Stereoselective Synthesis of *N*-Alkylaziridines from *N*-Chloroamines

Bew, S. P.; Hughes, D. L.; Palmer, N. J.; Savic, V.; Soapi, K. M.; Wilson, M. A. *Chem. Commun*. **2006**, 4338-4340

Presented by:
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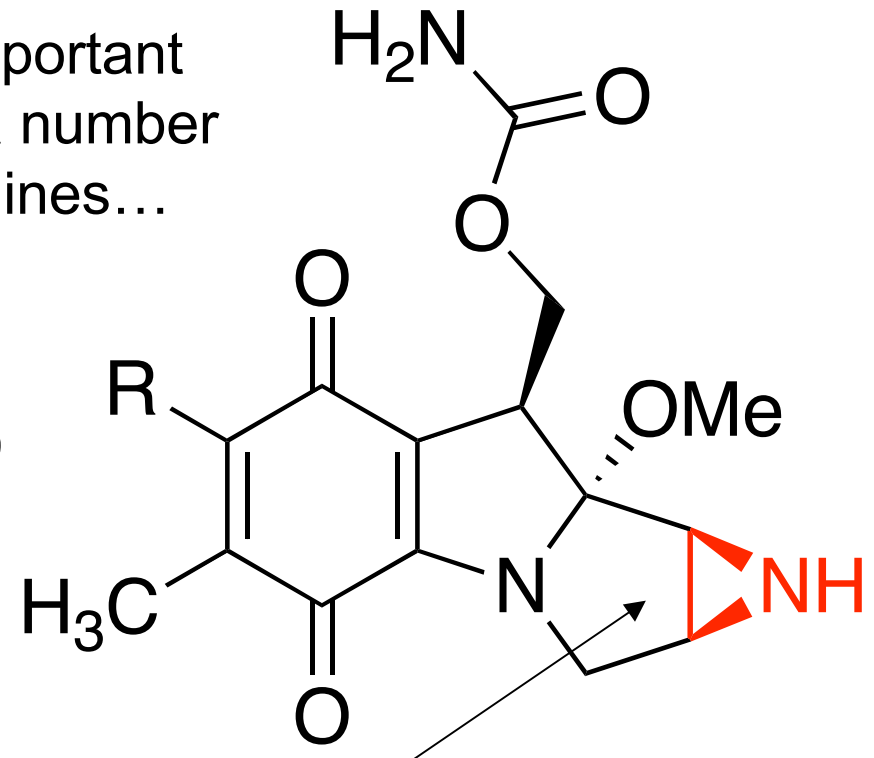
Wipf Group
University of Pittsburgh
October 28, 2006

Naturally Occurring Aziridines

In addition to serving as important building blocks, there are a number of naturally occurring aziridines…

Mitomycin A (R=OCH_3)
Mitomycin C (R=NH_2)

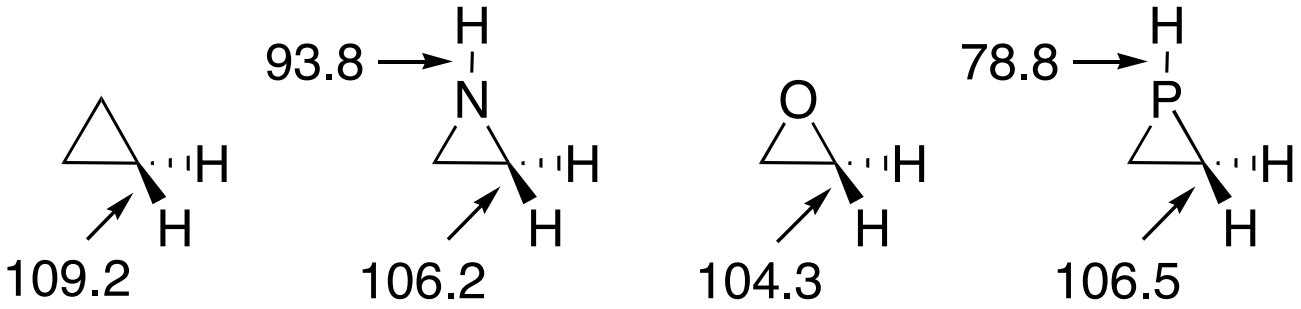
antitumor agents



Aziridine typically constructed via intramolecular displacement

Physical Properties of Aziridine

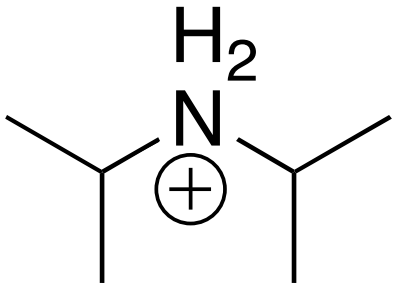
BDE:
kcal/mol (G3)

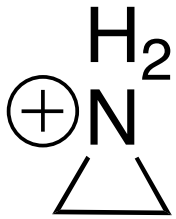


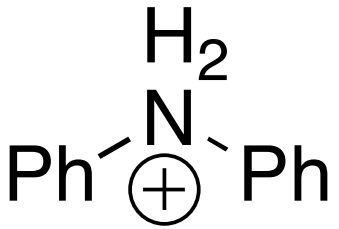
Calculated SE: kcal/mol (G3)	27.8	27.0	25.7	23.1
experimental:	(27.5)			

JACS, **2006**, *128*, 4598.

Basicity of Aziridine



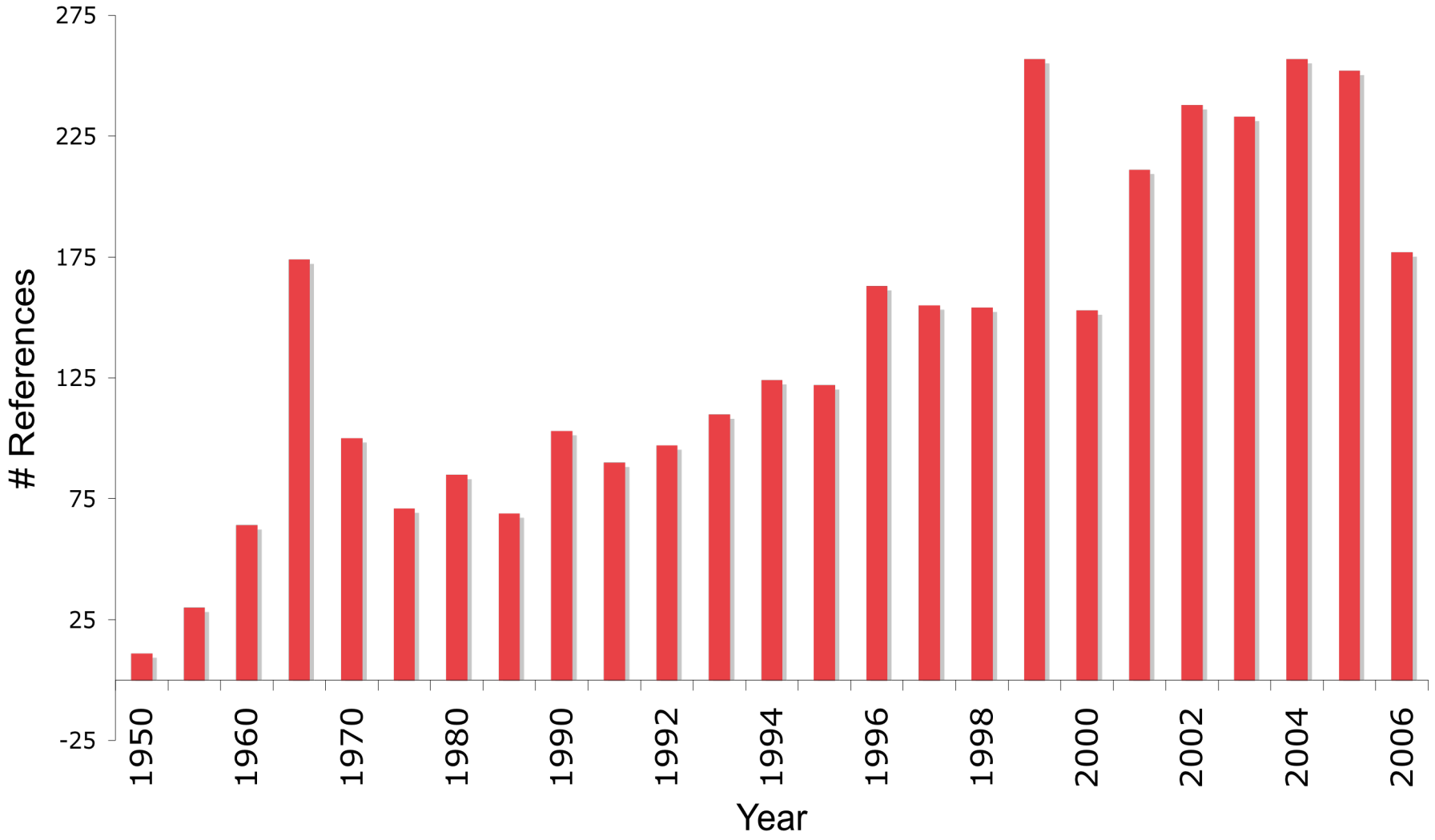




pKa: (H_2O)	11.05	7.98	0.78

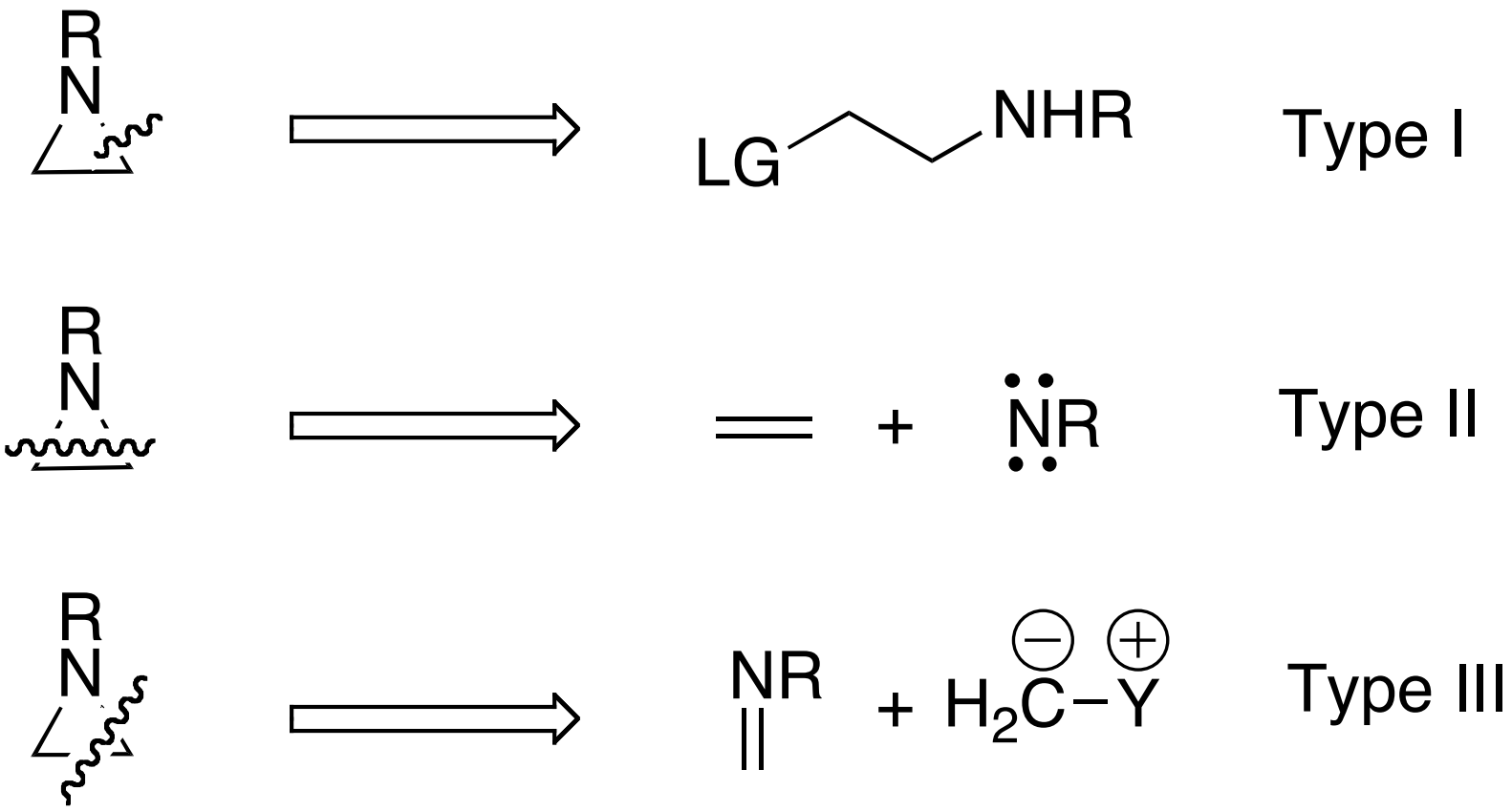
The Chemistry of Heterocycles, Eicher, T. and Hauptmann, T. 1995.
http://ccc.chem.pitt.edu/wipf/MechOMs/evans_pKa_table.pdf

Aziridine Synthesis Papers / Year

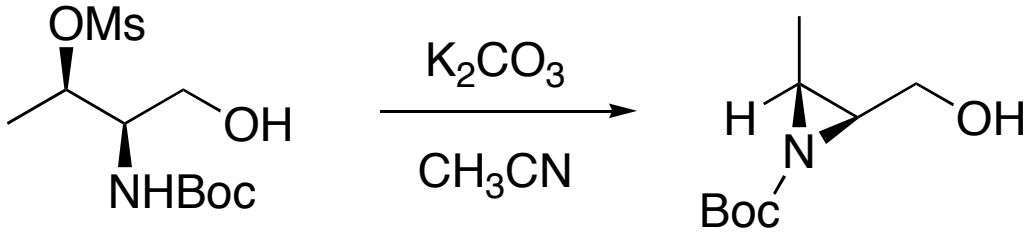


SciFinder Scholar

Typical Aziridine Disconnections

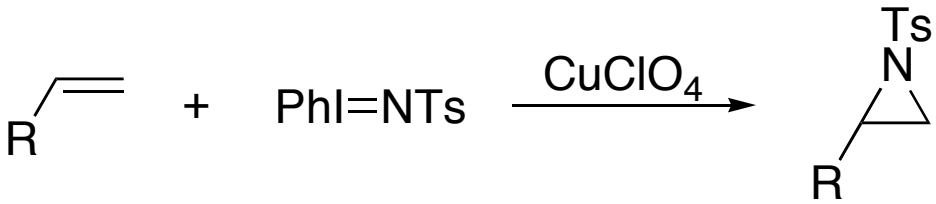


Examples of Aziridinations



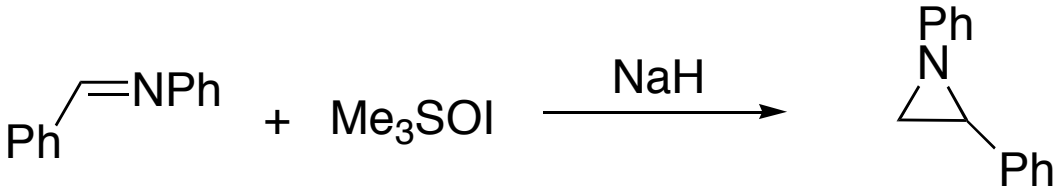
Type I

Wipf, et. al. *J. Org. Chem.* **1994**, *59*, 4875.



Type II

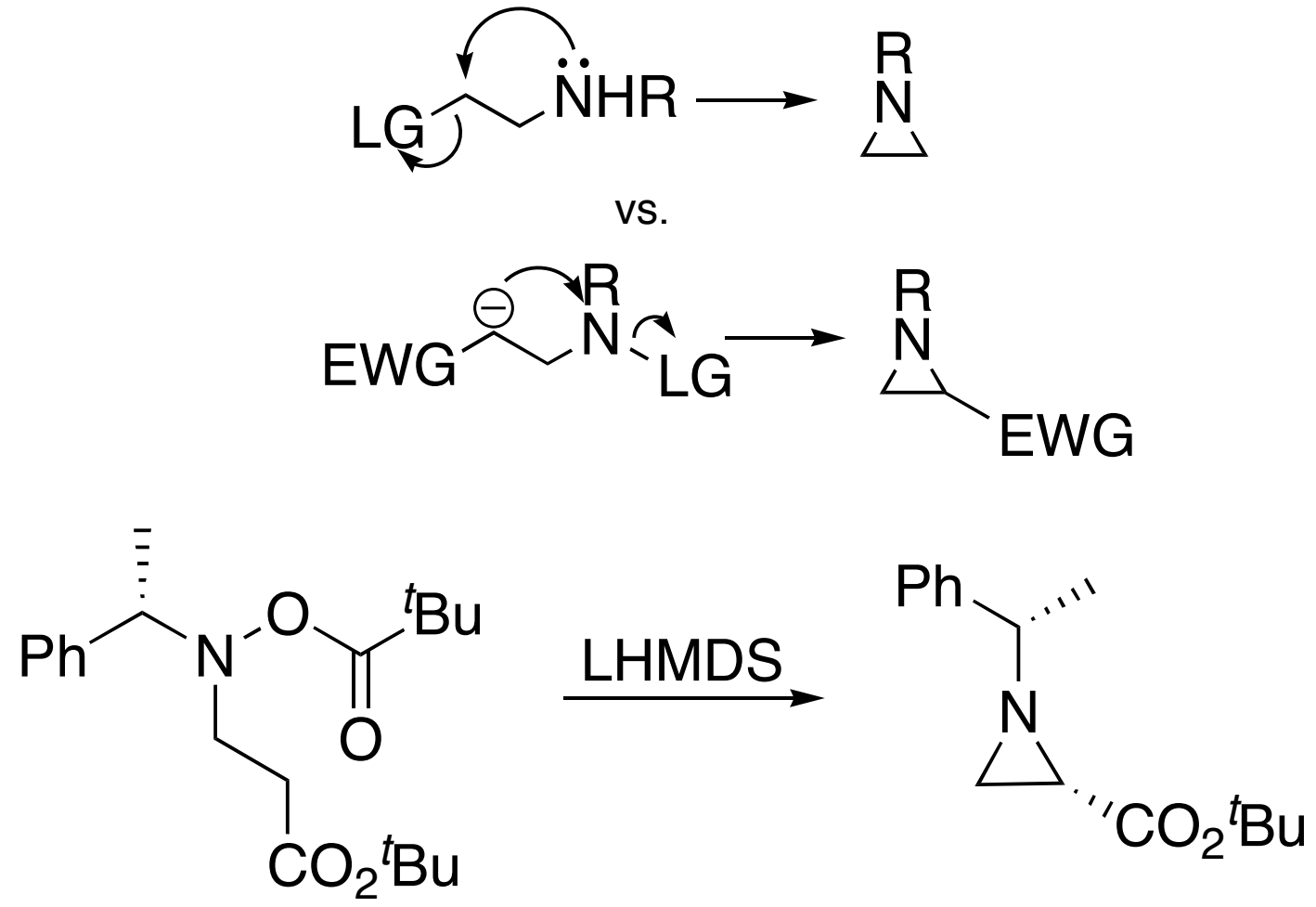
Evans, et. al. *J. Am. Chem. Soc.* **1994**, *116*, 2742



Type III

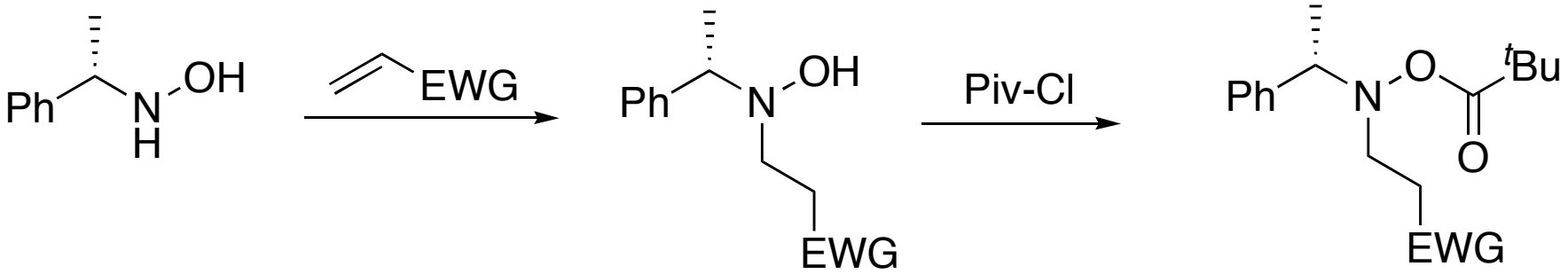
Corey, et. al. *J. Am. Chem. Soc.* **1965**, *87*, 1353

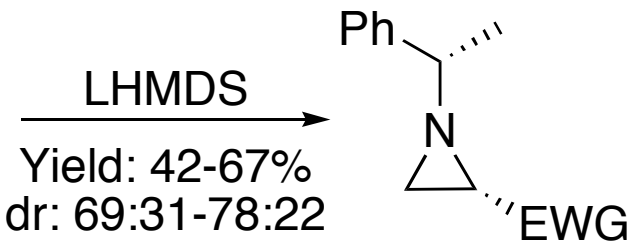
An Unusual Approach…



Chem. Commun. **2006**, 3513.

Aziridines from Hydroxylamines

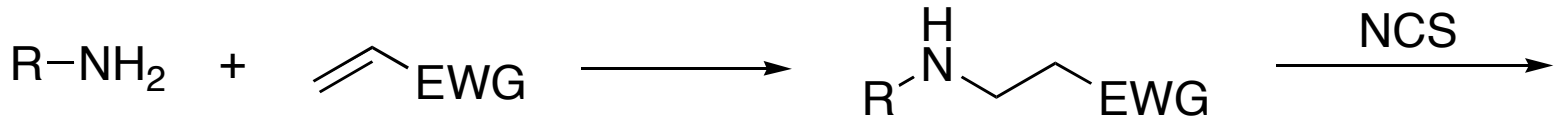


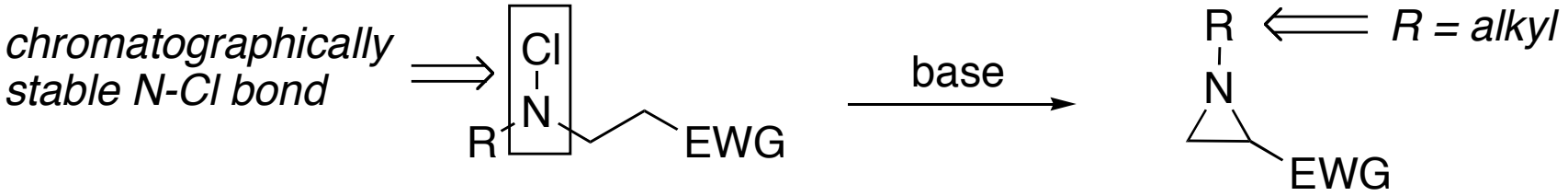


EWG: $CO_2{}^tBu$
CO_2Et
SO_2Ph
CN

Chem. Commun. **2006**, 3513.

Current Work

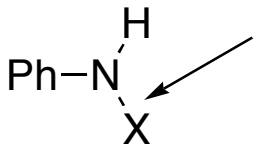




Chem. Commun. **2006**, 4338.

N-Cl Bonds

JOC, **2003**, *68*, 262.

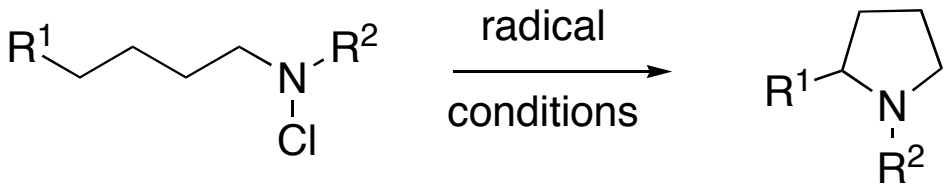


Calculated (G3) BDE (kcal/mol):

X = H	91.4
X = Me	71.8
X = Cl	47.4

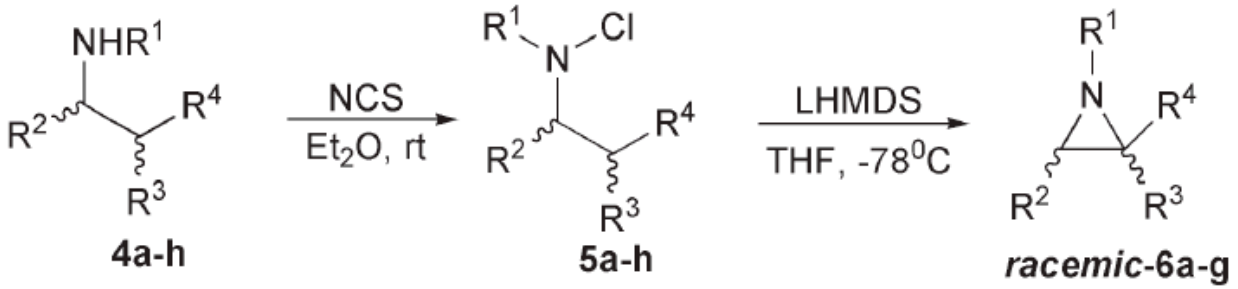
Weak bond...radical reactions

Hofmann-Loffler-Freytag Reaction:



"...no special precautions...on exceptionally sunny days the flask was wrapped in foil."
Chem. Commun. **2006**, 4338.

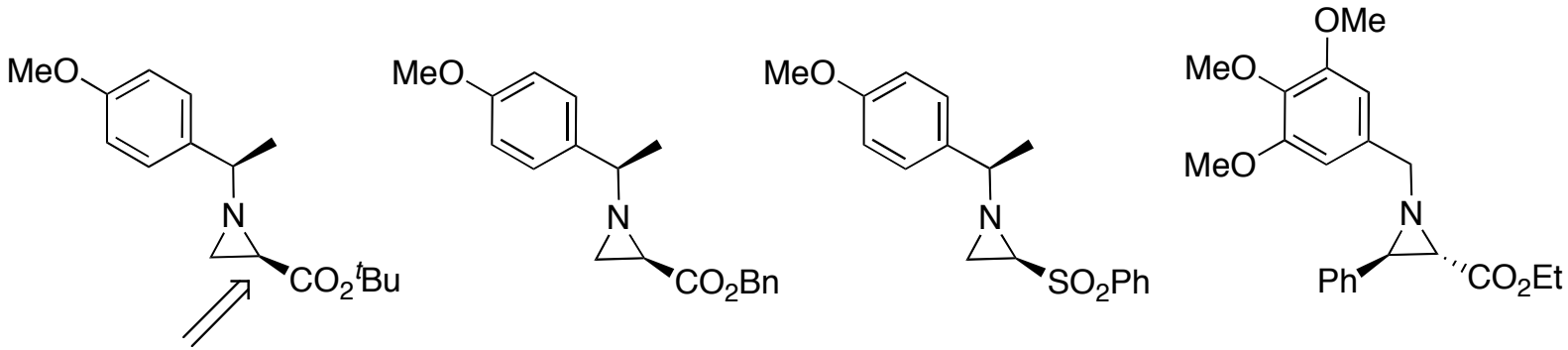
Results of Racemic Aziridination



R^1	R^2	R^3	R^4	4	5	6
4-$MeOC_6H_4CH_2$	H	H	$-CO_2Me$	**4a** 89%	**5a** 94%	**6a** 72%
4-$MeOC_6H_4CH_2$	H	H	–CN	**4b** 84%	**5b** 93%	**6b** 70%
4-$MeOC_6H_4CH_2$	H	H	$-CO_2{}^tBu$	**4c** 87%	**5c** 65%	**6c** 39%
4-$MeOC_6H_4CH_2$	Me	H	$-CO_2Me$	**4d** 87%	**5d** 64%	**6d** 79%
Allyl	H	H	$-CO_2Me$	**4e** 92%	**5e** 78%	**6e** 58%
tert-Bu	H	H	$-CO_2{}^tBu$	**4f** 94%	**5f** 82%	**6f** 90%
4-MeOBn	Me	H	$-CO_2{}^tBu$	**4g** 97%	**5g** 64%	**6g** 63%
4-MeOBn	H	Me	$-CO_2Me$	**4h** 99%	**5h** 99%	—

Chem. Commun. **2006**, 4338.

Asymmetric Version

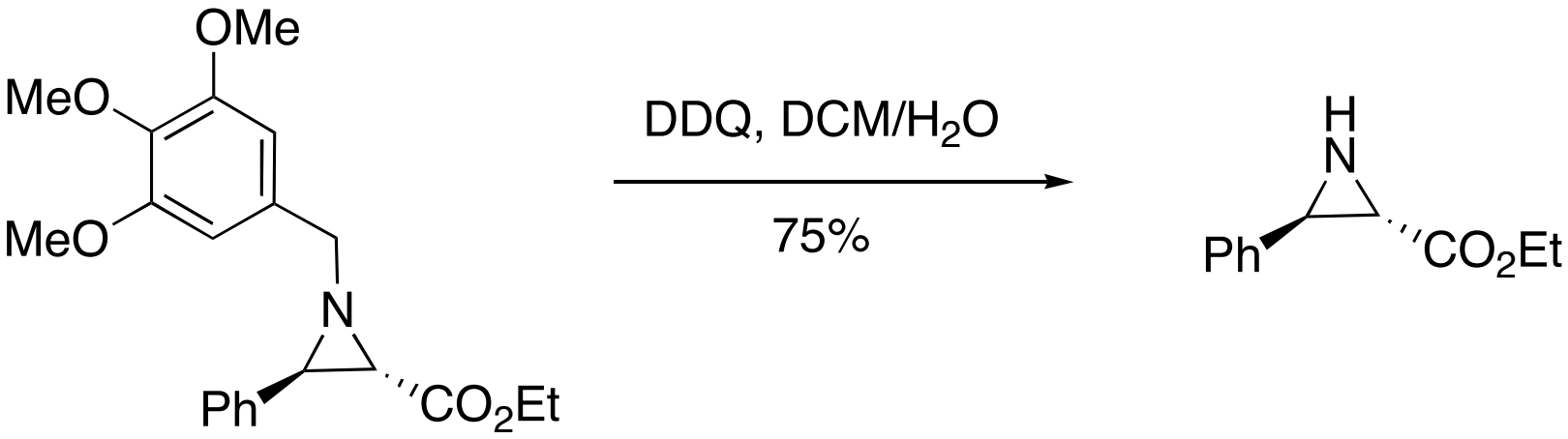


Yield:	88%	87%	65%	70%
dr:	93:7	75:25	75:25	*from chiral β-amino ester*

Optimization: 1) Hydrocarbon solvents best for selectivity and yield
2) Temperature variation exhibits little effect

Chem. Commun. **2006**, 4338.

Protecting Group Removal



Note: Attempted removal of PMB group was unsuccessful.

Summary

- Unusual synthesis of *N*-alkyl aziridines
- S_N2 attack onto nitrogen center
- Utilized non-stabilized *N*-chloramines
- Simple chiral protecting groups give moderate diastereoselectivity