Solid-Phase Synthesis of a Peptide-Based P,S-Ligand System Designed for Generation of Combinatorial Catalyst Libraries

Christian A. Christensen and Morten Meldal*

Carlsberg Laboratory, SPOCC-Centre, Gamle Carlsbergvej 10, DK-2500 Valby, Denmark

Received May 4, 2006

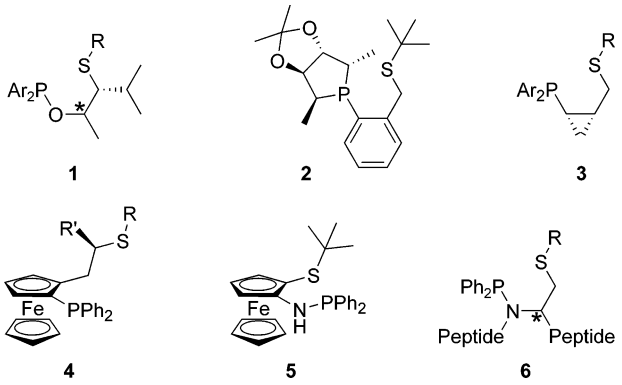
An efficient methodology for the solid-phase synthesis of diverse combinatorial peptide-based P,S-ligand libraries based on a modular approach was developed. Chiral thioethers were introduced into a series of peptide scaffolds using commercially available Fmoc-protected cysteine derivatives, and secondary amines were incorporated into the peptide backbones by reductive alkylation using readily available Fmoc-protected amino aldehydes. Phosphinylation of the secondary amines of the scaffolds, applying two different reagents, yielded two different types of ligands. Subsequent complexation with palladium afforded six- or seven-membered chelates, respectively. The selectivity, in an asymmetric allylic substitution reaction, of the two different types of chelates, derived from the same peptide scaffold, was complementary in all cases studied, affording the product as opposite stereoisomers with up to 60% ee. These results hold great promise for the identification of highly selective catalysts upon screening of larger P,S-based catalyst libraries.

Introduction

Much effort has gone into the development of new transition metal catalysts for asymmetric organic synthesis, especially in the design of ligands.[1] In that context, bidentate, mixed heteroatom ligands have proven to be very useful. One class of such ligands is the P,S-ligands,[2] which have been successfully applied in the palladium-catalyzed allylic substitution reaction.[3] Recent examples include **1** by Evans et al.,[2a] mannitol-derived ligand **2**,[2b] cyclopropane-based ligands **3**,[2c] and ferrocenyl ligands **4**[2d] and **5**[2e] (see Chart 1). Even though rational and iterative design of ligands has led to highly selective catalysts, these catalysts have been optimized for a single reaction type and often fine-tuned for a single substrate in a process that is time-consuming. Furthermore, such catalysts are rarely very selective for other substrates or types of reactions. Alternatively, high-throughput screening of combinatorial libraries of potential catalysts would be a more general method for rapid selection of a highly selective catalyst for each new reaction or synthetic challenge.[4] Immobilization of library members on individual beads would greatly facilitate this screening.

To generate catalyst libraries, it is obvious to utilize the methodologies developed for the solid-phase synthesis of combinatorial peptide libraries.[5] The synthesis is modular, and it benefits from the readily available chiral pool of both natural and synthetic amino acids. Furthermore, being of intermediate size, peptide-based catalysts would possibly inherit some of the selectivity and increased reactivity known from enzymes, due to binding of the substrate by a folded peptide scaffold. Thus, it was decided to develop and study a new P,S-ligand system, **6**, inspired by the homogeneous ligands **1**−**5**, which was incorporated into a peptide sequence and which could be synthesized in a combinatorial manner on solid support.

Chart 1. Examples of P,S-Ligands



Results and Discussion

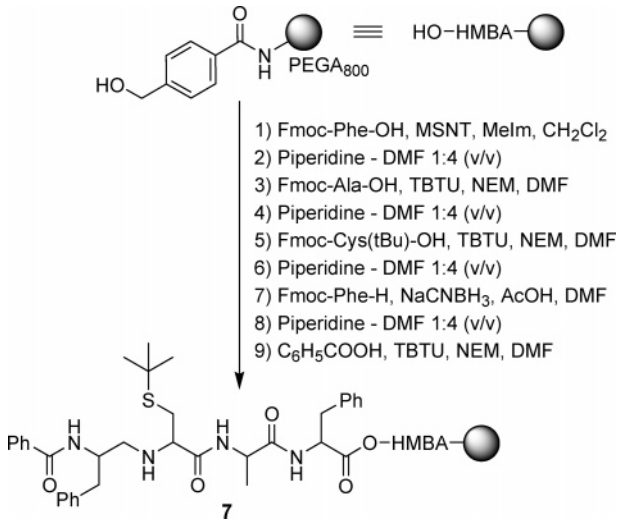
We recently reported a methodology developed for the solid-phase synthesis of combinatorial libraries of peptide-based bidentate phosphine ligands.[6] The key step was the solid-phase phosphinomethylation of secondary amines, which were incorporated into the backbone of a peptide scaffold by reductive alkylation. For the synthesis of **6**, the many readily available cysteine derivatives could be a rich source of chiral thioethers, and reductive alkylation of the cysteine amine would subsequently furnish a secondary amine and thereby a peptide scaffold that could serve as a precursor for ligand **6**. Thus, peptide scaffold **7** was synthesized following the Fmoc protocol[7] for solid-phase peptide synthesis (Scheme 1).

For the synthesis of scaffold **7**, $PEGA_{800}$ resin[8] and the base labile hydroxymethylbenzoic acid (HMBA) linker were used. PEGA resin has good swelling properties in a wide range of organic solvents as well as in water, and it has

* To whom correspondence should be addressed. E-mail: mpm@crc.dk.

10.1021/cc0600627 CCC: $37.00
Published on Web 12/22/2006

Scheme 1. Solid-Phase Synthesis of a Peptide Scaffold[a]



[a] PEGA = poly(ethylene glycol) polyacrylamide copolymer, MSNT = 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole, MeIM = methylimidazole, DMF = *N*,*N*-dimethylformamide, TBTU = *N*-[(1*H*-benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide, NEM = *N*-ethylmorpholine.

proven to be well-suited as a support for catalysts.[6] The cysteine derivative used for **7** was *tert*-butyl-substituted, since for most of the ligand systems **1**−**5**, bulky substituents on sulfur yielded the highest selectivities. The secondary amine of **7** was obtained by reductive alkylation of the cysteine residue using Fmoc-protected phenylalaninal,[9] making the amine relatively sterically hindered. Capping using benzoic acid afforded **7**.

In total, a series of four different scaffolds, **7a**−**d** (Scheme 2), were synthesized. They differed only in the configuration of the cysteine residue and the phenyl alanine residue that was introduced by reductive alkylation, that is, the two residues making up the substituents of the formed secondary amine. This was done to investigate which residues were more important for the selectivity of the derived catalyst.

To obtain a ligand affording a favored six-membered chelate, as for ligands **1**, **2**, **3**, and **5**, scaffolds **7a**−**d** were phosphinylated using diphenylphosphine chloride in the presence of *N*-ethylmorpholine to give resin-bound ligands **8a**−**d**. This solid-phase reaction had previously been performed only on the relatively unhindered secondary amine of a terminal proline,[10] but by raising the concentration, the hindered amines of **7a**−**d** could also be fully converted.

Since a methodology for the phosphinomethylation of hindered secondary amines such as **7a**−**d** had already been developed,[6] ligands **9a**−**d** were also synthesized and investigated for their catalytic properties on solid support. Compounds **9a**−**d** were obtained in an overnight condensation reaction using hydroxymethyldiphenylphosphine.[11] The complexes derived from ligands **8a**−**d** are six-membered chelates, whereas ligands **9a**−**d** afford seven-membered chelates; however, both ligand series can be obtained from the same precursor scaffolds **7a**−**d**. For the generation of combinatorial libraries, this provides an extra point of diversity. Thus, a library of scaffolds could be functionalized not only using differently substituted phosphine chlorides, but also using different hydroxymethylphosphines, affording phosphinomethylene moieties instead of phosphine moieties.

For solution-phase analysis, samples of the ligands **8a**−**d** and **9a**−**d** were oxidized using a dilute aqueous solution of hydrogen peroxide before cleavage from the solid support, affording oxidized ligands **12a**−**d** and **13a**−**d**, respectively (Scheme 3). Oxidation was performed to avoid partial oxidation of the ligands **8a**−**d** and **9a**−**d** during analysis, which would give rise to several species and, thus, not represent a true picture of the purity of the synthesized ligands on solid support.[12]

In Figure 1, the crude HPLC chromatograms of cleaved peptide scaffold **7a** and the oxidized ligands **12a** and **13a** are shown. As can be seen, the starting material **7a** was fully converted to either **12a** or **13a**, affording the oxidized ligands in high purity. Furthermore, synthesis of the oxidized ligands **12a**−**d** and **13a**−**d** was repeated several times, and in all cases, the high purity could be reproduced. This is important, since the ligands should remain immobilized on solid support during catalysis, which prohibits purification of the products.

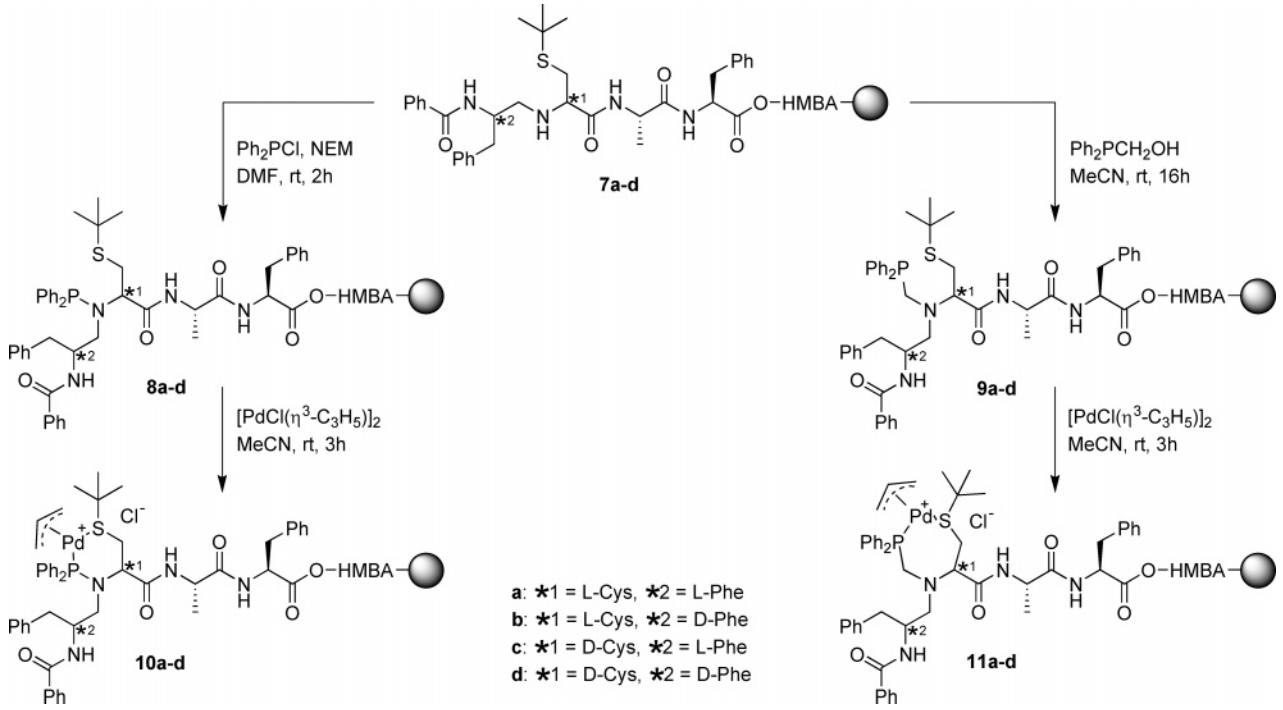
Freshly prepared portions of ligands **8a**−**d** and **9a**−**d** were treated with a solution of allyl palladium chloride dimer in acetonitrile to give the six-membered chelates **10a**−**d** and the seven-membered chelates **11a**−**d**, respectively. To study the catalytic properties of the resin-bound complexes, a palladium-catalyzed asymmetric allylic substitution reaction[3] was carried out. Not only is this a common model reaction for evaluation of mixed P,S-ligands, it has also found widespread use in the synthesis of a number of bioactive targets.[13] Thus, freshly prepared **10a**−**d** and **11a**−**d** were used in 5 mol % (based on the initial resin loading reported by the manufacturer) for the reaction of 1,3-diphenylpropenyl acetate **14** with dimethylmalonate **15** under basic conditions[14] (Scheme 4).

After 3 h, the reactions were worked up, and **16** was isolated as a mixture of enantiomers. The enantiomeric excess was determined by ^{1}H NMR using the chiral shift reagent [Eu(hfc)$_3$].[15] Isolated yields after column chromatography and ee values are listed in Table 1.

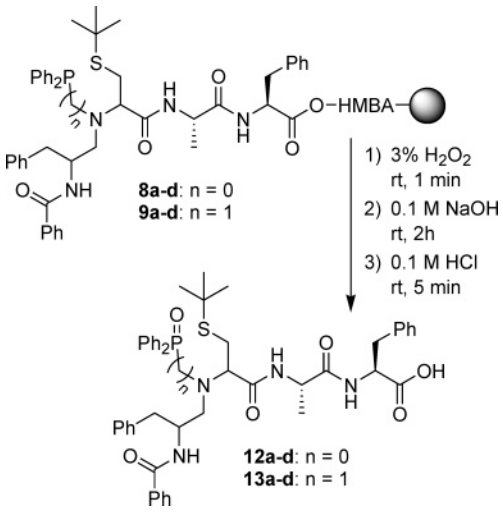
The enantioselectivities range from 28 to 60%, and the yields are near quantitative for **11a**−**d**, but slightly lower for **10a**−**d**. Both the yields and the enantioselectivities were reproducible; however, a fresh batch of catalyst was needed for each experiment.[16] Interestingly, a change in the configuration of the cysteine residue changes the configuration of the product **16**, whereas the configuration of the phenylalanine residue only influences the catalyst selectivity to a lesser extent. This makes good sense, since the cysteine residue is part of the chelate ring, whereas the phenylalanine residue is only a neighboring group.

Even more interesting is the comparison of the different catalysts **10** and **11** originating from the same scaffold **7**. In all four cases, **a**−**d** going from the six-membered chelate **10** to the seven-membered chelate **11** causes inversion of product configuration (i.e., **10a** affords (*R*)-**16**, whereas **11a** affords (*S*)-**16**, etc.), due to insertion of only a single methylene spacer in the chelate ring. The highest selectivity is observed for catalyst **11c** (60%, *R*) whereas its counterpart **10c** affords the lowest selectivity (28%, *S*), even though both

Scheme 2. Two Series of Two Different Types of Catalysts Derived from the Same Series of Peptide Scaffolds



Scheme 3. Oxidation and Cleavage of Ligands for Analysis



catalysts are derived from the same peptide scaffold **7c**. These results could not have been predicted, and rational design would hardly have suggested the insertion of a methylene spacer to completely invert the selectivity of the catalysts. This underlines the strengths of using a modular and highly diverse methodology designed for the generation of combinatorial libraries of potential catalysts.

Conclusions

A new methodology for the synthesis of solid-supported peptide-based P,S-ligands was successfully developed, exploiting the readily available chiral pool of cysteine derivatives and the possibility of using two different types of phosphinylation reagents for the solid-phase phosphinylation of peptides. Thus, from a series of four peptide scaffolds, a collection of eight catalysts was obtained. The strength of this combinatorial approach was proven by the very different selectivities of the catalysts, in that it was possible to obtain both enantiomers of the product of the trial asymmetric allylic substitution reaction with an enantioselectivity of up to 60% ee. The unpredictable relationship between catalyst structure and enantioselectivity further emphasizes the need for combinatorial approaches to synthesize highly selective catalysts for a wide range of reactions and substrates. Together with the development of new general high-throughput screening methods, this should lead to a very powerful tool in organic synthesis.

Experimental Section

ESMS spectra were recorded on a Micromass QTOF Global Ultima instrument, and high-resolution MS was determined using an appropriate internal reference. ^{1}H NMR and ^{31}P NMR spectra were recorded on a Bruker DRX250 250-MHz instrument. Chemical shifts for ^{1}H spectra are reported in parts per million relative to the internal solvent peak (2.50 ppm for DMSO-d_6 and 7.26 for chloroform-*d*) and for ^{31}P spectra referenced against H_3PO_4. For the oxidized ligands **12**−**13**, NMR spectra were recorded of their sodium salts to avoid zwitterionic species and since the P−N bond in **12** is very acid-labile. Solid-phase reactions were performed in flat-bottomed polyethylene syringes equipped with sintered Teflon filters (50 μm pores), Teflon tubing, Teflon valves for flow control, and suction to drain the syringes from below. For solid-phase reactions carried out under argon, the syringes were equipped with a rubber septum and an argon inlet.

Analytical and preparative RP-HPLC were performed on a Waters HPLC system using Merck Chromolith SpeedROD RP-18e (4.6 × 50 mm) and Delta PAK (20 × 200 mm) C_{18} columns with a flow rate of 5 and 10 cm^3 min^{-1}, respectively. Detection was at 215 nm on a multiwavelenght detector (Shimadzu SPD-6A) for analytical purposes and a photodiode

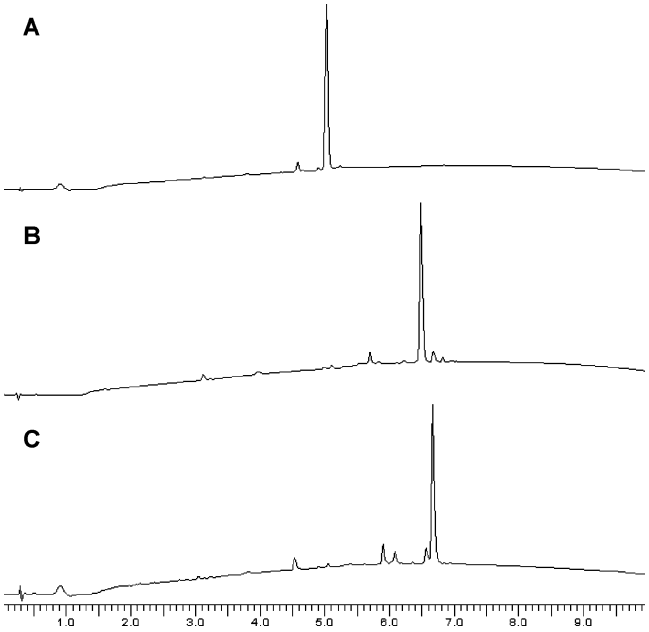


Figure 1. Reversed-phase HPLC chromatograms of crude compounds: (A) cleaved peptide scaffold **7a**, (B) oxidized ligand **12a**, and (C) oxidized ligand **13a**.

Scheme 4. Palladium-Catalyzed Asymmetric Allylic Substitution

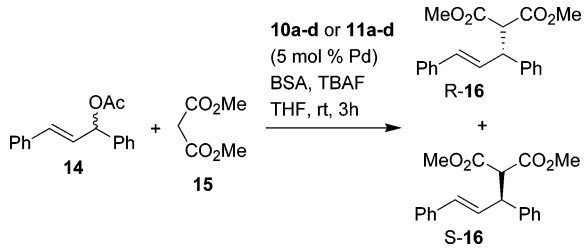


Table 1. Palladium-Catalyzed Asymmetric Allylic Substitution[a]

entry	catalyst	yield of **16** (%)[b]	ee of **16** (%)[c]	configuration
1	**10a**	88	41	R
2	**10b**	94	32	R
3	**10c**	85	28	S
4	**10d**	77	39	S
5	**11a**	96	44	S
6	**11b**	98	55	S
7	**11c**	94	60	R
8	**11d**	95	41	R

[a] All reactions were performed at room temperature in acetonitrile using 5 mol % Pd, based on the initial resin loading. [b] Isolated yield. [c] Determined by ^{1}H NMR using a chiral shift reagent.

array detector (Waters M991) for preparative separations. All RP-HPLC procedures were carried out using buffers A (0.1% TFA in H_2O) and B (0.1% TFA in MeCN−H_2O, 9:1) with a linear gradient (for analytical RP-HPLC: 100% A → 100% B in 10 min, t_R values refer to this system).

$PEGA_{800}$ was from VersaMatrix, Denmark. All solvents were HPLC grade. Anhydrous solvents were obtained by storing over 3-Å activated molecular sieves. Degassed solutions were obtained by bubbling with argon for 30 min. All other starting materials from suppliers were used without further purification.

General Procedure for Peptide Couplings. *N*-[(1*H*-Benzotriazol-1-yl)-(dimethylamino)methylene]-*N*-methylmethanaminium tetrafluoroborate *N*-oxide (TBTU) couplings, were performed by dissolving the acid (3 equiv) in *N*,*N*-dimethylformamide with NEM (4 equiv), followed by addition of TBTU (2.9 equiv). The resulting solution was left for preactivation for 5 min before being added to the resin (reaction time 2−3 h). Peptide couplings were generally run in an amount of solvent just sufficient to cover the resin. After reaction, the resin was washed with *N*,*N*-dimethylformamide (×6) and methanol (×2) and, finally, checked using the Kaiser test.[17]

General Procedure for Fmoc Deprotection. Fmoc deprotection was achieved with 20% piperidine in *N*,*N*-dimethylformamide (v/v) for 2 + 18 min, followed by washing of the resin with *N*,*N*-dimethylformamide (×6) and methanol (×2). The cleavage was checked using the Kaiser test.[17]

General Procedure for Cleavage of Resin-Supported Peptides. Cleavage of peptides was achieved with 0.1 M aqueous NaOH for 2 h, followed by neutralization with 0.1 M aqueous HCl.

Typical Procedure for the Synthesis of Peptide Scaffolds 7a−d. $PEGA_{800}$ (1.00 g, loading 0.38 mmol/g, 0.38 mmol) was coupled with Fmoc-Gly−OH using TBTU activation according to the general procedure, whereupon the Fmoc groups were removed. The HMBA linker was attached by TBTU coupling, whereupon the resin was dried in vacuo in the presence of phosphorus pentaoxide overnight. A solution of Fmoc-Phe−OH (3 equiv) and *N*-methylimidazole (2.25 equiv) in dry dichloromethane was added to 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT, 3 equiv), and the resulting solution was transferred to the dry resin and reacted for 1 h. The resin was washed with dry dichloromethane (×3), and the MSNT coupling was repeated. The resin was washed with dichloromethane (×6) and *N*,*N*-dimethylformamide (×6), whereupon the Fmoc groups were removed. Elongation with Fmoc-Ala−OH and Fmoc-Cys(*t*Bu)−OH by TBTU coupling was followed by reductive alkylation using Fmoc-phenylalaninal. Two solutions of the same volume were prepared so that the total volume was just enough to cover the resin. Solution 1: sodium cyanoborohydride (20 equiv) and 4% (v/v) glacial acetic acid were dissolved in *N*,*N*-dimethylformamide. Solution 2: Fmoc-phenylalaninal[9] (10 equiv) was dissolved in *N*,*N*-dimethylformamide. Solution 1 was added to the resin possessing the free amine of the cysteine residue. The resin was stirred for 1 min, whereupon solution 2 was added while stirring. The resin was left to react for 3 h, drained, and washed with *N*,*N*-dimethylformamide (×6) and methanol (×2). The reaction was checked using the Kaiser test.[17] Removal of Fmoc groups and TBTU coupling of benzoic acid afforded peptide scaffold **7**. A small sample of **7** was cleaved for analytical HPLC and HRMS.

Phenyl-L-Phe-ψ[CH_2N]-L-Cys(*t*Bu)-L-Ala-L-Phe−OH (7a). Analytical RP-HPLC: t_R = 5.02 min, >95% purity; HRMS (ES) calcd for $C_{35}H_{45}N_4O_5S$ $[MH]^+$, 633.3105; found, 633.3098.

Phenyl-D-Phe-ψ[CH$_2$N]-L-Cys(*t*Bu)-L-Ala-L-Phe−OH (7b). Analytical RP-HPLC: t_R = 5.02 min, >95% purity; HRMS (ES) calcd for $C_{35}H_{45}N_4O_5S$ [MH]$^+$, 633.3105; found, 633.3102.

Phenyl-L-Phe-ψ[CH$_2$N]-D-Cys(*t*Bu)-L-Ala-L-Phe−OH (7c). Analytical RP-HPLC: t_R = 5.04 min, >95% purity; HRMS (ES) calcd for $C_{35}H_{45}N_4O_5S$ [MH]$^+$, 633.3105; found, 633.3097.

Phenyl-D-Phe-ψ[CH$_2$N]-D-Cys(*t*Bu)-L-Ala-L-Phe−OH (7d). Analytical RP-HPLC: t_R = 5.05 min, >95% purity; HRMS (ES) calcd for $C_{35}H_{45}N_4O_5S$ [MH]$^+$, 633.3105; found, 633.3100.

Typical Procedure for the Synthesis of Ligands 8a−d: Phosphinylation. Resin **7** was dried in vacuo over phosphorus pentaoxide overnight and flushed with argon. To a dry, degassed 0.75 M solution of NEM in DMF (30 mL) was added diphenylphosphine chloride (1.39 mL, 7.5 mmol), making the solution 0.25 M relative to diphenylphosphine chloride. The reagent mixture was stirred under argon at room temperature for 5 min, whereupon a fraction of it (3× the swelling volume of the resin) was added to the dry resin (25 equiv). The resin was kept under argon and allowed to react for 2 h, after which time it was drained and washed under argon with a dry degassed 0.75 M solution of NEM in DMF (×2) and dry degassed acetonitrile (×4). At this stage, the batch of resin was used directly for the synthesis of either oxidized ligand **12** or the palladium complex **10** (see below).

Typical Procedure for the Synthesis of Ligands 9a-d: Phosphinomethylation. Neat paraformaldehyde (1 equiv) and diphenylphosphine (1 equiv) were heated at 110 °C for 1.5 h under argon, affording hydroxymethyldiphenylphosphine. The resin was dried in vacuo overnight and flushed with argon. To the resin was added a 0.20 M solution of hydroxymethyldiphenylphosphine in degassed acetonitrile (3× the volume needed to swell the resin, 20 equiv). The resin was allowed to react under argon for 12 h at room temperature, drained, and washed with degassed acetonitrile (×6) under argon. At this stage, the batch of resin was used directly for the synthesis of either oxidized ligand **13** or the palladium complex **11**, see below.

General Procedure for Oxidation of Phosphine Ligands. The freshly prepared resin-bound phosphine ligand was washed with a 3% aqueous solution of hydrogen peroxide (×1), whereupon the hydrogen peroxide solution was added to cover the resin for 1 min. The resin was drained and washed with methanol (×2), *N*,*N*-dimethylformamide (×6), methanol (×2), and dichloromethane (×2), whereupon it was dried in vacuo.

Oxidized Phosphine Ligands (12a−d) . Freshly prepared resins **8a−d** (from 200 mg of resin **7a−d**, 0.058 mmol) were oxidized following the general procedure to give the oxidized resin-bound ligands **12a−d**. The oxidized ligands **12a−d** (from 200 mg of resin **7a−d**, 0.058 mmol) were cleaved to give amorphous colorless solids.

12a. The crude product was purified by preparative RP-HPLC (39 mg, 81%). Analytical RP-HPLC: t_R = 6.49 min; ^{1}H NMR (DMSO-d_6): δ 8.55 (d, J = 7.5 Hz, 1H; amide), 8.30 (d, J = 7.8 Hz, 1H; amide), 7.90−7.35 (m, 16H; amide, arom. H), 7.24−7.00 (m, 10H; arom. H), 4.53−4.41 (m, 1H; Phe CH$^\alpha$), 4.36−4.22 (m, 1H; Ala CH$^\alpha$), 4.17−4.05 (m, 1H; Phe CH$^\alpha$), 4.05−3.95 (m, 1H; Cys CH$^\alpha$), 3.40−2.78 (m, 7H; Phe CH$_2$N, Phe CH$_2$, Cys CH$_2$), 2.38−2.22 (m, 1H; Phe CH$_2$), 1.10 (d, J = 6.8 Hz, 3H; Ala CH$_3$), 1.06 (s, 9H; *t*Bu CH$_3$); ^{31}P NMR (DMSO-d_6): δ = 34.8; HRMS (ES) calcd for $C_{47}H_{54}N_4O_6PS$ [MH]$^+$, 833.3496; found, 833.3524.

12b. The crude product was purified by preparative RP-HPLC (40 mg, 83%). Analytical RP-HPLC: t_R = 6.69 min; ^{1}H NMR (DMSO-d_6): δ 8.97 (d, J = 7.8 Hz, 1H; amide), 8.44 (d, J = 9.3 Hz, 1H; amide), 8.21−8.13 (m, 2H; arom. H), 8.02−7.37 (m, 14H; amide, arom. H), 7.16−7.03 (m, 8H; arom. H), 6.73 (d, J = 6.8 Hz, 2H; arom. H), 4.43−4.37 (m, 1H; Ala CH$^\alpha$), 4.17−4.10 (m, 1H; Phe CH$^\alpha$), 4.04−3.91 (m, 1H; Phe CH$^\alpha$), 3.70−3.61 (m, 1H; Cys CH$^\alpha$), 3.18−2.79 (m, 5H; Phe CH$_2$, Cys CH$_2$, Phe CH$_2$N), 2.49−2.38 (m, 1H; Phe CH$_2$), 2.06−1.99 (m, 1H; Phe CH$_2$), 1.89−1.85 (m, 1H; Cys CH$_2$), 1.25 (d, J = 6.8 Hz, 3H; Ala CH$_3$), 0.56 (s, 9H; *t*Bu CH$_3$); ^{31}P NMR (DMSO-d_6): δ = 35.1; HRMS (ES) calcd for $C_{47}H_{54}N_4O_6PS$ [MH]$^+$, 833.3496; found, 833.3503.

12c. The crude product was purified by preparative RP-HPLC (42 mg, 88%). Analytical RP-HPLC: t_R = 6.83 min; ^{1}H NMR (DMSO-d_6): δ 9.06 (d, J = 7.3 Hz, 1H; amide), 8.38 (d, J = 9.0 Hz, 1H; amide), 8.18−7.00 (m, 24H; amide, arom. H), 6.74 (d, J = 6.5 Hz, 2H; arom. H), 4.39−4.28 (m, 1H; Ala CH$^\alpha$), 4.21−4.12 (m, 1H; Phe CH$^\alpha$), 3.91−3.79 (m, 1H; Phe CH$^\alpha$), 3.72−3.61 (m, 1H; Cys CH$^\alpha$), 3.34−2.92 (m, 5H; Phe CH$_2$, Cys CH$_2$, Phe CH$_2$N), 2.41−2.31 (m, 1H; Phe CH$_2$), 1.94−1.89 (m, 2H; Phe CH$_2$, Cys CH$_2$), 1.23 (d, J = 7.0 Hz, 3H; Ala CH$_3$), 0.58 (s, 9H; *t*Bu CH$_3$); ^{31}P NMR (DMSO-d_6): δ = 34.8; HRMS (ES) calcd for $C_{47}H_{54}N_4O_6PS$ [MH]$^+$, 833.3496; found, 833.3497.

12d. The crude product was purified by preparative RP-HPLC (43 mg, 90%). Analytical RP-HPLC: t_R = 6.67 min; ^{1}H NMR (DMSO-d_6): δ 8.47 (d, J = 6.5 Hz, 1H; amide), 8.32 (d, J = 7.5 Hz, 1H; amide), 8.02−7.36 (m, 16H; amide, arom. H), 7.16−7.03 (m, 10H; arom. H), 4.47−4.31 (m, 2H; Ala CH$^\alpha$, Phe CH$^\alpha$), 4.24−4.09 (m, 1H; Phe CH$^\alpha$), 4.07−3.90 (m, 1H; Cys CH$^\alpha$), 3.34−2.74 (m, 6H; Phe CH$_2$N, Phe CH$_2$, Cys CH$_2$), 2.61 (dd, J_1 = 12.5 Hz, J_2 = 6.0 Hz, 1H; Cys CH$_2$), 2.41−2.32 (m, 1H; Phe CH$_2$), 1.24 (d, J = 6.8 Hz, 3H; Ala CH$_3$), 1.01 (s, 9H; *t*Bu CH$_3$); ^{31}P NMR (DMSO-d_6): δ = 35.0; HRMS (ES) calcd for $C_{47}H_{54}N_4O_6PS$ [MH]$^+$, 833.3496; found, 833.3489.

Oxidized Phosphine Ligands (13a−d). Freshly prepared resins **9a−d** (from 200 mg of resin **7a−d**, 0.058 mmol) were oxidized following the general procedure to give the oxidized resin-bound ligands **13a−d**. The oxidized ligands **13a−d** (from 200 mg of resin **7a−d**, 0.058 mmol) were cleaved to give amorphous colorless solids.

13a. The crude product was purified by preparative RP-HPLC (40 mg, 82%). Analytical RP-HPLC: t_R = 6.67 min; ^{1}H NMR (DMSO-d_6): δ 8.50 (d, J = 7.8 Hz, 1H; amide), 8.10 (d, J = 7.5 Hz, 1H; amide), 7.89−7.72 (m, 6H; arom. H), 7.58−7.05 (m, 20H; amide, arom. H), 4.37−4.21 (br m, 1H; Phe CH$^\alpha$), 4.09 (pentet, J = 7.0 Hz, 1H; Ala CH$^\alpha$), 3.93 (q, J = 5.0 Hz, 1H; Phe CH$^\alpha$), 3.84−3.69 (m, 3H; Cys CH$^\alpha$, PCH$_2$), 3.11−3.04 (m, 2H; Phe CH$_2$N, Phe CH$_2$), 2.94−2.55

(m, 6H; Phe CH_2N, Phe CH_2, Cys CH_2), 1.15 (s, 9H; *t*Bu CH_3), 0.95 (d, $J = 7.0$ Hz, 3H; Ala CH_3); ^{31}P NMR (DMSO-d_6): $\delta = 27.8$; HRMS (ES) calcd for $C_{48}H_{56}N_4O_6PS$ $[MH]^+$, 847.3653; found, 847.3628.

13b. The crude product was purified by preparative RP-HPLC (39 mg, 80%). Analytical RP-HPLC: $t_R = 6.56$ min; ^{1}H NMR (DMSO-d_6): δ 8.51 (d, $J = 7.5$ Hz, 1H; amide), 8.34 (d, $J = 7.8$ Hz, 1H; amide), 7.86−7.71 (m, 6H; arom. H), 7.56−7.01 (m, 20H; amide, arom. H), 4.31−4.21 (m, 2H; Ala CH^α, Phe CH^α), 4.07−3.99 (m, 2H; Phe CH^α, PCH_2), 3.69 (dd, $J_1 = 8.5$ Hz, $J_2 = 6.0$ Hz, 1H; Cys CH^α), 3.61−3.54 (m, 1H; PCH_2), 3.11 (dd, $J_1 = 13.0$ Hz, $J_2 = 5.0$ Hz, 1H; Phe CH_2), 2.95−2.64 (m, 6H; Phe CH_2, Cys CH_2, Phe CH_2N), 2.23 (dd, $J_1 = 12.5$ Hz, $J_2 = 5.5$ Hz, 1H; Cys CH_2), 1.11 (d, $J = 7.0$ Hz, 3H; Ala CH_3), 1.01 (s, 9H; *t*Bu CH_3); ^{31}P NMR (DMSO-d_6): $\delta = 27.9$; HRMS (ES) calcd for $C_{48}H_{56}N_4O_6PS$ $[MH]^+$, 847.3653; found, 847.3639.

13c. The crude product was purified by preparative RP-HPLC (43 mg, 88%). Analytical RP-HPLC: $t_R = 6.57$ min; ^{1}H NMR (DMSO-d_6): δ 8.54−8.48 (m, 2H; amide), 7.89−6.98 (m, 26H; amide, arom. H), 4.47−4.38 (br m, 1H; Phe CH^α), 4.19 (pentet, $J = 7.0$ Hz, 1H; Ala CH^α), 4.05−3.97 (m, 2H; PCH_2, Phe CH^α), 3.68−3.57 (m, 2H; Cys CH^α, PCH_2), 3.13−2.65 (m, 7H; Phe CH_2, Cys CH_2, Phe CH_2N), 1.88 (dd, $J_1 = 12.5$ Hz, $J_2 = 4.0$ Hz, 1H; Cys CH_2), 1.21 (d, $J = 7.0$ Hz, 3H; Ala CH_3), 0.93 (s, 9H; *t*Bu CH_3); ^{31}P NMR (DMSO-d_6): $\delta = 29.1$; HRMS (ES) calcd for $C_{48}H_{56}N_4O_6PS$ $[MH]^+$, 847.3653; found, 847.3639.

13d. The crude product was purified by preparative RP-HPLC (42 mg, 86%). Analytical RP-HPLC: $t_R = 6.67$ min; ^{1}H NMR (DMSO-d_6): δ 8.71 (d, $J = 8.3$ Hz, 1H; amide), 8.03 (d, $J = 7.3$ Hz, 1H; amide), 7.95−7.72 (m, 6H; arom. H), 7.59−6.88 (m, 20H; amide, arom. H), 4.25−4.14 (m, 2H; Ala CH^α, Phe CH^α), 4.02−3.73 (m, 4H; Phe CH^α, Cys CH^α, PCH_2), 3.14−2.63 (m, 7H; Phe CH_2, Cys CH_2, Phe CH_2N), 2.21 (dd, $J_1 = 12.5$ Hz, $J_2 = 4.8$ Hz, 1H; Cys CH_2), 1.14−1.11 (m, 12H); ^{31}P NMR (DMSO-d_6): $\delta = 28.5$; HRMS (ES) calcd for $C_{48}H_{56}N_4O_6PS$ $[MH]^+$, 847.3653; found, 847.3645.

General Procedure for Formation of Resin-Bound Palladium(II) Allyl Complexes. The freshly prepared resin-bound phosphine ligand, still under argon and swollen in acetonitrile, was drained. A solution of allyl palladium chloride dimer (1 equiv) in dry degassed acetonitrile was added, whereupon it was left under argon for 3 h, in which time the resin attained a yellow color. The resin was drained and washed with dry degassed acetonitrile (×1). The drained resin was used immediately for palladium-catalyzed asymmetric allylic substitution.

General Procedure for Palladium Catalyzed Asymmetric Allylic Substitution: Synthesis of 16. Dimethyl malonate **15** (3 equiv) was dissolved in dry degassed acetonitrile (0.5 mL/mmol) under argon. To the solution was added tetrabutylammonium fluoride (3 equiv of a 1.0 M solution in tetrahydrofuran) and *N*,*O*-bis(trimethylsilyl)-acetamide (3 equiv), whereupon the solution was stirred for 15 min at room temperature. To the freshly prepared drained catalyst resin **10a**−**d** or **11a**−**d** (5 mol % Pd, based on the initial resin loading reported by the manufacturer), still under argon, was added 1,3-diphenylpropenyl acetate **14** (1 equiv, typically 48 mg, 0.19 mmol) in dry degassed acetonitrile (1.0 mL/mmol) and then the malonate solution. The resin mixture was shaken under argon for 3 h, whereupon it was drained and washed with ethyl acetate (×3). The combined organic phases were concentrated in vacuo and purified by column chromatography (silica gel, eluent: pentane-diethyl ether, 3:1, v/v) affording compound **16** as a colorless oil, which solidified upon standing. ^{1}H NMR ($CDCl_3$): $\delta = 7.17-7.33$ (m, 10 H; Ph), 6.46 (d, $J = 16$ Hz, 1 H; C_1 CH), 6.31 (dd, $J_1 = 16$ Hz, $J_2 = 8$ Hz, 1 H; C_2 CH), 4.25 (dd, $J_1 = 11$ Hz, $J_2 = 8$ Hz, 1 H; C_3 CH), 3.93 (d, $J = 11$ Hz, 1 H; C_4 CH), 3.69 (s, 3 H; CO_2CH_3), 3.50 (s, 3 H; CO_2CH_3). The ^{1}H NMR spectrum was identical to that described in the literature.[15] The enantiomeric excess was determined by ^{1}H NMR using the chiral shift reagent [Eu(hfc)$_3$] (see Supporting Information).

For Catalyst 10a. Using **14** (33 mg, 0.13 mmol) and **10a** (0.0065 mmol Pd), compound **16** was isolated in 88% yield, 37 mg, and 41% ee (*R*).

For Catalyst 10b. Using **14** (48 mg, 0.19 mmol) and **10b** (0.0095 mmol Pd), compound **16** was isolated in 94% yield, 58 mg, and 32% ee (*R*).

For Catalyst 10c. Using **14** (48 mg, 0.19 mmol) and **10c** (0.0095 mmol Pd), compound **16** was isolated in 85% yield, 53 mg, and 28% ee (*S*).

For catalyst 10d. Using **14** (48 mg, 0.19 mmol) and **10d** (0.0095 mmol Pd), compound **16** was isolated in 77% yield, 48 mg, and 39% ee (*S*).

For Catalyst 11a. Using **14** (40 mg, 0.16 mmol) and **11a** (0.0080 mmol Pd), compound **16** was isolated in 96% yield, 50 mg, and 44% ee (*S*).

For Catalyst 11b. Using **14** (48 mg, 0.19 mmol) and **11b** (0.0095 mmol Pd), compound **16** was isolated in 98% yield, 61 mg, and 55% ee (*S*).

For Catalyst 11c. Using **14** (48 mg, 0.19 mmol) and **11c** (0.0095 mmol Pd), compound **16** was isolated in 94% yield, 58 mg, and 60% ee (*R*).

For Catalyst 11d. Using **14** (48 mg, 0.19 mmol) and **11d** (0.0095 mmol Pd), compound **16** was isolated in 95% yield, 59 mg, and 41% ee (*R*).

Acknowledgment. We are grateful to the Danish National Research Foundation for financial support.

Supporting Information Available. HPLC chromatograms of crude cleaved compounds **7a**−**d**, **12a**−**d**, and **13a**−**d** and ^{1}H NMR spectra of compounds **12a**−**d** and **13a**−**d**. ^{1}H NMR spectra of **16** and of **16** with chiral shift reagent added, for ee determination (1 example). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999.

(2) (a) Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905−7920. (b) Yan, Y.-Y.; RajanBabu, T. V. *Org. Lett.* **2000**, *2*, 199−202. (c) Molander, G. A.; Burke, J. P.; Carroll, P. J. *J. Org. Chem.* **2004**, *69*, 8062−8069. (d) Enders, D.; Peters, R.;

Runsink, J.; Bats, J. W. *Org. Lett.* **1999**, *1*, 1863−1866. (e) Mancheño, O. G.; Priego, J.; Cabrera, S.; Arrayás, R. G.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679−3686. (f) Nakano, H.; Okuyama, Y.; Yanagida, M.; Hongo, H. *J. Org. Chem.* **2001**, *66*, 620−625. (g) Sugama, H.; Saito, H.; Danjo, H.; Imamoto, T. *Synthesis* **2001**, 2348−2353. (h) Albinati, A.; Pregosin, P. S.; Wick, K. *Organometallics* **1996**, *15*, 2419−2421.

(3) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.

(4) (a) Reetz, M. T. *Angew. Chem. Int. Ed.* **2001**, *40*, 284−310. (b) Gennari, C.; Piarulli, U. *Chem. Rev.* **2003**, *103*, 3071−3100. (c) Stambuli, J. P.; Hartwig, J. F. *Curr. Opin. Chem. Biol.* **2003**, *7*, 420−426. (d) Fonseca, M. H.; List, B. *Curr. Opin. Chem. Biol.* **2004**, *8*, 319−326.

(5) Excluding purely organocatalytic examples, see: (a) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657−2658. (b) Hird, A. W.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 1276−1279. (c) Landis, C. R.; Clark, T. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5428−5432. (d) Agarkov, A.; Uffman, E. W.; Gilbertson, S. R. *Org. Lett.* **2003**, *5*, 2091−2094. (e) Greenfield, S. J.; Agarkov, A.; Gilbertson, S. R. *Org. Lett.* **2003**, *5*, 3069−3072. (f) Agarkov, A.; Greenfield, S. J.; Ohishi, T.; Collibee, S. E.; Gilbertson, S. R. *J. Org. Chem.* **2004**, *69*, 8077−8085.

(6) Christensen, C. A.; Meldal, M. *Chem.—Eur. J.* **2005**, *11*, 4121−4131.

(7) Sheppard, R. *J. Pept. Sci.* **2003**, *9*, 545−552.

(8) Meldal, M. *Tetrahedron Lett.* **1992**, *33*, 3077−3080.

(9) Diness, F.; Beyer, J.; Meldal, M. *QSAR Comb. Sci.* **2004**, *23*, 130−144.

(10) Benito, J. M.; Christensen, C. A.; Meldal, M. *Org. Lett.* **2005**, *7*, 581−584.

(11) Hellmann, H.; Bader, J.; Birkner, H.; Schumacher, O. *Liebigs Ann. Chem.* **1962**, *659*, 49−63.

(12) Prolonged oxidation also afforded species in which the cysteine sulfur was oxidized, but this was avoided by restricting the oxidation time to 1 min.

(13) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813−5837.

(14) For the basic conditions, see: Gilbertson, S. R.; Chang, C.-W. T. *J. Org. Chem.* **1998**, *63*, 8424−8431.

(15) Brenchley, G.; Fedouloff, M.; Mahon, M. F.; Molloy, K. C.; Wills, M. *Tetrahedron* **1995**, *51*, 10581−10592.

(16) The active catalyst could not be recovered after catalysis. Possible leaching of palladium during catalysis was not determined.

(17) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595−598.

CC0600627