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Notable Coordination Effects of 2-Pyridinesulfonamides Leading to Efficient Aziridination and Selective Aziridine Ring Opening

Hoon Han, Imhyuck Bae, Eun Jeong Yoo, Junseong Lee, Youngkyu Do, and Sukbok Chang*

Center for Molecular Design and Synthesis, Department of Chemistry and School of Molecular Science (BK21), Korea Advanced Institute of Science and Technology (KAIST), Daejon 305-701, Republic of Korea

sbchang@kaist.ac.kr

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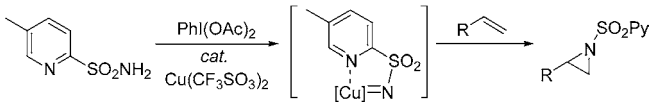
ABSTRACT



We have developed, on the basis of a chelation-strategy, an efficient copper-catalyzed aziridination protocol with the use of 5-methyl-2-pyridinesulfonamide and $PhI(OAc)_2$. The reaction proceeds smoothly under mild conditions to give aziridines in moderate to good yields in the absence of external ligands or bases. The coordination-assisted approach offers the additional benefits that efficient deprotection of the N-substituent and selective aziridine ring-opening are effectively achieved.

Setting a properly chosen directing group in an appropriate position influences reaction pathways significantly leading to noticeable changes in efficiency and selectivity.[1] Recently, the 2-pyridyl group has drawn much attention as an efficient directing group, and intensive research has been undertaken to utilize the coordination-assisted approach with the moiety, making a large number of synthetically useful organic transformations possible.[2] Aziridines are important building blocks in organic synthesis, and they are also responsible for diverse biological activities in natural products. This has stimulated the development of numerous preparative procedures of aziridines either by conventional synthesis or by catalytic routes.[3] Despite remarkable advances in the metal-catalyzed addition of nitrene derivatives to alkenes, which would be one of the most attractive aziridination routes,[4,5] some challenges still remain. For example, available nitrene sources in the catalytic reactions are rather limited, and *N*-tosyliminophenyliodinane (TsN═IPh) has been employed in most cases, which is an unstable and capricious compound being prepared via two steps. Efficient deprotection and selective ring-opening of *N*-tosyl aziridines consist of additional formidable tasks to be improved. Changes in the steric and electronic properties of nitrene source have been proposed as one of the feasible breakthrough of these limitations.[6] Described herein are our recent findings that a practical protocol of aziridination, efficient deprotection, and

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(5) For some examples of aziridination methods catalyzed by other metals than copper: (a) Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C. M. *J. Am. Chem. Soc.* **1999**, *121*, 9120. (b) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672. (c) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507. (d) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202.

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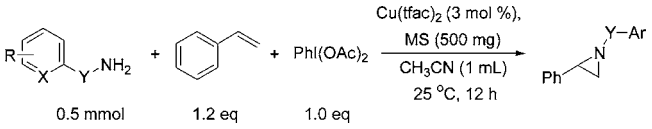
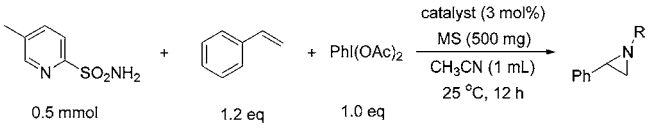
Table 1. Aziridination of Styrene with Various Sulfonamides



entry	R	X	Y	yield[a] (%)
1	H	N	SO_2	76
2	5-Me	N	SO_2	84
3	6-Me	N	SO_2	73[b]
4	4-Me	CH	SO_2	NR[c]
5	H	CH	SO_2	15
6	H	CH	CO	NR[c]
7	H	N	CO	NR[c]

[a] NMR yield. [b] 3.0 equiv of styrene was used. [c] NR = no reaction.

Table 2. Aziridination of Styrene with Various Metal Catalysts



entry	catalyst	yield[a] (%)
1	$Cu(OTf)_2$	71
2	$Cu(OTf)\cdot PhH$	66
3	$CuBr\cdot(CH_3)_2S$	8
4	$Cu(CH_3CN)_4PF_6$	58
5	$CuCl_2$	10
6	CuBr	6
7	CuI	trace
8	$Cu(acac)_2$	78
9	$Cu(tfac)_2$	84
10	$Cu((hfac)_2\cdot H_2O$	48
11	Cu(OAc)	10
12	$Cu(OAc)_2$	5
13	$[Rh(OAc)_2]_2$	63[b]
14	$RuCl_2(CO)_2(PPh_3)_2$[d]	NR[c]
15	$Ru(acac)_3$[d]	NR[c]
16	$CpRu(PPh_3)_2Cl$[d]	NR[c]
17	$RuCl_3$[d]	NR[c]
18	$RuCl_2(C_{10}H_8N_2)_2\cdot 2H_2O$[d]	NR[c]

[a] NMR yield. [b] 10 equiv of styrene was used. [c] NR = no reaction. [d] 10 mol % of catalyst was employed.

selective aziridine ring-opening were achieved on the basis of a chelation strategy.[7]

At the outset of our studies, we intended to develop a practical aziridination system by using readily available sulfonamides or amides as a nitrogen source in combination with an easily handled oxidant such as $PhI(OAc)_2$ for the generation of nitrene precursor that is catalytically transferred to alkenes (Table 1). In initial experiments with styrene, it was found that certain copper complexes effectively catalyzed the aziridination when 2-pyridinesulfonamides (X = N, Y = SO_2) were employed *in combination with PhI(OAc)$_2$ alone in the absence of any external ligands or bases* (entry 1). Introduction of a methyl group at the C5 position slightly improved reaction efficiency to afford the corresponding aziridine in the highest yield (entry 2). Interestingly, use of 6-methyl-2-pyridinesulfonamide gave less satisfactory results even under more forcing conditions (3.0 equiv of styrene, entry 3). On the other hand, aziridination reaction of styrene with *p*-toluenesulfonamide (R = 4-Me, X = CH, Y = SO_2) or benzenesulfonamide (R = H, X = CH, Y = SO_2) turned out to be sluggish under the employed conditions (entry 4 and 5, respectively), thus strongly implying that *a driving force for the reaction is the coordination of Cu to the pyridyl N atom of 2-pyridinesulfonamides*. During preparation of this manuscript, Che et al. reported that addition of external ligands is highly important for giving high efficiency and enantioselectivity in $Cu(CH_3CN)_4ClO_4$-catalyzed aziridination of olefins using sulfonamides and $PhI(OAc)_2$ systems.[8] In the meantime, carboxamides turned out to be poor nitrene donors under the present catalyst systems (entries 6 and 7).

Efficiency of catalysts was next investigated in the aziridination of styrene with the use of 5-methyl-2-pyridinesulfonamide (**1**) and $PhI(OAc)_2$ system (Table 2, R: 5-methyl-2-pyridinesulfonyl). It was immediately found that certain Cu complexes showed higher catalytic activities compared to other transition-metal species which exhibited either lower or almost no reactivities. Among Cu catalysts tested, copper(II) trifluoroacetylacetonate yielded the best results (entry 9).

Table 3 shows results of the coordination-assisted aziridination of a range of olefins with sulfonamide **1** under the optimized conditions (R: 5-methyl-2-pyridinesulfonyl). Aromatic olefins were smoothly reacted irrespective of their electronic and steric properties to afford the corresponding aziridines in good yields (entries 1−8). Interestingly, a ring-opened compound was isolated from the reaction with *O*-silyl styrene (entry 9), which was presumably derived by a subsequent reaction of aziridine with acetate released from the oxidant, $PhI(OAc)_2$. While a reaction of *trans*-β-methylstyrene afforded only *E*-aziridine, that of *cis*-olefin took place nonstereoselectively so that a mixture of *cis*/*trans*-isomeric products were generated (entries 11 and 12). This strongly suggests that the nitrene-transfer process in our system proceeds stepwise via a radical pathway.[9]

Aliphatic olefins were rather less reactive so the corresponding aziridines were obtained in moderate yields under more forcing conditions (entries 13 and 14). In the case of norbornene, only *exo*-aziridine was produced, confirmed by a single-crystal X-ray diffraction study (Figure 1).[10] Intrigu-

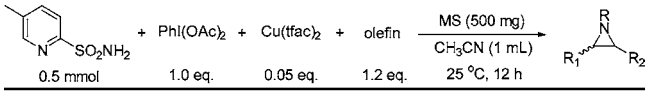
(6) (a) Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tetrahedron Lett.* **1997**, *38*, 6897. (b) Dauban, P.; Dodd, R. H. *J. Org. Chem.* **1999**, *64*, 5304.

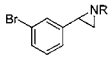
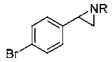
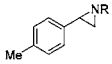
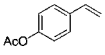
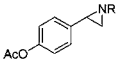
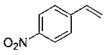
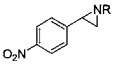
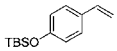
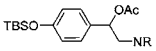
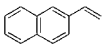
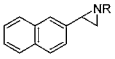
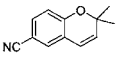
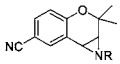
(7) Recent reports from this laboratory regarding on the chelation approach: (a) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750. (b) Ko, S.; Lee, C.; Choi, M.-G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607. (c) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687. (d) Na, Y.; Ko, S.; Hwang, L. K. *Tetrahedron Lett.* **2003**, *44*, 4475.

(8) Kwong, H.-L.; Liu, D.; Chan, K.-Y.; Lee, C.-S.; Huang, K.-H.; Che, C.-M. *Tetrahedron Lett.* **2004**, *45*, 3965.

(9) For mechanistic studies in Cu-catalyzed aziridination, see: (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (b) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889. (b) Brandt, P.; Södergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013.

Table 3. Coordination-Assisted Aziridination of Various Olefins



entry	substrate	product	yield (%)[a]
1			84
2			60
3			68
4			74
5			59
6			69
7			75
8			52
9			64
10			68[b]
11			68[b]
12			49[b] (c/t= 1/2)
13			58[b,c]
14			44[b,c,d]
15			58[b]

[a] Isolated yield. [b] 5.0 equiv of olefin was used. [c] Run at 40 °C. [d] $Cu(CH_3CN)_4PF_6$ was employed as a catalyst.

ingly, Cu(I) catalyst was found to be marginally superior to Cu(II) catalyst in the reaction of cyclooctene. It should be

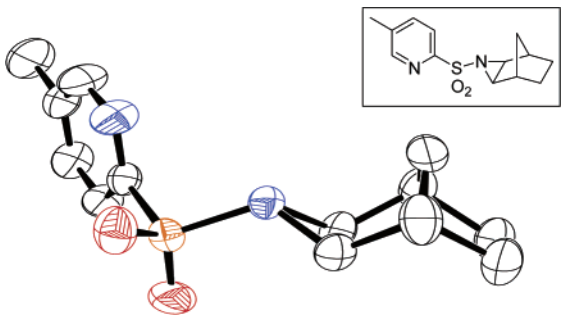
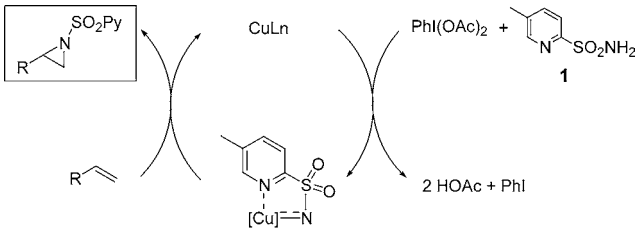


Figure 1. X-ray structure of *N*-(5-methyl-2-pyridinesulfonyl)-norbonylaziridine.

Scheme 1. Proposed Pathway for the Aziridination Using **1** and $PhI(OAc)_2$

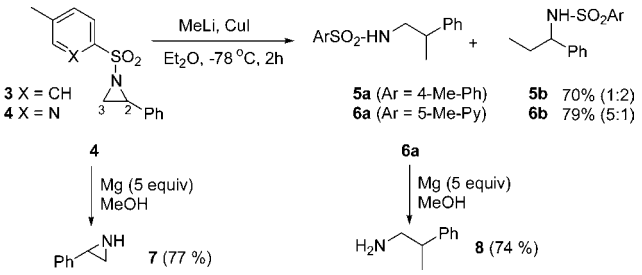


mentioned that the aziridination procedure developed herein is highly flexible and practical so that a large-scale process is readily operational. For example, reaction of styrene in gram scale (12 mmol, 1.2 equiv to sulfonamide **1**) proceeded smoothly, giving the aziridine (2.2 g, 81%) using 3.0 mol % of $Cu(tfac)_2$.[10]

Although the involvement of a metallonitrene intermediate is now well accepted in the catalytic aziridination,[9] the direct experimental evidence for active species is limited. On the basis of the results obtained from Table 1, it might be anticipated that the presence of 2-pyridyl group coordinated to copper would stabilize the speculative nitrene intermediates represented as **2** (Scheme 1).

Nucleophilic ring opening of aziridines is of great interest in that it furnishes a broad range of amine functionalities.[11] While reaction of *N*-tosylphenylaziridine **3** with in situ generated methyl cuprate exhibited poor selectivity favoring at less hindered 3-position (**5a/5b**, 1:2), consistent with the literature (Scheme 2),[12] *a completely reversed regioselectivity*

Scheme 2. Stereoselective Ring Opening and Deprotection



was observed from the reaction of aziridine ***4*** *bearing the N-pyridine sulfonyl group*. The preferential opening at C2 (**6a/6b**, 5:1) of **4** could be attributed to a pre-coordination of cuprate complex to the pyridyl nitrogen atom followed by the transfer of a methyl group into more electrophilic benzylic position via intramolecular manner. At the present stage, however, other possibilities than chelation effects that govern the observed regioselectivity in the aziridine ring-opening reaction still remain to be elucidated.

(10) For details, see the Supporting Information.
(11) For a review, see: Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
(12) Kozikowski, A. P.; Ishida, H.; Isobe, K. *J. Org. Chem.* **1979**, *44*, 2788.

Deprotection of the *N*-pyridinesulfonyl group from both aziridine **4** and ring-opened moieties **6a**/**6b** were readily achieved using magnesium in methanol.[13] This mild and efficient reductive deprotection is likely related to its lower LUMO energy level of the pyridinesulfonyl group compared to toluenesulfonyl group.[14] It should be addressed that removal of the *N*-toluenesulfonyl group from *N*-tosylaziridines is not so easy up to date that it is regarded as a major drawback with these most frequently studied aziridines.[15] Therefore, the observed rather mild and facile deprotection procedure from the *N*-pyridinesulfonyl adducts demonstrates an additional significant advantage of pyridinesulfonyl moiety facilitated herein.

In conclusion, we have developed an efficient, practical, and external ligand-free Cu-catalyzed aziridination protocol based on the chelation-approach for the first time, which also allows mild and selective deprotection as well as aziridine ring-opening.

Acknowledgment. This research was supported by KOSEF (R02-2003-000-10075-0) through the Basic Research Program.

Supporting Information Available: Spectral data and copies of ^{1}H and ^{13}C NMR spectra for new compounds and crystallographic data for compound *N*-(5-methyl-2-pyridinesulfonyl)norbonyl aziridine (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0481784

(13) Pak, C. S.; Lim, D. S. *Synth. Commun.* **2001**, *31*, 2209.

(14) Mazéas, D.; Skrydstrup, T.; Doumeix, O.; Beau, J. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1383 and references therein.

(15) In fact, the desulfonylation from **3** and **5a**/**5b** was incomplete and nonselective under the same conditions as for **4** and **6a**/**6b**. For a relevant method of deprotection of *N*-tosyl group from aziridines, see: Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455.