



# Selected Recent Applications of Low-Valent Titanium Chemistry

Bill Darrow

Denmark Lab Group Meeting

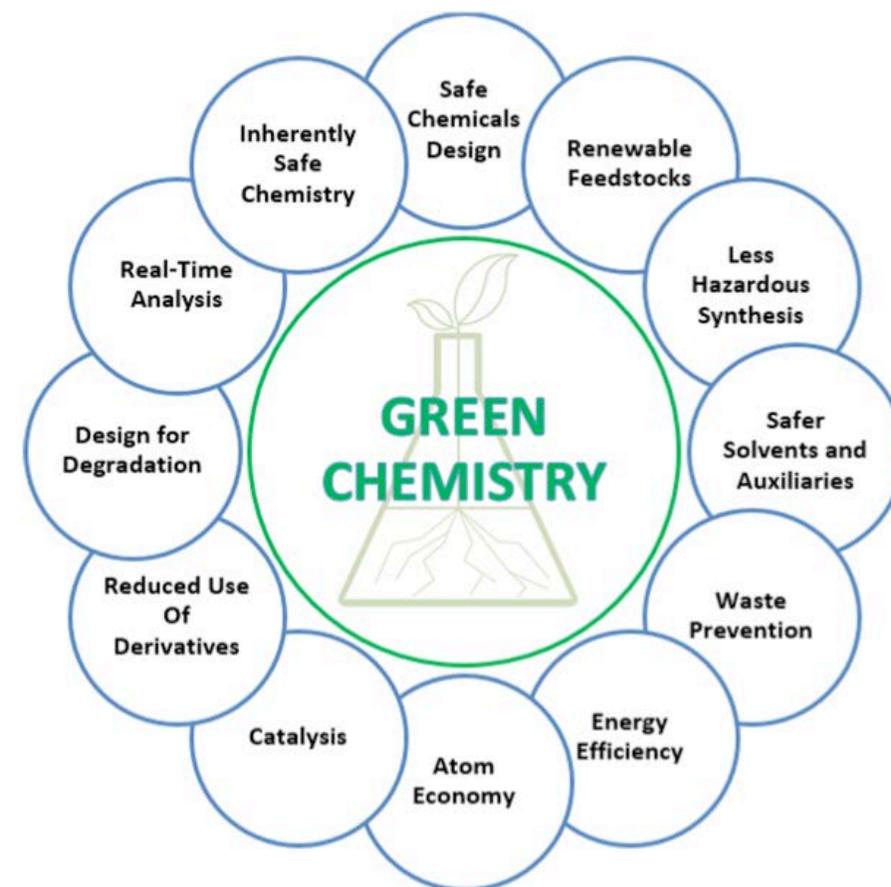
April 23, 2019



- Titanium and Its Common Uses in Organic Chemistry
- Titanium(II) and (III): Structure and Relevance
- Generation of Pyrroles by a Ti(II)/(IV) Catalytic Cycle
- Oxidative Carboamination of Alkynes with Alkenes and Diazenes
- TMS-Protected Alkynes as Substrates for [2+2+1] Pyrrole Synthesis
- Mechanism Of Ti-Catalyzed Oxidative Nitrene Transfer
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- Applications of Ti(III) in Recent Total Syntheses
- Conclusions

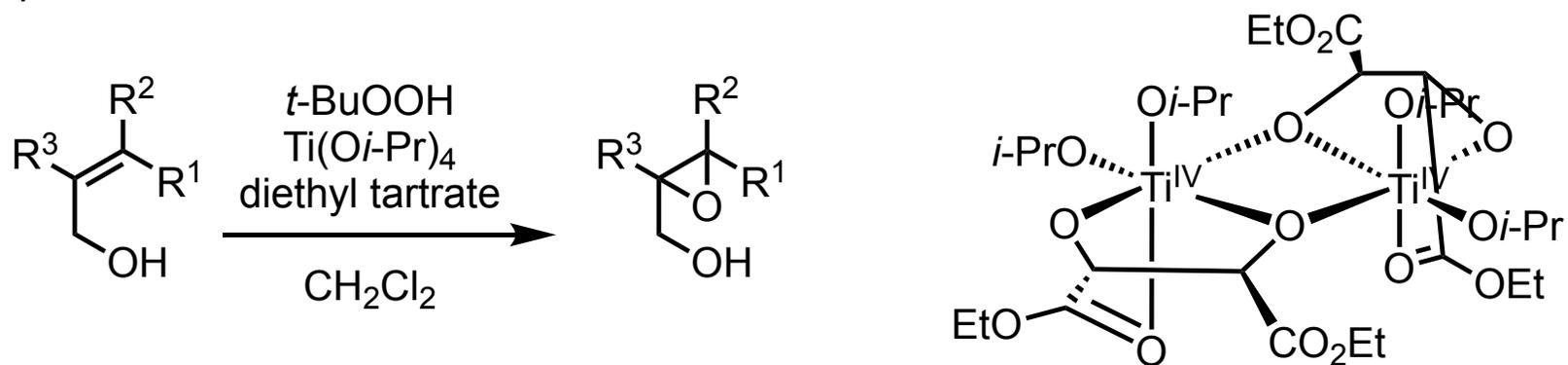
## Why Titanium?

- Abundant (0.6% abundance in Earth's crust)
- Cheap (100 g bottle of  $\text{TiCl}_4$  is \$44 from Oakwood)
- Non-toxic
- Satisfies several of the 12 principles of green chemistry
  - Amenable to catalysis
  - Compatible with safer solvents (THF, toluene, etc)
  - Atom economy
  - Minimization of Energy Consumption (many rxns run at rt)

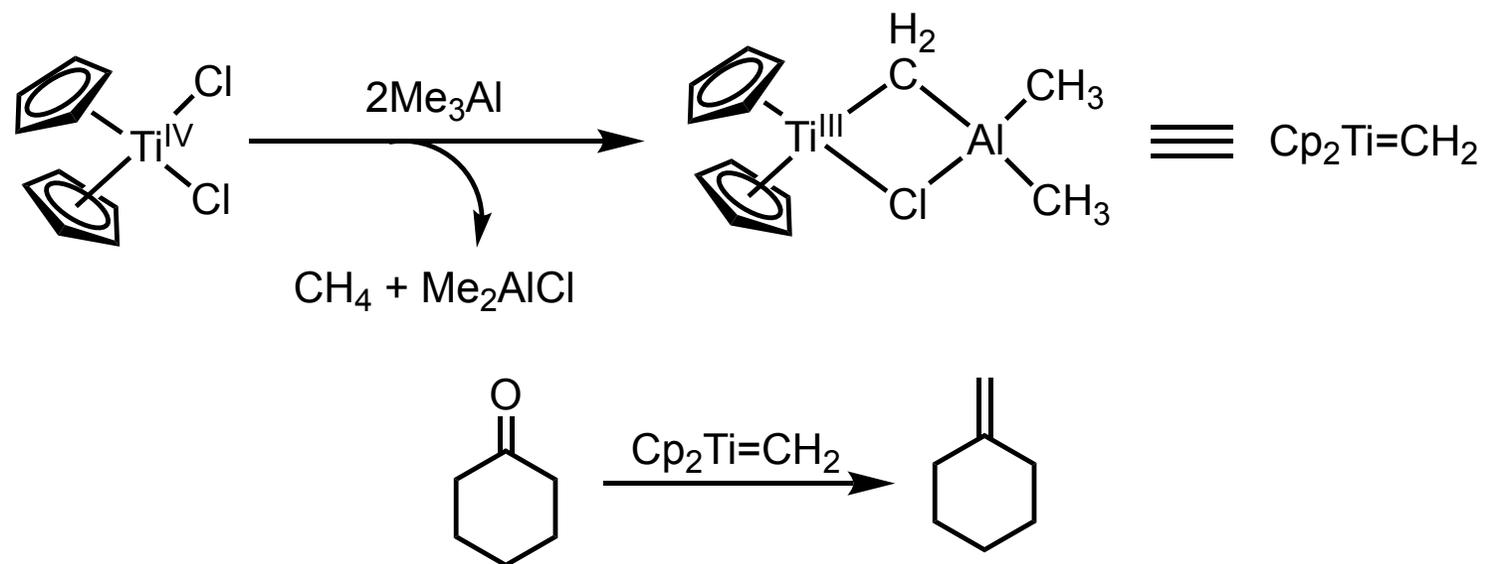


# Titanium and Its Common Uses in Organic Chemistry

- Sharpless Epoxidation

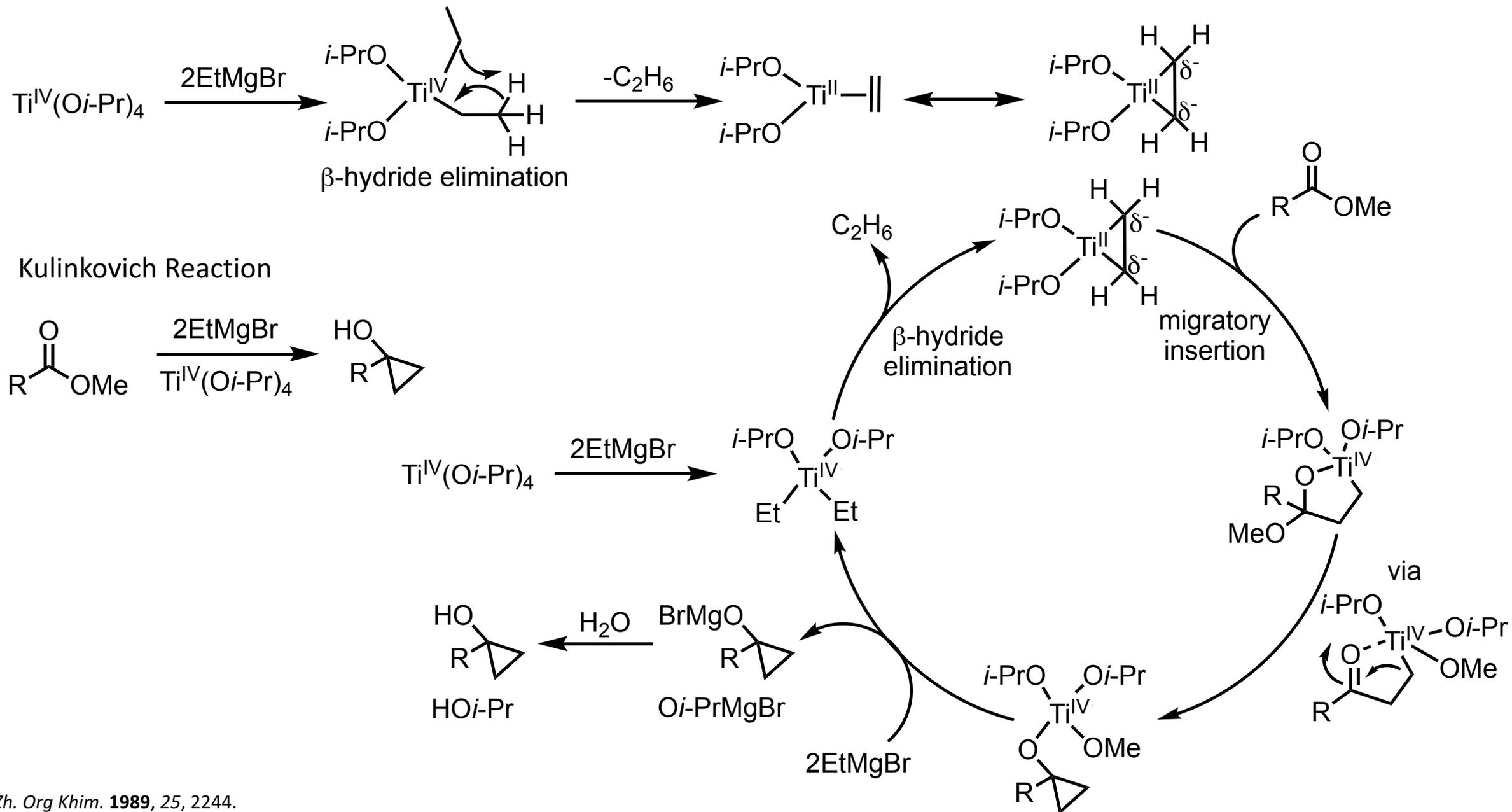


- Tebbe Reagent





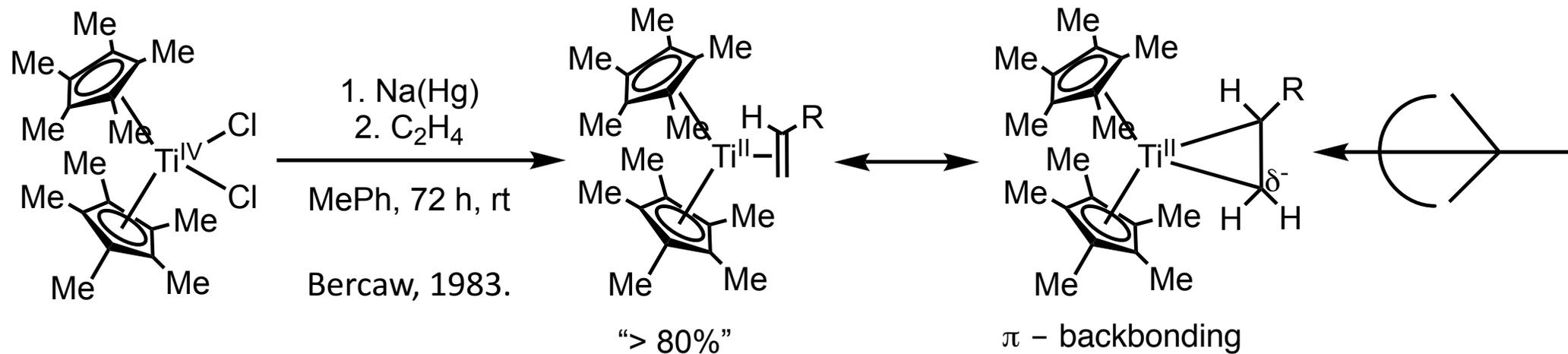
# Titanium and Its Common Uses in Organic Chemistry



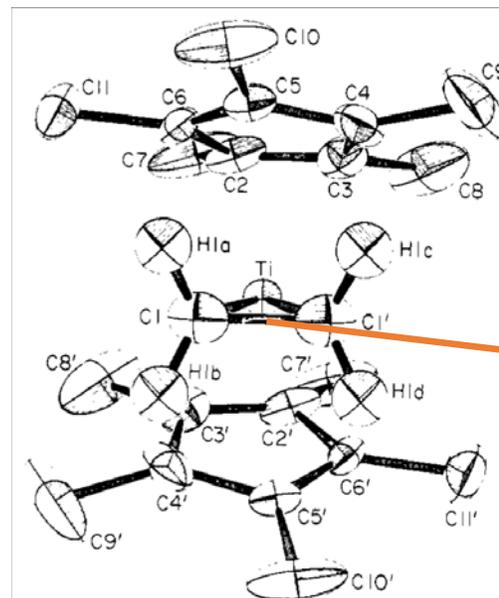


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# Titanium(II): Structure and Relevance



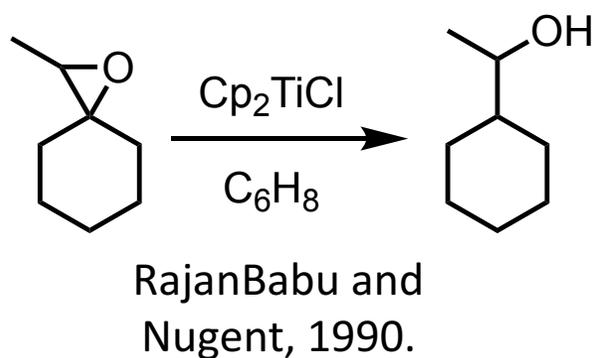
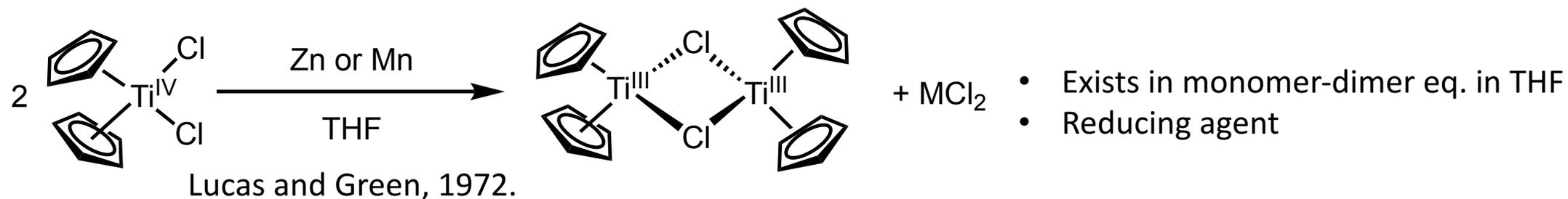
- First isolable Ti<sup>II</sup>-olefin complex and crystal structure
- Complex can undergo ox. add. with H<sub>2</sub> unlike Ti(IV) complexes
- Electron rich Ti<sup>II</sup>-olefin complexes readily undergo migratory insertion
- Driving force of oxidizing Ti<sup>II</sup> to Ti<sup>IV</sup> can turn over catalytic cycles



1.337 Å for ethylene

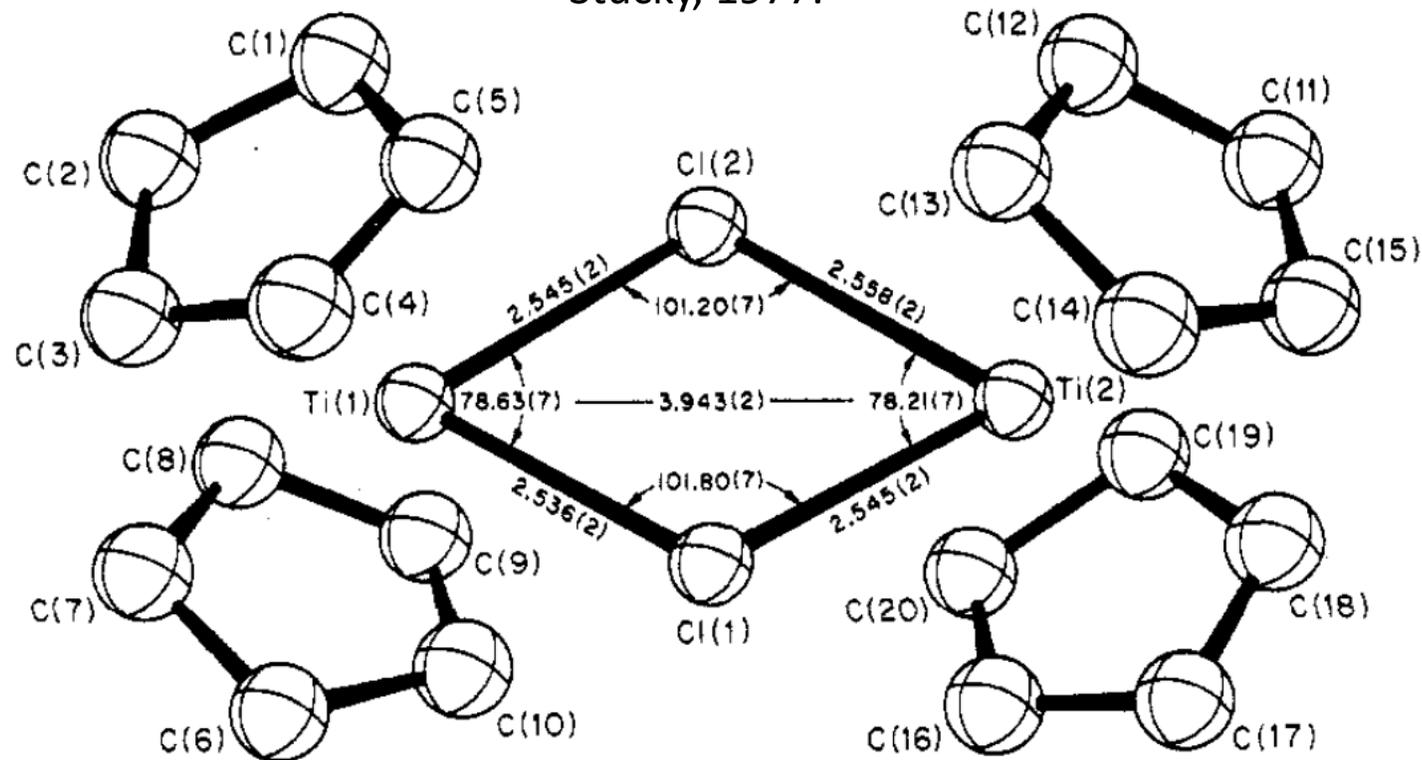
1.438 Å  
(similar to analogous low val. e<sup>-</sup> rich metal complexes; Nb = 1.406 Å)

# Titanium(III): Structure and Relevance



- $\text{Cp}_2\text{TiCl}$  engages in SET chemistry
- Resulting radicals trapped with olefins, alkynes, hydrogen atoms, etc

Stucky, 1977.

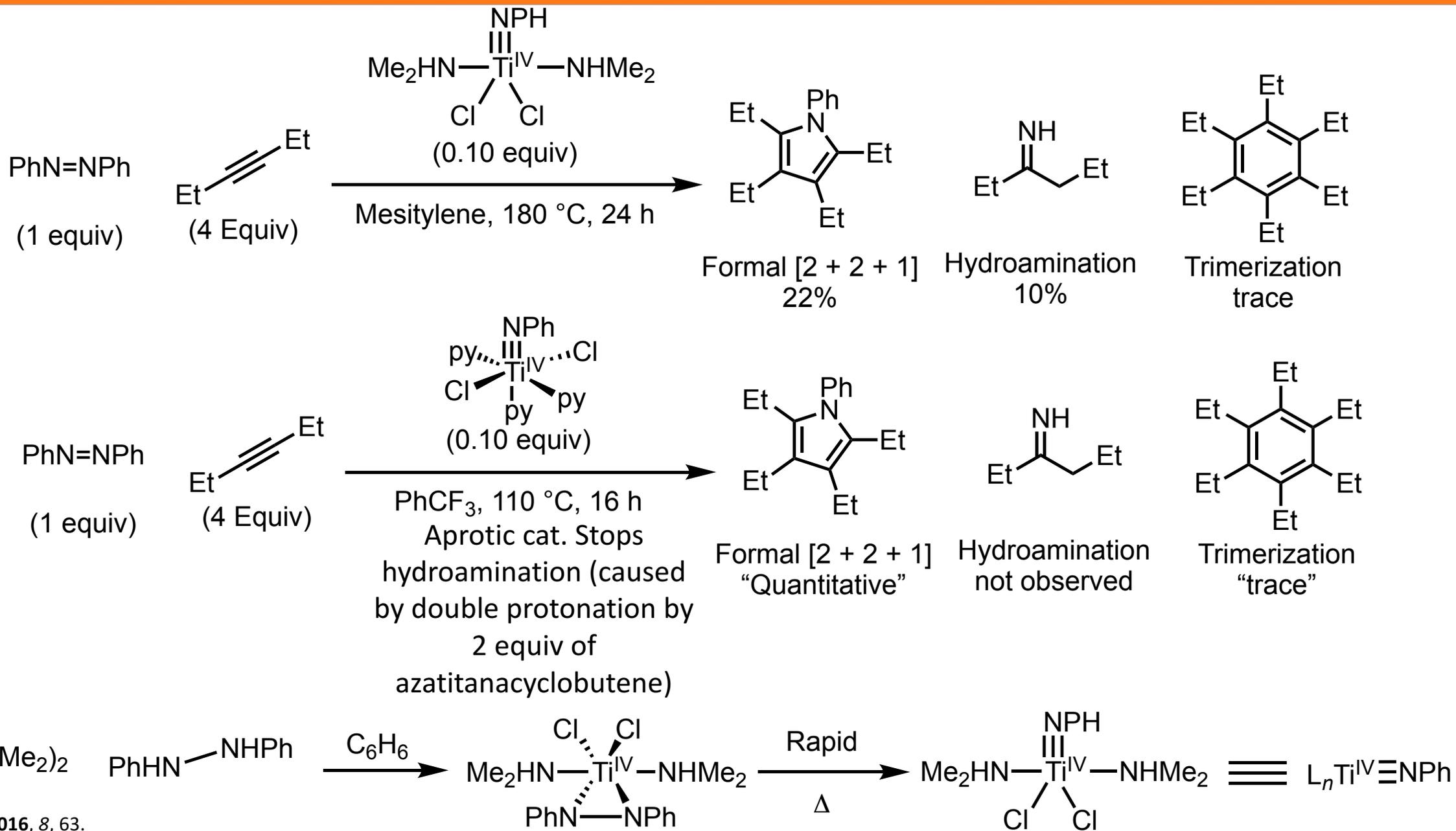




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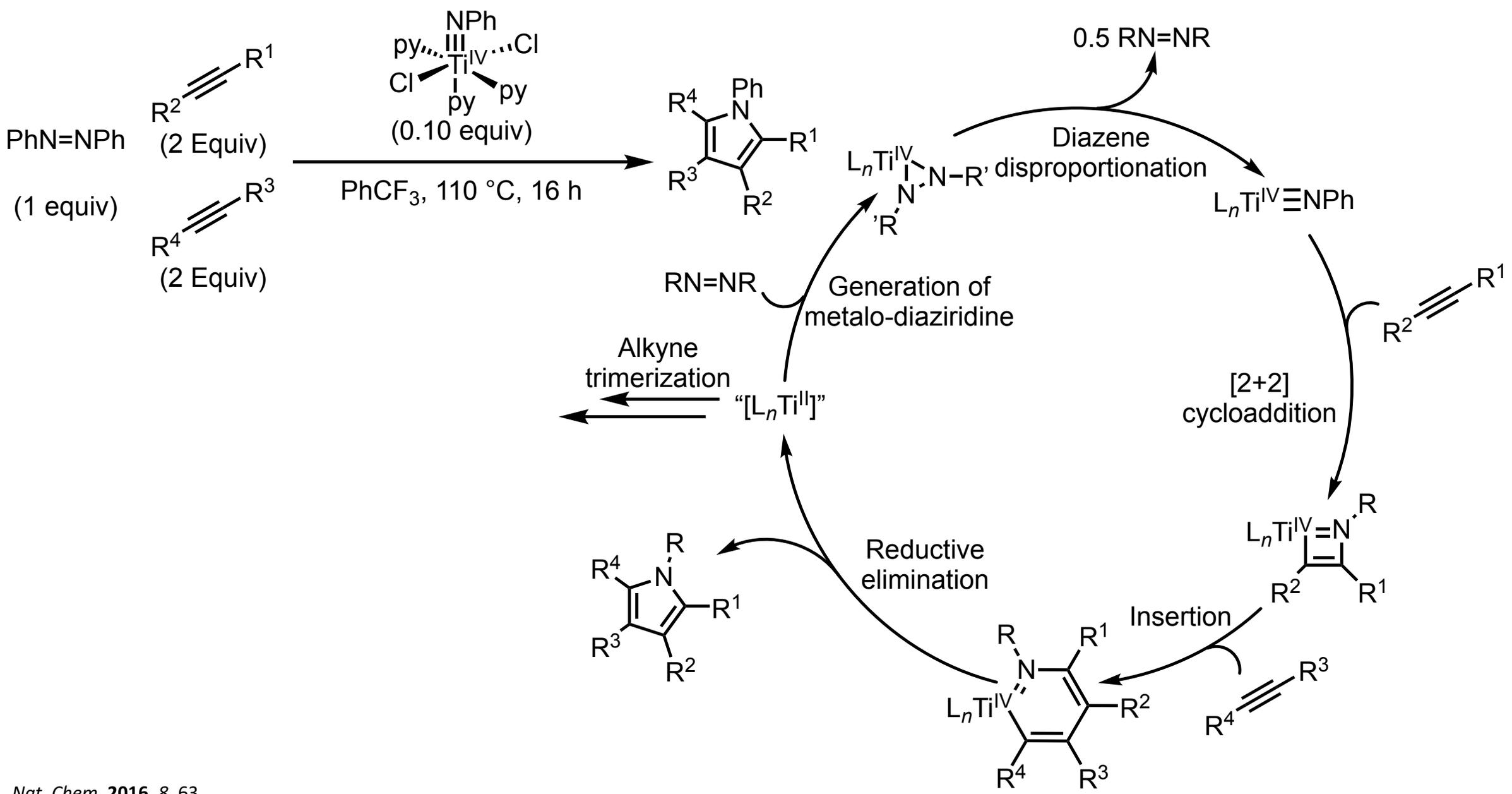


# Generation of Pyrroles by a Ti(II)/(IV) Catalytic Cycle



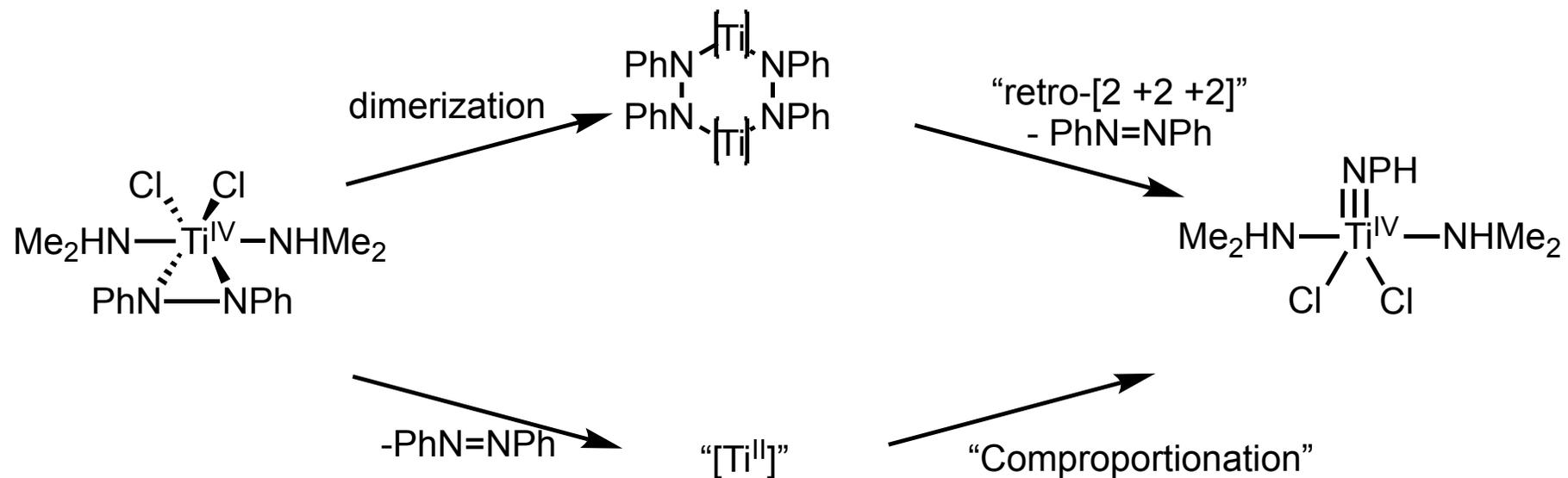


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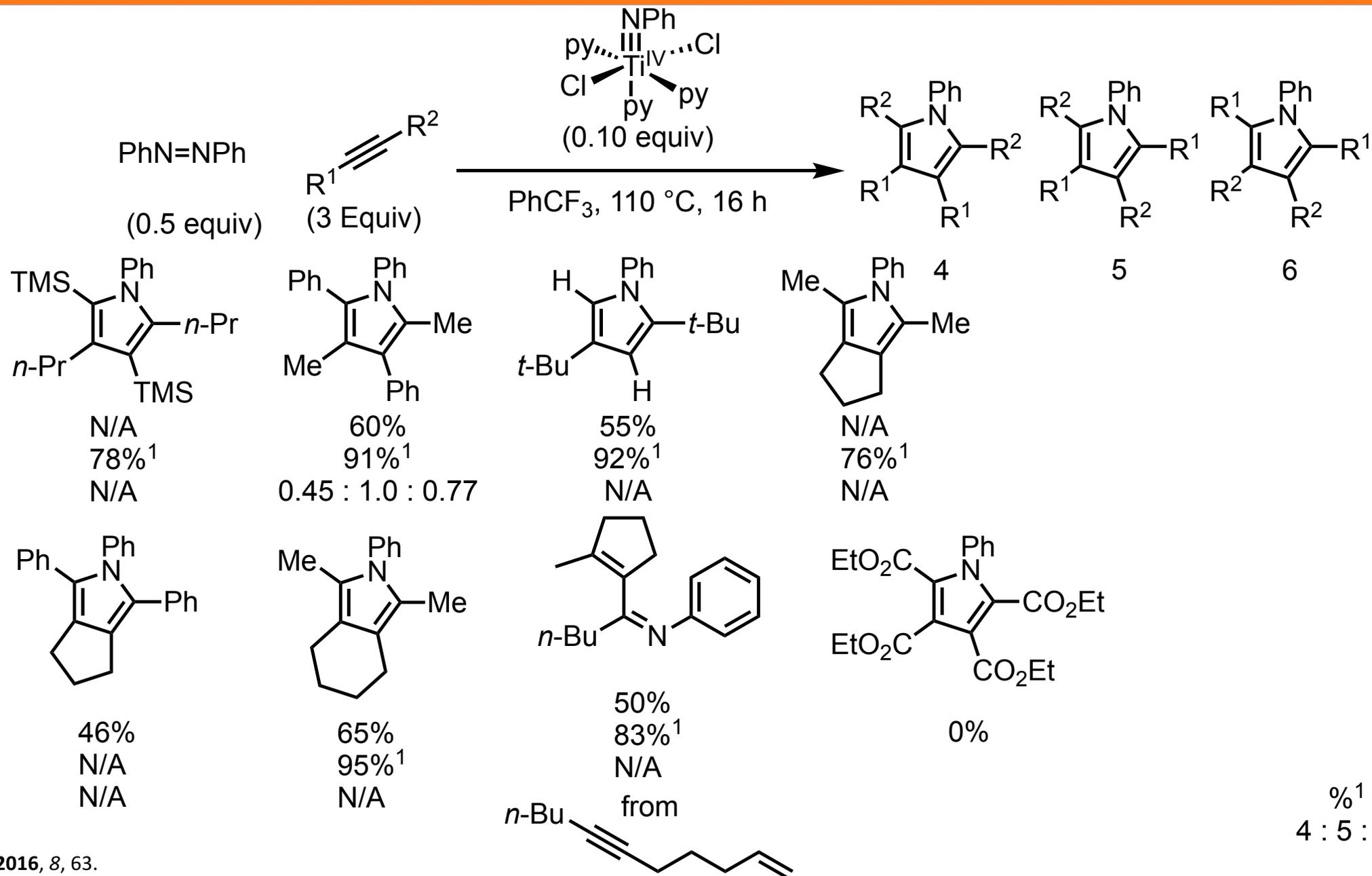




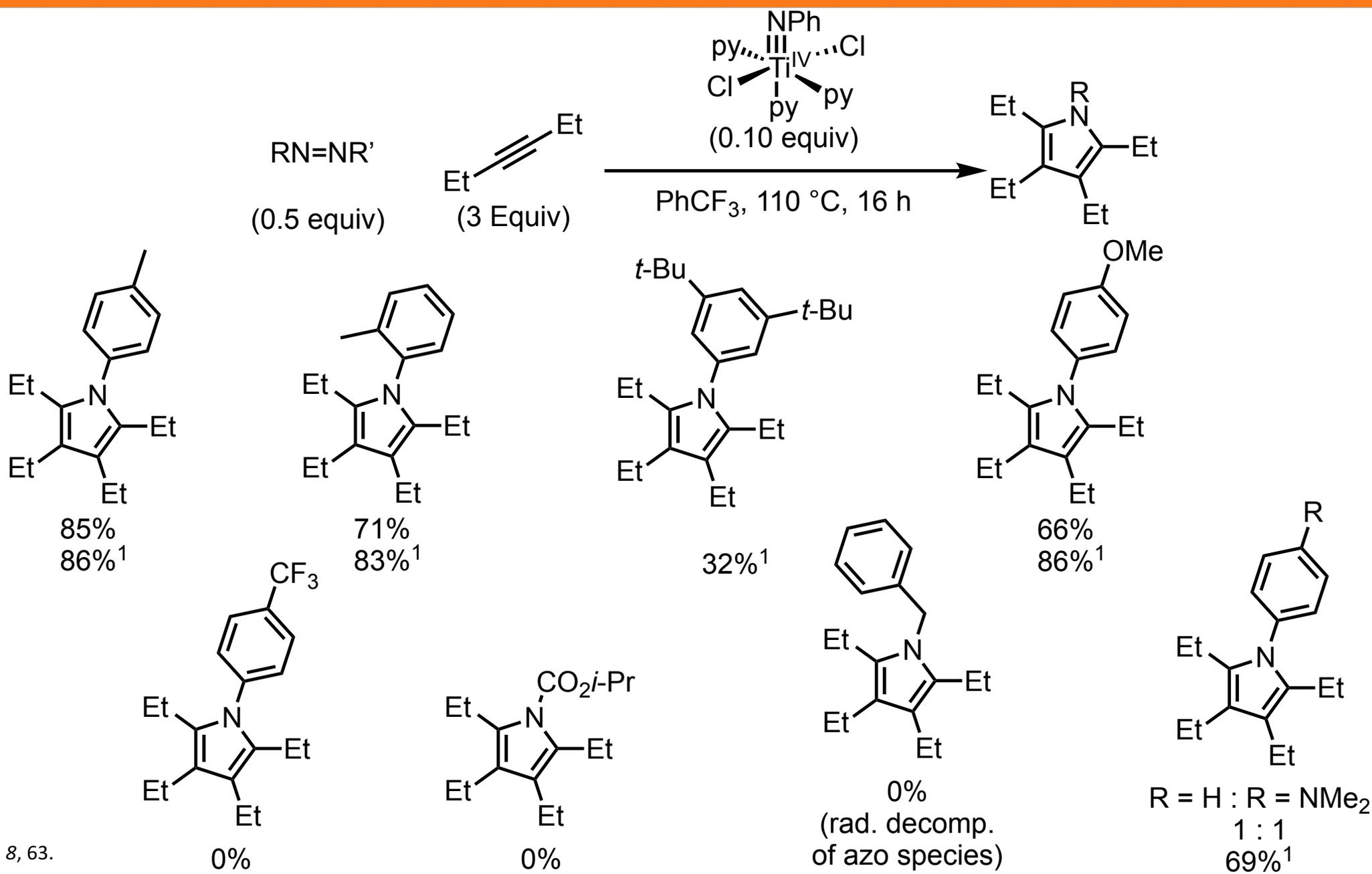
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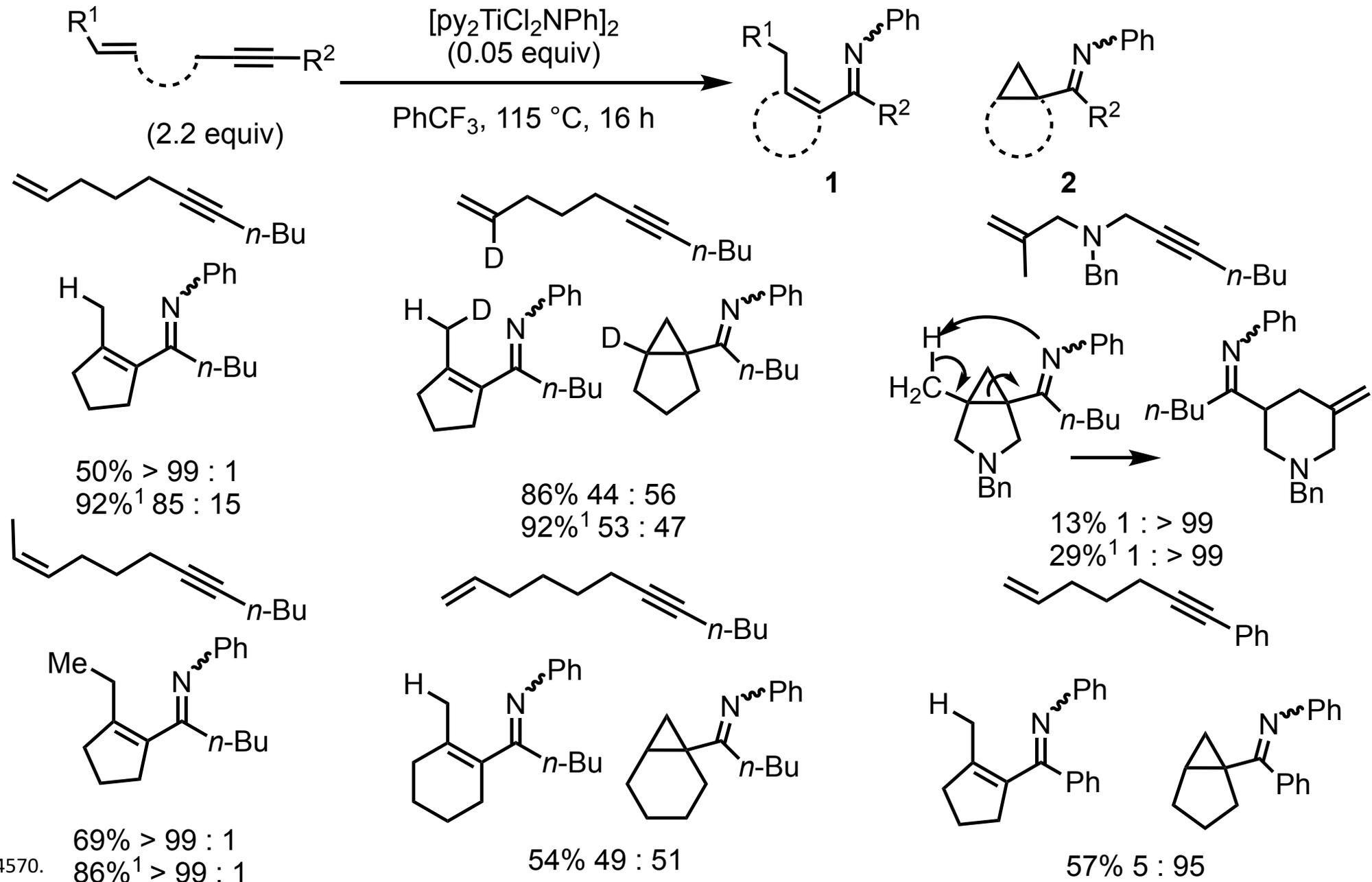
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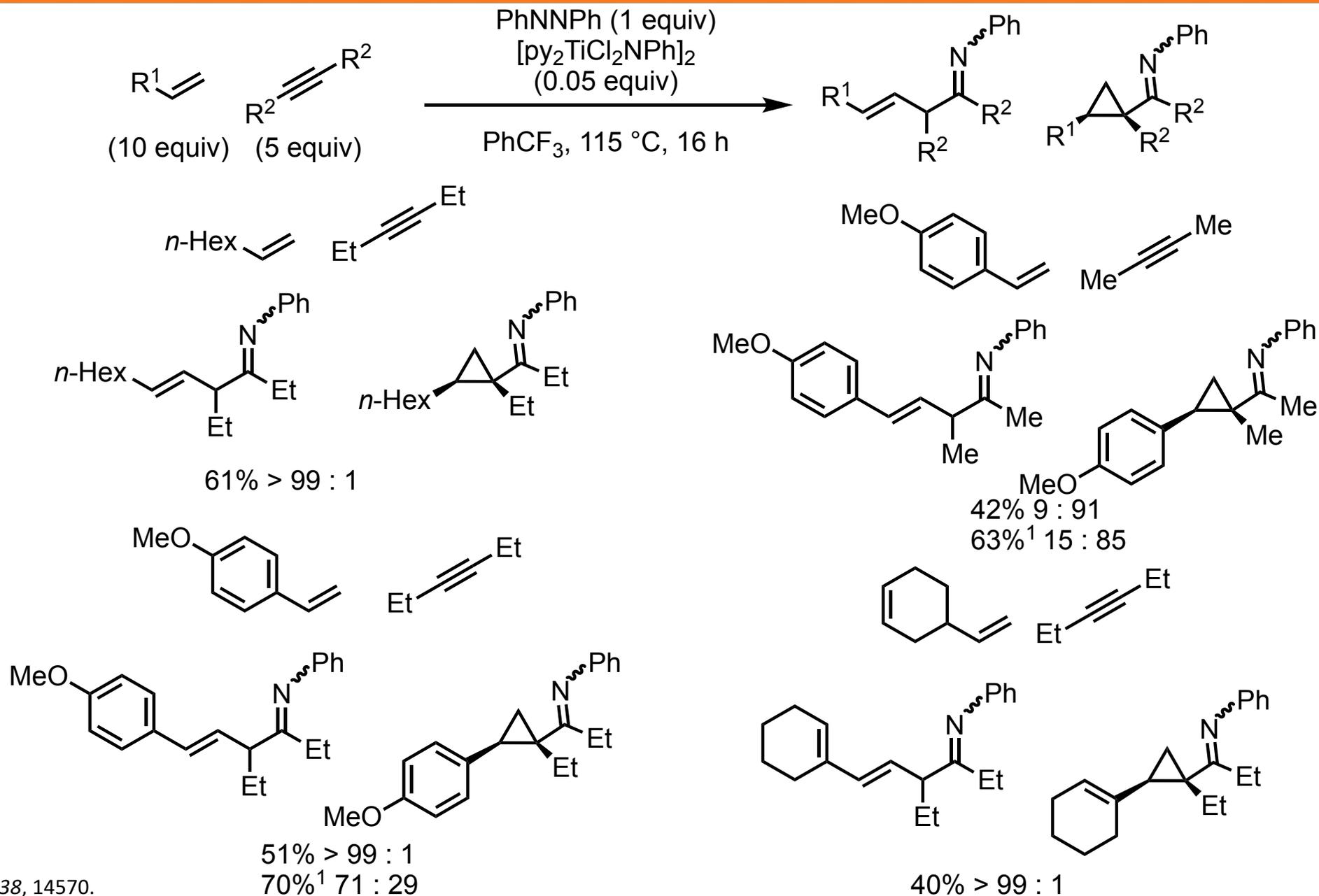
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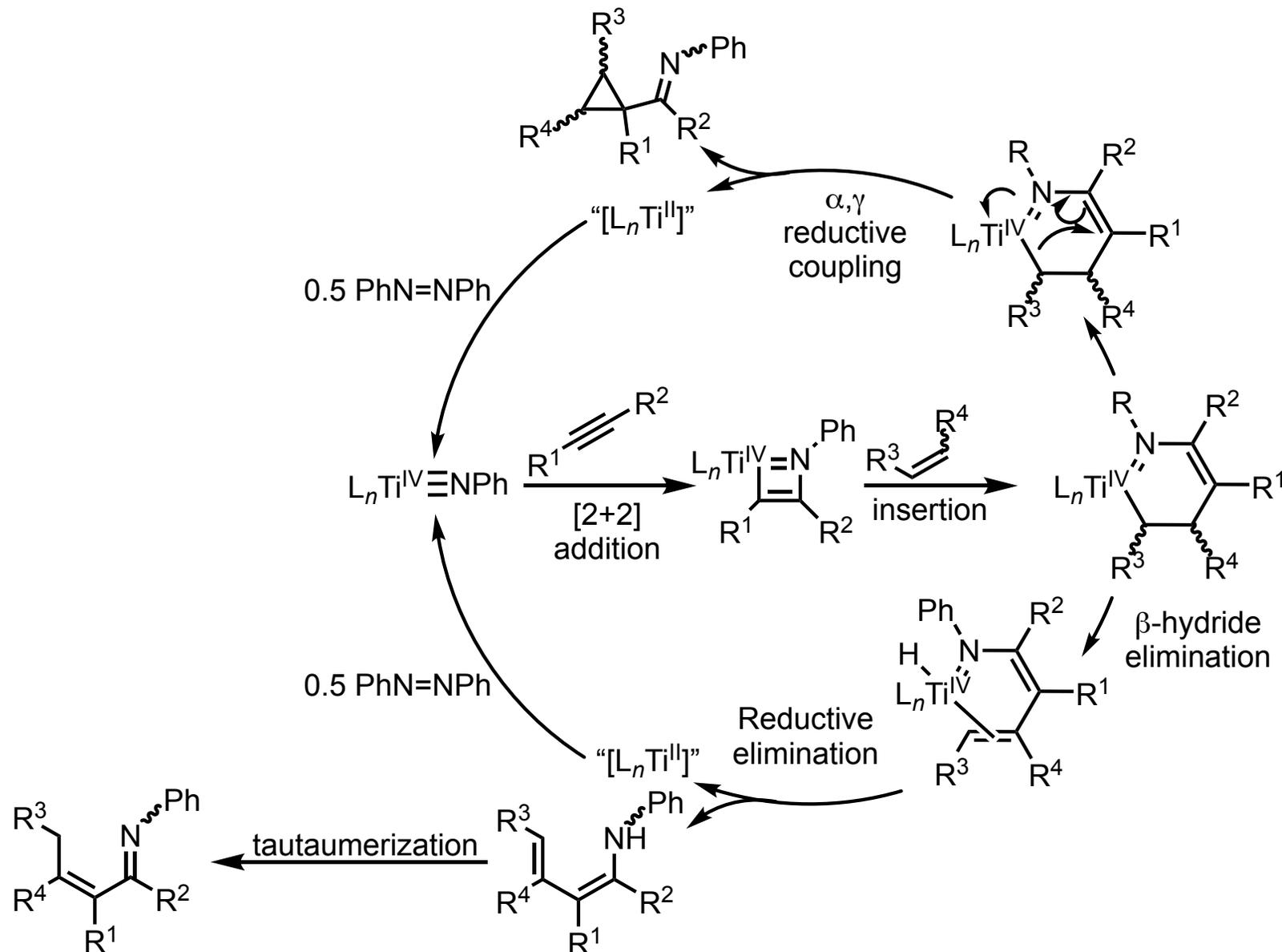


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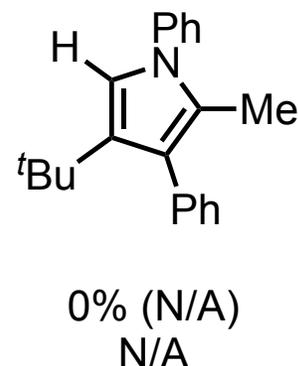
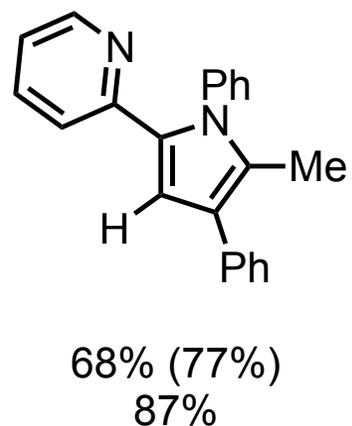
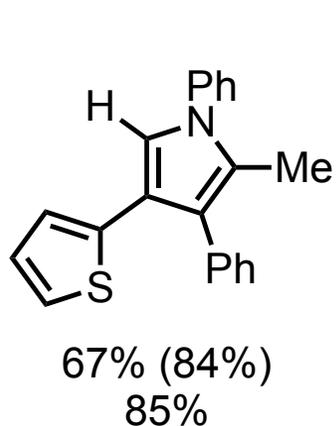
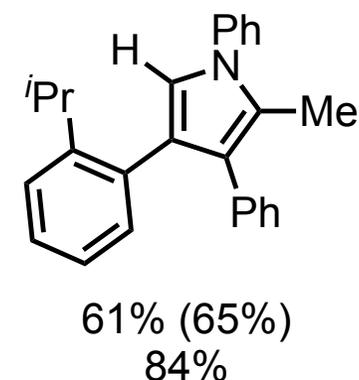
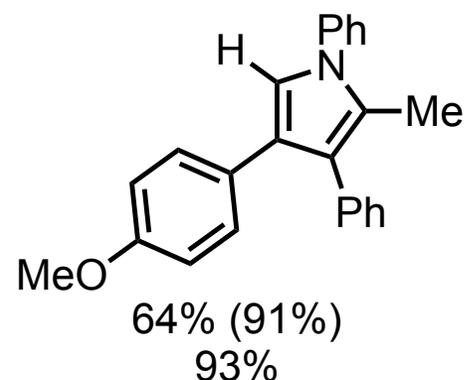
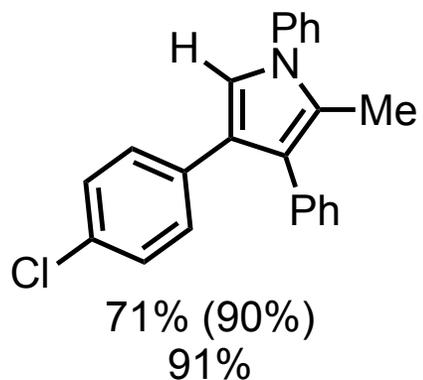
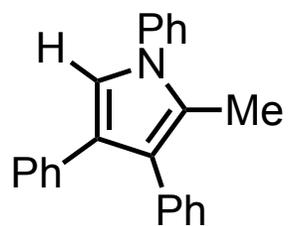
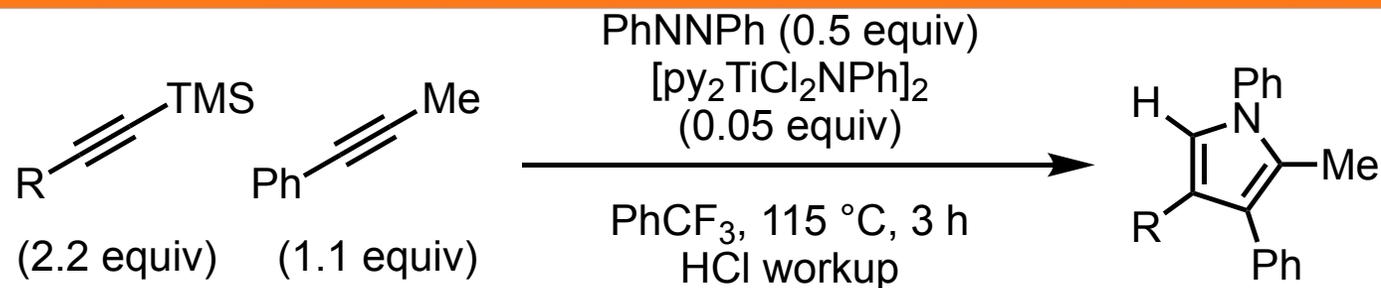
- Both cycles go through azatitanacyclohexene
- Product formed determined by sterics of azatitanacyclohexene





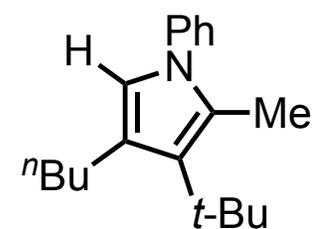
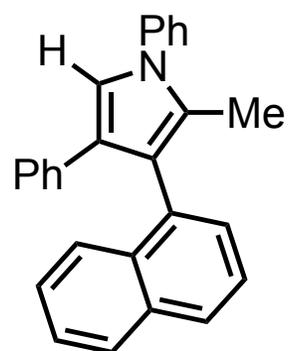
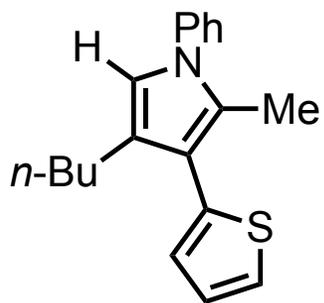
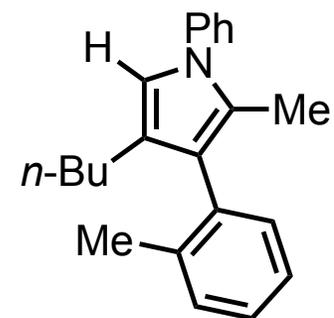
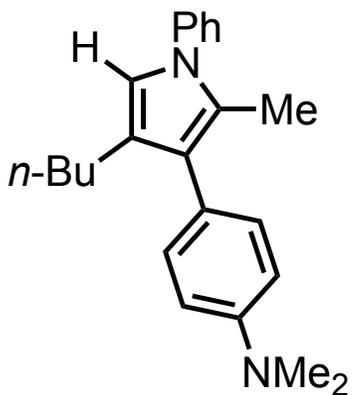
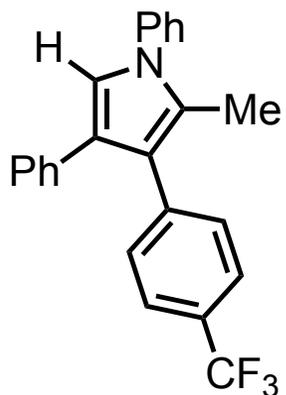
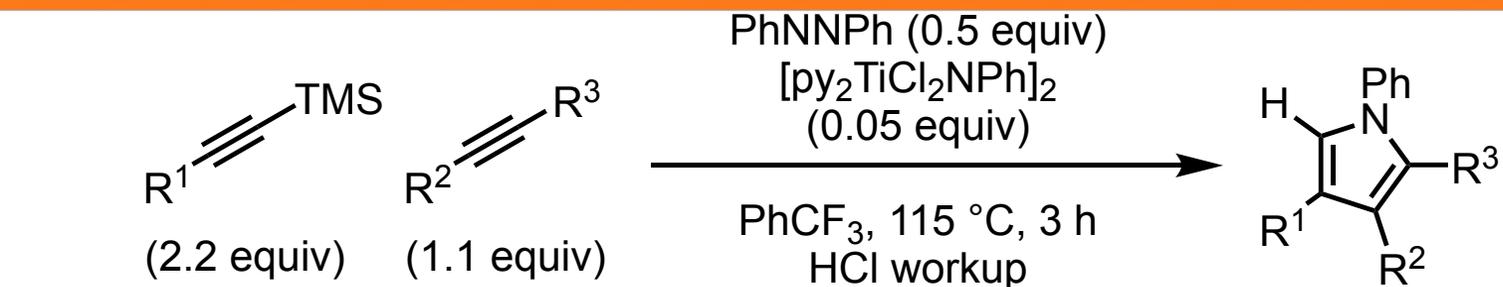
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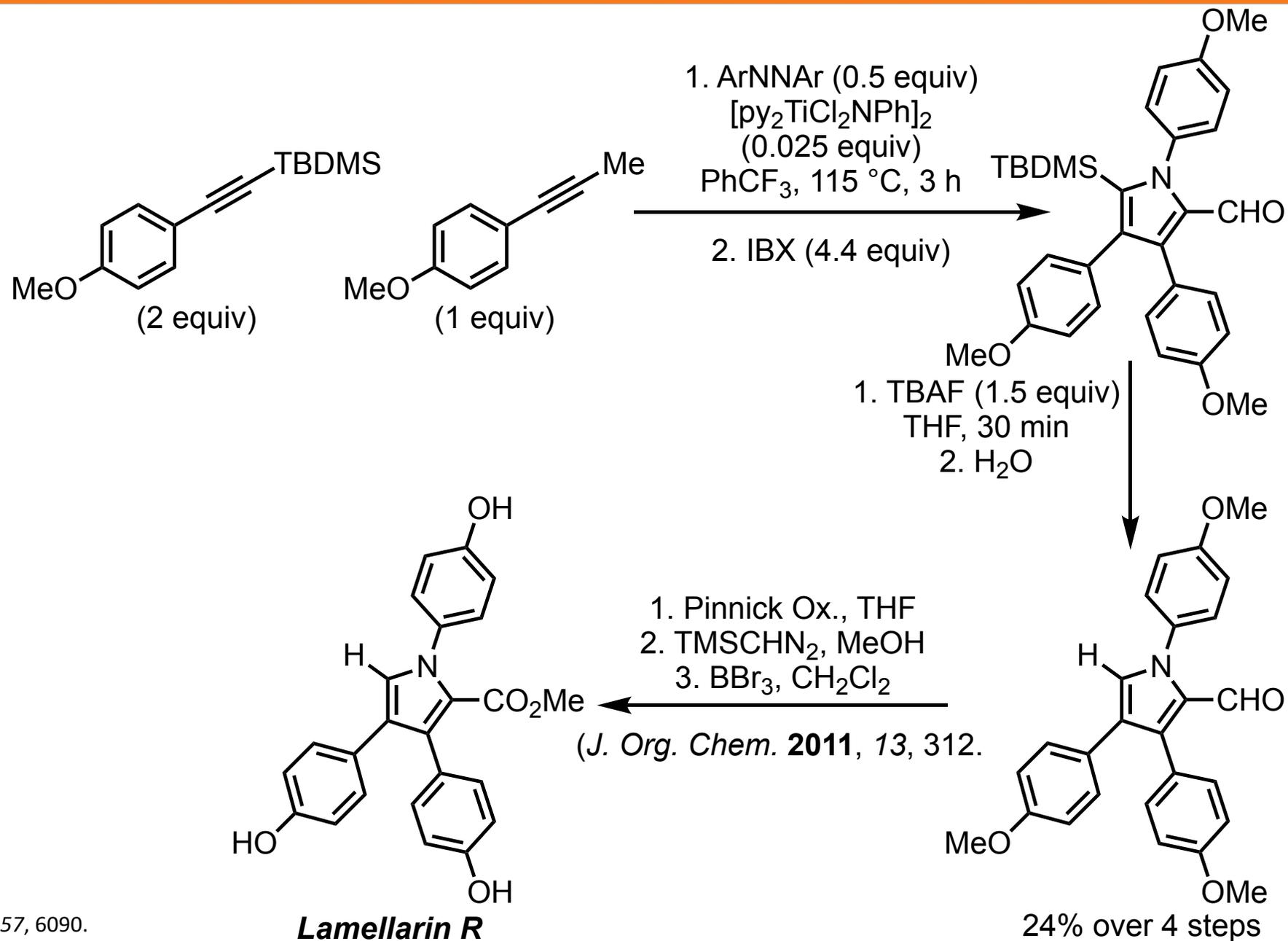
*isolated yield (GC yield)*  
*selectivity w.r.t. all possible pyrrole ptds*

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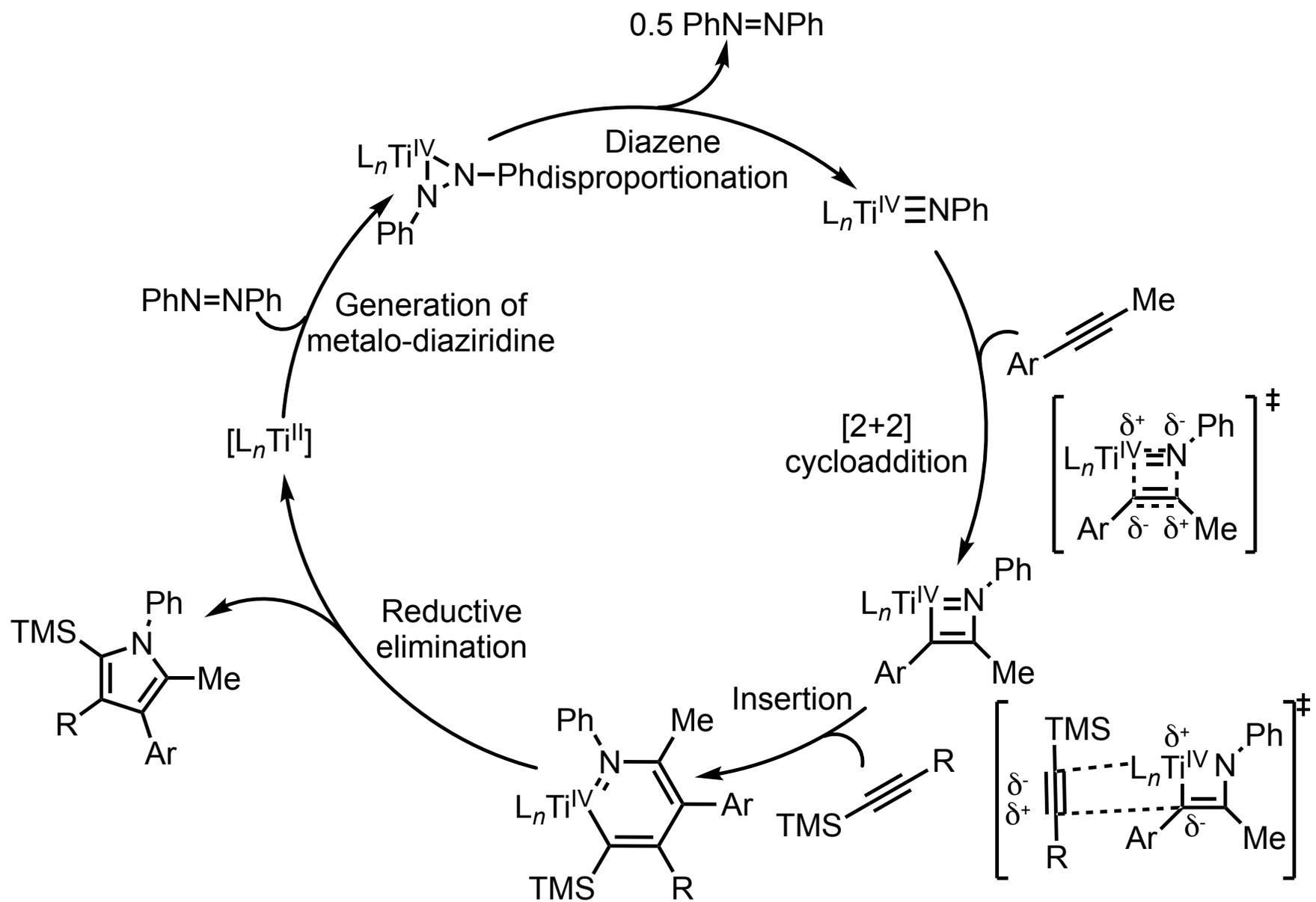


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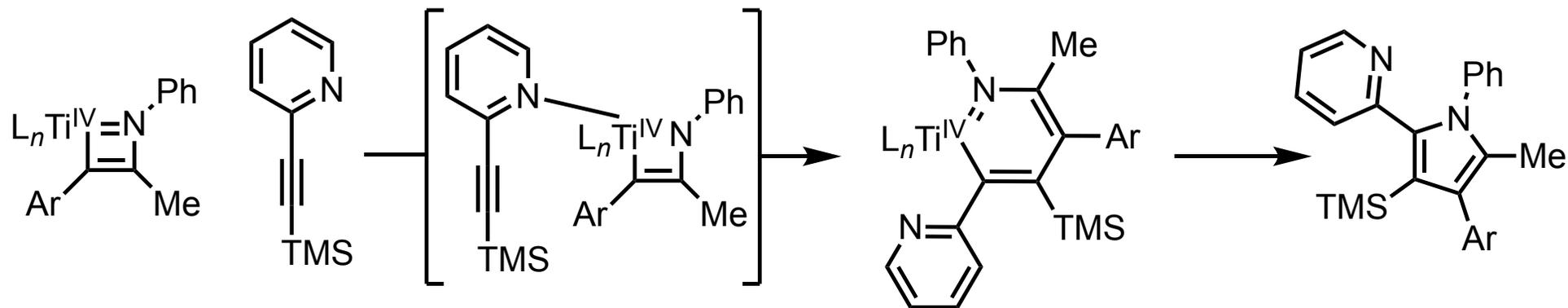
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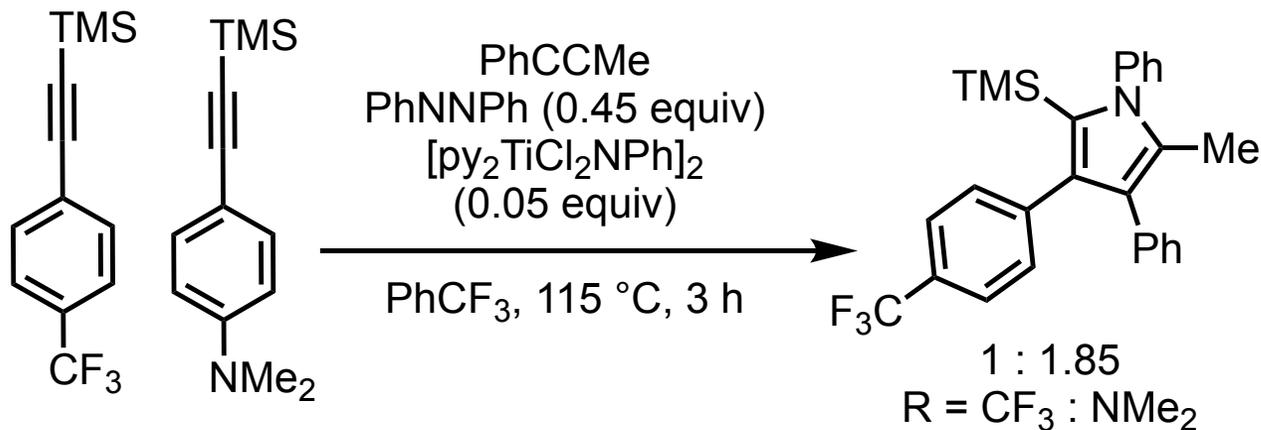
# TMS-Protected Alkynes as Substrates for [2+2+1] Pyrrole Synthesis



# TMS-Protected Alkynes as Substrates for [2+2+1] Pyrrole Synthesis



- LB functionalities direct second cycloaddition
- Thiophene gives opposite selectivity due to HSAB mismatch of Ti/S
- Electron-rich substrates outcompete electron-deficient substrates



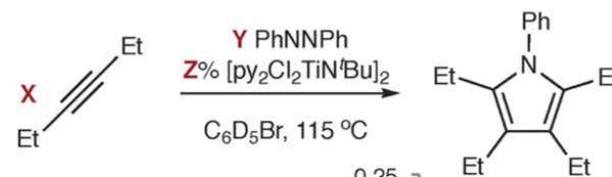
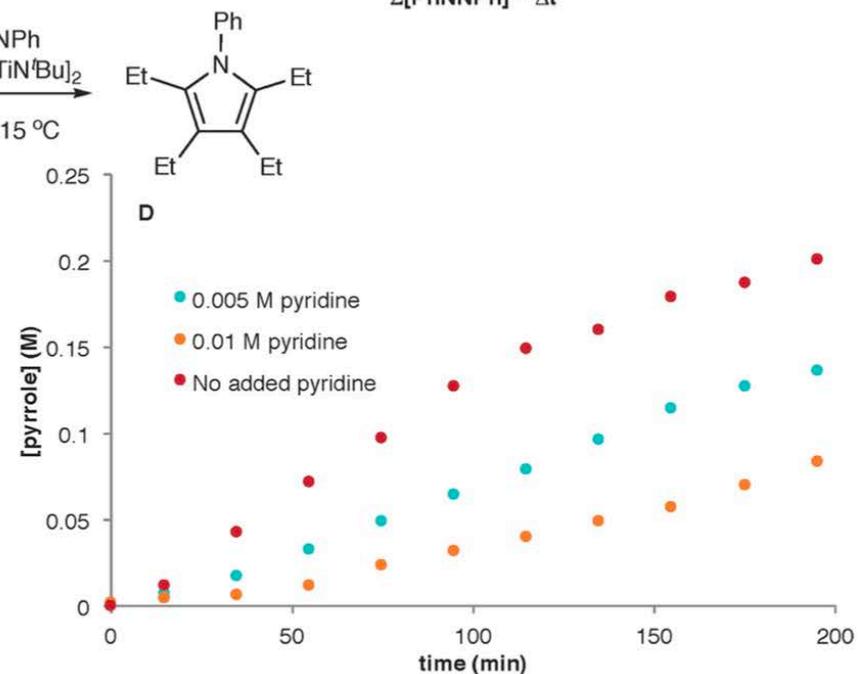
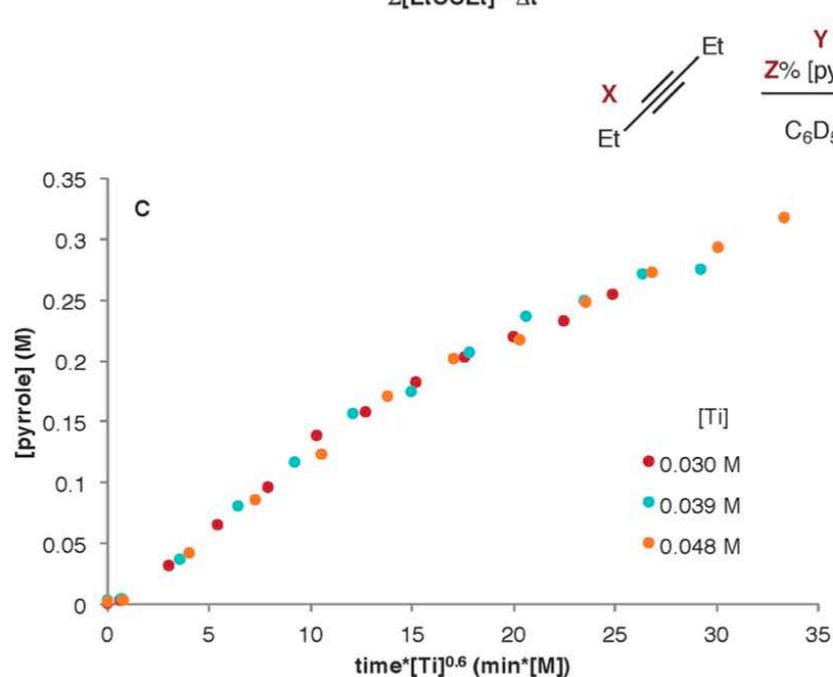
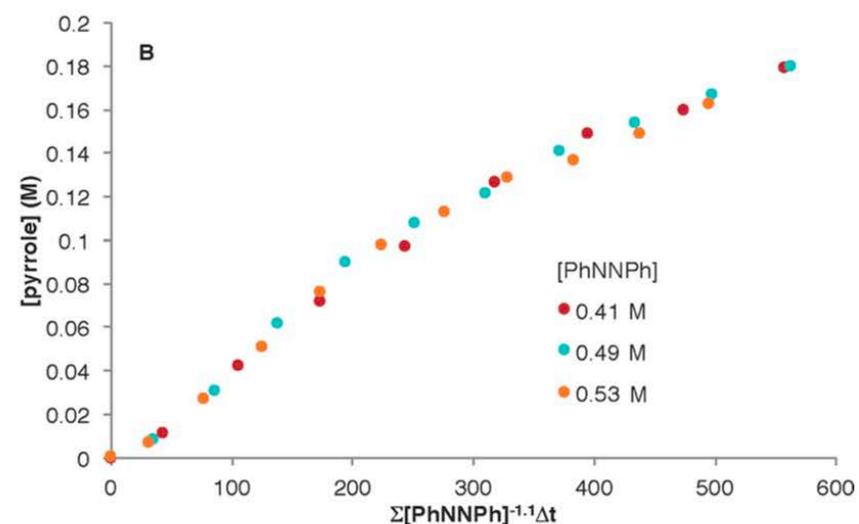
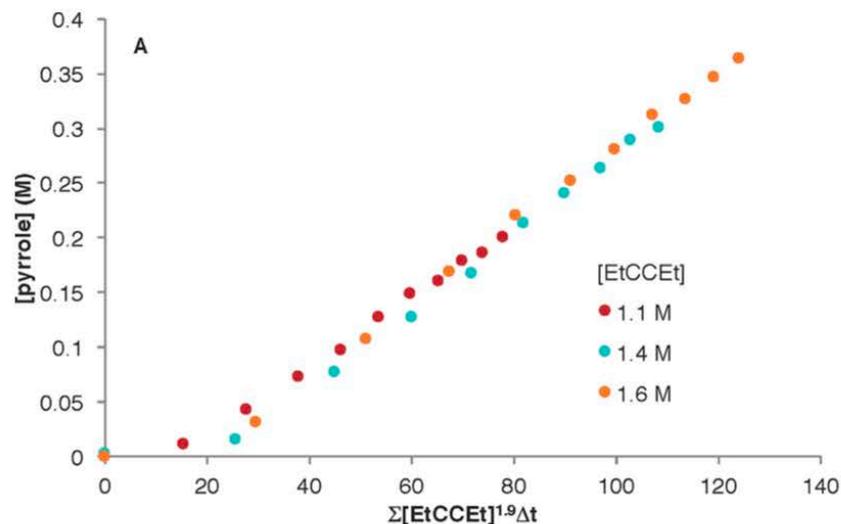


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# Mechanism Of Ti-Catalyzed Oxidative Nitrene Transfer

$$rate = k \frac{[Ti]^{0.5}[alkyne]^2}{[PhNNPh][pyridine]}$$

- Variable time normalization analysis
- 0.5 order in Ti due to monomer-dimer equilibrium
- PhNNPh could competitively bind alkyne
- Second alkyne insertion or red. elim. is rate-determining.
- Ti monomer-dimer eq. prior to reversible [2+2] cycloaddition followed by RD, irreversible second alkyne insertion or RE.





# Mechanism Of Ti-Catalyzed Oxidative Nitrene Transfer

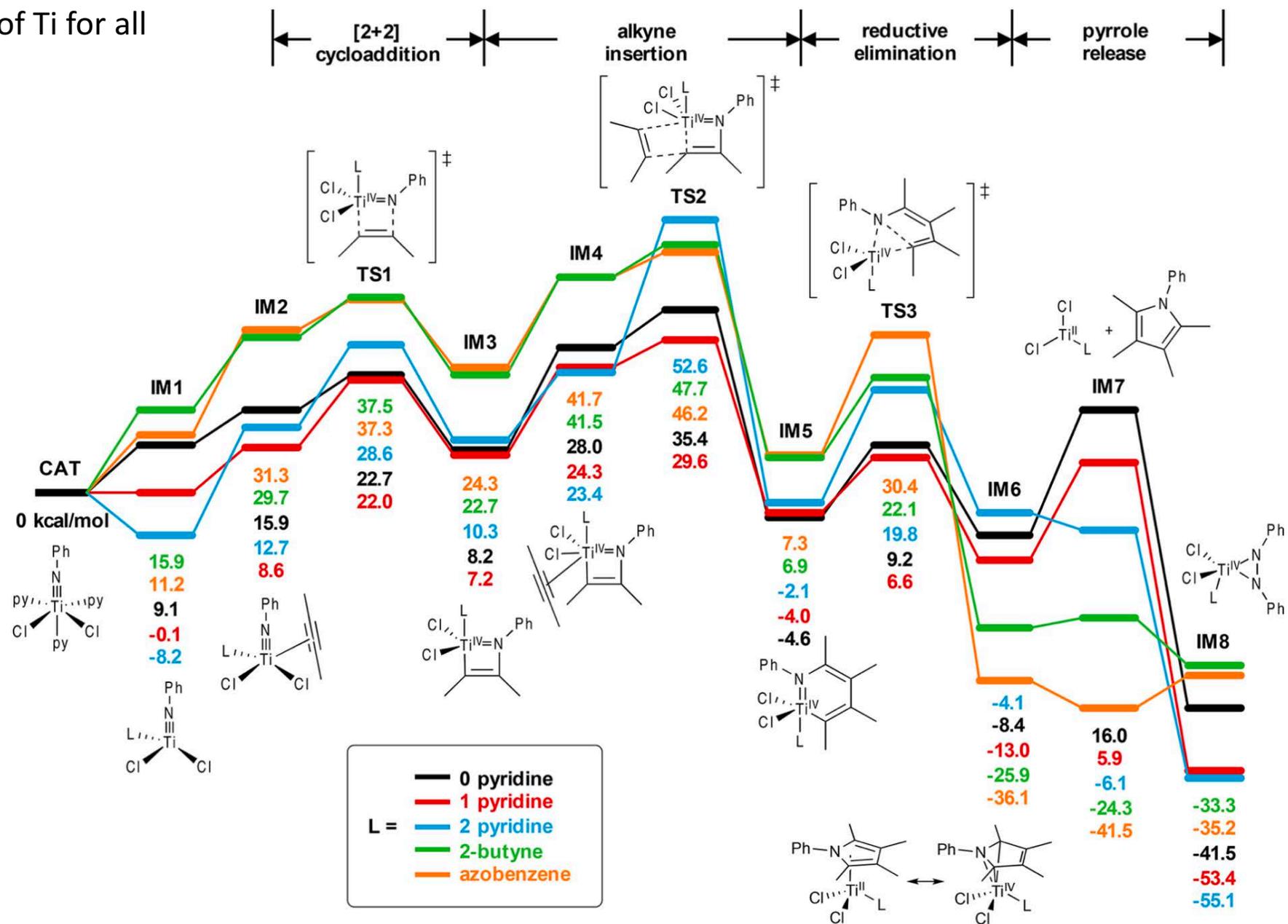
- Geometry optimizations: Gaussian 09
- M06 functional
- 6-311G(d,p) basis set
- Ultrafine grid
- SMD solvation model
  
- Natural Bond Orbital (NBO) calculations
  - NBO 5.G program
  
- Intrinsic Bond Orbital (IBO) calculations
  - MOLPRO 2015.1
  - M06/def2-TZVP

# Mechanism Of Ti-Catalyzed Oxidative Nitrene Transfer

Occ. # correlates with ox. state of Ti for all comp. species

Table 1. Occupation Number of the 3d<sub>z</sub><sup>2</sup> Orbital Compared with the Formal Oxidation State of the Ti Atom in the Complex<sup>a</sup>

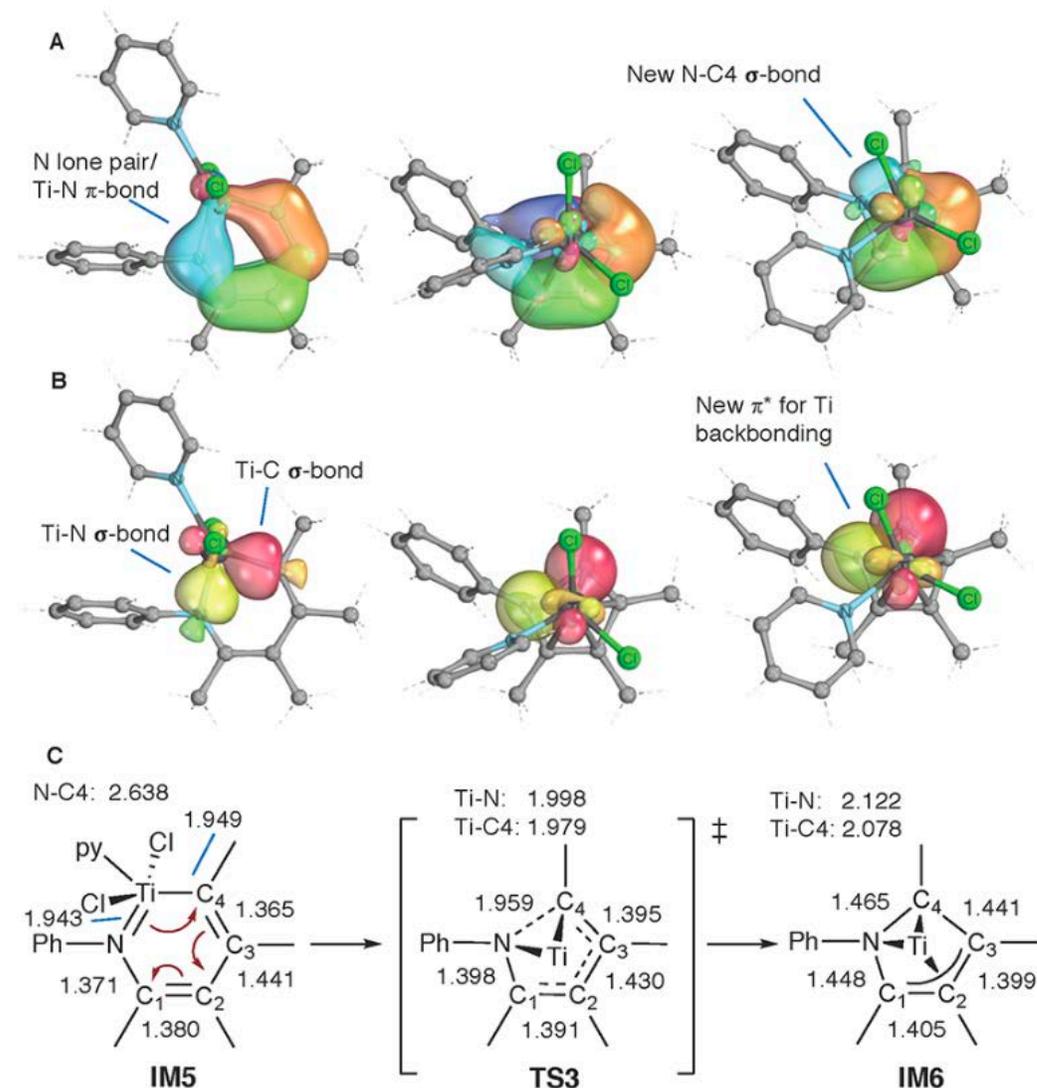
Species	Occupation numbers (3d <sub>z</sub> <sup>2</sup> orbital)	Formal Oxidation State
IM1	0.31	+4
IM2	0.30	+4
TS1	0.35	+4
IM3	0.38	+4
IM4	0.37	+4
TS2	0.40	+4
IM5	0.44	+4
TS3	0.54	+2/+4
IM6	0.61	+2
IM7	0.72	+2
IM8	0.38	+4
TiCl <sub>2</sub>	0.82	+2
[TiCl <sub>4</sub> ] <sup>2-</sup>	0.77	+2
TiCl <sub>2</sub> py <sub>2</sub>	0.68	+2
TiCl <sub>2</sub> py <sub>4</sub>	0.65	+2
TiCl <sub>4</sub>	0.29	+4



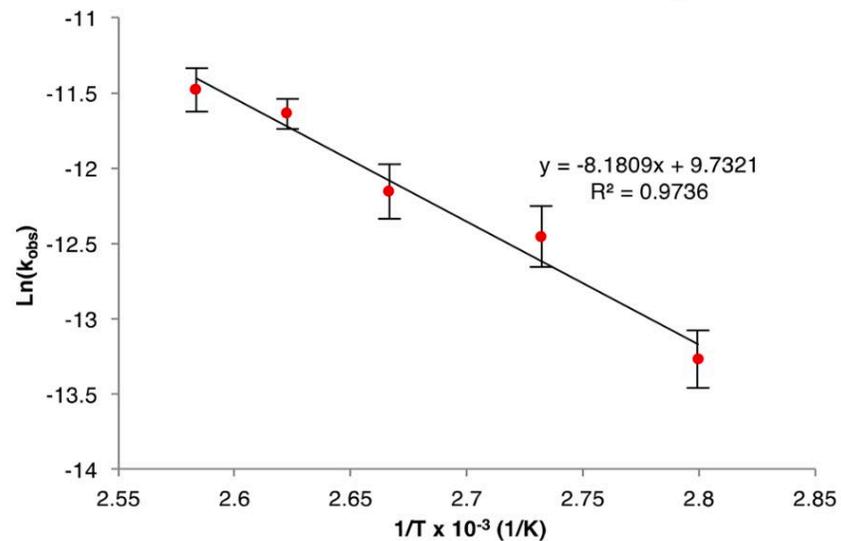
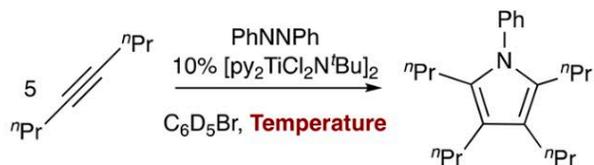
# Mechanism Of Ti-Catalyzed Oxidative Nitrene Transfer

IBO calcs show:

- LPE on N attacks C4 in an electrocyclic fashion
- Orange and magenta  $\pi$ -bonds of C1-C2 and C3-C4 become localized on C1, C2, and C3
- Ti-C and Ti-N  $\sigma$ -bonding orbitals rotate orth. to the pyrrole and become a  $\pi$ -backbonding interaction
- Pyrrole pdt binds to Ti in an  $\eta^3$ -fashion via C1, C2, and C3 and  $\pi$ -backbonding via C4 and N.



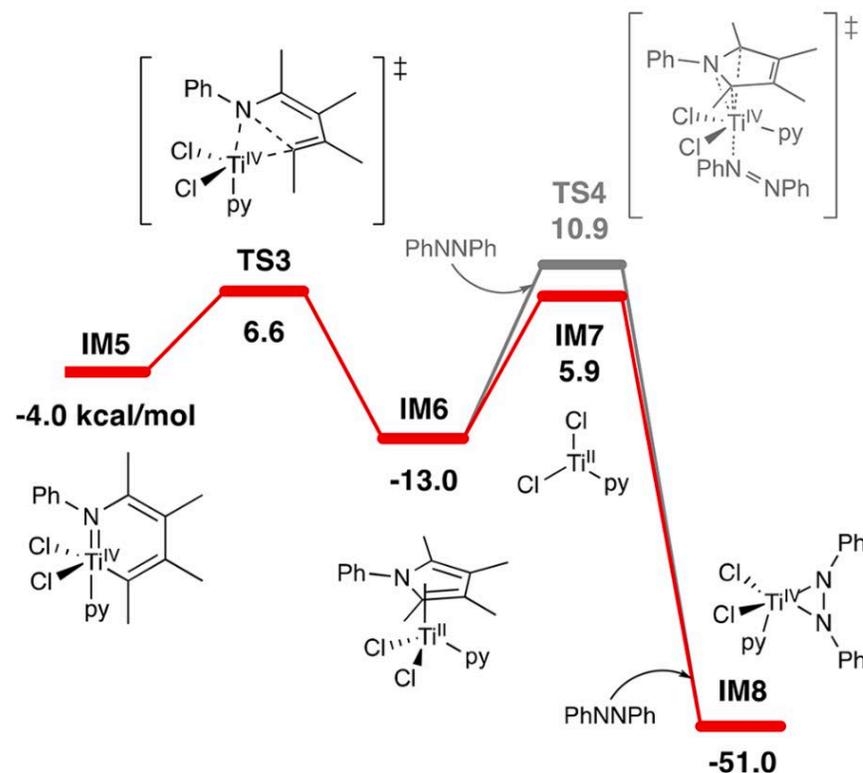
# Mechanism Of Ti-Catalyzed Oxidative Nitrene Transfer



$$\Delta H_{Act,exp} = 16.3 \pm 0.6 \text{ kcal/mol}$$

$$\Delta H_{Act,comp} = 21.1 \text{ for CAT to TS2}$$

(2<sup>nd</sup> insertion)



Barrier to dissociate pyrrole from unbound Ti lower than barrier for Ti with bound PhNNPh => PhNNPh inhibits catalysis. Better nitrene transfer reagent?



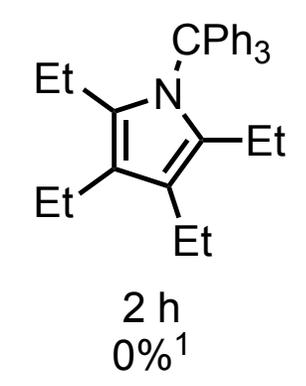
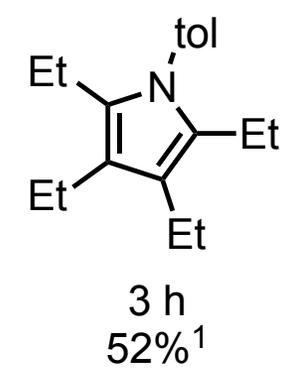
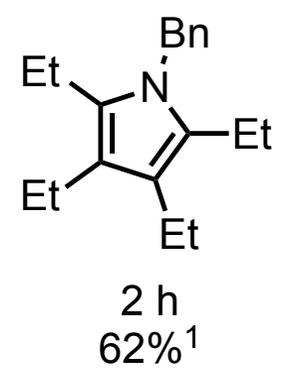
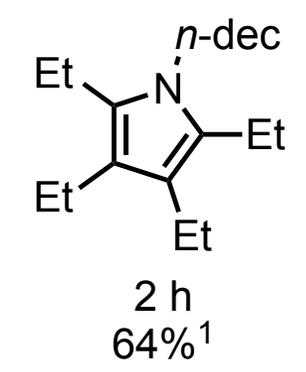
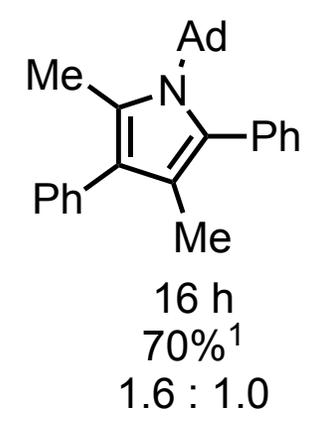
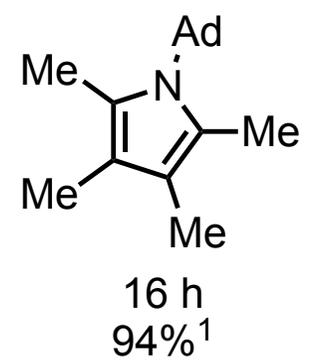
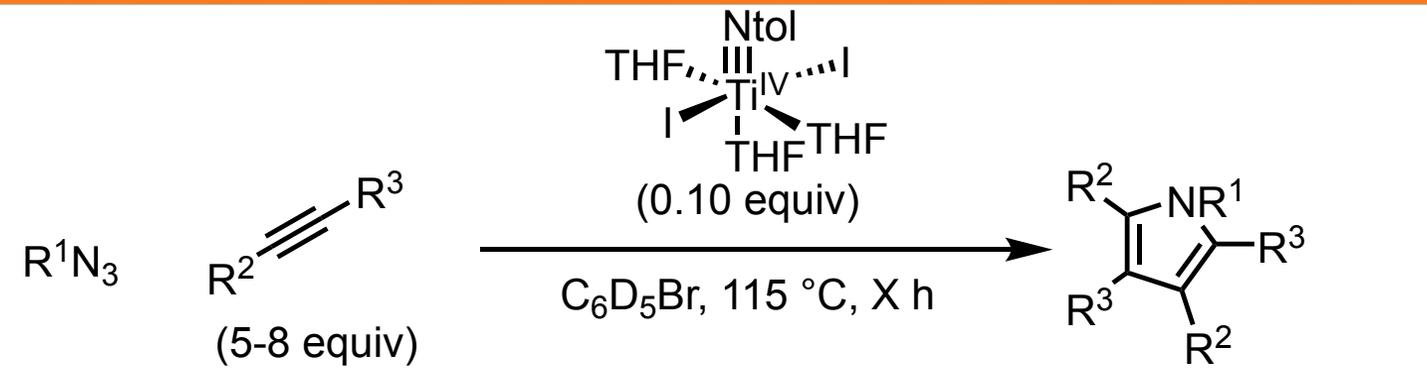
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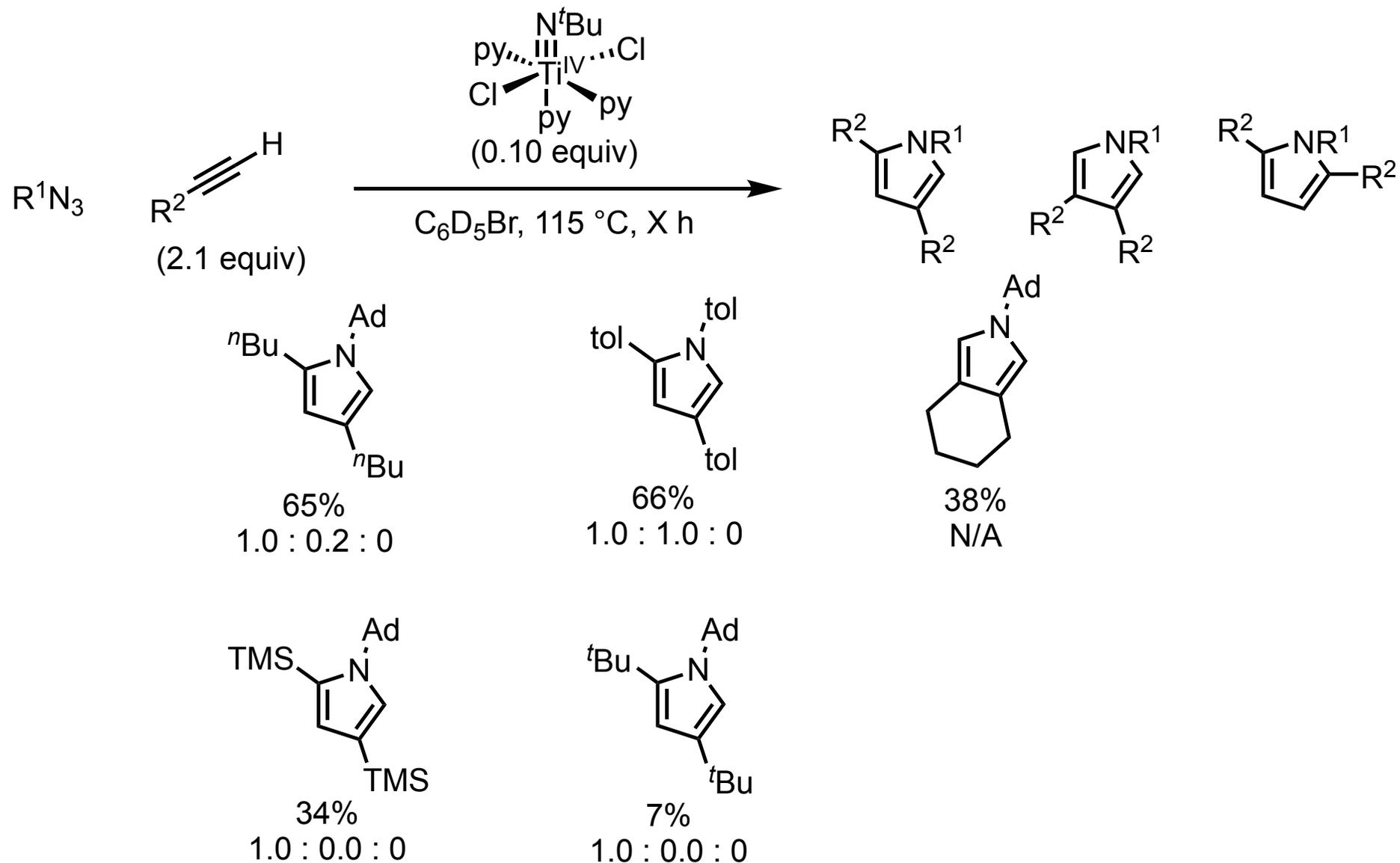


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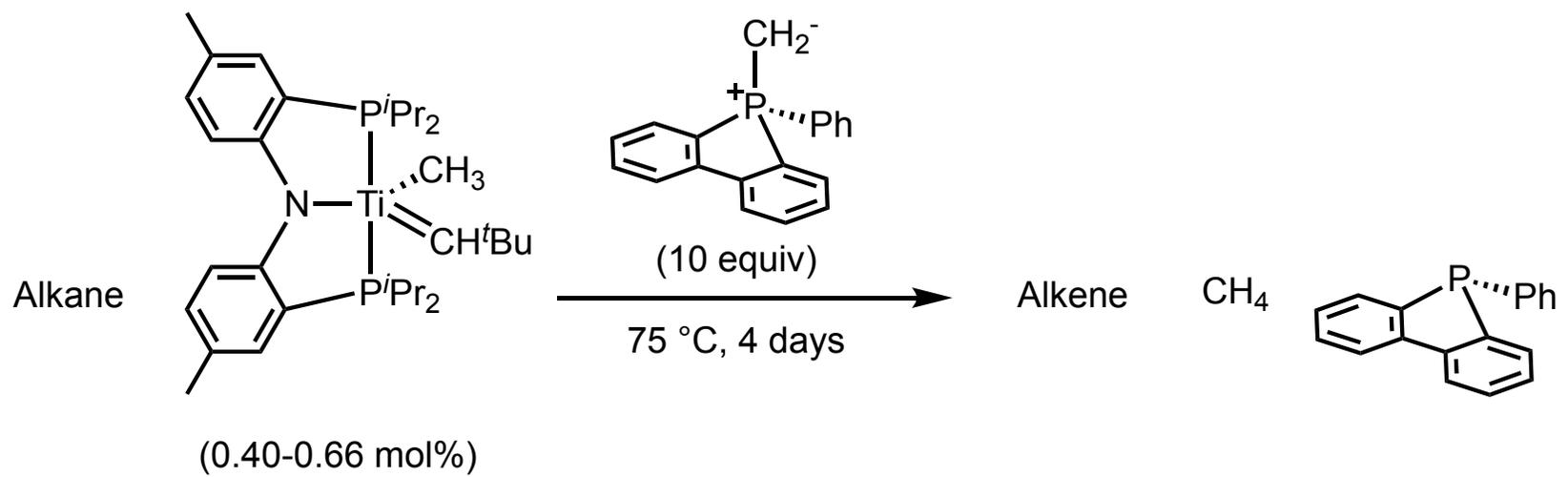
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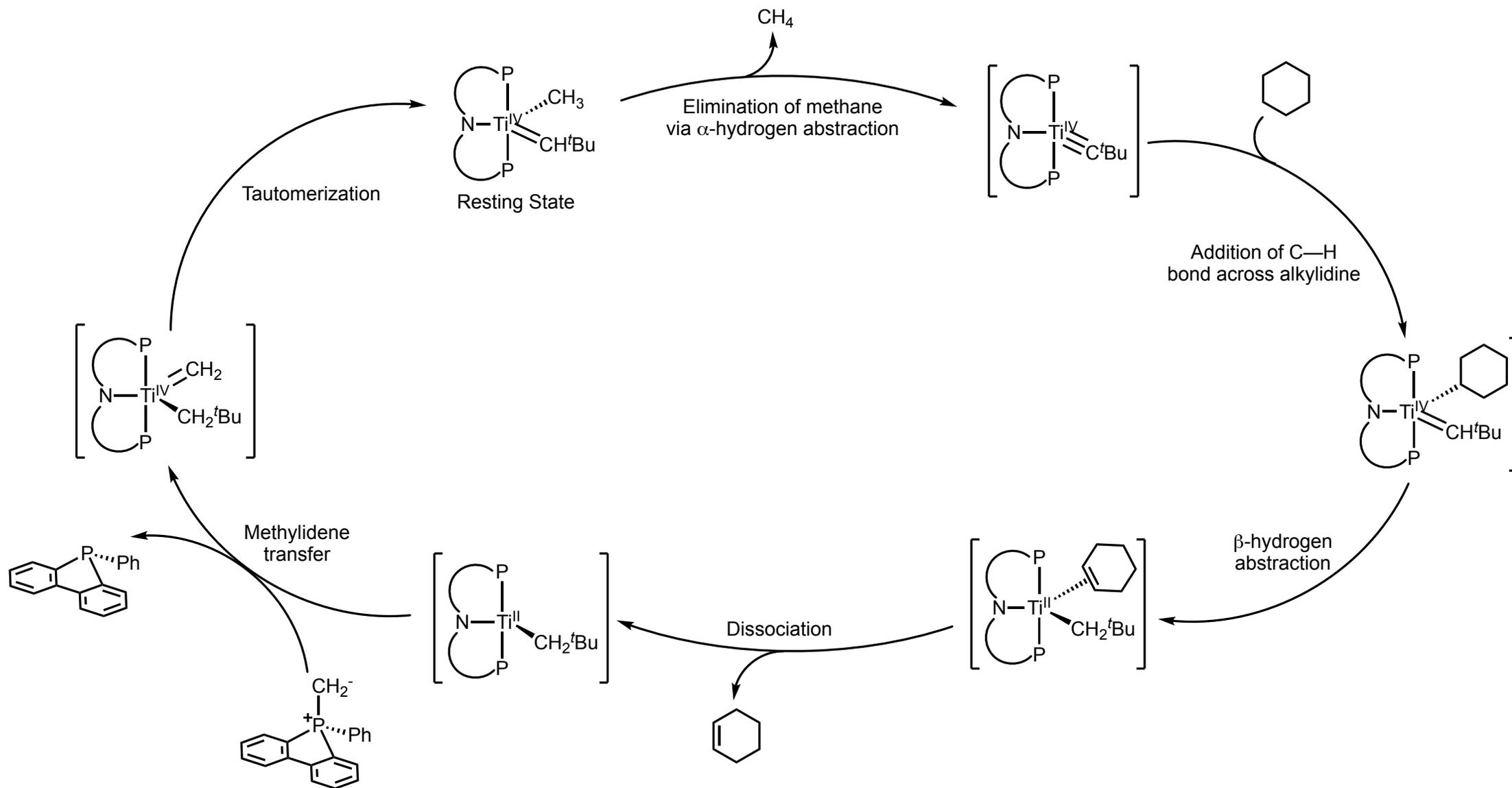
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- **Titanium(II) as a Dehydrogenation Catalyst**
- Applications of Ti(III) in Recent Total Syntheses
- Conclusions

# Titanium As a Dehydrogenation Catalyst



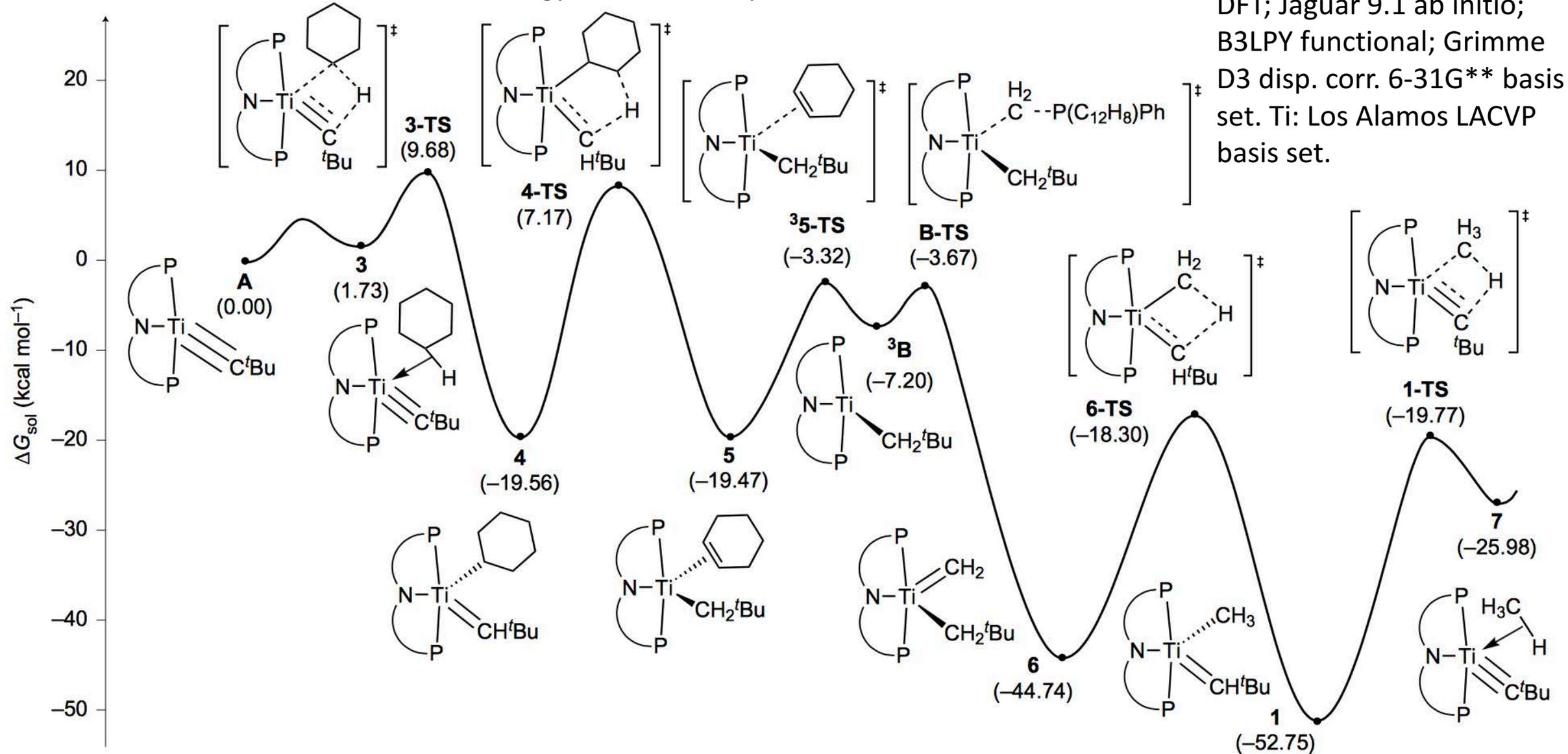
Alkane	Alkene	TON
		2.8
		2.5
		1.5
		3.2
		3.0
		2.7
in C <sub>6</sub> H <sub>12</sub>		0.2

# Titanium As a Dehydrogenation Catalyst



# Titanium As a Dehydrogenation Catalyst

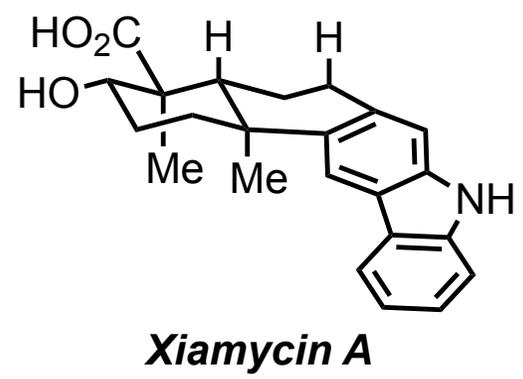
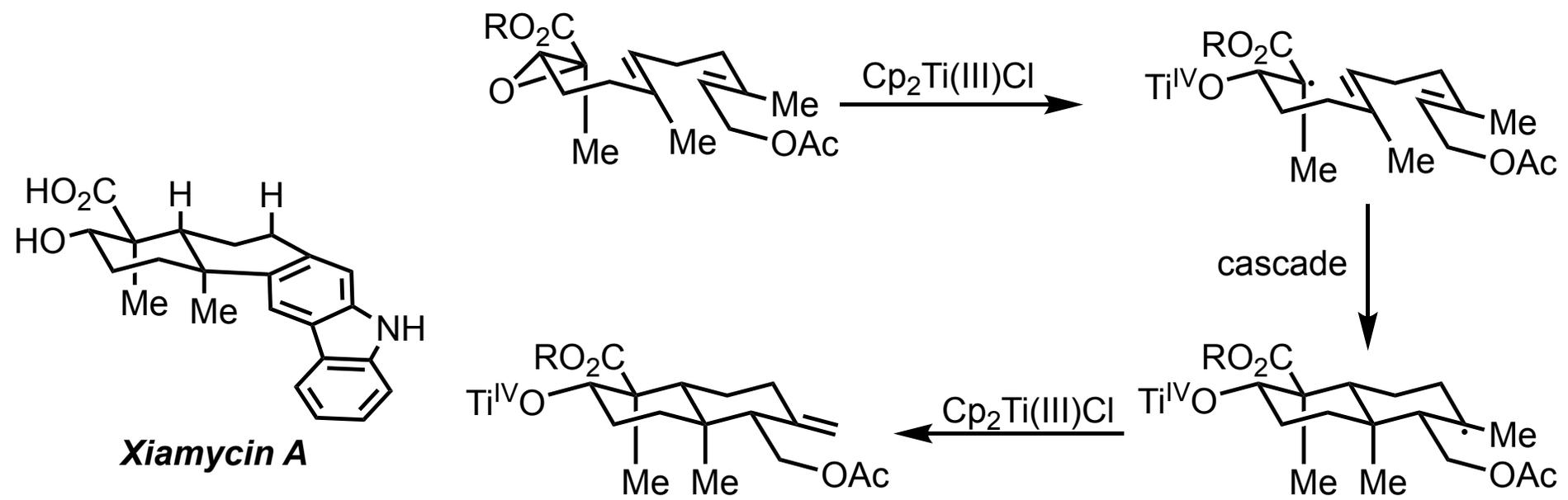
Gibbs Free Energy Profile with Optimized Structures



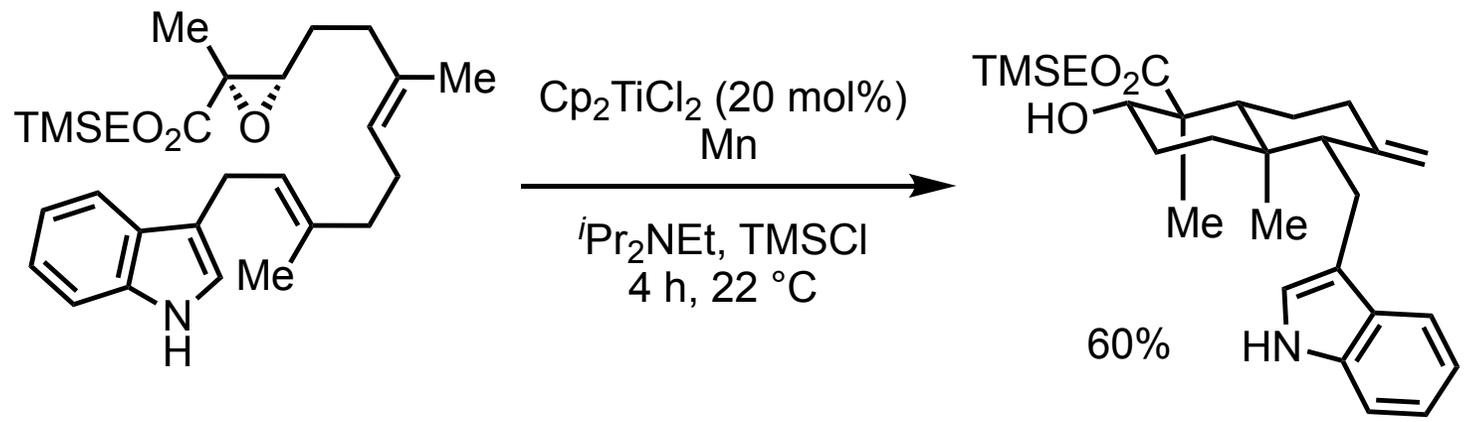


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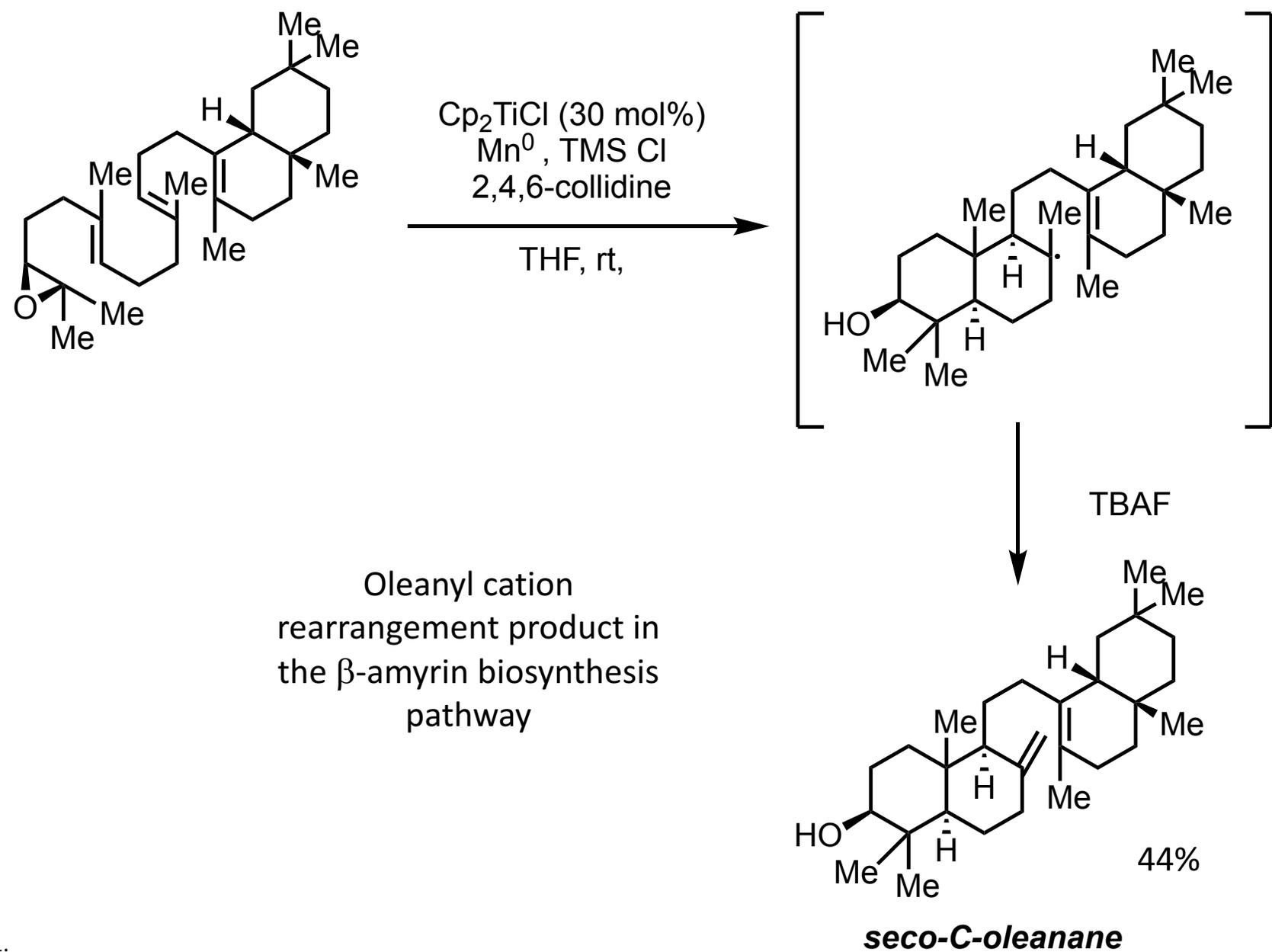
# Applications of Ti(III) in Recent Total Syntheses



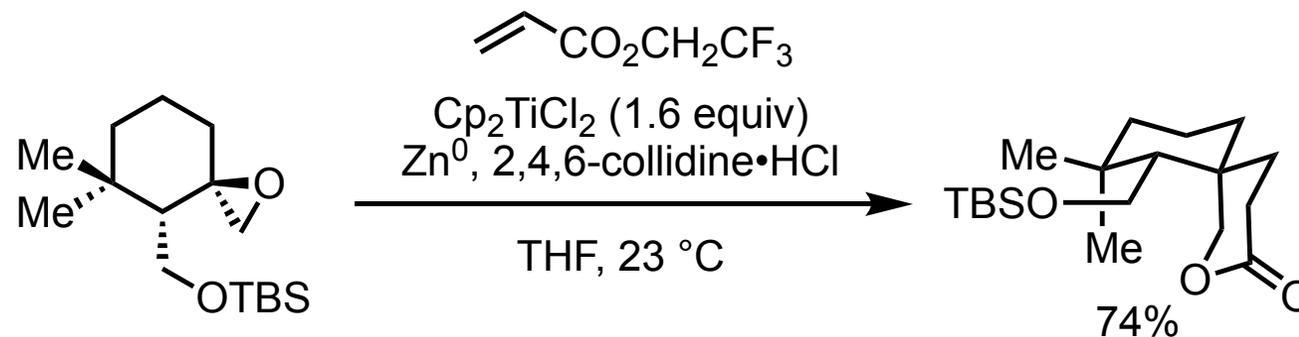
Potent inhibitor  
against herpes  
simplex virus



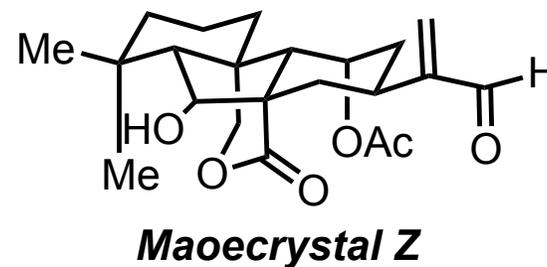
# Applications of Ti(III) in Recent Total Syntheses



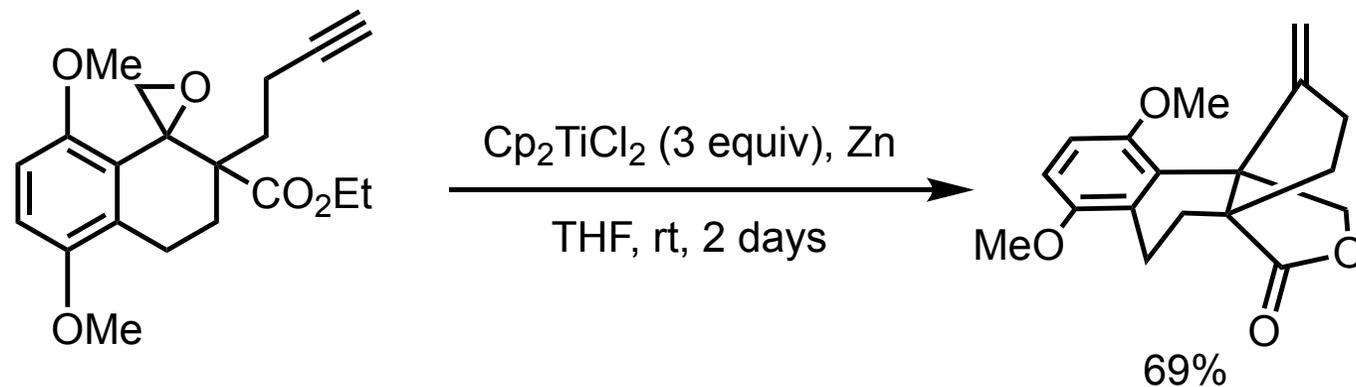
# Applications of Ti(III) in Recent Total Syntheses



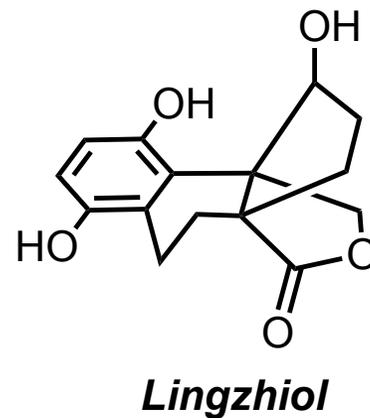
- Diastereoselective reductive coupling was key to synthesis
- Isolated from Chinese medicinal herb *Isodon eriocalyx*
- Potent cytotoxicity toward ovarian cancer cell lines



# Applications of Ti(III) in Recent Total Syntheses



Natural product  
 isolated from medicinal  
 mushrooms of the  
 genus *Ganoderma*





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- Low-valent Ti has found wide use in organic chemistry and has a bright future
- Energetic drive of  $Ti^{II}/Ti^{III}$  to be  $Ti^{IV}$  is useful
- Future directions of the field should include more catalytic transformations using Ti
- Other applications: hydrogenation, hydrodefluorination, other C—C bond forming reactions
- Other metals are also worth mentioning: Zr, Hf, V, Nb, Ta
- For more information, please see *Nat. Rev. Chem.* **2019**, 3, 15. written by Prof. Ian Tonks