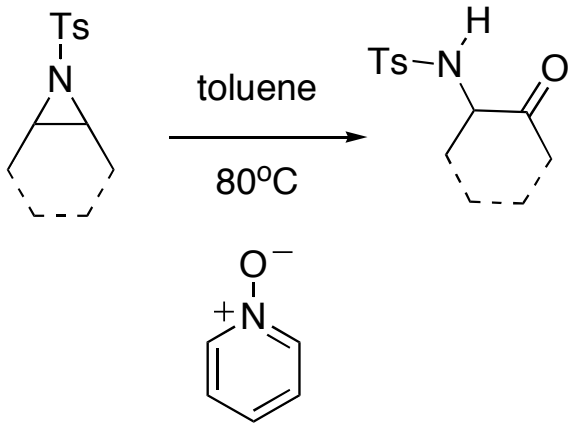
Facile preparation of α-amino ketones from oxidative ring-opening of aziridines by pyridine *N*-oxide

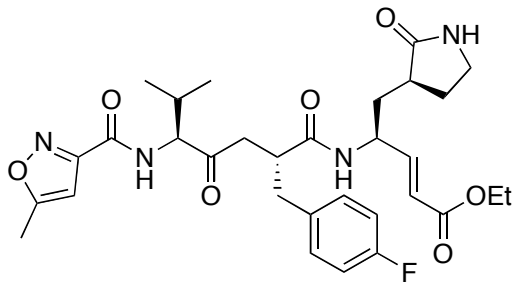
Org. Biomol. Chem., **2007**, *5*, 3428
Luo, Z.-B.; Wu, J.-Y.; Hou, X.-L.; Dai, L.-X.



John Maciejewski

Current literature
01/05/08

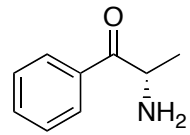
α-Amino ketones



Rupintrivir

Shown to treat symptoms assoc. with common cold

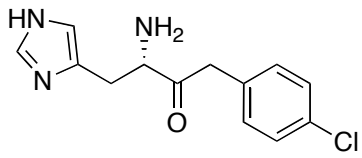
Tetrahedron: Asymmetry **2005**, *16*, 699



(*S*)-2-amino-1-phenylpropan-1-one

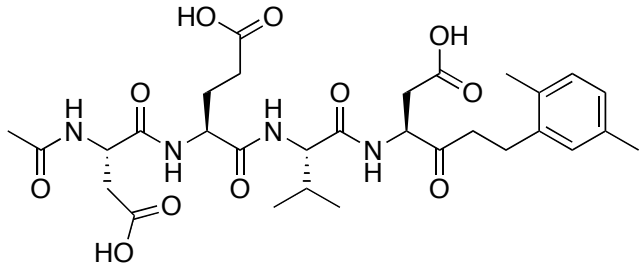
Natural product found in leaves of *Catha edulis* Forsk

J. Org. Chem. **1994,** *59,* 8288



Active against brucellosis (Malta fever)

AAC **2007**, *51*, 3752



K_i values

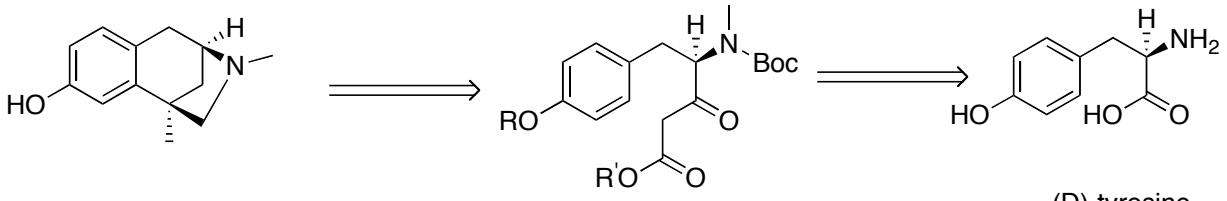
Caspase-3	Caspase-7
0.2 nM	4.0 nM

Potent caspase inhibitors

Org. Lett. **2005**, *7*, 3529

α-Amino ketone preparation

Often important synthetic intermediates



(-)-aphanorphin

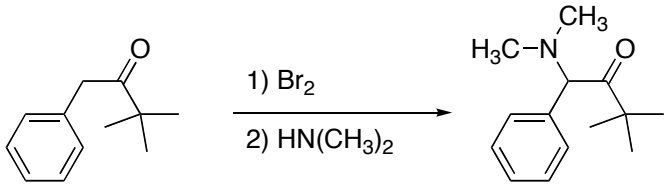
key synthetic intermediate

(D)-tyrosine

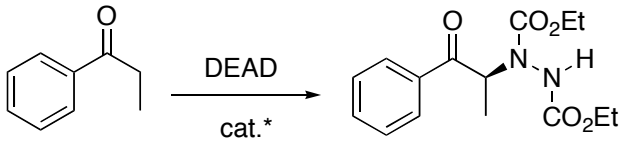
Synthesis **2007**, *1,* 55

Begin from chiral pool

Other methodologies include the following:



J. Het. Chem. **1984**, *21*, 1509

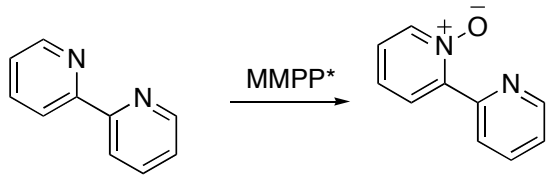


Org. Lett. **2007**, *9*, 3671

Cinchona alkaloids afford α–amino ketones in high enantioselectivity

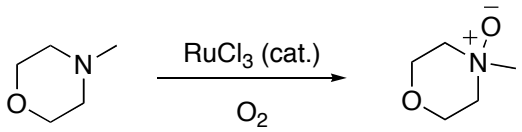
Preparation of *N*-oxides

Mild oxidants, easily prepared



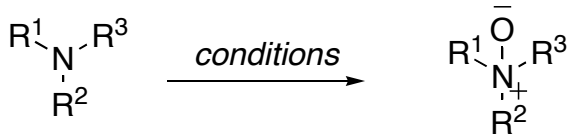
*magnesium monoperoxyphthalate

J. Org. Chem., **2007**, *72, 6653*

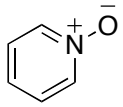


Chem. Commun., **2002**, 1040

Other methods of *N*-oxide preparation include use of peracids, H_2O_2, and O_2 with catalysts



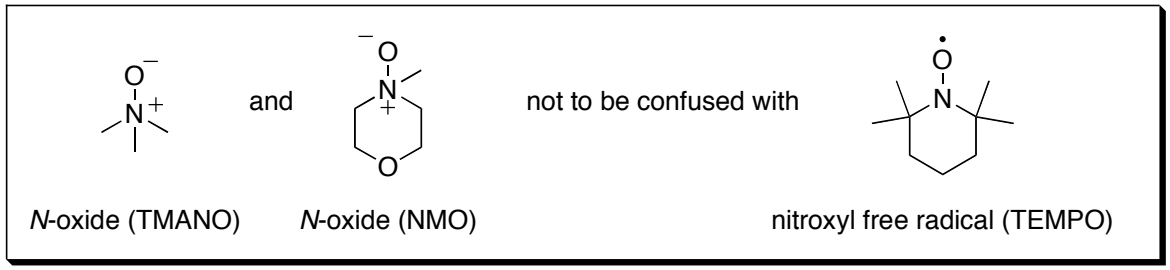
Synthesis **1993**, *3*, 263 (and references therein)

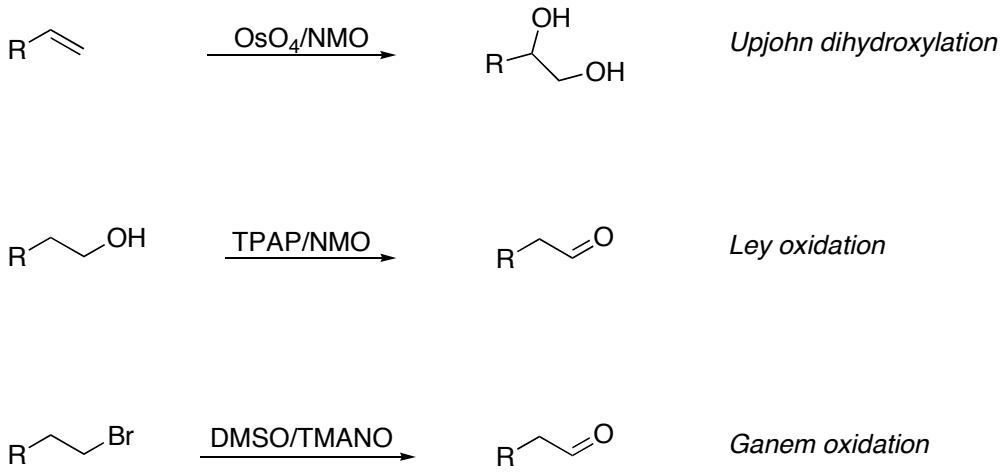


~71 kcal/mol

J. Chem. Thermodynamics **1995**, *27*, 391

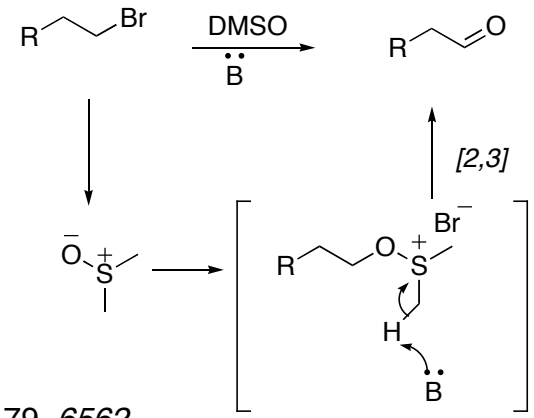
Applications for *N*-oxides





N-oxides used to regenerate transition metal catalysts

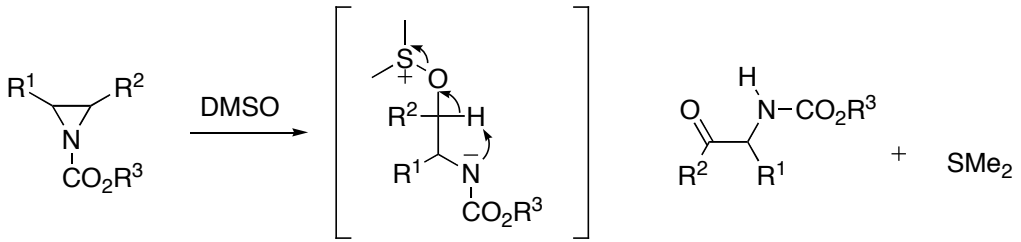
Applications for oxides of sulfur



Kornblum oxidation

J. Am. Chem. Soc., ***1957****,* 79*, 6562*

Applications with aziridines



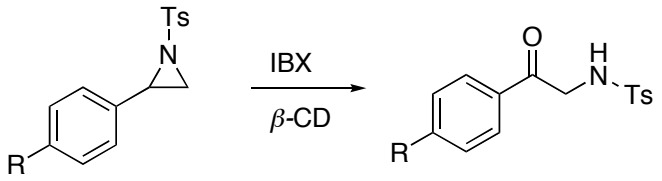
Tetrahedron **1970**, *26*, 4347

Aziridine opened with DMSO, followed by loss of SMe_2 to afford amino ketone

Drawbacks: DMSO is often difficult to remove, in addition to noxious byproduct (SMe_2)

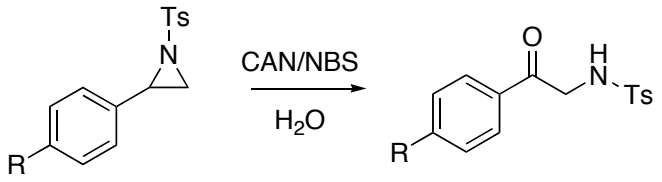
Oxidative ring-opening of aziridines

Recent advances



J. Org. Chem., **2003**, *68*, 9119

IBX promotes amino ketone formation, which is facilitated by β-CD

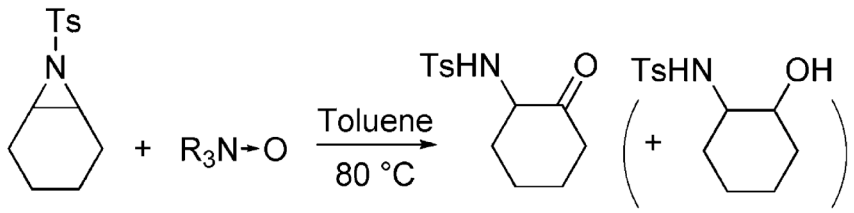


Tetrahedron Lett., **2005**, *46*, 4111

The CAN/NBS system allows selective oxidation to the amino ketone

Oxidative ring-opening of aziridines

Org. Biomol. Chem., **2007**, *5*, 3428.



Initial investigations tested 1-10 equiv. of DMSO in CH_2Cl_2, THF, MeCN, benzene, EtOAc, and Et_2O

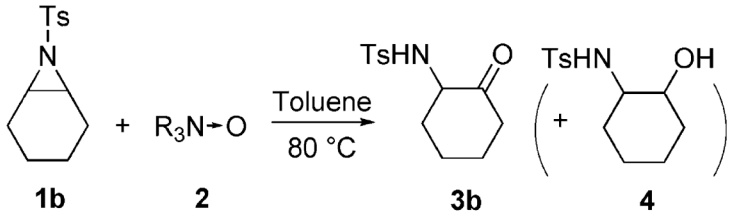
Investigations using pyridine *N*-oxide (1.2 equiv.) DMF at 80°C provided the desired α-amino ketone in 60% yield

Toluene at 80°C proved to give best results (70-80% yields)

Increasing oxidant loading to 2-3 equiv. did not improve yields

Oxidative ring-opening of aziridines

Table 1 Oxidative ring opening of aziridine **1b** with different amine oxides[a]



1b **2** **3b** **4**

Entry	Amine *N*-oxide **2**	Time/h	Yield of **3b** (%)
1	Pyridine *N*-oxide	24	76
2	4-Methoxypyridine *N*-oxide	5	75
3	4-Acetylpyridine *N*-oxide	40	Trace
4	3-Methylpyridine *N*-oxide	15	62
5	Collidine *N*-oxide	24	41
6	Quinoline *N*-oxide	15	60
7	Me_3N *N*-oxide	4	22[b]
8	*N*-Morpholine *N*-oxide	5	14[b]

[a] Run at 80 °C in toluene using 1.2 eq. of amine oxide. [b] 60% yield of product **4** was also separated.

Electron donating pyridines accelerated reaction, but did not increase yield

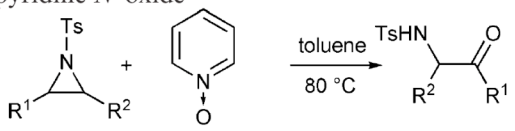
Electron withdrawing pyridines resulted in trace product after 40 h

Sterically hindered substrates such as collidine gave low yields

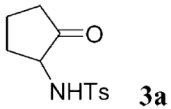
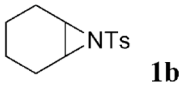
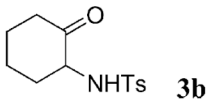
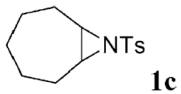
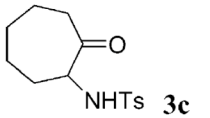
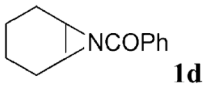
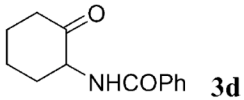
Aliphatic amines gave low yields of α-amino ketones, with undesired amino alcohol in moderate yields

Oxidative ring-opening of aziridines

Table 2 Oxidative ring-opening of aziridines using pyridine *N*-oxide[8]



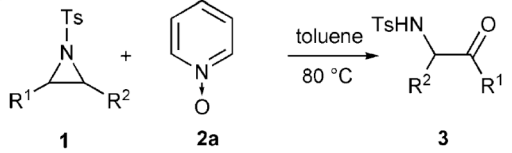
1 2a 3

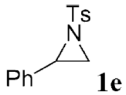
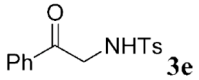
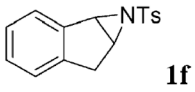
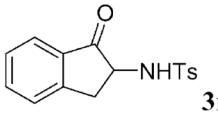
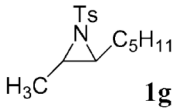
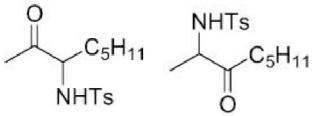
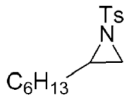
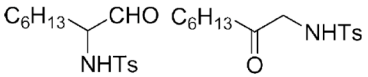
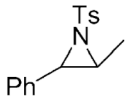
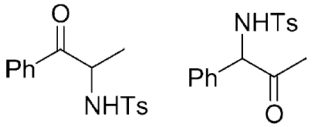
Entry	Aziridine	Time/h	Product	Isolated yield (%)
1	 **1a**	24	 **3a**	77
2	 **1b**	48	 **3b**	76
3	 **1c**	64	 **3c**	Trace
4	 **1d**	12	 **3d**	80

Oxidation proceeds in good yields with 5- and 6-membered rings

Oxidative ring-opening of aziridines

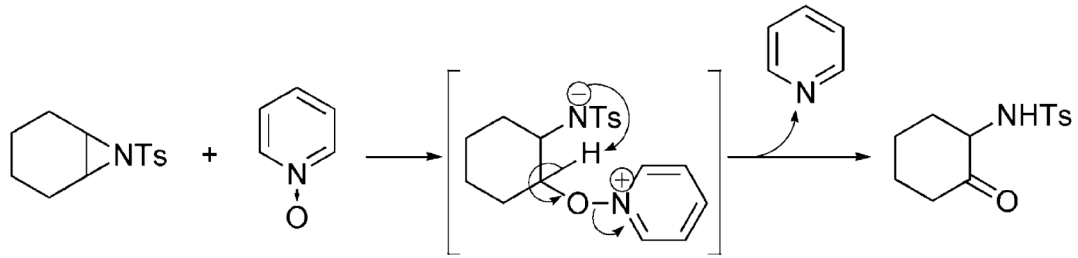
Table 2 Oxidative ring-opening of aziridines using pyridine *N*-oxide[8]



Entry	Aziridine	Time/h	Product	Isolated yield (%)
5	 **1e**	10	 **3e**	40
6	 **1f**	10	 **3f**	55
7[a]	 **1g**	20	 61 : 39 **3g** **3g´**	74
8[a]	 **1h**	24	 60 : 40 **3h** **3h´**	20
9[a]	 **1i**	24	 81 : 19 **3i** **3i´**	82

Oxidative ring-opening of aziridines

Mechanism of oxidation



1b **2a** **A** **3b**

Mechanism explains formation of amino ketone, but not amino alcohol.

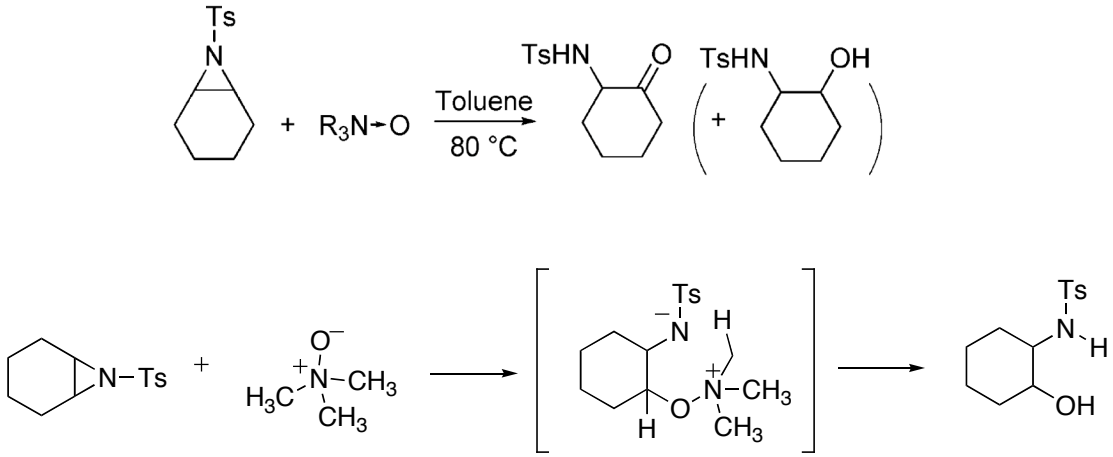
Aliphatic amine oxides provide low yields of desired amino ketone, but moderate yields of amino alcohol

7	Me_3N *N*-oxide	4	22[b]
8	*N*-Morpholine *N*-oxide	5	14[b]

[a] Run at 80 °C in toluene using 1.2 eq. of amine oxide. [b] 60% yield of product **4** was also separated.

Oxidative ring-opening of aziridines

Proposed mechanism of oxidation



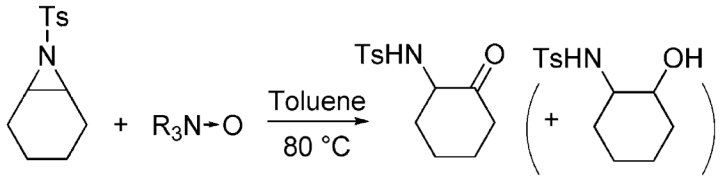
Aliphatic amine oxides have acidic hydrogen, where pyridine *N*-oxides do not

Authors did not address (or reference) the mechanism for the formation of amino alcohols

Interesting method for preparing amino alcohols

Summary and Conclusions

Oxidative ring-opening of aziridines



Pyridine *N*-oxides are efficient reagents for the oxidative ring-opening of aziridines

The desired α-amino ketones were obtained in good yields on various substrates

Aliphatic *N*-oxides primarily afford the amino alcohol over the α-amino ketone

Future work includes the development of an asymmetric version (chiral amines?)