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Metal-Free Aziridination of Styrene Derivatives with Iminoiodinane Catalyzed by a Combination of Iodine and Ammonium Iodide

Kensuke Kiyokawa, Tomoki Kosaka, and Satoshi Minakata*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University,
Yamadaoka 2-1, Suita, Osaka 565-0871, Japan

minakata@chem.eng.osaka-u.ac.jp

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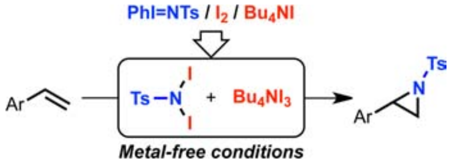
ABSTRACT



The metal-free catalytic aziridination of styrene derivatives with *N*-tosyliminophenyliodinane (PhI=NTs) in the presence of a combination of I_2 and tetrabutylammonium iodide (TBAI) is reported. In situ generated $TBAI_3$ from I_2 and TBAI dramatically promotes the reaction of alkenes with *N*,*N*-diiodotosylamide, which is formed in situ.

Aziridines represent an important structural motif in natural products and are also a useful building block in organic synthesis.[1] Therefore, numerous synthetic methodologies for preparing aziridines have been reported in the past decades. The direct aziridination of alkenes, the transfer of a nitrogen atom to alkenes, are currently one of the most practical and useful methods for the synthesis of aziridines.[1a,2,3] Significant progress has been achieved to date in the transition-metal-catalyzed aziridination of alkenes using several nitrogen sources such as organic azides, *N*-sulfonyliminophenyliodinanes, and *N*-haloamine salts. Among these reagents, iminoiodinanes have been widely used for aziridination reactions including asymmetric versions, since the discovery of a practical method for the synthesis of *N*-tosyliminophenyliodinane (PhI = NTs).[4]

Recently, the benign metal-free aziridination of alkenes has attracted considerable attention from practical,

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(1) (a) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (c) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Aldrichimica Acta* **2003**, *36*, 39. (d) Shipman, M. *Synlett* **2006**, 3205. (e) Hou, X. L.; Wu, J.; Fan, R. H.; Ding, C. H.; Luo, Z. B.; Dai, L. X. *Synlett* **2006**, 181. (f) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, 1. (g) Ismail, F. M. D.; Levitsky, D. O.; Dembitsky, V. M. *Eur. J. Med. Chem.* **2009**, *44*, 3373.

(2) Minakata, S.; Takeda, Y.; Kiyokawa, K. In *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*; Nishiwaki, N., Ed.; Wiley-VCH: Weinheim, Germany, Chapter 2; ISBN 978-1-118-29988-3.

(3) For selected reviews, see: (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (c) Driver, T. G. *Org. Biomol. Chem.* **2010**, *8*, 3831. (d) Chang, J. W. W.; Ton, T. M. U.; Chan, P. W. H. *Chem. Rec.* **2011**, *11*, 331. (e) Jenkins, D. M. *Synlett* **2012**, 1267.

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(5) For an example of metal-free aziridinations using an organic azide, see: Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354.

(6) For selected examples of metal-free aziridinations using haloamine salts, see: (a) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844. (b) Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1998**, *54*, 13485. (c) Kano, D.; Minakata, S.; Komatsu, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3186. (d) Minakata, S.; Kano, D.; Oderaotoshi, Y.; Komatsu, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 79. (e) Minakata, S.; Murakami, Y.; Tsuruoka, R.; Kitanaka, S.; Komatsu, M. *Chem. Commun.* **2008**, 6363. (f) Murakami, Y.; Takeda, Y.; Minakata, S. *J. Org. Chem.* **2011**, *76*, 6277. (g) Saikia, I.; Kashyap, B.; Phukan, P. *Chem. Commun.* **2011**, *47*, 2967.

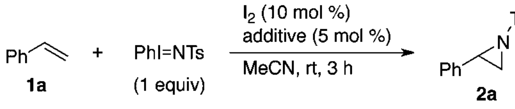
(7) For selected examples of metal-free aziridinations using *N*-aminophthalimide, see: (a) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530. (b) Li, J.; Liang, J.-L.; Hong Chan, P. W.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 2685. (c) Li, J.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2005**, *7*, 5801. (d) Shen, Y.-M.; Zhao, M.-X.; Xu, J.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8005. (e) Krasnova, L. B.; Yudin, A. K. *Org. Lett.* **2006**, *8*, 2011. (f) Richardson, R. D.; Desaize, M.; Wirth, T. *Chem.—Eur. J.* **2007**, *13*, 6745. (g) Yoshimura, A.; Middleton, K. R.; Zhu, C.; Nemykin, V. N.; Zhdankin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 8059.

10.1021/ol402276f

economical, and environmental points of view.[5–9] However, to the best of our knowledge, aziridination using iminoiodinanes under metal-free conditions, which would be highly desirable, has not been developed, although the direct amidation of a C–H bond in the presence of an I_2 catalyst has been achieved.[10] Herein, we report on the metal-free catalytic aziridination of styrene derivatives using an equimolar amount of PhI = NTs in the presence of I_2 and tetrabutylammonium iodide (TBAI). Although the aziridination of alkenes generally requires an excess amount of either the alkene or the nitrogen source to produce a satisfactory yield, this is not needed in this protocol.

Previously, our group reported on the catalytic aziridination of alkenes with chloramine-T in the presence of I_2.[6b] On the basis of the conditions in that report, we first examined the addition of 10 mol % of I_2 in the reaction of styrene (1 equiv) with PhI = NTs (1 equiv) in acetonitrile at room temperature, to produce the corresponding aziridine **2a** in moderate yield (Table 1, entry 1). During further investigations of the catalytic system, we were pleased to find that the use of TBAI (5 mol %) in combination with I_2 (10 mol %) resulted in a dramatically increased yield of **2a** up to 94% (Table 1, entry 2). Only a trace amount of **2a** was produced in the absence of I_2 (Table 1, entry 3), suggesting that I_2 plays a critical role in the aziridination reaction. Other ammonium iodides, such as $BnEt_3NI$, Et_4NI, and Me_4NI in addition to TBAI, were also highly effective (Table 1, entries 4–6). The use of TBABr gave **2a** in 85% yield, while TBACl, $TBABF_4$, and $TBABPh_4$ inhibited the reactions (Table 1, entries 7–10). Employing alkali metal iodides (LiI, NaI, and KI) instead of ammonium salts resulted in slightly lower yields compared to reactions using TBAI (Table 1, entries 11–13). When the reaction was conducted in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), a radical inhibitor, the yield of the product was greatly depressed (Table 1, entry 14). Furthermore, when the reaction was run in the dark, it was suppressed (Table 1, entry 15). These results indicate that the reaction involves a radical pathway that is promoted by visible light (ambient laboratory light).

Table 1. Screening of Additives[a]



entry	additive	yield (%)[b]
1	none	55
2	Bu_4NI	94 (93)[c]
3[d]	Bu_4NI	<5
4	$BnEt_3NI$	94
5	Et_4NI	90
6	Me_4NI	94
7	Bu_4NBr	85
8	Bu_4NCl	17
9	Bu_4NBF_4	21
10	Bu_4NBPh_4	<5
11	LiI	85
12	NaI	89
13	KI	89
14[e]	Bu_4NI	<5
15[f]	Bu_4NI	61

[a] Reaction conditions: styrene (0.5 mmol), PhI = NTs (0.5 mmol), I_2 (0.05 mmol), additive (0.025 mmol), MeCN (2 mL), rt, 3 h. [b] Yields of crude products determined by ^1H NMR analysis. [c] Isolated yield. [d] I_2 was not added. [e] TEMPO (1 equiv) was added. [f] The reaction was carried out in the dark.

With the optimal conditions in hand, we next investigated the scope of alkenes in metal-free aziridination (Table 2). Styrene derivatives bearing various types of functional groups at the para position were suitable substrates (Table 2, entries 1–9).[11] It is noteworthy that electron-deficient styrenes as well as electron-rich derivatives could also be used in the reaction. Substituents at the ortho or meta position on the phenyl ring had a negligible effect on reactivity (Table 2, entries 10 and 11). α-Methylstyrene (**1m**) was also applicable (Table 2, entry 12).[11] Cyclic alkenes such as indene (**1n**) and 1,2-dihydronaphthalene (**1o**) provided the corresponding aziridines selectively without amidation of the C–H bond at the secondary benzylic position (Table 2, entries 13 and 14).[10] Disappointingly, a very low yield was obtained when an aliphatic alkene was used in the reaction (Table 2, entry 15).

Interestingly, in the reaction of C_{60} with PhI = NTs in *o*-dichlorobenzene (*o*-DCB), the azafulleroid **3** was the major product, rather than the aziridinofullerene **4** (37% yield (combined isolated yield of **3** and **4**), 69% selectivity),[12,13] which is contrary to the result when a copper catalyst is used, in which **4** is produced selectively (Scheme 1).[14] Furthermore, the yield and selectivity were similar, even when TBAI was not employed in the reaction.

The reactions of *cis*- and *trans*-disubstituted alkenes **1p** and **1q** gave insights into the stereochemistry of the aziridination reaction (Table 3). The reaction of *trans*-β-methylstyrene (*trans*-**1p**) provided the corresponding aziridine **2p** in 89% overall yield in a *cis*/*trans* ratio of 39:61 (Table 3, entry 1). No isomerization of either the starting alkene (*trans*-**1p**) or the aziridine product (*trans*-**2p**) was observed with the I_2/TBAI catalyst in acetonitrile

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(8) For selected examples of metal-free aziridinations using amides, see: (a) Minakata, S.; Morino, Y.; Oderaotoshi, Y.; Komatsu, M. *Chem. Commun.* **2006**, 3337. (b) Fan, R.; Pu, D.; Gan, J.; Wang, B. *Tetrahedron Lett.* **2008**, *49*, 4925. (c) Deiana, L.; Zhao, G.-L.; Lin, S.; Dziedzic, P.; Zhang, Q.; Leijonmarck, H.; Córdova, A. *Adv. Synth. Catal.* **2010**, *352*, 3201.

(9) For an example of metal-free aziridination using ammonia, see: Varszegi, C.; Ernst, M.; van Laar, F.; Sels, B. F.; Schwab, E.; De Vos, D. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 1477.

(10) Lamar, A. A.; Nicholas, K. M. *J. Org. Chem.* **2010**, *75*, 7644.

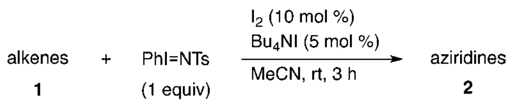
(11) Products **2b** and **2m** were unstable and partially decomposed during their isolation by column chromatography using silica gel.

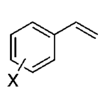
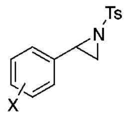
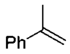
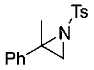
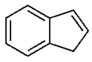
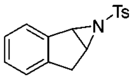
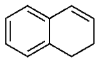
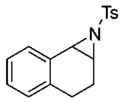
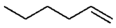
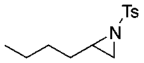
(12) The term "selectivity" is defined using the following equation: selectivity = [yield of product]/[conversion of C_{60}] × 100.

(13) Nagamachi, T.; Takeda, Y.; Nakayama, K.; Minakata, S. *Chem.—Eur. J.* **2012**, *18*, 12035.

(14) Nambo, M.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 2402.

Table 2. Scope of Alkenes[a]



entry	1		2		yield (%)[b]
					
1	X = 4-OMe	**1b**		**2b**	51 (86)[c]
2	X = 4-Me	**1c**		**2c**	90
3	X = 4-OAc	**1d**		**2d**	89
4	X = 4-Cl	**1e**		**2e**	86
5	X = 4-Br	**1f**		**2f**	75
6	X = 4-CO_2Me	**1g**		**2g**	81
7	X = 4-CN	**1h**		**2h**	80
8	X = 4-CF_3	**1i**		**2i**	74
9	X = 4-NO_2	**1j**		**2j**	60
10	X = 2-Me	**1k**		**2k**	92
11	X = 3-Me	**1l**		**2l**	85
12		**1m**		**2m**	58 (74)[c]
13[d]		**1n**		**2n**	64
14[d]		**1o**		**2o**	46
15					(6)[c]

[a] Reaction conditions: alkene (0.5 mmol), PhI = NTs (0.5 mmol), I_2 (0.05 mmol), TBAI (0.025 mmol), MeCN (2 mL), rt, 3 h. [b] Isolated yields. [c] Yields of crude products determined by ^1H NMR analysis. [d] I_2 (20 mol %) and TBAI (10 mol %) were used.

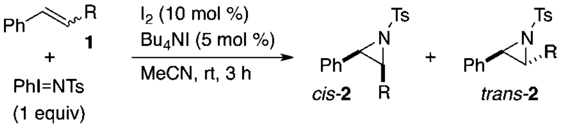
Scheme 1. Reaction of C_{60} with PhI = NTs

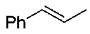
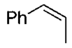
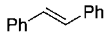
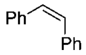
3 **4**

37% (**3**/**4** = 84:16), 69% selectivity
without Bu_4NI: 40% (**3**/**4** = 85:15), 73% selectivity

(see the Supporting Information for details). These results strongly suggest that the aziridination proceeds via a stepwise process, in which the stereochemistry of the starting alkene is lost. Similarly, starting from the *cis* isomer **1p**, **2p** was obtained in 92% yield as a mixture of *cis*/*trans* isomers (Table 3, entry 2). Furthermore, in the case of stilbene (*trans*-**1q** and *cis*-**1q**), the reactions also proceeded in a nonstereospecific manner (Table 3, entries 3 and 4), consistent with a stepwise process.[15]

Table 3. Reactions of *cis* and *trans*-Disubstituted Alkenes[a]

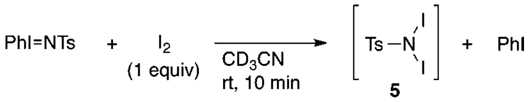


entry	1		2	*cis*/*trans*[b]	yield (%)[c]
1		*trans*-**1p**	**2p**	39/61	89
2		*cis*-**1p**	**2p**	36/64	92
3		*trans*-**1q**	**2q**	90/10	78
4		*cis*-**1q**	**2q**	92/8	67

[a] Reaction conditions: alkenes (0.5 mmol), PhI = NTs (0.5 mmol), I_2 (0.05 mmol), TBAI (0.025 mmol), MeCN (2 mL), rt, 3 h. [b] Determined by ^1H NMR analysis of crude products. [c] Isolated yields.

To investigate the active species of the reaction, the reaction was run using a mixture of PhI = NTs and an equimolar amount of I_2 in [D_3]acetonitrile and was monitored by NMR spectroscopy. In the ^{13}C NMR spectrum of the mixture, characteristic signals ($\delta(^{13}C)$ = 145.6, 130.5, 130.4, 128.6, and 21.6 ppm), indicating the generation of *N*,*N*-diiodotosylamide **5** or its oligomeric species,[10] were observed along with signals corresponding to iodobenzene (Scheme 2) (see the Supporting Information for details). Amide **5**, which acts as an amidyl radical precursor,[10,12] is considered to be the active species in the aziridination.

Scheme 2. Reaction of PhI = NTs with I_2 in Acetonitrile



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It is known that ammonium tri-iodide ($TBAI_3$) is in equilibrium with I_2 and TBAI in acetonitrile (eq 1), and tri-iodide (I_3^-) is excited by a visible light to generate an iodine radical ($I^\bullet$) and an iodine radical anion ($I_2^{-\bullet}$) (eq 2).[16] However, to the best of our knowledge, the application of such a system for organic synthesis has not been reported.[17] We speculated that $TBAI_3$ would be generated in situ from I_2 and TBAI and then functions as a radical promoter in the aziridination reaction. To confirm this hypothesis, control experiments were conducted, as shown in Scheme 3. Although the aziridine **2a** was obtained in 94% yield under the standard conditions (Table 1, entry 2),

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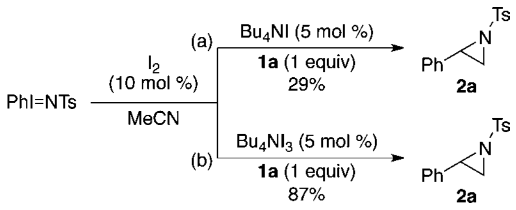
(15) When the reaction of an aliphatic alkene, *trans*-3-hexene, was conducted under optimized conditions (see, Table 1, entry 2), the corresponding aziridine was obtained with a *cis*/*trans* ratio of 36:64 in 5% yield, as determined by ^1H NMR analysis of the crude product.

(16) (a) Gardner, J. M.; Abrahamsson, M.; Farnum, B. H.; Meyer, G. J. *J. Am. Chem. Soc.* **2009**, *131*, 16206. (b) Boschloo, G.; Hagfeldt, A. *Acc. Chem. Res.* **2009**, *42*, 1819.

(17) The reaction using tri-iodide (I_3^-) generated in situ from $Cu(ClO_4)_2$ and NaI as an electrophile has been reported; see: Brotherton, W. S.; Clark, R. J.; Zhu, L. *J. Org. Chem.* **2012**, *77*, 6443.

Scheme 3. Control Experiments Using TBAI or $TBAI_3$



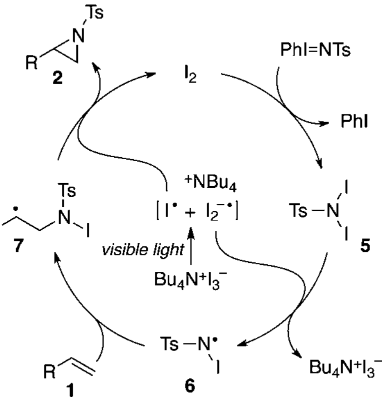
where PhI = NTs and styrene (**1a**) were added to a mixture of I_2 and TBAI in acetonitrile, when PhI = NTs and I_2 were mixed in advance of the addition of TBAI and **1a**, the reaction was suppressed, and **2a** was produced in only 29% yield (Scheme 3, method a). In contrast, the use of $TBAI_3$ instead of TBAI afforded **2a** in 87% yield (Scheme 3, method b), similar to the yield under the optimized conditions described above, clearly showing that $TBAI_3$ played a significant role in promoting the reaction. In the case of method a, the rapid and complete consumption of I_2 in the initial reaction with PhI = NTs, to provide the diiodoamide **5**, would inhibit the generation of $TBAI_3$.

$$Bu_4NI + I_2 \rightleftarrows Bu_4NI_3 \qquad (1)$$

$$I_3^- \xrightarrow{\text{visible light}} [I_3^-]^* \rightarrow I^\bullet + I_2^{-\bullet} \qquad (2)$$

On the basis of the above experiments, a plausible reaction mechanism for the radical aziridination is shown in Scheme 4. Initially, PhI = NTs reacts with I_2, providing *N*,*N*-diiodotosylamide **5** (or its oligomeric species). Simultaneously, $TBAI_3$, generated in situ from I_2 and TBAI, is excited by visible light to provide $I^\bullet$ and $I_2^{-\bullet}$. When $I_2^{-\bullet}$ promotes the homolytic cleavage of the N–I bond of **5** via the abstraction of an iodine atom, the amidyl radical **6** is generated along with the regeneration of tri-iodide ($TBAI_3$). The amidyl radical **6** is rapidly trapped by the alkene **1**, followed by the intramolecular cyclization of **7** assisted by $I^\bullet$ to furnish the aziridine product **2** with regeneration of I_2. An alternative pathway is also possible, in which $I^\bullet$ participates in the N–I bond cleavage of **5** to give **6** and I_2, and $I_2^{-\bullet}$ reacts with **7** instead, affording **2** and the tri-iodide ($TBAI_3$).[18] It is interesting to note that TBAI appears to function as a precursor for $TBAI_3$ rather than as a phase-transfer catalyst.[6c,e,f]

Scheme 4. Plausible Mechanism



In conclusion, the novel metal-free aziridination of styrene derivatives with PhI = NTs has been developed by employing a I_2/TBAI catalyst system. Various functional groups were compatible with this catalytic system. The aziridination proceeds via a radical mechanism, where in situ generated $TBAI_3$ dramatically promotes the reaction of alkenes with *N*,*N*-diiodotosylamide, which is formed in situ. Further investigations of the mechanism and the application of the procedure to organic synthesis including enantioselective reactions are currently in progress.

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Supporting Information Available. Experimental details and spectra data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] A mechanism involving a single-electron transfer between $I^\bullet$ (or $I_2^{-\bullet}$) and **5**, leading to **6** with I_2 (or I_3^-), cannot be ruled out, based on the available data.

The authors declare no competing financial interest.