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Silicon-based aromatic transferring linkers for traceless solid-phase synthesis of aryl-, polyaryl-, and heteroaryl-containing compounds

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Abstract—A number of arylsilane-based linkers are prepared for traceless solid-phase synthesis. General methodologies for introduction of the silyl group and various functional groups to aromatic, polyaromatic, and heteroaromatic rings are developed. Also, broad utilities of the linkers are demonstrated by on-resin preparation of small organic molecules and subsequent cleavage of the products either by protiodesilylation (TFA) or ipso-substitution (Br_2). © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The practical applications of combinatorial chemistry and high-throughput screening are apparent in medicinal chemistry.[1] To support the need for a variety of chemistries on solid phase, much of the current effort is focused on the development of new linkers. The most widely used supports, such as Merrifield, Wang, and Rink resins, require specific polar functional groups (e.g. COOH, NHR, OH) for attachment of the desired molecule to the resin. Upon cleavage of the product obtained after a given sequence of reactions, the polar group remains on the target molecules. For the design of lead compounds for certain biological activities, such polar functionalities may have unfavorable pharmacological or pharmacokinetic properties, and more lipophilic groups are required. A traceless linker strategy in which a hydrophobic group is attached to a polymeric support, then, after elaboration of the group, is cleaved from the resin intact, would avoid the incorporation of an unwanted polar group and leave no trace or 'memory' of its attachment to the solid support.[1]

We previously reported silicon-based linking strategies[2] to attach the aromatic side chain of phenylalanine[3] and β-phenylalanine,[4] which were ultimately used for the efficient synthesis of small peptides and a cyclic peptide.[5] By taking advantage of side chain tethered amino acids, modification of both the N- and C-termini of the peptides is possible, which is desired for the maximum diversification of a library. Given that nonpolar aromatic moieties play important roles in numerous therapeutic agents, we envisioned synthetic protocols which would be generally applicable to the construction of a wide range of aromatic building blocks utilizing silicon-based traceless linker strategy. We report here these solid-phase strategies.

2. Results and discussion

2.1. Phenylsilane linkers

Our synthetic approach to various phenylsilane linker systems started from 1,4-dibromobenzene, which was readily converted into 4-allyldimethylsilyl-1-bromobenzene (**1**) by treatment with *n*-butyllithium followed by allylchlorodimethylsilane.[4] As shown in Scheme 1, treatment of **1** with magnesium in THF generated the Grignard reagent, which was treated with paraformaldehyde to afford the benzyl alcohol derivative **2**. Mitsunobu reaction of **2** with *N*-Boc protected ethyl oxamate and subsequent hydrolysis provided an *N*-Boc protected benzylamine building block **3**.[6] The mild reaction conditions for the conversion of the alcohol to the amino group was also found to be efficiently adapted to solid-phase reactions. Bromination of **2** was carried out with triphenylphosphine and carbon tetrabromide. The resulting benzyl bromide analogue **4** was previously used as a key intermediate for the polymer-bound phenylalanine derivative **5**.[3] Quenching of the Grignard reagent generated from **1** with carbon dioxide followed by acidic workup, then esterification [MeOH, $SOCl_2$ (cat)] gave the methyl benzoate analogue **6**. Lithium–halogen exchange of **1** with *t*-butyllithium at −78°C followed by addition of dry DMF afforded a

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Keywords: traceless solid-phase synthesis; aromatic; polyaromatic; heteroaromatic compounds.

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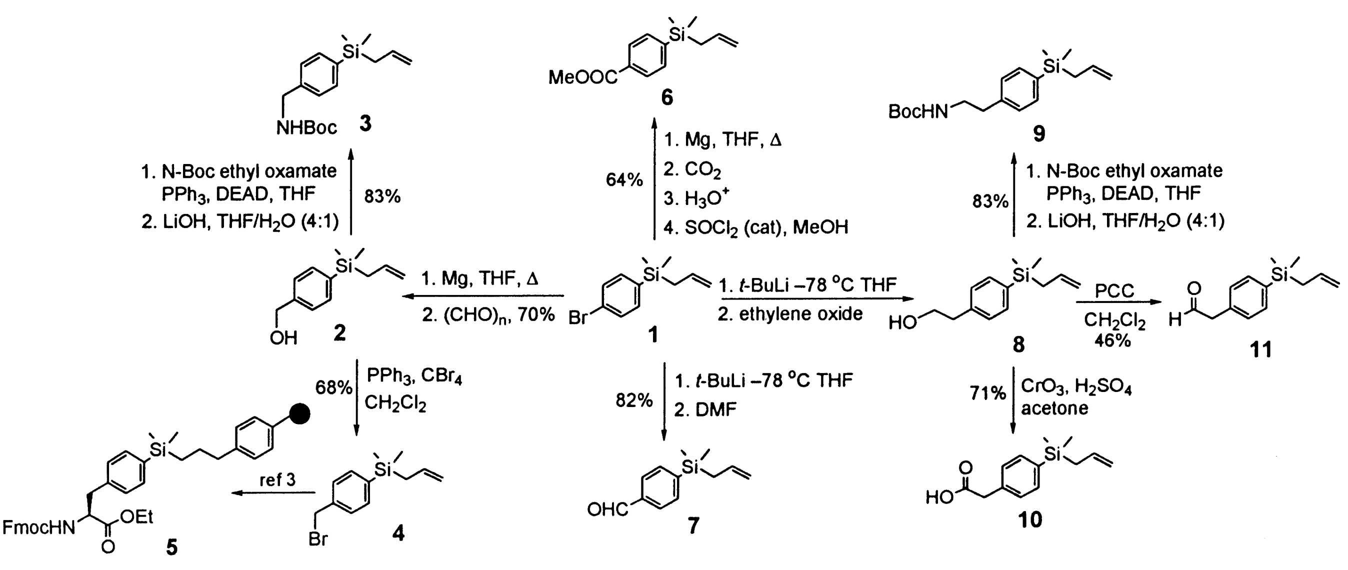
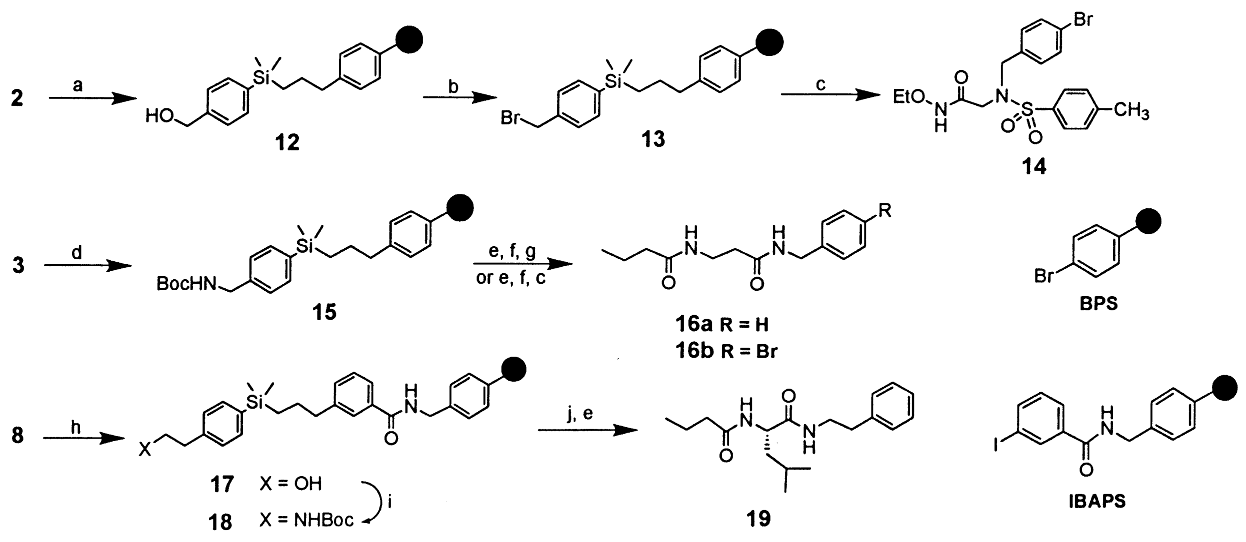


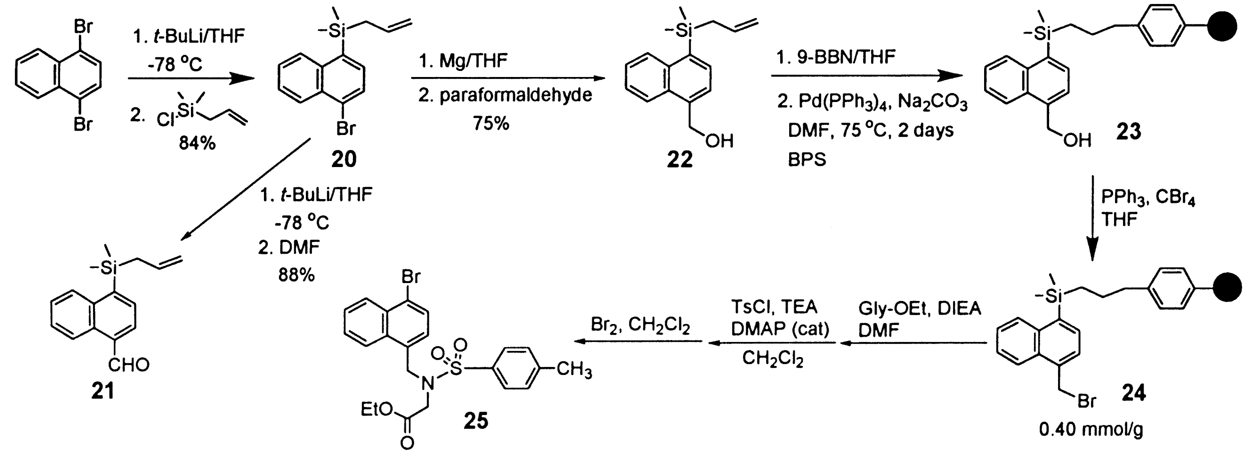
Scheme 1.

4-allyldimethylsilylbenzaldehyde (**7**). The two carbon homologated product **8** was obtained when the lithiated form of **1** was exposed to ethylene oxide. Compound **8** was also converted to the *N*-Boc protected phenylethylamine derivative **9** under the same conditions employed for the preparation of **3**. Jones oxidation and PCC reactions of **8** resulted in carboxylic acid **10** and aldehyde **11**, respectively. Compounds **2**, **3**, and **8** were loaded onto the polymer (either bromopolystyrene (BPS) or iodobenzoylaminomethylpolystyrene [IBAPS[7]]) in one-pot, two-step reactions: hydroboration of the terminal olefin with 9-BBN followed by in situ Suzuki coupling[2e,8] (Scheme 2).

Resin-bound benzyl alcohol **12** was treated with PPh_3 and CBr_4 to give benzyl bromide **13**, which was subjected to the following solid-phase reaction sequence: (1) reaction with glycine ethyl ester to give a secondary amino group; (2) sulfonylation of the secondary amine; (3) hydrolysis of the ester with LiOH (5 equiv.) in aqueous THF; (4) coupling of the acid with *O*-ethyl hydroxylamine; (5) cleavage of the product with Br_2 in CH_2Cl_2 to provide a hydroxamic acid analogue **14**. Hydroxamic acids are known inhibitors of matrix metalloproteinases. Deprotection of the *N*-Boc protecting group of **15** with TFA afforded a resin-bound benzylamine which was coupled to Fmoc-protected β-alanine. After removal of the Fmoc group with 20% piperidine in DMF, the resulting amino group was coupled to butyric acid, then the product was cleaved from the resin under two different conditions, 50% TFA in CH_2Cl_2 and Br_2 in CH_2Cl_2, to give highly pure **16a** (82% yield) and **16b** (92% yield), respectively. Solid-phase conversion of alcohol **17** to *N*-Boc protected amine **18** was carried out under the same conditions employed for the preparation of **3**. After deprotection of the Boc-protecting group, the



Scheme 2. *Reagents and conditions*: (a) 9-BBN, THF, rt, 5 h, then BPS, DMF, $Pd(PPh_3)_4$, 2N Na_2CO_3, 75°C, 2 days (b) PPh_3, CBr_4, CH_2Cl_2 (c) 1. H-Gly-OEt, DMF 2. TsCl, TEA, DMAP (cat), CH_2Cl_2 3. LiOH, THF/H_2O (8:1) 4. NH_2OEt, EDC, HOBt, TEA, DMF 5. Br_2, CH_2Cl_2 (d) 9-BBN, THF, rt, 5 h, then BPS, DMF, $Pd(PPh_3)_4$, K_3PO_4, 75°C, 2 days (e) 50% TFA in CH_2Cl_2 (f) 1. Fmoc-βAla-OH, EDC, HOBt, TEA, DMF 2. 20% piperidine in DMF 3. butyric acid, EDC, HOBt, TEA, DMF (g) 50% TFA in CH_2Cl_2 (h) 9-BBN, THF, rt, 5 h, then IBAPS, DMF, $Pd(PPh_3)_4$, K_3PO_4, 75°C, 2 days (i) N-Boc ethyl oxamate, PPh_3, DEAD, THF, then LiOH, THF/H_2O (8:1) (j) 1. Fmoc-Leu-OH, EDC, HOBt, TEA, DMF 2. 20% piperidine in DMF 3. butyric acid, EDC, HOBt, TEA, DMF.



Scheme 3.

resulting amine was subjected to coupling reaction with Fmoc-Leu-OH followed by Fmoc deprotection. Subsequent coupling of the amine group with butyric acid and cleavage of the product (50% TFA in CH_2Cl_2) afforded **19**.

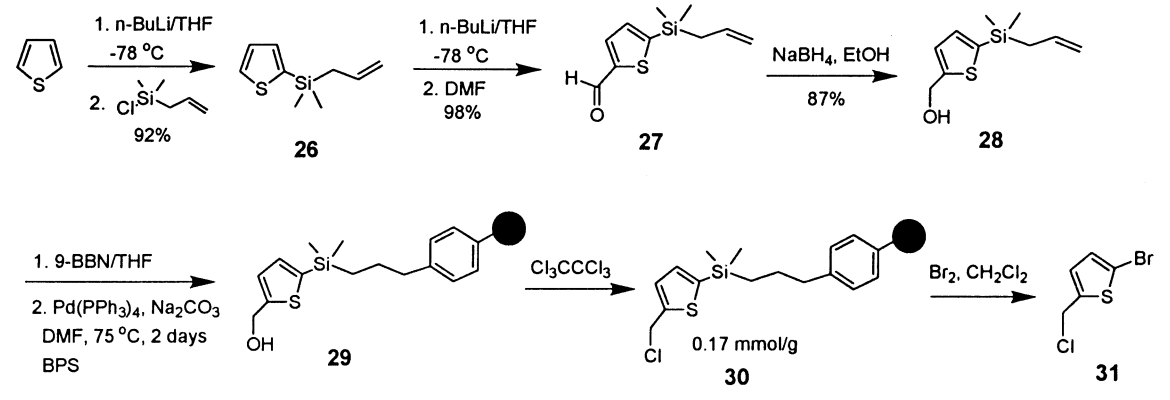
2.2. Polyaromatic linkers

To expand the scope of aromatic systems tolerated by the methodology, the functional group transformation strategy developed for the silylated benzene ring was applied to other aromatic systems. This would allow for construction of a variety of polyaromatic compounds. As illustrated in Scheme 3, lithium–halogen exchange of 1,4-dibromonaphthalene followed by treatment with allylchlorodimethylsilane at −78°C afforded silylated intermediate **20** in an 84% yield. Quenching of the lithiated **20** with DMF provided aldehyde derivative **21**. Alternatively, formation of the Grignard reagent of **20** and subsequent treatment with paraformaldehyde provided naphthalene methanol **22**. Loading of **22** onto bromopolystyrene under the usual Suzuki conditions provided polymer-bound naphthalene methanol **23**. Solid-phase conversion of the alcohol to bromide **24** was carried out by treatment with PPh_3 and CBr_4 in THF. The loading level of this resin (0.40 mmol/g) was determined by the mass balance of the 4-bromonaphthalene-1-methyl bromide, which was obtained by cleavage of the resin-bound product with Br_2.

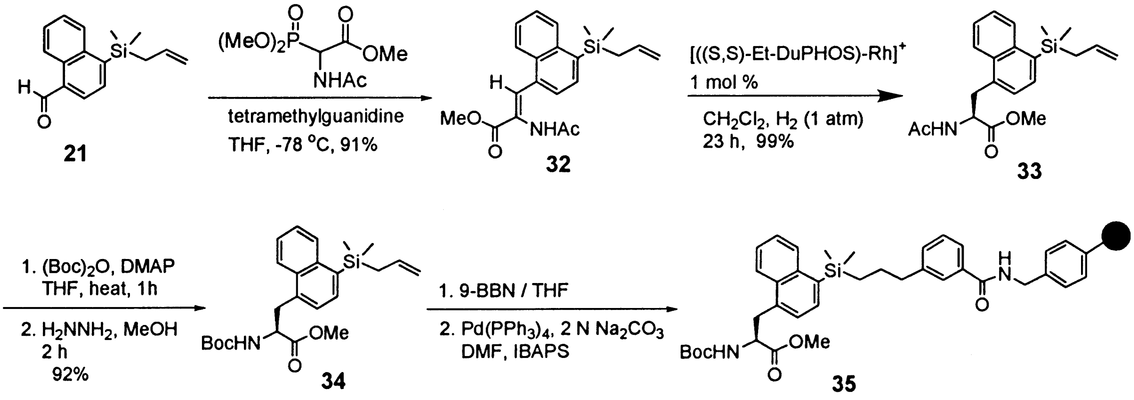
Nucleophilic substitution reaction of **24** with glycine ethyl ester generated a secondary amino ester intermediate which was allowed to react with TsCl in the presence of a catalytic amount of DMAP. The sulfonamide **25** was obtained by *ipso*-substitution of the arylsilyl linker with bromine.

2.3. Heteroaromatic linkers

As a representative model for a heteroaromatic system, thiophene transferring building block **30** was prepared as shown in Scheme 4. Lithiation of thiophene with *n*-butyllithium followed by treatment with allylchlorodimethylsilane afforded 2-allyldimethylsilylthiophene (**26**) in 92% yield. Lithiation of **26** with *n*-butyllithium followed by quenching with anhydrous DMF resulted in 2-allyldimethylsilylthiophene-5-carboxaldehyde (**27**) in a 98% yield. Reduction of the aldehyde group to alcohol **28** with sodium borohydride in ethanol and subsequent coupling with bromopolystyrene under the usual Suzuki conditions provided polymer-bound thiophenemethyl transferring building block **29**, which was further derivatized to the reactive chloride analogue **30** (0.17 mmol/g). Final cleavage of the resin-bound product with bromine afforded **31**. This and the previous Schemes 1–3 demonstrate that various aromatic transferring building blocks could be utilized for solid-phase synthesis of molecules containing the desired aromatic moiety.



Scheme 4.



Scheme 5.

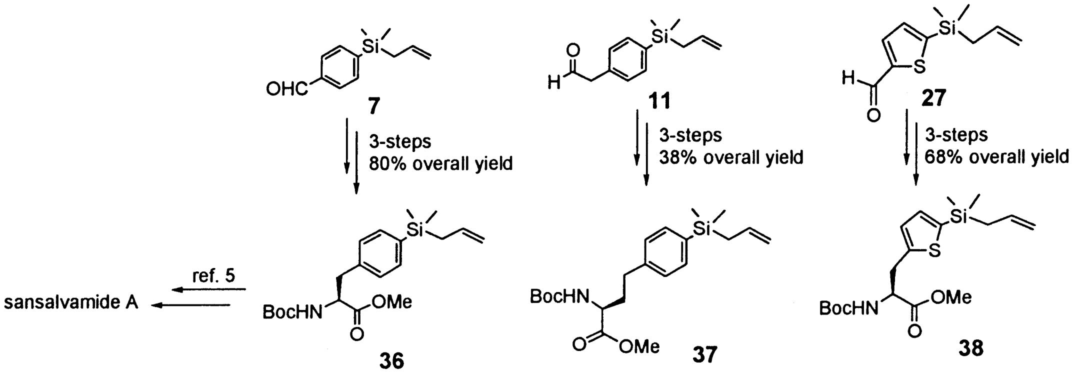
2.4. Aryl-, polyaryl-, and heteroarylalanine derivatives

In our continuing interest in side-chain tethered amino acids as building blocks with two diversity points as well as in the synthesis of cyclic peptides, various amino acid derivatives with aromatic side chains attached to the polymer through a silyl linkage were prepared (Scheme 5). A tetramethylguanidine-mediated Horner–Emmons olefination reaction of naphthylaldehyde **21** with methyl 2-acetamido-2-(dimethoxyphosphinyl)acetate in THF resulted in exclusively the (*Z*)-isomer of the α-eneamide ester (**32**) in a 91% yield.[9] Asymmetric catalytic hydrogenation of **32** proceeded to completion to give the chiral α-amino acid precursor **33** in a high yield (99%).[10] The N-acetyl protecting group of **33** was converted to a Boc protecting group by treatment with di-*tert*-butyl dicarbonate in THF under refluxing conditions in the presence of a catalytic amount of DMAP followed by treatment with excess hydrazine in THF/MeOH (1:1) to afford the desired *N*-Boc-protected naphthylalanine methyl ester **34** in 92% yield for the two-step, one-pot reaction.[11] Hydroboration and Suzuki coupling of **34** under the usual conditions produced the polymer-bound building block **35** (0.10 mmol/g). The principal reason for the low loading amount obtained was that the polymer (IBAPS) was used in a 2.5-fold excess over **34**. This was done for two reasons: (1) **34** was economically more valuable than the IBAPS resin and (2) the polymer-bound building block was designed for use in cyclic peptide synthesis; a low loading level of a linear peptide would be desirable at the cyclization step to avoid a dimerization or oligomerization side reaction. The unreacted iodine of excess IBAPS is inert to most reaction conditions, so the excess polymer does not interfere.

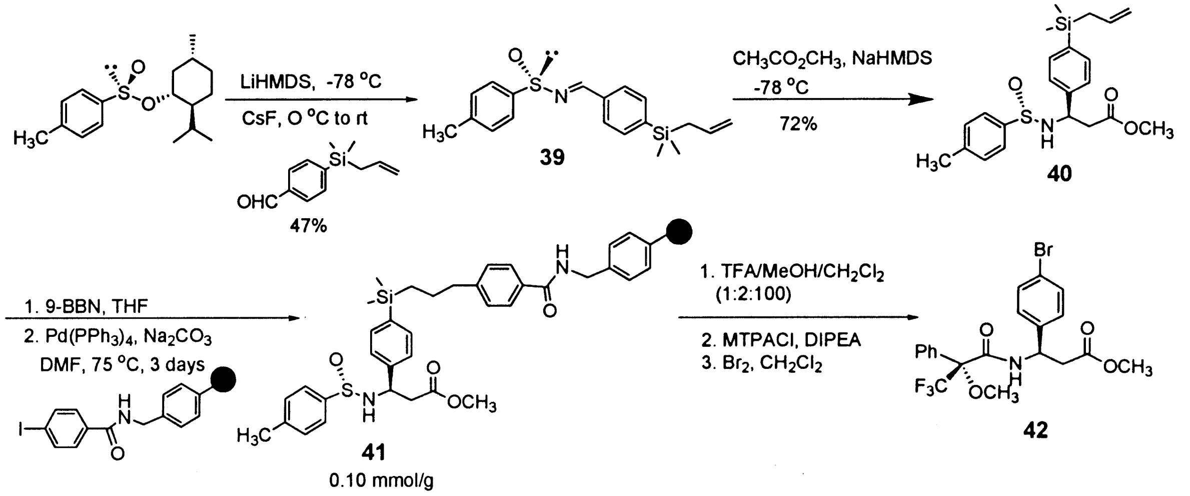
The same reaction sequence as described in Scheme 5 was repeated to prepare other chiral amino acid analogues with silylated aromatic side chain (**36**–**38**) from the corresponding aldehyde precursors (Scheme 6). The silylated phenylalanine derivative **36** was loaded (0.12 mmol/g) onto the IBAPS resin under the usual Suzuki conditions and subjected to ten solid-phase reactions leading to the synthesis of the cytotoxic pentadepsipeptide sansalvamide A in a 68% yield with 95% purity requiring no purification.[5] On the basis of this observation, other side chain modified amino acid building blocks could be used for solid-phase synthesis of cyclic peptides in an automated fashion.

2.5. β-Arylamino acids

β-Amino acids are frequently found components in many natural products and in therapeutic agents. As an efficient tool for solid-phase synthesis of β-phenylalanine-containing molecules, we recently reported a side-chain tethered β-phenylalanine synthesis and its use in the preparation of tripeptide analogues.[4] Enantiomerically pure (*R*)-(+)-*tert*-butylsulfinamide[12] was used as an essential chiral auxiliary/protecting group for asymmetric induction of (*R*)-β-phenylalanine. Prior to our knowledge of the availability of the (*S*)-(−)-enantiomer we developed an alternative strategy of silylated (L)-β-phenylalanine as a potential resin-bound



Scheme 6.



Scheme 7.

building block for the solid-phase synthesis of cyclic natural products such as andrimid,[13] dihydroperiphylline[14] and the family of astins.[15] As shown in Scheme 7, commercially available (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate was treated with LiHMDS (1.5 equiv.) at −78°C in THF, then treated with 4-allyldimethylsilylbenzaldehyde in the presence of cesium fluoride.[16] The resulting (S_R,*R*)-(+)-methyl *N*-(*p*-tolylsulfinyl)-3-amino-3-(4-allyldimethylsilylphenyl)propanoate (**39**) was allowed to react with the sodium enolate of methyl acetate (2 equiv.) at −78°C for 7 h to provide the silylated (L)-β-phenylalanine precursor **40**. Loading onto the IBAPS resin afforded the polymer bound β-amino acid derivative **41**. Hydrolysis of the sulfinamide group under acidic conditions and subsequent coupling of the resulting amino group with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid chloride (MTPACl)[17] provided the Mosher amide **42** after cleavage from the resin using Br_2 in CH_2Cl_2. The loading level of **41** (0.10 mmol/g) was determined by the mass balance of **42**. Analysis of both the ^1H NMR and ^{19}F NMR spectra of the Mosher amide showed less than 2% of the minor diastereomer. As described in the previous report, **41** can be used as a building block for combinatorial libraries of (L)-β-phenylalanine containing molecules.[4]

2.6. Summary

In summary, we have developed general synthetic strategies for disubstitution of aromatics with the allyldimethylsilyl group and various functional groups. Under mild reaction conditions (9-BBN and Suzuki coupling), the allyl group was attached to a halide-substituted polymer, and the other functional groups on the aromatics were elaborated by solid-phase reactions. This process proves to be useful for the rapid preparation of aromatic-, polyaromatic- and heteroaromatic-containing molecules. If a certain nonpolar aromatic moiety plays an important role in the biological activity of a compound, an efficient way to synthesize a multitude of analogues would be to attach the aromatic moiety to the polymer and derivatize other parts of the molecule by either parallel or combinatorial methods. The silylated building block strategy we described here can provide various polymer-bound aromatics with a variety of functional groups for incorporation into parallel synthetic schemes.

3. Experimental

3.1. General methods

Conventional organic solvents were purchased from Fisher. All of the chemicals were purchased from Aldrich Chemical Co and used without further purification unless stated otherwise. Aminomethylated polystyrene (1.02 mmol/g, 100–200 mesh) and 4-bromopolystyrene (BPS, 1.94 mmol/g, 50–100 mesh) were obtained from NovaBiochem (San Diego). [(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf was purchased from Strem Chemical, Inc. (Newburyport, MA). Tetrahydrofuran (THF) was distilled under N_2 from sodium/benzophenone ketyl and methylene chloride from calcium hydride. Flash chromatography was performed with Merck silica gel (230–400 mesh). TLC plates (silica gel 60-F254) were purchased from VWR Scientific. All ^1H NMR spectra were recorded on Varian Gemini 300 MHz, Mercury 400, or Inova 500 spectrometers (75, 100, or 125 MHz for ^{13}C NMR spectra). Chemical shifts (δ) are reported downfield from tetramethylsilane (Me_4Si) in parts per million (ppm). Compounds were visualized with a ninhydrin spray reagent or a UV/vis lamp. Mass spectra (EI and FAB) were recorded on a VG Instrument VG70–250SE high-resolution mass spectrometer. Mass spectra (APCI) were performed on a Micromass Quattro II instrument.

3.1.1. 1-Allyldimethylsilyl-4-bromobenzene (1). To a solution of 1,4-dibromobenzene (28.3 g, 120 mmol) in dried THF (300 mL) at −78°C was added *n*-butyllithium (40.0 mL, 2.5 M solution in hexanes, 100 mmol) over a period of 20 min. After being stirred at −78°C for 30 min, allylchlorodimethylsilane (13.5 g, 100 mmol) in THF (50 mL) was added dropwise over a period of 20 min, and the reaction mixture was warmed to room temperature. After stirring for 1 h at room temperature the reaction mixture was concentrated, and the residue was extracted with ether and brine. The organic layer was dried (Na_2SO_4) and distilled under reduced pressure to provide a colorless liquid (21.9 g, 82%, bp 72°C/0.1 mmHg); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.31 (s, 6H), 1.77 (d, J=8.07 Hz, 2H), 4.87 (m, 1H), 4.92 (m, 1H), 5.78 (ddt, J=17.55, 9.51, and 8.07 Hz, 1H), 7.41 (d, J=8.28 Hz, 2H), 7.52 (d, J=8.28 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) −3.5 (2 C), 23.6, 113.8, 123.9, 130.9 (2 C), 134.2, 135.3 (2 C), 137.5; HRMS calcd for $C_{11}H_{15}BrSi$ 254.0127 and 254.0107, found 254.0128 and 256.0109.

3.1.2. Methyl 4-allyldimethylsilylbenzyl alcohol (2). To a suspension of activated magnesium turning (294 mg, 12 mmol) in dry THF (20 mL) were added a piece of I_2 and ethyl iodide (50 μL). The reaction mixture was heated to reflux until the red color disappeared. Heating (65°C) of the suspension was continued while a solution of 1-allyldimethylsilyl-4-bromobenzene (**1**, 2.6 g, 10 mmol) in THF (20 mL) was added over a period of 15 min. Upon completion of the addition, the gray solution was heated further for 20 min. After the reaction was cooled to room temperature, paraformaldehyde (0.9 g, 30 mmol) was added, and the reaction mixture was stirred for 3 h at room temperature. The clear solution was poured into a saturated NH_4Cl (10 mL) with vigorous stirring, and the suspension was filtered through a short pad of Celite. The solution was diluted with ethyl acetate (20 mL), and the organic layer was separated, dried over Na_2SO_4 and concentrated to leave a colorless liquid (1.4 g, 70%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.30 (s, 6H), 1.77 (dt, J=8.10, 1.05 Hz, 2H), 2.28 (bs, OH, 1H), 4.66 (s, 2H), 4.85 (s, 1H), 4.92 (dt, J=8.10, 1.05 Hz, 1H), 5.81 (ddt, J=10 20, 8.70, 8.10 Hz, 1H), 7.36 (d, J=8.10 Hz, 2H), 7.53 (d, J=8.10 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) −3.3 (2C), 23.8, 65.2, 113.5, 126.4 (2C), 134.0 (2C), 134.6, 138.0, 141.8.

3.2. Reaction of 4-allyldimethylsilylbenzyl alcohol with *N*-Boc-ethyl oxamate

To a stirred mixture of 4-allyldimethylsilylbenzyl alcohol (**2**, 413 mg, 2 mmol), *N*-Boc-ethyl oxamate (478 mg, 2.2 mmol), and triphenylphosphine (577 mg, 2.2 mmol) in dry THF (15 mL) was added diethyl azodicarboxylate (350 μL, 2.2 mmol). After being stirred for 1 h at room temperature, the reaction mixture was concentrated, and the residue was triturated with 1:6 ethyl acetate/hexanes. The precipitated triphenylphosphine oxide was filtered. The filtrate was concentrated, and the residue was purified on silica gel with 1:6 ethyl acetate/hexanes to afford a colorless oil (722 mg, 89%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.27 (s, 2H), 1.36 (t, J=7.50 Hz, 3H), 1.43 (s, 9H), 1.73 (d, J=8.40 Hz, 2H), 4.35 (q, J=7.50 Hz, 2H), 4.80–4.87 (4H), 5.74 (m, 1H), 7.29 (d, J=7.50 Hz, 2H), 7.47 (d, J=7.50 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) −3.3, 14.0, 23.9, 27.9, 46.4, 62.4, 85.6, 113.6, 127.0, 127.7, 133.7, 134.5, 134.9, 137.4, 151.8, 162.0, 163.6; HRMS (EI) calcd for $C_{21}H_{31}NO_5Si$ 405.1973, found 405.1972.

3.2.1. *N*-Boc-4-allyldimethylsilylbenzylamine (3). The oxamate derivative obtained above (406 mg, 1 mmol) was vigorously stirred in a heterogeneous solution of LiOH (210 mg, 5 mmol) in THF/H_2O (4:1, 25 mL) for 2 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with methylene chloride (40 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to leave a colorless oil (287 mg, 94%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.30 (s, 6H), 1.47 (s, 9H), 1.76 (d, J=7.83 Hz, 2H), 4.28 (d, J=6.02 Hz, 2H), 4.86 (s, 1H), 4.90 (d, J=6.61 Hz), 5.31 (bs, *NH*, 1H), 5.78 (ddt, J=16.53, 10.23, 8.14 Hz, 1H), 7.27 (d, J=7.86 Hz, 2H), 7.49 (d, J=7.86 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) −3.2 (2C), 23.9, 28.7 (3C), 44.8, 79.4, 113.7, 127.1 (2C), 134.1 (2C), 134.7, 137.5, 140.3, 156.3; HRMS (EI) calcd for $C_{17}H_{27}NO_2Si$ 305.1811, found 305.1795.

3.2.2. 4-Allyldimethylsilylbenzyl bromide (4). To a mixture of 4-allyldimethylsilylbenzyl alcohol (**2**, 17.7 g, 86 mmol) and triphenylphosphine (22.5 g, 86 mmol) in dichloromethane (200 mL) at 0°C was added carbon tetrabromide (28.4 g, 86 mmol) portionwise. The reaction mixture was stirred at room temperature for 2 h and concentrated. The residue was triturated with ethyl acetate (200 mL) and the precipitated solid was removed by filtration. The filtrate was concentrated, and the residue was triturated with ethyl acetate/hexanes (1:1), then the precipitated solid was removed by filtration (this procedure was repeated three times). After drying and concentration of the residue, column chromatography (1:20 ethyl acetate/hexanes) gave a colorless liquid (15.7 g, 68%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.40 (s, 6H), 1.87 (d, J=8.01 Hz, 2H), 4.57 (s, 2H), 4.96 (s, 1H), 5.00 (m, 1H), 5.88 (ddt, J=16.95, 10 47, 8.01 Hz, 1H), 7.48 (d, J=8.01 Hz, 2H), 7.61 (d, J=8.01 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) −3.3 (2C), 23.7, 33.7, 113.8, 128.4 (2C), 134.3 (2C), 134.5, 138.5, 139.3; HRMS calcd for $C_{12}H_{17}BrSi$ 268.0283 and 270.0263, found 268.0216 and 270.0232.

3.2.3. Methyl 4-allyldimethylsilylbenzoate (6). To a suspension of activated magnesium turning (490 mg, 20 mmol) in dry THF (20 mL) were added a piece of I_2 and ethyl iodide (50 μL). The reaction mixture was heated to reflux until the red color disappeared. Heating (65°C) of the suspension was continued while a solution of 1-allyldimethylsilyl-4-bromobenzene (1, 2.6 g, 10 mmol) in THF (20 mL) was added over a period of 15 min. Upon completion of the addition, the gray solution was heated further for 20 min. After the reaction was cooled to room temperature, anhydrous CO_2 was gently bubbled through the reaction mixture for 5 min and stirred further for 10 min. The clear solution was poured into a saturated solution of NH_4Cl (10 mL) with vigorous stirring, and the suspension was filtered through a short pad of Celite. The solution was diluted with ethyl acetate (20 mL), and the organic layer was separated, dried over Na_2SO_4 and concentrated to leave a white solid on standing. Without further purification, the solid was dissolved in MeOH (40 mL), and the solution was treated with a catalytic amount of thionyl chloride (50 μL), then stirred for 16 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the resulting crude product was purified by column chromatography (1:20 ethyl acetate/hexanes) to afford a colorless oil (1.5 g, 64%); ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.33 (s, 6H), 1.79 (d, J=8.0 Hz, 2H), 3.93 (s, 1H), 4.87 (s, 1H), 4.90 (d, J=5.0 Hz, 1H), 5.77 (m, 1H), 7.61 (d, J=8.0 Hz, 2H), 8.03 (d, J=8.0 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) −3.4, 23.6, 52.3, 114.1, 128.7, 130.7, 133.9, 134.3, 145.2, 167.4. HRMS (EI) calcd for $C_{13}H_{18}O_2Si$ 234.1076, found 234.1077.

3.2.4. 4-Allyldimethylsilylbenzaldehyde (7). To a solution of 1-allyldimethylsilyl-4-bromobenzene (**1**, 1.3 g, 5 mmol) in dry THF (70 mL) at −78°C was added *t*-butyllithium (3.0 mL, 1.7 M solution in pentane, 5.1 mmol) over a period of 10 min. After 30 min of stirring at −78°C, anhydrous DMF (750 μL, 10 mmol) was added dropwise. The reaction mixture was stirred further for 1 h and warmed to room temperature. Concentrated NH_4Cl (2 mL) was added to the solution, and the reaction mixture was concentrated. The residue was extracted with ethyl acetate (20 mL) and brine (5 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (1:15 ethyl acetate/hexanes) to afford a colorless oil (860 mg, 82%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.32 (s, 6H), 1.78 (d, *J*=8.10 Hz, 2H), 4.84 (s, 1H), 4.89 (m, 1H), 5.76 (m, 1H), 7.67 (d, *J*=8.10 Hz, 2H), 7.85 (d, *J*=8.10 Hz, 2H), 10.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.4 (2C), 23.5, 114.2, 128.8 (2C) 133.7, 134.4, (2C), 136.9, 147.6, 192.8; HRMS calcd for $C_{12}H_{16}OSi$ 204.0971, found 204.0972.

3.3. 4-Allyldimethylsilylphenethyl alcohol (8)

To a solution 1-allyldimethylsilyl-4-bromobenzene (**1**, 5.1 g, 20 mmol) in dried THF (30 mL) at −78°C was added *t*-butyllithium (12.9 mL, 1.7 M solution in pentane, 22 mmol) over a period of 5 min. The reaction mixture was allowed to warm to room temperature and stirred further for 1 h. The solution was cooled to −78°C and transferred to a cooled (−78°C) solution of ethylene oxide (3.5 g, 78 mmol) in dry THF (50 mL) via cannula. The reaction mixture was warmed to room temperature over 30 min and quenched with saturated NH_4Cl (5 mL). After evaporation of THF, the residue was extracted with ethyl acetate and water. The organic layer was dried (Na_2SO_4) and concentrated to give an oil which was distilled to afford the desired product as a colorless oil (2.9 g, 67%, bp 100°C/0.1 mmHg); ^1H NMR (300 MHz, $CDCl_3$) δ 0.32 (s, 6H), 1.72 (bs, OH, 1H), 1.79 (d, *J*=8.01 Hz, 2H), 2.90 (t, *J*=6.60 Hz, 2H), 3.89 (t, *J*=6.60 Hz, 2H), 4.88 (m, 1H), 4.92 (m, 1H), 5.83 (ddt, *J*=16.83, 10.20, 8.04 Hz, 2H), 7.27 (d, *J*=8.04 Hz, 2H), 7.52 (d, *J*=8.04 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.3 (2C), 23.8, 39.3, 63.6, 113.5, 128.6 (2C), 134.0 (2C), 134.7, 136.5, 139.5; HRMS ($M-CH_3$) calcd for $C_{12}H_{17}OSi$ 205.1048, found 205.1045.

3.3.1. *N*-Boc-4-allyldimethylsilylphenethylamine (9). This compound was synthesized according to the procedure for **3** and purified by column chromatography (1:8 ethyl acetate/hexanes) to afford a colorless oil (83%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.32 (s, 6H), 1.48 (s, 9H), 1.79 (d, *J*=7.5 Hz, 2H), 2.83 (app t, *J*=6.9 Hz, 2H), 3.42 (m, 2H), 4.74 (bs, NH, 1H), 4.88 (s, 1H), 4.92 (d, *J*=7.8 Hz, 1H), 5.81 (m, 1H), 7.24 (d, *J*=7.8 Hz, 1H), 7.50 (d, *J*=7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.1, 24.0, 28.7, 36.5, 42.0, 79.4, 113.7, 128.6, 134.2, 134.9, 136.6, 140.2, 156.2; HRMS (EI) calcd for $C_{18}H_{29}NO_2Si$ 319.1967, found 319.1984.

3.4. 4-Allyldimethylsilylphenylacetic acid (10)

To a solution of 4-allyldimethylsilylphenethyl alcohol (**8**, 2.8 g, 12.7 mmol) in acetone (60 mL) was added a stock solution of oxidizing agent [mixed solution of CrO_3 (13 g), H_2SO_4 (11 mL), and water (40 mL)]. Upon addition of each portion of Jones reagent to the vigorously stirred reaction mixture, the orange color of the solution rapidly changed to light green, and the end point was determined when the orange color persisted. Acetone was carefully decanted from the flask and evaporated to leave an orange colored oil which was extracted with brine/ethyl acetate (1:4, 50 mL). The organic layer was dried (Na_2SO_4), concentrated, and the residue was purified by column chromatography (1:4 ethyl acetate/hexanes) to afford a colorless oil (2.1 g, 71%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.36 (s, 6H), 1.84 (d, *J*=8.10 Hz, 2H), 3.72 (s, 2H), 4.92 (m, 1H), 4.97 (m, 1H), 5.86 (ddt, *J*=16.80, 10.35, 8.01 Hz, 1H), 7.36 (d, *J*=7.98 Hz, 2H), 7.58 (d, *J*=7.98 Hz, 2H) 11.38 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.3 (2C), 23.7, 41.2, 113.6, 128.9 (2C), 134.0, 134.1 (2C), 134.6, 137.7, 178.3; HRMS ($M-CH_3$) calcd for $C_{12}H_{15}O_2Si$ 219.0841, found 219.0846.

3.4.1. 4-Allyldimethylsilylphenyacetaldehyde (11). To a suspension of pyridinium chlorochromate (8.6 g, 40 mmol) in dry CH_2Cl_2 (150 mL) was added 4-allyldimethylsilylphenethyl alcohol (**8**, 4.4 g, 20 mmol) in one portion, and the mixture was stirred for 3 h at room temperature under an N_2 atmosphere. The reaction mixture was filtered through Celite, and the combined solution of filtrate and washings (CH_2Cl_2) were concentrated and purified by column chromatography (1:10 ethyl acetate/hexanes) to afford a colorless oil (2.0 g, 46%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.34 (s, 6H), 1.81 (d, *J*=8.40 Hz, 2H), 3.72 (s, 2H), 4.89 (s, 1H), 4.93 (d, *J*=7.20 Hz, 1H), 5.81 (m, 1H), 7.26 (d, *J*=7.80 Hz, 2H), 7.57 (d, *J*=7.80 Hz, 2H), 9.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.2 (2C), 23.9, 50.8, 113.8, 129.3 (2C), 132.9, 134.6 (2C), 134.7, 138.0, 199.6.

3.4.2. Preparation of resin 12. To a solution (4-allyldimethylsilyl)benzyl alcohol (**2**, 2.1 g, 10 mmol) in dry THF (50 mL) under an N_2 atmosphere was added 9-BBN (20 mL, 0.5 M solution in THF, 10 mmol) dropwise at 0°C. The mixture was gradually warmed to room temperature and stirred for 5 h. $Pd(PPh_3)_4$ (70 mg), 4-bromopolystyrene (5.0 g, 1.94 mmol/g), 2N aqueous Na_2CO_3 (10 mL, 20 mmol), and DMF (20 mL) were added. The reaction flask and reflux condenser were wrapped with aluminum foil, and the mixture was refluxed for 24 h. $Pd(PPh_3)_4$ (70 mg) was added to the reaction mixture which was refluxed for an additional 24 h. The resin was filtered and washed with THF (once), 1:1 THF/water (twice), water (twice), methanol (twice), and CH_2Cl_2 (twice).

3.4.3. Polymer bound (4-alkyldimethylsilyl)benzyl bromide (13). To the above described resin (**12**, 3 g) swelled in CH_2Cl_2 (120 mL) at 0°C was added PPh_3 (2.6 g, 10 mmol) and CBr_4 (3.3 g, 10 mmol), and the reaction mixture was stirred for 4 h at 0°C. The resin was filtered and washed with CH_2Cl_2 (twice), methanol (twice), 1:1 methanol/water (twice), methanol (twice), CH_2Cl_2 (twice), then dried under reduced pressure. An aliquot of the resin (200 mg) was treated with a solution of CH_2Cl_2 (7 mL) and Br_2 (150 μL) for 5 min. The cleavage solution was removed, and the resin was rinsed with CH_2Cl_2 (3 mL). Concentration of the combined filtrates gave the known 4-bromobenzyl bromide (18.5 mg, 0.37 mequiv./g; purity was determined to be greater than 95% based on the ^{1}H NMR spectrum).

3.4.4. *N*-Hydroxy-α-[[(4-methylphenyl)sulfonyl](4-bromobenzyl)amino] acetamide (14) from polymer bound (4-alkyldimethylsilyl)benzyl bromide. To an aliquot of resin **13** (150 mg, 0.37 mequiv./g) swelled in DMF (7 mL) were added glycine ethyl ester hydrochloride (10 equiv.) and DIPEA (10 equiv.). The reaction mixture was agitated for 16 h at room temperature, then washed with DMF (twice), water (twice), methanol (twice), CH_2Cl_2 (twice). To the resin swelled in CH_2Cl_2 (7 mL) were added *p*-toluenesulfonyl chloride (10 equiv.), Et_3N (10 equiv.), and DMAP (cat). After agitation for 20 h at room temperature the resin was washed with CH_2Cl_2 (twice), methanol (twice), CH_2Cl_2 (twice). The resin was agitated with LiOH (5 equiv.) in THF/H_2O (8:1, 9 mL) for 8 h, then washed with THF (twice), CH_2Cl_2 (twice), methanol (twice) and dried. Coupling of the resin bound amine was performed with *O*-ethyl hydroxylamine (3 equiv.), EDC (3 equiv.), HOBT·H_2O (3 equiv.), Et_3N (3 equiv.) in DMF (8 mL) for 20 h at room temperature. After washing with DMF, MeOH/H_2O, MeOH, CH_2Cl_2, and drying, the resin swelled in CH_2Cl_2 (7 mL) was added Br_2 (100 μL), and the mixture was stirred for 10 min at room temperature. Filtration of the cleavage solution from the resin followed by evaporation yielded **14** (21 mg, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J=7.05 Hz, 3H), 2.44 (s, 3H), 3.65 (bs, 2H), 3.72 (q, J=7.05 Hz, 2H), 4.31 (bs, 2H), 7.16 (d, J=8.40 Hz, 2H), 7.34 (d, J=7.80 Hz, 2H), 7.44 (d, J=8.40 Hz, 2H), 7.72 (d, J=7.80 Hz, H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.5, 21.8, 49.8, 53.5, 72.5, 122.7, 127.7 (2C), 130.3 (2C), 130.9 (2C), 132.3 (2C), 133.9, 134.8, 144.7, 169.6.

3.4.5. Preparation of resin 15. To a solution of *N*-Boc-4-allyldimethylsilylbenzylamine (**3**, 611 mg, 2 mmol) in dry THF (4 mL) under a N_2 atmosphere was added 9-BBN (4 mL, 0.5 M solution in THF, 2 mmol) dropwise at 0°C. The mixture was gradually warmed to room temperature and stirred for 2 h. THF was evaporated under reduced pressure, and the reaction intermediate was dissolved in toluene (8 mL). After adding ground K_3PO_4 (424 mg, 2 mmol), 4-bromopolystyrene (1.0 g, 1.94 mmol/g), and $Pd(PPh_3)_4$ (70 mg), the reaction mixture was degassed by bubbling with N_2 and sealed. The reaction flask was wrapped with aluminum foil and heated at 75°C for 2 days. The resin was filtered and washed with MeOH (once), 1:1 MeOH/water (twice), water (twice), methanol (twice), CH_2Cl_2 (twice), then dried under reduced pressure.

3.4.6. *N*-Benzyl-3-butyrylamidopropanamide (16a). An aliquot of the resin **15** (500 mg) was treated with a solution of thioanisole (100 μL) and 50% TFA/CH_2Cl_2 (7 mL) for 5 min followed by washing with CH_2Cl_2 (4×8 mL). The resin was further washed with DMF (4×8 mL) and treated with Fmoc-β-Ala-OH (312 mg, 1 mmol), EDC (192 mg, 1 mmol), HOBT·H_2O (135 mg, 1 mmol), and Et_3N (140 μL, 1 mmol) in DMF (8 mL) for 15 h at room temperature and washed. The loading level of dried resin determined by the Fmoc release UV/vis assay was 0.1 mmol/g. The resin was stirred in 20% piperidine/DMF (8 mL) for 20 min, then washed with DMF, MeOH, CH_2Cl_2, and DMF. Peptide coupling of the resin bound amine was performed with butyric acid (91 mL, 1 mmol), EDC (1 mmol), HOBT·H_2O (1 mmol), and Et_3N (1 mmol) in DMF (8 mL) for 16 h at room temperature. After washing with DMF, MeOH/H_2O, MeOH, CH_2Cl_2, and drying, a portion of the resin (250 mg) was treated with TFA/CH_2Cl_2 (1:1, 14 mL) for 24 h at room temperature. The cleavage solution was separated, and the resin was rinsed with CH_2Cl_2 (3 mL). Concentration of the filtrates gave a white solid (**16a**, 5.1 mg, 82%, purity was determined to be higher than 95% based on the ^{1}H NMR spectrum); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J=6.3 Hz, 3H), 1.59 (m, 2H), 2.23 (m, 2H), 2.71 (m, 2H), 3.59 (m, 2H), 4.44 (s, 2H), 7.20–7.38 (5H); ^{13}C NMR (125 MHz, $CDCl_3$) 13.5, 19.3, 35.0, 36.8, 37.6, 44.8, 128.1, 128.4, 129.1, 136.3, 173.8, 178.2; HRMS (EI) calcd for $C_{14}H_{20}N_2O_2$ 248.1524, found 248.1525.

3.4.7. *N*-(4-Bromobenzyl)-3-butyrylamidopropanamide (16b). The same procedure as described above was repeated except that the cleavage of the final product on the resin (250 mg) was carried out with a solution of Br_2 (100 μL) in CH_2Cl_2 (8 mL) for 20 min. The cleavage solution was filtered, and the resin was rinsed with CH_2Cl_2 (3 mL). Concentration of the combined filtrates gave an orange powder (**16b**, 11.5 mg, 92%, purity was determined to be higher than 95% based on the ^{1}H NMR spectrum); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (t, J=7.25 Hz, 3H), 1.78 (app q, J=7.25 Hz, 2H), 2.57 (t, J=7.25 Hz, 2H), 3.21 (bs, 2H), 3.71 (bs, 2H), 4.53 (d, J=4 Hz, 2H), 7.29 (d, J=8.00 Hz, 2H), 7.51 (d, J=8.00 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 13.9, 19.3, 35.9, 37.0, 45.1, 122.6, 130.5, 132.3, 134.3, 176.0, 180.4; HRMS calcd for $C_{14}H_{19}BrN_2O_2$ 326.0630 and 328.0609, found 326.0630 and 328.0625.

3.4.8. Preparation of (3-iodobenzoylamidomethyl)polystyrene (IBAPS). To pre-swelled aminomethylated polystyrene resin (7 g, 1.02 mmol/g) in DMF (100 mL) were added 3-iodobenzoic acid (12.4 g, 50 mmol), HOBT·H_2O (6.8 g, 50 mmol), diisopropylethylamine (8.7 mL, 50 mmol), and 1,3-diisopropylcarbodiimide (7.8 mL, 50 mmol). The suspension was stirred for 2 days at 40°C, and the resin was washed with DMF, MeOH, dichloromethane, and MeOH and dried under reduced pressure to provide the functionalized resin.

3.4.9. Hydroboration and Suzuki coupling of 4-allyldimethylsilylphenethylalcohol (8) to IBAPS. To a solution of 4-allyldimethylsilylphenethyl alcohol (**8**, 440 mg, 2 mmol) in dry THF (4 mL) under a N_2 atmosphere was added 9-BBN (4 mL, 0.5 M solution in THF, 2 mmol) dropwise at 0°C. The mixture was gradually warmed to room temperature and stirred for 4 h. THF was evaporated under reduced pressure, and the reaction intermediate was dissolved in toluene (8 mL). After adding ground K_3PO_4 (424 mg, 2 mmol), the IBAPS resin prepared above (1.1 g), and $Pd(PPh_3)_4$ (70 mg), the reaction mixture was degassed by bubbling with N_2 and sealed. The reaction flask was wrapped with aluminum foil and heated at 80°C for 24 h. The resin (**17**) was filtered and washed with MeOH (once), 1:1 MeOH/water (twice), water (twice), methanol (twice), CH_2Cl_2 (twice), then dried under reduced pressure. An aliquot of resin (100 mg) was treated with a solution of Br_2 (50 μL) in CH_2Cl_2 (8 mL) for 20 min. The cleavage solution was filtered, and the resin was rinsed with CH_2Cl_2 (3 mL). Concentration of the combined filtrates gave 2-bromophenethyl alcohol (4 mg, loading level was determined to be 0.20 mmol/g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (bs, OH, 1H), 2.86 (t, J=6.5 Hz, 2H), 3.88 (t, J=6.5 Hz, 2H), 7.14 (d, J=8.0 Hz, 2H), 7.46 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 38.7, 63.7, 129.9, 131.0, 131.9, 132.3.

To an agitated mixture of resin prepared above (500 mg, 2.0 mmol/g), triphenylphosphine (4 equiv.) and *N*-Boc-ethyl oxamate (4 equiv.) in THF (8 mL) was added diethylazodicarboxylate (4 equiv.), and the mixture was further agitated for 16 h at room temperature. After washing with THF, the resin was transferred to a round bottomed flask and stirred with LiOH (5 equiv.) in THF/H_2O (5:1, 12 mL) at 40°C for 16 h. The resin was washed with THF, MeOH, and CH_2Cl_2 and treated with a solution of thioanisole (50 μL) and 50% TFA/CH_2Cl_2 (8 mL) for 5 min, then washed again with CH_2Cl_2. The resin was further washed with DMF and treated with Fmoc-Leu-OH (4 equiv.), EDC (4 equiv.), HOBT·H_2O (4 equiv.), and Et_3N (4 equiv.) in DMF (8 mL) for 16 h at room temperature and washed with DMF, MeOH, and CH_2Cl_2. The loading level of dried resin, determined by the Fmoc release UV/vis assay, was 0.18 mmol/g. The resin was stirred in 20% piperidine/DMF (8 mL) for 20 min, then washed with DMF, MeOH, CH_2Cl_2, and DMF. Peptide coupling of the resin bound amine was performed with butyric acid (4 equiv.), EDC (4 equiv.), HOBT·H_2O (4 equiv.), and Et_3N (4 equiv.) in DMF (8 mL) for 16 h at room temperature. After being washed with DMF, MeOH/H_2O, MeOH, and CH_2Cl_2, and dried, a portion of the resin (100 mg) was treated with TFA/CH_2Cl_2 (1:1, 8 mL) for 24 h at room temperature. The cleavage solution was separated, and the resin was rinsed with CH_2Cl_2 (3 mL). Concentration of the combined filtrates gave a colorless oil (**19**, purity was determined to be higher than 95% based on the ^{1}H NMR spectrum); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0. 0.86 (m, 6H), 0.94 (t, J=7.50 Hz, 3H), 1.20–1.63 (3H), 1.65 (q, J=7.5 Hz, 2H), 2.27 (t, J=7.5 Hz, 2H), 2.84 (m, 2H), 3.57 (m, 2H), 4.51 (m, 1H), 7.17 (d, J=7.5 Hz, 2H), 7.31 (d, J=7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 13.5, 19.3, 22.2, 22.6, 24.9, 35.1, 38.1, 40.7, 41.5, 127.0, 128.9, 129.0, 137.9, 173.6, 176.3.

3.4.10. 1-Allyldimethylsilyl-4-bromonaphthalene (20). To a solution 1,4-dibromonaphthalene (28.6 g, 0.1 mol) in dry THF (800 mL) at −78°C was added *t*-butyllithium (59.0 mL, 1.7 M solution in pentane, 0.1 mol) over a period of 20 min. After 30 min stirring at −78°C, allylchlorodimethylsilane (13.5 g, 0.1 mol) in THF (25 mL) was added dropwise over a period of 30 min. The reaction mixture was stirred further for 1 h and warmed to room temperature. Concentrated NH_4Cl (5 mL) was added to the solution, and the reaction mixture was concentrated. The resulting yellow oil was concentrated, extracted with ethyl acetate/water, and the organic layer was dried and concentrated. The crude product was Kugelrohr distilled to give a colorless oil (25.6 g, 84%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.57 (s, 6H), 2.07 (d, J=8.10 Hz, 2H), 4.94–5.04 (2H), 5.87 (ddt, J=16.80, 10.20, 8.10 Hz, 1H), 7.56 (d, J=7.20 Hz, 1H), 7.61–7.70 (2H), 7.83 (d, J=7.20 Hz, 1H), 8.19 (m, 1H), 8.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −1.5 (2 C), 24.5, 114.3, 126.0, 126.9, 127.1, 128.6, 128.8, 129.7, 132.2, 134.2, 134.7.

3.4.11. 1-Allyldimethylsilyl-4-naphthaldehyde (21). To a solution 1-allyldimethylsilyl-4-bromonaphthalene (**20**, 3.0 g, 10 mmol) in dry THF (150 mL) at −78°C was added *t*-butyllithium (6.0 mL, 1.7 M solution in pentane, 10.2 mmol) over a period of 10 min. After 30 min of stirring at −78°C, anhydrous DMF (1.5 mL, 20 mmol) was added dropwise. The reaction mixture was stirred further for 1 h and warmed to room temperature. Concentrated NH_4Cl (5 mL) was added to the solution, and the reaction mixture was concentrated. The residue was extracted with ethyl acetate (50 mL) and brine (10 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (1:20 ethyl acetate/hexanes) to afford a colorless oil (2.1 g, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53 (s, 6H), 2.03 (d, J=7.80 Hz, 2H), 4.88–4.97 (2H), 5.79 (m, 1H), 7.60–7.70 (2H), 7.84 (d, J=7.50 Hz, 1H), 7.89 (d, J=6.90 Hz, 1H), 8.20 (d, J=8.10 Hz, 1H), 9.35 (d, J=8.10 Hz, 1H), 10.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −1.7 (2C), 24.2, 114.5, 126.1, 126.9, 128.6, 128.7, 132.9, 134.3, 135.4, 137.6, 146.8, 194.1.

3.4.12. 1-Allyldimethylsilyl-4-naphthalenemethanol (22). To a vigorously stirred suspension of activated magnesium turnings (480 mg, 20 mmol) in dry THF (70 mL) were added a piece of I_2 and ethyl iodide (50 μL). The reaction mixture was heated to reflux until the red color disappeared. Heating (65°C) of the suspension was continued while a solution of 1-allyldimethylsilyl-4-bromonaphthalene (**20**, 3.0 g, 10 mmol) in THF (20 mL) was added over a period of 15 min. Upon completion of the addition, the gray solution was heated further for 10 min and transferred via cannula to a separate flask containing paraformaldehyde (700 mg) in THF (20 mL). After stirring the reaction mixture at 50°C for 30 min, concentrated NH_4Cl (10 mL) was added to the solution, and the reaction mixture was concentrated. The residue was extracted with ethyl acetate (70 mL) and brine (30 mL), and the organic layer was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (1:5 ethyl acetate/hexanes) to afford a colorless oil (1.8 g, 75%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.58 (s, 6H), 2.08 (d, J=7.50 Hz, 2H), 3.21 (s, OH, 1H), 4.93–5.03 (2H), 5.04 (s, 2H), 5.89 (m, 1H), 7.47 (d, J=7.20 Hz, 2H), 7.53–7.64 (2H), 7.69 (d, J=6.90 Hz, 1H), 8.11 (d, J=8.80 Hz, 1H), 8.23 (d, J=8.80 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −1.50 (2 C), 24.6, 63.5, 114.1, 124.5, 124.8, 125.9, 126.8, 129.1, 131.4, 133.7, 135.0, 137.3, 137.5, 138.3.

3.4.13. Preparation of resin 23. To a solution 1-allyldimethylsilyl-4-naphthalenemethanol (**22**, 750 mg, 3.1 mmol) in dry THF (20 mL) under a N_2 atmosphere was added 9-BBN (6.2 mL, 0.5 M solution in THF, 3.1 mmol) dropwise at 0°C. The mixture was gradually warmed to room temperature and stirred for 5 h. $Pd(PPh_3)_4$ (60 mg), 4-bromopolystyrene (1.5 g, 1.94 mmol/g), 2N aqueous Na_2CO_3 (3.1 mL, 6.2 mmol), and DMF (10 mL) were added. The reaction flask and reflux condenser were wrapped with aluminum foil, and the mixture was heated to 65°C for 24 h. $Pd(PPh_3)_4$ (60 mg) was added to the reaction mixture which was heated to 65°C for 24 h. The resin was filtered and washed with THF (once), 1:1 THF/water (twice), water (twice), methanol (twice), and CH_2Cl_2 (twice). The resin was used directly for the next reaction.

3.4.14. Preparation of resin 24. To dried resin **23** (100 mg) swelled in dry THF (8 mL) was added PPh_3 (52 mg, 0.2 mmol) and CBr_4 (66 mg, 0.2 mmol), and the reaction mixture was agitated for 1 h at room temperature. The resin was filtered and washed with CH_2Cl_2 (twice), methanol (twice), and CH_2Cl_2 (twice), then dried under reduced pressure. The resin was treated with a solution of CH_2Cl_2 (7 mL) and Br_2 (150 μL) for 10 min. The cleavage solution was removed, and the resin was rinsed with CH_2Cl_2 (3 mL). Concentration of the combined filtrates gave the known 4-bromo-1-(bromomethyl)naphthalene (12 mg, 0.40 mequiv./g); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (s, 2H), 7.39 (d, J=7.60 Hz, 1H), 7.60–7.70 (2H), 7.72 (d, J=7.80 Hz, 1H), 8.14 (m, 1H), 8.32 (m, 1H).

3.4.15. Ethyl *N*-(4-bromonaphthyl)methyl-*N*-(4-methylphenylsulfonyl)glycinate (25). To resin **23** (dried, 100 mg) swelled in dry THF (8 mL) was added PPh_3 (52 mg, 0.2 mmol) and CBr_4 (66 mg, 0.2 mmol), and the reaction mixture was agitated for 1 h at room temperature. The resin was filtered and washed with CH_2Cl_2 (twice), methanol (twice), and CH_2Cl_2 (twice), then dried under reduced pressure. To the resin swelled in DMF (7 mL) were added glycine ethyl ester hydrochloride (10 equiv.) and diisopropyl ethyl amine (10 equiv.). The reaction mixture was agitated for 16 h at room temperature, then washed with DMF (twice), water (twice), methanol (twice), and CH_2Cl_2 (twice). To the resin swelled in CH_2Cl_2 (7 mL) were added *p*-toluenesulfonyl chloride (10 equiv.), Et_3N (10 equiv.), and DMAP (30 mg). After agitation for 20 h at room temperature the resin was washed with CH_2Cl_2 (twice), methanol (twice), and CH_2Cl_2 (twice). To the resin swelled in CH_2Cl_2 (7 mL) was added Br_2 (100 μL), and the mixture was stirred for 10 min at room temperature. Filtration of the cleavage solution from the resin followed by evaporation yielded **25** (14 mg, 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, J=7.20 Hz, 3H), 2.46 (s, 3H), 3.79 (s, 2H), 3.88 (q, J=7.20 Hz, 2H), 4.94 (s, 2H), 7.15 (d, J=7.50 Hz, 2H), 7.30–7.70 (3H), 7.56–7.82 (4H), 8.22–8.35 (2H).

3.4.16. 2-Allyldimethylsilylthiophene (26). To a solution of thiophene (8.4 g, 0.1 mol) in dried THF (300 mL) at −78°C was added *n*-butyllithium (40 mL, 2.5 M solution in hexanes, 0.1 mol) over a period of 5 min. After 30 min of further stirring at −78°C, allylchlorodimethylsilane (13.5 g, 0.1 mol) was added dropwise over a period of 20 min, and the reaction mixture was warmed to room temperature. After 1 h of further stirring at room temperature, concentrated NH_4Cl (3 mL) was added, and the reaction mixture was concentrated. Kugelrohr distillation of the crude oil under reduced pressure afforded a colorless oil (16.7 g, 92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.39 (s, 6H), 1.84 (dd, J=8.10, 1.20 Hz, 2H), 4.92 (s, 1H), 4.97 (m, 1H), 5.85 (m, 1H), 7.24 (m, 1H), 7.33 (dd, J=3.30, 1.50 Hz, 1H), 7.65 (dd, J=5.70, 1.20 Hz, 1H); ^{13}C NMR (75M Hz, $CDCl_3$) −2.0 (2C), 24.8, 114.2, 128.4, 131.0, 134.4, 134.8, 138.3; HRMS (EI) calcd for $C_9H_{15}SSi$ 182.0585, found 182.0583.

3.4.17. 2-Allyldimethylsilylthiophene-5-carboxaldehyde (27). To a solution of 2-allyldimethylsilylthiophene (**26**, 10.6 g, 58.5 mmol) in dry THF (300 mL) at −78°C was added *n*-butyllithium (23.4 mL, 2.5 M solution in hexanes, 58.5 mmol) over a period of 10 min. After 30 min of stirring at −78°C, anhydrous DMF (6.8 mL, 87.8 mmol) was added dropwise. The reaction mixture was stirred for 1 h and warmed to room temperature. Concentrated NH_4Cl (4 mL) was added to the solution, and the reaction mixture was concentrated. The residue was extracted with ethyl acetate (150 mL) and brine (20 mL), and the organic layer was dried (Na_2SO_4) and concentrated to afford a colorless oil (12.1 g, 98%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.32 (s, 6H), 1.76 (dd, J=8.10, 1.20 Hz, 2H), 4.85 (m, 1H), 4.89 (s, 1H), 5.72 (m, 1H), 7.30 (d, J=3.60 1H), 7.77 (dd, J=3.60, 1.50 Hz, 1H), 9.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −2.4 (2C), 24.0, 114.9, 133.3, 135.4, 137,0, 148.7, 150.7, 182.7; HRMS (EI) calcd for $C_{10}H_{14}OSSi$ 210.0533, found 210.0531.

3.4.18. 2-Allyldimethylsilyl-5-hydroxymethylthiophene (28). To a solution of 2-allyldimethylsilylthiophene-5-carboxaldehyde (**27**, 8.6 g, 40.8 mmol) in EtOH (150 mL) was added sodium borohydride (3.0 g, 82 mmol) portionwise for 10 min at room temperature. After being stirred for 30 min, excess sodium borohydride was quenched by slow addition of acetone (5 mL) to the reaction mixture. The solvent was evaporated, and the residue was extracted with ethyl acetate/brine. The organic layer was dried (Na_2SO_4) and concentrated to afford a colorless oil (7.5 g, 87%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.36 (s, 6H), 1.81 (d, J=8.10, 2H), 2.85 (bs, OH, 1H), 4.81 (s, 2H), 4.91 (s, 1H), 4.96 (m, 1H), 5.84 (ddt, J=16.50, 10.50, 8.10 Hz, 1H), 7.08 (d, J=3.30 Hz, 1H), 7.17 (d, J=3.30 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −2.1 (2C), 24.6, 59.9, 114.2, 127.0, 134.3, 134.8, 138.8, 149.9; HRMS (EI) calcd for $C_{10}H_{16}OSSi$ 212.0692, found 212.0690.

3.4.19. 2-Bromo-5-chloromethylthiophene (31). To a solution of **28** (850 mg, 4 mmol) in dry THF (8 mL) under a N_2 atmosphere was added 9-BBN (8 mL, 0.5 M solution in THF, 2 mmol) under a N_2 atmosphere. After stirring for 5 h at room temperature, $Pd(PPh_3)_4$ (140 mg), 4-bromopolystyrene (2.0 g, 1.94 mmol/g), 2N aqueous Na_2CO_3 (4 mL, 8 mmol), and DMF (20 mL) were added. The reaction mixture was degassed by bubbling with N_2 and sealed. The mixture was heated to 75°C for 24 h. The resin (**29**) was filtered and washed with THF (once), 1:1 THF/water (twice), water (twice), methanol (twice), and CH_2Cl_2 (twice), then dried under reduced pressure. To an aliquot of resin **29** (300 mg) in CH_2Cl_2 (8 mL) were added hexachloroethane (236 mg, 1 mmol) and triphenylphosphine (262 mg, 1 mmol), then the reaction vessel was gently swirled for 16 h at room temperature. After washing with CH_2Cl_2 (8 mL×4) resin **30** was treated with a solution of Br_2 (150 μL) in CH_2Cl_2 (8 mL) for 20 min. The cleavage solution was filtered, and the resin was rinsed with CH_2Cl_2 (3 mL). Concentration of the combined filtrates gave 2-bromo-5-chloromethylthiophene (10.7 mg, loading level was determined to be 0.17 mequiv./g); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (s, 2H), 6.86 (d, J=3.9 Hz, 1H), 6.93 (d, J=3.9 Hz, 1H).

3.4.20. (2*Z*)-Methyl-2-acetamido-3-(2-allyldimethylsilyl-4-naphthyl)prop-2-enoate (32). This compound was synthesized according to the procedure described for **36** except that **21** was used instead of 4-allyldimethylsilylbenzaldehyde and the product was purified by column chromatography (1:1 ethyl acetate/hexanes) to afford a colorless oil (91%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.50 (s, 6H), 1.83 (s, 3H), 2.00 (d, J=7.80 Hz, 2H), 3.83 (s, 3H), 4.86–4.96 (2H), 5.81 (m, 1H), 7.45–7.58 (4H), 7.66 (d, J=7.20 Hz, 1H), 7.79 (s, 1H), 7.99 (d, J=7.80 Hz, 1H), 8.13 (d, J=7.80 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −1.6, 22.9, 24.4, 52.9, 114.2, 125.5, 125.7, 126.3, 128.1, 128.9, 131.3, 132.6, 133.3, 134.7, 137.3, 139.0, 165.7, 170.0; HRMS (EI) calcd for $C_{21}H_{25}NO_3Si$ 367.1603, found 367.1605.

3.4.21. (*S*)-Methyl-2-acetamido-3-([4-allyldimethylsilyl]-naphthyl)propanoate (33). This compound was synthesized according to the procedure as described for **36** and purified to afford a colorless oil (99%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.49 (s, 6H), 1.97 (s, 3H), 2.00 (d, J=7.80 Hz, 2H), 3.61 (m, 2H), 3.67 (s, 3H), 4.80–4.94 (2H), 5.05 (m, 1H), 5.80 (bd, J=7.20 Hz, NH, 1H), 7.22 (d, J=6.60, 1H), 7.54–7.61 (3H), 8.10–8.18 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) −1.5, 23.1, 24.5, 35.5, 52.5, 53.5, 114.0, 124.7, 125.9, 126.1, 127.0, 129.2, 132.4, 133.5, 134.7, 136.6, 137.7, 172.8; HRMS (EI) calcd for $C_{21}H_{27}NO_3Si$ 369.1757, found 369.1756.

3.4.22. (*S*)-Methyl-3-([4-allyldimethylsilyl]naphthyl)-2-(*tert*-butoxycarbamido)propanoate (34). This compound was synthesized according to the procedure as described for **36** and purified by column chromatography (1:5 ethyl acetate/hexanes) to afford a colorless oil (92%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48 (s, 6H), 1.41 (s, 9H), 2.00 (d, J=8.40 Hz, 2H), 3.40–3.66 (2H), 3.67 (s, 3H), 4.75 (m, 1H), 4.85–4.95 (2H), 5.09 (bd, NH, 1H), 5.82 (m, 1H), 7.25–7.28 (2H), 7.50–7.63 (3H), 8.10–8.17 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) −1.5, 24.5, 28.6, 36.1, 52.4, 54.6, 80.1, 114.0, 124.8, 125.8, 126.1, 127.1, 129.2, 132.5, 133.5, 134.7, 135.0, 136.5, 137.7, 155.4, 172.9; HRMS (EI) calcd for $C_{24}H_{32}NO_4Si$ 427.2180, found 427.2180.

3.4.23. Preparation of resin 35. To a solution **34** (427 mg, 1 mmol) in dry THF (6 mL) under a N_2 atmosphere was added 9-BBN (2 mL, 0.5 M solution in THF, 1 mmol) dropwise at room temperature, and the mixture was stirred for 5 h. The IBAPS resin (3 g), DMF (6 mL), and 2N aqueous Na_2CO_3 (1.0 mL, 2 mmol) were added to the reaction mixture which was bubbled with a slow stream of argon for 10 min. After the addition of $Pd(PPh_3)_4$ (70 mg), the reaction flask and reflux condenser were wrapped with aluminum foil, then stirred at 75°C for 24 h. Additional $Pd(PPh_3)_4$ (40 mg) was added to the reaction mixture, and stirring was continued further for 48 h. The resin was washed sequentially with CH_2Cl_2, DMF, 1N HCl/THF (1:7, 16 mL, 30 min), MeOH, and CH_2Cl_2, and dried.

3.5. (*S*)-Methyl-3-([4-allyldimethylsilyl]phenyl)-2-(*tert*-butoxycarbamido)propanoate (36)

3.5.1. (2*Z*)-Methyl-2-acetamido-3-([4-allyldimethylsilyl]-phenyl)prop-2-enoate. To a solution of methyl-2-acetamido-2-(dimethoxyphosphinyl)-acetate (4.8 g, 20.0 mmol) in THF (50 mL) at −78°C was added tetramethylguanidine (3.2 mL, 26 mmol), and the mixture was stirred for 15 min. 4-Allyldimethylsilylbenzaldehyde (**7**, 4.1 g, 20.0 mmol) in THF (10 mL) was added, and the mixture was stirred for 1 h at −78°C and 4 h at room temperature. The mixture was diluted with EtOAc, washed with 1N HCl, 1N $CuSO_4$, and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (1:3 ethyl acetate/CH_2Cl_2) to afford a white powder (5.5 g, 86%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 6H), 1.76(d, J=8.40 Hz, 2H), 2.15 (s, 3H), 3.85 (s, 3H), 4.84 (s, 1H), 4.89 (m, 1H), 5.77 (m, 1H), 7.12 (bs, NH, 1H), 7.37 (s, 1H), 7.44 (d, J=7.80 Hz, 2H), 7.52 (d, J=7.80 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.3, 23.3, 23.7, 52.8, 113.9, 125.1, 129.2, 132.8, 134.0, 134.3, 134.5, 141.1, 166.0, 169.8. HRMS (EI) calcd for $C_{17}H_{23}NO_3Si$ 317.1448, found 317.1451.

3.5.2. (*S*)-Methyl-2-acetamido-3-([4-allyldimethylsilyl]-phenyl)propanoate. To a round bottomed flask containing (2*Z*)-methyl-2-acetamido-3-(4-allyldimethylsilylphenyl)-prop-2-enoate (3.2 g, 10 mmol) in deoxygenated CH_2Cl_2 (40 mL) was added [(COD)Rh(*S*,*S*)-Et-DuPHOS]OTf (7 mg). After eight vacuum/H_2 cycles, the reaction was stirred for 23 h at room temperature under H_2 (1 atm). Once the reaction was finished, the solution was passed through a short plug of silica to remove the catalyst and afford a colorless oil (3.2 g. 100%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.25 (s, 6H), 1.72 (dd, J=8.10 Hz, 2H), 1.98 (s, 3H), 3.10 (m, 2H), 3.72 (s, 3H), 4.81 (d, J=1.2 Hz, 1H), 4.83–4.92 (2H), 5.76 (m, 1H), 5.94 (bd, J=7.80 Hz, NH, 1H), 7.06 (d, J=7.20 Hz, 2H), 7.42 (d, J=7.20 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.2, 23.3, 23.9, 37.9, 52.6, 53.3, 113.7, 128.9, 134.1, 134.8, 136.9, 137.5, 170.1, 172.5; HRMS (EI) calcd for $C_{17}H_{25}NO_3Si$ 319.1600, found 319.1602.

3.5.3. (*S*)-Methyl-3-([4-allyldimethylsilyl]phenyl)-2-(*tert*-butoxycarbamido)propanoate (36). To a solution of (*S*)-methyl-2-acetamido-3-(4-allyldimethylsilylphenyl)propanoate (1.5 g, 4.7 mmol) and DMAP (115 mg, 0.94 mmol) in THF (16 mL) was added di-*tert*-butyl dicarbonate (2.0 g, 9.4 mmol), and the mixture was heated to reflux for 1 h. After the solution was cooled to room temperature, MeOH (15 mL) and hydrazine monohydrate (912 μL, 18.8 mmol) were added, and the mixture was stirred for 2 h at room temperature. The solvent was evaporated by rotary evaporation, and the residue was subjected to high vacuum to remove the remaining volatile materials. The oily residue was purified by column chromatography (1:7 ethyl acetate/hexanes) to afford a colorless oil (1.7 g, 93%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 6H), 1.43 (s, 9H), 1.76 (d, J=7.80 Hz, 2H), 3.09 (m, 2H), 3.73 (s, 3H), 4.62 (m, 1H), 4.84 (s, 1H), 4.88 (d J=6.60 Hz, 1H), 5.20 (bd, NH, 1H), 5.78 (m, 1H), 7.14 (d, J=7.50 Hz, 2H), 7.46 (d, J=7.50 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.2, 23.9, 28.5, 38.6, 52.5, 54.6, 80.1, 113.7, 129.0, 134.1, 134.8, 137.1, 137.3, 153.3, 172.6; HRMS (EI) calcd for $C_{20}H_{32}NO_4Si$ 378. 2100, found 378.2101.

3.6. (*S*)-Methyl-4-([4-allyldimethylsilyl]phenyl)-2-(*tert*-butoxycarbamido)butanoate (37)

3.6.1. (2*Z*)-Methyl-2-acetamido-4-([4-allyldimethylsilyl]-phenyl)but-2-enoate. To a solution of methyl-2-acetamido-

2-(dimethoxyphosphinyl)-acetate (1.2 g, 5.0 mmol) in THF (15 mL) at −78°C was added tetramethylguanidine (815 μL, 6.5 mmol) and the mixture was stirred for 15 min. (4-Allyldimethylsilylphenyl)acetaldehyde (1.1 g, 5.0 mmol) in THF (4 mL) was added, and the mixture was stirred for 1 h at −78°C and 4 h at room temperature. The mixture was diluted with EtOAc, washed with 1N HCl, 1N $CuSO_4$, and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (1:1 ethyl acetate/hexanes) to afford a colorless oil (760 mg, 45%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 6H), 1.76(d, J=7.80 Hz, 2H), 2.17 (s, 3H), 3.52 (d, J=7.20 Hz, 2H), 3.78 (s, 3H), 4.85 (s, 1H), 4.91 (d, J=8.10 Hz, 1H), 5.77 (m, 1H), 6.84 (t, J=7.20 Hz, 1H), 7.21 (d, J=7.50 Hz, 2H), 7.47 (d, J=7.50 Hz, 2H), 7.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.2 (2C), 23.5, 23.9, 35.3, 52.7, 113.7, 125.8, 128.4 (2C), 134.3 (2C), 134.8, 136.8, 137.1, 165.4, 169.5; HRMS (EI) calcd for $C_{18}H_{25}NO_3Si$ 331.1605, found 331.1606.

3.6.2. (*S*)-Methyl-2-acetamido-3-([4-allyldimethylsilyl]-phenyl)butanoate. This compound was synthesized according to the procedure as described for **36** and purified to afford a colorless oil (96%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 6H), 1.75 (d, J=7.50 Hz, 2H), 2.01 (s, 3H), 2.00–2.30 (2H), 2.65 (m, 2H), 3.75 (s, 3H), 4.71 (m, 1H), 4.85 (s, 1H), 4.89 (d, J=8.70 Hz, 1H), 5.79 (m, 1H), 5.97 (bd, J=8.10 Hz, NH, 1H), 7.19 (d, J=7.80 Hz, 2H), 7.45 (d, J=7.80 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.2, 23.1, 23.9, 32.1, 33.8, 52.3, 52.4, 113.7, 128.2, 134.1, 134.8, 136.2, 141.9, 170.8, 173.3; HRMS (EI) calcd for $C_{18}H_{27}NO_3Si$ 333.1757, found 333.1755.

3.6.3. (*S*)-Methyl-4-([4-allyldimethylsilyl]phenyl)-2-(*tert*-butoxycarbamido)butanoate (37). This compound was synthesized according to the procedure as described for **36** and purified by column chromatography (1:5 ethyl acetate/hexanes) to afford a colorless oil (88%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 6H), 1.47 (s, 9H), 1.75 (d, J=7.80 Hz, 2H), 1.98 (m, 1H), 2.17 (m, 1H), 2.69 (m, 2H), 3.73 (s, 1H), 4.38 (m, 1H), 4.84 (s, 1H), 4.88 (d, J=8.10 Hz, 1H), 5.21 (bd, NH, 1H), 5.78 (m, 1H), 7.19 (d, J=7.80 Hz, 2H), 7.45 (d, J=7.80 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) −3.2, 24.0, 28.6, 31.9, 34.4, 52.5, 53.5, 80.1, 113.6, 128.2, 134.1, 134.9, 136.2, 142.0, 155.7, 173.4; HRMS (EI) calcd for $C_{21}H_{33}NO_4Si$ 391.2178, found 391.2180.

3.7. (*S*)-Methyl-3-(2-[5-allyldimethylsilyl]thiophenyl)-2-(*tert*-butoxycarbamido)propanoate (38)

3.7.1. (2*Z*)-Methyl-2-acetamido-3-(2-allyldimethylsilyl-5-thiophenyl)prop-2-enoate. This compound was synthesized according to the procedure as described for **36** except that 2-allyldimethylsilylthiophene-5-carboxaldehyde was used instead of 4-allyldimethylsilylbenzaldehyde and purified by column chromatography (1:1 ethyl acetate/hexanes) to afford a colorless oil (78%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.32 (s, 6H), 1.77 (d, J=8.10 Hz, 2H), 2.21 (s, 3H), 3.78 (s, 3H), 4.87 (s, 1H), 4.91 (m, 1H), 5.76 (m, 1H), 7.19 (d J=3.30 Hz, 1H), 7 32 (d, J=3.30 Hz, 1H), 7.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −2.3, 23.7, 24.3, 52.7, 114.6, 122.0, 129.4, 133.8, 134.5, 134.7, 141.5, 145.3, 165.7, 170.3; HRMS (EI) calcd for $C_{15}H_{21}NO_3SSi$ 323.1011, found 323.1012.

3.7.2. (*S*)-Methyl-2-acetamido-3-(2-allyldimethylsilyl-5-thiophenyl)propanoate. This compound was synthesized according to the procedure as described for **36** and purified to afford a colorless oil (98%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 6H), 1.74 (d, J=7.80 Hz, 2H), 2.03 (s, 3H), 3.39 (d, J=4.80 Hz, 2H), 3.76 (s, 3H), 4.80–4.90 (3H), 5.75 (m, 1H), 6.24 (bd, J=7.20 Hz, NH, 1H), 6.83 (d, J=3.30 Hz, 1H), 7.07 (d, J=3.30 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −2.1, 23.4, 24.6, 32.1, 52.8, 53.3, 114.1, 128.3, 134.2, 134.9, 138.4, 143.3, 170.0, 171.8; HRMS (EI) calcd for $C_{15}H_{23}NO_3SSi$ 325.1168, found 325.1165.

3.7.3. (*S*)-Methyl-3-(2-[5-allyldimethylsilyl]thiophenyl)-2-(*tert*-butoxycarbamido)propanoate (38). This compound was synthesized according to the procedure as described for **36** and purified by column chromatography (1:5 ethyl acetate/hexanes) to afford a colorless oil (90%); ^1H NMR (300 MHz, $CDCl_3$) δ 0.30 (s, 6H), 1.45 (s, 9H), 1.75 (d, J=8.10 Hz, 2H), 3.38 (m, 2H), 3.75 (s, 3H), 4.60 (m, 1H), 4.86 (s, 1H), 4.90 (m, 1H), 5.19 (d, J=7.50 Hz, NH, 1H), 5.78 (m, 1H), 6.87 (d, J=3.00 Hz, 1H), 7.08 (d, J=3.00 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) −2.1, 24.6, 28.6, 32.6, 52.6, 54.5, 80.2, 100.3, 114.1, 128.3, 134.3, 134.9, 138.1, 143.5, 155.3, 172.0; HRMS (EI) calcd for $C_{18}H_{29}NO_4SSi$ 383.1586, found 383.1585.

3.7.4. (*S*)-(+)-*N*-(4-Allyldimethylsilylbenzylidene)-*p*-toluenesulfinamide (39). To a solution of (1*R*,2*S*,5*R*)-(−)-menthyl-(*S*)-*p*-toluenesulfinate (2.9 g, 10 mmol) in dry THF (100 mL) at −78°C was added LiHMDS (1 M solution in THF, 15 mL, 15 mmol) dropwise. After 15 min the reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was cooled to 0°C, and **7** (3.0 g, 15 mmol) was added dropwise, followed by the addition of powdered CsF (3.0 g, 20 mmol). After being stirred overnight at room temperature, the reaction mixture was quenched with saturated NH_4Cl (10 mL) and diluted with ethyl acetate (150 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated to give an orange oil which was purified by silica gel chromatography using EtOAc/hexanes (1:8) as eluent to obtain a yellow oil (1.6 g, 47%); ^1H NMR (400 MHz, $CDCl_3$) δ 0.29 (s, 6H), 1.75 (d, J=8.4 Hz, 2H), 2.38 (s, 3H), 4.82 (s, 1H), 4.86 (d, J=4.0 Hz, 1H), 5.73 (m, 1H), 7.29 (d, J=8.0 Hz, 2H), 7.61 (d, J=8.0 Hz, 2H), 7.63 (d, J=8.0 Hz, 2H), 7.81 (d, J=8.0 Hz, 2H), 8.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) −3.1, 21.8, 23.7, 114.1, 125.0, 128.7, 130.0, 134.1, 134.3, 141.9, 145.0, 160.8; HRMS (EI) calcd for $C_{19}H_{23}NOSSi$ 341.1269, found 341.1268.

3.7.5. (S_R,*R*)-(+)-Methyl 3-(*p*-tolylsulfinamido-3-([4-allyldimethylsilyl]phenyl)propanoate (40). To a solution of NaHMDS (1 M solution in THF, 22.4 mL, 22.4 mmol) in dry ether (100 mL) at −78°C was added methyl acetate (2.2 mL, 28.0 mmol), and the mixture was stirred for 30 min. A solution of **39** (4.8 g, 14 mmol) in ether (15 mL) was added over a period of 15 min at −78°C.

After being stirred for 7 h at −78°C, the reaction was quenched with saturated NH_4Cl (20 mL) at −78°C and warmed to room temperature. The organic layer was dried (Na_2SO_4), and concentrated to give an oil which was purified by silica gel chromatography using EtOAc/hexanes (1:2) as eluent to obtain a white solid (4.2 g, 72%); mp 82–85°C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.25 (s, 6H), 1.71 (d, J=8.0 Hz, 2H), 2.33 (s, 3H), 2.81 (m, 3H), 3.51 (s, 3H), 4.80–4.85 (3H), 5.34 (bs, NH, 1H), 5.75 (m, 1H), 7.20 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H), 7.48 (d, J=8.0 Hz, 2H), 7.52 (d, J=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) −3.0, 21.8, 24.0, 42.4, 52.1, 55.1, 113.7, 125.7, 126.7, 129.6, 134.2, 134.6, 138.4, 141.3, 141.6, 142.3, 171.2; HRMS (EI) calcd for $C_{22}H_{28}NO_3SSi$ 441.1559, found 414.1559.

3.7.6. Preparation of resin 41. To a solution of **40** (1.1 g, 2.6 mmol) in dry THF (20 mL) under a N_2 atmosphere was added 9-BBN (5.2 mL, 0.5 M solution in THF, 2.6 mmol) dropwise at room temperature, and the mixture was stirred for 3 h. The IBAPS resin (5 g, 0.96 mmol/g), DMF (15 mL), and 2N aqueous Na_2CO_3 (2.0 mL, 4 mmol) were added to the reaction mixture which was bubbled with a slow stream of argon for 10 min. After the addition of $Pd(PPh_3)_4$ (260 mg), the reaction flask and reflux condenser were wrapped with aluminum foil, then stirred at 75°C for 48 h. Additional $Pd(PPh_3)_4$ (140 mg) was added to the reaction mixture, and stirring was continued further for 24 h. The resin product (**41**) was washed sequentially with THF, CH_2Cl_2, MeOH, and CH_2Cl_2, then dried in vacuo.

3.7.7. Determination of the loading level and enantiopurity of the resin 41 by MPTA amide derivatization. An aliquot of resin **41** (200 mg) was treated with a solution (10 mL) of TFA/MeOH/CH_2Cl_2=1:2:100 for 3 h, then washed with CH_2Cl_2, THF, MeOH, and CH_2Cl_2. The resin was suspended in dry CH_2Cl_2 (8 mL), then treated with (R)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid chloride (76 mg, 0.3 mmol)) and DIPEA (87 μL, 0.5 mmol) for 5 h. After successive washing with CH_2Cl_2, MeOH, and CH_2Cl_2, the resin was treated with a solution of Br_2 (15 μL) in CH_2Cl_2 (8 mL) for 20 min. The cleavage solution was filtered, and the resin was rinsed with CH_2Cl_2 (3 mL). Concentration of the combined filtrates gave the MTPA amide as a colorless oil (**42**, 9.5 mg, the loading level of resin **41** was determined to be 0.10 mmol/g); ^1H NMR (400 MHz, $CDCl_3$) δ 2.85 (dd, J=16.4, 6.0 Hz, 1H), 2.90 (dd, J=16.0, 6.8 Hz, 1H), 3.46 (d, J=0.8 Hz, 3H), 3.63 (s, 3H), 5.39 (dd, J=14.4, 6.4 Hz, 1H), 7.05 (d, J=8.8 Hz, 2H), 7.33–7.44 (7H), 7.80 (8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.9, 49.5, 52.4, 55.5, 121.9, 127.6, 128.1, 128.7, 129.7, 132.0, 132.5, 139.1, 165.8, 171.1; Analysis of the ^1H NMR and ^{19}F NMR spectral integration of the crude **42** showed less than 2% of the minor diasteromer. HRMS (EI) calcd for $C_{20}H_{19}BrF_3NO_4$ 473.0450 and 475.0431, found 473.0450 and 475.0463.

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