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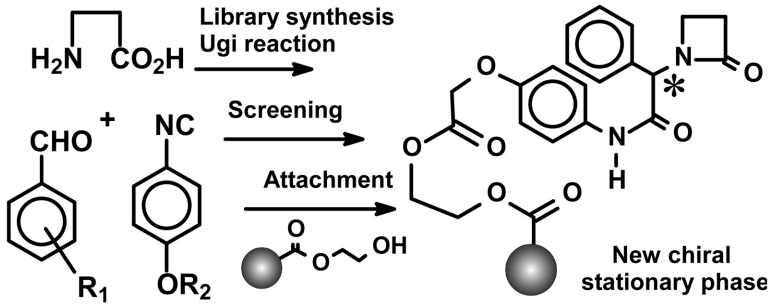

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Chiral Recognition: Design and Preparation of Chiral Stationary Phases Using Selectors Derived from Ugi Multicomponent Condensation Reactions and a Combinatorial Approach

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Combinatorial approaches together with high-throughput screening have been used to develop highly selective stationary phases for chiral recognition. Libraries of potential chiral selectors have been prepared by the Ugi multicomponent condensation reactions and screened for their enantioselectivity using the reciprocal approach involving a chiral stationary phase with immobilized model target compound *N*-(3,5-dinitrobenzoyl)-α-L-leucine. The best candidates were identified from the library of phenyl amides of 2-oxo-azetidineacetic acid derivatives. This screening also enabled specification of the functionalities of the selector desired to achieve the highest level of chiral recognition. The substituents of the phenyl ring adjacent to the chiral center of the selector candidates exhibited the most profound effect on the chiral recognition. The best candidate was then synthesized on a larger scale, resolved into single enantiomers using preparative enantioselective HPLC, and attached to porous poly(2-hydroxyethyl methacrylate-*co*-ethylene dimethacrylate) beads via an ester linkage to afford the desired stationary phase. Selectivities α as high as 3.2 were found for the separation of a variety of amino acid derivatives.

Introduction

The continuing trend to replace racemic drugs, agrochemicals, flavors, food additives, and numerous other products with their single enantiomers is driven by increasingly restrictive regulatory requirements and attempts to limit pollution of organisms and environment with inactive chemicals. For example, the development of single enantiomer drugs replacing their racemic forms ("racemic switch") has been prompted by the awareness that the human body may respond differently to individual enantiomers.[1] These safety concerns, along with the desire to achieve novelty in intellectual property or to extend the patent life of current "blockbuster" drugs,[2] have advanced the techniques for obtaining single enantiomers and the tools used to study their pharmacological properties. Single enantiomer compounds can be obtained by synthesis from natural chiral starting materials, by using enantioselective reactions, and by their separation from racemic mixtures using methods such as crystallization via diastereomers, enzymatic or chemical kinetic resolution, and chromatography. In recent years, the high-performance liquid chromatographic (HPLC) separation of racemates using chiral stationary phases (CSPs) has emerged as an economical and efficient technique applicable even to the large scale isolation of highly purified single enantiomers.[3] Owing to its high efficiency, ease of implementation, and scalability, chromatography has already been used for both analytical and preparative separations.[4] During the last two decades, hundreds of CSPs have been developed, and many of them are now commercially available.[5]

CSPs typically contain chiral polymers or small molecule selectors. These chiral selectors are either covalently linked or adsorbed onto solid support, usually porous silica beads. Large macromolecular selectors, such as proteins,[6] polysaccharides,[7] synthetic polymers,[8] cyclodextrins,[9] and macrocyclic antibiotics,[10] have been used to afford CSPs with selectivities sufficient for the enantioseparations of a wide variety of racemates. However, the mechanism of separation for some of these CSPs is not completely understood, which makes it difficult to develop new, more powerful stationary phases. In contrast, CSPs based on low-molecular weight synthetic selectors,[11] such as Pirkle's "brush-type" stationary phases,[12] have several advantageous features, including better kinetic performance, inertness, broad applicability, and compatibility with a wider range of mobile phases. Moreover, unlike the CSPs based on optically active polymers, the chromatographic behaviors of brush-type CSPs can be rationalized by chiral "recognition" models. These phenomenological descriptions allow the design and development of novel classes of selectors by identifying the specific functionalities enabling the desired interactions, such as donor−acceptor, dipole−dipole, and π-stacking, that are necessary for attaining the optimal level of recognition by the selector.

The separation of enantiomers on a CSP results from the diastereomeric interactions that occur between the analytes and the CSP. The chiral recognition with a brush-type CSP is assumed to be the result of three simultaneous interactions,

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such as H-bonding, π-stacking, and dipole−dipole interactions between the selectors of the analyte, with the condition that one of the interactions is stereochemically dependent and prefers one of the enantiomers.[12]

Despite enormous progress made in the area of theoretical calculations,[13] the models currently used are not yet sufficient to predict a priori the enantioselectivity of a CSP for a specific separation. Therefore, extensive preparation and evaluation of potential chiral selectors cannot be obviated for the development of new CSPs. Combinatorial chemistry together with high-throughput screening may shorten the discovery process considerably. This "high-speed chemistry" has already found widespread applications in pharmaceutical and materials research[14] and has also been used for the development of materials for recognition of chirality.[15,16]

We have previously designed and demonstrated two new approaches to the development of CSPs using high-speed methods. First, the "library-on-bead" approach involved a mixed library of potential chiral selectors *all* attached to porous polymer beads and tested for the separation of the target analyte. The selector with highest selectivity was then identified in a few deconvolution steps.[17] Alternatively, we prepared a novel CSP derived from a library of low molecular weight selectors, dihydropyrimidines, obtained in solution using the Biginelli three-component condensation reaction.[18] The lead selector was then identified by a reciprocal screening using a column with immobilized target enantiomers.[19]

Clearly, the availability of a large number of structurally different compounds increases the probability of finding selectors for chiral HPLC, enabling the separation of a wide range of specific targets. Screening of these molecules also helps one to understand the mechanism of chiral recognition by monitoring the effects of individual substituents decorating the persisting scaffold structure.

In the present work, we describe the use of another multicomponent condensation reaction, the Ugi reaction;[20] to create a library of potential selectors, its screening for selectors, enabling the rapid design of CSPs amenable to the HPLC separations of racemic compounds; and the preparation of a highly selective CSP via attachment of the single enantiomer of specified lead compound to specially designed noninteracting porous polymer beads.

Experimental Section

Materials. All aldehydes were obtained commercially or prepared according to literature procedures. Ethyl isocyanoacetate, *tert*-butyl isocyanide, 4-amino phenol, carbon tetrabromide, *tert*-butyl dimethylsilyl chloride (TBDMSCl), tetrabutylammonium fluoride (TBAF) (1 M solution in THF), benzyl 2-bromoacetate and *tert*-butyl 2-bromoacetate, diisopropyl carbodiimide (DIC), 4-dimethyl aminopyridine (DMAP), and 2,6-dimethyl phenyl isocyanide were obtained from commercial sources. 4-Dimethylaminopyridinium *p*-toluenesulfonate (DPTS) was purchased from Aldrich. Isonitrile **33** was synthesized using literature procedure.[21] Dichloromethane (CH_2Cl_2) was distilled over CaH_2 under inert atmosphere, and tetrahydrofuran (THF) was freshly distilled over sodium benzophenone ketyl under N_2 atmosphere. *N*,*N*-Dimethyl formamide (DMF) was distilled over CaH_2 under reduced pressure and stored over molecular sieves. All moisture or air-sensitive reactions were carried out under N_2 atmosphere in dry solvent. The 7-μm monodisperse porous poly(2-hydroxyethyl methacrylate-*co*-ethylene dimethacrylate) beads containing 60 wt % of cross-linker were prepared using a staged templated suspension polymerization method previously developed in our group.[22] These beads have a median pore size of 30 nm, a pore volume of 0.3 mL g^{-1}, and a specific surface area of 140 m^2 g^{-1}.

Instrumentation. ^1H and ^{13}C NMR spectra were recorded on Fourier transform spectrometers (Bruker AMX-300 or Bruker AMX-400). Infrared spectra were recorded on Nicolet Mattson Genesis II FT-IR spectrophotometer using KBr technique.

General Procedure for Ugi Three- and Four-Component Condensation Reactions. To a stirred solution of aldehyde (1 mmol) and amine or amino acid (1 mmol) in methanol (5 mL) at 0 °C was added a solution of isonitrile (1−1.2 mmol) in MeOH (1 mL), and the mixture was stirred at room temperature. Upon completion of the reaction (TLC monitoring), the solvent was evaporated, and the residue was purified by flash chromatography (1:1 hexanes/EtOAc) or by crystallization to afford products in 60−90% yields.

Preparation of Aryl Isonitriles. *tert*-Butyl [4-(formylamino)phenoxy] Acetate (43). To a stirred solution of 4-hydroxy-*N*-formanilide **41**[21] (3.3 g, 24.2 mmol) and *tert*-butyl 2-bromoacetate (6.6 g, 33.3 mmol, 1.4 equiv) at 0 °C in DMF (70 mL) was added finely ground K_2CO_3 (4.6 g, 33.8 mmol). The mixture was allowed to stir for 6 h and then was filtered to remove solid material, which was washed with EtOAc. The filtrate was diluted with H_2O (100 mL) and then extracted with Et_2O (3 × 100 mL). The organic extracts were combined, washed with H_2O, and dried over Na_2SO_4. Evaporation of the solvent and purification of the crude product by flash chromatography (2:3 hexanes/EtOAc) gave **43** (4.7 g, 77%) as a light pink solid. mp: 72−74 °C. IR ν: 3326, 1727, 1687, 1608, 1541, 1508 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.49 (s, 9H), 4.53 (s, 2H), 6.86 (d, J = 9 Hz, 2H), 7.32 (d, J = 9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 65.8, 83.0, 115.4 (2C), 127.9 (2C), 158.3, 167.4. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.46; H, 6.75; N, 5.66.

***tert*-Butyl (4-Isocyanophenoxy) Acetate (34).** To a stirred solution of *N*-formyl derivative **43** (2.47 g, 9.62 mmol) in dry CH_2Cl_2 (75 mL) was added carbon tetrabromide (4.76 g, 4.5 mmol, 1.5 equiv), triphenyl phosphine (3.72 g, 14.5 mmol, 1.5 equiv), and triethylamine (1.45 g, 14.4 mmol, 1.5 equiv) at 0 °C. After stirring the mixture for 4 h, the solvent was evaporated, and the residue was taken into cold EtOAc. The insoluble phosphine oxide was removed by filtration, and the filtrate was condensed to give a crude product, which was then purified by flash chromatography (10:1 hexanes/EtOAc) to afford isonitrile **34** (804 mg, 77%). mp 60−62 °C. IR ν: 3105, 2120, 1720, 1680, 1514 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.49 (s, 9H), 4.66 (s, 2H), 6.87 (d, J = 9 Hz, 2H), 7.32 (d, J = 9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 65.8, 83.0, 115.4 (2C), 127.9, 158.3, 167.4.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.77; H, 6.46; N, 5.93.

Benzyl [4-(Formylamino)phenoxy] Acetate (44). This compound was prepared according to procedures similar to those described above for **43**. Using benzyl 2-bromoaceate as the alkylating reagent, **44** was obtained as a brown oil (25% yield after flash chromatography). IR (neat): ν 3297, 1756, 1684, 1603, 1511 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.64 (s, 2H), 5.23 (s, 2H), 6.87 (t, $J = 5.1$ Hz, 2H), 7.00 (d, $J = 6.6$ Hz, 1H), 7.35 (m, 5H), 7.44 (d, $J = 6.6$ Hz, 1H), 8.31 (s, 1H), 8.50 (d, $J = 8.7$ Hz, 1H). Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.47; H, 5.40; N, 4.83.

Benzyl (4-Isocyanophenoxy) Acetate (35). The benzyl-protected isonitrile **35** was prepared from the above material using the procedure described for the substrate **34** to give a pale yellow solid in 72% isolated yield. mp 81−83 °C. IR ν: 3105, 2123, 1744, 1605, 1503 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.67 (s, 2H), 5.29 (s, 2H), 6.86 (d, 6.6 Hz, 2H), 7.30 (d, $J = 6.6$ Hz, 2H), 7.37−7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.3, 67.2, 115.3, 127.8 (2C), 128.4 (2C), 128.7 (2C), 134.9, 157.9, 168.0. Anal. Calcd C, 71.90; H, 4.90; N, 5.24. Found: C, 71.75; H, 4.92; N, 5.32.

***tert*-Butyl (4-{[(2-Oxoazetidin-1-yl)(phenyl)acetyl]amino}-phenoxy) Acetate (47).** To a stirred solution of β-alanine (247 mg, 2.7 mmol) and benzaldehyde (295 mg, 2.78 mmol) in MeOH was added isonitrile **34** (650 mg, 2.78 mmol) at room temperature. After stirring for 24 h, the solvent was evaporated, and the residue was purified by flash chromatography (1:1 hexanes/EtOAc) to give **47** (690 mg, 61%) as a white solid. mp 60−62 °C. IR ν: 3324, 1750, 1675, 1611, 1517 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 9H), 2.90−3.03 (m, 2H), 3.23−3.27 (m, 1H), 3.67−3.71 (m, 1H), 4.47 (s, 2H), 5.57 (s, 1H), 6.82 (d, $J = 9.0$ Hz), 7.36 (d, $J = 9$ Hz), 7.38−7.43 (m, 5 Hz), 8.49 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.9, 35.9, 39.3, 59.7, 65.8, 82.2, 114.7, 121.3, 127.9, 128.5, 128.9, 131.6, 134.3, 154.5, 166.7, 167.9, 168.2. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.46; H, 6.49; N, 6.70.

Benzyl (4-{[(2-Oxoazetidin-1-yl)(phenyl)acetyl]amino}-phenoxy) Acetate (48). This compound was prepared from isonitrile **35** to obtain compound **48** as a white solid (60% yield) using the same procedure described for compound **48**. mp 56−57 °C. IR ν: 3311, 1733, 1605, 1684, 1507 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.44−2.98 (m, 2H), 3.21−3.24 (m, 1H), 3.73−3.75 (m, 1H), 4.60 (s, 2H), 5.22 (s, 2H), 5.76 (s, 1H), 6.76 (d, $J = 6.6$ Hz, 2H), 7.28−7.32 (m, 10H), 7.37−7.45 (m, 2H), 9.14 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.1, 39.3, 59.5, 65.6, 67.0, 114.9, 121.5, 128.1, 128.4, 128.5, 128.6, 129.1, 132.1, 134.5, 135.1, 154.4, 167.0, 168.3, 168.8. Anal. Calcd for $C_{26}H_{24}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.46; H, 6.49; N, 6.70.

***N*-(4-*tert*-Butyldimethylsilyloxyphenyl)-2-(2-oxoazetidin-1-yl)-2-phenylacetamide (50).** This compound was prepared from isonitrile **33** to obtain compound **50** (64% yield) according to the same procedure described for **47**. mp 60−62 °C. IR ν: 3309, 1733, 1690, 1605, 1507, 1407, 1240, 915 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.16 (s, 6H), 0.96 (s, 9H), 2.89−2.92 (m, 1H), 2.98−3.01 (m, 1H), 3.26−3.29 (m, 1H), 3.75−3.77 (m, 1H), 5.72 (s, 1H), 6.74 (d, $J = 6$ Hz, 2H), 7.34−7.45 (m, 7H), 8.84 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 4.3, 18.3, 25.8, 26.2, 39.5, 60.0, 120.3, 121.5, 128.2, 128.8, 129.2, 131.6, 134.6, 152.5, 166.9, 168.4. Anal. Calcd for $C_{26}H_{24}N_2O_5$: C, 67.28; H, 7.36; N, 6.82. Found: C, 67.04; H, 7.29; N, 6.84.

***N*-(4-Hydroxyphenyl)-2-(2-oxoazetidin-1-yl)-2-phenylacetamide (51).** To a stirred solution of **50** (150 mg, 0.35 mmol) in dry THF (10 mL) with or without the presence of 2-bromoacetic acid was added 0.4 mL of TBAF (0.4 mmol, 1 M in THF) at 0 °C. After stirring the mixture at room temperature for 30 min, the solvent was evaporated, and the crude product was purified by a flash chromatography (5% MeOH in CH_2Cl_2) to give **51** as a white crystalline solid (70 mg, 68%). mp 225−227 °C. IR ν: 3252, 1721, 1644, 1563, 1517, 1249 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$−DMSO-d_6): δ 2.69−2.84 (m, 2H), 3.04−3.09 (m, 1H), 3.57−3.62 (m, 2H), 5.53 (s, 1H), 6.62 (d, $J = 8$, 2H), 7.21 (d, $J = 8$ Hz, 2H), 7.22−7.31 (m, 5H), 8.50 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.5, 38.3, 58.0, 114.8, 120.9, 121.1, 127.5, 127.7, 128.2, 129.5, 134.6, 153.4, 166.3, 166.8. Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.74; H, 5.57; N, 9.33.

Conversion of Aryl Silyl Ethers to Alkyl Ethers. To a mixture of aryl silyl ether **50** (860 mg, 2.0 mmol), and benzyl 2-bromoacetate (720 mg, 3.14 mmol) in dry THF (30 mL) was added 2.5 mL of TBAF solution (2.5 mmol, 1 M in THF) at 0 °C. After stirring the mixture at room-temperature overnight, the solvent was evaporated, and the crude product was purified by flash chromatography (1:1 hexanes/EtOAc) to afford **48** (880 mg, 99%) as a white crystalline solid. The spectral data is identical to the one prepared by the Ugi reaction. Similarly, when *tert*-butyl 2-bromoacetate was used as the electrophile, the product **47** was obtained in 77% isolated yield.

(4-{[(2-Oxoazetidin-1-yl)(phenyl)acetyl]amino}phenoxy)-acetic Acid (49). Benzyl ester **48** (870 mg, 1.9 mmol) was dissolved in EtOAc (15 mL) and was evacuated by applying vacuum in the presence of H_2 gas to remove all of the atmospheric O_2. Pd (10%) on charcoal (15 mg) was then added, followed by 2−3 drops of MeOH. The mixture was allowed to stir under pressurized H_2 gas for 3 h. The catalyst was removed by filtration, and the filtrate was evaporated to afford acid **49** (605 mg, 90%) as a white crystalline solid. mp 160 °C (dec). IR (KBr): 3297, 1730, 1881, 1604, 1553, 1510, 1411, 1209 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.77 (d, $J = 12.4$ Hz, 1H), 2.93 (d, $J = 12.4$ Hz, 1H), 3.14 (d, $J = 2$ H, 1H), 3.68 (d, $J = 2$ Hz, 1H), 4.47 (s, 2H), 5.73 (s, 1H), 6.60 (d, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 8.8$ Hz, 2H), 7.31−7.39 (m, 5H), 7.64 (br s, 1H), 8.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.78, 39.59, 59.73, 60.65, 65.21, 72.16, 114.90, 121.98, 128.45, 129.01, 129.27, 131.68, 134.00, 154.60, 167.22, 169.27, 172.14. Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.48; H, 5.46; N, 7.79.

Preparation of Chiral Stationary Phases. To a suspension of poly(2-hydroxyethyl methacrylate-*co*-ethylene dimethacrylate) beads **52** (1.5 g) in CH_2Cl_2 (15 mL) was added sequentially acid **49** (450 mg, 1.2 mmol), DMAP (24 mg,

0.2 mmol), DPTS (59 mg, 0.2 mmol), and DIC (151 mg, 1.2 mmol), and the mixture was shaken at room temperature overnight. The beads were filtered and repeatedly washed with CH_2Cl_2, THF, water, methanol, THF, CH_2Cl_2, and acetone and then dried under vacuum. The beads were end-capped by treatment with acetic anhydride (100 mg) in CH_2Cl_2 (5 mL) and pyridine (100 mg) overnight. The beads were then washed and dried under vacuum to afford the CSP. A selector content of 0.5 mmol g^{-1} in the CSP is based on the elemental analysis of nitrogen.

Chromatographic Evaluation. Once the CSPs were end-capped, they were dispersed in hexane and slurry-packed at a constant pressure of 15.0 MPa into 150 × 4.6-mm-i.d. stainless steel columns. Preparative separations were carried out on 60 × 0.8-cm-i.d. column packed with (*S*)-3,5-(dinitrobenzoyl)leucine-functionalized CSP. A Waters HPLC system (Alliance 2690 XE), a 486 UV detector, and a Jasco OR-990 chiral detector controlled by Millennium 2010 software were used for all of the chromatographic measurements.

Normal phase chiral separations were carried out using CH_2Cl_2/hexane as the mobile phases. The separation factors α (selectivity) were calculated using the following equation,

$$\alpha = k'_2/k'_1 \tag{3}$$

where k'_1 and k'_2 are the retention factors of the enantiomers defined as

$$k'_r = (t_R - t_0)/t_0 \tag{4}$$

where t_R and t_0 represent the retention times of the compound and 1,3,5-tri-*tert*-butylbenzene (void volume marker), respectively. The racemic analytes *N*-3,5-dinitroanilides were prepared using methods reported elsewhere.[23]

Results and Discussion

Synthesis of Libraries. Multicomponent condensation reactions are organic reactions in which three or more compounds react in a "single-pot" mode to give a durable scaffold structure that features highly variable pendent functionalities.[24] This versatility makes multicomponent condensations particularly valuable for generating diverse combinatorial libraries of small molecules from readily available building blocks. The Ugi multicomponent condensation reaction[20,25] has been used extensively for the synthesis of libraries of druglike molecules with a peptidic core structure.[26] Depending on the number of components involved, this reaction can be classified as a three-,[20,27] four-,[28] or even five-component condensation[29] and typically involves equimolar ratios of an amine, a carboxylic acid, a carbonyl compound, and an isonitrile. A cyclic product is formed when two of these functionalities are part of the same molecule, as is the case with an amino acid. More than two dozen core structures[30] have already been obtained using Ugi type reactions. This approach has also been successfully adopted for solid phase and fluorous phase synthesis.[21] The uniqueness of the Ugi reaction lies in the remarkable reactivity of the isonitrile functionality, which undergoes both

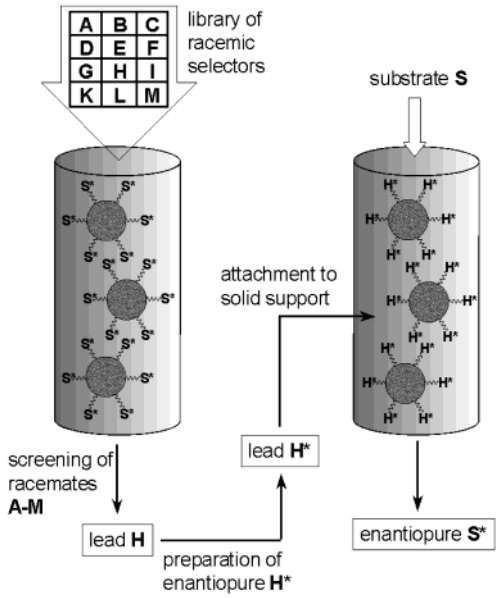
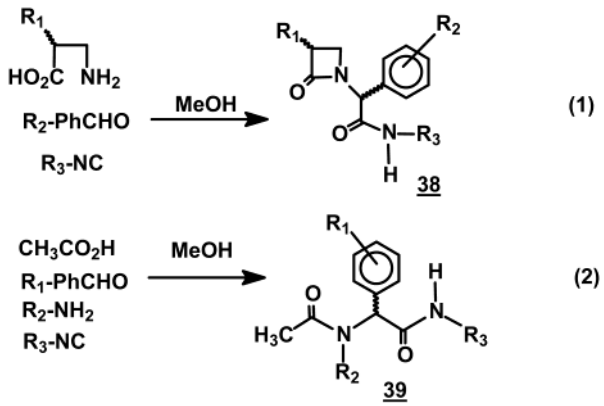


Figure 1. Concept of reciprocal screening to identify best selector for the preparation of chiral stationary phases.

Scheme 1



α-addition by a nucleophile and electrophile attack on the same carbon.

To increase the diversity of our library of potential chiral selectors, we used both three- and four-component Ugi reactions involving compounds **1**−**37** in the parallel synthesis protocol shown in eqs 1 and 2, respectively (Scheme 1). The three-component condensation reaction involves *β*-alanine and its reaction with an aldehyde and isonitrile to afford the *β*-lactam scaffold **38**, a key structure found in many families of antibiotics[31] and antibacterial agent.[32] In contrast, isonitrile, acetic acid, benzylamine or 4-methoxy benzylamine, and an aldehyde are combined in the four-component reaction to afford the peptide-like molecule **39**.

The building blocks used in our study are shown in Figure 2. All of the aldehydes **1**−**29** are commercially available or readily prepared. Similarly, isonitriles **30**−**32** were purchased, but **33**−**35** with protected hydroxyl or acid functionalities were synthesized from 4-aminophenol **40** (Scheme 2). These isonitriles were specifically designed to enable postcondensation deprotection while also providing a handle for later attachment of the selector to the beads. They were synthesized using modified literature procedures[33,34] by first reacting compound **40** with acetic formic anhydride to give

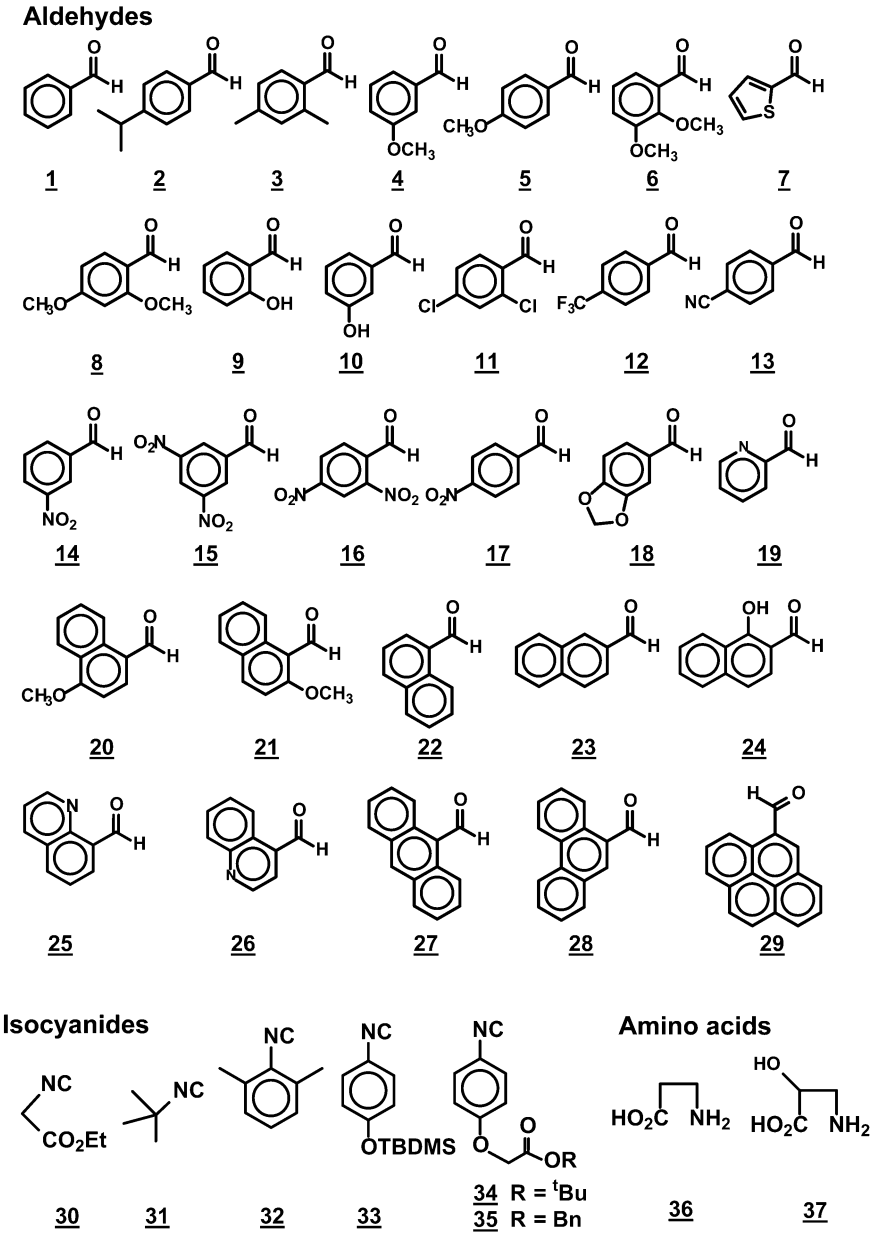
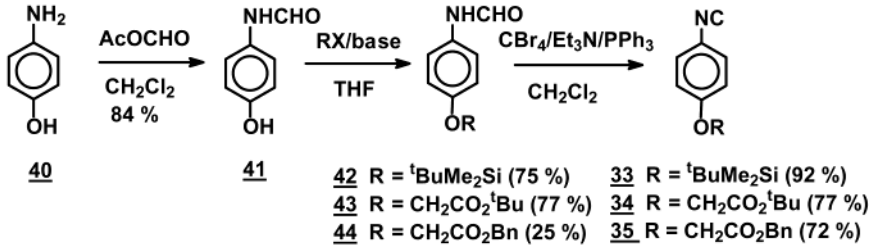


Figure 2. Building blocks for the synthesis of library of selectors using the Ugi reaction.

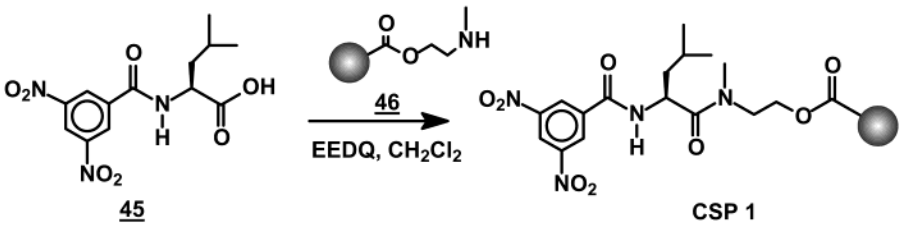
Scheme 2



the *N*-formyl derivative **41**, followed by subsequent reaction with specific reagents to afford intermediates **42**−**44** (Scheme 2). Reaction with *tert*-butyldimethylsilyl chloride (TBDMSCl) and *tert*-butyl 2-bromoacetate affords products in yields exceeding 75%. In contrast, the yield of the reaction with benzyl 2-bromoacetate is substantially lower, perhaps due to saponification of the benzyl ester under the basic reaction conditions. The derivatives **42**−**44** were then converted to the respective isonitriles **33**−**35** using dehydration conditions (Scheme 2).[35]

The condensation reactions were carried out in parallel on a 5−10 mmol scale, and the library was diversified by using a large set of aromatic aldehydes. The three component Ugi reactions involved an amino acid added to 1 equiv of aldehyde in methanol. After stirring for a few minutes, the mixture was treated with the desired isonitrile at 0 °C. For

Scheme 3



the four-component reactions, acid followed by isonitrile was added to a stirred solution of a mixture of amine and aldehyde in methanol. All reaction mixtures were then stirred for 24 h at room temperature, with monitoring by TLC, and the product was isolated by flash chromatography or, in some cases, by recrystallization. Typically, the racemic Ugi adducts were obtained in 60−90% yield with a purity of >90% according to ^{1}H NMR. All para- and meta-substituted aldehydes used in our reactions afforded the desired products in high yields. In contrast, ortho-substituted aromatic aldehydes afforded little or no product.

Screening of the Library of Selectors. Figure 1 outlines schematically the reciprocal screening procedure that we used to identify the best potential selector. First, an analytical chiral HPLC column must be prepared using a stationary phase CSP **1** with the selector derived from a single enantiomer of the model target (*S*)-(3,5-dinitrobenzoyl)leucine **45** attached to monodisperse macroporous poly((*N*-methyl)-aminoethyl methacrylate-*co*-methyl methacrylate-*co*-ethylene dimethacrylate) beads **46**[36] (Scheme 3). The selector loading was 0.33 mmol/g. A racemic library of potential selectors is then screened on this column to identify the lead compound that is best separated on a CSP containing the target compound. This lead is then synthesized in racemic form on a larger scale and separated to obtain individual enantiomers.

The results of screening using CSP **1** in normal phase chromatographic mode using a 30:70 mixture of hexanes and dichloromethane as the mobile phase are summarized in Table 1. This table lists only the compounds that afforded separations with selectivity factors α of >1.1. The results indicate that the incorporation of aromatic rings and their substitution pattern strongly affect the selectivity. Several racemic β-lactams from the library were resolved with separation factors as high as 2.7. The chromatographic separation of enantiomers of lactam derivative **49** is shown in Figure 3. In contrast, none of the compounds prepared using the four-component Ugi condensation reaction could be resolved on CSP **1**.

Our observations obtained while screening the library reveal some general trends with respect to the structural requirements necessary to achieve good chiral recognition. As expected, changes in the substituents of selectors strongly affect the enantiorecognition of the β-lactams. For example, enantiomers derived from aromatic isonitriles **32**−**35** were separated better than those made from aliphatic isonitriles **30** and **31**. This can be ascribed to the additional π−π interactions between the immobilized selector and the lactams in which a second aromatic ring is present. In contrast to the 4-alkoxyphenyl isonitrile (**33**−**35**)-based compounds,

Table 1. Retention Factors k_1' and Separation Factors α of β-Lactam Selectors Derived from Ugi-3CC Reaction (Scheme 1) on CSP **1** Derived from (*S*)-(3,5-Dinitrobenzoyl)leucine[a]

entry	aldehyde	isonitrile	k_1'	α
1	2-naphthyl	**30**	0.22	1.63
2	9-phenanthryl	**30**	0.35	1.58
3	4-OMe-1-naphthyl	**30**	0.25	1.47
4	1-pyrenyl	**30**	0.53	1.36
5	3-OMePh	**32**	0.22	1.40
6	4-OMePh	**33**	0.21	2.22
7	3-OMePh	**33**	0.25	1.78
8	3,5-$(OMe)_2$Ph	**33**	0.26	1.45
9	3-NO_2Ph	**33**	0.40	2.04
10	phenyl	**33**	0.24	2.08
11	4-OMe-2-naphthyl	**33**	0.44	1.11
12	2-naphthyl	**33**	0.43	1.13
13	4-OMePh	**34**	1.58	2.38
14	3-OMePh	**34**	1.13	2.06
15	phenyl	**34**	1.02	2.46
16	3-NO_2Ph	**34**	2.07	2.18
17	4-NO_2Ph	**34**	2.05	2.18
18	2-naphthyl	**34**	1.55	1.52
19	4-OMe-1-naphthyl	**34**	1.52	1.58
20	isobutyl	**34**	0.25	1.00
21	phenyl	**35**	1.38	2.72

[a] Conditions: column 150 × 4.6 mm i.d; mobile phase, CH_2Cl_2/hexanes (70:30); flow rate, 1 mL/min.

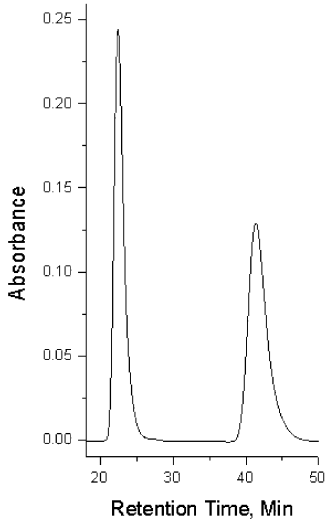
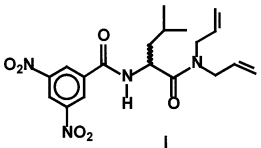
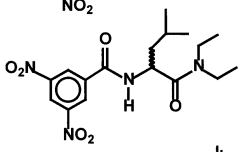
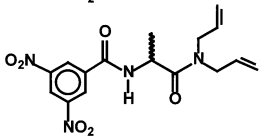
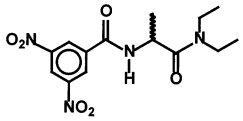


Figure 3. Separation of selector **48** on CSP **1**. Chromatographic conditions: column, 60 × 0.8 cm i.d.; mobile phase, 70/30 dichloromethane/hexanes; flow rate, 1 mL/min. UV detection at 254 nm.

lactams derived from 2,6-dimethylphenyl isonitrile **32** (entry 5) were not well separated.

The lactam derived from ethyl isocyanoacetate **30** and unsubstituted 2-naphthaldehyde **23** was separated with better selectivity than its benzaldehyde **1**, phenanthrene-9-carbox-

Table 2. Chromatographic Separation of Analytes on CSPs **2** and **3**[a]

entry	analyte	t_1[b]	k_1'	α	t_1[c]	k_1'	α
		CSP 2 (-)			CSP 3 (+)		
1		2.79	0.64	3.03	3.34	1.01	3.00
2		2.83	0.80	2.84	3.50	1.09	2.80
3		2.83	0.66	2.88	3.50	1.09	2.78
4		2.70	0.58	3.20	3.55	1.12	3.1

[a] Conditions: column, 150 × 4.6 i.d.; mobile phase, CH_2Cl_2/hexanes (70:30); flow rate, 1 mL/min; 25 °C. [b] Retention time of first eluted (+) enamtiomer. [c] Retention time of first eluted (−) enantiomer.

aldehyde **28**, and 1-pyrenecarboxaldehyde **29** counterparts (Table 2, entries 2−4). However, after substitution of the alkyl isonitrile with an aromatic silyl derivative **33**, the benzaldehyde-derived products were separated better than those prepared from the higher aromatic aldehydes. In addition, introduction of an electron-donating group at the para position of the benzaldehyde significantly enhances the chiral recognition (entry 6). Remarkably, an electron-withdrawing group placed at the meta position of the aldehyde also contributes to the increase of selectivity (entry 9).

Selectors derived from 4-alkoxyphenyl isonitriles **34**−**35** were well separated; however, the type and substitution pattern of the aldehyde again plays an essential role. Generally, lactams derived from benzaldehyde are better separated than those prepared from higher aromatic aldehydes. However, any substitution on the phenyl ring has a deleterious effect on the separation, and only the benzaldehyde-derived compounds showed highest selectivity among the series of all other lactams (Table 2, entry 15). Replacing the *tert*-butyl group of the isonitrile with a benzyl group further improves the separation (entry 20). The position of substitution with electron-donating groups has a moderate effect. For example, the lactam derived from 4-methoxybenzaldehyde was better separated than its counterpart prepared from 3-methoxybenzaldehyde (entries 13−14). However, with electron-withdrawing substituents, such as the nitro group, the position of substitution had no effect on the separation (entries 16−17).

Finally, entry 20 in Table 2 shows that the Ugi adduct derived from an aliphatic aldehyde, isovaleraldehyde, was not separated, in contrast to those derived from aromatic aldehydes. This confirms that the presence of an aromatic ring directly connected to the chiral center is essential for chiral recognition of the selected target.

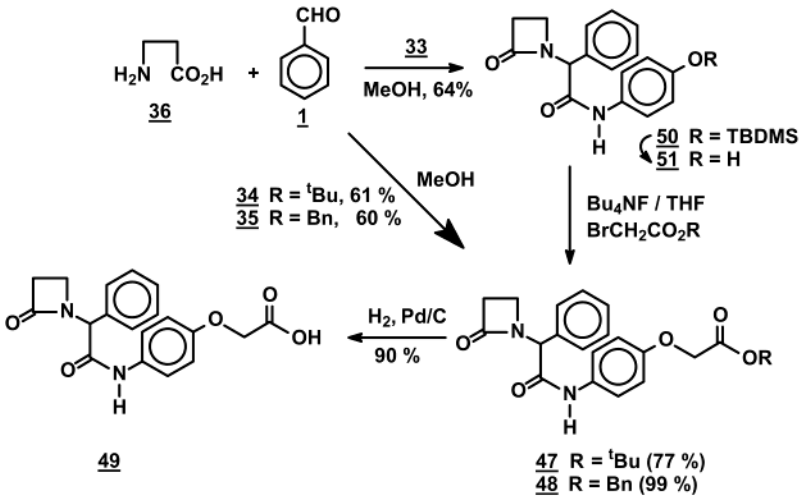
Preparation of Chiral Stationary Phases. Having identified the best potential selectors from the library, a suitable reactive handle was needed to attach the compound onto polymer beads. Although hydrolysis of *tert*-butyl ester **47** (Scheme 4) using trifluoroacetic acid would provide direct access to acid **49**, the product obtained in this reaction was a mixture of compounds, possibly as a result of the occurrence of additional cleavage reactions. Even the use of carbocation scavengers, such as anisole or triethylsilane, as suggested in the literature,[37] did not afford the desired product. A trimethylsilyl iodide-mediated reaction that enables hydrolysis of *tert*-butyl esters presumably under neutral conditions[38] also led to a mixed product. In contrast, benzyl ester **48**, synthesized from isonitrile **35** (Scheme 4), was easily deprotected under neutral conditions using Pd-catalyzed hydrogenolysis. However, the overall yield of this four-step route was only 7.5%, primarily because of the low yield obtained for compound **35**. Thus, silyl derivative **50** was synthesized to finally obtain selector **48** in overall 40% yield.

Compound **50** was derived from a known isonitrile **33**.[34] This strategy is based on the chemistry of desilylation of aryl silyl ethers in the presence of electrophiles, leading to the direct formation of an alkyl ether using tetrabutylammonium fluoride (TBAF) as the reagent.[39] Thus, the treatment of **50** with TBAF in the presence of benzyl 2-bromoacetate gave the aryl alkyl ether **48** in almost quantitative yield (Scheme 4). This reaction sequence was repeated several times in gram quantities with consistent yields. Similarly, this route can also be extended to alkylation with *tert*-butyl 2-bromoacetate for the synthesis of compound **47** in high yield. However, attempts to use 2-bromoacetic acid as the alkylating agent to prepare acid **49** failed, and only the protodesilylated product **51** was isolated (Scheme 4). This is likely due to the rapid protonation of the intermediate phenoxide ion by the carboxylic acid functionality.

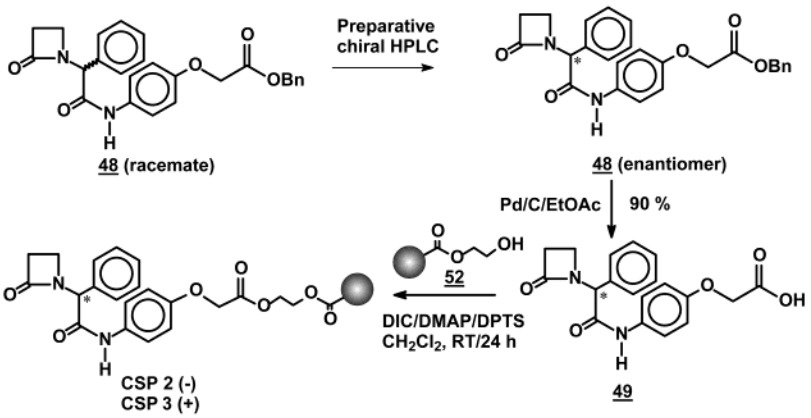
The next important task in the preparation of the desired CSP was the large scale resolution of the racemic selector into single enantiomers and their immobilization onto an appropriate noninteracting solid support. Since the analytical column containing CSP **1** proved to be very efficient for the screening of our library, a semipreparative 60 × 0.8-cm-i.d. stainless steel column was prepared using CSP **1** as a packing material. Using this column, benzyl ester **48** was resolved, and both enantiomers could be obtained with ee exceeding 98% in quantities of over 600 mg, sufficient for the preparation of chiral columns. Independent hydrogenolysis of both enantiomers of **48** using 10% palladium on carbon in ethyl acetate afforded the desired products **49** in 90% yield (Scheme 4).

The enantiomeric acids **49** were then separately immobilized onto poly(2-hydroxyethyl methacrylate-*co*-ethylene dimethacrylate) beads **52** via an ester linkage to obtain two new CSPs, each containing a chiral β-lactam selector. Reaction of the two acids (−)-**49** and (+)-**49** with the porous polymer beads was achieved in the presence of DIC/DMAP/DPTS coupling agents in CH_2Cl_2 at room temperature for

Scheme 4



Scheme 5



24 h. The beads were then thoroughly washed to remove excess reagents and treated with acetic anhydride and 1 equiv of pyridine in CH_2Cl_2 to end-cap the residual hydroxyl groups, affording the desired chiral phases CSP **2** and CSP **3**, respectively.

Successful immobilization of the individual selectors onto the insoluble and highly cross-linked solid support was monitored by IR spectrometry. In addition, nitrogen elemental analyses of CSPs **2** and **3** indicated a loading of 0.51 mmol g^{-1}, assuming that all of the nitrogen in the beads originates from the chiral selector.

Separation of Enantiomers with the *β*-Lactam Chiral Stationary Phases. CSPs **2** and **3** were packed in 150 × 4.6-mm-i.d. stainless steel columns, and their ability to separate the enantiomers of various racemates was evaluated in normal phase HPLC mode (Table 2). Both CSPs exhibited good enantioselectivities for certain analytes derived from amino acids. In fact, the selectivities observed were higher than those obtained during the reciprocal screening on CSP **1**. It is also worth noting that the retention times observed on both CSP **2** and CSP **3** are significantly shorter than was the case with CSP **1**. Clearly, the columns involved in the two phases of this reciprocal scheme cannot be directly compared to each other because of the ancillary structural modifications required for the attachment of selector **48** onto the solid support. The highest separation factor, $\alpha = 3.2$,

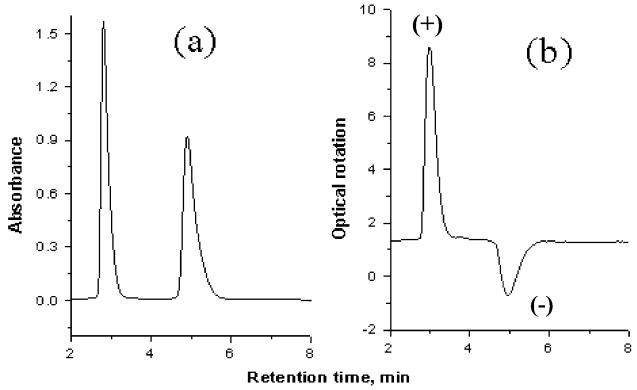


Figure 4. Separation of (3,5-dinitrobenzoyl)-alanine-*N*,*N*-diethylamide on *β*-lactam derived CSP **2** (−). Chromatographic conditions: column, 150 × 4.6 mm i.d.; mobile phase, 70/30 dichloromethane/hexanes; flow rate, 1 mL/min. UV detection at 254 nm (a) and chiral detection (b).

was obtained with CSP **2** for the enantiomers of DNB−Ala−diethyl amide (Figure 4). Not surprisingly, elution times for the (−) enantiomers of the analytes were longer with CSP **2**, whereas the (+) enantiomers were more retained on CSP **3.** Columns packed with CSPs **2** and **3** exhibit very similar elution times of 1.65 and 1.68 min for the unretained marker, respectively, which indicates that both columns are packed similarly. Since the column efficiency is 11 000 plates/m for both columns, the peaks shown in Figure 4 are sharp and

well resolved. Table 2 summarizes the separation factors for several amino acid derivatives. Interestingly, they are not equal, as might be expected for CSPs differing only in configurations of the selector. This can be ascribed to the lower enantiomeric excess (ee) of the attached selectors. The ee of the (−) enantiomer was 99.7, but the ee for the (+) enantiomer was 97.7. As a result, CSP **3** containing the latter affords separations with a lower selectivity, thus demonstrating the significant effect of selector purity.

Conclusion

The Ugi multicomponent condensation reaction together with the reciprocal screening is a powerful strategy in designing new brush-type CSPs. By introducing the β-lactam chemistry that provides the required chiral selectivity, this study further extends and corroborates the utility of library approaches in enantioseparations. At the same time, our results also contribute to a better understanding of the molecular recognition process through the specification of effects that may be attributed to individual functionalities decorating the chiral scaffold. Our current work involves a combination of modeling and synthetic approaches for the design of highly discriminating selectors for specific target drugs.

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