Toward the Synthesis of *E*-Alkene Peptide Isosteres

Bryan Wakefield

Research Topic Seminar

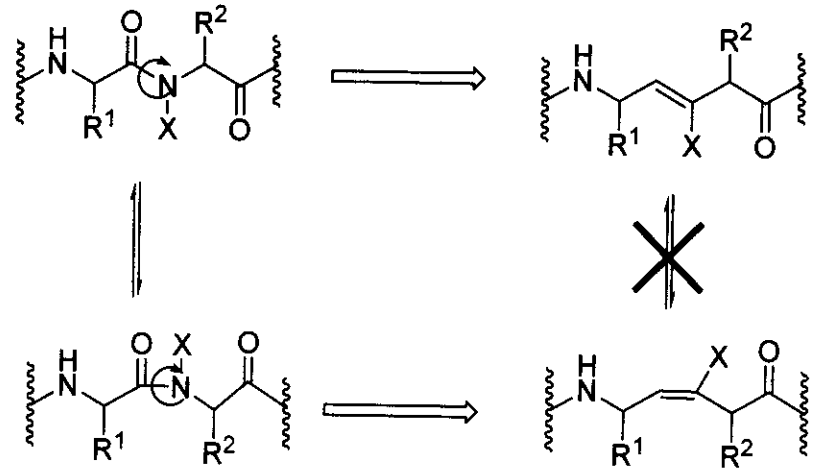
Outline

- Introduction to Peptide Isosteres
  - *E*-Alkene Peptide Isosteres
- Synthesis of *E*-Alkene Isosteres
- Synthesis of Aziridines
- Previous Wipf Group Work
- Current Approach

Peptide Mimetics

- Expected to have the same biological activities of their natural counterparts, due to their structural similarities.
- Should posses great metabolic stability.
- Replacement of the amide bond has been a focus of this work.
  - To increase rigidity of the molecule
  - Mimic β-turns

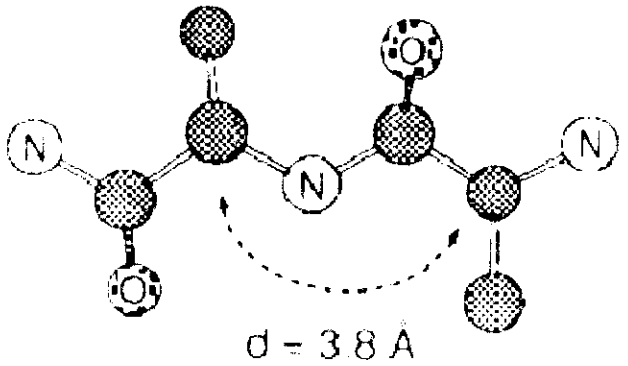
Alkene Dipeptide Mimetics

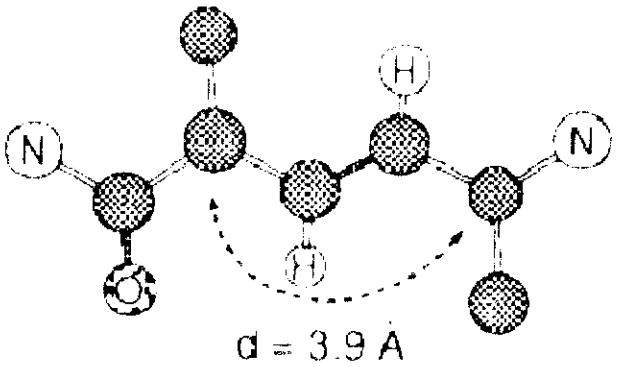


Fujii, N. *JOC* 2002, 67, 6162

- Used to eliminate trans/cis conversion of the amide bond
- Replaces the amide bond, thus increasing metabolic stability by eliminating a site of hydrolysis.

Comparing *E*-Alkene Isosteres to Amide Bonds

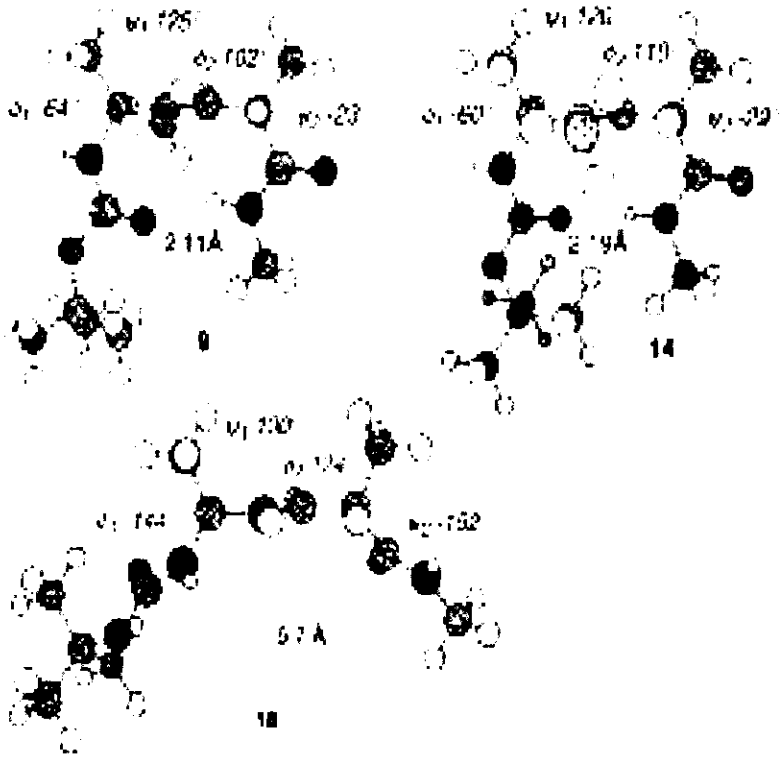




- Alkenes closely resemble amides in bond length, angle and rigidity.

Wipf, P, *JOC* 1994, 59, 4875

β-Turn Mimics

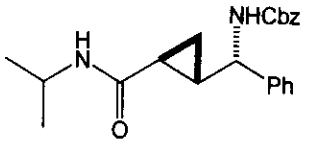


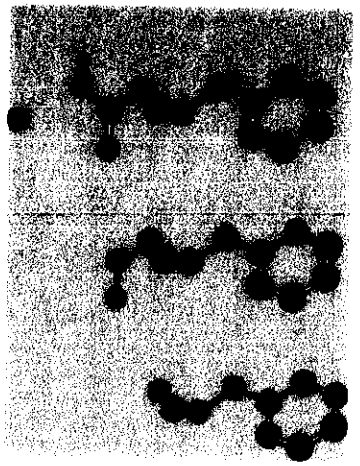
- More highly substituted E-Alkenes mimic β-turns better.
- The β-turn is caused by $A^{1,3}$ and $A^{1,2}$ strain.

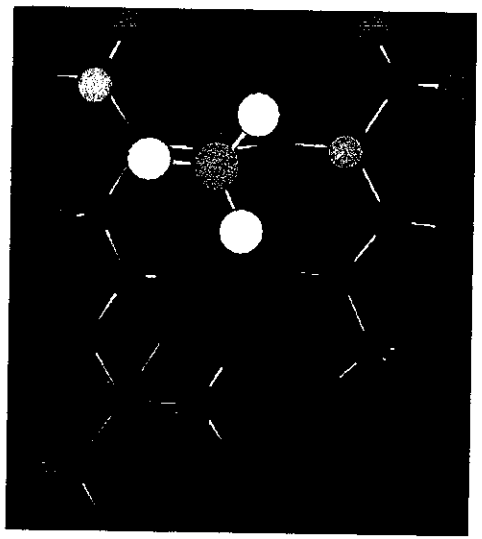
Wipf, P, *JOC* 1998, 63, 6088

Work in the Wipf Group

- Mimetics used in the Wipf group include:
  - cyclopropanes
  - vinyl CF_3
  - *E*-alkenes.

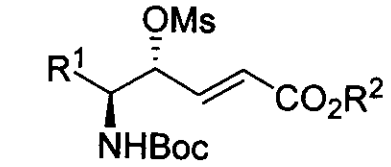


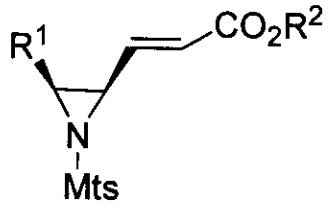


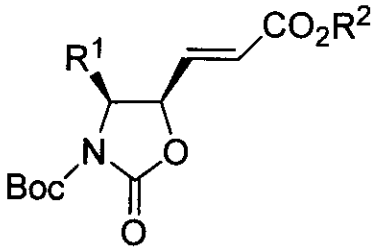


Routes to *E*-Alkene Dipeptide Isosteres

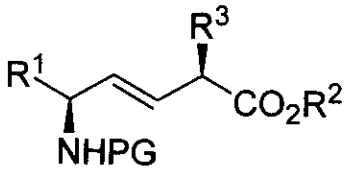
Anti-S_N2' Cuprate Addition





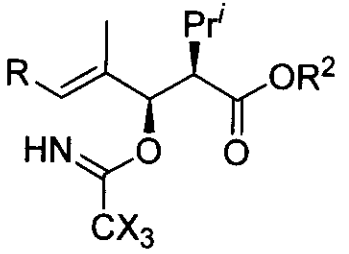


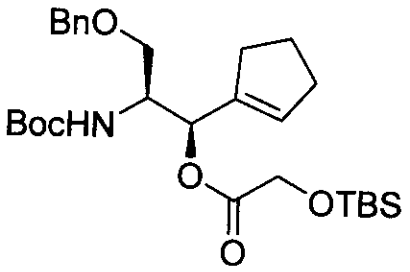
"R^3Cu"
anti-S_N2'

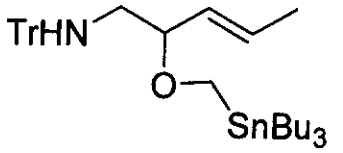


Steps

Rearrangements

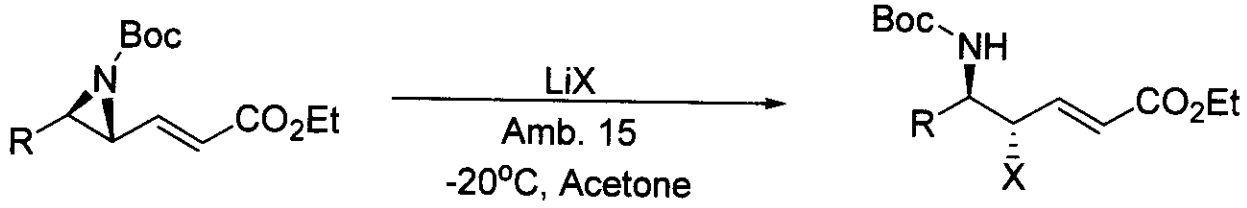






Fujii, N. *JOC* 2002, 67, 6162

Metal Halide Aziridine Openings



R=Pr^n

X=Cl 84%
X=Br 94%
X=I 70%

R=Cyclohexane

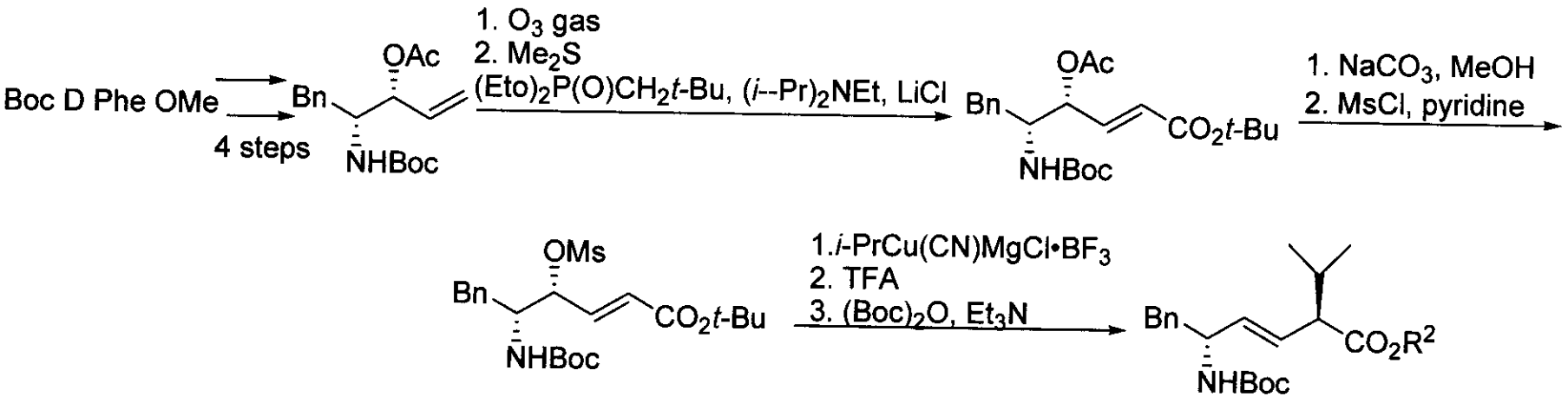
X=Cl 86%
X=Br 94%
X=I 72%

R=Bu^t

X=Cl 82%
X=Br 87%
X=I 67%

Righi, G. *Tet Let* 2002 43, 5867

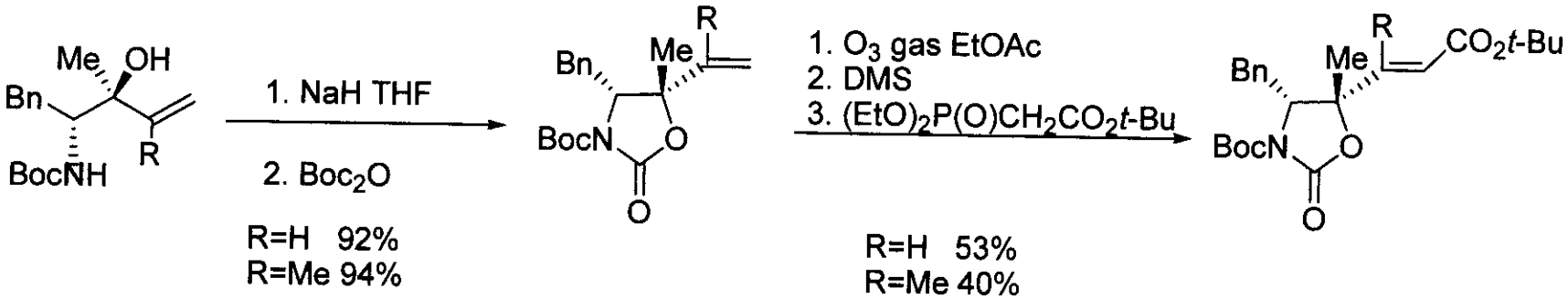
E-Alkene Peptide Isosteres via *Anti*-S_N2' Cuprate Additions

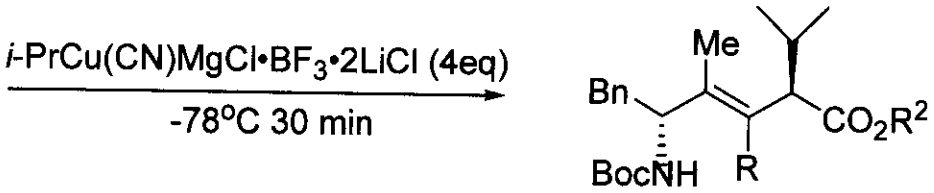


Fujii, N. *Org Let* 2002, 7, 1055

Fujii, N. *JOC* 2002, 67, 6162

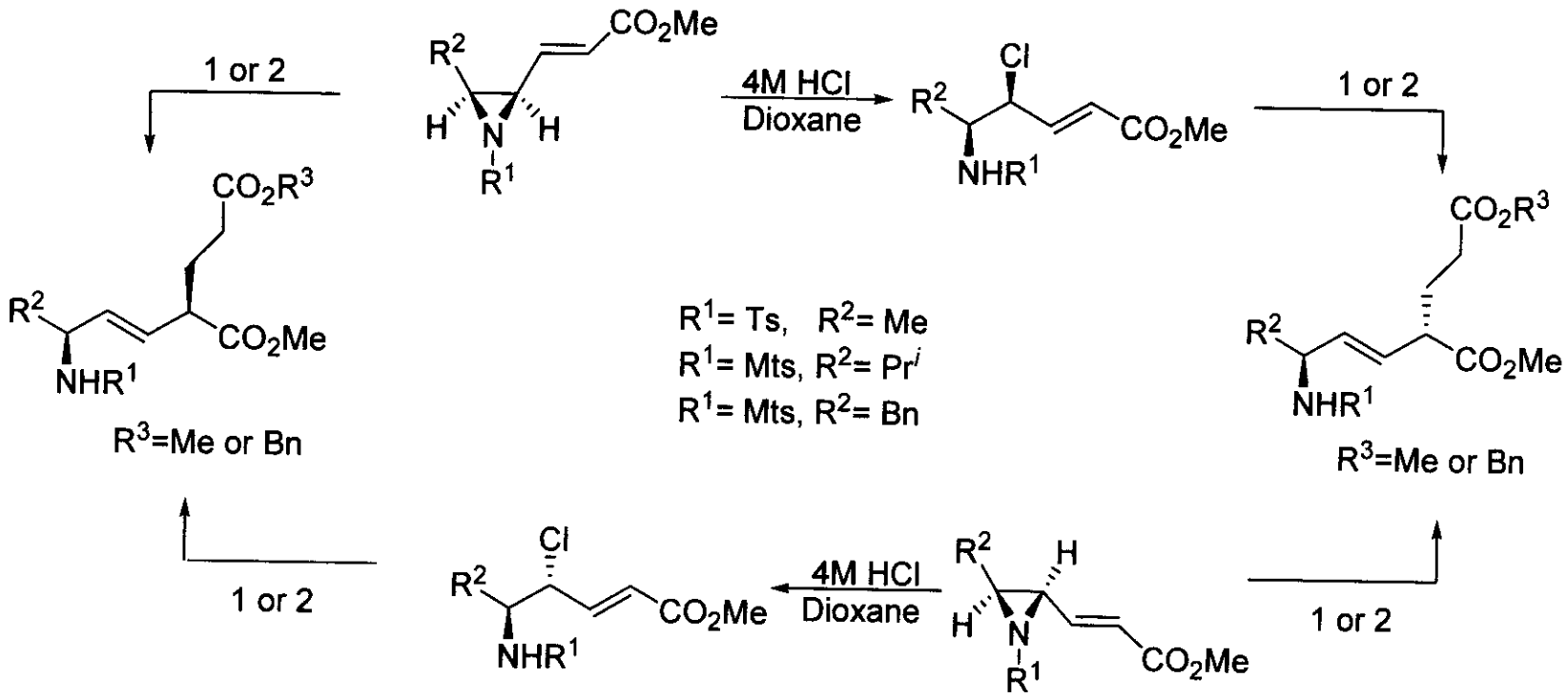
E-Alkene Dipeptide Isosteres via Oxazolidinone Opening





Fujii, N. *Org Let* 2002, 7, 1055

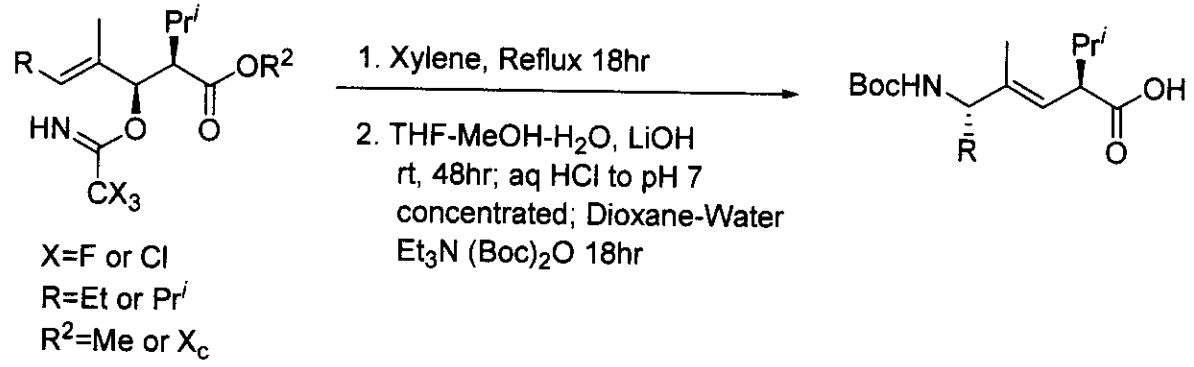
Halide Aziridine Openings and Cuprate Additions



1. $IZn(CN)CuCH_2CH_2CO_2Me \cdot 2LiCl$
2. $IZN(CN)CuCH_2CH_2CO_2Bn \cdot 2LiCl$

Fujii, N. *JCS Perkin Trans 1* 2001, 2445

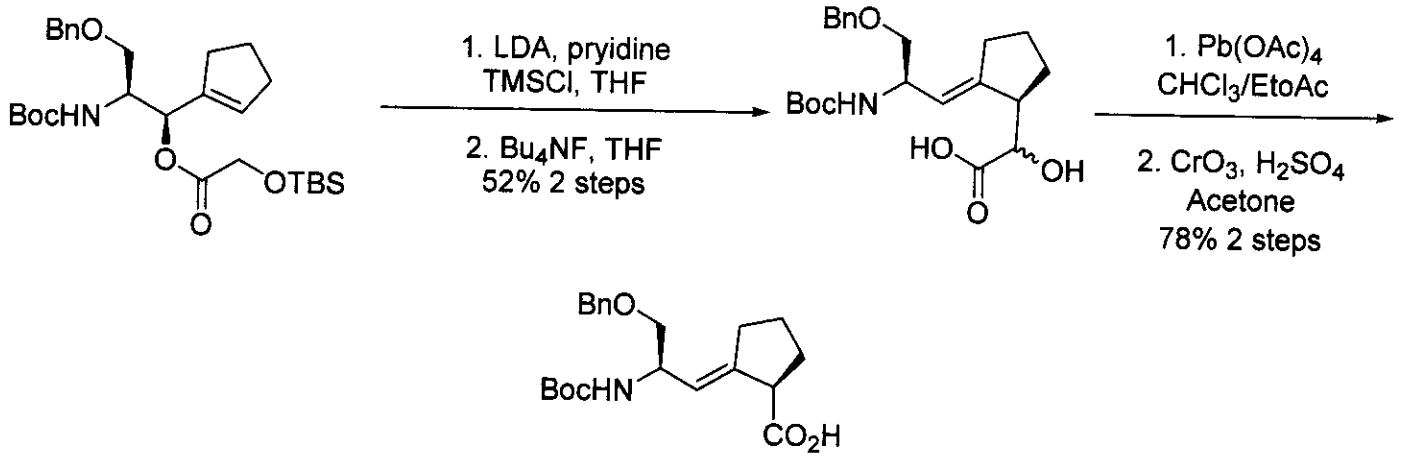
E-Alkene Peptide Isosteres via [3,3] Sigmatropic Rearrangement



X=F or Cl
R=Et or Pr^i
R^2=Me or X$_c$

Wai, J *Tet Let* 1995, 36, 3461

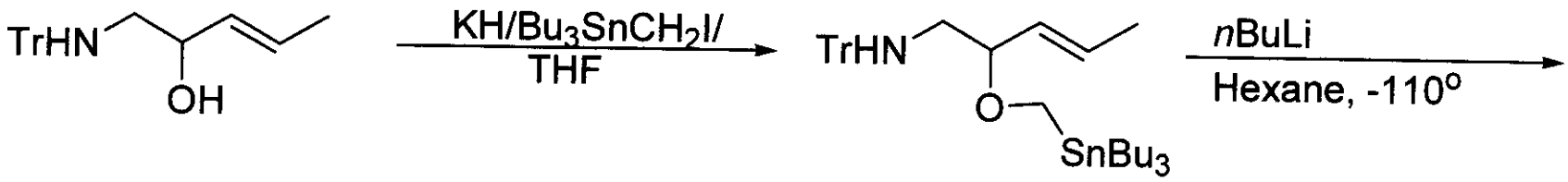
Ireland-Claisen Rearrangement

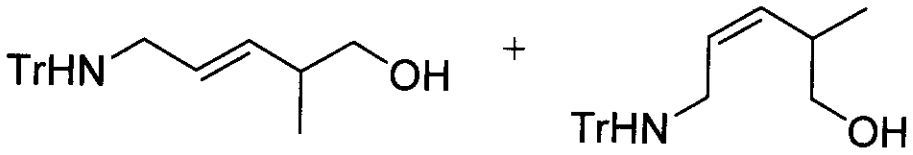


Etzkor, F.A. *JOC* 2003 68, 2343

E-Alkene Peptide Isosteres via Wittig-Still Rearrangement

Wittig-Still Rearrangement



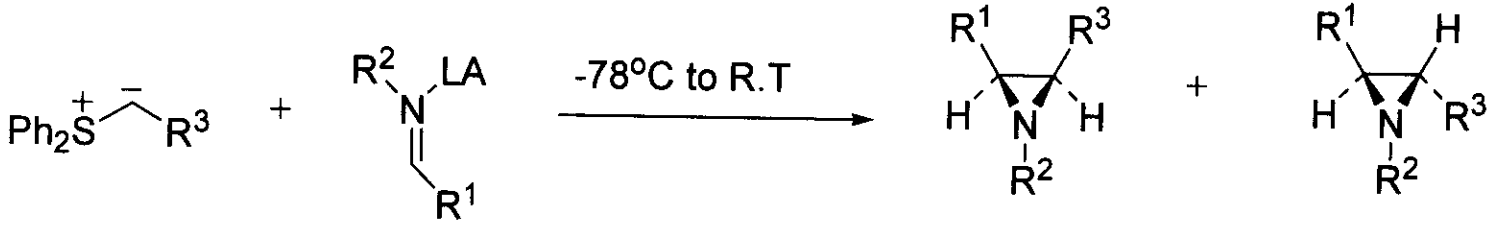


1.5 1

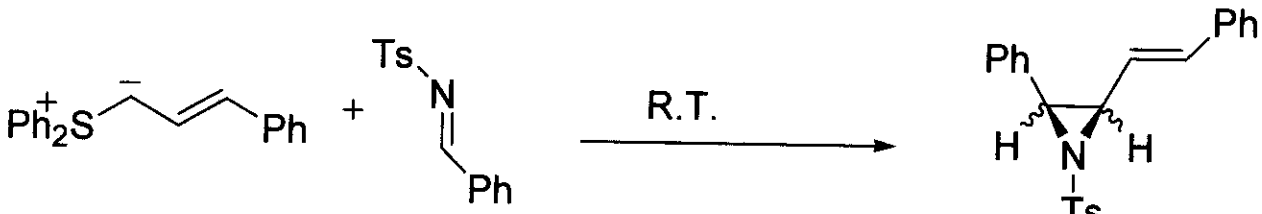
80% combined yield

Bol, K.M. *Tet* 1992, 48, 6425

Aziridine Formation via Sulfur Yildes



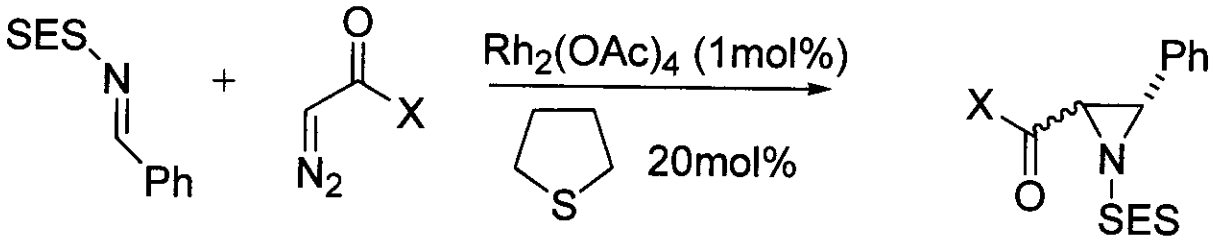
Hou, X.L. *Chem Comm* 1997, 1231



Trans/Cis 63/37

Hou, X.L. *JOC* 1996, 61, 4641

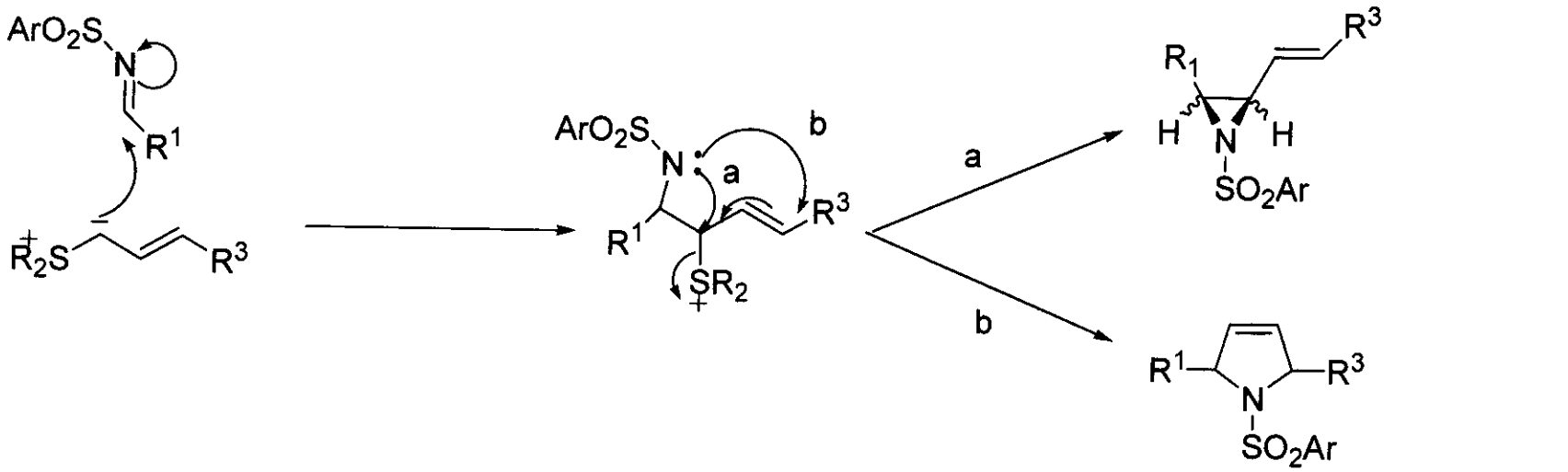
Aziridine Formation via Sulfur Ylides cont.



X	Yield(%)	Ratio (Trans:Cis)
NEt_2	91	2:1
OEt	57	1:3

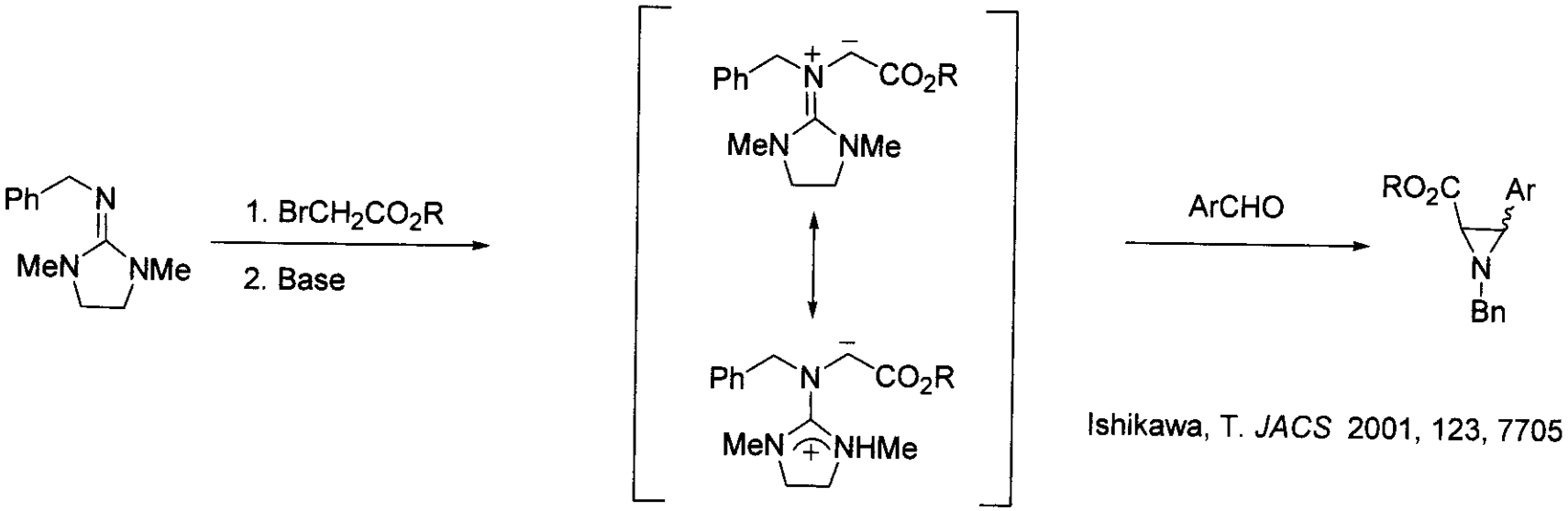
Aggarwal, V.K. *JOC* 1996, 61, 8368

Mechanism of Aziridine Formation via Sulfur Ylides



Hou, X.L. *JOC* 1996, 61, 4641

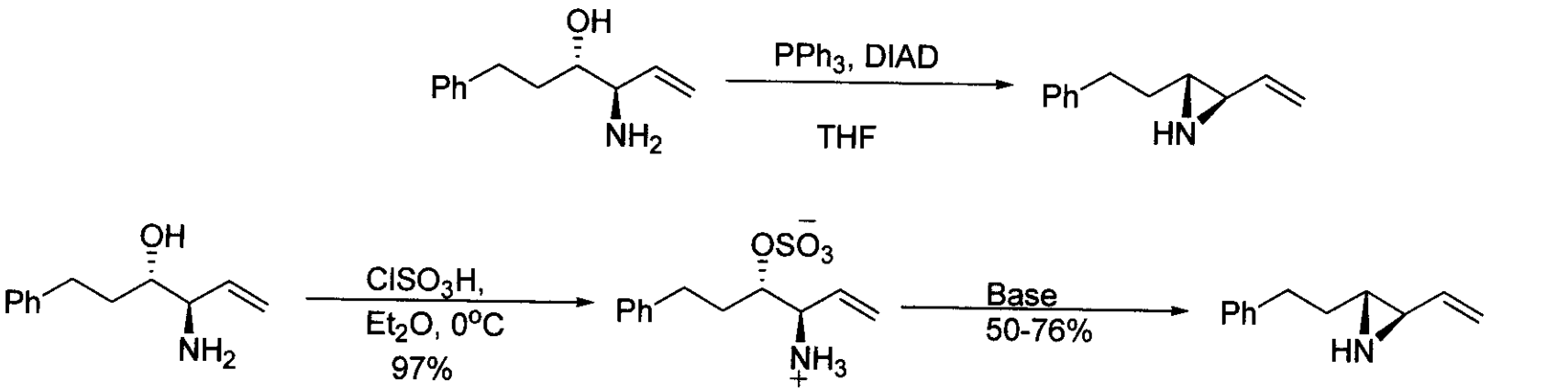
Aziridine Formation via Guanidinium Ylides



Guanidinium ylide

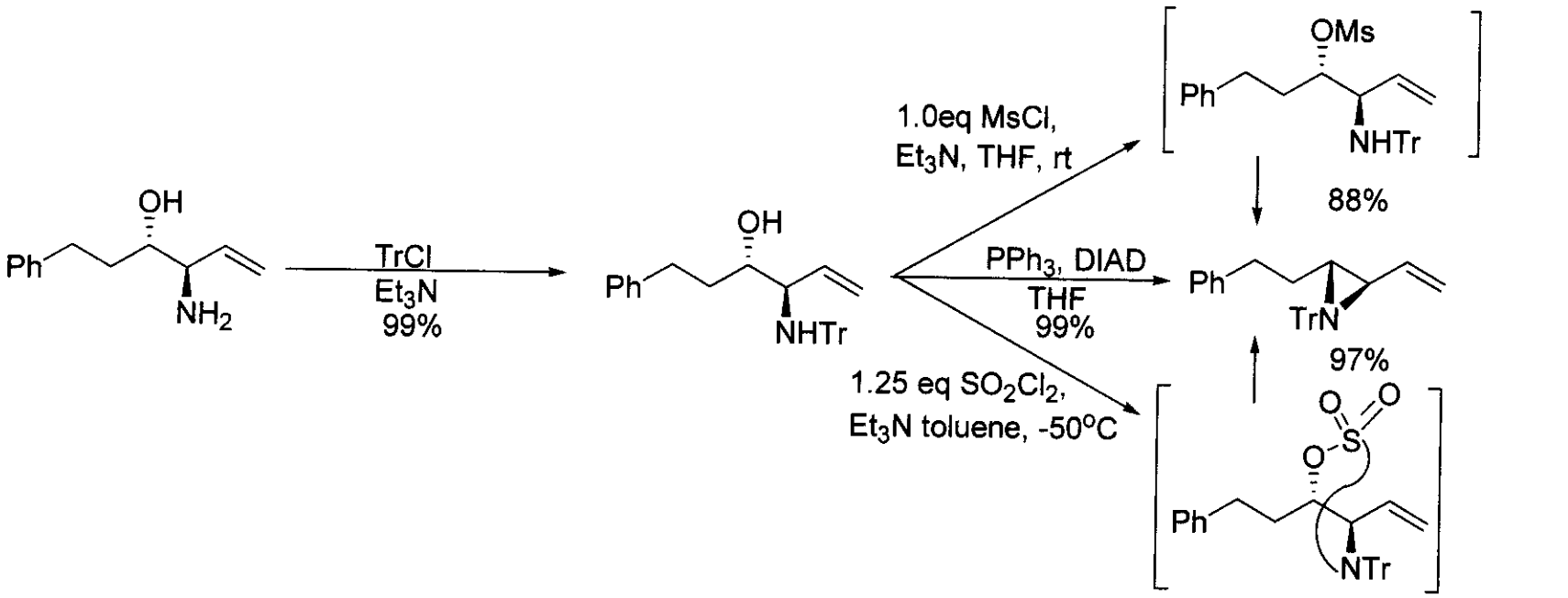
Ishikawa, T. *JACS* 2001, 123, 7705

N-H Aziridine Formation via Displacement



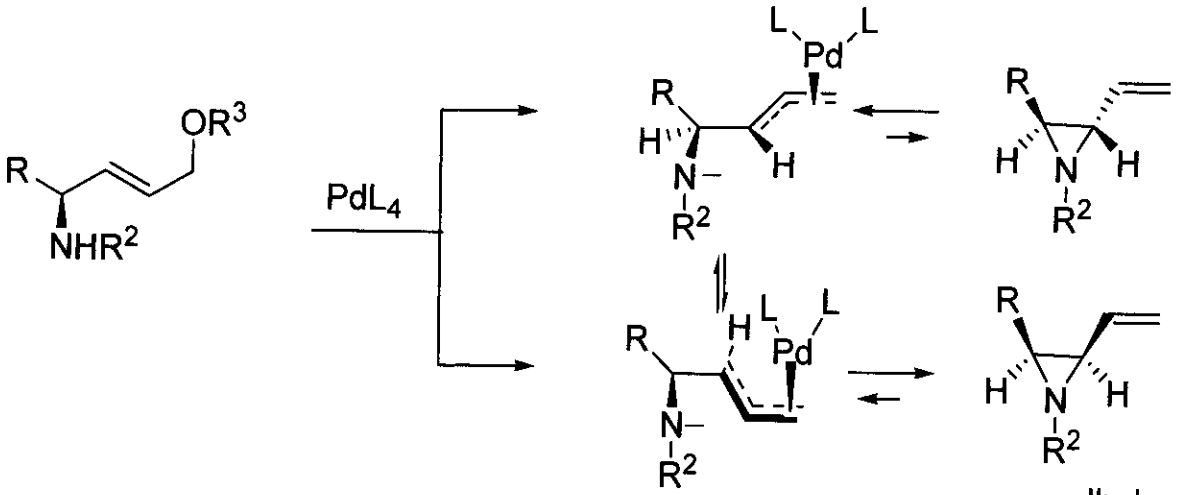
Somfai, P *Tet* 2002, 58, 5979

Aziridine Formation via Displacement



Somfai, P *Tet* 2002, 58, 5979

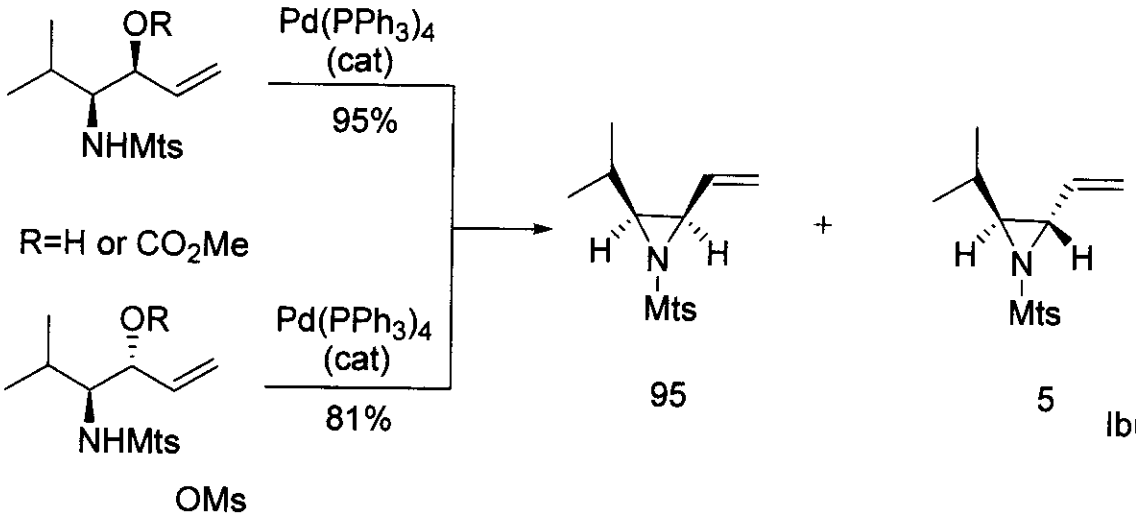
Pd Mediated Aziridine Formation



R=alkyl or aryl
R^2=Boc or Ts
R^3=Ms, Ts, etc.
L= PPh_3

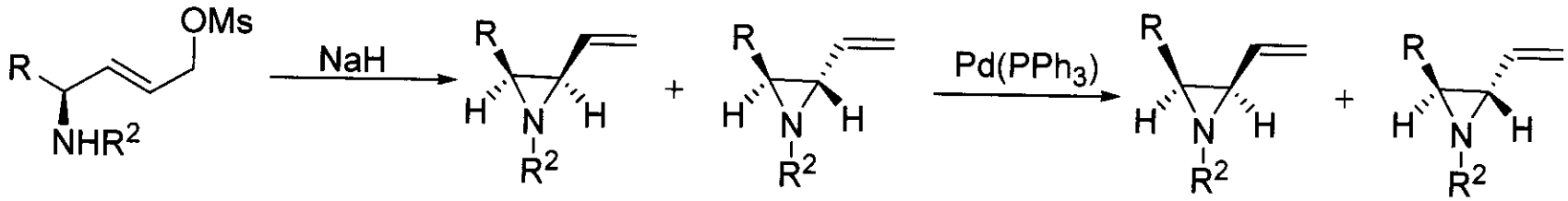
Ibuka, T *JCS Perkin Trans 1* 1998, 3703

Pd Mediated Aziridine Formation



Ibuka, T *JCS Perkin Trans 1* 1998, 3703

Displacement and Pd Isomeration

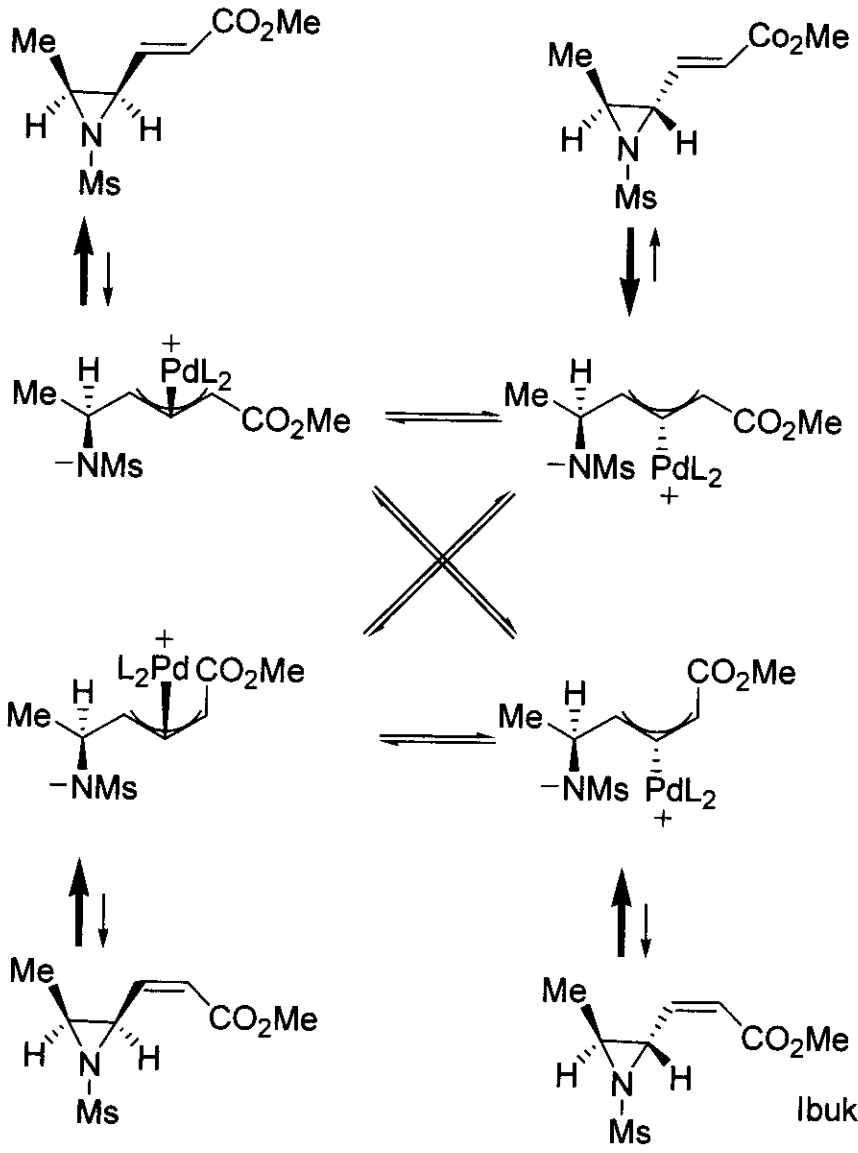


R=Pr^{i} R_2=Mts
R=Bu^{i} R_2=Ts
R=Bu^{i} R_2=Pmc
R=Bn R_2=Mts

Mixtures favoring trans

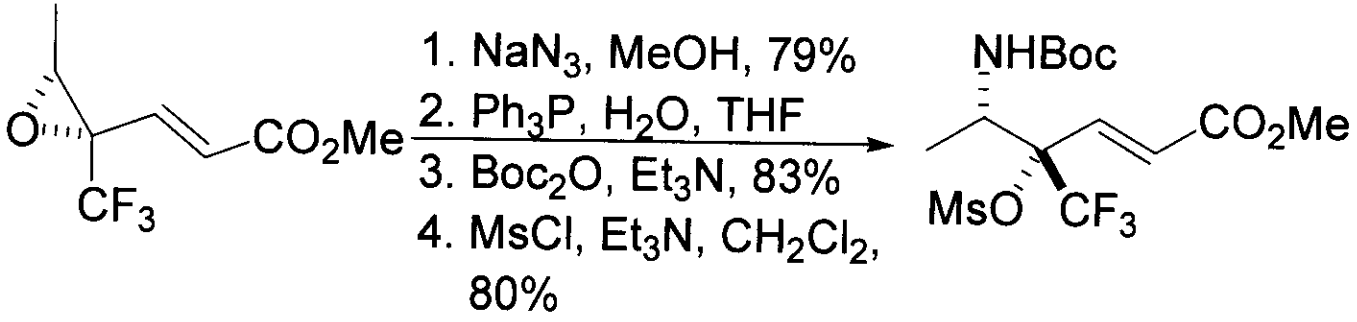
92:8 to 96:4

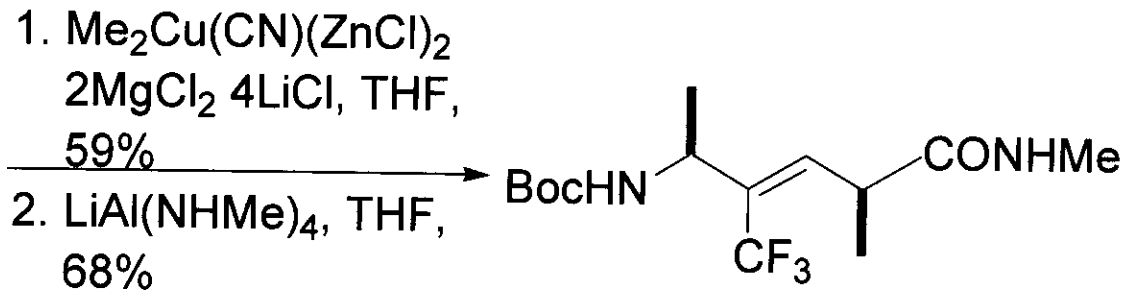
Pd Mediated Isomerization



Ibuka, T. *JOC* 1997, 62, 2982

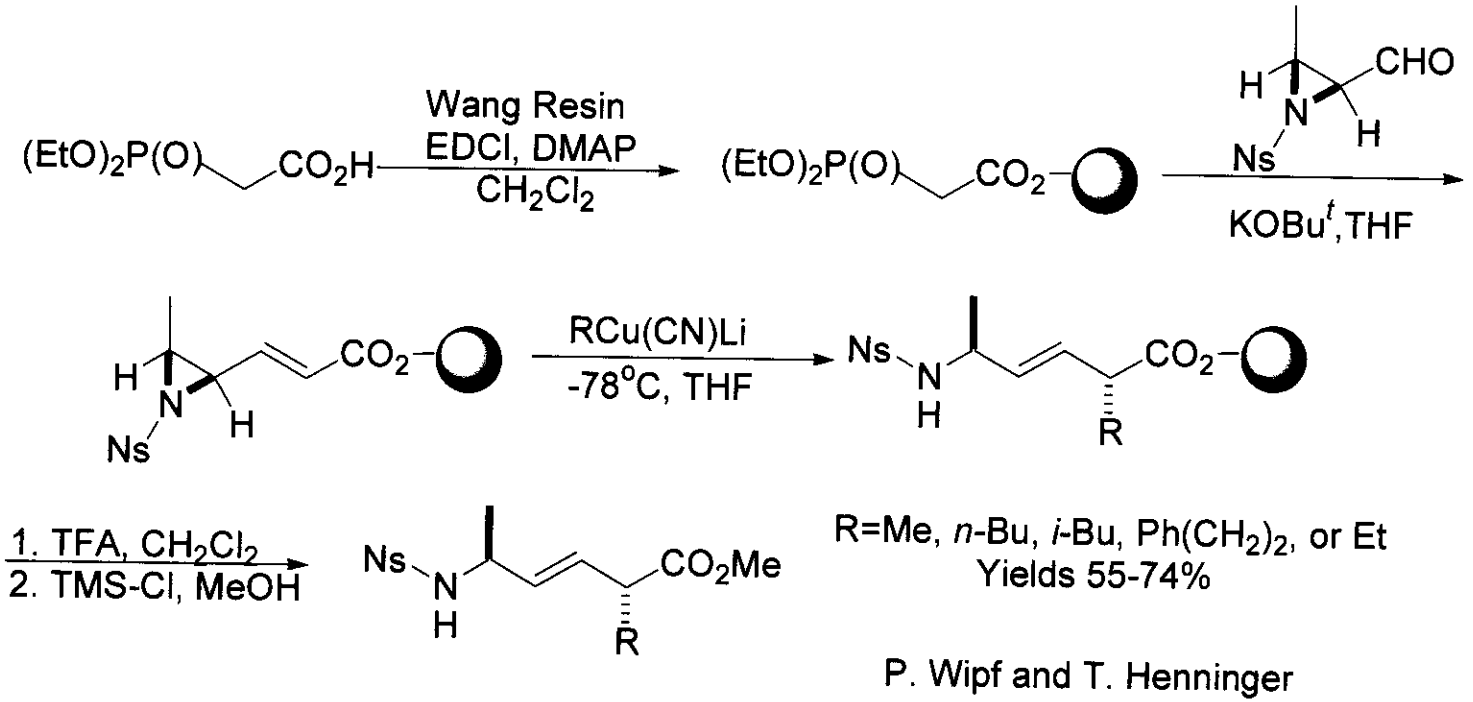
Previous Group Work: Vinyl CF_3





P. Wipf, T. Henninger, and S. Geib

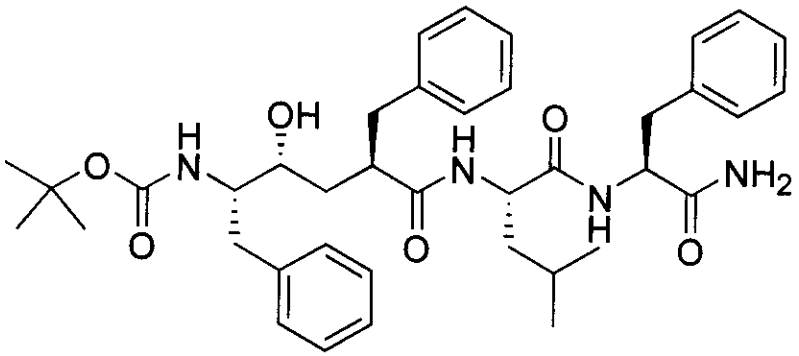
Previous Group Work:Aziridine Opening on Solid Support



R=Me, *n*-Bu, *i*-Bu, $Ph(CH_2)_2$, or Et
Yields 55-74%

P. Wipf and T. Henninger

Biological Activity of L-685,458



L-685,458

- Specific γ-secretase inhibitor, thus lowering the amount of Aβ protein
- Functions as a transition state analogue mimic at the catalytic site of an aspargyl protease.