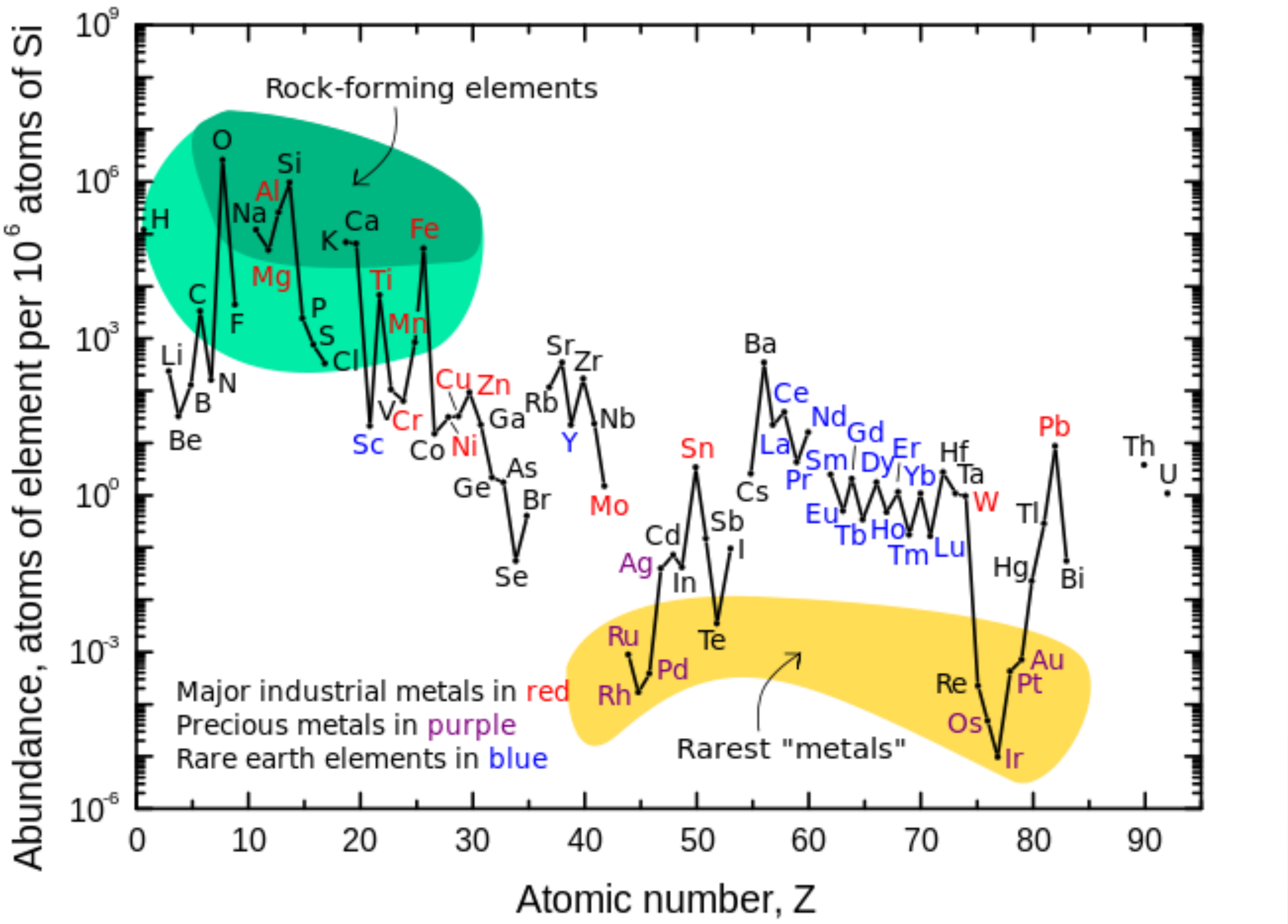
Catalytic [2+2+1] synthesis of pyrroles from alkynes and diazines via Ti^{II}/Ti^{IV} redox catalysis

Gilbert, Z. W.; Hue, R. J.; Tonks, I. A.
Nat. Chem. **2015**, DOI: 10.1038/NCHEM.2386

John Milligan
Current Literature
Wipf Group Meeting- December 19, 2015

Earth abundant transition metals in catalysis: a hot topic



Earth abundant transition metals in catalysis: a hot topic

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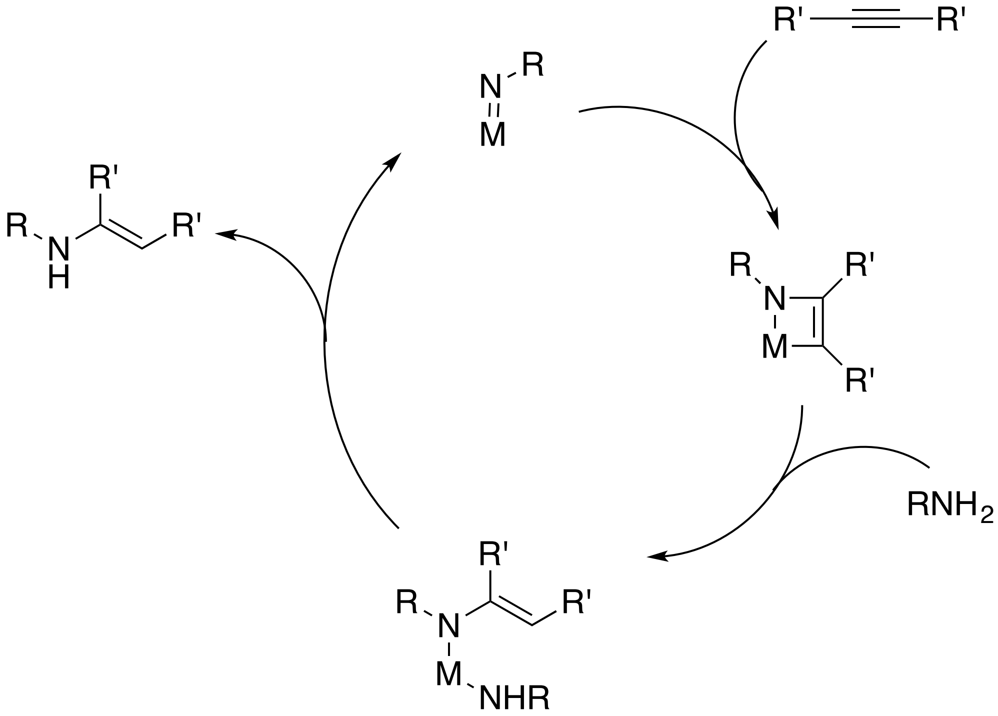
Special Issue, 2015
Earth Abundant Metals
in Homogeneous Catalysis

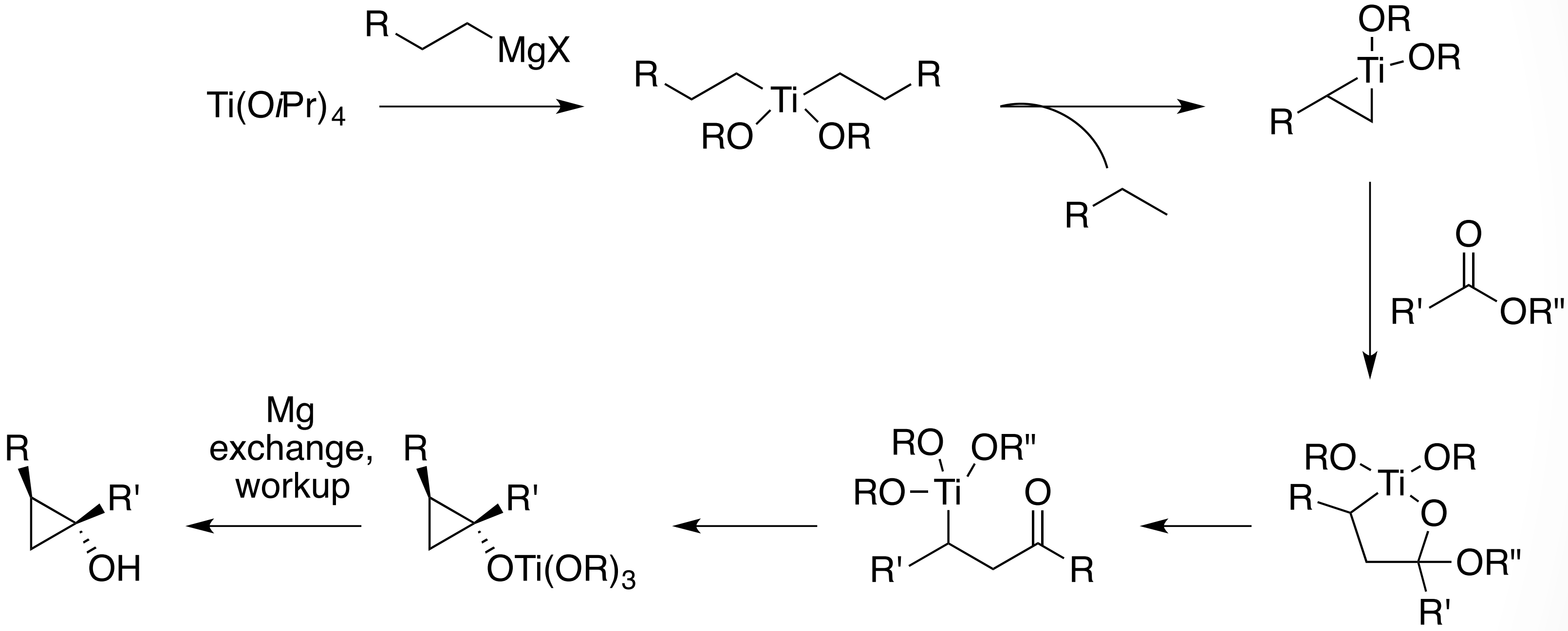
Ti: Redox neutral catalysis

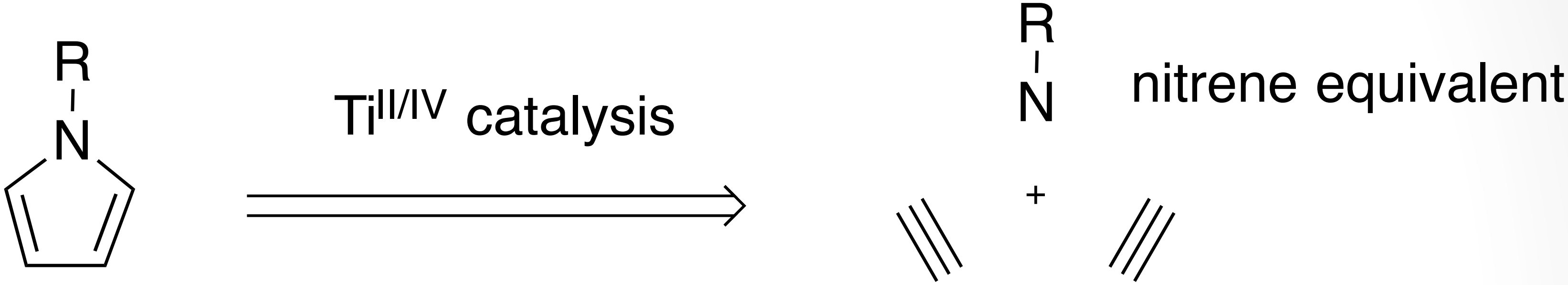
- Ti is oxophilic; the majority of Ti-mediated transformations are redox-neutral
- Example: the Bergman hydroamination mechanism



Odom, A. L. *Dalton Trans.* **2005**, 225-233.
Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708

The Kulinkovich reaction: a Ti redox active process



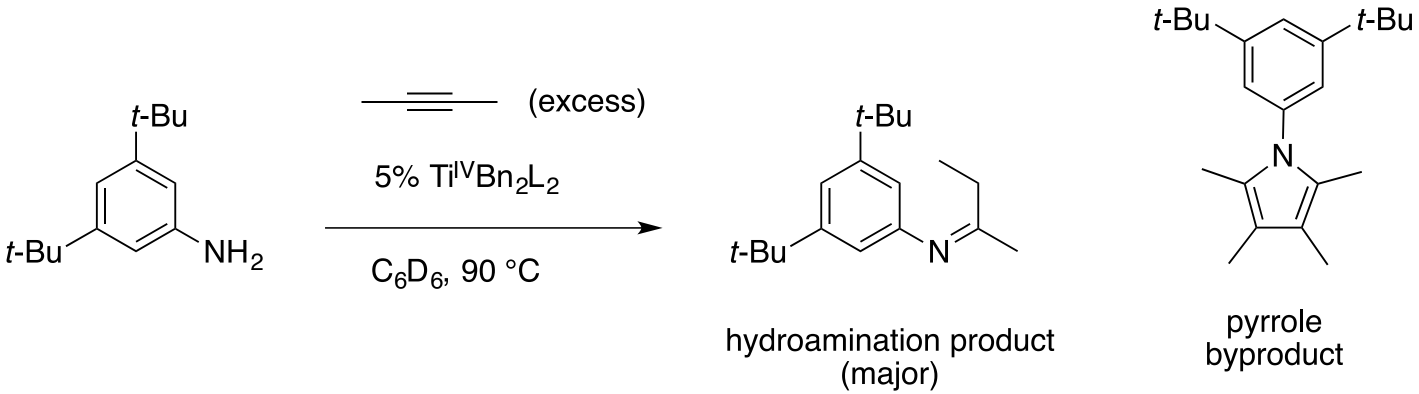


Ti$^{III/IV}$ catalysis

nitrene equivalent

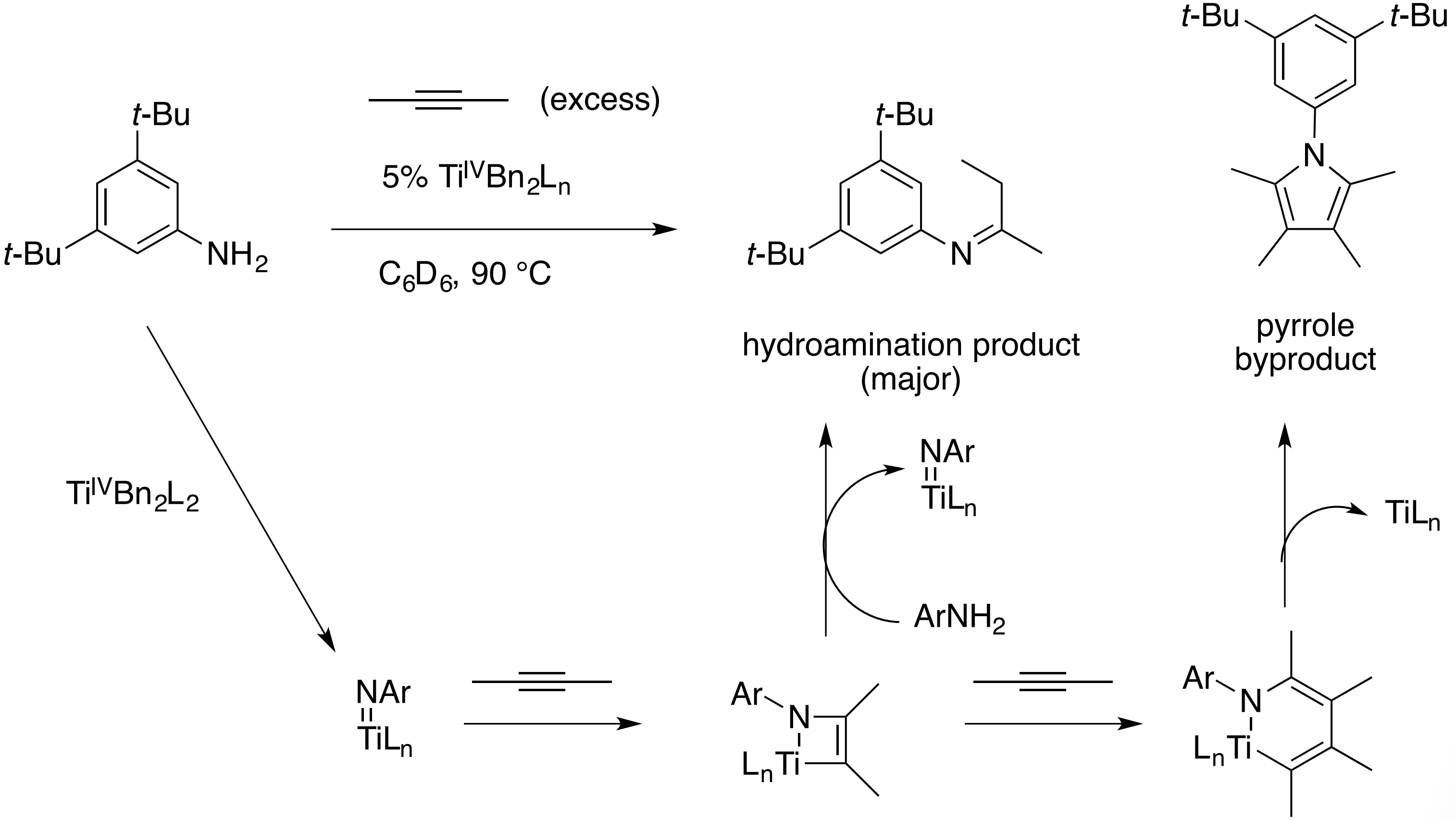
Can oxidative C-N bond formation be mediated by Ti to make pyrroles?

Previous work: Stoichiometric oxidative pyrrole formation with Ti



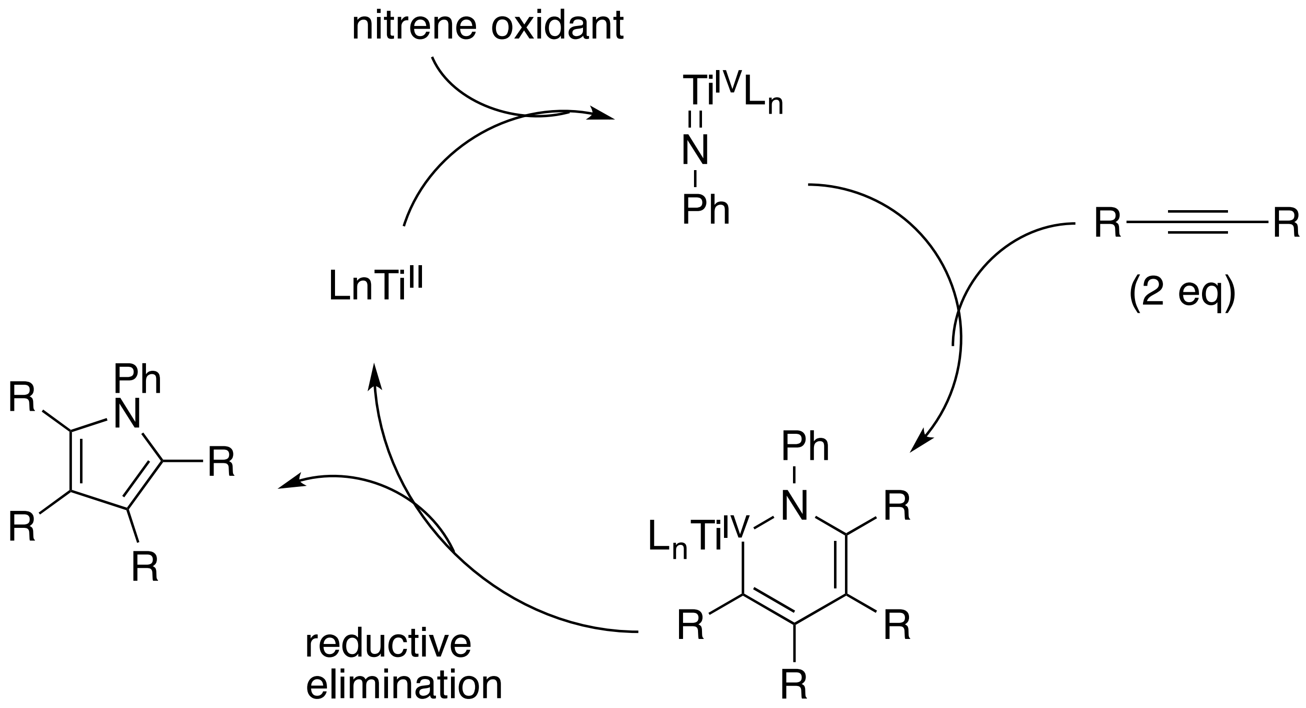
Tonks, I. A.; Meier, J. C.; Bercaw, J. E. *Organometallics* **2013**, *32*, 3451-3457

Previous work: Stoichiometric oxidative pyrrole formation with Ti

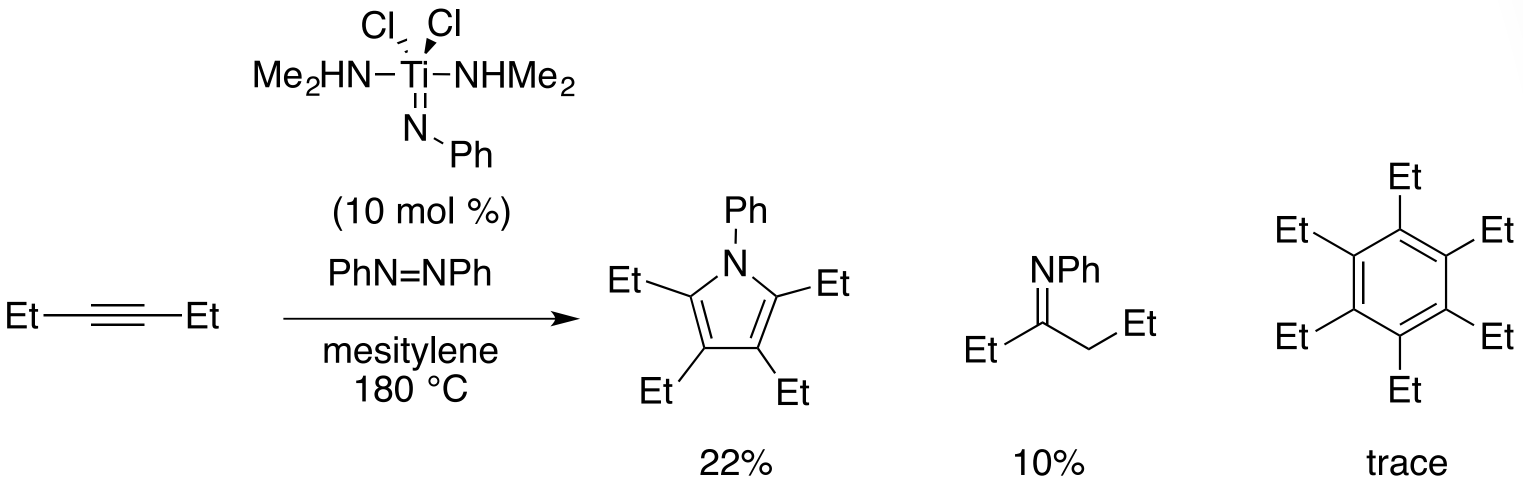


Tonks, I. A.; Meier, J. C.; Bercaw, J. E. *Organometallics* **2013**, *32*, 3451-3457

This work: Creating a Ti catalytic cycle



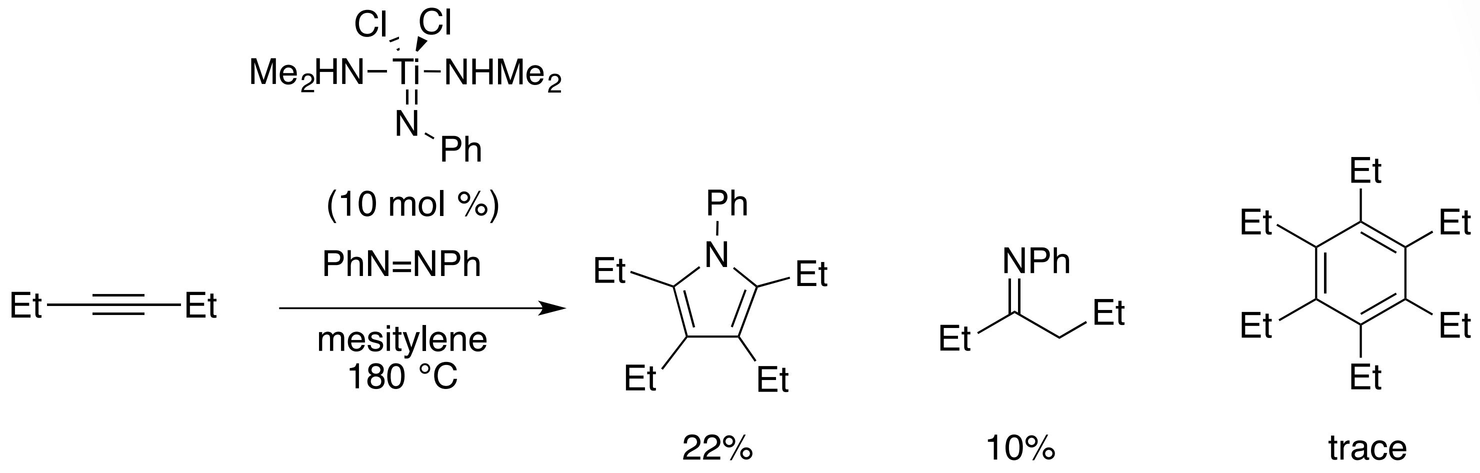
Initial result

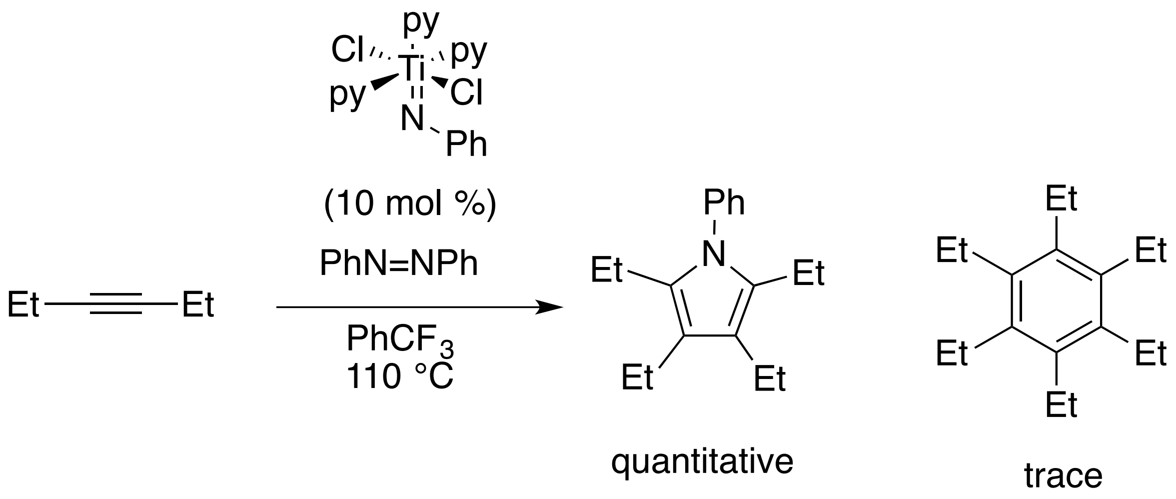


Conclusions:

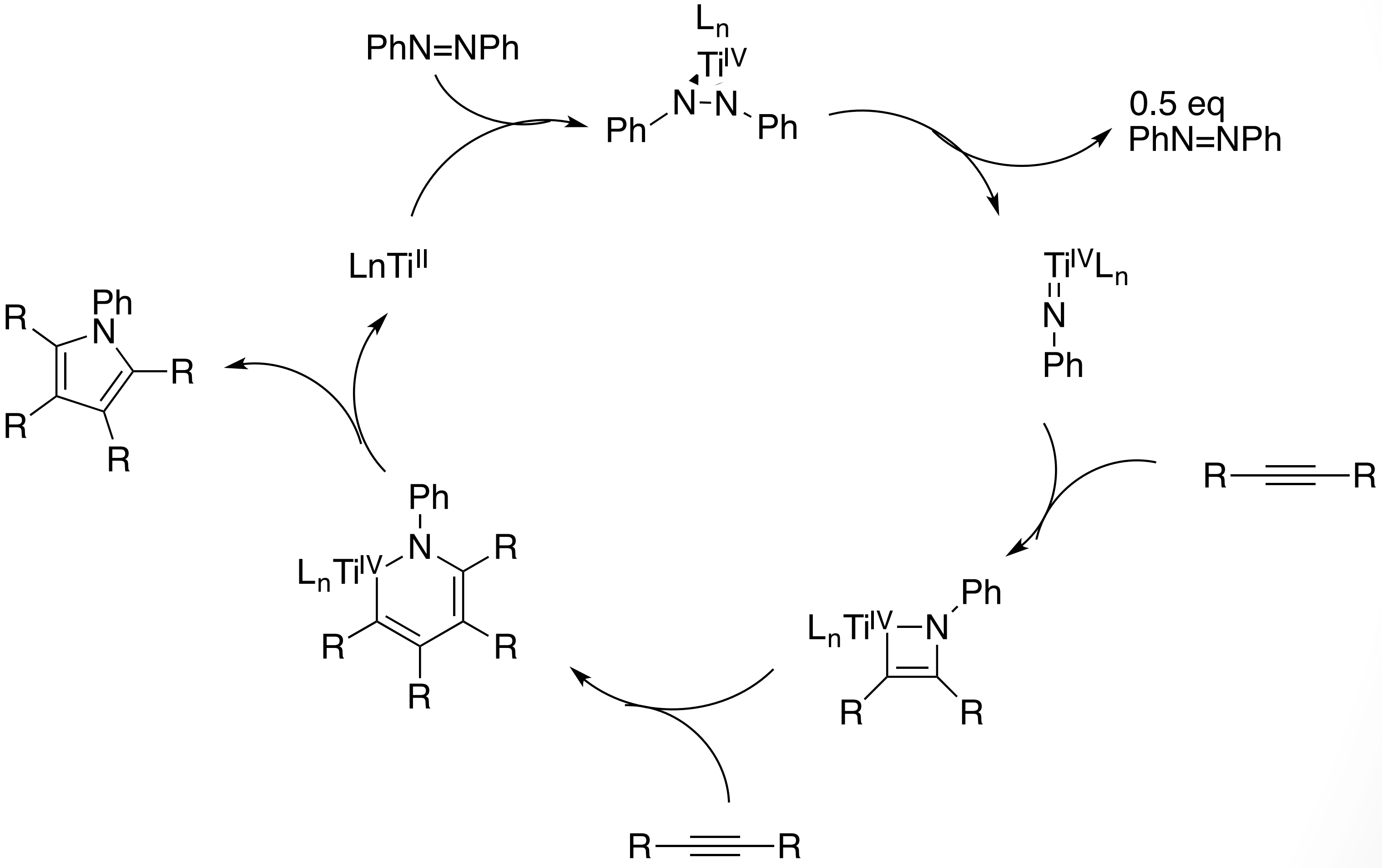
- Azobenzene can turn over the cycle to oxidize Ti
- The [2+2+1] and hydroamination are competing and may share a common intermediate
- The trimerization product (arene) sugguests Ti^{II} is involved

Catalyst effect

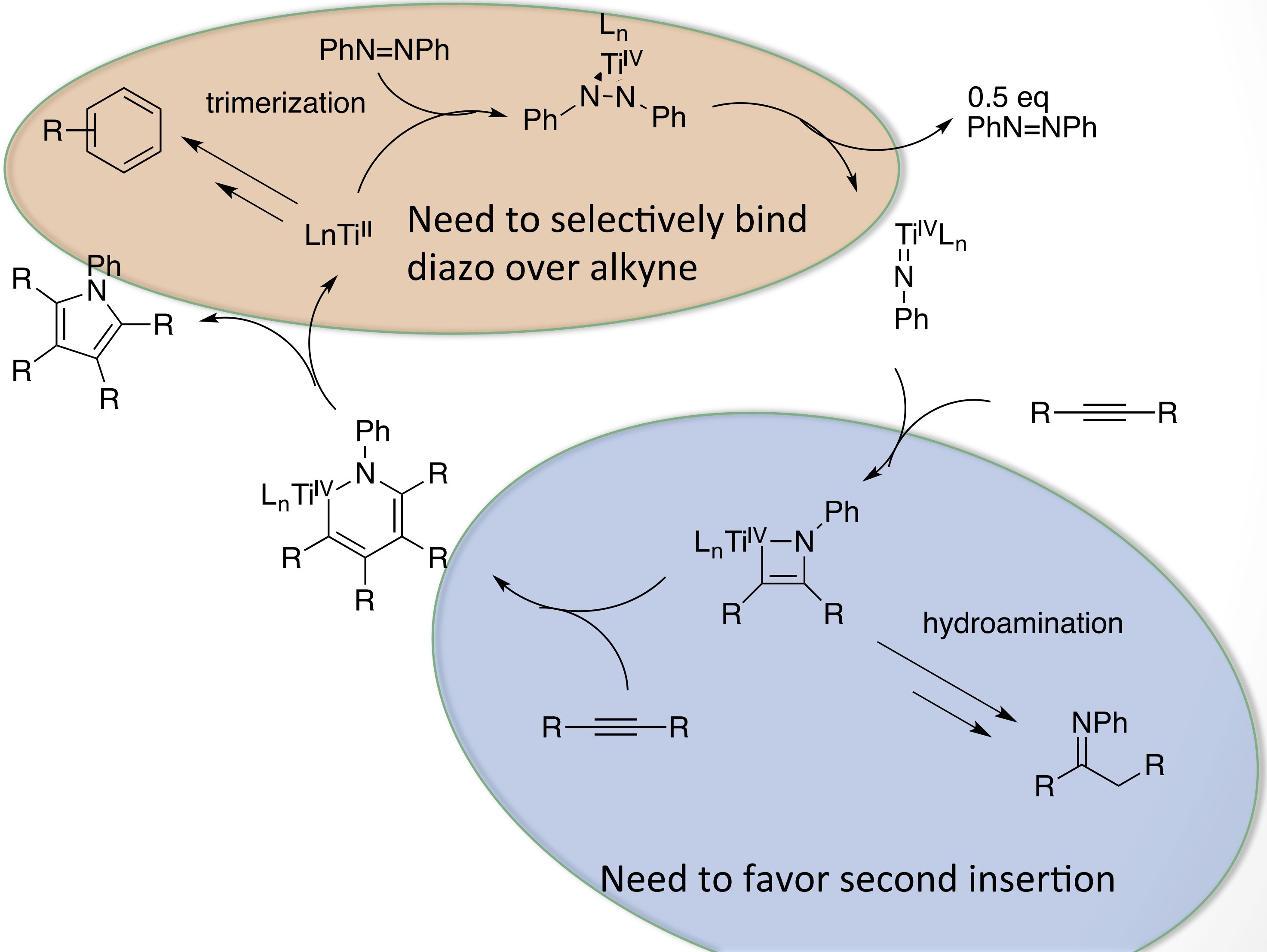




Mechanism


PhN=NPh
L$_n$
Ti^{IV}
Ph N–N Ph
0.5 eq
PhN=NPh
Ti^{IV}L$_n$
N
Ph
R–≡–R
L$_n$Ti^{IV}–N Ph
R R
R–≡–R
Ph
L$_n$Ti^{IV} N R
R R
R
LnTi^{II}
R Ph N R
R R

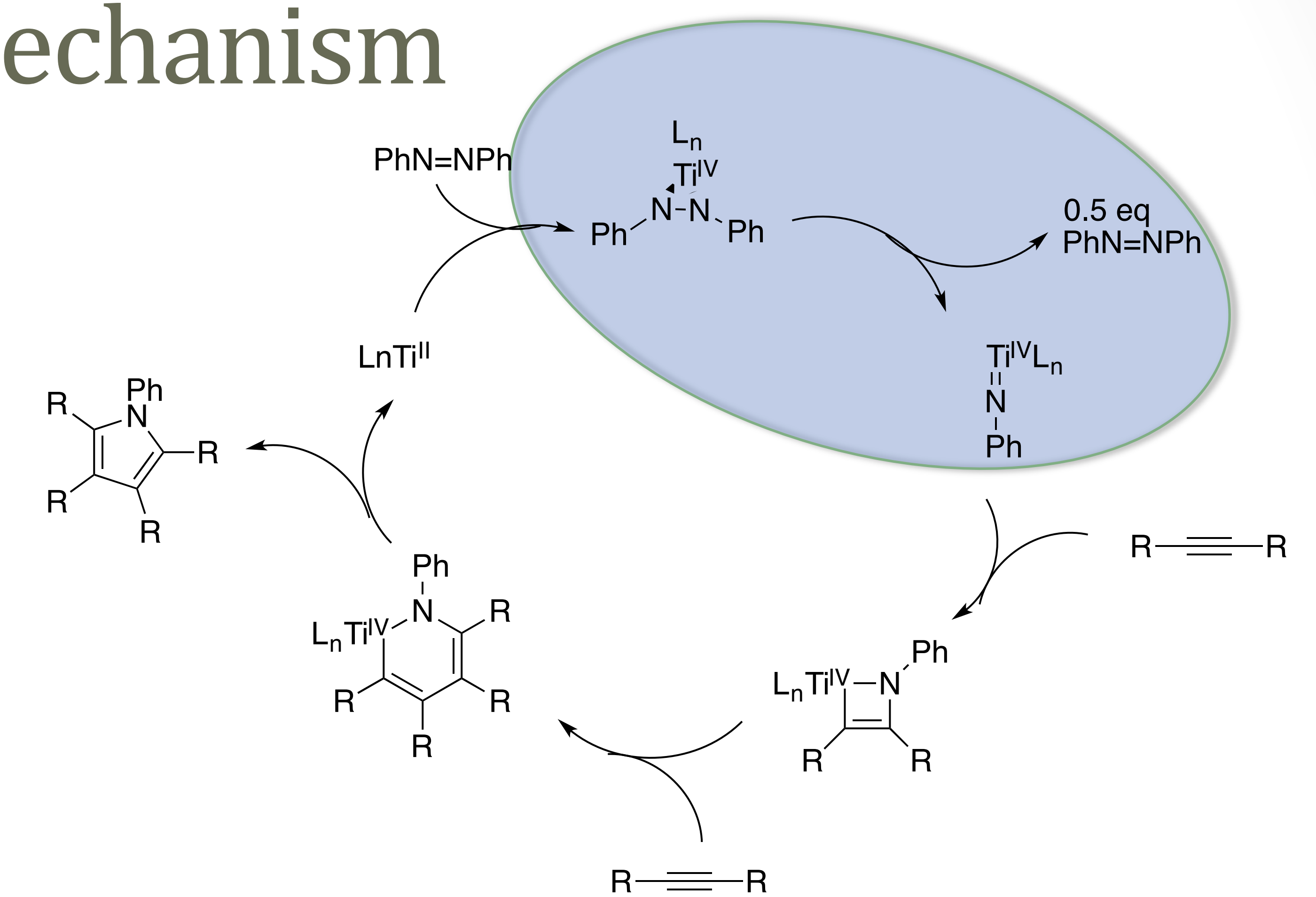
Mechanism: selectivity



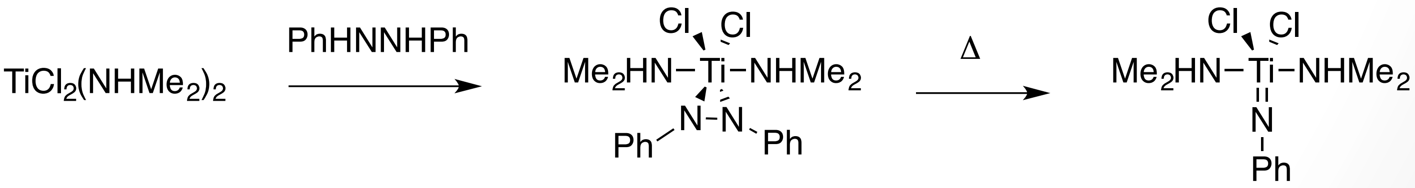
Need to selectively bind diazo over alkyne

Need to favor second insertion

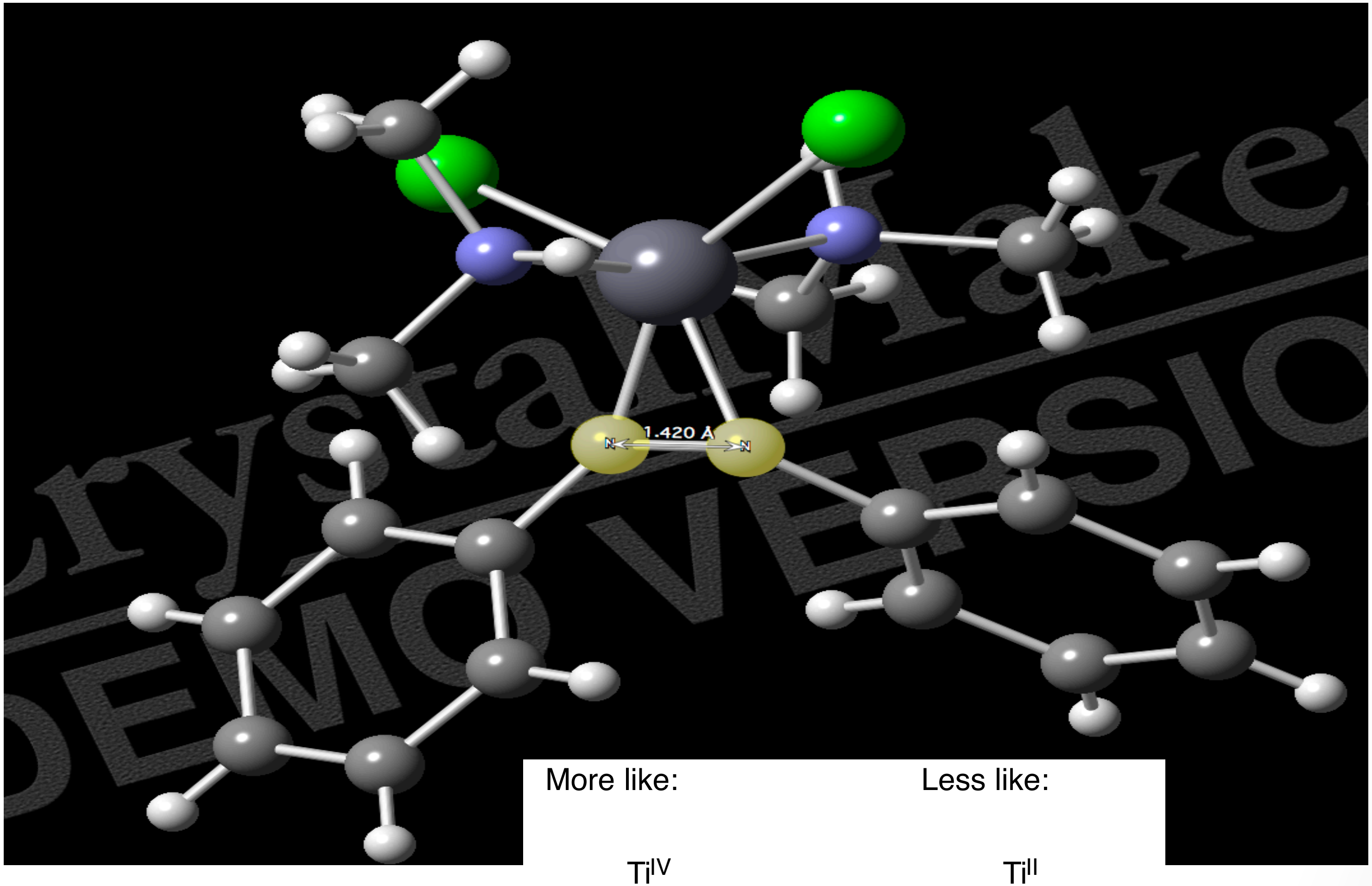
Mechanism



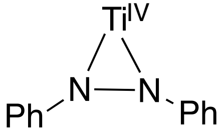
Mechanistic verification:



Crystal structure: evidence for Ti^{IV}

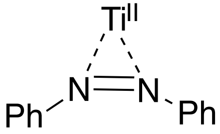


More like:



w/ N-N @ ~1.42 A

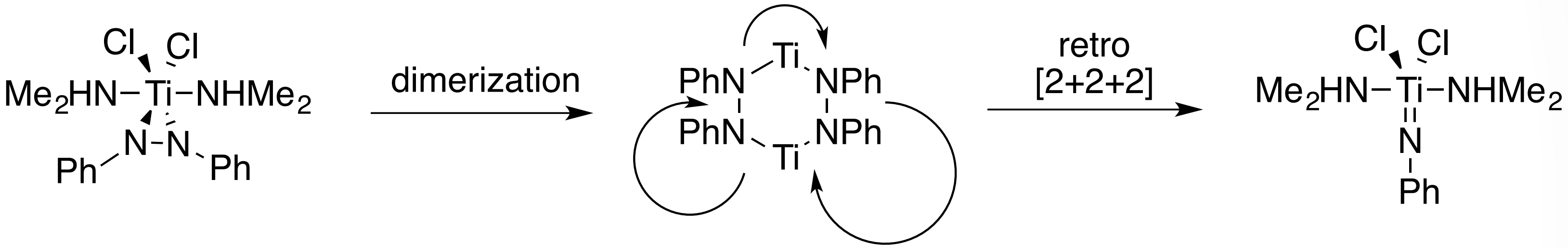
Less like:

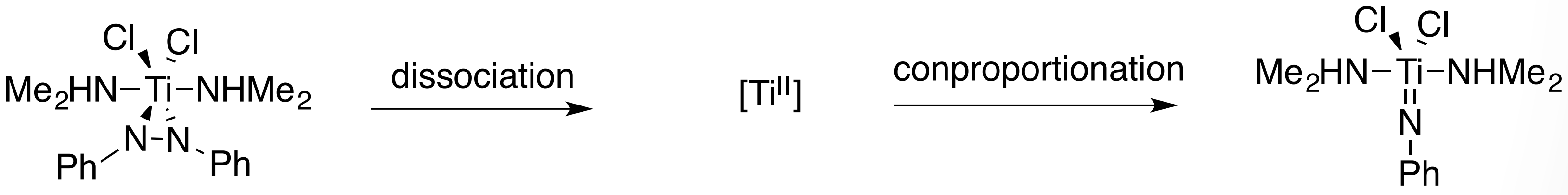


w/ N=N @~ 1.25 A

Disporportionation

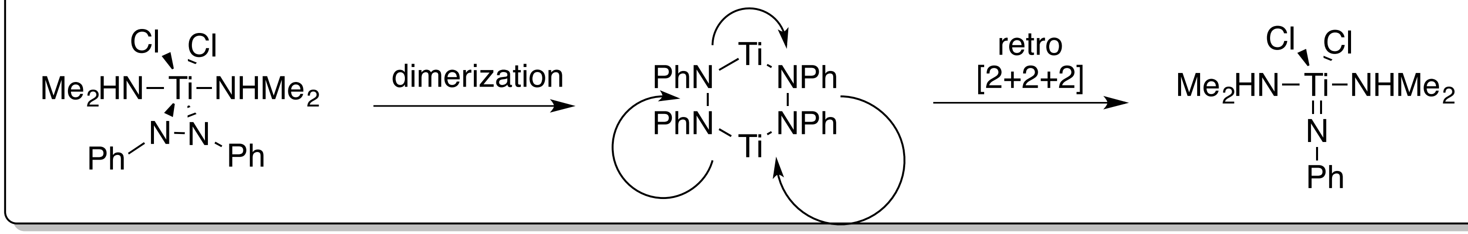
- Possible mechanisms:

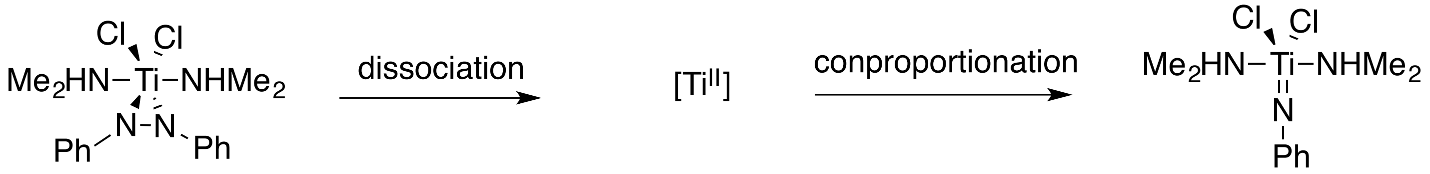




Disproportionation mechanism

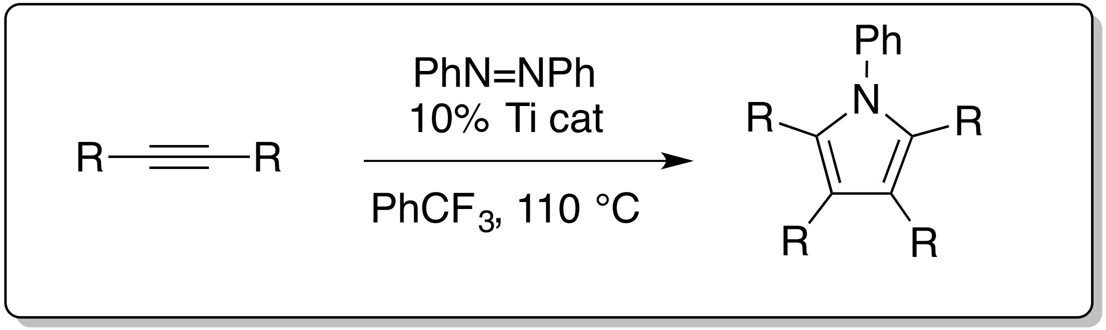
More likely:





- No crossover product when TolN=NTol is added, thus no dissociation

Substrate scope



$\mathrm{Et}-\equiv-\mathrm{Et}$

85%

$\mathrm{Me}-\equiv-\mathrm{Me}$

76%

$\mathrm{Ph}-\equiv-\mathrm{Ph}$

26%

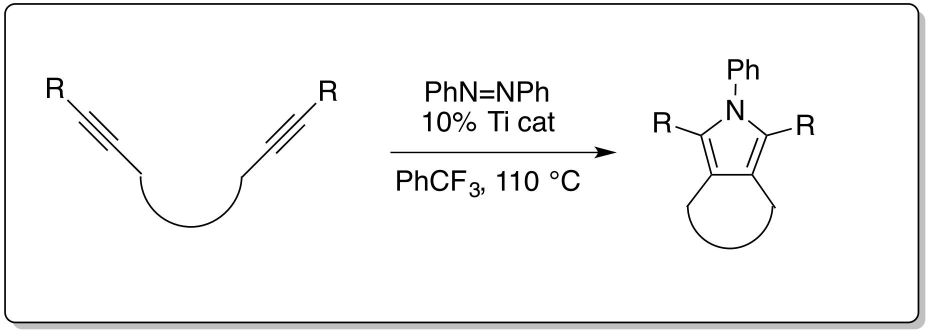
$\mathrm{TMS}-\equiv-\mathrm{TMS}$

NR

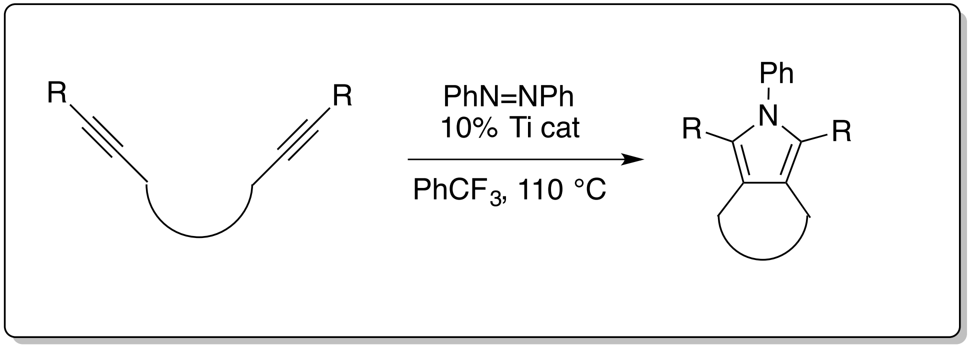
$\mathrm{MeO_2C}-\equiv-\mathrm{CO_2Me}$

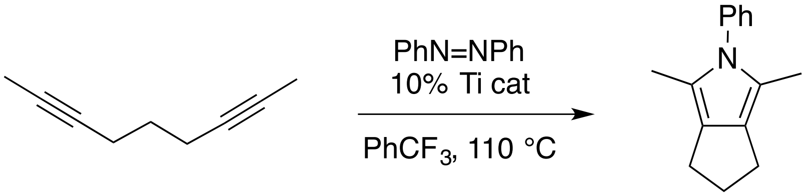
NR

Tethered alkynes

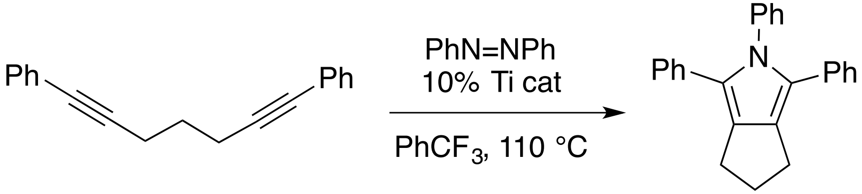


Tethered alkynes

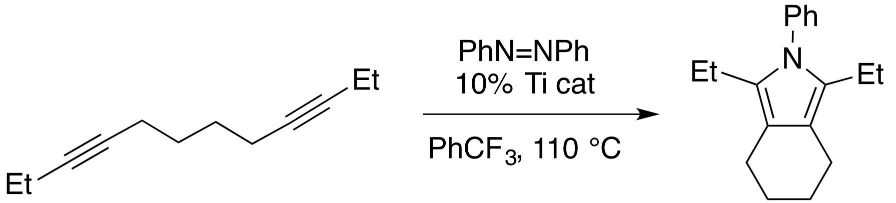




76%

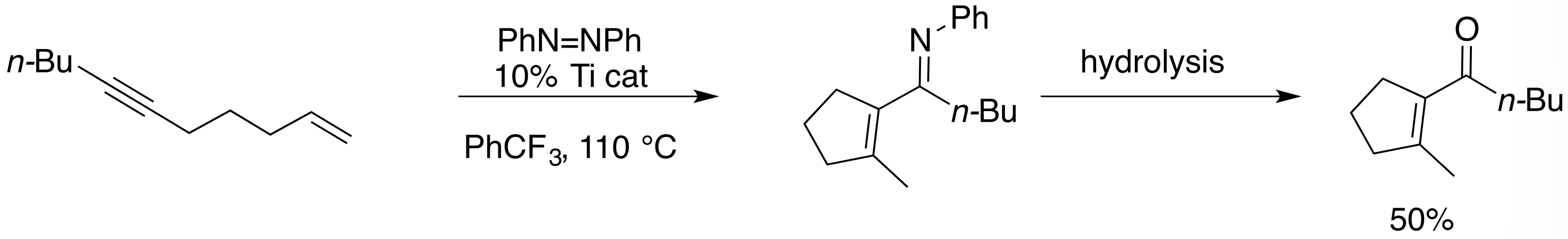


46%

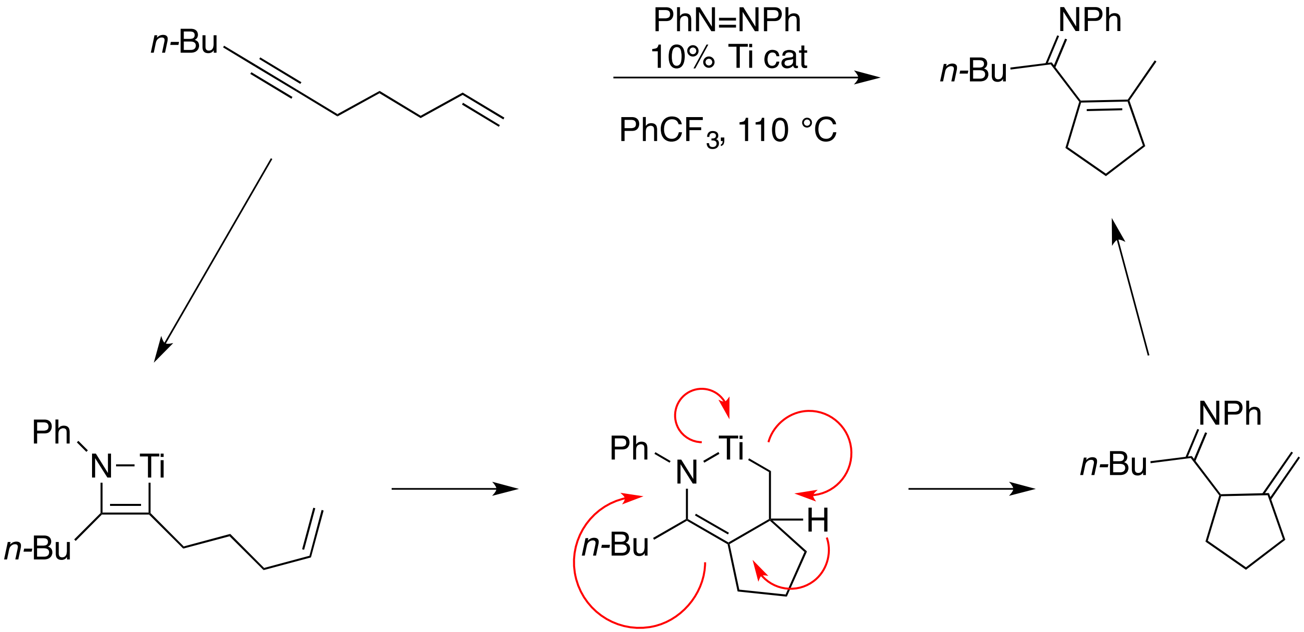


65%

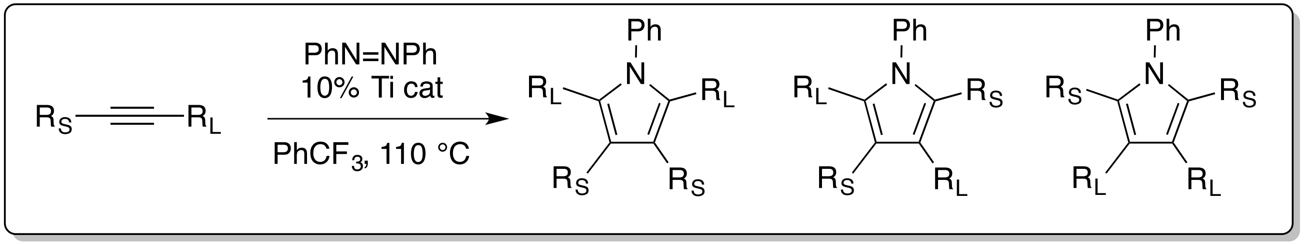
Enyne substrate



Enyne substrate

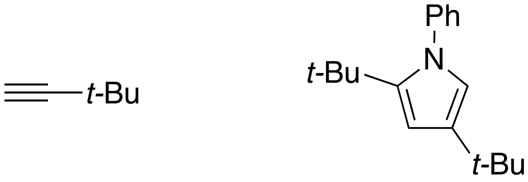


Asymmetric alkynes: Regioselectivity

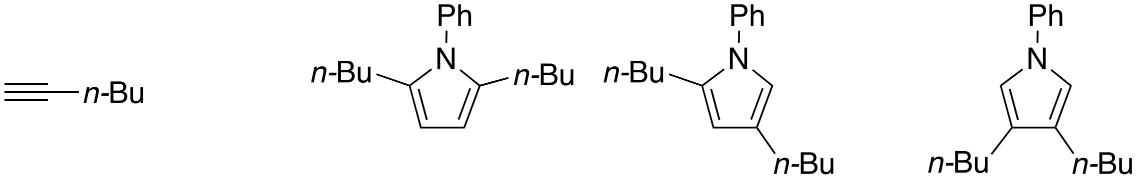


Alkyne Product(s)

32%

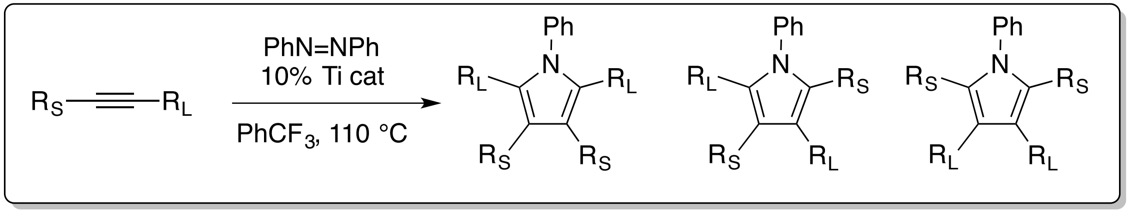


55%



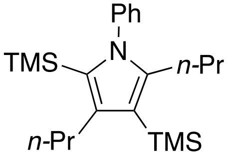
13:100:13 (36% combined)

Asymmetric alkynes: Regioselectivity



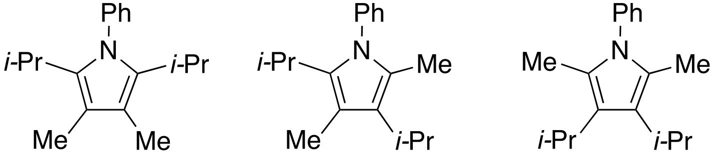
Alkyne | Product(s)

n-Pr—≡—TMS



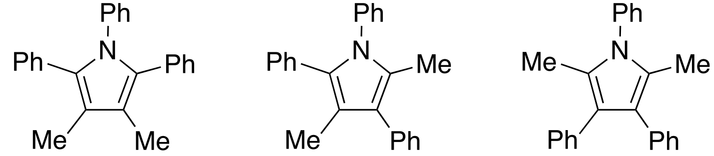
78% (NMR yield)

Me—≡—i-Pr



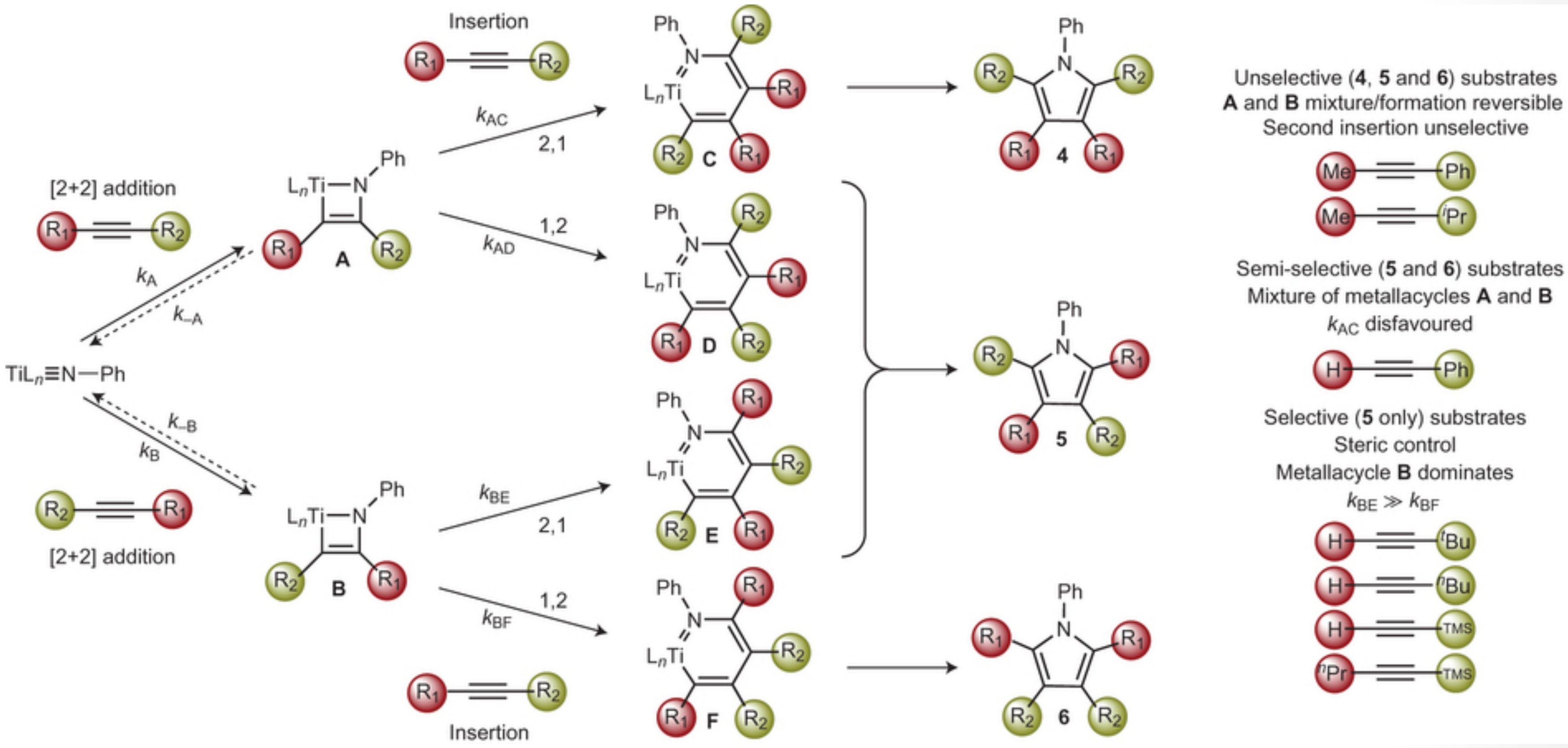
13:100:13 (36% combined)

Me—≡—Ph



45:100:77 (60% combined)

Regioselectivity rationale

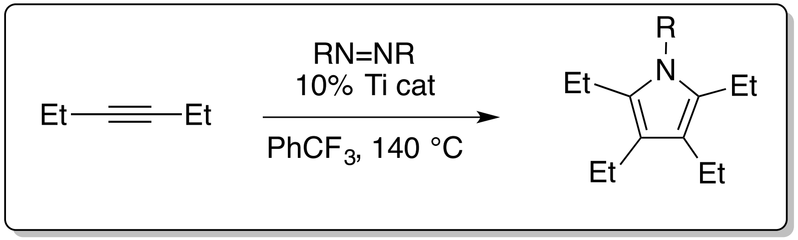


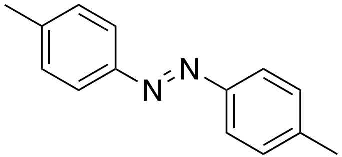
Unselective (**4**, **5** and **6**) substrates
A and **B** mixture/formation reversible
Second insertion unselective

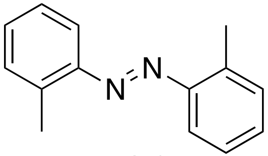
Semi-selective (**5** and **6**) substrates
Mixture of metallacycles **A** and **B**
k_{AC} disfavoured

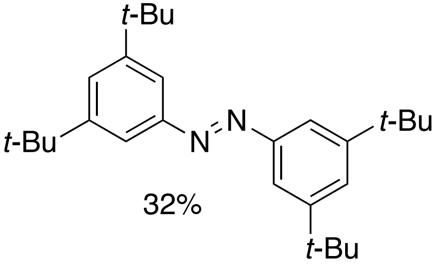
Selective (**5** only) substrates
Steric control
Metallacycle **B** dominates
$k_{BE} \gg k_{BF}$

Diazo scope

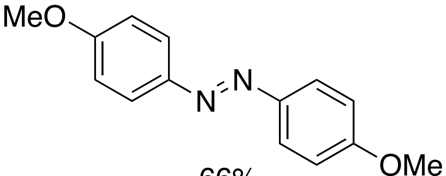



85%

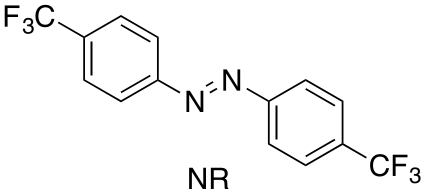

71%



32%

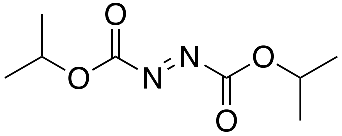


66%



NR

NR



NR

Conclusion

- A unique [2+2+1] Ti-mediated pyrrole synthesis was developed
- Mechanistic experiments prove a Ti(II)/Ti(IV) cycle involving diazo activation
- Future directions include exploring ligands on Ti to enable catalyst controlled regioselectivity