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$PhI(OAc)_2$ induced intramolecular oxidative bromocyclization of homoallylic sulfonamides with KBr as the bromine source

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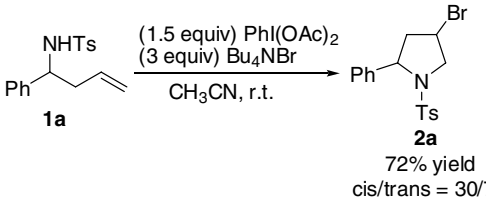
Abstract—(Diacetoxyiodo)benzene ($PhI(OAc)_2$) was found to be a powerful reagent to induce the intramolecular oxidative bromocyclization of homoallylic sulfonamides utilizing KBr as the bromine source. The reaction affords 2-substituted-4-bromo-pyrrolidines in moderate to excellent yields under a mild metal-free condition, and offers good manipulability by avoiding the use of highly toxic and caustic bromine (Br_2).

The aminohalogenation of alkenes has attracted a lot of attention owing to their efficiency, selectivity, and the synthetic value for the vicinal haloamines, which are important building blocks in organic and medicinal chemistry.[1–3] *N*-halo,[4] *N*-halocarbamates,[5] *N*,*N*-dihalophosphoramides,[6] and *N*,*N*-dihaloarylsulfonamides[1f,i] have been used as the nitrogen source as well as the halogen source in the aminohalogenation of alkenes. Despite the great advantages of these approaches, they are not suitable for the intramolecular aminohalogenations. The intramolecular aminohalogenation of homoallylic amines provides a great potential for the synthesis of functionalized pyrrolidine derivatives,[7] which are found in numerous natural products and medicinally relevant compounds.[8] In contrast to the extensive studies on the iodocyclization of homoallylic amines,[9] the bromocyclization of homoallylic amines has received much less scrutiny.[10] I_2 is used as the iodine source in most of the iodocyclization of homoallylic amines. However, it is hazardous for the bromocyclization of homoallylic amines under the same conditions owing to the high toxicity and causticity of bromine (Br_2). *N*-Bromosuccinimide (NBS)[11] and *N*-bromoacetamide[12] have been used as the bromine source in the intermolecular aminobromination of alkenes, but a metal catalyst (Os, Mn, V, or Cu) is required in the reaction, and no intramolecular aminobromination under these conditions has been reported. We herein present a highly efficient (diacetoxyiodo)benzene ($PhI(OAc)_2$) induced oxidative bromocyclization of homoallylic sulfonamides utilizing KBr as the bromine source under a mild metal-free condition.

$PhI(OAc)_2$ is a well investigated, and practically useful organic derivative of iodine(III).[13] A noteworthy feature of $PhI(OAc)_2$ is its ability to undergo the ligand exchange reaction with various nucleophiles and the subsequent reductive elimination reaction, which is common for the transition metals. The combinations of $PhI(OAc)_2$ with KSCN, TMSNCS, Et_4NBr, Ph_4PI, and PhSeSePh are useful for the oxidative functionalization of alkenes.[14] In these reactions, the nucleophilic anions are oxidized by $PhI(OAc)_2$ to the corresponding electrophilic species via the ligand exchange and subsequent reductive elimination. As a part of our program to develop the synthetic utilities of sulfonamides in the presence of organic polyvalent iodine compounds, we found that homoallylic sulfonamide **1a** underwent a bromocyclization reaction with $PhI(OAc)_2/Bu_4NBr$ to give 2-phenyl-4-bromo-pyrrolidine **2a** in good yield (Eq. 1). Cis- and trans-products were formed and could be separated by flash column chromatography. The structure of *trans*-**2a** was verified by its X-ray diffraction (Fig. 1).



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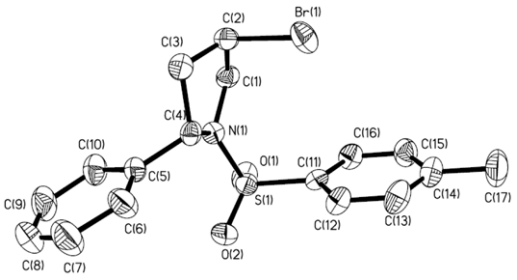


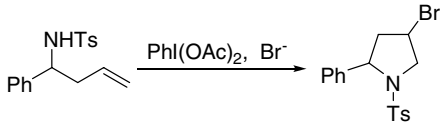
Figure 1. ORTEP diagram of *trans*-**2a**.

Control experiments indicated that no bromocyclization reaction occurred when $PhI(OAc)_2/Bu_4NBr$ was replaced with NBS.[15] As shown in Table 1, subsequent investigations revealed that the best ratio among homoallylic sulfonamide **1a**, $PhI(OAc)_2$ and Bu_4NBr was 1:2:4, in which the yield of **2a** increased to 83% (Table 1, entry 3). The desired product could be obtained but in a low yield (23%) when 4 equiv KBr was used as the bromine source (Table 1, entry 6). Bu_4NBr (0.5 equiv) could efficiently promote the reaction with KBr (Table 1, entry 8). No product was detected when DMSO was used as the solvent, while the reaction could proceed in toluene, THF, DCE, and DMF with varied efficiency and selectivity (Table 1, entries 9–13). Drastic decrease in yields occurred when the reaction was warmed up (Table 1, entries 14 and 15), and the starting material **1a** was recovered in high yield. The reaction became sluggish at 0 °C, but also led to product **2a** in 74% yield with a better selectivity after 48 h (Table 1, entry 16). It was noteworthy that Bu_4NBr was not necessary to finish the reaction when DMF was used as the solvent. The reaction was complete after 12 h, and generated 2-phenyl-4-bromo-pyrrolidine **2a** in slightly reduced yield (Table 1, entry 17).

The scope of the $PhI(OAc)_2$ induced bromocyclization of homoallylic amines was explored (Table 2). The reactions of the aryl substrates with electron-withdrawing groups on their aromatic rings gave higher yields than those of substrates with electron-donating groups (Table 2, entries 1–9). For heteroaryl homoallylic sulfonamides, thiophen and pyridine derivatives were good substrates to the reaction (Table 2, entries 11 and 12). However, in the case of the furan derivative, the reaction product was too complicated to be purified (Table 2, entry 10). Aliphatic homoallylic sulfonamide showed a lower reactivity, and gave product **2m** in moderate yield (Table 2, entry 13). The N-substituent of homoallylic amines played an important role in the reaction. When *N*-phenyl, *N*-benzyl, and *N*-Bu homoallylic amines were used as the substrates, no expected product was obtained from the reactions.[16]

When $PhI(OAc)_2$ was mixed with KBr in DMF at room temperature, a yellow solution was obtained after 30 min. The TLC of the reaction mixture showed the formation of PhI and the disappearance of $PhI(OAc)_2$. The yellow color indicated the formation of a bromate (I) species.[14g] It might be acetylhypobromite (AcOBr) or bromine (Br_2). Control experiments indicated that no bromocyclization reaction occurred when $PhI(OAc)_2/Bu_4NBr$ was replaced with 2 equiv bromine (Br_2). Product **2a** was isolated in 34% yield when 2 equiv bromine and 4 equiv AcONa were used in the reaction. As shown in Scheme 1, acetylhypobromite, which was

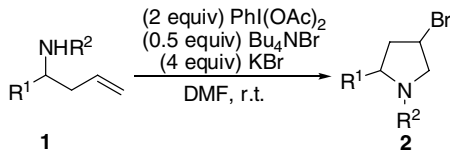
Table 1. The condition screening experiments[a]



Entry	Conditions (equiv)	Yield (cis/trans)[b,c]
1	(1.5) $PhI(OAc)_2$, (3) Bu_4NBr, CH_3CN, rt, 5 h	72 (30/70)
2	(1.1) $PhI(OAc)_2$, (2.2) Bu_4NBr, CH_3CN, rt, 5 h	53 (21/79)
3	(2) $PhI(OAc)_2$, (4) Bu_4NBr, CH_3CN, rt, 5 h	83 (31/69)
4	(3) $PhI(OAc)_2$, (6) Bu_4NBr, CH_3CN, rt, 5 h	82 (28/72)
5	(2) $PhI(OAc)_2$, (2) Bu_4NBr, CH_3CN, rt, 5 h	43 (22/78)
6	(2) $PhI(OAc)_2$, (4) KBr, CH_3CN, rt, 5 h	23 (15/85)
7	(2) $PhI(OAc)_2$, (0.1) Bu_4NBr (4) KBr, CH_3CN, rt, 5 h	50 (22/78)
8	(2) $PhI(OAc)_2$, (0.5) Bu_4NBr (4) KBr, CH_3CN, rt, 5 h	71 (28/72)
9	(2) $PhI(OAc)_2$, (0.5) Bu_4NBr (4) KBr, DMSO, rt, 5 h	N.R.[d]
10	(2) $PhI(OAc)_2$, (0.5) Bu_4NBr (4) KBr, Toluene, rt, 5 h	69 (17/83)
11	(2) $PhI(OAc)_2$, (0.5) Bu_4NBr (4) KBr, THF, rt, 5 h	21 (28/72)
12	(2) $PhI(OAc)_2$, (0.5) Bu_4NBr (4) KBr, DCE, rt, 5 h	48 (35/65)
13	(2) $PhI(OAc)_2$, (0.5) Bu_4NBr (4) KBr, DMF, rt, 5 h	84 (34/66)
14	(2) $PhI(OAc)_2$, (0.5) Bu_4NBr (4) KBr, DMF, reflux, 5 h	9 (38/62)
15	(2) $PhI(OAc)_2$, (0.5) Bu_4NBr (4) KBr, DMF, 60 °C, 5 h	17 (35/65)
16	(2) $PhI(OAc)_2$, (0.5) Bu_4NBr (4) KBr, DMF, 0 °C, 48 h	74 (18/82)
17	(2) $PhI(OAc)_2$, (4) KBr, DMF, rt, 12 h	78 (25/75)

[a] All reactions were conducted in 0.5 mmol scale.
[b] Isolated yield.
[c] Ratio based on the isolated yield.
[d] No reaction was observed, and **1a** was recovered in 88% yield.

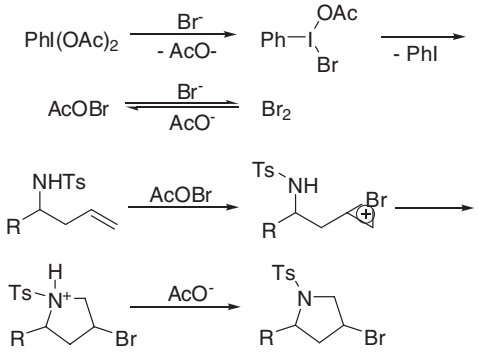
Table 2. Bromocyclization of homoallylic sulfonamides[a]



1 **2**

Entry	R^1	R^2	**2** Yield (cis/trans)[b,c]
1	Ph	Ts	**2a** 84 (34/66)
2	*p*-CH_3–C_6H_4	Ts	**2b** 79 (37/63)
3	*p*-CH_3O–C_6H_4	Ts	**2c** 71 (31/69)
4	*o*,*m*-Di–CH_3O–C_6H_3	Ts	**2d** 75 (40/60)
5	*o*-Cl–C_6H_4	Ts	**2e** 78 (45/55)
6	1-Nap	Ts	**2f** 86 (46/54)
7	*o*-CF_3–C_6H_4	Ts	**2g** 85 (63/37)
8	*p*-F–C_6H_4	Ts	**2h** 88 (48/52)
9	*p*-NO_2-C_6H_4	Ts	**2i** 92 (29/71)
10	2-Furan	Ts	**2j**[d]
11	2-Thiophen	Ts	**2k** 90 (50/50)
12	3-Pyridin	Ts	**2l** 93 (48/52)
13	3-Hept	Ts	**2m** 55 (50/50)
14	Ph	Ph	[e]
15	Ph	Bn	[e]
16	Ph	*n*-Bu	[e]

[a] All reactions were conducted in 0.5 mmol scale.
[b] Isolated yield.
[c] Ratio based on the ^{1}H NMR of the corresponding products.
[d] Reaction is complex, and product is hard to be purified.
[e] The reaction was complex, and no expected product was obtained from the reactions.



Scheme 1. Plausible reaction pathway.

formed from the ligand exchange between $PhI(OAc)_2$ with KBr and the subsequent reductive elimination, was the reaction intermediate, and the acetate anion generated in the ligand exchange step could act as a base to promote the bromocyclization of homoallylic sulfonamides. Because acetylhypobromite was sensitive to the temperature, low conversion of the starting material was observed when the reaction was warmed up.

In summary, we have developed a $PhI(OAc)_2$ induced intramolecular oxidative bromocyclization of homoallylic sulfonamides for the synthesis of 2-substituted-4-bromo-pyrrolidine with KBr as the bromine source under a mild metal-free condition. The procedure offers good manipulability by avoiding the use of highly toxic and caustic bromine. The further investigation of the scope, mechanism, synthetic applications, and asymmetric reactions is ongoing and will be reported in due course.

Acknowledgments

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16. *Representative experimental procedure and spectroscopic data for* **2a**: A solution of homoallylic amine (0.5 mmol) in anhydrous DMF (2 mL) was treated with $PhI(OAc)_2$ (322 mg, 1 mmol), Bu_4NBr (161 mg, 0.25 mmol), and KBr (238 mg, 2 mmol). The reaction mixture was stirred at room temperature under N_2 for 5 h (determined by TLC), and then quenched with the saturated solution of $Na_2S_2O_3$. The mixture was extracted with DCM, dried over anhydrous Na_2SO_4, and the crude product was purified by flash column chromatography to provide the corresponding product. *cis-4-Bromo-2-phenyl-1-tosylpyrrolidine* **2a**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.16–2.26 (m, 1H), 2.41 (s, 3H), 2.82–2.87 (m, 1H), 3.64 (dd, $J = 11.4$, 9.2 Hz, 1H), 3.78–3.84 (m, 1H), 4.16 (dd, $J = 11.5$, 6.8 Hz, 1H), 4.73 (t, $J = 8.3$ Hz, 1H), 7.21–7.32 (m, 7H), 7.56 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 40.1, 46.3, 57.1, 63.0, 126.3, 127.2, 127.5, 128.3, 129.6, 135.1, 141.0, 143.6; IR (neat) ν 1162, 1353, 1593 2924 cm^{-1}; MS (ESI) m/z (rel intensity) 381 (5, $M+H^+$), 300 (10, M^+-Br); Anal. Calcd for $C_{17}H_{18}BrNO_2S$: C, 53.69; H, 4.77; N, 3.68. Found: C, 53.88; H, 4.69; N, 3.62. *trans-4-Bromo-2-phenyl-1-tosylpyrrolidine* **2a**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.34–2.45 (m, 5H), 3.86 (dd, $J = 11.9$, 3.2 Hz, 1H), 4.16 (dd, $J = 12.3$, 5.0 Hz, 1H), 4.35–4.38 (m, 1H), 4.90 (t, $J = 7.4$ Hz, 1H), 7.24–7.33 (m, 7H), 7.63 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 43.7, 47.3, 58.4, 62.7, 126.4, 127.6, 127.7, 128.5, 129.5, 134.7, 141.2, 143.6; IR (neat) ν 1161, 1350, 1599, 3154 cm^{-1}; MS (ESI) m/z (rel intensity) 381 (24, $M+H^+$), 300 (100, M^+-Br); Anal. Calcd for $C_{17}H_{18}BrNO_2S$: C, 53.69; H, 4.77; N, 3.68. Found: C, 53.92; H, 4.54; N, 3.79.