Titanium-Catalyzed Radical Opening of *N*-Acylated Aziridines

Reporter: Jie Wang
Checker: Hong-Qiang Shen
Date: 2017-10-17

Hao, W.; Wu, X.; Sun, J. Z.; Siu, J. C.; MacMillan, S. N.; Lin, S.
J. Am. Chem. Soc. **2017**, *139*, 12141.
Zhang, Y.-Q.; Vogelsang, E.; Qu, Z.-W.; Grimme, S.; Gansäuer, A.
Angew. Chem. Int. Ed. **2017**, *56*, 12654.

Contents

CV of Song Lin

Song Lin

Education:

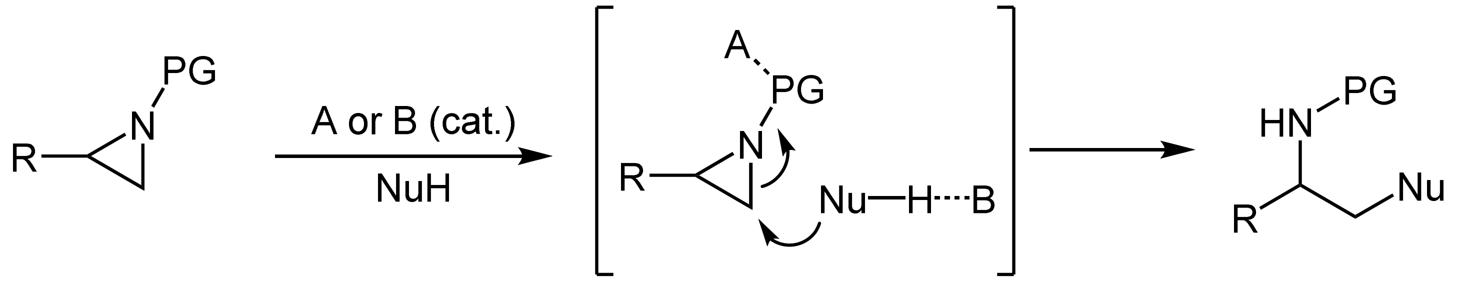
- B.S., Peking University (2004-2008)
- Ph.D., Harvard University
  with Eric N. Jacobsen (2008-2013)
- Postdoctoral Fellow., University of California, Berkeley
  with Christopher J. Chang (2013-2016)
- Cornell University (2016)

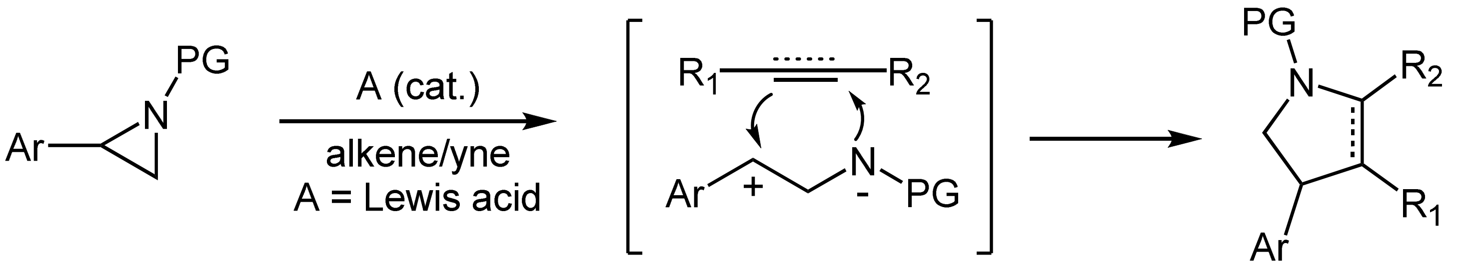
Research:

The research in the Lin Lab lies in the broadly defined area of organic chemistry, with specific interests in electrosynthesis, asymmetric catalysis and organic materials.

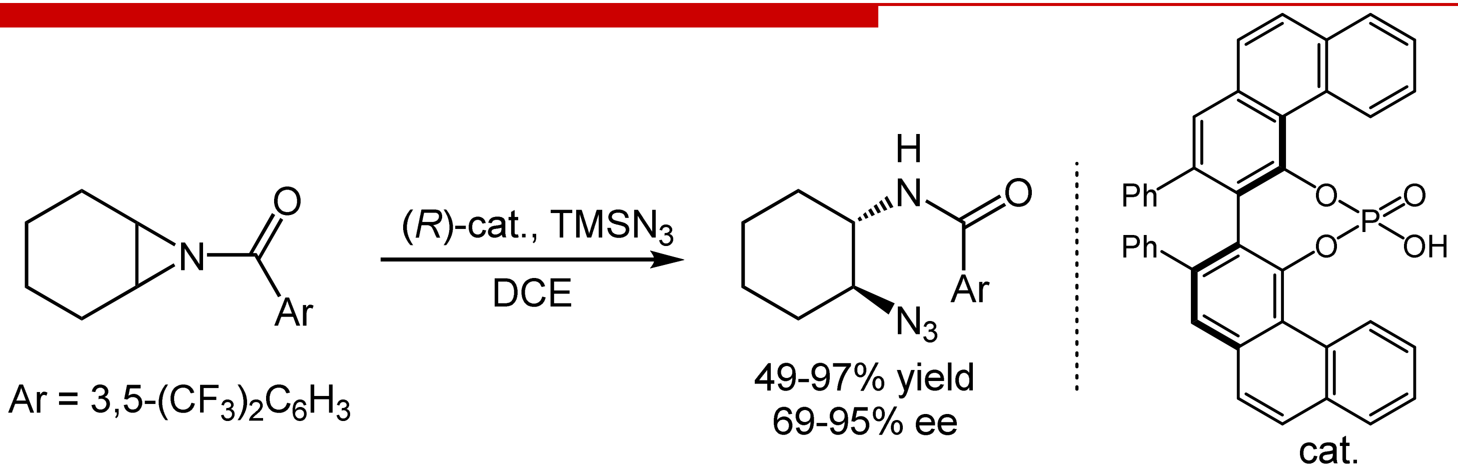
Introduction

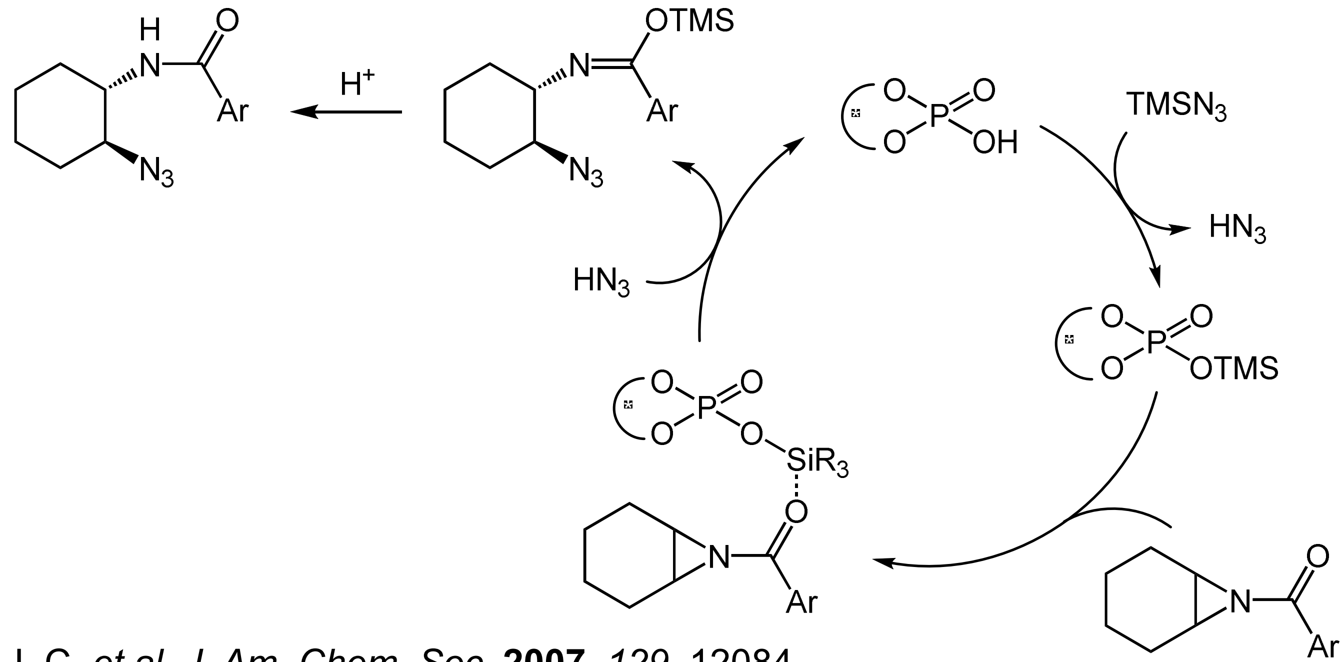
Acid or base catalysis:





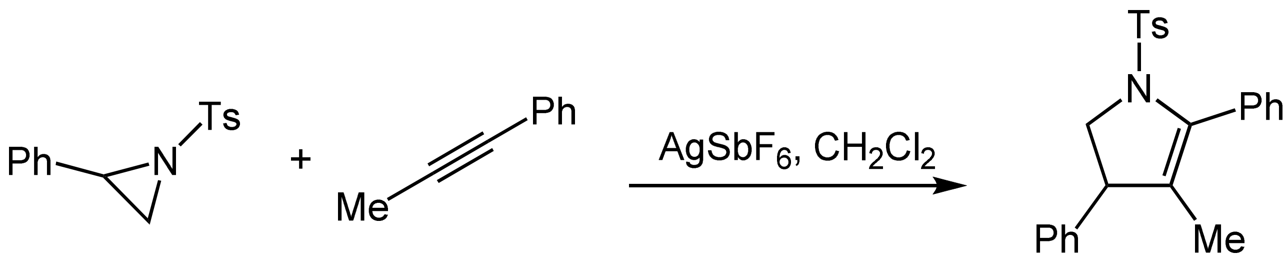
Introduction





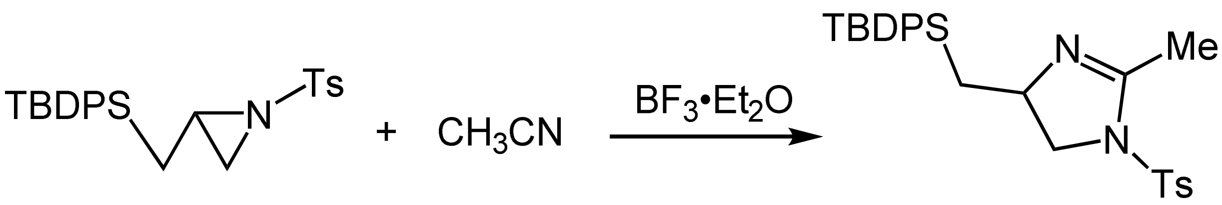
Antilla, J. C. *et al. J. Am. Chem. Soc.* **2007**, *129*, 12084.

Introduction



28-89% yield

Wender, P. A. *et al. J. Am. Chem. Soc*. **2009**, *131,* 7528.

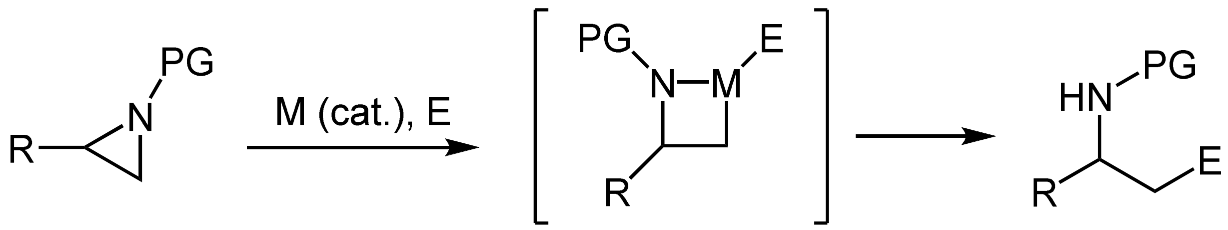


62-95% yield

Yadav, V. K. *et al. J. Am. Chem. Soc*. **2005**, *127*, 16366.

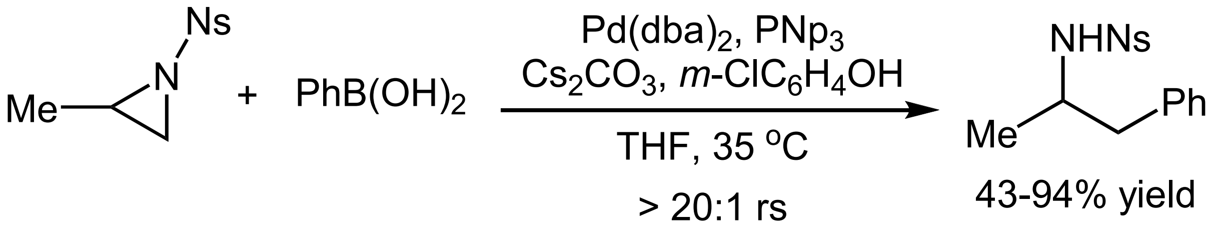
Introduction

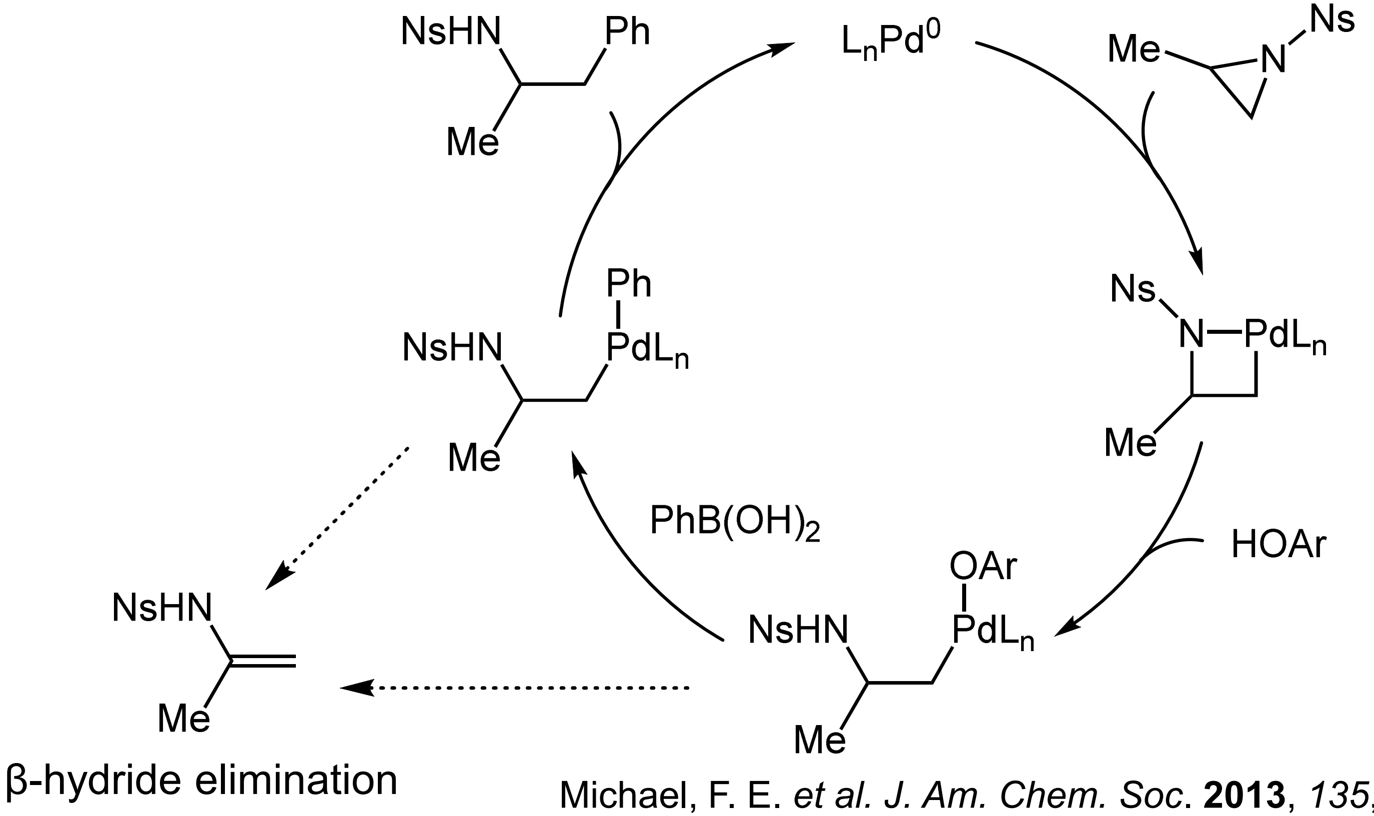
Transition-metal catalysis:



M = transition metal

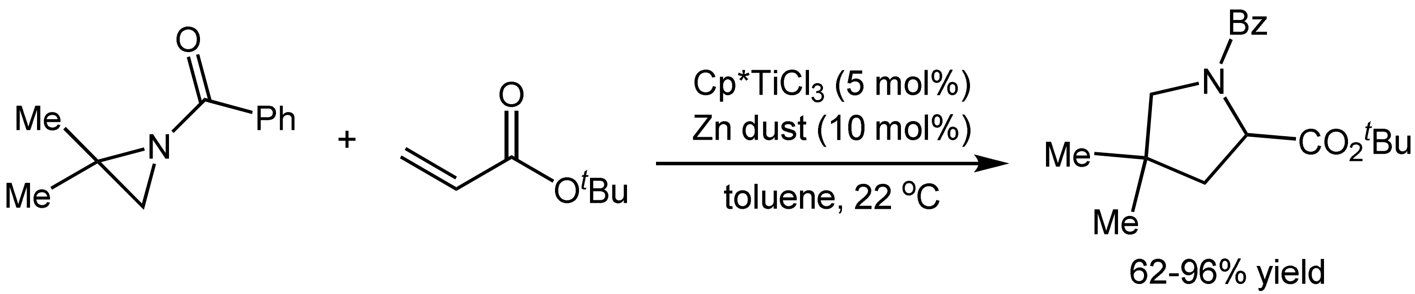
Introduction





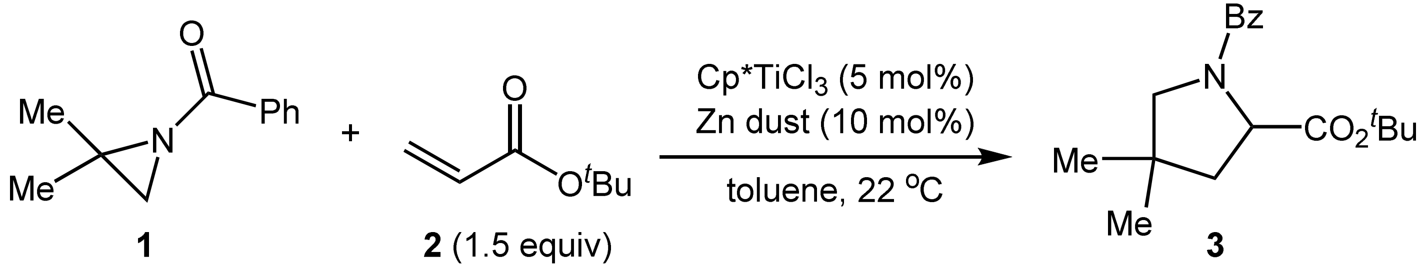
Michael, F. E. *et al. J. Am. Chem. Soc.* **2013**, *135*, 18347.

Redox-Neutral Radical Opening of Aziridines



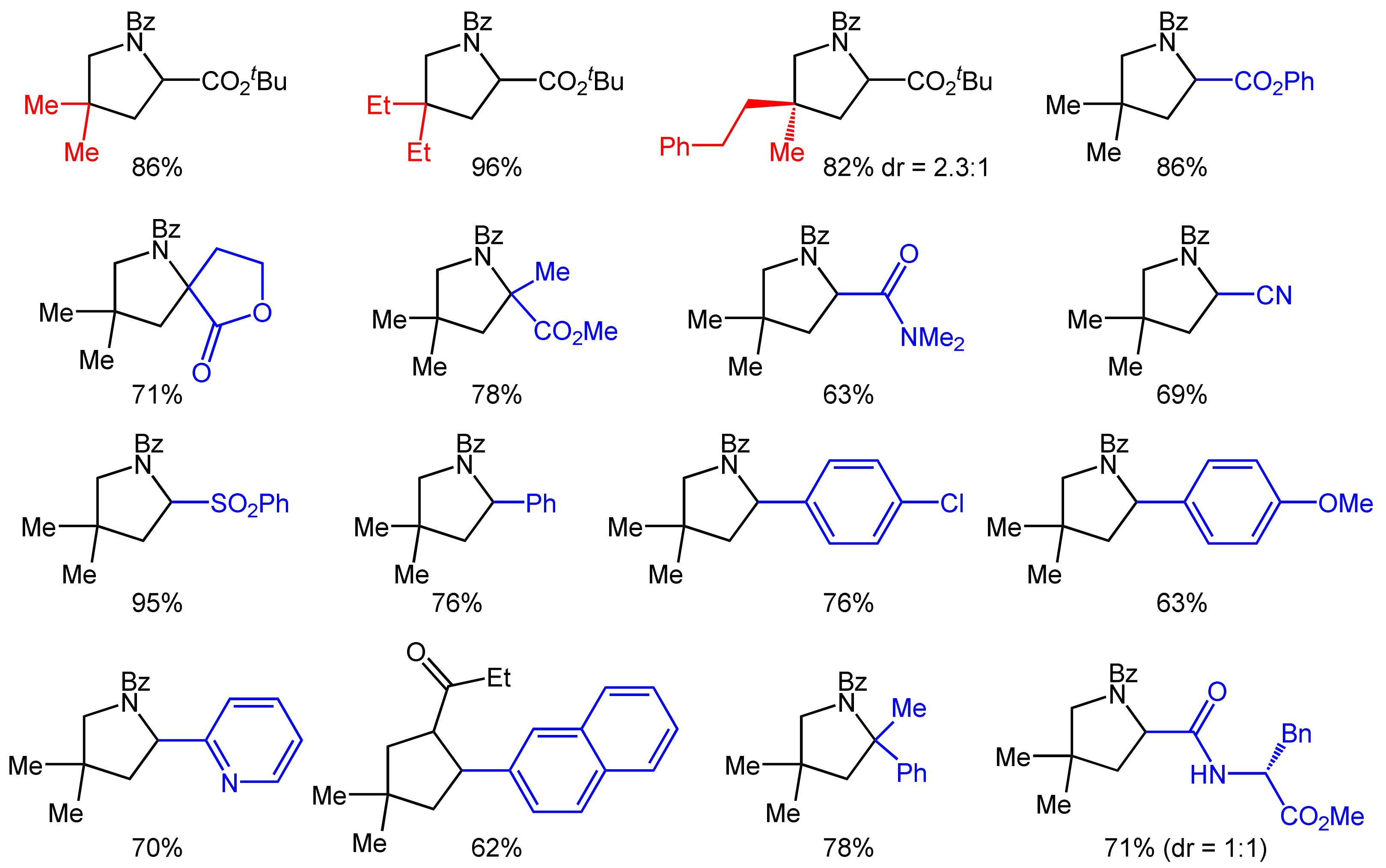
Lin, S. *et al. J. Am. Chem. Soc.* **2017**, *139*, 12141.

Evaluation Conditions



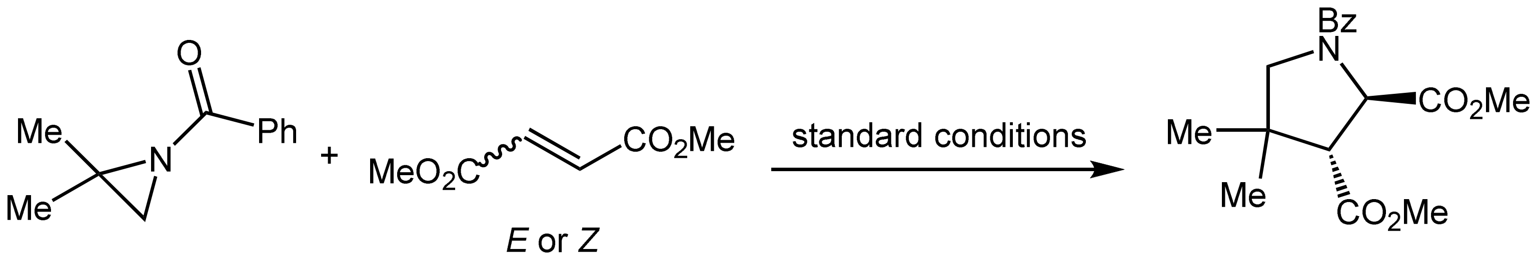
entry	variation from standard conditions	yield (%)
1	none	94
2	$CpTiCl_3$ instead of Cp^*TiCl_3	20
3	Cp_2TiCl_2 instead of Cp^*TiCl_3	<5
4	$TiCl_4$ instead of Cp^*TiCl_3	<5
5	without Zn dust	<5
6	Mn dust instead of Zn dust	82
7	$ZnCl_2$ instead of Cp^*TiCl_3 and Zn dust	<5
8	DCM instead of toluene	82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

Substrate Scope



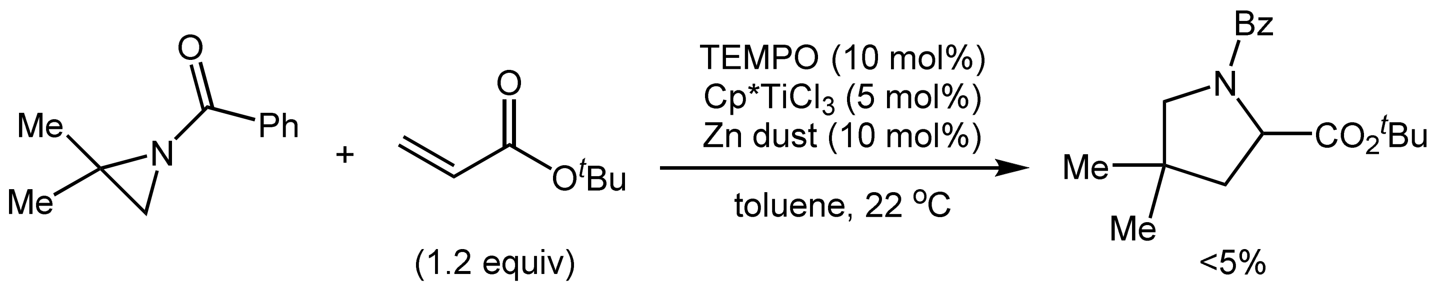
Mechanistic Experiments

A. Stereochemical infidelity of the [3+2] cycloaddition



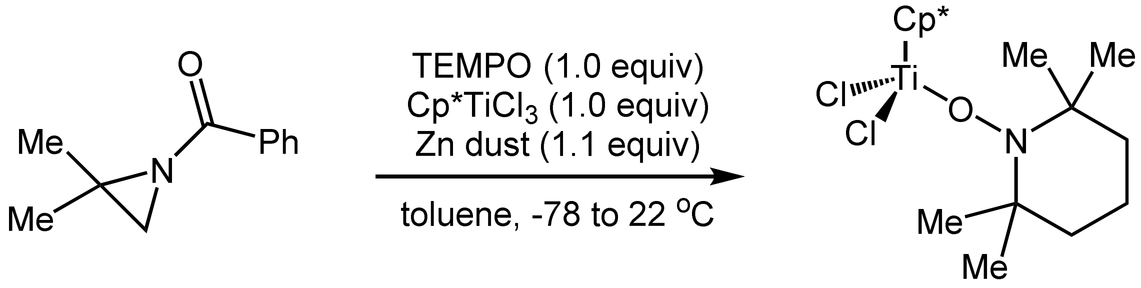
from *Z*: 36%, dr > 19:1
from *E*: 34%, dr > 19:1

B. Spin trapping with TEMPO

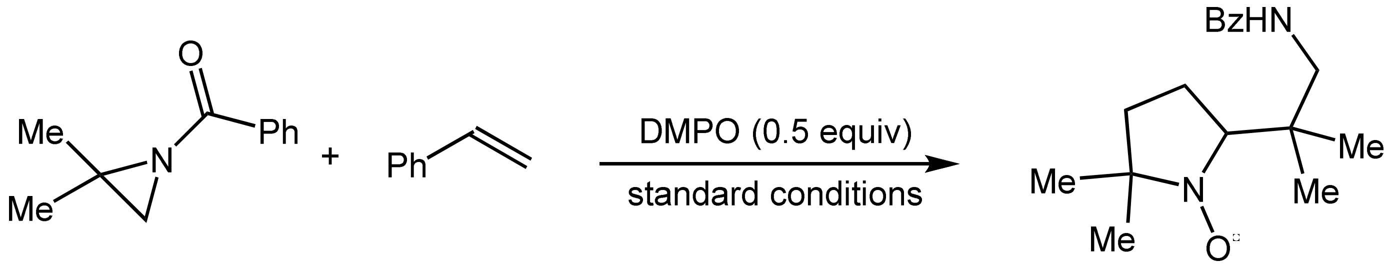


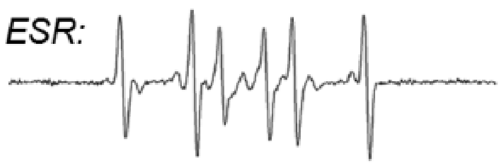
<5%

Mechanistic Experiments



confirmed with X-ray

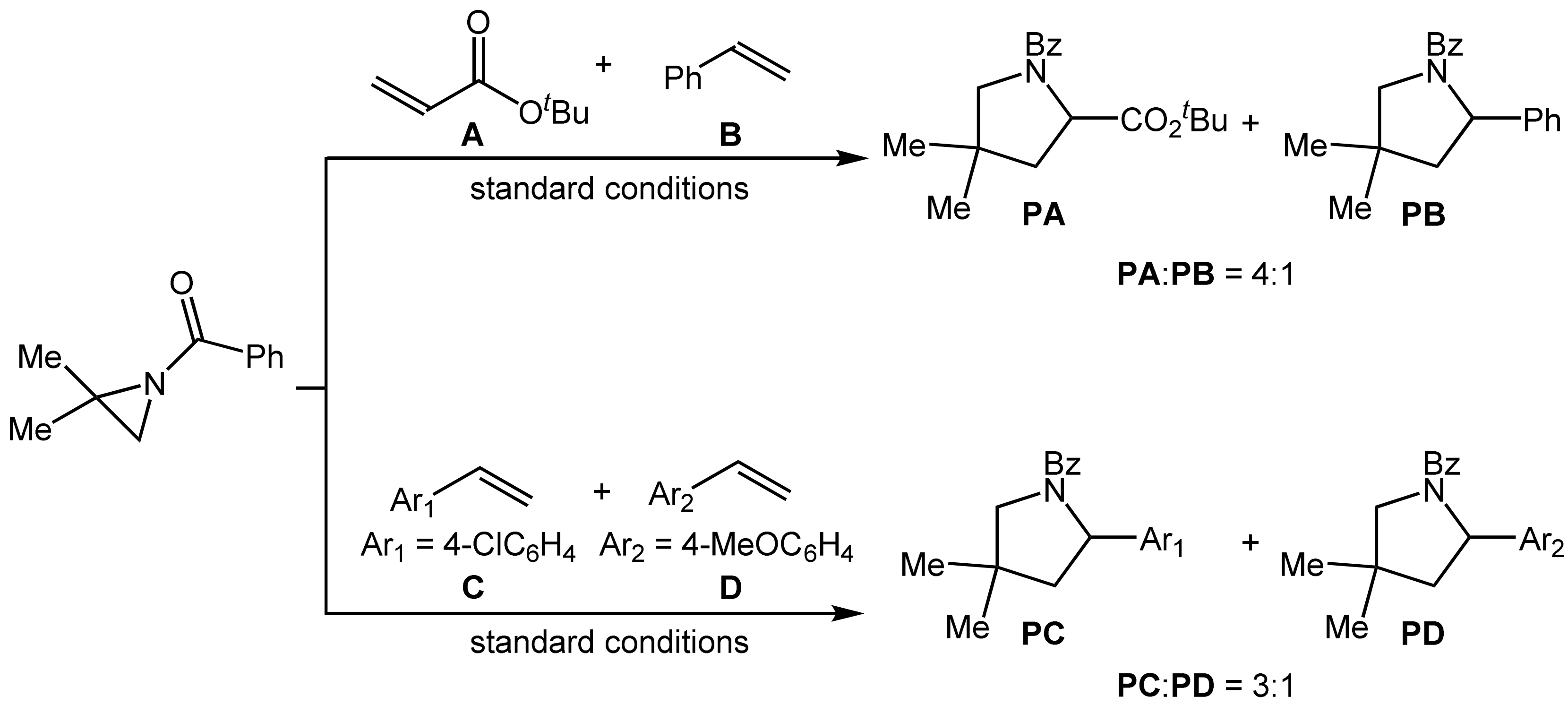




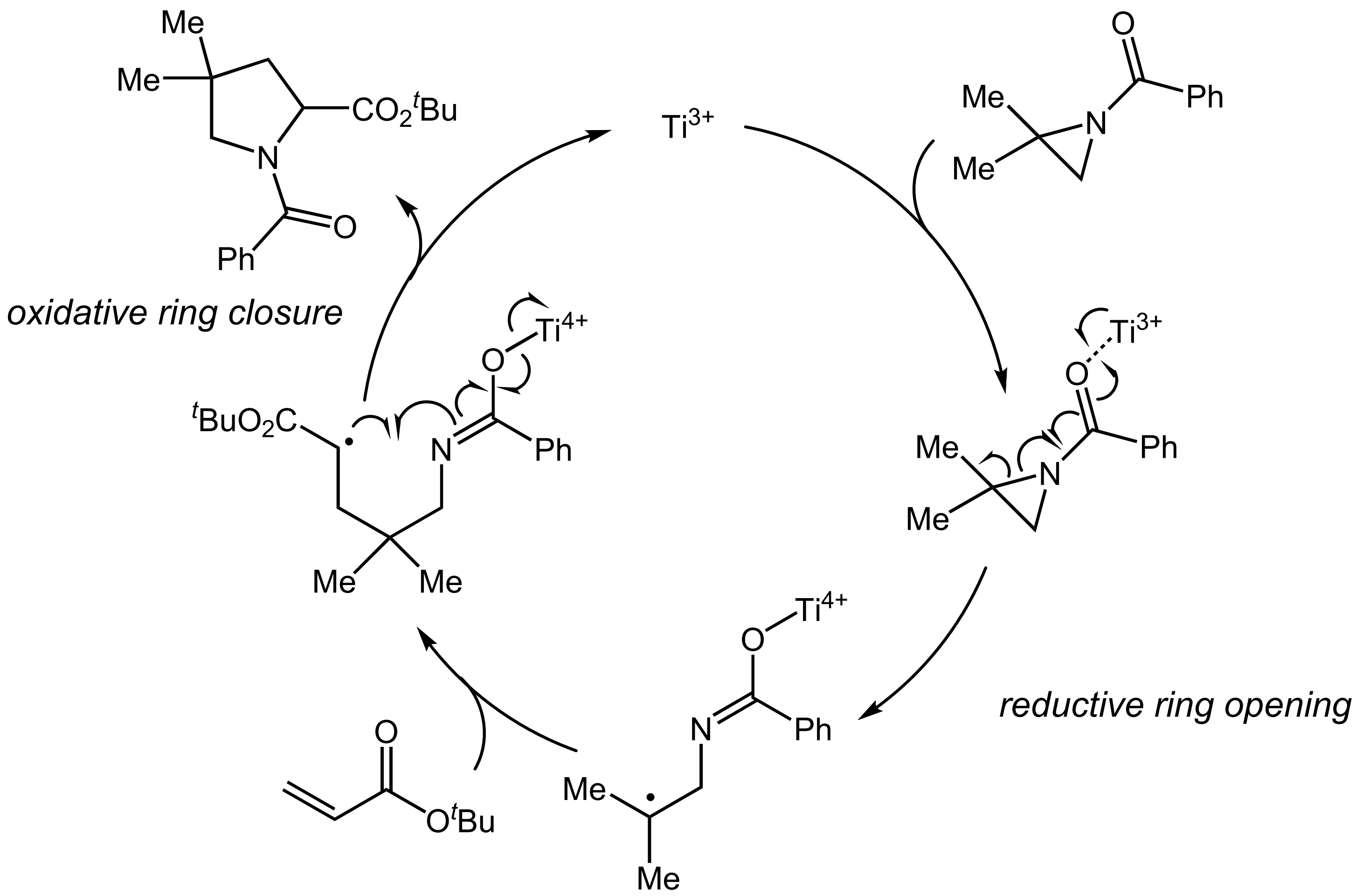
g value = 2.0059, mass = 289.18995

Mechanistic Experiments

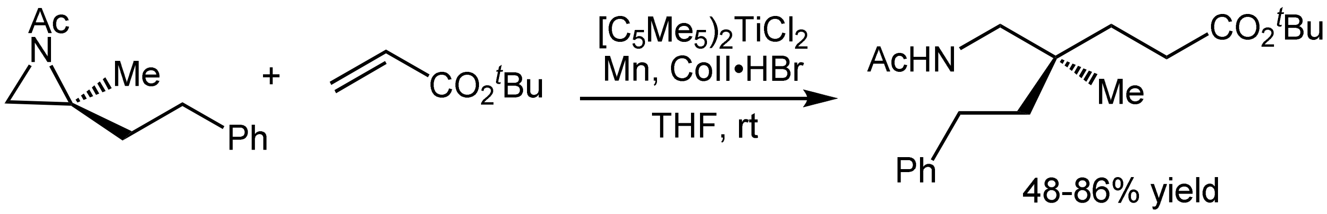
C. Competition experiments using alkenes



Proposed Mechanism

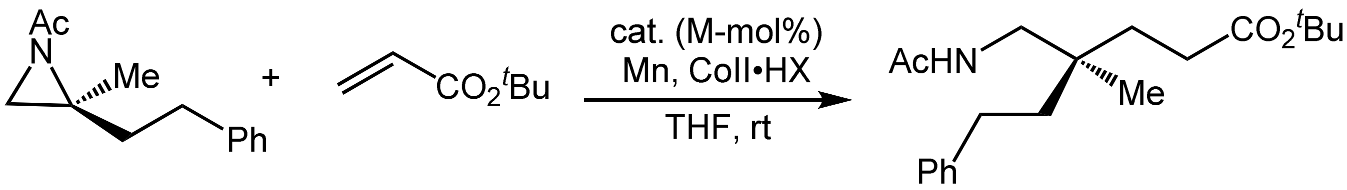


Reductive Radical Opening of Aziridines



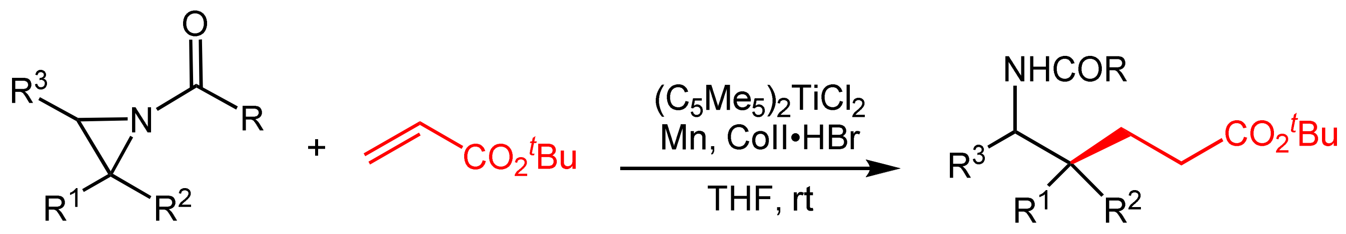
Gansäuer, A. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 12654.

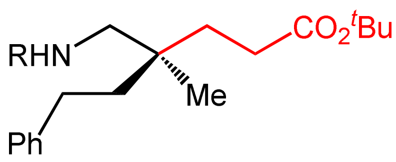
Evaluation Conditions



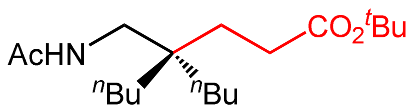
entry	cat.	mol%	Coll•HX	yield (%)
1	Cp_2TiCl_2	10	Coll•HCl	22
2	(salen)$TiCl_2$	10	Coll•HCl	-
3	$(C_5H_4Me)_2TiCl_2$	10	Coll•HCl	46
4	$(C_5H_4{}^tBu)_2TiCl_2$	10	Coll•HCl	<5
5	$(C_5H_4Cl)_2TiCl_2$	10	Coll•HCl	<5
6	$(C_5Me_5)_2TiCl_2$	10	Coll•HCl	80
7	$(C_5Me_5)_2TiCl_2$	10	Coll•HBr	82
8	$(C_5Me_5)_2TiCl_2$	10	Coll•HI	38
9	$(C_5Me_5)_2TiCl_2$	5	Coll•HBr	76

Substrate Scope

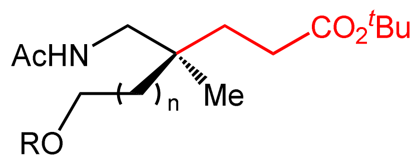




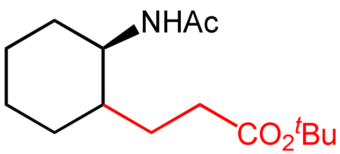
R = Ac, 82%
R = CHO, 65%
R = CO_2Et, 77%
R = Boc, 86%



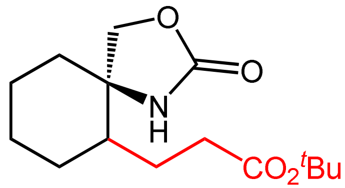
86%



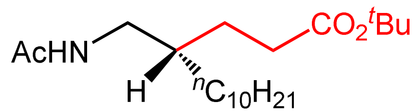
n = 1, R = Bn, 83%
n = 8, R = TBS, 77%
n = 8, R = Piv, 68%
n = 8, R = Bz, 66%



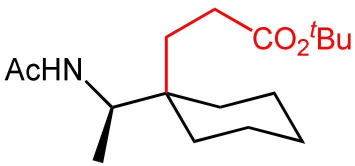
63%, *trans*:*cis* = 58:42



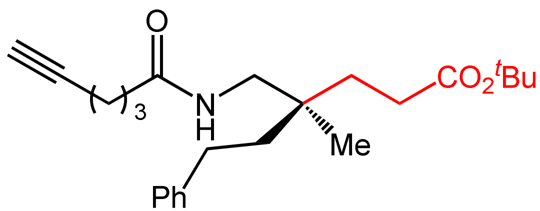
73%, dr = 60:40



48%

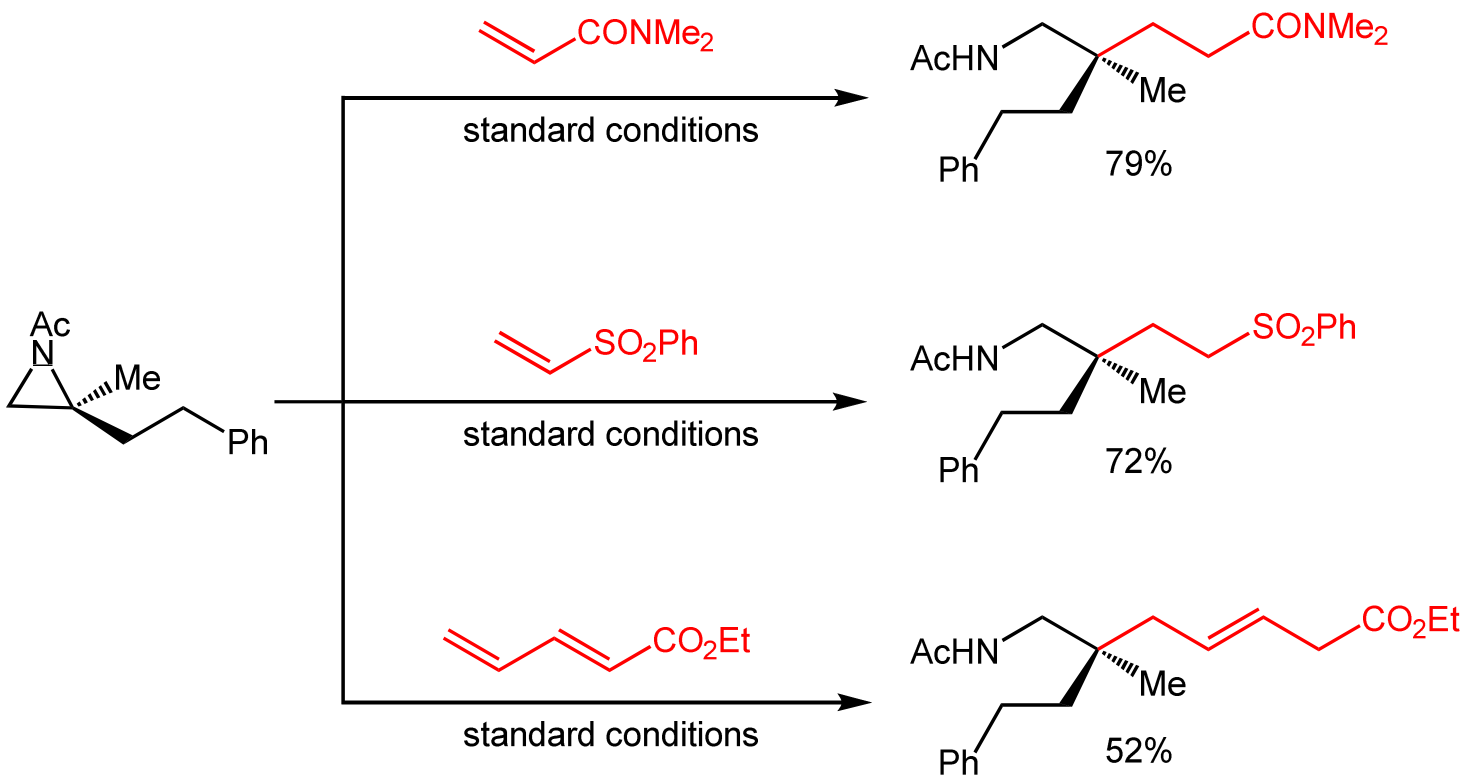


51%

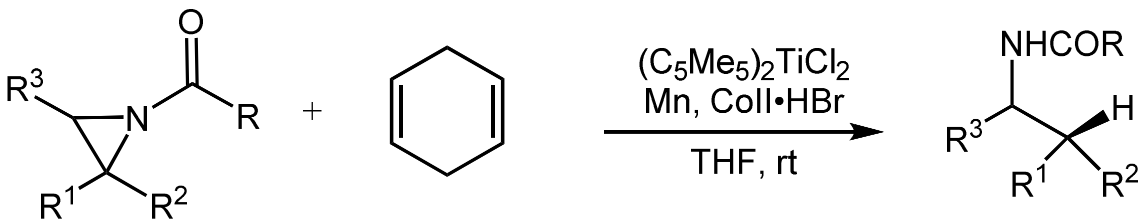


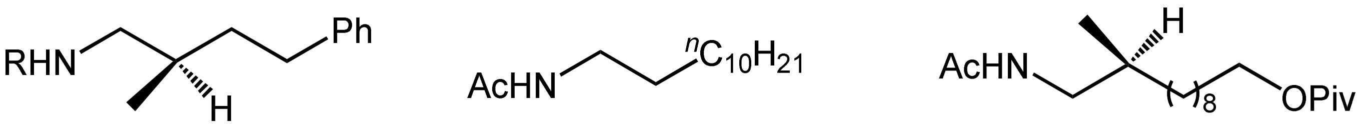
84%

Substrate Scope



Hydrogen-atom Transfer





R = Ac, 76%
R = Boc, 84%

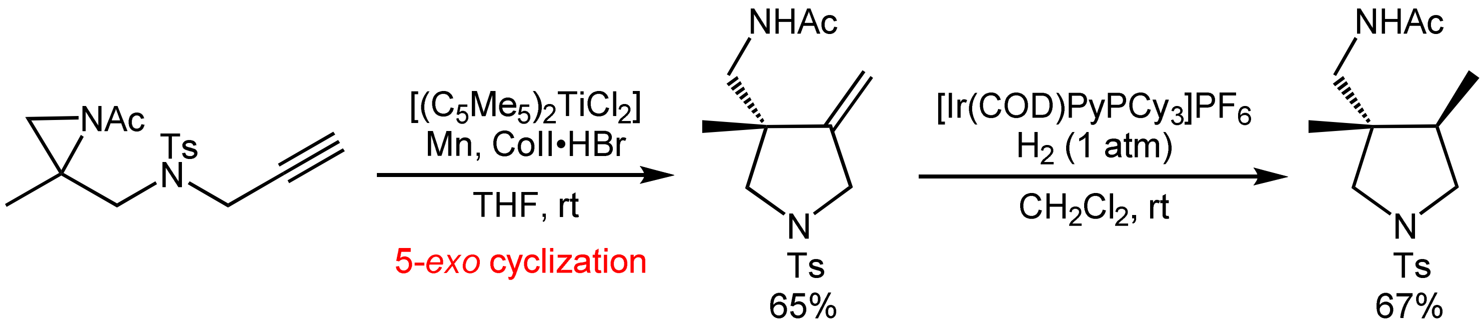
55%

78%

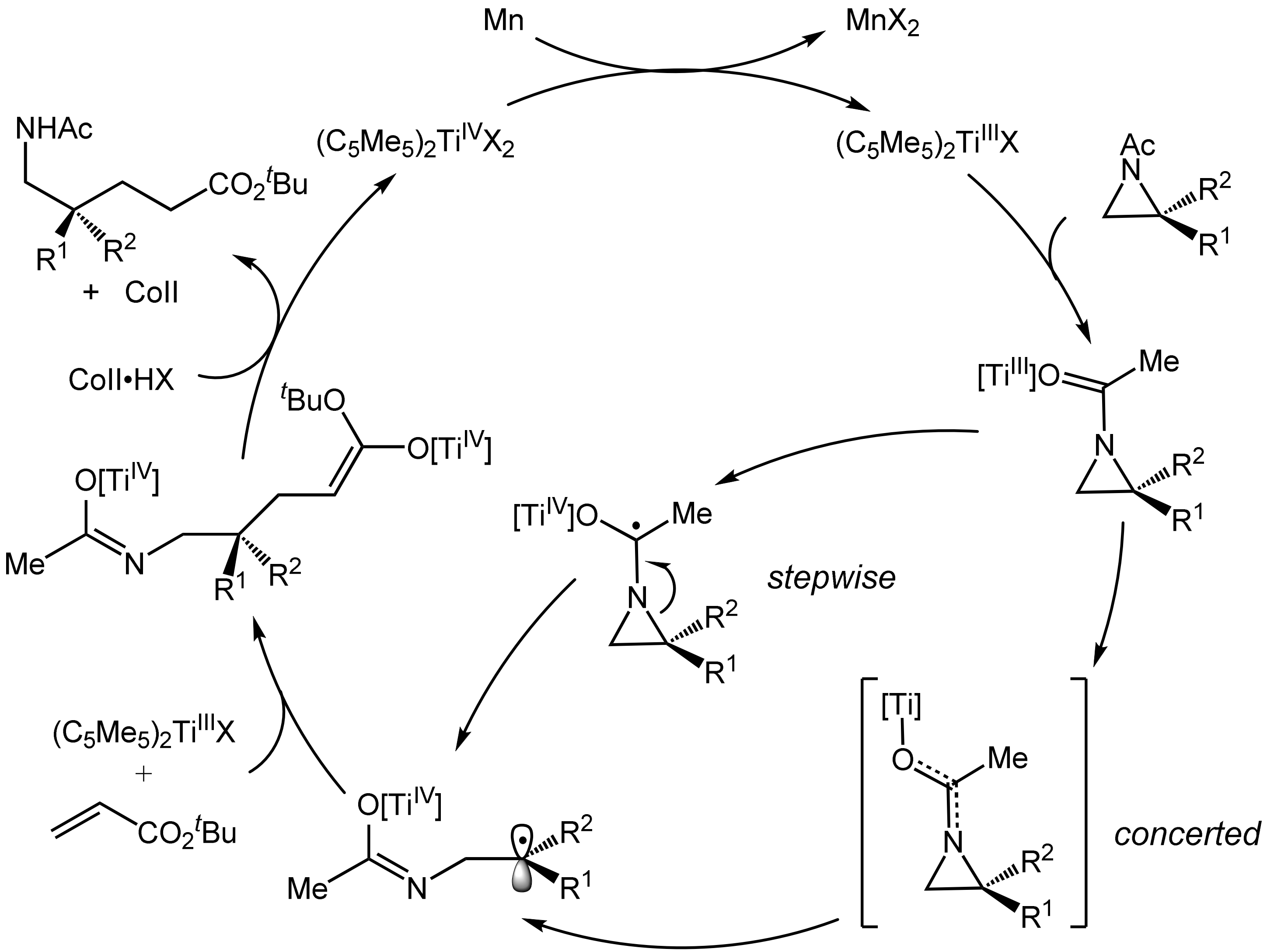
74%

79%

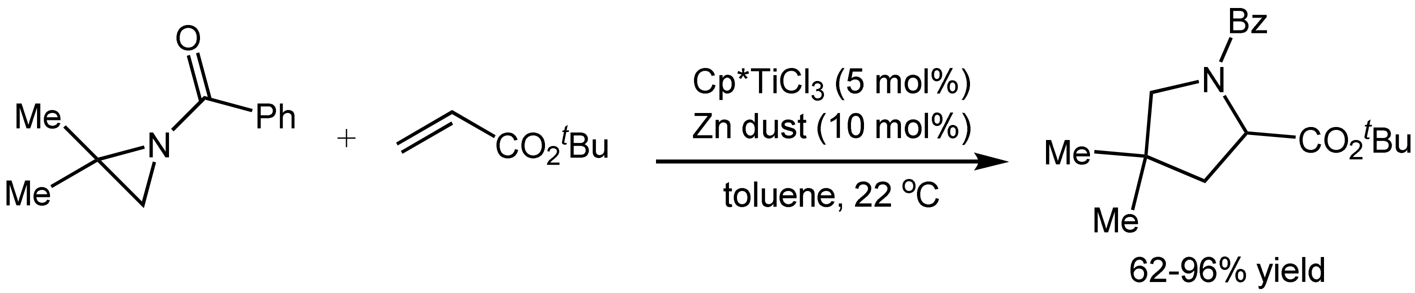
Cyclization of Aziridines



Proposed Mechanism



Summary



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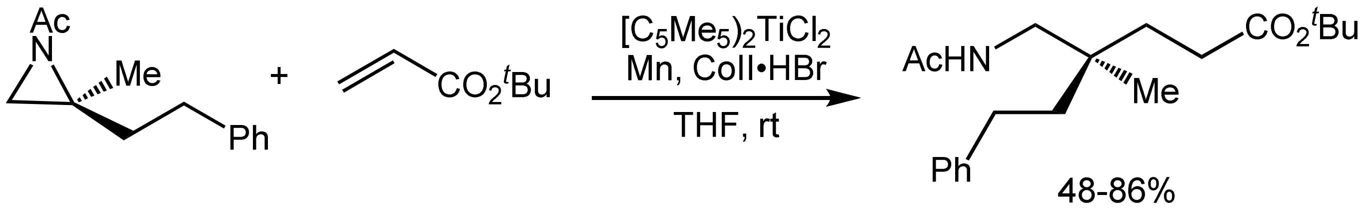

Gansäuer, A. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 12654.

The first paragraph

Owing to the presence of nitrogen-containing motifs in the vast majority of medicinally relevant synthetic targets, the development of efficient, selective, and sustainable technologies for constructing these organic structures is of critical importance. The ring opening of aziridines represents an attractive approach for the synthesis of novel nitrogenous molecules. The tendency of these strained heterocycles to rupture at two distinct reactive sites offers unique opportunities for the efficient introduction of new functionalities.

The last paragraph

In summary, we developed a Ti-catalyzed radical formal [3+2] cycloaddition of *N*-acylaziridines with alkenes in high yield and with complete regioselectivity. This method offers an efficient approach to the synthesis of pyrrolidines: structural motifs frequently observed in bioactive natural products, synthetic pharmaceuticals, and molecular catalysts. The overall redox-neutral reaction was achieved using a redox-relay strategy, harnessing radical intermediates for selective C-N cleavage and formation. We anticipate that this new strategy will be widely applicable for overcoming other synthetic challenges involving overall redox-neutral reactions.