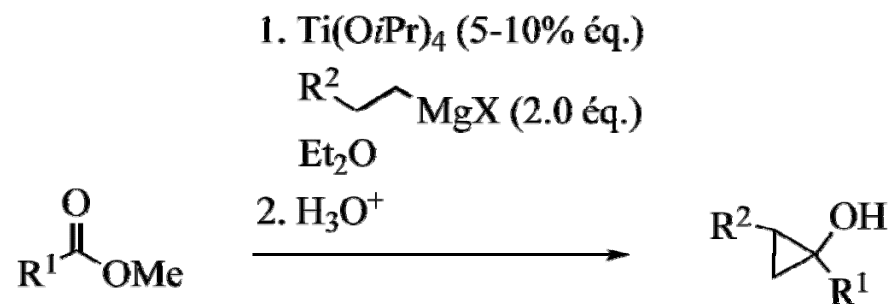


Kulinkovich Reaction



Zhang Wang

Synthesis Literacy Group Meeting

July 11, 2008

Background

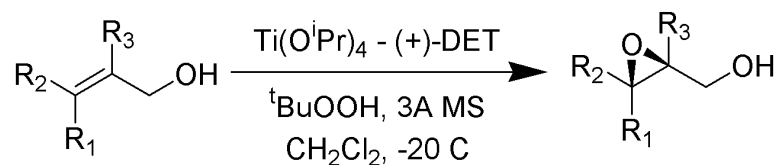
- Born May 11, 1948
- PhD (1975, Belarusian State U.)
- Full Professor (1987, Belarusian State U.)
- Famous for cyclopropane and titanium chemistry



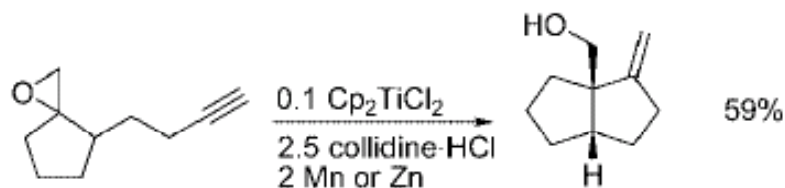
Prof. Oleg Grigor'evich Kulinkovich

Organotitanium Chemistry

- Ti(IV)

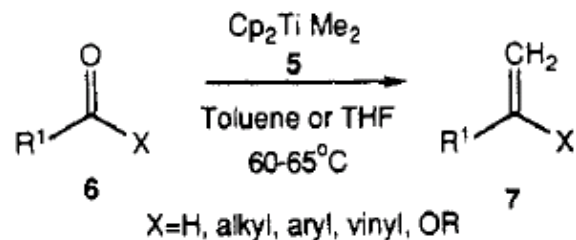
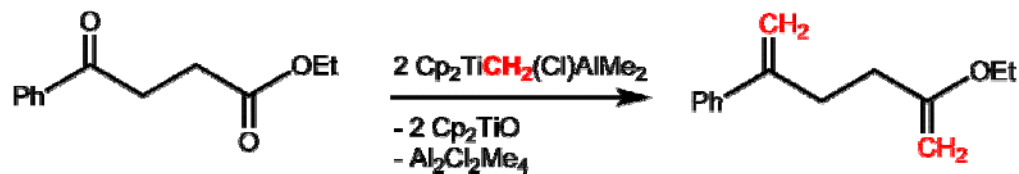


- Ti(III)



Eur. J. Org. Chem. 2006, 1627–1641

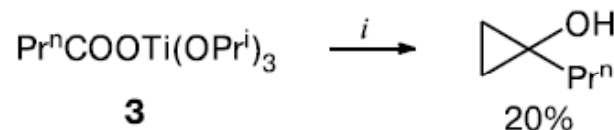
- Ti(II)



J. Am. Chem. Soc.; 1990; 112(17); 6392-6394

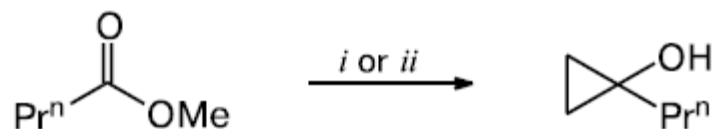
Introduction

- First discovery



i. 1) EtMgBr (3 equiv.), 2) H₃O⁺.

- Modification



Reagents and conditions: *i.* 1) EtMgBr (3 equiv.), Ti(OPr^{*i*})₄ (1 equiv.), -78 °C → 0 °C, 2) H₃O⁺, 90% yield; *ii.* 1) EtMgBr (2 equiv.), Ti(OPr^{*i*})₄ (0.1 equiv.), ~20 °C, 2) H₃O⁺, 91% yield.

Synthesis 1991, 234

- Further development...

TiCl(O*i*-Pr)₃
Ti(O*i*-Pr)₄

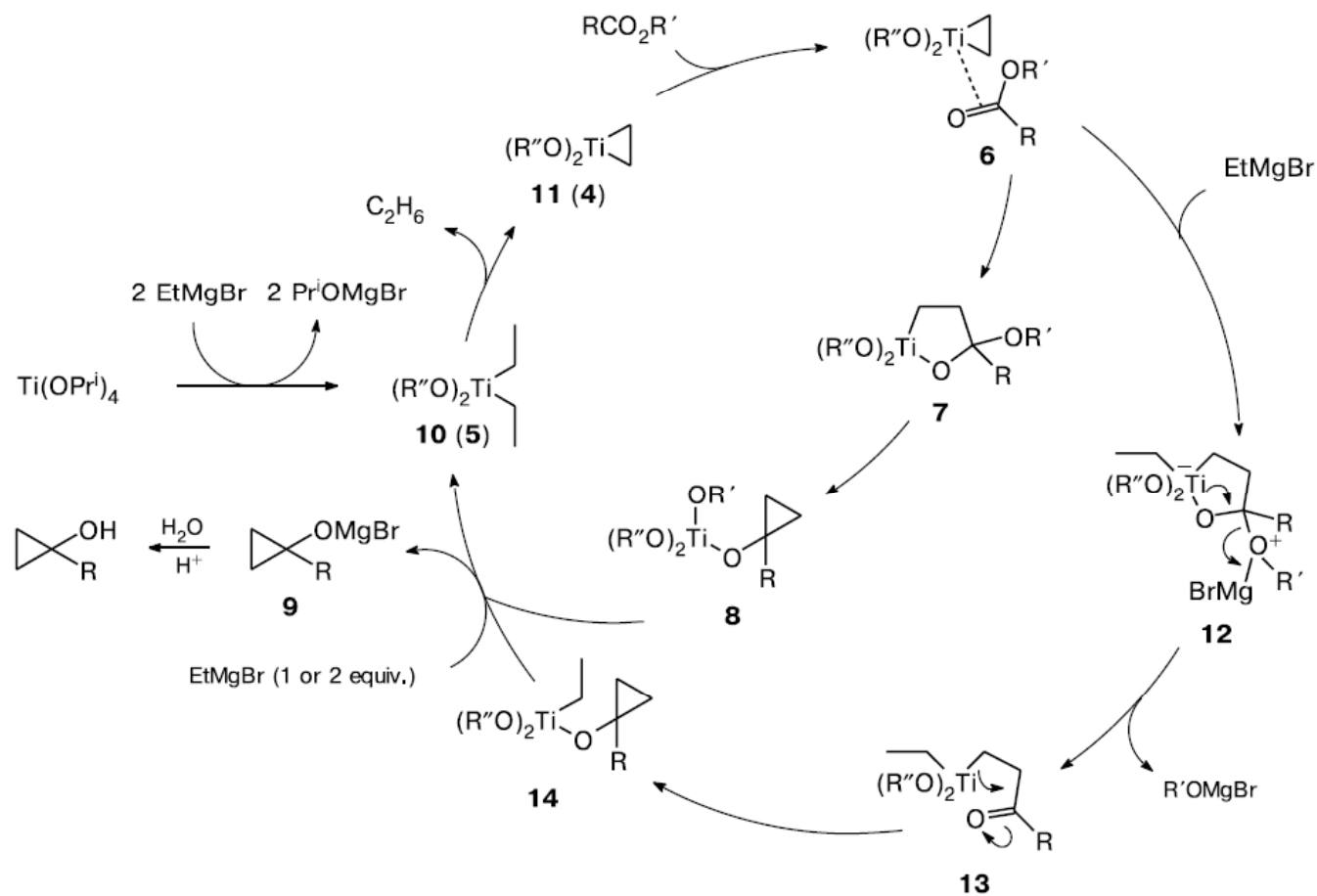
.....

RCH₂CH₂MgBr
c-alkyl-MgBr

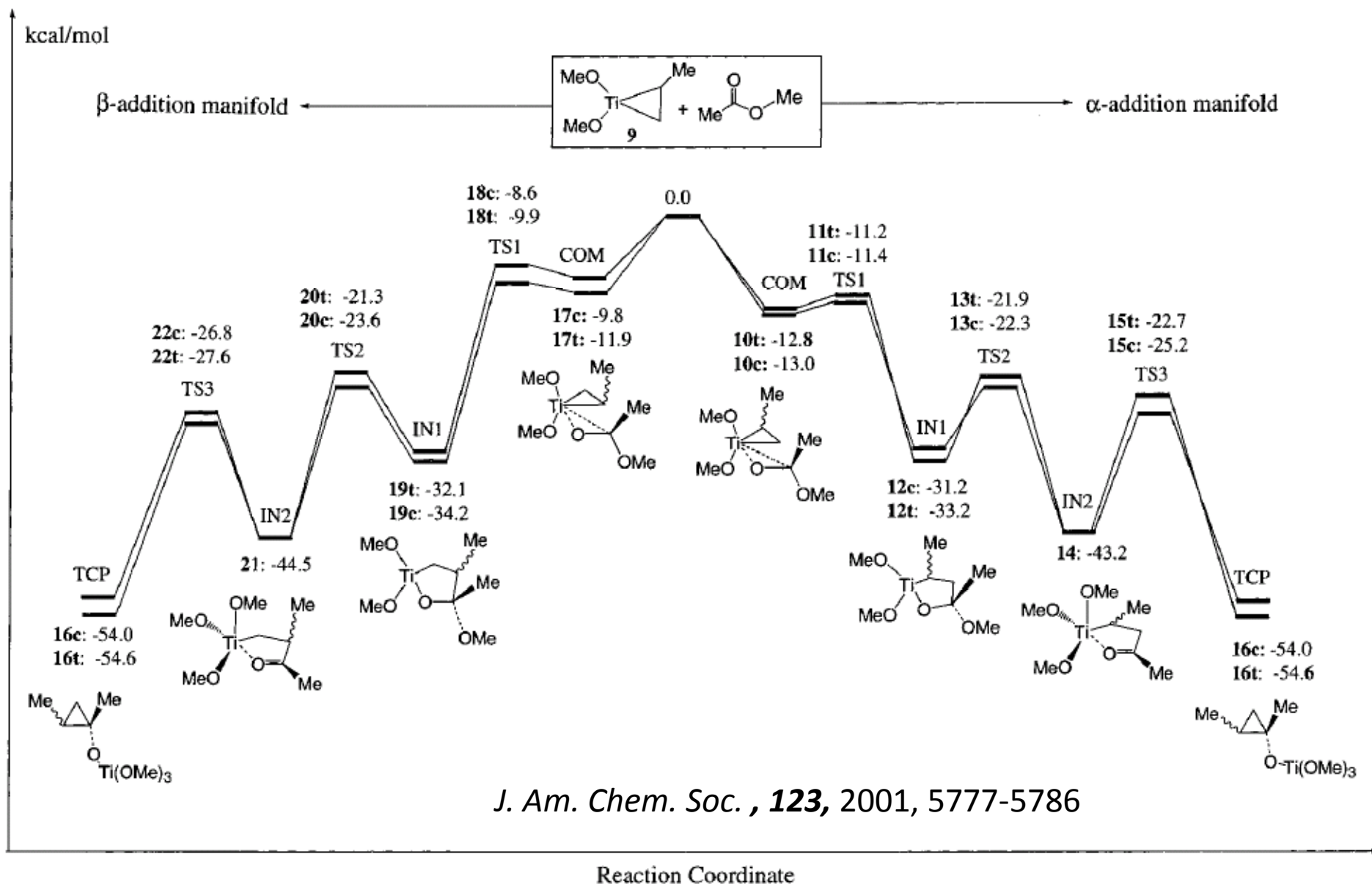
.....

Different substrates
.....

Mechanism

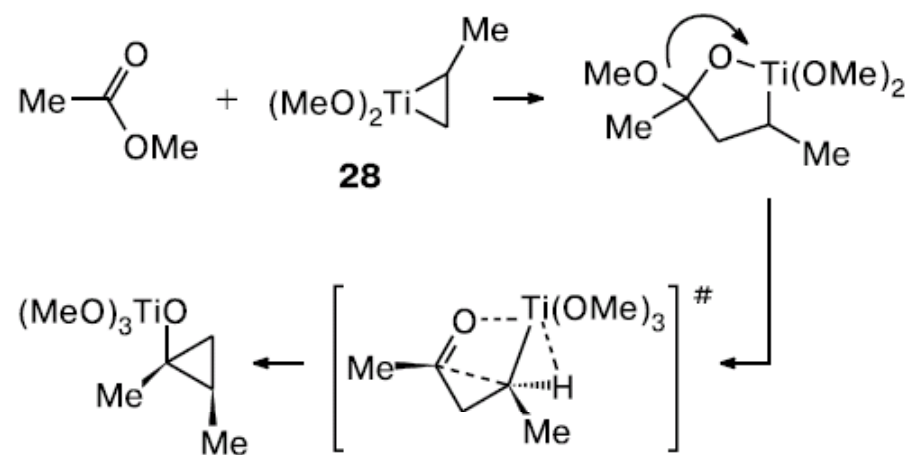
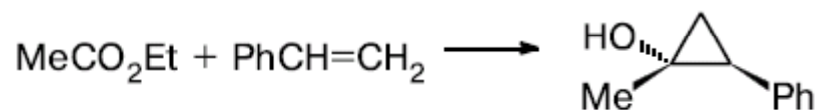


“Chemoselectivity”



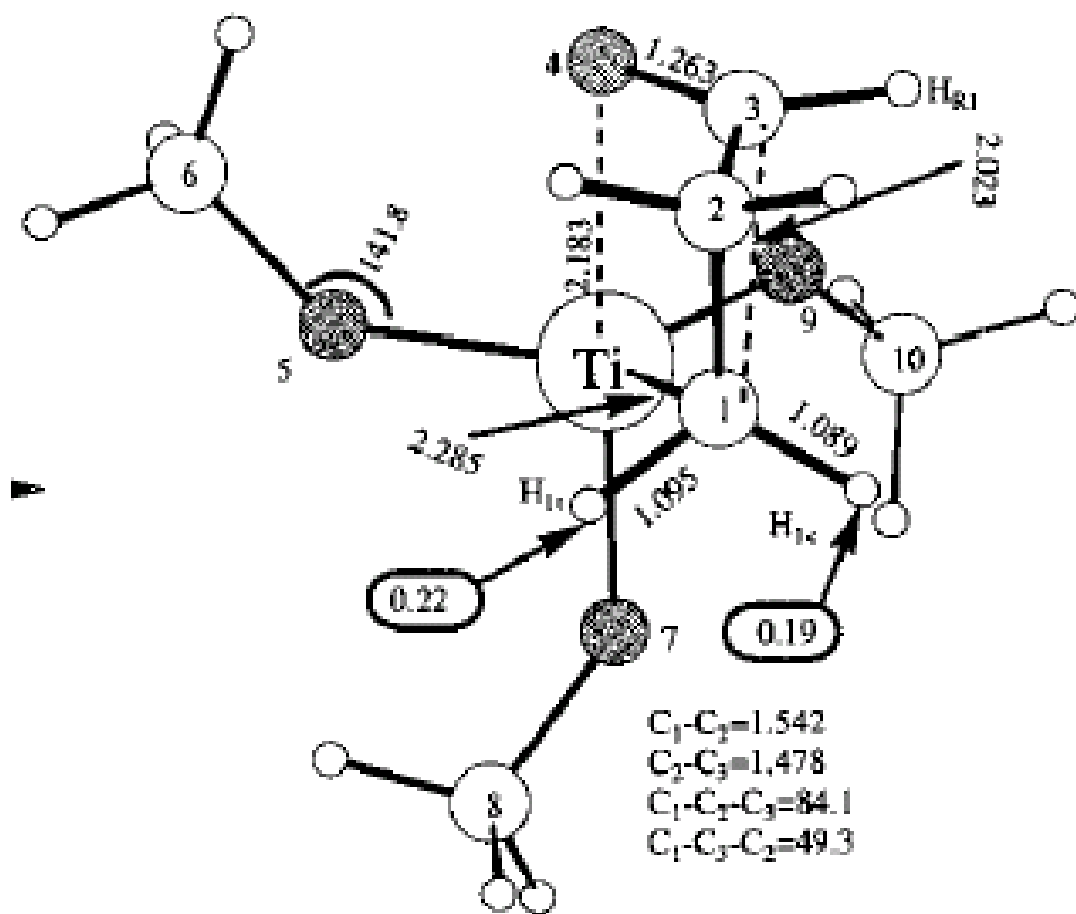
Diastereoselectivity-1

- *cis*-dialkylcyclopropanol

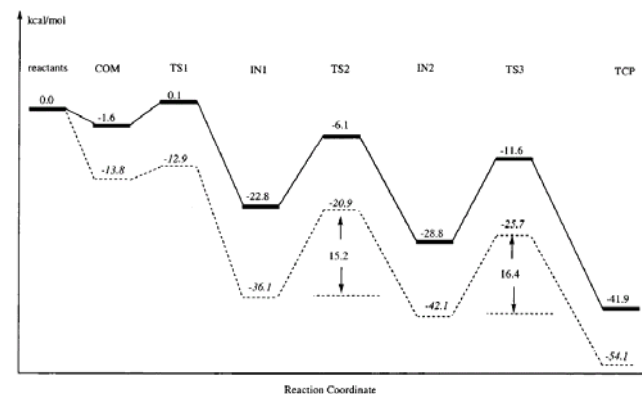
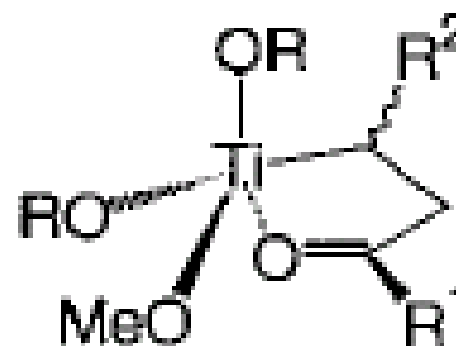


J. Org. Chem. USSR, 1991, 27, 250

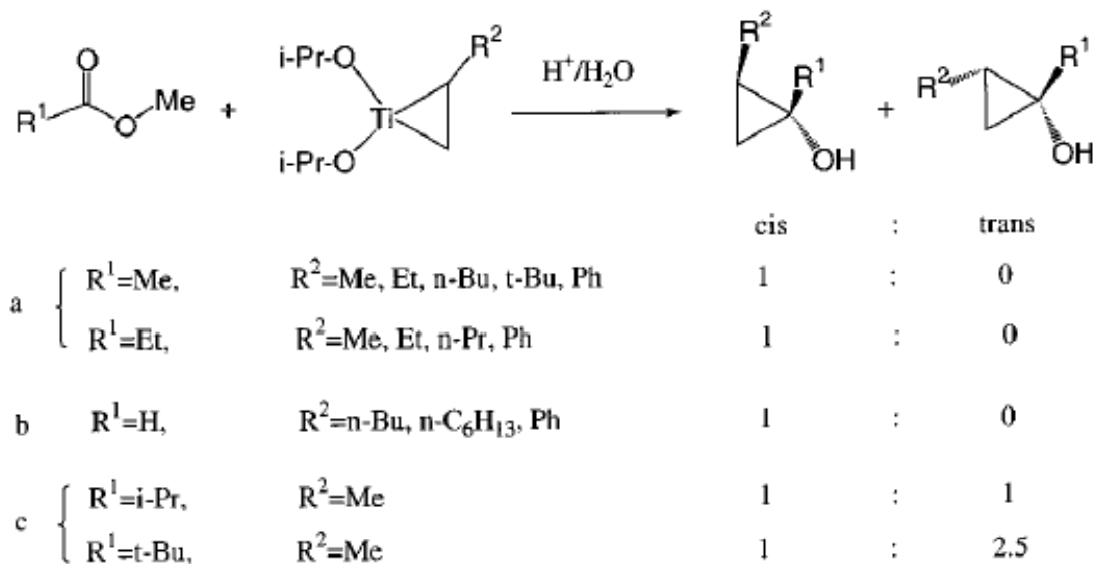
Diastereoselectivity-2



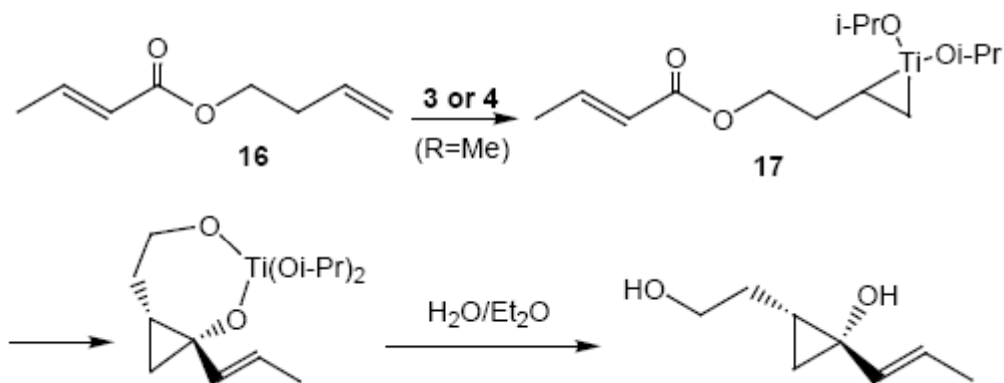
7 (TS3)



Diastereoselectivity-3

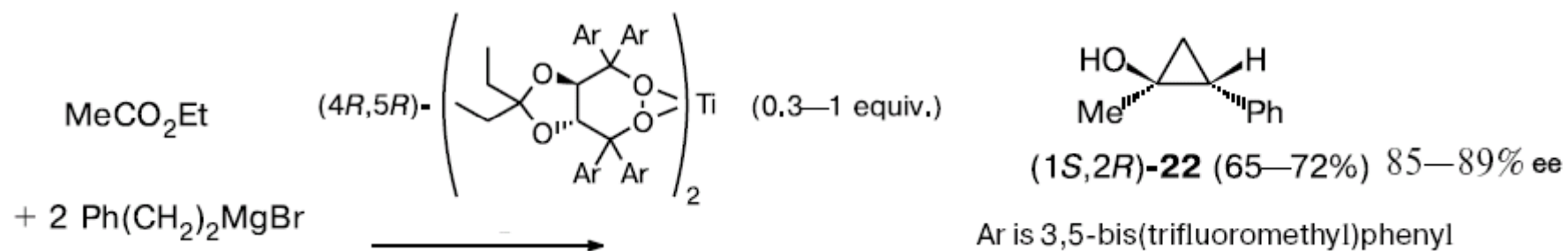


J. Am. Chem. Soc., **123**, 2001, 5777-5786



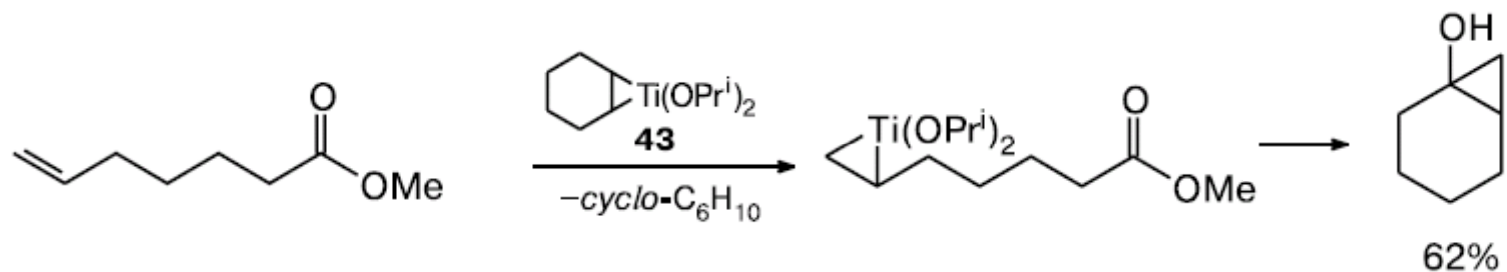
Synlett 2000 12, 1729-1732

Asymmetric Version

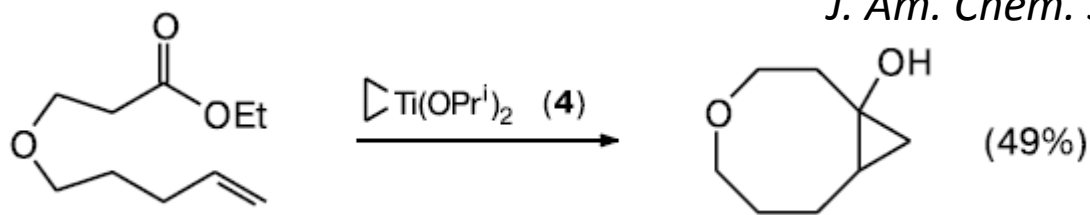


J. Am. Chem. Soc., 1994, 116, 9345

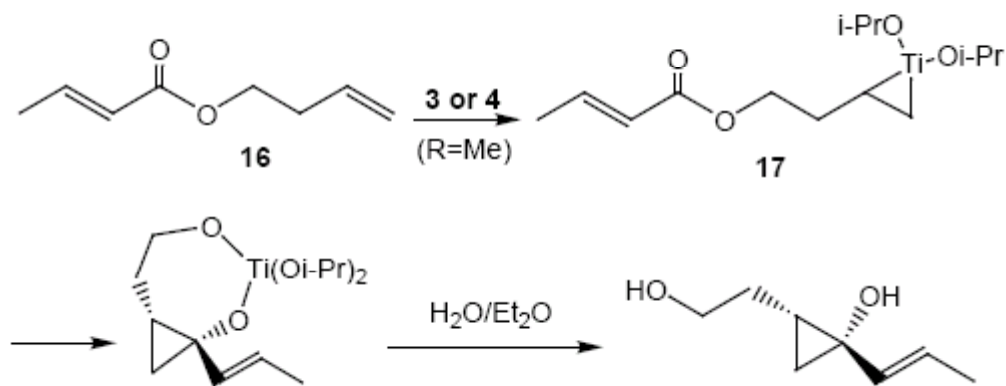
Intramolecular Version



J. Am. Chem. Soc.; 1996; 118(1); 291-292



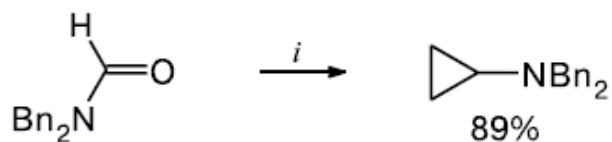
Org. Biomol. Chem., 2003, 1, 3600



Synlett, 2000, 1729

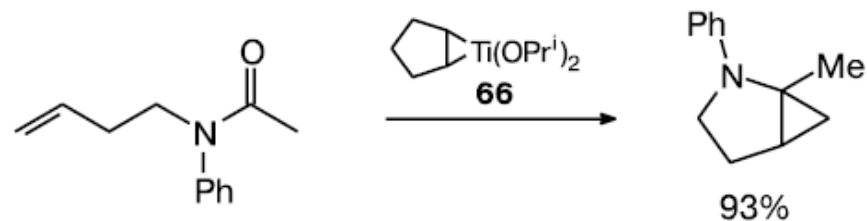
Variations

de Meijere variation:



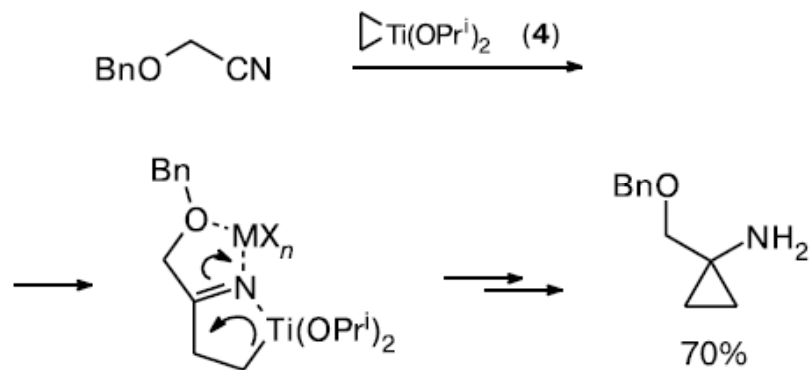
Org. Lett., 2003, 5, 753

i. $\text{MeTi}(\text{OPr}^i)_3$ (1 equiv.), Et_2Zn (2 equiv.), NaOPr^i (2 equiv.).

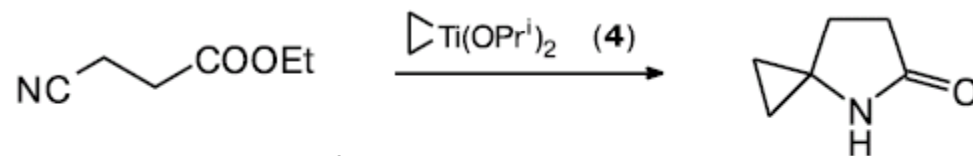


Chem. Eur. J., 2002, 8, 3789.

Szymoniak variation:

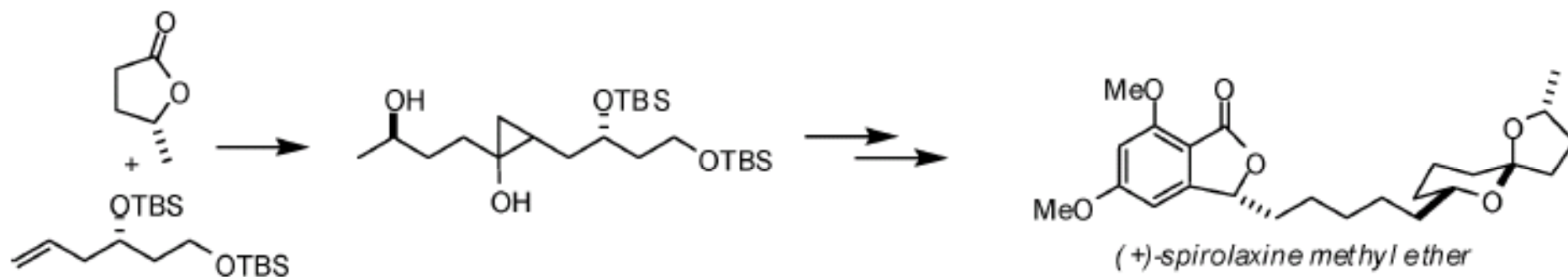
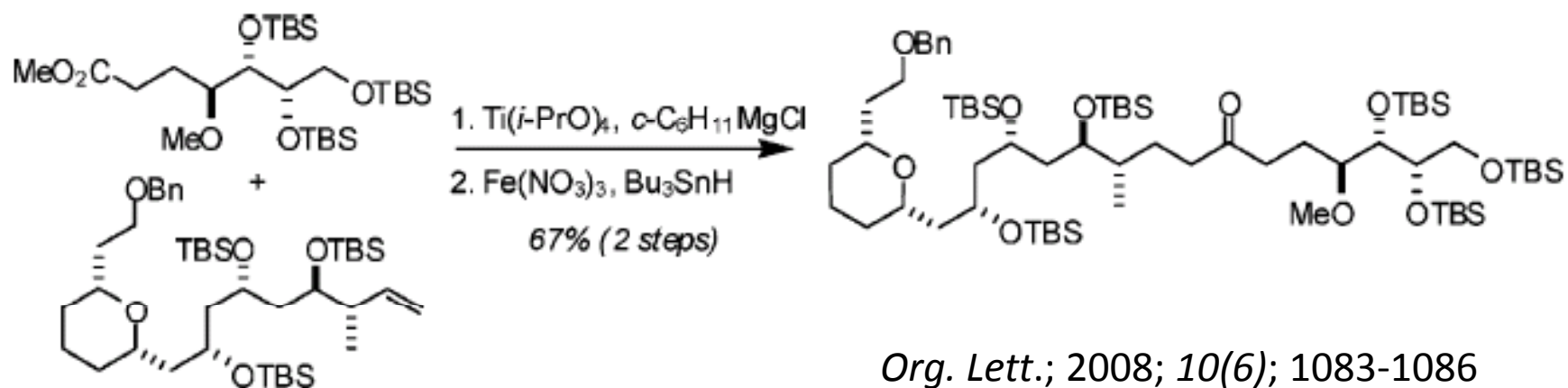


J. Org. Chem., 2002, 67, 3965.



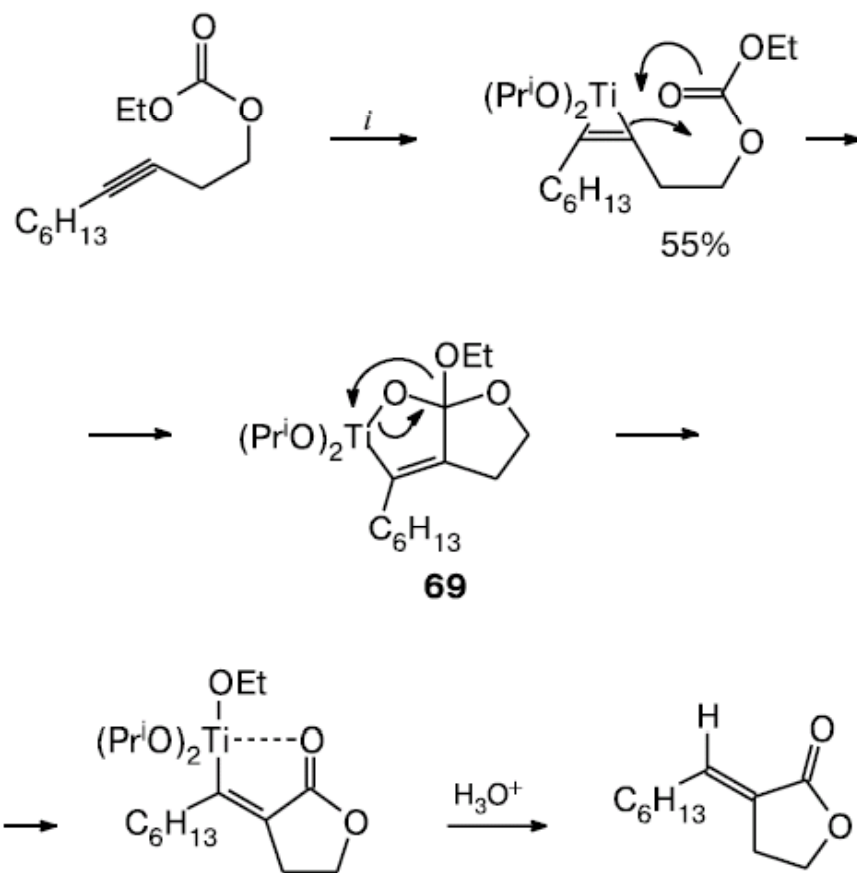
Synlett, 2003, 265.

Total Synthesis



Org. Lett.; 2007; 9(14); 2717-2719

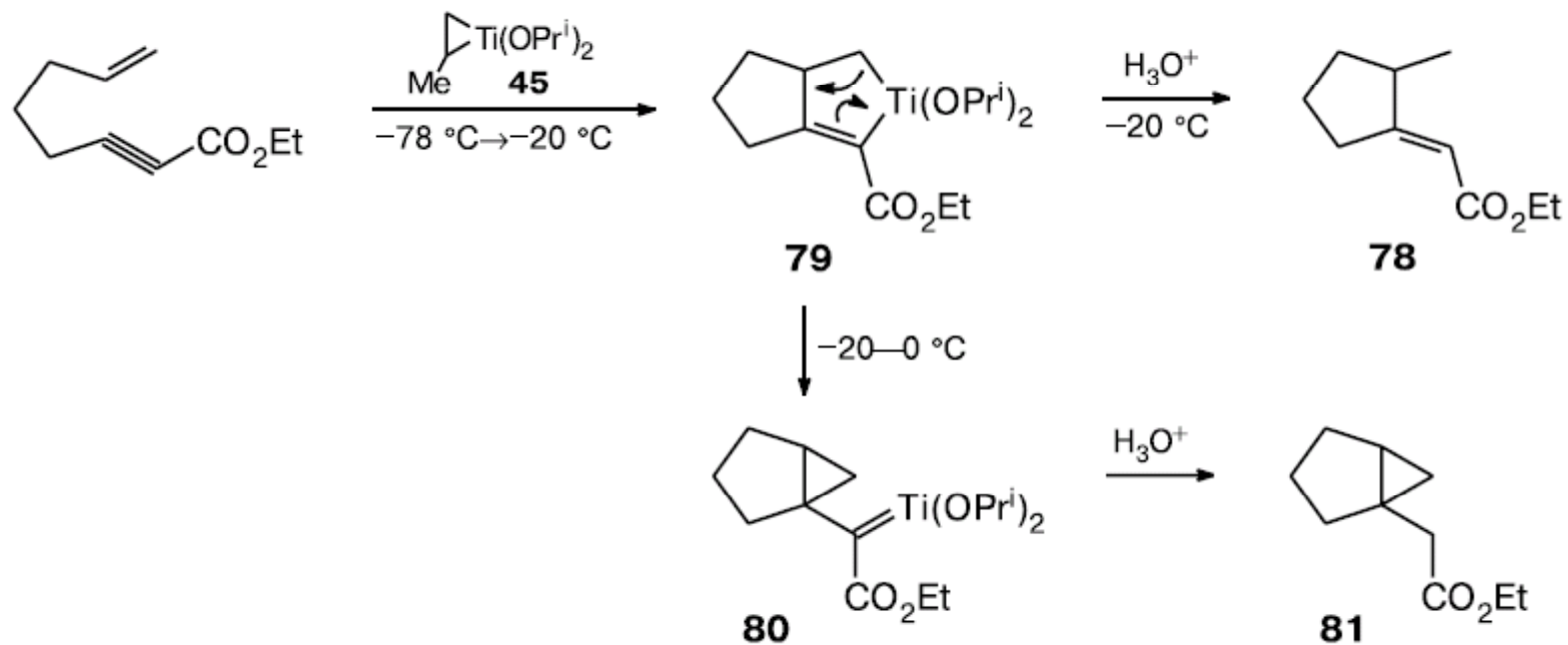
More than the Reaction-1



i. Pr^iMgBr (2 equiv.), $\text{ClTi}(\text{OPr}^i)_3$.

Tetrahedron Lett., 1995, 36, 6075

More than the Reaction-2



J. Am. Chem. Soc.; 1996; 118(36); 8729-8730

Limitations

- Enantioselective Versions
- Mono-substituted nucleophile
- Further transformations based on the product needed