Intramolecular Cyclization of Alkenyl Substrates Using Oxidative Umpolung of Alkali Metal Bromides by Inorganic Oxidants

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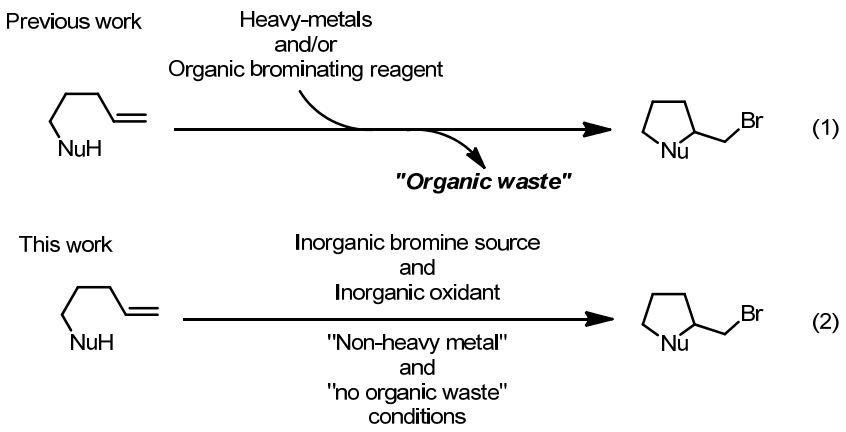
Contents

1. Oxidative Intramolecular Bromo-Amination of *N*-Alkenyl Sulfonamides via Umpolung of Alkali Metal Bromides.

Introduction

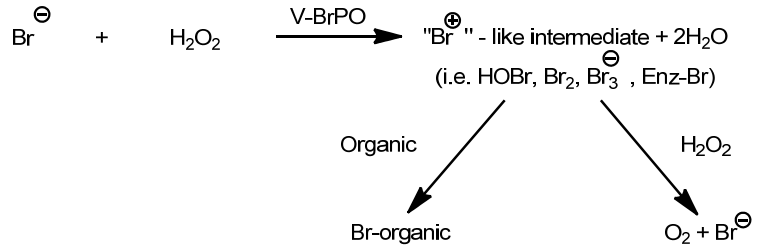
Intramolecular halo-cyclization[1] is an important tool for the synthesis of nitrogen- or oxygene-containing heterocycles, which are useful building blocks of biologically active natural products and pharmacological products.[2] In particular, some bromo compounds have been also noted in the biosynthesis of halogenated marine natural products[3] and medicinal plants.[3a,4] As for the bromo-amination of alkenes by both intermolecular and intramolecular reactions with *N*-protected amines, straightforward methods using transition metal catalysts and stoichiometric amounts of brominating reagents have been developed. However, those methods present a disadvantage in that toxic heavy metals (Os,[5] Mn,[6] V,[6] Cu,[6,7] or Pd[7,8]) are required. On the other hand, such organic brominating reagents as *N*-bromosuccinimide (NBS),[9] 1,3-dibromo-5,5-dimethyl hydantoin (DBDMH),[10] 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO),[11] and bromodiethylsulfonium bromopentachloroantimonate (BDSB)[12] have been used as active bromo sources for chemoselective bromo-cyclization reactions. However, they present a particular problem in that the stoichiometric amount of the corresponding organic waste is increased (Scheme 1, eq. 1). To overcome this problem, it is very important to develop a bromo cyclization using non-organic bromo reagents under heavy-metal-free conditions. Therefore, we focused on the oxidative bromo-cyclization via umpolung of alkali metal bromides, which can oxidize bromide ion (Br^-) (inorganic bromide) to activated bromonium-like species (Br^+) using various kinds of oxidants (Scheme 1, eq. 2).[13]

Scheme 1. Intramolecular Bromocyclization of Alkenes



The oxidative umpolumg reaction of bromide anion is related closely to the biosynthesis of vanadium bromoperoxydase (V-BrPO), which is used to synthesize halogenated organic compounds in seaweeds and marine algae. The V-BrPO catalyze the oxidation of a bromide anions (Br-) by hydrogen peroxide to produce the corresponding bromonium ion intermediate (Br^+ or its equivalent) through two-electron oxidation. Continuously, the oxidized intermediate can halogenate an appropriate organic substrates, or react with another equivalent of hydrogen peroxide to form singlet oxygen (**Scheme 2**). In recent years, these oxidative bromination with vanadium catalyst has been reported.

Scheme 2. A Mechanism of Vanadium Bromoperoxydases (V-BrPO)

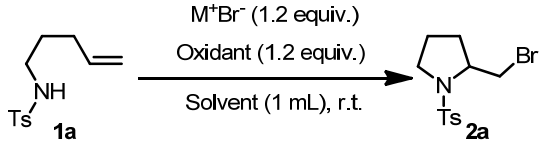


In the past, the *exo*-selective intramolecular bromo-amination was developed. However, the reaction required NBS as the bromo reagent.[14] The author report here an *exo*-selective intramolecular bromo-amination of *N*-alkenyl sulfonamides and *N*-alkenoxyl sulfonamides via umpolung of inorganic bromides.

Results and Discussion.

First, the author screened a series of bromo reagents and oxidants for the intramolecular bromo-amination with **1a** (**Table 1**). The use of Br_2 as bromo reagent for intramolecular bromo-amination was not suitable to give **2a** in moderate yield together with many by-products (entry 1). In contrast, the use of NBS gave **2a** in 90% yield (entry 2). When **1a** was treated with KBr as the bromo reagent with *m*-CPBA or Oxone® as the oxidant in CH_2Cl_2, **2a** was obtained in low yields (entries 3 and 4). Then, solvent effects on the intramolecular bromo-amination using KBr/Oxone® were investigated (entries 5-7). Whereas the treatment of **1a** in THF and AcOEt gave **2a** in 70% and 92% yields, respectively (entries 5 and 6), the reaction in MeCN gave **2a** in >99% yield as the best result (entry 7). Use of other oxidants, such as *m*-CPBA, H_2O_2, $PhI(OAc)_2$, or *t*-BuOCl, in this reaction with **1a** decreased the yield of **2a** (entries 8-11). Furthermore, use of NaBr instead of KBr also decreased the yield of **2a** (entry 12) and the use of KBr alone was totally ineffective for the transformation of **1a** into **2a** (entry 13).

Table 1. Screening of Intramolecular Bromo-amination with *N*-4-Pentenyl Sulfonamide (**1a**)



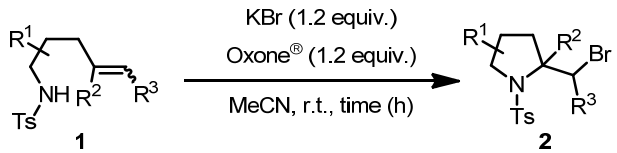
Entry	Br	Oxidant	Solvent	Time (h)	Conv. (%)	Yield[a] (%)
1	Br_2		MeCN	1	>99	57
2	NBS		MeCN	3	>99	90
3	KBr	*m*-CPBA	CH_2Cl_2	2	>99	37
4	KBr	Oxone	THF	20	>99	19
5	KBr	Oxone	AcOEt	8	>99	70
6	KBr	Oxone	MeCN	24	>99	92
7	KBr	Oxone	MeCN	2	>99	>99
8	KBr	*m*-CPBA	MeCN	2	>99	32
9	KBr	H_2O_2	MeCN	64	0	0
10	KBr	$PhI(OAc)_2$	MeCN	12	>99	75
11	KBr	*t*-BuOCl	MeCN	24	>99	82
12	NaBr	Oxone	MeCN	3	>99	60
13	KBr		MeCN	64	0	0

[a] Isolated yield

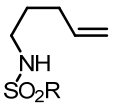
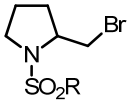
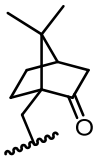
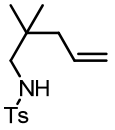
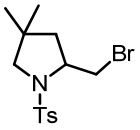
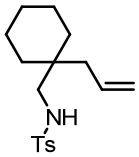
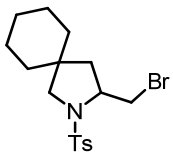
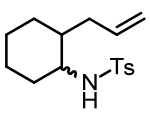
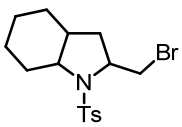
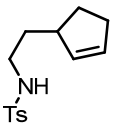
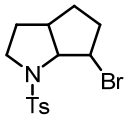
Next, the author investigated the scope of the intramolecular bromo-amination of *N*-alkenyl sulfonamides **1** via the umpolung reaction of KBr under optimized reaction conditions (**Table 2**). The reaction of *N*-alkenyl sulfonamides bearing other sufonyl groups, such as benzenesulfonyl (**1b**), 1-naphthalenesulfonyl (**1c**),

4-fluorobenzenesulfonyl (**1d**), *n*-butanesulfonyl (**1e**), and (1*S*)-camphorsulfonyl (**1f**), also gave the corresponding products in excellent yields (**Table 2**, entries 1-5). A variety of substituted alkenes underwent the intramolecular bromo-amination to give the corresponding aminobromides. When *N*-(2,2-dialkyl)substituted and *N*-(1,2-dialkyl) substituted 4-penten-1-yl sulfonamides **1g**, **1h**, **1i**, and **1j** were used, cyclization products **2g**, **2h**, **2i**, and **2j** were obtained in >99%, 97%, >99%, and 96% yields, respectively (entries 6-9). *N*-Alkenyl sulfonamides with cyclic alkene **1k** and internal alkenes *(E)*-**1l** and *(Z)*-**1m** were efficiently converted into corresponding products **2k**, **2l**, and **2m** in high yields (89–91%) with good diastereoselectivities (dr = 77:23–>99:<1) (entries 10-12). Disubstituted terminal alkene **1n** could be also used and corresponding product **2n** with a quaternary carbon center was obtained in 90% yield (entry 13). Moreover, the same treatment of the chiral *N*-alkenyl sulfonamides (**1o** and **1p**) derived from α-amino acids also provided corresponding products **2o** and **2p** in excellent yields with moderate diastereoselectivities (>99% and 93% yields, dr = 77:23 and 57:43), respectively (entries 14 and 15). Once the optimized conditions were established, other substrates were examined, and the scope of the intramolecular bromo-amination for several *N*-alkenyl sulfonimides is shown in **Table 2** and **Table 3**.

Table 2. *Exo*-selective Intramolecular Bromo-amination of Various *N*-Alkenyl Sulfonamides (**1**).

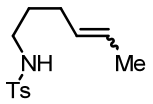
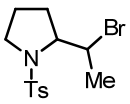
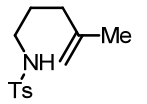
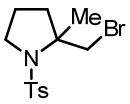
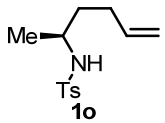
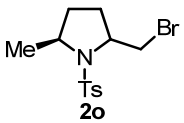
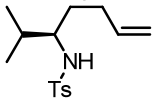
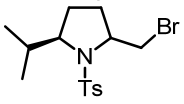


1 **2**

Entry	Substrate	Product	Time (h)	Yield of **2** (%)[a]
				
1[c]	R = Ph (**1b**)	**2b**	2	95
2[d]	R = 1-Naphthyl (**1c**)	**2c**	16	96
3[d]	R = 4-F-C_6H_4 (**1d**)	**2d**	17	93
4[d]	R = *n*-Bu (**1e**)	**2e**	12	>99
5[e]	R =  **1f**	**2f**	3	98 (dr = 64:36)
6[b]	 **1g**	 **2g**	1	>99
7[b]	 **1h**	 **2h**	3	97
				
8[c]	*cis*-**1i**	**2i**	8	>99 (dr = 68:32)
9[c]	*trans*-**1j**	**2j**	5	96 (dr = 84:16)
10[b]	 **1k**	 **2k**	8	91 (dr = >99:<1)

[a]Isolated yield. [b]Reaction was carried out in MeCN (2 mL).

[c]Reaction was carried out under dark conditions.

Entry	Substrate	Product	Time (h)	Yield of **2**(%)[a]
11[d]	 *(E)*-**1l**	 **2l**	24	89 (dr = 77:23)
12[c]	*(Z)*-**1m**	**2m**	20	90 (dr = >99:<1)
13	 **1n**	 **2n**	2	90
14	 **1o**	 **2o**	8	>99 (dr = 77:23)
15	 **1p**	 **2p**	1	93 (dr =57:43)

[a]Isolated yield. [b]Reaction was carried out in MeCN (2 mL).

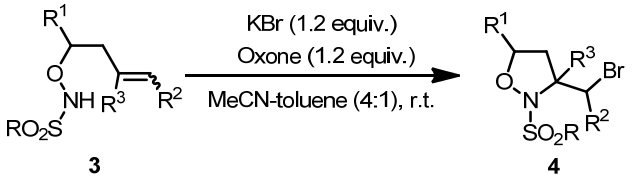
[c]Reaction was carried out under dark conditions.

[d]Reaction was carried out with Oxone (2.0 equiv.) in a mixture of MeCN and toluene (4 :1) (1 mL).

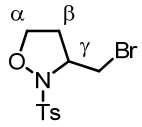
The present method for the oxidative intramolecular bromo-amination of *N*-alkenyl sulfonamides was applied to the synthesis of bromo isoxazolidines from *N*-alkenoxyl sulfonamide derivatives. Isoxazolidines are useful for the synthesis of biologically active compounds.[15] They also serve as precursors to *γ*-amino alcohols,[16] *γ*-amino ketones,[17] *β*-amino acids,[18] and 3-isoxazolidines.[19] Isoxazolidines have been synthesized via the 1,3-dipolar cycloaddition reaction of nitrones with alkenes[16a,20] and the Pd-catalyzed cyclization of *N*- or *O*-homoallyl hydroxylamines.[21] To the best of his knowledge, however, there has been no report of the synthesis for bromo isoxazolidines. The author reports here the first synthesis of bromo isoxazolidines via the oxidative intramolecular bromo-amination of *N*-alkenoxyl sulfonamide derivatives **3** (**Table 3**). Treatment of **3a** ($R^1 = R^2 = R^3 = H$) with KBr and Oxone® in a 4:1 mixture of MeCN and toluene gave **4a** in 93% yield. The same treatment of 2-aryl substituted *N*-alkenoxyl sulfonamides bearing H, MeO, and CF_3 at aryl group **3b**, **3c**, and **3d** (R^1 = Ph, 4-MeO-C_6H_4, and 4-CF_3-C_6H_4, $R^2 = R^3 = H$) also provided corresponding products **4b**, **4c**, and **4d** in excellent yields (90–97%) with moderate diastereoselectivities (dr = 4:1). Use of disubstituted internal alkene **3e** (R^1 = 1-naphthyl, R^2 = Me, R^3 = H) and terminal alkene **3f** (R^1 = 4-Cl-C_6H_4, R^2 = H, R^3 = Me) provided corresponding products **4e** and **4f** in 91%

and 95% yields, respectively. Moreover, treatment of 2-thienyl substituted *N*-alkenoxyl sulfonamides **3g** (R^1 = 2-thienyl, R^2 = R^3 = H) and 2-butyl substituted *N*-alkenoxyl sulfonamides **3h** (R^1 = *n*-butyl, R^2 = R^3 = H) also gave desired products **4g** and **4h** in 82% and 98% yields, respectively.

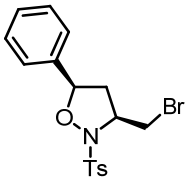
Table 3. *Exo*-selective Intramolecular Bromo-amination of Various *N*-alkenoxyl Sulfonamides (**3**).



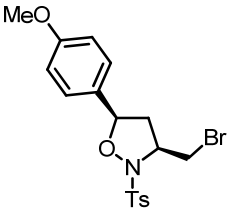
Product, Time (h), Yield of **4** (%)[b]



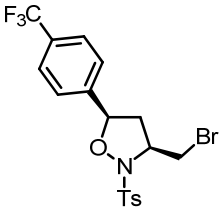
4a, 4 h, 93%



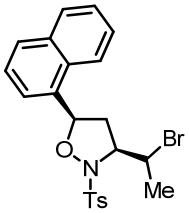
4b, 4h 97%
(dr = 84 :16)



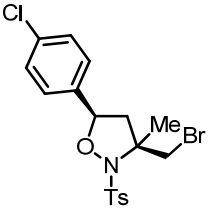
4c[c], 10 h, 90%
(dr = 90:10)



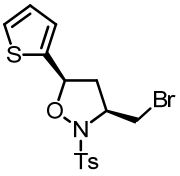
4d[c], 20 h, 91%
(dr = 83:17)



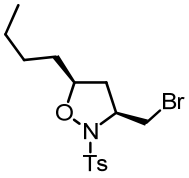
4e[c,d], 3 h, 91%
(dr = 53:36:11)



4f[c], 2 h, 95%
(dr = 81:19)



4g[c,e]18 h, 82%
(dr = 81:19)



4h[c],8 h, 98%
(dr = 82:18)

[c]Reaction was carried out under dark conditions.

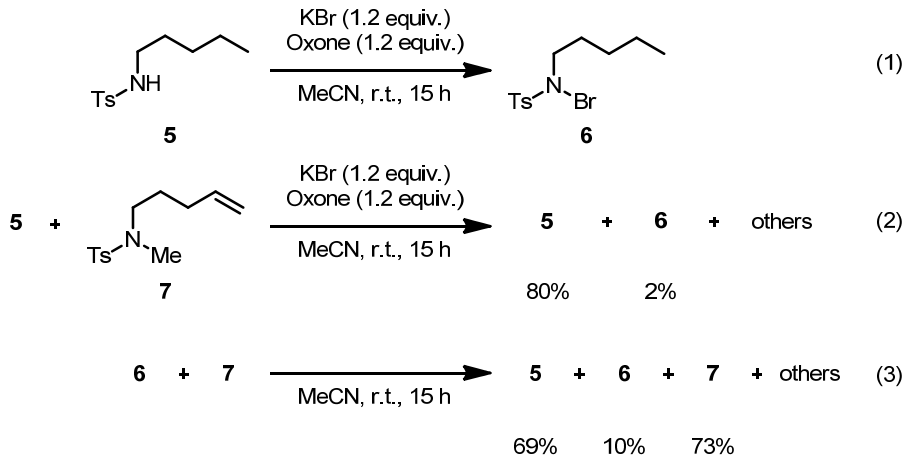
[d]Starting materials with a 2:1 mixture of E/Z isomers were used.

[e] Reaction was carried out in a mixture of MeCN and toluene (1:1) (1 mL).

Next, the author carried out three experiments in order to further illuminate the mechanistic picture (**Scheme 3**). First, the treatment of *N*-pentyltosylamide (**5**) with KBr and Oxone® in MeCN gave *N*-bromo-*N*-pentyltosylamide (**6**) in 88% yield (**Scheme 3**, **eq. 1**). Second, when a mixture of **5** and *N*-methyl-*N*-(4-penten-1-yl)tosylamide (**7**) was

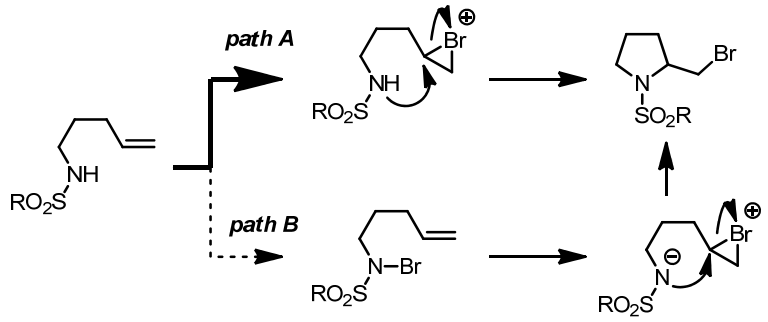
treated with KBr and Oxone in MeCN, only **7** was converted into some of unknown products (**Scheme 3**, **eq. 2**). In contrast, a mixture of **6** and **7** in MeCN were less converted than the reaction in **eq. 3** (27% consumption of **7**).

Scheme 3. Preparation of *N*-Alkenylsulfonpyrrolidines from Various *N*-Alkenyl sulfonamides.



The proposed reaction mechanism is depicted in Scheme 4. The key step is the generation of the activated bromonium-like species (Br^+), but not Br_2, via oxidative umpolung of KBr with Oxone® in MeCN at room temperature (Table 1, entries 1 vs 7). The author speculates that there are two pathways for the bromo-amination of *N*-alkenyl sulfonamides **1** with Br^+. First, the reaction may occur via intermolecular bromination of the olefin moiety and then, the bromonium cation intermediate may be intramolecularly attacked by the sulfonamide group to form cyclization products **2** (**path A**). Alternatively, sulfonamides may undergo direct bromination to form *N*-bromo sulfonamides, followed by intramolecular bromonium ion transfer to the olefin moiety, and the cyclization of bromonium cation intermediate proceeds to afford desired products **2** (**path B**). Some of the mechanistic approaches to the intramolecular bromo-amination indicate that the activated bromonium-like species first brominate the olefin moiety of the substrates (**path A**).

Scheme 4. Plausible Reaction Mechanism



In conclusion, the author has developed an oxidative intramolecular cyclizations using the unpolung of alkali metal bromide with Oxone®. These reactions provides the desired products without generating the stoichiometric amount of the corresponding organic wastes, thus contributing to green sustainable chemistry. And, these reactions proceeded to generate the *N*-containing heterocycles in high yields.

Experimental Section

^{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).

General Procedure for the Intramolecular Bromo-amination of *N*-Alkenyl Sulfonamides with a Metal Bromide / Oxone System (Table 1, entry 7). To a solution of **1a** (59.8 mg, 0.25 mmol) and Oxone® (184.4 mg, 0.30 mmol) in acetonitrile (1 mL) was added KBr (35.7 mg, 0.30 mmol) under argon atmosphere. The solution was stirred at room temperature for 3 h. Saturated $NaHCO_3$ aqueous solution (10mL) was added to the reaction mixture, and the product was extracted with AcOEt (15 mL × 3). The combined extracts were washed by brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure and the crude product was purified by silica-gel column chromatography (eluent: hexane/AcOEt = 5/1), to give the desired product **2a** (79.2 mg, >99% yield).

2-(Bromomethyl)-1-tosylpyrrolidine (2a): ^{1}H NMR (400 MHz,$CDCl_3$) δ 1.51-1.61 (m, 1H), 1.69-1.80 (m, 1H), 1.81-1.89 (m, 1H), 1.90-1.98 (m, 1H), 2.44 (s, 3H), 3.15 (dt, *J* = 10.1, 7.1 Hz, 1H), 3.36 (t, *J* = 9.7 Hz, 1H), 3.51-3.44 (m, 1H), 3.74-3.79 (m, 1H), 3.80-3.87 (m, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.7, 30.2, 36.0, 49.8, 60.3, 127.5 (2C), 129.8 (2C), 134.0, 143.8. IR (neat) 1338, 1161, 1091, 1034, 986 cm^{-1}. MS (ESI) calcd for $C_{12}H_{17}BrNO_2S$ $[M + H]^+$ 318.0158, found 318.0151. Anal. calcd for $C_{12}H_{16}BrNO_2S$: C, 45.29; H, 5.07; N, 4.40%. Found: C, 45.60; H, 5.16; N, 4.27%.

2-(Bromomethyl)-1-(phenylsulfonyl)pyrrolidine (2b): yield 95%, 72.2mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51-1.61 (m, 1H), 1.68-1.80 (m, 1H), 1.80-1.90 (m, 1H), 1.91-2.00 (m, 1H), 3.17 (dt, *J* = 10.1, 7.5Hz, 1H), 3.37 (t, *J* = 9.8 Hz, 1H), 3.46-3.53 (m, 1H), 3.78 (dd, *J*

= 10.1, 3.3 Hz, 1H), 3.81-3.89 (m, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.60-7.66 (m, 1H), 7.86 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 30.1, 35.9, 49.7, 60.3, 127.3 (2C), 129.1 (2C), 132.9, 136.7. IR (KBr) 1337, 1199, 1162, 1092, 1030 cm^{-1}. MS (ESI) calcd for$C_{11}H_{15}BrNO_2S$ $[M+H]^+$ 304.0001, found 304.0005.

2-(Bromomethyl)-1-(naphthalen-1-ylsulfonyl)pyrrolidine (2c): yield 96%, 85.0 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63-1.73 (m, 1H), 1.82-1.92 (m, 2H), 1.93-2.04 (m, 1H), 3.36 (t, *J* = 9.7 Hz, 1H), 3.30-3.43 (m, 2H), 3.68 (dd, *J* = 10.1, 3.2 Hz, 1H), 4.12-4.20 (m, 1H), 7.52-7.64 (m, 2H), 7.64-7.71 (m, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 8.86 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 30.4, 35.6, 49.5, 59.7, 124.2, 125.1, 126.9, 128.2, 128.9, 129.0, 130.0, 133.5, 134.3, 134.6. IR (neat) 1347, 1159, 1133, 1029, 989 cm^{-1}.MS (ESI) calcd for$C_{15}H_{17}BrNO_2S$ $[M+H]^+$ 354.0158, found 354.0152.

2-(Bromomethyl)-1-[(4-fluorophenyl)sulfonyl]pyrrolidine (2d): yield 93%, 74.9 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52-1.65 (m, 1H), 1.71-1.82 (m, 1H), 1.82-1.93 (m, 1H), 1.93-2.02 (m, 1H), 3.15 (dt, *J* = 10.1, 7.3 Hz, 1H), 3.37 (t, *J* = 9.8 Hz, 1H), 3.44-3.52 (m, 1H), 3.76 (dd, *J* = 9.8, 3.1 Hz, 1H), 3.79-3.87 (m, 1H), 7.23 (t, *J* = 8.7 Hz, 2H), 7.84-7.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 30.2, 35.8, 49.8, 60.4, 116.5 (d, *J* = 22.0 Hz, 2C) 130.1 (d, *J* = 8.6 Hz, 2C), 133.2, 165.3 (d, *J* = 256.8 Hz). IR (KBr) 1343, 1231, 1169, 1093, 1057 cm^{-1}.MS (ESI) calcd for $C_{11}H_{14}BrFNNaO_2S$ $[M + Na]^+$ 343.9727, found 343.9722.

2-(Bromomethyl)-1-(butylsulfonyl)pyrrolidine (2e): yield >99%, 71.1mg. ^{1}H NMR(400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.47 (sext, *J* = 7.5Hz, 2H), 1.75-2.18 (m, 6H), 2.95-3.02 (m, 2H), 3.35-3.48 (m, 3H), 3.64 (dd, *J* = 10.3, 3.2 Hz, 1H), 4.04-4.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 21.7, 24.6, 25.2, 30.4, 36.2, 49.4, 50.2, 59.7. IR (KBr) 1334, 1142, 1067, 1035, 989 cm^{-1}.MS (ESI) calcd for $C_9H_{18}BrNNaO_2S$ $[M+Na]^+$ 306.0134, found 306.0133.

2-(Bromomethyl)-1-[(*1S*)-10-camphorsulfonyl]pyrrolidine (2f, Diastereomeric Mix -ture): yield 98%, 92.7 mg. Major-diastereomer: ^{1}H NMR 400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.14 (s, 3H), 1.39-1.48 (m, 1H), 1.62-1.71 (m, 1H), 1.88-2.22 (m, 7H), 2.34-2.45 (m, 1H), 2.47-2.58 (m, 1H), 2.88 (d, *J* = 14.9 Hz, 1H), 3.33-3.43 (m, 2H), 3.43-3.54 (m, 2H), 3.67 (dd, *J* = 10.3, 3.3Hz, 1H), 4.02-4.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 20.0, 24.3, 25.2, 26.9, 30.4, 36.1, 42.6, 42.8, 45.8, 47.9, 49.4, 58.3, 60.1, 215.5.

Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.15 (s, 3H), 1.39-1.48 (m, 1H), 1.62-1.71 (m, 1H), 1.88-2.22 (m, 7H), 2.34-2.45 (m, 1H), 2.47-2.58 (m, 1H), 2.84 (d, *J* = 14.6 Hz, 1H), 3.33-3.43 (m, 2H), 3.43-3.54 (m, 2H), 3.70 (dd, *J* = 10.1, 3.2 Hz, 1H), 3.99-4.08 (m, 1H). ^{13}C NMR (100MHz, $CDCl_3$) δ 19.8, 20.0, 24.2, 25.1, 26.9, 30.5, 35.9, 42.6, 42.8, 45.1, 47.9, 49.6, 58.2, 60.1, 215.3. IR (KBr) 1745, 1341, 1200, 1146, 1037 cm^{-1}.MS (ESI) calcd for $C_{15}H_{24}BrNNaO_3S$ $[M + Na]^+$ 400.0552, found 400.0550.

2-(Bromomethyl)-4,4-dimethyl-1-tosylpyrrolidine (2g): yield >99%, 86.5 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 1.05 (s, 3H), 1.70 (dd, *J* = 13.0, 8.5 Hz, 1H), 1.88 (dd, *J* = 13.0, 7.6 Hz, 1H), 2.44 (s, 3H), 3.14 (d, *J* = 10.8 Hz, 1H), 3.19 (d, *J* = 10.8 Hz, 1H), 3.52 (t, *J* = 9.6 Hz, 1H), 3.82-3.91 (m, 1H), 3.94 (dd, *J* = 9.6, 3.0 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 25.7, 26.0, 37.4, 37.5, 45.8, 60.0, 61.8, 127.5 (2C), 129.7 (2C), 134.8, 143.7. IR (KBr) 1345, 1157, 1092, 1043, 1024 cm^{-1}.MS (ESI) calcd for $C_{14}H_{21}BrNO_2S$ $[M + H]^+$ 346.0471, found 346.0463.

3-(Bromomethyl)-2-tosyl-2-azaspiro[4.5]decane (2h): yield 97%, 93.7mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59-0.69 (m, 1H), 0.74-0.84 (m, 1H), 1.05-1.50 (m, 8H), 1.63 (dd, *J* = 13.3, 8.5 Hz, 1H), 1.95 (dd, *J* = 13.3, 7.5 Hz, 1H), 2.43 (s, 3H), 3.15 (d, *J* = 11.0 Hz, 1H), 3.35 (d, *J* = 11.0 Hz, 1H), 3.50 (dd, *J* = 9.8, 9.0 Hz, 1H), 3.75-3.84 (m, 1H), 3.94 (dd, *J* = 9.8, 3.0 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.7, 23.6, 25.7, 33.9, 36.1, 37.7, 41.4, 44.0, 59.0, 59.2, 127.4 (2C), 129.7 (2C), 134.6, 143.7. IR (KBr) 1350, 1220, 1160, 1090, 1031 cm^{-1}. MS (ESI) calcd for $C_{17}H_{25}BrNO_2S$ $[M + H]^+$ 386.0784, found 386.0776. Anal. calcd for $C_{17}H_{24}BrNO_2S$: C, 52.85; H, 6.26;N, 3.63%. Found: C, 52.81; H, 6.27; N, 3.55%.

***cis*-2-(Bromomethyl)-1-tosyloctahydro-1*H*-indole (2i, Diastereomeric Mixture):** yield >99%, 93.0 mg. Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99-1.31 (m, 2H), 1.32-1.48 (m, 2H), 1.48-1.74 (m, 4H), 1.80-2.04 (m, 2H), 2.07-2.18 (m, 1H), 2.44 (s, 3H), 3.41 (t, *J* = 9.8 Hz, 1H), 3.62-3.71 (m, 1H), 3.71-3.78 (m, 1H), 4.00 (dd, *J* = 9.8, 3.6 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 21.6, 24.3, 25.7, 31.1, 34.1, 36.2, 37.8, 60.7, 61.4, 127.4 (2C), 129.8 (2C), 134.7, 143.6. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.99 (m, 1H), 0.99-1.31 (m, 2H), 1.32-1.48 (m, 2H), 1.48-1.74 (m, 4H), 1.80-2.04 (m, 2H), 2.43 (s, 3H), 3.28 (t, *J* = 10.8 Hz, 1H), 3.82-3.89 (m, 1H), 3.92-4.02 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* =8.2Hz, 2H). ^{13}C NMR(100 MHz, $CDCl_3$) δ 20.0, 21.5, 23.5, 25.6, 27.9, 31.6, 34.5, 35.5,

59.0, 61.6, 127.3 (2C), 129.6 (2C), 138.4, 143.2. IR (KBr) 1345, 1162, 1096, 1032, 1004 cm^{-1}. MS (ESI) calcd for $C_{16}H_{23}BrNO_2S$ $[M + H]^+$ 372.0627, found 372.0624.

***trans*-2-(Bromomethyl)-1-tosyloctahydro-1*H*-indole (2j, Diastereomeric Mixture):** yield 96%, 89.4 mg. Major-diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 0.98-1.48 (m, 6H), 1.55-1.73 (m, 1H), 1.73-1.88 (m, 2H), 2.25-2.34 (m, 2H), 2.43 (s, 3H), 2.90 (dt, *J* = 10.8, 3.2 Hz, 1H), 3.60 (dd, *J* = 9.8, 8.2 Hz, 1H), 3.88 (dd, *J* = 9.8, 3.2 Hz, 1H), 4.27 (dq, *J* = 8.2, 3.2 Hz, 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, 25.0 (2C), 29.3, 29.6, 36.4, 38.4, 45.3, 60.2, 66.3, 127.0 (2C), 129.6 (2C), 139.6, 143.0. Minor-diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 0.98-1.48 (m, 6H), 1.55-1.88 (m, 3H), 1.99 (dd, *J* = 12.6, 5.5 Hz, 1H), 2.25-2.34 (m, 1H), 2.46 (s, 3H), 2.46-2.52 (m,1H), 3.29 (dd, *J* = 11.4, 10.6 Hz, 1H), 3.76-3.84 (m, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 24.5, 25.2, 29.4, 32.4, 33.1, 35.8, 42.7, 61.3, 67.3, 127.8 (2C), 129.7 (2C), 133.0, 143.8. IR (KBr) 1333, 1148, 1118, 1088, 1035 cm^{-1}. MS (ESI) calcd for $C_{16}H_{23}BrNNaO_2S$ $[M + Na]^+$ 394.0447, found 394.0443.

***cis*-6-Bromo-1-tosyloctahydrocyclopenta[b]pyrrole (2k):** yield 91%, 78.3 mg. ^1H NMR(400 MHz, $CDCl_3$) δ 1.45-1.54 (m, 2H), 1.67-1.76 (m, 1H), 2.00-2.07 (m, 1H), 2.13-2.28 (m, 2H), 2.45 (s, 3H), 2.74-2.82 (m, 1H), 3.01 (td, *J* = 10.1, 7.3 Hz, 1H), 3.45 (td, *J* = 10.1, 6.1 Hz, 1H), 3.89 (d, *J* = 7.6 Hz, 1H), 4.77 (d, *J* = 3.9 Hz, 1H), 7.35 (d, *J* = 8.5Hz, 2H), 7.73 (d, *J* = 8.5Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 29.8, 30.7, 33.9, 41.9, 50.0, 57.6, 73.3, 127.9 (2C), 129.8 (2C), 132.8, 143.9. IR (KBr) 1345, 1157, 1094, 1026 cm^{-1}.MS(ESI) calcd for $C_{14}H_{18}BrNNaO_2S$ $[M + Na]^+$ 366.0134, found 366.0126. Anal. calcd for $C_{14}H_{18}BrNO_2S$: C, 48.84; H, 5.27; N, 4.07%. Found: C, 48.96; H, 5.20; N, 4.02%.

***syn*-2-(1-Bromomethyl)-1-tosylpyrrolidine (2l):** yield 89%, 73.9 mg. ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (dt, *J* = 12.1, 7.6 Hz, 1H), 1.68 (d, *J* = 7.1 Hz, 1H), 1.68-1.80 (m, 1H), 1.82-1.92 (m, 1H), 1.95-2.03 (m, 1H), 2.43 (s, 3H), 3.34 (dd, *J* = 7.6, 5.9 Hz, 2H), 3.69 (dt, *J* = 8.2, 4.7 Hz, 1H), 4.61 (dq, *J* = 7.1, 4.7 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.1, 24.5, 27.9, 49.4, 55.1, 65.0, 127.5 (2C), 129.7 (2C), 135.1, 143.6. IR (KBr) 1343, 1156, 1092, 1044, 996 cm^{-1}. MS (ESI) calcd for $C_{13}H_{19}BrNO_2S$ $[M+ H]^+$ 332.0314, found 332.0314.

***anti*-2-(1-Bromomethyl)-1-tosylpyrrolidine (2m):** yield 90%, 74.8 mg. ^1H NMR (400 MHz, $CDCl_3$) δ 1.37-1.49 (m, 1H), 1.66 (d, *J* = 7.1 Hz, 3H), 1.71-1.83 (m, 2H), 1.95-2.05 (m,

1H), 2.45 (s, 3H), 3.26 (dt, J= 10.7, 7.1 Hz, 1H), 3.47 (dt, J= 10.7, 6.2 Hz, 1H), 3.93 (dt, J = 8.0, 4.1 Hz, 1H), 4.68 (dq, J= 7.1, 4.1 Hz, 1H), 7.34 (d, J= 8.1 Hz, 2H), 7.73 (d, J= 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 21.5, 24.5, 27.0, 50.8, 51.0, 64.1, 127.6 (2C), 129.8 (2C), 133.6, 143.8. IR (KBr) 1341, 1160, 1087, 1004, 978 cm^{-1}. MS (ESI) calcd for $C_{13}H_{19}BrNO_2S$ $[M + H]^+$ 332.0314, found 332.0307.

2-(Bromomethyl)-2-methyl-1-tosylpyrrolidine (2n): yield 90%, 74.8 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.67-1.92 (m, 3H), 2.25-2.33 (m, 1H), 2.42 (s, 3H), 3.31-3.39 (m, 1H), 3.39-3.46 (m, 1H), 3.76 (d, J= 10.3Hz, 1H), 3.86 (d, J= 10.3Hz, 1H), 7.29 (d, J= 8.3Hz, 2H), 7.76 (d, J= 8.3Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.5, 24.0, 39.3, 41.0, 49.8, 67.3, 127.3 (2C), 129.5 (2C), 137.8, 143.1. IR (KBr) 1338, 1155, 1120, 1064, 1005 cm^{-1}. MS (ESI) calcd for $C_{13}H_{19}BrNO_2S$ $[M + H]^+$ 332.0314, found 332.0309.

***(5S)*-2-(Bromomethyl)-5-methyl-1-tosylpyrrolidine (2o, Diastereomic Mixture):** yield >99%, 83.0 mg. Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J= 6.4 Hz, 3H), 1.50-1.57 (m, 2H), 2.07-2.12 (m, 2H), 2.43 (s, 3H), 3.23 (t, J= 10.1 Hz, 1H), 3.90 (dd, J= 9.8, 3.3 Hz, 1H), 4.02-4.16 (m, 2H), 7.30 (d, J= 8.1 Hz, 2H), 7.75 (d, J= 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 21.6, 27.8, 30.9, 34.6, 57.4, 60.6, 127.1 (2C), 129.7 (2C), 138.9, 143.3. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 6.4 Hz, 3H), 1.58-1.74 (m, 2H), 2.02-2.20 (m, 2H), 2.44 (s, 3H), 3.33 (t, J= 10.8 Hz, 1H), 3.71 (q, J= 6.4 Hz, 1H), 3.80 (dd, J= 9.6, 3.2 Hz, 1H), 3.79-3.87 (m, 1H), 7.33 (d, J= 8.2 Hz, 2H), 7.73 (d, J= 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 23.2, 28.9, 31.8, 36.4, 58.3, 62.1, 127.6 (2C), 129.9 (2C), 134.4, 143.8. IR (neat) 1340, 1157, 1095, 1040 cm^{-1}. MS (ESI) calcd for $C_{13}H_{18}BrNNaO_2S$ $[M + Na]^+$ 354.0134, found 354.0125.

***(5R)*-2-(Bromomethyl)-5-isopropyl-1-tosylpyrrolidine (2p, Diastereomeric Mixture):** yield 93%, 83.8 mg. Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (d, J= 6.9 Hz, 3H), 0.81 (d, J= 6.9 Hz, 3H), 1.23-1.34 (m, 1H), 1.60-1.72 (m, 1H), 1.72-1.85 (m, 1H), 1.85-2.00 (m, 1H), 2.00-2.10 (m, 1H), 2.42 (s, 3H), 3.28 (t, J = 10.0 Hz, 1H), 3.85-3.89 (m, 1H), 4.03 (dd, J= 9.7, 2.2 Hz, 1H), 4.15-4.21 (m, 1H), 7.29 (d, J= 8.1 Hz, 2H), 7.73 (d, J= 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 19.8, 21.5, 22.9, 29.3, 31.2, 34.6, 61.9, 65.7, 126.8 (2C), 129.5 (2C), 138.9, 143.1. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, J= 7.0 Hz, 3H), 0.99 (d, J= 7.0 Hz, 3H), 1.60-1.72 (m, 1H), 1.72-1.85 (m, 1H), 1.85-2.00 (m, 1H), 2.00-2.10 (m, 1H), 2.30-2.41 (m, 1H), 2.44 (s, 3H), 3.25 (t, J= 11.2 Hz, 1H), 3.41-3.47 (m, 1H), 3.76-3.84 (m, 2H), 7.34 (d, J=

8.1 Hz, 2H), 7.72 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 20.0, 21.5, 25.2, 28.9, 29.3, 35.9, 62.0, 68.1, 127.6 (2C), 129.8 (2C), 134.3, 143.7. IR (KBr) 1330, 1214, 1154, 1096, 989 cm^{-1}. MS (ESI) calcd for $C_{15}H_{23}BrNO_2S$ $[M + H]^+$ 360.0627, found 360.0620.

3-(Bromomethyl)-2-tosylisoxazolidine (4a): yield 93%, 74.7 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17-2.30 (m, 1H), 2.46 (s, 3H), 2.43-2.53 (m, 1H), 3.35 (t, J = 9.7 Hz, 1H), 3.66 (dd, J = 10.2, 4.9 Hz, 1H), 3.94-4.06 (m, 2H), 4.44-4.53 (m, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.86 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 34.2, 34.3, 59.9, 70.2, 129.2 (2C), 129.8 (2C), 132.5, 145.3. IR (KBr) 1349, 1308, 1169, 1088, 1011 cm^{-1}.MS (ESI) calcd for $C_{11}H_{15}BrNO_3S$ $[M+H]^+$ 319.9951, found 319.9944. Anal. calcd for $C_{11}H_{14}BrNO_3S$: C, 41.26; H, 4.41; N, 4.37%. Found: C, 41.57; H, 4.22; N, 4.29%.

3-(Bromomethyl)-5-phenyl-2-tosylisoxazolidine (4b, Diastereomeric Mixture): yield 97%, 96.1 mg. Data are for the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (ddd, J = 12.6, 10.8, 7.8 Hz, 1H), 2.45 (s, 3H), 2.90 (ddd, J = 12.6, 7.8, 6.0 Hz, 1H), 3.51 (t, J = 10.1 Hz, 1H), 3.79 (dd, J = 10.1, 4.8 Hz, 1H), 4.58-4.68 (m, 1H), 5.14 (dd, J = 10.8, 6.0 Hz, 1H), 7.23-7.39 (m, 7H), 7.89 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 34.8, 42.5, 60.9, 83.7, 126.9 (2C), 128.7 (2C), 129.0, 129.3 (2C), 129.8 (2C), 132.5, 135.9, 145.4. IR (KBr) 1358, 1172, 1087, 1027, 1006 cm^{-1}. MS (ESI) calcd for $C_{17}H_{18}BrNNaO_3S$ $[M + Na]^+$ 418.0083, found 418.0071. Anal. calcd for $C_{17}H_{18}BrNO_3S$:C, 51.52; H, 4.58; N, 3.53%. Found: C, 51.66; H, 4.54; N, 3.36%.

3-(Bromomethyl)-5-(4-methoxyphenyl)-2-tosylisoxazolidine (4c, Diastereomeric Mixtu -re): yield 90%, 95.9 mg. Data are for the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (ddd, J = 12.8, 10.8, 8.0 Hz, 1H), 2.45 (s, 3H), 2.84 (ddd, J = 12.8, 7.8, 5.5 Hz, 1H), 3.52 (t, J = 10.4 Hz, 1H), 3.78 (s, 3H), 3.79 (dd, J = 10.4, 4.6 Hz, 1H), 4.57-4.68 (m, 1H), 5.06 (dd, J = 10.8, 5.5Hz, 1H), 6.86 (d, J = 8.8Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 7.88 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 34.9, 42.2, 55.3, 61.0, 83.5, 114.0 (2C), 127.4, 128.5 (2C), 129.3 (2C), 129.8 (2C), 132.5, 145.3, 160.2. IR (KBr) 1517, 1356, 1254, 1166, 1030 cm^{-1}. MS (ESI) calcd for $C_{18}H_{21}BrNO_4S$ $[M+H]^+$ 426.0369, found 426.0356.

3-(Bromomethyl)-2-tosyl-5-[4-(trifluoromethyl)phenyl]isoxazolidine (4d, Diastereomeric Mixture): yield 91%, 105.6 mg. Data are for the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (ddd, J = 12.8, 10.2, 8.9 Hz, 1H), 2.46 (s, 3H), 2.97 (ddd, J = 12.8, 8.0, 6.1

Hz, 1H), 3.49 (dd, J= 10.2, 8.9Hz, 1H), 3.76 (dd, J= 10.2, 4.6Hz, 1H), 4.64-4.74 (m, 1H), 5.28 (dd, J= 10.5, 6.1Hz, 1H), 7.37 (d, J= 8.2 Hz, 2H), 7.42 (d, J= 8.2 Hz, 2H), 7.60 (d, J = 8.2 Hz, 2H), 7.88 (d, J= 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 34.7, 42.7, 60.7, 82.7, 125.6 (d, J= 3.8 Hz, 2C), 127.0 (2C), 127.3, 129.3 (2C), 129.7 (d, J= 15.3 Hz), 129.9 (2C), 132.3, 140.3, 145.6. IR (KBr) 1363, 1332, 1168, 1124, 1036 cm^{-1}. MS (ESI) calcd for $C_{18}H_{18}BrF_3NO_3S$ $[M+H]^+$ 464.0137, found 464.0127.

3-(1-Bromoethyl)-5-(naphthalen-1-yl)-2-tosylisoxazolidine (4e, Diastereomeric Mixtu -re): yield 91%, 104.73 mg. Major-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.66 (d, J= 7.3 Hz, 3H), 2.44 (s, 3H), 3.16-3.26 (m,1H), 3.49 (dd, J= 11.4, 10.1 Hz, 1H), 3.96 (dd, J =10.1,4.5 Hz, 1H), 4.52-4.60 (m, 1H), 5.53 (d, J = 4.5 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.40-7.53 (m, 4H), 7.56 (d, J= 7.3 Hz, 1H), 7.80 (d, J= 8.2 Hz, 1H), 7.87 (d, J= 8.4 Hz, 1H), 7.91 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 8.2, 21.7, 29.8, 41.8, 65.5, 82.0, 121.9, 123.8, 125.1, 125.7, 126.3, 128.4, 129.0, 129.6 (3C), 129.8, 129.9 (2C), 131.3, 133.3, 145.5. Minor-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, J = 6.6 Hz, 3H), 2.43 (s, 3H), 2.88-2.99 (m, 1H), 3.73-3.88 (m, 2H), 4.32 (dt, J= 7.5, 4.1 Hz, 1H), 5.57 (d, J= 10.3Hz, 1H), 7.33 (d, J= 8.0 Hz, 2H), 7.42-7.58 (m, 3H), 7.85 (t, J= 7.6 Hz, 2H), 7.93 (d, J= 8.4 Hz, 2H), 8.03 (d, J= 8.5 Hz, 1H), 8.11 (d, J= 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 21.7, 34.5, 48.1, 66.1, 85.9, 123.3, 125.1, 125.2, 125.9, 126.5, 128.8, 129.2 (2C), 129.8 (3C), 129.9, 131.9, 132.9, 133.8, 145.2. IR(KBr) 1362, 1334, 1168, 1091, 1038 cm^{-1}. MS (ESI) calcd for $C_{22}H_{23}BrNO_3S$ $[M+H]^+$ 460.0577, found 460.0563.

3-(Bromomethyl)-5-(4-chlorophenyl)-3-methyl-2-tosylisoxazolidine (4f, Diastereomeric Mixture): yield 95%, 105.6 mg. Data are for the major diastereomer: ^{1}H NMR(400 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.43 (s, 3H),2.63 (dq, J= 12.8, 7.3Hz, 2H), 3.61 (d, J= 10.5Hz, 1H), 3.74 (d, J= 10.5Hz, 1H), 5.55 (t, J= 8.0 Hz, 1H), 7.21 (d, J= 8.6 Hz, 2H), 7.26-7.34 (m, 4H), 7.85 (d, J= 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 21.9, 41.4, 48.8, 70.8, 81.7, 128.0 (2C), 128.8 (4C), 129.5 (2C), 134.5, 135.1, 135.5, 144.8. IR (neat) 1494, 1333, 1161, 1092 cm^{-1}. MS (ESI) calcd for $C_{18}H_{20}BrClNO_3S$ $[M+H]^+$ 444.0030, found 444.0018.

3-(Bromomethyl)-5-(thiophen-2-yl)-2-tosylisoxazolidine (4g, Diastereomeric Mixture): yield 82%, 82.5 mg. Data are for the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (ddd, J= 12.8, 9.8, 7.1 Hz, 1H), 2.45 (s, 3H), 2.97 (ddd, J= 12.8, 7.8, 6.3 Hz, 1H), 3.51 (t, J= 10.1 Hz, 1H), 3.77 (dd, J= 10.1, 4.9 Hz, 1H), 4.64-4.74 (m, 1H), 5.50 (dd, J=

9.8, 6.3 Hz, 1H), 6.97 (dd, J = 5.0, 3.6 Hz, 1H), 7.04-7.08 (m, 1H), 7.32 (dd, J = 5.0, 1.1 Hz, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 34.5, 42.4, 60.9, 79.4, 126.8, 126.9, 127.5, 129.3 (2C), 129.8 (2C), 132.4, 138.3, 145.4. IR (KBr) 1354, 1326, 1169, 1092, 1032 cm^{-1}. MS (ESI) calcd for $C_{15}H_{17}BrNO_3S_2$ $[M + H]^+$ 401.9828, found 401.9817.

3-(Bromomethyl)-5-butyl-2-tosylisoxazolidine (4h, Diastereomeric Mixture): yield 98%, 92.2 mg. Data are for the major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 3H), 1.16-1.37 (m, 4H), 1.41-1.69 (m, 2H), 1.79 (ddd, J = 12.5, 10.2, 7.8 Hz, 1H), 2.46 (s, 3H), 2.59 (ddd, J = 12.5, 7.8, 5.5 Hz, 1H), 3.38 (t, J = 9.7 Hz, 1H), 3.71 (dd, J = 10.2, 4.6 Hz, 1H), 3.98-4.07 (m, 1H), 4.37-4.48 (m, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.7, 22.4, 28.1, 32.2, 34.9, 40.4, 60.7, 82.4, 129.2 (2C), 129.8 (2C), 132.5, 145.2. IR (neat) 1454, 1360, 1167, 1091, 1017 cm^{-1}. MS (ESI) calcd for $C_{15}H_{23}BrNO_3S$ $[M+H]^+$ 376.0577, found 376.0565.

Mechanicstic Study for Oxidative Intramolecular Bromo-amination of *N*-Alkenyl Sulfonamides *via* Umpolung of Alkali Metal Bromides (Table 2). *N*-Bromination of *N*-pentenyltosylamide (**5**) via oxidative umpolung of KBr (**eq 1**): To a solution of 5 (60.3 mg, 0.25 mmol) and Oxone® (184.4 mg, 0.30 mmol) in acetonitrile (1 mL) was added KBr (35.7mg, 0.30 mmol) under argon atmosphere. The solution was stirred at room temperature for 15 h. Saturated $NaHCO_3$ aqueous solution (10 mL) was poured into the reaction mixture, and the product was extracted with AcOEt (15 mL × 3). The combined extracts were washed by brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the residue was the pure desired product (**6**) (70.7 mg, 88% yield) without further purification.

***N*-Pentyltosylamide (5):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 6.9 Hz, 3H), 1.18-1.28 (m, 4H), 1.41-1.49 (m, 2H), 2.43 (s, 3H), 2.91 (q, J = 6.9 Hz, 2H), 4.71 (brd, J = 5.0 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 21.5, 22.1, 28.6, 29.1, 43.1, 127.0 (2C), 129.6 (2C), 136.9, 143.3. IR (neat) 3281, 1425, 1325, 1160, 1094 cm^{-1}. MS (ESI) calcd for $C_{12}H_{20}NO_2S$ $[M + H]^+$ 242.1209, found 242.1201.

***N*-Bromo-*N*-pentyltosylamide (6):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.1 Hz, 3H), 1.28-1.37 (m, 4H), 1.58-1.68 (m, 2H), 2.47 (s, 3H), 3.14 (t, J = 7.1Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.83 (d, J =8.2Hz, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 13.9, 21.7, 22.1, 27.8,

28.0, 57.8, 129.4 (2C), 129.5 (2C), 130.6, 144.9. IR (neat) 1441, 1354, 1166, 1089 cm^{-1}.MS (ESI) calcd for $C_{12}H_{19}BrNO_2S$ $[M+H]^+$ 320.0314, found 320.0304.

General Procedure for the Competitive Bromination of *N*-Sulfonamides (eq 2): To a solution of **5** (60.3 mg, 0.25 mmol), **7** (63.3 mg, 0.25 mmol) and Oxone® (184.4 mg, 0.30 mmol) in acetonitrile (1 mL) was added KBr (35.7 mg, 0.30 mmol) under argon atmosphere. The solution was stirred at room temperature for 15 h. Saturated $NaHCO_3$ aqueous solution (10 mL) was poured into the reaction mixture, and the product was extracted with AcOEt (15 mL × 3). The combined extracts were washed by brine (10 mL) and dried over Na_2SO_4. The organic phase was concentrated under reduced pressure, and the residue was a mixture of products **5** (48.5 mg, 80% yield), **7** (1.4 mg, 2% yield), and unknown products, yield (%) of which was estimated by ^1H NMR analysis.

***N*-Methyl-*N*-(4-penten-1-yl)tosylamide (7):** ^1H NMR (400 MHz, $CDCl_3$) δ 1.58-1.68 (m, 2H), 2.06-2.14 (m, 2H), 2.43 (s, 3H), 2.71 (s, 3H), 2.99 (t, J = 7.3 Hz, 2H), 4.96-5.08 (m, 2H), 5.80 (ddt, J = 17.2, 10.4, 6.6 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.8, 30.6, 34.7, 49.6, 115.3, 127.4 (2C), 129.6 (2C), 134.4, 137.5, 143.2. IR (neat) 1460, 1341, 1160, 1091 cm^{-1}.MS (ESI) calcd for $C_{13}H_{20}NO_2S$ $[M+H]^+$ 254.1209, found 254.1201.

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(19) Piperno, A.; Chiacchio, U.; Iannazzo, D.; Giofrè, S. V.; Romeo, G.; Romeo, R. *J. Org. Chem.* **2007**, *72*, 3958-3960.

(20) For reviews, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863-910. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Comm.* **2000**, 1449-1458.

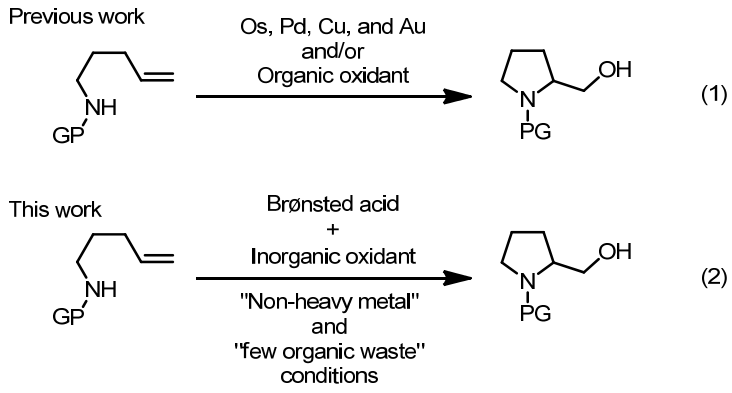
(21) For recent contributions to the Pd-catalyzed cyclization, see the following selected samples: (a) Peng, J.; Jiang, D.; Lin, W.; Chen, Y. *Org. Biomol. Chem.* **2007**, *5*, 1391-1396. (b) Peng, J.; Lin, W.; Yuan, S.; Chen, Y. *J. Org. Chem.* **2007**, *72*, 3145-3148. (c) Hay, M. B.; Wolfe, J. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 6492-6494. (d) Jiang, D.; Peng, J.; Chen, Y. *Tetrahedron* **2008**, *64*, 1641-1647. (e) Lemen, G. S.; Giampietro, N. C.; Hay, M. B.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 2533-2540.

2. Bronsted Acid-assisted Intramolecular Aminohydroxylation of *N*-Alkenylsulfonamides under Heavy Metal-free Conditions

Introduction

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 such as bis(trifluoroacetoxyiodo)benzene(I(III), PIFA)[8], NIS[9], iodosylbenzene[10], and chiral aryliodine diacetate(I(III))[11] were developed as sustainable strategies. However, the reactions with *N*-alkenylamides produced a stoichiometric amount of organic waste derived from the organic oxidant. The author reports here a heavy metal-free intramolecular aminohydroxylation of *N*-alkenyl sulfonamides 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).

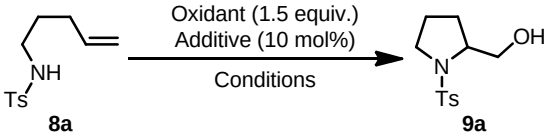
Scheme 5. Intramolecular Aminooxygenation of *N*-Protected Alkenes



Results and Discussion

Initially, the author optimized the reaction conditions for the intramolecular aminohydroxylation of *N*-alkenyl sulfonamides (**Table 5**). When **8a** 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, **9a** 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 **9a** (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 **9a** (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 **8a** into **9a** (entry 9). Raising the reaction temperature to 50 °C furnished **9a** 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).

Table 5. Screening of Optimal Conditions for Intramolecular Aminohydroxylation of **8a**



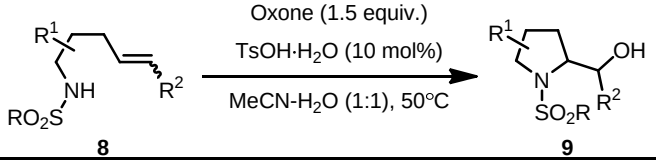
8a **9a**

Entry	Oxidant	Additive	Solvent	Time (h)	Yield (%)
1	Oxone		MeCN:H_2O(1:1), rt	24	74
2	Oxone	$TsOH \cdot H_2O$	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	$TsOH \cdot H_2O$	$MeNO_2$:H_2O(1:1), rt	24	6
7	Oxone	$TsOH \cdot H_2O$	AcOEt:H_2O(1:1), rt	24	14
8	Oxone	$TsOH \cdot H_2O$	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		MeCN:H_2O(1:1), 50°C	10	93
11	Oxone	$TsOH \cdot H_2O$	MeCN:H_2O(1:1), 50°C	10	>99
12	Oxone	$TsOH \cdot H_2O$	MeCN:H_2O(2:1), 50°C	10	92
13	Oxone	$TsOH \cdot H_2O$	MeCN:H_2O(1:2), 50°C	10	91
14	Oxone	$TsOH \cdot H_2O$	H_2O, 50°C	20	81
15	H_2O_2	$TsOH \cdot H_2O$	MeCN:H_2O(1:1), 50°C	20	0
16	TBHP	$TsOH \cdot H_2O$	MeCN:H_2O(1:1), 50°C	20	0
17	*t*-BuOCl	$TsOH \cdot H_2O$	MeCN:H_2O(1:1), 50°C	10	84

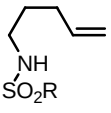
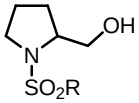
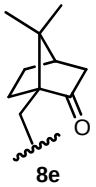
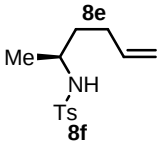
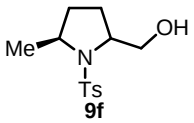
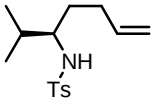
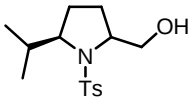
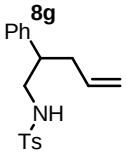
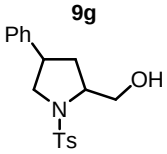
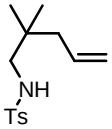
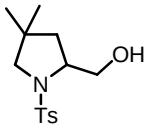
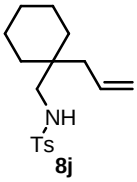
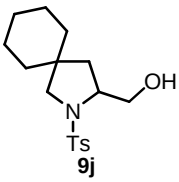
[a] Yield of **9a** with K_2CO_3 (1.5 equiv), and **8a** was recovered in 56% yield.
[b] Yield of **9a** with K_2CO_3 (3.0 equiv), and **8a** was recovered in 99% yield.

Then, the author investigated the scope of the heavy metal-free intramolecular aminohydroxylation of *N*-alkenyl sulfonamides **8** under the optimized reaction conditions (**Table 5**). The reaction of *N*-alkenyl sulfonamides bearing other sulfonyl groups, such as 4-fluorobenzenesulfonyl (**8b**), 4-nitrobenzenesulfonyl (**8c**), *n*-butanesulfonyl (**8d**), and (*S*)-camphorsulfonyl (**8e**), gave corresponding products (**9b**–**9e**) in high yields (78–97%) (entries 1–4). When monoalkyl- and dialkyl-substituted alkenylsulfonamides (**8f**–**8j**) were treated with Oxone® (1.5 or 2.0 equiv), cyclization products (**9f**–**9j**) were obtained in excellent yields (91–98%) (entries 5–9). The reaction of *N*-sulfonyl-2-allylcyclohexylamines (**8k** and **8l**) and *N*-sulfonyl-2-allylaniline (**8m**) with Oxone® (2.0 equiv) in a 2:1 mixture of MeCN and H_2O also provided hexahydroindoline derivatives (**9k** and **9l**) and the indoline derivatives (**9m**) in high yields (78–90%), respectively (entries 10–12). π-Electron-rich disubstituted internal alkenes (**8n** and **8o**) and disubstituted terminal alkene (**8p**) were efficiently converted into prolinol derivatives bearing a secondary alcohol group (**9n** and **9o**) and a quaternary carbon center (**9p**), respectively, in high yields (78–91%) (entries 13–15). Moreover, *N*-alkenyl sulfonamide bearing a hydroxy group (**8q**) also provided 4-hydroxyprolinol derivative (**9q**) in 91% yield (entry 16). Unfortunately, the reaction of diastereotopic *N*-alkenyl sulfonamides gave moderate to low diastereoselectivities (dr = 77:23–54:46).

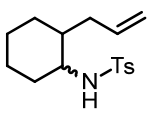
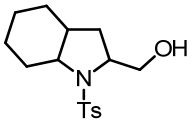
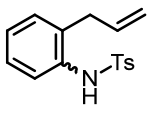
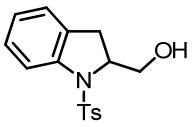
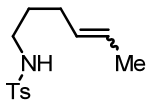
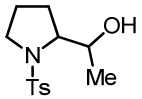
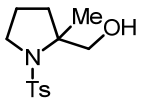
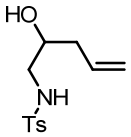
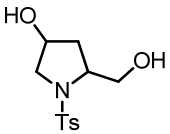
Table 5. Intramolecular Aminohydroxylation of *N*-Alkenyl Sulfonamides (**8**).



8 **9**

Entry	Substrate	Product	Time (h)	Yield of **9** (%)[a]
				
1	R = 4-F-C_6H_4 (**8b)**	**9b**	13	90
2	R = 4-NO_2-C_6H_4 (**8c**)	**9c**	10	78
3[a]	R = 4-NO_2-C_6H_4 (**8d**)	**9d**	72	97
4	R =  **8e**	**9e**	24	91 (dr = 55:45)
5	 **8f**	 **9f**	22	94 (dr = 50:50)
6[b]	 **8g**	 **9g**	78	91 (dr =52:48)
7	 **8h**	 **9h**	72	93 (dr =54:46)
8[b]	 **8i**	 **9i**	74	96
9[b]	 **8j**	 **9j**	72	98

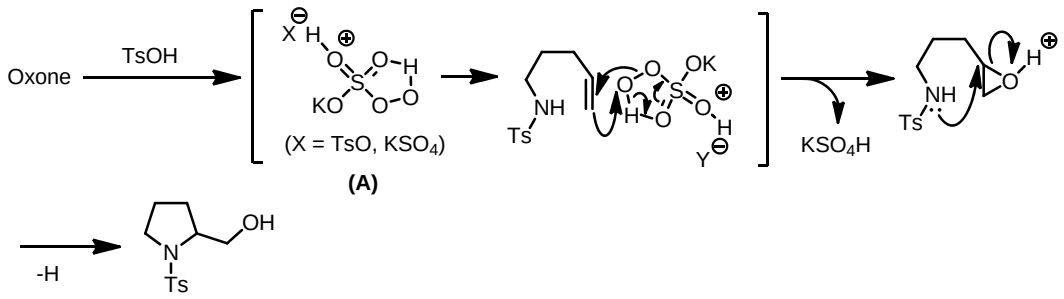
[a]Reaction was carried out at room temperature. [b]Oxone (2.0 equiv.) was used.
[c]Oxone (2.0 equiv) was used in a 2:1 mixture of MeCN and H_2O.
[d]Reaction was carried out without TsOH·H_2O at 0 °C.

Entry	Substrate	Product	Time (h)	Yield of **9**(%)[a]
				
10[c]	*cis*-**8k**	**9k**	75	90 (dr = 54:46)
11[c]	*trans*-**8l**	**9l**	58	78 (dr = 66:34)
12[c]	 **8m**	 **9m**	74	88
13[d]	 (*Z*)-**8n**	 **9n**	56	91 (dr = >99:<1)
14[d]	(*E*)-**8o**	**9o**	72	82 (dr = 77:23)
15[d]	 **8p**	 **9p**	71	78
16[d]	 **8q**	 **9q**	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 $TsOH \cdot H_2O$ at 0 °C.

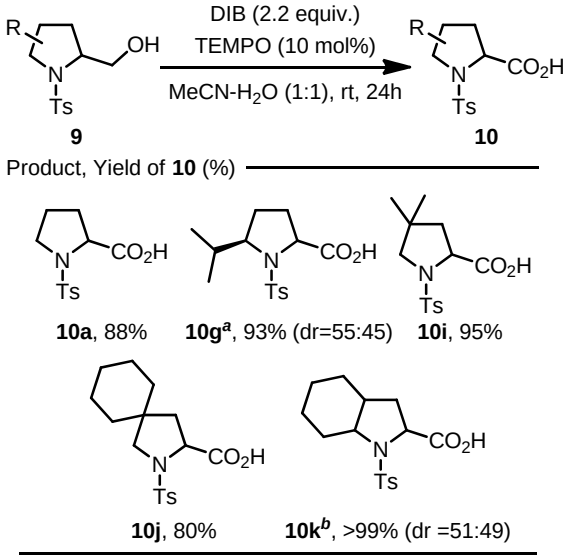
The catalytic Brønsted acid (TsOH or KSO_4H) activates Oxone® as an electrophilic oxidant to form activated peroxymonosulfate intermediate (**A**)[12] in situ. Intermediate (**A**) promotes the intramolecular aminohydroxylation of *N*-alkenylsulfonamides, particularly electron-poor mono-substituted olefins. This reaction proceeds through a tandem reaction via the epoxidation of olefins, followed by the *exo*-selective intramolecular amination of epoxides (**Scheme 6**).[12,13]

Scheme 6. Plausible Reaction Mechanism for Intramolecular Aminohydroxylation of *N*-Alkenyl Sulfonamides.



Once prolinol derivatives **9** are formed, they are readily transformed into *N*-sulfonyl proline derivatives **10** 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 (**Table 6**).[14] The reactions of **9a**, **9c**, **9d**, **9f**, and **9g** gave corresponding products **10a**, **10c**, **10d**, **10 f**, and **10g** in high yields (80–>99%), respectively.

Table 6. Oxidative Transformation of **9** into **10**.

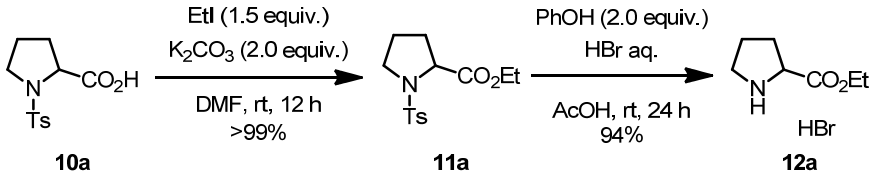


[a] **9g** (dr = 52:48) was used. [b] **9k** (dr = 54:46) was used.

Finally, the author investigated the possibility of synthesizing of proline ethyl ester **12a** through the cleavage of the sulfonyl groups of *N*-sulfonylproline **11a** under mild conditions (**Scheme 7**). Thus, **10a** was treated with EtI and K_2CO_3 to obtain *N*-tosyl-protected proline ethyl ester **11a** in a quantitative yield. Removal of the tosyl

group in **11a** with phenol in aqueous HBr solution and AcOH[15] provided desired proline ethyl ester **12a** as a hydrogen bromide salt in 94% yield.

Scheme 7. Synthesis of Proline Ethyl Ester (**12a**) by Desulfonylation of *N*-Sulfonamide (**11a**).



In conclusion, the author has developed an intramolecular aminohydroxylation of *N*-alkenyl sulfonamides (**8**) 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 (**9**). Moreover, **9** were transformed into *N*-sulfonyl proline derivatives (**10**) by oxidation using a DIB/TEMPO system and **11** was, in turn, converted into proline ethyl ester (**12**) 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 **8a**–**8e**, **8h**–**8j**, and **8n**–**8p**,[16a] **8f** and **8g**,[16b] **8k** and **8l**,[16c,d] **8m**,[16e] and **8q**[4g] were prepared according to the literature procedure. Spectroscopic data of **9a**[6b], **9h**[17a], **9i**[6b], **9m**[6b], **9q**[4g], **10a**[17b], and **11a**[17c] were in accord with those reported in the literature.

4-Fluoro-*N*-(pent-4-en-1-yl)phenylsulfonamide (8b): 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)butan-1-ylsulfonamide (8d):** 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, $CDCl_3$) δ 13.6, 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 (8e):** 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.

General Procedure for the Intramolecular Aminohydroxylation of *N*-Alkenyl Sulfonamides (8) (Table 8, entry 10 and Table 9). To a solution of **8a** (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 silica-gel column chromatography (eluent: hexane/AcOEt = 2/1) to give desired product **9a** (63.8 mg, >99% yield) as a colorless oil.

(±)-{1-[(4-Fluorophenyl)sulfonyl]pyrrolidin-2-yl}methanol (9b): 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, JC–F = 23.0 Hz) (2C), 130.2 (d, JC–F = 9.6 Hz) (2C), 133.0 (d, JC–F = 3.8 Hz), 165.3 (d, JC–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.

(±)-{1-[(4-Nitrophenyl)sulfonyl]pyrrolidin-2-yl}methanol (9c): 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, found287.0694.

(±)-[1-(Butylsulfonyl)pyrrolidin-2-yl]methanol (9d): 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 0(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-Camphorsulfonylpyrrolidin-2-yl]methanol (9e, Diastereomeric Mixture): 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 (9f, Diastereomeric Mixture). 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 (9g): 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 (9j): 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-1*H*-indol-2-yl)methanol (9k, Diastereomeric Mixture): Colorle -ss 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-1*H*-indol-2-yl)methanol (9l, Diastereomeric Mixture): 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 (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 (9n): 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 (9o): 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 (9p): 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 (9) into *N*-Sulfonyl Proline Derivatives (10) by Oxidation with a DIB/TEMPO System (Scheme 3). To a solution of **9a** (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 1M NaOH aq., and washed with AcOEt (15 mL × 3). The aqueous layer was acidified to pH 3 with 1M 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 **10a** (59.2 mg, 88% yield) as a white solid without further purification.

***(5R)*-5-Isopropyl-1-tosylpyrrolidine-2-carboxylic acid (10g, Diastereomeric Mixture):** 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 (10i): 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 (10j): 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-1*H*-indole-2-carboxylic acid (10k, Diastereomeric mixture): 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 (10a) into Proline Ethyl Ester (12a) by Detosylation under Mild Conditions (Scheme 8).

To a solution of *N*-tosyl proline (**10a**) (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. 1M 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 silica-gel column chromatography (eluent: hexane/AcOEt = 4/1) to give *N*-tosyl proline ethyl ester (**11a**) (59.4 mg, >99% yield) as a white solid. The solution of *N*-tosyl proline ethyl ester (**11a**) (74.3 mg, 0.25 mmol), 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 (**12a**) (52.6 mg, 94%) as a brown oil.

(±)-Ethyl pyrrolidine-2-carboxylate hydrobromide (12a). ^{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.

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3. Preparation of α-Bromoketones and Thiazoles from Ketones with NBS and Thioamides in Ionic Liquids.

Introduction

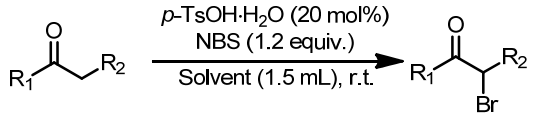
Thiazoles are one of the most important heterocycles and known for their broad spectrum of biological activities.[1] Many natural and synthetic molecules containing the thiazole moiety play a significant role in the pharmaceutical industry due to their anti-inflammatory,[2] anti-HIV,[3] anti-bacterial,[4] anti-cancer[5] properties. Today, there are many methods for the preparation of the thiazole moiety.[6] One of the most excellent and efficient methods is the Hantzsch thiazole synthesis[7] that employs the reaction of *α*-haloketones or *α*-tosyloxyketones with thioamides. For the preparation of *α*-bromonoketones from ketones, NBS (*N*-bromosuccinimide) is well used,[8] whereas HTIB [(hydroxy)(tosyloxy)iodobenzene] is the sole reagent for the direct preparation of α-tosyloxyketones from ketones.[9]

On the other hand, ionic liquids have grown in popularity as organic reaction media due to the promotion of ionic reactions and in view of environmental safety.[10] Ionic liquids offer interesting and useful features that are advantageous to organic reactions such as negligible vapor pressure, nonflammability, high thermal stability, and easy reusability. In this regard, ionic liquids have been successfully used in the Friedel-Crafts reaction,[11] hydrogenation,[12] Diels-Alder reactions,[13] Mizoroki-Heck, Suzuki-Miyaura, Sonogashira, and olefin metathesis reactions,[14] Michael additions,[15] oxidation,[16] condensation reaction,[17] formation of imines,[18] 1,2-rearrangement,[19] esterification of carboxylic acids and carboxylates,[20] Williamson ether synthesis,[21] and the Grignard reaction.[22] The author labolatory has reported efficient methods for the esterification of carboxylic acids and phosphonic acids with trialkyl orthoacetate in ionic liquid,[23a] the demethylation of *N,N*-dimethylanilines with phenyl chloroformate in ionic liquids,[23b] and the *3-exo-tet* cyclization of 2,2-disubstituted 1,3-dihalopropanes with indium in ionic liquid,[23c] The α-bromination of *β*-dicarbonyls and cyclic ketones with NBS in ionic liquids,[24] and the aromatic ring bromination with NBS in ionic liquids[25] have been reported as well. However, to the best of his knowledge, there are no synthetic studies that deal with the preparation of thiazoles from ketones with NBS and thioamides in ionic liquids. Here, as a part of his synthetic study of ionic liquids, The author would like to report the preparation of *α*-bromoketones and thiazoles from ketones, with NBS and thioamides in typical room-temperature ionic liquids.

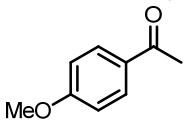
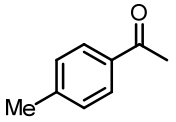
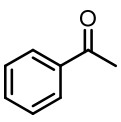
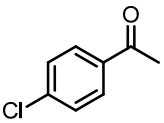
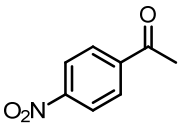
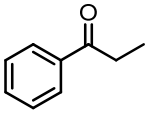
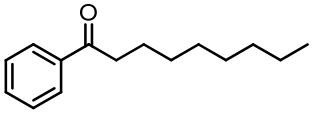
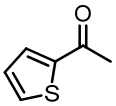
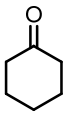
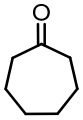
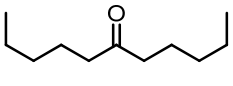
Result and discussion

The α-bromination of ketones **13** with NBS in the presence of a catalytic amount of *p*-toluenesulfonic acid mono hydrate (*p*-TsOH · H_2O) was carried out at room temperature in both chloroform and typical room-temperature ionic liquids, such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim] PF_6), *N*-butyl-*N*-methyl -pyrrolidinium bis(trifluoromethanesulfonyl)imidate ([bmpy]Tf_2N), and 1-butyl-3-me -thylimidazolium tetrafluoroborate ([bmim]BF_4), as shown in **Table 7**. As a result, the corresponding α-bromoketones **14** were obtained in good to high yields in chloroform, [bmim]PF_6, and [bmpy]Tf_2N, respectively. In contrast, the α-bromination of ketones did not proceed at all in [bmim]BF_4. It is probable that the proton derived from *p*-TsOH could not promote the formation of enol forms of ketones due to the interaction between the proton of *p*-TsOH and BF_4^-. Practically, chemical shift of a hydrogen atom

Table 7. α-Bromination of Ketones (**19**) in Several Ionic Liquids and $CHCl_3$.

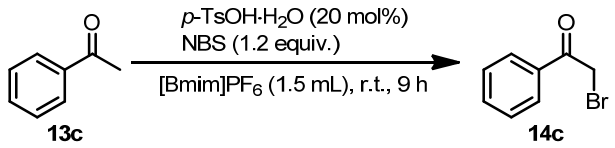


13 **14**

Substrate, Yield of **20** (%)				
				
	13a	**13b**	**13c**	**13d**
[Bmim]PF_6	86	84	90	93
[Bmim]BF_4	0	0	0	0
[Bmpy]Tf_2N	85	89	84	95
$CHCl_3$	92	96	81	94
				
	13e	**13f**	**13g**	
[Bmim]PF_6	85	74	83	
[Bmim]BF_4	0	0	0	
[Bmpy]Tf_2N	96	75	92	
$CHCl_3$	62	26	53	
				
	13h	**13i**	**13j**	**13k**
[Bmim]PF_6	81	78	73	82
[Bmim]BF_4	0	0	0	0
[Bmpy]Tf_2N	74	68	68	83
$CHCl_3$	67	57	64	66

at 2-position of [bmim]BF_4 is 9.42 ppm ($CDCl_3$, TMS), and is lower field than that of [bmim]PF_6 (8.42 ppm, $CDCl_3$, TMS). This suggests that BF_4^- in [bmim]BF_4 interacts strongly with a proton of *p*-TsOH. Moreover, the yields of *α*-bromoketones in [bmim]PF_6 and [bmpy]Tf_2N are higher overall than those in chloroform, especially when propiophenone and nonanophenone were used as substrate (**13f, 13g**). When an ionic liquid such as [bmim]PF_6 was used, α-bromoketone was obtained in good yields with good purity (>80%) by simple ether extraction of the reaction mixture and the ionic liquid reaction medium could be reused for the same reaction up to the 7th time while maintaining the high yields of α-bromoketone, as shown in **Table 8**.

Table 8. Reuse of [Bmim]PF_6 in *α*-Bromination of Acetophenone



13c **14c**

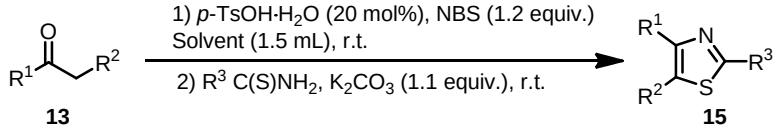
Reuse	0	1	2	3	4	5	6	7
Yield(%)	90	81	78	91	92	96	93	95

Then, the one-pot conversion of ketones **13** to thiazoles **15** in both chloroform and ionic liquids, such as [bmim]PF_6 and [bmpy]Tf_2N, was studied, as shown in **Table 9**. After the *α*-bromination of ketones with NBS, thioamide and potassium carbonate were added to the reaction mixture, and the obtained mixture was stirred at room temperature. Overall, the yields in [bmim]PF_6 and [bmpy] Tf_2N were higher than those in chloroform, particularly, when propiophenone with thiobenzamide (**15f**), acetophenone with *p*-methoxythiobenzamide (**15a**), and acetophenone with thioacetamide (**15o**) were used. In the reaction with acetophenone in [bmim]PF_6, thiazoles were obtained in good yields with moderate purity (>70%) by ether extraction, and the ionic liquid reaction medium could be reused for the same reaction, maintaining the good yields of thiazole up to the 5th time, as shown in **Table 10**.

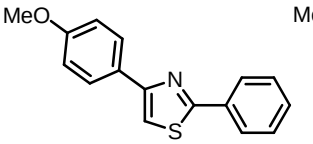
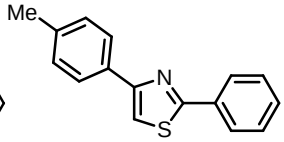
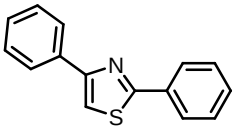
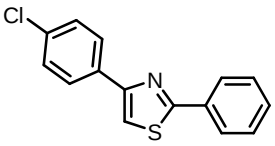
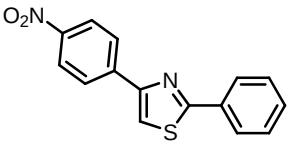
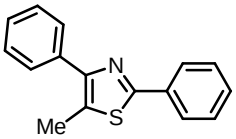
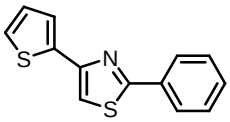
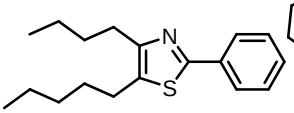
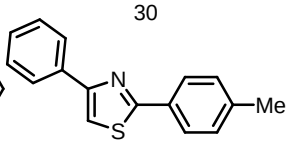
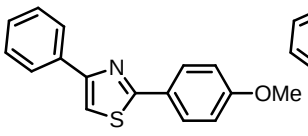
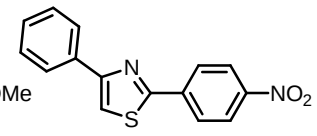
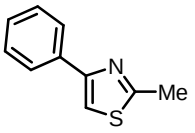
In conclusion, typical room temperature ionic liquids, such as [bmim] PF_6 and [bmpy]Tf_2N could be used for the conversion of ketones to *α*-bromoketones with NBS and the conversion of ketones to thiazoles with NBS and subsequently thioamides in a one-pot manner. *α*-Bromoketones and thiazoles could be obtained in good yields with good purity by simple ether extraction, and the ionic liquid reaction media could be reused for the same reaction while maintaining good yields and purity of the products. The present method offers a green approach to the preparation of α-bromoketones and thiazoles in good yields with good purity from ketones with NBS and subsequently

thioamides at room temperature.

Table 9. One-pot Synthesis of Thiazols (**13**) in Several Ionic Liquid and $CHCl_3$.

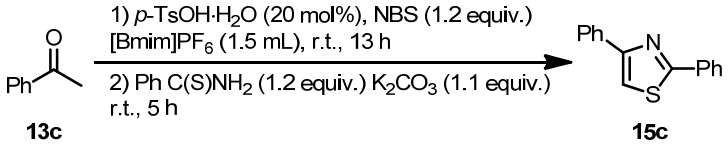


13 **15**

Product, Yield of **15** (%)			
			
	15a	**15b**	**15c**
$[Bmim]PF_6$	86	94	96
$[Bmpy]Tf_2N$	89	96	94
$CHCl_3$	86	87	73
			
	15d	**15e**	**15f**
$[Bmim]PF_6$	89	85	73
$[Bmpy]Tf_2N$	69	83	63
$CHCl_3$	73	74	30
			
	15h	**15k**	**15l**
$[Bmim]PF_6$	99	77[a]	94
$[Bmpy]Tf_2N$	-	71	-
$CHCl_3$	71	64	90
			
	15m	**15n**	**15o**
$[Bmim]PF_6$	84	85	83
$[Bmpy]Tf_2N$	61	-	75
$CHCl_3$	26	78	44

[a] Reaction temperature was 50°C.

Table 10. Reuse of [Bmim]PF_6 for preparation of 2,4-Diphenylthiazol (**15c**)



13c **15c**

Reuse	0	1	2	3	4	5
Yield(%)	95	97	91	85	89	96

Experimental Section

General procedure

^{1}H NMR and ^{13}C NMR spectra were obtained on JEOL-JNM-ECX400, JEOL-JNM-ECS400, and JEOL-JNM- ECA500 spectrometers. All chemical shifts were expressed in ppm, δ units down field from TMS (Me_4Si). Mass spectra were recorded on JEOL-HX-110 and JEOL- JMS-AT15 spectrometers. Melting points were determined on Yamato melting points apparatus Model MP-21. Silica Gel 60 (Kanto Kagaku Co.) and Wakogel B5F were used for column chromatography and preparative TLC, respectively.

Typical Procedure for Conversion of Acetophenone (13a) into *α*-Bromoacetophenone (14a) with NBS and *p*-TsOH·H_2O in Ionic Liquids: To a solution of acetophenone (**13a**, 1 mmol) in [Bmim]PF_6 (1.5 mL) were added *p*-TsOH·H_2O (0.2 mmol) and NBS (1.2 mmol). The mixture was stirred for 9.5 h at room temperature. After the reaction, the reaction mixture was extracted with diethyl ether (10 mL × 7). Then, the extract was poured into sat. aq. Na_2SO_3 solution. The organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, *α*-bromoacetophenone was obtained in the crude state. Purity was estimated by ^{1}H-NMR to be in the range of 70% - 80%. Pure α-bromoacetophenone (**14a**) was obtained by flash short column chromatography on silica gel ($CHCl_3$:Hexane = 1:1) in 90% yield.

Typical Reuse of [Bmim]PF_6:

After the extraction of the reaction mixture with diethyl ether, the ionic liquid was dried with a vacuum pump for 2 h at 80°C. To a solution of acetophenone (1 mmol) in [Bmim]PF_6 (1.5 mL) were added *p*-TsOH·H_2O (0.2 mmol) and NBS (1.2 mmol). The mixture was stirred for 9 h at room temperature. After the reaction, the reaction mixture was extracted with diethyl ether (10 mL × 7). Then, extract was poured into sat. aq. Na_2SO_3 solution. The organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, α-bromoacetophenone (**14a**) was obtained in the crude state. Purity was estimated by ^{1}H NMR to be in the range of 70% - 80%. Pure α-bromoacetophenone was obtained by flash short column chromatography on silica gel ($CHCl_3$:Hexane = 1:1) in 91 % yield.

α-Bromoacetophenone (14c): mp 54°C - 55°C (lit.[26] mp 49°C - 50°C); IR(Nujol) 2319, 1690, 1594, 1308, 1276, 1199, 991, 745, 685 cm^{-1}; ^{1}H NMR(500 MHz, $CDCl_3$): δ = 7.99 (d, 2H, *J* = 7.4 Hz, ArH), 7.62 (t, 1H, *J* = 7.4 Hz, ArH), 7.50 (t, 2H, *J* = 7.4 Hz, ArH), 4.46 (s, 2H, -CH_2-); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 133.9 (3C), 128.9, 128.8, 30.8.

α-Bromo-4'-chloroacetophenone (14d): mp 101°C - 103°C (lit.[27] mp 95°C - 96°C); IR(Nujol) 3853, 3749, 3648, 1690, 1540, 1507, 1092, 721, 509 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ = 7.99 (d, 2H, *J* = 7.3 Hz, ArH), 7.62 (t, 1H, *J* = 7.3 Hz, ArH), 7.50 (t, 2H, *J* = 8.0 Hz, ArH), 4.46 (s, 2H, -CH_2Br); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.2, 140.5, 132.2, 130.3, 129.2, 30.3.

α-Bromo-4'-methoxyacetophenone (14a): mp 70°C (lit.[28] mp 69°C - 73°C); IR(Nujol) 3853, 3749, 3648, 2309, 1683, 1598, 1508, 1322, 1306, 1260, 1205, 1170, 1116, 1020, 986, 840, 816, 721 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ = 7.97 (d, 2H, *J* = 7.8 Hz, ArH), 6.96 (d, 2H, *J* = 7.8 Hz, ArH), 4.40 (s, 2H, -CH_2-), 3.88 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.8, 163.9, 131.1, 126.7, 113.9, 55.5, 30.7.

α-Bromo-4'-methylacetophenone (14b): mp 56°C - 58°C (lit.[29] mp 48°C - 50°C); IR(Nujol) 1687, 1608, 1282, 1179, 799, 723 cm^{-1}; ^1H NMR(500 MHz, $CDCl_3$): δ = 7.88 (d, 2H, *J* = 8.6 Hz, ArH), 7.28 (d, 2H, *J* = 8.6 Hz, ArH), 4.42 (s, 2H, -CH_2Br), 2.42 (s, 3H, -CH_3) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.9, 144.9, 131.4, 129.5, 129.0, 30.9, 21.7.

α-Bromo-4'-nitroacetophenone (14e): mp 98°C - 101°C (lit.[30] mp 98°C); IR(Nujol) 3853, 3748, 3647, 2309, 1698, 1507, 966, 844, 720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.35 (d, 2H, *J* = 8.9 Hz, ArH), 8.16 (d, 2H, *J* = 8.44 Hz, ArH), 4.46 (s, 2H, -CH_2Br); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.8, 150.7, 138.3, 130.0, 124.0, 30.1.

α-Bromopropiophenone (14f): Oil; IR(Neat) 3062, 2978, 2925, 1686, 1595, 1448, 1346, 1238, 1160, , 994, 949, 707 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, 2H, *J* = 7.4 Hz, ArH), 7.59 (t, 1H, *J* = 6.9 Hz, ArH), 5.29 (q, *J* = 6.30 Hz, 1H, -CH-), 1.91 (d, *J* = 6.30 Hz, 3H, -CH3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.2, 134.0, 133.6, 128.8, 128.6, 41.4, 20.0.

α-Bromononanophenone (14g): Oil; IR(Neat) 2926, 2855, 1687, 1264, 702, 685 cm^{-1} ; ^1H NMR(500 MHz, $CDCl_3$): δ = 8.01 (d, 2H, *J* = 7.4 Hz, ArH), 7.59 (t, 1H, *J* = 7.4 Hz, ArH), 7.48 (t, 2H, *J* = 7.4 Hz, ArH), 5.13 (t, 1H, *J* = 6.8 Hz, -CHBr-), 2.24-2.07 (m, 2H, -CH_2-), 1.53-1.48 (m, 1H, -CH-), 1.43-1.27 (m, 9H, -CH_2-), 0.89-0.86 (t, 3H, *J* = 6.8 Hz, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.3, 134.5, 133.6, 128.8, 128.7, 47.3, 33.5, 31.6, 29.1, 29.0, 27.5, 22.5, 14.0.

2-(α-Bromacetyl)thiophene (14h): Oil; IR(Neat) 3544, 3297, 3091, 2942, 2469, 2319,

1660, 1517, 1412, 1355, 1289, 1238, 1193, 1112, 1079, 1061, 1041, 972, 940, 885, 859, 727, 686, 664, 632, 614 cm^{-1}; ^1H NMR(500 MHz, $CDCl_3$): δ = 7.81 (d, 1H, *J* = 4.0 Hz, thiophene), 7.72 (d, 1H, *J* = 4.6 Hz, thiophene), 7.17 (t, 1H, *J* = 4.5 Hz, thiophene), 4.36 (s, 2H, -CH_2Br); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 184.3, 140.7, 135.2, 133.5, 128.3, 30.5.

α-Bromocyclohexanone (14i): Oil; IR(Neat) 2927, 2867, 1715, 1448, 1430, 962 cm^{-1} ; ^1H NMR(400 MHz, $CDCl_3$): δ = 4.44 (t, 1H, *J* = 5.1 Hz, -CHBr-), 3.01 - 2.95 (m, 1H, -CH_2-), 2.36 - 2.29 (m, 2H, -CH_2-), 2.27 - 2.19 (m, 1H, -CH_2-), 2.06 - 1.92 (m, 2H, -CH_2-), 1.85 - 1.70 (m, 2H, -CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.4, 53.4, 37.9, 36.7, 26.7, 22.1

α-Bromocycloheptanone (14j): Oil; IR(Neat) 2933, 2857, 1709, 1454, 1322, 1186, 1159, 935 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ = 4.38 (q, 1H, *J*=4.6 Hz, -CHBr-), 2.89 - 2.82 (m, 1H, -CH-), 2.49 (qd, 1H, *J* = 8.0 Hz, *J* = 2.96, -CH-), 2.40 - 2.32 (m, 1H, -CH-), 2.06 - 1.90 (m, 3H, -CH-), 1.81 - 1.73 (m, 1H, -CH-), 1.62 - 1.51 (m, 2H, -CH-), 1.43 - 1.34 (m, 1H, -CH-); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 53.6, 39.3, 34.2, 29.5, 26.7, 24.9.

5-Bromoundecan-6-one (14k): Oil ; IR (Neat) 2958, 2860, 1717, 1464, 1406, 1377, 1241, 1125, 1053, 731; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.23 (dd, 1H, *J* = 6.6 Hz, *J* = 8.2 Hz,-CHBr-), 2.74 - 2.58 (m, 2H, -CH_2-), 2.04 - 1.88 (m, 2H, -CH_2-), 1.62 (quant, 2H, *J* = 7.3 Hz,-CH_2-), 2.04 - 1.27 (m, 8H, -CH_2-), 0.90 (q, *J* = 5.5 Hz, 6H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.4, 53.7, 38.9, 33.1, 31.2, 29.4, 23.6, 22.4, 22.1, 13.9, 13.8.

Typical Procedure for Conversion of Acetophenone (13a) into 2,4-Diphenylthiazole (15c) in Ionic Liquid with NBS and Benzthioamide: To a solution of acetophenone (**13a**) (1 mmol) in [Bmim]PF_6 (1.5 mL) were added *p*-TsOH H_2O (0.2 mmol) and NBS (1.2 mmol). The mixture was stirred for 9 h at room temperature. Then, benzthioamide (1.2 mmol) and K_2CO_3 (1.1 mmol) were added to the reaction mixture and the obtained mixture was stirred for 5 h at room temperature. After the reaction, the reaction mixture was extracted with diethyl ether (10 mL × 10). Then, the extract was washed with sat. aq. Na_2SO_3 solution. The organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, 2,4-diphenylthiazole was obtained in the crude state. Pure 2,4-diphenylthiazol (**15c**) was obtained by flash short column chromatography on silica gel ($CHCl_3$:Hexane = 1:1) in 96 % yield.

Reuse of [Bmim]PF_6:

After extraction of the reaction mixture with diethyl ether, the ionic liquid was washed

with water (1 mL). The mixture was dried with a vacuum pump for 2 h at 80°C. To a solution of acetophenone (1 mmol) in [Bmim]PF_6 (1.5 mL) were added *p*-TsOH H_2O (0.2 mmol) and NBS (1.2 mmol). The mixture was stirred for 12.5 h at room temperature. Then, benzthioamide and K_2CO_3 (1.1 mmol) were added and the obtained mixture was stirred for 5h at room temperature. After the reaction, the reaction mixture was extracted with diethyl ether (10 mL × 10). Then, the extract was washed with sat. aq. Na_2SO_3 solution. The organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, 2,4-diphenylthiazole was obtained in the crude state. Pure 2,4-diphenylthiazole was obtained by flash short column chromatography on silica gel ($CHCl_3$:Hexane = 1:1) in 97% yield

2-Phenyl-4-(4'-methoxyphenyl)thiazole (15a): mp 126°C - 127°C (lit.[31] mp 134°C - 135°C). IR(Nujol); 3748, 3648, 2309, 1607, 1520, 1307, 1255, 1172, 1029, 979, 833, 737, 722 cm^{-1}; ^1H NMR(500 MHz, $CDCl_3$): δ = 8.03 (d, 2H, *J* = 6.3 Hz, ArH), 7.93 (d, 2H, *J* = 8.6 Hz, ArH), 7.45-7.43 (m, 3H, ArH), 7.34 (s, 1H, thiazole), 6.97 (d, 2H, *J* = 9.1 Hz, ArH), 3.86 (s, 3H, -OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6, 159.6, 156.1, 133.8, 129.9, 128.8, 127.7, 127.5, 126.5, 114.0, 110.8, 55.3.

2-Phenyl-4-(4'-methylphenyl)thiazole (15b): mp 108°C (lit.[32] mp 116°C); IR(Nujol) 3853, 3749, 3648, 2309, 1698, 1540, 1507, 973, 722 cm^{-1} ; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.04 - 8.02 (d, 2H, *J* = 6.3 Hz, ArH), 7.89 - 7.87 (d, 2H, *J* = 8.0 Hz, ArH), 7.46 - 7.41 (m, 3H, ArH), 7.40 (s, 1H, thiazole), 7.25 - 7.23 (d, 2H, *J* = 6.3 Hz, ArH), 2.39 (s, 3H, -CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6, 156.3, 137.9, 133.8, 131.8, 129.9, 129.3, 128.8, 126.5, 126.3, 111.8, 21.2.

2,4-Diphenylthiazole (15c): mp 78°C (lit.[32] mp 75°C - 78°C). IR(Nujol) 760, 725, 465 cm^{-1}; ^1H NMR(500 MHz, $CDCl_3$): δ = 8.05 (d, 2H, *J* = 8.0 Hz, ArH), 8.00 (d, 2H, *J* = 8.0 Hz, ArH), 7.49 - 7.42 (m, 6H, thiazole, ArH), 7.35 (t, 1H, *J* = 7.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 156.2, 134.4, 133.7, 130.0, 128.8, 128.7, 128.1, 126.5, 126.4, 112.5.

2-Phenyl-4-(4'-chlorophenyl)thiazole (15d): mp 128°C (lit.[31] mp 131°C - 132°C). IR(Nujol) 1235, 1051, 766, 722 cm^{-1}; ^1H NMR(500 MHz, $CDCl_3$): δ = 8.03 (d, 2H, *J* = 8.0 Hz, ArH), 7.93 (d, 2H, *J* = 8.5 Hz, ArH), 7.48-7.44 (m, 4H, ArH, thiazole), 7.41 (d, 2H, *J* = 8.5 Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.1, 155.0, 133.9, 133.5, 132.9, 130.1, 128.9, 128.8, 127.6, 126.5,112.8.

2-Phenyl-4-(4'-nitrophenyl)thiazole (15e): mp 125°C - 127°C (lit.[33] mp 122°C); IR (Nujol) 1597, 1509, 1341, 1058, 974, 842, 734, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, 2H, *J* = 8.8 Hz, ArH), 8.17 (d, 2H, *J* = 8.8 Hz, ArH), 8.06 - 8.03 (m, 2H, ArH), 7.69 (s, 1H, thiazole), 7.52 - 7.48 (m, 3H, ArH); ^{13}C NMR (125 MHz,$CDCl_3$): δ = 168.7, 153.7, 147.2, 140.2, 133.1, 130.5, 129.0, 126.9, 126.6, 124.1, 115.9.

2,4-Diphenyl-5-methylthiazole (15f): mp 75°C - 76°C (lit.[34] mp 76°C); IR(Nujol) 2723, 1306, 970, 760, 721, 690 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ = 7.96 (d, 2H, *J* = 6.4 Hz, ArH), 7.73 (d, 2H, *J* = 6.8 Hz, ,ArH), 7.48 - 7.39 (m, 6H, ArH, thiazole), 2.61 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 151.9, 135.1, 133.8, 129.5, 128.7, 128.6, 128.3, 127.5, 126.2, 12.8.

2-Phenyl-4-(2'-thienyl)thiazole (15h): mp 58 - 60 (lit.[35] mp 69°C - 71°C); IR(Nujol) 1664, 1024, 970, 763, 691, 740 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ = 8.04 - 8.01 (m, 2H, ArH), 7.53 (dd, 1H, *J* = 3.6 Hz, *J* = 1.1 Hz, thienyl), 7.49 - 7.45 (m, 3H, ArH), 7.35 (s, 1H, thiazol), 7.32 (dd, 1H, *J* = 5.0 Hz, *J* = 1.1 Hz, thienyl), 7.10 (dd, 1H, *J* = 3.6 Hz, *J* = 5.2 Hz, thienyl); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 150.7, 138.3, 133.3, 130.1, 128.9, 127.6, 126.6, 125.3, 124.2, 111.3.

4-Butyl-2-phenyl-5-pentylthiazole (15k): Oil. IR (neat) 2928, 2857, 1536, 1461, 1248, 991, 760, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, 2H, *J* = 6.6 Hz, ArH), 7.41-7.33 (m, 3H, ArH), 2.75 (t, 2H, *J* = 7.5 Hz, $-CH_2-$), 2.68 (t, 2H, *J* = 7.5 Hz, $-CH_2-$), 1.71 (quant, 2H, *J* = 7.5 Hz, $-CH_2-$), 1.63 (quant, 2H, *J* = 7.8 Hz, $-CH_2-$), 1.46 - 1.33 (m, 6H, $-CH_2-$), 0.95 (t, 3H, *J* = 7.3 Hz, $-CH_3$), 0.90 (t, 3H, *J* = 7.1 Hz, $-CH_3$) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.5, 153.4, 134.2, 132.7, 129.2, 128.7, 126.1, 34.2, 31.7, 29.6, 29.2, 26.1, 22.5, 22.2, 14.0, 13.8; HRMS Calcd for $C_{18}H_{26}NS$ 288.1780, Found; 288.1774.

4-Phenyl-2-(4'-methylphenyl)thiazole (15l): mp 120°C - 122°C (lit. [36] mp 127°C - 128°C); IR(Nujol) 1056, 972, 814, 739, 689 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ = 7.99 (d, 2H, *J* = 7.3 Hz, ArH), 7.93 (d, 2H, *J* = 8.2 Hz, ArH), 7.46 - 7.42 (m, 2H, ArH, thiazol), 7.34 (t, 1H, *J* = 7.3 Hz, ArH) 7.26 (d, 1H, *J* = 6.4 Hz, ArH) 2.41 (s, 3H, $-CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0, 156.1, 140.2, 134.6, 131.1, 129.5, 128.6, 128.0, 126.5, 126.4, 112.1, 21.4.

4-Phenyl-2-(4'-methoxyphenyl)thiazole (15m): mp 96°C - 98°C (lit.[36] mp 101°C); IR(Nujol) 1519, 1254, 979, 833, 737 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ = 7.98 (d, 2H, *J* =

9.1 Hz, ArH), 7.44 (t, 2H, *J* = 7.3 Hz, ArH), 7.41 (s, 1H, thiazole), 7.34 (t, 1H, *J* = 7.3 Hz, ArH), 3.86 (s, 3H, -OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.6, 161.1, 155.9, 134.6, 128.6, 128.0, 126.7, 126.3, 114.2, 111.7, 55.3.

2-(4'-Nitrophenyl)-4-Phenylthiazol (15n): mp 162°C - 164°C (lit.[36] mp 164°C - 165°C); IR(Nujol) 1595, 1512, 1340, 848, 751, 722, 687 cm^{-1}; ^1H NMR(500 MHz, $CDCl_3$): δ = 8.33 (d, 2H, *J* = 9.2 Hz, ArH), 8.22 (d, 2H, *J* = 9.2 Hz, ArH), 8.00 (d, 2H, *J* = 6.8 Hz, ArH), 7.62 (s, 1H, thiazol), 7.47 (t, 1H, *J* = 7.4 Hz, ArH), 7.39 (t, 1H, *J* = 7.4 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 157.3, 148.4, 139.1, 133.8, 128.8, 128.6, 127.1, 126.4, 124.3, 114.5.

2-Methyl-4-phenylthiazole (15o): mp 64°C (lit.[37] mp 64°C); IR(Nujol) 740, 726, 692, 675 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$): δ = 7.87 (d, 2H, *J* = 6.8 Hz, ArH), 7.41 (t, 2H, *J* = 7.8 Hz, ArH), 7.33-7.30 (m, 2H, ArH, thiazole), 2.78 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 155.1, 134.5, 128.6, 127.9, 126.2, 112.2, 19.3.

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List of Publications

Papers

1) Izumisawa, Y.; Togo, H. "Preparation of *α*-Bromoketones and Thiazoles from Ketones with NBS and Thioamides in Ionic Liquids", *Green and Sustainable Chemistry*, *1* (3), p54-62, **2011**

2) Moriyama, K.; Izumisawa, Y.; Togo, H. "Oxidative Intramolecular Bromo-Amination of *N*-Alkenyl Sulfonamides via Umpolung of Alkali Metal Bromides", *J. Org. Chem.*, *76* (17), p7249-7255, **2011**

3) Moriyama, K.; Izumisawa, Y.; Togo, H. "Brønsted Acid-assisted Intramolecular Aminohydroxylation of *N*-Alkenylsulfonamides under Heavy Metal-free Conditions", *J. Org. Chem.*, 77 (21), p9846-9851, **2012**

Poster

1) *α*-Bromination of Ketones Using NBS in Ionic Liquids and its application of preparation of Thiazoles.
The 90th Annual Meeting of Japan Chemical Society, Osaka, March 26, **2010**.

2) Intramolecular Amidehydroxylation of *N*-alkenyl sulfonamides with Inorganic Reagent.
The 92th Annual Meeting of Japan Chemical Society, Tokyo, March 27, **2012**.

3) Intramolecular Bromo-oxygenation of Alkenylcarboxylic acids and Alkenylalcohols *via* Oxidative Umpolung of Alkali Metal Bromides.
The 93th Annual Meeting of Japan Chemical Society, Shiga, March 24, **2013**.

4) Intramolecular Aminohydroxylation of *N*-Alkenyl Sulfonamides with Inorganic Reagent.
IKCOC-12, Kyoto, PC-063, November 15, **2012**.

Oral

1) Intramolecular Bromoamidation of *N*-alkenylsulfonamides *via* Oxidative Umpolung Reaction of Inorganic Bromides.
The 91th Annual Meeting of Japan Chemical Society, Kanagawa, March 29, **2011**

2) Intramolecular Bromo-etherification *via* the Oxidative Umpolung of Bromide Ion. The 94th Annual Meeting of Japan Chemical Society, Kanagawa, March 29, **2014**