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Copper iodide-catalyzed aziridination of alkenes with sulfonamides and sulfamate esters

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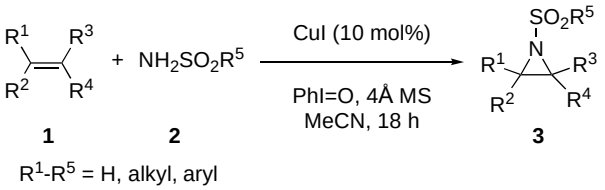
ABSTRACT

An efficient copper iodide-catalyzed aziridination of a variety of alkenes with sulfonamides and sulfamate esters as the nitrogen source and iodosylbenzene (PhI=O) as the oxidant is reported herein. The reaction is operationally straightforward, applicable to a variety of alkenes containing electron-withdrawing, electron-donating, and sterically encumbered substrate combinations, and proceeds under mild conditions at room temperature in good to excellent yields.

Aziridines are found in a myriad of bioactive natural products, and are compounds of current therapeutic interest exhibiting a variety of biological properties, such as antibiotic and antitumor activities.[1–11] The ability of aziridines to undergo regio- and stereoselective ring opening reactions also renders this class of compounds as invaluable building blocks in organic synthesis. For this reason, the development of novel synthetic routes for the preparation of aziridines has received significant attention. Among the various strategies developed for preparing aziridines, transition metal-catalyzed aziridination of C=C bonds has been reported to be a mild and efficient approach. In recent years, these methods have relied heavily on the use of metal catalysts such as Fe,[5] Mn,[6] Ru,[7] Rh_2,[8] Ag,[9] Au,[10] and Co[11] with preformed iminoiodinanes ($PhI{=}NSO_2R$, typically R = Ar) or sulfonamide, sulfamate and carbamate esters in combination with a hypervalent iodine(III) oxidant[12] as the nitrogen source. However, a drawback of many of these methodologies has been the need to prepare the metal catalyst, which can be expensive, arduous and time-consuming. In addition, a competitive C–H insertion process and, in many instances, the need for an excess of the alkene substrate, which are often invaluable intermediates in natural product synthesis, to achieve high conversions and yields have been reported. In this regard, attempts to overcome such limitations have led to a resurgence in interest toward exploring catalytic systems that employ copper salts.[13–16] In a recent notable advance, Lebel and co-workers demonstrated that the aziridination of alkenes with *N*-tosyloxycarbamates proceeds smoothly in the presence of a pyridylcopper(II) complex as catalyst.[14] At about the same time, Fleming and co-workers described the intramolecular aziridination of carbamates catalyzed by $(CF_3SO_3Cu)_2{\cdot}C_6H_6$.[15] More recently, Appella and co-workers reported that N-heterocyclic carbene copper complexes could facilitate alkene aziridination with 2,2,2-trichloroethyl sulfamate and iodosylbenzene (PhI=O) as oxidant.[16] In contrast, a synthetic approach that relies on the exceptional activity offered by copper catalysis, but makes use of CuI as the source of the metal catalyst is not known. In general, such nitrogen-transfer reactions across a C=C bond have often relied upon making use of copper complexes derived from more expensive and moisture-sensitive copper triflate salts. As part of an ongoing program on C–N bond formation in our group,[17] we present herein a CuI-catalyzed method for the aziridination of a wide variety of alkenes with sulfonamides and sulfamate esters and PhI=O as oxidant (Scheme 1). The reaction proceeds under mild conditions at room temperature in good to excellent yields of up to 99%.

Initially, we examined the effect of various oxidizing agents and solvents on the aziridination of styrene **1a** in the presence of 10 mol % CuI as catalyst and *p*-toluenesulfonamide **2a** as the nitrene source to establish the reaction conditions (Table 1). Our studies showed that the best yields were obtained when 1.5 equiv of PhI=O was employed as the oxidant in the presence of powdered 4 Å molecular sieves in MeCN at room temperature for 18 h.[18] Under these conditions, aziridine **3a** was obtained in 99% yield (entry 1). Further investigations revealed that reducing the loading of PhI=O to 1.25 equiv gave the desired aziridine product in a lower yield of 79% (entry 4). A further reduction in oxidant loading to 1 equiv resulted in a respective decrease in product yield to 56%



Scheme 1. CuI-catalyzed aziridination of alkenes.

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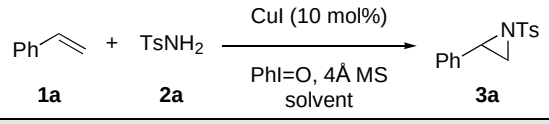
Table 1
Optimization of the reaction conditions[a]



1a **2a** **3a**

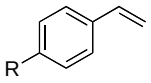
Entry	PhI=O (equiv)	Solvent	Yield[b] (%)
1	1.5	MeCN	99
2[c]	1.5	MeCN	81
3[d]	1.5	MeCN	19
4	1.25	MeCN	79
5	1	MeCN	56
6	2	C_6H_6	21
7	2	CH_3NO_2	66
8	2	1,4-Dioxane	54
9	2	$ClCH_2CH_2Cl$	29
10	2	$CHCl_3$	99
11	2	CH_2Cl_2	99
12[d]	1.5	CH_2Cl_2	99

[a] Unless otherwise stated, all reactions were carried out with 0.5 mmol of **1a** and 2 equiv of **2a** for 18 h at room temperature.
[b] Isolated yield.
[c] Reaction conducted with 1.5 equiv of **2a**.
[d] Reaction conducted with 5 mol % of CuI.

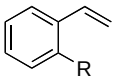
(entry 5). The use of 2 equiv of $TsNH_2$ was also found to be necessary for the aziridination to proceed smoothly, when $TsNH_2$ was reduced to 1.5 equiv, a slightly lower product yield of 81% was afforded (entry 2). A decrease of catalyst loading to 5 mol % in MeCN resulted in a drastic drop in product yield to 19%, the analogous reaction repeated at the same catalyst loading in CH_2Cl_2 afforded **3a** in 99% yield (entries 3 and 12). On the other hand, replacing PhI=O with other hypervalent iodine reagents, such as 2-iodobenzoic acid, hydroxyl(tosyloxy)iodobenzene (HTIB), iodobenzene diacetate [$PhI(OAc)_2$], bis(^{t}butylcarbonyloxy)iodobenzene [$PhI(OCO^tBu)_2$], and 2-iodoxybenzoic acid (IBX), resulted in no reaction and near quantitative recovery of the starting materials. Under similar conditions, the use of inorganic oxidants such as Oxone®, $K_3Fe(CN)_6$, $K_2Cr_2O_7$, KIO_4, and $K_2S_2O_8$ in place of PhI=O was also found to give no reaction. With an oxidant loading of 2 equiv, an examination of solvent effects showed that reactions carried out in $CHCl_3$ and CH_2Cl_2 gave the desired aziridine **3a** in near quantitative yields (entries 10 and 11). In contrast, lower product yields of 21–66% were obtained when C_6H_6, $MeNO_2$ 1,4-dioxane, and 1,2-dichloroethane were employed as solvents (entries 6–9).

To define the scope of the present procedure, we applied this process to a variety of internal and terminal alkenes **1a–k** and nitrogen sources **2a–f** (Table 2). These reactions gave the corresponding aziridines in good to excellent yields (entries 2–19). This included near quantitative product yields obtained for the reactions of **1f** with **2a** and **1a** with **2b**, which was found to be consistent with our earlier findings on the aziridination of **1a** with **2a** (cf. entry 1 with entries 6 and 12). More notably, the electronic nature of either the C=C bond or aryl sulfonamide was found to have no effect on the reaction yield. A competitive rate study of a number of *para*-substituted styrenes [X = Me (**1b**), ^{t}Bu (**1c**), F (**1d**), Cl (**1e**), and Br (**1f**)] gave $\log K_X/K_H$ values of 0.057 (**1b**), 0.026 (**1c**),

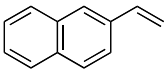
Table 2
CuI-catalyzed aziridination of alkenes **1a–k** with sulfonamides **2a–c** and sulfamate ester **2d**[a]



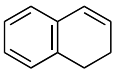
1a, R = H
1b, R = Me
1c, R = ^{t}Bu
1d, R = F
1e, R = Cl
1f, R = Br



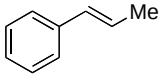
1g, R = Me
1h, R = Br



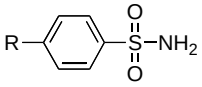
1i



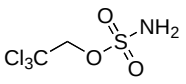
1j



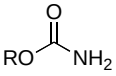
1k



2a, R = Me
2b, R = OMe
2c, R = Cl



2d



2e, R = ^{t}Bu
2f, R = Bn

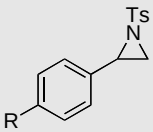
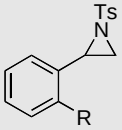
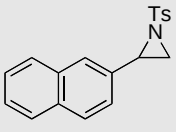
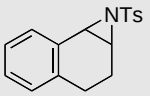
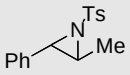
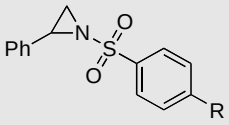
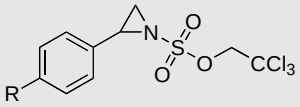
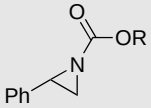
Entry	Substrates	Product	Yield[b] (%)	
1	**1a** + **2a**		**3a**, R = H	99
2	**1b** + **2a**		**3b**, R = Me	68
3	**1c** + **2a**		**3c**, R = ^{t}Bu	93
4	**1d** + **2a**		**3d**, R = F	79
5	**1e** + **2a**		**3e**, R = Cl	83
6	**1f** + **2a**		**3f**, R = Br	99
7	**1g** + **2a**		**3g**, R = Me	63
8	**1h** + **2a**		**3h**, R = Br	40
9	**1i** + **2a**		**3i**	92

Table 2 (*continued*)

Entry	Substrates	Product	Yield[b] (%)	
10	**1j** + **2a**		**3j**	25 (56)[c]
11	**1k** + **2a**		**3k**	– (90)[c]
12	**1a** + **2b**		**3l**, R = OMe	99
13	**1a** + **2c**		**3m**, R = Cl	84
14	**1a** + **2d**		**3n**, R = H	69
15	**1b** + **2d**		**3o**, R = Me	41
16	**1c** + **2d**		**3p**, R = ^{t}Bu	50
17	**1d** + **2d**		**3q**, R = F	67
18	**1e** + **2d**		**3r**, R = Cl	60
19	**1f** + **2d**		**3s**, R = Br	68
20	**1a** + **2e**		**3t**, R = ^{t}Bu	–[d]
21	**1a** + **2f**		**3v**, R = Bn	–[d]

[a] All reactions were carried out at room temperature in MeCN for 18 h with CuI:**1**:**2**:PhI=O molar ratio = 1:10:20:15.
[b] Isolated yields.
[c] Values in parentheses denote yields from reactions conducted in CH_2Cl_2.
[d] No reaction was observed based on TLC and ^{1}H NMR analysis of the crude reaction mixture.

−0.034 (**1d**), −0.079 (**1e**) and −0.061 (**1f**), which implied that electron-deficient alkenes accelerated aziridination more rapidly than electron-rich alkenes.[19] Steric effects of the alkene substrate may also play a role since increasingly bulky groups, such as an *o*-methylphenyl or *o*-bromophenyl, were found to provide **3g** and **3h** in lower yields of 63% and 40%, respectively (entries 7 and 8). In addition, both **1j** and **1k** were found to be poor substrates under the standard conditions. In our hands, reaction of **1j** was found to afford **3j** in a low yield of 25% while no reaction was observed when we examined **1k**. However, in both cases, good to excellent product yields were obtained on changing the solvent from MeCN to CH_2Cl_2, although the reasons for this stark difference in reactivity remain unclear (entries 10 and 11). On the other hand, the present procedure was shown to work well for the aziridinations of alkenes **1a**–**f** with the sulfamate ester **2d** as the nitrogen source (entries 14–19). In these reactions, the corresponding aziridines **3n**–**s** were furnished in 41–69% yields. However, the analogous reactions of **1a** with carbamates, such as *t*-butyl carbamate **2e** and benzyl carbamate **2f**, were found to be ineffective. Under our standard conditions, TLC and ^{1}H NMR analysis of the crude mixtures only detected the presence of the starting materials, which were subsequently recovered in near quantitative yields (entries 20 and 21).

In summary, we have demonstrated a CuI-catalyzed process for the aziridination of alkenes in good to excellent yields. The present protocol was shown to be applicable to a variety of alkenes and sulfonamide and sulfamate ester nitrogen sources. Further examination of the scope and applications of this reaction is currently underway, and will be reported in due course.

Acknowledgments

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References and notes

1. (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247; (b) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999.
2. (a) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; (b) Zwanenburg, B.; ten Holte, P. *Top. Curr. Chem.* **2001**, *216*, 93; (c) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347.
3. (a) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657; (b) Fructos, M. R.; Belderrain, T. R.; Nicasio, M. C.; Nolan, S. P.; Kaur, H.; Diaz-Requejo, M. M.; Perez, P. *J. Am. Chem. Soc.* **2004**, *126*, 10846; (c) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
4. For recent reviews, see: (a) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194; (b) Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 379. Chapter 17; (c) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905; (d) Dodd, P.; Dauban, R. H. *Synlett* **2003**, 1571.
5. Selected examples on Fe-catalyzed reactions: (a) Vyas, R.; Gao, G. Y.; Harden, J. D.; Zhang, P. X. *Org. Lett.* **2004**, *6*, 1907; (b) Mansuy, D.; Mahy, J. P.; Dureault, A.; Bedi, G.; Battioni, P. *Chem. Commun.* **1984**, 1161; (c) Groves, J. T.; Takahashi, T. *J. Am. Chem. Soc.* **1983**, *105*, 2073.
6. Selected examples on Mn-catalyzed reactions: (a) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 1563; (b) Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245; (c) Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1993**, 469; (d) Breslow, R.; Gellman, S. H. *Chem. Commun.* **1982**, 1400.
7. Selected examples on Ru-catalyzed reactions: (a) Fantauzzi, S.; Gallo, E.; Caselli, A.; Piangiolino, C.; Ragaini, F.; Cenini, S. *Eur. J. Org. Chem.* **2007**, 6053; (b) Kawabata, H.; Omura, K.; Katsuki, T. *Tetrahedron Lett.* **2006**, *47*, 1571; (c) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610; (d) Leung, S. K.-Y.; Huang, J.-S.; Liang, J.-L.; Che, C.-M.; Zhou, Z.-Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 340.
8. Selected examples on Rh-catalyzed reactions: (a) Müller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* **1996**, *52*, 1543; (b) Fruit, C.; Robert-Peillard, F.; Bernardinelli, G.; Müller, P.; Dodd, R. H.; Dauban, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3484; (c) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198; (d) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377; (e) Liang,

J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2003**, *44*, 5917; (f) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728.
9. Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202.
10. Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 5876.
11. Selected examples on Co-catalyzed reactions: (a) Ruppel, J. V.; Jones, J. E.; Huff, C. A.; Kamble, R. M.; Chen, Y.; Zhang, P. X. *Org. Lett.* **2008**, *10*, 1995; (b) Gao, G.-Y.; Harden, J. D.; Zhang, P. X. *Org. Lett.* **2005**, *7*, 3191.
12. Selected examples: (a) Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; Du Bois, J. *Tetrahedron* **2006**, *62*, 11331; (b) Kwong, H.-L.; Liu, D.; Chan, K.-Y.; Lee, C.-S.; Huang, K.-H.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 3965; (c) Han, H.; Bae, I.; Yoo, E. J.; Lee, J.; Do, Y.; Chang, S. *Org. Lett.* **2004**, *6*, 4109; (d) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507; (e) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672; (f) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481; (g) Dauban, P.; Saniere, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707.
13. (a) Mohr, F.; Binfield, S. A.; Fettinger, J. C.; Vedernikov, A. N. *J. Org. Chem.* **2005**, *70*, 4833; (b) Sun, W.; Herdtweck, E.; Kuhn, F. E. *New J. Chem.* **2005**, *29*, 1577; (c) DiChenna, P. H.; Robert-Peillard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2004**, *6*, 4503; (d) Leca, D.; Toussaint, A.; Mareau, C.; Fensterbank, L.; Lacote, E.; Malacria, M. *Org. Lett.* **2004**, *6*, 3573; (e) Mairena, M. A.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *Organometallics* **2004**, *23*, 253; (f) Vedernikov, A. N.; Caulton, K. G. *Org. Lett.* **2003**, *5*, 2591; (g) Gillespie, K. M.; Sanders, C. J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C. P.; Scott, P. *J. Org. Chem.* **2002**, *67*, 3450; (h) Brandt, P.; Sodergren, M. J.; Andersson, P. G.; Norrby, P. O. *J. Am. Chem. Soc.* **2000**, *122*, 8013; (i) Sanders, C. J.; Gillespie, K. M.; Bell, D.; Scott, P. *J. Am. Chem. Soc.* **2000**, *122*, 7132; (j) Dauban, P.; Dodd, R. H. *J. Org. Chem.* **1999**, *64*, 5304; (k) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742; (l) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326; (m) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744.
14. Lebel, H.; Lectard, S.; Parmentier, M. *Org. Lett.* **2007**, *9*, 4797.
15. Liu, R.; Herron, S. R.; Fleming, S. A. *J. Org. Chem.* **2007**, *72*, 5587.
16. Xu, Q.; Appella, D. H. *Org. Lett.* **2008**, *10*, 1497.
17. (a) Rao, W.; Chan, P. W. H. *Chem. Eur. J.* **2008**. doi:10.1002/chem.200801242; (b) Wu, W.; Rao, W.; Er, Y. Q.; Loh, J. K.; Poh, C. Y.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2620; (c) Chang, J. W. W.; Chan, P. W. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1138; (d) Rao, W.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 3789; (e) Chang, J. W. W.; Xu, X.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 245.
18. *General experimental procedure*: To a suspension of PhI=O (0.75 mmol), RSO_2NH_2 **2** (1 mmol), CuI (0.05 mmol), and powdered 4 Å molecular sieves in dry MeCN (2 mL) was added the alkene **1** (0.5 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 18 h, after which the suspension was filtered through Celite®, washed with EtOAc, and evaporated to dryness. The residue was purified via silica gel flash column chromatography to afford the title compound **3**.
19. Anderson, D. J.; Gilchrist, T. L.; Horwell, D. C.; Rees, C. W. *J. Chem. Soc. (C)* **1970**, *4*, 576.