ORGANIC LETTERS

2010
Vol. 12, No. 2
364−366

Metal-Free Intramolecular Aziridination of Alkenes Using Hypervalent Iodine Based Sulfonyliminoiodanes

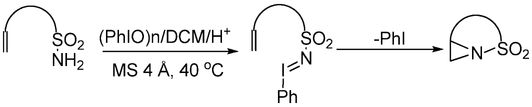
Robert M. Moriarty* and Sachin Tyagi

*Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street,
Chicago, Illinois 60607-7061*

moriarty@uic.edu

Received November 23, 2009

ABSTRACT



Intramolecular aziridination of alkenyl sulfonyliminoiodanes occurs thermally in the absence of conventional metal catalysts such as Rh(II) and Cu(II). In rigid molecular systems, conversions are near quantitative. The scope of the nonmetal process is related to the conformational flexibility of the alkenyl sulfonyliminoiodane. A mechanism is proposed involving formal 2 + 2 cycloaddition of the $RSO_2N{=}IPh$ group to the double bond followed by reductive elimination of PhI to yield the sulfonylaziridine. Green chemistry aspects of the process are highlighted.

Transition-metal-catalyzed cyclopropanation[1] and aziridination[2] of alkenes using hypervalent iodonium ylides and iminoiodanes, respectively, have proven to be exceptionally useful. Earlier we and others found that in the case of certain intramolecular cyclopropanation processes, conventionally effected using copper or rhodium catalysis, the reaction occurred efficiently in the absence of these metals.[1a,3] Originally treated as an undesirable complication in examples using chirally modified copper catalysts for stereoselective syntheses,[1a] but now viewed in a more current societal context, the significance of this phenomenon requires reevaluation. Contemporary organic synthesis strives to be metal free.[4] General environmental awareness, i.e., green chemistry, and more specifically concerns around the exigencies of drug manufacture, i.e., pharmacovigilance, drive this search for metal-free cognate reactions of synthetic processes that are conventionally metal catalyzed.[4a−d]

Transition-metal-catalyzed aziridination[5] of alkenes has been largely developed on the basis of $ArSO_2N{=}IPh$, and apparently the deletion of metal from this type of reactions

---

(1) For reviews, see: (a) Müller, P *Acc. Chem. Res.* **2004**, *37*, 243. (b) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (d) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (e) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893.

(2) (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Guthikonda, K.; When, P. M.; Caliando, B. J.; DuBois, J. *Tetrahedron* **2006**, *62*, 11331. (c) Dauban, P.; Dodd, R. H. *Syn. Lett.* **2003**, *11*, 1571. (d) First example of Cu(I) or Cu(II) catalysis: Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (e) Evans, D. A.; Bilodeau, M. T.; Faul, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (f) Rovis, T.; Evans, D. A. *Prog. Inorg. Chem.* **2001**, *50*, 1. (g) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361. (h) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. Use of Rh(II): (i) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507.

(3) For the first example of this intramolecular thermal nonmetal process, see: (a) Moriarty, R. M.; Prakash, O.; Vaid, R. K.; Zhao, L. *J. Am. Chem. Soc.* **1989**, *111*, 6443. Erratum *J. Am. Chem. Soc.* **1990**, *112*, 1297. (b) Gallos, J. K.; Koftis, T. V.; Massen, Z. S.; Dellios, C. C.; Mourtzinos, I. T.; Coutouli-Argyropoulou, E.; Koumbis, A. E. *Tetrahedron* **2002**, *58*, 8043. For a comparison of the intramolecular cyclopropanation using Cu(I), Rh(II), and nonmetal, see: (c) Müller, P.; Bolėa, C. *Synlett* **2000**, 826. (d) Müller, P.; Bolėa, C. *Helv. Chim. Acta* **2001**, *84*, 1093.

(4) A recent example of this effort is the achievement of a copper-free Sonogashira coupling: (a) Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Eur. J. Org. Chem.* **2003**, 4713. (b) Leadbeater, N. E.; Marco, M.; Tominack, B. J. *Org. Lett.* **2003**, *5*, 3919. (c) Luque, R.; Macquarrie, D. J. *Org. Bio. Chem.* **2009**, *7*, 1627. For toxicity of copper, see: (d) Flemming, C. A.; Trevors, J. T. *Water Air Soil Poll.* **1989**, *44*, 143. (e) Use of organohypervalent iodine reagents as substitutes for Pb(IV), Tl(III), and Hg(II) has been pursued (ref 1e). Use of the Dess−Martin reagent, IBX, and PhIO as oxidants in place of Cr(VI) (ref 1c) and use of IBX as a substitute for Se(IV) for conjugated carbonyl compound synthesis are relevant advances. (f) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 75960. (g) A striking example of metal replacement is the use of fullerene inplace of noble metals in catalytic hydrogenation: Li, B.; Xu, Z. *J. Am. Chem. Soc.* **2009**, *131*, 16380.

(5) (a) Evans, D. A.; Bilodeau, M. T.; Faul, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.

10.1021/ol9026655

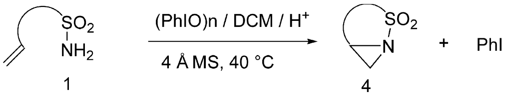
has not been investigated.[6,7] Because of the obvious similarity between the cyclopropanation and the aziridination reaction, we decided to study the metal-free reaction. Apart from environmental reasons, synthetically the aziridine group serves as a synthon for a wide range of functional groups,[2c] and a noncatalytic route would obviously be valuable.

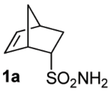
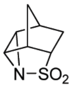
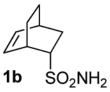
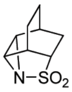
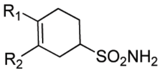
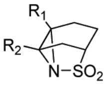
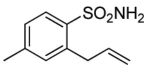
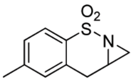
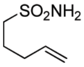
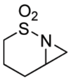
Reference to Table 1 reveals the realization of the nonmetal route for intramolecular sulfonylaziridination. Bridged bicyclic systems **1a** and **1b** proceeded with quantitative conversions affording aziridines **4a** and **4b** (entries 1 and 2). Cyclohexenyl systems **1c**−**e** provided **4c**−**e** in very high yields (entries 3−5). Entry 6 (**1f**) is instructive in that a degree of conformational flexibility of the alkenyl group is present relative to the cycloalkenyl examples; nonetheless, efficient aziridination occurs. Also, a comparison with the CuOTf-catalyzed reaction[8a] reveals that the nonmetal reaction proceeds in higher yield, 83% vs 61%, while the $Rh_2(OAc)_4$[8b] reaction is slightly inferior, 95% vs 100% conversion. Entry 7 (**1g**), 0% conversion, illustrates the effect of the intramolecular proximity of the reacting groups and presages the synthetic scope and limitations of the nonmetal intramolecular aziridination relative to the metal-catalyzed process. Together with example **1g**, control experiments of **1h**−**1j** provide an insight into the mechanism of the process.

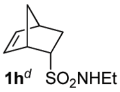
The results shown in Table 1 can be discussed on the basis of Scheme 1, and these data enable formulation of a tentative competitive metal-catalyzed process. The relevant processes are: reversible formation of iminoiodanes[9] (**1**→**2**), intramolecular reaction of iminoiodanes (**2**→**4**) with adjacent double bond, Cu(I) or Rh(II) exchange (**2**→**3**), aziridination formation of metal nitrenoids (**3**→**4**), initial double bond hyperiodination followed by intramolecular cyclization (**1**→**4** via **5**→**6**),[10] and consumption of PhIO by disproportionation.[11] Entries 1−6 of Table 1 correspond to capture of the equilibrium concentration of the iminoiodanes by the adjacent double bond to yield aziridine.

The fact that the *N*-ethylsulfonamide (**1h**) is recovered unreacted proves that initial reaction at the double bond is not the route to the aziridination. It can be implied that **1h**, **1i**, and **1j** form the iminoiodanes because of the obtention of PhI and $PhIO_2$. Finally, entry 6 instantiates the importance of equilibrium **1**→**2**; 1-pentenylsulfonamide (**1g**) forms the iminoiodane, but the rate of intramolecular addition to the double bond is slower than the rate of reversion to the starting alkene.

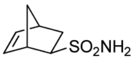
Table 1. Metal-Free Intramolecular Aziridination of Unsaturated Sulfonamides with I(III)[a]



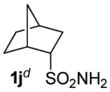
entry	sulfonamide	aziridine	conversion (%)[b]	yields (%)[c]
1	 **1a**	 **4a**	100	80
2	 **1b**	 **4b**	100	80
				
3	**1c**, R1 = H, R2 = H	**4c**	70	60
4	**1d**, R1 = CH_3, R2 = H	**4d**	90	78
5	**1e**, R1 = CH_3, R2 = CH_3	**4e**	100	92
6	 **1f**	 **4f**	95 100 100	83 61 (CuOTf) 98 ($Rh_2(OAc)_4$)
7	 **1g**	 **4g**	0 90	0 61 (CuOTf) 80 ($Rh_2(OAc)_4$)



1h[d]



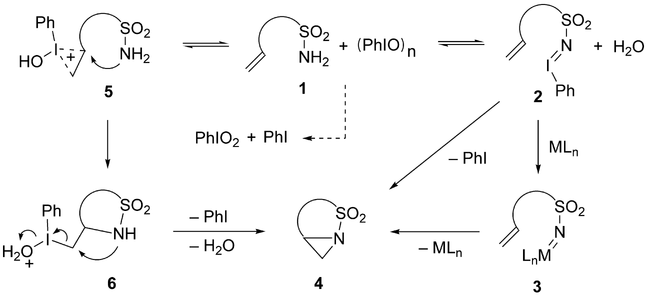
1i[d]



1j[d]

[a] Reactions were done under thermal conditions, unless catalyst is mentioned in parentheses. [b] Conversion on the basis of crude ^{1}H NMR. [c] Isolated yield after column chromatography. [d] Almost 100% of starting material was retrieved.

Scheme 1. Pathways for the Intramolecular Aziridination of Alkenylsulfonamides with I(III)



By contrast, the capture of the iminoiodane by Cu(I) or Rh(II) is assumed to be faster (**2**→**3**) than reversion, and

---

(6) An example of the Rh(II) and nonmetal intramolecular cyclization of a cycloalkenyl carbamate with I(III) has been reported: Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137.

(7) The focus of the present metal-free reactions of alkenes is on organohypervalent iodine and transition metals. Of course, metal-free aziridination[7] can be accomplished via thermal or photochemical generation of nitrenes from azides just as cyclopropanation can be effected by thermal or photochemical decomposition of diazocompounds. For other metal-free intermolecular alkene aziridination processes, see: (a) Li, J.; Liang, J.-L.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 2685. (b) Li, J.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2005**, *7*, 5801. (c) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844. (d) Minakata, S.; Morino, Y.; Oderaotoshi, Y.; Komatsu, M. *J. Chem. Soc., Chem. Commun.* **2006**, 3337. (e) Minakata, S. *Acc. Chem. Res.* **2009**, *42*, 1172.

(8) (a) Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327. (b) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507.

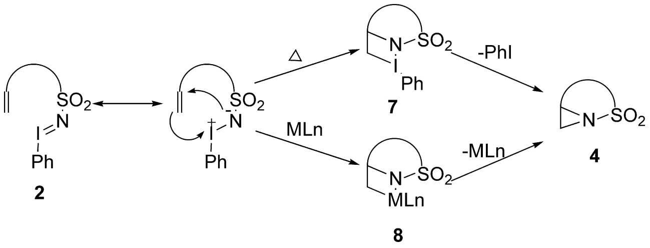
(9) White, R. E. *Inorg. Chem.* **1987**, *26*, 3916.

(10) For an example of (**1**→**5**→**6**→**4**), see: Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 5039.

(11) Bressan, M.; Morvillo, A. *Inorg. Chem.* **1989**, *28*, 950.

subsequent intramolecular reaction with the double bond yields the aziridine (**3**→**4**). One salient feature of the nonmetal intramolecular aziridination is that conformationally rigid systems are most favored candidates for successful aziridination. Thus, the alkenyl group in **1f** (83%) is comparatively conformationally fixed relative to the more conformationally flexible linear alkenyl system of **1g** (0%). Ochiai[12] has shown that the more reactive alkyl iminobromanes undergo intermolecular aziridination with alkene via a nitrenoid mechanism. This pathway is unlikely in the present system because **1g**, **1i**, and **1f** all should react if a nitrenoid intermediate occurred.

Scheme 2. Aziridination via a Formal [2 + 2] Cycloaddition Step



The pathway from the iminoiodane **2**→**4** may involve an electrophilic addition of the tethered double bond to the PhI^+ center with concomitant neutralization of the thus formed carbocation by the anionic nitrogen center (**2**→**7**) (Scheme 2). Within the limits of synchronicity, this devolves into a [2 + 2] cycloaddition, and the observed rather strict geometric requirements for the reaction agree with this pathway. A similar process has been discussed for the addition of $R_2C{=}CuL_n$ to alkenes[2e] to form a metallocyclobutane (**2**→**8**). In the instant case, the resulting incipient azaiodoniocyclobutane[13] (**7**) yields the aziridine by reductive elimination of PhI (**7**→**4**).

In conclusion, a search for nonmetal variants of classically metal-catalyzed reactions was productively pursued guided by mechanistic insight. In the present case, the stability of the iminoiodane is the key.[14] The scope of the nonmetal aziridination can be broadened by variations in the stability of the iminoiodane. More reactive Cl(III)[15] and Br(III)[12] iminohalogans are also potentially useful in this regard.

Finally, we envision the most interesting applications will be in total synthesis of complex molecules. In such cases, critical intramolecular distances between $RSO_2N{=}IPh$ and the double bond will be fixed in favorable orientations for aziridination because of the rigid molecular framework. A very clever example of the use of intramolecular aziridination followed by ring opening is found in the recent total synthesis of (−)-Agelastatin A.[16]

Acknowledgment. We thank KYTHERA Biopharmaceuticals, Inc., Calabasas, California, for the support of this work. We also thank Professor Daesung Lee of the Department of Chemistry, University of Illinois at Chicago, for insightful discussions.

Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9026655

---

[12] Ochiai, M.; Kaneaki, T.; Tada, N.; Miyamoto, K.; Chuman, H.; Shiro, M.; Hayashi, S.; Nakanishi, W. *J. Am. Chem. Soc.* **2007**, *129*, 12938.

[13] For an example of stable four-membered tricoordinated iodine(III) heterocycle, see: Kawashima, T.; Hoshiba, K.; Kano, N. *J. Am. Chem. Soc.* **2001**, *123*, 1507.

[14] Sodergren, M. J.; Alonso, D. A.; Andersson, P. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3563.

[15] Moriarty, R. M.; Tyagi, S.; Ivanov, D.; Constantinescu, M. *J. Am. Chem. Soc.* **2008**, *130*, 7564.

[16] Wehn, P. M.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3802.