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Brønsted Acid-assisted Intramolecular Aminohydroxylation of *N*-Alkenylsulfonamides under Heavy Metal-free Conditions

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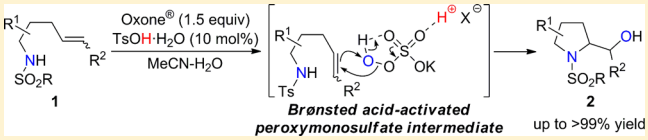
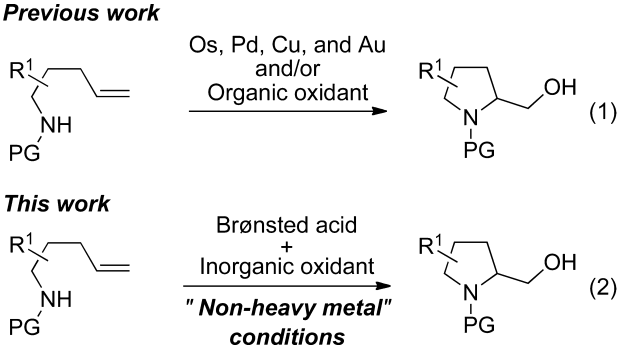
Supporting Information

ABSTRACT: The intramolecular aminohydroxylation of *N*-alkenylsulfonamides proceeded under heavy metal-free conditions to give substituted prolinol derivatives in high yields. Oxone activated by catalytic Brønsted acid worked well as an electrophilic oxidant for this reaction.



The aminooxygenation of olefins is a very important strategy to directly provide 1,2-aminoalcohol derivatives that serve as useful bulding blocks in the synthesis of drugs and natural products.[1,2] In particular, the intramolecular aminooxygenation of *N*-protected alkenes furnishes nitrogen-containing heterocycles that possess a variety of biological activities.[3] Previously, reported methods required the use of heavy metals, such as Os,[4] Pd,[5] Cu,[6] and Au,[7] for the intramolecular aminooxygenation of *N*-protected alkenes (Scheme 1, eq 1). Heavy metal-free reactions of *N*-protected amines with iodine reagents (phenyliodine(III) bis(trifluoroacetate) (PIFA),[8] NIS,[9] iodosylbenzene,[10] and chiral aryliodine(III) diacetate[11]) were developed as sustainable strategies. However, the reactions with *N*-alkenylamides produced a stoichiometric amount of organic waste derived from the organic oxidant. We report here a heavy metal-free intramolecular aminohydroxylation of *N*-alkenylsulfonamides using a Brønsted acid-assisted inorganic oxidant, which is the simplest aminooxygenation method and produces no stoichiometric amount of organic waste (Scheme 1, eq 2).

Scheme 1. Intramolecular Aminohydroxylation of *N*-Protected Alkenes



Initially, we optimized the reaction conditions for the intramolecular aminohydroxylation of *N*-alkenylsulfonamides (Table 1). When **1a** was treated with Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) in a mixture of MeCN and H_2O (1:1) at room temperature, **2a** was obtained in 74% yield (entry 1). The addition of $TsOH \cdot H_2O$ as Brønsted acid to activate the cyclization increased the yield of **2a** (entry 2). The use of other Brønsted acids, such as $PhCO_2H$, $(PhO)_2P(O)OH$, and $(CF_3SO_2)_2NH$, decreased the yield of **2a** (entries 3–5). The use of $MeNO_2$, AcOEt, and CH_2Cl_2 instead of MeCN as organic solvent was not effective as a organic solvent for the intramolecular aminohydroxylation (entries 6–8). Under basic conditions, the reaction with K_2CO_3 (1.5 equiv) became less effective, and increasing the amount of K_2CO_3 to 3.0 equiv had no effect whatsoever on the transformation of **1a** into **2a** (entry 9). Raising the temperature of the reaction to 50 °C furnished **2a** in a quantitative yield (entry 10). The use of other oxidants and changing the ratio of MeCN to H_2O as solvent at 50 °C had negligible effects compared to the use of Oxone in a 1:1 mixture of MeCN and H_2O (entries 11–16). Interestingly, the reaction in H_2O produced a cyclization product in 81% yield (entry 13).

Then, we investigated the scope of the heavy metal-free intramolecular aminohydroxylation of *N*-alkenylsulfonamides **1** under the optimized reaction conditions (Table 2). The reaction of *N*-alkenylsulfonamides bearing other sulfonyl groups, such as 4-fluorobenzenesulfonyl (**1b**), 4-nitrobenzenesulfonyl (**1c**), *n*-butanesulfonyl (**1d**), and (*S*)-camphorsulfonyl (**1e**), gave corresponding products (**2b**–**2e**) in high yields (78–97%) (entries 1–4). When monoalkyl- and dialkyl-substituted alkenylsulfonamides (**1f**–**1j**) were treated with Oxone (1.5 or 2.0 equiv), cyclization products (**2f**–**2j**) were obtained in excellent yields (91–98%) (entries 5–9). The reaction of *N*-sulfonyl-2-allylcyclohexylamines (**1k** and **1l**) and *N*-sulfonyl-2-allylaniline (**1m**) with Oxone (2.0 equiv) in a 2:1 mixture of MeCN and H_2O also provided hexahydroindoline derivatives (**2k** and **2l**) and the indoline derivatives (**2m**) in high yields (78–90%), respectively (entries 10–12). π-Electron-rich disubstituted internal alkenes (**1n** and **1o**) and disubstituted terminal alkene (**1p**) were efficiently converted into prolinol derivatives bearing a secondary alcohol group (**2n** and **2o**) and a quaternary carbon center (**2p**), respectively, in high yields (78–91%) (entries 13–15). Moreover, *N*-alkenylsulfonamide bearing a

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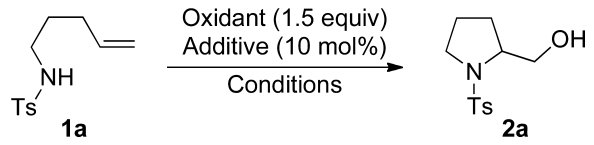
Table 1. Screening of Optimal Conditions for Intramolecular Aminohydroxylation of 1a



entry	oxidant	additive	conditions	time (h)	yield of **2a** (%)
1	Oxone		MeCN:H_2O (1:1), rt	24	74
2	Oxone	TsOH·H_2O	MeCN:H_2O (1:1), rt	24	84
3	Oxone	$PhCO_2H$	MeCN:H_2O (1:1), rt	24	59
4	Oxone	$(PhO)_2P(O)OH$	MeCN:H_2O (1:1), rt	24	68
5	Oxone	$(CF_3SO_2)_2NH$	MeCN:H_2O (1:1), rt	24	66
6	Oxone	TsOH·H_2O	$MeNO_2$:H_2O (1:1), rt	24	6
7	Oxone	TsOH·H_2O	AcOEt:H_2O (1:1), rt	24	14
8	Oxone	TsOH·H_2O	CH_2Cl_2:H_2O (1:1), rt	24	5
9	Oxone	K_2CO_3	MeCN:H_2O (1:1), rt	24	44[a] (0)[b]
10	Oxone	TsOH·H_2O	MeCN:H_2O (1:1), 50 °C	10	>99
11	Oxone	TsOH·H_2O	MeCN:H_2O (2:1), 50 °C	10	92
12	Oxone	TsOH·H_2O	MeCN:H_2O (1:2), 50 °C	10	91
13	Oxone	TsOH·H_2O	H_2O, 50 °C	20	81
14	H_2O_2	TsOH·H_2O	MeCN:H_2O (1:1), 50 °C	20	0
15	TBHP	TsOH·H_2O	MeCN:H_2O (1:1), 50 °C	20	0
16	*t*-BuOCl	TsOH·H_2O	MeCN:H_2O (1:1), 50 °C	10	84

[a]Number indicates the yield when the reaction was carried out with K_2CO_3 (1.5 equiv) and obtained 56% recovery of **1a**. [b]Number in parentheses indicates the yield when the reaction was carried out with K_2CO_3 (3.0 equiv) and obtained >99% recovery of **1a**.

hydroxy group (**1q**) also provided 4-hydroxyprolinol derivative (**2q**) in 91% yield (entry 16). Unfortunately, the reaction of diastereotopic *N*-alkenyl sulfonamides gave moderate to low diastereoselectivities (dr = 77:23−54:46).

The proposed reaction mechanism for the Brønsted acid catalyzed intramolecular aminohydroxylation of *N*-alkenylsulfonamides is depicted in Scheme 2.

The catalytic Brønsted acid (TsOH or KSO_4H) activates Oxone as an electrophilic oxidant to form activated peroxymonosulfate intermediate (**A**)[12] in situ. Intermediate (**A**) promotes the intramolecular aminohydroxylation of *N*-alkenylsulfonamides, particularly electron-poor monosubstituted olefins. This reaction proceeds through a tandem reaction via the epoxidation of olefins, followed by the *exo*-selective intramolecular amination of epoxides.[12,13]

Once prolinol derivatives **2** are formed, they are readily transformed into *N*-sulfonyl proline derivatives **3** by the treatment with (diacetoxyiodo)benzene (DIB) (2.2 equiv) and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) (10 mol %) in a 1:1 mixture of MeCN and H_2O at room temperature (Scheme 3).[14] The reactions of **2a**, **2g**, **2i**, **2j**, and **2k** gave corresponding products **3a**, **3g**, **3i**, **3j**, and **3k** in high yields (80−>99%), respectively.

Finally, we investigated the possibility of synthesizing of proline ethyl ester **5a** through the cleavage of the sulfonyl groups of *N*-sulfonylproline **3a** under mild conditions (Scheme 4). **3a** was treated with EtI and K_2CO_3 to obtain *N*-tosyl-protected proline ethyl ester **4a** in a quantitative yield. Removal of the tosyl group in **4a** with phenol in aqueous HBr solution and AcOH[15] provided desired proline ethyl ester **5a** as a hydrobromide salt in 94% yield.

In conclusion, we have developed an intramolecular aminohydroxylation of *N*-alkenylsulfonamides (**1**) that proceeds under heavy metal-free conditions. This reaction, which was promoted by a Brønsted acid catalyst, activated a peroxymonosulfate complex to obtain *N*-sulfonyl prolinol derivatives (**2**). Moreover, **2** were transformed into *N*-sulfonyl proline derivatives (**3**) by oxidation using a DIB/TEMPO system and **3** was, in turn, converted into proline ethyl ester (**5a**) by desulfonylation under mild conditions.

EXPERIMENTAL SECTION

General Procedure. ^{1}H NMR spectra were measured on a 400 MHz spectrometer. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on a 100 MHz spectrometer. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). High-resolution mass spectra (HRMS) were performed by orbitrap mass spectrometers. Characteristic peaks in the Infrared (IR) spectra are recorded in wave numbers, cm^{-1}. Melting points are reported as uncorrected. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plate (60F-254). The products were purified by column chromatography on silica gel 60 (63−200 mesh). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. *N*-Alkenyl sulfonamides **1a**−**1e**, **1h**−**1j**, and **1n**−**1p**,[16a] **1f** and **1g**,[16b] **1k** and **1l**,[16c,d] **1m**,[16e] and **1q**[4g] were prepared according to the literature procedure. Spectroscopic data of **2a**,[6b] **2h**,[17a] **2i**,[6b] **2m**,[6b] **2q**,[4g] **3a**,[17b] and **4a**[17c] were in accord with those reported in the literature.

*4-Fluoro-N-(pent-4-en-1-yl)benzenesulfonamide (**1b**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (quin, J = 7.1 Hz, 2H), 2.05 (q, J = 6.8 Hz, 2H), 2.96 (q, J = 7.1 Hz, 2H), 4.91 (brs, 1H), 4.92−5.00 (m, 2H), 5.70 (ddt, J = 17.2, 10.5, 6.8 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 7.90 (dd, J = 8.8, 5.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 30.5, 42.6, 115.6, 116.3 (d, J_{C-F} = 23.0 Hz) (2C), 129.7 (d, J_{C-F} = 8.6 Hz) (2C), 136.0 (d, J_{C-F} = 3.8 Hz), 137.0, 165.0 (d, J_{C-F} = 254.8 Hz). IR (neat) 3286, 2938, 1422, 1328, 1237, 1155 cm^{-1}. MS (ESI) calcd for $C_{11}H_{15}FNO_2S$ $[M + H]^+$ 244.0802, found 244.0801.

*N-(Pent-4-en-1-yl)butane-1-sulfonamide (**1d**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H), 1.46 (sext, J = 7.4 Hz, 2H), 1.67 (quin, J = 7.2 Hz, 2H), 1.73−1.82 (m, 2H), 2.13 (q, J = 7.1 Hz, 2H), 2.97−3.04 (m, 2H), 3.12 (q, J = 7.2 Hz, 2H), 4.39−4.49 (brm, 1H), 4.99−5.09 (m, 2H), 5.79 (ddt, J = 17.2, 10.3, 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ13.6, 21.5, 25.6, 29.4, 30.7, 42.6, 52.3, 115.6, 137.2. IR (neat) 3289, 2962, 1432, 1322, 1144, 1082 cm^{-1}. MS (ESI) calcd for $C_9H_{20}NO_2S$ $[M + H]^+$ 206.1209, found 206.1212.

*(1S)-10-Camphor-N-(pent-4-en-1-yl)sulfonamide (**1e**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.03 (s, 3H), 1.42−1.50 (m, 1H), 1.71 (quin, J = 7.3 Hz, 2H), 1.91−2.09 (m, 3H), 2.10−2.27 (m, 4H), 2.36−2.43 (m, 1H), 2.91 (d, J = 15.2 Hz, 1H), 3.10−3.24 (m, 2H), 3.39 (d, J = 15.2 Hz, 1H), 4.97−5.10 (m, 2H), 5.13−5.20 (brm, 1H), 5.80 (ddt, J = 17.2, 10.5, 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 19.9, 26.6, 27.0, 29.2, 30.7, 42.8, 42.9, 43.1, 48.8, 49.3, 59.2, 115.4, 137.4, 217.0. IR (neat) 3295, 2959, 1742, 1329, 1146, 1069 cm^{-1}. MS (ESI) calcd for $C_{15}H_{26}NO_3S$ $[M + H]^+$ 300.1628, found 300.1624.

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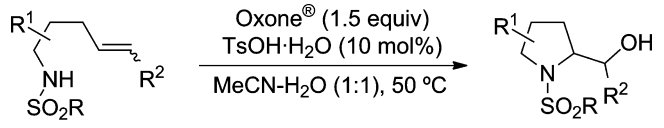
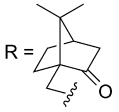
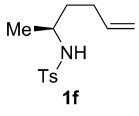
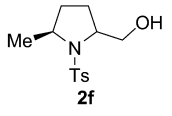
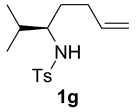
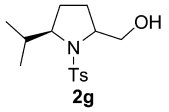
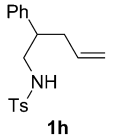
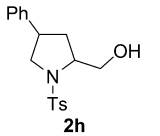
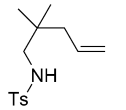
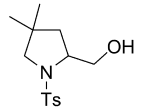
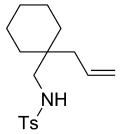
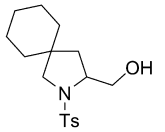
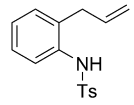
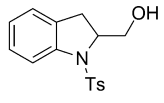
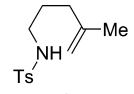
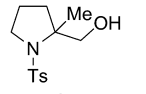
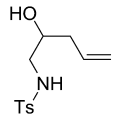
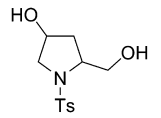
Table 2. Intramolecular Aminohydroxylation of *N*-Alkenylsulfonamides

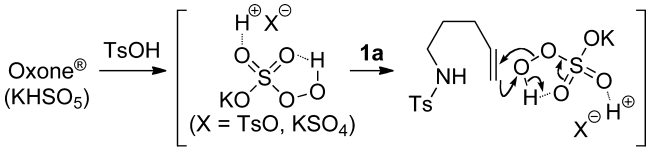


1 **2**

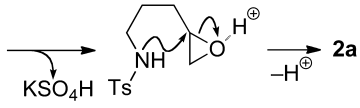
entry	substrate	product	time (h)	yield (%)
1	R = 4-F-C_6H_4 (**1b**)	**2b**	13	90
2	R = 4-NO_2-C_6H_4 (**1c**)	**2c**	10	78
3[a]	R = Bu (**1d**)	**2d**	72	97
4	R =  **1e**	**2e**	24	91 (dr = 55:45)
5	 **1f**	 **2f**	22	94 (dr = 50:50)
6[b]	 **1g**	 **2g**	78	91 (dr = 52:48)
7	 **1h**	 **2h**	72	93 (dr = 54:46)
8[b]	 **1i**	 **2i**	74	96
9[b]	 **1j**	 **2j**	72	98
10[c]	*cis*-**1k**	**2k**	75	90 (dr = 54:46)
11[c]	*trans*-**1l**	**2l**	58	78 (dr = 66:34)
12[c]	 **1m**	 **2m**	74	88
13[d]	(*Z*)- **1n**	**2n**	56	91 (dr = >99:<1)
14[d]	(*E*)- **1o**	**2o**	72	82 (dr = 77:23)
15[d]	 **1p**	 **2p**	71	78
16[a]	 **1q**	 **2q**	99	91 (dr = 51:49)

[a]Reaction was carried out at room temperature. [b]Oxone (2.0 equiv) was used. [c]Oxone (2.0 equiv) was used in a 2:1 mixture of MeCN and H_2O. [d]Reaction was carried out without TsOH·H_2O at 0 °C.

Scheme 2. Plausible Reaction Mechanism for Intramolecular Aminohydroxylation of *N*-Alkenylsulfonamides



***Brønsted acid–activated peroxymonosulfate intermediate* (A)**



General Procedure for the Intramolecular Aminohydroxylation of *N*-Alkenyl Sulfonamides (1) (Table 1, entry 10 and Table 2). To a solution of **1a** (59.8 mg, 0.25 mmol) and Oxone (230.5 mg, 0.375 mmol) in a 1:1 mixture (1.5 mL) of MeCN and H_2O was added TsOH·H_2O (4.8 mg, 0.025 mmol). The solution was stirred at 50 °C for 10 h. Saturated $NaHCO_3$ aqueous solution (10 mL) was added to the reaction mixture, and the product was extracted with AcOEt (15 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was purified by silicagel column chromatography (eluent: hexane/AcOEt = 2/1) to give desired product **2a** (63.8 mg, >99% yield) as a colorless oil.

(±)-(1-((4-Fluorophenyl)sulfonyl)pyrrolidin-2-yl)methanol (**2b**). White solid (58.3 mg, 90% yield) mp 69–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45–1.54 (m, 1H), 1.65–1.77 (m, 2H), 1.77–1.89 (m, 1H), 2.68 (brs, 1H), 3.24 (dt, J = 10.4, 7.1 Hz, 1H), 3.48 (dt, J = 10.4, 6.2 Hz, 1H), 3.59–3.66 (m, 1H), 3.66–3.76 (m, 2H), 7.19–7.28 (m, 2H), 7.85–7.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.9, 50.0, 61.9, 65.7, 116.5 (d, J_{C-F} = 23.0 Hz) (2C), 130.2 (d, J_{C-F} = 9.6 Hz) (2C), 133.0 (d, J_{C-F} = 3.8 Hz), 165.3 (d, J_{C-F} = 256.8 Hz). IR (KBr) 3534, 1493, 1332, 1237, 1155, 1093, 1042 cm^{-1}. MS (ESI) calcd for $C_{11}H_{14}FNNaO_3S$ $[M + Na]^+$ 282.0571, found 282.0567.

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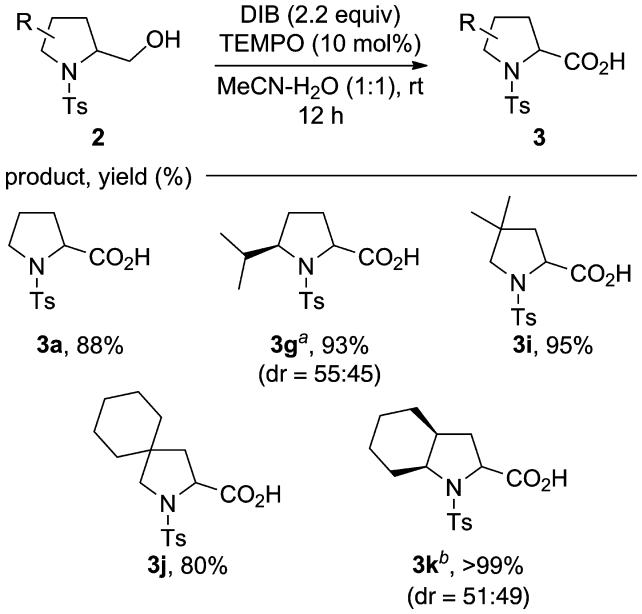
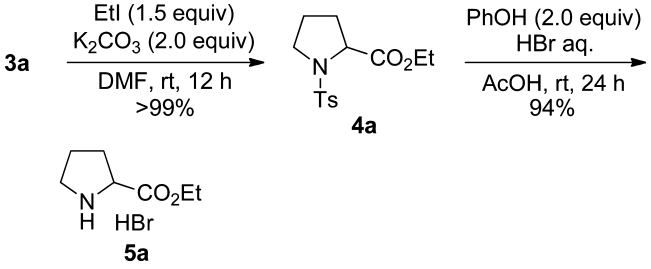
Scheme 3. Oxidative Transformation of 2 into 3



[a] **2g** (dr = 52:48) was used. [b] **2k** (dr = 54:46) was used.

Scheme 4. Synthesis of Proline Ethyl Ester 5a by Desulfonylation of *N*-Sulfonamide 4a



*(±)-(1-((4-Nitrophenyl)sulfonyl)pyrrolidin-2-yl)methanol (**2c**).* Yellow solid (55.8 mg, 78% yield) mp 93–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–1.60 (m, 1H), 1.67–1.77 (m, 1H), 1.77–1.96 (m, 2H), 2.51 (brs, 1H), 3.27 (dt, J = 10.6, 7.1 Hz, 1H), 3.53 (dt, J = 10.6, 6.3 Hz, 1H), 3.64–3.78 (m, 3H), 8.06 (d, J = 8.9 Hz, 2H), 8.40 (d, J = 8.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 28.8, 50.0, 62.1, 65.5, 124.4 (2C), 128.7 (2C), 142.9, 150.2. IR (neat) 3567, 1532, 1349, 1163, 1095 cm^{-1}. MS (ESI) calcd for $C_{11}H_{15}N_2O_5S$ $[M + H]^+$ 287.0696, found 287.0694.

*(±)-(1-(Butylsulfonyl)pyrrolidin-2-yl)methanol (**2d**).* Colorless oil (53.7 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.6 Hz, 3H), 1.47 (sext, J = 7.6 Hz, 2H), 1.78–1.92 (m, 4H), 1.92–2.00 (m, 1H), 2.01–2.12 (m, 1H), 2.67 (brs, 1H), 2.99 (dd, J = 9.0, 7.1 Hz, 2H), 3.35–3.49 (m, 2H), 3.55–3.69 (m, 2H), 3.82–3.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 21.7, 24.8, 25.1, 29.1, 48.9, 49.5, 61.5, 65.8. IR (neat) 3504, 1327, 1144, 1050 cm^{-1}. MS (ESI) calcd for $C_9H_{20}NO_3S$ $[M + H]^+$ 222.1158, found 222.1161.

*(1-(1S)-10-Camphorsulfonyl)pyrrolidin-2-yl)methanol (**2e**, Diastereomer Mixtures).* Colorless oil (71.7 mg, 91% yield, dr = 55:45). Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.14 (s, 3H), 1.38–1.49 (m, 1H), 1.61–1.72 (m, 1H), 1.81–2.16 (m, 7H), 2.34–2.44 (m, 1H), 2.47–2.59 (m, 1H), 2.81 (brs, 1H), 2.83 (d, J = 14.6 Hz, 1H), 3.42 (d, J = 14.6 Hz, 1H), 3.45–3.56 (m, 2H), 3.57–3.76 (m, 2H), 3.82–3.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.1, 24.8, 25.4, 27.0, 29.3, 42.7, 42.9, 44.6, 48.2, 49.9, 58.5, 61.9, 65.8, 215.7. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.13 (s, 3H), 1.38–1.49 (m, 1H), 1.61–1.72 (m, 1H), 1.81–2.16 (m, 7H), 2.34–2.44 (m, 1H), 2.47–2.59 (m, 1H), 2.91 (d, J = 14.6 Hz, 1H), 2.92 (brs, 1H), 3.36 (d, J = 14.6 Hz, 1H), 3.39–3.45 (m, 1H), 3.45–3.56 (m, 1H), 3.57–3.76 (m, 2H), 3.90–3.98 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.1, 25.0, 25.4, 27.0, 29.0, 42.7, 42.9, 45.8, 48.0, 49.6, 58.4, 62.1, 65.6, 216.0. IR (neat) 3502, 1743, 1146, 1050 cm^{-1}. MS (ESI) calcd for $C_{15}H_{26}NO_4S$ $[M + H]^+$ 316.1577, found 316.1572.

*((5S)-5-Methyl-1-tosylpyrrolidin-2-yl)methanol (**2f**, Diastereomer Mixtures).* Colorless oil (63.2 mg, 94% yield, dr = 50:50). Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.6 Hz, 3H), 1.56–1.66 (m, 1H), 1.79–1.89 (m, 1H), 2.02–2.19 (m, 2H), 2.43 (s, 3H), 2.60 (brs, 1H), 3.58–3.78 (m, 3H), 4.16–4.25 (m, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 21.5, 27.9 31.8, 57.8, 61.3, 65.5, 127.1 (2C), 129.6 (2C), 138.4, 143.2. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (d, J = 6.4 Hz, 3H), 1.43–1.54 (m, 2H), 1.55–1.78 (m, 2H), 2.44 (s, 3H), 2.87 (brs, 1H), 3.58–3.67 (m, 2H), 3.67–3.85 (m, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.2, 27.2, 31.7, 58.3, 63.3, 66.1, 127.6 (2C), 129.8 (2C), 134.3, 143.7. IR (neat) 3512, 1332, 1156, 1095, 1049 cm^{-1}. MS (ESI) calcd for $C_{13}H_{20}NO_3S$ $[M + Na]^+$ 270.1158, found 270.1155.

*((5R)-5-Isopropyl-1-tosylpyrrolidin-2-yl)methanol (**2g**).* The diastereomers were separeted by column chromatography. White solid (67.6 mg, 91% yield, dr = 52:48). Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 7.9 Hz, 3H), 1.02 (d, J = 7.9 Hz, 3H), 1.16–1.27 (m, 1H), 1.50–1.69 (m, 3H), 1.92–2.02 (m, 1H), 2.44 (s, 3H), 3.00 (brs, 1H), 3.49 (td, J = 7.6, 3.9 Hz, 1H), 3.58–3.68 (m, 3H), 7.33 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 20.1, 21.5, 25.7, 27.1, 31.4, 63.0, 66.0, 68.4, 127.7 (2C), 129.7 (2C), 134.3, 143.7. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.49 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H), 1.68–1.76 (m, 1H), 1.77–2.02 (m, 3H), 2.42 (s, 3H), 2.36–2.46 (m, 1H), 2.61–2.68 (m, 1H), 3.76–3.85 (m, 3H), 3.94–4.00 (m, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 19.8, 21.5, 23.8, 29.6, 29.8, 63.0, 65.3, 66.5, 126.8 (2C), 129.5 (2C), 138.5, 143.0. IR (KBr) 3520, 1469, 1328, 1155, 1045 cm^{-1}. MS (ESI) calcd for $C_{15}H_{24}NO_3S$ $[M + H]^+$ 298.1471, found 298.1472.

*(±)-(2-Tosyl-2-azaspiro[4.5]decan-3-yl)methanol (**2j**).* Colorless oil (79.2 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.51–0.59 (m, 1H), 0.66–0.76 (m, 1H), 1.05–1.47 (m, 8H), 1.51 (dd, J = 12.9, 9.7 Hz, 1H), 1.73 (dd, J = 12.9, 7.5 Hz, 1H), 2.44 (s, 3H), 3.16 (d, J = 11.2 Hz, 1H), 3.29 (dd, J = 8.3, 5.1 Hz, 1H), 3.33 (d, J = 11.2 Hz, 1H), 3.51–3.59 (m, 1H), 3.66–3.74 (m, 1H), 3.74–3.83 (m, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.7, 23.7, 25.7, 33.8, 36.2, 40.7, 41.5, 59.6, 61.5, 66.0, 127.5 (2C), 129.7 (2C), 134.0, 143.8. IR (neat) 3500, 1450, 1336, 1157, 1092, 1036 cm^{-1}. MS (ESI) calcd for $C_{17}H_{26}NO_3S$ $[M + Na]^+$ 324.1628, found 324.1624.

*(±)-(cis-1-Tosyloctahydro-1H-indol-2-yl)methanol (**2k**, Diastereomer Mixtures).* Colorless oil (69.6 mg, 90% yield, dr = 54:46). Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99–1.02 (m, 1H), 1.02–1.30 (m, 2H), 1.31–1.75 (m, 5H), 1.85–1.88 (m, 1H), 2.21–2.24 (m, 2H), 2.43 (s, 3H), 2.64 (t, J = 6.8 Hz, 1H), 3.62–3.73 (m, 1H), 3.73–3.86 (m, 2H), 3.96 (dt, J = 11.0, 5.8 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 21.5, 23.6, 25.8, 27.5, 30.8, 35.6, 59.7, 62.1, 66.6, 127.3 (2C), 129.6 (2C), 137.9, 143.2. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02–1.30 (m, 3H), 1.31–1.75 (m, 7H), 1.92–2.03 (m, 1H), 2.44 (s, 3H), 3.17 (dd, J = 8.2, 4.8 Hz, 1H), 3.52–3.61 (m, 1H), 3.62–3.73 (m, 2H), 3.73–3.86 (m, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 21.5, 24.3, 25.6, 30.9, 31.8, 36.0, 61.7, 62.6, 66.3, 127.4 (2C), 129.8 (2C), 134.6, 143.6. IR (neat) 3502, 1335, 1157, 1095, 1049 cm^{-1}. MS (ESI) calcd for $C_{16}H_{24}NO_3S$ $[M + H]^+$ 310.1471, found 310.1465.

*(±)-(trans-1-Tosyloctahydro-1H-indol-2-yl)methanol (**2l**, Diastereomer Mixtures).* Colorless oil (60.3 mg, 78% yield, dr = 66:34). Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84–1.47 (m, 6H), 1.57–1.74 (m, 3H), 1.75–1.88 (m, 2H), 2.35 (td, J = 10.5, 3.4 Hz, 1H), 2.45 (s, 3H), 2.49–2.59 (m, 1H), 3.61–3.77 (m, 3H), 7.35 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 24.6, 25.2, 29.8, 32.6, 33.1, 43.8, 62.1, 66.9, 67.4, 128.0 (2C), 129.7 (2C), 133.0, 143.7. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84–1.47 (m, 6H), 1.57–1.74 (m, 3H), 1.75–1.88 (m, 2H), 2.05–2.15

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(m, 1H), 2.43 (s, 3H), 2.84 (ddd, J = 11.6, 10.5, 3.4 Hz, 1H), 3.04 (brs, 1H), 3.77−3.85 (m, 1H), 4.00−4.08 (m, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 25.06, 25.07, 29.5, 29.8, 33.8, 44.7, 62.9, 66.0, 66.6, 127.0 (2C), 129.7 (2C), 139.1, 143.1. IR (neat) 3505, 1340, 1157, 1095, 1045 cm^{-1}. MS (ESI) calcd for $C_{16}H_{24}NO_3S$ $[M + H]^+$ 310.1471, found 310.1468.

*(±)-syn-1-(1-Tosylpyrrolidin-2-yl)ethanol (**2n**).* White solid (61.2 mg, 91% yield, dr = >99:<1) mp 73−74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, J = 6.2 Hz, 3H), 1.28−1.39 (m, 1H), 1.51−1.63 (m, 2H), 1.66−1.77 (m, 1H), 2.44 (s, 3H), 3.32−3.45 (m, 3H), 3.45−3.53 (m, 1H), 3.67−3.76 (m, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 21.5, 24.5, 28.4, 49.8, 66.4, 69.7, 127.6 (2C), 129.8 (2C), 134.2, 143.9. IR (KBr) 3523, 1327, 1153, 1105, 1079 cm^{-1}. MS (ESI) calcd for $C_{13}H_{20}NO_3S$ $[M + H]^+$ 270.1158, found 270.1158.

*(±)-anti-1-(1-Tosylpyrrolidin-2-yl)ethanol (**2o**).* Colorless oil (55.2 mg, 82% yield, dr =77:23). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 6.4 Hz, 3H), 1.24−1.32 (m, 1H), 1.59−1.69 (m, 1H), 1.69−1.89 (m, 2H), 2.44 (s, 3H), 2.62 (brs, 1H), 3.32−3.43 (m, 2H), 3.48−3.54 (m, 1H), 4.15−4.24 (m, 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 21.5, 24.5, 26.0, 50.5, 65.7, 69.0, 127.6 (2C), 129.7 (2C), 133.9, 143.7. IR (KBr) 3506, 1337, 1158, 1092, 999 cm^{-1}. MS (ESI) calcd for $C_{13}H_{19}NNaO_3S$ $[M + Na]^+$ 292.0978, found 292.0973.

*(±)-(2-Methyl-1-tosylpyrrolidin-2-yl)methanol (**2p**).* White solid (52.5 mg, 78% yield) mp 64−65 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.58−1.68 (m, 1H), 1.71−1.93 (m, 2H), 2.14 (dt, J = 12.4, 7.9 Hz, 1H), 2.43 (s, 3H), 2.66 (brs, 1H), 3.33−3.41 (m, 1H), 3.48 (dt, J = 9.4, 7.2 Hz, 1H), 3.59 (dd, J = 11.7, 5.4 Hz, 1H), 3.89 (dd, J = 11.7, 3.8 Hz, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.2, 22.4, 38.1, 50.3, 68.9, 69.1, 127.2 (2C), 129.6 (2C), 137.8, 143.2. IR (KBr) 3527, 1325, 1152, 1094, 1052 cm^{-1}. MS (ESI) calcd for $C_{13}H_{19}NNaO_3S$ $[M + Na]^+$ 292.0978, found 292.0970.

General Procedure for the Transformation of *N*-Sulfonyl Prolinol Derivatives (2) into *N*-Sulfonyl Proline Derivatives (3) by Oxidation with DIB/TEMPO System (Scheme 3). To a solution of **2a** (63.8 mg, 0.25 mmol) and DIB (177.1 mg, 0.55 mmol) in a 1:1 mixture (1.5 mL) of MeCN and H_2O was added TEMPO (3.9 mg, 0.025 mmol), and the solution was stirred at room temperature for 12 h. Saturated $NaHCO_3$ aqueous solution (10 mL) was added to the reaction mixture. The product was basified to pH 10 with 1N NaOH aq., and washed with AcOEt (15 mL × 3). The aqueous layer was acidified to pH 3 with 1N HCl aq., extracted with $CHCl_3$ (15 mL × 3), and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure to give the desired product **3a** (59.2 mg, 88% yield) as a white solid without further purification.

*(5R)-5-Isopropyl-1-tosylpyrrolidine-2-carboxylic acid (**3g**, Diastereomer Mixtures).* White solid (72.3 mg, 93% yield, dr = 55:45). Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J = 6.9 Hz, 3H), 1.00 (d, J = 6.9 Hz, 3H), 1.34−1.45 (m, 1H), 1.71−1.87 (m, 2H), 2.02−2.17 (m, 2H), 2.45 (s, 3H), 3.53 (dd, J = 11.9, 7.1 Hz, 1H), 4.17 (dd, J = 8.3, 6.2 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 9.25 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 20.1, 21.6, 26.0, 28.3, 31.1, 62.0, 68.1, 127.7 (2C), 129.9 (2C), 133.8, 144.3, 175.2. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.51 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H), 1.70−1.84 (m, 1H), 1.96−2.19 (m, 3H), 2.24−2.37 (m, 1H), 2.43 (s, 3H), 3.98−4.04 (m, 1H), 4.51 (d, J = 7.3 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 9.25 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 19.7, 21.5, 23.7, 29.5, 29.8, 62.3, 64.9, 127.0 (2C), 129.4 (2C), 138.1, 143.2, 178.5. IR (KBr) 2965, 1728, 1344, 1159, 1090, 1019 cm^{-1}. MS (ESI) calcd for $C_{15}H_{22}NO_4S$ $[M + H]^+$ 312.1264, found 312.1258.

*(±)-4,4-Dimethyl-1-tosylpyrrolidine-2-carboxylic acid (**3i**).* White solid (70.6 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (s, 3H), 1.09 (s, 3H), 1.91−2.02 (m, 2H), 2.44 (s, 3H), 3.10 (d, J = 10.0 Hz, 1H), 3.21 (t, J = 10.0 Hz, 1H), 4.29 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 10.43 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 25.5, 25.7, 38.8, 44.2, 60.4, 60.7, 127.7 (2C), 129.7 (2C), 134.4, 144.0, 177.2. IR (KBr) 2963, 1729, 1345, 1159, 1093 cm^{-1}. MS (ESI) calcd for $C_{14}H_{20}NO_4S$ $[M + H]^+$ 298.1108, found 298.1104.

*(±)-2-Tosyl-2-azaspiro[4.5]decane-3-carboxylic acid (**3j**).* Colorless oil (75.9 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86−0.95 (m, 1H), 0.95−1.05 (m, 1H), 1.14−1.51 (m, 9H), 1.88−1.97 (m, 1H), 1.97−2.06 (m, 1H), 2.44 (s, 3H), 3.22 (d, J = 10.6 Hz, 1H), 3.25 (d, J = 10.6 Hz, 1H), 4.22 (t, J = 8.2 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.9, 23.5, 25.6, 34.1, 35.3, 42.2, 42.7, 58.1, 59.8, 127.7 (2C), 129.7 (2C), 134.2, 144.0, 176.8. IR (neat) 3545, 1729, 1346, 1156, 1093, 1056 cm^{-1}. MS (ESI) calcd for $C_{17}H_{24}NO_4S$ $[M + H]^+$ 338.1421, found 338.1411.

*(±)-cis-1-Tosyloctahydro-1H-indole-2-carboxylic acid (**3k**, diastereomer mixtures).* White solid (80.8 mg, >99% yield, dr = 51:49). Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01−1.35 (m, 3H), 1.36−1.72 (m, 4H), 1.72−1.82 (m, 1H), 2.03−2.13 (m, 2H), 2.19 (td, J = 12.6, 8.9 Hz, 1H), 2.45 (s, 3H), 2.54−2.65 (m, 1H), 3.66 (dt, J = 11.0, 6.3 Hz, 1H), 4.20 (t, J = 8.9 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.5, 23.4, 25.6, 29.5, 32.4, 37.3, 59.1, 60.5, 127.6 (2C), 129.5 (2C), 137.7, 143.4, 178.3. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01−1.35 (m, 3H), 1.36−1.72 (m, 6H), 1.82−1.92 (m, 1H), 1.94 (dd, J = 13.1, 6.3 Hz, 1H), 2.33 (td, J = 13.1, 9.6 Hz, 1H), 2.43 (s, 3H), 3.75−3.86 (m, 1H), 4.40 (d, J = 9.6 Hz, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 21.5, 23.7, 25.6, 28.5, 32.6, 35.8, 59.7, 60.7, 127.6 (2C), 129.8 (2C), 135.0, 143.9, 177.6. IR (KBr) 2932, 1725, 1340, 1157, 1096 cm^{-1}. MS (ESI) calcd for $C_{16}H_{22}NO_4S$ $[M + H]^+$ 324.1264, found 324.1256.

Transformation of *N*-Tosyl Proline (3a) into Proline Ethyl Ester (5a) by Detosylation under Mild Conditions (Scheme 4). The solution of *N*-tosyl proline (**3a**) (53.8 mg, 0.20 mmol) and K_2CO_3 (55.2 mg, 0.40 mmol) in DMF (1.0 mL) was added EtI (24.1 μL, 0.30 mmol). The solution was stirred at room temperature for 14 h under argon atmosphere. 1N HCl solution (3 mL) was added to the reaction mixture, and the product was extracted with AcOEt (10 mL × 3). The combined extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was purified by silicagel column chromatography (eluent: hexane/AcOEt = 4/1) to give *N*-tosyl proline ethyl ester (**4a**) (59.4 mg, >99% yield) as a white solid.

The solution of *N*-tosyl proline ethyl ester (**4a**) (74.3 mg, 0.25 mmol) and phenol (47.0 mg, 0.50 mmol) and 25% HBr in acetic acid (1 mL) was stirred at room temperature for 24 h under argon atmosphere. This reaction mixture was concentrated under reduced pressure to give proline ethyl ester (**5a**) (52.6 mg, 94%) as a brown oil.

*(±)-Ethyl pyrrolidine-2-carboxylate hydrobromide (**5a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.3 Hz, 3H), 2.02−2.27 (m, 3H), 2.41−2.53 (m, 1H), 3.53−3.69 (m, 2H), 4.32 (q, J = 7.3 Hz, 2H), 4.49−4.60 (m, 1H), 8.52 (brs, 1H), 10.3 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 23.7, 28.8, 46.2, 59.3, 63.3, 168.7. IR (neat) 3427, 1739, 1630, 1241, 1043 cm^{-1}. MS (ESI) calcd for $C_7H_{14}NO_2$ $[M]^+$ 144.1019, found 144.1015.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of compounds in the intramolecular aminohydroxylation, in the oxidation using a DIB/TEMPO system, and in the derivatization in Scheme 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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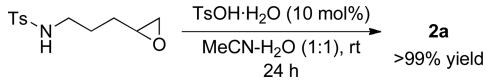

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