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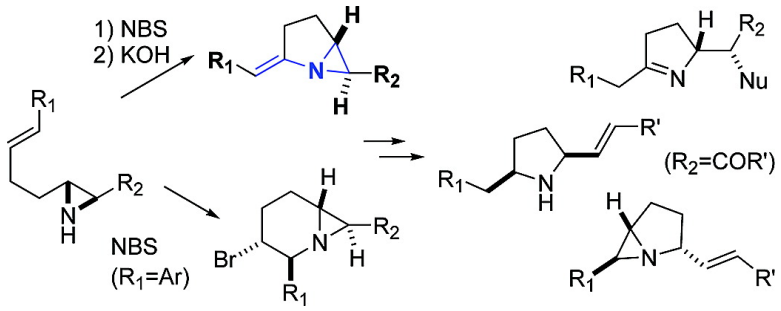

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Oxidative Cycloamination of Olefins with Aziridines as a Versatile Route to Saturated Nitrogen-Containing Heterocycles

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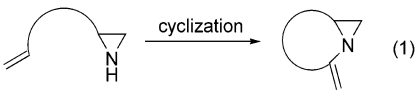
Selective transfer of nitrogen-containing fragments to readily available olefins is one of the fundamental ways of incorporating nitrogen atoms into the frameworks of organic molecules.[1] Our interest in synthetic applications of functionalized aziridines[2] has led to the investigation of their utility in the synthesis of larger nitrogen-containing heterocycles. Known for the difficulties in controlling their reactivity, aziridines are rarely used in complex molecule synthesis.[3] If functionalization of an aziridine-containing building block is required during synthesis, nitrogen protection and deprotection sequences are unlikely to be successful due to aziridines' susceptibility to acidic reagents and harsh reaction conditions.

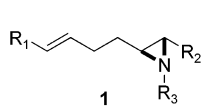
We reasoned that despite its basic character, aziridine nitrogen should be quite resistant to oxidative degradation so that transformations of aziridine-containing building blocks can be realized. At the outset of our investigations, we had observed a significant (0.8 V) difference in the oxidation potential of cyclohexene imine compared to the value recorded for a typical secondary amine such as piperidine, known for its low stability toward oxidation.[4] This finding can be explained on the basis of thermodynamically uphill formation of the iminium species in the case of aziridine oxidation, which opens a range of opportunities to explore the NH-containing aziridines in oxidative nitrogen transfer under nonacidic conditions.[5] Of particular value are intramolecular versions of such amination protocols (eq 1) because they should allow for straightforward syntheses of a wide range of larger ring heterocycles. The resulting enamine-containing compounds have not received attention in synthesis.



(1)

Toward this goal, aziridine-containing building blocks (**1a**−**e**, Figure 1) were synthesized from commercially available starting materials.[6] The NH portion of **1a**−**e** is separated from the olefin by the $(CH_2)_2$ linker, positioned toward cyclization to give pyrrolidine- and piperidine-containing heterocycles. The pyrrolidine and piperidine rings are incorporated into the structures of a wide range of natural products and pharmaceuticals, which makes them an important class of targets for stereoselective synthesis.[9] If relative stereochemistry of the products can be controlled during cyclization and subsequent ring-opening steps, the oxidative aziridine cycloamination methodology should be a valuable addition to the established methods.[10]

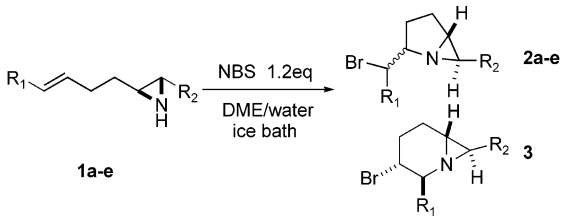
The double bond functionalization of **1a** can be achieved by the Heck reaction[6,7] or by the cross-metathesis.[6,8] In the case of metathesis, protection of the NH aziridine was found to be mandatory, whereas the Heck reaction took place on the parent NH system using $Pd(OAc)_2/P(o\text{-tolyl})_3$ catalyst. Our further studies revealed that aziridines **1a**−**e** are converted into 1-azabicyclo[3.1.0]hexane derivatives **2a**−**e** in good yields upon treatment with *N*-bromosuccinimide (NBS) in DME and water.[11] The TLC analysis indicated complete conversion of the NH aziridine to the corresponding N−Br species within the first 2 min of the reaction.[12] The bromoamine **1f** (Figure 1) thus formed attacked the double bond of the molecule to give the cycloamination product. Table 1 shows the scope of the reaction. The products are [5,3] bicyclic rings in the case of the terminal double bond-containing substrates, whereas aryl-substituted double bonds preferentially give six-membered-ring products.



1a : R_1=H, R_2=PhCO, R_3=H
1b : R_1=Me, R_2=PhCO, R_3=H
1c : R_1=CH_2OH, R_2=PhCO, R_3=H
1d : R_1=Ph, R_2=PhCO, R_3=H
1e : R_1=H, R_2=PhCH(OH), R_3=H
1f : R_1=H, R_2=PhCO, R_3=Br

Figure 1. Aziridine-Containing Building Blocks.

Table 1. Intramolecular Cycloamination of Olefins



entry	R_1	R_2	product[a]	yield[b]
1	H	PhCO	**2a**	76
2	Me	PhCO	**2b**	51
3	CH_2OH	PhCO	**2c**	54
4	Ph	PhCO	**3**[c]	67
5	H	PhCH(OH)	**2e**	55

[a] Structures were determined by NMR analysis (NOE, HMBC, and COSY). [b] The diastereomeric ratios were as follows: for **2a**, 41:59; for **2b**, 33:67; for **2c**, 33:67; for **3**, 19:81. [c] 23% of **2d** was also isolated.

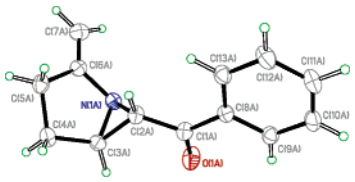


Figure 2. X-ray Structure of Bicyclic Aziridine **4a**.

The resulting bicycles **2a**−**b** were converted into exo-methylene bicyclic aziridines **4a**−**b** in quantitative yields by dehydrobromination (eq 2). We attribute surprisingly high stability of the resulting enamines to the orthogonal orientation of the nitrogen electron pair in relation to the double bond, evident from the single crystal X-ray analysis (Figure 2). The X-ray data shows that the bond length between C(6A) and C(7A) is 1.32 Å, which is typical of an olefin

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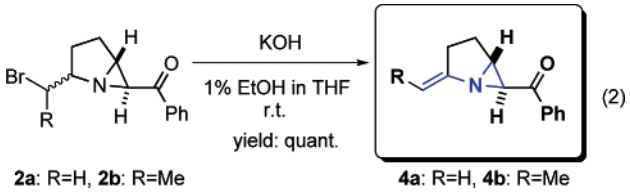
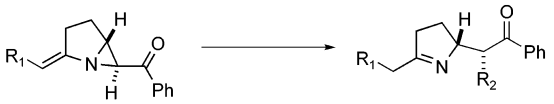


(2)

system. Worthy of note, this interesting and uncommon structural motif is present in the azinomycin family of antibiotics.[13]

Table 2. Ring Opening Reactions of Bicyclic Aziridines **4**



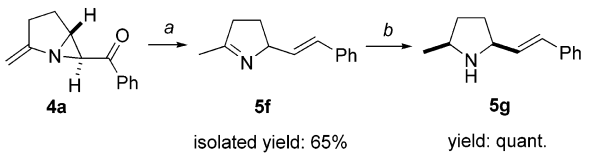
entry	R_1	condition	R_2	yield
1	H	$TMSN_3$ 2 equiv, H_2O 10 equiv, DCM, r.t.	N_3	99
2	Me	$TMSN_3$ 2 equiv, H_2O 10 equiv, DCM, r.t.	N_3	95
3	H	HBF_4 1.5 equiv, MeOH, r.t.	OMe	65
4	H	AcOH 5 equiv, DCM, r.t.	OAc	73
5	H	10% Pd/C (0.1 wt %), H_2	H	99

The bicyclic aziridines **4a**−**b** possess considerable synthetic potential because of the enamine-like aziridine ring that can be transformed into an imine/enamine system upon ring opening. The ring-opening reactions were found to proceed with high yields and excellent diastereoselectivities. The reactions are regioselective and afford the corresponding pyrrolidine derivatives. The resulting enamines are in situ tautomerized into cyclic imines. The reductive ring opening of aziridine **4a** by hydrogen on Pd/C gives five-membered cyclic imine in excellent yield (Table 2, entry 5).

Aziridine ring opening was also triggered under the reductive conditions. Upon treatment with hydrazine, valuable 2-allylamine derivatives can be obtained in good yields (Scheme 1). The resulting cyclic imines can be readily reduced to pyrrolidines using DIBAL-H. For example, **5f** was reduced to *cis*-2,5-disubstituted pyrrolidine **5g** in excellent yield and diastereoselectivity (Scheme 1). The 2,5-disubstituted fragments similar to **5g** are often seen in natural products, for example, in pinidine.[14]

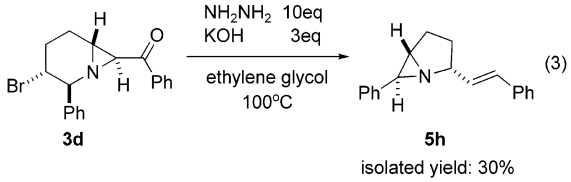
The reactions of [6,3] bicyclic aziridine **3** were also investigated under hydrazinolysis conditions. The presence of endocyclic bromine substituent in compound **3** suggested further relay of the aziridine functionality within the bicyclic ring system. Under the hydrazinolysis conditions, compound **3d** was converted into bicyclic aziridine **5h**, another valuable precursor to functionalized pyrrolidines, via ring-opening reaction followed by a ring closing step (eq 3).

Scheme 1. Hydrazine Reduction of Bicyclic Aziridine **4a**



[a] NH_2NH_2 10 equiv, KOH 3 equiv, ethylene glycol, 100 °C. [b] DIBAL 3 equiv, toluene, −78 °C.

In summary, we have shown that versatile chemistry of functionalized bicyclic aziridines enables rapid construction of a variety



(3)

of heterocyclic products with high levels of stereocontrol. Notably, the starting materials can be prepared in enantiomerically pure form using the Julia−Colonna epoxidation reaction followed by epoxide conversion into aziridine.[15] The cycloanimation strategy should be a valuable addition to existing methods for the construction of substituted pyrrolidines and piperidines, especially since stereocontrol still poses significant challenges with known methods. Transition metal-catalyzed versions of these reactions are under investigation.

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Supporting Information Available: Experimental procedures and characterization data for all unknown compounds (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000.
(2) (a) Siu, T.; Yudin, A. K. *J. Am. Chem. Soc.* **2002**, *124*, 530. (b) Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 2597. (c) Sasaki, M.; Dalili, S.; Yudin, A. K. *J. Org. Chem.* **2003**, *68*, 2045. (d) Watson, I. D. G.; Yudin, A. K. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 906.
(3) For use of aziridines in complex molecule synthesis, see: Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
(4) For a one-electron process, the 0.8 V anodic shift corresponds to the 18 kcal/mol increase in oxidative stability.
(5) Iminium ions are known to form during secondary amine oxidation processes: Gilchrist, T. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, p 735.
(6) See Supporting Information for experimental details.
(7) Heck, R. F. *Palladium Reagents in Organic Syntheses*; Academic Press: London, 1985.
(8) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
(9) For example, see: (a) Dewick, P. M. *Medicinal Natural Products*: *A Biosynthetic Approach*; Wiley & Sons: Chichester, U.K., 1997; Chapter 6. (b) Hagan, D. O. *Nat. Prod. Rep.* **2000**, *17*, 435.
(10) For reviews, see: (a) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862 and references therein. (b) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927 and references therein. (c) Higasio, Y.; Shoji, T. *Appl. Catal., A* **2001**, *221*, 197. For the synthesis of [5, 3] bicyclic aziridines, see: (d) Coleman, R. S.; Kong, J.-S.; Richardson, T. E. *J. Am. Chem. Soc.* **1999**, *121*, 9088. (e) Mulzer, J.; Becker, R.; Brunner, E. *J. Am. Chem. Soc.* **1989**, *111*, 7500. (f) Guillemin, J. C.; Denis, J. M. *Angew. Chem.* **1982**, *94*, 715. (g) Chaabouni, R.; Laurent, A.; Marquet, B. *Tetrahedron* **1980**, *36*, 877.
(11) Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5491.
(12) We were able to isolate and characterize the N−Cl-containing intermediate. See Supporting Information.
(13) (a) Nagaoka, K.; Matsumoto, M.; Ono, J.; Yokoi, K.; Ishizeki, S.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 1527. (b) Coleman, R. S.; Li, J.; Navarro, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 1736.
(14) Tallent, W. H.; Horning, E. C. *J. Am. Chem. Soc.* **1956**, *78*, 4467.
(15) For highly enantioselective Julia−Colonna epoxidation followed by conversion into aziridine, see: (a) Nemoto, T.; Ohshima, T.; Shibasaki, M. *Yuki Gosei Kagaku Kyokaishi* **2002**, *60*, 94 and references therein. For ring opening by azide and reductive ring closing to aziridine, see: (b) Jin, X. L.; Sugihara, H.; Daikai, K.; Tateishi, H.; Jin, Y. Z.; Furuno, H.; Inanaga, J. *Tetrahedron* **2002**, *58*, 8321−8329. (c) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, *30*, 4881−4.

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