

The Kulkinovich Reaction

Modern Routes to Cyclopropyl Derivatives
Using Titanium- “Lord of the Small Rings”

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Literature Presentation

21 June 2011

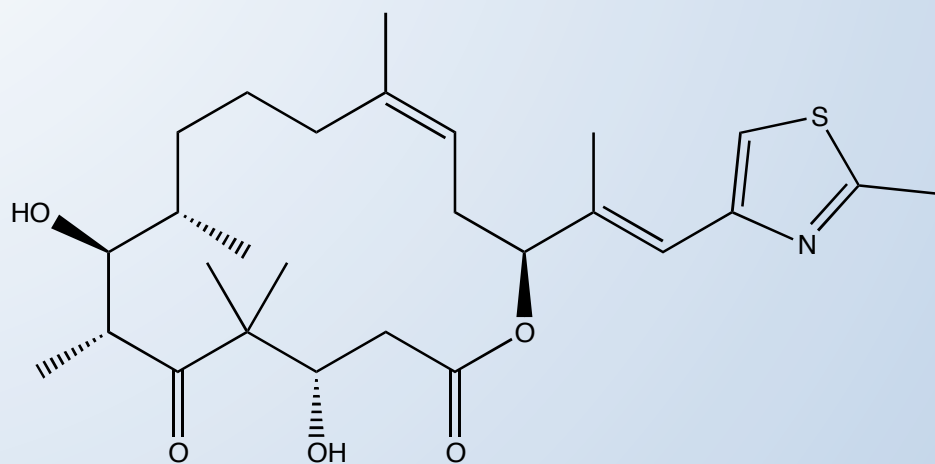
Cyclopropanes



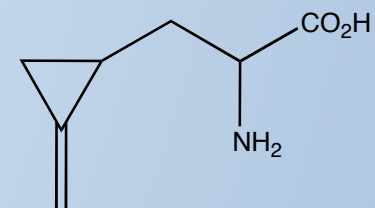
$X = \text{OH}, \text{NR}_2, \text{NH}_2$

- Common drug and agrochemical targets
- Important intermediates in complex molecular synthesis
- Present in more than 4,000 natural products

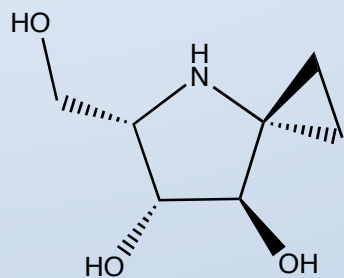
Cyclopropanes in Nature



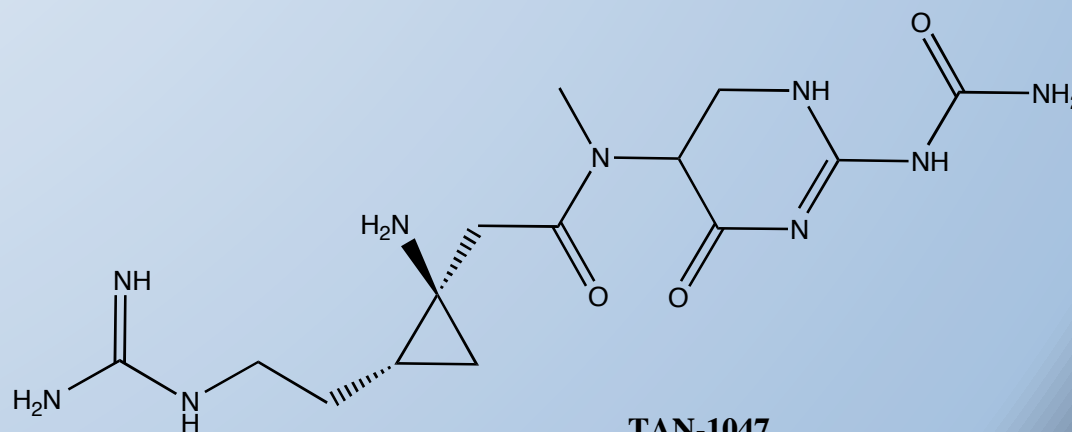
Epothilone D



Hypoglycine A

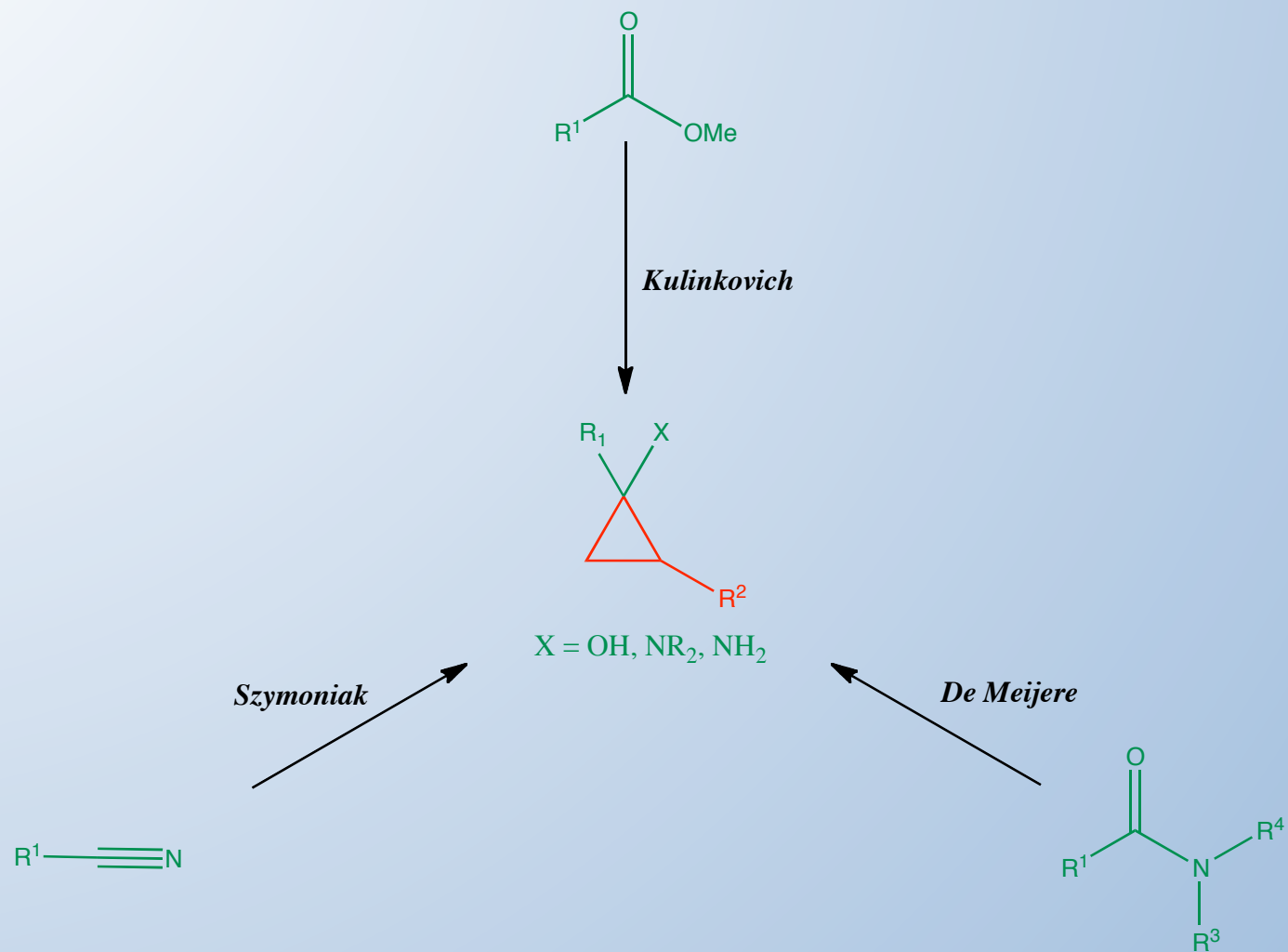


Iminosugars

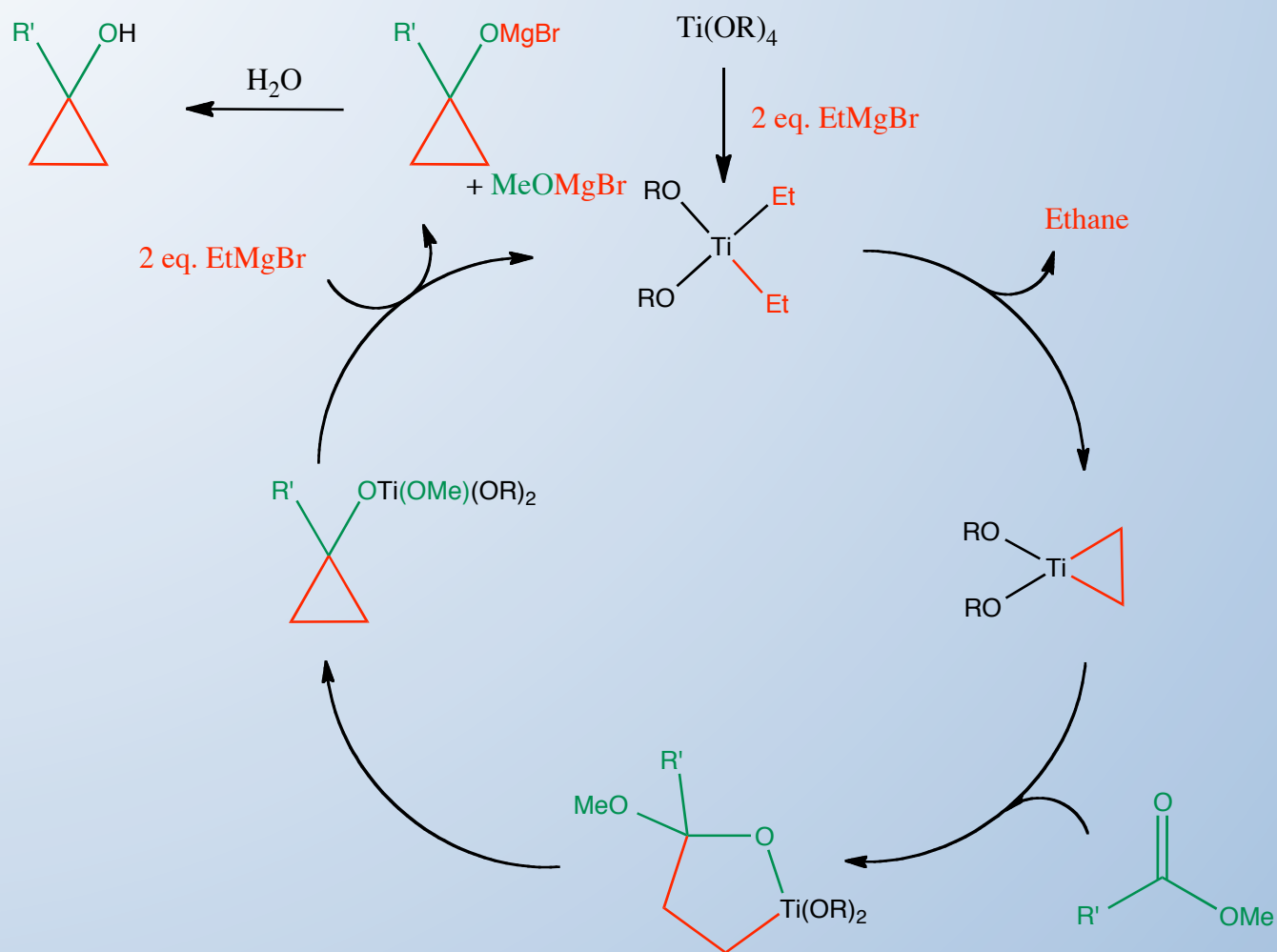


TAN-1047
(β-aminoacid analogue)

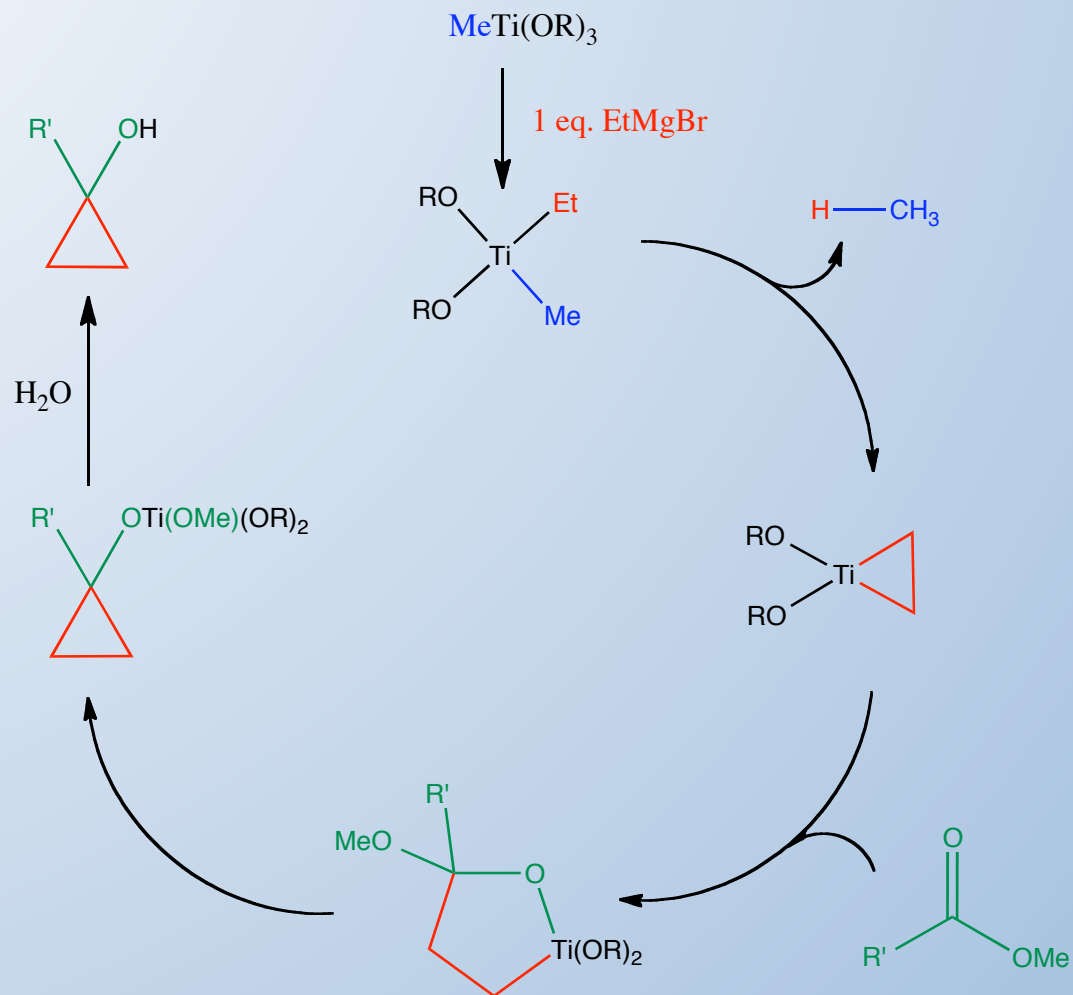
Kulinkovich Reaction



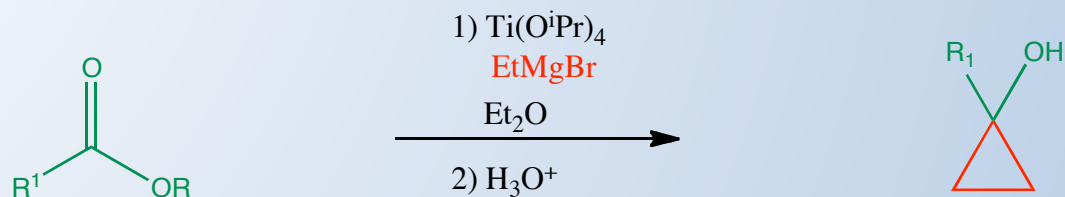
Mechanism



Mechanism

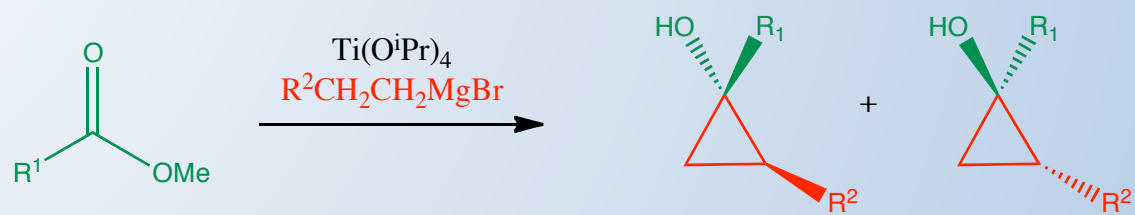


Substituted Cyclopropanols



R_1	R	Yield
Me	OMe	76
$n\text{-C}_9\text{H}_{19}$	OMe	98
$i\text{Pr}$	OMe	88
c-Hex	OMe	85
$\text{HC}=\text{CH}_2$	OMe	11
Ph	OEt	93
$\text{CH}_2\text{CH}_2\text{Br}$	OMe	86
CH_2SiMe_3	OMe	67
$\text{CH}_2\text{CH}_2\text{P}(\text{O})(\text{O}^i\text{Pr})_2$	OMe	67

1,2-Disubstituted Cyclopropanols



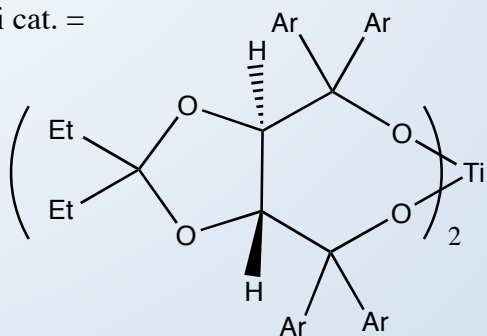
R_1	R^2	Yield
$n\text{-C}_3\text{H}_7$	C_2H_5	79
$n\text{-C}_6\text{H}_{13}$	C_2H_5	81
$n\text{-C}_6\text{H}_{13}$	$n\text{-C}_6\text{H}_{13}$	88
H	$n\text{-C}_6\text{H}_{13}$	72
$\text{CH}_2\text{CH}_2\text{P}(\text{O})(\text{O}^i\text{Pr})_2$	Et	71
	$\text{CH}_2\text{CH}_2\text{OTIPS}$	77

Corey, E. J.; Rao, S. A.; Noe, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 9345-9346

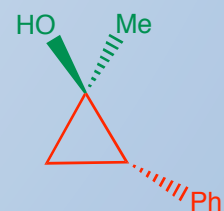
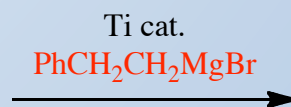
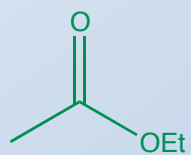
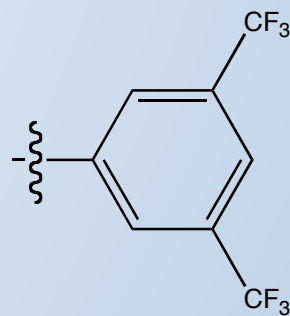
De Meijere, A.; Kulinkovich, O. *Chem Rev.*, **2000**, *100*, 2789-83

Asymmetric Variant

Ti cat. =

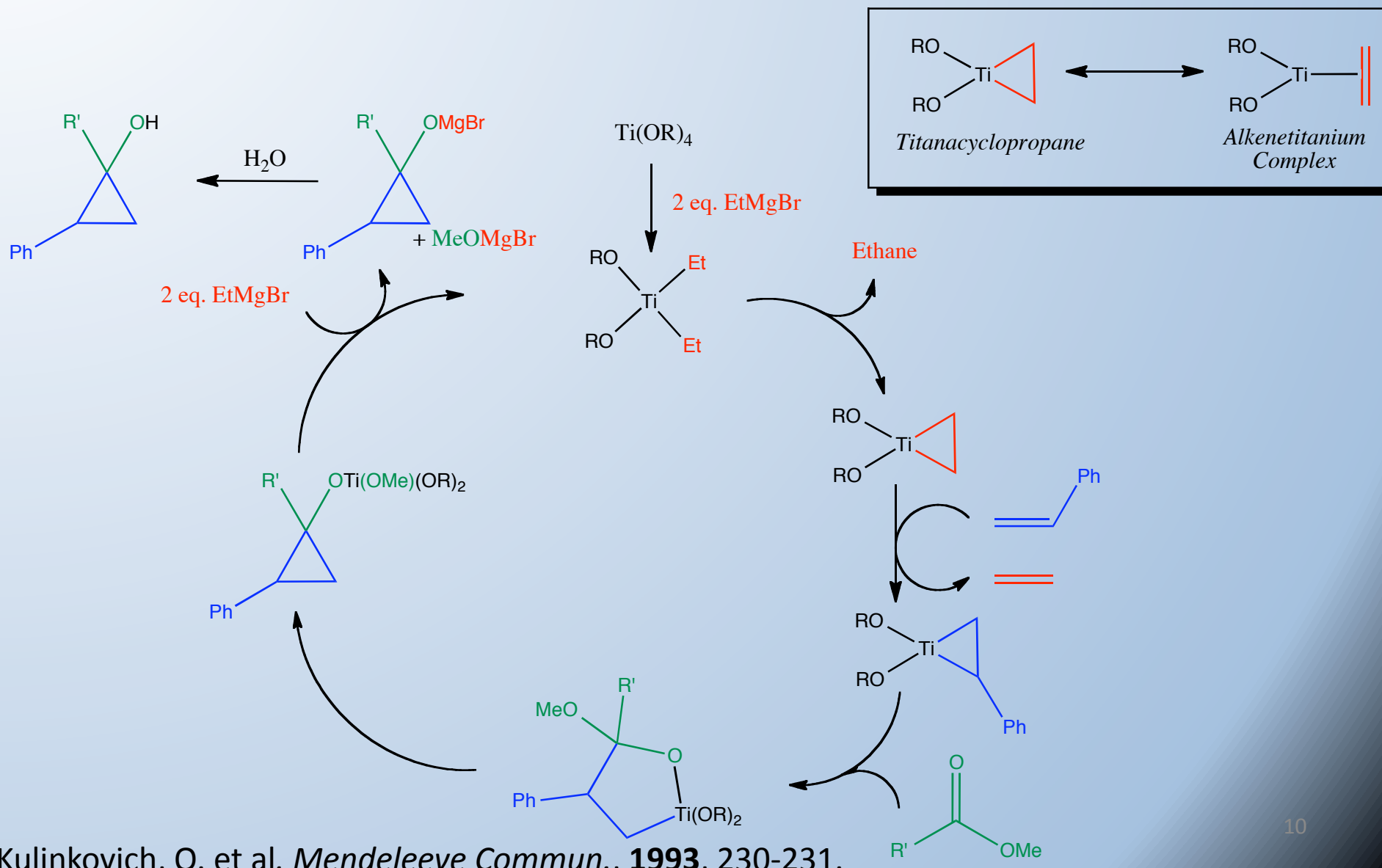


Ar =

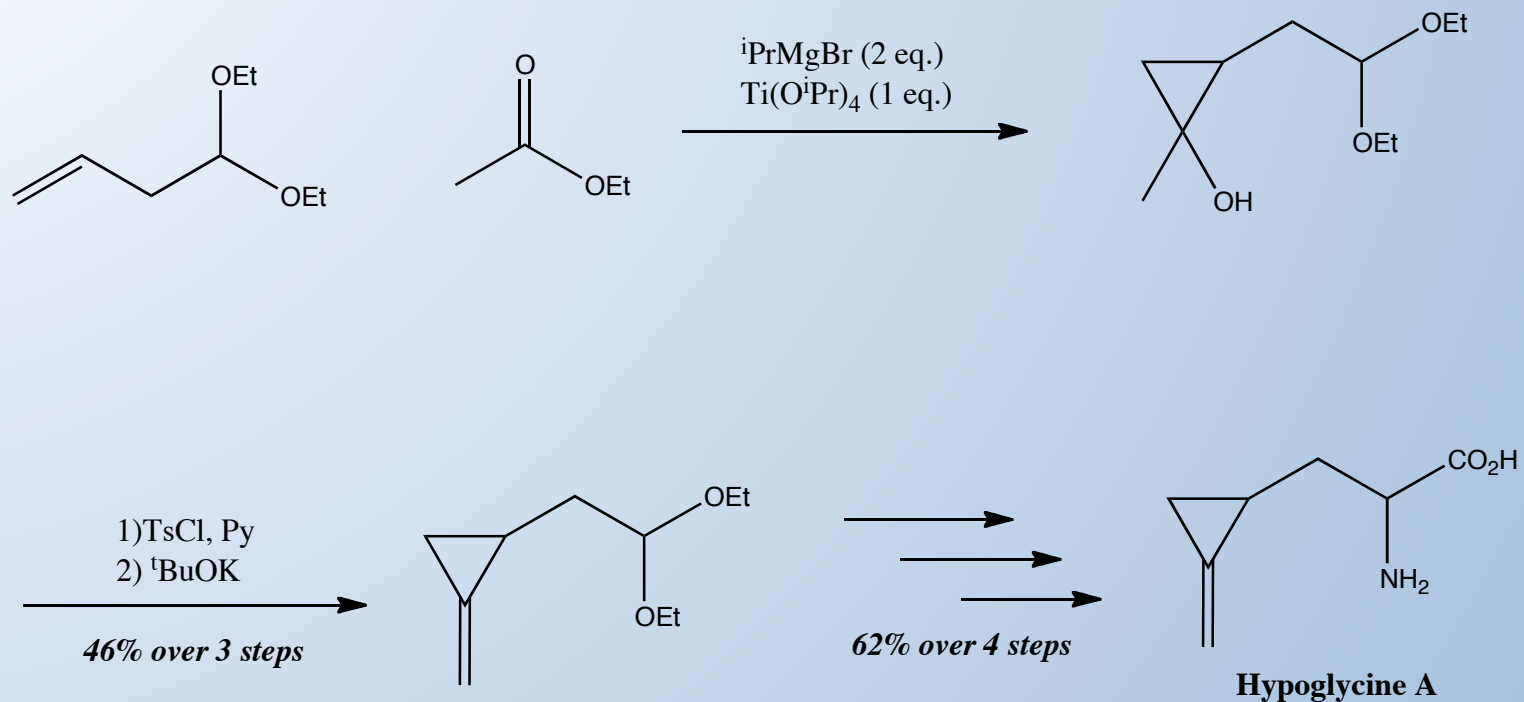


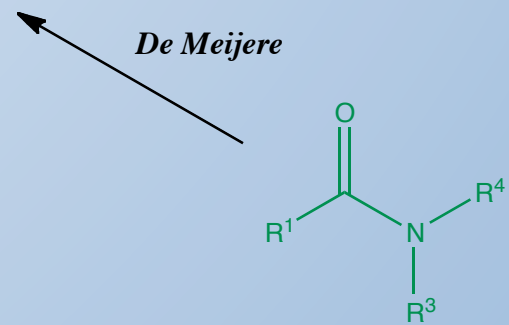
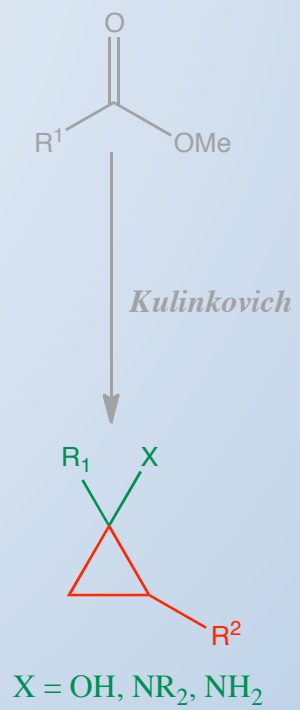
up to 78% ee

Hydroxycyclopropanation of Alkenes

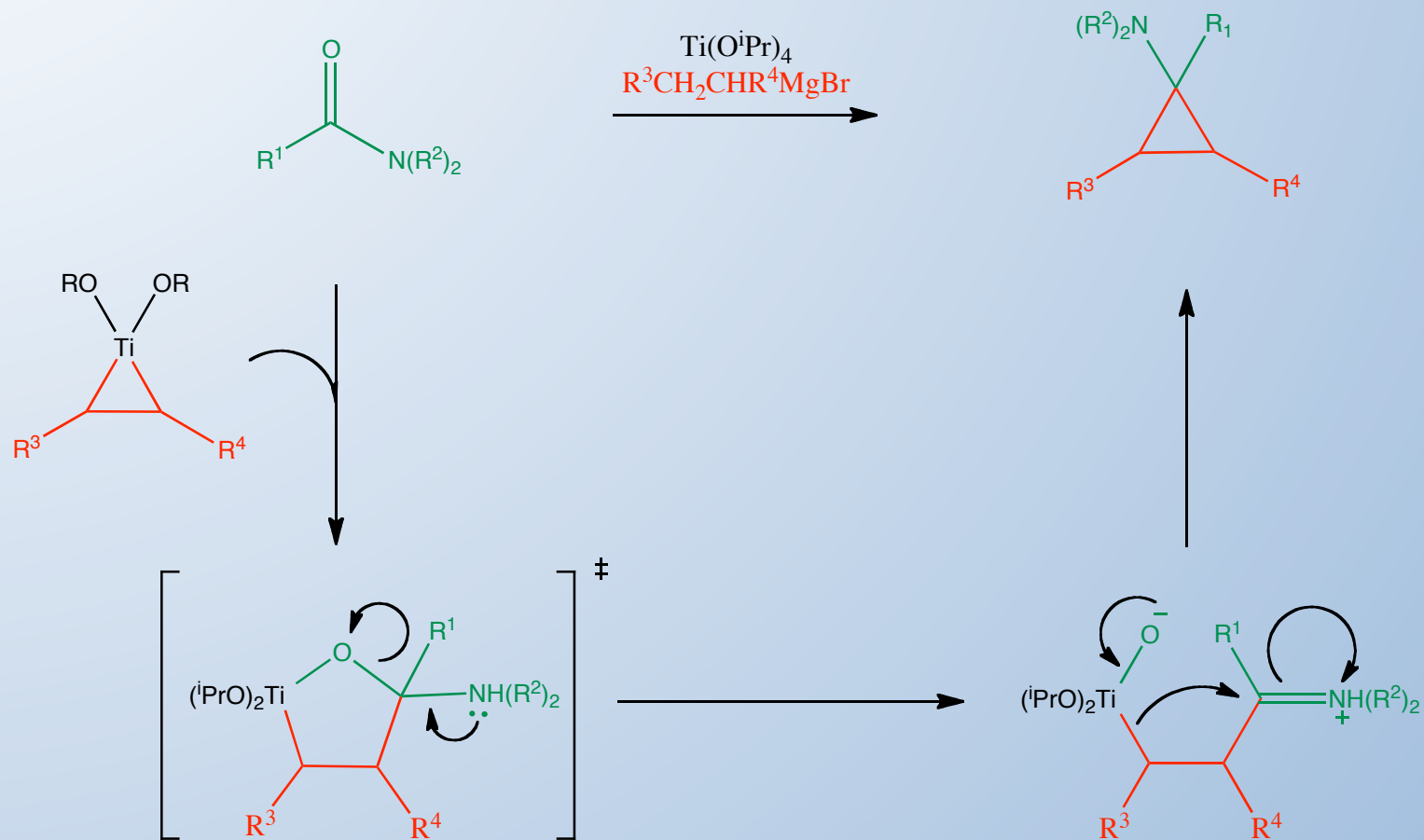


Hypoglycine A

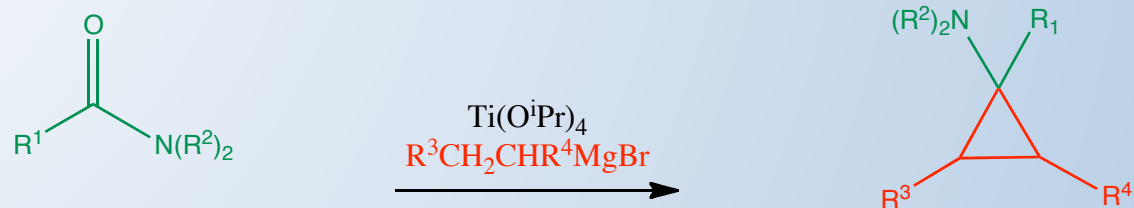




De Meijere Modification

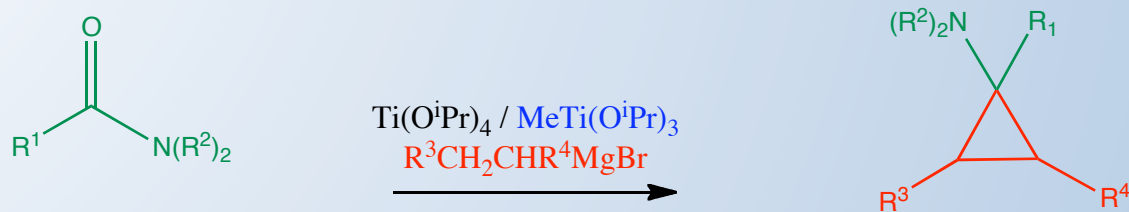


De Meijere Scope



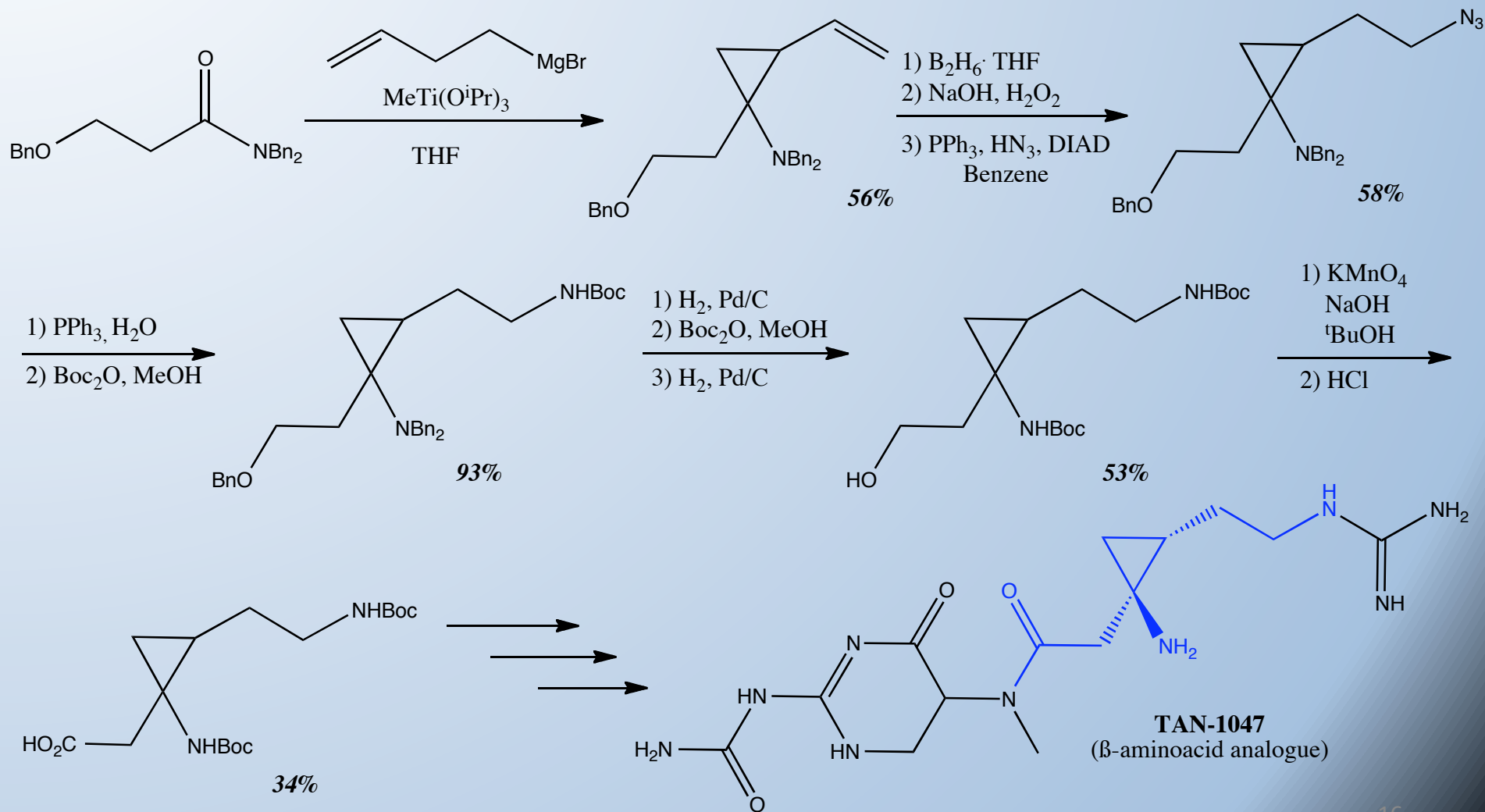
R ¹	R ²	R ³	R ⁴	Yield
H	Bn	H	H	73
H	<i>t</i> -Bu	H	H	20
Et	Bn	H	H	63
<i>n</i> -Pr	Bn	<i>n</i> -Bu	H	35

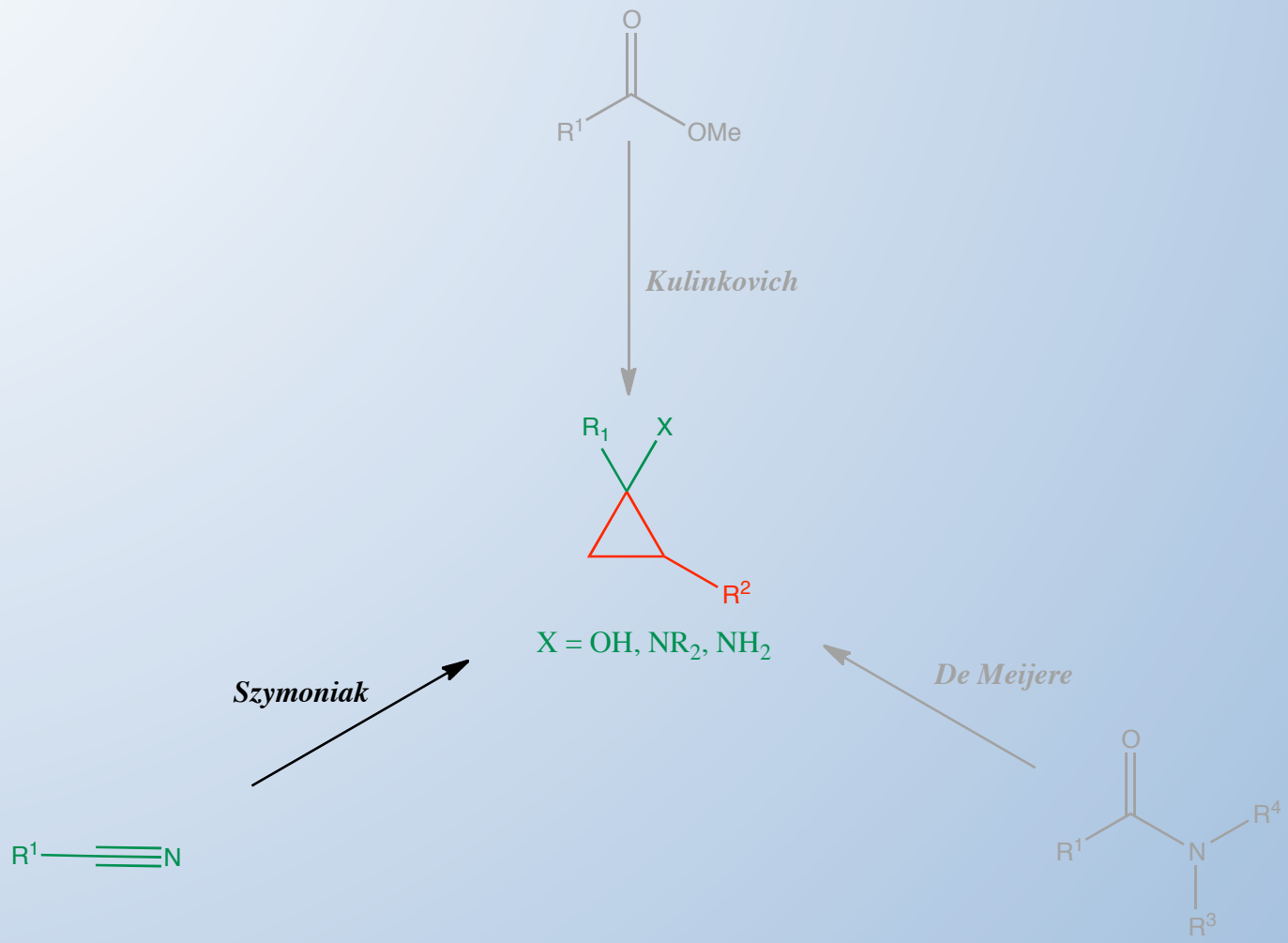
De Meijere Scope



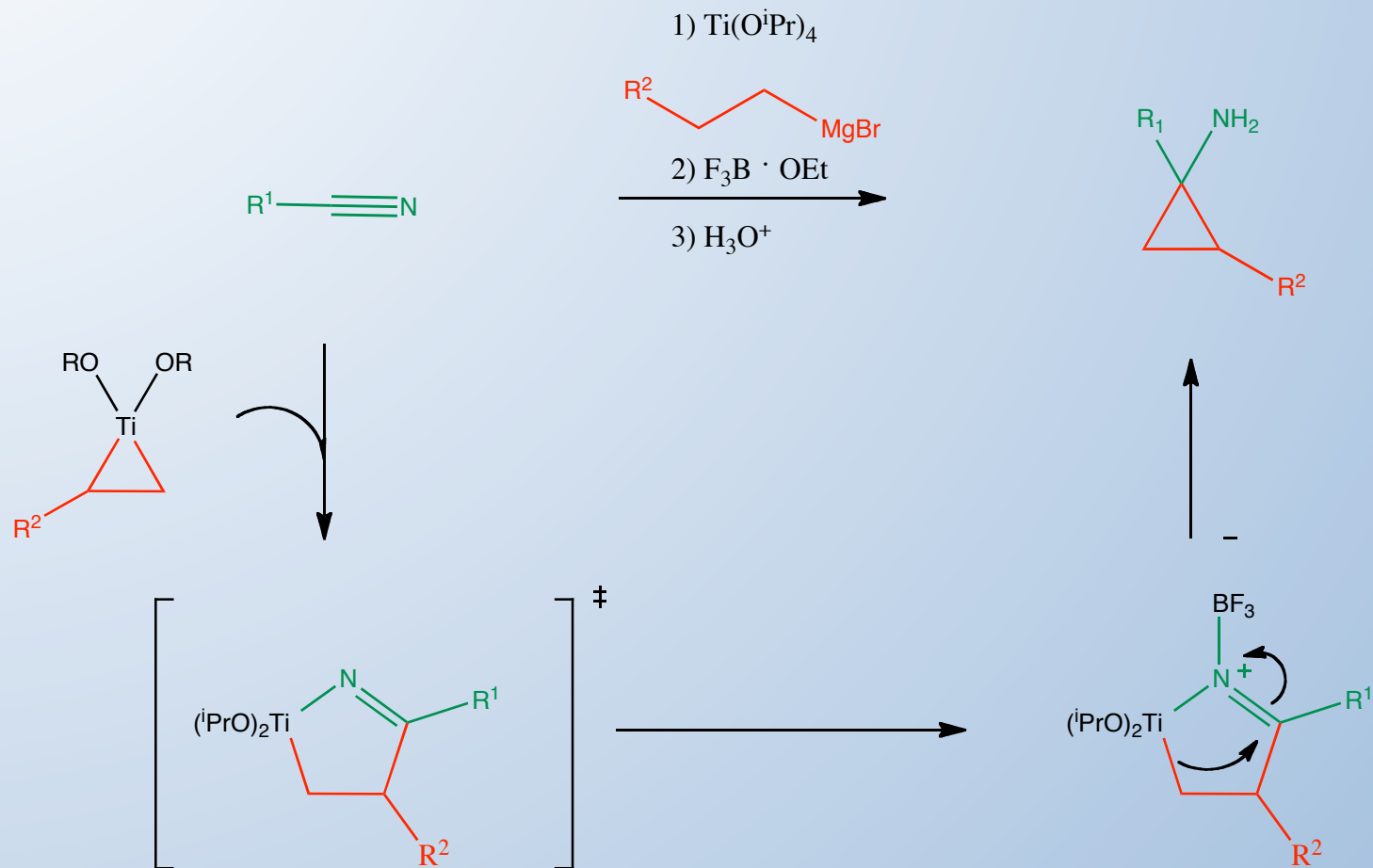
R ¹	R ²	R ³	R ⁴	Yield	Yield
H	Bn	H	H	73	-
H	<i>t</i> -Bu	H	H	20	-
Et	Bn	H	H	63	-
<i>n</i> -Pr	Bn	<i>n</i> -Bu	H	35	-
H	Bn	H	H	-	95
CH ₂ CH ₂ Cl	Bn	H	H	-	49
CH(OMe)CH ₃	Bn	H	H	-	63
CH ₂ CH ₂ P(O)Ph ₂	CH ₃	CH ₃	H	-	80 (1:3.5)

TAN-1047 Analogues

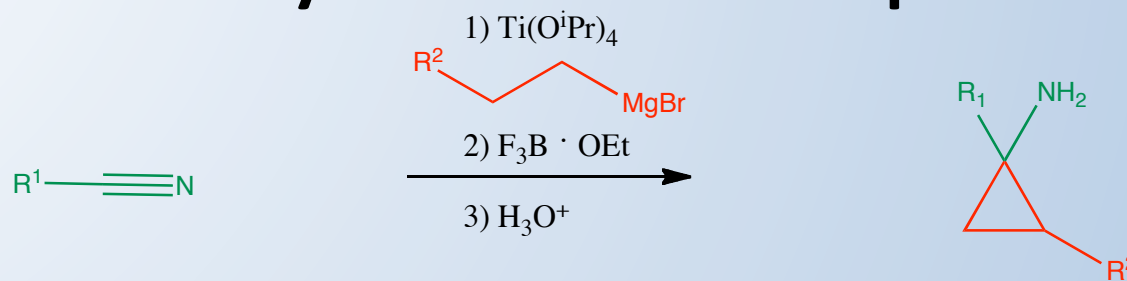




Szymoniak Modification



Szymoniak Scope

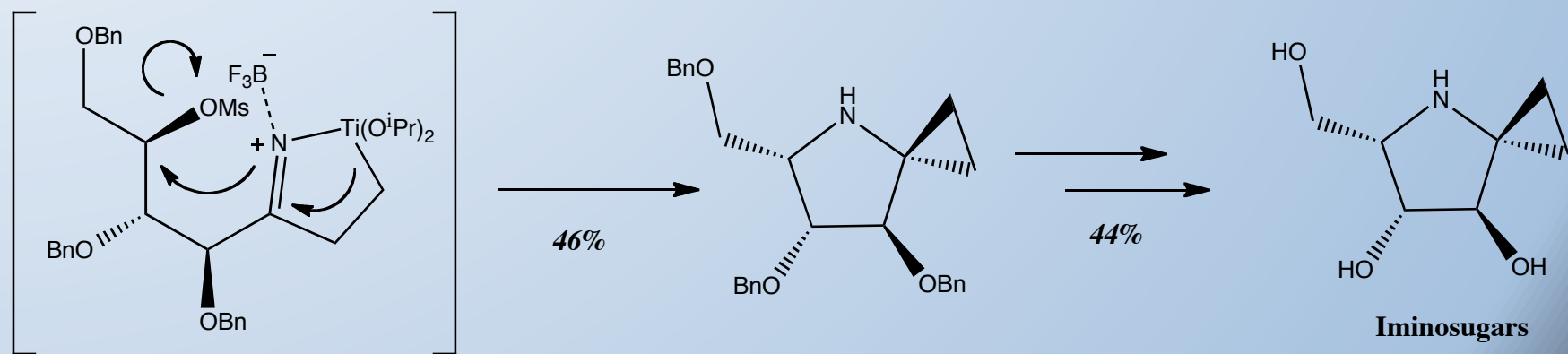
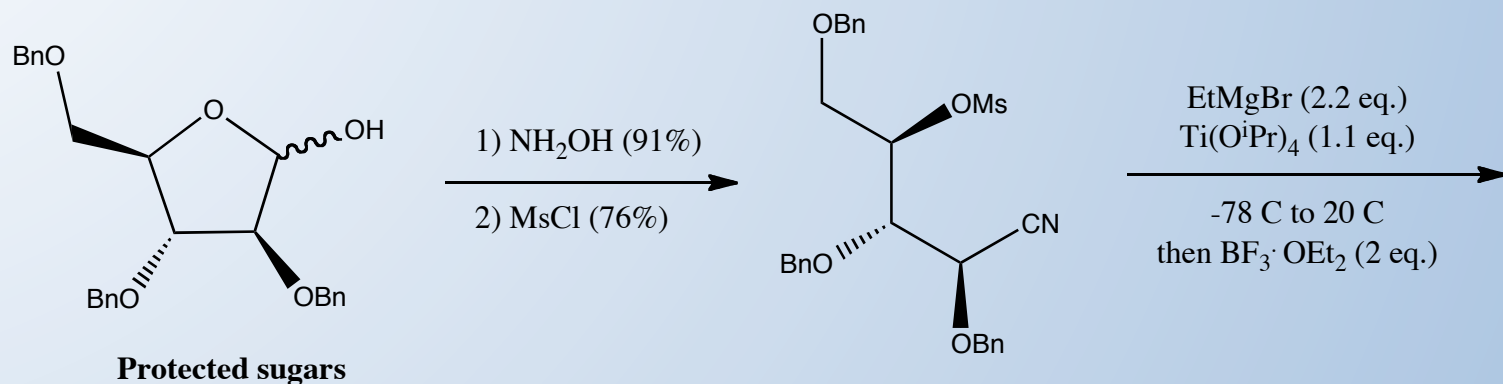


R ¹	R ²	Yield
	R = OMe	43
	R = Me	73
	R = F	64
Bn	H	70
<i>n</i> -C ₉ H ₁₉	H	70
C ₆ H ₁₁	H	52
Bn	<i>n</i> -Bu	57 (64:36)
Bn	<i>s</i> -Bu	54 (55:45)

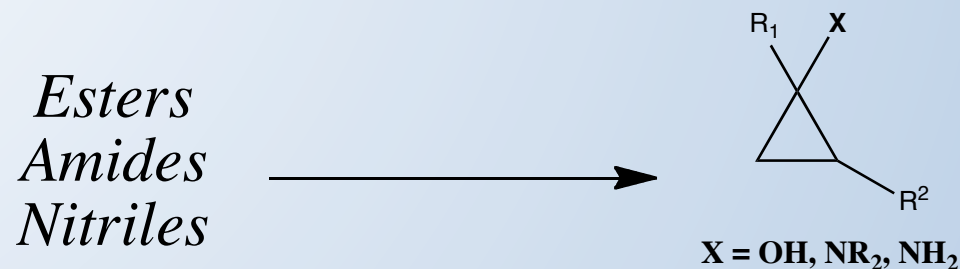
Bertus, P.; Szymoniak, J. *Chem. Commun.*, **2001**, 1792-1793

Bertus, P.; Szymoniak, J. *J. Org. Chem. Note*, **2003**, 7133-7136

Imino Sugars



Conclusion



- Kulinkovich: Esters to cyclopropanols
 - De Meijere: Amides to cyclopropylamines
 - Szymoniak: Nitriles to cyclopropylamines
- Enantioselective variants using TADDOL based ligands