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Copper(I)-catalyzed asymmetric alkene aziridination mediated by $PhI(OAc)_2$: a facile one-pot procedure

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Abstract—A facile one-pot procedure for copper-catalyzed $PhI(OAc)_2$-mediated asymmetric alkene aziridination had been developed. Commercially available $PhI(OAc)_2$ and sulfonamides were used to generate the nitrene precursors (PhI=NR) in situ for olefin aziridination. This one-pot procedure had been optimized using 4-nitrobenzenesulfonamide as the nitrene source. With 5 mol% of the chiral copper catalyst, these conditions afforded 94% yield of the isolated product with 75% ee. We had also developed a simple and rapid method to monitor the rate of this one-pot aziridination.

Chiral aziridines are used widely in organic synthesis.[1] The readily available methods for stereo- and regioselective ring opening or expansion of the strained aziridine rings allow quick access to a variety of chiral amines, which would be useful building blocks for natural product synthesis. Moreover, chiral aziridines have been utilized as ligands and auxiliaries in asymmetric synthesis.[1b,c] Due to the versatile utilities of chiral aziridines in organic synthesis, the development of efficient enantioselective synthetic methods for chiral aziridines has received considerable interest. Among all the reported methods, transition metal-catalyzed asymmetric alkene aziridination has drawn a lot of attention in the past decade.[2] In 1993, Evans et al. and Jacobsen and co-workers independently reported the copper-catalyzed asymmetric alkene aziridination using [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NR) as the nitrene source.[2a,c] This process had been successfully applied to the total synthesis of some natural or biologically active products.[3] However, one of the drawbacks of this method is the need to isolate the nitrene precursors (PhI=NR), some of which were reported to be unstable and explosive.[2f,4] To simplify the procedure for preparation of the nitrene precursor, Dauban et al. and Dodd and co-workers recently reported a modified procedure for the copper-catalyzed asymmetric alkene aziridination.[2h,i] In their procedures, PhI=NR was generated in situ by treating sulfonamides with iodosyl-benzene (PhI=O).[2h] In our laboratory, we found that PhI=NR can be generated simply by treating sulfonamides with a commercially available reagent, iodobenzene diacetate [$PhI(OAc)_2$].[5] We, herein, report a very simple and efficient one-pot procedure for the copper-catalyzed $PhI(OAc)_2$-mediated asymmetric alkene aziridination (Scheme 1), and the study on the effect of the nature of sulfonamides and olefin substrates under the employed reaction conditions.

Our initial study was to examine the effects of various copper catalysts on aziridination of styrene using 4-methylbenzenesulfonamide and stoichiometric amount of $PhI(OAc)_2$ in CH_3CN at room temperature. Among all the copper catalysts used, $[Cu(CH_3CN)_4]ClO_4$ gave the best yield of the aziridine product (55%), while other copper catalysts gave only 15–29% yields (Table 1). To develop a chiral version of this procedure, Evan's chiral bis(oxazoline) ligand[6] (L^*) was introduced to the system. However, addition of 6 mol% of the chiral ligand gave no enantioselectivity in CH_3CN. Switching the reaction solvent to CH_2Cl_2 increased the

Keywords: One-pot asymmetric aziridination; Copper catalyst; Styrene; Iodobenzene diacetate; Sulfonamides.
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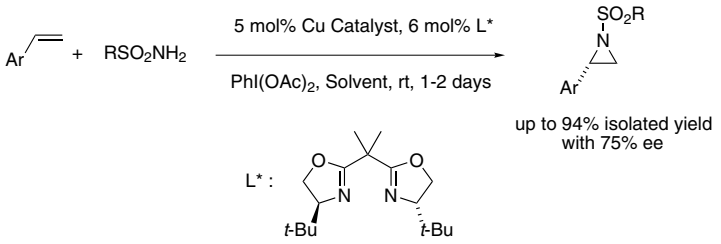


Scheme 1. One-pot copper-catalyzed $PhI(OAc)_2$-mediated asymmetric alkene aziridination.

Table 1. Effects of solvents and copper catalysts[a]

Entry	Copper catalyst	Solvent	L* mol%	Yield[b] %	% Ee[c]
1	CuCl	CH_3CN	—	15	—
2	Cu(OTf)	CH_3CN	—	27	—
3	$Cu(CH_3CN)_4PF_6$	CH_3CN	—	28	—
4	$Cu(CH_3CN)_4ClO_4$	CH_3CN	—	56	—
5	$Cu(CH_3CN)_4ClO_4$	CH_3CN	6	59	0
6	$Cu(CH_3CN)_4ClO_4$	CH_2Cl_2	6	82	29
7	$Cu(CH_3CN)_4ClO_4$	C_6H_6	6	75	48

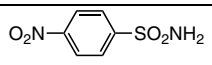
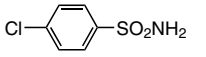
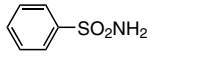
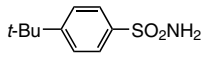
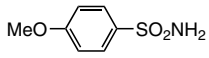
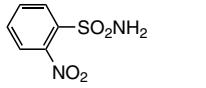
[a] The representative procedures in Ref. 7 were followed with 0 or 6 mol% of L*, 5 mol% of copper salt, 1 equiv of 4-methylbenzenesulfonamide and $PhI(OAc)_2$, 5 equiv of styrene and 3 mL of the solvent.
[b] Isolated yield.
[c] The absolute configuration of all compounds were assigned to be (*S*) based on the order of elution in HPLC.

yield to 82% with 29% ee. The enantioselectivity was further improved to 49% ee with 75% yield by using benzene as the solvent (Table 1, entry 7). The two-step aziridination procedure under slightly different conditions (Cu(OTf) as the catalyst at 0 °C) gave 65% overall yield of the aziridination product with 52% ee.[2f,g] The highest achievable results from the two-step procedure were obtained using CuOTf as the catalyst at 0 °C with excess olefin as the solvent (73% overall yield with 63% ee).[2a,f]

With these encouraging results, we investigated the effect of different sulfonamides as the nitrene source. As shown in Table 2, all sulfonamides gave good to excellent yields with enantioselectivity up to 75% ee. The nature of the sulfonamides exhibited a strong influence on the yields and enantioselectivities under our one-pot conditions. Benzene-sulfonamides with an electron withdrawing group at the 4-position generally gave higher product yields and ee's than those with an electron donating group. This trend is reverse in the two-step protocol (Table 2, entries 1 and 5).[2f,g] The best result was obtained with 4-nitro-benzenesulfonamide as the nitrene precursor, in which 94% of the aziridine product with 75% ee was obtained. Interestingly, moving the nitro group from the 4- (Table 2, entry 1) to the 2-position (Table 2, entry 6) of the benzene-sulfonamide led to a significant decrease in ee. Moreover, aziridination of styrene using methane-sulfonamide also gave good yield of the aziridine product with moderate enantioselectivity (Table 2 entry 7).

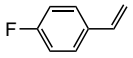
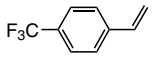
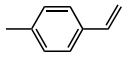
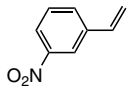
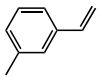
According to the literature, some of the sulfonamides failed to form the nitrene precursor (PhI=NR) in the conventional two-step aziridination protocol.[2f,g] For example, $PhI{=}NSO_2$-[*p*-(*t*-Bu)C_6H_4] could not be obtained from treatment of 4-(*t*-butyl)benzenesulfonamide with $PhI(OAc)_2$ in the presence of a basic methanolic solution.[2f] This problem is solved by using our one-pot procedure, which would give the aziridine product in 75% yield with 44% ee (Table 2, entry 4). This result suggests that the unstable nitrene precursor (PhI=NR) generated in situ could lead to the formation of the chiral aziridine product in a one-pot procedure.

Table 2. Effects of sulfonamides[a]

Entry	Sulfonamide	% Yield[b]	% Ee[c]
1		94 (91)[d]	75 (66)[d]
2		90	52
3		82	50
4		75	44
5		55 (73)[d]	33 (78)[d]
6		66	22
7	$CH_3SO_2NH_2$	86	36

[a] The representative procedures in Ref. 7 were followed with 6 mol% of L*, 5 mol% of $[Cu(CH_3CN)_4]ClO_4$, 1 equiv of sulfonamide and $PhI(OAc)_2$, 5 equiv of styrene and 3 mL of benzene.
[b] Isolated yield.
[c] The absolute configuration of all compounds were assigned to be (*S*) based on the order of elution in HPLC.
[d] Results obtained by the two-step procedure with CuOTf as the catalyst at 0 °C.[2f,g]

Table 3. Effects of olefin substrates[a]

Entry	Substrate	Aziridine	% Yield[b]	% Ee[c]
1		**1a**: R = 4-NO_2–Ph	95	72
		1b: R = 4-Cl–Ph	95	51
		1c: R = 4-Me–Ph	84	40
2		**2a**: R = 4-NO_2–Ph	64	51
		2b: R = 4-Cl–Ph	68	43
		2c: R = 4-Me–Ph	43	38
3		**3a**: R = 4-NO_2–Ph	78	45
		3b: R = 4-Cl–Ph	80	43
		3c: R = 4-Me–Ph	61	32
4		**4a**: R = 4-NO_2–Ph	82	52
		4b: R = 4-Cl–Ph	89	48
		4c: R = 4-Me–Ph	77	45
5		**5a**: R = 4-NO_2–Ph	68	57
		5b: R = 4-Cl–Ph	78	42
		5c: R = 4-Me–Ph	76	37

[a] The representative procedures in Ref. 7 were followed with 6 mol% of L*, 5 mol% of $[Cu(CH_3CN)_4]ClO_4$, 1 equiv of sulfonamide and $PhI(OAc)_2$, 5 equiv of substituted styrene and 3 mL of benzene.
[b] Isolated yield.
[c] The absolute configuration of all compounds were assigned to be (*S*) based on the order of elution in HPLC.

To investigate the effect of the substrates, various alkenes were employed for aziridination with different sulfonamides. The results are tabulated in Table 3. All the substituted styrenes gave good to excellent yields of the aziridine products with enantioselectivities up to 72% ee. Aziridination using 4-chlorobenzenesulfonamide gave the highest yield of the aziridine products and 4-nitrobenzenesulfonamide gave the best enantioselectivity for all the substituted styrene substrates. The optimal result was obtained from aziridination of 4-fluorostyrene using 4-nitrobenzenesulfonamide. Although the most electron deficient substrate gave the best results in terms of product yield and ee, the effect of the substrates remained not clear.

A detailed study of the electronic effect of the sulfonamides and olefin substrates would rely on a direct and rapid method to monitor the aziridination reaction. However, aziridines were found to be unstable for gas chromatography (GC) analysis. Here, this problem was solved by using naphthalene as an internal standard and monitoring the rate of formation of the by-product, iodobenzene, in GC-FID spectra. Preliminary study on the kinetics of aziridination showed that the rate of aziridination using 4-nitrobenzenesulfonamide as the nitrene source is faster than those using 4-chlorobenzenesulfonamide or methane-sulfonamide (Fig. 1). Though the reaction rate did not appear to have great impact on the product yields (86–94%, Table 2), it might have some bearing on the enantioselectivity of the aziridine products. Detailed studies on the kinetics of the alkene aziridination reaction are still ongoing.

In conclusion, we have developed a facile and convenient one-pot procedure for copper-catalyzed $PhI(OAc)_2$-mediated asymmetric alkene aziridination. The optimal conditions were found to be using 4-nitrobenzene-sulfonamide and $PhI(OAc)_2$ for generation of the nitrene precursor. With 5 mol% of the chiral copper catalyst, our one-pot procedure afforded 94% yield of the isolated aziridine in 74% ee. We have also developed a simple and rapid method for monitoring the rate of aziridination. Preliminary study on the aziridination profile suggested a correlation between the reaction rate and the enantioselectivity. Further studies on this interesting kinetic issue are ongoing in our laboratory.

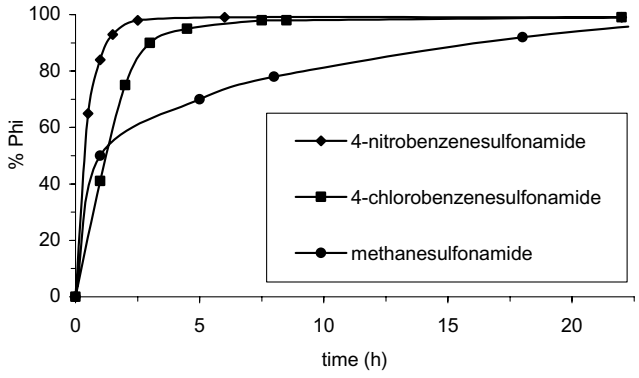


Figure 1. Rate of aziridination with different sulfonamides.[8]

Acknowledgements

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References and notes

1. (a) Tanner, D. *Pure Appl. Chem.* **1993**, *65*, 1319–1328; (b) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619; (c) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365.
2. (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328–5329; (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742–2753; (c) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326–5327; (d) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676–678; (e) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889–5890; (f) Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, *38*, 6897–6900; (g) Södergren, M. J.; Alonso, D. A.; Andersson, P. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3563–3565; (h) Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707–7708; (i) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481–2483.
3. (a) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752–10765; (b) Masse, C. E.; Knight, B. S.; Stavropoulos, P.; Panek, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 6040–6047; (c) Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 4039–4040; (d) Sudau, A.; Münch, W.; Bats, J. W.; Nubbemeyer, U. *Chem. Eur. J.* **2001**, *7*, 611–621.
4. Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178.
5. (a) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233–2236; (b) Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* **2000**, *65*, 7858–7864; (c) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 1563–1572.
6. (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726–728; (b) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541–4544.
7. Representative procedures for the one-pot aziridination: A mixture of 2,2-bis[2-[(4*S*)-*t*-butyl-1,3-oxazolinyl]] propane ligand (18 mg, 0.06 mmol) and $Cu(CH_3CN)_4ClO_4$ (16 mg, 0.05 mmol) in benzene (3 mL) was stirred at room temperature under nitrogen for 1 h. To this stirred solution was added iodobenzene diacetate (320 mg, 1.0 mmol) and 4-nitrobenzenesulfonamide (202 mg, 1.0 mmol) in one portion followed by styrene (0.57 mL, 5.0 mmol). The resulting mixture was stirred at room temperature for 1 day. After removal of the volatiles under reduced pressure, the residue was purified by flash column chromatography (*n*-hexane–ethyl acetate = 5:1) to give a pale yellow solid (287 mg, 0.94 mmol, 94%) as the product, which was characterized by ^1H NMR and MS. Ee's were determined by HPLC with Whelk-O1 column eluting with *n*-hexane–isopropanol (97:3).
8. Representative procedures for monitoring the rate of the one-pot aziridination: The above procedures were followed with naphthalene (128 mg, 1.0 mmol) added as the internal standard after the copper–ligand complex formation. Upon the complete dissolution of naphthalene, the mixture of 4-nitrobenzenesulfonamide, $PhI(OAc)_2$ and styrene was added in one portion. Then a drop of the reaction mixture was taken every 30 min and filtered through a short silica gel column to remove the unreacted $PhI(OAc)_2$. The resulting solution was submitted for GC-FID analysis with Ultra 2 (5% cross-linked with triphenylsilane) column. The percentage of iodobenzene generated was calculated by comparing with the area of the peak for naphthalene.