Solid-phase synthesis of chiral 3,4-diazaphospholanes and their application to catalytic asymmetric allylic alkylation

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Functionalized chiral diazaphospholanes ligate to a variety of transition metals, yielding chiral, catalytically active, metal complexes. Previous work has established that amino acid derivatization of the carboxyl groups of (R,R)-N,N'-phthaloyl-2,3-(2-carboxyphenyl)-phenyl-3,4-diazaphospholane (1) yields phosphines that are excellent ligands for palladium-catalyzed asymmetric allylic alkylation reactions. Alanine functionalization is particularly effective for allylic alkylation of 1,3-dimethylallyl acetate. Standard Merrifield resins and amino acid coupling methods are used to synthesize the bead-attached phosphine having the topology bead-linker-Ala-(R,R)-1-Ala-OMe, as a 1:1 mixture of linkage isomers. Use of this supported phosphine in Pd-catalyzed asymmetric allylic alkylation yields 92% enantiomeric excess, matching prior results. A 20-member collection of amino acid-functionalized phosphines on beads with the topology bead-linker-AA2-AA1-1-AA1-AA2 was synthesized by using parallel solid-phase methods and screened for efficacy in allylic alkylation. Resulting enantioselectivities indicate that the AA1 position has the strongest effect on the reaction. Catalyst activities can vary widely with the nature of the phosphine ligand and the reaction conditions. Meaningful analysis of intrinsic catalytic activities awaits identification of the structure and abundance of the active catalyst.

Unfortunately, the existing syntheses of such phosphines were not tolerant of most functional groups. This problem was overcome by creating a simple, rapid, and general synthesis of phospholane analogs, 3,4-diazaphospholanes (5–7).

Racemic 3,4-diazaphospholanes form in high yield upon condensing a primary phosphine with azines and an acid dichloride (5) (Fig. 2). Azines are simply synthesized from aldehydes and hydrazine. The reaction generally exhibits remarkable selectivity for the rac product and tolerates the presence of functional groups in the azine (basic functional groups such as amines are the primary exception). Bis-3,4-diazaphospholanes also can be synthesized by using bis primary phosphines and can be isolated as pure rac materials, although in somewhat low overall yields (∼30%). This chemistry demonstrates that a wide variety of highly functionalized chiral phospholane structures can be synthesized rapidly from simple starting materials. However, enantioselective catalysis requires access to a wide range of resolved chiral ligands.

The synthesis of the diazaphospholane 1 derived from 2-carboxybenzaldehyde provides an easily resolved diazaphospholane bearing a carboxylic acid that can be further derivatized by using many available methods for coupling and reducing carboxylic acid groups (7). Most importantly, the racemic diazaphospholane is resolved in >99% enantiomeric excess (ee) by simple crystallization of diastereomeric salts made with α-methylbenzylation enantiomers. Furthermore, the presence of the carboxylic acid groups permits further functionalization by coupling with amines and amino acids. Attachment of several amino acids or other bifunctional fragments enables truly combinatorial ligand development from a single phosphine precursor.

Although hundreds of chiral phosphine ligands have been reported in the literature, the creation of combinatorial libraries (for a general review of combinatorial library synthesis see ref. 8; see also refs. 9–13) of phosphine ligands is a recent phenomenon (14–23). Mannich condensation reactions for the combinatory synthesis of chiral phosphines are covered in this article.

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Abbreviations: AAA, asymmetric allylic alkylation; ee, enantiomeric excess; MAS-NMR, magic-angle spinning NMR; PS, polystyrene; EBES (2,2'-ethylenedioxy)bis(ethylamino)monosuccinimide; Boc, tert-butoxycarbonyl; Fmoc, fluorenylmethoxycarbonyl; DMF, dimethylformamide; HOBt, hydroxybenzotriazole; DIC, N,N'-diisopropylcarbodiimide; MBHA, methylbenzhydrylamine.

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that catalysis with such libraries may be evaluated in solution and in the solid phase, based on unnatural phosphine-functionalized polypeptides (20). Most relevant to this work, Gilbertson and coworkers have reported by LaPointe (14) and by Portnoy and coworkers (15) chemical combinatorial synthesis of achiral phosphine ligand collections have been reported. This seminal work has demonstrated that catalysis with such libraries may be evaluated “on-bead,” and the discovery of effective new phosphine ligands based on β-hairpin structures has been reported.

Of the many applications of chiral phosphines to enantioselective catalysis, we have focused on AAA (see Fig. 3) for testing simple monophosphine ligand libraries derived from 1 (7). In particular, we have focused on the substrate 1,3-dimethylyallyl acetate, because so few ligands are capable of effecting this transformation with >85% ee at ambient or higher temperatures (24–26). Our recently reported results for this AAA reaction demonstrated several notable features for small libraries based on 1: (i) High ee (92%) is obtained with the alanine-derivatized ligand, a value that is similar to the state of the art. (ii) Chemical yields and especially enantioselectivities are exquisitely sensitive to minor variations in the amino acid structure; e.g., alanine gives very high ee but phenylglycine and phenylalanine of the same group have pio-

Solution-phase synthesis of ligand libraries involves extensive manual manipulations and purification steps. Solid-phase synthesis has the advantages of facilitated purification and adaptability to both parallel and split-pool combinatorial synthetic strategies (27–33). Our construction of chiral solid-supported phosphine ligands involves coupling of common cross-linked Merrifield resins, by a linker, to amino acids and phosphines with the general topology bead-linker-αααα-αααα (Fig. 4). The first application of this strategy is to synthesize a high-purity chiral immobilized phosphine with αααα = Ala and n = 1, characterize this ligand on-bead, by means of magic-angle spinning NMR (MAS-NMR) methods, and explore the efficiency of supported-Pd AAA catalysts. A second application involves application of combinatorial techniques to synthesize a small demonstration library of supported phosphines for the purpose of screening potentially interesting candidates for further study.

Materials and Methods
Synthesis of diazaphospholane 1 followed previously reported procedures (7). Solution-phase syntheses used the general procedures reported previously. Full details of the synthesis and characterization of all new synthetic intermediates are reported in Supporting Materials and Methods, which is published as supporting information on the PNAS web site.

General Synthesis of Immobilized Array. Fig. 4 outlines the overall procedure for solid-phase synthesis of the amino acid-functionalized phosphines. Methylbenzhydrolamine (MBHA)-functionalized PS resin (75 mg) was placed in 20 PolyPrep chromatography columns (Bio-Rad). Each coupling step was performed in parallel by using the DIC/HOBt coupling protocol in 1:4 DMF/CH₂Cl₂, and the reactions were mixed overnight on a shaker. All reactants were added in large excess relative to the immobilized material (4–5 eq). The resins were isolated after each coupling cycle by thorough washings with DMF, CH₂Cl₂, and MeOH. Removal of the Fmoc protecting group was effected by adding 20% piperidine in DMF solutions to the resins and mixing for 30 min. The Boc and t-buty1 ester protecting groups were removed by treatment with trifluoroacetic acid. A t-buty1 cation scavenger mixture of 2.5% trisopropylsilane and 2.5% water was also used during the ester deprotection. MAS-NMR characterization of products indicated that scavengers are necessary to minimize the appearance of additional phosphine-containing impurities as identified by 31P NMR. The final products exhibit little oxygen sensitivity; 31P NMR spectroscopy reveals that moderate exclusion of oxygen during the coupling steps involving the diazaphospholane prevents oxidation.

Allylic Alkylation Procedure. Methylene chloride (2.0 ml) was added to a septum-sealed 3-dram (11-ml) vial containing [(η⁵-C₅H₅)₂PdCl₂] (1.8 mg, 5 μmol), phosphine (10 μmol or 15–20 mg of resin), tetra-n-butylammonium fluoride trihydrate (~5 mg), and NaPF₆ under N₂. After stirring the solution at room temperature for 5 min, N,O-bis(trimethylsilyl)acetamide (0.70 ml, 3.0 mmol), dimethyl malonate (0.30 ml, 3.0 mmol), and 1,3-dimethyllyl acetate (0.15 ml, 1.0 mmol) were added. The mixture was stirred for 17 h at room temperature. The products were diluted with 6 ml of 5:1 hexane/ethyl acetate and filtered twice through plugs of silica. The enantiomeric excess of the product was determined by chiral GC (Supelco β-DEX 120 column, 30 m × 0.25 mm i.d., column temperature 70°C, flow rate 1.8 ml/min). The absolute configuration of products was determined by comparison of GC retention times with results obtained previously (7).

Results and Discussion
Solid-Phase Synthesis of Alanine Diazaphospholane (Bead-Linker-Ala-1-Ala). Incorporation of amino acid-functionalized 3,4-diazaphospholanes onto PS beads used a combination of Fmoc and Boc amino acid coupling techniques. Starting with MBHA-PS resin, chosen for stability to the trifluoroacetic acid and basic treatments, a polyethylene glycol-like linker, EBES (34), was attached to the resin. This linker enables high-quality NMR characterization by MAS-NMR spectroscopy and yields a more homogeneous environment for the immobilized phosphine sites.

Landis and Clark
Four coupling steps are necessary to synthesize the immobilized L-alanine diazaphospholane analog. Because there is little selectivity over which of the two inequivalent phospholane carboxylic acids couples with the amino acid-functionalized resin, two linkage isomers result. Correspondingly, characterization with $^{31}$P MAS-NMR reveals two resonances (Fig. 5). The $^1$H MAS-NMR spectra exhibit reasonably narrow lines but are less useful for detailed characterization because of overlap of the Ala-1-Ala-OMe resonances with the resin and linker resonances.

Asymmetric allylic alkylation of dimethylallyl acetate with dimethylmalonate in the presence of 0.5 mol % [Pd(allyl)Cl]$_2$, $\approx$1 mol % immobilized PS-linker-Ala-1-Ala, N,O-bis(trimethylsilyl)acetamide, sodium hexafluorophosphate, and tetrabutylammonium fluoride in dichloromethane solution at room temperature for 17 h gives the alkylated allyl in 92% ee and 67% yield. Importantly, the immobilized monophosphine matches the enantioselectivity previously demonstrated for its homogeneous counterpart (93%). Although others have reported difficulty matching homogeneous selectivities and activities with ligands immobilized on standard Merrifield resins (27, 28), this work demonstrates that the combination of bead cross-linking, EBES linker, and amino acids yields active immobilized catalysts with solution-like properties.

Results with immobilized 1 support our previous formulation of the catalytically active species (7). Previously we postulated that the active AAA catalyst consists of a Pd center bound to one molecule of 1. In support, the crude kinetics of allylic alkylation and the enantioselectivities were independent of the ratio of 1 to Pd over the range of 1:1 to 4:1. Immobilization of 1 on resin beads provides high isolation of phosphine sites, essentially preventing formation of bis(phosphine)Pd complexes. Thus, the observation of identical enantioselectivities in solution and with immobilized 1 virtually requires that the active catalyst is a 1:1 phosphine:Pd adduct.

**Design and Synthesis of 3 × 7 Array of Tetrapeptide Diazaphospholanes (Bead-Linker-AA$_2$-AA$_1$-1-AA$_1$-AA$_2$).** Previous solution work found functionalization of 1 with amino acids bearing small alkyl side chains to be most effective in the AAA reaction. Therefore, we chose to explore three simple apolar residues, Ala, Leu, and Val, in the positions (AA$_1$ in Fig. 4) adjacent to 1. With the goal of further fine-tuning the catalyst selectivity, seven different amino acids of varying bulk and functionality were attached in the AA$_2$ position. Building the immobilized ligand in one
direction requires a switch from N-protected to C-protected amino acids after the diaacid phospholane is incorporated. Empirically we found the r-butyli ester to perform better than the methyl ester in the last deprotection step. Deprotection of r-butyli esters spontaneously proceeds under standard conditions for Boc-group removal. As before, each bead contains two linkage isomers. The diazaphospholane structure is quite robust under acidic conditions, and solution-phase testing shows no decomposition of the diazaphospholane under the deprotection conditions.

To minimize oxidation at phosphorus of the 20-member array, each reaction involving the phosphine was prepared and sealed while inside a glove bag. A solvent mixture of 4:1 methylene chloride/DMF provides enough polarity to dissolve all reactants and has sufficient density to suspend the resins, ensuring maximum agitation. Resins were dried overnight and stored in a glove box.

**Allylic Alkylation with Solid-Phase 3 × 7 Array of Tetrapeptide Diazaphospholanes**. Fig. 6 displays the enantioselectivities obtained with the small library. All products have the S configuration. As expected, the impact of the second amino acid (AA 2) was much less than AA 1. Large unpredictable variations in selectivities and rates accompanied changes in AA 1, with Ala clearly superior. With Ala at AA 1, the best selectivities were obtained with either Met or Val at AA 2. Significantly poorer results were obtained with Leu or Phe at AA 2. The general unpredictability of the results demonstrates the need for empirical screening.

**Solution Phase Allylic Alkylation with Tetrapeptide Diazaphospholanes**. Soluble versions of three of the phosphines from the screen were synthesized: Ala × Met, Ala × Ala, and Val × Ala (listed as AA 1 × AA 2). The purpose of this study was to compare solution and solid-phase behavior for a representative sample from the small library with a special eye toward evaluating whether poor performance of solid-phase materials originated from impurities accumulated during solid-phase synthesis. In agreement with solid-phase data, the Val × Ala diazaphospholane yielded poor enantioselectivity (47% ee solution, 50% ee solid phase). The solution diazaphospholanes containing Ala in the AA 1 position, Ala × Met and Ala × Ala, catalyzed the reaction with high selectivities, 91% and 71% ee, respectively. As far as enantioselectivity is concerned, bead and solution-phase behaviors are identical.

Overall activities on-bead appear to be lower than solution activities by factors of 1.5–4. This observation does underscore the advantage of examining a reaction, such as asymmetric allylic alkylation, that is “ligand accelerated” (refs. 24 and 25; we thank one of the manuscript reviewers for pointing this out) when screening bead-based ligand libraries. Even if not all immobilized ligand sites are accessible to the catalyst precursor, nonligated metal species do not form significant product and lower the overall reaction selectivity, although the apparent activities may be lower. At this point it is unclear why the supported catalysts exhibit lower activity. It appears that effective catalysis of asymmetric allylic alkylation with amino acid-functionalized diazaphospholanes requires ionization of the catalyst precursor Pd–Cl bonds as indicated by the requirement for sodium or silver hexafluorophosphate salts. Future work should focus on broader screening with halide-free catalysts and more detailed mechanistic investigations of the catalytic process.

In summary, 3,4-diazaphospholanes are versatile ligands for asymmetric catalysis. The readily resolved diacid 1 enables synthesis of both solution and solid-phase ligands by using well developed amino acid chemistry. This work complements Gilbertson and coworkers’ pioneering work in the sense that the diazaphospholane is intrinsically chiral and relies on small peptides for tuning of the catalyst environment. In contrast, Gilbertson’s ligands involve rather simple phosphine fragments that rely on peptide secondary structure for the development of asymmetry. Both approaches lend themselves to combinatorial modification.

The synthesis and screening of the small library reported herein demonstrates that (i) solid-phase synthetic techniques using MBHA-functionalized PS beads are suitable for making libraries of diazaphospholanes; (ii) AAA with these ligands can lead to state-of-the-art selectivity for a difficult substrate under both homogeneous and supported catalyst conditions; and (iii) ligands derived from 1 exhibit exquisite sensitivity to amino acid modification that is difficult to predict a priori, thus validating a screening approach. Significantly, the strategy outlined here should be generalizable to a large number of metal–phosphine-promoted transformations. Continuing to explore diazaphospholane modifications and applications to asymmetric catalysis should prove fruitful. With respect to asymmetric alkylations, the foci are expanding the range of substrates and nucleophiles as well as probing mechanistic features of the reactions.

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