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Synthesis of 3-Hydroxy and 3-Amino 2-Substituted *N*-Heterocycles *via* Enamine Oxidation and Aziridination

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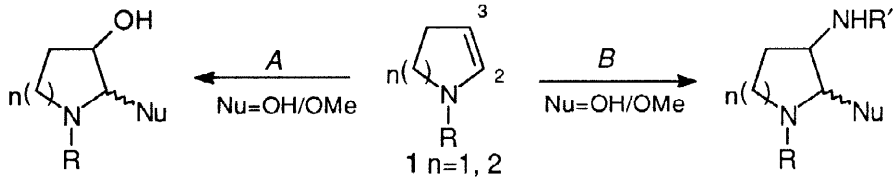
Abstract: Reaction of the *N*-sulfonyl heterocyclic enamines (**1a/b**) under asymmetric epoxidation and dihydroxylation reaction conditions leads to 2,3-dihydroxypyrrolidines and piperidines, (**2a**) and (**2b**). Only diols are observed under aminohydroxylation conditions, but Mn-mediated aziridination of (**1a**) provides a route to the 3-amino-2-methoxypyrrolidine derivatives (**6**) and (**7**).

The π-bond of *N*-substituted heterocyclic enamines (**1**, n=1,2) offers a versatile basis for elaboration to more highly substituted and functionalised pyrrolidines and piperidines respectively.[1] Oxidation processes involving (**1**) are especially attractive since this not only allows introduction of a heteroatom at *C(3)*, but by trapping of the resulting iminium intermediate with a nucleophile (water or an alcohol), retains valuable reactivity at *C(2)*.[2] The potential of this chemistry is aptly illustrated by the recent work of Correia[3] and, prompted by this publication, we disclose our own studies in this area. Like Correia, we have examined both epoxidation and dihydroxylation of (**1**) (*path A*, **Scheme 1**) and our results are presented here. We also have an interest in 3-aminopyrrolidines and piperidines and the amination of (**1**) *via* either aminohydroxylation or aziridination (*path B*, **Scheme 1**) has, in addition, been evaluated.



Scheme 1. *A = Epoxidation or dihydroxylation; B = Aminohydroxylation or aziridiniation*

Using the *N*-toluenesulfonyl derivatives (**1a**) and (**1b**), epoxidation has been carried out under Jacobsen's conditions[4] with NMMO/mCPBA as stoichiometric oxidants. Methanol work-up afforded the corresponding 3-hydroxy-2-methoxypyrrolidine and piperidine derivatives, (**2a**) (**2b**) respectively which were isolated as *cis/trans* mixtures.[5] Enantiomeric ratios (%e.e.) of (**2a**) and (**2b**) were determined by derivatisation of the alcohols as the corresponding Mosher ester.

Asymmetric dihydroxylation of (**1a**) and (**1b**) was examined under the Sharpless conditions[6] (using Admix-β). The crude diols (corresponding to (**3a**) and (**3b**) respectively - *see Scheme 2*) were then treated with methanol, in the presence of pyridinium tosylate (PyHTs), to give the 2-methoxy adducts (**2a**) and (**2b**)

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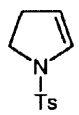
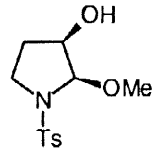
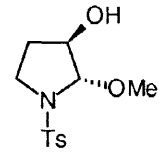
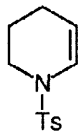
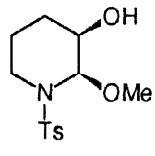
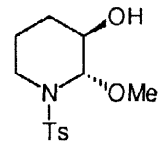
which were analysed as described above. Results for both asymmetric epoxidation and dihydroxylation of (**1a**) and (**1b**) are summarised in **Table 1**.

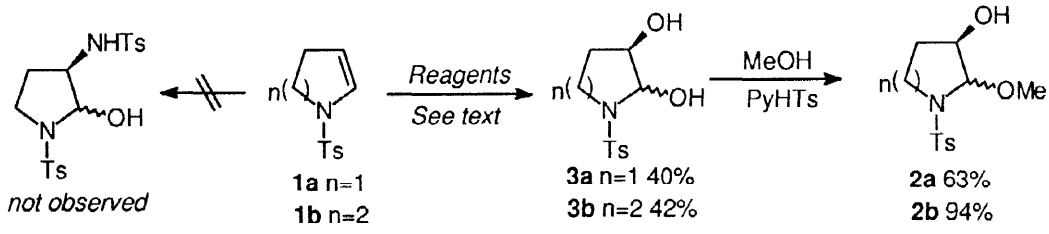
TABLE 1. Asymmetric Epoxidation and Dihydroxylation of (**1a**) and (**1b**).

Substrate	Products (%e.e.; % yield)[a]
 (**1a**)	 *cis*-(**2a**)  *trans*-(**2a**)
Jacobsen Epoxidation -78 °C	84 %e.e.; 46 % overall yield (*cis trans* = 1: 5.4)
25 °C	82 %e.e.; 21 % overall yield (*cis:trans* = 1 : 5.4)
Sharpless Dihydroxylation (0 °C)[b]	9 %e.e; 48 % overall yield (*cis:trans* = 1: 5.4)
 (**1b**)	 *cis*-(**2b**)  *trans*-(**2b**)
Jacobsen Epoxidation -78 °C	84 %e.e.; 28 % overall yield (*cis:trans* = 1: 1)
25 °C	62 %e.e.; 14 % overall yield (*cis:trans* = 1 : 1)
Sharpless Dihydroxylation (0 °C)[c]	28 %e.e; 83 % overall yield (*cis trans* = 1: 1)

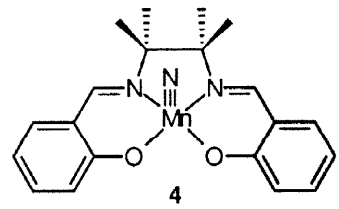
[a] *cis*- and *trans*-(**2a**) were analysed as a mixture but *cis*- and *trans*-(**2b**) were separated prior to analysis. Within each series [*cis*/*trans*-(**2a**) and *cis*/*trans*-(**2b**)], the %e.e. determined for the *cis* and *trans* isomers was the same (however, see ref. 3) and "overall yield" refers to the two-step oxidation+methanolysis; [b]initial product is (**3a**); [c]initial product is (**3b**). For the yields associated with (**3**) → (**2**), see Scheme 2.

Aminohydroxylation of electron rich alkenes raises interesting issues of reactivity and regioselectivity.[7] Asymmetric aminohydroxylation of (**1a**) and(**1b**) was evaluated again using the Sharpless procedure[8] (OsO_4, $(DHQD)_2PHAL$, chloramine-T, $MeCN/H_2O$) (**Scheme 2**). In the event, we have not been able to detect *C(3)* amination with the only products observed corresponding to the 2,3-diols (**3a**) and (**3b**); these were characterised by conversion to the methoxy adducts (**2a**) and (**2b**) respectively. These results suggest that either direct dihydroxylation of enamines is the favoured pathway or, if aminohydroxylation is occurring, then this places the sulfonamido residue at *C(2)* which undergoes nucleophilic exchange under the reaction conditions. The same level of asymmetric induction was observed for both dihydroxylation (Table 1) and attempted aminohydroxylation, however, this does not allow differentiation of these possible pathways.

Scheme 2. Attempted Asymmetric Aminohydroxylation of (**1a**) and (**1b**).



Formal aziridination of electron rich enol ethers has recently been reported by Carreira using the manganese nitrido complex (saltmen)Mn(N) (**4**).[9] It is not clear what intermediate(s) are involved in this process (e.g. an aziridine or bicyclic oxazoline) but translating the regioselectivity observed by Carreira to heterocyclic enamines opens an entry to the corresponding *racemic* 3-amino-2-methoxy derivatives.



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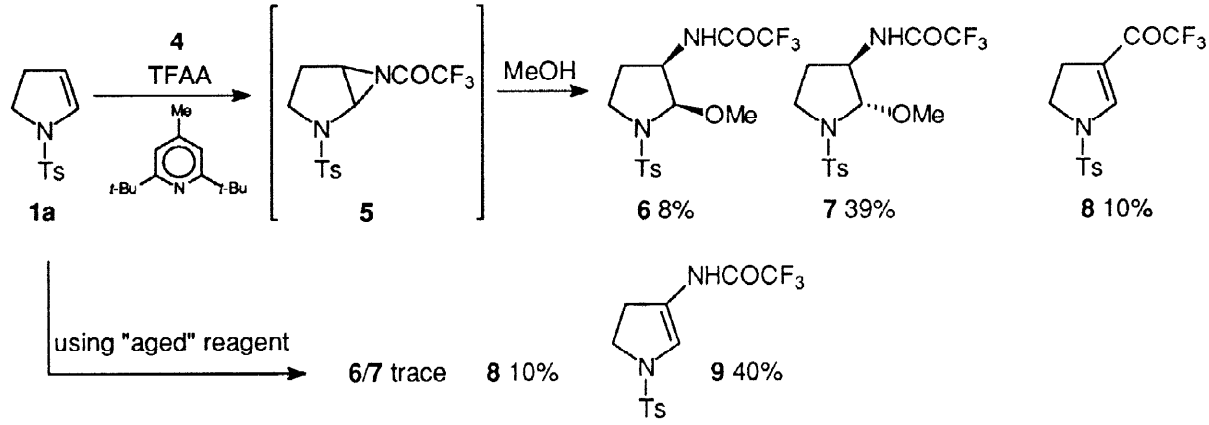
Exposure of (**1a**) to the Mn≡N complex (**4**)[9] (activated using TFAA, 2,6-di(*tert*-butyl)-4-methylpyridine, -78 °C to r.t., then addition of MeOH) gave a separable mixture of racemic *cis*- and *trans*-2-methoxy-3-*N*-(trifluoroacetyl)aminopyrrolidine derivatives (**6**) (8 %) and (**7**) (39 %) respectively, formation of which may be rationalised in terms of the intermediacy of aziridine (**5**) (**Scheme 3**). The structure of (**7**) has been confirmed by single crystal X-ray crystallographic analysis and the major by-product observed under these conditions was the trifluoroacetylated enamine (**8**) (10%); a control experiment showed that (**1a**) reacted with TFAA in the presence of 2,6-di(*tert*-butyl)-4-methylpyridine to give (**8**).[10] Attempts to suppress formation of (**8**) by "ageing" the aziridinating agent (allowing a longer period to complete the reaction between (**4**) and TFAA) were unsuccessful. Under these "aged" conditions, trace amounts of (**6**)/(**7**) were detected, with (**8**) (10%), but the major product was the 3-*N*-(trifluoroacetyl)amino enamine (**9**) (40%).

Scheme 3. Mn-Mediated Aziridination of Enamine (**1a**)



Control experiments[11] suggest that "ageing" the (**4**)/TFAA reagent results in a different, but as yet poorly defined species. Surprisingly, attempted aziridination of piperidine (**1b**) led only to the trifluoroacetylated enamine (the homologue of (**8**)) in 20% yield with "normal" reagent and 40% yield using "aged" reagent.

In summary, our studies support those of Correia[3] for the asymmetric epoxidation and dihydroxylation of heterocyclic enamines. Aminohydroxylation failed to introduce a *C(3)* amino residue, but this may be achieved using an aziridination pathway. This is the first time that this type of enamine aziridination has been described and, while requiring further study, this process offers potential as an alternative entry to the pyrrolidine *trans*-lactams, a recently disclosed class of protease inhibitors.[12]

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References and Notes.

1. For some recent synthetic applications of heterocyclic enamines see Shono, T.; Matsumura, Y.; Onomura, O.; Ogaki, M.; Kanazawa, T.; *J. Org. Chem.* 1987; **52**, 536. Nilsson, K.; Hallberg, A. *J. Org. Chem.* 1990, **55**, 2464. Van Broeck, P. I.; Van Doren, P. E.; Toppet, S. M.; Hoornaert, G. J. *J. Chem. Soc. Perkin Trans.1* 1992, 415. Ozawa, F.; Hayashi, T. *J. Organomet. Chem.* 1992, **428**, 267. de Faria, A. R.; Matos, C. R. R.; Correia, C. R. D. *Tetrahedron Lett.* 1993, **34**, 27. Grotjahn, D. B.; Vollhardt, K. P. C. *Synthesis* **1993**; 579.
2. The oxidation of enamines with dimethyl dioxirane has been reported: Burgess, L. E.; Gross, E. K. M.; Jurka, J. *Tetrahedron Lett.* 1996, **37**, 3255. Electrochemical oxidation has also been described: Matsumura, Y.; Takeshima, Y.; Okita, H. *Bull. Chem. Soc. Jpn.* 1994, **67**, 304.
3. Sugisaki, C. H.; Carroll, P. J.; Correia, C. R. D. *Tetrahedron Lett.* 1998, **39**, 3413. These authors indicate that different levels of asymmetric induction were associated with the *cis* and *trans* diol derivatives.
4. Palucki, M.; Pospisil, P. J.; Zhang, W.; J.; Jacobsen, E. N. *J. Am. Chem. Soc.* 1994, **116**, 9333. Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* 1995, **36**, 5457. Jacobsen, E. N. In Comprehensive Organometallic Chemistry II, Abel, E. W.; Stone, F. G. A.; Wilkinson, G., eds.; Pergamon: New York, 1996 Vol. 12, pp. 1097-1135.
5. The *cis* and *trans* isomers of (**2a**) could not be separated and were analysed as the mixture. The isomers of (**2b**) were separated prior to conversion to the corresponding Mosher esters, and in both series the corresponding racemates were prepared and used as standards.
6. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* 1992, **57**, 2768. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* 1994, **94**, 2483.
7. Asymmetric aminohydroxylation of silyl enol ethers, see Phukan, P.; Sudalai, A. *Tetrahedron: Asymmetry*, 1998, **9**, 1001.
8. Li, G.; Chang, H.-T. Sharpless, K. B. *Angew. Chem. Int, Ed. Engl.* 1996, **35**, 451.
9. Du Bois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* 1996, **118**, 915. Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* 1997, **119**, 3179. Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *Acc. Chem. Res.* 1997, **30**, 364. See also Groves, J. T.; Takahashi, T. *J. Am. Chem. Soc.* 1983, **105**, 2073.
10. (**6**): m.p. 118 °C (petrol/EtOAc) δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.3), 7.34 (2H, d, *J* 8.3), 6.74 (1H, br s, NH), 4.98 (1H, d, J 5.1 H-2), 3.78 (1H, m, H-3), 3.56 (3H, s, OMe), 3.56 (1H, m, H-5), 3.08 (1H, td, *J* 11.0 and 7.3, H-5), 2.46 (3H, s, Me), 2.26 (1H, m, H-4) and 1.92 (1H, qd, *J* 11.0 and 9.0, H-4); (**7**): m.p. 138 °C (petrol/EtOAc) δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.3), 7.34 (2H, d, *J* 8.3), 6.00 (1H, br s, NH), 5.30 (1H, s, H-2), 4.31 (1H, br t, *J* 6.5, H-3), 3.43 (3H, s, OMe), 3.49-3.37 (2H, m, H-5), 2.44 (3H, s, Me), 2.46 (1H, m, H-4) and 1.90 (1H, m, H-4). Clearly the [Mn=NCOCF$_3$] complex could also act as a trifluoroacetylating agent and may represent a source of (**8**). (**9**): δ_H (250MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.3), 7.34 (3H, m, incl. NH), 7.08 (1H, br t, *J* 2.1, H-2), 3.54 (2H, t, *J* 9.4, H-5) and 2.72 (2H, td, *J* 9.4 and 2.1, H-4). *Crystal data* for (**7**): $C_{15}H_{19}F_3N_2O_4S$, M = 388.4, triclinic, space group $P\bar{1}$, a = 10.432(2), b = 10.561(2), c = 18.594(3) Å, α = 83.054(10), β = 76.100(11), γ = 65.186(12) °, U = 1804.5(6) Å^3, Z = 4, D_c = 1.43 g cm^{-3}, μ = 0.234 mm^{-1}, 8144 unique data , $\theta < 27.4$ °, R_1 = 0.044.
11. "Normal" aziridination conditions involved addition of TFAA to a mixture of (**1a**), (**4**), and 2,6-di(*tert*-butyl)-4-methylpyridine in CH_2Cl_2 at -78 °C and the mixture was then allowed to warm to r.t. over 5 h prior to addition of MeOH(D). The "aged" reagent was generated by addition of TFAA to (**4**) and 2,6-di(*tert*-butyl)-4-methylpyridine in CH_2Cl_2 at -78 °C, then warming to 0 °C (over 2h). The mixture was then re-cooled to -78 °C and (**1a**) was added (over 2h *via* syringe pump) and the mixture was then warmed to r.t. over 4h, after which time MeOH(D) was added. Interestingly, when both "normal" and "aged" reactions were monitored by TLC, (**8**) and (**9**) were the major components observed. However, when these reactions were subsequently quenched with MeOD, (**6**) and (**7**) isolated contained no incorporation of deuterium at *C(3)*. This suggests *(i)* that (**9**) is not involved in the pathway leading to (**6/7**) (although the species present in solution appears to break down to (**9**) on TLC), *(ii)* the "aged" reagent is quite distinct to that produced under "normal" conditions and *(iii)* that two discreet amination pathways are available. We have been unsuccessful in converting (**9**) to (**6/7**) using MeOH and PyHTs (pyridinium tosylate) but thermolysis (PhMe, PyHTs, 100°C) of (**7**) gave (**9**) (20%) together with (**6**) (30%) and recovered (**7**) (15%).
12. The *trans* lactam-based protease inhibitors were discovered by GlaxoWellcome: Macdonald, S. J. F.; Belton, D. J.; Spooner, J. E.; Anson, M. S.; Harrison, L. A.; Mills, K.; Upton, R. J.; Dowle, M. D.; Smith, R. A.; Molloy, C.; Risley, C. *J. Med Chem.* in press.
13. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. J. *J. Chem. Inf. Comput. Sci.* 1996, **36**, 746.