UNIVERSITÄT BERN

Radical Redox-Relay Catalysis: Formal [3+2] Cycloaddition of N-Acylaziridines and Alkenes

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J. Am. Chem. Soc. **2017**, *139*, 12141−12144

Journal Club, Renaud Group_Eloïse_30.04.2020

The Song Lin group – Research focus

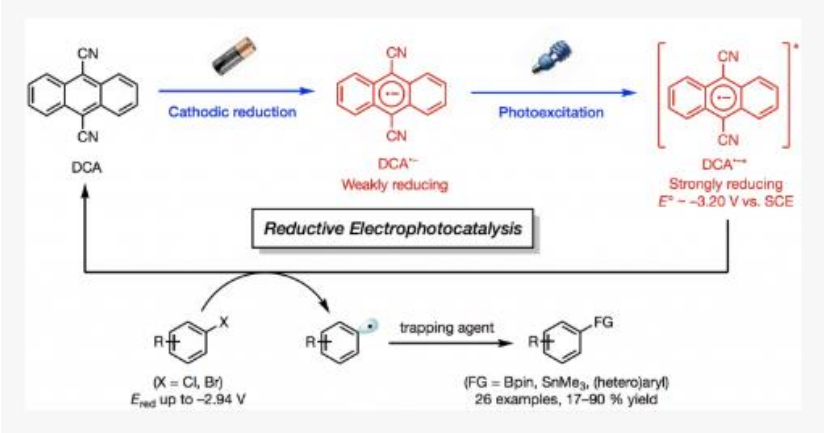
Song Lin

- Since 2016, independent career at Cornwell University
- 2013 – 2016: Postdoctoral fellow, University of California, Berkeley (Advisor: Christopher J. Chang)
- 2008 – 2013: M.A. & Ph.D., Harvard University (Advisor: Eric N. Jacobsen)

« photoelectrocatalysis »

Angew. Chem., Int. Ed. **2020**, *59*, 409-417 - "Electrochemistry Broadens the Scope of Flavin Photocatalysis: Photoelectrocatalytic Oxidation of Unactivated Alcohols"

Acc. Chem. Res. **2020**, *53*, 547-560 - "Catalyzing Electrosynthesis: A Homogeneous Electrocatalytic Approach to Reaction Discovery"

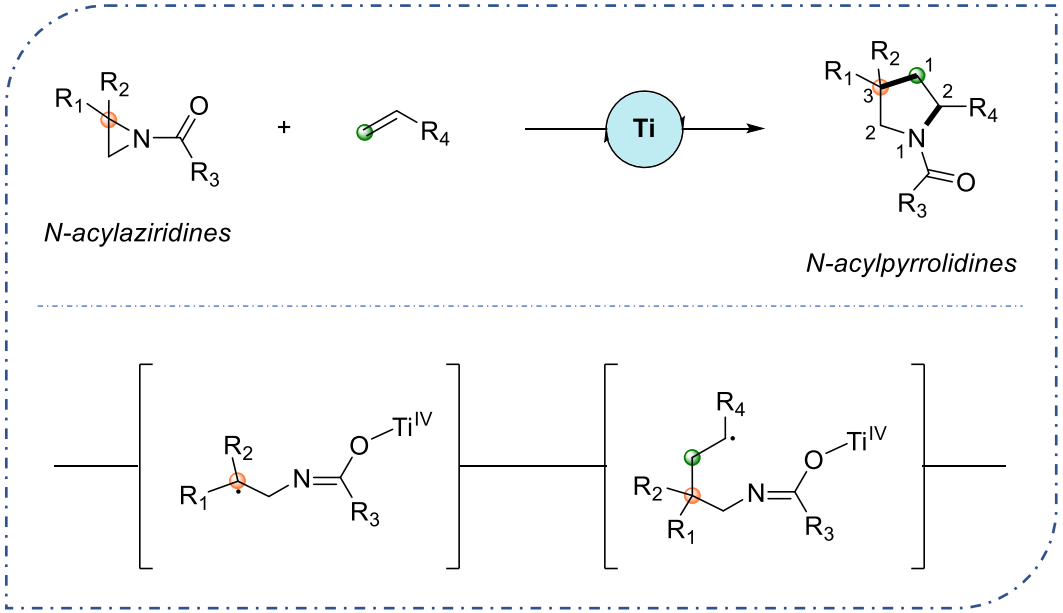


J. Am. Chem. Soc. **2020**, *142*, 2087-2092 - "Reductive Electrophotocatalysis: Merging Electricity and Light to Achieve Extreme Reduction Potentials"

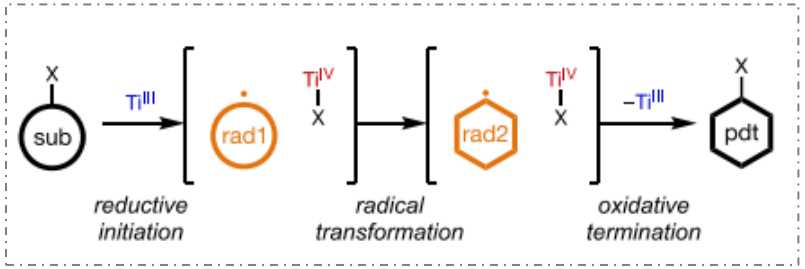
Titanocene catalysis

J. Org. Chem. **2019**, *84*, 22, 14369-14380 (Recent Advances in Titanium Radical Redox Catalysis)

General principle



Radical Redox-Relay Catalysis by $Ti^{IV/III}$

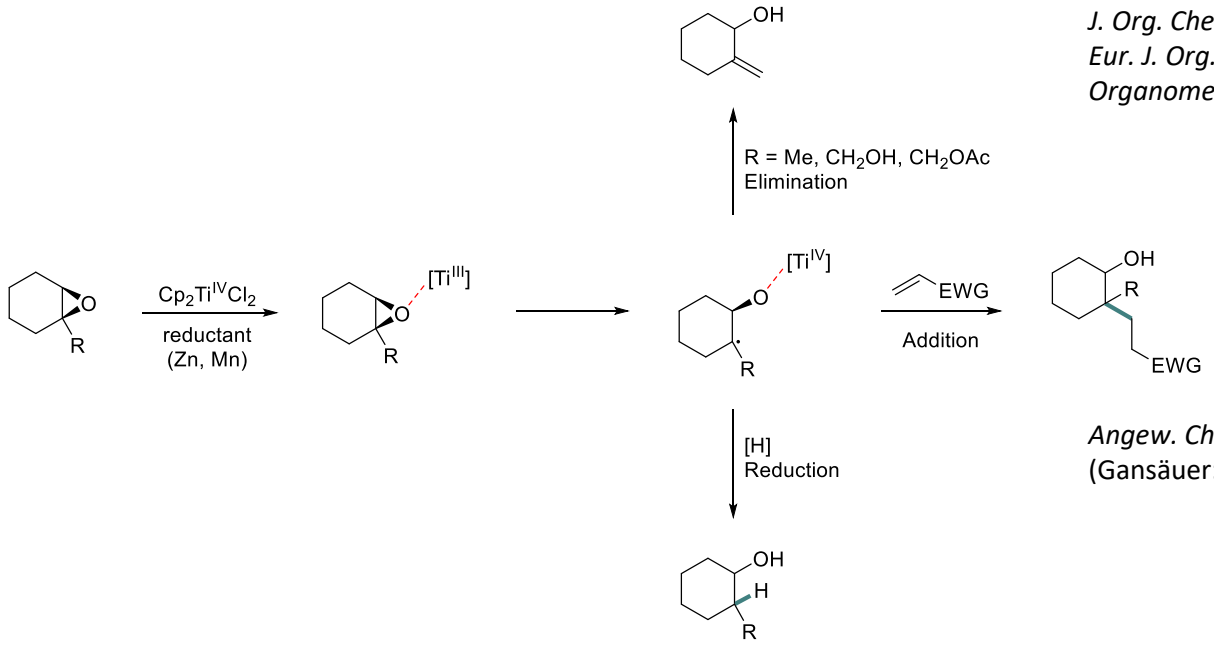


Chem. Soc. Rev., **2019**, *48*, 4626-4638 (Procter)

✓ Formal radical [3+2] cycloaddition

✓ Complete regioselectivity towards both alkene addition and aziridine opening

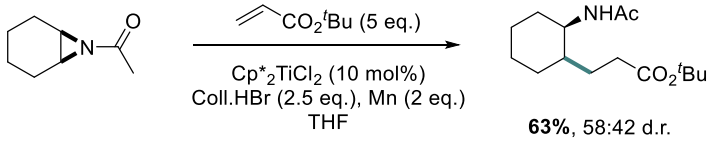
Literature precedence – Ti-mediated epoxide opening and extension to N-acylaziridines



J. Org. Chem. **2004**, *69*, 5275–5280
Eur. J. Org. Chem. **2010**, 856–861
Organometallics **2018**, *37*, 4801–4809

J. Am. Chem. Soc. **1988**, *110*, 8561–8562 (Nugent & RajanBabu)
J. Am. Chem. Soc. **1994**, *116*, 986– 997

Angew. Chem., Int. Ed. **1999**, *38*, 2909–2010 & *Adv. Synth. Catal.* **2001**, *343*, 785–787
(Gansäuer: desymmetrization and enantioselective opening of meso-epoxides)

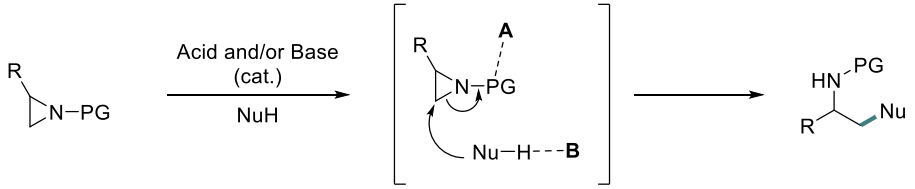


63%, 58:42 d.r.

Angew. Chem., Int. Ed. **2017**, *56*, 12654–12657 (Gansäuer)

Literature precedence – two-electron methods

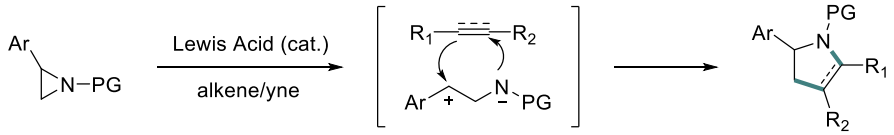
Acid and/or base catalysis



Angew. Chem., Int. Ed. **2009**, *48*, 1149–1152
(Aggarwal, synthesis of β-amino alcools from aziridines and boronic esters)

J. Am. Chem. Soc. **2007**, *129*, 12084–12085
(Antilla, Brønsted Acid-Catalyzed Desymmetrization of meso-Aziridines with HN_3)

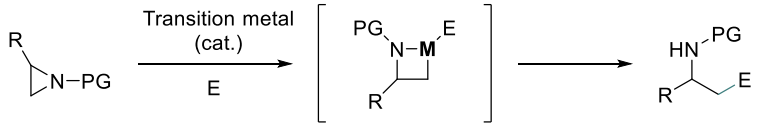
J. Am. Chem. Soc. **2005**, *127*, 11252–11253
(Shibasaki, Catalytic Enantioselective Desymmetrization of meso-N-Acylaziridines with TMSCN)



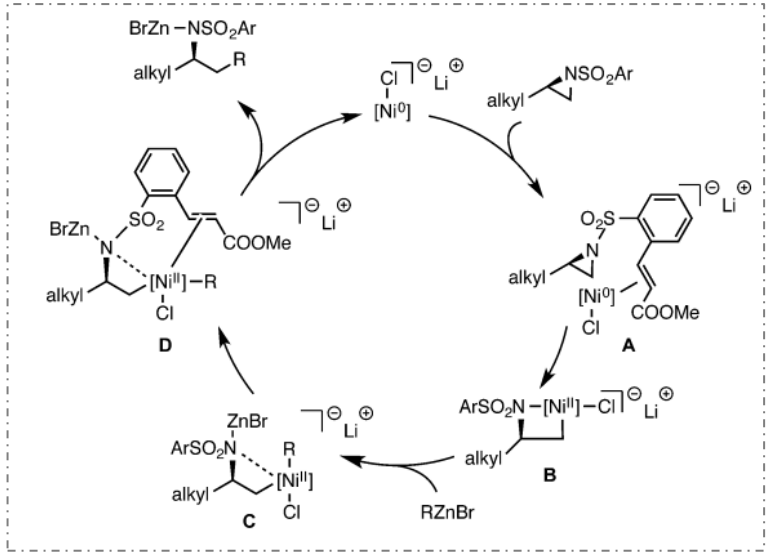
Eur. J. Org. Chem. **2012**, 6479–6501 (review)

Literature precedence – two-electron methods

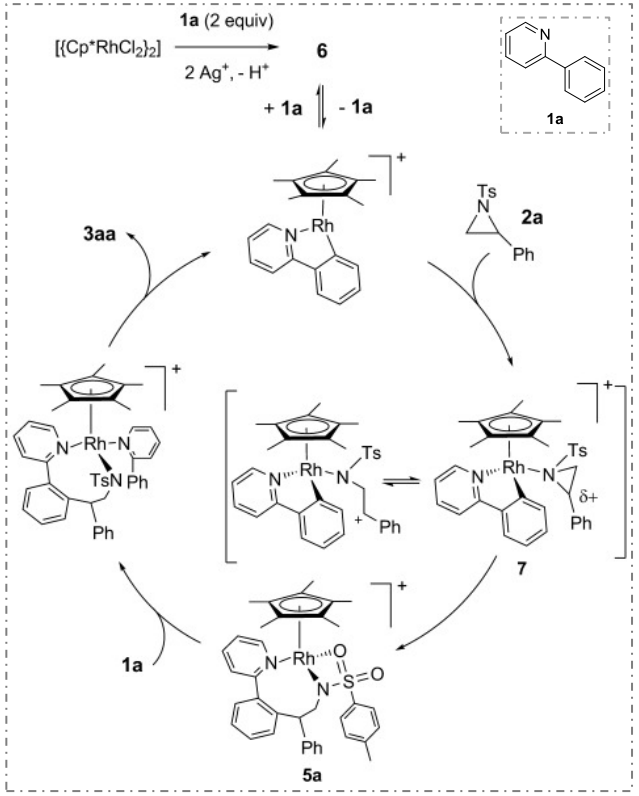
Transition-metal catalysis



J. Am. Chem. Soc. **2012**, *134*, 9541−9544 (aryl subsituent)
J. Am. Chem. Soc. **2013**, *135*, 36, 13605-13609 (alkyl substituent)
(Doyle, Directed Nickel-Catalyzed Negishi Cross Coupling of Aziridines)

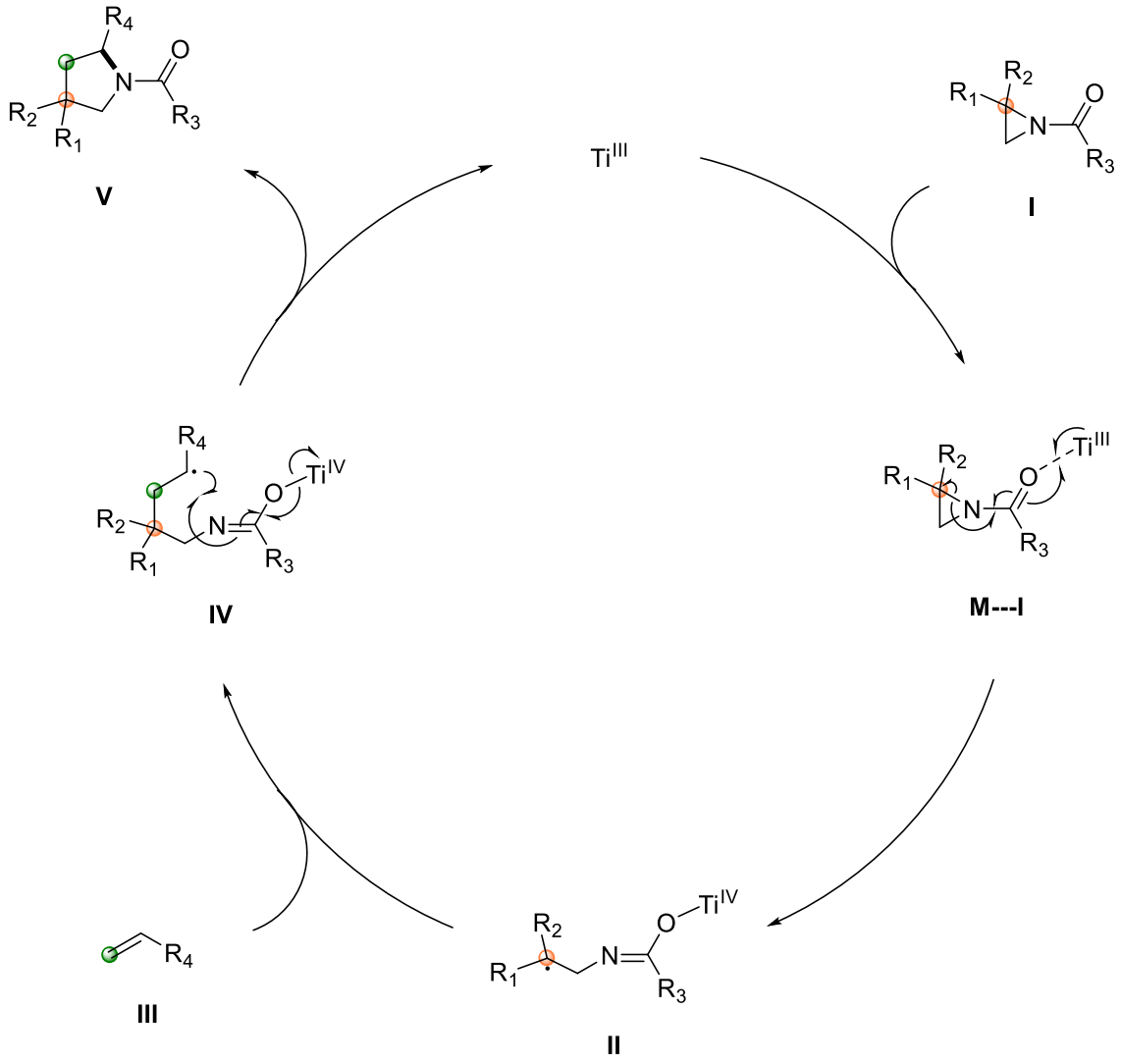


Angew. Chem. Int. Ed. **2013**, *52*, 2577 –2580
(Yu, Rh^{III}-catalyzed C-C Coupling between Arenes and Aziridines by C-H Activation)

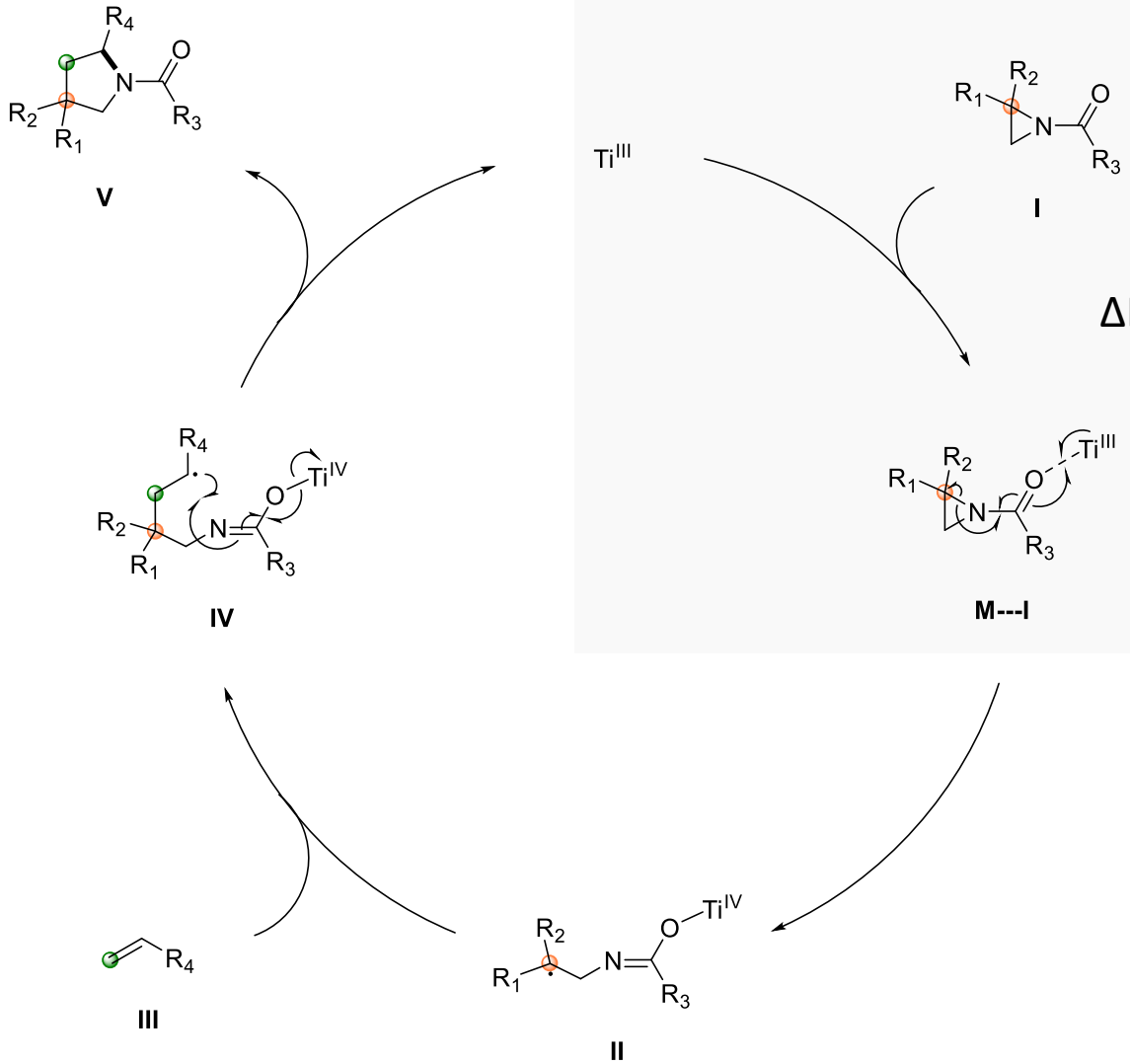


J. Am. Chem. Soc. **2013**, *135*, 18347−18349
(Michael, Palladium-Catalyzed Cross-Coupling of N-Sulfonylaziridines with Boronic Acids)

Mechanism

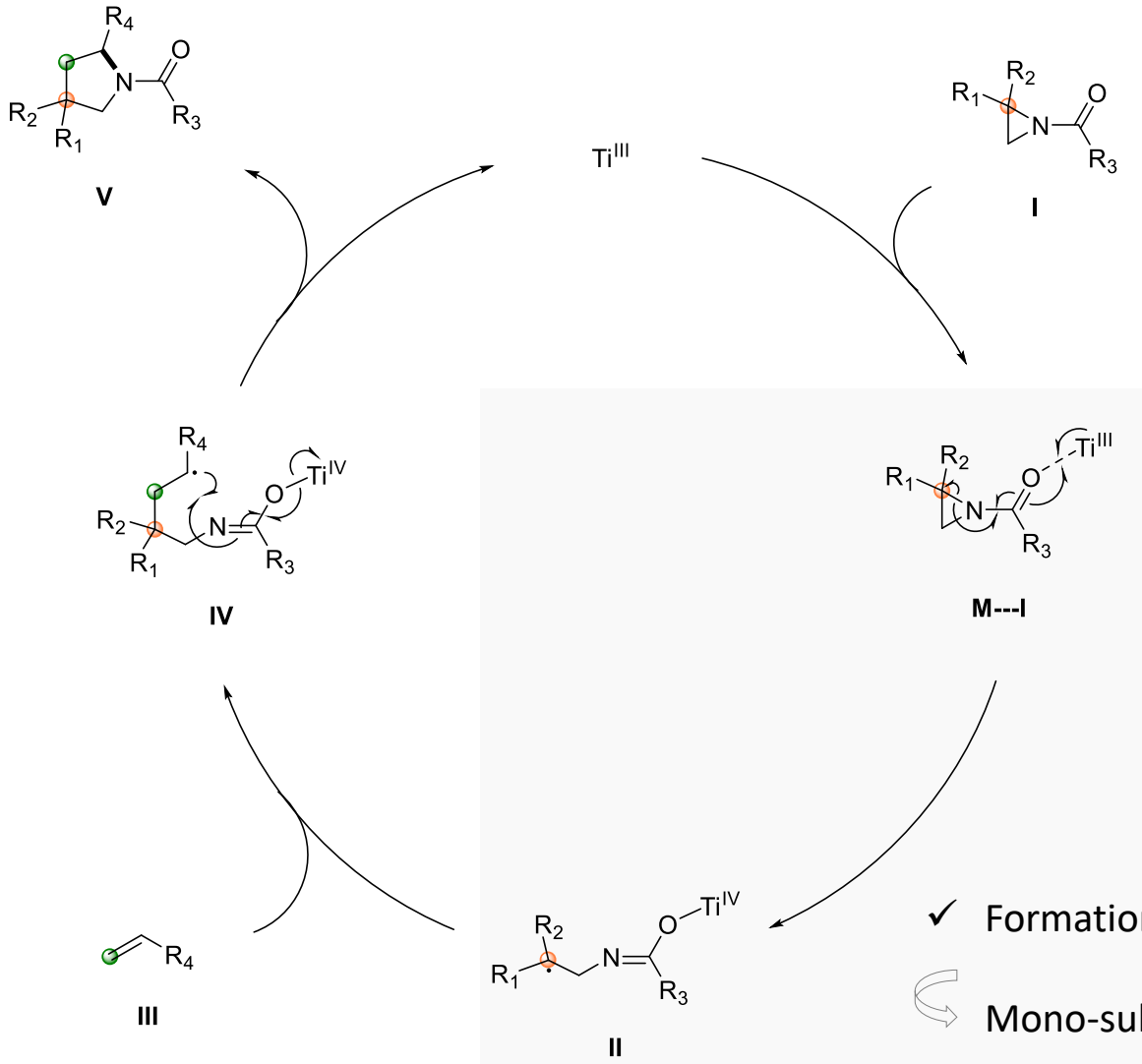


1/ Coordination of oxophile metal center



$\Delta BDE_{C—N/C—N\text{-}Acyl}$ = 22,4 kcal/mol

J. Am. Chem. Soc. **2015**, *137*, 6440–6443
(Ti mediated cleavage of N—H carbamate bonds)



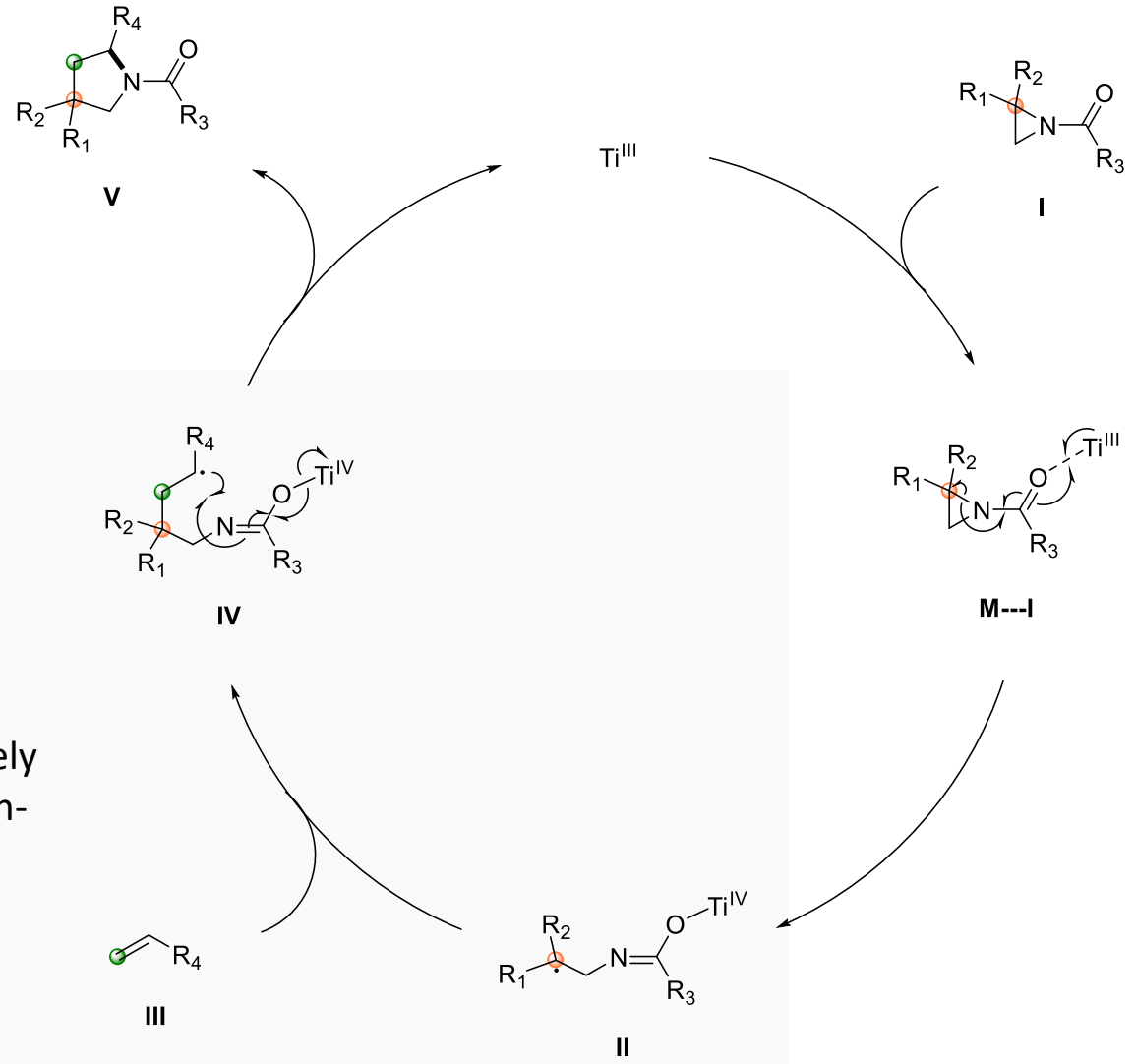
2/ Single electron reductive opening

✓ Electron-rich Ti cat. needed for efficient reaction → this step may be involved in the rate-limiting process

✓ Formation of an azaenolate and nucleophilic tertiary alkyl radical

Mono-substituted aziridines were not amenable to the reaction

3/ Radical addition



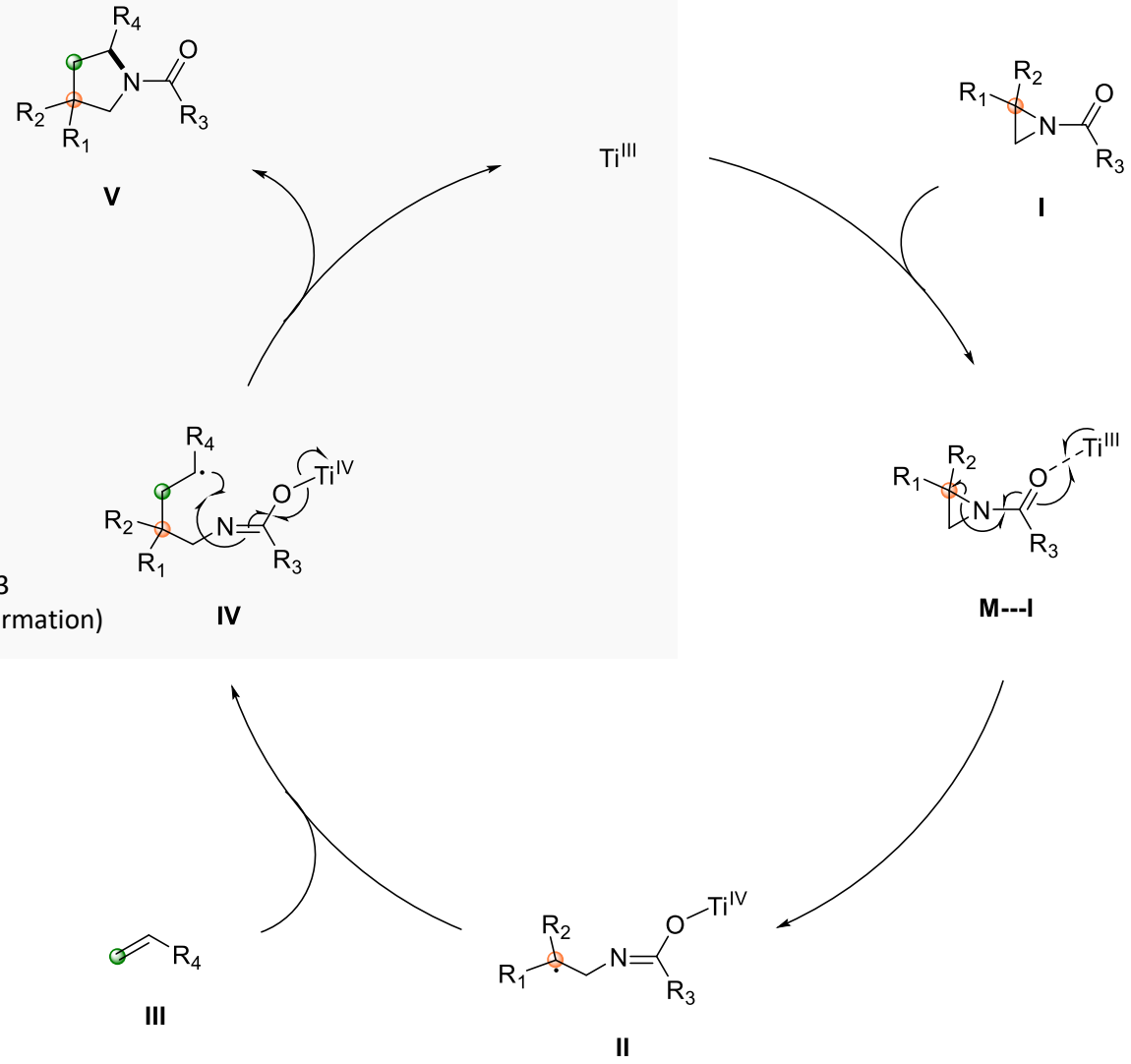
- ✓ Rate of reaction positively correlated with electron-deficiency of alkene

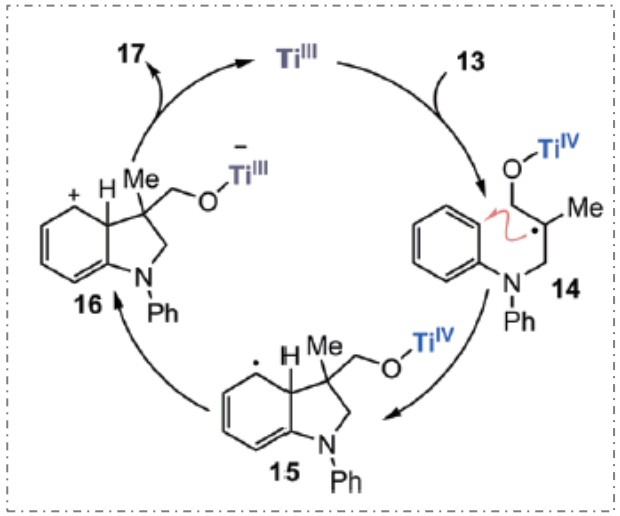
Angew. Chem., Int. Ed., **2012**, *51*, 4739–4742

4/ Oxidative ring closure

- ✓ Unprecedented C-centered radical addition to an azaenolate
- ✓ SET from C-radical to Ti^{IV}-azaenolate followed by polar addition not thermodynamically favorable

J. Am. Chem. Soc. **2010**, *132*, 1482–1483
(Ti-enolates as radical acceptors for C-C bond formation)

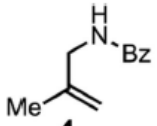




Optimization

entry	variation from standard conditions	yield (%)[a]
1	none	94
2	$CpTiCl_3$ instead of Cp^*TiCl_3	20[b]
3	Cp_2TiCl_2 instead of Cp^*TiCl_3	<5[b]
4	$TiCl_4$ instead of Cp^*TiCl_3	<5[b] (11% **4**)
5	without Zn dust	<5 (>99% **4**)
6	Mn dust instead of Zn dust	82%
7	$ZnCl_2$ instead of Cp^*TiCl_3 and Zn dust	<5[b]
8	DCM instead of toluene	82%
9	THF or MeCN instead of toluene	<5[b]
10	1.0 equiv **2**	92
11	**4** or **5** instead of **1**	<5[b]

[a]Determined with ^{1}H NMR. [b]Unreacted starting material observed.



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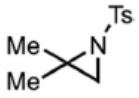
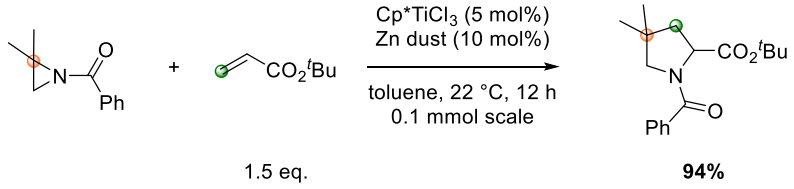
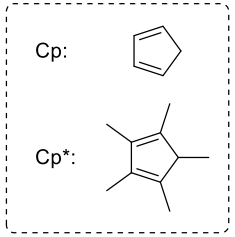


5

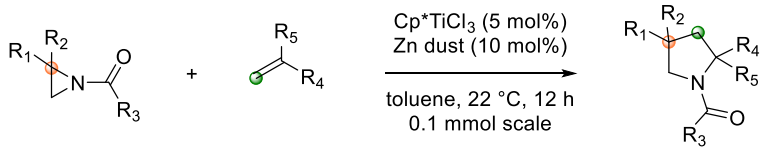
Optimized conditions





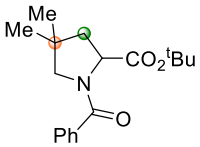
$E_{1/2}(Cp_2TiCl) = -0.65$ V vs SCE
$E_{1/2}(CpTiCl_2) = -0.82$ V vs Fc^+/Fc
$E_{1/2}(Cp^*TiCl_2) = -1.10$ V vs Fc^+/Fc

Scope

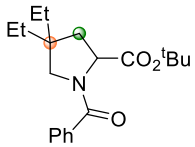


N-acylaziridines + 1.0 - 1.2 eq. → *N-acylpyrrolidines*
24 examples
62 - 96 %

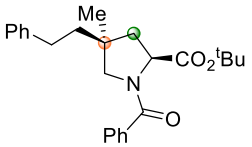
Variation of the aziridine substituents



86%
(91% on 1 mmol scale)

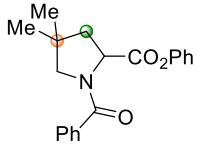


96%

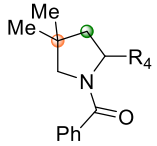


82%, 2.3:1 d.r.

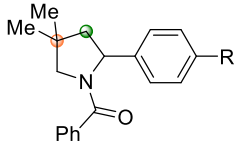
Variation of the alkene



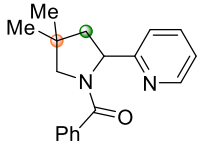
86%



R_4 = $CONMe_2$, **63%**
= CN, **69%**
= SO_2Ph, **95%**

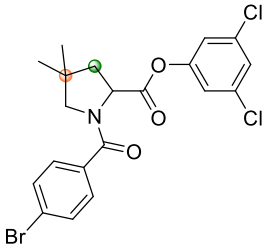


R = H, **76%**
= Cl, **76%**
= OMe, **63%**

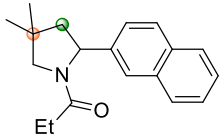


70%

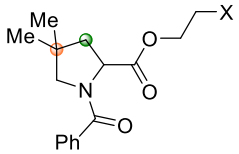
Variation of the acyl group



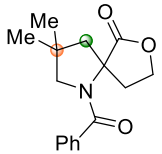
88%



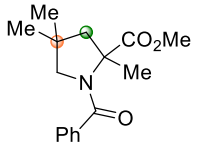
62%



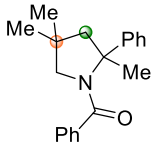
X = Cl, **93%**
X = NMe_2, **78%**
X = THF, **75%**



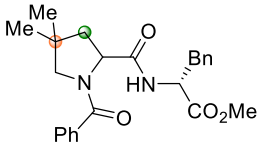
71%



78%

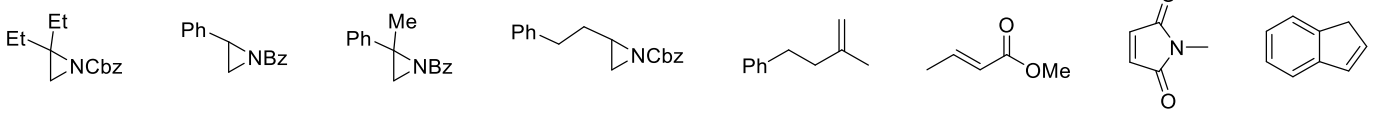


78%

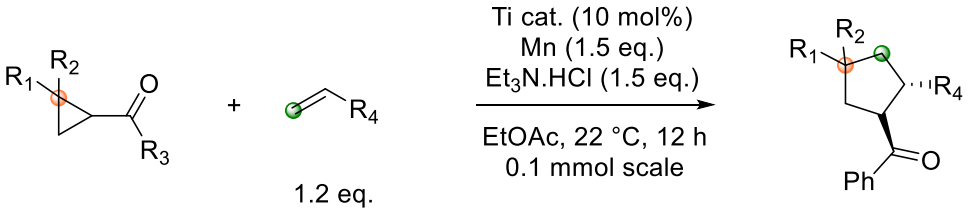


71%, 1:1 d.r.

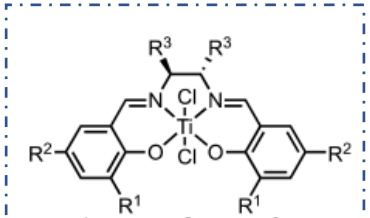
Unreactive substrates



Futher developement – cyclopropyl ketones

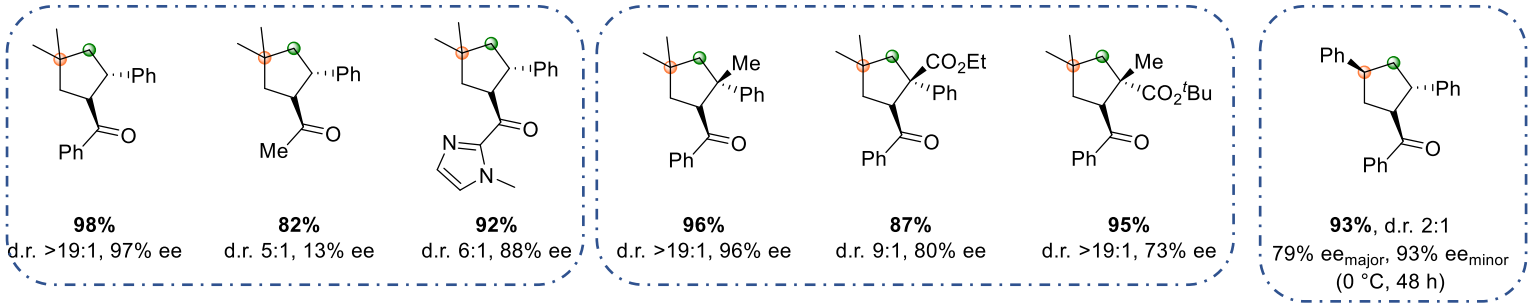


30 examples
53 - 98%
9:1 - >19:1 d.r.
45 - 98% ee



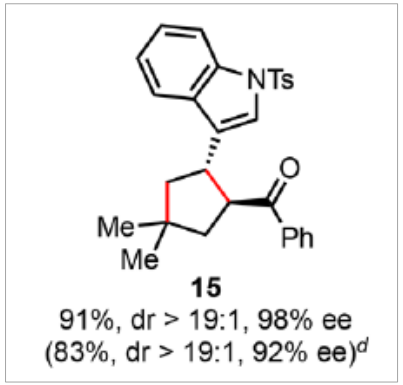
3, R^1 = 1-Ad, R^2 = Me, R^3 = Ph

Representative examples:



98%	**82%**	**92%**	**96%**	**87%**	**95%**
d.r. >19:1, 97% ee	d.r. 5:1, 13% ee	d.r. 6:1, 88% ee	d.r. >19:1, 96% ee	d.r. 9:1, 80% ee	d.r. >19:1, 73% ee

93%, d.r. 2:1
79% ee_{major}, 93% ee_{minor}
(0 °C, 48 h)



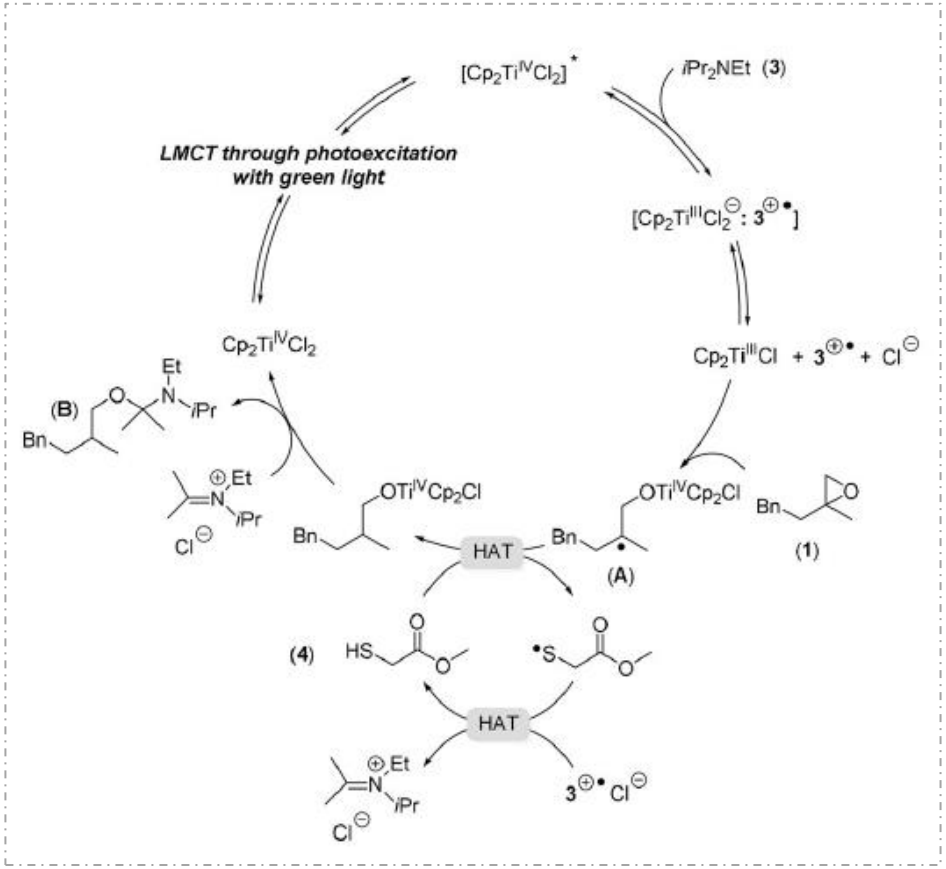
15
91%, dr > 19:1, 98% ee
(83%, dr > 19:1, 92% ee)[d]

Scale up from 0.1 to 1 mmol

J. Am. Chem. Soc. **2018**, *140*, 10, 3514-3517

See also *J. Am. Chem. Soc.* **2018**, *140*, 14836−14843 (Ti^{III}-mediated Cl atom abstraction and subsequent radical addition to electron-deficient alkenes)

Futher developement – titanocene as photoredox catalyst



Angew. Chem. Int. Ed. **2020**, *59*, 1–6

Conclusion

- Ti-catalyzed radical formal [3+2] cycloaddition of N-acylaziridines with alkenes
- High yield and complete regioselectivity
- Redox-relay strategy with selective C—N bond breaking and formation
  - Efficient protocol for pyrrolidine synthesis
- Scope limited to di-substituted N-acylaziridines
- Not a stereoselective protocol
- Could however be stereoselectively applied to cyclopropyl ketones

UNIVERSITÄT BERN

Radical Redox-Relay Catalysis: Formal [3+2] Cycloaddition of N-Acylaziridines and Alkenes

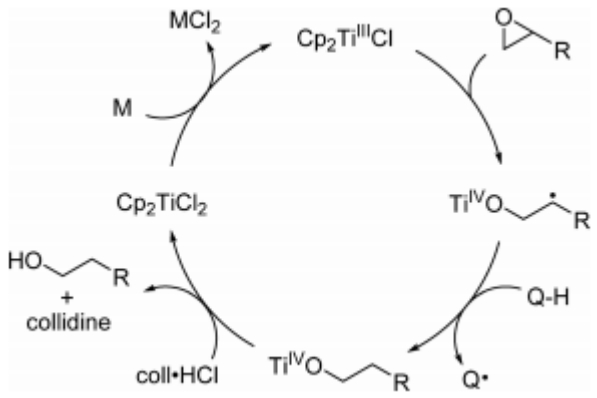
Wei Hao, Xiangyu Wu, James Z. Sun, Juno C. Siu, Samantha N. MacMillan, and Song Lin

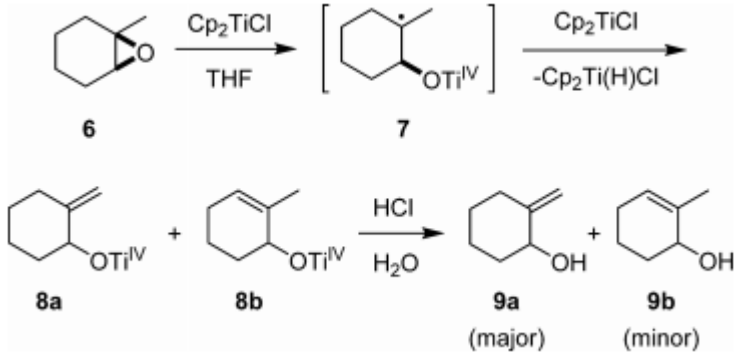
J. Am. Chem. Soc. **2017**, *139*, 12141−12144

Journal Club, Renaud Group_Eloïse_30.04.2020

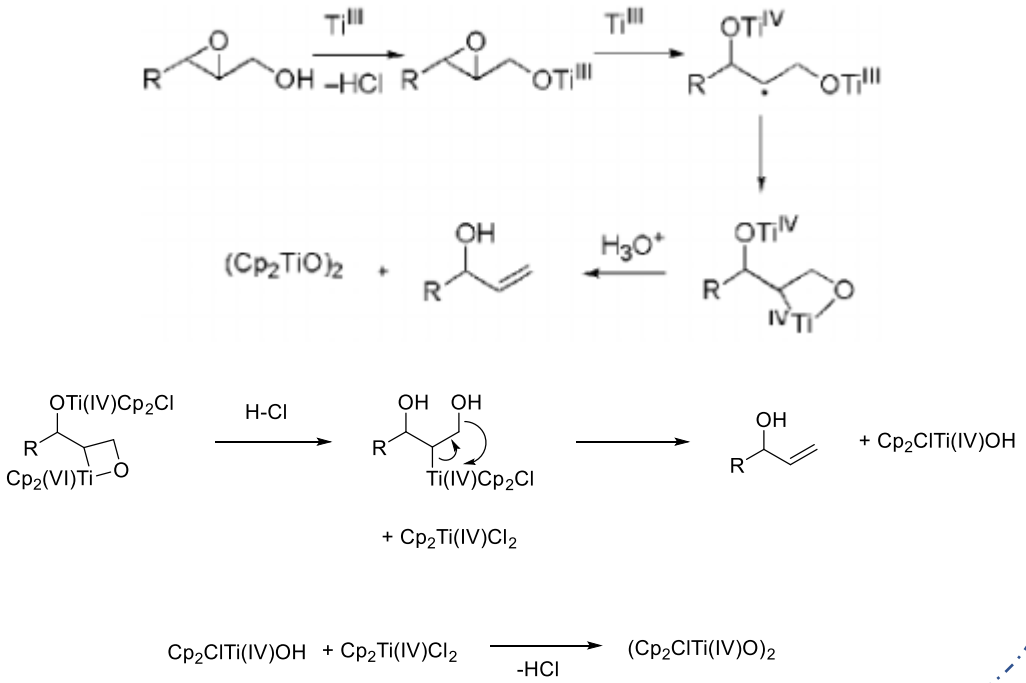
Elimination reactions

Organometallics **2018**, *37*, 4801−4809

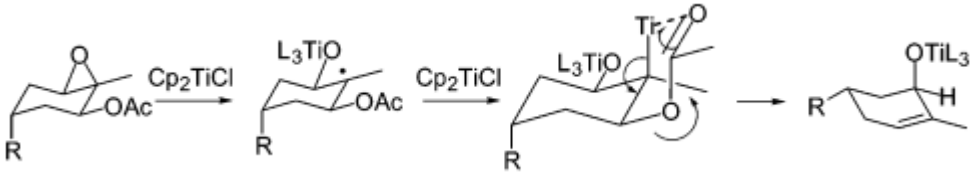




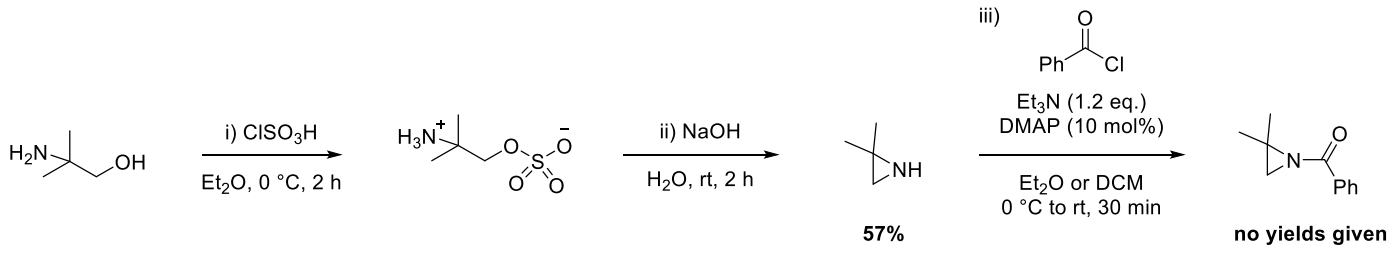
Eur. J. Org. Chem. **2010**, 856−861



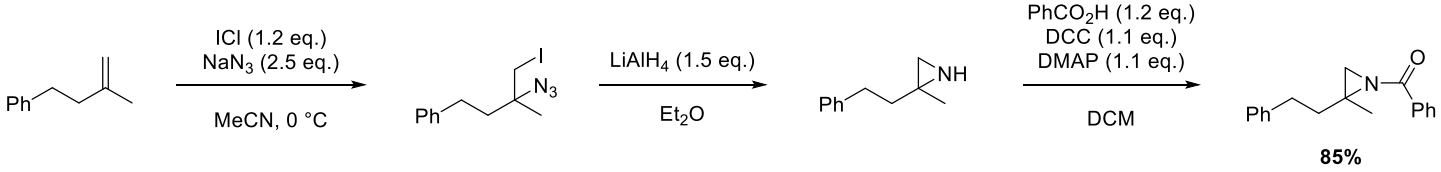
J. Org. Chem. **2004**, *69*, 5275−5280



Synthesis of the precusors



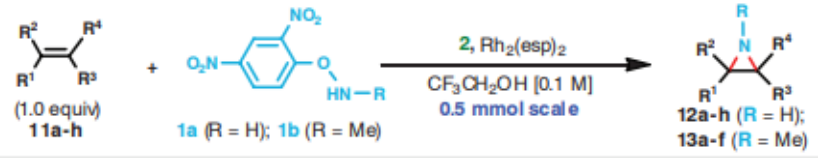
Adv. Synth. Catal. **2019**, *361*, 1647 –166

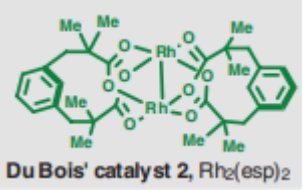


For recent developments in alkene aziridination see for example:
Science **2014**, *343*, 61−65
J. Am. Chem. Soc. **2003**, *125*, 44, 13350-13351
J. Am. Chem. Soc. **2002**, *124*, 530−531

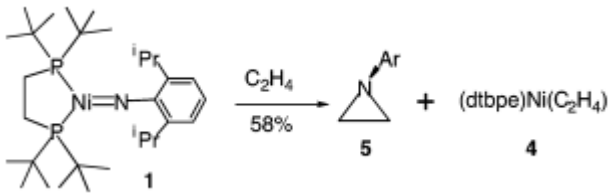
Alkene Aziridination

Science **2014**, *343*, 61–65





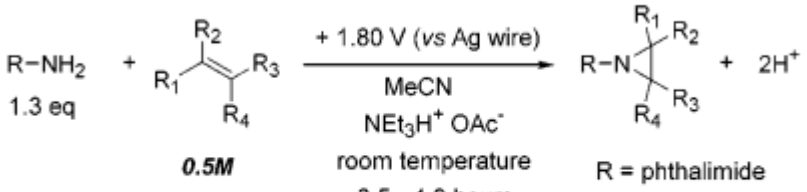
J. Am. Chem. Soc. **2003**, *125*, 44, 13350-13351



Nickel-imido complex

J. Am. Chem. Soc. **2002**, *124*, 530–531

Platinum Anode:



Platinum Cathode:

$2\,H^+ \longrightarrow H_2$