HETEROCYCLES, Vol. 103, No. , 2021, pp. -. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 8th June, 2020, Accepted, 13th July, 2020, Published online, 27th August, 2020
DOI: 10.3987/COM-20-S(K)20

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

Kensuke Kiyokawa,* Shogo Nakamura, and Satoshi Minakata*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan; E-mail: kiyokawa@chem.eng.osaka-u.ac.jp, minakata@chem.eng.osaka-u.ac.jp

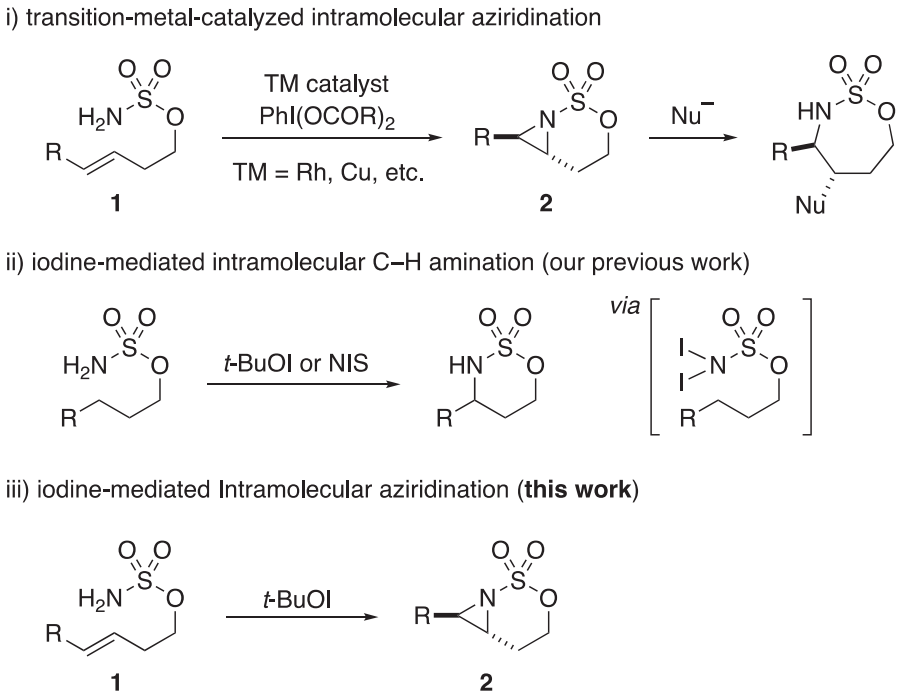
Abstract – The transition-metal-free aziridination of alkenes with sulfamate in the presence of *tert*-butyl hypoiodite (*t*-BuOI) is reported. The reaction can be used in intra- and intermolecular reactions, offering a practical and environmentally benign method for the synthesis of valuable aziridine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

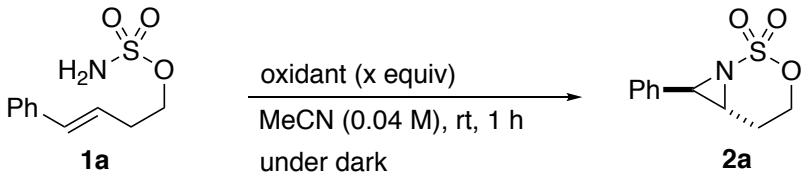


Scheme 1. Intramolecular oxidative cyclization involving C−N bond formation in sulfamate esters

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]

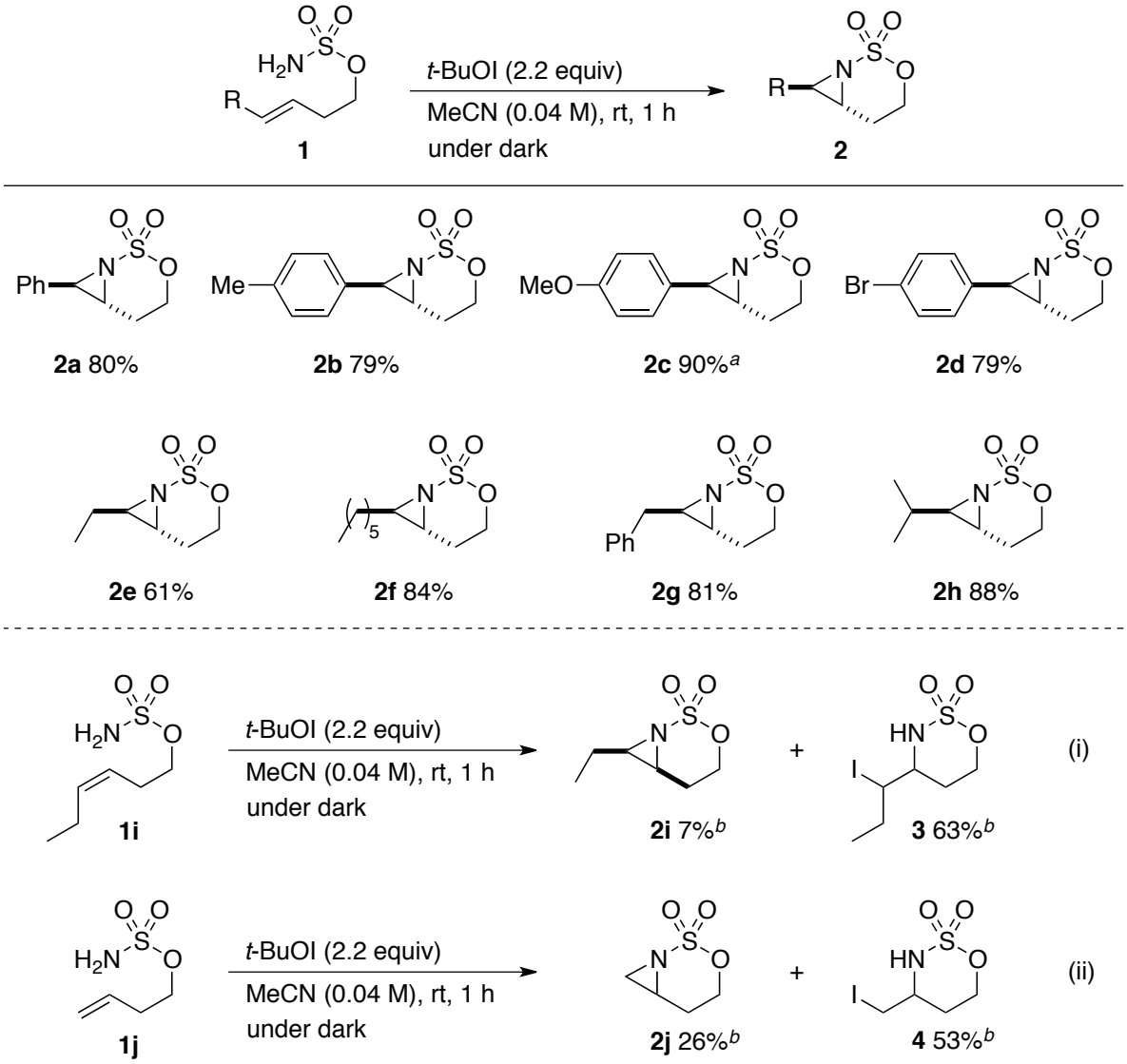


entry	oxidant (x equiv)	yield (%)[b]
1[c,d]	*t*-BuOI (2.2)	56
2[c]	*t*-BuOI (2.2)	68
3	*t*-BuOI (2.2)	90
4	*t*-BuOI (1.5)	57
5	*t*-BuOI (1.0)	40
6	DIH (2.2)	41
7	NIS (2.2)	0
8	*t*-BuOCl (2.2)	0
9	NBS (2.2)	0

[a] Reactions were performed on a 0.2 mmol scale. [b] Determined by ^{1}H 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

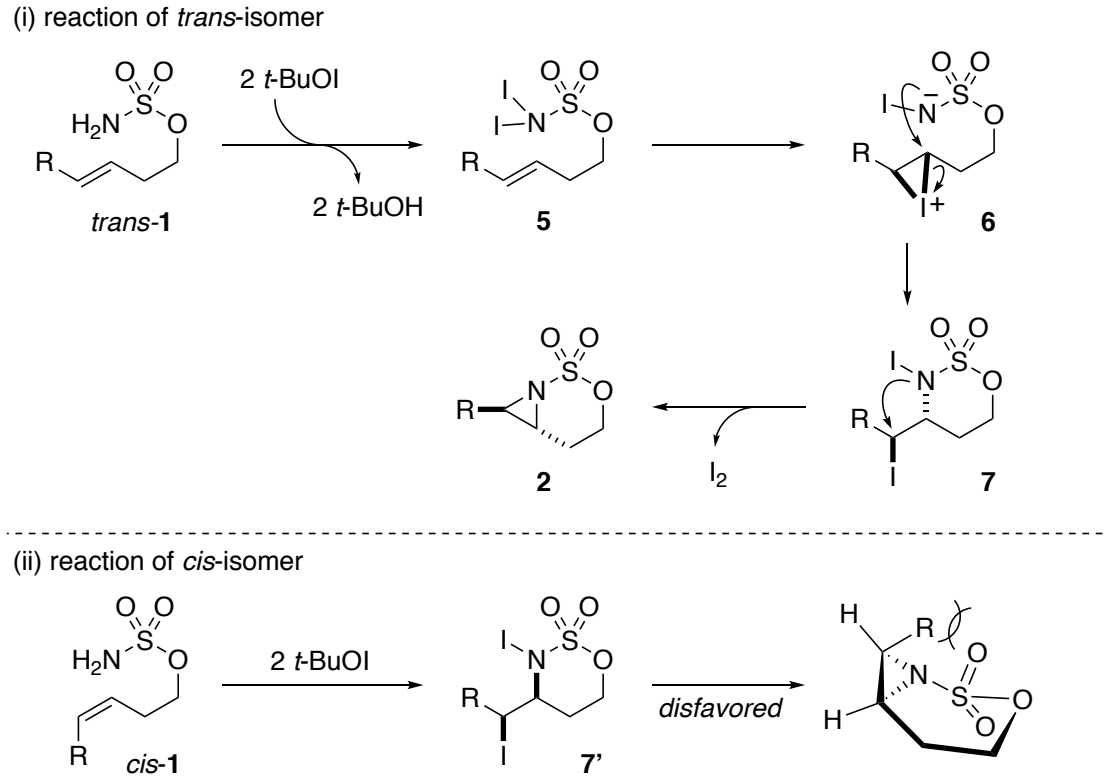
the main product, the structure of which was unambiguously determined by NMR experiments (Scheme 2i).[13] Prolonging the reaction time failed to improve the yield of **2i**. We hypothesize that a cyclization leading to the formation of the *cis*-aziridine **2i** is retarded by steric repulsion between 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 ^{1}H NMR analysis of the crude product using 1,1,2,2-tetrachloroethane as an internal standard.

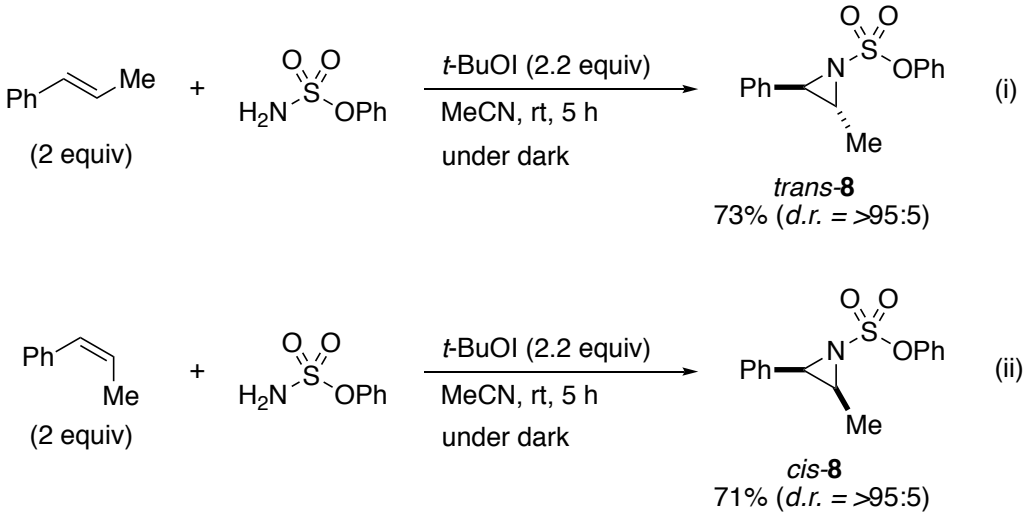
A plausible reaction pathway is depicted in Scheme 3, based on the experimental results and the previously reported mechanism of iodine-mediated aziridination reactions,[10] The sulfamate ester *trans*-**1** initially reacts with *t*-BuOI, providing the *N*,*N*-diiodo species **5**, the cationic iodine atom of which is transfered 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).



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

ACKNOWLEDGEMENTS

This work was supported by JSPS KAKENHI Grant Numbers 19H02716 (S.M.) and 20K05511 (K.K.)

REFERENCES AND NOTES

1. 'Aziridines and Epoxides in Organic Synthesis' ed. by A. K. Yudin, Wiley-VCH, Weinheim, Germany, 2006.
2. (a) F. M. D. Ismail, D. O. Levitsky, and V. M. Dembitsky, *Eur. J. Med. Chem.*, 2009, **44**, 3373; (b) C. J. Thibodeaux, W. Chang, and H. Liu, *Chem. Rev.*, 2012, **112**, 1681; (c) K. C. Nicolaou, D. Rhoades, Y. Wang, R. Bai, E. Hamel, M. Aujay, J. Sandoval, and J. Gavrilyuk, *J. Am. Chem. Soc.*, 2017, **139**, 7318; (d) K. C. Nicolaou, Y. G. Shelke, B. D. Dherange, A. Kempema, B. Lin, C. Gu, J. Sandoval, M. Hammond, M. Aujay, and J. Gavrilyuk, *J. Org. Chem.*, 2020, **85**, 2865.
3. For reviews, see: (a) D. Tanner, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 599; (b) X. E. Hu, *Tetrahedron*, 2004, **60**, 2701; (c) W. McCoull and F. A. Davis, *Synthesis*, 2000, 1347; (d) M.

Shipman, *Synlett*, 2006, 3205; (e) X. L. Hou, J. Wu, R. H. Fan, C. H. Ding, Z. B. Luo, and L. X. Dai, *Synlett*, 2006, 181; (f) C. Schneider, *Angew. Chem. Int. Ed.*, 2009, **48**, 2082; (g) P. Lu, *Tetrahedron*, 2010, **66**, 2549; (h) S. Stanković, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. Van Speybroeck, N. De Kimpe, and H.-J. Ha, *Chem. Soc. Rev.*, 2012, **41**, 643; (i) C. Y. Huang and A. G. Doyle, *Chem. Rev.*, 2014, **114**, 8153; (j) B. H. Rotstein, S. Zaretsky, V. Rai, and A. K. Yudin, *Chem. Rev.*, 2014, **114**, 8323.

4. S. Minakata, Y. Takeda, and K. Kiyokawa, 'In Methods and Applications of Cycloaddition Reactions in Organic Syntheses' ed. by N. Nishiwaki, Wiley-VCH: Weinheim, Germany, Chapter 2.
5. For reviews, see: (a) J. B. Sweeney, *Chem. Soc. Rev.*, 2002, **31**, 247; (b) H. Pellissier, *Tetrahedron*, 2010, **66**, 1509; (c) P. Müller and C. Fruit, *Chem. Rev.*, 2003, **103**, 2905; (d) G. S. Singh, M. D'hooghe, and N. De Kimpe, *Chem. Rev.*, 2007, **107**, 2080; (e) T. G. Driver, *Org. Biomol. Chem.*, 2010, **8**, 3831; (f) J. W. W. Chang, T. M. U. Ton, and P. W. H. Chan, *Chem. Rec.*, 2011, **11**, 331; (g) D. M. Jenkins, *Synlett*, 2012, 1267; (h) L. Degennaro, P. Trinchera, and R. Luisi, *Chem. Rev.*, 2014, **114**, 7881; (i) Y. Zhu, Q. Wang, R. G. Cornwall, and Y. Shi, *Chem. Rev.*, 2014, **114**, 8199; (j) H. Pellissier, *Adv. Synth. Catal.*, 2014, **356**, 1899; (k) S. Sabir, G. Kumar, and J. L. Jat, *Asian J. Org. Chem.*, 2017, **6**, 782; (l) E. Roma, E. Tosi, M. Miceli, and T. Gasperi, *Asian J. Org. Chem.*, 2018, **7**, 2357.
6. (a) F. Durán, L. Leman, A. Ghini, G. Burton, P. Dauban, and R. H. Dodd, *Org. Lett.*, 2002, **4**, 2481; (b) K. Guthikonda and J. Du Bois, *J. Am. Chem. Soc.*, 2002, **124**, 13672; (c) P. M. Wehn, J. Lee, and J. Du Bois, *Org. Lett.*, 2003, **5**, 4823; (d) K. Guthikonda, P. M. Wehn, B. J. Caliando, and J. Du Bois, *Tetrahedron*, 2006, **62**, 11331; (e) A. Estéoule, F. Durán, P. Retailleau, R. H. Dodd, and P. Dauban, *Synthesis*, 2007, 1251; (f) R. Lorpitthaya, Z.-Z. Xie, J.-L. Kuo, and X.-W. Liu, *Chem. Eur. J.*, 2008, **14**, 1561; (g) R. Lorpitthaya, K. B. Sophy, J.-L. Kuo, and X.-W. Liu, *Org. Biomol. Chem.*, 2009, **7**, 1284; (h) G. Malik, A. Estéoule, P. Retailleau, and P. Dauban, *J. Org. Chem.*, 2011, **76**, 7438; (i) M. M. Hoque, K. Miyamoto, N. Tada, M. Shiro, and M. Ochiai, *Org. Lett.*, 2011, **13**, 5428; (j) G. H. Huang, J.-M. Li, J.-J. Huang, J.-D. Lin, and G. J. Chuang, *Chem. Eur. J.*, 2014, **20**, 5240.
7. For examples of intramolecular aziridination of sulfonamides, see: (a) P. Müller, C. Baud, and Y. Jacquier, *Can. J. Chem.*, 1998, **76**, 738; (b) P. Dauban and R. H. Dodd, *Org. Lett.*, 2000, **2**, 2327; (c) P. Dauban and R. H. Dodd, *Tetrahedron Lett.*, 2001, **42**, 1037; (d) P. Dauban, L. Sanière, A. Tarrade, and R. H. Dodd, *J. Am. Chem. Soc.*, 2001, **123**, 7707; (e) J.-L. Liang, S.-X. Yuan, P. W. H. Chan, and C.-M. Che, *Org. Lett.*, 2002, **4**, 4507; (f) R. M. Moriarty and S. Tyagi, *Org. Lett.*, 2010, **12**, 364.
8. For examples of intramolecular aziridination of carbamates, see: (a) A. Padwa and T. Stengel, *Org. Lett.*, 2002, **4**, 2137; (b) A. Padwa, A. C. Flick, C. A. Leverett, and T. Stengel, *J. Org. Chem.*, 2004, **69**, 6377; (c) H. Lebel, K. Huard, and S. Lectard, *J. Am. Chem. Soc.*, 2005, **127**, 14198; (d) M. Ju, C. D. Weatherly, I. A. Guzei, and J. M. Schomaker, *Angew. Chem. Int. Ed.*, 2017, **56**, 9944; (e) Q.-H. Deng, J.-C. Wang, Z.-J. Xu, C.-Y. Zhou, and C.-M. Che, *Synthesis*, 2011, 2959.
9. For representative examples of transition-metal-free intermolecular aziridination of alkenes, see: (a)

J. U. Jeong, B. Tao, I. Sagasser, H. Henniges, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1998, **120**, 6844; (b) T. Ando, D. Kano, S. Minakata, I. Ryu, and M. Komatsu, *Tetrahedron*, 1998, **54**, 13485; (c) T. Siu and A. K. Yudin, *J. Am. Chem. Soc.*, 2002, **124**, 530; (d) J. Li, P. W. H. Chan, and C.-M. Che, *Org. Lett.*, 2005, **7**, 5801; (e) S. Minakata, Y. Morino, Y. Oderaotoshi, and M. Komatsu, *Chem. Commun.*, 2006, 3337; (f) Y.-M. Shen, M.-X. Zhao, J. Xu, and Y. Shi, *Angew. Chem. Int. Ed.*, 2006, **45**, 8005; (g) A. Yoshimura, K. R. Middleton, C. Zhu, V. N. Nemykin, and V. V. Zhdankin, *Angew. Chem. Int. Ed.*, 2012, **51**, 8059; (h) C. Varszegi, M. Ernst, F. van Laar, B. F. Sels, E. Schwab, and D. E. De Vos, *Angew. Chem. Int. Ed.*, 2008, **47**, 1477; (i) K. Kiyokawa, T. Kosaka, and S. Minakata, *Org. Lett.*, 2013, **15**, 4858; (j) S. L. Johnson and M. K. Hilinski, *J. Org. Chem.*, 2019, **84**, 8589; (k) Q.-Q. Cheng, Z. Zhou, H. Jiang, J. H. Siitonen, D. H. Ess, X. Zhang, and L. Kürti, *Nat. Catal.*, 2020, **3**, 386.

10. (a) S. Minakata, *Acc. Chem. Res.*, 2009, **42**, 1172; (b) K. Kiyokawa and S. Minakata, *Synlett*, 2020, **31**, 845.
11. (a) S. Minakata, I. Sasaki, and T. Ide, *Angew. Chem. Int. Ed.*, 2010, **49**, 1309; (b) Y. Takeda, S. Okumura, and S. Minakata, *Angew. Chem. Int. Ed.*, 2012, **51**, 7804.
12. K. Kiyokawa, S. Nakamura, K. Jou, K. Iwaida, and S. Minakata, *Chem. Commun.*, 2019, **55**, 11782.
13. Product **3** was obtained as a single isomer, whose configuration has not been determined.