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AN EFFECTIVE PROCEDURE TO PROMOTE AZA–PRINS CYCLIZATION REACTIONS EMPLOYING A COMBINATION OF FERRIC CHLORIDE AND AN IMIDAZOLIUM SALT IN BENZOTRIFLUORIDE

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Abstract – Aza–Prins cyclization reactions of *N*-tosyl-3-butenylamine with *p*-methoxybenzaldehyde, 1-naphthaldehyde and 2-naphthaldehyde take place efficiently using a combination of ferric chloride and 1-butyl-3-methylimidazolium hexafluorophosphate in benzotrifluoride (FeIm–BTF procedure). The new methodology, leading to formation of target *N*-tosyl-4-chloro-2-substituted piperidines, is superior to the one using 1-butyl-3-methylimidazolium tetrachloroferrate. The FeIm–BTF procedure was also applied to aza–Prins cyclization reactions of other aldehydes. Finally, the effects of imidazolium salts on aza–Prins cyclization reaction promoted by boranetrifluoride-diethyl ether complex, leading to formation of fluorinated piperidines, were explored.

INTRODUCTION

Piperidines are biologically and pharmaceutically relevant nitrogen heterocycles. As a result, they have attracted interest as synthetic targets.[1] The aza–Prins cyclization reaction is among the most useful methods to construct piperidines.[2,3] We recently reported that the use of a combination of ferric chloride ($FeCl_3$) and 1-butyl-3-methylimidazolium hexafluorophosphate ($BmimPF_6$) or tetrachloroferrate

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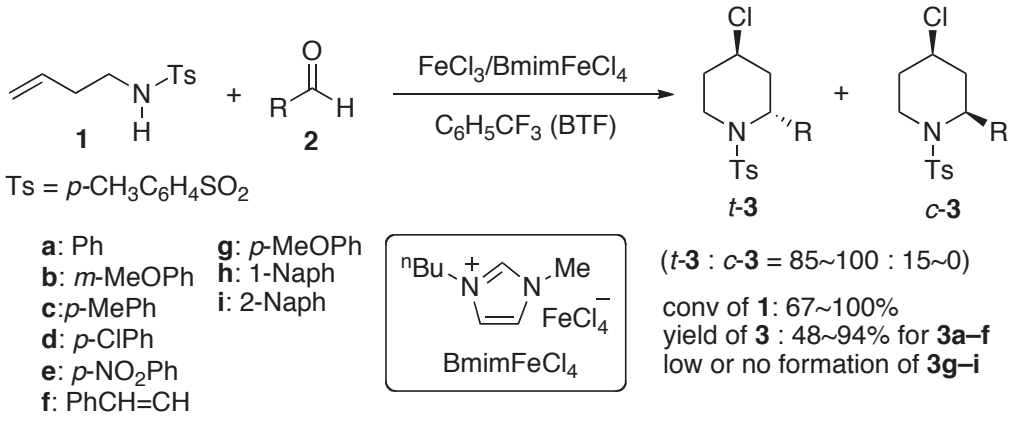
Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday

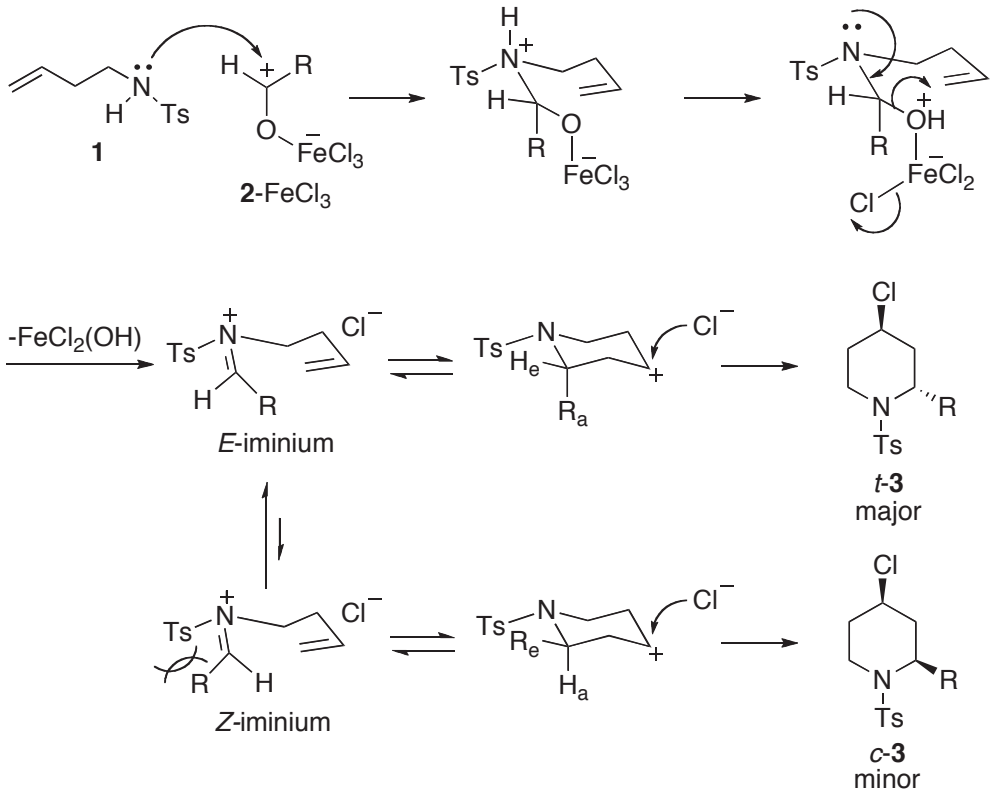
($BmimFeCl_4$) in benzotrifluoride (BTF) (named as FeIm–BTF procedure)[4] is effective in promoting aza–Prins cyclization reactions.[5] The FeIm–BTF procedure has several attractive features, including the employment of a liquid-liquid biphasic reaction mixtures, and the fact that both the imidazolium salts[6] and BTF[7] are environmentally benign solvents and $FeCl_3$ is an inexpensive and nontoxic iron reagent. Therefore, the FeIm–BTF procedure for carrying out the aza–Prins process is compatible with green sustainable chemistry.[8]

Application of the FeIm–BTF procedure using $BmimFeCl_4$ to the reaction of *N*-tosyl-3-butenylamine **1** and aromatic aldehydes **2a–f** results in formation of the desired *N*-tosyl-4-chloro-2-substituted piperidines **3a–f** in good to excellent yields with high levels of diastereoselectivity (Scheme 1).[5]



Scheme 1

Observed diastereoselectivity is rationalized by the plausible reaction pathways described in Scheme 2.[5] $FeCl_3$ activated aldehyde (**2**–$FeCl_3$) is attacked by **1** to give the zwitterionic ammonium intermediate. Proton transfer in the ammonium produces the hydroxonium intermediate. Releasing the ferric salt gives the iminium intermediate whose *E*-form and *Z*-form are in the equilibrium with each other. Since *E*-form is more stable than *Z*-form due to the steric repulsion between Ts and R groups, the formation of the piperidine cation possessing axial R is more favorable than that of the piperidine cation possessing equatorial R, and then in situ generated chloride ion attacks to these piperidine cations from the less crowded upper side. Consequently, *t*-**3** is exclusively formed.



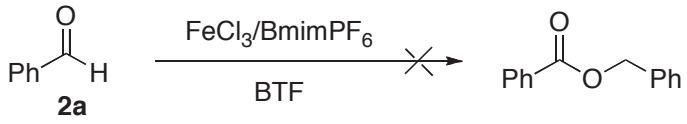
Scheme 2

On the other hand, it was also found that *p*-methoxybenzaldehyde **2g**, 1-naphthaldehyde **2h**, and 2-naphthaldehyde **2i** are much less reactive under these conditions (Scheme 1). In fact, only 8% of *t*-**3i** is obtained at 8% conversion of **1**, and neither **2g** nor **2h** undergo the desired reactions. We have undertaken an effort to uncover suitable reaction conditions that would promote the inefficient reactions described above. The results of the studies described below have shown that piperidines **3g–i** can be generated by using the FeIm–BTF procedure when $BmimFeCl_4$ is replaced by $BmimPF_6$. The improved procedure was applied to aza–Prins cyclization reactions of other aldehydes including **2f**. In this effort, the effects of imidazolium salts on aza–Prins cyclization reaction of **1** with **2a** promoted by boranetrifluoride-diethyl ether complex and leading to formation of fluorinated piperidines, were also explored.

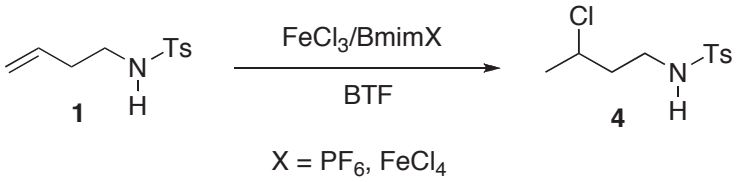
RESULTS AND DISCUSSION

Preliminary observations made in this investigation suggest that an increase in the quantity of $FeCl_3$ and a decrease in the volume of BTF leads to increased yields of **3a** in the reaction of **1** and **2a** using $BmimPF_6$.[5] Thus, we decided to conduct the reactions using $BmimPF_6$. An exploratory study was carried out with the aim of identifying possible side products formed in the reaction of **1** and **2a** with $FeCl_3$. Although it is known that **2a** undergoes a Lewis acid promoted Tishchenko reaction,[9] when **2a** (0.75 mmol) is treated with $FeCl_3$ (2.0 equiv) and $BmimPF_6$ (1.0 equiv) in BTF (1.0 mL) at room temperature

for 24 h, the expected Tishchenko-type ester product is not generated and, instead, only a mixture of unidentifiable substances were produced together with recovered **2a** (Scheme 3). On the other hand, treatment of **1** (0.50 mmol) with $FeCl_3$ (3.0 equiv for X = PF_6, 1.5 equiv for X = $FeCl_4$) and an imidazolim salt ($BmimPF_6$ or $BmimFeCl_4$, 1.5 equiv) in BTF (1.0 mL) at room temperature for 24 h leads to formation of **4** in yields of 82% for $BmimPF_6$ and 60% (85% conversion of **1**) for $BmimFeCl_4$ (Scheme 4). Although not proven, the mechanism for this process likely involves formal electrophilic addition to the alkene moiety of **1** by HCl, generated from water present in the reaction mixture.



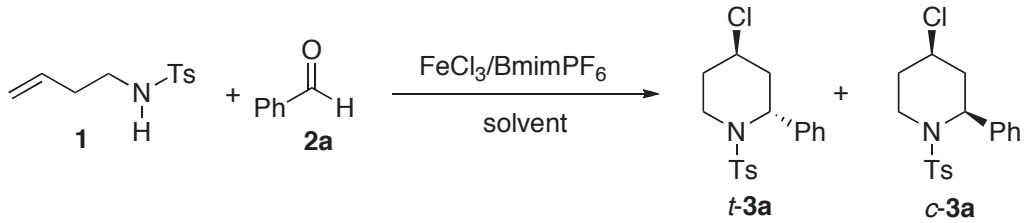
Scheme 3



Scheme 4

Factors that influence the yields of the reaction of **2a** with **1**, promoted by $BmimPF_6$, were explored next (Table 1). The results show that an increase in the concentration of $FeCl_3$ significantly shortens the reaction time without decreasing the yield of **3a** (compare entries 2, 3 with 1, also see Scheme 1). Moreover, the reaction does not occur to completion, the yield of **3a** significantly decreases, and **4** (11%) is also produced when $BmimPF_6$ is not included in the reaction mixture (entry 4). An exploration of other solvents for the reaction promoted by FeIm reagent revealed that $FeCl_3$ and $BmimPF_6$, while not being soluble in toluene and cyclohexane, dissolve in CH_2Cl_2, MeCN, and DMF. Although heterogeneous reactions in the former solvents lead to moderate to good yields of **3a**, purification of the product is difficult (entries 5 and 6). Moreover, while the yield of **3a** formed by homogeneous reaction in CH_2Cl_2 is comparable with that in BTF (compare entry 7 with 3), the efficiency of the process in MeCN is low and the reaction does not proceed in DMF (entries 9 and 10). Another notable observation is that **4** (43%) is produced to a considerable extent when $BmimPF_6$ is not present in the reaction conducted in CH_2Cl_2 (entry 8).

Table 1. Aza–Prins cyclization reaction of **1** with benzaldehyde **2a** promoted by $FeCl_3$ with $BmimPF_6$[a]

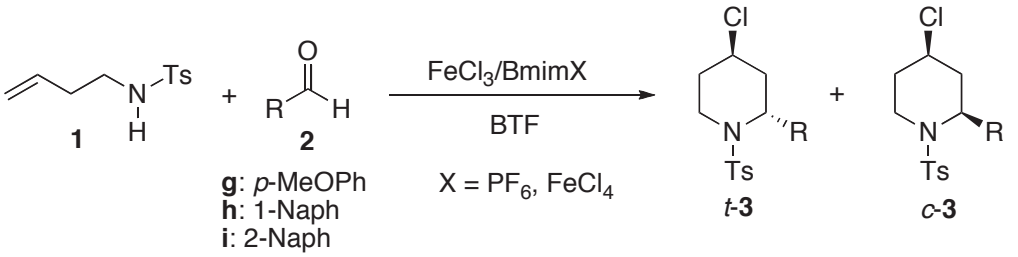


Entry	$BmimPF_6$ (equiv vs **1**)	Solvent	Reaction time (h)	Conversion of **1** (%)	Yield of **3a** (*t*-**3a** : *c*-**3a**) (%)[b]
1[c]	1.5	BTF	24	100	82 (90 : 10)
2	1.5	BTF	6	100	88 (86 : 14)
3	1.5	BTF	4	100	84 (87 : 13)
4	0	BTF	4	49	~26[d](83 : 17)[f]
5	1.5	$PhCH_3$	4	100	~88[d](e)
6	1.5	*c*-C_6H_{12}	4	100	~50[d](e)
7	1.5	CH_2Cl_2	4	100	85 (87 : 13)
8	0	CH_2Cl_2	4	71	~12[d](e)[f]
9	1.5	MeCN	4	~82[d]	~24[d](e)
10	1.5	DMF	4	0	0

[a]Tosylamine **1** (0.50 mmol), **2a** (1.5 equiv vs **1**), $FeCl_3$ (3.0 equiv vs **1**), Solvent (1.0 mL), at room temperature. [b]Isolated yields. [c]Ref. 5 (also see Scheme 1). [d]Small quantities of impurities are included. [e]Not determined. [f]**4** was obtained.

Based on the results described above, we have designed studies aimed at improving FeIm–BTF promoted aza–Prins cyclization reactions (Table 2).[10] The observations made in this effort show that when quantity of BTF is decreased by one fifth, product **3** still forms (compare entry 3 with 1, 6 with 5, and 9 with 8, respectively), but when 3.0 equivalents of $FeCl_3$ are used along with $BmimFeCl_4$, **3** is not generated and **4** is formed exclusively (see entries 2 and 10). In contrast, conditions utilizing 3.0 equivalents of $FeCl_3$ with $BmimPF_6$ lead to a significantly accelerated reaction and an increased yield of **3** (entries 4, 7 and 11). While the use of CH_2Cl_2 is comparable to BTF as solvent for the reaction promoted by $BmimPF_6$ (compare 13 with 11), CH_2Cl_2 is a better solvent than BTF for the $BmimFeCl_4$ induced process (compare 12 with 9).

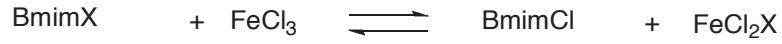
Table 2. Aza–Prins cyclization reactions of **1** with aldehydes **2g–i** promoted by $FeCl_3$ with BmimX[a]



Entry	**2**	X	$FeCl_3$ (equiv vs **1**)	Solvent (mL)	Conversion of **1** (%)	Yield of **3** (*t*-**3** : *c*-**3**) (%)[b]
1[c]	**2g**	$FeCl_4$	1.5	BTF (5.0)	0	0
2	**2g**	$FeCl_4$	3.0	BTF (5.0)	e	0
3	**2g**	$FeCl_4$	1.5	BTF (1.0)	39	33 (91 : 9)
4	**2g**	PF_6	3.0	BTF (1.0)	100	73 (92 : 8)[g]
5[c]	**2h**	$FeCl_4$	1.5	BTF (5.0)	0	0
6	**2h**	$FeCl_4$	1.5	BTF (1.0)	8	~8[f] (53 : 47)
7	**2h**	PF_6	3.0	BTF (1.0)	~94[f]	~70[f] (43 : 57)
8[c]	**2i**	$FeCl_4$	1.5	BTF (5.0)	8	8 (100 : 0)
9	**2i**	$FeCl_4$	1.5	BTF (1.0)	46	42 (89 : 11)
10	**2i**	$FeCl_4$	3.0	BTF (1.0)	e	0
11	**2i**	PF_6	3.0	BTF (1.0)	100	79 (87 : 13)
12	**2i**	$FeCl_4$	1.5	CH_2Cl_2 (1.0)	77	68 (89 : 11)
13	**2i**	PF_6	3.0	CH_2Cl_2 (1.0)	100	80 (87 : 13)
14	**2i**	d	1.5	CH_2Cl_2 (1.0)	50	43 (89 : 11)

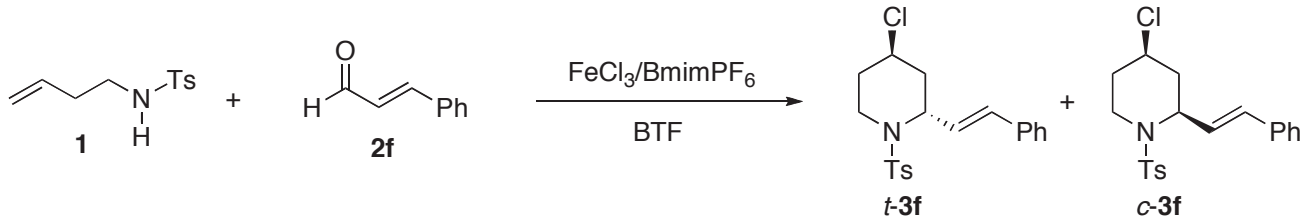
[a]Tosylamine **1** (0.50 mmol), **2** (1.5 equiv vs **1**), at room temperature, for 24 h. [b]Isolated yields. [c]Ref. 5 (also see Scheme 1). [d]No BmimX was added. [e]Some recovery of **1** and formation of **4** were observed. [f]Small quantities of impurities are included. [g]Determined by ^{1}H-NMR.

The results clearly show that the presence of an imidazolium salt accelerates the reaction (compare entry 14 with 12, also see entries 3, 4, 7, and 8 in Table 1). Although the exact role of the salts is not clear, mixing of $FeCl_3$ with BmimX may cause an ion pair exchange process to occur[11] to give another more reactive Fe(III) species ($FeCl_2X$) (Scheme 5). When 1.5 equivalents of $BmimPF_6$ and 3.0 equivalents of $FeCl_3$ are employed to promote reaction of 1.0 equivalents of **1** (see Table 1 and 2), $FeCl_2PF_6$ is likely present in the reaction mixture. Thus, it is possible that $FeCl_2PF_6$ is a more effective promoter of the aza–Prins cyclization reaction than is $FeCl_3$, which itself leads to a process that forms **4** (Table 1, entries 4 and 8; Table 2, entries 2 and 10).

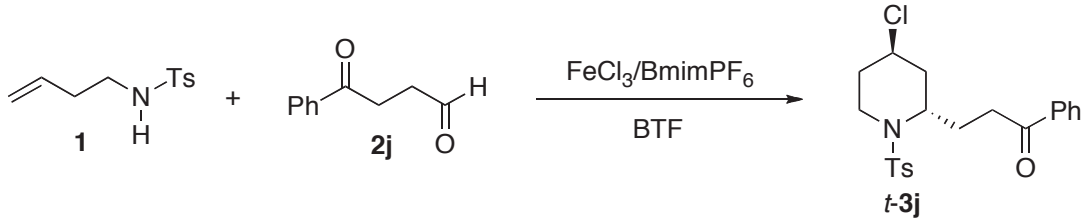


Scheme 5

In order to explore advantageous feature of the FeIm–BTF procedure further (entries 4, 7, and 11 in Table 2), it was applied to the reaction of **2f** with **1** (Scheme 6). While the reaction time (5 h) was shorter than that (24 h) in Table 2, this process generates piperidine **3f** in 74% yield (*t*-**3f** : *c*-**3f** = 78 : 22) at 89% conversion of **1**, which is greater than that previously reported (48% yield at 62% conversion of **1**, see Scheme 1). This procedure was also applied to the reaction of keto-aldehyde **2j** (Scheme 7), which was found to form *trans*-**3j** in 80% yield while *cis*-**3j** could not be isolated. This observation suggests that ketone carbonyl is unaffected under the FeIm–BTF conditions.

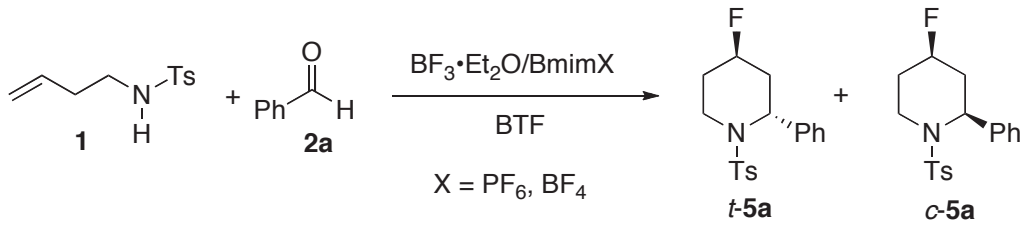


Scheme 6



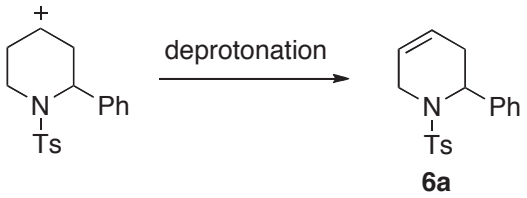
Scheme 7

In order to determine if imidazolium salts effect other Lewis acid promoted reactions, we studied the fluorinated piperidine forming aza–Prins cyclization reaction promoted by the boranetrifluoride-diethyl ether complex.[12,13] Treatment of a mixture of **1** (0.50 mmol) and **2a** (1.5 equiv vs **1**) with BF_3•Et_2O (1.5 equiv vs **1**) in the presence of an imidazolim salt (BmimX: 1.5 equiv vs **1**) in BTF (1.0 mL) at room temperature for 24 h, leads to generation of the fluorinated piperidine **5a** as a mixture of diastereoisomers (*t*-**5a** : *c*-**5a**) in moderate yields, 53% (*t*-**5a** : *c*-**5a** = 24 : 76) and 54% (*t*-**5a** : *c*-**5a** = 23 : 77) for the respective $BmimPF_6$ and $BmimBF_4$ induced reactions (Scheme 8).[14] Reaction in the absence of BmimX generates **5a** but in only 29% yield (*t*-**5a** : *c*-**5a** = 32 : 68).



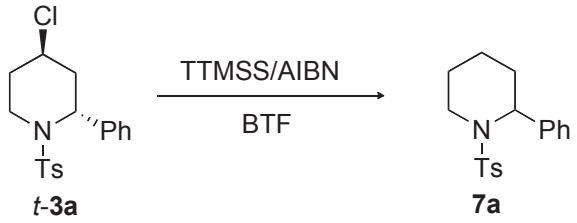
Scheme 8

It should be noted that the reaction of **1** with **2a** promoted by $BmimPF_6$ also affords a small quantity of tetrahydropyridine **6a** (6%), which is perhaps produced via deprotonation of a cationic intermediate (Scheme 9).



Scheme 9

In order to explore possible derivatization reactions of the piperidines produced in the aza–Prins cyclization reactions, a transformation of **3a** was briefly explored. We observed that free radical reaction of *t*-**3a** using $[(CH_3)_3Si]_3SiH$ (TTMSS)[15] and AIBN at 85 ºC for 24 h proceeds smoothly to give dechlorinated piperidine **7a** in 97% (Scheme 10).



Scheme 10

In conclusion, the investigation described above has led to the development of the FeIm–BTF procedure for promotion of aza–Prins cyclization reactions of *N*-tosyl-3-butenylamine with *p*-methoxybenzaldehyde, 1-naphthaldehyde and 2-naphthaldehyde, processes that do not take place efficiently under the previously devised conditions.[5] Significant improvements in the yields of the desired *N*-tosyl-4-chloro-2-substituted piperidines were achieved. A combination of an imidazolium salt and BTF was also applied to carry out the boranetrifluoride-diethyl ether complex promoted aza–Prins cyclization reaction. Among noteworthy observations made in this effort are that addition of imidazolium salts accelerate the Lewis acid promoted aza–Prins cyclization in both BTF and CH_2Cl_2, and that $BmimPF_6$ is a more effective additive than $BmimFeCl_4$ in this regard. Although not extensively explored yet, a homolytic cleavage of the carbon-chlorine bond in the aza–Prins cyclization product *t*-**3a** via a free radical pathway, suggests an interesting method to form and utilize piperidine radicals as synthetically useful intermediates.

EXPERIMENTAL

NMR spectra were recorded in $CDCl_3$ with Me_4Si as an internal standard at 270 MHz, 400 MHz and 700 MHz for ^{1}H-NMR, and 68 MHz, 100 MHz and 176 MHz for ^{13}C-NMR. Benzotrifluoride (BTF, –63.7 ppm) was used as an internal standard for ^{19}F–NMR spectra (376 MHz). Column chromatography was performed with silica gel (Wakogel C-200). Preparative TLC was performed on 20 cm x 20 cm plates

coated with silica gel (Wakogel B-5F). $FeCl_3$ and BF_3•Et_2O were purchased and used for the aza-Prins cyclization reactions. BTF, DMF, *c*-C_6H_{12}, $BmimPF_6$, and $BmimFeCl_4$ were purchased and used without distillation. CH_2Cl_2 and toluene were treated with H_2SO_4, water, 5% NaOH, water, $CaCl_2$, and then distilled with CaH_2. MeCN was distilled over P_2O_5 and subsequently distilled with K_2CO_3. Other reagents and solvents were purchased and used without further purification.

Starting Materials. 1-Phenyl-1,4-butanedione **(2j)** were prepared by previously reported procedures.[16] Other aldehydes **2** were purchased and used without purifications.

Preparation of *N*-(3'-Buthenyl)phthalimide. 4-Bromo-1-butene (2.23 mL, 22.0 mmol) was added to the suspention of potassium phthalimide (3.71 g, 20.0 mmol) in anhydrous DMF (30 mL). The mixture was stirred under N_2 at 80 °C for 20 h. The reaction was quenched by water (30 mL) and extracted with Et_2O. The combined organic extracts were washed with water, sat. aqueous $Na_2S_2O_3$, sat. aqueous $NaHCO_3$ and sat. aqueous NaCl. The Et_2O solution was dried over $MgSO_4$, and the filtrated to give crude *N*-(3'-Butenyl)phthalimide (4.04 g, 20.1 mmol); yellow oil; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.87-7.82 (m, 2H), 7.73-7.68 (m, 2H), 5.86-5.73 (m, 1H), 5.09-5.00 (m, 2H), 3.77 (t, *J* = 6.4 Hz, 2H), 2.45 (q, *J* = 6.4, 14.8 Hz, 2H).

Preparation of *N*-(3'-Butenyl)-4-toluenesulfonamide (1). *N*-(3'-Buthenyl)phthalimide (4.04 g, 20.1 mmol) was added to 50 mL EtOH to 50 °C. Hydrazine monohydrate (1.94 mL, 40.0 mmol) was then added, and this mixture was stirred under N_2 for 1 h. The white suspension was quenched with 2M HCl (20 mL). The resulting solution was stirred for another 10 min. The white solid was filtered off and the remaining solution was concentrated. The residue was added 20% NaOH (12 g) and water (80 mL), the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with water (2 times) and sat. aqueous NaCl. The solution was dried over $MgSO_4$, and then the filtrate was concentrated to about 70 mL. To this CH_2Cl_2 solution containing crude 3-buten-1-amine were added Et_3N (8.4 mL, 60.4 mmol) and TsCl (7.63g, 40.0 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred under N_2 for 24 h. The mixture was quenched with sat. aqueous $Na_2S_2O_3$ (40 mL) and extracted with Et_2O. The combined organic extracts were washed with water, sat. aqueous $Na_2S_2O_3$ and sat. aqueous NaCl. The ether solution was dried over $MgSO_4$, and concentrated. This crude reaction mixture was purified by silica gel column chromatography (EtOAc/*n*-hexane = 1/3) and distillation to give **1** (1.63 g, 7.21 mmol, 36%); pale yellow oil; IR (liquid film) 3524, 3052, 1590, 1300, 1138 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 5.68-5.57 (m, 1H), 5.09-5.01 (m, 2H), 4.51 (brd, 1H), 3.02 (q, *J* = 6.4 Hz, 2H), 2.43 (s, 3H), 2.20 (q, *J* = 6.7 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 68 MHz) δ 143.5 (s), 137.0 (s), 134.4 (d), 129.8 (d, 2C), 127.2 (d, 2C), 118.1 (t), 42.4 (t), 33.9 (t), 21.8 (q).

General reaction procedure of aza–Prins cyclization. A BTF solution of **1** (112.7 mg, 0.50 mmol) and **2** (0.75 mmol) was added to Lewis acid ($FeCl_3$: 0.75 or 1.50 mmol, BF_3•Et_2O: 0.75 mmol) and

BmimX (X = $FeCl_4$, PF_6, BF_4, 0.75 mmol) in BTF under N_2. In case a solid aldehyde is not completely dissolved in an appropriate volume of BTF, the aldehyde is placed with $FeCl_3$ and BmimX. This devised operation was used for **2i**. The resulting mixture was stirred under N_2 at room temperature for 4-24 h. Then, it was extracted with Et_2O after addition of water. The extract was treated with water, sat. aqueous $Na_2S_2O_3$, sat. aqueous $NaHCO_3$, sat. aqueous NaCl, and dried over anhydrous $MgSO_4$. The residue obtained after concentration was purified by silica-gel column chromatography (EtOAc/*n*-hexane, etc., volume ratio varied), and then subjected to TLC (EtOAc/*n*-hexane, EtOAc/benzene, etc., volume ratio varied).

The X-ray crystallographic analysis of related piperidines such as *trans-N*-tosyl-2-benzyl-4-chloropiperidine and *trans-N*-tosyl-4-chloro-2-isobutylpiperidine is previously reported,[3e] and characterization of the obtained piperidines **3** and determination of their relative stereochemistry were performed by the comparison of their spectral data with those of the reported piperidines. Thus, characterizations of *t*-**3a**, *c*-**3a**, *t*-**3b**, *c*-**3b**, *t*-**3c**, *c*-**3c**, *t*-**3d**, *c*-**3d**, *t*-**3e** and *t*-**3f** were completed and reported in our previous publication.[5]

***trans-N*-Tosyl-4-chloro-2-(*trans*-styryl)piperidine (*t*-3f)**[5]: pale yellow solid; mp 125.9-129.2 °C; IR (KBr) 2959, 2924, 2862, 1595, 1494, 1447, 1332, 1156, 1089, 936, 726 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, *J* = 10.3 Hz, 2H), 7.37-7.14 (m, 7H), 6.42 (d, *J* = 16.4 Hz, 1H), 5.91 (dd, *J* = 17.1, 6.9 Hz, 1H), 4.86 (broad s, 1H), 4.12-4.00 (m, 1H), 3.92-3.82 (m, 1H), 3.11 (t, *J* = 12.6 Hz, 1H), 2.38 (s, 3H), 2.30-2.27 (m, 1H), 2.16-2.09 (m, 1H), 1.98 (dt, *J* = 12.4, 5.7 Hz, 1H), 1.76 (dq, *J* = 16.4, 3.4 Hz, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.5 (s), 137.1 (s), 135.9 (s), 132.9 (d), 129.7 (d), 128.5 (d), 128.0 (d), 127.3 (d), 126.4 (d), 125.1 (d), 55.5 (d), 53.0 (d), 41.4 (t), 40.6 (t), 35.6 (t), 21.4 (q) ppm; HRMS (ESI) Calcd for $C_{20}H_{23}{}^{35}ClNO_2S$ $[M+H]^+$ = 376.1133, found $[M+H]^+$ = 376.1137; Calcd for $C_{20}H_{23}{}^{37}ClNO_2S$ $[M+H]^+$ = 378.1103, found $[M+H]^+$ = 378.1107.

***cis-N*-Tosyl-4-chloro-2-(*trans*-styryl)piperidine (*c*-3f)**: white solid; mp 93.5-96.3 °C; IR (KBr) 3429, 3029, 2959, 2920, 2863, 1598, 1493, 1450, 1341, 1296, 1259, 1159, 1092, 1065, 1037, 971, 942, 896, 831, 813, 751, 732, 693, 656, 610 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.26-7.15 (m, 7H), 6.29-6.27 (m, 2H), 4.46-4.42 (m, 1H), 4.34-4.29 (m, 1H), 3.62-3.56 (m, 1H), 3.53-3.47 (m, 1H), 2.34-2.28 (m, 4H), 2.18-2.08 (m, 2H), 2.01-1.96 (m, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.3, 136.5, 136.3, 130.5, 129.4, 128.4, 127.7, 127.7, 127.6, 126.4, 55.9, 54.2, 39.8, 38.9, 33.7, 21.4 ppm; HRMS (ESI) Calcd for $C_{20}H_{22}{}^{35}ClNO_2S$ $[M+Na]^+$ = 398.0952, found $[M+Na]^+$ = 398.0954; Calcd for $C_{20}H_{22}{}^{37}ClNO_2S$ $[M+Na]^+$ = 400.0922, found $[M+Na]^+$ = 400.0920.

***trans-N*-Tosyl-4-chloro-2-(*p*-methoxylphenyl)piperidine (*t*-3g)**: pale yellow solid; mp 108.5-109.2 °C; IR (KBr) 3049, 2957, 2931, 2871, 2837, 1605, 1511, 1452, 1334, 1249, 1152, 1087, 1033, 954, 929, 844, 730, 658, 612 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.23

(d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 6.8 Hz, 2H), 5.34 (broad s, 1H), 3.97-3.89 (m, 2H), 3.79 (s, 3H), 3.02 (ddd, *J* = 14.0, 2.8 Hz, 1H), 2.68 (dd, *J* = 13.7 Hz 1H), 2.45 (s, 3H), 1.93-1.80 (m, 2H), 1.60-1.49 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 158.7, 143.5, 137.9, 129.9, 129.0, 127.7, 126.8, 114.2, 55.5, 55.2, 52.8, 41.2, 37.5, 35.1, 21.5; HRMS(ESI) Calcd for $C_{19}H_{22}{}^{35}ClNO_3S$ $[M+Na]^+$ = 402.0901, found $[M+Na]^+$ = 402.0900; Calcd for $C_{19}H_{22}{}^{37}ClNO_3S$ $[M+Na]^+$ = 404.0872, found $[M+H]^+$ = 404.0864.

***cis*-*N*-Tosyl-4-chloro-2-(*p*-methoxyphenyl)piperidine (*c*-3g)**: white solid; mp 126.0-127.8 °C; IR (KBr) 3006, 2920, 2848, 1611, 1514, 1450, 1347, 1302, 1283, 1250, 1160, 1091, 1066, 1036, 866, 818, 735, 721, 654 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.57 (t, *J* = 5.8 Hz, 1H), 4.12-4.06 (m, 1H), 3.94-3.88 (m, 1H), 3.78 (s, 3H), 3.41-3.35 (m, 1H), 2.44-2.36 (m, 4H), 2.26-2.20 (m, 1H), 2.17-2.10 (m, 1H), 1.94-1.86 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 158.7, 143.1, 136.8, 131.1, 129.4, 128.3, 127.3, 113.3, 57.6, 55.2, 54.2, 41.8, 40.0, 34.1, 21.5; HRMS(ESI); Calcd for $C_{19}H_{22}{}^{35}ClNO_3S$ $[M+Na]^+$ = 402.0901, found $[M+Na]^+$ = 402.0903; Calcd for $C_{19}H_{22}{}^{37}ClNO_3S$ $[M+Na]^+$ = 404.0872, found $[M+Na]^+$ = 404.0869.

***trans*-*N*-Tosyl-4-chloro-2-(1'-naphthyl)piperidine (*t*-3h)**: pale yellow white turbidness oil; IR (KBr) 3052, 2928, 1597, 1509, 1450, 1398, 1339, 1258, 1157, 1092, 935, 859, 802, 778, 721, 664 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.49-7.42 (m, 2H), 7.34-7.25 (m, 4H), 6.96 (d, *J* = 8.0 Hz, 2H), 5.92 (t, *J* = 5.2 Hz, 1H), 4.25-4.19 (m, 1H), 4.06-4.00 (m, 1H), 3.90-3.83 (m, 1H), 2.93-2.88 (m, 1H), 2.31-2.20 (m, 5H), 1.99-1.90 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 142.8, 136.7, 134.2, 133.9, 130.7, 129.0, 128.9, 128.5, 126.9, 126.3, 125.5, 125.0, 124.6, 123.1, 54.6, 54.0, 43.6, 39.6, 34.8, 21.3; HRMS (ESI); Calcd for $C_{22}H_{22}{}^{35}ClNO_2S$ $[M+Na]^+$ = 422.0952, found $[M+Na]^+$ = 422.0955; Calcd for $C_{22}H_{22}{}^{37}ClNO_2S$ $[M+Na]^+$ = 424.0922, found $[M+Na]^+$ = 424.0919.

***cis*-*N*-Tosyl-4-chloro-2-(1'-naphthyl)piperidine (*c*-3h)**: yellow oil; IR (KBr) 3048, 2930, 2863, 1597, 1510, 1448, 1397, 1340, 1317, 1260, 1213, 1154, 1092, 1068, 1033, 1007, 944, 823, 800, 779, 728, 711, 657 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.83-7.81 (m, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.37-7.33 (m, 3H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 4.92 (dd, *J* = 10.6, 3.4 Hz, 1H), 4.42-4.36 (m, 1H), 4.17-4.11 (m, 1H), 3.33 (dt, *J* = 12.2, 3.2 Hz 1H), 2.86 (dq, *J* = 13.3, 2.8 Hz, 1H), 2.47-2.41 (m, 1H), 2.38-2.34 (m, 1H), 2.24-2.13 (m, 4H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 142.3, 135.8, 133.7, 133.5, 131.1, 128.8, 128.6, 128.4, 127.0, 126.4, 126.0, 125.1, 124.9, 123.2, 58.3, 55.7, 46.4, 40.4, 35.7, 21.2; HRMS (ESI); Calcd for $C_{22}H_{22}{}^{35}ClNO_2S$ $[M+Na]^+$ = 422.0952, found $[M+Na]^+$ = 422.0955; Calcd for $C_{22}H_{22}{}^{37}ClNO_2S$ $[M+Na]^+$ = 424.0922, found $[M+Na]^+$ = 424.0919.

***trans*-*N*-Tosyl-4-chloro-2-(2'-naphthyl)piperidine (*t*-3i)**[5]: white solid; mp 123.5-126.5 °C; IR (KBr) 3442, 3054, 2974, 2929, 2874, 1598, 1504, 1493, 1449, 1338, 1302, 1288, 1261, 1201, 1159, 1122, 1092, 1079, 1044, 1006, 969, 939, 861, 845, 816, 784, 752, 731, 662 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ

7.76-7.66 (m, 5H), 7.56 (s, 1H), 7.46-7.34 (m, 3H), 7.26 (d, *J* = 9.1 Hz, 2H), 5.46 (broad s, 1H), 3.96-3.87 (m, 2H), 3.02(dt, *J* = 12.8, 2.2 Hz, 1H), 2.81-2.77 (m, 1H), 2.38 (s, 3H), 2.01-1.80 (m, 2H), 1.64-1.44 (m, 2H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.6 (s), 138.0 (s), 134.8 (s), 133.2 (s), 132.5 (s), 130.0 (d), 128.9 (d), 127.9 (d), 127.5 (d), 127.0 (d), 126.4 (d), 126.3 (d), 125.5 (d), 124.4 (d), 56.2 (d), 52.8 (d), 41.6 (t), 37.8 (t), 35.2 (t), 21.5 (q) ppm; HRMS (ESI); Calcd for $C_{22}H_{23}{}^{35}ClNO_2S$ $[M+H]^+$ = 400.1133 found, $[M+H]^+$ = 400.1118; Calcd for $C_{22}H_{23}{}^{37}ClNO_2S$ $[M+H]^+$ = 402.1103, found $[M+H]^+$ = 402.1088.

***cis*-*N*-Tosyl-4-chloro-2-(2'-naphthyl)piperidine (*c*-3i)**: white solid; mp 167.3-169.0 °C; IR (KBr) 3056, 2953, 2860, 1598, 1505, 1448, 1345, 1291, 1161, 1092, 1063, 832, 730, 656 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.80-7.76 (m, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.67-7.63 (m, 1H), 7.53-7.50 (m, 3H), 7.46-7.42 (m, 2H), 7.36 (dd, *J* = 8.8, 1.6Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.85 (t, *J* = 5.8 Hz, 1H), 4.19-4.13 (m, 1H), 4.00-3.93 (m, 1H), 3.55-3.49 (m, 1H), 2.60-2.53 (m, 1H), 2.35-2.30 (m, 4H), 2.20-2.13 (m, 1H), 1.97-1.89 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.3, 136.8, 136.7, 132.9, 132.5, 129.4, 127.8, 127.6, 127.5, 127.2, 125.9, 125.9, 125.6, 125.1, 57.7, 54.2, 41.4, 39.6, 33.9, 21.4; HRMS(ESI); Calcd for $C_{22}H_{22}{}^{35}ClNO_2S$ $[M+Na]^+$ = 422.0952, found $[M+Na]^+$ = 422.0954; Calcd for $C_{22}H_{22}{}^{37}ClNO_2S$ $[M+Na]^+$ = 424.0922, found $[M+Na]^+$ = 424.0918.

***trans*-*N*-Tosyl-4-chloro-2-(3'-phenyl-3'-propione)piperidine (*t*-3j)**: brown solid; mp 73.5-78.0 °C; IR (KBr) 3060, 2959, 1683, 1595, 1491, 1448, 1379, 1330, 1208, 1154, 1096, 1033, 991, 911, 842, 814, 749, 692, 650, 605 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 700 MHz) δ 7.93 (d, *J* = 7.7 Hz, 2H), 7.70 (d, *J* = 9.8 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.29-7.26 (m, 2H), 4.22-4.19 (m, 1H), 4.14-4.10 (m, 1H), 3.96 (dd, *J* = 14.7, 4.2 Hz, 1H), 3.14-3.05 (m, 3H), 2.41 (s, 3H), 2.15-2.09 (m, 1H), 2.00 (ddd, *J* = 37.5, 13.0, 4.2 Hz, 2H), 1.88-1.83 (m, 1H), 1.63-1.58 (m, 1H), 1.44-1.37 (m, 1H); ^{13}C-NMR ($CDCl_3$, 175 MHz) δ 199.2, 143.5, 138.0, 136.7, 133.1, 129.9, 128.5, 128.0, 126.8, 53.6, 52.8, 40.3, 39.0, 35.1, 35.0, 24.4, 21.5; HRMS(ESI); Calcd for $C_{21}H_{24}{}^{35}ClNO_3S$ $[M+Na]^+$ = 428.1058, found $[M+Na]^+$ = 428.1060; Calcd for $C_{21}H_{24}{}^{37}ClNO_3S$ $[M+Na]^+$ = 430.1028, found $[M+Na]^+$ = 430.1029.

***trans*-*N*-Tosyl-4-fluoro-2-phenylpiperidine (*t*-5a)**[12a]: pale yellow solid; mp 107.9-110.0 °C; IR (KBr) 3055, 2963, 2928, 1596, 1493, 1450, 1346, 1321, 1254, 1154, 1086, 1027, 949, 921, 878, 809, 779, 756, 729, 699, 651 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.31-7.18 (m, 7H), 5.24 (d, *J* = 6.4 Hz, 1H), 4.93-4.75 (m, $J_{H,F}$ = 49.2 Hz, 1H), 3.75 (d, *J* = 14.4 Hz, 1H), 3.39 (dt, *J* = 13.4, 3.2 Hz, 1H), 2.69-2.61 (m, 1H), 2.41 (s, 3H), 2.07-1.88 (m, *J* = 46.0 Hz, 1H), 1.77-1.56 (m, 2H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.3, 139.4, 137.9, 129.7, 128.2, 127.0, 126.8, 126.5, 126.5, 86.2 (d, *J* = 171.8 Hz), 53.3, 36.7, 32.1 (d, *J* = 19.4 Hz), 29.2 (d, *J* = 21.5 Hz), 21.5 ppm; ^{19}F-NMR ($CDCl_3$, 376 MHz) δ -181.9 ~ -182.4 (m); HRMS (ESI); Calcd for $C_{18}H_{20}FNO_2S$ $[M+Na]^+$ = 356.1091, found $[M+Na]^+$ = 356.1093.

***cis*-*N*-Tosyl-4-fluoro-2-phenylpiperidine (*c*-5a)**[12a]: white solid; mp 114.5-119.0 °C; IR (KBr) 3058, 3030, 2973, 2945, 2885, 1596, 1492, 1448, 1340, 1305, 1281, 1249, 1203, 1156, 1092, 1058, 1013, 984,

938, 815, 796, 760, 722, 696, 672 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.36-7.20 (m, 7H), 5.44 (broad s, 1H), 4.69-4.50 (m, $J_{H,F}$ = 48.7 Hz, 1H), 3.98 (d, *J* = 14.8 Hz, 1H), 3.03 (t, *J* = 13.2 Hz, 1H), 2.70-2.64 (m, 1H), 2.46 (s, 3H), 1.87-1.84 (m, 1H), 1.75-1.66 (m, 1H), 1.51-1.39 (m, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.5, 137.9, 137.7, 129.9, 128.8, 127.4, 126.9, 126.4, 86.7 (d, *J* = 172.6 Hz), 55.4 (d, *J* = 13.4 Hz), 39.9 (d, *J* = 12.7 Hz), 33.4 (d, *J* = 18.6 Hz), 31.0 (d, *J* = 18.6 Hz), 21.5 ppm; ^{19}F-NMR ($CDCl_3$, 376 MHz) δ -175.9~-176.0 (m); HRMS (ESI) Calcd for $C_{18}H_{20}FNO_2S$ $[M+Na]^+$ = 356.1091, found $[M+Na]^+$ = 356.1092.

***N*-Tosyl-2-phenyl-1,2,3,6-tetrahydropyridine (6a)**[17]: white solid; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.31-7.23 (m, 5H), 5.83-5.75 (m, 1H), 5.62-5.55 (m, 1H), 5.32-5.28 (m, 1H), 4.16-4.07 (m, 1H), 3.39 (d, *J* = 18.0 Hz, 1H), 2.48-2.34 (m, 5H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.1, 139.1, 137.7, 129.5, 128.3, 127.4, 127.3, 127.0, 123.9, 123.7, 52.7, 40.8, 26.3, 21.5; HRMS (ESI) Calcd for $C_{18}H_{19}NO_2S$ $[M+Na]^+$ = 336.1029, found $[M+Na]^+$ = 336.1027.

Reaction of benzaldehyde (2a) with $FeCl_3$. A BTF solution of **2a** (0.75 mmol) was added to $FeCl_3$ (1.50 mmol) and $BmimPF_6$ (0.75 mmol) in BTF under N_2. The resulting mixture was stirred under N_2 at room temperature for 24 h. Then, it was extracted with Et_2O after addition of water. The extract was treated with water, sat. aqueous $Na_2S_2O_3$, sat. aqueous $NaHCO_3$, sat. aqueous NaCl, and dried over anhydrous $MgSO_4$. The residue obtained after concentration was purified by TLC (EtOAc/benzene = 1/3).

Reaction of *N*-(3'-Butenyl)-4-toluenesulfonamide (1) with $FeCl_3$. A BTF solution of **1** (112.7 mg, 0.50 mmol) was added to $FeCl_3$ (0.75 or 1.50 mmol) and BmimX (X = $FeCl_4$, PF_6, 0.75 mmol) in BTF under N_2. The resulting mixture was stirred under N_2 at room temperature for 24 h. Then, it was extracted with Et_2O after addition of water. The extract was treated with water, sat. aqueous $Na_2S_2O_3$, sat. aqueous $NaHCO_3$, sat. aqueous NaCl, and dried over anhydrous $MgSO_4$. The residue obtained after concentration was purified by TLC (EtOAc/benzene or EtOAc/*n*-hexane, volume ratio varied) to give *N*-(3'-chlorobuthyl)-4-toluenesulfonamide (**4**): yellow oil; IR 3565, 3281, 2975, 2928, 2872, 2359, 1598, 1495, 1445, 1380, 1325, 1158, 1094, 815, 666, 610, 551 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.98 (broad s, 1H), 4.11-4.03 (m, 1H), 3.13-3.08 (m, 2H), 2.44 (s, 3H), 1.99-1.91 (m, 1H), 1.84-1.75 (m, 1H), 1.48 (d, *J* = 6.4 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 143.5, 136.6, 129.7, 127.0, 55.5, 40.6, 39.7, 25.3, 21.5; HRMS (ESI) Calcd for $C_{11}H_{16}{}^{35}ClNO_2S$ $[M+Na]^+$ = 284.0482, found $[M+H]^+$ = 284.0486. HRMS (ESI); Calcd for $C_{11}H_{16}{}^{37}ClNO_2S$ $[M+Na]^+$ = 286.0453, found $[M+H]^+$ = 286.0454.

Free radical dechlorination of *trans*-*N*-tosyl-4-chloro-2-phenylpiperidine (*t*-3a): α,α'-Azobisisobutyronitrile (AIBN, 4.9 mg, 0.030 mmol) and tris(trimethylsilyl)silane (TTMSS, 0.14 mL, 0.45 mmol) was added to *t*-**3a** (105.0 mg 0.30 mmol) in BTF (3.0 mL). The mixture was heated at 85 °C under N_2 for 24 h. The residue obtained after concentration was purified by silica-gel column

chromatography (CH_2Cl_2/*n*-hexane = 5/1), and then subjected to TLC (CH_2Cl_2/*n*-hexane = 5/1) to give *N*-tosyl-2-phenylpiperidine (**7a**)[18]: pale yellow solid; mp 128.8-131.6 °C; IR (KBr) 3049, 2953, 2926, 2865, 1596, 1493, 1449, 1373, 1327, 1297, 1220, 1151, 1099, 1049, 1026, 947, 817, 756, 722, 662, 631 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 7.7 Hz, 2H), 7.36-7.21 (m, 7H), 5.27 (broad s, 1H), 3.84 (d, *J* = 14.1 Hz, 1H), 3.01 (dt, *J* = 13.5, 3.0 Hz, 1H), 2.43 (s, 3H), 2.21 (d, *J* = 13.4 Hz, 1H), 1.68-1.60 (m, 1H), 1.52-1.25 (m, 4H); ^{13}C-NMR ($CDCl_3$, 175 MHz) δ 142.9, 138.8, 138.6, 129.6, 128.5, 126.9, 126.9, 126.7, 55.2, 41.8, 27.1, 24.2, 21.5, 18.9; HRMS(ESI); Calcd for $C_{18}H_{21}NO_2S$ $[M+Na]^+$ = 338.1185, found $[M+Na]^+$ = 338.1186.

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