Aziridination

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Hypoiodite-Mediated Metal-Free Catalytic Aziridination of Alkenes**

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Aziridination of alkenes is an important chemical transformation and is a convenient method for accessing various nitrogen-containing products and synthetic intermediates.[1] Particularly useful aziridinating reagents are *N*-tosyliminoiodanes (ArINTs), which are important representatives of the rapidly growing field of hypervalent-iodine reagents.[2] Numerous synthetically useful aziridination methods are based on the use of metal salts or complexes as catalysts (for example, derivatives of Cu, Mn, Fe, and Rh) and ArINTs as nitrenium precursors.[3] However, from both environmental and economical viewpoints, avoiding toxic metals and performing reactions under metal-free conditions, is critically important in the development of "green" synthetic methodologies. Recently, the research groups of Che[4a,b] and Yudin[4c–e] reported metal-free conditions for aziridination using (diacetoxyiodo)benzene and *N*-aminoheterocycles. Che and co-workers have also reported aziridination using in situ generated hypervalent-iodine reactive species.[4b] However, the attempted realization of the catalytic version of aziridination was not successful. Likewise, Wirth and co-workers were unsuccessful in their broad search for reaction conditions to effect organocatalytic alkene aziridination using *N*-aminophthalimide ($PhthNH_2$) as the nitrenium source.[5] To the best of our knowledge, the organocatalytic aziridination of alkenes using $PhthNH_2$ as the nitrenium precursor has not yet been developed.

Herein we report the first metal-free catalytic aziridination using catalytic amounts of tetrabutylammonium iodide (TBAI), *m*-chloroperoxybenzoic acid (*m*CPBA) as the terminal oxidant, and $PhthNH_2$ as the nitrenium precursor. This new catalytic reaction has an advantage over the commonly used reactions that employ stoichiometric amounts of *N*-tosyliminoiodanes, because it employs the common inexpensive reagents, TBAI and *m*CPBA. Very recently, the research group of Ishihara reported the use of quaternary ammonium iodides as catalysts for the oxidative cycloetherification of ketophenol and intra- and intermolecular organocatalytic oxidative-coupling reactions mediated by the in situ generated tetrabutylammonium hypoiodite.[6] Several other research groups have also reported reactions using catalytic amounts of TBAI and common oxidants.[7]

In a search for iodine-mediated organocatalytic aziridination reaction conditions, we investigated the reactions of alkenes and $PhthNH_2$ as a nitrenium precursor with a broad range of oxidants (for example, Oxone, sodium perborate, and *m*CPBA) in the presence of iodine-containing precatalysts (various aryl iodides, I_2, NaI, and Bu_4NI) under different reaction conditions using various solvents and other additives (for more details see the Supporting Information, Table S1).

In the absence of iodine-containing pre-catalysts, the reactions of alkenes with $PhthNH_2$ and *m*CPBA afford mainly epoxides and do not produce any significant amounts of aziridines. The addition of 0.5 equivalents of an aryl iodide (PhI, 4-$MeOC_6H_4I$, 2,4,6-$Me_3C_6H_2I$, 2-$MeOC_6H_4I$, 4-MeC_6H_4I, 4-$CF_3C_6H_4I$, 4-ClC_6H_4I, and 3-$HO_2CC_6H_4I$ were tested) results in the formation of moderate amounts (below 40%) of the desired aziridines, a result, which is in agreement with previously reported observations of Che and co-workers,[4b] and is indicative of a noncatalytic reaction.

We were pleased to find that the addition of TBAI dramatically changes the outcome of this reaction, in that the desired aziridines were now formed in high yields. We investigated the aziridination of styrene as a model alkene in the presence of TBAI at 40°C under different reaction conditions (see Table 1; for more details see the Supporting Information, Table S1). Out of several solvents tested (see the Supporting Information, Table S1), ethyl acetate was found to be the best solvent. In particular, the reaction of styrene (**1a**) with $PhthNH_2$ (**2**), *m*CPBA, and 0.5 equivalents of TBAI in the presence of potassium carbonate in ethyl acetate afforded aziridine **3a** in 62% yield (Table 1, entry 1). Under these reaction conditions, but using a longer reaction time, aziridine **3a** was obtained in 71% yield (Table 1, entry 2). When the amount of TBAI was reduced from 50 mol% to 20 mol%, **3a** was obtained in a slightly lower yield (69%; Table 1, entry 3). Decreasing the amount of *m*CPBA from five to three equivalents resulted in further improvement of the yield to 79% (Table 1, entry 6). Lower amounts of *m*CPBA or TBAI and a lower reaction temperature lead to reduced yields of **3a** (Table 1, entries 9–11). A further increase in reaction time does not improve the yields (Table 1, entries 7, 8, and 12). Only trace amounts of **3a** are observed in the absence of TBAI (Table 1, entry 13). The presence of a base, potassium carbonate, is critically important (also see the Supporting Information, Table S1), probably because the aziridine product **3a** is unstable under acidic reaction conditions.

Using the optimized reaction conditions with 20 mol% TBAI, we investigated the conversion of various substituted alkenes **1** into the respective aziridines **3** (Table 2). In general,

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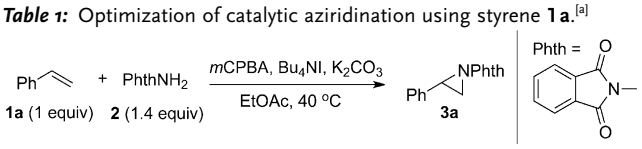
Table 1: Optimization of catalytic aziridination using styrene **1a**.[a]



1a (1 equiv) **2** (1.4 equiv) **3a**

Entry	*t* [h]	*m*CPBA [equiv]	TBAI [equiv]	**3a** [%][b]
1	4	5	0.5	(62)
2	12	5	0.5	(71)
3	12	5	0.2	64 (69)
4	24	5	0.2	(64)
5	6	3	0.2	70 (72)
6	12	3	0.2	76 (79)
7	24	3	0.2	68 (73)
8	48	3	0.2	61 (63)
9[c]	12	3	0.2	(46)
10	12	2	0.2	(51)
11	12	3	0.1	55 (56)
12	24	3	0.1	55 (59)
13	12	3	0	(<2)

[a] The aziridination of styrene was performed in ethyl acetate at 40 °C for several hours by using styrene **1a** (1 equiv), *N*-aminophthalimide **2** (1.4 equiv), K_2CO_3 (3 equiv), TBAI (0–0.5 equiv), and *m*CPBA (2–5 equiv). [b] Yields of products after isolation by column chromatography; NMR-determined yields are shown in parentheses. [c] Reaction was performed at room temperature.

all styrenes with either electron-donating or electron-withdrawing substituents afforded products in good yields (Table 2, entries 1–8). This reaction also gave good yields for α- or β-substituted styrenes (Table 2, entries 9–12). In the reactions of nonhindered cycloalkenes, the products were obtained in moderate yields (Table 2, entries 13 and 14), although a substituted cycloalkene, 1-methylcyclohexene (Table 2, entry 15) and seven- or eight-membered cycloalkenes (Table 2, entries 16 and 17) gave lower yields of aziridines. Reactions of 1-decene (Table 2, entry 18) and α,β-unsaturated cyclic ketone (Table 2, entry 19) under these conditions afforded corresponding aziridines in low yield, and these yields were not improved upon using stoichiometric amounts of TBAI. In general, the observed trend in yields is in agreement with that of Cu-catalyzed aziridination reactions of alkenes in previous studies.[3a,f] For comparison, the Cu-catalyzed aziridination reactions of 1-methylcyclohexene and cyclohexene give the corresponding aziridines in 32–51 and 30–60% yield, respectively.[3a] Likewise, the previously reported conversion of 1-nonene—using $PhI(OAc)_2$ and $PhthNH_2$—into the corresponding aziridine was only 29% (see Table 2, entry 18).[4a] The structure of the aziridination product **3e** (Table 2, entry 5) was established by a single-crystal X-ray analysis (see the Supporting Information for details). This structure (Figure 1), in combination with ^{1}H NMR data, confirms the *trans* configuration of the Phth group and the substituent in the aziridine ring (Table 2, entries 1–8 and 18). In the reaction of 1,1-disubstituted alkene (Table 2, entry 10), a mixture of two diastereomers is formed.

Several mechanisms can be considered for this new reaction. A control experiment has shown that epoxides are not intermediates in this reaction: a reaction of styrene oxide with $PhthNH_2$ under standard reaction conditions did not

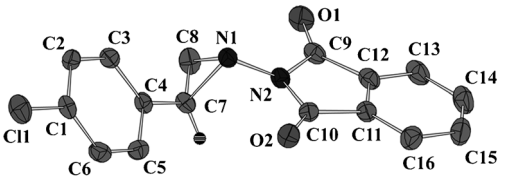


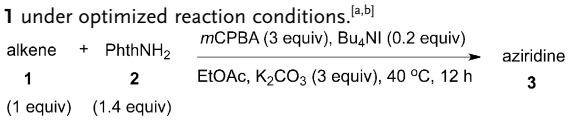
Figure 1. X-ray crystal structure of *N*-(aminophthalimide)-2-(4-chlorophenyl)aziridine (**3e**). Thermal ellipsoids are shown at 50% probability and some hydrogen atoms have been omitted for clarity.

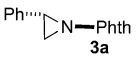
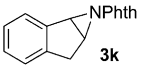
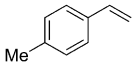
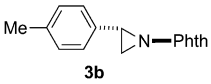
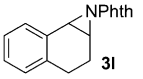
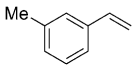
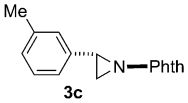
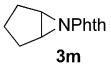
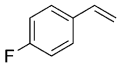
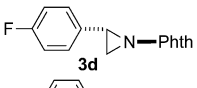
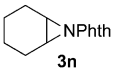
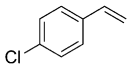
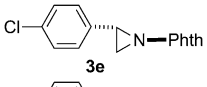
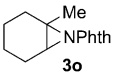
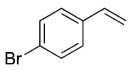
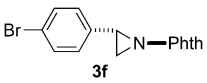
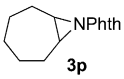
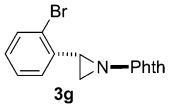
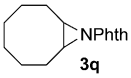
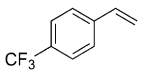
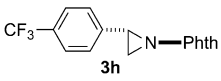
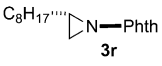
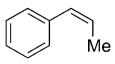
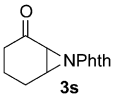
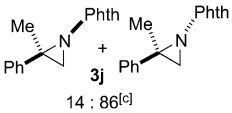
afford the aziridine product in detectable amounts. Another possible mechanism may involve the formation of reactive *N*-benzoyloxyaminophthalimide intermediates (PhthNHOCOAr) from $PhthNH_2$ and *m*CPBA in the presence of TBAI under the reaction conditions. Previously, a mechanism via PhthNHOCOR was proposed by the research groups of Che[4b] and Yudin[4e] for alkene aziridination using hypervalent-iodine species and $PhthNH_2$. The reported reactions via PhthNHOCOR intermediates worked particularly well for α,β-unsaturated ketones and chalcone.[4] However, in contrast to the studies of the research groups of Che[4b] and Yudin,[4e] the reactions catalyzed by TBAI gave a very small yield of aziridine for the α,β-unsaturated ketone (Table 2, entry 19), and did not afford any products of aziridination for chalcone. Based on this observation, we ruled out this mechanism.

Most likely, the mechanism of this reaction involves an oxidized iodine species generated in situ from Bu_4NI and *m*CPBA. To understand the nature of these active iodine species we performed several control experiments. These experiments showed that the aziridination products are not formed when stoichiometric amounts of iodate(V) or periodate(VII) salts are used in combination with $PhthNH_2$ under standard reaction conditions. Likewise, aziridines were not detected when the reaction was conducted in the presence of molecular iodine. However, we could detect the aziridine product when a combination of I_2 and Bu_4NOH was used without any additional oxidant added. This implies that the in situ generated hypoiodous acid, HOI, may be the active species in this reaction. The involvement of hypoiodous acid or hypoiodite anion as an active species is in agreement with the research group of Ishihara's proposal for the mechanism of a Bu_4NI-catalyzed oxidative cycloetherification reaction.[6]

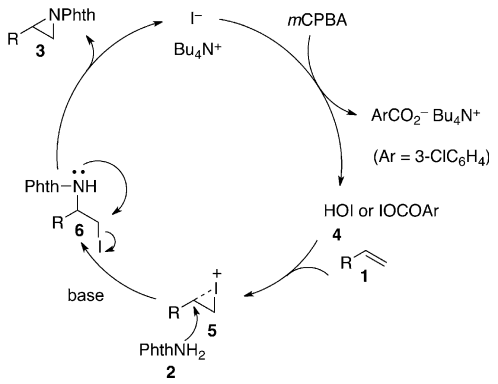
From these controls experiment, we propose the catalytic aziridination mechanism outlined in Scheme 1. The active species, hypoiodous acid **4** (or iodine 3-chlorobenzoate, IOCOAr), which is generated from Bu_4NI and *m*CPBA, reacts with alkene to give the iodonium ion **5**, which is then opened at the benzylic position by $PhthNH_2$ **2** (or by the corresponding potassium salt, PhthNHK, formed from **2** in the presence of K_2CO_3). This sequence of reactions gives β-iodo-*N*-aminophthalimide **6**, the cyclization of which affords the aziridine product **3** and iodide anion. The regenerated iodide anion continues the catalytic cycle. A similar reaction mechanism was previously proposed for the aziridination of olefins by chloramine-T in the presence of a Br^+ source[8a,b] or iodine.[8c]

Table 2: Catalytic aziridination of alkenes **1** under optimized reaction conditions.[a,b]



Entry	Alkene **1**	Product **3**	Yield [%][b]	Entry	Alkene **1**	Product **3**	Yield [%][b]
1		 **3a**	76	11		 **3k**	69
2		 **3b**	71	12		 **3l**	69
3		 **3c**	74	13		 **3m**	72
4		 **3d**	80	14		 **3n**	53
5		 **3e**	76	15		 **3o**	44
6		 **3f**	79	16		 **3p**	38
7		 **3g**	77	17		 **3q**	44
8		 **3h**	69	18		 **3r**	32
9		 **3i**	63	19		 **3s**	16
10		 **3j** 14 : 86[c]	69				

[a] The aziridination of alkenes was performed in ethyl acetate at 40 °C for 12 h by using alkene **1** (1 equiv), *N*-aminophthalimide **2** (1.4 equiv), K_2CO_3 (3 equiv), TBAI (0.2 equiv), and *m*CPBA (3 equiv). [b] Yields of products after isolation by column chromatography. [c] Ratio of invertomers was determined by ^{1}H NMR spectroscopy.



Scheme 1. Proposed mechanism of TBAI-catalyzed aziridination.

In conclusion, we have found reaction conditions for a catalytic aziridination of alkenes. This metal-free catalytic procedure gives good results for the aziridination of substituted styrenes and some cycloalkenes. The mechanism of this reaction probably involves in situ generated hypoiodous acid, which is generated from the oxidation of TBAI by *m*CPBA.

Experimental Section

General procedure for tetrabutylammonium-iodide-mediated catalytic aziridination of alkenes **1**: *m*CPBA (0.375 mmol), K_2CO_3 (0.375 mmol), alkene **1** (0.125 mmol), and tetrabutylammonium iodide (0.025 mmol) was added to a solution of *N*-aminophthalimide **2** (0.175 mmol) in 1.5 mL of EtOAc. The reaction mixture was stirred at 40 °C for 12 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (5 mL) and extracted with dichloromethane, and the organic phase was dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography over silica gel gave aziridine **3**.

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Keywords: aziridination · hypoiodous acid · iodine · organocatalysis · oxidation

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Communications

Aziridination

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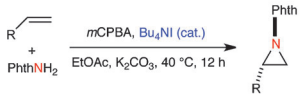
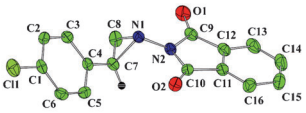
Hypoiodite-Mediated Metal-Free Catalytic Aziridination of Alkenes





Look, no metal: A metal-free catalytic procedure for aziridination of alkenes using tetrabutylammonium iodide as the catalyst, *m*-chloroperoxybenzoic acid (*m*CPBA) as the terminal oxidant, and *N*-aminophthalimide as the nitrenium precursor has been developed (see scheme; right: X-ray structure of one of the products). Control experiments suggests that the active oxidant is in situ generated hypoiodous acid (HIO).