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Asymmetric Garratt–Braverman Cyclization: A Route to Axially Chiral Aryl Naphthalene–Amino Acid Hybrids

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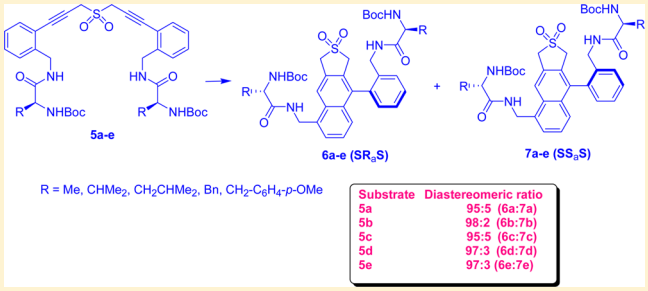
Supporting Information

ABSTRACT: We report the first example of a highly diastereoselective Garratt–Braverman cyclization leading to the synthesis of chiral aryl naphthalene–amino acid hybrids in excellent yields. The stereogenecity in the amino acid has induced high diastereoselectivity for the reaction. Computations based on density functional theory indicated a lower activation free energy barrier for the **M** isomer as compared to that for the **P** diastereomer ($\Delta\Delta G$ = 3.48 kcal/mol). Comparison of the recorded CD spectrum of the product with the calculated one also supported the preferential formation of the **M** diastereomer.



INTRODUCTION

Garratt–Braverman (GB) cyclization,[1] discovered in the 1970s, has recently drawn keen interest, specifically focusing on two aspects: finding additional support for the biradical mechanism[2] and exploration of its synthetic potential.[3] While many elegant studies are there in pursuit of the mechanistic aspects of the reaction, synthetic endeavors exploiting the reaction have started to appear only in recent years.[4] Some of the advantages of GB cyclization in organic synthesis include formation of two carbon–carbon bonds, as depicted in Scheme 1, in high yields (especially from aryl-substituted systems) and the easy availability of starting materials. However, at the same time, the reaction suffers from some selectivity issues which can lower its synthetic potential to a large extent.

One common selectivity problem encountered in the case of GB cyclization of unsymmetrical sulfones is the formation of four possible products (excluding atropisomerism) arising from participation of both aryl rings. Even for some symmetrical sulfones, two products can be obtained, as the aryl double bond can participate in two possible orientations. All these possibilities are shown in Scheme 2. Recently,[4a] by a judicious choice of aryl groups with distinctly different electronic characters, the number of possible products have been minimized and one product predominates. However, until now, to the best of our knowledge, there is no report of asymmetric GB reaction which leads to only one stereoisomeric axially chiral aryl naphthalene. In this communication, we report the first example of a highly diastereoselective GB reaction that led to the synthesis of aryl naphthalene–amino acid hybrids[4b] in high yields.

RESULTS AND DISCUSSION

The idea behind making the aryl naphthalene–amino acid hybrid was 2-fold: first, to exploit the influence of chirality of the amino acid moiety on the axial chirality of the biaryl system, and second, the use of such skeletons as privileged structures for combinatorial drug design.[5] Previously,[6,7] we have shown that the substrates **I** and **J**, upon base-treatment, did not follow the GB reaction pathway; instead these produced products arising from intramolecular nucleophilic addition (INA) or 6π-electrocyclization (6π-EC) as shown (Scheme 3). To suppress these non-GB pathways, we made a tertiary amide **K** involving piperidine. Expectedly, **K** produced only the GB product in high yield when treated with Et_3N.

Having sorted out the structural requirement of *o*-amido propargyl sulfones to undergo the GB pathway using a tertiary amide, we incorporated different chiral oxazolidinones at the ortho-position of propargyl sulfones (**1a–c**) and studied the diastereoselectivity of the resulting GB process (Scheme 4). However, in none of these cases was the distereoselectivity found to be satisfactory. The best ratio (1.8:1) was obtained with phenylalanine derived oxazolidinone in benzene (entry **10**, Table 1). The structure of the major isomer from **1c** was confirmed by single crystal X-ray crystallography,[8] and its absolute configuration was determined to be **M**. Use of a chiral base or performing the reaction in different solvents and temperatures to enhance the selectivity did not improve the scenario. Attempts to raise the rotational barrier between the two atropisomers by placing a substituent at C-4 of the starting

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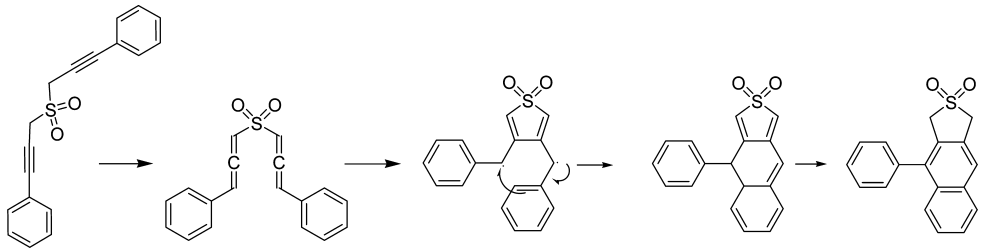
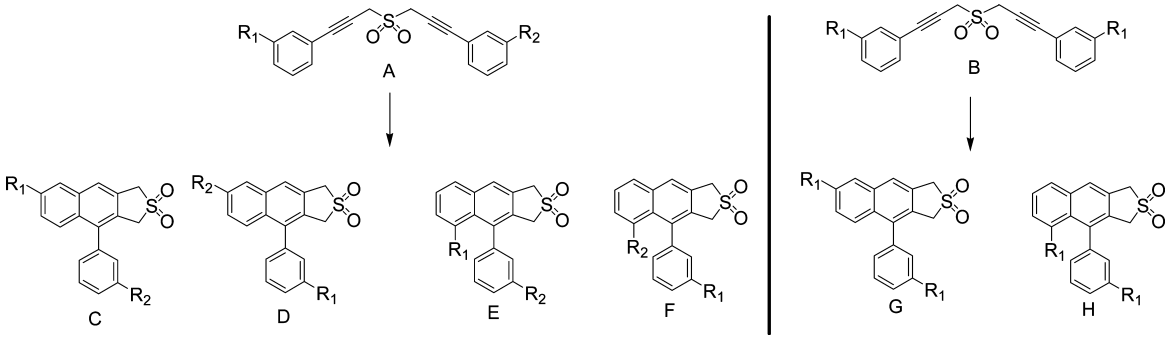
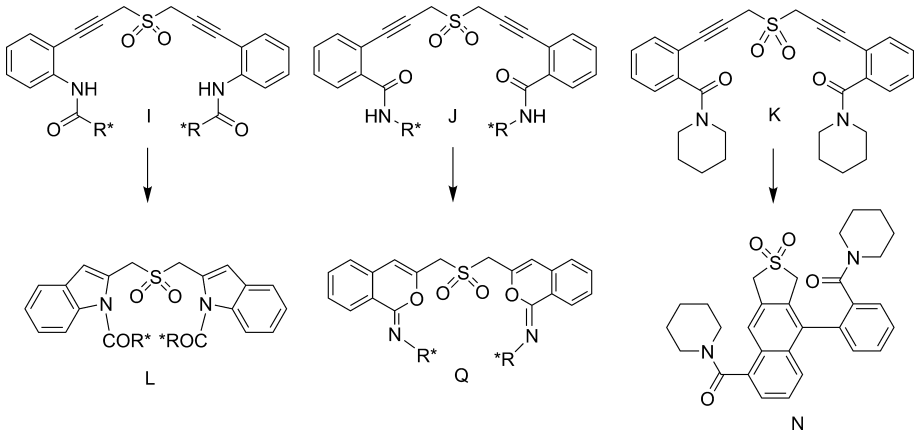
Scheme 1. GB Cyclization of Bis-propargyl Sulfone



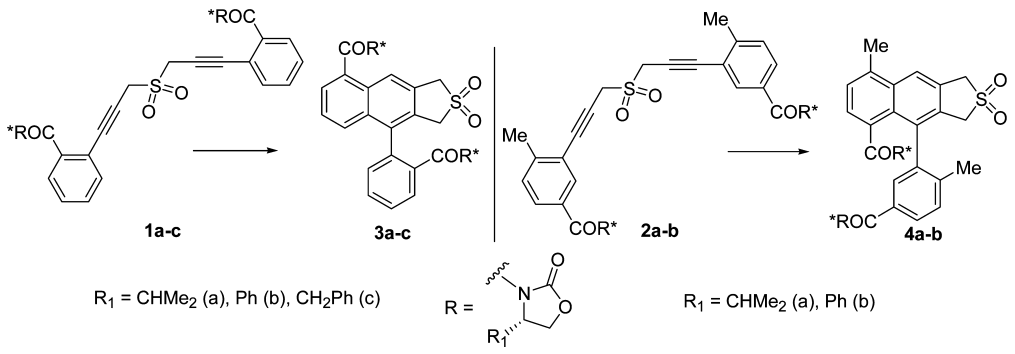
Scheme 2. Various Possible Products of GB Cyclization of Unsymmetrical (A) and Symmetrical (B) Sulfones



Scheme 3. Reactivity of Sulfones with Different Amide Linkages



Scheme 4. Reactivity of Sulfones with Oxazolidinone Auxiliaries



bisaryl propargyl ether (**2a,b**) (that ultimately ended up at C-8 of the final aryl naphthalene **4a,b**) was only marginally successful (compare entries **14**, **15** vis-a-vis entries **1** and **2**).

As attempts to increase the distereoselectivity via the oxazolidinone approach failed, we turned our attention to a different strategy. Retrospection of the reactivity of previously synthesized *o*-amido sulfones which underwent intramolecular addition or 6π-EC indicated generation of highly stabilized indole or isochromene systems to be the probable cause for such type of reactivity (computational analysis described later). We reasoned that incorporation of a methylene linker in the form of a homologous amide will remove the possibility of such

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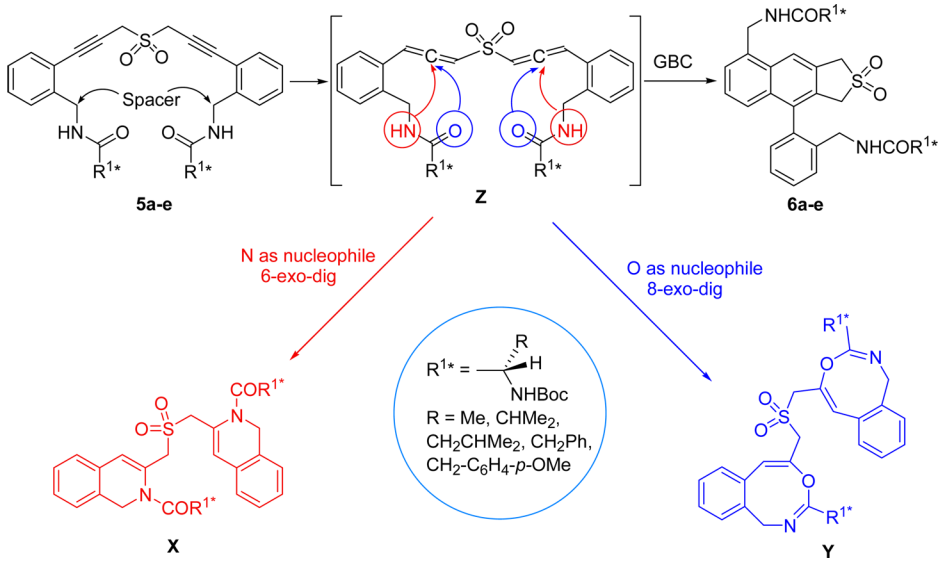
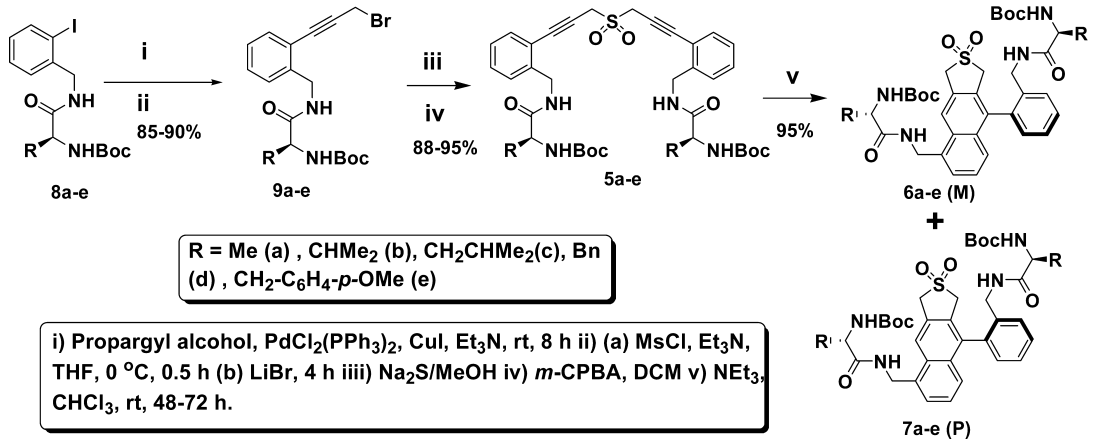
Table 1. GB Cyclization of Different Sulfones

entry	starting sulfone	base	solvent	temperature	product	ratio of diastereomers
1	**1a**	Et_3N	$CHCl_3$	rt	**3a**	1.7:1
2	**1b**	Et_3N	$CHCl_3$	rt	**3b**	1:1
3	**1c**	Et_3N	$CHCl_3$	rt	**3c**	1.65:1
4	**1c**	Et_3N	$CHCl_3$	0 °C	**3c**	1.61:1
5	**1c**	Et_3N	$CHCl_3$	65 °C	**3c**	1.63:1
6	**1c**	Et_3N	$CHCl_3$	−20 °C	**3c**	no reaction
7	**1c**	Et_3N	PhMe	−4 °C	**3c**	1.64:1
8	**1c**	Et_3N	DMSO	rt	**3c**	decomposed
9	**1c**	Et_3N	CH_3CN	rt	**3c**	1:1
10	**1c**	Et_3N	C_6H_6	rt	**3c**	1.8:1
11	**1c**	(−)-spartein	C_6H_6	rt	**3c**	1.5:1
12	**1c**	(+)-cinchonine	C_6H_6	rt	**3c**	1.7:1
13	**1c**	(−)-cinchonidine	C_6H_6	rt	**3c**	1.65:1
14	**2a**	Et_3N	C_6H_6	rt	**4a**	2:1
15	**2b**	Et_3N	$CHCl_3$	rt	**4b**	1.14:1

Scheme 5. Reactivity of N-Boc-Aminoacylated *o*-Aminomethyl Bispropargyl Sulfones with Different Amino Acids



Scheme 6. Synthesis and GB Cyclization of 5a−e



processes occurring, as those cannot lead to a stabilized aromatic system (Scheme 5). These molecules are thus expected to follow the GB cyclization pathway. Computations (as described later) also supported such an assertion and showed a difference of 12.64 kcal/mol between the GB process and intramolecular nucleophilic addition. It also predicted an activation energy difference of 3.48 kcal/mol between the two possible diastereomers, with **M** having lower activation energy.

To check the validity of our prediction, a series of N-Boc-aminoacylated *o*-aminomethyl bispropargyl sulfones **5a−e** were

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prepared using different amino acids (Scheme 6) starting from *o*-iodo aminoacyl benzylamine derivatives **8a−e**.[9] Sonogashira coupling with propargyl alcohol followed by functional group transformation provided the bromides **9a−e**. The latter on treatment with Na_2S followed by oxidation with *m*-CPBA furnished the sulfones **5a−e** which were then subjected to GB conditions (Et_3N in $CHCl_3$). To our expectation, the reaction followed only the GB pathway; no non-GB product could be isolated. The other striking feature of the reaction was the excellent diastereoselectivity in addition to the high yield (de > 90%, yield >95%). The results are compiled in Table 2. The

Table 2. Diastereselective GB Cyclization

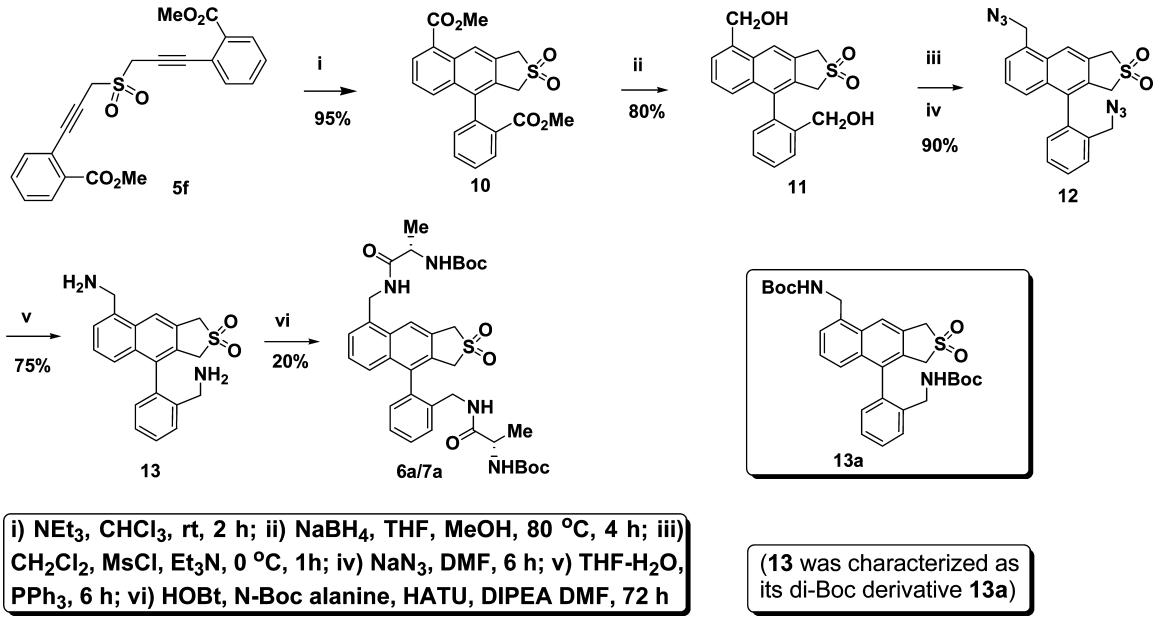
substrate	amino acid	overall yield (%)	diastereomeric ratio
5a	Ala	97	95:5 (**6a:7a**)
5b	Val	97	98:2 (**6b:7b**)
5c	Leu	95	95:5 (**6c:7c**)
5d	Phe	95	97:3 (**6d:7d**)
5e	MeO-tyr	97	97:3 (**6e:7e**)

structure of the GB products was confirmed by comparing the ^{1}H NMR with those made from the diamine **13** via HATU-mediated coupling with the Boc-amino acids. Incidentally, the diamine **13** was prepared from the diester **10** for which an X-ray structure was available[8] (Scheme 7). The diastereomeric ratios were calculated from the HPLC analysis. The absolute configuration of the major diastereomer could not be determined by single crystal X-ray because none of the diastereomers gave crystals which met the quality and size required for such analysis. In view of that, we chose to compare the electronic circular dichroism (ECD) spectra with the experimental one[10] (Figure 1). The computed CD spectrum showing a positive Cotton effect for the **M** diastereomer matched that observed experimentally for the diastereomer **6d**. A negative Cotton effect was computationally predicted for the other diastereomer **P**. For **M**, the major positive rotatory strength is at 386 nm and for **P** at 426 nm. Lowest excited state ($\pi \rightarrow \pi^*$ transiton from HOMO to LUMO) contributed to the Cotton effect.

As the complexity of the system increases, the rule of thumb predictions based on electronic or steric effects becomes highly difficult. In our system, complexity arises from a multitude of possible intramolecular interactions between aromatic groups and among the N−H···O hydrogen bonds and also from the various possible conformations of the substrate. Therefore, we tried to understand the energy requirements for the possible reaction pathways by computational methods.[11] To address the conformational space, we have made Short Molecular Dynamics Conformational Search for the bisallenic sulfones **Z**, the active species for the cyclization (Scheme 4).[10] Conformations resulting from the MD runs were further fully optimized with density functional theory calculations. Most stable conformations were chosen for further calculation for each of the substrates (**I**, **J**, **K**, and **5a**).

The conformational geometry has a very important role in the course of subsequent steps in the reaction. In our system, ortho-substituted bisallenic sulfones may undergo biradical GB cyclization, 6π-EC, or INA. For **I** and **J**, from the computed energies, it is observed that the allenyl moieties are away from each other in most stable bisallenic sulfones geometries. Such substrate conformations with distant allenyl groups will have lesser tendencies for GB cyclization. We have calculated the activation free energy for the competitive pathways. **I** has a barrier of 25.61 kcal/mol for INA, whereas for GB cyclization, the barrier is twice (51.07 kcal/mol) that for INA. Similarly for **J**, the barriers are 12.69 and 22.20 kcal/mol for 6π-EC and GB cyclization, respectively. Such large differences in barriers for competitive reactions indicate exclusive non-GB cyclizations for **I** and **J**. But for **K**, the situation is reversed; the barrier is 10.73 kcal/mol for GB cyclization and 16.8 kcal/mol for intramolecular nucleophilic addition, showing a preference for the GB cyclization pathway. Because there is no H attached to N, it cannot participate in aromatization. Therefore, there was no driving force for intramolecular nucleophilic addition. For further study, we have performed similar calculations on the

Scheme 7. Alternate Synthesis of GB Products 5a−e



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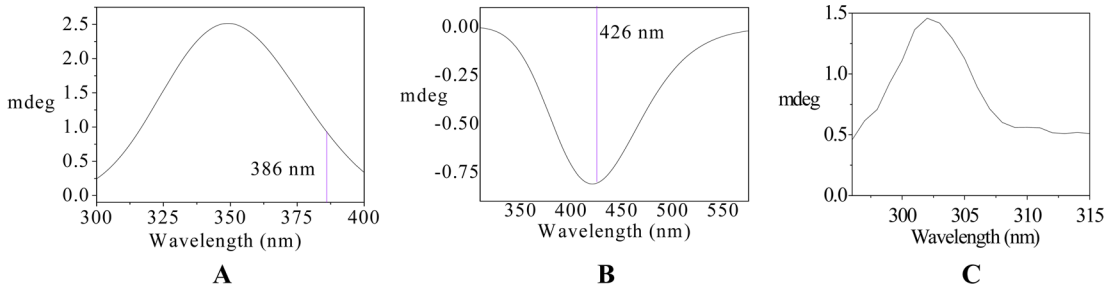

Figure 1. (A) Computed electronic CD spectrum of **6d** (**M**; rotatory strength is shown at 386 nm). (B) Computed electronic CD spectrum of **7d** (**P**; rotatory strength is shown at 426 nm). (C) Experimentally recorded CD spectrum of the cyclized product of **5d**.

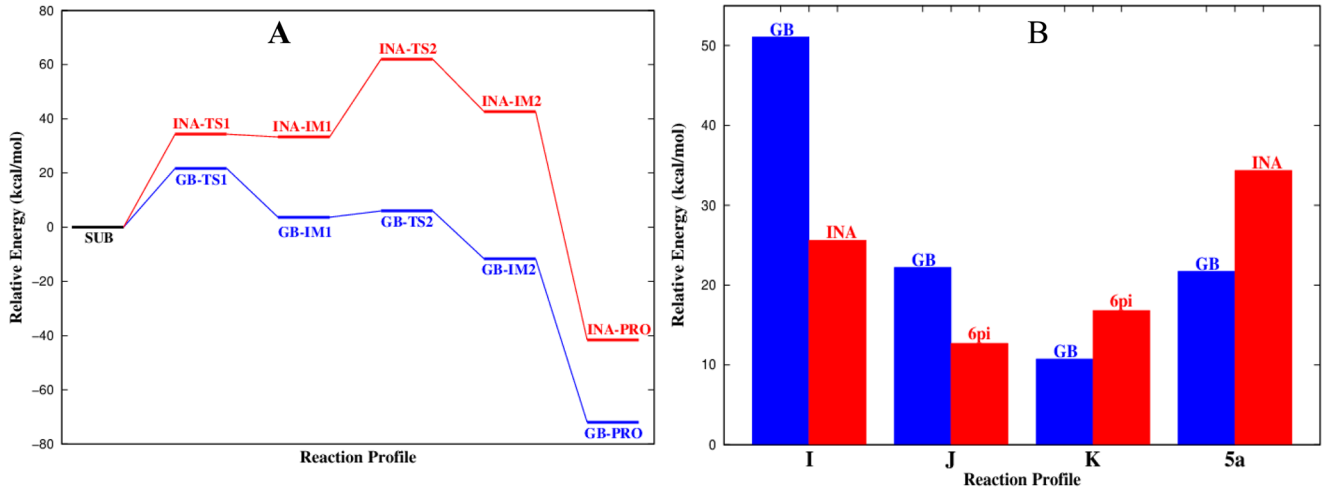

Figure 2. (A) Free energy profile (ΔG in kcal/mol; BP86-D3/def2-SVP) of INA and GB cyclization reaction of **5a**. Red colored line describes the energy diagram for INA, and the blue colored line stands for GB cyclization. Here the energy of substrate conformation was taken as reference. (B) Relative free energies of activation (at BP86-D3/def2-SVP level; in kcal/mol) for the first intermediate formation from bisallenic sulfones in different mechanistic pathways. Blue colored bars stand for free activation barrier of GB cyclization, and the red colored bars are for INA or 6π-EC. The energy of the most stable bisallenic sulfone was taken as the reference (0.0 kcal/mol) for each case.

methylene-linked molecule **5a**. Again, **5a** has the option of undergoing GB cyclization and intramolecular nucleophilic addition. But the activation free energy for GB cyclization is 21.70 kcal/mol, which is much lower than the required activation energy for intramolecular nucleophilic addition (34.34 kcal/mol). Such a high energy difference will lead to the formation of GB cyclization exclusively. The energy profiles for the competing processes are shown in Figure 2.

Axial chirality arises from unsymmetrically substituted aryl rings, e.g., ortho-substitution at the phenyl rings attached to the terminal alkyne systems. If both ortho substituents are the same, bispropargyl sulfones can produce two GB-cyclized products under base treatment, which are diastereomers with axial chirality. When the ortho substituent is large, geometry of the active substrate (bisallenic form) conformation determines the selection of pathways for the GB cyclization. The rearrangement after the first step is unlikely when the ortho-substituted group is bulky, and therefore the **P**/**M** conversion is not possible. Two of the stable substrate conformations are shown in Figure 3. The conformation **A** leads to **M** isomer and **B** leads to **P** isomer. Conformation **A** is 9.58 kcal/mol more stable than the conformation **B**, and the energy of the transition state for the reaction from **A** is lower by 3.48 kcal/mol than that from conformation **B**. This is because of greater π-stacking interactions between the aryl rings of the two propargyl arms. Thus, on the basis of computation results, the reaction should prefer to form the isomer with **M** axial chirality which

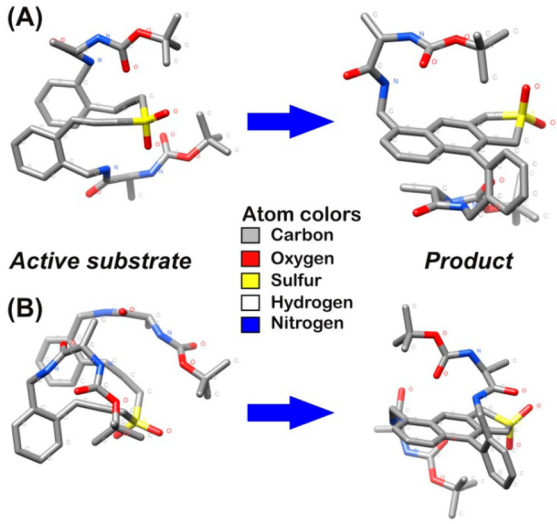

Figure 3. Optimized geometry of bisallenic sulfones of **5a**. **A** and **B** are two conformations, where **A** is more stable than **B**. For clarity, hydrogen atoms are not shown.

corresponded to the experimental result. The activation barrier for the conversion from **M** to **P** for the **6a**/**7a** pair was estimated from a relaxed surface scan to be 50.67 kcal/mol, which is too high for a conversion at the reaction conditions.

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In conclusion, we have successfully carried out an asymmetric GB reaction leading to the synthesis of aryl naphthalene–amino acid hybrids with predominantly one axial chirality. To the best of our knowledge, this is the first example of an asymmetric GB reaction. Computational results supported well the observed selectivity. Considering the importance of the aryl naphthalene skeleton, the strategy to have access to the latter in one chiral form should be of importance to the synthetic community.

EXPERIMENTAL SECTION

All the reactions were monitored by TLC using Polygram SILG/UV_{254} precoated (0.25 mm) silica gel TLC plates. Column chromatography was done with silica gel (60–120 or 230–400 mesh). NMR data were obtained with 200 and 400 MHz NMR instruments. Proton and carbon spectra were referenced internally to solvent signals, using values of δ = 7.26 for proton and δ = 77.0 for carbon (middle peak) in $CDCl_3$. The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, sex. = sextet, m = multiplet, app = apparent, and bs = broad signal. All coupling constants (J) are given in hertz.

Synthesis of Sulfones 1a–c, 2a–,b, 5a–f. To an ice-cold solution of the sulfide (0.05 mmol, 1.0 equiv) in dry DCM (2 mL) was added *m*-CPBA (2.0 equiv, 75%, 0.1 mmol, 45 mg) under inert conditions. After 20 min, the ice was removed and the reaction mixture was left to attain room-temperature. The reactions were complete within 10–15 min. The reactions were quenched by diluting the reaction mixture with water and DCM and washed with saturated solutions of Na_2SO_3 and Na_2CO_3 successively. DCM layers were dried over anhyd Na_2SO_4, and the solutions were concentrated and subjected to column chromatography (silica gel, petroleum ether–ethyl acetate mixture as eluent).

Compound ***1a***. White solid; yield 90% (27 mg), mp 180–182 °C; δ_H (400 MHz): 7.56–7.32 (m, 8H), 4.67–4.59 (m, 2H), 4.45 (t, J = 8.6 Hz, 2H, 4.27–4.16 (m, 6H), 2.63–2.47 (m, 2H), 0.97 (d, J = 2.6 Hz, 6H), 0.93 (d, J = 2.6 Hz, 6H), $^{13}C\{^1H\}$ (50 MHz): 168.1, 153.3, 138.2, 132.4, 129.8, 129.1, 126.7, 118.6, 85.1, 79.6, 79.6, 63.8, 58.7, 44.2, 28.4, 17.9, 14.8. HRMS: m/z [M + Na^+] Calcd for $C_{32}H_{32}N_2O_3SNa$ 627.1777; found 627.1782.

Compound ***1b***. White solid; yield 90% (30 mg), mp 183–185 °C; δ_H (400 MHz): 7.51–7.23 (m, 18H), 5.65–5.56 (m, 2H), 4.92–4.67 (m, 4H), 4.24–4.13 (m, 4H), $^{13}C\{^1H\}$ (50 MHz): 167.5, 153.0, 138.7, 137.6, 132.4, 130.1, 129.2, 129.1, 128.7, 127.0, 126.1, 118.9, 85.3, 79.7, 70.4, 58.0, 44.3. HRMS: m/z [M + Na^+] Calcd for $C_{38}H_{28}N_2O_8SNa$ 695.1464; found 695.1467.

Compound ***1c***. White solid; yield 90% (31 mg), mp 190–192 °C; δ_H (400 MHz): 7.43–7.24 (m, 18H), 4.94–4.85 (m, 2H), 4.45–4.32 (m, 4H), 4.24–4.15 (4H), 4.49 (dd, J = 3.2 Hz, 13.2 Hz, 2H), 2.98 (dd, J = 9.4 Hz, 13.3 Hz, 2H), $^{13}C\{^1H\}$ (50 MHz): 168.2, 152.9, 137.8, 135.4, 132.6, 130.2, 129.5, 129.2, 129.0, 127.3, 127.2, 119.0, 85.2, 79.6, 66.7, 55.4, 44.3, 37.6. HRMS: m/z [M + Na^+] Calcd for $C_{40}H_{32}N_2O_8SNa$ 723.1777; found 723.1781.

Compound ***2a***. White solid; yield 92% (29 mg), mp 194–195 °C; δ_H (400 MHz): 7.76 (d, J = 1.6 Hz, 2H), 7.57 (dd, J = 8.0 Hz, 1.6 Hz, 2H), 7.32–7.28 (m, 4H), 4.71–4.66 (m, 2H), 4.4–4.39 (m, 6H), 4.29–4.26 (m, 2H), 2.53 (s, 6H), 2.52–2.47 (m, 2H), 0.97 (d, J = 7.2 Hz), $^{13}C\{^1H\}$ (100 MHz): 168.7, 153.7, 145.6, 133.0, 130.9, 129.8, 129.2, 121.2, 86.0, 80.5, 63.5, 58.6, 44.4, 28.2, 20.9, 17.8, 15.1. HRMS: m/z [M + Na^+] Calcd for $C_{34}H_{36}N_2O_8SNa$ [M + Na^+] 655.2090; found 655.2088.

Compound ***2b***. White solid; yield 92% (32 mg), mp 205–207 °C; δ_H (400 MHz): 7.77 (s, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.42–7.28 (m, 10H), 7.28 (s, 4H), 5.61 (t, J = 7.2 Hz, 2H), 4.77 (t, J = 8.0 Hz, 2H), 4.36 (s, 4H), 4.32 (t, J = 8.0 Hz, 2H), 2.50 (t, J = 10.0 Hz), $^{13}C\{^1H\}$ (100 MHz): 168.3, 153.8, 146.3, 137.7, 133.5, 130.2, 129.5, 129.2, 126.6, 126.3, 121.5, 86.2, 80.8, 70.1, 59.0, 44.8, 21.2. HRMS: m/z [M + Na^+] Calcd for $C_{40}H_{32}N_2O_8SNa$ [M + Na^+] 723.1777; found 723.1779.

Compound ***5a***. White solid; yield 90% (31 mg), mp 125–126 °C; δ_H (200 MHz): 7.42 (d, J = 7.6 Hz, 2H), 7.32–7.29 (m, 4H), 7.23–7.19 (m, 2H), 5.27 (bs, 2H), 4.54–4.45 (m, 8H), 4.21–4.11 (bs, 2H), 1.36 (s, 18H), 0.89–0.83 (m, 3H); $^{13}C\{^1H\}$ (50 MHz): 172.9, 155.5, 140.8, 132.5, 129.6, 128.4, 127.4, 120.4, 86.1, 80.6, 79.9, 49.9, 45.1, 42.1, 25.2, 18.5. HRMS (ESI-TOF) m/z [M + Na^+] Calcd for $C_{36}H_{46}N_4O_8SNa$ 717.2934; found 717.2937.

Compound ***5b***. White solid; yield 90% (34 mg), mp 120–122 °C; δ_H (200 MHz): 7.41 (d, J = 7.6 Hz, 2H), 7.35–7.26 (m, 6H), 7.18 (t, J = 7.6 Hz, 2H), 5.28 (d, J = 6.4 Hz, 2H), 4.58–4.40 (m, 8H), 3.96 (bs, 2H), 2.05–2.02 (m, 2H), 1.35 (s, 18H), 0.91–0.85 (bm, 12H); $^{13}C\{^1H\}$ (50 MHz): 172.2, 156.2, 141.2, 132.7, 129.8, 128.9, 127.5, 120.6, 86.4, 80.9, 79.9, 60.1, 45.1, 42.3, 31.2, 28.4, 19.5, 18.1; HRMS m/z [M + Na^+] Calcd for $C_{40}H_{54}N_4O_8SNa$ 773.3560; found 773.3562.

Compound ***5c***. White solid; yield 88% (34 mg); mp 118–120 °C; δ_H (200 MHz): 7.60 (bs, 1H), 7.41 (d, J = 7.6 Hz, 2H), 7.33–7.26 (m, 3H), 7.19–7.17 (m, 2H), 5.28–5.27 (m, 1H), 4.65–4.62 (m, 1H), 4.51–4.35 (m, 5H), 4.23 (bs, 1H), 1.67–1.48 (m, 6H), 1.32 (bs, 18H), 0.95–0.81 (bs, 12H); $^{13}C\{^1H\}$ (50 MHz): 173.4, 156.1, 141.2, 132.7, 129.8, 128.1, 127.4, 120.5, 86.1, 81.1, 80.0, 53.3, 45.0, 42.1, 41.6, 28.4, 24.1, 23.2; HRMS (ESI-TOF) m/z [M + Na^+] Calcd for $C_{42}H_{58}N_4O_8SNa$ 801.3873; found 801.3877.

Compound ***5d***. White solid; yield 90% (38 mg); mp 125–127 °C; δ_H (200 MHz): 7.40–7.08 (m, 20H), 5.27 (d, J = 6.8 Hz, 2H), 4.50–4.22 (m, 10H), 3.03–2.98 (m, 4H), 1.28 (s, 18H); $^{13}C\{^1H\}$ (50 MHz): 155.7, 140.8, 136.8, 132.7, 129.8, 129.5, 128.6, 127.5, 126.9, 120.5, 86.3, 80.9, 55.8, 45.0, 42.3, 38.9, 28.4; HRMS (ESI-TOF) m/z [M + Na^+] Calcd for $C_{48}H_{54}N_4O_8SNa$ 869.3560; found 869.3566.

Compound ***5e***. White solid; yield 90% (40 mg), mp 120–122 °C; δ_H (200 MHz): 7.4 (d, J = 7.2 Hz, 2H), 7.25–6.99 (m, 12H), 6.71 (d, J = 8.0 Hz, 4H), 5.32–5.27 (m, 2H), 4.56–4.53 (m, 2H), 4.39–4.28 (m, 8H), 3.73 (s, 6H), 2.97–2.91 (m, 4H), 1.32 (s, 18H); $^{13}C\{^1H\}$ (50 MHz): 171.8, 158.6, 155.6, 140.8, 132.6, 129.7, 128.8, 127.5, 120.6, 114.1, 86.3, 80.9, 80.1, 55.3, 45.0, 42.2, 38.0, 28.4; HRMS (ESI-TOF) m/z [M + Na^+] Calcd for $C_{50}H_{58}N_4O_{10}SNa$ 929.3771; found 929.3774.

Compound ***5f***. Yellowish white solid: yield 95% (19 mg), mp 124–125 °C; δ_H (200 MHz): 7.93 (dd, J = 7.2 Hz, 1.3 Hz, 2H), 7.59–7.33 (m, 6H), 4.61 (s, 4 H), 3.90 (s, 6H); $^{13}C\{^1H\}$ (50 MHz): 166.1, 134.5, 132.0, 131.9, 130.4, 128.8, 86.1, 81.6, 52.5, 44.7; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{22}H_{19}O_6S$ 411.0902; found 411.0910.

Synthesis of Aryl Naphthalenes 3a–c, 4a,b, 6a–e, and 10 by Garratt–Braverman Cyclization. The aryl naphthalenes were obtained simply by treating the sulfones (0.05 mmol, 1.0 equiv) with triethylamine (0.05 mmol, 7 μL as a solution in $CHCl_3$, 1.0 equiv) in $CHCl_3$ (2 mL). The time for the completion of the reactions varied from 48 to 72 h for different substrates. The reaction mixtures, after evaporation to dryness, were directly subjected to column chromatographic purification (silica gel, hexane–ethyl acetate 1:1 mixture as eluent).

Compound ***3a*** *(diastereomeric mixture)*. White solid; Combined yield 80% (24 mg); δ_H (400 MHz): 8.30 (d, J = 4.0 Hz), 8.95 (s, major diastereomer), 8.89 (s, minor diastereomer), 7.77–7.71 (m), 7.66–7.61 (m), 7.59–7.52 (m), 7.49–7.43 (m), 7.35–7.32 (m), 6.77 (m), 4.80–4.78 (m), 4.59–4.53 (m), 4.47–4.42 (m), 4.36–4.31 (m), 4.15 (t, J = 16.0 Hz), 4.06–4.04 (m), 3.97–3.74 (m), 2.71–2.65 (m), 1.96 (bs), 1.09–1.06 (m), 0.75 (d, J = 7.2 Hz), 0.62 (d, J = 6.8 Hz); HRMS (ESI-TOF) m/z [M + Na^+] Calcd for $C_{32}H_{32}N_2O_8SNa$ 627.1777; found 627.1778.

Compound ***3b*** *(diastereomeric mixture)*. White solid; Combined yield 85% (28 mg); δ_H (400 MHz): 8.28 (s, characteristic of one axial diastereomer), 8.26 (s, characteristic of another axial distereomer), 7.76–7.71 (m), 7.65–7.23 (m), 7.13–7.07 (m), 6.76 (s), 6.66 (bs), 6.62 (bs), 5.79–5.73 (m), 5.68 (bs), 5.02–4.75 (m), 4.73 (t, J = 8.8 Hz), 4.48–4.16 (m), 4.05–4.01 (m), 3.94–3.90 (m); HRMS (ESI-TOF) m/z [M + Na^+] Calcd for $C_{38}H_{28}N_2O_8SNa$ 695.1464; found 695.1464.

Compound ***3c*** *(P)*. White crystalline solid; yield 45% (16 mg); δ_H (400 MHz): 7.91 (s, 1H), 7.64–7.59 (m, 4H), 7.51–7.49 (m, 1H), 7.44–7.09 (m, 10H), 7.08 (d, J = 6.8 Hz, 2H), 5.03–5.00 (m, 1H),

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4.62−4.50 (m, 3H), 4.40−4.36 (m, 1H), 4.31−4.23 (m, 2H), 4.17 (d, J = 16.4 Hz, 1H), 3.85−3.82 (m, 1H), 3.73−3.69 (m, 1H), 3.59 (dd, J = 16.0 Hz, 2.8 Hz, 1H), 3.03 (dd, J = 13.2 Hz, 9.6 Hz, 1H), 2.94 (d, J = 12.0 Hz, 1H); $^{13}C\{^1H\}$ (100 MHz): 169.0, 168.4, 152.7, 152.4, 135.6, 135.3, 134.9, 134.8, 134.6, 132.0, 131.3, 131.0, 130.5, 130.2, 129.9, 129.7, 129.5, 129.4, 129.3, 129.1, 128.8, 128.4, 128.2, 127.6, 127.2, 125.6, 121.8, 76.6, 66.4, 57.0, 55.9, 55.5, 54.8, 37.7, 36.9, 29.6; HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{40}H_{33}N_2O_8S$ 701.1958; found 701.1959.

Compound ***3c*** *(****M****).* White solid; yield 52% (18 mg); δ_H (400 MHz): 7.91 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.69−7.56 (m, 4H), 7.52−7.48 (m, 1H), 7.41−7.31 (m, 6H), 7.22−7.15 (m, 3H), 7.00−6.98 (m, 2H), 5.04−4.98 (m, 1H), 4.54−4.48 (m, 3H), 4.44−4.36 (m, 1H), 4.32−4.29 (m, 1H), 4.15−4.11 (m, 2H), 3.75−3.73 (m, 2H), 3.59 (dd, J = 13.2 Hz, 3.2 Hz, 1H), 3.06 (dd, J = 12.8 Hz, 9.6 Hz, 1H), 2.68 (d, J = 12.8 Hz, 1H); $^{13}C\{^1H\}$ (100 MHz): 168.0, 168.6, 152.6, 152.5, 135.7 (2C), 135.0, 134.7, 134.3, 132.1, 131.4, 130.8, 130.4, 130.3, 129.8, 129.5, 129.2, 129.1, 128.7, 128.6, 127.9, 127.6, 127.2, 127.0, 125.7, 121.7, 66.5, 66.4, 56.8, 55.8, 55.3, 55.0, 37.8, 36.4; HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{40}H_{33}N_2O_8S$ 701.1958; found 701.1957.

Compound ***4a*** *(one diastereomer; axial stereochemistry is undetermined).* White solid; yield 27% (8 mg); δ_H (400 MHz): 8.08 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 4.61 (s, 2H), 4.53−4.50 (m, 1H), 4.38 (t, J = 1.2 Hz, 1H), 4.32−4.28 (m, 2H), 4.02 (d, J = Hz, 1H), 4.92−4.90 (m, 2H), 3.68 (d, J = Hz, 1H), 2.77 (s, 3H), 2.70 (bs, 1H), 2.22 (bs, 1H), 1.66 (s, 3H), 1.01 (d, J = 8.0 Hz, 3H), 0.96 (d, J = 8.0 Hz, 3H), 0.89−0.83 (m, 6H); $^{13}C\{^1H\}$ (100 MHz): 169.3, 168.7, 153.5, 152.9, 144.2, 136.6, 136.5, 135.7, 133.1, 132.1, 131.4, 130.7, 130.6, 129.4, 129.2, 128.0, 127.4, 126.7, 126.2, 122.3, 62.8, 62.4, 58.1, 57.3, 57.2, 56.3, 27.7, 27.6, 20.4, 20.3, 18.0, 17.7, 14.8, 14.3; HRMS (ESI-TOF) m/z [M + Na$^+$] Calcd for $C_{34}H_{36}N_2O_8SNa$ 655.2090; found 655.2090.

Compound ***4a*** *(another diastereomer; axial stereochemistry is undetermined).* White solid; yield 54% (17 mg); δ_H (400 MHz): 8.08 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.41 (dd, J = 12.0 Hz, 8.0 Hz, 2H), 7.35 (s, 1H), 7.11 (d, J = 4.0 Hz, 1H), 4.69 (sex., J = 4.0 Hz, 1H), 4.64, 4.58 (ABq, J = 16.0 Hz, 2H), 4.32−4.26 (m, 2H), 4.19−4.13 (m, 2H), 3.93 (dd, J = 12.0, 4.0 Hz, 1H), 3.77 (d, J = 16.0 Hz, 1H), 3.62 (t, J = 4.0 Hz, 1H), 2.75 (s, 3H), 2.38−2.30 (m, 2H), 2.17 (s, 3H), 0.90 (m, 6H), 0.83 (d, J = 8.0 Hz, 6H); $^{13}C\{^1H\}$ (100 MHz): 169.3, 168.7, 153.5, 152.9, 144.2, 136.6, 136.5, 135.7, 133.1, 132.1, 131.4, 130.7, 130.6, 129.4, 129.2, 128.0, 127.43, 126.7, 126.2, 122.3, 62.8, 62.4, 58.1, 57.3, 57.2, 56.3, 27.7, 27.6, 20.4, 20.3, 18.0, 17.7, 14.8, 14.3; HRMS (ESI-TOF) m/z [M + Na$^+$] Calcd for $C_{34}H_{36}N_2O_8SNa$ 655.2090; found 655.2090.

Compound ***4b*** *(diastereomeric mixture).* White solid; Combined yield 80% (28 mg); mp 200−205 °C; δ_H (400 MHz): 8.10 (s), 8.08 (s), 7.84−7.77 (m), 7.57 (s), 7.45 (d, J = 7.6 Hz), 7.46−7.26 (m), 7.11 (d, J = 6.8 Hz), 6.98 (d, J = 7.6 Hz), 5.75 (t, J = 8.8 Hz, minor diastereomer), 5.63 (t, J = 8.8 Hz, major diastereomer), 4.82−4.57 (m), 4.40−4.33 (m), 4.29−4.22 (m), 4.12 (q, J = 7.2 Hz), 4.00−3.97 (m), 3.90 (t, J = 9.2 Hz), 3.81 (d, J = 4.8 Hz), 3.76 (d, J = 4.8 Hz), 3.58 (q, J = 4.4 Hz), 2.76 (s), 2.07 (s), 2.05 (s), 1.74 (s); HRMS (ESI-TOF) m/z [M + Na$^+$] Calcd for $C_{40}H_{32}N_2O_8SNa$ 723.1777; found 723.1777.

Compounds ***6a*** *and* ***7a****.* White solid; yield 95% (33 mg); mp 120−125 °C; δ_H (acetone-d_6, 400 MHz): 8.23 (s, 1H), 7.72 (bs, 1H), 7.59−7.57 (m, 2H), 7.49−7.37 (m, 4H), 7.24 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 7.2 Hz, 1H), 6.16 (bs, 1H), 6.06 (bs, 1H), 4.92 (m, 2H), 4.69−4.64 (m, 2H), 4.30−3.94 (m, 6H), 1.42−1.28 (m, 24H); $^{13}C\{^1H\}$ (100 MHz): 174.0, 173.7, 155.8, 155.7, 137.0, 136.9, 136.1, 134.5, 131.9, 130.8, 130.1, 129.2, 128.7, 127.6, 127.4, 126.5, 126.4, 125.2, 120.8, 79.0, 56.7, 55.4, 50.4, 50.1, 40.7, 40.6, 40.0, 28.6, 17.4; $[\alpha]^{25}_D$ −65.3 (c 0.25, $CHCl_3$); HRMS (ESI-TOF) m/z [M + Na$^+$] Calcd for $C_{36}H_{46}N_4O_8SNa$ 717.2934; found 717.2939.

Compounds ***6b*** *and* ***7b****.* White solid; yield 95% (36 mg); mp 115−117 °C; δ_H (acetone-d_6, 400 MHz):8.24 (s, 1H), 7.81 (bs, 1H), 7.59−7.55 (m, 3H), 7.49−7.35 (m, 3H), 7.25−7.23 (m, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.00 (bs, 1H), 5.90 (bs, 1H), 4.91 (bs 2H), 4.73−4.61 (m, 2H), 4.35−4.27 (m, 1H), 4.12−3.85 (m, 6H), 2.04−1.97 (m, 1H), 1.39−1.37 (m, 24H), 0.94−0.91 (m, 6H), 0.87−0.82 (m, 6H); $^{13}C\{^1H\}$ (100 MHz): 171.5, 171.4, 155.7, 137.5, 136.2, 136.2, 136.1, 134.9, 132.1, 131.0, 130.3, 129. 4, 129.3, 128.5, 127.5, 127.4, 126.7, 126.4, 125.4, 125.3, 121.0, 78.2, 60.0, 56.8, 55.5, 40.8, 40.1, 30.8, 30.5, 29.5, 29.3, 29.1, 28.9, 28.7, 28.5, 28.3, 27.6, 18.9, 17.4, 17.3; $[\alpha]^{25}_D$ −67.6 (c 0.25, $CHCl_3$); HRMS (ESI-TOF) m/z [M + Na$^+$] Calcd for $C_{40}H_{54}N_4O_8SNa$ 773.3560; found 773.3562.

Compound ***6c*** *and* ***7c****.* White solid; yield 95% (37 mg); mp 118−120 °C; δ_H (acetone-d_6, 400 MHz): 8.21 (s, 1H), 7.82 (d, J = 5.6 Hz, 1H), 7.59−7.54 (m, 3H), 7.48−7.33 (m, 3H), 7.22 (d, J = 6.0 Hz, 1H), 7.14 (d, J = 6.8 Hz, 1H), 6.18 (bs, 1H), 6.10 (bs, 1H), 4.90−4.88 (m, 2H), 4.73−4.62 (m, 2H), 4.33−4.21 (m, 2H), 4.12−4.08 (m, 2H), 4.01−3.93 (m, 2H), 1.72−1.63 (m, 2H), 1.39−1.35 (m, 18H), 0.92−0.84 (m, 12H); $^{13}C\{^1H\}$ (100 MHz): 172.6, 172.5, 155.6, 137.6, 137.5, 136.2, 135.0, 132.1, 131.0, 130.3, 129.3, 129.2 (2C), 128.5, 127.4, 126.5, 126.3 (2C), 120.9, 120.9, 78.3, 56.9, 55.5, 53.2, 53.1, 41.2, 41.0, 40.9, 40.8, 40.1 (2C), 27.7, 24.5 (2C), 22.5 (2C), 21.1; $[\alpha]^{25}_D$ −75.2 (c 0.25, $CHCl_3$); HRMS (ESI-TOF) m/z [M + Na$^+$] Calcd for $C_{42}H_{58}N_4O_8SNa$ 801.3873; found 801.3869.

Compounds ***6d*** *and* ***7d****.* White solid; yield 95% (40 mg), mp 116−118 °C; δ_H (acetone-d_6, 400 MHz): 8.22 (s, 1H), 7.80 (bs, 1H), 7.46−7.16 (m, 17H), 6.15 (bs, 1H), 6.05 (s, 1H), 4.90−4.88 (m, 2H), 4.68−4.66 (m, 2H), 4.43 (bs, 1H), 4.29−4.26 (m, 2H), 4.14−4.07 (m, 2H), 3.98−3.87 (m, 2H), 2.95−2.87 (m, 4H), 1.31 (s, 18H); $^{13}C\{^1H\}$ (100 MHz): 172.3, 155.8, 137.6, 137.3, 137.2, 136.4, 136,3, 132.2, 131.2, 130.4, 129.5, 129.4, 129.3, 128.9, 128.4, 128.3, 128.1, 127.8, 127.7, 126.6, 126.5, 125.5, 121.2, 79.2, 57.1, 56.2, 56.1, 55.7, 40.9, 40.4, 40.3, 38.2, 38.0, 29.9, 29.7, 29.5, 29.4, 29.2, 28.9, 28.8, 27.8; $[\alpha]^{25}_D$ −72.3 (c 0.25, $CHCl_3$); HRMS (ESI-TOF) m/z [M + Na$^+$] Calcd for $C_{48}H_{54}N_4O_8SNa$ 869.3560; found 869.3562.

Compounds ***6e*** *and* ***7e****.* White solid; yield 95% (43 mg); mp 123−125 °C; δ_H (acetone-d_6, 400 MHz): 8.21 (s, 1H), 7.78 (bs, 1H), 7.45−6.73 (m, 15H), 6.12 (bs, 1H), 6.01 (bs, 1H), 4.86 (bs, 2H), 4.60−4.65 (m, 2H), 4.37−3.9 (m, 6H), 3.77 (s, 6H), 3.06 (bs, 1H), 2.98−2.92 (m, 4H), 1.32 (s, 18H); $^{13}C\{^1H\}$ (100 MHz): 171.4, 158.4, 158.3, 155.4, 155.2, 137.4, 137.3, 136.3, 136.2, 134.8, 132.0, 129.4, 129.3, 128.5, 128.1, 127.7, 127.5, 127.4, 126.5, 126.4, 125.2, 120.8, 113.6, 113.5, 78.4, 56.8, 56.2, 55.5, 55.3, 54.5, 54.4, 40.7, 40.1, 37.2, 37.1, 36.9, 29.5, 29.3, 29.1, 28.9, 28.7, 28.5, 28.3, 27.6; $[\alpha]^{25}_D$ −68.9 (c 0.25, $CHCl_3$); HRMS (ESI-TOF) m/z [M + Na$^+$] Calcd for $C_{50}H_{58}N_4O_{10}SNa$ 929.3771; found 929.3771.

Synthesis of Compounds 9a−e. A 0.5 mmol amount of the product of Sonogashira coupling between **8a−e** and propargyl alcohol was taken in 15 mL of anhyd THF and cooled in an ice-bath. Et_3N (2.0 equiv, 1.0 mmol, 140 μL) and MsCl (1.1 equiv, 0.55 mmol, as a solution of 45 μL in 1.0 mL CH_2Cl_2) were added in succession. The progress of the reaction was monitored by TLC. After the completion of the reaction (maximum 30 min), anhyd LiBr (2.5 mmol, 5.0 equiv, 215 mg) was added and the reaction was sirrred at rt for 4 h. The reaction mixture was concentrated, and the product was purified by column chromatography (silica gel 60−120 mesh, PE:EA = 4:1).

Compound ***9a****.* Colorless liquid; yield 90% (175 mg); δ_H (200 MHz): 7.38−7.13 (m, 4H), 6.78 (bs, 1H), 5.12−5.14 (m, 1H), 4.51 (d, J = 5.8, 2H), 4.15 (s, 2H), 1.35 (s, 9H), 1.24−1.21 (m, 3H); $^{13}C\{^1H\}$ (50 MHz): 172.7, 155.6, 140.4, 132.5, 129.3, 128.2, 127.4, 121.2, 89.3, 84.6, 80.2, 42.1, 29.7, 28.3, 18.5, 15.2; HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{18}H_{24}BrN_2O_3$ 395.0970; found 395.0972.

Compound ***9b****.* Colorless liquid; yield 90% (190 mg); δ_H (200 MHz): 7.41−7.15 (m, 4H), 6.73(bs, 1H), 5.19 (d, J = 8.2, 1H), 4.53 (d, J = 5.8, 2H), 4.17 (m, 2H), 3.98−3.91 (m, 1H), 1.38 (s, 9H), 0.93−0.85 (m, 6H); $^{13}C\{^1H\}$ (50 MHz): 171.8, 156.1, 140.4, 132.6, 129.4, 128.4, 127.5, 121.3, 89.3, 84.7, 42.2, 31.0, 28.5, 19.5, 17.9, 15.3; HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{20}H_{28}BrN_2O_3$ 423.1283; found 423.1285.

Compound ***9c****.* Colorless liquid; yield 90% (195 mg); δ_H (200 MHz): 7.36−7.21 (m, 4H), 5.46 (d, J = 7.8, 1H), 4.47−4.36 9m, 2H), 4.14 (s, 2H), 1.64−1.48 (m, 3H), 1.36 (s, 9H), 0.89−0.87 (m, 6H); $^{13}C\{^1H\}$ (50 MHz): 173.0, 155.8, 140.4, 132.3, 129.2, 127.5, 127.1,

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120.9, 89.23, 84.4, 79.7, 53.1, 41.7, 41.4, 28.3, 24.7, 22.9, 22.0, 15.2; HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{21}H_{30}BrN_2O_3$ 437.1440; found 437.1443.

Compound ***9d***. Colorless liquid; yield 90% (210 mg); δ_H (200 MHz): 7.35−7.32 (m, 1H), 7.22−7.07 (m, 8H), 6.59 (m,1H), 5.23 (bs, 1H), 4.41−4.31 (m, 3H), 4.09 (s, 2H), 3.58 (t, J = 6.4, 1H), 2.99 (d, J = 6.6, 2H), 1.37 (s, 9H); $^{13}C\{^1H\}$ (50 MHz): 171.4, 155.6, 140.2, 136.7, 132.5, 129.4, 128.7, 18.3,127.4, 126.9, 121.2, 89.3, 84.6, 80.5, 61,8, 42.0, 38.8, 28.4, 15.3; HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{24}H_{28}BrN_2O_3$ 471.1283; found 471.1285.

Compound ***9e***. Colorless liquid; yield 85% (212 mg); δ_H (200 MHz): 7.34−7.22 (m, 3H), 7.05 (d, J = 7.8, 3H), 6.76−6.69 (m, 3H), 5.36−5.32 (m, 1H), 4.51−4.36 (m, 3H), 4.14 (s, 2H), 3.75 (s, 3H), 2.99 (d, J = 6.6, 2H), 1.38 (s, 9H); $^{13}C\{^1H\}$ (50 MHz): 171.5, 158.5, 155.5, 140.2, 130.4, 129.2, 128.7, 128.1, 127.3, 121.1, 114.1, 89.3, 84.5, 80.1, 55.3, 41.9, 37.9, 28.4, 15.2; HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{25}H_{30}BrN_2O_3$ 501.1389; found 501.1391.

Compound ***10***. White crystalline solid; yield 95% (19 mg); mp 225−227 °C; δ_H (400 MHz): 9.02 (s, 1H), 8.21 (d, J = 6.8 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H), 7.71−7.67 (m, 1H), 7.63−7.59 (m, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.40−7.36 (m, 1H), 7.25 (d, J = 6.8 Hz, 1H), 4.67, 4.62 (ABq, J = 16.2 Hz, 1H), 4.16, 4.07 (ABq, J = 16.2 Hz, 1H), 4.01 (s, 3H), 3.50 (s, 3H); $^{13}C\{^1H\}$ (100 MHz): 167.8, 166.6, 138.3, 137.8, 132.9, 132.5, 131.6, 131.2, 131.0, 131.0, 130.5, 130.3, 129.0, 128.4, 127.0, 125.6, 122.8, 105.3, 57.6, 56.2, 52.5, 52.3; HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{22}H_{19}O_6S$ 411.0902; found 411.0900.

Synthesis of Compound 11. A solution of **10** (0.5 mmol, 205 mg) in THF (15 mL) was taken in a two-neck round-bottom flask. Eight equivalents of finely ground $NaBH_4$ (4 mmol, 152 mg) was added. Dropwise addition of 10 mL of MeOH followed at 60 °C for 4 h. The reaction was quenched with NH_4Cl (aq), extracted with EtOAc, dried over anhyd Na_2SO_4, concentrated, and subjected to column chromatographic purification (silica gel 60−120 mesh, PE:EA = 1:1). Isolated as white solid; yield 80% (140 mg); mp 230−232 °C; δ_H (400 MHz): 8.21 (s, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.56−7.52 (m, 2H), 7.48−7.45 (m, 1H), 7.38−7.35 (m, 1H), 7.30−7.26 (m, 1H), 7.16 (d, J = 7.2 Hz, 1H), 5.16 (s, 2H), 4.61 (s, 2H), 4.28−4.11 (m, 4H); $^{13}C\{^1H\}$ (100 MHz): 138.7, 136.7, 136.3, 136.2, 132.5, 131.2, 129.5, 129.0, 128.9, 128.8, 128.4, 126.7, 126.6, 126.4, 121.4, 63.9, 62.8, 57.3, 56.1. HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{20}H_{19}O_4S$ 355.1004; found 355.1006.

Synthesis of Compound 12. The diol **11** (0.5 mmol, 177 mg) was treated with 3.0 equiv of mesyl chloride (1.5 mmol, 115 μL in 1 mL of CH_2Cl_2) and 3.0 equiv of Et_3N (1.5 mmol, 210 μL) in CH_2Cl_2 at 0 °C for 15 min. The solvent was evaporated in vacuum, and the reaction crude was directly treated with 5.0 equiv of NaN_3 (2.5 mmol, 162 mg) in anhyd DMF for 6 h. The reaction mixture was poured into water, extracted with EtOAc, washed with brine, dried over anhyd Na_2SO_4, evaporated in vacuum, and purified by column chromatography (silica gel 60−120 mesh, PE:EA = 2:1). Isolated as colorless viscous liquid; yield 90% (180 mg); δ_H (400 MHz): 8.08 (s, 1H), 7.56−7.22 (m, 7H), 4.79 (s, 2H), 4.65 (s, 2H), 4.15 (s, 2H), 4.04, 3.89 (ABq, J = 13.6 Hz, 2H); $^{13}C\{^1H\}$ (100 MHz): 136.9, 136.2, 134.1, 133.4, 131.4, 131.1, 130.0, 129.8, 129.4, 129.2, 128.4, 126.9, 126.6, 121.3, 57.2, 56.0, 53.0, 52.6; HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{20}H_{17}N_6O_2S$ 405.1134; found 405.1137.

Synthesis of Compound 13. The diazide **12** (0.05 mmol, 20 mg) was treated with 3.0 equiv of TPP (0.15 mmol, 40 mg) in 5 mL of THF−H_2O (10:1) for 6 h at room temperature. The product was purified by column chromatography (silica gel 60−120 mesh, DCM:MeOH = 4:1). Isolated as brown viscous oil; yield 75% (13 mg); δ_H (400 MHz): 8.06 (s, 1H), 7.51−7.02 (m, 7H), 4.53 (s, 2H), 4.28 (bs, 2H), 4.05 (s, 2H), 3.36−3.53 (m, 3H).

Synthesis of Compound 13a. The diazide **12** (0.5 mmol, 200 mg) was treated with 3.0 equiv of TPP (1.5 mmol, 400 mg) in 15 mL of THF−H_2O (10:1) for 6 h at room temperature. A 2.0 equiv amount of Et_3N (1.0 mmol, 140 μL) and 2.2 equiv of Boc anhydride (1.1 mmol, 240 μL) were added in succession at rt and stirred for 4 h. The product was purified by column chromatography (silica gel 60−120 mesh, PE:EA = 2:1). Isolated as white solid; yield 45% (125 mg); mp 140−142 °C; δ_H (400 MHz): 8.13 (s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.51−7.40 (m, 3H), 7.34 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 6.8 Hz, 1H), 4.89 (bs, 1H), 4.78 (s, 2H), 4.60 (bs, 3H), 4.16−4.07 (m, 2H), 3.86−3.83 (m, 2H), 1.49 (s, 9H), 1.35 (s, 9H); $^{13}C\{^1H\}$(100 MHz) 155.8 (2 signals), 137.5, 137.1, 136.4, 134.9, 132.7, 131.5, 129.8, 129.5, 129.3, 128.8, 128.3, 127.7, 127.0, 126.4, 121.4, 80.1, 79.8, 57.7, 56.3, 43.3, 42.4, 28.6, 28.5; HRMS (ESI-TOF) m/z [M + H$^+$] Calcd for $C_{30}H_{37}N_2O_6S$ 553.2372; found 553.2369

Procedure of HATU-Mediated Coupling for Synthesis of 6a/7a. A solution of N-Boc L-alanine (95 mg, 0.5 mmol, 2.0 equiv), HATU (2.0 equiv 0.5 mmol, 190 mg), and HOBt (2.0 equiv, 0.5 mmol, 70 mg) was prepared in anhyd DMF (2 mL) at 0 °C, and an ice-cold solution of the diamine (1.0 equiv, 0.25 mmol, 88 mg) and anhyd DIPEA (4 equiv, 1.0 mmol, 175 μL) in anhyd DMF (2 mL) was added dropwise to it. The reaction was left for 72 h to gradually attain room-temperature. The workup of the reaction was performed according to the usual procedure with water and EtOAc. The reaction product was purified by column chromatography (silica gel 60−120 mesh, PE:EA = 1:1). Isolated yield was 35 mg (20%).

■ ASSOCIATED CONTENT

Supporting Information

Spectral data for all new compounds;various ^1H and ^{13}C NMR spectra, crystallographic data and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) CCDC Numbers for compound **3c** and for compound **10** are 943869 and 943891, respectively.
(9) The aminoacyl *o*-iodobenzylamine derivatives were prepared from *o*-iodobenzylamine via EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide)-mediated coupling with various Boc-amino acids.
(10) Experimental condition of the ECD measurement: (C) 250 μM in MeOH, path length 0.1 cm, bandwidth 1.0 nm, data pitch 0.5 nm, temperature 25 °C.
(11) For computational details and references, see Supporting Information.