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TRANSITION-METAL-FREE AZIRIDINATION OF ALKENES WITH SULFAMATE ESTERS USING *tert*-BUTYL HYPOIODITE

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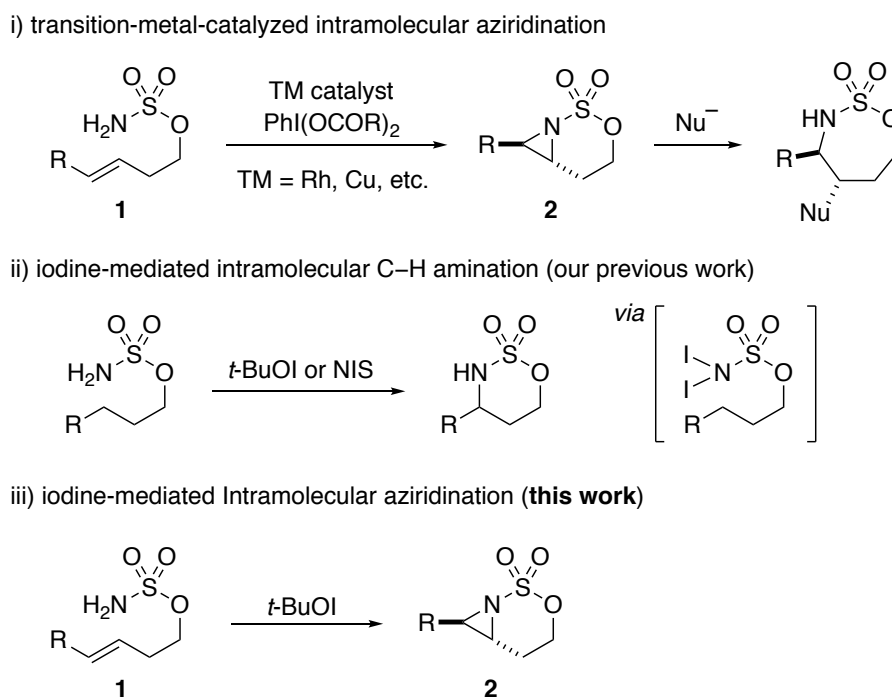
Abstract – The transition-metal-free aziridination of alkenes with sulfamate esters in the presence of *tert*-butyl hypoiodite (*t*-BuOI) is reported. The reaction can be used in intra- and intermolecular reactions, offering a practical and environmentally benign method for the synthesis of valuable aziridine compounds.

Aziridines are an important class of compounds that are frequently found in natural products and biologically active compounds.^{1,2} In addition, owing to their high ring strain, aziridines readily undergo ring opening with a wide variety of nucleophiles, thus representing a useful synthetic intermediate for preparing nitrogen-containing organic compounds.^{1,3} Because of this, substantial efforts have been devoted to the development of new methodologies for the synthesis of aziridines in the past decades.^{1,4,5}

The intramolecular aziridination of unsaturated sulfamate esters **1** provides synthetically useful bicyclic aziridines **2** (Scheme 1i).⁶ In particular, compound **2** can react with various nucleophiles, resulting in regioselective ring opening to provide the corresponding seven-membered ring products that can then be further elaborated to multi-functionalized amines.⁶ Conventional approaches to the intramolecular aziridination of **1** have involved a transition-metal-catalyzed nitrene transfer reaction, in which **1** is in-situ converted into an iminoiodane intermediate by reaction with a hypervalent iodine oxidant.^{6–8} A transition-metal-free version of the aziridination has, however, not been explored to date although it would be highly desirable from practical, economical, and environmental points of view.^{6i,7f,9}

During our ongoing studies on the development of oxidative amination reactions in which iodine reagents are used,^{10,11} we recently found that the intramolecular C–H amination of sulfamate esters proceeds effectively in the presence of monovalent iodine reagents such as *tert*-butyl hypoiodite (*t*-BuOI) or *N*-iodosuccinimide (NIS), affording six-membered oxathiazinane derivatives (Scheme 1ii).¹² Mechanistic investigations revealed that an *N,N*-diiodosulfamate ester is generated in-situ as a reactive intermediate through hydrogen–iodine exchange between the starting sulfamate ester and the iodine reagent being used.

Based on this finding and our previous studies on iodine-mediated aziridination reactions,^{9e} we hypothesized that the intramolecular aziridination of **1** should be feasible through the formation of an *N,N*-diiodosulfamate ester. Herein, we report on the transition-metal-free intramolecular aziridination of unsaturated sulfamate esters **1** in the presence of *t*-BuOI (Scheme 1iii). In addition, *t*-BuOI was found to be applicable to the intermolecular aziridination of alkenes with a sulfamate ester.

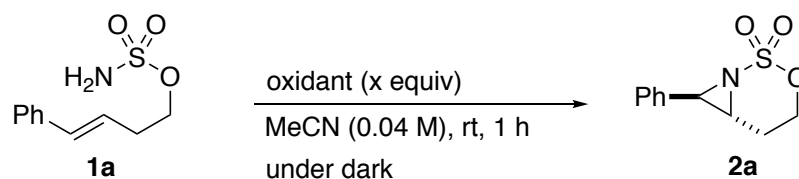


Scheme 1. Intramolecular oxidative cyclization involving C–N bond formation in sulfamate esters

We began our investigation by examining the intramolecular aziridination of the sulfamate ester **1a** using *t*-BuOI as an oxidant, which permits the iodination of the acidic protons on the nitrogen atom (Table 1).¹⁰ Based on the reaction conditions used in our previous work on the intramolecular C–H amination of sulfamate esters,¹² we used 2.2 equivalents of *t*-BuOI, prepared in situ from *t*-BuOCl and NaI, in MeCN (0.2 M) in the presence of a fluorescent light on the ceiling and found that **1a** was converted into the *trans*-aziridine **2a** in moderate yield but with a low mass balance (<5% recovery of **1a**) (entry 1). In an attempt to minimize potential intermolecular side reactions, the concentration in MeCN was decreased to 0.04 M, which was effective in improving the yield of **2a** (entry 2). The in situ generated *N,N*-diiodosulfamate ester shows radical reactivity as a nitrogen-centered radical due to the homolytic cleavage of an N–I bond when irradiated with visible light,¹² and this reactivity is the source of the side reaction. By conducting the reaction in the dark, the yield of **2a** was increased up to 90% (entry 3). Decreasing the amount of *t*-BuOI decreased the product yield (entries 4 and 5). The use of

1,3-diiodo-5,5-dimethylhydantoin (DIH) in the reaction provided **2a** in moderate yield (entry 6), while the use of NIS (entry 7) and other halogen-based oxidants, *t*-BuOCl and NBS, did not give **2a** (entries 8 and 9). Therefore, the aziridination was most efficient when we used *t*-BuOI in MeCN and conducted the reaction in the dark, and would proceed stereospecifically via an ionic pathway through the formation of a three-membered cyclic iodonium intermediate.¹⁰

Table 1. Optimization of the reaction conditions for the intramolecular aziridination of sulfamate ester **1a**^a

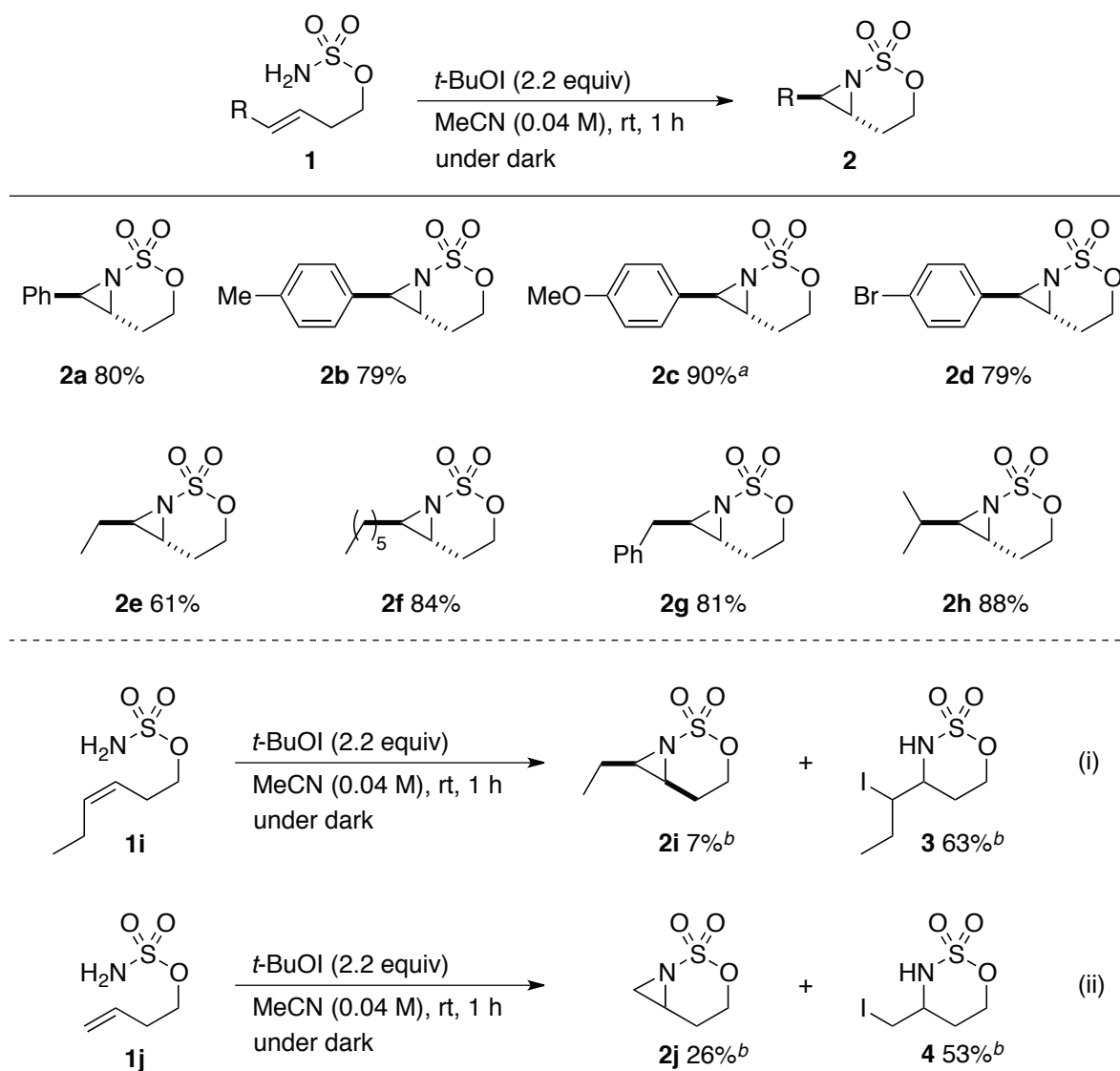


entry	oxidant (x equiv)	yield (%) ^b
1 ^{c,d}	<i>t</i> -BuOI (2.2)	56
2 ^c	<i>t</i> -BuOI (2.2)	68
3	<i>t</i> -BuOI (2.2)	90
4	<i>t</i> -BuOI (1.5)	57
5	<i>t</i> -BuOI (1.0)	40
6	DIH (2.2)	41
7	NIS (2.2)	0
8	<i>t</i> -BuOCl (2.2)	0
9	NBS (2.2)	0

^a Reactions were performed on a 0.2 mmol scale. ^b Determined by ¹H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. ^c Reaction was conducted on the benchtop in the presence of a fluorescent light on the ceiling for 7 h. ^d The reaction concentration was 0.2 M.

With the optimized conditions in hand, we next explored the substrate scope in the reaction (Scheme 2). The aziridination of sulfamate esters bearing a *trans*-alkene moiety was first examined. The reaction of styryl-type substrates bearing electron-rich aromatic rings as well as bromo-substituted phenyl groups proceeded smoothly to provide the corresponding *trans*-aziridines (**2a–d**). Substrates bearing an aliphatic alkene moiety also reacted well (**2e–h**). The efficiency of this aziridination was strongly affected by the *E/Z* configuration of the alkene. Contrary to the aziridination of the *trans*-alkene **1e**, the reaction of the *cis*-alkene **1i** provided the aziridine **2i** in low yield, with the iodoamination product **3** being produced as

the main product, the structure of which was unambiguously determined by NMR experiments (Scheme 2i).¹³ Prolonging the reaction time failed to improve the yield of **2i**. We hypothesize that a cyclization leading to the formation of the *cis*-aziridine **2i** is retarded by steric repulsion between the ethyl group and the cyclic unit (*vide infra*). In the case of the reaction of **1j** bearing a terminal alkene moiety, unexpectedly, a mixture of the aziridine **2j** and the iodoamination product **4** was obtained (Scheme 2ii).

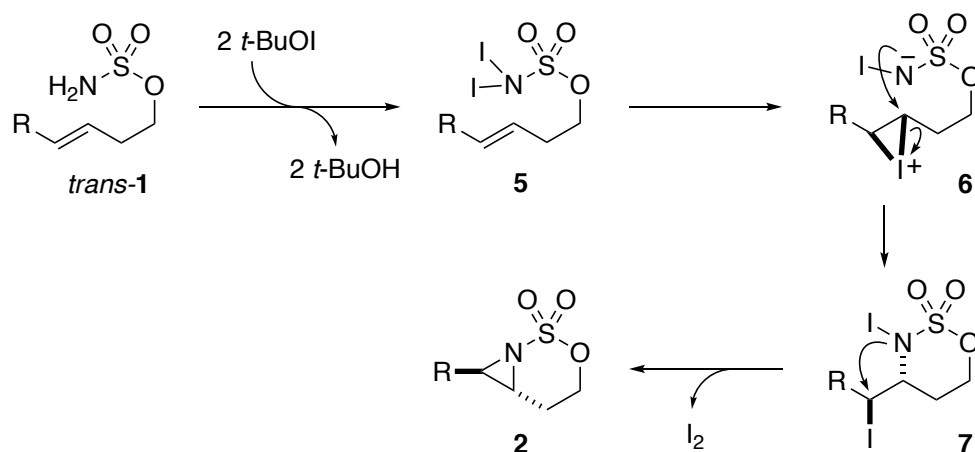


Scheme 2. Substrate scope for unsaturated sulfamate esters. Reactions were performed on a 0.2 mmol scale. Yields are isolated yields. ^a Reaction was conducted at 0 °C. ^b Determined by ¹H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.

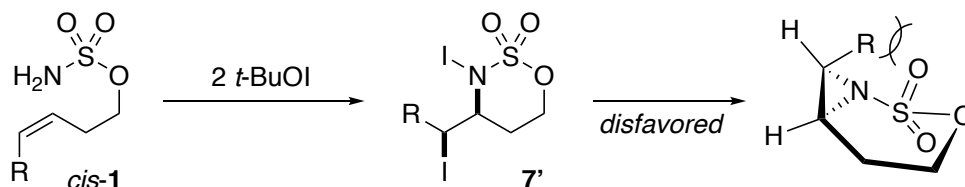
A plausible reaction pathway is depicted in Scheme 3, based on the experimental results and the previously reported mechanism of iodine-mediated aziridination reactions.¹⁰ The sulfamate ester *trans*-**1** initially reacts with *t*-BuOI, providing the *N,N*-diiodo species **5**, the cationic iodine atom of which is transferred to the alkene moiety to form a three-membered cyclic iodonium intermediate **6** (Scheme 3i). A

subsequent nucleophilic attack of a nitrogen atom provides the iodoaminated compound **7**. Finally, intramolecular substitution leads to the formation of the aziridine **2**, along with the generation of I_2 . This proposed pathway is consistent with the stereospecific formation of *trans*-aziridines from *trans*-alkenes. Meanwhile, the reaction of a *cis*-alkene gives the iodoaminated compound **7'**, the cyclization of which leading to the *cis*-aziridine would be disfavored due to steric repulsion (Scheme 3ii).

(i) reaction of *trans*-isomer

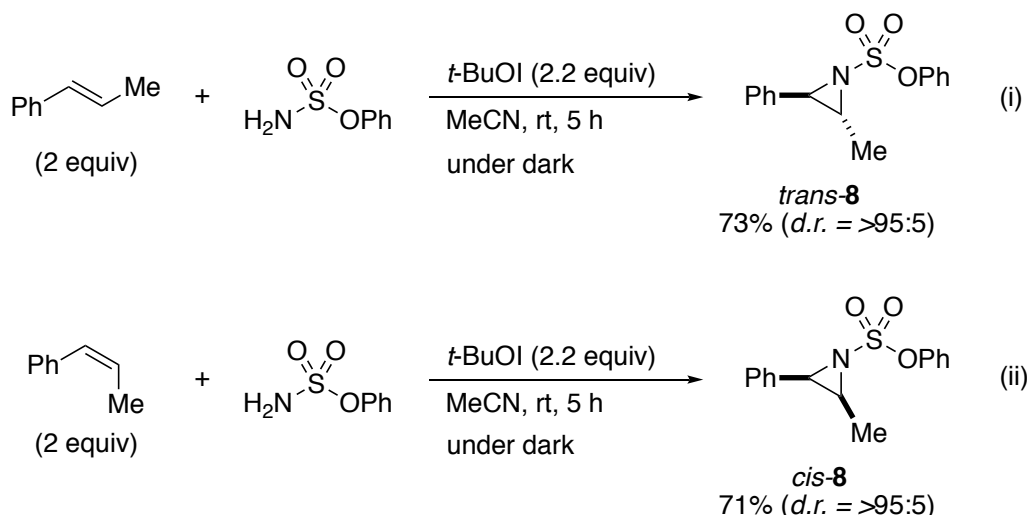


(ii) reaction of *cis*-isomer



Scheme 3. Plausible reaction pathway

The successful transition-metal-free intramolecular aziridination of sulfamate esters allowed us to examine the intermolecular version of this method.^{6b,9e} We tested the reaction using *trans*- β -methylstyrene as a substrate and phenyl sulfamate as a nitrogen source under the conditions used for the intramolecular reaction. The reaction resulted in an efficient aziridination to give the *trans*-aziridine **8** in 73% isolated yield (*d.r.* = >95:5) (Scheme 4i). Pleasingly, in the intermolecular reaction, a *cis*-alkene also smoothly participated in a stereospecific aziridination (Scheme 4ii).



Scheme 4. Intermolecular aziridination of alkenes with phenyl sulfamate

In conclusion, we report on the development of the transition-metal-free intramolecular aziridination of unsaturated sulfamate esters using *t*-BuOI. We also demonstrate that the method can be applied to the intermolecular aziridination of alkenes. The present aziridination proceeds stereospecifically under mild reaction conditions, thus offering a practical method for the synthesis of aziridine compounds.

SUPPORTING INFORMATION

Supplementary data (experimental procedures and characterization data) associated with this article can be found, in the online version, at URL:

<https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26700/103/1>

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