Combinatorial Chemistry for Ligand Development in Catalysis: Synthesis and Catalysis Screening of Peptidosulfonamide Tweezers on the Solid Phase

Arwin J. Brouwer, Heiko J. van der Linden, and Rob M. J. Liskamp*

Department of Medicinal Chemistry, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, P.O. Box 80082, NL-3508 TB Utrecht,The Netherlands

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On the basis of a pyrrolidine tweezer **1**, a library of peptidosulfonamide tweezers (**15a**−**e**, **16a**−**e**) was synthesized on the solid phase. This library was screened in a simultaneous substrate screening procedure for the ability to enantioselectively catalyze the Ti(O-*i*-Pr)$_4$-mediated addition of diethylzinc to aldehydes. One of the best solid-phase tweezer catalyst (i.e., **16d**, giving an ee of 32% in solid-phase catalysis) was resynthesized in solution (compounds **20** and **21**). The now homogeneous solution-phase catalysis showed even better enantioselectivity (i.e., up to 66%).

Introduction

Combinatorial chemistry is now widely integrated in the drug discovery and optimization processes, and it is now progressing rapidly in a number of other molecular areas.[1a] The possibilities to generate and screen a number of compounds as well as optimize conditions for studying these compounds (e.g., reaction conditions) in an iterative manner make combinatorial chemistry extremely attractive for finding and optimizing ligands for catalysis.[1b]

In principle, there are two approaches for screening of a catalyst ligand: screening in solution[1a−c] or screening on the solid phase.[1a,b,d−f] Although screening an immobilized solid-phase catalyst ligand clearly has disadvantages compared to solution screening, such as the heterogeneous nature of a solid-phase bead causing unfavorable kinetics and possible interactions of the reactants with the solid phase, the very same heterogeneous nature of the bead has the advantages that catalyst and product can be easily separated and the catalyst recovered. In addition, solid-phase chemistry enables, in principle, the convenient preparation of libraries of compounds.

Therefore, our approach was to synthesize ligands for catalysis on the solid phase, screen them for catalytic activity, and resynthesize the best ligand in solution and determine its catalytic activity. Thus, the solid-phase approach is used here for synthesis and screening of ligands, which will be applied in solution.

Recently, we found that peptidosulfonamide-containing tweezer-like molecules were capable of selective binding of tripeptides from a combinatorial library.[2a] In addition, we found that a more rigid hinge preorganized toward a tweezer structure led to a considerable increase in binding affinity.[2b] One of these tweezers was the pyrrolidine containing synthetic receptor **1** (Figure 1). There is clear similarity between the amine−sulfonamide part of this compound with the very well-known bisulfonamide ligand derived from 1,2-diaminocyclohexane[3] **2**. This ligand has been used in the very efficient enantioselective addition of diethylzinc to aldehydes (e.g., benzaldehyde).[3] The pyrrolidine tweezer-like synthetic receptor has an additional handle for attachment of a dye[2] or to a solid-phase bead. In this paper, the handle is attached to a solid-phase bead enabling solid-phase synthesis of the peptidosulfonamide tweezer-ligand as well as a facile screening of enantioselective catalytic properties. Advantages of a solid-phase ligand are easy removal after completion of the reaction and catalyst reuse.

Results and Discussion

To determine if the pyrrolidine hinge would give rise to a catalytically active ligand showing at least some degree of enantioselectivity, the triflate containing hinge **3** was first synthesized in solution. Indeed, it was found that the triflate pyrrolidine ligand gave rise to catalysis, and to some degree of enantioselectivity. The next step was to introduce a linker for attachment to a solid-phase resin to give compound **4.** This compound, as well as a compound containing a different sulfonamide (**5**), was catalytically active showing that the pyrrolidine hinge containing a linker can, in principle, be used for different catalytically active ligands and that a linker is compatible with catalytic activity (Figure 1).

Before moving to a solid-phase synthesis of the peptidosulfonamide ligands, it was necessary to evaluate if

* To whom correspondence should be addressed Fax: (+31)30-2536655. E-mail: R.M. J.Liskamp@pharm.uu.nl.

(1) (a) For a recent review, see: Jandeleit, B.; Scheafer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2495−2532. (b) For a nice overview of seminal work of several researchers, see, e.g.: Shimizu, K. D.; Snapper, M. L.; Hoveyda, A. H. *Chem. Eur. J.* **1998**, *4*, 1885 and references therein. (c) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668. (d) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704−1707. (e) Taylor, S. J.; Morken, J. P *Science* **1998**, *280*, 267−270. (f) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901−4902.

(2) (a) Löwik, D. W. P. M.; Mulders, S. J. E.; Cheng, Y.; Shao, Y.; Liskamp, R. M. J. *Tetrahedron Lett.* **1996**, *37*, 8253−8256. (b) Löwik, D. W. P. M.; Weingarten, M. D.; Broekema, M.; Brouwer, A. J.; Still, W. C.; Liskamp, R. M. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1846−1850.

(3) See e.g. Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 7095; Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691. A modified bissulfonamide ligand derived from **2** has been used as a cross-linker in the successfull preparation of a polymeric catalytically active ligand for the enantioselective alkylation of benzaldehyde: Halm, C.; Kurth, M. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 510−512.

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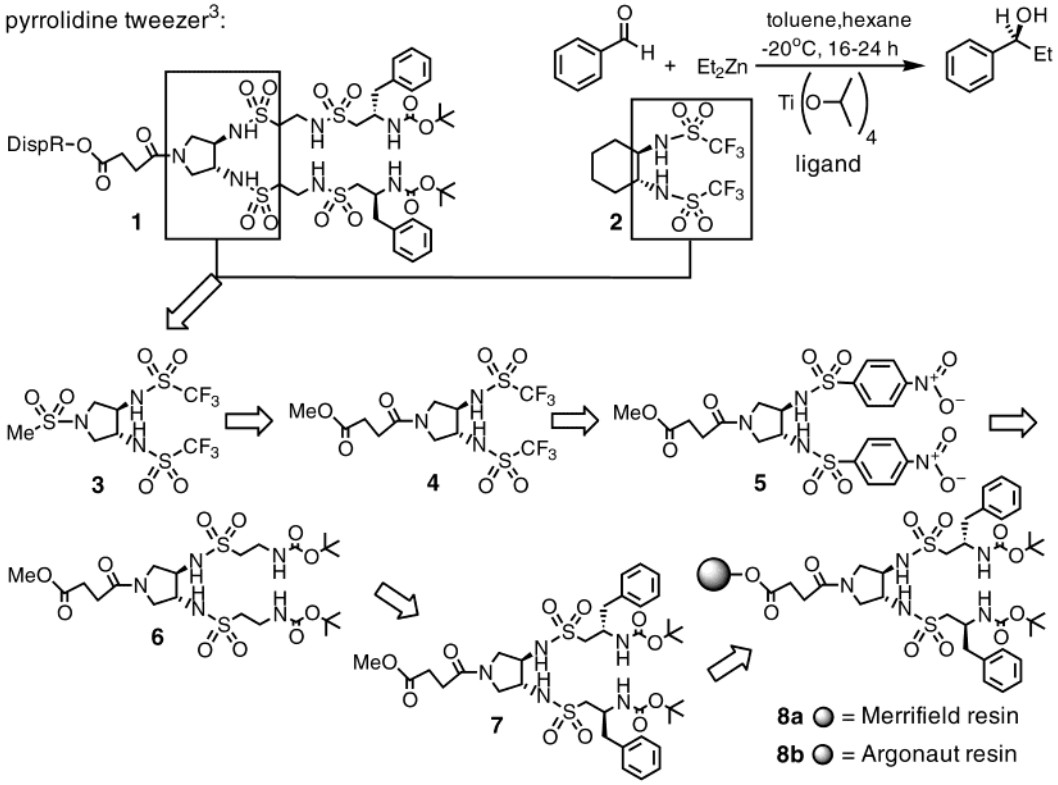


Figure 1. Pyrrolidine-containing synthetic receptor **1** and bistriflate catalyst **2** as starting points for the development of solid-phase attached tweezer catalysts.

these ligands showed at least some catalytic activity in solution. Therefore, taurine-containing tweezer **6** as well as the phenylalanine sulfonamide (Phe^s) containing tweezer **7** were synthesized. The latter displayed a promising ee of 30% in preliminary experiments in the catalyzed diethylzinc addition (vide infra).

However, in initial experiments with the sulfonamide ligand attached to the solid phase, it was found that the resin type and the amount of the used catalyst was quite essential. In these experiments, benzaldehyde was used as the substrate in the Ti(O-*i*-Pr)$_4$-mediated addition of diethylzinc. The sulfonamide ligand attached to a Merrifield resin (**8a)** was completely devoid of catalytic activity. After changing the resin to a poly(ethylene glycol)-polystyrene (Argonaut resin) to give **8b**, catalysis did take place using 16 mol % of ligand. Based on a loading of 0.30 mmol/g resin, this amounted to 40 mg of resin.

These encouraging results justified the solid-phase preparation and screening for catalytic activity of peptidosulfonamide tweezers.[4] Five β-amino sulfonic acid derivatives were selected for solid-phase synthesis of pyrrolidine-containing peptidosulfonamides. To determine the influence of ligand handedness on enantioselectivity, the pyrrolidine ring was synthesized starting from L- as well as D-tartaric acid (Scheme 1). Thus, the pyrrolidine hinge[5] was prepared as follows, from pyrrolidine diol **9**.[6] This diol was converted into the diazide[7] and reduced, and the resulting amino groups were protected to afford **10**. The spacer was introduced after hydrogenolysis of the benzyl group[8] by treatment with succinic anhydride. Coupling of the resulting pyrrolidine ring containing system **11** to the Argonaut resin was achieved in a BOP coupling to give **12**. After removal of the Boc-protecting groups, the peptidosulfonamide moieties were introduced in **13** by the sulfonyl chloride approach (Scheme 1). The required Fmoc-protected β-aminosulfonyl chlorides **14a**−**e** were synthesized as described.[9] By cleavage of the Fmoc group, the loading of the resin was determined followed by introduction of the base-stable Boc group.[10] According to this procedure, a library of 10 peptidosulfonamide tweezers **15a**−**e** and **16a**−**e** on the solid phase was obtained.

Instead of screening each resin-bound peptidosulfonamide tweezer with one substrate, we decided to use a mixture of substrates (Scheme 2). This mixture was chosen in such a way that (a) the GC retention times of the individual substrates were different, (b) the retention times of the individual enantiomeric mixtures of the products were different, and (c) the retention times of the substrates and products were different. In this way, in a single run four data points were obtained with

(4) While this work was in progress, the synthesis in solution and parallel screening of chiral sulfonamide containing diamines was described: Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C. A. G. N.; Jackson, R. F. W. *J. Org. Chem.* **1998**, *63*, 5312−5313.

(5) This hinge was successfully applied in the synthetic receptors of Still et al.; see, e.g.: (a) Yoon, S. S.; Still, W. C. *Tetrahedron* **1995**, *51*, 567−578. (b) Shao, Y.; Still, W. C. *J. Org. Chem.* **1996**, *62*, 6086−6087. (c) Pan, Z.; Still, W. C.*Tetrahedron Lett.* **1996**, *37*, 8699−8702. (d) Torneiro, M.; Still, W. C.*Tetrahedron* **1997**, *53*, 8739−8750.

(6) Nagel, U.; Kinzel, E.; Andrade, J.; Prescher, G. *Chem. Ber.* **1986**, *119*, 3326−3343.

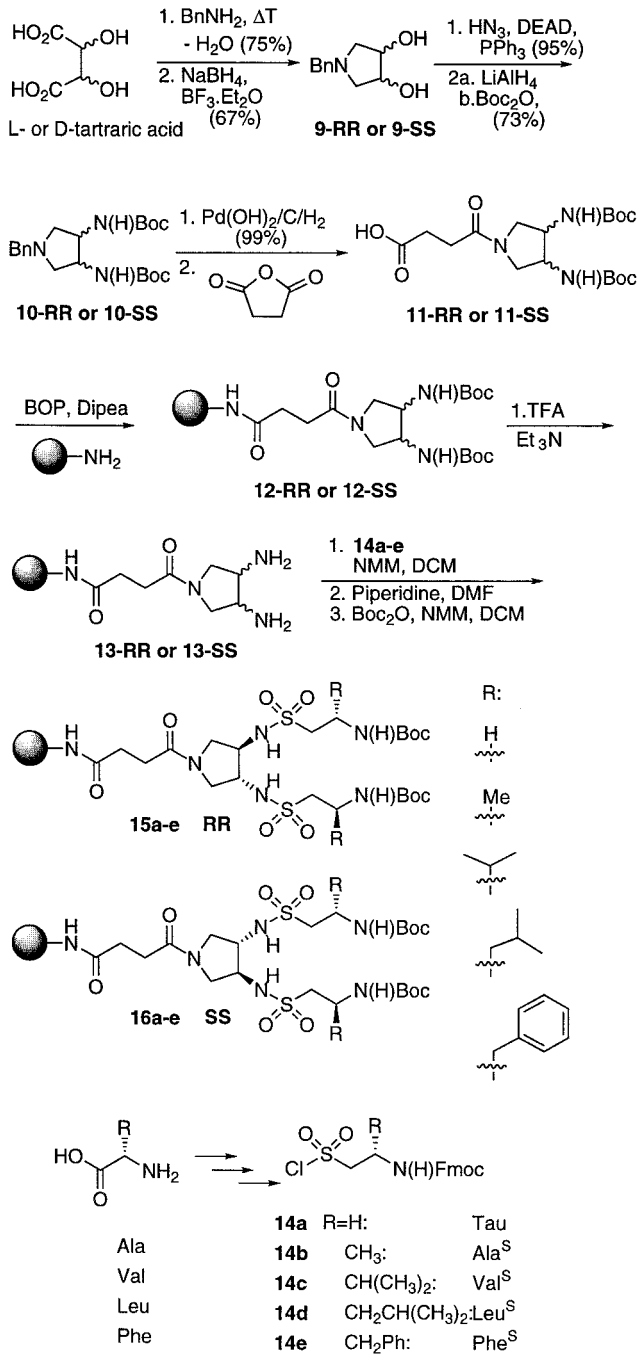
(7) Skarzewski, J.; Gupta, A. *Tetrahedron*: *Assymetry* **1997**, *8*, 1861−1867.

(8) See ref 5a.

(9) (a) De Bont, D. B. A.; Dijkstra, G. D. H.; Den Hartog, J. A. J.; Liskamp, R. M. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3035−3040. (b) Brouwer, A. J.; Monnee, M. C. F.; Liskamp, R. M. J. Manuscript in preparation.

(10) We have now shown that although upon storage the Fmoc group is less stable, it gave rise to comparable conversions and ee.

Scheme 1. Synthesis of a Library of Peptidosulfonamide Tweezers on the Solid Phase

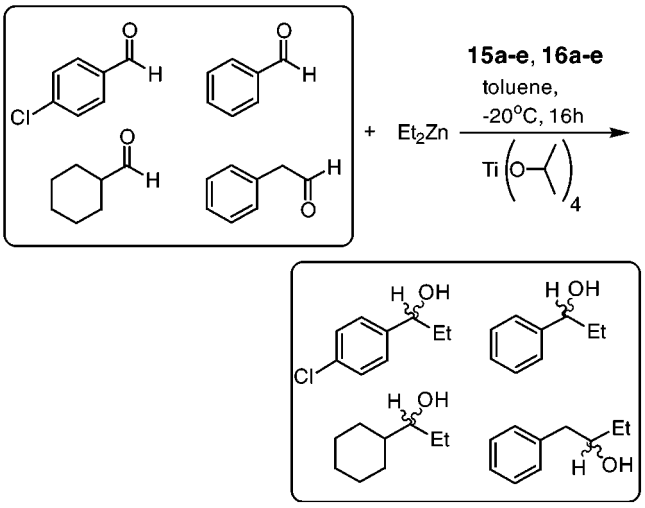


respect to the conversion and four data points were obtained with respect to the enantioselectivity (expressed as ee).

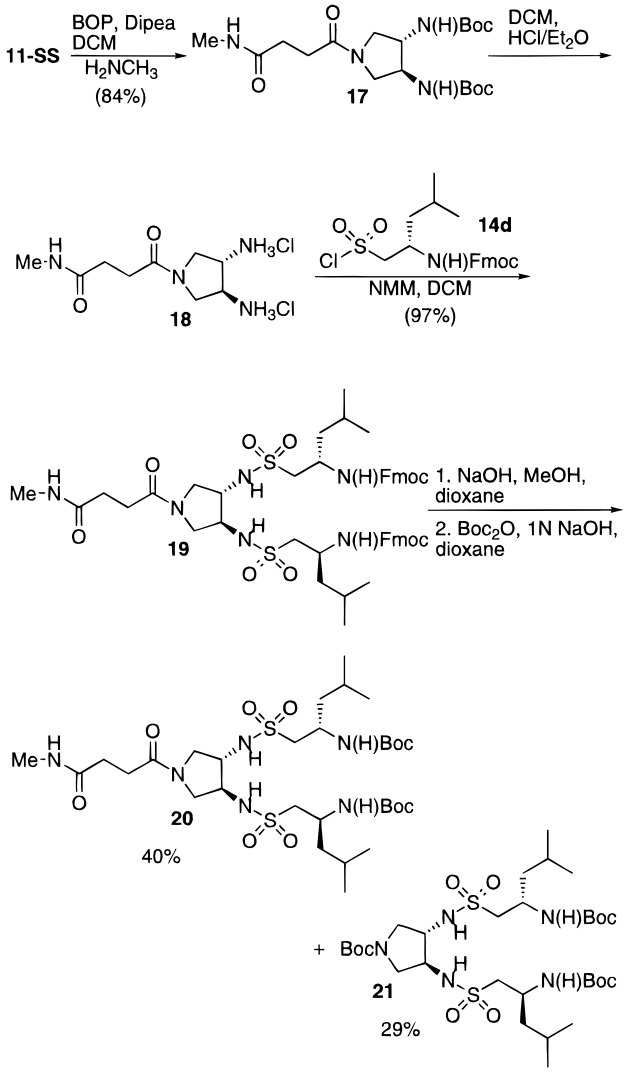
The Ti(O-*i*-Pr)$_4$-mediated diethylzinc addition reactions were carried out in toluene on a 0.0125 mmol scale, for each substrate, using 20 mg of resin corresponding to 10−16 μmol of resin bound chiral peptidosulfonamide ligand. The substrates were benzaldehyde, *p*-Cl-benzaldehyde, cyclohexylaldehyde, and phenylacetaldehyde. The reactions were run overnight at −20 °C, quenched, and analyzed by GC using a chiral capillary GC column. A typical GC trace of a reaction mixture is shown in Figure 2.

The results of the conversion and ee values are shown in Figures 3 and 4, respectively.

Scheme 2. Library Screening in a Simultaneous Substrate Screening Procedure for the Ability To Enantioselectively Catalyze the Ti(O-*i*-Pr)$_4$ Mediated Addition of Diethylzinc



Scheme 3. Resynthesis in Solution of Solid Phase Attached Peptidosulfonamide Tweezer 16d



From a comparison of the bargraphs in Figures 3 and 4, it is immediately apparent that high conversion was paralleled by high ee. Furthermore, the two aromatic

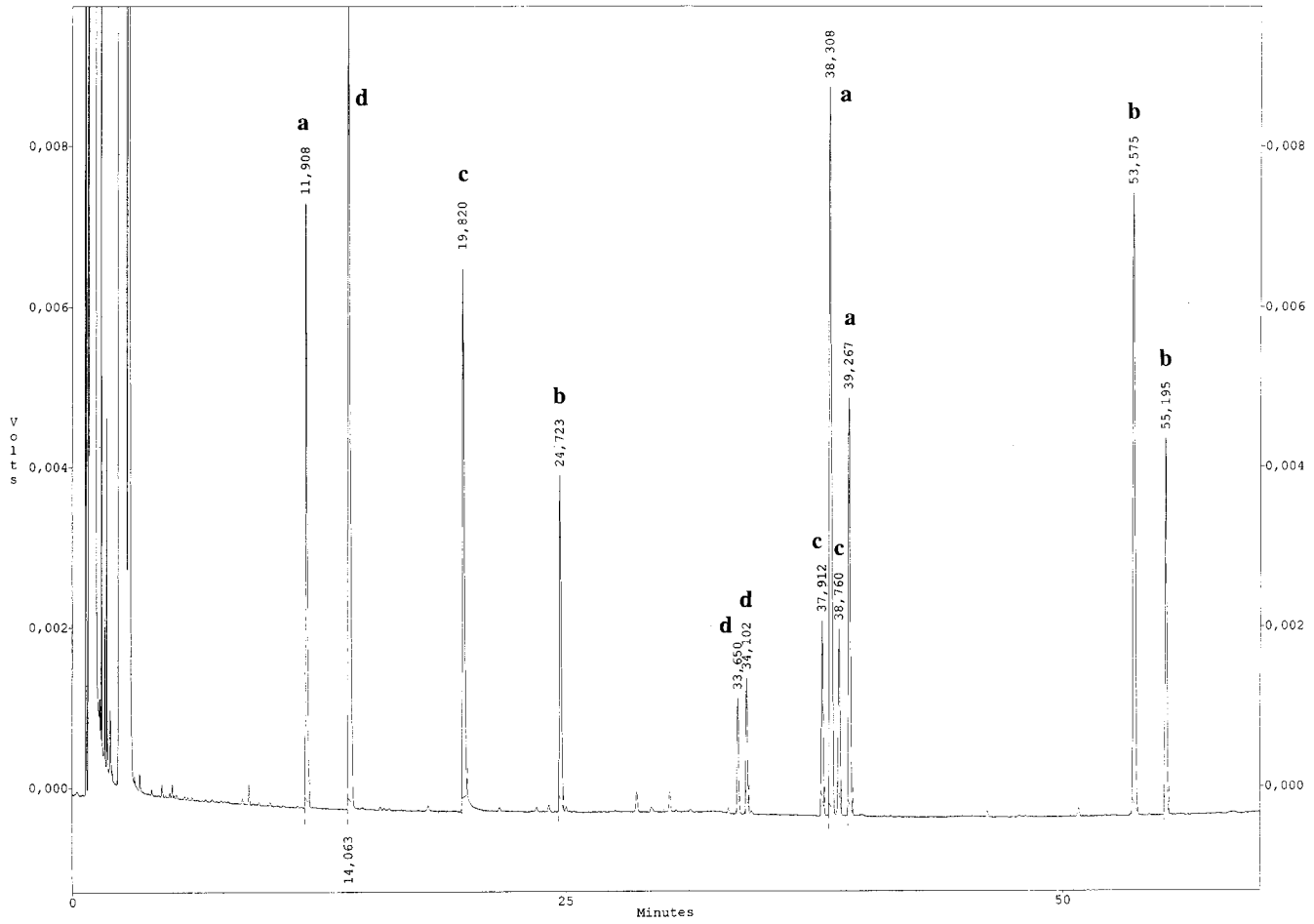
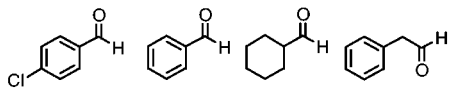


Figure 2. Typical GC-trace (CP-Chiracil-Dex CB column) of the enantioselective addition of diethylzinc to a mixture of benzaldehyde (a), 4-chlorobenzaldehyde (b), phenylacetaldehyde (c), and cyclohexylaldehyde (d) catalyzed by solid-phase tweezer **16d** giving rise to the corresponding enantiomeric mixtures of alcohols (aa−dd).

Table 1



20	66	56	14	8
16d	32	32	12	6
21	58	58	10	4

aldehydes showed the highest conversions and highest ee's. It is also important to emphasize that the same enantiomer is always formed in excess, irrespective of the peptidosulfonamide and the chirality of the pyrrolidine moiety.

The influence of the configuration of the chiral centers in pyrrolidine is not very great. However, the highest ee's are generally observed with the *RR*-pyrrolidine. This is paralleled by the conversions, which are generally greater for the *RR*-pyrrolidine with the distinct exception of the valine-derived sulfonamide. Here, the *SS* diastereomer resulted in a higher conversion, whereas the *RR* diastereomer gave a higher ee. Clearly, the chirality of the pyrrolidine is not sufficient for a high enantioselectivity since taurine-containing pyrrolidine tweezers **15a** and **16a** did not show an appreciable ee. The best ee's were observed with the aromatic substrates using the leucine-derived peptidosulfonamide (Leu[s]) pyrrolidine tweezers **15d** and **16d**. The ee's are largely determined by the side chains in the peptidosulfonamide, since both pyrrolidine enantiomers give rise to a similar ee. Apparently, size of the side chain is not the only factor, since the phenylalanine-derived peptidosulfonamide **15e** and **16e** do not give rise to the highest ee. The less the influence of the side chain, the more distinct the influence of the pyrrolidine ring on the ee as is nicely illustrated by the phenylalanine derived peptidosulfonamide containing tweezers (Figure 4).

Not unexpectedly, both the ee and the conversions using the resin-bound tweezer are lower than in solution. Therefore, it was expected once the best catalytically resin-bound tweezer was found, the corresponding "solution" tweezer would give better enantiomeric ratio's and higher yields. There are literature data[1d] supporting this assumption. Thus, the resin-bound tweezer containing the leucine-derived peptidosulfonamide, which gave the best ee, was synthesized in solution (Scheme 3). Instead of attaching the pyrrolidine-spacer molecule to the resin, the methyl amide **17** was now prepared, followed by removal of the Boc group to **18** and preparation of the peptidosulfonamide **19**. Surprisingly, removal of the

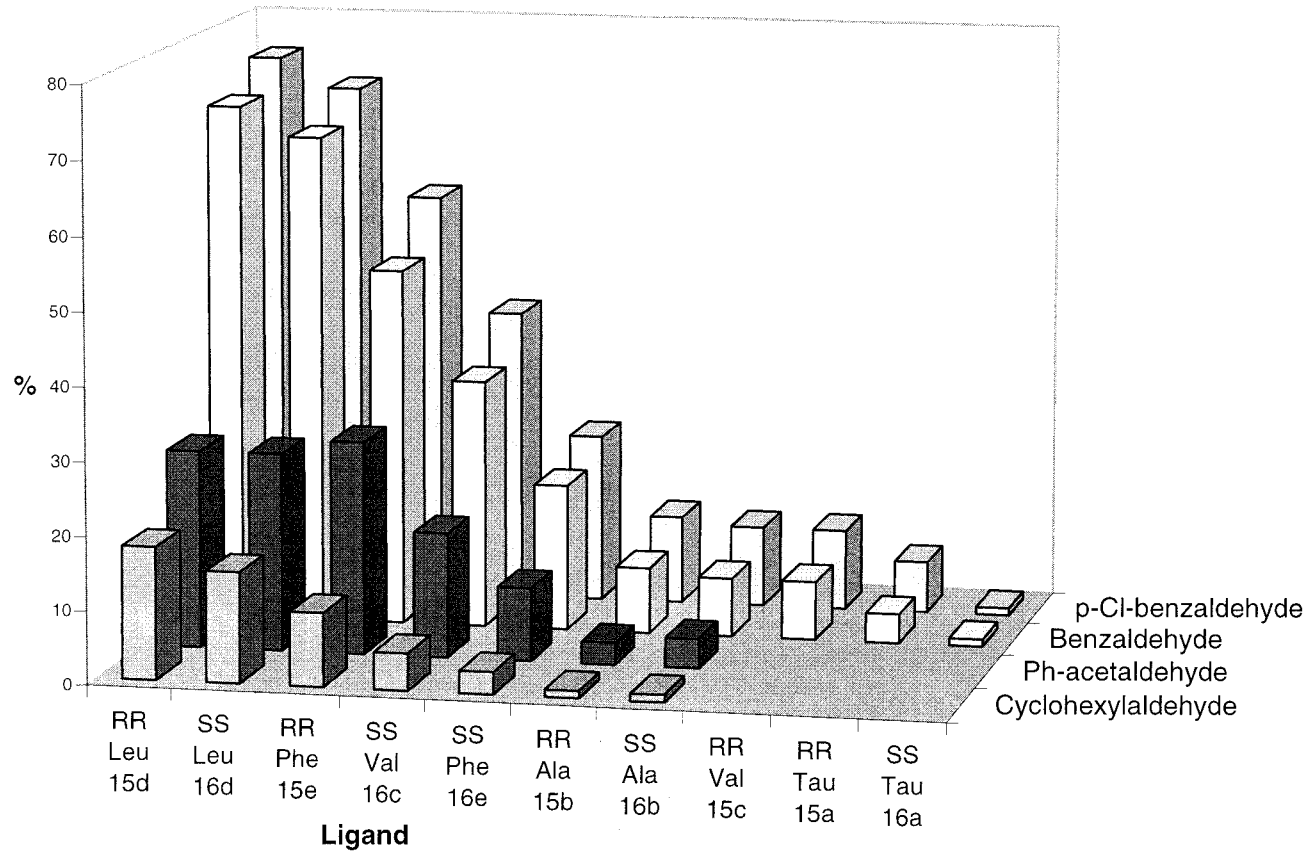


Figure 3. Aldehyde conversions catalyzed by peptidosulfonamide tweezers on the solid phase.

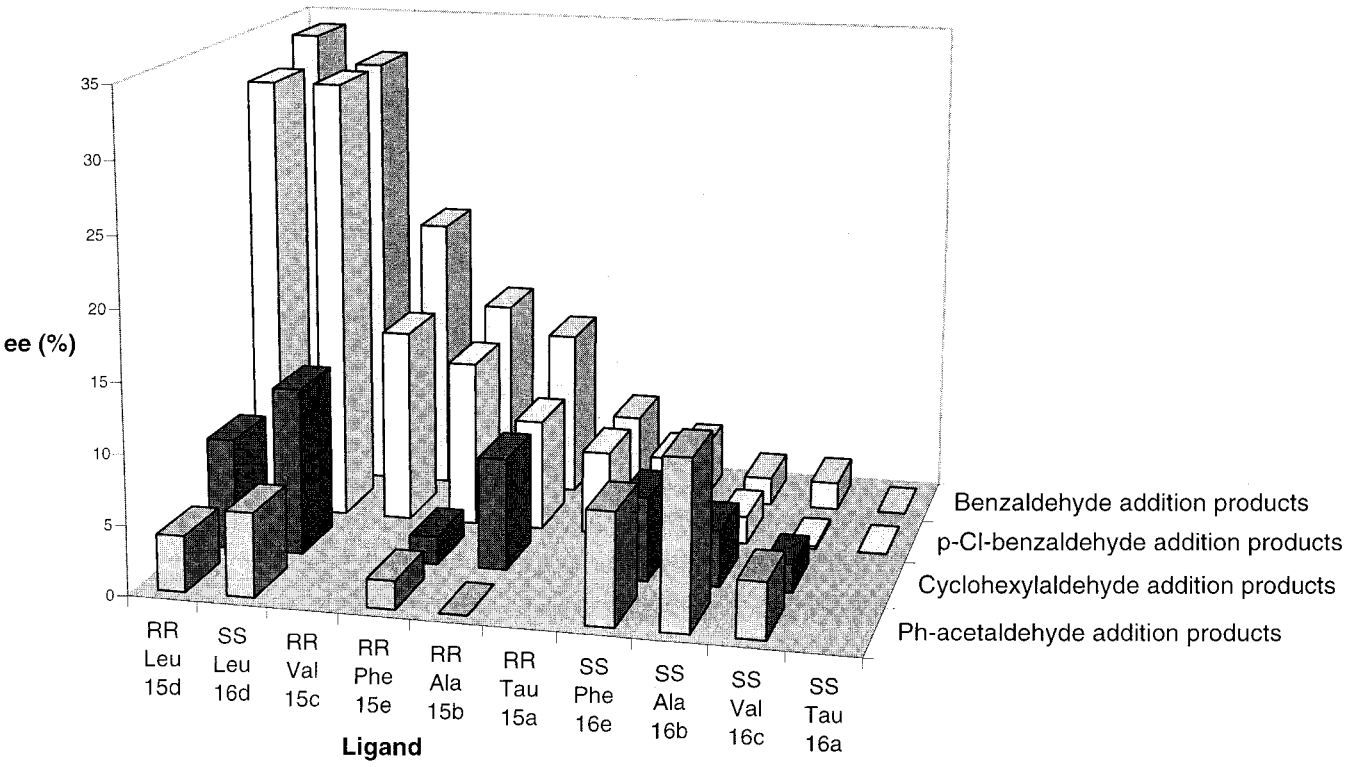


Figure 4. Ee of the diethylzinc addition products catalyzed by peptidosulfonamide tweezers on the solid phase.

Fmoc group followed by introduction of the Boc group to give **20** was accompanied by formation of a product (**21**) resulting from cleavage of the spacer-pyrrolidine amide. Be this as it may, both products **20** and **21** were tested for their ability to catalyze the diethylzinc addition. Indeed, it was found that under homogeneous conditions

the tweezer containing leucine-derived peptidosulfonamides gave rise to notably increased ee values (56−66%) as compared to the resin-bound ligand (32%), thus confirming the earlier assumption (Table 1).

Conclusion

We have shown that the solid-phase synthesis approach is a versatile approach to rapidly prepare a library of peptidosulfonamide tweezers, which can be conveniently screened in a simultaneous screening procedure for finding the optimal tweezer as well as determination of the substrate specificity. Furthermore, it was shown that the best ligand in the solid-phase catalysis is even better in solution-phase catalysis. Since this approach is amenable to additional combinatorial chemistry applications, it offers perspectives for further optimization of the tweezer, determination of substrate range, and reuse of the library in other catalytic reactions.

Experimental Section

General Methods. Solvents were distilled prior to use. If necessary, the commercial reagents were purified according to Perrin and Armarego.[11] Et_2Zn was obtained as a 1 M solution in hexanes (Aldrich, Zwijndrecht, The Netherlands). *N*-Methylmorpholine (NMM) was distilled from CaH_2. Argogel-NH_2 resin was purchased from Argonaut Technologies Inc. (San Carlos, CA). The aldehydes, Ti(O-*i*-Pr)$_4$, and methylamine in THF (2 M) were obtained from Aldrich; the Ti(O-*i*-Pr)$_4$ was distilled. Reactions were carried out at ambient temperature unless stated otherwise. TLC analysis was performed on Merck precoated silicagel 60 F-254 (0.25 mm) plates. Spots were visualized with UV light, ninhydrin, or Cl_2-TDM.[12] Solvents were evaporated under reduced pressure at 40 °C. Column chromatography was performed on Merck Kieselgel 60 (40−63 μm). Electrospray mass spectra were recorded on a LCMS spectrometer. Elemental analyses were carried out at Janssen Pharmaceutica (Beerse, Belgium). For gas chromatography, a gas chromatograph with split injector and a CP-Chirasil-Dex CB column was used. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer. ^{13}C spectra were recorded using the attached proton test (APT) pulse sequence. Compounds were pure according to TLC.

Ligand 3. 1-Mesyl-3,4-di(Boc-amino)pyrrolidine (688 mg, 1.98 mmol), obtained by hydrogenolysis and subsequent mesylation of **10-RR**, was dissolved in 4 mL of DCM, and 4 mL of ether, saturated with HCl, was added. After the mixture was stirred for 10 min, the solvent was removed in vacuo, and the residue was dried on KOH under reduced pressure. The HCl salt was obtained in 95% as a white solid (474 mg, 1.88 mmol). To a suspension of HCl salt (252 mg, 1.0 mmol) in DMF (10 mL) at 0 °C was added DIPEA (766 μL, 4.4 mmol), under a nitrogen atmosphere. After being stirred for 10 min, the mixture was cooled to −40 °C and trifluoromethanesulfonyl chloride (212 μL, 2.0 mmol) was added slowly. The mixture was stirred for 1 h at room temperature. The solvent was evaporated, and the residue was dissolved in EtOAc. After being washed with 1 M $KHSO_4$, water, and brine, the organic layer was dried on Na_2SO_4 and evaporated to dryness in vacuo. Column chromatography (eluent 10% MeOH in DCM, v/v) afforded **3** as a white solid (82 mg, 19%, 0.185 mmol): R_f 0.19 (eluent: 10% MeOH in DCM, v/v); ^{1}H NMR ($CDCl_3$/CD_3OD) δ 2.92, 2.93 (2s, 3H), 3.21 (m, 2H), 3,76 (m, 2H), 4.03 (m, 2H), 4.33 (bs, 2H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 35.3, 49.8, 57.5, 113.1, 118.0, 121.6, 125.9.

Ligand 4. To a solution of *N*-succinyl-3,4-di-(Boc-amino)-pyrrolidine **11-RR** (380 mg, 0.946 mmol) in MeOH (10 mL) was added a diazomethane solution in diethyl ether until the reaction mixture remained yellow. After the mixture was stirred for 5 min, a few drops of glacial acetic acid were added to destroy the excess diazomethane. Subsequently, the solvent was evaporated, and the Boc groups were removed by dissolving the residue in DCM (20 mL) and TFA (20 mL) and by stirring for 5 min. Evaporation to dryness gave a yellow oil that was dried on KOH under reduced pressure. The oil was dissolved in DCM (4 mL), and DIPEA (1.07 mL, 6.15 mmol) was added. After the mixture was cooled to −40 °C, trifluoromethanesulfonyl chloride (201 μL, 1.89 mmol) in DCM (0.5 mL) was slowly added. Stirring was continued at 4 °C for 2 h. Then the solvent was evaporated, and EtOAc (40 mL) was added. The resulting solution was washed with $KHSO_4$, water, and brine and dried on Na_2SO_4 followed by concentration. After purification by column chromatography (eluent: 5% MeOH/DCM, v/v), the product was obtained as a white foam (185 mg, 44%, 0.414 mmol): R_f 0.37 (eluent: 10% MeOH in DCM, v/v); ^{1}H NMR ($CDCl_3$) δ 2.54−2.67 (2m, 4H), 3.28−3.47 (m, 2H), 3.70 (s, 3H), 3.87−4.13 (m, 4H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 28.1, 28.2, 47.9, 49.2, 51.7, 56.3, 57.8, 113.1, 117.4, 121.6, 125.9, 171.0, 174.0.

Ligand 5. To a solution of *N*-succinyl-3,4-di(Boc-amino)-pyrrolidine **11-RR** (385 mg, 0.958 mmol) in MeOH (9.6 mL) was added a diazomethane solution in diethyl ether until the reaction mixture remained yellow. After the mixture was stirred for 5 min, a few drops of glacial acetic acid were added to destroy the excess of diazomethane. Evaporation of the solvent gave a colorless oil (417 mg) that was dissolved in DCM (3.0 mL), followed by addition of diethyl ether (3.0 mL), saturated with HCl. After the mixture was stirred for 10 min, the solvent was removed, and the product was dried on KOH under reduced pressure, which gave a sticky white solid (290 mg, 0.964 mmol, 101%). To a solution of this residue (86.5 mg, 0.3 mmol) in DCM (3 mL) were added Et_3N (167.3 μL, 1.2 mmol) and 4-nitro-phenylsulfonyl chloride (133 mg, 0.6 mmol). After the mixture was stirred for 3 h, the solvent was evaporated and the product was purified by column chromatography (eluent: 5% MeOH in DCM, v/v) affording a yellow foam (89 mg, 0.152 mmol, 51%): R_f 0.37 (eluent: 7% MeOH in DCM, v/v); ^{1}H NMR ($CDCl_3$/CD_3OD) δ 2.41−2.63 (m, 4H), 3.16 (dd, 1H), 3.33 (dd, 1H), 3.50 (dd, 1H), 3.66 (s, 3H), 3.71 (4 lines, 1H), 3.78 (dd, 1H), 3.89 (4 lines, 1H), 8.08 (m, 4H, 8.36 (m, 4H); ^{13}C NMR ($CDCl_3$/CD_3OD) δ 28.4, 48.0, 51.9, 55.9, 57.5, 124.5, 128.2, 128.3, 145.5, 145.6, 150.2, 170.9, 173.9.

Ligand 6. TFA salt (0.30 mmol), prepared from **11-RR** according to the procedure described for **4**, was dissolved in DCM (2.2 mL). NMM was added, until the apparant pH of the solution was 8, and then Boc-tauryl chloride was added (168 mg, 0.69 mmol). After the mixture was stirred for 12 h, the solvent was removed in vacuo. Purification by column chromatography (eluent: 6% MeOH in DCM, v/v) afforded a colorless oil (80 mg, 43%, 0.129 mmol): R_f 0.44 (eluent: 10% MeOH in DCM); ^{1}H NMR ($CDCl_3$/CD_3OD) δ 1.43 (s, 18H), 2.55, 2.64 (2m, 4H), 3.31 (m, 5H), 3.43 (m, 1H), 3.56 (m, 4H), 3.68 (s, 3H), 3.90−4.02 (m, 4H), 5.56 (m, 2H), 6.64 (bs, 2H); ^{13}C NMR ($CDCl_3$) δ 28.2, 28.5, 48.6, 50.1, 51.8, 52.4, 52.7, 55.5, 56.9, 80.1, 156.2, 170.8, 173.8; $[M + H]^+ = 630.25$.

Ligand 7. TFA salt (0.30 mmol), prepared from **11-RR** according to the procedure described for **4**, was dissolved in DCM (2.2 mL). NMM was added, until the apparent pH of the solution was 8, and then Boc-benzyltauryl chloride was added (230 mg, 0.69 mmol). After the mixture was stirred for 12 h, the solvent was removed in vacuo. Purification by column chromatography (eluent: 4% MeOH in DCM, v/v) afforded a white foam (46 mg, 19%, 0.057 mmol): R_f 0.53 (eluent: 10% MeOH in DCM); ^{1}H NMR ($CDCl_3$) δ 1.40, 1.41 (2s, 18H), 2.52, 2.66 (2m, 4H), 2.83−3.04 (2m, 4H), 3.10−3.42 (m, 6H), 3.68 (s, 3H), 3.70−3.92 (m, 2H), 4.11−4.24 (m, 4H), 4.91 (bs, 2H), 7.15−7.33 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 28.2, 28.5, 38.7, 48.2, 50.0, 51.7, 54.0, 81.4, 127.2, 129.0, 129.4, 129.5, 136.3, 155.8, 170.1, 173.5; $[M + H]^+ = 810.40$.

***N*-Benzyl-3,4-di(Boc-amino)pyrrolidine 10-RR and 10-SS.** A solution of *N*-benzyl-3,4-diazidopyrrolidine (2.4 g, 9.9 mmol), prepared from **9-RR** according to Skarzewski and

(11) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed,; Pergamon Press: Oxford, 1988.

(12) Arx, E. von; Faupel, M.; Bruggen, M., *J. Chromatogr.* **1976**, *120*, 224.

Gupta,[7] in dried THF (9.9 mL), was added dropwise to a stirring mixture of $LiAlH_4$ (992 mg, 26.1 mmol) in THF (9.9 mL). The mixture was refluxed for 30 min, followed by cooling to 0 °C in an ice bath. NaOH (1 M, 6.4 mL) and water (6.4 mL) were carefully added. The mixture was filtrated and concentrated to ca. 15 mL. Then dioxane (15 mL) and Boc_2O (4.3 g, 19.8 mmol) in dioxane (15 mL) were added. After the mixture was stirred for 2 h at room temperature, the solvent was removed and EtOAc was added. The organic layer was washed with water (twice) and brine, dried (Na_2SO_4), and evaporated. Crystallization from EtOAc afforded a white crystalline solid (1.5 g, 79%, 7.82 mmol): ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 18H), 2.40 (m, 2H), 2.99 (m, 2H), 3.58 (s, 2H), 3.85 (m, 2H), 4.89 (bs, 2H), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.4, 57.2, 59.0, 59.8, 79.6, 127.2, 128.3, 128.7, 138.0, 155.5.

***N*-Succinyl-3,4-di(Boc-amino)pyrrolidine 11-RR and 11-SS.** To a solution of *N*-benzyl-3,4-di(Boc-amino)pyrrolidine **10-RR** (3.95 g, 10.1 mmol) in *t*-BuOH/H_2O (4:1, v/v, 150 mL) was added $Pd(OH)_2$/C (10%, 250 mg). The mixture was shaken overnight under a 3 Bar hydrogen atmosphere in a Parr apparatus. The catalyst was removed by filtration over Hyflo. Evaporation of the solvent followed by coevaporation of the residue with benzene (three times) afforded the amine as a white solid (2.96 g, 97%, 9.80 mmol). This amine was dissolved in DCM (93 mL), and succinic anhydride (936 mg, 9.35 mmol) and Et_3N (1.56 mL, 11.22 mmol) were added. After the mixture was stirred for 1 h at room temperature, the solvent was removed and EtOAc was added. The organic layer was washed with 1 M $KHSO_4$ (twice), water, and brine and dried (Na_2SO_4). Removal of the solvent gave a white foam (4.0 g, 102%, 9.54 mmol) that contained unexplained varying amounts (2−8%) of 1-butanol; ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 18H), 1.6 (m, 4H), 3.2 (bs, 2H), 3.8−4.1 (m, 4H), 5.5, 5.6 (2bs, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3, 28.3, 28.6, 28.9, 48.4, 50.3, 55.9, 80.2, 156.1, 171.1, 175.6; $[M + Na]^+ = 424.15$, $[M - H + 2Na]^+ = 446.10$.

Resin 12a,b. Argogel-NH_2 (600 mg, 0.41 mmol/g) was loaded with pyrrolidine **11-RR** or **11-SS** (296 mg, 0.738 mmol) using BOP (327 mg, 0.738 mmol) and DIPEA (514 μL, 2.95 mmol) dissolved in DCM (7 mL). The resin was gently shaken overnight, filtrated, and washed three times with DCM (2 min each).

General Procedure for Library Synthesis 15a−e, 16a−e. DCM (1 mL) and TFA (1 mL) were added to resin **12a,b** (100 mg, 0.041 mmol), and the mixture was gently shaken for 30 min. The resin was filtrated and washed three times with DCM (2 min each), three times with 10% Et_3N/DCM (2 min each), and three times with DCM (2 min). To the resin were added 8 equiv of sulfonyl chloride **14a−e**[9] (0.32 mmol), NMM (30 μL, 0.32 mmol), and DCM (0.5 mL). After the mixture was shaken for 4−16 h, the resin was washed with DCM three times (2 min each). The resin was dried overnight on P_2O_5, and the loading of the resin was determined from the absorbance of the dibenzofulvene-piperidine adduct at 301 nm.[13] The Fmoc groups were cleaved by adding 20% piperidine in DCM (2 mL) and shaking for 30 min. The resin was filtrated, washed with DCM three times (2 min each), and Boc_2O (0.32 mmol) and NMM (0.32 mmol) in DCM (0.5 mL) were added followed by gentle shaking of the resin overnight. After being washed with DCM three times (2 min each), the resin was dried on P_2O_5.

***N*-Methylaminosuccinyl-3,4-di(Boc-amino)pyrrolidine 17.** To a solution of *N*-succinyl-3,4-di(Boc-amino)pyrrolidine **11-SS** (502 mg, 1.25 mmol), BOP (608 mg, 1.37 mmol), and DIPEA (479 μL, 2.75 mmol) in DCM (2.5 mL) was added dropwise a solution of methylamine in THF (2 M, 3.13 mL, 6.25 mmol) at 0 °C. After the mixture was stirred for 1 h at 0 °C, the solvent was evaporated and the residue redissolved in EtOAc. This solution was washed twice with 1 M $KHSO_4$, twice with 1 M NaOH, and once with brine and dried on Na_2SO_4. The EtOAc was removed in vacuo, and the product was purified by column chromatography (eluent: 6% MeOH in DCM, v/v) yielding pyrrolidine **17** (435 mg, 1.05 mmol, 84%) as a white foam: R_f 0.19 (eluent: 6% MeOH in DCM, v/v); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 18H, 2 × $C(CH_3)_3$), 2.53 (m, 4H, CH_2CH_2), 2.75 (d, 3H, NCH_3), 3.20−3.40 (m, 2H, 2 × NCH^aCH), 3.84−4.06 (m, 4H, 2 × NCH^bCH, 2 × NCH_2CH), 5.89 (bd, 2H, 2 × NHBoc), 6.93 (bs, 1H, $NHCH_3$); ^{13}C NMR ($CDCl_3$) δ 26.1 (NCH_3), 28.2 ($C(CH_3)_3$), 29.1, 30.5 (CH_2CH_2), 48.3, 49.9, (NCH_2-CH), 53.2, 55.4 (NCH_2CH), 79.6 ($C(CH_3)_3$), 155.8 ($NHCO_2$), 171,0 (CH_2C=O), 172.7 (CH_3NHC=O); $[M + Na]^+ = 437.40$, $[2M + Na]^+ = 851.20$. Anal. Calcd for $C_{19}H_{34}N_4O_6 \cdot H_2O$: C, 52.76; H, 8.39; N, 12.95. Found: C, 52.66; H, 7.94; N, 12.71.

Ligand 19. To a solution of *N*-methylamidosuccinyl-3,4-di(Boc-amino)pyrrolidine **17** (145 mg, 0.35 mmol) in DCM (1.0 mL) was added diethyl ether (1.0 mL), saturated with HCl. The mixture was stirred for 30 min followed by the evaporation of the solvent and drying of the residue in vacuo. Then, to a solution of this residue in DCM (3.0 mL) were added NMM (169 μL, 1.54 mmol) and Leucine derived sulfonyl chloride **14d** (409 mg, 1.05 mmol). After the mixture was stirred for 2 h, the solvent was evaporated and the product was purified by column chromatography (eluent: 6% MeOH in DCM v/v) affording **19** (335 mg, 0.32 mmol, 97%) as a white foam: R_f 0.38 (eluent: 10% MeOH in DCM); ^{1}H NMR($CDCl_3$) δ 0.74−0.88 (m, 12H, 2 × $CH(CH_3)_2$), 1.43−1.57 (m, 6H, 2 × CH_2CH-$(CH_3)_2$), 2.32 (bs, 4H, CH_2CH_2), 2.64 (d, 3H, NCH_3), 3.00−3.30 (m, 6H, 2 × SCH_2, NCH_2CH, 3.82 (m, 4H, NCH_2CH, 2 × NCH_2CH) 4.15 (m, 4H, 2 × NCH, 2 × CH (Fmoc)), 4.35−4.55 (2m, 4H, 2 × CH_2 (Fmoc)), 5.51, 5.67, 5.96, 6.02, 6.25, 6.45, 6.60, (7 × bs), 5H, 2 × NHFmoc, $NHCH_3$, 2 × SNH), 7.26 (m, 8H, Ar-CH (Fmoc)), 7.56 (t, 4H, Ar-CH (Fmoc)), 7.72 (d, 4H, Ar-CH (Fmoc)); ^{13}C NMR ($CDCl_3$) δ 21.5, 21.6, 23.0, 23.1 ($CHCH_3$), 24.6 ($CHCH_3$), 26.3 ($NHCH_3$), 28.8, 30.1 (CH_2CH_2), 43.3 (CH_2CHCH_3), 46.1 (FmocNHCH), 47.1 (CH (Fmoc)), 48.7, 49.8 (NCH_2CH), 56.0 (NCH_2CH), 57.3 (SCH_2), 119.9, 126.1, 127.0, 126.6 (Ar-CH (Fmoc)), 141.2, 143.6, 143.9 (Ar-C (Fmoc)), 156.2 ($NHCO_2$), 171.2 (CH_2NC=O), 172.9 (CH_3NHC=O); $[M + H]^+ = 985.20$, $[M + Na]^+ = 1007.00$. Anal. Calcd for $C_{51}H_{64}N_6O_{10}S_2 \cdot H_2O$: C, 61.06; H, 6.63; N, 8.38; S, 6.39. Found: C, 60.93; H, 6.61; N, 8.26; S, 6.09.

Ligand 20. Fmoc-ligand **19** (197 mg, 0.20 mmol) was dissolved in Tesser's base (dioxane/MeOH/4M NaOH 14:5:2, v/v/v, 2 mL) and was stirred for 2.5 h. Then 1 M HCl was added until pH ≈ 6, and the solvents were evaporated. Ether was added to the solid residue, and after being stirred overnight, the mixture was filtrated. To the resulting solid, dioxane (2 mL), 1 M NaOH (2 mL) and Boc_2O (98 mg, 0.44 mmol) were added. After being stirred overnight, the mixture was concentrated and dissolved in DCM. The solution was extracted with 1 M $KHSO_4$, H_2O, and brine and dried on Na_2SO_4. Evaporation of the solvent and column chromatography (eluent: 6% MeOH in DCM, v/v) gave a white foam (54 mg, 0.08 mmol, 40%): R_f 0.28 (eluent: 10% MeOH in DCM, v/v); ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 12H, 2 × $CH(CH_3)_2$), 1.42 (m, 22H, 2 × $C(CH_3)_3$, 2 × $CH_2CH(CH_3)_2$, 1.67 (bs, 2H, 2 × $CHCH_3$), 2.50 (m, 4H, CH_2CH_2), 2,73 (d, 3H, $NHCH_3$), 3.22−3.49 (m, 6H, 2 × SCH_2, 2 × NCH^aCH), 3.86−4.11 (m, 6H, 2 × NCH^bCH, 2 × NCH_2CH, 2 × BocNHCH), 5.23, 5.29, 5.34 (bs (3 ×), 2H, 2 × NHBoc), 6.37, 6.62, 6.91 (bs (3 ×), 3H, $NHCH_3$, 2 × $NHSO_2$); ^{13}C NMR ($CDCl_3$) δ 21.6, 23.0 ($CHCH_3$), 24.6 ($CHCH_3$), 26.3 ($NHCH_3$), 28.4 ($C(CH_3)_3$), 29.1, 30.5 (CH_2CH_2), 43.4 (CH_2CHCH_3), 45.7 (BocNHCH), 49.1, 50.3 (NCH_2CH), 56.0, NCH_2CH), 57.3 (SCH_2), 79.9 ($C(CH_3)_3$), 155.9 ($NHCO_2$), 171.3 (CH_2NC=O), 173 (CH_3NHC=O); $[M + H]^+ = 741.20$, $[M + Na]^+ = 763.20$. Anal. Calcd for $C_{31}H_{60}N_6O_{10}S_2$: C, 50.25; H, 8.16; N, 11.34; S, 8.65. Found: C, 49.95; H, 8.26; N, 11.04; S, 8.12.

Ligand 21. Ligand **21** was obtained as an unexpected product from Fmoc-ligand **19** (197 mg, 0.20 mmol) according to the procedure described for **20**. The product was purified by column chromatography (eluent: 6% MeOH in DCM, v/v) which gave a white foam (42 mg, 0.058 mmol, 29%): R_f 0.70 (eluent: 10% MeOH in DCM); ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 12H, 1.42 (bs, 31H), 1.67 (bs, 2H), 3.23 (m, 6H), 3.83 (m, 4H), 4.15 (bs, 2H), 4.93, 5.60, 6.12 (bs (3×), 4H); ^{13}C NMR ($CDCl_3$) δ 21.6, 23.0, 24.7, 28.4, 43.5, 45.7, 49.0, 56.3, 58.4, 80.1, 153.9, 156.2; $[M + Na]^+ = 750.20$.

(13) Meienhofer, J.; Waki, M.; Heimer, E. P.; Lambros, T. J.; Makofske, R. C.; Chang, C.-D., *Int. J. Peptide Protein Res.* **1979**, *13*, 35−42.

General Procedure for the Enantioselective Addition of Diethylzinc to Aldehydes. Under an argon atmosphere $Ti(O\text{-}i\text{-}Pr)_4$ solution in toluene (1 M, 0.06 mL, 0.06 mmol) was added to the ligand (0.002 mmol) (ligand on resin: 20 mg, 0.010−0.016 mmol, additional toluene (0.04 mL) was added). After being stirred at 40 °C for 30 min, the mixture was cooled to −78 °C and Et_2Zn in hexanes (1 M solution, 110 μL, 0.110 mmol) was added followed by a mixture of benzaldehyde, 4-chlorobenzaldehyde, phenylacetaldehyde, and cyclohexylaldehyde (50 μL, 0.0125 mmol each, in toluene). The reaction mixture was stirred overnight at −20 °C and quenched by adding 1 M HCl (0.5 mL) and EtOAc (1 mL). The EtOAc layer was removed and dried on Na_2SO_4. This solution was directly used for GC analysis.

Supporting Information Available: Experimental procedures containing NMR peak assignments. Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **3**, **5**, **6**, **7**, **10**, **11**, and **21**, a ^{13}C NMR spectrum for **4**, and COSY spectra for **17**, **19**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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