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Copper-Catalyzed Alkene Aziridination with *N*-Tosyloxycarbamates

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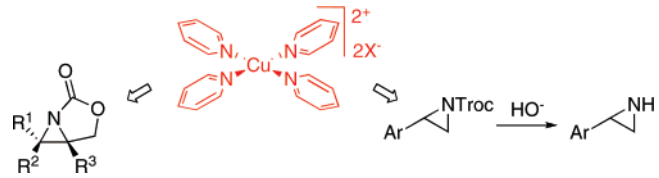
ABSTRACT



Pyridine copper complexes were found as active catalysts for the intramolecular aziridination of allylic *N*-tosyloxycarbamates and the intermolecular aziridination of styrenes with trichloroethyl *N*-tosyloxycarbamates. Free aziridines were easily obtained by basic deprotection of the trichloroethyl group.

Aziridines are attractive synthetic targets, as they are found in a number of natural products exhibiting various biological properties, such as antitumor and antibiotic activities.[1] Since these are the nitrogen analogues of epoxides, they also display similar electrophilic reactivity. Various synthetic methods have been developed to prepare aziridines, typically starting from alkenes or imines.[2] The discovery of hypervalent iodinane reagents for nitrene transfer to alkenes by means of transition metal complexes, such as copper[3] or rhodium[4] complexes, has led to the development of efficient catalytic processes[5] including asymmetric systems.[6] The major drawback of these methods is the generation of a full equivalent of iodobenzene. Alternative reagents have been developed, although with limited applicability.[7,8] Recently, we have reported the use of *N*-tosyloxycarbamates as an alternative to produce rhodium nitrenes that can undergo C−H insertion and aziridination reactions.[9] Indeed, the decomposition of allylic *N*-tosyloxycarbamates in the pres-

(1) (a) Jacobsen, E. N. in *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, pp 607. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347−1365. (c) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247−258. (d) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919. (e) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571−1586. (f) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657−669. (g) Li, Z. G.; He, C. *Eur. J. Org. Chem.* **2006**, 4313−4322. (h) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH, Weinheim, 2006.

(2) (a) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1995**, *34*, 676−678. (b) Juhl, K.; Hazell, R. G.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293−2297. (c) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518−4521. (d) Hanessian, S.; Cantin, L. D. *Tetrahedron Lett.* **2000**, *41*, 787−790. (e) Aggarwal, V. K.; Alonso, E.; Fang, G. Y.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433−1436. (f) Yang, X. F.; Mang, M. J.; Hou, X. L.; Dai, L. X. *J. Org. Chem.* **2002**, *67*, 8097−8103. (g) Davis, F. A.; Wu, Y. Z.; Yan, H. X.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410−2419.

(3) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742−2753. (b) Brookhart, M.; DiazRequejo, M. M.; Perez, P. J.; Templeton, J. L. *Organometallics* **1997**, *16*, 4399−4402. (c) Brandt, P.; Sodergren, M. J.; Andersson, P. G.; Norrby, P. O. *J. Am. Chem. Soc.* **2000**, *122*, 8013−8020. (d) Sanders, C. J.; Gillespie, K. M.; Bell, D.; Scott, P. *J. Am. Chem. Soc.* **2000**, *122*, 7132−7133. (e) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481−2483. (f) Vedernikov, A. N.; Caulton, K. G. *Org. Lett.* **2003**, *5*, 2591−2594. (g) Di Chenna, P. H.; Robert-Peillard, F.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2004**, *6*, 4503−4505. (h) Leca, D.; Toussaint, A.; Mareau, C.; Fensterbank, L.; Lacote, E.; Malacria, M. *Org. Lett.* **2004**, *6*, 3573−3575. (i) Mairena, M. A.; Diaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Perez, P. J. *Organometallics* **2004**, *23*, 253−256. (j) Mohr, F.; Binfield, S. A.; Fettinger, J. C.; Vedernikov, A. N. *J. Org. Chem.* **2005**, *70*, 4833−4839. (k) Sun, W.; Herdtweck, E.; Kuhn, F. E. *New J. Chem.* **2005**, *29*, 1577−1580.

(4) (a) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728−6729. (b) Muller, P.; Baud, C.; Jacquier, Y. *Can. J. Chem.* **1998**, *76*, 738−750. (c) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672−13673. (d) Levites-Agababa, E.; Menhaji, E.; Perlson, L. N.; Rojas, C. M. *Org. Lett.* **2002**, *4*, 863−865. (e) Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137−2139. (f) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377−6386. (g) Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; Du Bois, J. *Tetrahedron* **2006**, *62*, 11331−11342.

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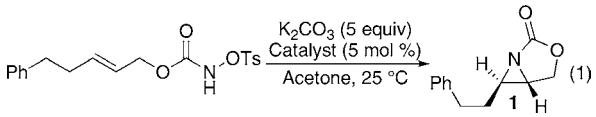
ence of potassium carbonate and rhodium(II) acetate dimer catalyst leads to the intramolecular nitrene transfer, thereby generating the corresponding aziridine in good to excellent yields. However, this method would greatly benefit from the use of a cheaper catalyst, such as copper complexes.[3,10] In this communication, we wish to report the use of pyridine copper complexes for *intra-* and *intermolecular* alkene aziridinations using *N*-tosyloxycarbamate reagents.

Sulfonyloxycarbamates are known to react with electron-deficient alkenes via an AZA-Michael-initiated ring closing (AZA-MIRC) process to give the corresponding aziridines in good yields.[8] The reaction of such reagents with non-activated alkenes (in the absence of catalyst) leads to low yields and unselective processes typically observed with free nitrenes.[1c,11] Conversely, the use of the rhodium(II) acetate dimer catalyst allowed the intramolecular aziridination of allylic *N*-tosyloxycarbamates (Table 1, entries 1 and 2).[9] Copper complexes are known to promote aziridination of alkenes in the presence of sulfonyliminoiodinane reagents.[3]

Table 1. Copper-Catalyzed Aziridination of (*E*)-5-Phenylpent-2-enyl *N*-Tosyloxycarbamate (eq 1)



entry	catalyst	yield[a]
1	none	<10%
2	$Rh_2(OAc)_4$	74%[b]
3	$Cu(OTf)_2$	45%
4	$Cu(OTf)_2$·Benzene	50%
5	$Cu(pyridine)_2Cl_2$	53%
6	$Cu(pyridine)_4(OTf)_2$	74%
7	**$Cu(pyridine)_4(OTf)_2$[c]**	**84%**
8	$Cu(pyridine)_4(OTf)_2$[d]	72%
9	$Cu(pyridine)_2(BAr^F{}_4)_2$[e]	82%
10	$Cu(pyridine)_4(BF_4)_2$	74%

[a] Isolated yield by flash chromatography. [b] 7 equiv of K_2CO_3 was used, see ref 9a. [c] 2 mol % of catalyst. [d] 1 mol % of catalyst. [e] $BAr^F{}_4$ = tetra[3,5-di(trifluoromethyl)phenyl]borate.

However, the use of copper(II) triflate for the intramolecular aziridination of allylic *N*-tosyloxycarbamates led to aziridination product **1** with only moderate yields (entries 3 and 4). We postulated that the solubility of the copper species might be an issue, as the reaction between copper(II) triflate and potassium carbonate could generate a very insoluble copper carbonate species. We then studied the use of ligands to make a more soluble species and to accelerate the reaction. We chose to investigate pyridine copper complexes as these are known to efficiently catalyze the aziridination of alkenes with PhINTs.[3j] However, we did not observed an improvement using $Cu(pyridine)_2Cl_2$ (entry 5). Conversely, complexes containing less coordinating anionic ligands, such as triflate,[12] tetra[3,5-di(trifluoromethyl)phenyl]borate ($BAr^F{}_4$), or tetrafluoroborate, led to the desired aziridine **1** with 74−84% yields (entries 6, 8−10). However, no significant difference was detected between the use of the more expensive $BAr^F{}_4$ over the triflate and the tetrafluoroborate anionic ligand. Thus, the study was pursued with the triflate complex. Not only are copper complexes cheaper than rhodium complexes, but it was also possible to decrease the catalyst loading of $Cu(pyridine)_4(OTf)_2$ to 2 mol % without affecting the yield (entry 7). Optimization with $Cu(pyridine)_4(OTf)_2$ showed that no yield improvement was observed when changing either the solvent or the base.

A variety of allylic *N*-tosyloxycarbamates were then treated with 2 mol % of $Cu(pyridine)_4(OTf)_2$ in the presence of 5 equiv of potassium carbonate in acetone. Under these reaction conditions, the corresponding aziridine was isolated with a good yield (Table 2). Aliphatic and aromatic *E*-disubstituted alkenes reacted stereospecifically to produce *trans*-aziridines with 66% and 51% yield, respectively (entries 1 and 2). Conversely, the aziridination of *Z*-disubstituted allylic *N*-

(5) Transition metals other than Cu and Rh: (a) Breslow, R.; Gellman, S. H. *Chem. Commun.* **1982**, 1400−1401. (b) Groves, J. T.; Takahashi, T. *J. Am. Chem. Soc.* **1983**, *105*, 2073−2074. (c) Mahy, J. P.; Battioni, P.; Mansuy, D. *J. Am. Chem. Soc.* **1986**, *108*, 1079−1080. (d) Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1993**, 469−471. (e) Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245−9248. (f) Liang, J. L.; Huang, J. S.; Yu, X. Q.; Zhu, N. Y.; Che, C. M. *Chem. Eur. J.* **2002**, *8*, 1563−1572. (g) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202−16203. (h) Li, Z. G.; Ding, X. Y.; He, C. *J. Org. Chem.* **2006**, *71*, 5876−5880.

(6) (a) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326−5327. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328−5329. (c) Jacobsen, E. N.; Li, Z.; Quan, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 5889−5890. (d) Sanders, C. J.; Gillespie, K. M.; Bell, D.; Scott, P. *J. Am. Chem. Soc.* **2000**, *122*, 7132−7133. (e) Fruit, C.; Robert-Peillard, F.; Bernardinelli, G.; Muller, P.; Dodd, R. H.; Dauban, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3484−3487. (f) Ma, L. G.; Jiao, P.; Zhang, Q. H.; Xu, J. X. *Tetrahedron: Asymmetry* **2005**, *16*, 3718−3734. (g) Wang, X. S.; Ding, K. L. *Chem. Eur. J.* **2006**, *12*, 4568−4575.

(7) For alternative methods, see: (a) Sharpless, K. B.; Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H. *J. Am. Chem. Soc.* **1998**, *120*, 6844−6845. (b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852−2859. (c) Chanda, B. M.; Vyas, R.; Landge, S. S. *J. Mol. Catal.* **2004**, *223*, 57−60. (d) Siu, T.; Picard, C. J.; Yudin, A. K. *J. Org. Chem.* **2005**, *70*, 932−937. (e) Catino, A. J.; Nichols, J. M.; Forslund, R. E.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 2787−2790. (f) Kawabata, H.; Omura, K.; Katsuki, T. *Tetrahedron Lett.* **2006**, *47*, 1571−1574.

(8) AZA-MIRC: (a) Fazio, A.; Loreto, M. A.; Tardella, P. A. *Tetrahedron Lett.* **2001**, *42*, 2185−2187. (b) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synthesis* **2001**, 1975−1978. (c) Fioravanti, S.; Mascia, M. G.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Eur. J. Org. Chem.* **2002**, 4071−4074. (d) Gasperi, T.; Loreto, M. A.; Tardella, P. A.; Gambacorta, A. *Tetrahedron Lett.* **2002**, *43*, 3017−3020. (e) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **2002**, *67*, 4972−4974. (f) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Eur. J. Org. Chem.* **2003**, 4549−4552. (g) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synlett* **2004**, 1083−1085. (h) Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354−1355. (i) Shen, Y. M.; Zhao, M. X.; Xu, J. X.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8005−8008. (j) Vesely, J.; Ibrahem, I.; Zhao, G. L.; Rios, R.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778−781.

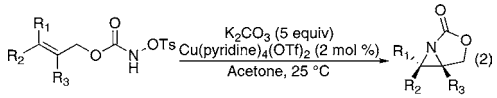
(9) (a) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198−14199. (b) Lebel, H.; Leogane, O.; Huard, K.; Lectard, S. *Pure Appl. Chem.* **2006**, *78*, 363−375. (c) Lebel, H.; Huard, K. *Org. Lett.* **2007**, *9*, 639−642.

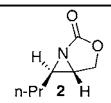
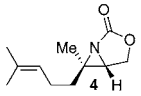
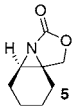
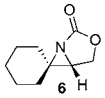
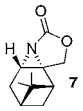
(10) During the course of preparing this manuscript, Fleming and coworkers reported the use of a copper(I) catalyst for the intramolecular aziridination of allylic tosyloxycarbamates; see: Liu, R.; Herron, S. R.; Fleming, S. A. *J. Org. Chem.* **2007**, *72*, 5587−5591.

(11) For examples, see: (a) Barani, M.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1994**, *50*, 11235−11238. (b) Fioravanti, S.; Luna, G.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **1997**, *53*, 4779−4786.

(12) Haynes, J. S.; Rettig, S. J.; Sams, J. R.; Trotter, J.; Thompson, R. C. *Inorg. Chem.* **1988**, *27*, 1237−1241.

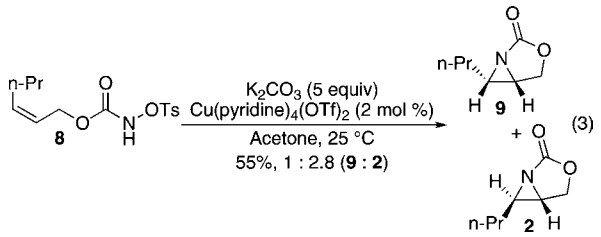
Table 2. Intramolecular Aziridination of Allylic *N*-Tosyloxycarbamates with Cu(pyridine)$_4$(OTf$_2$) (eq 2)



entry	product	yield[a]
1		66%
2		51%
3		61%[b]
4		79%
5		84%
6		78%[c]

[a] Isolated yield by flash chromatography. [b] 2 mol % of Cu(pyridine)$_2$-(BAr$^F_4$)$_2$. [c] 5 mol % of Cu(pyridine)$_4$(OTf)$_2$.

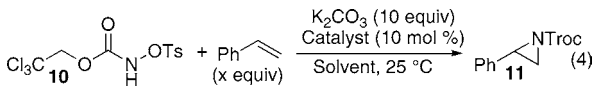
tosyloxycarbamates led to a mixture of *cis*- and *trans*-aziridines (eq 3).



These results suggest that a stepwise mechanism, involving presumably a triplet metal nitrene intermediate, is taking place.[11] Trisubstituted allylic *N*-tosyloxycarbamates also reacted with Cu(pyridine)$_4$(OTf)$_2$ to produce the corresponding aziridines with good to excellent yields (entries 3−6). Only one diastereomer was observed for the aziridination of the *N*-tosyloxycarbamate derived from (−)-myrtenol, aziridine **7** arisen from the attack of the metal nitrene on the less hindered side of the alkene.

A more challenging task is to achieve the *intermolecular* aziridination reaction with alkenes because a reagent that will not react *intramolecularly* is required. Recently, we have shown that rhodium-catalyzed intermolecular C−H amination proceeds efficiently using trichloroethyl *N*-tosyloxycarbamate (**10**).[9c] This reagent was thus used to test the copper-catalyzed

Table 3. Copper-Catalyzed Intermolecular Aziridination of Styrene with Trichloroethyl *N*-Tosyloxycarbamate (**10**) (eq 4)

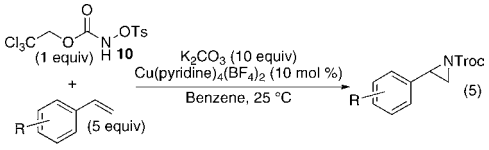


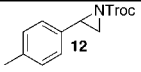
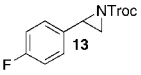
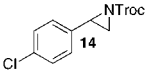
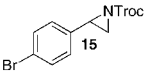
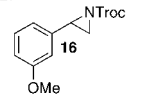
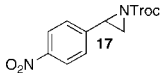
entry	equiv of styrene	catalyst	solvent	yield[a]
1	3	Cu(pyridine)$_4$(OTf)$_2$	acetone[b]	<5%
2	5	Cu(pyridine)$_4$(OTf)$_2$	benzene	47%
3	2	Cu(pyridine)$_4$(BF$_4$)$_2$	benzene	55%
4	**5**	**Cu(pyridine)$_4$(BF$_4$)$_2$**	**benzene**	**74%**
5	5	Cu(pyridine)$_4$(BF$_4$)$_2$	toluene	34%
6	5	Cu(pyridine)$_4$(BF$_4$)$_2$	PhCF$_3$	42%
7	5	Cu(pyridine)$_4$(BF$_4$)$_2$	PhCl	33%

[a] Isolated yield by flash chromatography. [b] 13 equiv of K_2CO_3 was used.

aziridination of styrene (Table 3). The first result was disappointing, as the reaction did not proceed in acetone using Cu(pyridine)$_4$(OTf)$_2$ as the catalyst and led exclusively to the decomposition of trichloroethyl *N*-tosyloxycarbamate (**10**) into the corresponding carbamate ($Cl_3CCH_2OC(O)NH_2$) (entry 1). We examined a variety of solvents and found that the reaction occurred in benzene with Cu(pyridine)$_4$(BF$_4$)$_2$ as the catalyst to give aziridine **11** in high yields (entry 4). Conversely, the use of other aromatic solvents produced the desired aziridine with only low to moderate yields (entries 5−7). Other styrene derivatives were reacted under these reaction conditions and produced the corresponding aziridines

Table 4. Intermolecular Aziridination of Various Styrenes with *N*-Tosyloxycarbamate **10** and Cu(pyridine)$_4$(BF$_4$)$_2$ (eq 5)

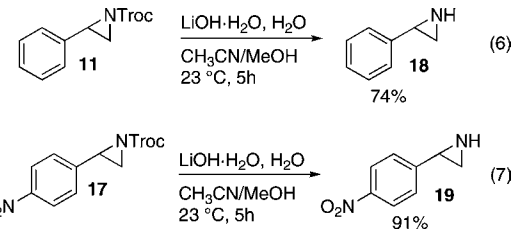


entry	product	yield[a]
1		68%
2		55%
3		62%
4		56%
5		62%
6		51%

[a] Isolated yield by flash chromatography.

with 51−68% yields. (Table 4). Methyl, halide, nitro, and methoxy groups were tolerated and did not affect the reaction. The reaction proceeded also with a good chemoselectivity, as neither the aziridination of the benzene ring nor the nitrene C−H insertion at the benzylic methyl group was observed.

Another important aspect in aziridine chemistry is to generate synthetically versatile derivatives that can be easily deprotected without opening the three-membered ring. Only a few examples of sulfonyliminophenyl iodinane reagents have been reported thus far that meet this requirement.[13] When using trichloroethyl *N*-tosyloxycarbamate as reagent, troc-protected aziridines are produced, and the protecting group can be easily cleaved under mild basic reaction conditions without opening the aziridine moiety. Indeed treatment with lithium hydroxide produced aziridines **18** and **19** with 74% and 91% yield, respectively.



In conclusion, we have developed a novel copper-catalyzed aziridination reaction based on the use of *N*-tosyloxycarbamates. These results correlate the work of Fleming and co-workers, who have also reported the use of a copper(I) catalyst for the intramolecular aziridination of allylic tosyloxycarbamates.[10] These reagents are advantageous in comparison to the use of hypervalent iodinane reagents, as they do not produce nonpolar, high molecular weight byproducts, such as iodobenzene. The formation of troc-protected aziridines is beneficial, as the troc protecting group is easily removed under mild basic conditions, without opening of the aziridine moiety. The use of copper catalysts is valuable in contrast to rhodium carboxylate dimer, as they are less expensive. We have shown that pyridine ligands are beneficial and clearly favor the aziridination reaction. The development of an enantioselective version based on chiral pyridine ligands is currently underway.

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Supporting Information Available: Experimental procedures, compound characterization data, and ^{1}H spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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