ORGANIC LETTERS

2005
Vol. 7, No. 11
2201−2204

Novel Ozone-Mediated Cleavage of the Benzhydryl Protecting Group from Aziridinyl Esters

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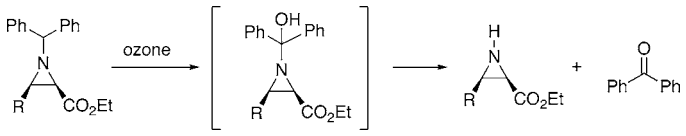
Received March 18, 2005

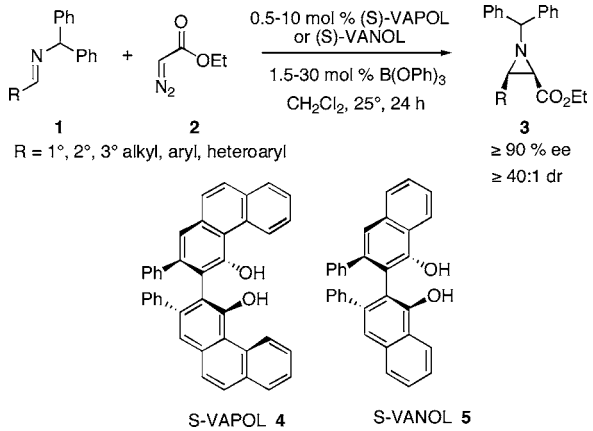
ABSTRACT



***N*-Benzhydryl aziridines-2-carboxylates can be readily obtained from the catalytic asymmetric aziridination reaction from *N*-benzhydrylimines and ethyl diazoacetate. Cleavage of the benzhydryl group by hydrogenolysis leads to ring opening when R = aryl. Surprisingly, ozone will selectively oxidize the benhydryl group in these aziridines even when R is an aryl group. This allows for a new deprotection strategy for these aziridines whose generality is explored.**

Chiral aziridines are very important synthetic targets as a result of their utility in providing access to unnatural optically pure amino acids and in general for the preparation of chiral amines.[1] Most chiral aziridines are prepared from compounds available in the chiral pool, and this may in part be due to the lack of asymmetric catalytic methods for the synthesis of aziridines.[2] We have developed a general method for the catalytic asymmetric synthesis of aziridine-2-carboxylic ethyl esters from benzhydryl imines and ethyl diazoacetate (Scheme 1).[3] The reaction selectively produces the cis diastereomers (≥40:1) of aziridines **3** in excellent enantioselectivities (≥90% ee) for imine substrates derived from aryl, heteroaryl, and primary, secondary, and tertiary alkyl aldehydes. Catalysts derived from either the VAPOL or VANOL ligand and triphenylborate are essentially equally effective in providing these levels of selectivity. To maximize the utility of this asymmetric aziridination, we realized that it would be necessary to develop methods for the deprotection of the benzhydryl group from these aziridines. Initially we examined hydrogenation methods, and this proved to be successful for 3-alkyl-substituted aziridines of the type **3** (Scheme 2). Pearlman's catalyst[4] would be the natural choice for this task since it is known to cleave benzhydryl groups from amines[5] and to selectively cleave benzylamines in the presence of benzyl ethers.[6] The hydrogenation was carried out under 1 atm of hydrogen in methanol at room temperature with 10% Pearlman's catalyst to give the primary, secondary, and

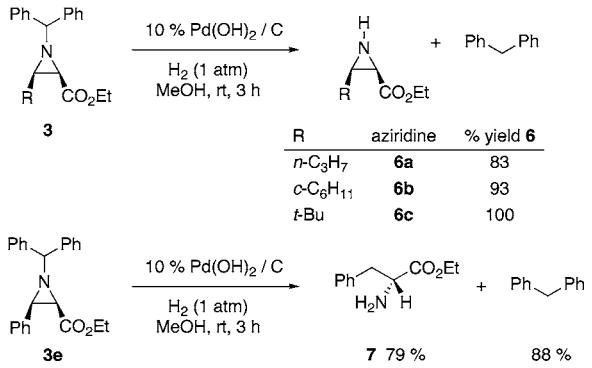
Scheme 1



(1) For a review and leading references, see: Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
(2) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.
(3) (a) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099. (b) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518. (c) Loncaric, C.; Wulff, W. D. *Org. Lett.* **2001**, *3*, 3675.
(4) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.
(5) Bacque, E.; Paris, J.-M.; Le Bitoux, S. *Synth. Commun.* **1995**, *25*, 803.

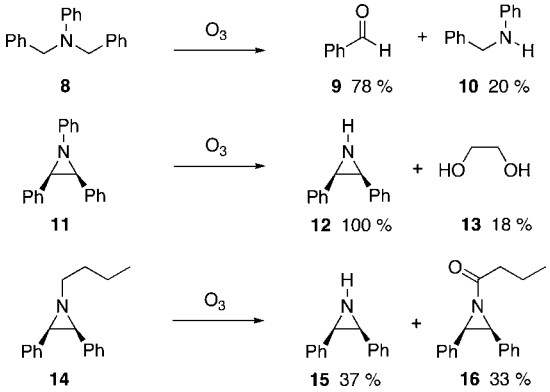
10.1021/ol050597t CCC: $30.25
Published on Web 05/07/2005

Scheme 2

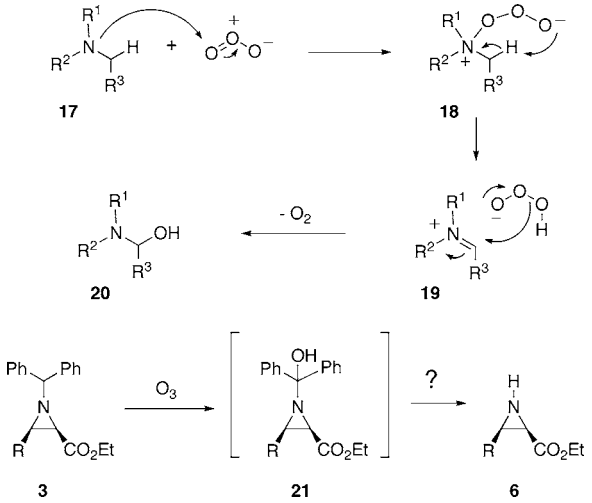


tertiary alkyl-substituted deprotected aziridines **6a**−**6c** in excellent yields. However, this protocol did not prove to be effective for the 3-phenyl-substituted aziridine **3e**. In this case, the deprotection occurs concomitant with the reductive opening of the aziridine to give the ethyl ester of phenylalanine in 79% yield.

Scheme 3

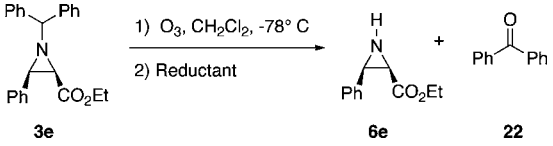


Scheme 4



In considering alternative strategies for the deprotection of 3-aryl-substituted azirdines of the type **3**, we were struck by the inertness of the aziridine ring system to ozone that was uncovered in the work of Ito and co-workers (Scheme 3).[7] They observed that the treatment of dibenzyl aniline with ozone only gave products that resulted from the cleavage of the benzyl groups. In direct contrast, *N*-phenyl aziridine **11** reacted with ozone to give the deprotected aziridine **12** in quantative yield. Clearly, the "benzylic" carbons in **11** are rendered inert to cleavage as a consequence of being in a three-membered ring. Even primary alkyl groups are oxidized in preference to the ring carbons, as evidenced by the ozonolysis of the *n*-butyl aziridine **14**, which gave the

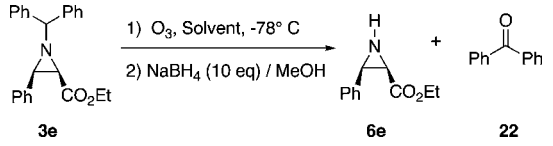
Table 1. Optimization of Reductant for Ozonolysis[a]



entry	reductant	% yield **6e**[b]	% yield **22**[b]
1	Me_2S	22	65
2	Zn/AcOH	42	75
3	DIBAL-H (1 equiv)	37	77
4	$NaBH_4$ (1 equiv) in MeOH	37	60
5	$NaBH_4$ (10 equiv) in MeOH	60[c]	77
6	$LiBH_4$ (10 equiv) in THF	43	82
7	PPh_3 (10 equiv)	47	73
8	H_2O	34	nd

[a] All reactions at 0.01 M in **3e**. [b] Isolated yields. [c] The yield varied from 54% to 60% over different runs. The use of 20 equiv of $NaBH_4$ did not improve the yield.

Table 2. Optimization of Solvent for Ozonolysis[a]

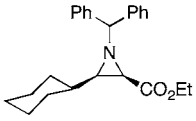
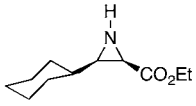
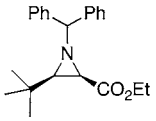
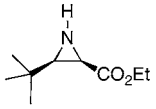
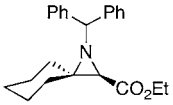
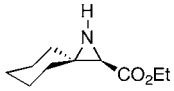
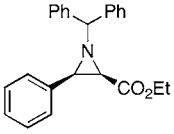
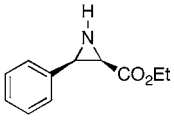
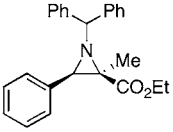
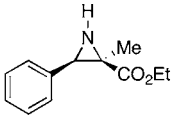
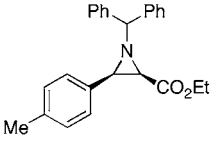
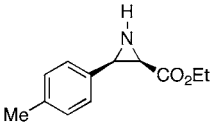
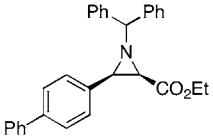
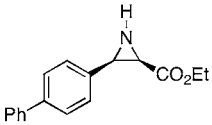
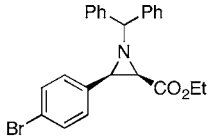
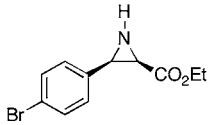


entry	solvent	% yield **6e**[b]	% yield **22**[b]
1	CH_2Cl_2	60	77
2	$CHCl_3$	59	80[c]
3	Et_2O		*d*
4	THF		*d*
5	MeOH	53	78
6	EtOH	39	74
7	EtOAc	57	82

[a] All reactions at 0.01 M in **3e**. [b] Isolated yields. [c] Reaction at −55 °C. [d] No conversion. In THF butyrolactone was formed.

(6) Bernotas, R. C.; Cube, R. V. *Synth. Commun.* **1990**, *20*, 1209.
(7) Ito, Y.; Ida, H.; Matsuura, T. *Tetrahedron Lett.* **1978**, 3119.

Table 3. Deprotection of 3-Alkyl and 3-Aryl-*N*-benzhydrylaziridine-2-carboxylate Esters[a]

substrate		product		% yield **6** [b]	% yield **22** [b]
3b		**6b**		60	77
3c		**6c**		55	81
3d		**6d**		40	80
3e		**6e**		60	77
3f		**6f**		50	78
3g		**6g**		51	80
3h		**6h**		60	77
3i		**6i**		40	78

[a] All reactions were in CH_2Cl_2 at −78 °C for 3 h and were quenched with 10 equiv of $NaBH_4$ in MeOH (0.2 M) at −78 °C. [b] Isolated yields.

aziridine **15** and the aziridinyl amide **16**. In this case, oxidation of the intermediate aminal competes with cleavage to the N-H aziridine.

The mechanism thought to account for the oxidation of aliphatic amines with ozone is presented in Scheme 4.[8] Attack of the amine on the ozone gives the zwitterionic intermediate **18**, which then ionizes to give the iminium/hydrozonide ion pair. Loss of oxygen and then recombination of the resulting new ion pair gives the aminal **20**. In the case of the *N*-butyl aziridine **14**, oxidation of aminal **20** competes with the formation of the free amine. In the case of *N*-benzhydryl aziridines **3**, the second oxidation to an *N*-acylaziridine would not be possible and thus cleavage to the N-H aziridine should be a more efficient process.

The initial study was on the ozonolysis of the 3-phenylaziridine **3e** in methylene chloride. The yield of the deprotected aziridine **6e** proved to be very dependent on the reductant used to quench the reaction. A survey of various reductants that are commonly used in ozonolysis reactions is presented in Table 1. The optimal quench of the reaction was found with 10 equiv of sodium borohydride in methanol, which gave **6e** in 60% yield. The yield was only 37% with 1 equiv of sodium borohydride, and no increase in yield was observed when 20 equiv was used. No silica gel mobile products were noted in these reactions other than the aziridine **6e**

(8) Bailey, P. S.; Carter, T. P., Jr.; Southwick, L. M. *J. Org. Chem.* **1972**, *57*, 2997.

and benzophenone, which was isolated in consistently higher yields than aziridine **6e** under all conditions in Table 1.

Typically chlorinated solvents are used in ozonolysis reactions.[9] However, there are reports of ozonolysis carried out in ethereal solvents,[10] ethyl acetate, and alcoholic solvents.[11] Thus we decided to screen a number of different solvents for the deprotection of aziridine **3e**, and the results are shown in Table 2. There was not a big difference between chlorinated solvents and ethyl acetate and methanol, but the ethereal solvents did not give any of the N-H aziridine **6e**. The *N*-benzhydryl aziridine **3e** did not undergo any conversion in these solvents. The ethereal solvents were very reactive toward ozone, and in the case of THF the product of this reaction was butyrolactone.

The optimum conditions of the deprotection of aziridine **3e** was thus to perform the reaction in methylene chloride at −78 °C and then to quench the reaction with 10 equiv of sodium borohydride in methanol, which gives the N-H aziridine **6e** in 60% yield. No other nitrogenous products were observed. The rest of the mass balance was suspected to be further oxidation of the N-H aziridine **6e**. In an effort to generate a more stable aziridine, the reaction was quenched with benzoyl chloride. However, no *N*-benzoylaziridine was observed and this reaction mixture was quite complex. In a more direct test of the stability of the product to the ozonolysis conditions, a pure sample of the N-H aziridine **6e** was subjected to the ozonolysis procedure and much to our surprise this aziridine was recovered in 95% mass balance. This indicates that the product aziridine is not being destroyed after it forms in the reaction mixture. At this point, we do not know the source of the missing mass balance.

The generality of the deprotection of *N*-benzhydryl aziridine by this ozonolysis procedure was explored with several other substrates, and the results are presented in Table 3. As the data reveal, the procedure is general for a 3-alkyl- and 3-aryl-substituted aziridines and with 3,3-disubstituted and 2,2-disubstituted aziridines as well. Although the yields are only moderate for all of the aziridines that were screened, this procedure is the only method we have found to date that will allow for the deprotection of an *N*-benzhydryl aziridine that has an aryl substituent. Essentially no optical activity is lost in the deprotection since a sample of **3e** of 98% ee gave **6e** of 97% ee. Thus, this procedure increases the utility of the *N*-benzhydryl aziridines that are produced in the asymmetric catalytic aziridination reaction.

Acknowledgment. This work was supported by the National Institutes of Health (GM 63019). The authors would like to thank Prof. Robert.Maleczka from the department of chemistry at Michigan State University for his generous help in giving access to the ozonolysis equipment and to the Michigan State University's Mass Spectrometry facility.

Supporting Information Available: Experimental procedures and characterization of compounds **6a**−**6i**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050597T

(9) Henry, H.; Zador, M.; Fliszar, S. *Can. J. Chem.* **1973**, *51*, 3398.
(10) Murry, R. W.; Su, J.-S. *J. Org. Chem.* **1983**, *48*, 817.
(11) Habib, R. M.; Chiang, C.-Y.; Bailey, P. S. *J. Org. Chem.* **1984**, *49*, 2780.