Bromine-Catalyzed Aziridination of Olefins. A Rare Example of Atom-Transfer Redox Catalysis by a Main Group Element

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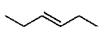
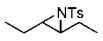
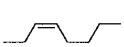
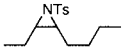
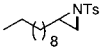
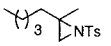
Due to their highly regio- and stereoselective ring-opening reactions, aziridines are valued as building blocks for the synthesis of a wide range of nitrogen-containing compounds.[1] Following Mansuy's seminal work,[2] several groups have also developed transition-metal-catalyzed aziridinations based on PhI═NTs as the nitrenoid source.[3] Despite these advances, catalytic aziridination has not yet entered the realm of practical organic synthesis, mainly due to the expense and inconvenience of PhI═NTs as a reagent.

Our long-standing interest in olefin oxidation processes led us to search sporadically over the past two decades for a transition-metal-catalyzed aziridination process using Chloramine-T (TsNClNa), a practical nitrogen source.[4] No effective transition-metal catalyst was found, but it was noticed that the presence of inorganic bromine seemed to coincide with the better yields of aziridine observed.[4a] Recent studies on this bromine effect revealed that a wide range of bromine sources (e.g., $ZnBr_2$, $HgBr_2$, $FeBr_2$, $CuBr_2$, Br_2, and NBS) act as catalysts for the aziridination of simple olefins using Chloramine-T.[4b] However, the substrate scope for all of these systems is limited, as is also the case for the interesting Chloramine-T/CuCl-catalyzed aziridination process just reported by Komatsu et al.[5]

Fortunately, additional screening experiments have identified a much more robust bromine-based catalyst system: *phenyltrimethylammonium tribromide (*$PhNMe_3^+Br_3^-$*, also known as PTAB)*. This catalyst provides good to excellent yields of aziridines across a wide range of olefin classes. Typical experimental conditions employ 10 mol % of PTAB and 1.1 equiv of anhydrous Chloramine-T[6] in acetonitrile[7] (0.2 M[8a]) at room temperature for 4−12 h. The PTAB functions as the source of the positive bromine species (Br-X) which initiates the catalytic cycle, and probably also as a solid−liquid phase transfer catalyst aiding the dissolution of Chloramine-T in acetonitrile. As depicted in Table 1,[8b] 1,2-disubstituted olefins (Table 1, entries 1−5) provided the corresponding aziridines stereospecifically and in excellent yield. The two monosubstituted olefins (entries 6 and 7) gave more modest yields, albeit still in the useful range. A disubstituted case, 2-methyl-1-heptene (entry 8), afforded 76% of the desired aziridine along with 10% of the allylic sulfonamide (**6**)[9] that is likely formed from an elimination process which competes with aziridine ring closure. An allylic sulfonamide (**7**)[9] was also a minor byproduct (5%) from the aziridination of 1-methylcyclohexene (entry 9).

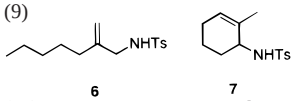
Table 1. Bromine-Catalyzed Aziridination of Olefins with TsNClNa[a]

entry	olefin	product	yield (%)[b]	mp (°C)[c]
1			93 (90)	69-70
2			76 (62)	85-87
3			95 (88)	*d*
4			89 (72)	82-83
5			86 (80[e])	71-72
6			54	*d*
7			68 (65)	88-89
8			76 (60)	*d*
9			51	90-91

[a] All reactions were run at 25 °C for 12 h on a 3 mmol scale and at 0.2 M [olefin] unless otherwise noted; *General procedure*: To a mixture of 3 mmol of olefin and 3.3 mmol of anhydrous Chloramine-T in 15 mL of CH_3CN were added 0.3 mmol of PTAB at 25 °C. After 12 h of vigorous stirring, the reaction mixture was concentrated and filtered through a short column of silica gel (3 × 4 cm, 10% EtOAc in hexane). After evaporation of the solvent, the resultant solid was purified by recrystallization. [b] Isolated yields after silica gel column chromatography. Yields in parentheses were obtained using $TsNClNa\cdot 3H_2O$ in place of anhydrous Chloramine-T. [c] See the Supporting Information for recrystallization solvents. [d] Colorless oil. [e] Use of the trihydrate of Chloramine-T in this case gave an 80% yield on a 3 mmol scale and also on a 0.5 mol scale, both run at 0.2 M concentration.

To establish the applicability of this "trihydrate" version to larger scale processes, a 0.5 mol scale reaction of cyclopentene (34 g) was undertaken with $TsNClNa\cdot 3H_2O$ (155 g) and 10 mol % PTAB (19 g) in CH_3CN (2.5 L, therefore ∼0.2 M). The

(9)



6 **7** **8** **9**

(1) (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (b) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, 5253. (c) Ibuka, T. *Chem. Soc. Rev.* **1998**, *27*, 145.

(2) Mansuy, D.; Mahy, J.-P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161.

(3) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, 7373. (c) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (d) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (e) Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, 9245. (f) Osborn, H. M. I.; Sweeny, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (g) Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, 6897 and references therein.

(4) Unpublished results: (a) Woodard, S. S.; Ho, P. T.; Sharpless, K. B., MIT and Stanford, 1977−1987. (b) Henniges, H.; Jeong, J. U.; Sharpless, K. B., Scripps, 1996−1997.

(5) Ando, T.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998**, 309. This appears to be the first bona fide case, using Chloramine-T, where the transition-metal center is directly involved in the aziridination step.

(6) The commercially available Chloramine-T trihydrate was dried to constant weight at ca. 80 °C for 12 h in a drying pistol. See also footnote 8 in Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O. *J. Am. Chem. Soc.* **1976**, *98*, 269.

(7) Purified by the Grubbs' method: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

(8) (a) When using *anhydrous Chloramine-T*, even higher reaction concentrations had only a small deleterious effect on the yield (e.g., *trans*-β-methylstyrene run at 0.5 M in acetonitrile afforded 71% of the azidine (cf., entry 2, 76% yield). (b) All aziridines were characterized by ^1H and ^{13}C NMR and by HRMS (see the Supporting Information).

(10) However, in contrast to the aziridination with anhydrous Chloramine-T, higher olefin concentration with Chloramine-T trihyrate gave lower yields of the aziridines. For example, the reaction of cyclopentene gave a 55% yield with Chloramine-T trihyrate at 0.5 M [olefin], and interestingly when this experiment was repeated in the presence of molecular sieves (4 Å), the yield was unchanged (i.e., 55%).

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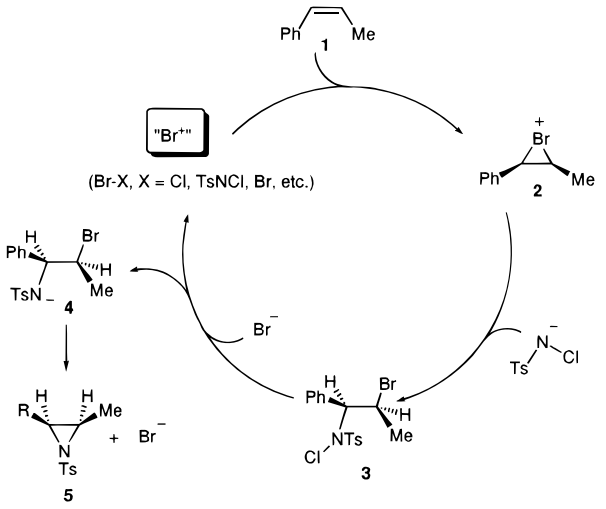
Scheme 1



aziridination product was easily isolated by crystallization of the crude reaction mixture (95 g, 80%, mp 71−72 °C) [see the Supporting Information].

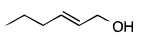
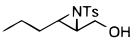
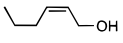
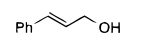
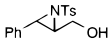
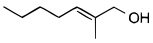
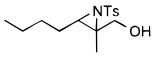
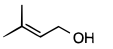
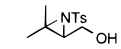
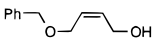
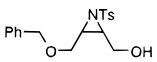
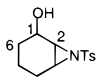
Our proposed pathway for this bromine-catalyzed aziridination process is shown in Scheme 1 taking *cis*-*β*-methylstyrene (**1)** as the specific case. Initially, the olefin reacts with a Br^+ source (Br-X) to give the bromonium ion **2**, which then suffers benzylic opening by $TsNCl^-$ forming the *β*-bromo-*N*-chloro-*N*-toluenesulfonamide **3**.[11] Attack of Br^- (or $TsNCl^-$) on the N−Cl group in putative intermediate **3** generates the anion **4** and a Br-X species. Expulsion of Br^- from the anion **4** finally yields the aziridine **5**, and the regenerated Br-X species (vide supra) is ready to initiate another turn of the catalytic cycle.

As revealed in Table 2, allylic alcohols are especially good substrates for this bromine-catalyzed aziridination process. Given that charged intermediates and reagents pervade the proposed catalytic cycle (Scheme 1), interesting mechanistic scenarios invoking important roles for the proximate hydroxyl group are easily imagined. For the moment, we note only one result of possible relevance to these considerations, which is the slight preference for *syn*-aziridination of 2-cyclohexen-1-ol, the sole cyclic case in Table 2 (entry 9, 2.5:1.0 = syn:anti).[12]

In the parent case (i.e., allyl alcohol, entry 6), 30% of the 2, 3-disulfonamide **8**[9] is also produced. This is not surprising since $TsNCl^-$ is an excellent nucleophile[11b] and the primary product, an aza-glycidol analogue, should be a reactive electrophile. However, the reaction of 2-methyl-2-propen-1-ol (entry 7) gave the corresponding aziridine in a 70% yield and only 12% of the disulfonamide **9**.[9] When these latter two reactions (entries 6 and 7) were repeated using 2.2 equiv of anhydrous Chloramine-T, only the disulfonamide products **8** (60%) and **9** (62%) were obtained.

In conclusion, we have found a simple bromine-catalyzed process for the direct formation of *N*-sulfonyl aziridines from olefins[13] with RSO_2NCl^- salts as the nitrogen source. Successful preliminary results have also been obtained with *p*-NO_2PhSO_2-NClNa,[14a] $MeSO_2NClNa$,[14b] *n*-$BuSO_2NClNa$,[14b] *t*-$BuSO_2NClNa$,[14c] and *N*-chloro-*N*-sodiobenzothiazole-2-sulfonamide,[14d] currently under investigation as alternative nitrogen sources due to the mild reaction conditions needed for subsequent deprotection of the resulting sulfonyl aziridines or their derivatives.[15] Thus bromine joins its third row neighbor selenium in catalyzing a selective atom transfer oxidation process of olefins.[16] Use of Chloramine-T (TsNClNa) is especially attractive because it is inexpensive and its aziridine derivatives tend to be crystalline. Since the process can be run fairly concentrated (e.g., 0.5 M), and in the case of crystalline products entails a very simple workup/isolation sequence, large scale applications can be considered.

Table 2. Bromine-Catalyzed Aziridination of Allylic Alcohols with *Anhydrous* TsNClNa[a]

entry	olefin	product	yield (%)[b, c]
1			97
2			95
3			70
4			73
5			94[d]
6			30[e]
7			70[f]
8			80
9			87[g]

[a] All reactions were performed on a 2 mmol scale and at 0.2 M [olefin]. [b] Isolated yields after silica gel column chromatography. [c] Colorless oil unless otherwise noted. [d] mp 63−64 °C. [e] 30% of the disulfonamide **8** was also obtained. [f] 12% of the disulfonamide **9** was also obtained. [g] Syn:anti = 2.5:1.0 (assignment of the configuration of the diastereomers was made by comparison of coupling constants with literature values:[12] syn, $J_{1,2}$ = 4.2 Hz, $J_{1,6}$ = 7.0 Hz; anti, $J_{1,6}$ = 6.8 Hz. Coupling constants of a similar pair of aziridine diastereomers:[12] syn, $J_{1,2}$ = 4.5 Hz, $J_{1,6A}$ = 9.0 Hz, $J_{1,6B}$ = 6.0 Hz; anti, $J_{1,2}$ = 1.0 Hz).

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Supporting Information Available: A discussion of the challenges faced in developing metalloid-main group elements as catalysts for atom transfer oxidation of olefins, experimental details, and spectral data (8 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981419G

(11) (a) Bromonium ions such as **2** and adducts such as **3** have been identified in the reactions of *N*, *N*-dihalosulfonamides with olefins, see: Mirskova, A. N.; Drozdova, T. I.; Levkovskaya, G. G.; Voronkov, M. G. *Russ. Chem. Rev.* **1989**, *58*, 250. (b) Studies have established that Chloramine-T is an exceptionally good nucleophile: Hardy, F. E. *J. Chem. Soc. B.* **1971**, 1899. Campell, M. M.; Johnson, G. *Chem. Rev.* **1978**, *78*, 65.

(12) The assignment of the configuration of the diastereomers was made by comparison of coupling constants with those of a very similar pair of aziridine diastereomers: Atkinson, R. S.; Kelly, B. J. *J. Chem. Soc., Chem. Commun.* **1988**, 624.

(13) (a) Unfortunately, electron-deficient olefins such as α,*β*-unsaturated esters and amides are beyond the scope of this reaction. (b) Interestingly, homoallylic and bishomoallylic alcohols gave less than 20% of the aziridination products under the standard conditions.

(14) (a) Heintzelman, R. W.; Swern, D. *Synthesis* **1976**, 731. (b) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810. (c) Gontcharov, A. V.; Liu, H.: Sharpless, K. B., unpublished results. (d) Schoenwald, R. D.; Eller, M. G.; Dixon, J. A.; Barfknecht, C. F. *J. Med. Chem.* **1984**, *27*, 810.

(15) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, 6373. (b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, 5831. (c) Vedejs, E.; Lin, S.; Klapars, A.; Wang, J. *J. Am. Chem. Soc.* **1996**, *118*, 9796.

(16) See the Supporting Information for discussion of the challenges faced in developing metalloid-main group elements (e.g., Se, Br, Te, and I) as catalysts for atom-transfer oxidation of olefins.