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Catalyst-free aminobromination of alkenes with *N*-methyl-*p*-toluenesulfonamide as nitrogen resource

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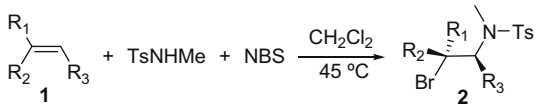
ABSTRACT

A catalyst-free electrophilic aminobromination system was described with *N*-methyl-*p*-toluenesulfonamide (*p*-TsNHCH$_3$) and *N*-bromosuccinimide (NBS) as nitrogen and bromine resources. The reaction can give vicinal haloamines in good yields, excellent regioselectivities, and stereoselectivities under convenient and mild condition. The existence of *N*-methyl group in the nitrogen resource was found to play an important role in the formation of vicinal haloamine product.

Aminohalogenation and related reactions of olefins have become an interesting topic in organic synthesis because the resulting vicinal haloamines are important building blocks in organic and medicinal chemistry.[1] The products resulting from these processes can easily be converted into numerous other derivatives by replacement of the halogen in intramolecular or intermolecular reactions. In recent years, several methodologies have been developed for the aminohalogenation of olefins in the presence of catalysts.[2,3] However, there still existed limitations, such as procedural difficulties, high catalyst loading, necessity of metal or metal salts as catalysts. In particular, the necessity of metal catalyst limits the attractiveness of these methodologies in their application for pharmaceuticals, because removal of the trace of residual metals from the resulting haloamines products is quite difficult.[4] Although several nonmetal catalysts have been developed for aminohalogenation reactions recently, these system usually need special auxiliary reagents, like ionic liquid,[5a] stoichiometric PhI(OAc)$_2$,[5b] sulfuric acid,[5c] or high pressure of CO_2.[5d] Developing more simple and efficient aminohalogenation system is still necessary.

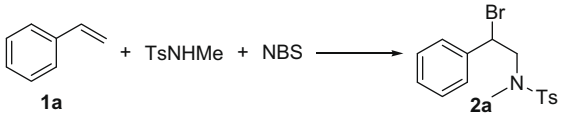
During our continuous investigation on aminohalogenation we turned our attentions to develop the catalyst-free aminohalogenation system, which could have great potential in pharmaceutical chemistry.[6,7] In this work we reported, for the first time, a simple and efficient catalyst-free aminobromination of olefins for the preparation of vicinal bromoamines with *N*-methyl-*p*-toluenesulfonamide (*p*-TsNHCH$_3$) and *N*-bromosuccinimide (NBS) as nitrogen and bromine sources (Scheme 1).

Initially, styrene was chosen as the model substrate to optimize the reaction conditions, and the results are shown in Table 1. Dichloromethane was proved to be the best solvent for this system, and gave the product in 94% yield (Table 1, entry 1). Very low yields were obtained when acetonitrile, toluene or 1,2-dichloroethane were used as solvent (Table 1, entries 2, 4, and 6). There was no haloamine product observed at all when the reaction was carried out in THF or DMF (Table 1, entries 3 and 5). The tempera-



Scheme 1. Catalyst-free aminohalogenation with TsNHMe as nitrogen resource.

Table 1
Aminobromination of styrene[a]



Entry	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	CH_2Cl_2	45	24	94
2	MeCN	45	24	11
3	THF	45	24	0
4	Toluene	45	24	24
5	DMF	45	24	0
6	$ClCH_2CH_2Cl$	45	24	18
7	CH_2Cl_2	25	24	13

[a] Conditions: 1.2 mmol of **1a**, 1 mmol of *p*-TsNHMe, and 1.4 mmol of NBS in solvent (3 mL).
[b] Isolated yields after chromatographic purification.

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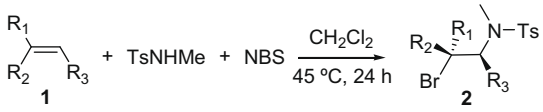
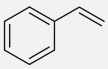
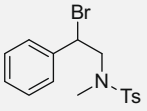
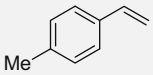
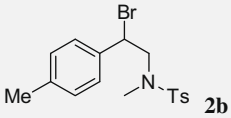
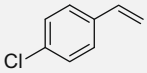
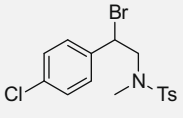
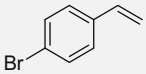
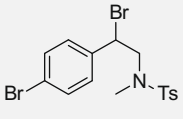
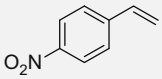
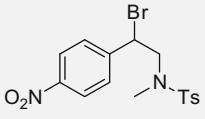
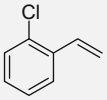
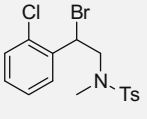
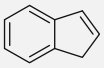
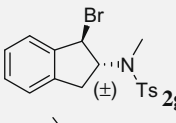
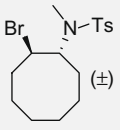
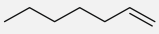
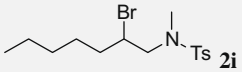
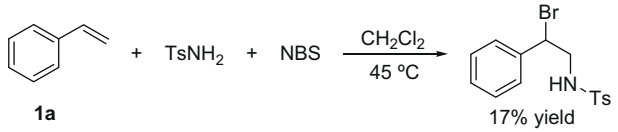
Table 2
Aminobromination of olefins with TsNHMe and NBS[a]



Entry	Substrate	Product	Yield[b] (%)
1		 **2a**	94
2		 **2b**	97
3		 **2c**	96
4		 **2d**	95
5		 **2e**	93
6		 **2f**	97
7		 **2g**	69[c]
8		 **2h**	43[c]
9		 **2i**	52

[a] Conditions: 1.2 mmol of alkenes, 1 mmol of *p*-TsNHMe, and 1.4 mmol of NBS in CH_2Cl_2 (3 mL) at 45 °C for 24 h.
[b] Isolated yields after chromatographic purification.
[c] Only *anti*-product was observed, estimated by crude ^1H NMR.

ture was also found to have an effect on the formation of haloamine product, because only 13% yield was obtained when the reaction was carried out at 25 °C.



Scheme 2. Aminohalogenation with $TsNH_2$/NBS.

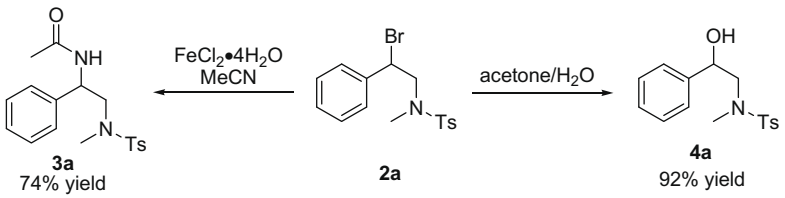
After obtaining the optimized reaction conditions, the scope and limitation of this system were then examined. Varieties of alkenes were subjected to the current aminobromination system, and the results were presented in Table 2.[8] The current catalyst-free system can be suitable for both aliphatic alkenes and aromatic alkenes, resulting in the corresponding haloamines in good yields. Especially for the aromatic alkenes, excellent yields were obtained (Table 2, entries 1–6). A cyclic olefin, cyclooctene, was also reacted effectively with TsNHMe/NBS in an acceptable yield (Table 2, entry 8). Long chain aliphatic alkene was also a good substrate for the current system, affording 52% yield (Table 2, entry 9). Only one regio-isomer was observed for each of these cases. The substrates showed excellent stereoselectivities, only the *anti* isomers were observed for two cyclic substrates (Table 2, entries 7 and 8).

To compare the current aminohalogenation system with previously reported aminohalogenation system using the combined $TsNH_2$/NBS as nitrogen and bromine resource,[9] we carried out the reaction between styrene and $TsNH_2$/NBS under the current reaction conditions (Scheme 2). Only 17% yield of desired haloamine product was obtained, and most of the starting materials were recovered. Comparing to 94% yield obtaining from the reaction with TsNHMe as nitrogen resource, we found that the introduction of *N*-methyl group into nitrogen resource plays an important role in the formation of haloamine product.

The mechanism of this reaction is believed to be similar to that of our previously reported aminohalogenation system.[2b–d] Firstly, NBS reacts with *p*-TsNHMe to form the *p*-TsNBrMe. The following step would be the formation of the aziridinium intermediate, and this positively charged intermediate would be S_N2 attacked by a bromide anion to give the aminohalogenation adducts. The existence of *N*-methyl group was believed to stable the aziridinium intermediate, which can promote the proceeding of reaction. The regio and stereoselectivity of this reaction can also be explained well on the basis of this mechanistic hypothesis involving these key aziridinium intermediates.

The presence of benzyl bromide functionality in the current haloamine products provided an easy access to other useful organic blocks by intermolecular reactions (Scheme 3). When the product **2a** was subjected $FeCl_2$/acetonitrile system[10] at room temperature, vicinal diamine **3a** was obtained in 74% yield. Product **2a** was also easily to be hydrolyzed by treatment with acetone/water, resulting in vicinal aminoalcohol **4a** with the yield of 92%.

In conclusion, we reported a first catalyst-free aminohalogenation system with TsNHMe as the nitrogen resource and NBS as bromine resource. The TsNHMe was found to be a good nitrogen resource for aminohalogenation reaction, and can react with varieties of alkenes to form haloamine product in good to excellent



Scheme 3. Nucleophilic substitutions.

yield without use of any catalyst. The introduction of *N*-methyl group into nitrogen resource was found to be very important for this aminohalogenation system, and can promote the formation of haloamine product.

Acknowledgments

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8. *General aminobromination procedure* (Table 2): A mixture of olefins (1.2 mmol), *p*-TsNHMe (0.185 g, 1 mmol), and NBS (0.249 g, 1.4 mmol) was added in CH_2Cl_2 (3 mL) with stirring at 45 °C under nitrogen atmosphere for 24 h. The reaction was quenched by dropwise addition of saturated aqueous Na_2SO_3 solution (3 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water and brine and dried over by anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography packed with silica gel to afford pure product.
N-(2-Bromo-2-phenylethyl)-N,4-dimethylbenzenesulfonamide (**2a**) isolated as a white solid (346 mg, 94% yield); mp 61–63 °C. IR (KBr): ν = 3418, 1618, 1491, 1384, 1334, 1159, 1088, 988, 934, 843, 812, 743, 705, 674, 644, 545 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.1 Hz, 2H), 7.29–7.45 (m, 7H), 5.15 (dd, *J* = 7.2, 8.4 Hz, 1H), 3.73 (dd, *J* = 7.2, 14.4 Hz, 1H), 3.53 (dd, *J* = 8.4, 14.4 Hz, 1H), 2.59 (s, 3H), 2.43 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7, 139.0, 134.6, 129.9, 129.0, 128.9, 128.1, 127.4, 57.7, 51.9, 36.8, 21.6 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{16}H_{18}BrNO_2SNa$: 392.01; found 392.25.
N-(2-Bromo-2-(p-tolyl)ethyl)-N,4-dimethylbenzenesulfonamide (**2b**) isolated as a white solid (370 mg, 97% yield); mp 92–94 °C. IR (KBr): ν = 3457, 1597, 1384, 1346, 1157, 1087, 985, 820, 733, 650, 571 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.4 Hz, 2H), 7.32–7.30 (m, 4H), 7.16 (d, *J* = 7.8 Hz, 2H), 5.13 (dd, *J* = 7.2, 8.4 Hz, 1H), 3.71 (dd, *J* = 7.2, 14.4 Hz, 1H), 3.54 (dd, *J* = 8.4, 14.4 Hz, 1H), 2.60 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7, 138.9, 136.1, 134.6, 129.8, 129.6, 127.9, 127.4, 57.6, 52.0, 36.8, 21.6, 21.3 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{17}H_{20}BrNO_2SNa$: 406.03; found 406.17.
N-(2-Bromo-2-(4-chlorophenyl)ethyl)-N,4-dimethylbenzenesulfonamide (**2c**) isolated as a white solid (387 mg, 96% yield); mp 81–82 °C. IR (KBr): ν = 3448, 1596, 1491, 1048, 1158, 1089, 985, 828, 746, 715, 547 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 6.6 Hz, 2H), 7.39–7.30 (m, 6H), 5.12 (dd, *J* = 6.6, 8.7 Hz, 1H), 3.67 (dd, *J* = 6.6, 14.4 Hz, 1H), 3.54 (dd, *J* = 8.7, 14.4 Hz, 1H), 2.60 (s, 3H), 2.43 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 137.5, 134.7, 134.5, 129.9, 129.5, 129.1, 127.3, 57.7, 50.6, 36.8, 21.6 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{16}H_{17}BrClNO_2SNa$: 425.97; found 426.17.
N-(2-Bromo-2-(4-bromophenyl)ethyl)-N,4-dimethylbenzenesulfonamide (**2d**) isolated as a white solid (425 mg, 95% yield); mp 108–110 °C. IR (KBr): ν = 3461, 1596, 1489, 1346, 1158, 984, 821, 664, 551 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 6.6 Hz, 2H), 7.33–7.29 (m, 4H), 5.10 (dd, *J* = 6.6, 8.7 Hz, 1H), 3.66 (dd, *J* = 6.6, 14.7 Hz, 1H), 3.53 (dd, *J* = 8.7, 14.7 Hz, 1H), 2.60 (s, 3H), 2.43 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9, 138.0, 134.4, 132.0, 129.9, 129.8, 127.4, 122.9, 57.6, 50.6, 36.8, 21.6 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{16}H_{17}Br_2NO_2SNa$: 469.92; found 470.00.
N-(2-Bromo-2-(4-nitrophenyl)ethyl)-N,4-dimethylbenzenesulfonamide (**2e**) isolated as a yellow gum (384 mg, 93% yield); IR (KBr): ν = 3450, 1599, 1524, 1346, 1160, 857, 742, 670, 550 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 9.0 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 4H), 7.32 (d, *J* = 8.4 Hz, 2H), 5.21 (t, *J* = 7.8 Hz, 1H), 3.64–3.62 (m, 2H), 2.62 (s, 3H), 2.43 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.0, 145.9, 144.1, 134.1, 130.0, 129.3, 127.4, 124.0, 57.5, 49.0, 36.9, 21.5 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{16}H_{17}BrN_2O_4SNa$: 437.00; found 437.00.
N-(2-Bromo-2-(2-chlorophenyl)ethyl)-N,4-dimethylbenzenesulfonamide (**2f**) isolated as a white solid (391 mg, 97% yield); mp 74–76 °C. IR (KBr): ν = 3445, 1596, 1335, 1156, 982, 751, 547 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.62 (m, 3H), 7.38–7.25 (m, 5H), 5.66 (dd, *J* = 7.2, 7.8 Hz, 1H), 3.83 (dd, *J* = 7.8, 14.4 Hz, 1H), 3.53 (dd, *J* = 7.2, 14.4 Hz, 1H), 2.72 (s, 3H), 2.43 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.8, 136.1, 134.4, 133.4, 130.0, 129.9, 129.9, 129.8, 127.6, 127.4, 56.2, 46.1, 36.0, 21.6 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{16}H_{17}BrClNO_2SNa$: 425.97; found 426.08.
N-(1-Bromo-2,3-dihydro-1H-inden-2-yl)-N,4-dimethylbenzenesulfonamide (**2g**) isolated as a white solid (262 mg, 69% yield); mp 127–129 °C. IR (KBr): ν = 3441, 1597, 1339, 975, 884, 810, 746, 693, 667, 549 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 6.6 Hz, 2H), 7.38–7.16 (m, 6H), 5.11–5.10 (m, 2H), 3.36–3.28 (m, 1H), 2.85–2.78 (m, 1H), 2.56 (s, 3H), 2.48 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7, 141.0, 140.3, 136.1, 129.9, 129.5, 127.9, 127.5, 125.4, 124.5, 66.6, 53.4, 33.8, 29.6, 21.7 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{17}H_{18}BrNO_2SNa$: 404.01; found 403.92.
N-(2-Bromocyclooctyl)-N,4-dimethylbenzenesulfonamide (**2h**) isolated as a white solid (161 mg, 43% yield); mp 102–104 °C. IR (KBr): ν = 3463, 2932, 2855, 1594, 1384, 1227, 1160, 985, 851, 801, 666, 645, 573, 547 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.37–4.27 (m, 2H), 2.69 (s, 3H), 2.41 (s, 3H), 2.25–2.16 (m, 2H), 1.95 (m, 1H), 1.64–1.40 (m, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 137.1, 129.4, 127.6, 56.9, 31.3, 31.1, 28.1, 26.0, 25.0, 25.0, 23.5, 23.5, 21.5 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{16}H_{24}BrNO_2SNa$: 398.06; found 398.08.
N-(2-Bromoheptyl)-N,4-dimethylbenzenesulfonamide (**2i**) isolated as a white solid (188 mg, 52 yield); mp 58–60 °C. IR (KBr): ν = 3417, 2953, 2857, 1638, 1618, 1384, 1342, 1162, 950, 907, 812, 752, 575, 552 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 4.14 (m, 1H), 3.46 (dd, *J* = 7.5, 14.1 Hz, 1H), 3.18 (dd, *J* = 6.3, 14.1 Hz, 1H), 2.81 (s, 3H), 2.44 (s, 3H), 2.00 (m, 1H), 1.74–1.61 (m, 2H), 1.44–1.29 (m, 5H), 0.91 (t, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7, 134.3, 129.8, 127.4, 57.2, 53.6, 36.8, 35.6, 31.1, 27.0, 22.5, 21.5, 14.0 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{15}H_{24}BrNO_2SNa$: 386.06; found 386.17.
N-(2-(N,4-Dimethylphenylsulfonamido)-1-phenylethyl)acetamide (**3a**) isolated as a white solid (256 mg, 74% yield); mp 132–134 °C. IR (KBr): ν = 3334, 1650, 1595, 1539, 1444, 1369, 1340, 1166, 941, 771, 705, 659, 578, 552 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.4 Hz, 2H), 7.32–7.29 (m, 7H), 6.70 (broad, 1H), 5.11 (m, 1H), 3.46 (dd, *J* = 6.6, 14.4 Hz, 1H), 3.01 (dd, *J* = 4.2, 14.4 Hz, 1H), 2.72 (s, 3H), 2.42 (s, 3H), 2.10 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 143.8, 139.4, 134.6, 129.9, 128.8, 127.8, 127.2, 126.5, 54.9, 51.4, 35.8, 23.3, 21.5 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{18}H_{22}N_2O_3SNa$: 369.12; found 369.42.
N-(2-Hydroxy-2-phenylethyl)-N,4-dimethylbenzenesulfonamide (**4a**) isolated as a colorless gum (281 mg, 92% yield); IR (KBr): ν = 3511, 3063, 3031, 2924, 1598, 1494, 1454, 1337, 1206, 1160, 1089, 972, 816, 760, 736, 701, 657, 550 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 6.6 Hz, 2H), 7.39–7.29 (m, 6H), 4.92 (dd, *J* = 3.3, 9.0 Hz, 1H), 3.28 (dd, *J* = 9.0, 14.1 Hz, 1H), 3.02 (dd, *J* = 3.3, 14.1 Hz, 1H), 2.80 (s, 3H), 2.41 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7, 141.2, 134.2, 129.8, 128.6, 128.0, 127.4, 126.1, 72.2, 58.3, 36.8, 21.5 ppm. MS (ESMS/[M+Na]$^+$): calcd for $C_{16}H_{19}NO_3SNa$: 328.10; found 328.25.
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