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# Stereoselective Synthesis of β-Amino Acid Derivatives by Asymmetric Mannich Reaction in Flow

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Takayuki Doi received his Ph.D. from Tokyo Institute of Technology in 1991. After his postdoctoral research under the guidance of Professor Gilbert Stork at Columbia University, he joined the groups of Professor Keiji Yamamoto in 1993 and Professor Takashi Takahashi in 1996 as an Assistant Professor. He was appointed to Associate Professor in 2001 and he has been a Full Professor at Tohoku University since 2008. He received Incentive Award in Synthetic Organic Chemistry, Japan in 2000 and The Pharmaceutical Society of Japan Award for Divisional Scientific Promotion in 2013.

**Abstract**

A continuous flow synthesis of β-amino acid derivatives has been demonstrated using an asymmetric Mannich reaction. An enolate of *tert*-butyl acetate was successfully prepared in 10 s at room temperature in a flow reactor, and the desired β-amino acid derivatives were stereoselectively obtained within a short residence time (40 s) in moderate-to-good yields. Sequential *N*-alkylation of the Mannich product in the flow reactor was also achieved in the presence of DMPU that provided *N*-alkylated β-amino acid derivatives in good yields.

## 1. Introduction

β-Amino acid derivatives are recognized as important building blocks in the structure of natural products and other biologically active molecules.[1] Several approaches for the synthesis of β-amino acid derivatives have been reported, for instance, the Arndt–Eistert homologation of α-amino acids and an asymmetric Mannich reaction.[2] In particular, the Mannich reaction using a chiral auxiliary has been widely utilized to prepare a variety of β-amino acid derivatives from chiral imine derivatives and the corresponding esters.[3] Sufficient formation of an enolate from ester is essential to obtain a Mannich product in a high yield without the generation of an acetoacetate derivative that can be formed by Claisen condensation. To enable reproducible production of β-amino acid derivatives by the Mannich reaction, we envisioned the use of a flow synthesis because flow systems allow a reproducible synthesis at different scales without further optimization of the reaction conditions.[4] To date, several research groups have reported a continuous-flow asymmetric Mannich reaction using organocatalysts.[5] However, the substrates are limited to ketones and alkanals as an acceptor and iminoglyoxylates as a donor. We have recently achieved a continuous-flow diastereoselective aldol reaction.[6] An enolate of an acetamide derivative in the flow reactor was successfully formed within a short residence time (150 s) at –40 °C, and the resulting enolate smoothly reacted with the aldehydes in 7.5 s at the same temperature to afford the aldol products in good yields. Thus, we assumed that the developed flow system could be applied to a reproducible synthesis of β-amino acid derivatives **1** by using an asymmetric Mannich reaction of an enolate of acetate with a variety of imine derivatives **2**,[3] as shown in Figure 1.

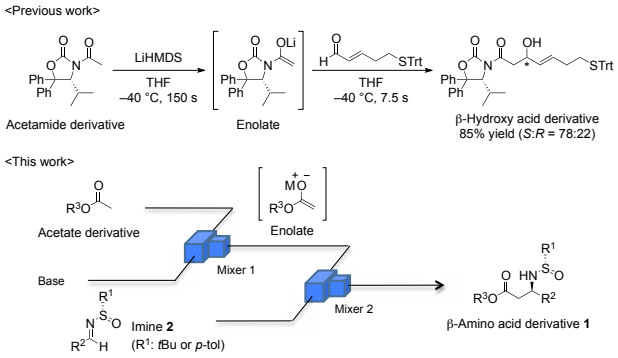
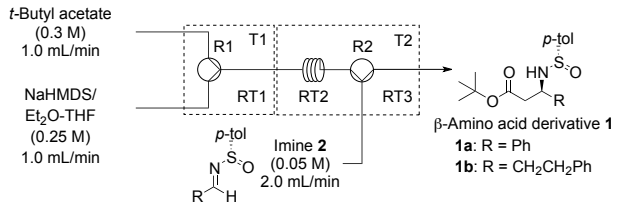



**Figure 1.** Outline for the Synthesis of β-Amino Acid Derivatives **1** by an Asymmetric Mannich Reaction in a Flow System

## 2. Results and Discussion

In order to avoid the Claisen condensation of an acetate derivative during the enolate formation, we chose steric hindered *tert*-butyl acetate as an ester source. The reaction conditions for the asymmetric Mannich reaction in the flow system were investigated, and the results are summarized in Table 1. A solution of *tert*-butyl acetate in the indicated solvent (0.3 M) was dispensed at a flow rate of 1 mL•min$^{-1}$ into reactor R1 (Comet-X01)[7] by a syringe pump, and a solution of NaHMDS in $Et_2O$-THF (7:1, 0.25 M, 1 mL•min$^{-1}$ by a syringe pump) was mixed at the appropriate temperature. The mixture was subsequently introduced into reactor R2 (Comet-X01), in which the chiral imine **2** (0.05 M in the indicated solvent) reacted with the resulting enolate at a flow rate of 2 mL•min$^{-1}$ through a precooling Teflon tube (0.5 m). The desired β-amino acid derivatives **1** were obtained from the outlet of reactor R2 after a conventional work-up. The solvent for the Mannich reaction in the flow system was initially investigated at −78°C (T1 and T2), and the use of THF resulted in a low yield (33%) of β-amino acid derivative **1a** with a moderate diastereoselectivity (8:1) (Table 1, entry 1). Conversely, the reaction performed in toluene afforded **1a** in 64% yield, and the diastereoselectivity was significantly improved (20:1, entry 2). Notably, the Mannich product **1a** was exclusively provided in 44% yield when $Et_2O$ was used as the solvent (entry 3).[8] Moreover, we found that the yield of **1a** was improved to 69% without a decrease in the diastereoselectivity when the reaction was performed at 0°C (entry 5), while the reaction at −40°C did not improve the yield of **1a** (entry 4).

**Table 1. Investigation of the Reaction Conditions for the Asymmetric Mannich Reaction in a Flow System**



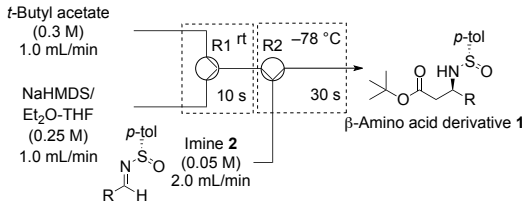

| Entry | Imine | Solvent | T1 (°C) | T2 (°C) | RT1 (s) | RT2 (s) | RT3 (s) | Product | Yield (%)[a] | dr |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **2a** | THF | | −78 | | 300 | 30 | **1a** | 33 | 8:1 |
| 2 | **2a** | Toluene | | −78 | | 300 | 30 | **1a** | 64 | 20:1 |
| 3 | **2a** | $Et_2O$ | | −78 | | 300 | 30 | **1a** | 44 | >20:1 |
| 4 | **2a** | $Et_2O$ | | −40 | | 300 | 30 | **1a** | 44 | >20:1 |
| 5 | **2a** | $Et_2O$ | | 0 | | 300 | 30 | **1a** | 69 | >20:1 |
| 6 | **2a** | $Et_2O$ | rt | −78 | 200 | 100 | 30 | **1a** | 87 | >20:1 |
| 7 | **2b** | $Et_2O$ | rt | −78 | 200 | 100 | 30 | **1b** | 80 | >20:1 |
| 8 | **2b** | $Et_2O$ | rt | −78 | 30 | 60 | 30 | **1b** | 73 | >20:1 |
| 9 | **2b** | $Et_2O$ | rt | −78 | 10 | 30 | 30 | **1b** | 81 | >20:1 |
| 10 | **2b** | $Et_2O$ | rt | −78 | 10 | 0 | 30 | **1b** | 80 | >20:1 |
| 11 | **2b** | $Et_2O$ | rt | –78 | 10 | 0 | 10 | **1b** | 59 | >20:1 |
| 12 | **2b** | $Et_2O$ | | rt | 10 | 0 | 30 | **1b** | 49 | >20:1 |

[a]Isolated yield

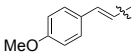
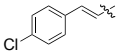
The above observation indicated that a higher temperature is required to generate an enolate or to perform the Mannich reaction in a flow reactor. To investigate the effect of temperature, we attempted the Mannich reaction at −78°C by using an enolate generated at room temperature. The enolate formed in the residence time RT1 (200 s) was introduced into the next reactor to react with imine **2a** at −78°C for 30 s after passing through a precooling coiled tube for the indicated residence time (Table 1, RT2). Interestingly, the yield of **1a** increased to 93% (entry 6, RT2, 100 s). The reaction with imine **2b** also proceeded to afford the corresponding **1b** in 80% yield with high diastereoselectivity (entry 7). Therefore, room temperature is crucial for enolate generation to provide the Mannich product **1** in a desirable yield. Having the good conditions for the enolate generation, we further investigated the residence time RT1 for the enolate formation and RT2 for precooling. We found that RT1 and RT2 could be reduced without affecting the yield of **1b** (entries 8–10). In particular, the enolate was smoothly generated in 10 s and the Mannich reaction proceeded in 30 s without precooling (entry 10). To our delight, the desired **1b** was stereoselectively obtained in 40 s in 80% yield. On the other hand, a decrease in the yield of **1b** was observed either reducing the residence time for the Mannich reaction (RT3: 10 s, entry 11) or performing the Mannich reaction at room temperature (T2: rt, entry 12).[9]

After determining the good reaction conditions for the stereoselective synthesis of β-amino acid derivatives (Table 1, entry 10), we investigated the substrate scope of imine **2** in the asymmetric Mannich reaction (Table 2). First of all, the reaction using imine **2a** was re-investigated under the optimized condition as mentioned in Table 1. Imine **2a** was completely consumed as well as entry 6 in Table 1, and the desired **1a** was afforded in 93% yield. Further, note that the Mannich reaction was performed in the continuous flow system for 4 min leading to 122 mg of **1a** (85% yield, 1.83 g•$h^{-1}$). A slightly lower yield of **1a** was observed by extension of the operation time. As a hydrolysate of **1a** was found in the resulting mixture, we assumed that the hydrolysis of the ester moiety in **1a** would partially occur at the time of quenching with saturated aqueous $NH_4Cl$ (entry 1). The reaction using imines **2c**–**2e** derived from benzaldehyde derivatives proceeded smoothly to provide **1c**–**1e** in good yields without any influence of the substituent on the aromatic ring (entries 2–4). Moreover, imines **2f**–**2h** prepared from cinnamaldehyde derivatives were tolerant in the Mannich reaction, and the corresponding products **1f**–**1h** were afforded in acceptable yields (71–89%, entries 5–7). However, a decrease in the yields of the Mannich products of **1i** and **1j** was observed in the reaction with alkyl imine derivatives **2i** and **2j** (entries 8 and 9). Conversely, the reaction with imine **2k** derived from pivalaldehyde was smoothly performed to obtain the corresponding **1k** in 85% yield (entry 10), resulting in the finding that the existence of acidic α-protons in the imine derivatives causes a decomposition or a decrease in the yield of the corresponding Mannich products.

**Table 2. Substrate Scope of Imine 2 in the Asymmetric Mannich Reaction in a Flow System**

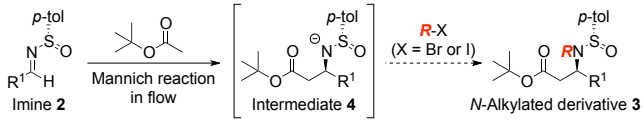



| Entry | Imine | R | Product | Yield (%)[a] (dr)[b] |
|---|---|---|---|---|
| 1 | **2a** |  | **1a** | 93 (85)[c, d] (>20:1) |
| 2 | **2c** |  | **1c** | 80 (>20:1) |

| | | | | |
|---|---|---|---|---|
| 3 | **2d** |  | **1d** | 79 (>20:1) |
| 4 | **2e** |  | **1e** | 77 (>20:1) |
| 5 | **2f** |  | **1f** | 89 (>20:1) |
| 6 | **2g** |  | **1g** | 84 (>20:1) |
| 7 | **2h** |  | **1h** | 71 (>20:1) |
| 8 | **2i** |  | **1i** | 51 (>20:1) |
| 9 | **2j** |  | **1j** | 55 (>20:1) |
| 10 | **2k** |  | **1k** | 85 |

[a]Isolated yield, [b]Determined by crude $^1$H NMR, [c]Operated for 4 min, [d]A hydrolysate of **1a** was observed in 5% yield.

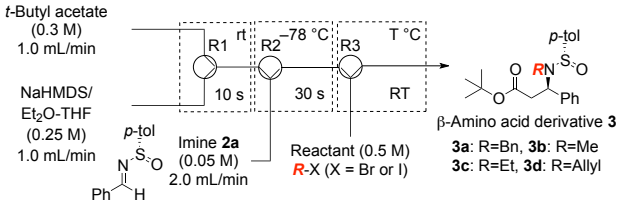
After successfully establishing a flow system for the stereoselective synthesis of β-amino acid derivatives, we investigated the synthesis of *N*-alkylated β-amino acid derivatives for a further application of this flow system. Focusing on the intermediate **4** generated by the Mannich reaction in the flow reactor, as shown in Scheme 1, we assumed that the anionic intermediate **4** was sufficiently nucleophilic to readily react with an alkyl halide, leading to the desired *N*-alkylated derivative **3**.[10]




**Scheme 1. Synthetic Plan for *N*-Alkylated β-Amino Acid Derivatives 3 in a Flow System**

First, benzyl bromide was subjected at 0°C as an electrophile for the sequential *N*-alkylation after the Mannich reaction performed at −78°C in the flow system; however, the *N*-alkylated product **3a** was not observed (Table 3, entry 1), but. the Mannich product **1a** was obtained in 93% yield. Therefore, we further investigated the reaction conditions such as the requirement of an additive. Note that the addition of DMPU[11] was essential to promote the *N*-alkylation and that the corresponding **3a** was obtained in 35% yield accompanied with the Mannich product **2a** recovered in 58% yield (entry 2). Then, we assumed that a higher temperature was required to promote the *N*-alkylation of the resulting sulfonamide moiety. As expected, the reaction in the flow reactor was smoothly conducted at room temperature and the corresponding **3a** was afforded in 53% yield (entry 3). Conversely, the yield of **3a** was not improved by an extension of the residence time because the sulfonamide moiety in the resulting **3a** was partially eliminated under the reaction conditions, leading to the formation of *tert*-butyl cinnamate (entry 4). As we successfully found the good conditions for sequential *N*-alkylation in the flow system, the reactions with several reactants were performed as follows. A methyl group was readily installed on a nitrogen atom by the *N*-alkylation in the flow system to afford **3b** in 72% yield, while the reaction with ethyl iodide was not complete within 120 s and the desired **3c** was provided in 28% yield with a recovery of the Mannich product **1a** in 55% yield (entries 5 and 6). The *N*-alkylation using allyl bromide proceeded smoothly, leading to the allylated **3d** (65%, entry 7); therefore, less hindered and reactive alkylating reagents were tolerated for the sequential *N*-alkylation in a flow system to provide the corresponding **3** in moderate-to-good yields.

**Table 3. Synthesis of *N*-Alkylated β-Amino Acid Derivatives 3 by Sequential Mannich-*N*-Alkylation in a Flow System**




| Entry | *R*-X | T (°C) | RT (s) | Additive | Product | Yield (%)[a, b] |
|---|---|---|---|---|---|---|
| 1 | BnBr | 0 | 120 | - | **3a** | 0 (93) |
| 2 | BnBr | 0 | 120 | DMPU | **3a** | 35 (58) |
| 3 | BnBr | rt | 120 | DMPU | **3a** | 53 |
| 4 | BnBr | rt | 150 | DMPU | **3a** | 50 |
| 5 | MeI | rt | 120 | DMPU | **3b** | 72 |
| 6 | EtI | rt | 120 | DMPU | **3c** | 28 (55) |
| 7 | AllylBr | rt | 120 | DMPU | **3d** | 65 |

[a]Isolated Yield, [b]Yield of recovered **1a** in the parenthesis.

## 3. Conclusion

We have demonstrated a continuous-flow stereoselective synthesis of β-amino acid derivatives by an asymmetric Mannich reaction using optically active sulfinimines. An enolate of *tert*-butyl acetate successfully formed in 10 s at room temperature in the flow reactor, and the asymmetric Mannich reaction with the resulting enolate proceeded smoothly within 30 s at −78°C to afford β-amino acid derivatives in moderate-to-good yields with high diastereoselectivity. Moreover, we found that the developed flow system could be operated continuously, leading to the formation of the corresponding Mannich product at the rate of 1.83 g•h$^{-1}$. For a further application of the flow system, the synthesis of *N*-alkylated β-amino acid derivatives was investigated. Continuous-flow *N*-alkylation of the resulting Mannich product was smoothly performed in the presence of DMPU to afford *N*-alkylated β-amino acid derivatives in good yields. This is the first example of a continuous-flow stereoselective synthesis of β-amino acid derivatives by a Mannich reaction using an enolate prepared from an acetate derivative in a flow reactor.

We are currently applying this method to a study on the synthesis and the structure–activity relationship of biologically active natural products, and the results will be reported in due course.

## 4. Experimental

**Generals.** All commercially available reagents were used as received. Dry THF and $CH_2Cl_2$ (Kanto Chemical Co.) were obtained by purchasing commercially available pre-dried, oxygen-free formulations. All reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) with UV light, visualized by *p*-anisaldehyde solution, phosphomolybdic acid solution. Column chromatography and flash column chromatography were carried out with silica gel 60 N (Kanto Chemical Co. 100-210 μm) and silica gel 60 N (Kanto Chemical Co. 40-50 μm), respectively. $^1$H NMR spectra (400 MHz and 600 MHz) and $^{13}$C NMR spectra (100 MHz and 150 MHz) were recorded on JEOL JNM-AL400 and JEOL ECA600 spectrometers in the indicated solvent. Chemical shifts are reported in units parts per million (ppm) relative to tetramethylsilane (0.00 ppm for $^1$H), chloroform (7.26 ppm for $^1$H), methanol (3.30 ppm for $^1$H), chloroform-*d* (77.0 ppm for $^{13}$C) and methanol-$d_3$ (49.0 ppm for $^{13}$C) when internal standard is not indicated. Multiplicities are reported by the following abbreviations: s; singlet, d; doublet, t; triplet, q; quartet, dd; double doublet, dt; double triplet, ddt; double double triplet, m; multiplet, br; broad, *J*; coupling constants in Hertz. Mass spectra and high-resolusion mass spectra were measured on JEOL JMS-DX303 (for EI), MS-AX500 (for FAB), and ThermoScientific™ Exactive™ Plus Orbitap Mass Spectrometer (for ESI). IR spectra were recorded on a JASCO FTIR-8400. Only the strongest and/or structurally important absorption are reported as the IR data afforded in cm$^{-1}$. Melting points were measured on Round Science RFS-10, and are uncorrected. Optical rotations were measured with a JASCO P-1010 polarimeter.

**General procedure for the synthesis of (*S*)-*N*-*p*-toluenesulfinylimine 2.** To a solution of *p*-tol-sulfinamine[12] (3.87 mmol, 1.0 equiv) in dry dichloromethane (7.7 mL, 2 mL/mmol) was added aldehyde (3.87 mmol, 1.0 equiv), $Ti(OEt)_4$ (19.4 mmol, 5.0 equiv) at room temperature under argon. After being stirred at reflux temperature for 3 h, the reaction mixture was poured into water. The mixture was filtered through a buchner funnel, and wash with dichloromethane. The filtrate was extracted with dichloromethane. The organic layer was washed with water, brine and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (5% ethyl acetate in hexane) to give (*S*)-*N*-(*p*-toluenesulfinyl)imine **2**.

**(*S*)-*N*-Benzylidene-*p*-toluenesulfinamide (2a):** Yield: 91% (0.856 g, 3.52 mmol), white solid; Melting point: 79–82 °C [lit.[13] mp 77−78 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.85 (d, 2H, *J* = 8.0 Hz), 7.64 (d, 2H, *J* = 8.3 Hz) 7.43−7.51 (m, 3H), 7.31 (d, 2H, *J* = 8.0 Hz), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.6, 141.8, 141.7, 133.9, 132.5, 129.8, 129.5, 128.8, 124.8, 21.4; IR (Solid) 3058, 1604, 1573, 1494, 1450, 1216, 1099, 1071, 809, 758, 721, 690 cm$^{-1}$; $[\alpha]_D^{28}$ +96.1 (*c* 1.17, $CHCl_3$) [lit.[13] $[\alpha]_D^{27}$ +120 (*c* 0.45, $CHCl_3$)]; HRMS(EI) calcd for $C_{14}H_{13}NOS$ $[M]^+$ 243.0718, found 243.0728.

**(*S*)-*N*-3-(Phenylpropylidene)-*p*-toluenesulfinamide (2b):** Yield: 68 % (0.714 g, 2.63 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.28 (t, 1H, *J* = 4.4 Hz), 7.50 (d, 2H, *J* = 8.3 Hz), 7.17−7.26 (m, 9H), 2.94 (t, 2H, *J* = 7.6 Hz), 2.79−2.84 (m, 2H), 2.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.1, 166.0, 141.6, 141.5, 140.1, 129.6, 128.4, 128.2, 126.1, 124.5, 37.2, 31.2, 21.33, 21.30; IR ($CHCl_3$) 3023, 2924, 1619, 1497, 1455, 1098, 1072, 809, 700 cm$^{-1}$; $[\alpha]_D^{24}$ +229 (*c* 0.950, $CHCl_3$) [lit.[14] $[\alpha]_D^{20}$ +196 (*c* 1.37, $CHCl_3$)]; HRMS(FAB) calcd for $C_{16}H_{18}NOS$ $[M+H]^+$ 272.1109, found 272.1115.

**(*S*)-*N*-(*p*-Methylbenzylidene)-*p*-toluenesulfinamide (2c):** Yield: 60 % (0.597 g, 2.32 mmol), white solid; Melting point: 96–99 °C [lit.[15] mp 100–102 °C], $^1$H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.74 (d, 2H, *J* = 8.0 Hz), 7.63 (d, 2H, *J* = 8.3 Hz) 7.24−7.31 (m, 4H), 2.39−2.40 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.5, 143.4, 142.0, 141.6, 131.4, 129.8, 129.6, 124.8, 21.7, 21.4; IR (Solid) 3030, 2953, 2922, 1599, 1566, 1494, 1452, 1304, 1210, 1173, 1103, 1073, 1040, 1017, 982, 809, 714, 702 cm$^{-1}$; $[\alpha]_D^{26}$ +77.7 (*c* 1.13, $CHCl_3$) [lit.[15] $[\alpha]_D^{25}$ +67 (*c* 0.50, $CHCl_3$)]; HRMS(EI) calcd for $C_{15}H_{15}NOS$ $[M]^+$ 257.0874, found 257.0864.

**(*S*)-*N*-(*p*-Chlorobenzylidene)-*p*-toluenesulfinamide (2d):** Yield: 63 % (0.677 g, 2.44 mmol), white solid; Melting point: 106–110 °C [lit.[13] mp 116–118 °C], $^1$H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.78 (d, 2H, *J* = 8.9 Hz), 7.62 (d, 2H, *J* = 8.2 Hz), 7.43 (d, 2H, *J* = 8.9 Hz), 7.31 (d, *J* = 8.2 Hz), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.3, 141.8, 141.5, 138.8, 132.3, 130.7, 129.8, 129.2, 124.7, 21.4; IR (Solid) 2921, 1608, 1592, 1566, 1489, 1405, 1104, 1087, 1014, 825, 809, 669 cm$^{-1}$; $[\alpha]_D^{28}$ +15.6 (*c* 0.975, $CHCl_3$); HRMS(EI) calcd for $C_{14}H_{12}ClNOS$ $[M]^+$ 277.0328, found 277.0330.

**(*S*)-*N*-(*p*-Trifluoromethylbenzylidene)-*p*-toluenesulfinamide (2e):** Yield: 37 % (0.446 g, 1.43 mmol), white solid; Melting point: 100–102 °C [lit.[16] 99–101 °C], $^1$H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.96 (d, 2H, *J* = 8.0 Hz), 7.71 (d, 2H, *J* = 8.3 Hz), 7.63 (d, 2H, *J* = 8.3 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.2, 141.9, 141.2, 136.7, 133.8 (q, *J* = 32.7 Hz), 129.9, 129.7, 125.8 (q, *J* = 3.6 Hz), 124.9, 124.7, 122.2, 21.4; IR (Solid) 1607, 1574, 1411, 1324, 1170, 1120, 1104, 1065, 838, 809 cm$^{-1}$; $[\alpha]_D^{24}$ +87.4 (*c* 1.06, $CHCl_3$) [lit.[16] $[\alpha]_D^{20}$ +86.2 (*c* 1.15, $CHCl_3$)]; HRMS(EI) calcd for $C_{15}H_{12}F_3NOS$ $[M]^+$ 311.0592, found 311.0591.

**(*S*)-*N*-{(*E*)-3-Phenylpropenylidene}-*p*-toluenesulfinamide (2f):** Yield: 82 % (0.855 g, 3.17 mmol), white solid; Melting point: 114–117 °C [lit.[17] mp 114–115 °C], $^1$H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, 1H, *J* = 9.2 Hz), 7.60 (d, 2H, *J* = 8.2 Hz), 7.52 (dd, 2H, *J* = 6.5, 2.9 Hz), 7.38−7.39 (m, 3H), 7.24−7.33 (m, 3H), 7.05 (dd, 1H, *J* = 15.8, 9.2 Hz), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.5, 146.8, 141.9, 141.7, 134.9, 130.3, 129.8, 128.9, 127.9, 125.1, 124.6, 21.4; IR (Solid) 3056, 1625, 1579, 1568, 1490, 1449, 1162, 1153, 1093, 1070, 998, 960, 809, 751, 704, 690 cm$^{-1}$; $[\alpha]_D^{28}$ +334 (*c* 0.980, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ +337 (*c* 1.49, $CHCl_3$)]; HRMS(EI) calcd for $C_{16}H_{15}NOS$ $[M]^+$ 269.0874, found 269.0872.

**(*S*)-*N*-{(*E*)-3-(*p*-Methoxyphenyl)propenylidene}-*p*-toluenesulfinamide (2g):** Yield: 76 % (0.881 g, 2.94 mmol), yellow solid; Melting point: 119–120 °C, $^1$H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, 1H, *J* = 9.3 Hz), 7.59 (d, 2H, *J* = 8.0 Hz), 7.46 (d, 2H, *J* = 7.3 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.20 (d, 1H, *J* = 15.6 Hz), 6.91−6.95 (m, 3H), 3.84 (s, 3H), 2.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.7, 161.4, 146.7, 142.1, 141.6, 129.8, 129.6, 127.6, 124.6, 123.3, 114.4, 55.3, 21.4; IR (Solid) 3030, 2998, 2956, 2840, 1626, 1602, 1578, 1569, 1513, 1315, 1307, 1299, 1265, 1180, 1153, 1096, 1070, 1022, 989, 954, 860, 821, 808, 705 cm$^{-1}$; $[\alpha]_D^{22}$ +240 (*c* 1.05, $CHCl_3$) [lit.[18] $[\alpha]_D^{25}$ +170 (*c* 1.00, $CHCl_3$)]; HRMS(EI) calcd for $C_{17}H_{17}NO_2S$ $[M]^+$ 299.0980, found 299.0983.

**(*S*)-*N*-{(*E*)-3-(*p*-Chlorophenyl)propenylidene}-*p*-toluenesulfinamide (2h):** Yield: 57 % (0.670 g, 2.21 mmol), white solid; Melting point: 117–120 °C, $^1$H NMR (400 MHz, $CDCl_3$) δ 8.51

(d, 1H, *J* = 9.3 Hz), 7.59 (d, 2H, *J* = 8.0 Hz), 7.43 (d, 2H, *J* = 8.5 Hz), 7.36 (d, 2H, *J* = 8.5 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.19 (d, 1H, *J* = 15.9 Hz), 7.01 (dd, *J* = 15.9, 9.3 Hz), 2.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.1, 145.1, 141.8, 141.7, 136.2, 133.4, 129.9, 129.2, 129.0, 126.0, 124.5, 21.4; IR (Solid) 3048, 2920, 1625, 1577, 1489, 1407, 1156, 1096, 1071, 809, 710, 677 cm$^{-1}$; $[\alpha]_D^{27}$ +227 (*c* 0.650, $CHCl_3$); HRMS(EI) calcd for $C_{16}H_{14}ClNOS$ $[M]^+$ 303.0485, found 303.0484.

**(*S*)-*N*-Propylidene-*p*-toluenesulfinamide (2i):** Yield: 44 % (0.333 g, 1.70 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.25 (t, 1H, *J* = 4.4 Hz), 7.56 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 2.47−2.55 (m, 2H) 2.40 (s, 3H), 1.16 (t, 3H, *J* = 7.4 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.9, 141.8, 141.5, 129.6, 129.4, 125.2, 124.5, 29.2, 21.3, 9.4; IR ($CHCl_3$) 2973, 2935, 2877, 1620, 1491, 1450, 1418, 1376, 1349, 1094, 1072, 809, 624 cm$^{-1}$; $[\alpha]_D^{22}$ +354 (*c* 1.04, $CHCl_3$) [lit.[13] $[\alpha]_D^{19}$ +341.1 (*c* 1.105, $CHCl_3$)]; HRMS(EI) calcd for $C_{10}H_{13}NOS$ $[M]^+$ 195.0718, found 195.0723.

**(*S*)-*N*-(2-Methylpropylidene)-*p*-toluenesulfinamide (2j):** Yield: 82 % (0.664 g, 3.17 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 1H, *J* = 4.6 Hz), 7.56 (d, 2H, *J* = 8.3 Hz), 7.30 (d, 2H, *J* = 8.3 Hz), 2.64−2.72 (m, 1H), 2.40 (s, 3H), 1.15 (d, 3H, *J* = 4.6 Hz), 1.14 (d, 3H, *J* = 4.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.1, 141.8, 141.5, 129.6, 129.4, 125.2, 124.5, 34.5, 21.3, 18.7, 18.6; IR ($CHCl_3$) 2966, 2929, 2871, 2360, 1617, 1491, 1457, 1095, 1072, 809 cm$^{-1}$; $[\alpha]_D^{22}$ +291 (*c* 1.30, $CHCl_3$) [lit.[17] $[a]_D^{20}$ +387 (*c* 2.1, $CHCl_3$)]; HRMS(EI) calcd for $C_{11}H_{15}NOS$ $[M]^+$ 209.0874, found 209.0875.

**(*S*)-*N*-(2,2-Dimethylpropylidene)-*p*-toluenesulfinamide (2k):** Yield: 53% (0.458 g, 2.05 mmol), white solid; Melting point: 69–74 °C [lit.[17] mp 73–75 °C], $^1$H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.55 (d, 2H, *J* = 8.3 Hz), 7.29 (d, 2H, *J* = 8.3 Hz), 2.40 (s, 3H), 1.13 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.4, 142.2, 141.5, 129.7, 124.7, 37.7, 26.5, 21.4; IR (Solid) 2969, 2930, 2903, 2867, 1932, 1618, 1593, 1495, 1477, 1463, 1364, 1342, 1300, 1209, 1202, 1086, 1072, 1040, 1013, 971, 963, 921, 855, 818, 799, 780, 703, 630 cm$^{-1}$; $[\alpha]_D^{23}$ +274 (*c* 1.07, $CHCl_3$) [lit.[17] $[\alpha]_D^{20}$ +371 (*c* 1.94, $CHCl_3$)]; HRMS(EI) calcd for $C_{12}H_{17}NOS$ $[M]^+$ 223.1031, found 223.1031.

**General procedure for the synthesis of β-amino acid derivatives 1 by the Mannich reaction in Flow:** The flow system was established with a syringe pump (HII-10B, Techno applications®), teflon tube, the flow reactor (Comet X-01-T, Techno applications®). Before use, the flow system was flushed with $Et_2O$ and dried under vacuum. A solution of NaHMDS (0.25 M) in $Et_2O$ was loaded into a teflon sample tube, and a solution of *tert*-butyl acetate (0.3 M) in $Et_2O$ was loaded into another teflon sample tube. Both two sample solutions were pumped at a flow rate of 1 mL/min, and mixed in the reactor (Comet X-01-T) at room temperature. The output of the reactor was connected with another reactor (Comet X-01-T) to mix with a solution of imine **2** in $Et_2O$ (0.05 M, 2 mL/min) at –78 °C. The resulting mixture was collected for 60 s and quenched with saturated aqueous $NH_4Cl$, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexane) to give Mannich product **1**.

***tert*-Butyl (*R*)-3-phenyl-3-{(*S*)-*p*-toluenesulfinylamino}propanoate (1a):** Yield: 93% (33.4 mg, 0.093 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2H, *J* = 8.0 Hz), 7.26−7.43 (m, 7 H), 5.00 (d, 1H, *J* = 4.6 Hz), 4.86 (m, 1H), 2.75 (d, 2H, *J* = 6.3 Hz), 2.41 (s, 3H), 1.32 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.0, 142.4, 141.3, 140.4, 129.5, 128.6, 127.9, 127.3, 125.3, 81.4, 55.0, 43.3, 27.9, 21.3; IR($CHCl_3$) 3181, 2976, 1730, 1455, 1366, 1150, 1089, 1056, 810, 700 cm$^{-1}$; $[\alpha]_D^{23}$ +53.3 (*c* 0.615, $CHCl_3$); HRMS(ESI) calcd for $C_{20}H_{25}NO_3SNa$ $[M+Na]^+$ 382.1447, found 382.1436.

***tert*-Butyl (*R*)-5-phenyl-3-{(*S*)-*p*-toluenesulfinylamino}pentanoate (1b):** Yield: 80 % (31.0 mg, 0.08 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 2H, *J* = 8.3 Hz), 7.22−7.28 (m, 7H), 4.73 (d, 1H, *J* = 9.0 Hz), 3.63−3.67 (m, 1H), 2.69−2.85 (m, 2H), 2.53−2.59 (m, 2H), 2.41 (s, 3H), 1.86−2.02 (m, 2H), 1.41 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.8, 142.5, 141.3, 141.2, 129.5, 128.5, 128.4, 125.9, 125.4, 81.2, 52.4, 41.6, 37.3, 32.3, 28.1, 21.3; IR ($CHCl_3$) 3191, 2976, 2929, 1725, 1367, 1149, 1089, 1056, 810, 700 cm$^{-1}$; $[\alpha]_D^{22}$ +42.2 (*c* 1.20, $CHCl_3$); HRMS(ESI) calcd for $C_{22}H_{29}NO_3SNa$ $[M+Na]^+$ 410.1760, found 410.1749.

***tert*-Butyl (*R*)-3-(*p*-methylphenyl)-3-{(*S*)-*p*-toluenesulfinylamino}propanoate (1c):** Yield: 80 % (29.9 mg, 0.08 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2H, *J* = 8.3 Hz), 7.28−7.32 (m, 4H), 7.18 (d, 2H, *J* = 7.8 Hz), 4.95 (d, 1H, *J* = 4.6 Hz), 4.81−4.84 (m, 1H), 2.72 (dd, 2H, *J* = 6.6, 3.7 Hz), 2.41 (s, 3H), 2.35 (s, 3H) 1.33 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.1, 142.4, 141.2, 137.6, 137.3, 129.4, 129.2, 127.3, 125.2, 81.3, 54.7, 43.3, 27.8, 21.3, 21.1; IR ($CHCl_3$) 3171, 2976, 1726, 1367, 1150, 1090, 1055, 951, 810 cm$^{-1}$; $[\alpha]_D^{23}$ +47.0 (*c* 1.37, $CHCl_3$); HRMS(ESI) calcd for $C_{21}H_{27}NO_3SNa$ $[M+Na]^+$ 396.1604, found 396.1595.

***tert*-Butyl (*R*)-3-(*p*-chlorophenyl)-3-{(*S*)-*p*-toluenesulfinylamino}propionate (1d):** Yield: 79 % (31.1 mg, 0.079 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2H, *J* = 8.3 Hz), 7.29−7.32 (m, 6H), 5.04 (d, 1H, *J* = 4.9 Hz), 4.80−4.83 (m, 1H), 2.71 (d, 2H, *J* = 6.1 Hz), 2.41 (s, 3H), 1.33 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.7, 142.1, 141.5, 139.0, 133.7, 129.5, 128.78, 128.77, 125.2, 81.6, 54.2, 43.1, 27.9, 21.3; IR ($CHCl_3$) 3186, 2977, 2924, 1726, 1491, 1450, 1367, 1257, 1151, 1090, 1056, 1014, 810 cm$^{-1}$; $[\alpha]_D^{24}$ +57.3 (*c* 1.01, $CHCl_3$); HRMS(ESI) calcd for $C_{20}H_{24}ClNO_3SNa$ $[M+Na]^+$ 416.1058, found 416.1046.

***tert*-Butyl (*R*)-3-{(*S*)-*p*-toluenesulfinylamino}-3-{*p*-(trifluoromethyl)phenyl}propanoate (1e):** Yield: 77 % (32.9 mg, 0.077 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.56−7.62 (m, 6H), 7.32 (d, 2H, *J* = 8.0 Hz), 5.14 (d, 1H, *J* = 5.4 Hz), 4.88 (m, 1H), 2.76 (d, 2H, *J* = 6.3 Hz), 2.42 (s, 3H), 1.32 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.7, 144.7, 141.9, 141.6, 129.8 (q, *J* = 32.1 Hz), 129.6, 127.7, 125.5 (q, *J* = 4.2 Hz), 125.3, 81.7, 54.4, 42.9, 27.8, 21.3; IR ($CHCl_3$) 3181, 2979, 2924, 1727, 1368, 1325, 1161, 1125, 1068, 842, 810 cm$^{-1}$; $[\alpha]_D^{21}$ +73.5 (*c* 0.900, $CHCl_3$); HRMS(ESI) calcd for $C_{21}H_{24}F_3NO_3SNa$ $[M+Na]^+$ 450.1321, found 450.1311.

***tert*-Butyl (*R*)-5-phenyl-3-{(*S*)-*p*-toluenesulfinylamino}-4-pentenoate (1f):** Yield: 89 % (34.3 mg, 0.089 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, 2H, *J* = 8.0 Hz), 7.29−7.35 (m, 7H), 6.66 (d, 1H, *J* = 15.9 Hz), 6.23 (dd, 1H, *J* = 15.9, 7.2 Hz), 4.83 (d, 1H, *J* = 5.9 Hz), 4.40−4.42 (m, 1H), 2.62 (d, 2H, *J* = 6.1 Hz), 2.41 (s, 3H), 1.40 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.1, 142.3, 141.3, 136.3, 132.5, 129.5, 128.7, 128.5, 127.8, 126.5, 125.4, 81.4, 53.5, 41.9, 28.0, 21.3; IR ($CHCl_3$) 3191, 2971, 2924, 1727, 1366, 1156, 1093, 1087, 1056, 962, 809, 694 cm$^{-1}$; $[\alpha]_D^{23}$ +96.2 (*c* 0.980, $CHCl_3$); HRMS(ESI) calcd for $C_{22}H_{27}NO_3SNa$ $[M+Na]^+$ 408.1604, found 408.1594.

***tert*-Butyl**

**(*R*)-5-(*p*-methoxyphenyl)-3-{(*S*)-*p*-toluenesulfinylamino}-4-pentenoate (1g):** Yield: 84 % (34.9 mg, 0.084 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 8.0 Hz), 7.26−7.34 (m, 4H), 6.85 (d, 2H, *J* = 8.5 Hz), 6.61 (d, 1H, *J* = 15.9 Hz), 6.08 (dd, 1H, *J* = 15.9, 7.3 Hz), 4.81 (d, 1H, *J* = 5.6 Hz), 4.38−4.40 (m, 1H), 3.80 (s, 3H), 2.60 (d, 2H, *J* = 6.1 Hz), 2.41 (s, 3H), 1.40 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.1, 159.4, 142.3, 141.2, 132.1, 129.5, 129.1, 127.7, 126.4, 125.4, 113.9, 81.3, 55.2, 53.6, 42.1, 28.0, 21.3, 21.2; IR ($CHCl_3$) 3202, 2971, 2929, 1724, 1607, 1510, 1366, 1297, 1250, 1152, 1034, 814, 625 cm$^{-1}$; $[\alpha]_D^{23}$ +103 (*c* 1.45, $CHCl_3$); HRMS(ESI) calcd for $C_{23}H_{29}NO_4SNa$ $[M+Na]^+$ 438.1710, found 438.1701.

***tert*-Butyl (*R*)-5-(*p*-chlorophenyl)-3-{(*S*)-*p*-toluenesulfinylamino}-4-pentenoate (1h):** Yield: 71 % (29.8 mg, 0.071 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 8.0 Hz), 7.29−7.31 (m, 6H), 6.60 (d, 1H, *J* = 15.9 Hz), 6.22 (dd, 1H, *J* = 15.9, 7.1 Hz), 4.86 (d, 1H, *J* = 5.9 Hz) 4.35−4.41 (m, 1H), 2.60 (d, 2H, *J* = 5.9 Hz), 2.41 (s, 3H), 1.40 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.0, 142.0, 141.3, 134.7, 133.5, 131.2, 129.54, 129.53, 128.7, 127.7, 125.4, 81.4, 53.3, 41.8, 28.1, 28.0, 21.3; IR ($CHCl_3$) 3190, 2976, 2929, 1725, 1490, 1367, 1152, 1089, 1058, 809 cm$^{-1}$; $[\alpha]_D^{23}$ +100 (*c* 1.67, $CHCl_3$); HRMS(ESI) calcd for $C_{22}H_{26}ClNO_3SNa$ $[M+Na]^+$ 442.1214, found 442.1203.

***tert*-Butyl (*R*)-3-{(*S*)-*p*-toluenesulfinylamino}pentanoate (1i):** Yield: 51 % (15.9 mg, 0.051 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2H, *J* = 8.3 Hz), 7.29 (d, 2H, *J* = 8.3 Hz), 4.61 (d, 1H, *J* = 8.3 Hz), 3.52−3.57 (m, 1H), 2.50 (d, 2H, *J* = 5.6 Hz), 2.41 (s, 3H), 1.64−1.71 (m, 2H), 1.41 (s, 9H) 0.99 (t, 3H, *J* = 7.4 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.9, 142.5, 141.1, 129.4, 125.5, 81.0, 53.9, 41.1, 28.5, 28.0, 21.3, 10.4; IR ($CHCl_3$) 3208, 2973, 2929, 2871, 1726, 1455, 1366, 1250, 1158, 1089, 1057, 811 cm$^{-1}$; $[\alpha]_D^{23}$ +64.7 (*c* 0.700, $CHCl_3$); HRMS(ESI) calcd for $C_{16}H_{25}NO_3SNa$ $[M+Na]^+$ 334.1447, found 334.1438.

***tert*-Butyl (*R*)-4-methyl-3-{(*S*)-*p*-toluenesulfinylamino}pentanoate (1j):** Yield: 55 % (17.9 mg, 0.055 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 2H, *J* = 8.3 Hz), 7.29 (d, 2H, *J* = 8.3 Hz), 4.57 (d, 1H, *J* = 8.5 Hz), 3.45−3.49 (m, 1H), 2.57 (dd, 2H, *J* = 5.6, 1.5 Hz), 2.40 (s, 3H), 1.94−1.97 (m, 1H), 1.42 (s, 9H) 0.97−0.99 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.1, 142.8, 141.1, 129.4, 125.3, 81.0, 58.6, 39.1, 31.9, 28.0, 21.3, 19.0, 18.6; IR ($CHCl_3$) 3202, 2965, 2929, 1726, 1367, 1156, 1089, 1058, 810 cm$^{-1}$; $[\alpha]_D^{23}$ +68.3 (*c* 1.16, $CHCl_3$); HRMS(ESI) calcd for $C_{17}H_{27}NO_3SNa$ $[M+Na]^+$ 348.1604, found 348.1595.

***tert*-Butyl (*R*)-4,4-dimethyl-3-{(*S*)-*p*-toluenesulfinylamino}pentanoate (1k):** Yield: 85 % (28.9 mg, 0.085 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 8.4 Hz), 7.29 (d, 2H, *J* = 8.4 Hz), 4.63 (d, 1H, *J* = 8.8 Hz), 3.55 (ddd, *J* = 8.8, 5.6, 5.6 Hz, 1H), 2.64 (dd, 1H, *J* = 16.0, 5.6 Hz), 2.52 (dd, 1H, *J* = 16.0, 5.6 Hz), 2.40 (s, 3H), 1.45 (s, 9H) 0.97 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.4, 143.3, 141.0, 129.4, 125.2, 81.1, 62.1, 38.1, 35.7, 27.9, 26.6, 21.3; IR ($CHCl_3$) 3197, 2972, 1731, 1366, 1152, 1090, 1065, 809 cm$^{-1}$; $[\alpha]_D^{24}$ +95.8 (*c* 1.08, $CHCl_3$); HRMS(ESI) calcd for $C_{18}H_{29}NO_3SNa$ $[M+Na]^+$ 362.1760, found 362.1750.

**General Procedure for the synthesis of *tert*-butyl (*R*)-3-[{(*S*)-*N*-alkyl-*N*-*p*-toluenesulfinyl}amino]-5-phenylpentanoate 3 in Flow:** The flow system was established with a syringe pump (HII-10B, Techno applications®), Teflon tube, the flow reactor (Comet X-01-T, Techno applications®). Before use, the flow system was flushed with $Et_2O$ and dried under vacuum. A solution of NaHMDS (0.25 M) in $Et_2O$-THF (7:1) was loaded into a teflon sample tube, and a solution of *tert*-butyl acetate (0.3 M) in $Et_2O$ was loaded into another teflon sample tube. Both two sample solutions were pumped at a flow rate of 1 mL/min, and mixed in the reactor (Comet X-01-T) at room temperature. The output of the reactor was connected with another reactor (Comet X-01-T) to mix with a solution of imine **2a** in $Et_2O$ (0.05 M, 2 mL/min) at −78 °C. The output of the reactor was connected with another reactor (T-shaped mixer) to react with an alkylating reagent (0.5 M solution in DMPU-$Et_2O$ (1:1)). The resulting mixture was collected for 60 s and quenched with saturated aqueous $NH_4Cl$, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, and dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (20% ethyl acetate in hexane) to give *N*-alkylated product **3**.

***tert*-Butyl (*R*)-{*N*-benzyl-*N*-(*S*)-*p*-toluenesulfinyl}amino-3-phenylpropanoate (3a):** Yield: 53% (23.8 mg, 0.053 mmol), yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, 2H, *J* = 8.3 Hz), 7.20−7.41 (m, 10H), 6.96 (d, 2H, *J* = 7.6 Hz), 4.71 (t, 1H, *J* = 7.8 Hz) 4.05 (d, 1H, *J* = 15.1 Hz), 3.62 (d, 1H, *J* = 15.1 Hz), 3.15 (dd, 1H, *J* = 15.9, 8.5 Hz), 2.85 (dd, 1H, *J* = 15.9, 7.1 Hz), 2.39 (s, 3H), 1.33 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.5, 141.2, 141.0, 138.3, 136.3, 129.5, 129.0, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.5, 127.3, 126.4, 126.1, 80.9, 60.2, 47.2, 41.7, 27.9, 21.3; IR ($CHCl_3$) 3023, 2976, 2924, 1728, 1494, 1455, 1367, 1149, 1090, 1068, 813, 754, 698 cm$^{-1}$; $[\alpha]_D^{23}$ +10.7 (*c* 1.31, MeOH); HRMS(ESI) calcd for $C_{27}H_{31}NO_3SNa$ $[M+Na]^+$ 472.1917, found 472.1909.

***tert*-Butyl (*R*)-{*N*-methyl-*N*-(*S*)-*p*-toluenesulfinyl}amino-3-phenylpropanoate (3b):** Yield: 72% (26.9 mg, 0.072 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46−7.51 (m, 4H), 7.38 (m, 2H), 7.27−7.31 (m, 3H), 5.02 (dd, 1H, *J* = 7.7, 7.7 Hz), 3.17 (dd, 1H, *J* = 15.9, 7.7 Hz), 2.99 (dd, 1H, *J* = 15.9, 7.7 Hz), 2.39 (s, 3H), 2.25 (s, 3H), 1.37 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.7, 140.9, 140.7, 139.0, 129.5, 128.5, 127.9, 127.7, 126.2, 81.1, 63.6, 39.8, 28.0, 27.9, 21.2; IR ($CHCl_3$) 2976, 2929, 1728, 1455, 1367, 1261, 1151, 1089, 1067, 813, 700 cm$^{-1}$; $[\alpha]_D^{22}$ +46.4 (*c* 0.610, $CHCl_3$); HRMS(ESI) calcd for $C_{21}H_{27}NO_3SNa$ $[M+Na]^+$ 396.1604, found 396.1596.

***tert*-Butyl (*R*)-{*N*-ethyl-*N*-(*S*)-*p*-toluenesulfinyl}amino-3-phenylpropanoate (3c):** Yield: 28% (10.9 mg, 0.028 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2H, *J* = 8.0 Hz), 7.52 (d, 2H, *J* = 8.0 Hz), 7.37 (m, 2H), 7.27−7.30 (m, 3H), 4.93 (t, 1H, *J* = 7.7 Hz), 3.15 (m, 1H), 2.93−2.98 (m, 2H), 2.60 (m, 1H), 2.40 (s, 3H), 1.38 (s, 9H), 0.81 (t, 3H, *J* = 7.2 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.8, 141.0, 140.8, 139.1, 129.3, 128.6, 127.9, 127.8, 126.5, 126.2, 81.0, 60.0, 41.8, 41.4, 38.1, 27.9, 21.3, 14.4, 13.8; IR($CHCl_3$) 2975, 2929, 1728, 1455, 1367, 1148, 1087, 1066, 809, 700 cm$^{-1}$; $[\alpha]_D^{19}$ +48.5 (*c* 0.910, $CHCl_3$); HRMS(ESI) calcd for $C_{22}H_{29}NO_3SNa$ $[M+Na]^+$ 470.1760, found 470.1753.

***tert*-Butyl (*R*)-{*N*-allyl-*N*-(*S*)-*p*-toluenesulfinyl}amino-3-phenylpropanoate (3d):** Yield: 65% (25.2 mg, 0.065 mmol), colorless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2H, *J* = 7.8 Hz), 7.50 (d, 2H, *J* = 7.8 Hz), 7.38 (m, 2H), 7.30−7.35 (m, 3H), 5.46 (m, 1H), 4.91−5.02 (m, 3H), 3.51 (dd, 1H, *J* = 15.5, 4.8 Hz), 3.22 (dd, 1H, *J* = 16.2, 9.1 Hz), 3.07 (dd, 1H, *J* = 15.5, 8.3 Hz), 2.92 (dd, 1H, *J* = 16.2, 6.7 Hz), 2.40 (s, 3H), 1.38 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.7, 141.1, 141.0, 138.8, 134.2, 129.4, 128.6,

127.98, 127.96, 126.5, 118.5, 81.0, 60.2, 46.5, 41.5, 27.9, 21.3; IR ($CHCl_3$) 2977, 2924, 1729, 1367, 1149, 1090, 1069, 813, 700 $cm^{-1}$; $[\alpha]_D^{22}$ +22.5 (*c* 0.550, $CHCl_3$); HRMS(ESI) calcd for $C_{23}H_{29}NO_3SNa$ $[M+Na]^+$ 422.1760, found 422.1749.

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