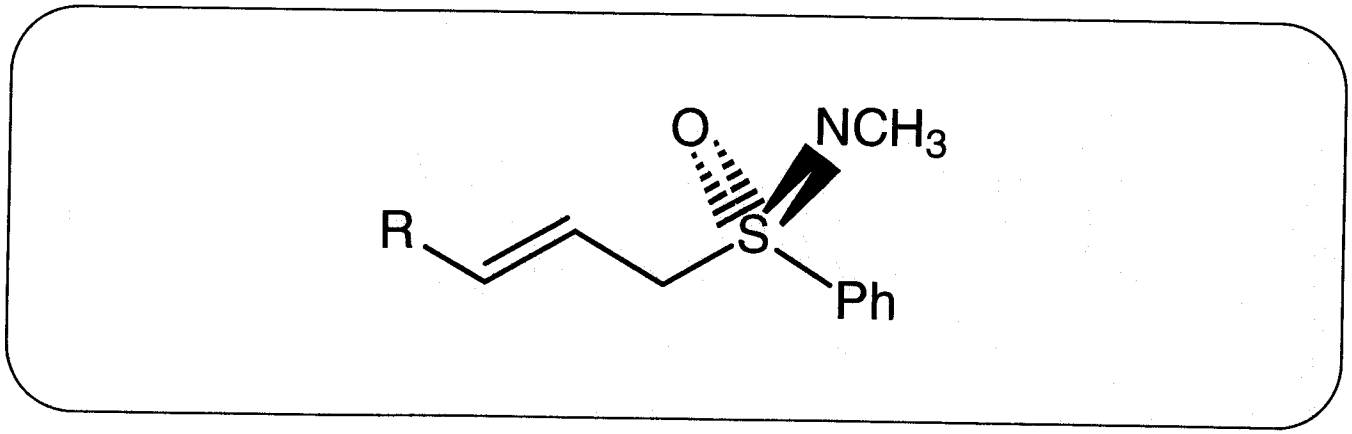
Structure, Hydroxy- and Aminoalkylation of Titanaallylsulfoximines: Enantioselective Synthesis of Unsaturated α-Amino Acids

Dissertation
Marcel Schleusner



Survey

- Part I: Hydroxy- and Aminoalkylation
  - Synthesis of sulfoximines, metallation and general reactivity

- Part II: Structure of Titanaallylsulfoximines■
  - General structure, possibilities and dynamic processes in solution

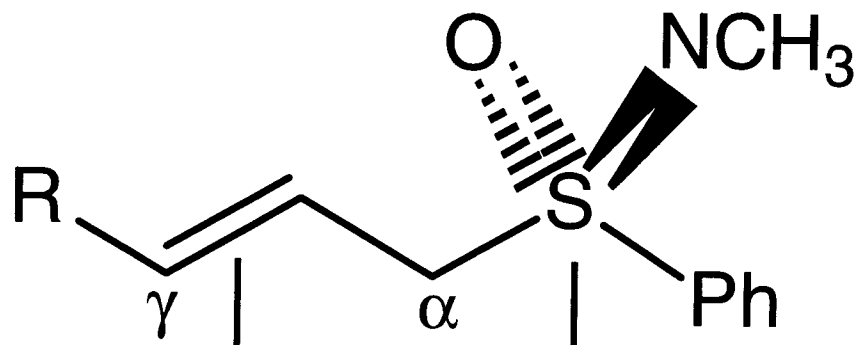
Part I

- Introduction
  - Sulfoximines, allylic sulfoximines and allylic titanasulfoximines
  - General reactivity of allylic titanasulfoximines

- Reactions of allylic alkoxytitanasulfoximines
  - γ-Hydroxyalkylation
  - γ-Aminoalkylation
  - Protecting groups
  - Further functionalizations

- Conclusion

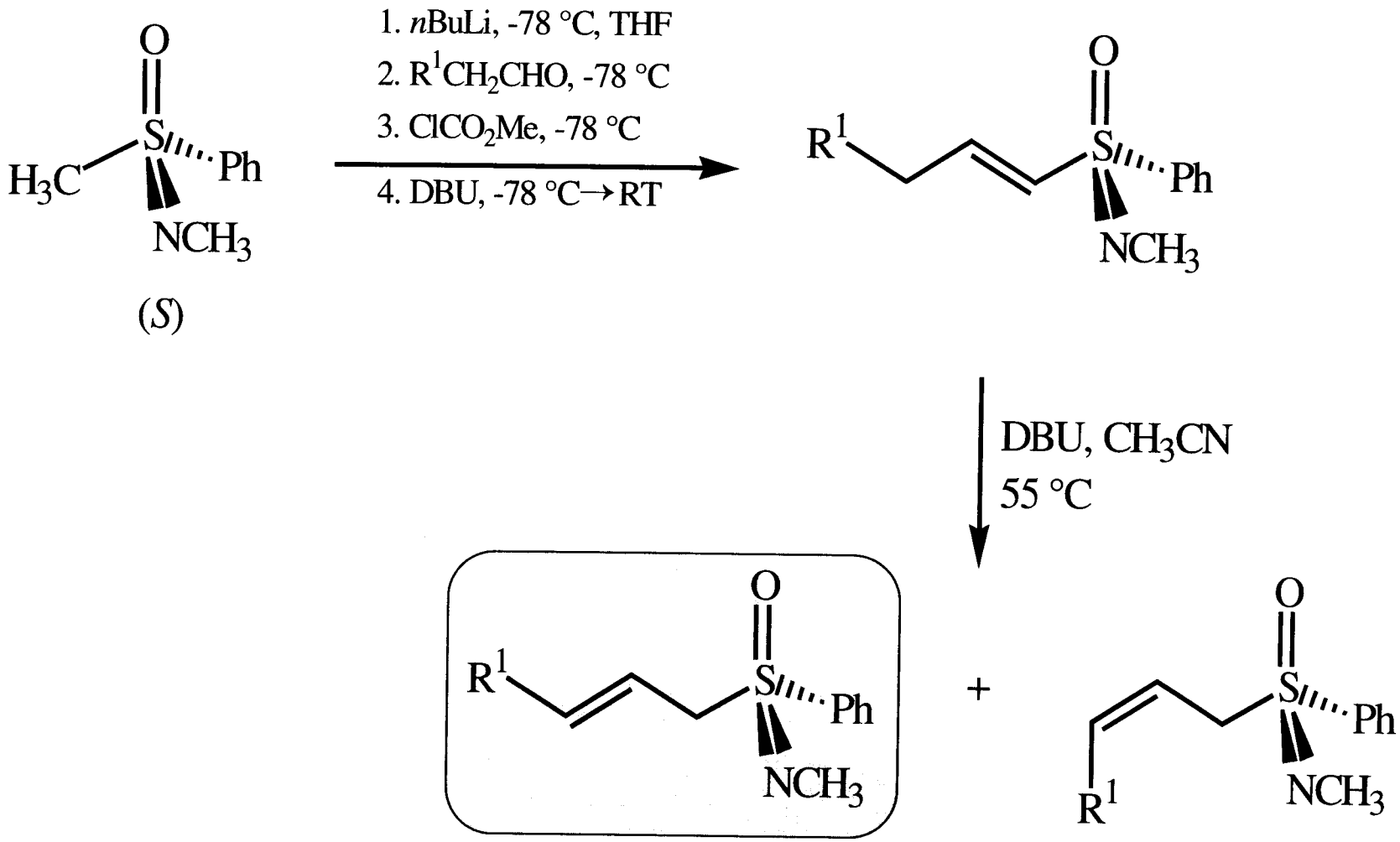
Properties of Allylic Sulfoximines



- Reactivity in α- and γ-position
- (*E*)- and (*Z*)-configuration
- Valuable functionalisation

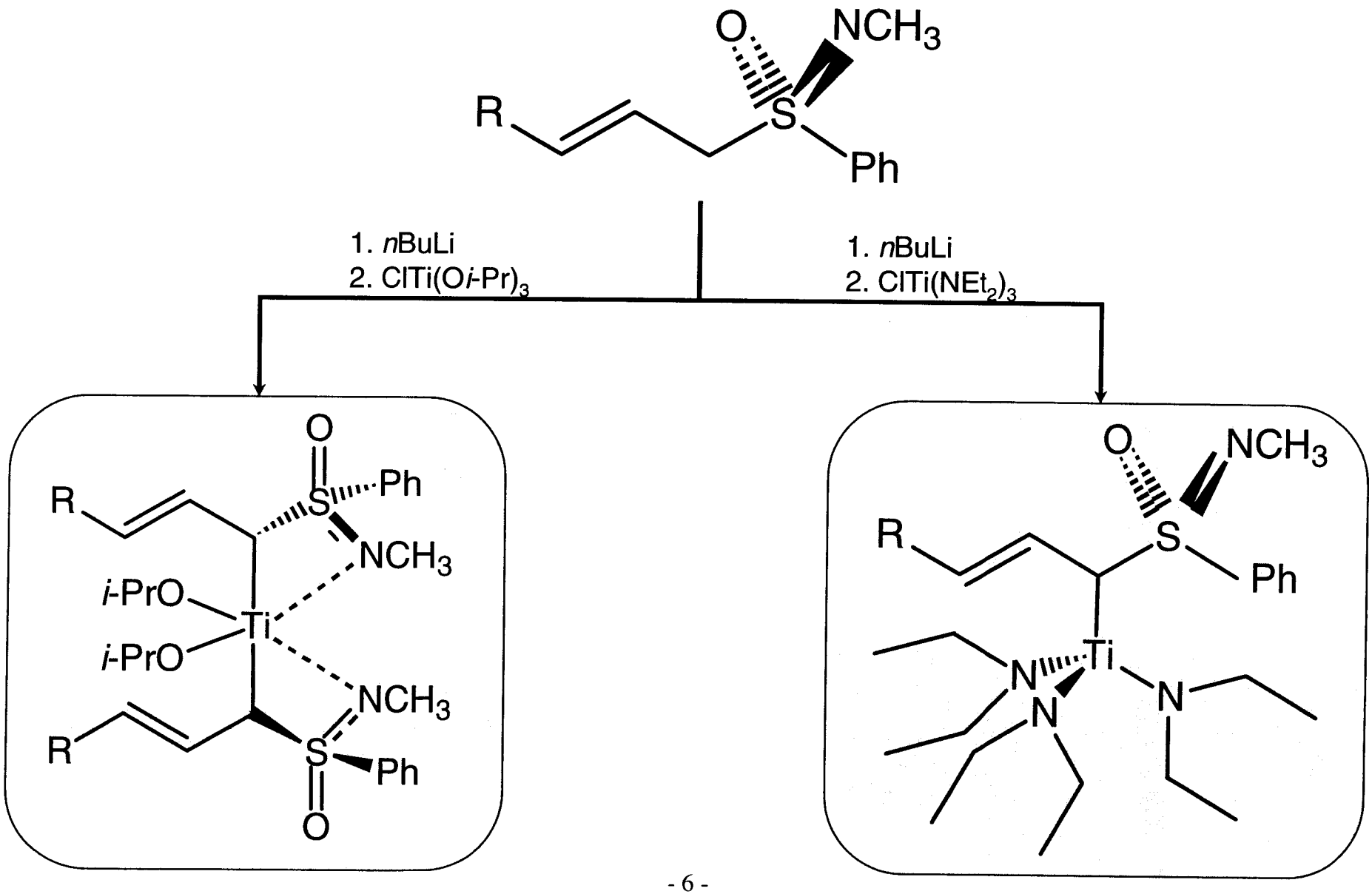
- Tetrahedral center of chirality
- Carbanion stabilisation
- Nucleofugacity
- Accessible in enantiopure form
- Basic nitrogen center

Synthesis of Allylic Sulfoximines

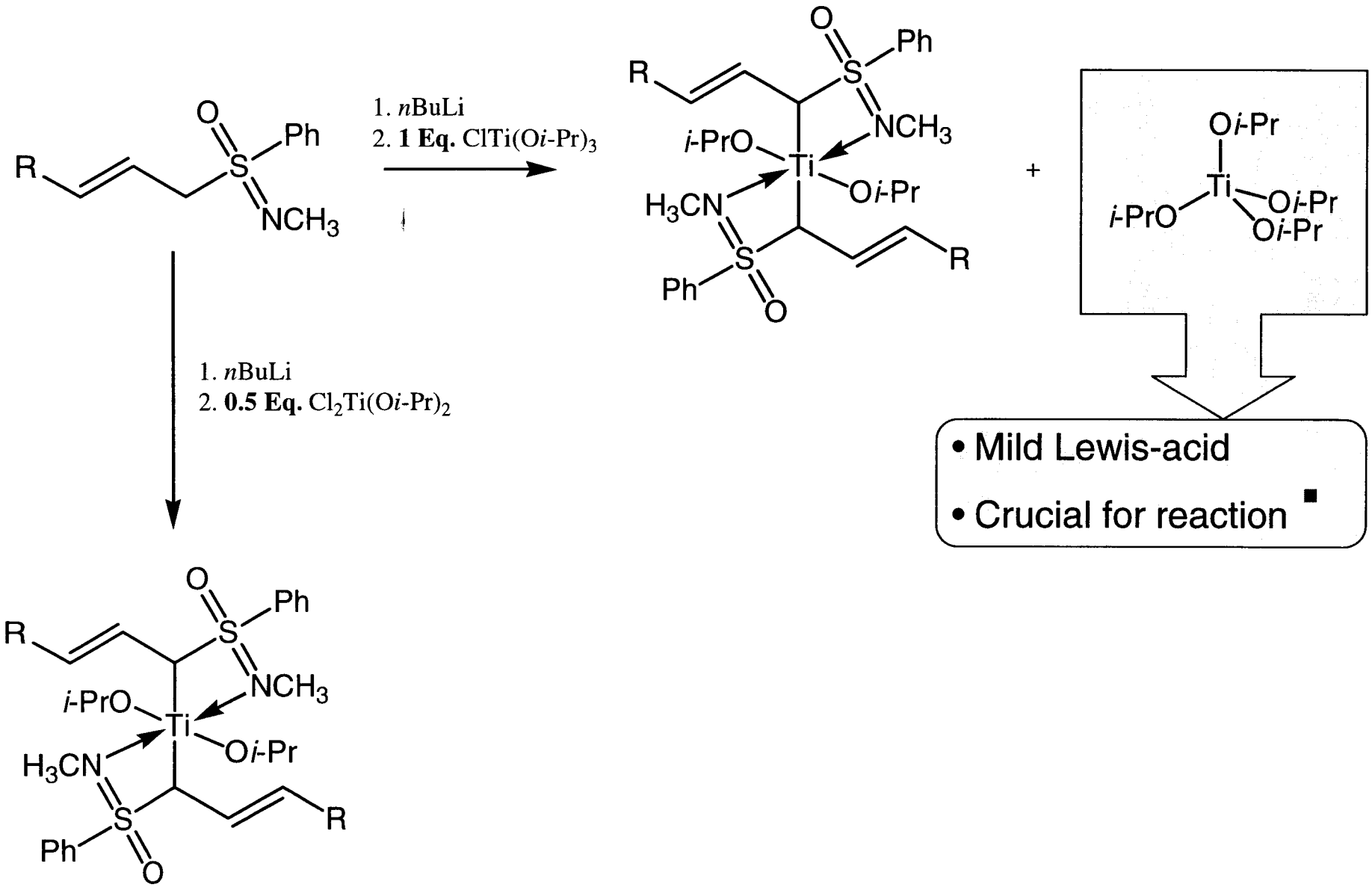


typical ratio: 7 : 1

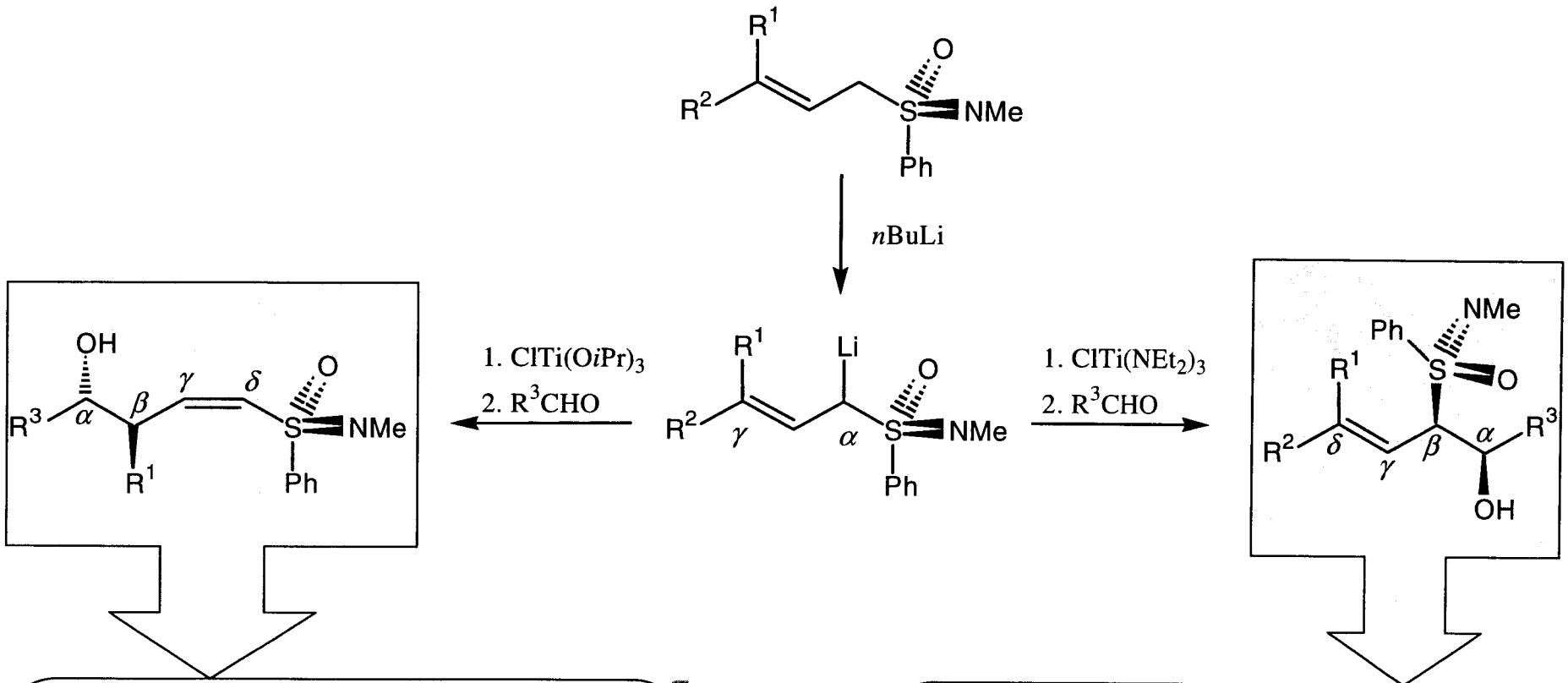
Allylic Titanasulfoximines



Formation of Alkoxytitanasulfoximines



General Reactivity



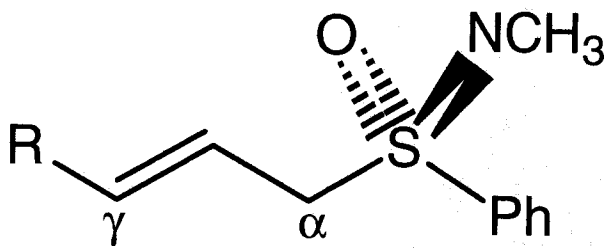
γ-Hydroxyalkylation

- (*Z*)-anti homoallylic alcohols
- δ-Sulfonimidoyl moiety
- *de* > 96%, c.y. 70–85%

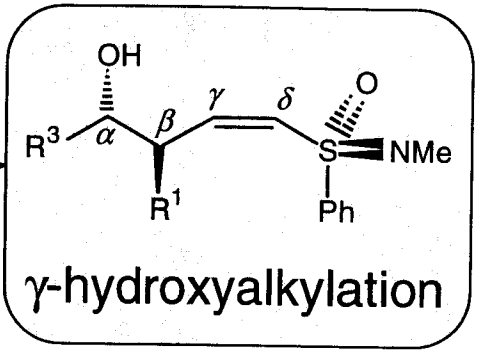
α-Hydroxyalkylation

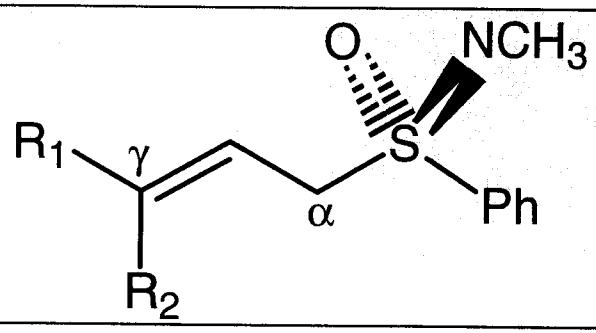
- (*E*)-syn homoallylic alcohols
- β-Sulfonimidoyl moiety
- *de* = 90-98%, c.y. 70–86%

Other Allylic Sulfoximine-Substrates



R= Cyclohexyl, *i*-Propyl, Methyl, Phenyl





(*Z*)-allyl: $\mathbf{R_1}$= H, $\mathbf{R_2}$= Cyclohexyl, *i*-Propyl

unselective

α-hydroxyalkylation

<u>disubstituted allylic sulfoximines:</u>

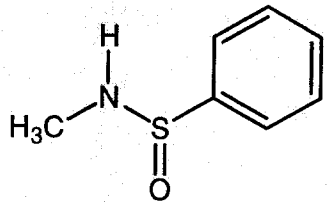
$\mathbf{R_1}$=$\mathbf{R_2}$= *i*-Propyl, Phenyl

$\mathbf{R_1}$= Cyclohexyl, $\mathbf{R_2}$= *i*-Propyl

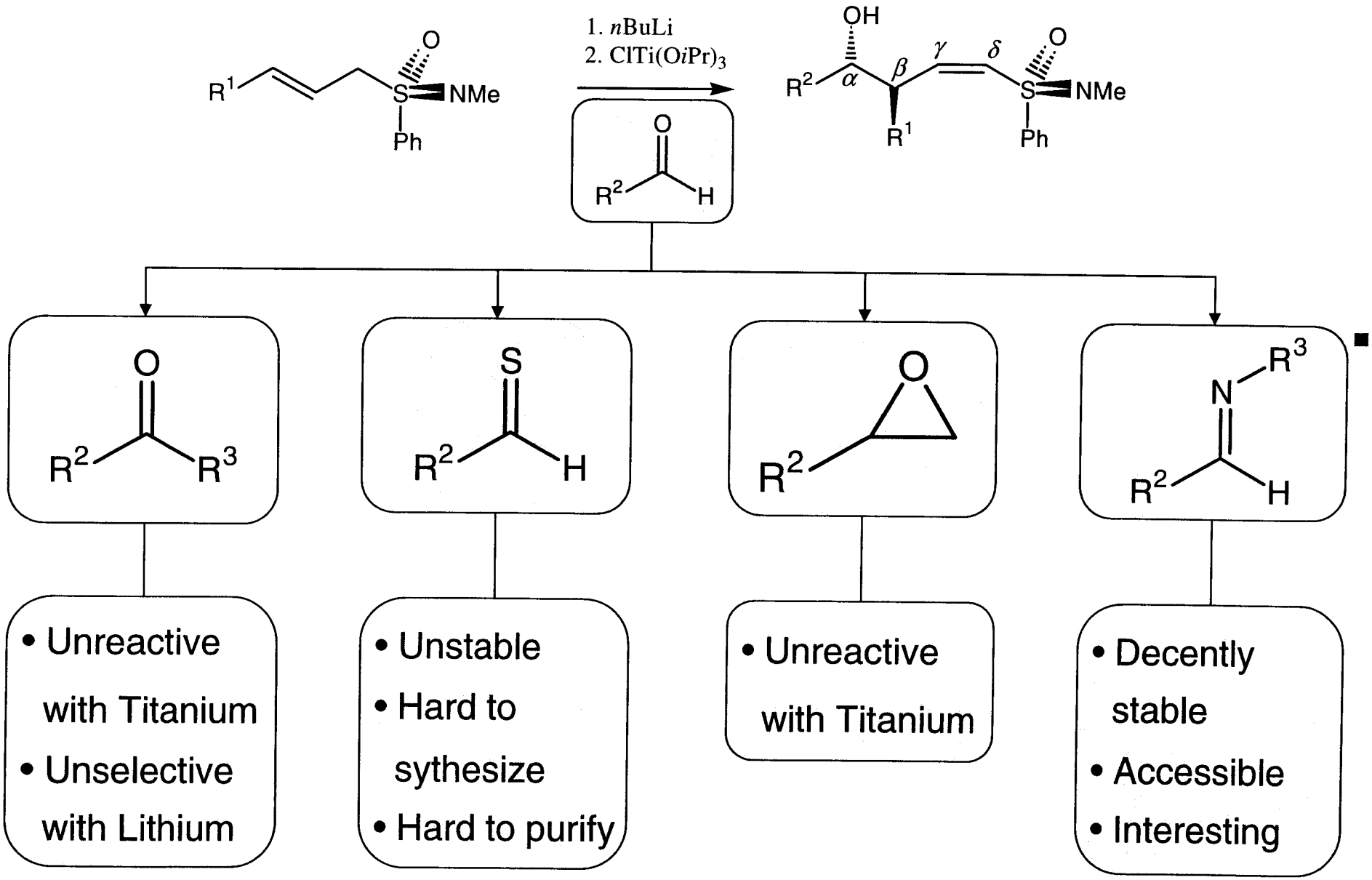
unselective

α-hydroxyalkylation

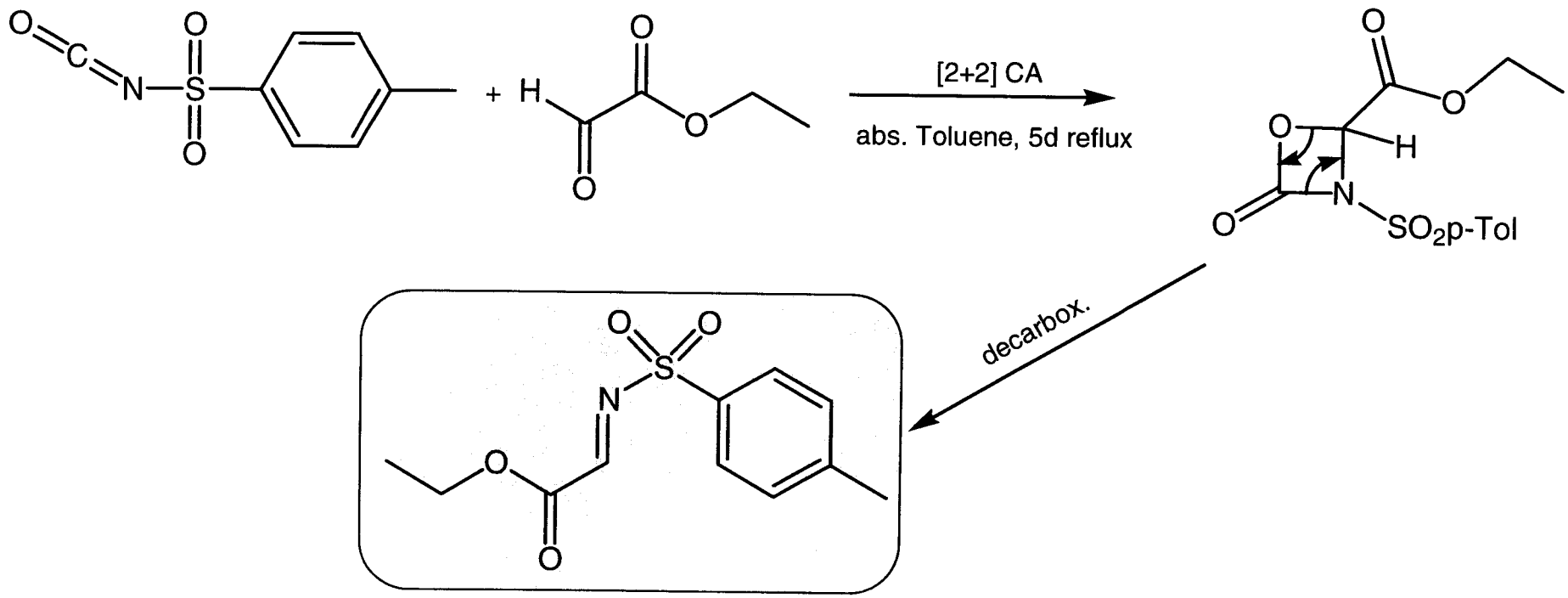
<u>and</u>



Is there more than just Aldehydes?

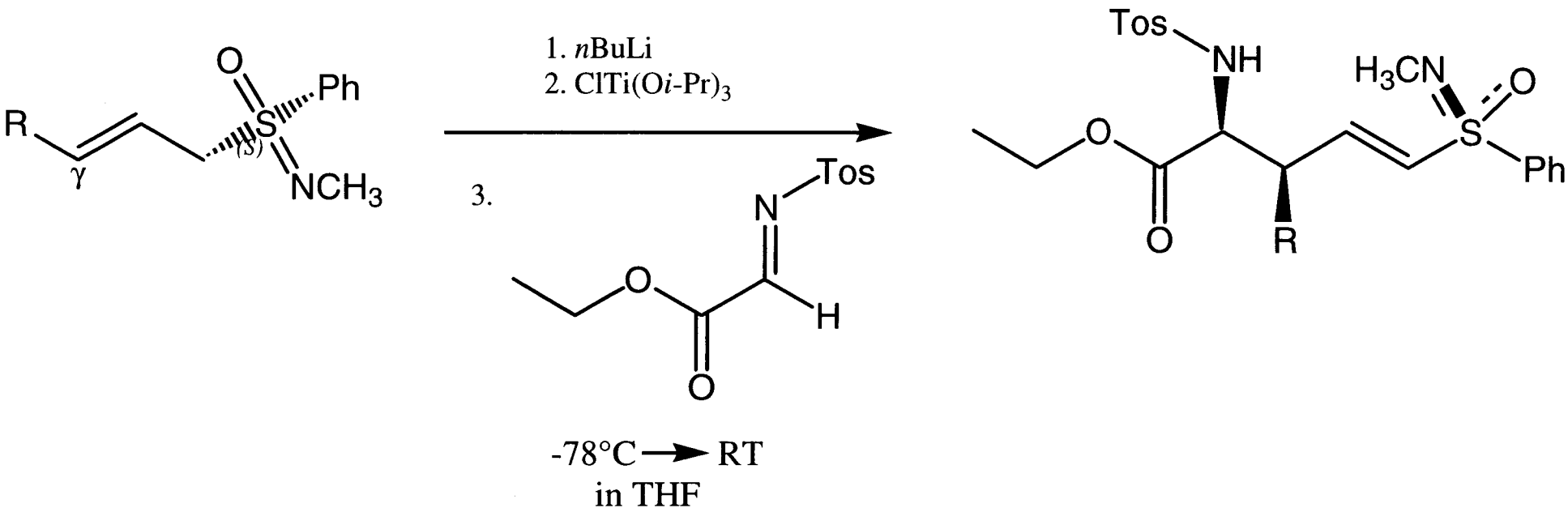


N-Tosylimino Acetate



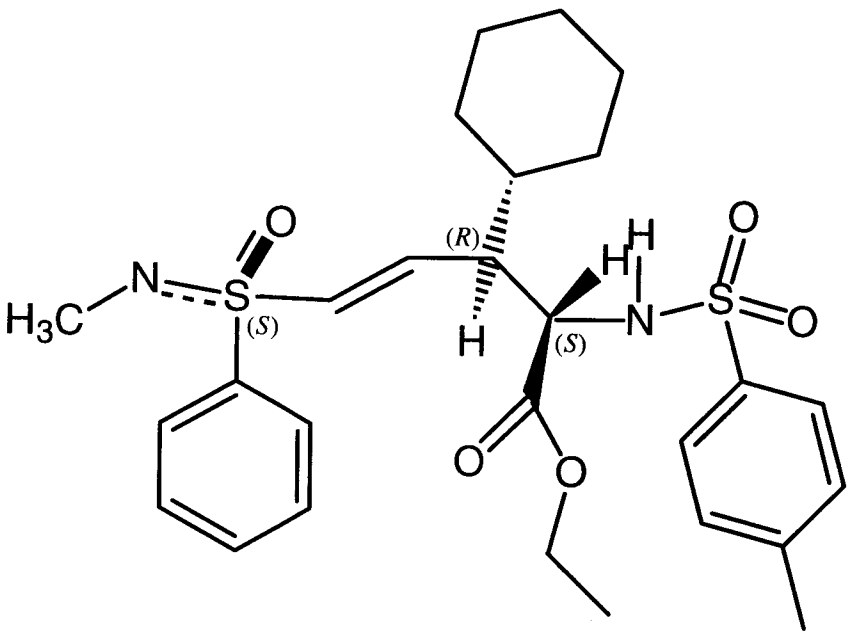
- Electron deficient (COOEt, SO_2)
- Highly reactive (hetero-diels-alder, ene-reactions, metallorganics)
- Stable and distillable (kugelrohr: 150–200 °C, 0.0001 mbar)
- Ester function ⟶ α-amino acids

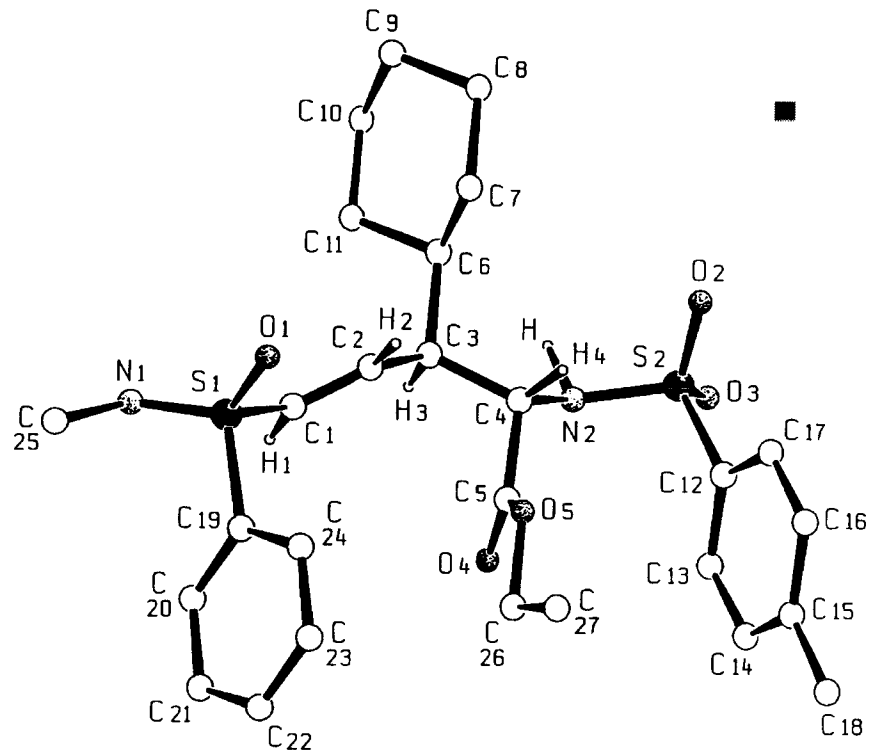
γ-Aminoalkylation with *N*-Tosylimine



- 79–85 % conversion, 59–65 % isolated yield
- *de* > 98%, single diastereomer found
- recrystallisation from ether provides analytically pure substance

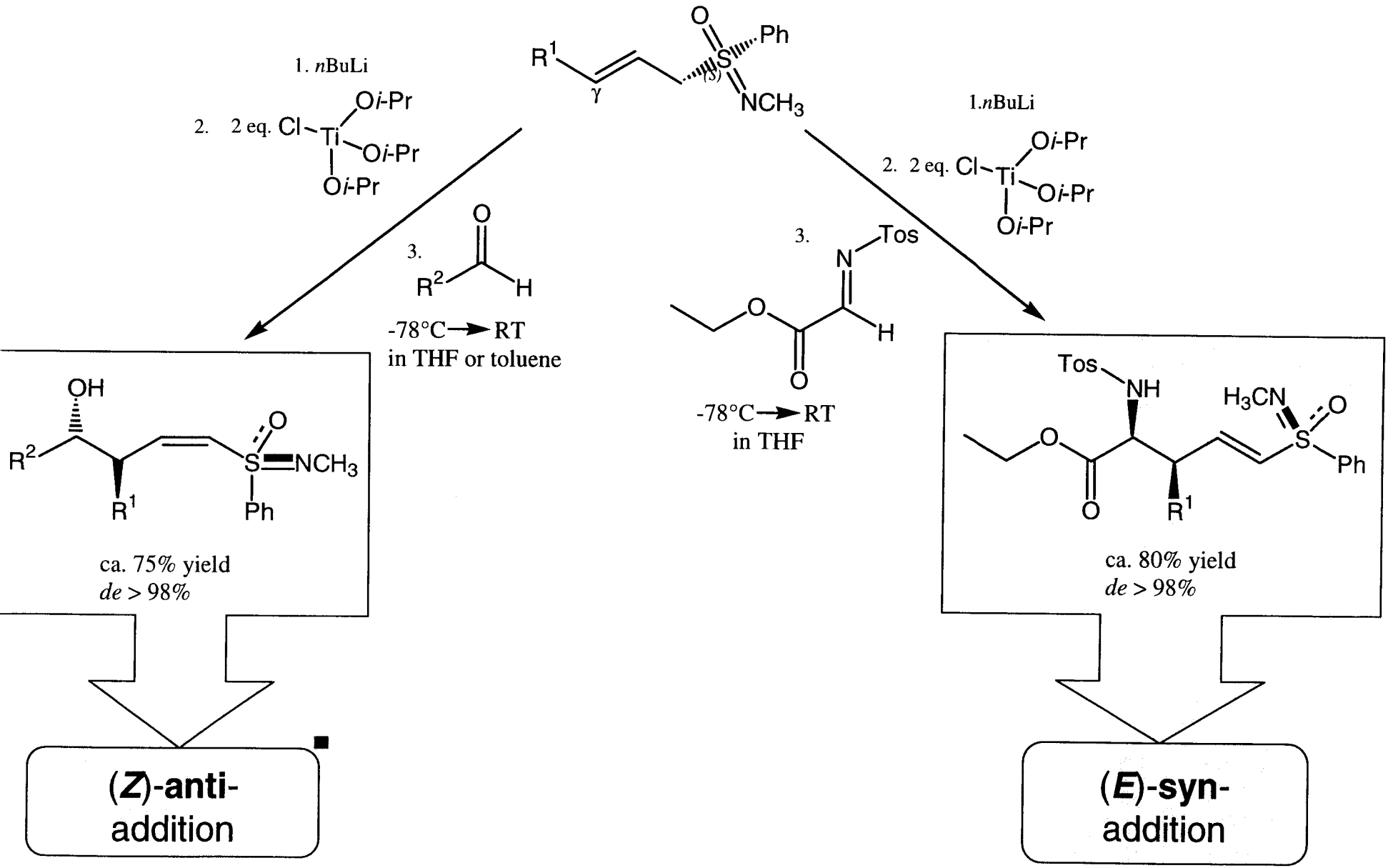
Stereochemistry of the γ-Aminoalkylation



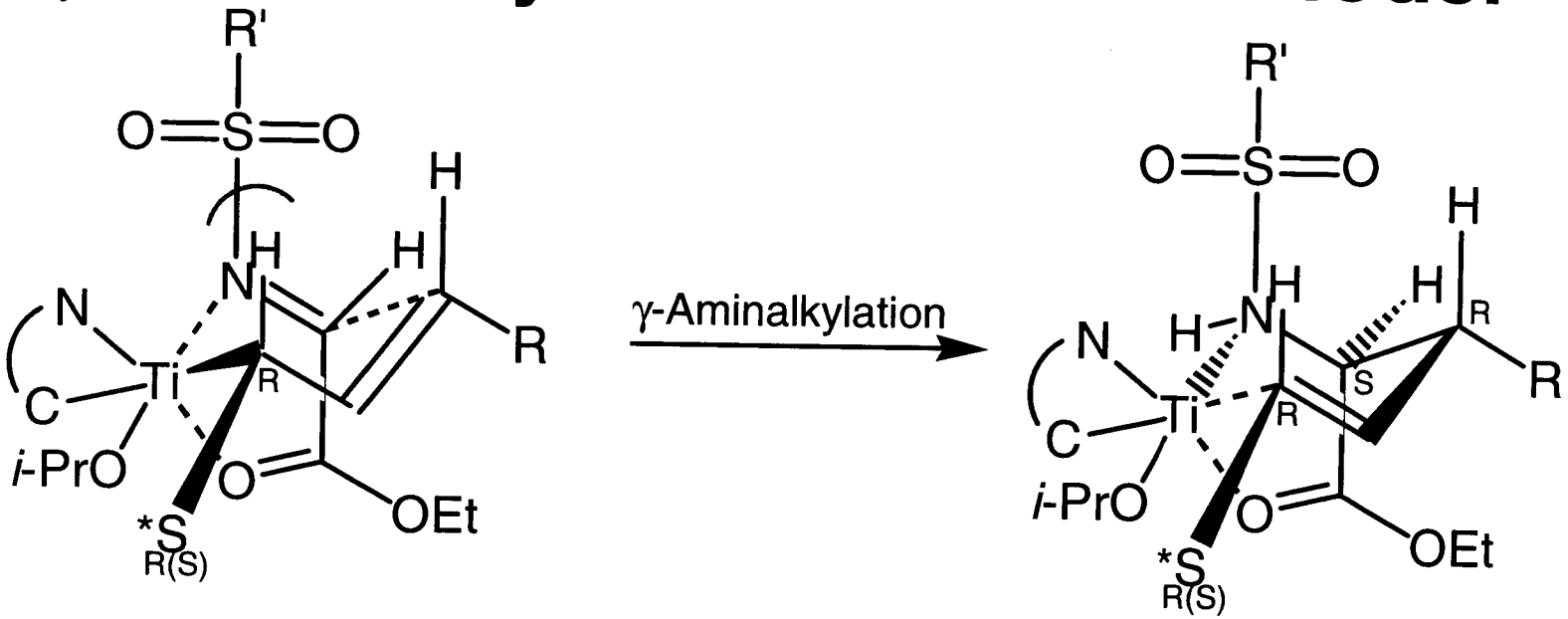


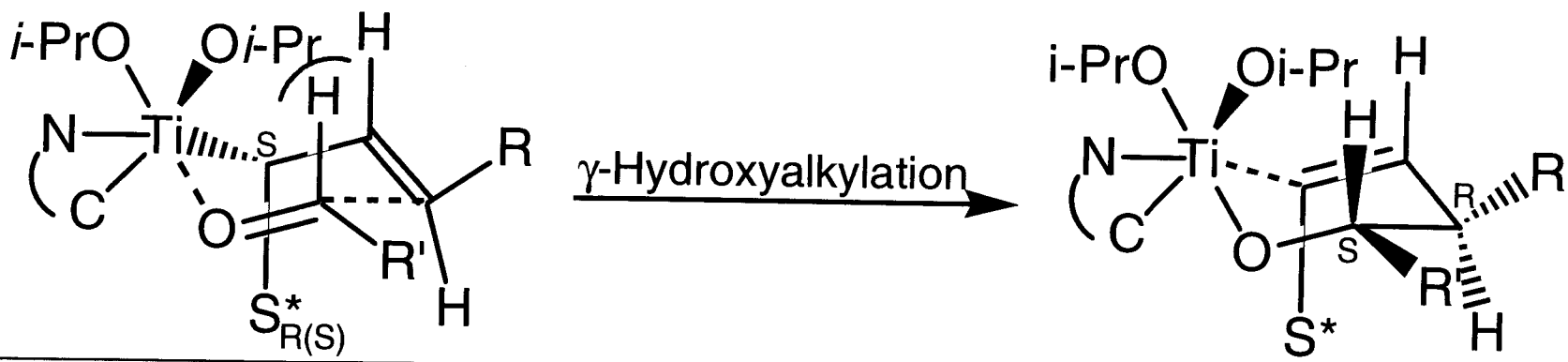
- (***E***)-(2*S*,3*R*)-**syn**-addition
- *de* > 98%, single diastereomer found
- However: other stereoconfiguration than γ-hydroxyalkylation

γ-Aminoalkylation vs γ-Hydroxyalkylation



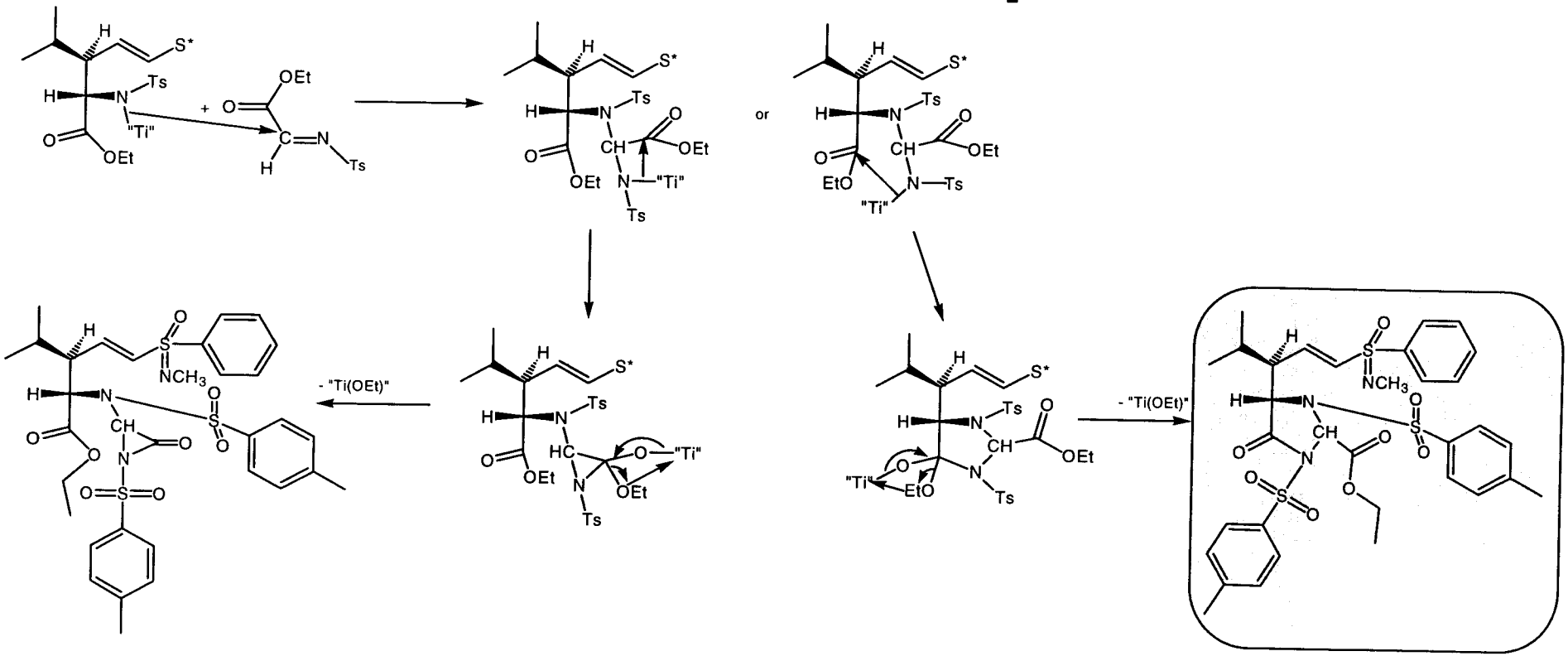
γ-Aminoalkylation: Reaction Model





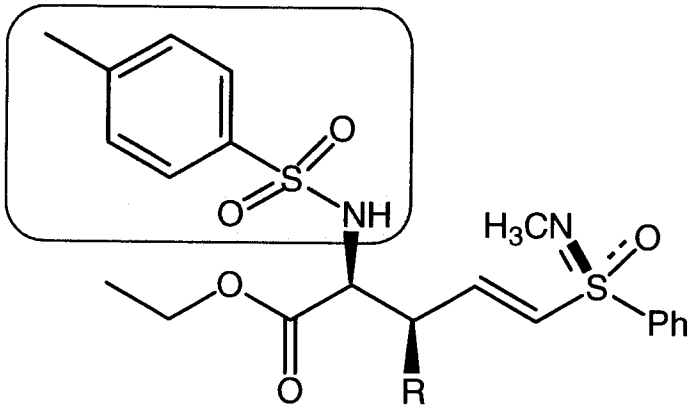
- (***E***)-configuration: S* in equatorial position,1-3 diaxial repulsion with *N*-tosyl
- **Syn**-addition: ester coordiantes to Ti **vs** R' of aldehyde points away from Ti

Side Product with 2 Eq. of Imine



- Demonstrates coordination of the ester function
- 5 membered imidazolidinone **vs** 3 membered α-lactame
- $^{1}J_{2\text{-}H,C\text{-}2}$ = 162 Hz indicates imidazolidinone structure

Removal of *N*-Tosyl



1. 2 eq. phenole
2. HBr or HI 30%
in AcOH or other homologues

→ no reaction

Na / NH_3 fl.

→ decomposition

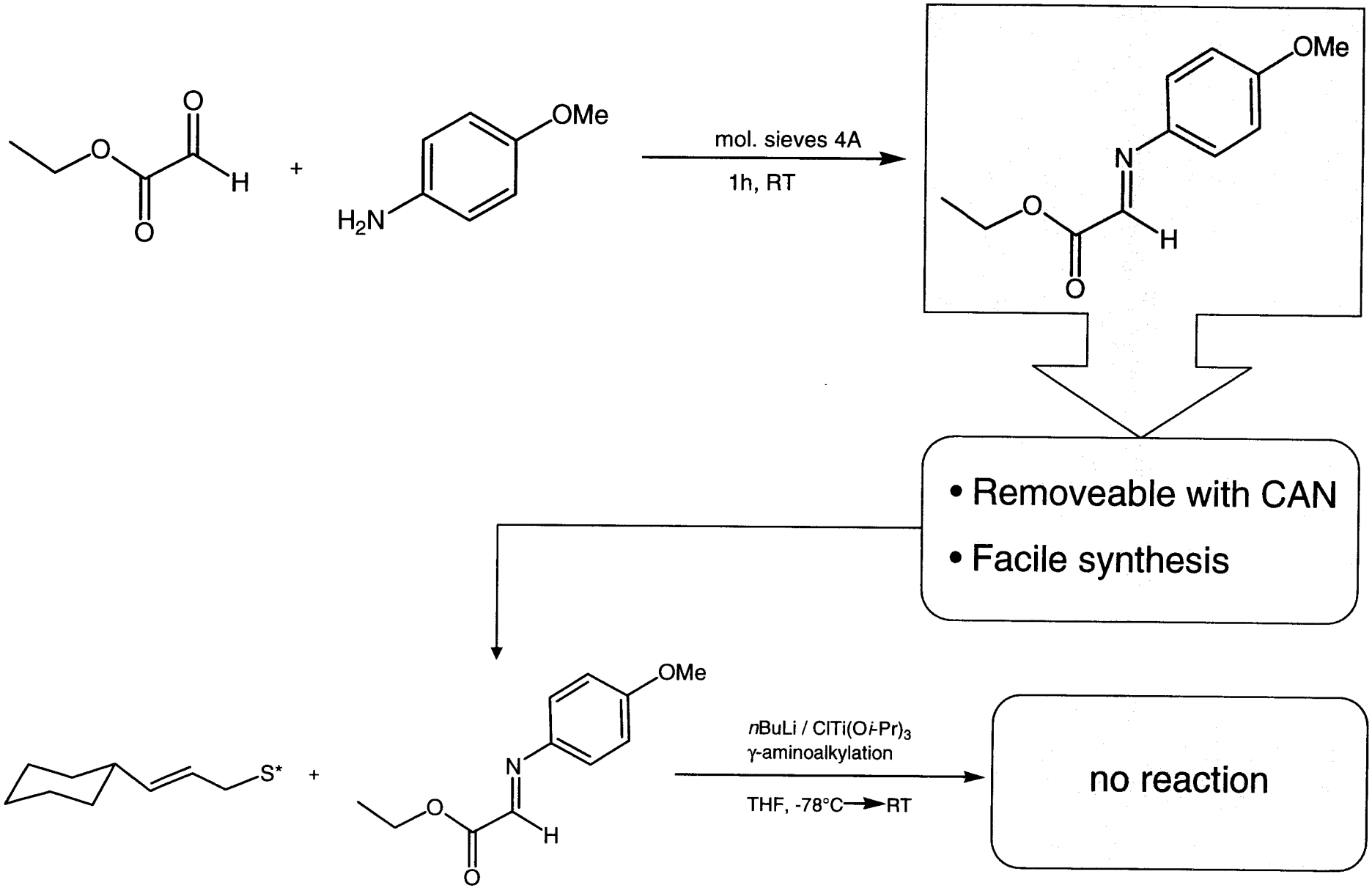
Reduction
Raney-Ni or
Na-Naphthalenide

→ 24h, RT

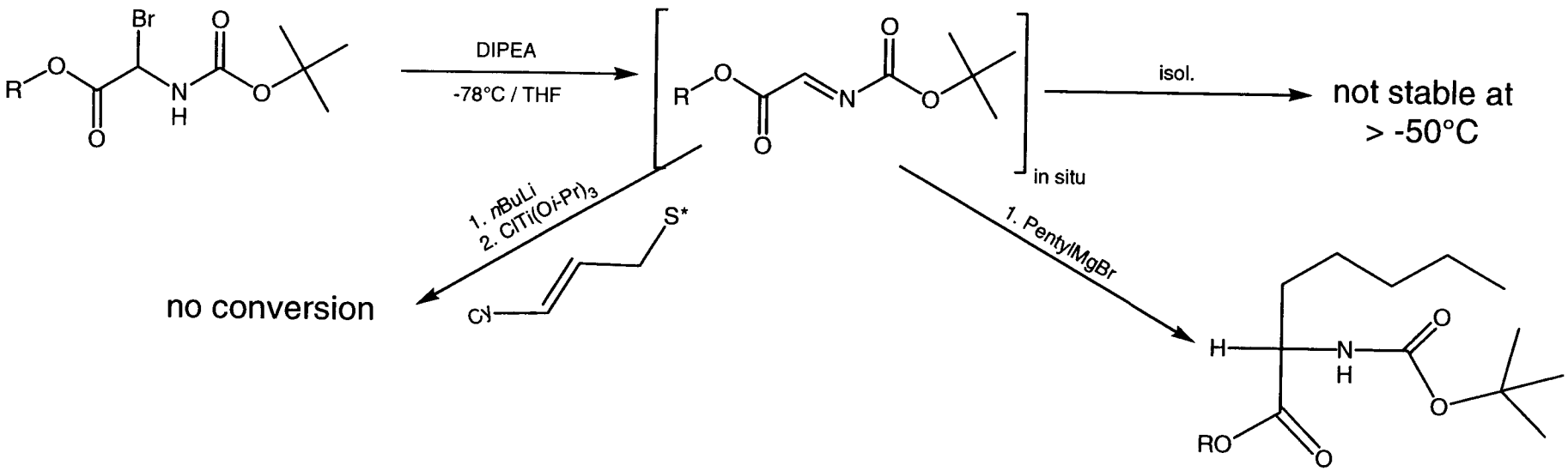
decomposition

- *N*-Tosyl bond too stable
- Other protecting groups (PG) needed

Other Protecting Groups: *N*-PMP

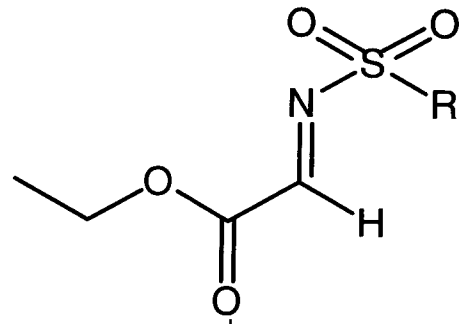


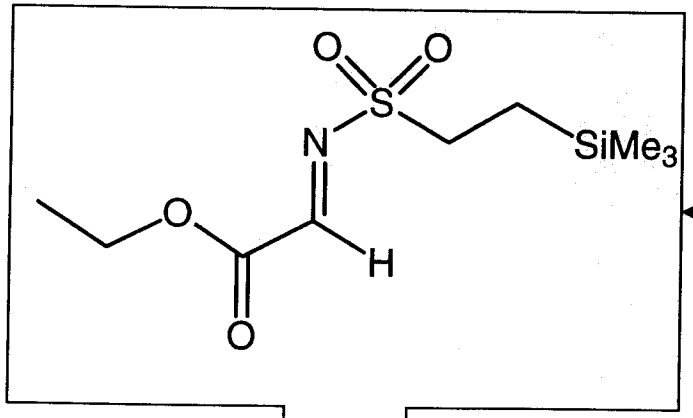
Other Protecting Groups: *N*-BOC

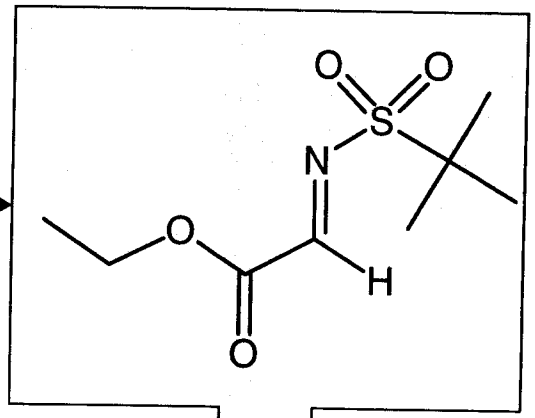


- *N*-BOC used in peptide chemistry, electron withdrawing
- Carried out for **R= Et, *t*-But**
- Trapping with PentylMgBr: ca. 50% yield
- No conversion at aminoalkylation-conditions
- <u>Conclusion</u>: SO_2-R as PG required ■

Other Sulfonyl-Protecting Groups







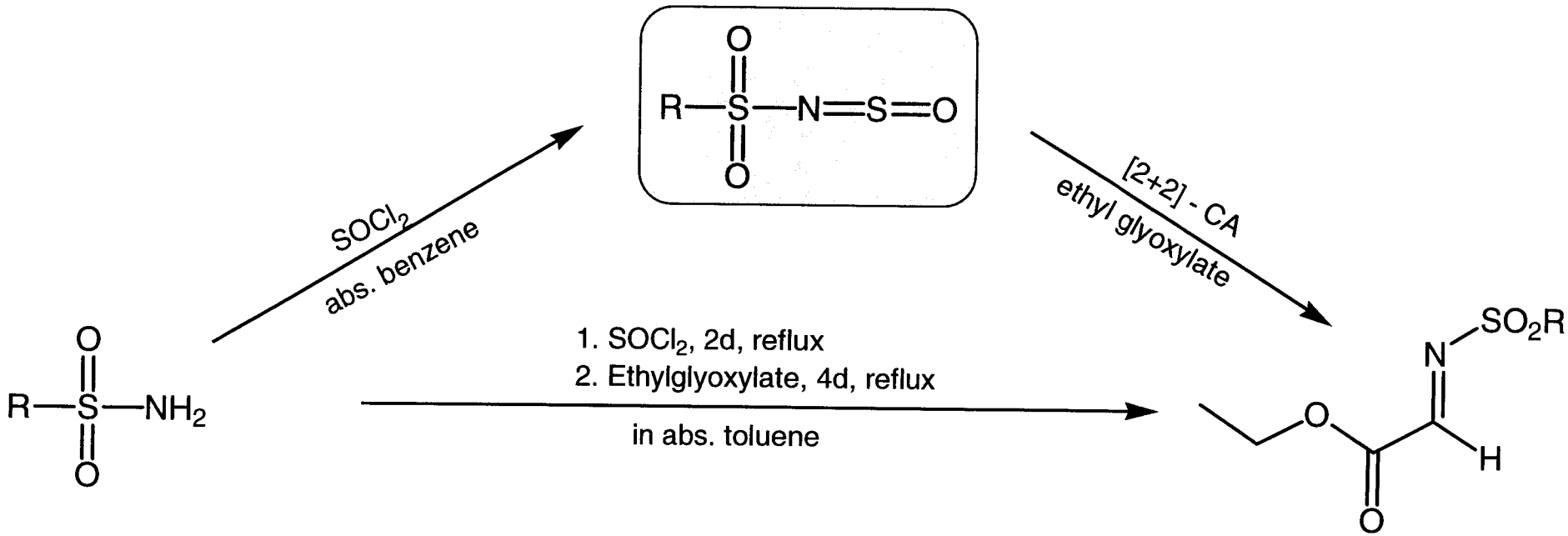
<u>*N*-SES</u>

- Removable with fluoride ions[■]
- Described as peptide-PG
- Stable

<u>*N*-Bus</u>

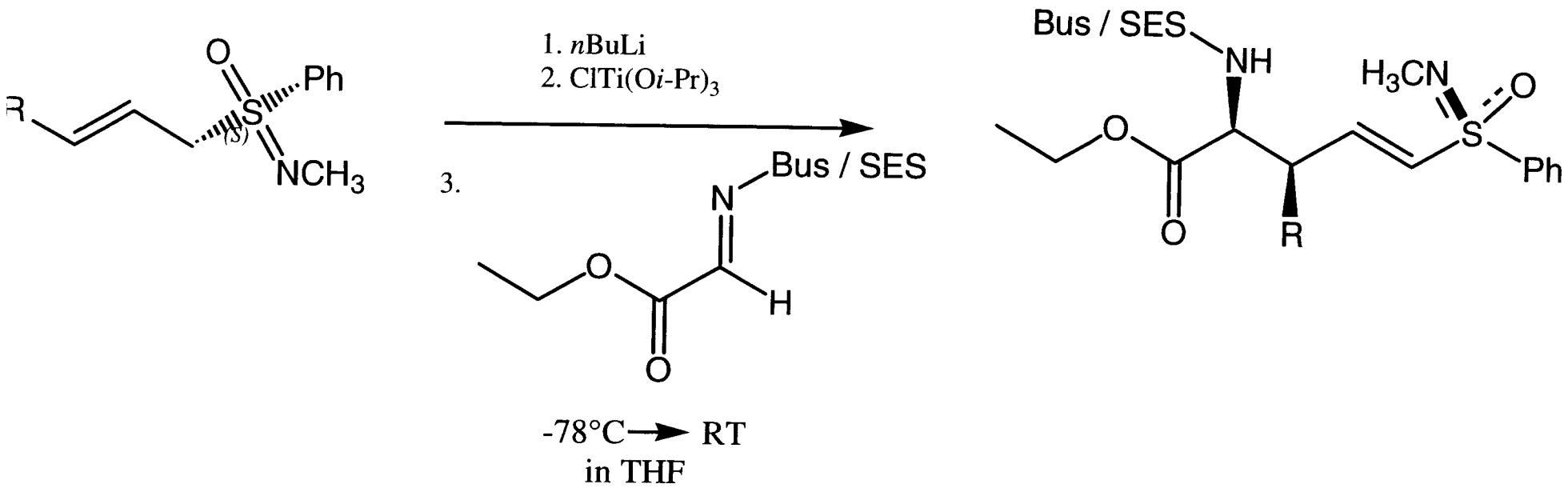
- Removable with diluted TfOH[■]
- Described as peptide-PG
- Stable

Synthesis of *N*-Bus and *N*-SES Imine



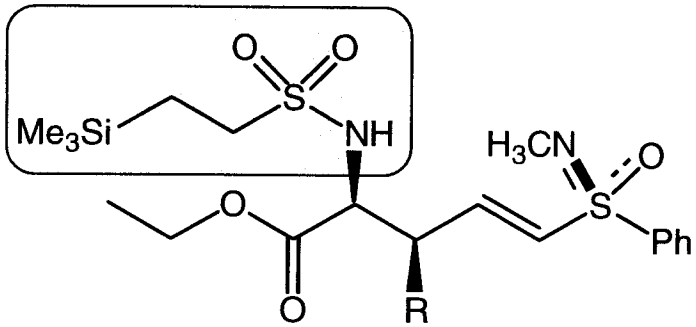
- Synthesis via thioisocyanate intermediate
- one pot procedure possible
- 38-61% isolated yield, >95% purity
- Decently stable at RT

γ-Aminoalkylation: Bus and SES Imines



- **R= Me, *i*-Propyl, Ph, Cyclohexyl**; protecting group: ***N*-SES**, ***N*-Bus**
- *de* > 98%, single diastereomer, (***E***)-(2*S*,3*R*)-**syn**-addition
- Recrystallisation from ether provides analytically pure substance
- 86–95 % conversion, 61–82 % isolated yield

Cleavage of SES-NH Bond



CsF or TBAF
in DMF or acetonitrile
> 50 °C

→ decomposition

CsF or TBAF
in DMF or acetonitrile
25 °C

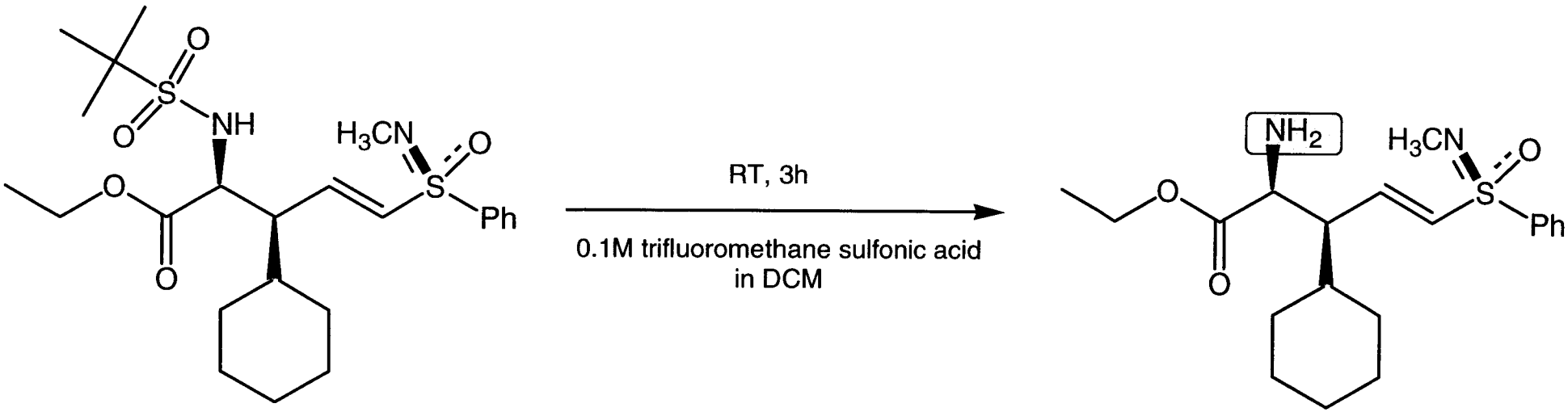
→ no reaction

TAS-F
DMF, RT

→ no reaction

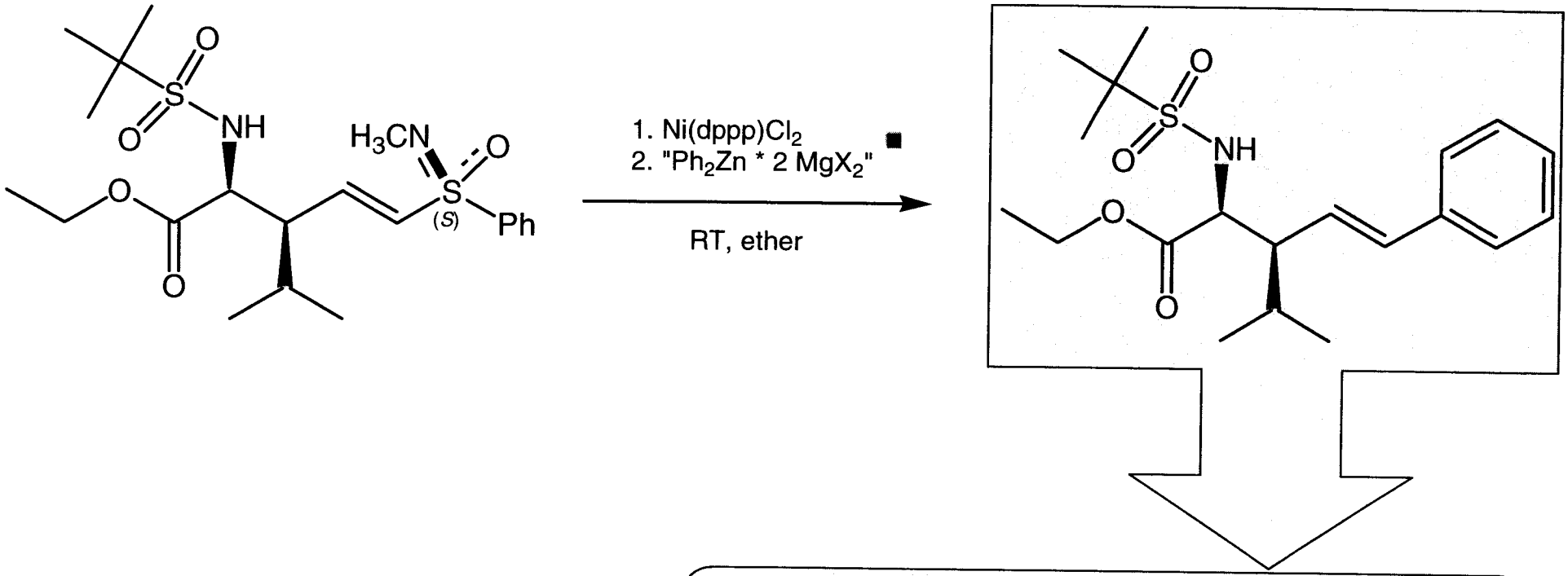
- Only cleavage conditions at RT possible
- Even TAS-F (Tris(dimethylamino)-sulfur-trimethylsilyldifluoride) fails
- Product too unstable for cleavage

Cleavage of Bus-NH Bond



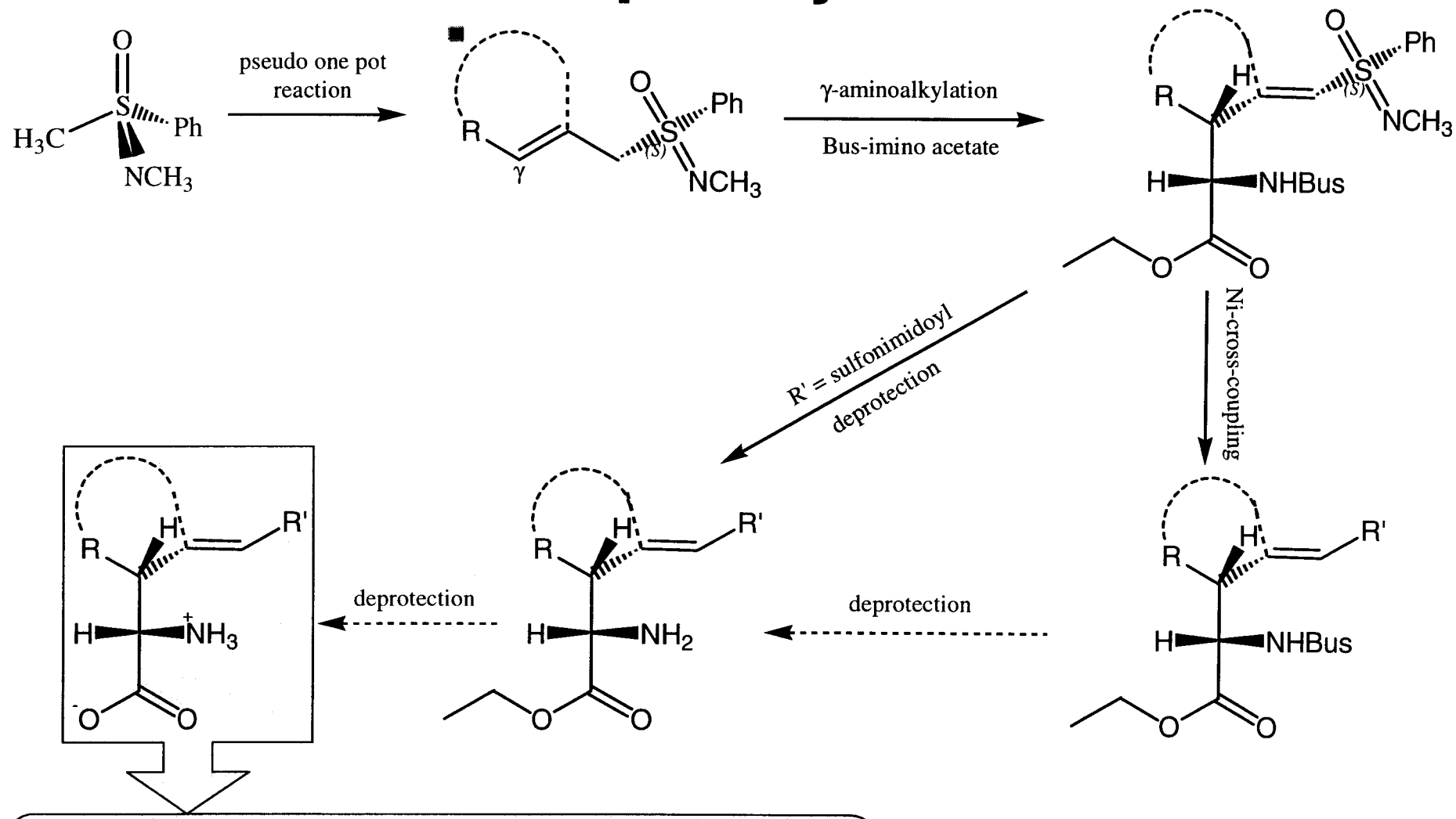
- Quantitative yield, >99% purity
- No purification needed
- Trifluoromethane sulfonic acid has to be water-free

Nickel Cross-Coupling Reaction



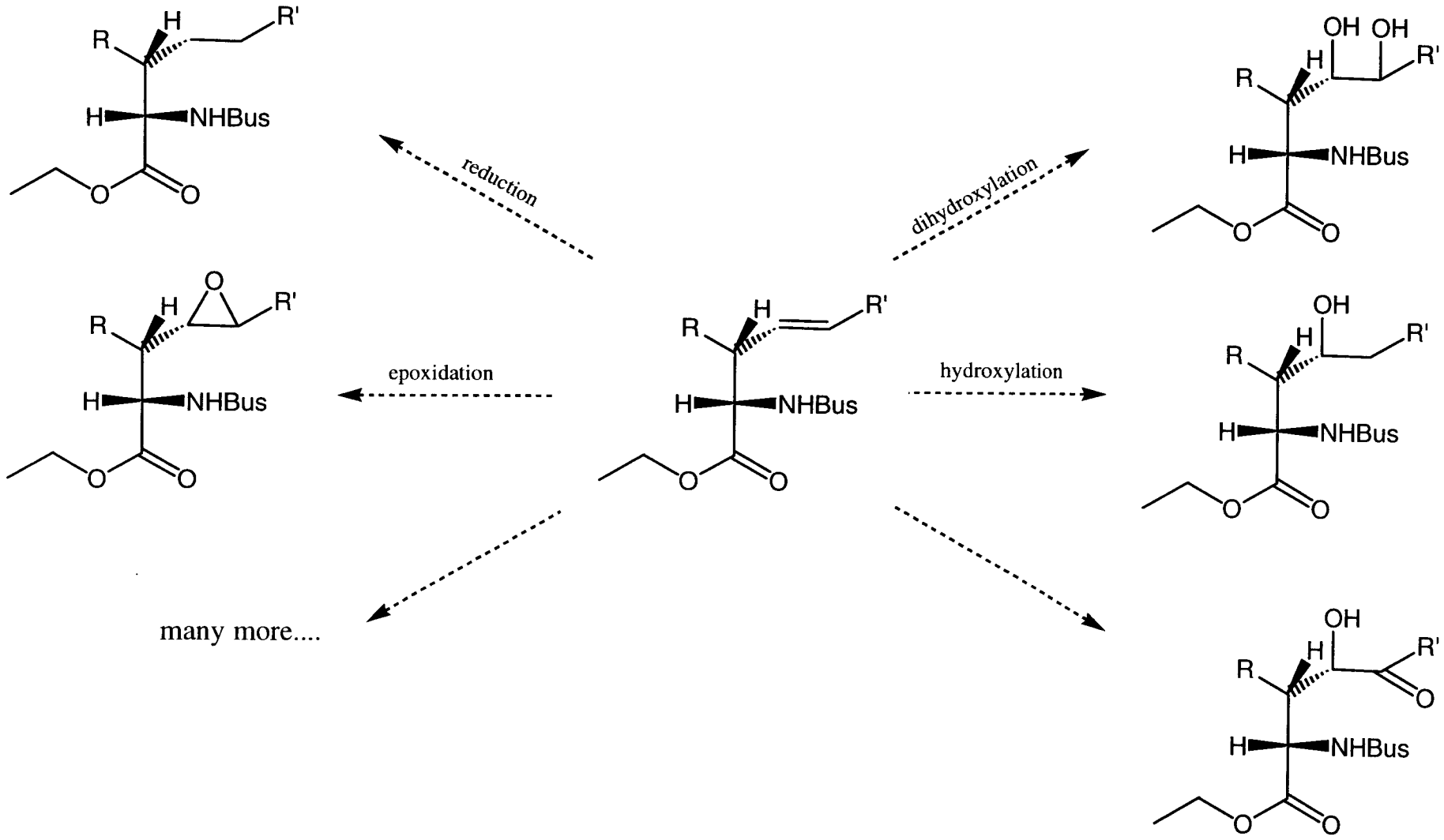
- Only (***E***)-configurated product, *de* > 98%
- 60% conversion, 48% isolated yield

Developed Synthesis

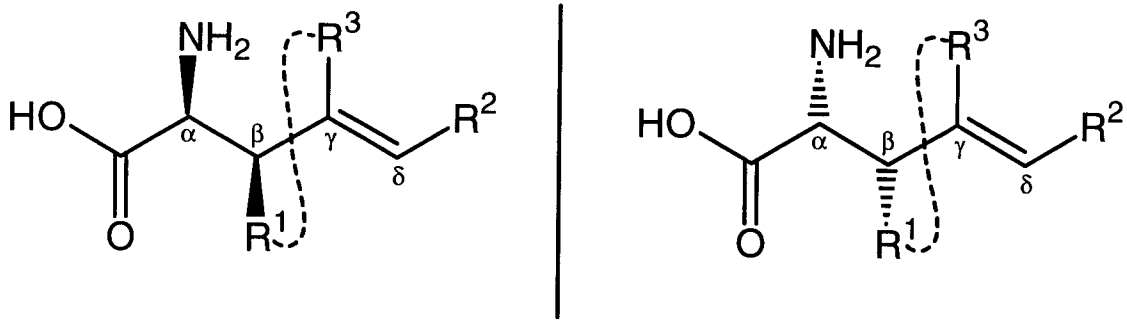


- γ,δ-Unsaturated β,δ-substituted α-amino acids
- Highly valuable substrates

Utility of Unsaturated Amino Acids



Other Methods in Literature: Overview



R^1 = Alkyl, (Aryl), (Alkyl / Aryl-X), cyclisch, ...
R^2 = H, Alkyl, Aryl, X, Alkyl-X, Aryl-X, ...
R^3 = H, Alkyl, cyclisch, ...

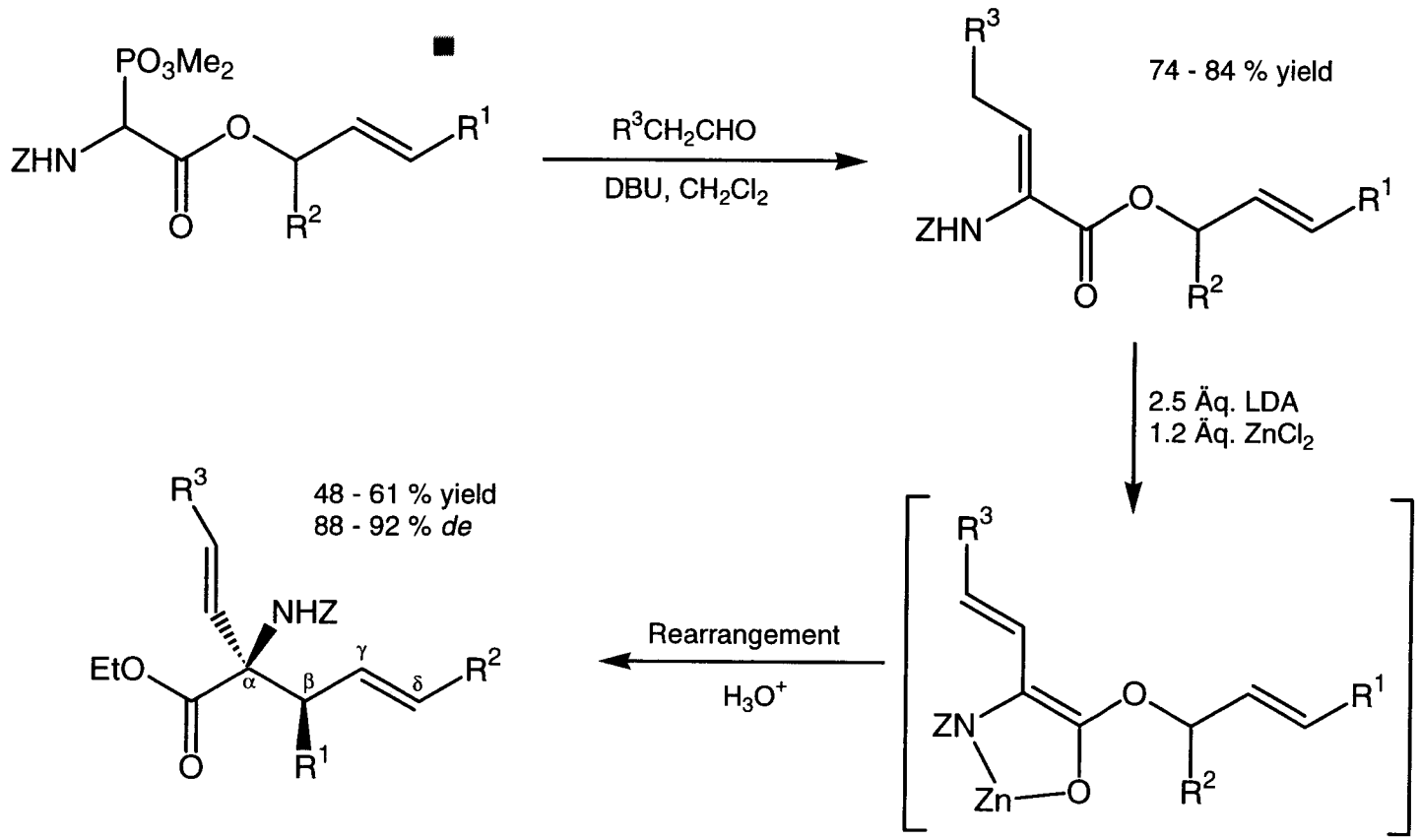
Aminoalkylation

Other Methods:

- Allylation of iminoesters and glycine derivatives: simple substitution patterns
- Imino-Ene-reaction: no β-substitution, mostly aromatic systems
- Pd-catalysed allylic substition of allylic carbonates: anti-products, mostly symmetric carbonates, unsymmetric: Prof. Kazmaier
- Ireland-Claisen-reaction of chelated ester enolates (Kazmaier)
- Regioselective hydrogenation of didehydro amino acids

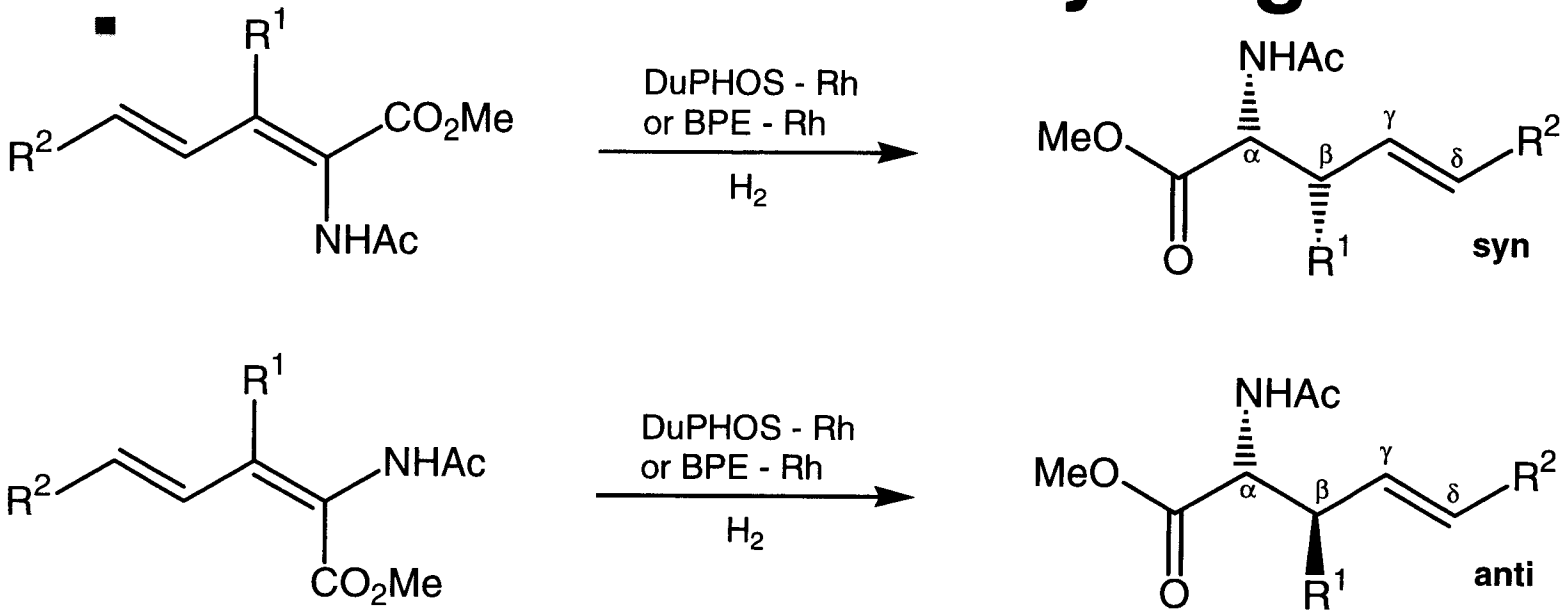
syn-products, substitution pattern

Other Methods: Ireland-Claisen-Reaction



- syn-configured products, good selectivities, moderate yields
- quarternary C-α carbon
- limitation: accessibility of precursors

Other Methods: Hydrogenation



47 - 100 % conv.
de = 73 - 93 %

17 - 100 % conv.
de = 85 - 96 %

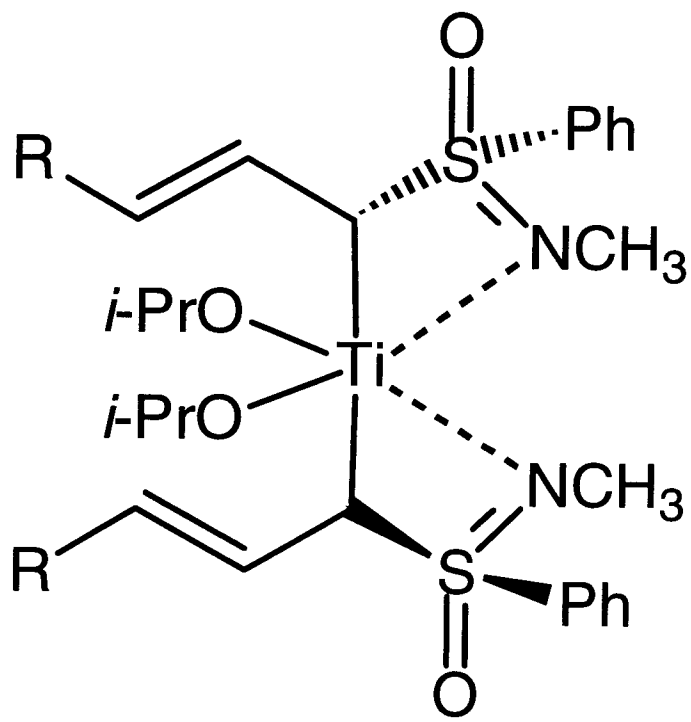
R^1 = Alkyl
R^2 = Alkyl, Aryl

- good selectivities, moderate – excellent yields
- both syn- and anti-configured products
- limitation: overreduction: carefull optimization crucial

Conclusion

- γ-Hydroxyalkylation
- Different allylic sulfoximines for the γ-hydroxyalkylation
- Other substrates: imines
- γ-Aminoalkylation
- Model for stereochemical course
- Protecting group: (SES), Bus
- Cleavage of protecting group
- Nickel cross-coupling
- Concept / Comparison

Structure of Allylic Alkoxytitanasulfoximines



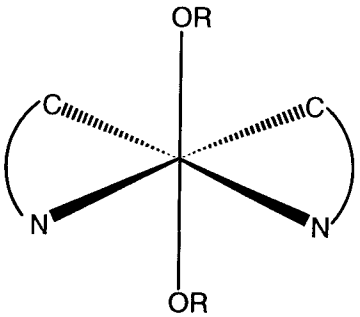
- Bis-(2-alkenyl)diisopropoxytitanium(IV) complex
- Titanium binds to α-C
- Double bond configuration is important

Part II: Structure of Titanaallylsulfoximines

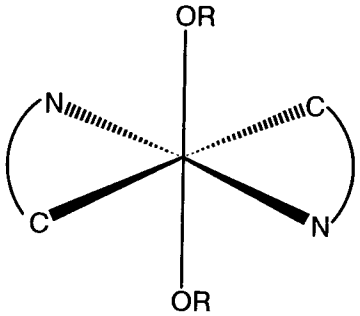
- Introduction
  - Chiralitity of octahedral titanium complexes
  - Aspect of chiral sulfoximine
  - Influence of Lewis-acids in reaction

- Structure of allylic alkoxytitanasulfoximines
  - Influence of Lewis-acid
  - Dynamic effects in solution
  - Model and conclusion

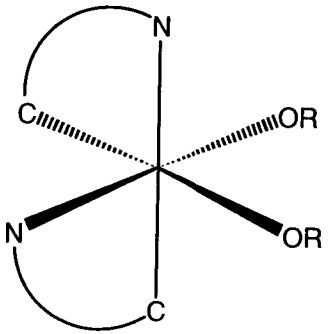
Octahedral Titanium-Complexes

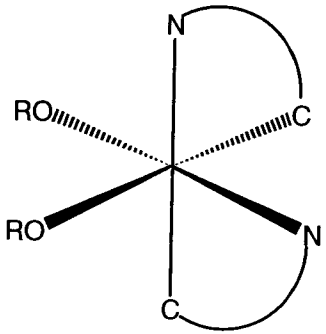


trans,cis,cis / C_{2v}

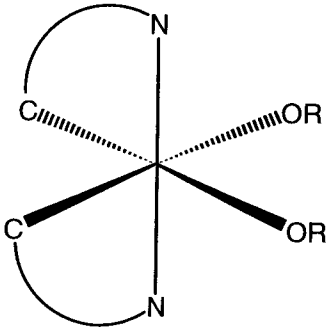


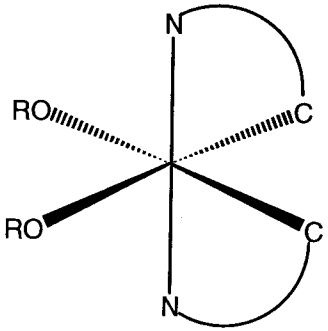
all-trans / C_{2h}



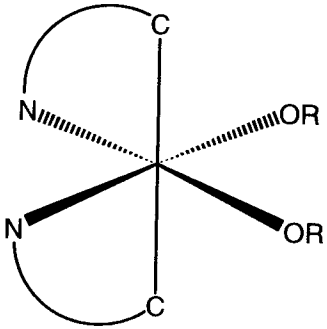


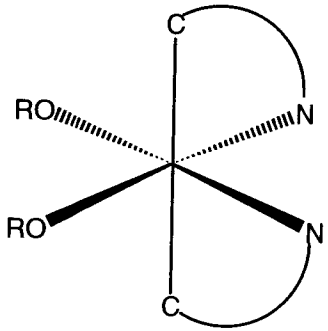
Λ all-cis / C_1 (2 NMR sets) Δ





Λ cis,trans,cis / C_2 Δ



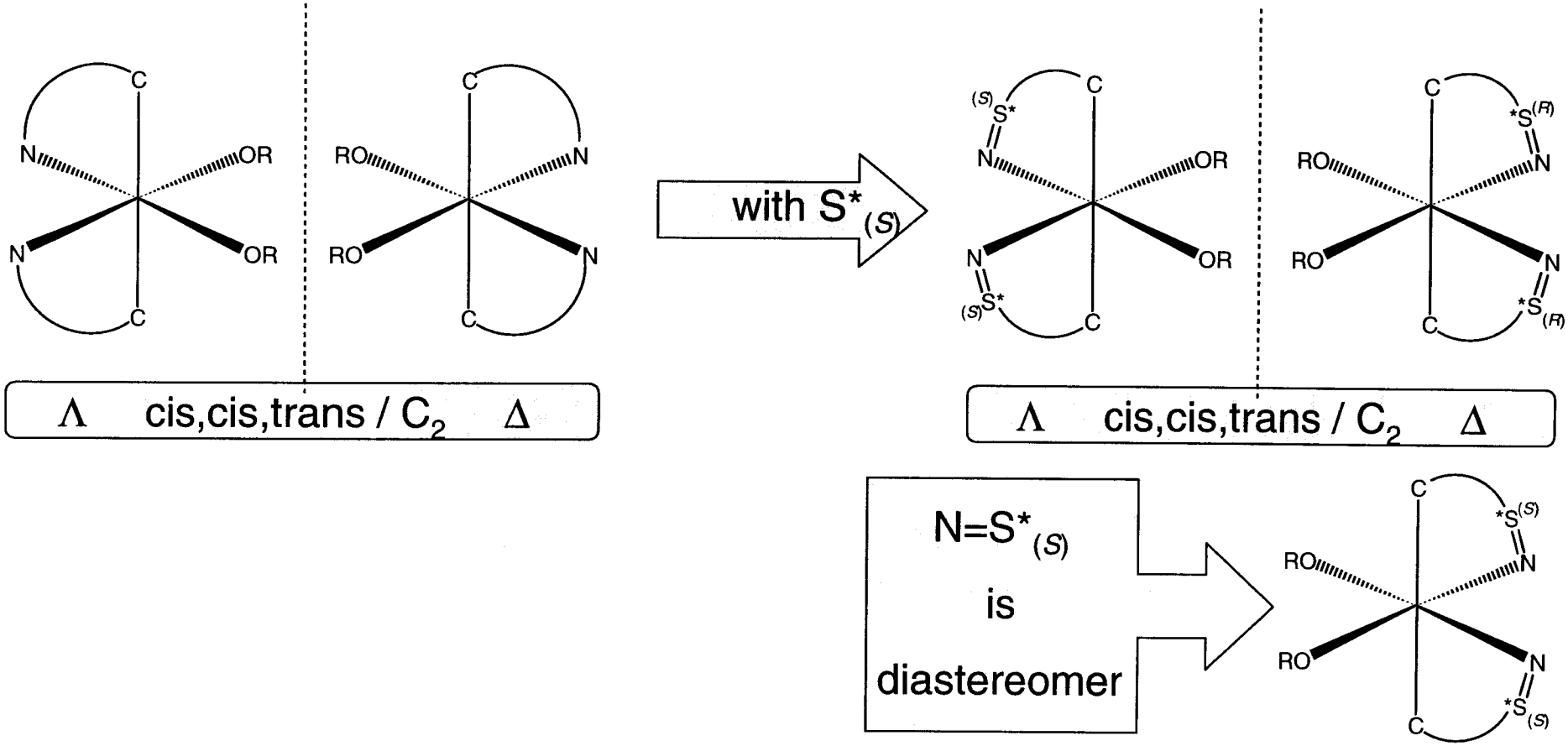


Λ cis,cis,trans / C_2 Δ

$Ti(OR)_2(uchel)_2$ →

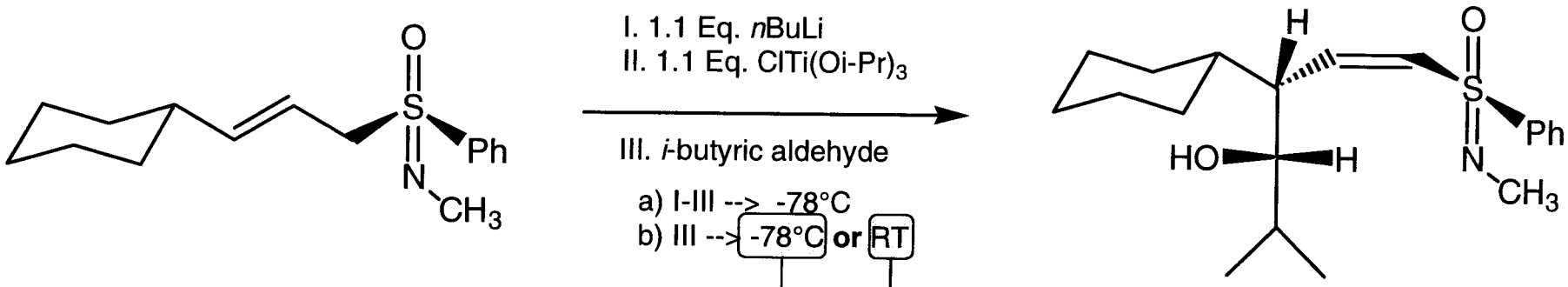
8 stereoisomers, hereof 5 diastereomers
2 trans OR → achiral, NMR: 1x OR, 1x C-N
3 cis OR → chiral, all-cis is C_1 (NMR: 2x)

Chiral Sulfonimidoyl Moiety



$Ti(OR)_2(uchel^*)_2$ → 8 stereoisomers, hereof 8 diastereomers
2 trans OR → chiral, C_{2v}/C_{2h} → C_2, NMR: 1x
3 cis OR → chiral, all-cis is C_1 (NMR: 2x)

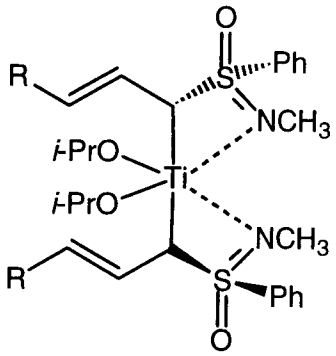
$Ti(O\mathit{i}\text{-}Pr)_4$ as Lewis-Acid*



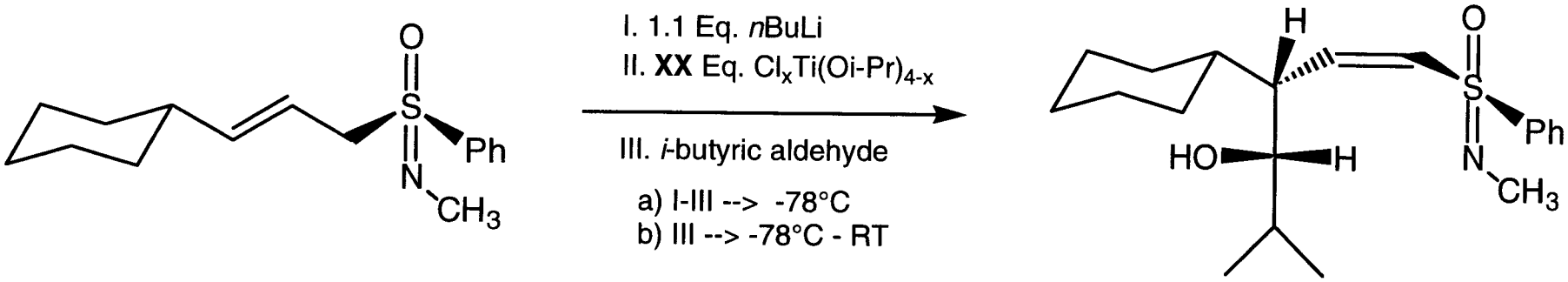
- 45-50% conversion
- ca. 50 % educt recovered
- No further conversion possible

- 45% γ-hydroxyalkylation
- ca. 50% unselective reaction
- α-Hydroxyalkylation products

$Ti(O\mathit{i}\text{-}Pr)_4$ too weak to transfer both organic fragments!



Importance of Lewis Acids



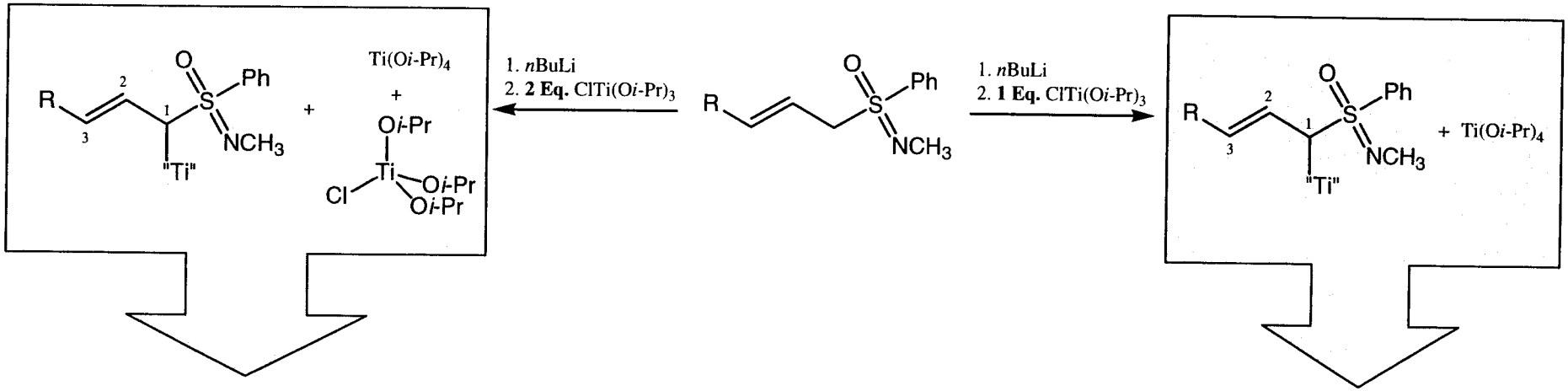
Substance	*0.55 Eq. $Cl_2Ti(Oi\text{-}Pr)_2$*	*0.65 Eq. $Cl_2Ti(Oi\text{-}Pr)_2$*	*0.8 Eq. $Cl_2Ti(Oi\text{-}Pr)_2$*	*1.1 Eq. $Cl_2Ti(Oi\text{-}Pr)_2$*
γ-Product	27.0 %	37.2 %	52.1 %	80.0 %
α-Product	52.2 %	43.2 %	24.7 %	≤ 1 %
Educt	14.0 %	12.9 %	13.6 %	15.0 %
Sulfine amide	6.8 %	6.7 %	9.6 %	5.0 %

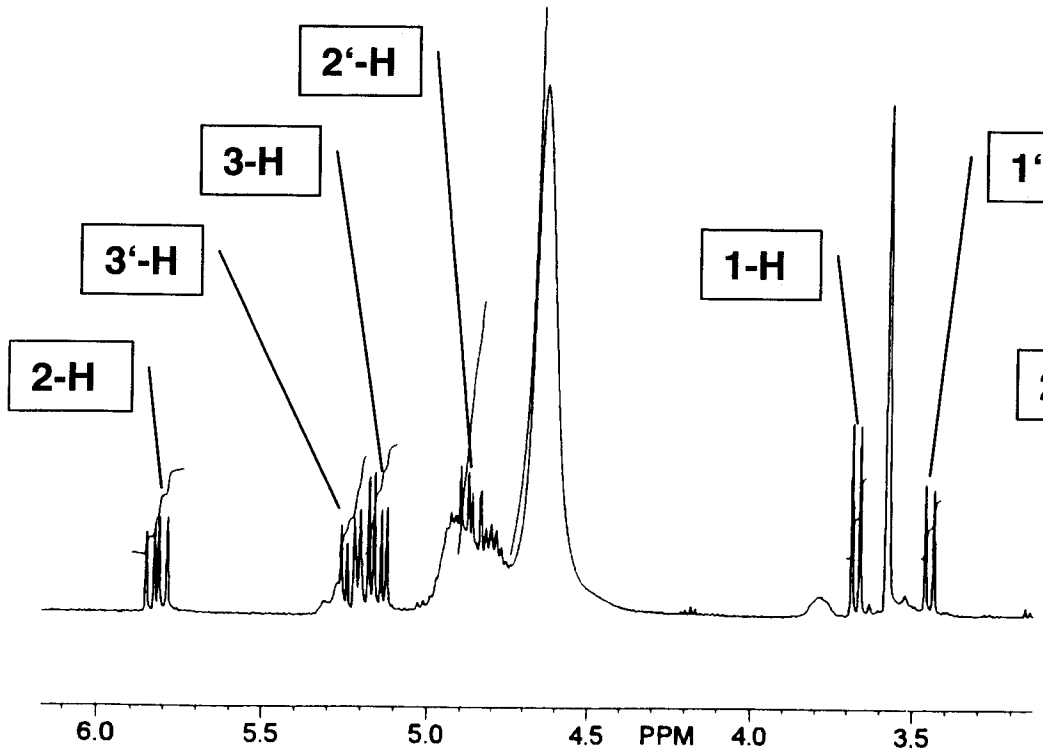
higher excess of lewis-acid

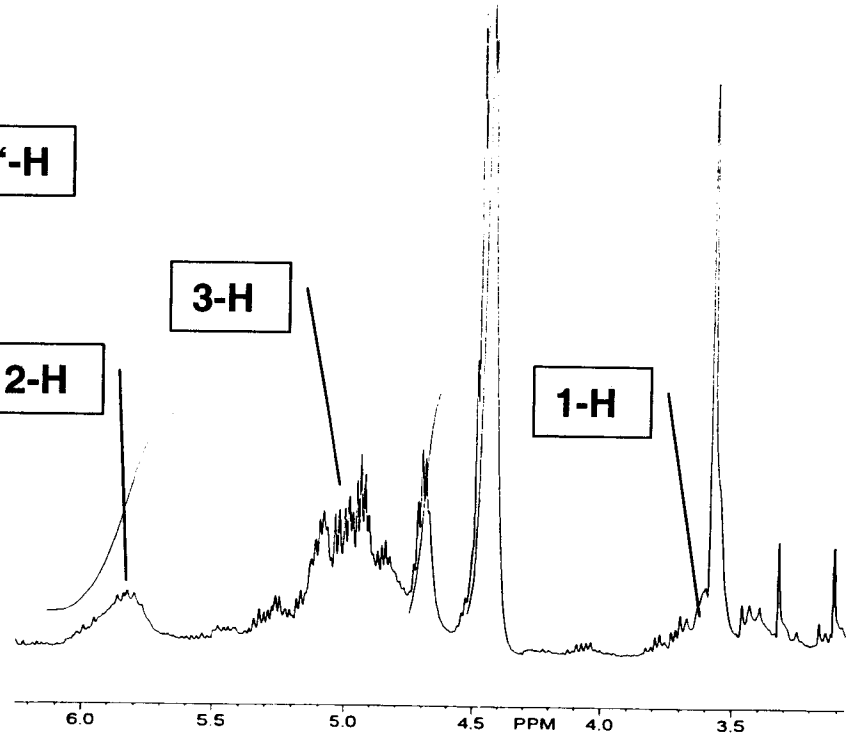
<u>same result:</u>

2.1 Eq. $ClTi(O\textit{i}\text{-}Pr)_3$

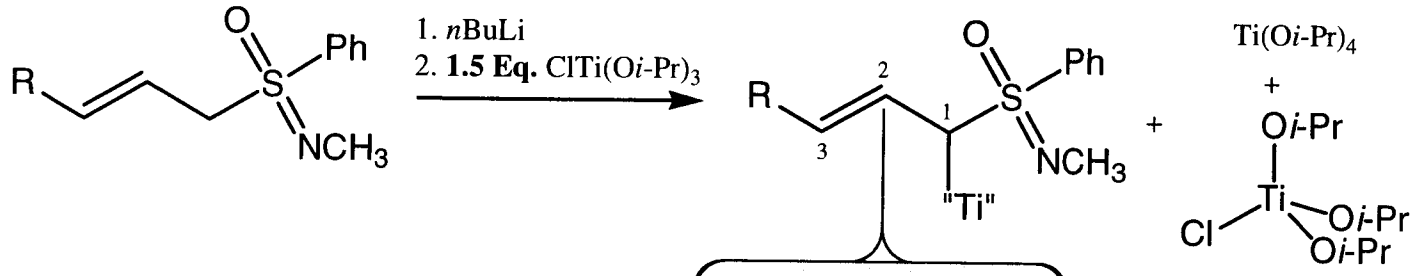
Influence of Lewis Acids





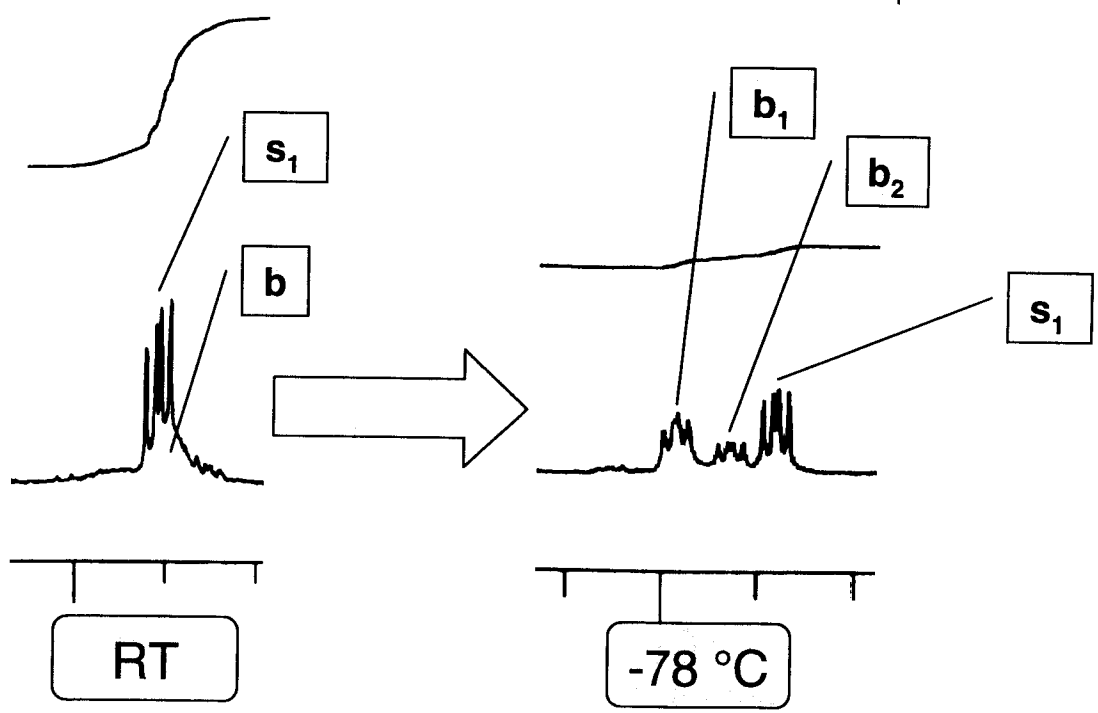


Dynamic Effect in Solution

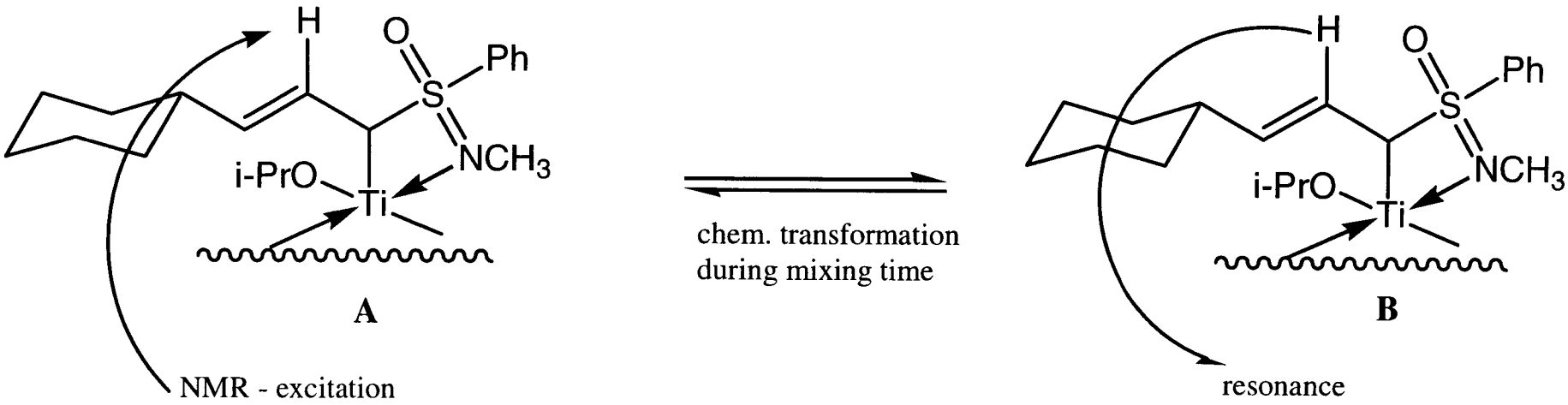


only **2-H** signals magnified

- b: ‚broad' species with 1 eq. of $ClTi(O\mathit{i}\text{-}Pr)_3$
- s: ‚slim' species with 2 eq. of $ClTi(O\mathit{i}\text{-}Pr)_3$
- Both species present
- At -78 °C: b → b_1 and b_2
- Ratio b_1 / b_2 ca. 2:1



NMR Exchange Experiments



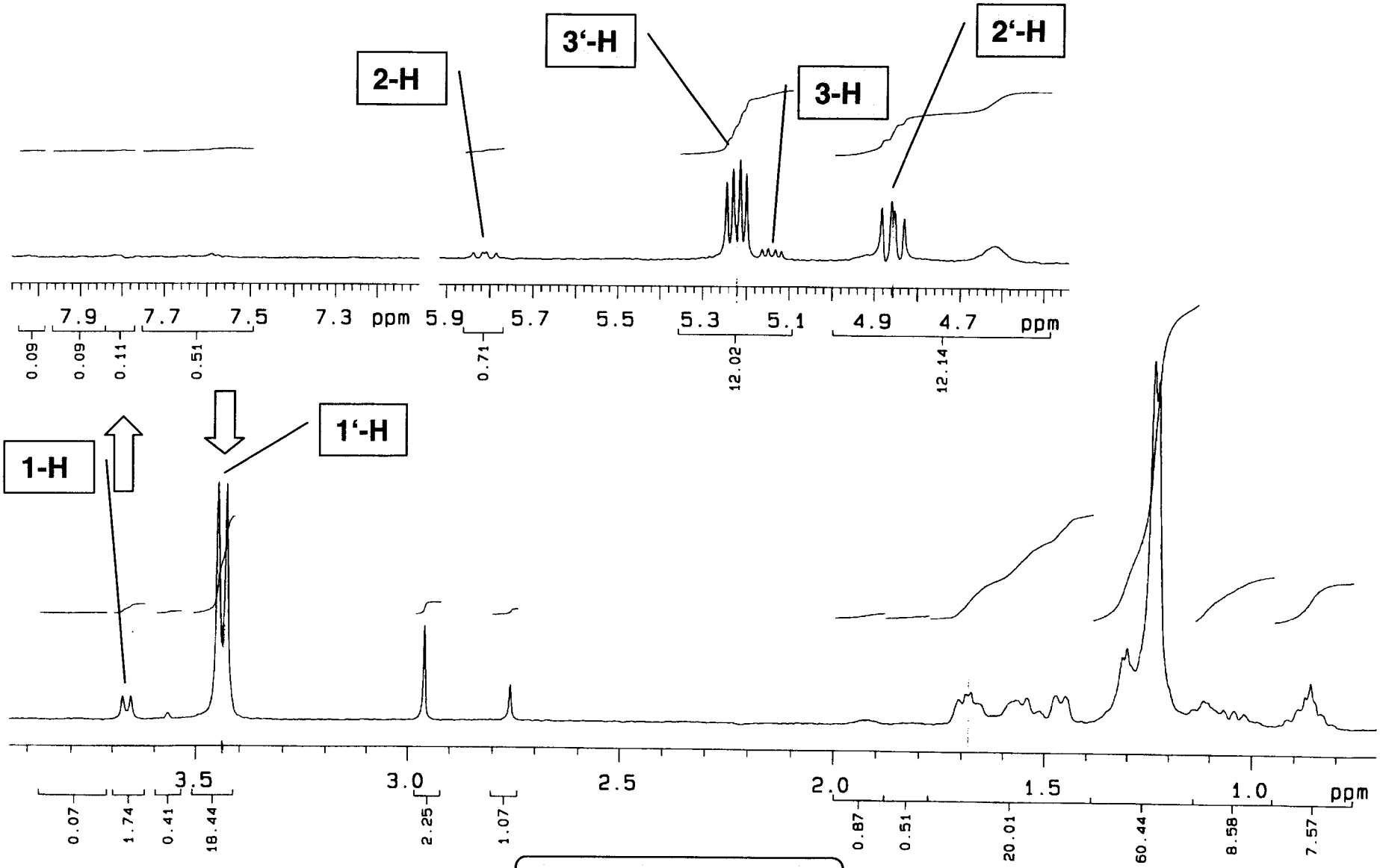
TOCSY: → magnetisation transfer via chemical bonds

NOESY: → magnetisation transfer through space

ROESY: → similar to NOE - effect

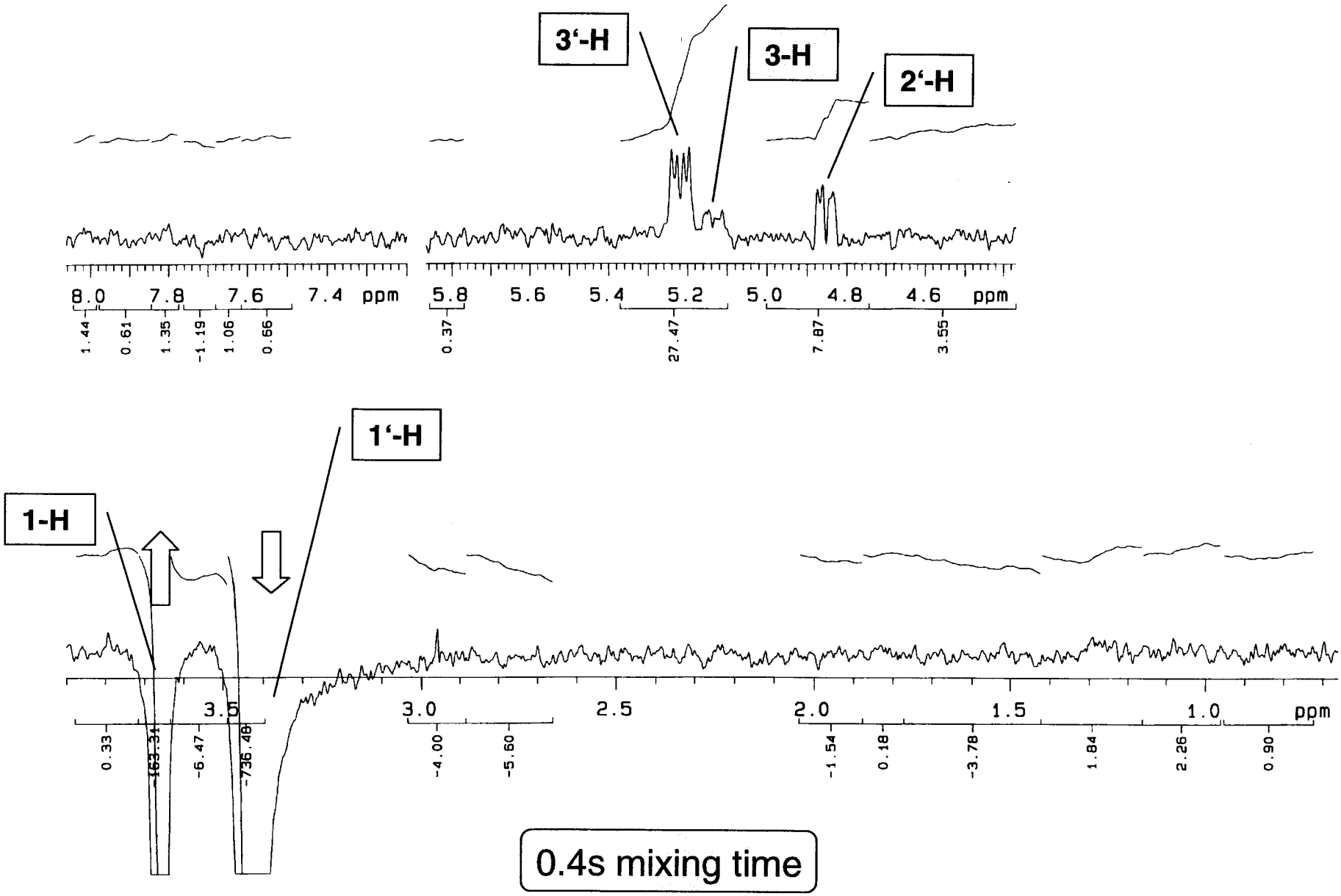
for allylic alkoxytitanasulfoximines <u>with lewis-acid excess</u>

1D-TOCSY

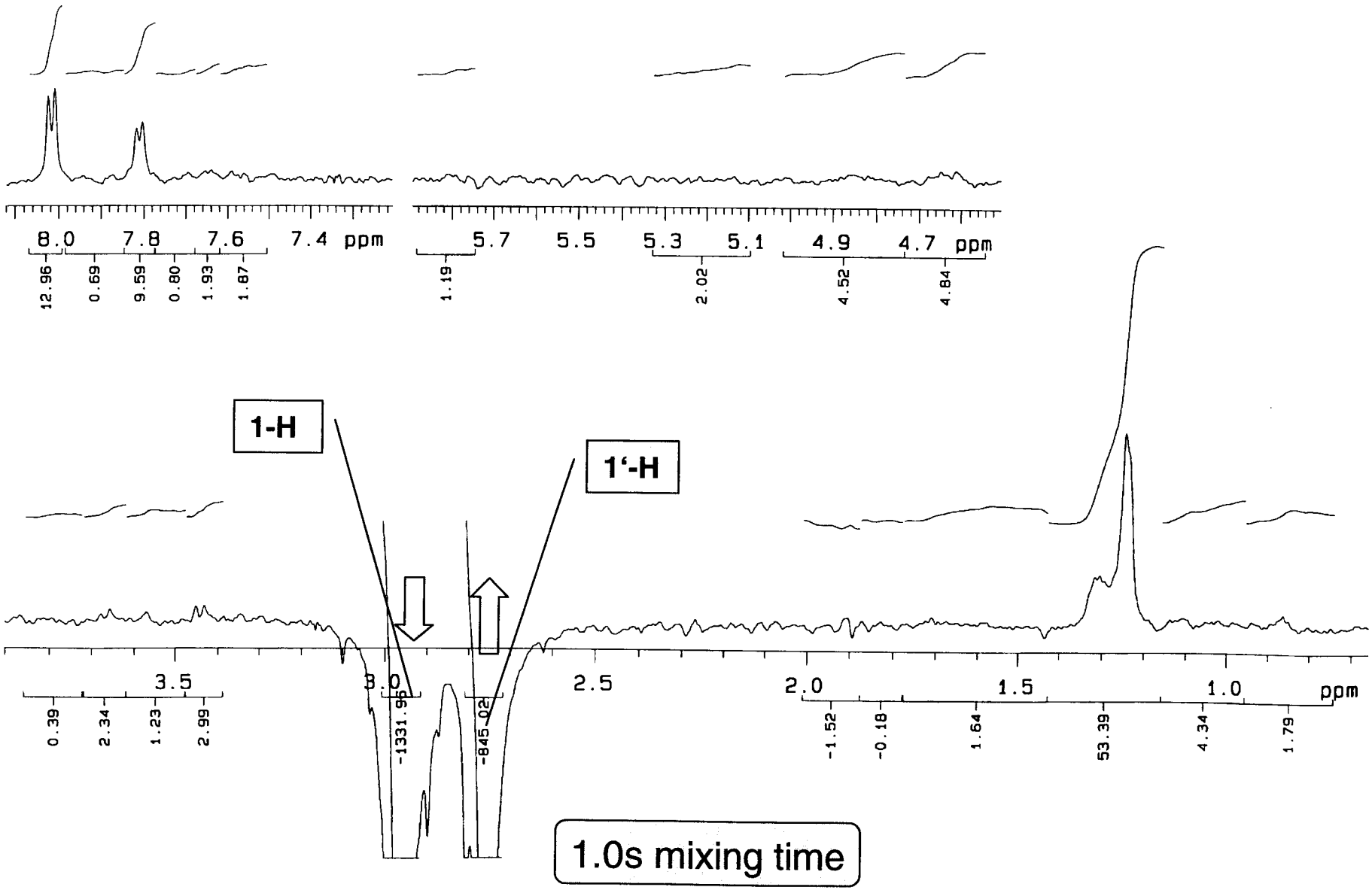


0.15s mixing time

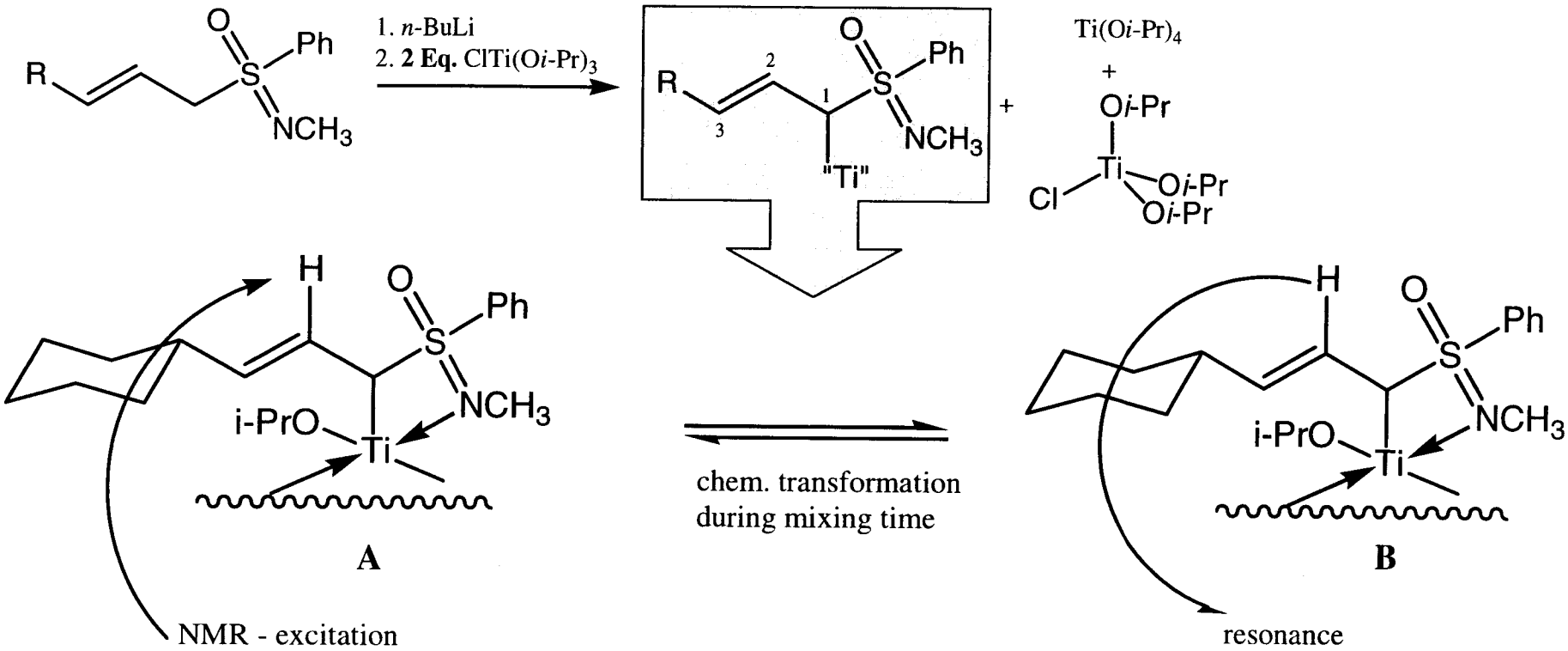
1D-ROESY (Difference)



1D-NOESY (Difference)

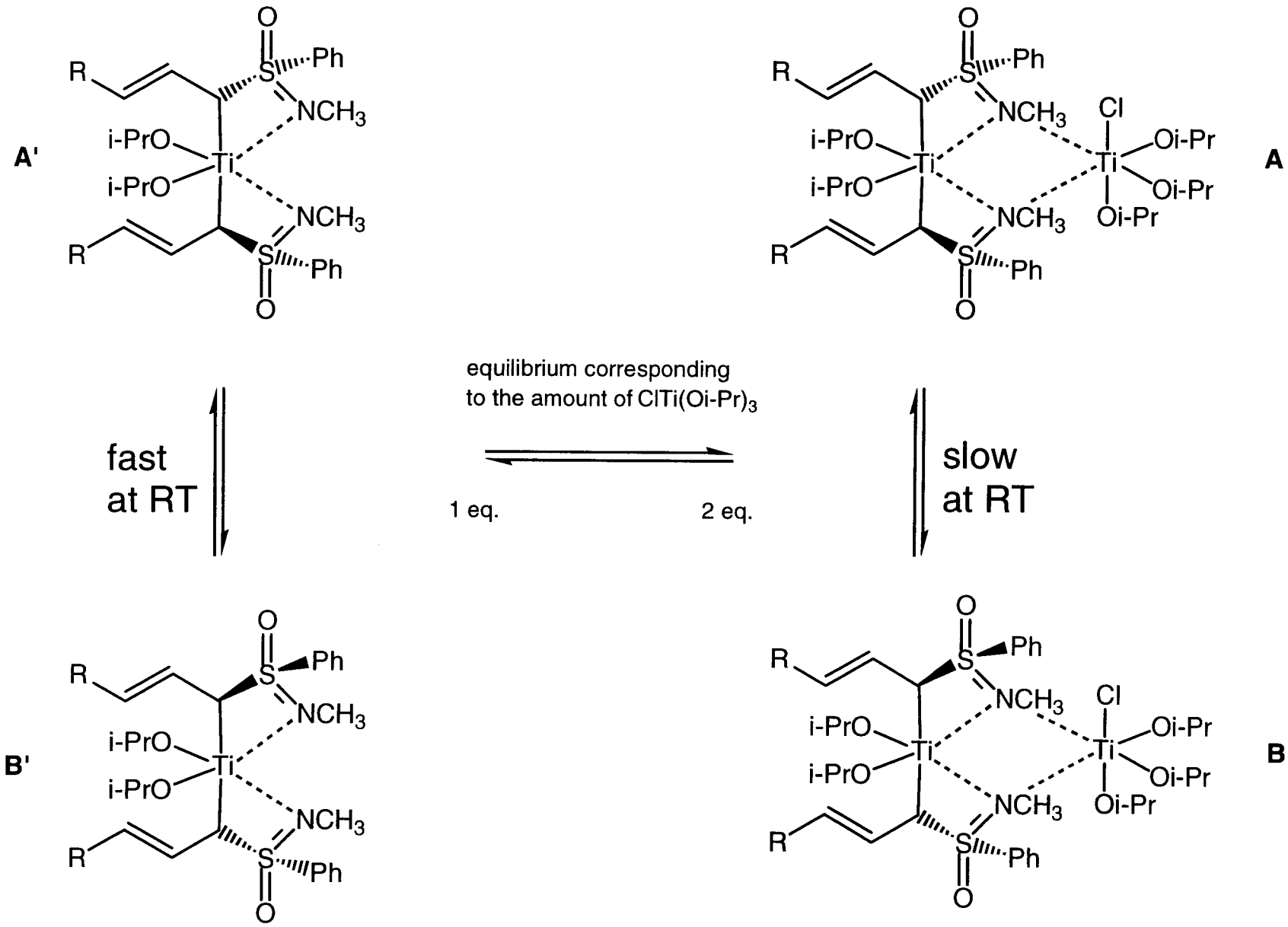


Exchange A - B

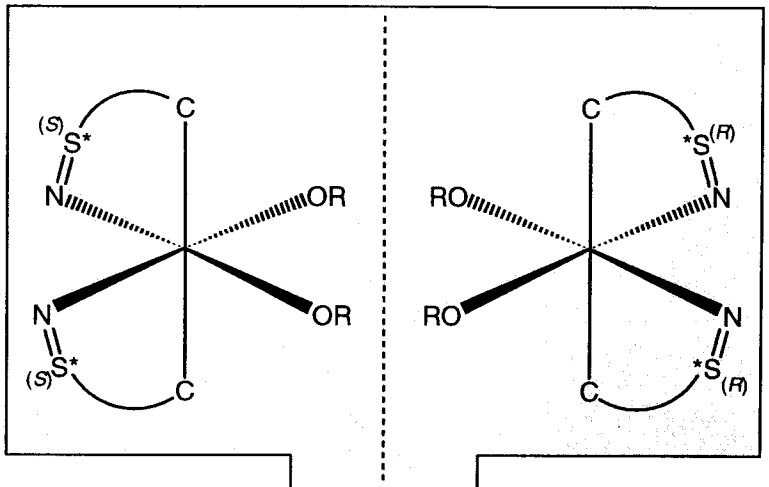


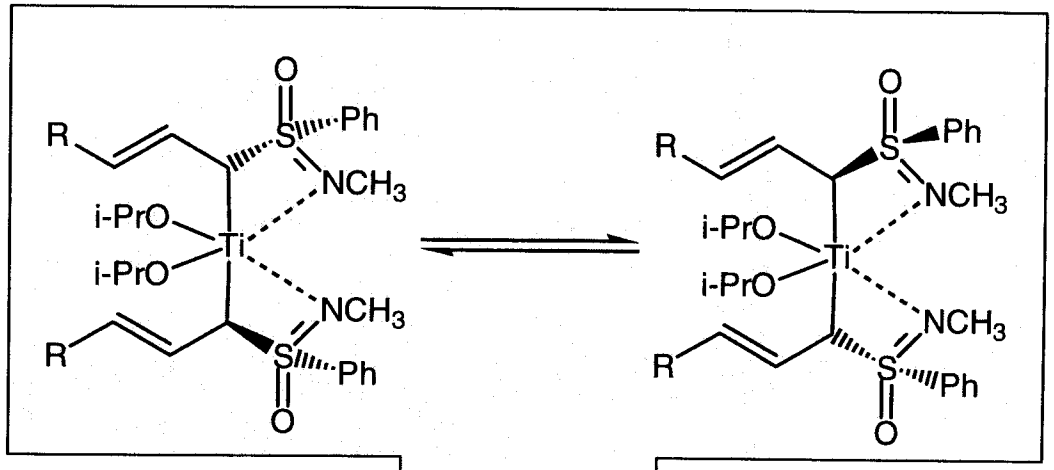
- Exchange during mixing time proven
- Equilibrium A - B exists, <u>slow</u> at room temperature

Model


A'
A
B'
B
fast
at RT
slow
at RT
equilibrium corresponding
to the amount of ClTi(Oi-Pr)3
1 eq.
2 eq.
R
Ph
NCH3
i-PrO
Ti
Cl
Oi-Pr
O
S

Comparison





- Ratio A/B not 1:1
- Only 2 out of 8 species
- Even at -80 °C
- Exchange should be fast

- 8 diastereomers: fast exchange or only 1
- Different configuration at 1-H (α-H)
- Fits to synthetic results (imines/aldehydes)
- Less complicated model

Acknowledgements

- Prof. Dr. H.-J. Gais
- My apprentice: D. Bayer
- Research group
- Analytics team of our research group and the institute
- SFB 380

Publications:

1. H.-J. Gais, R. Hainz, H. Müller, P. R. Bruns, N. Giesen, G. Raabe, J. Runsink, S. Nienstedt, J. Decker, M. Schleusner, J. Hachtel, R. Loo, C.-W. Woo, P. Das, *Eur. J. Org. Chem.*, **2000**, *24*, 3973-4009
2. Dissertation, M. Schleusner, RWTH Aachen 2002 (available on http://www.bth.rwth-aachen.de/job/disslist.pl)
3. H.-J. Gais, M. van Gumpel, M. Schleusner, G. Raabe, J. Runsink, C. Vermeeren, *Eur. J. Org. Chem.*, **2001**, 4275-4303
4. M. Schleusner, H.-J. Gais, S. Koep, G. Raabe, *J. Am. Chem. Soc.*, **2002**, *124*, 7789-7800