Stereoretentive Radical Cross-Coupling via a Redox-Neutral Mechanism

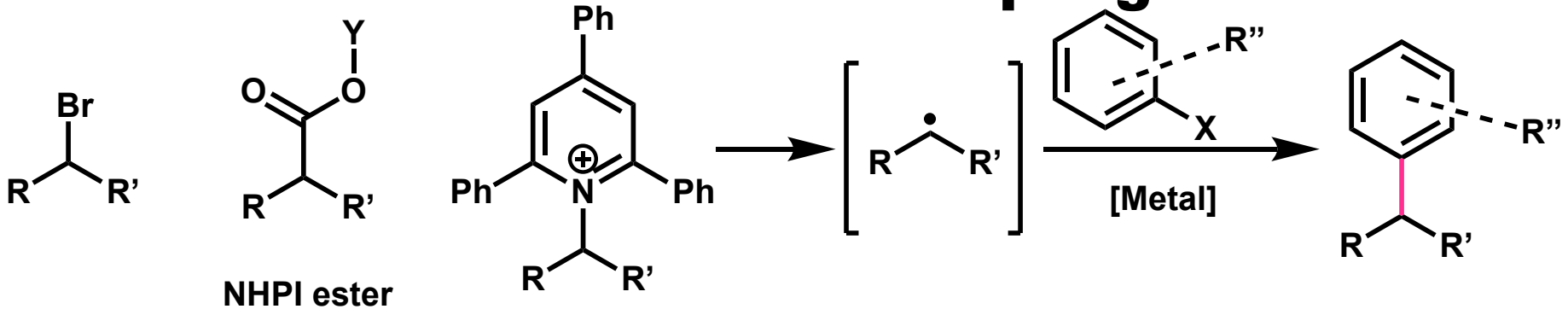
2025.12.6 Literature Seminar

M1 Kaede Ono

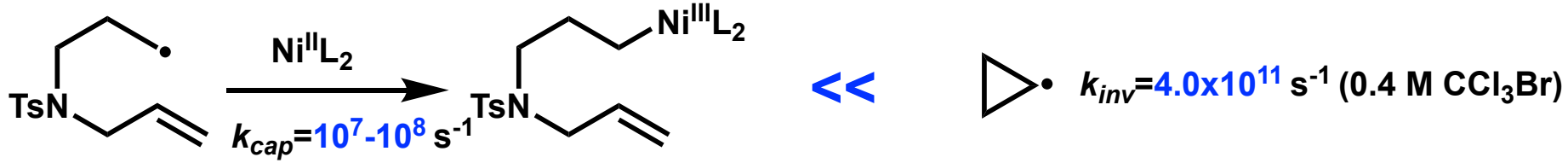
Contents

Contents

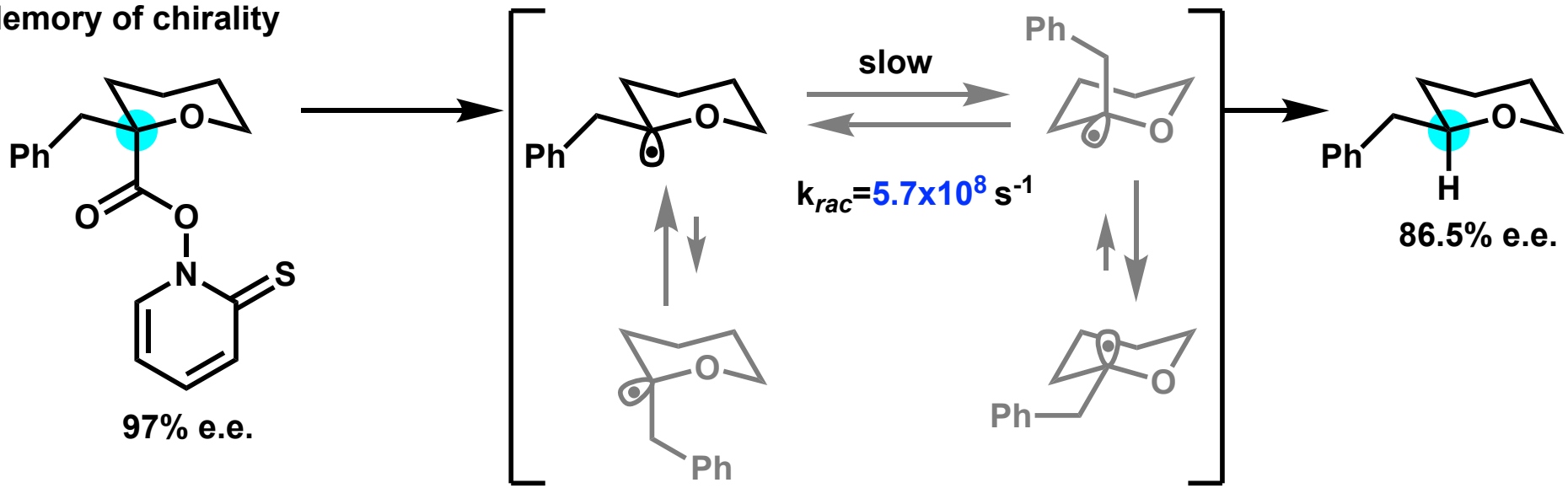
Radical Cross-Coupling



halide | NHPI ester carboxylic acid | Katrizky salt



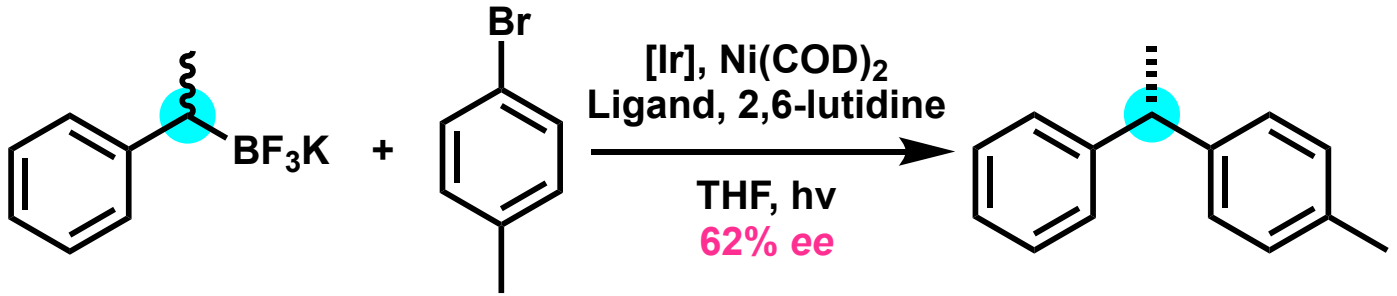
· Memory of chirality

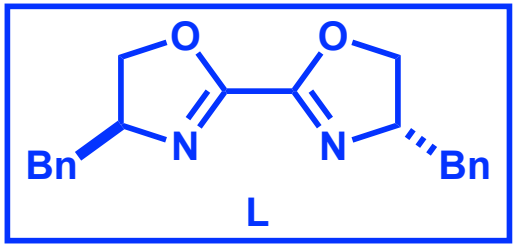


1) Kochi, J. K.; Morrell, D. G. *J. Am. Chem. Soc.* **1975**, *97*, 7262.
2) Gloor, C. S.; Dénès, F.; Renaud, P. *Free Radical Res.* **2016**, *50*, S102.
3) Spielvogel, E. H.; Yuan, J.; Hoffmann, N. M.; Diao, T. *J. Am. Chem. Soc.* **2025**, *147*, 19632.

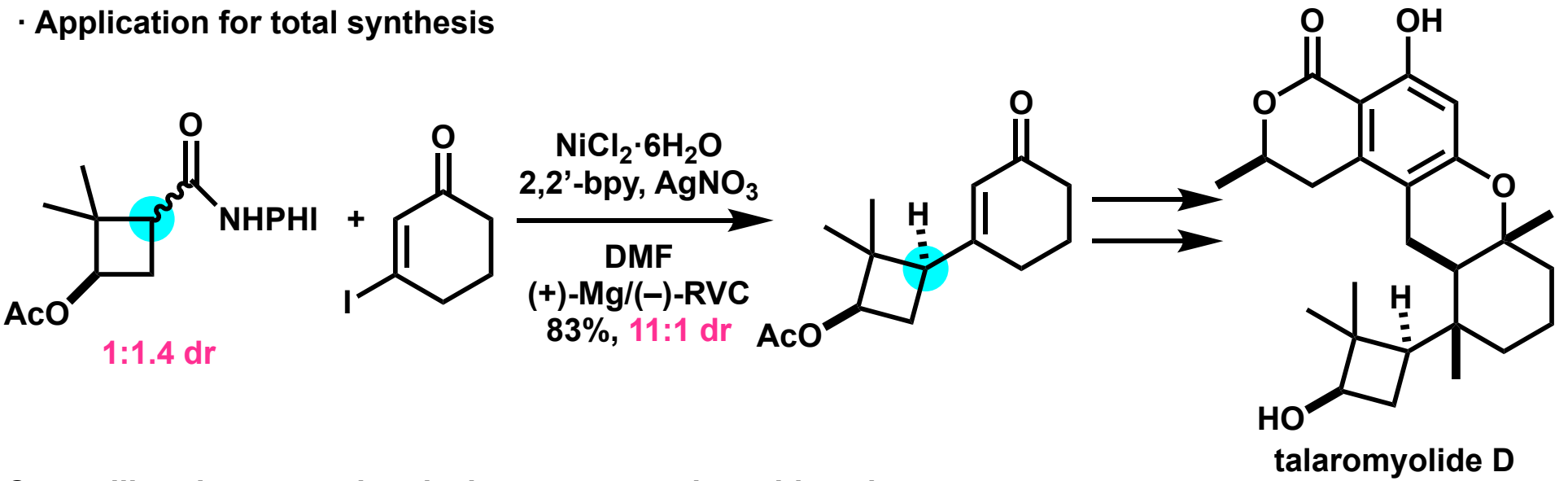
Stereo-selective Radical Cross-Coupling

· Enantio-selective radical cross-coupling





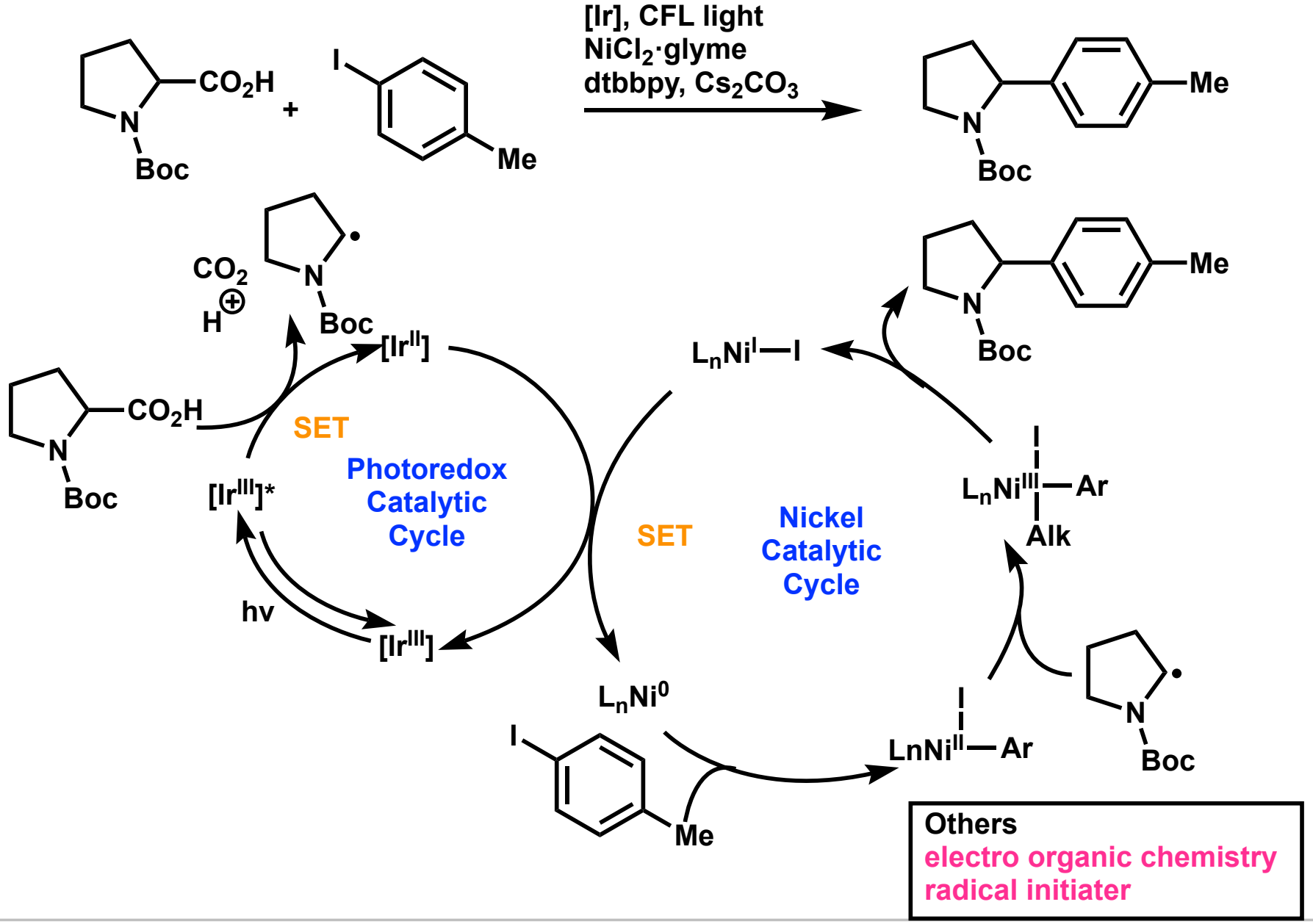
· Application for total synthesis



Controlling the stereochemical outcome can be achieved only on a case-by-case basis using chiral ligands or in a diastereoselective fashion guided by nearby stereocenters.

1) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2015**, 137, 4896.
2) Qin, B,; Szyperek, A.; Tomanik, M. *J. Am. Chem. Soc.,* **2025**, *147*, 31221.

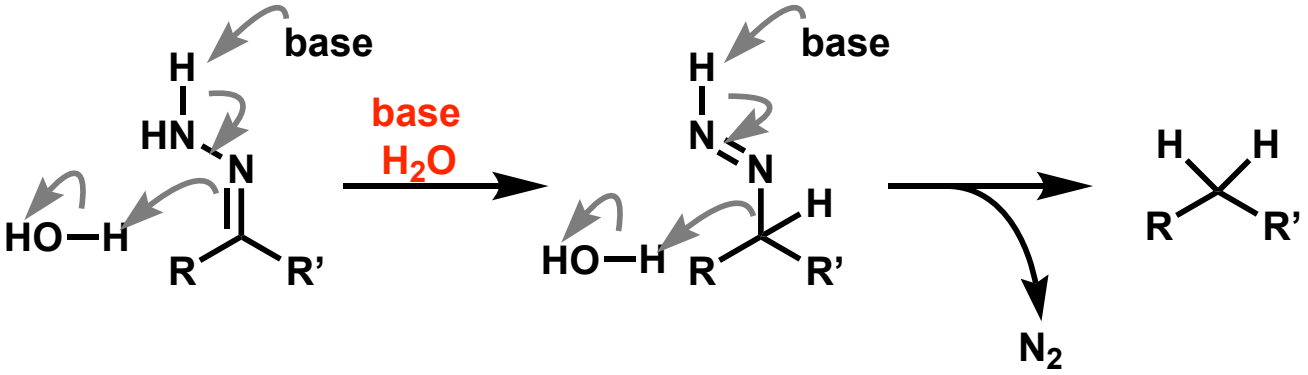
Iridium Catalyzed Decarboxylative Coupling



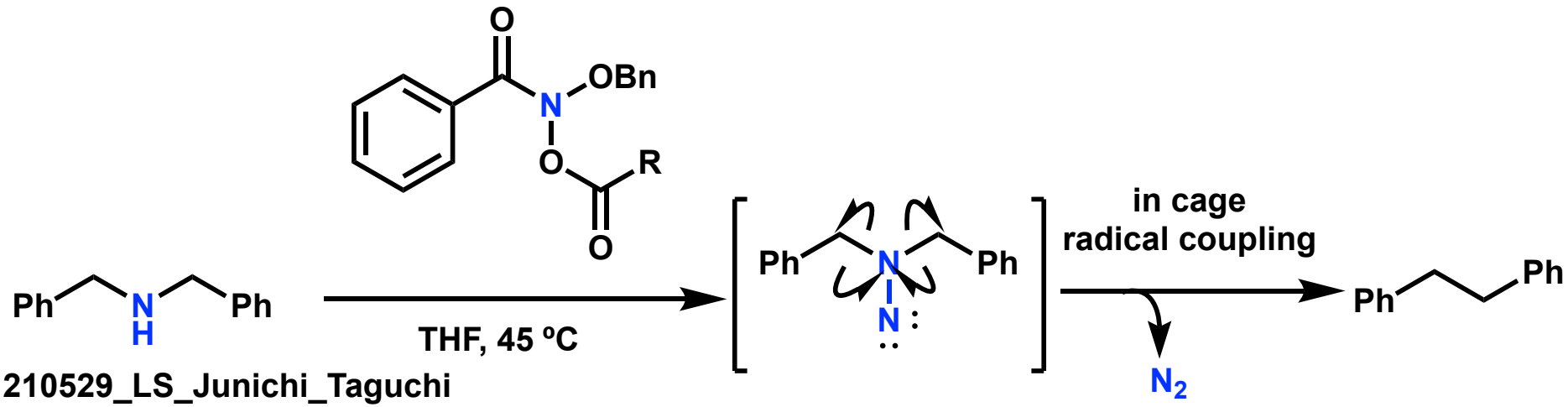
1) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437.

Nitrogen Deleting Reaction

· **Wolff-Kishner Reduction**



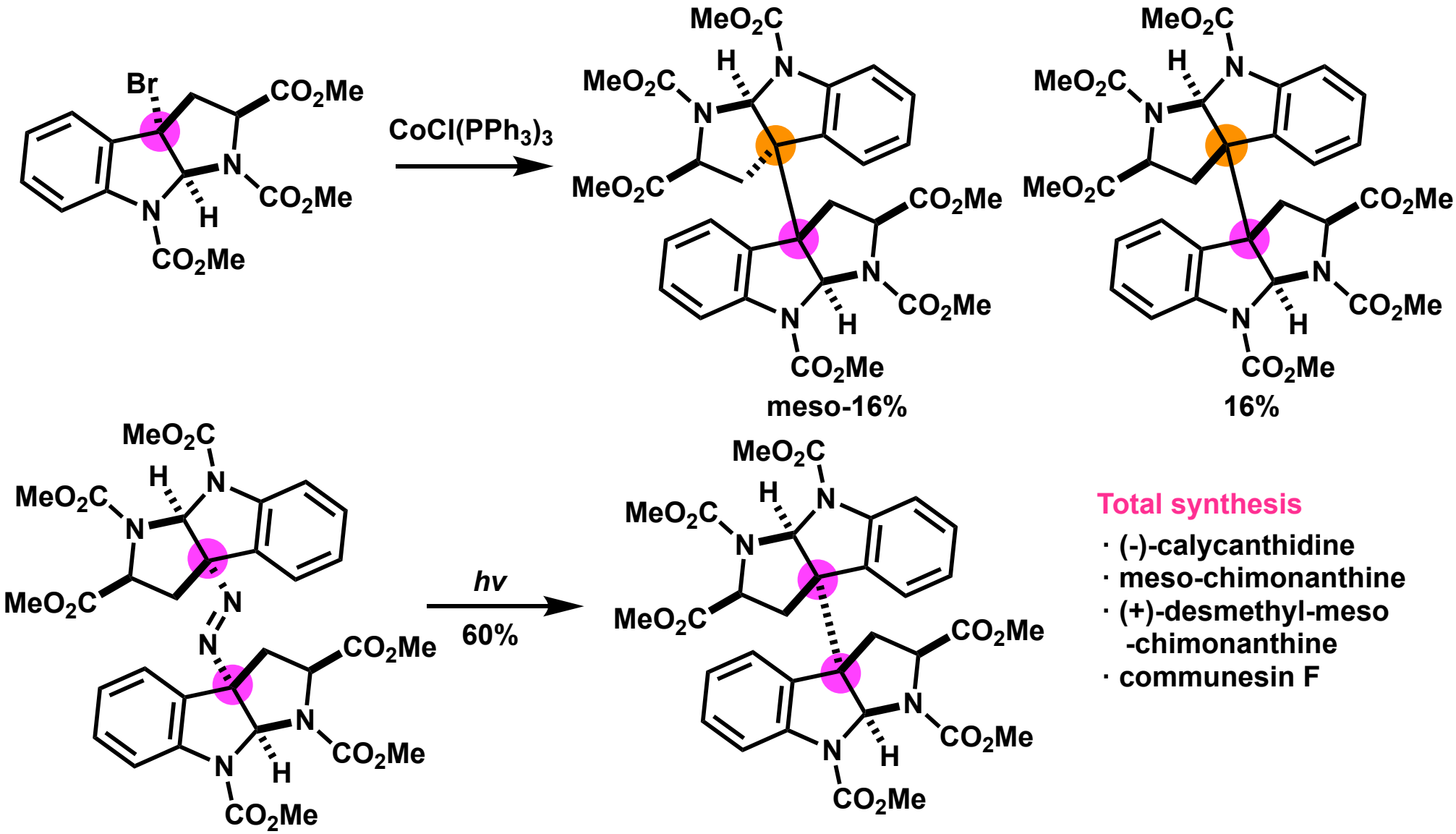
· **Skeltal editing through direct nitrogen deletion**



210529_LS_Junichi_Taguchi

1) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature* **2021**, *593*, 223.

Stereoretentive Nitrogen Deleting Coupling



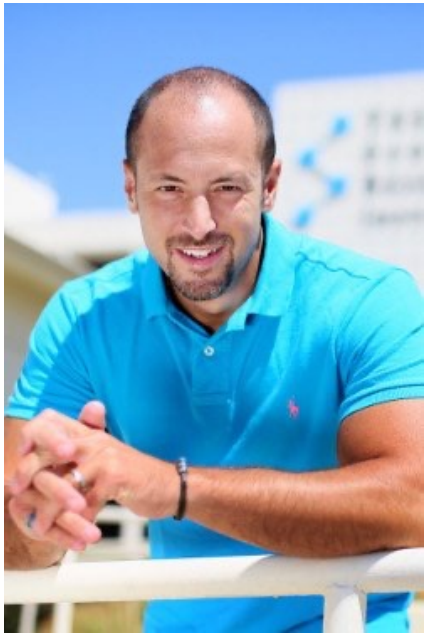
Total synthesis

- (-)-calycanthidine
- meso-chimonanthine
- (+)-desmethyl-meso -chimonanthine
- communesin F

1) Lathrop, S. P.; Kim, J.; Movassaghi, M. *Chimia* **2012**, *66*, 389.
2) Lathrop, S. P.; Movassaghi, M. *Chem. Sci*. **2014**, *5*, 333.
3) Lathrop, S. P.; Pompeo, M.; Chang, W. T. T. *J. Am. Chem. Soc.* **2016**, *138*, 7763.

Contents

Introduction of Prof. Baran



Prof. Phil S. Baran

Career:

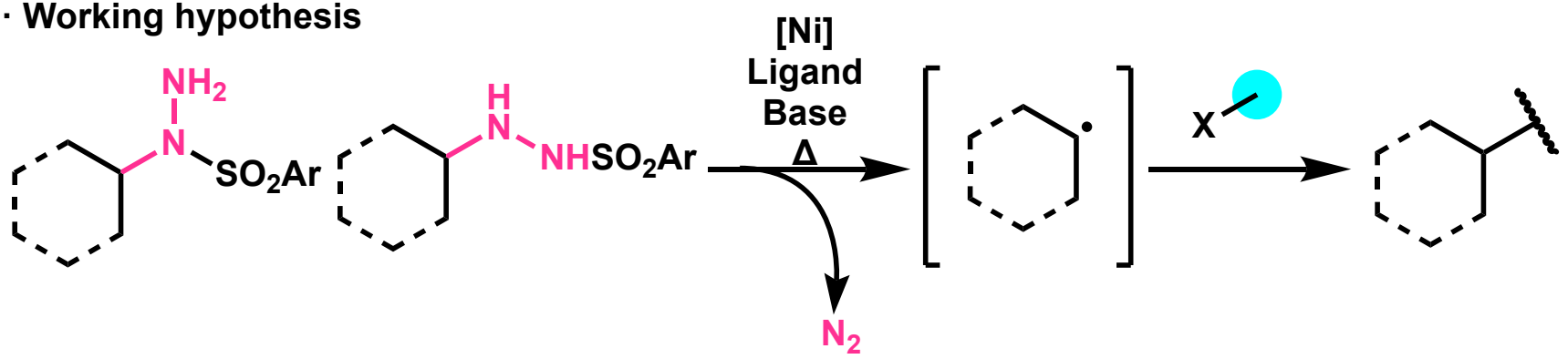
1995-1997 B.S. @New York University (Prof. D. I. Schuster)
1997-2001 Ph.D @the Scripps Research institute (Prof. K. C. Nicolaou)
2001-2003 Postdoc. @Harvard University (Prof. E. J. Corey)
2003-2006 Assistant Professor @the Scripps Research institute
2006-2008 Associate Professor @the Scripps Research institute
2008- Professor @the Scripps Research institute

Research topics:

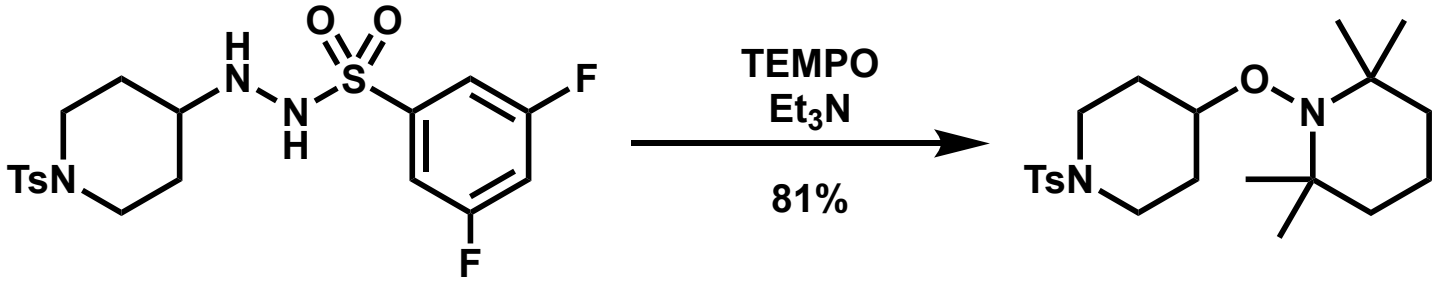
Total synthesis, New reaction methodology (electrochemistry)

Working Hypothesis

· Working hypothesis



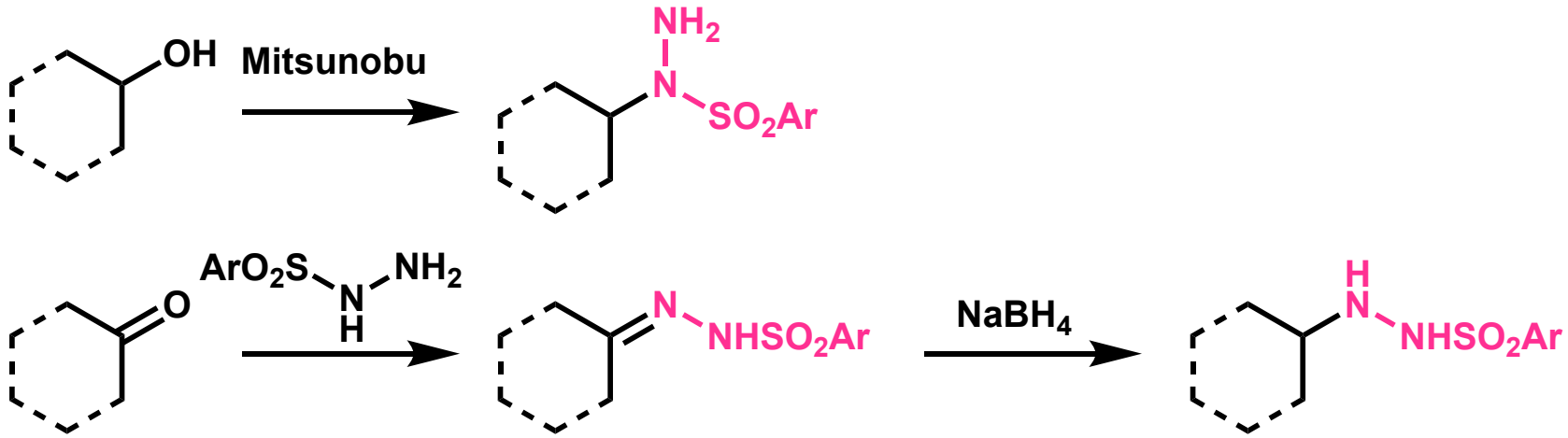
· Ni-free TEMPO trapping



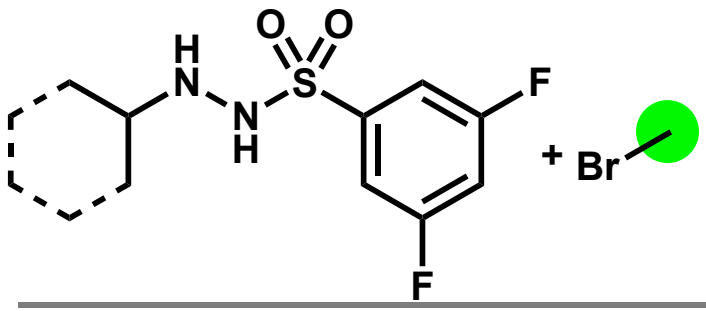
1) Sun, J.; Péter, A.´.; He, J.; Tsien, J.; Zhang, H.; Cagan, D. A.; Vokits, B. P.; Peters, D. S.; Oderinde, M. S.; Mandler, M. D.; Richardson, P.; Chen, D.; Palkowitz, M. D.; Raheja, N.; Kawamata, Y.; Baran, P. S. *Science* **2025**, *387*, 1377.

Substrate Scope (1)

· Preparation of substrates



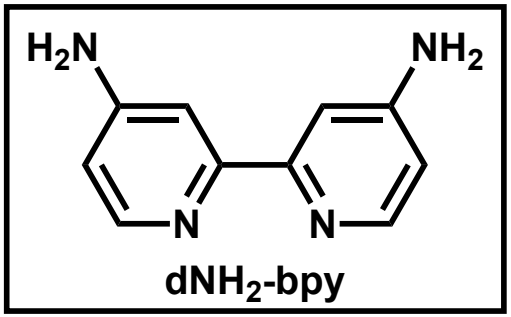
· Substrate scope



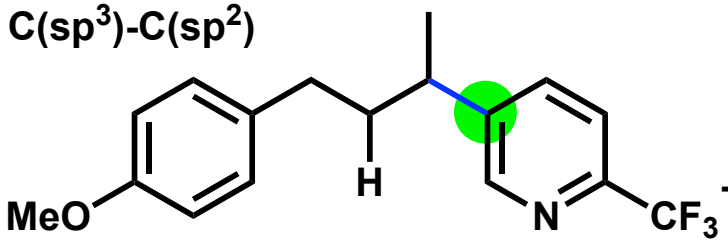
+ Br

Ni(dme)Cl_2 (20 mol%)
dNH_2-bpy (20 mol%)
Et_3N (3.0 equiv)

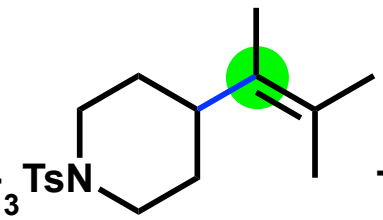
DMF
60 °C or 75 °C, 10-16 h



$C(sp^3)$-$C(sp^2)$

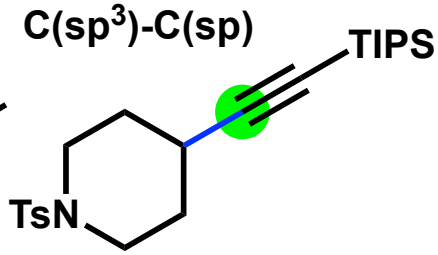


(63%)



(23%)

$C(sp^3)$-$C(sp)$

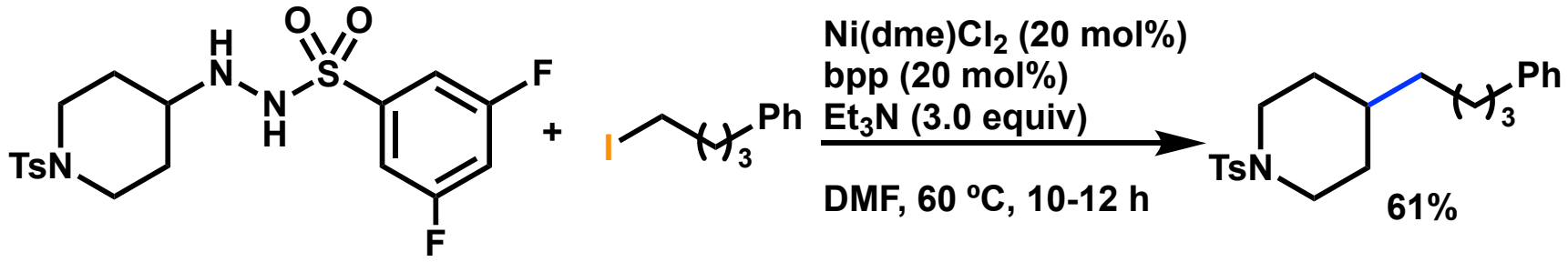


(40%)

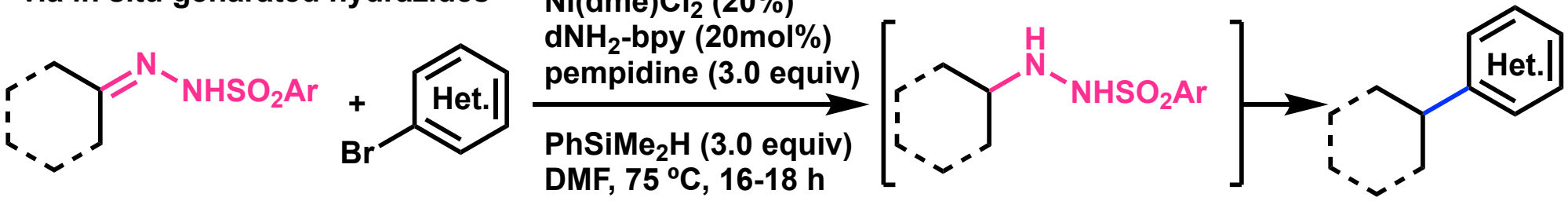
1) Sun, J.; et al. *Science* **2025**, *387*, 1377.

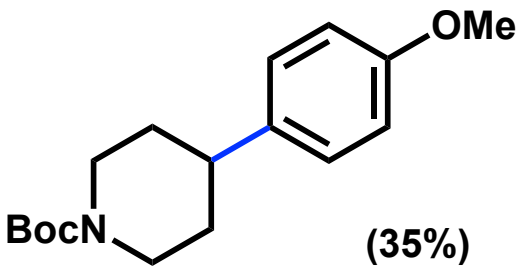
· C(sp^3)-C(sp^3)

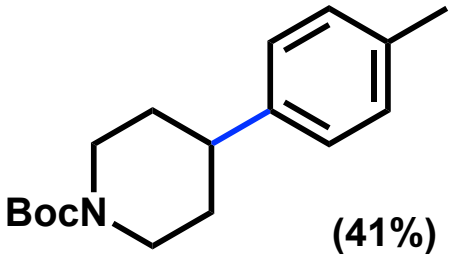
Substrate Scope (2)

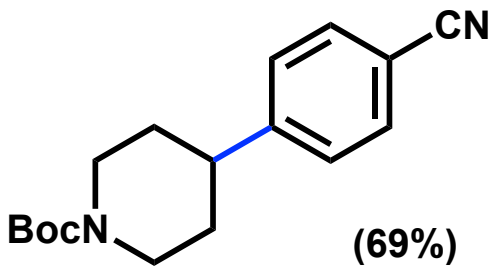


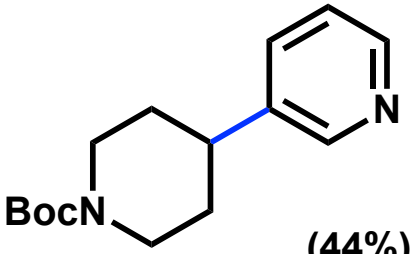
· via in situ genarated hydrazides

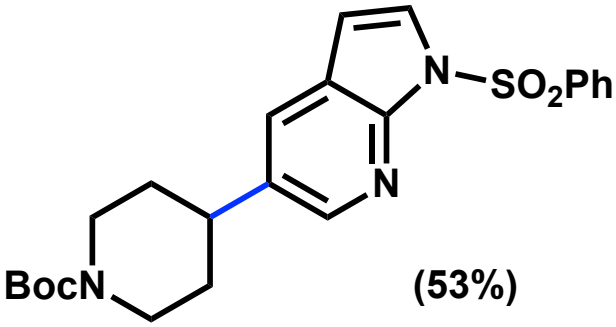


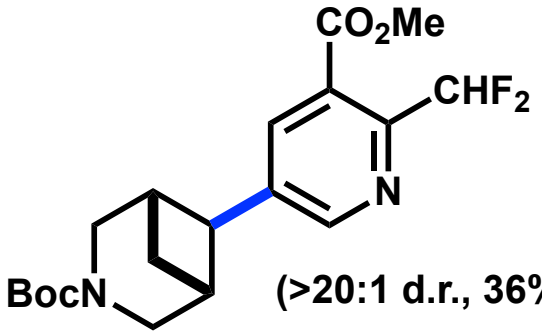

(35%)


(41%)


(69%)


(44%)

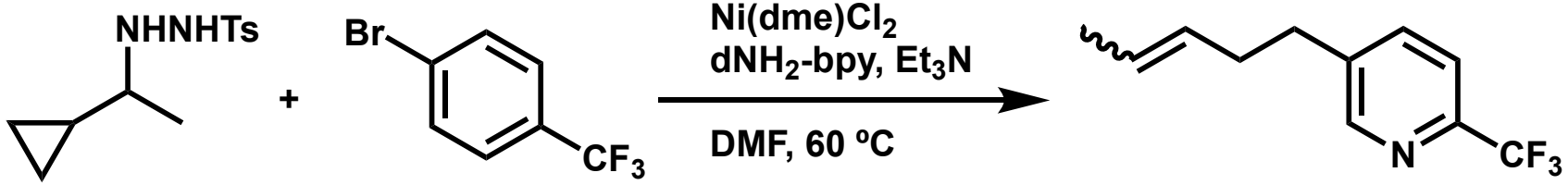

(53%)


(>20:1 d.r., 36%)

1) Sun, J.; et al. *Science* **2025**, *387*, 1377.

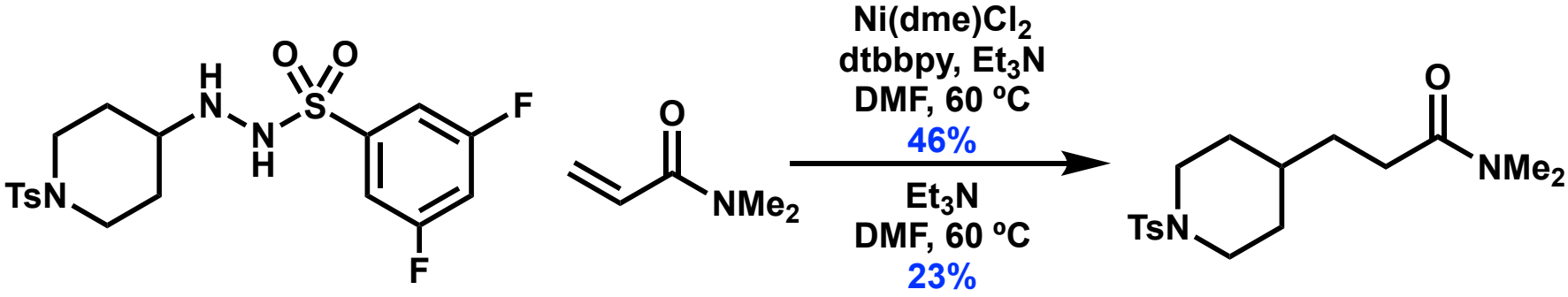
Mechanistic Study

· Cyclopropane opening



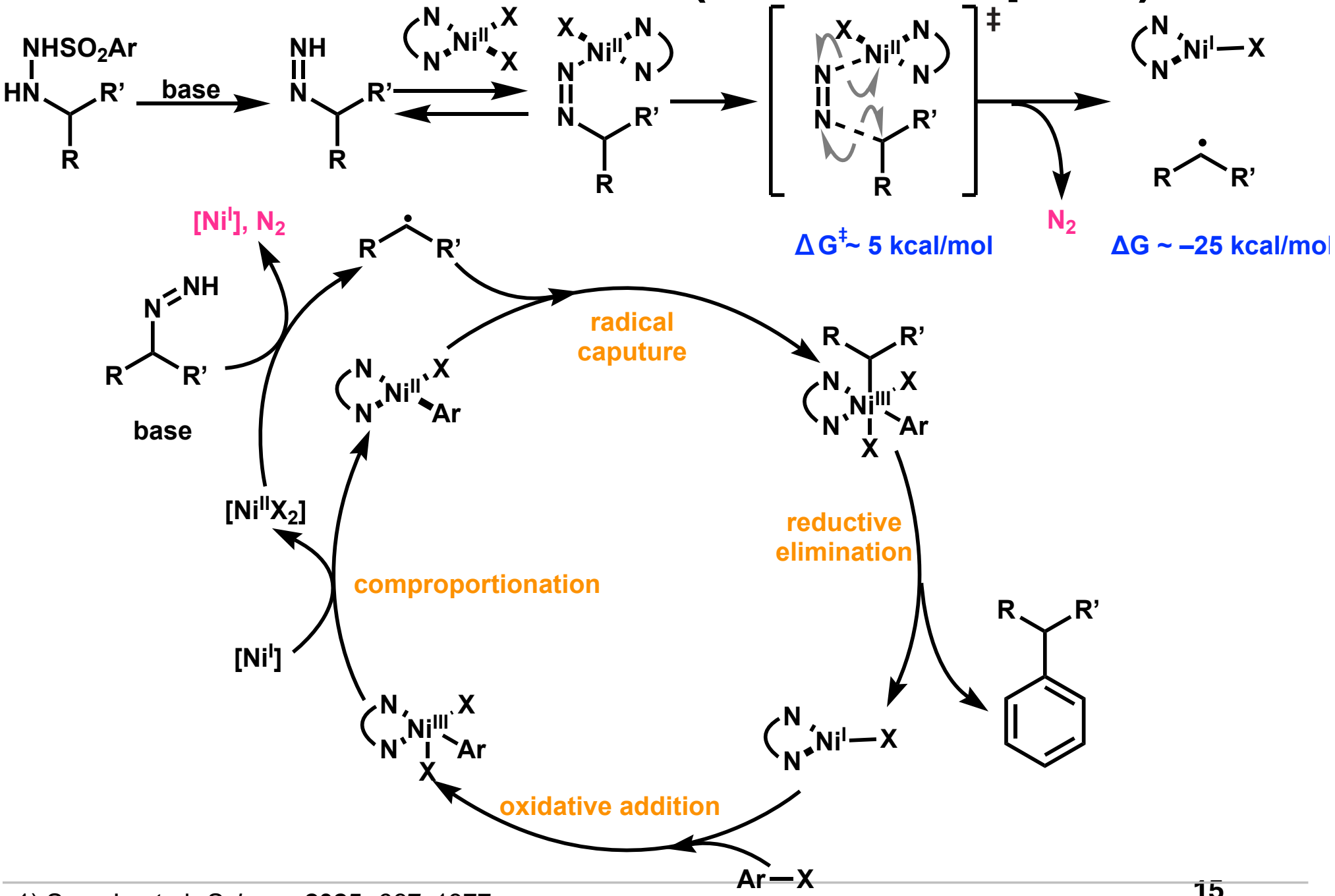
66% (Z/E, 1:1.4)

· Giese type reaction



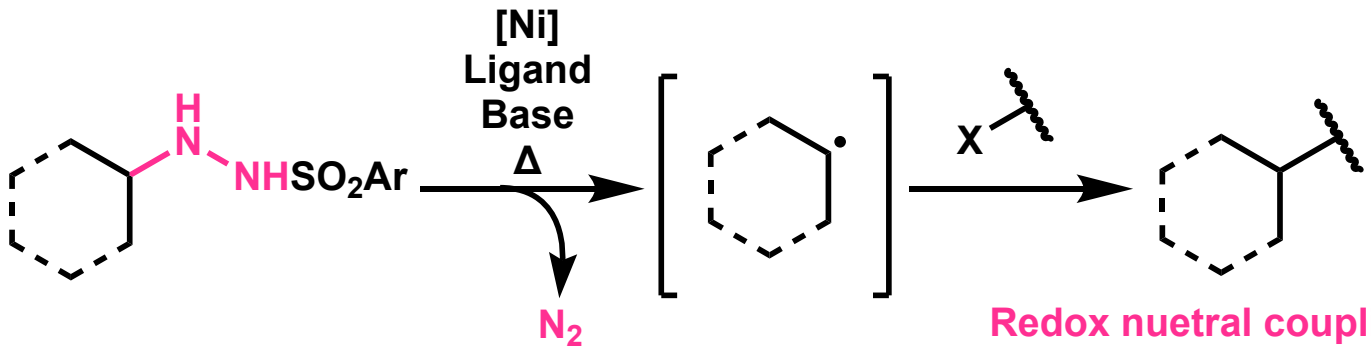
1) Sun, J.; et al. *Science* **2025**, *387*, 1377.

Reaction Mechanism (Author's Proposal)



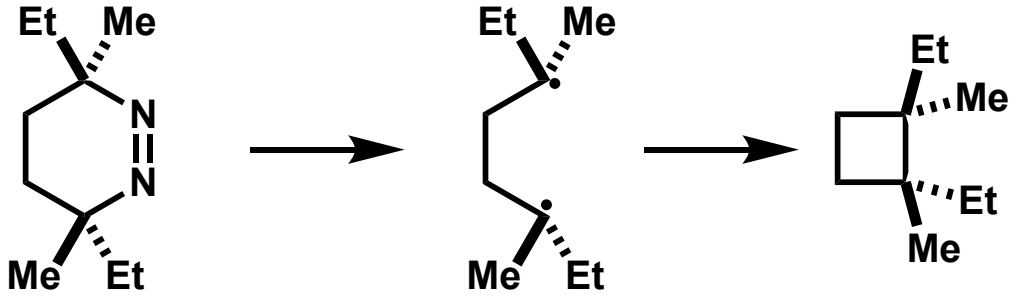
1) Sun, J.; et al. *Science* **2025**, *387*, 1377.

Key Point in This Lecture

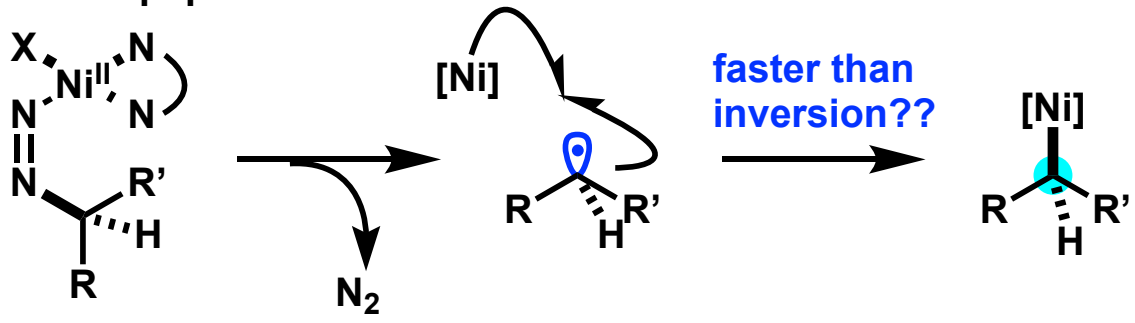


· In-cage enantiospecific couping

Enantioselective coupling is not achieved yet.



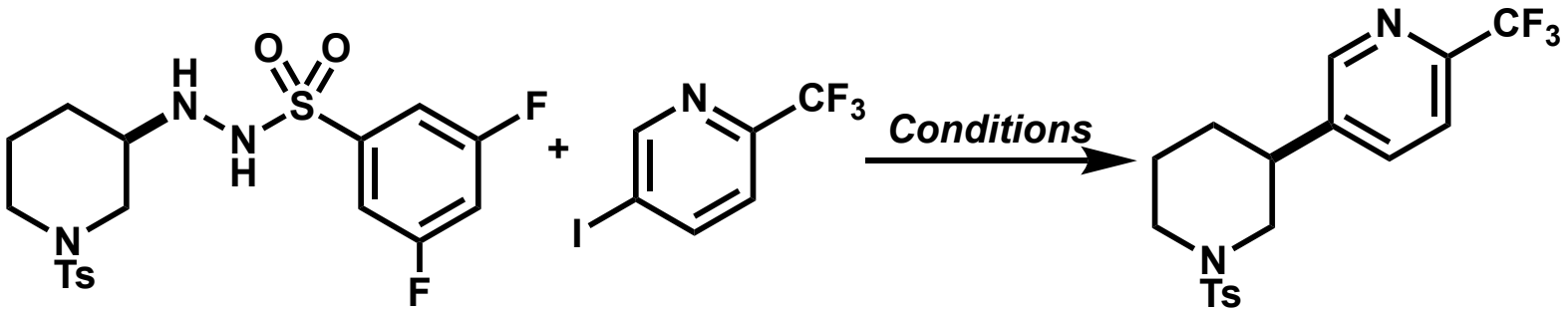
· Working hypothesis of main paper



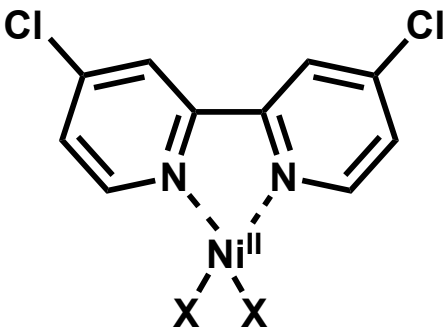
1) Sun, J.; et al. *Science* **2025**, *387*, 1377.
2) Hinsberg, W. D. I.; Schultz, P. G.; Dervan, P. B. *J. Am. Chem. Soc.***1982**, *104*, 766.

Contents

Effect of Reaction Conditions on Enantioretentivity



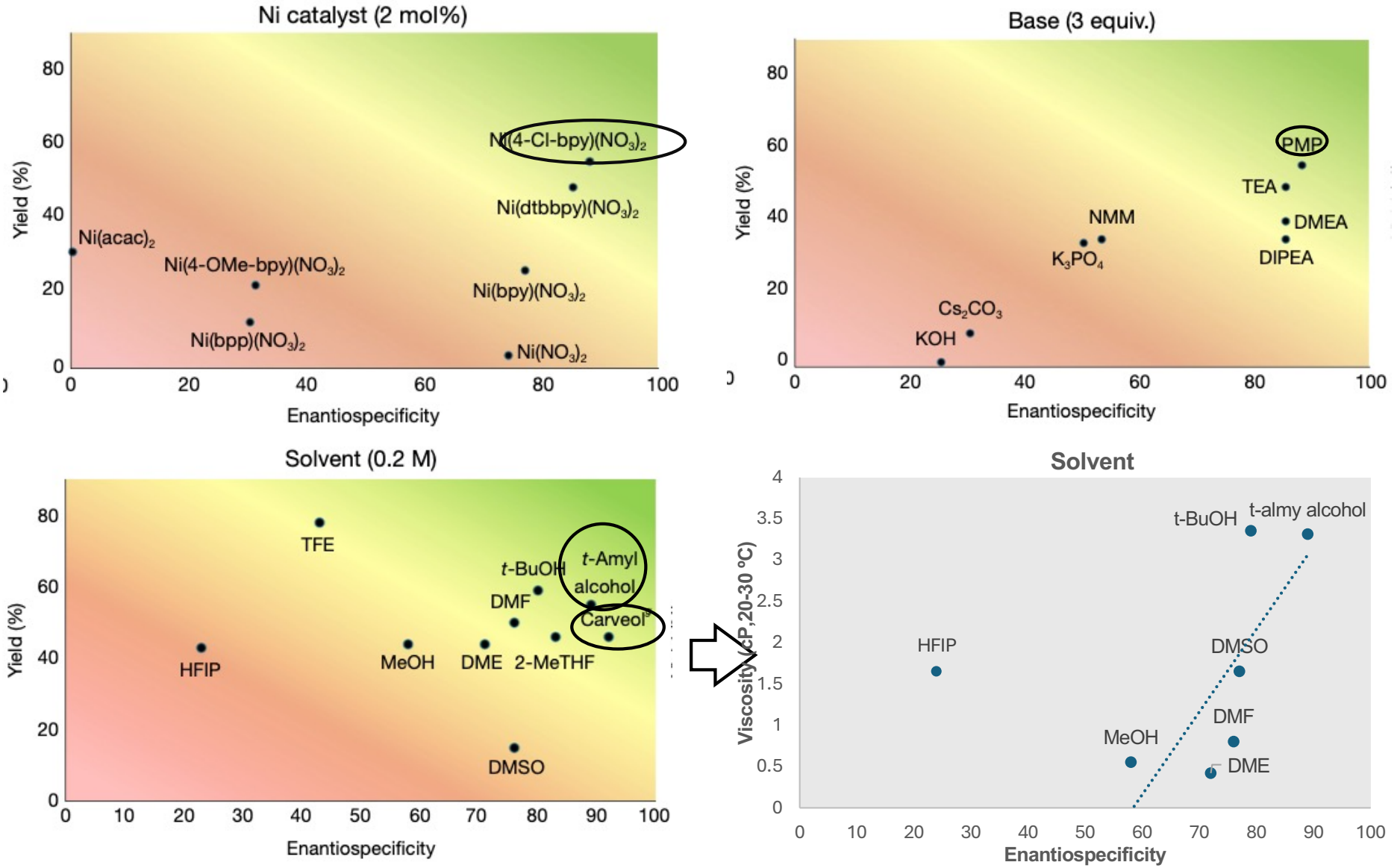
Conditions	yield	e.e.
$Ni^{II}(dme)Cl_2$ (20 mol%) dtbbpy (20 mol%) Et_3N (3.0 equiv) DMF, 60 °C	54%	39% e.e.
$Ni^{II}(4,4'\text{-Cl-bpy})(NO_3)_2$ (2 mol%) PMP (3.0 equiv) *t*-Amyl alcohol, 40 °C	55%	89% e.e.
$Ni^{II}(4,4'\text{-Cl-bpy})Br_2$ (2 mol%) PMP (3.0 equiv) *cis/trans*-(–)-carveol, 30 °C	46%	92% e.e.



$Ni^{II}(4,4'\text{-Cl-bpy})(X)_2$

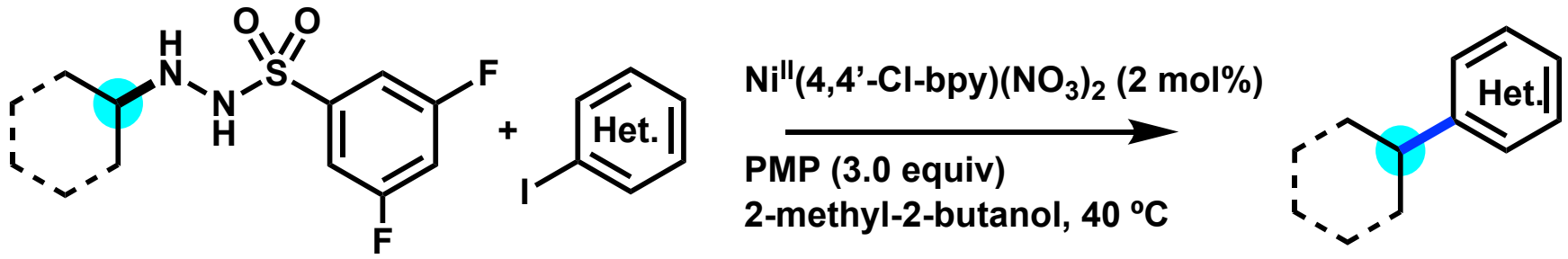
1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

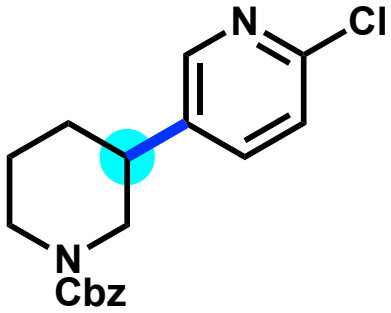
Optimization of the Conditions (1)



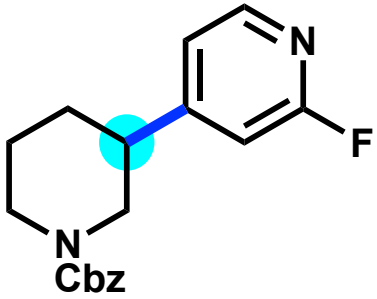
1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

Substrate Scope

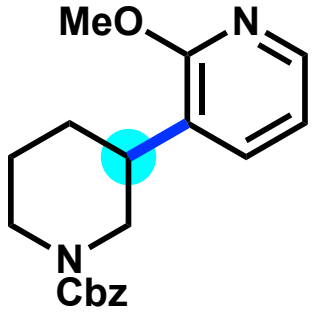




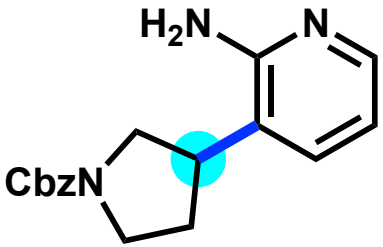
57%
85% e.e.



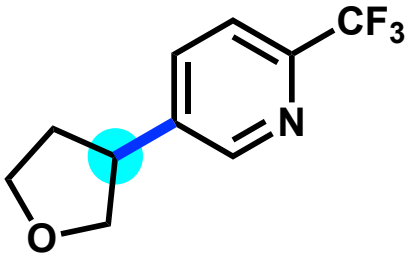
41%
86% e.e.



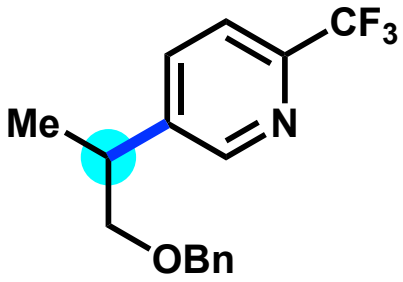
42%
84% e.e.



37%
88% e.e.



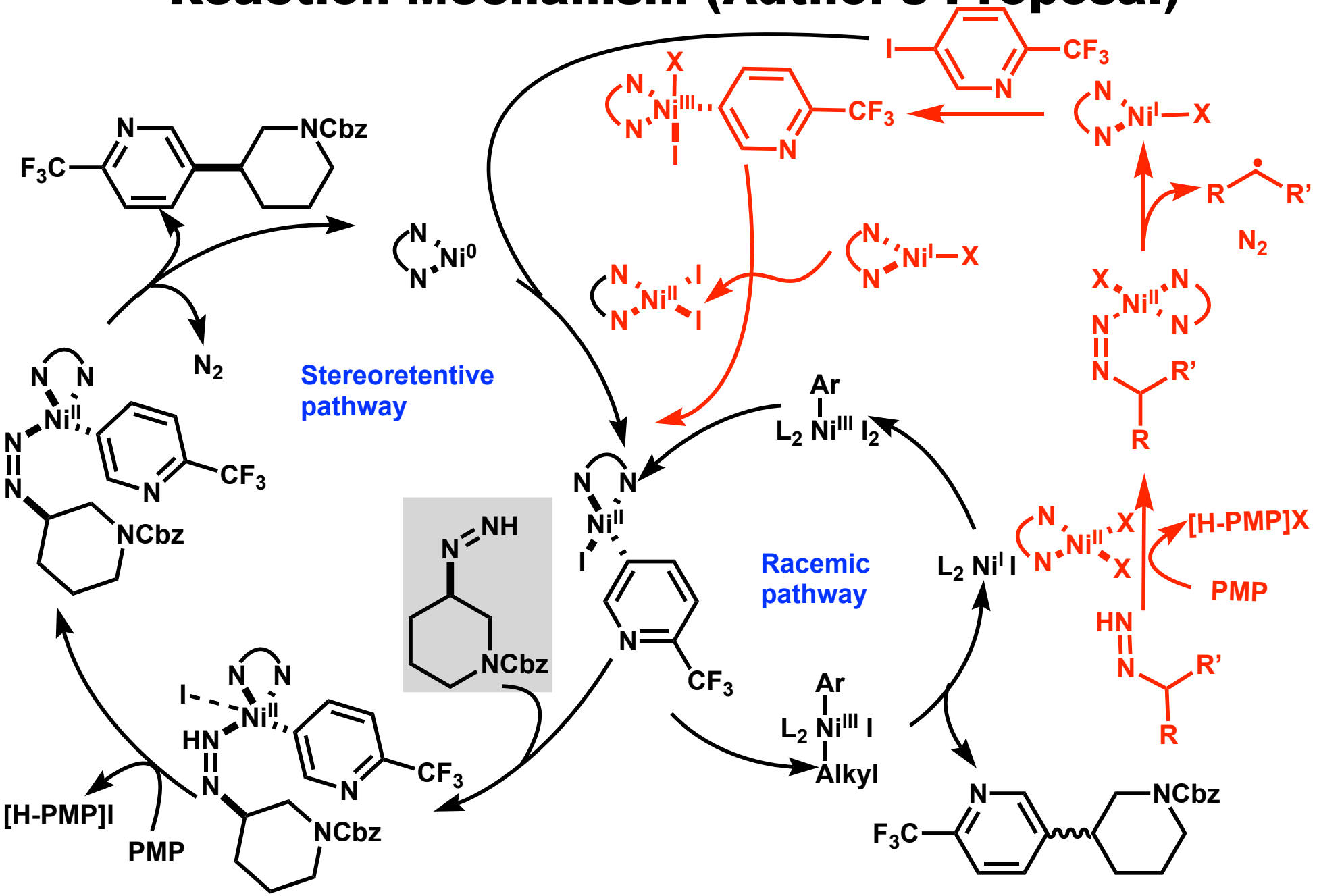
35%
67% e.e.



47%
56% e.e.

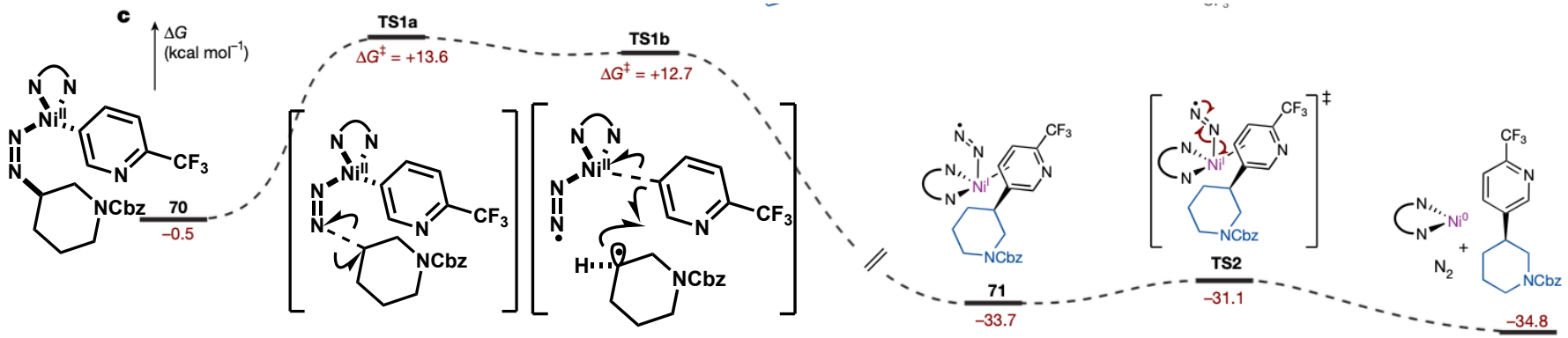
1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

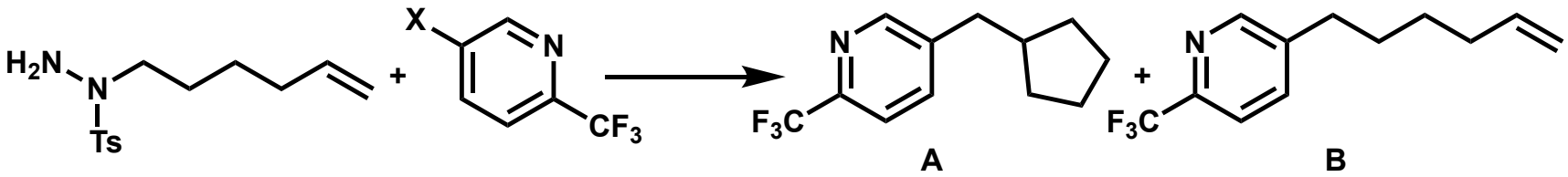
Reaction Mechanism (Author's Proposal)



1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

Mechanistic Study





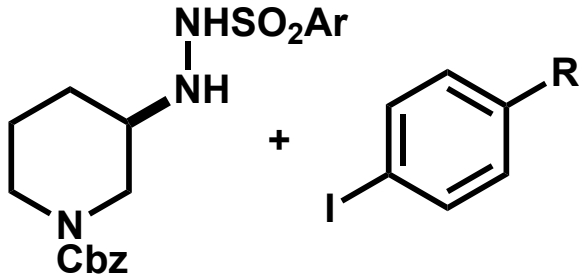
X	Conditions		A / B
Br	PMP (3 eq) Ni(dClbpy)$(NO_3)_2$ (1-10 mol%) 2-Methyl-2-butanol (0.2 M) 40 ºC		0.24~0.30
I	Et_3N (3 eq) Ni(DME)Cl_2 (20 mol%) dtbbpy (20 mol%) DMF (0.2 M), 70 ºC	t-Bu	1.75

The coupling occurs independently of the Ni catalyst concentration.

1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

Limitations (1)

· Limitation of Aryl halides



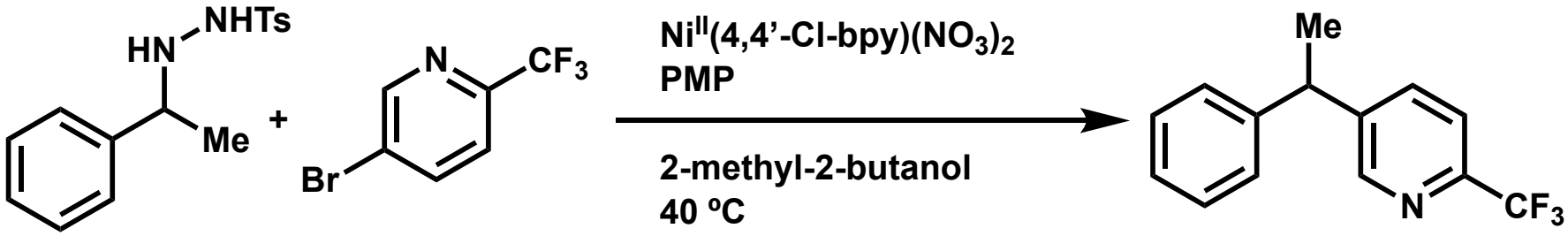
91% e.e.

electron-deficient

R	yield	e.e.
OMe	5%	61% e.e.
H	10%	64% e.e.
CHO	21%	72% e.e.
CN	34%	81% e.e.

Electron-deficient aryl groups give higher yields and ee.

· Limitation of Alkyl hydrazine

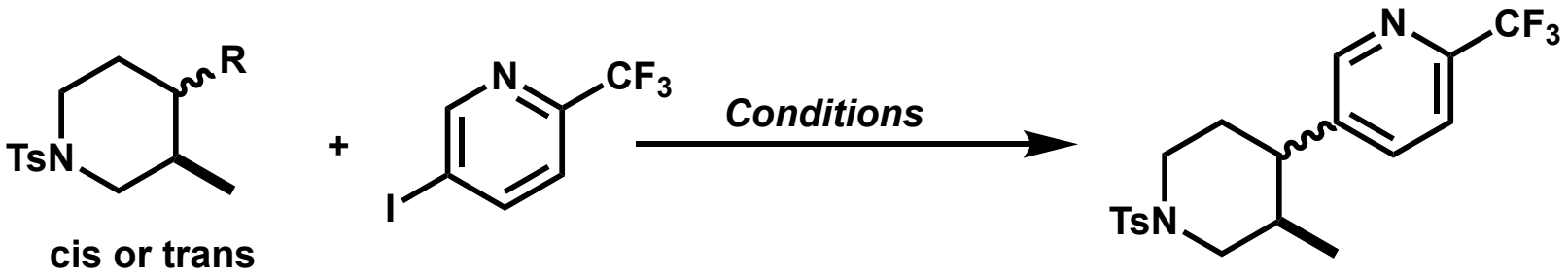


99% e.e.

50%, 7% e.e.

1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

Limitations (2)

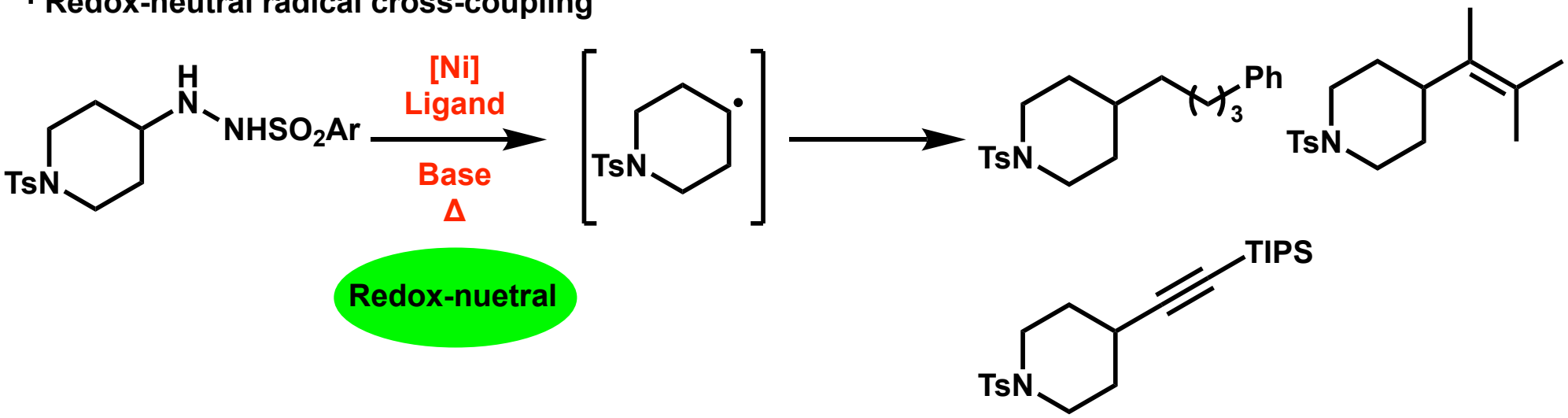


R	cis/trans	*Conditions*	yield	trans:cis
$NHNHSO_2Ar$	trans	Ni^{II}(4,4'-Cl-bpy)$(NO_3)_2$ PMP 2-methyl-2-butanol, 40 °C	46%	>20:1
I	cis	$Ni^{II}(dme)Cl_2$,bpy, $AgNO_3$ (*n*-Bu)$_4$NF, solvent (+)Mg/(–)RVC	33-43%	3:1~10:1
$NHNHSO_2Ar$	cis	Ni^{II}(4,4'-Cl-bpy)$(NO_3)_2$ PMP 2-methyl-2-butanol, 40 °C	44%	1:5

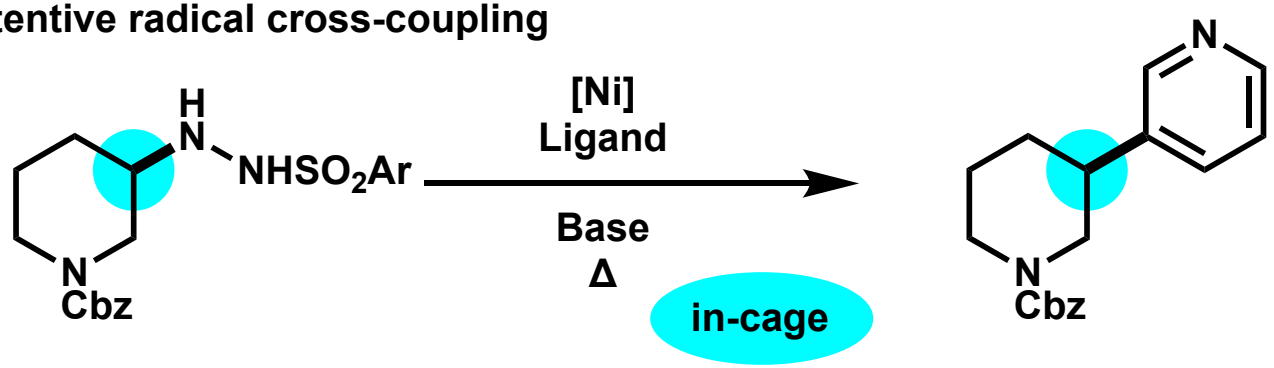
1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

Summary

· Redox-neutral radical cross-coupling



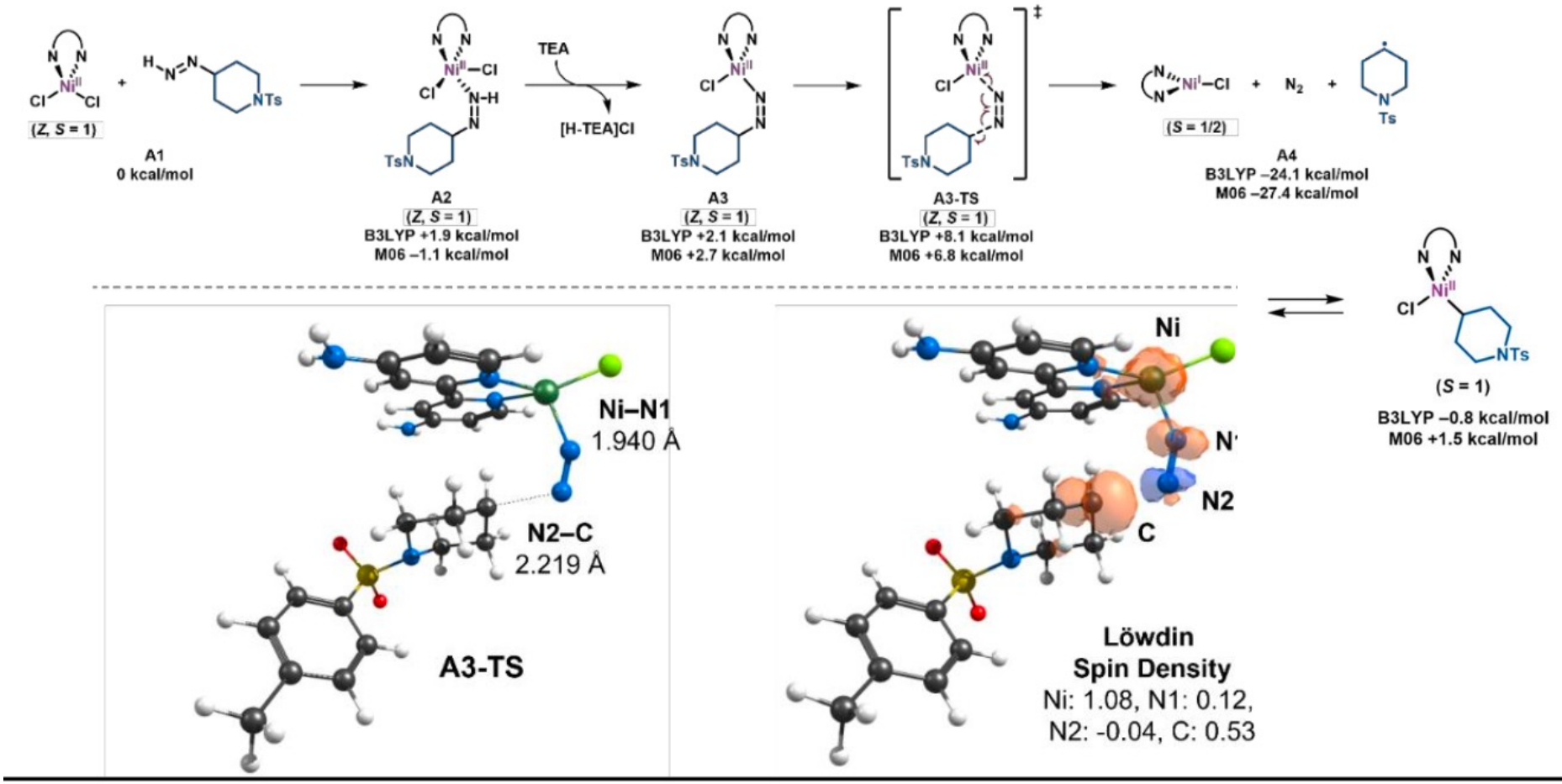
· Stereoretentive radical cross-coupling



1) Sun, J.; et al. *Science* **2025**, *387*, 1377.
2) Sun, J.; et al. *Nature* **2025**, *642*, 85.

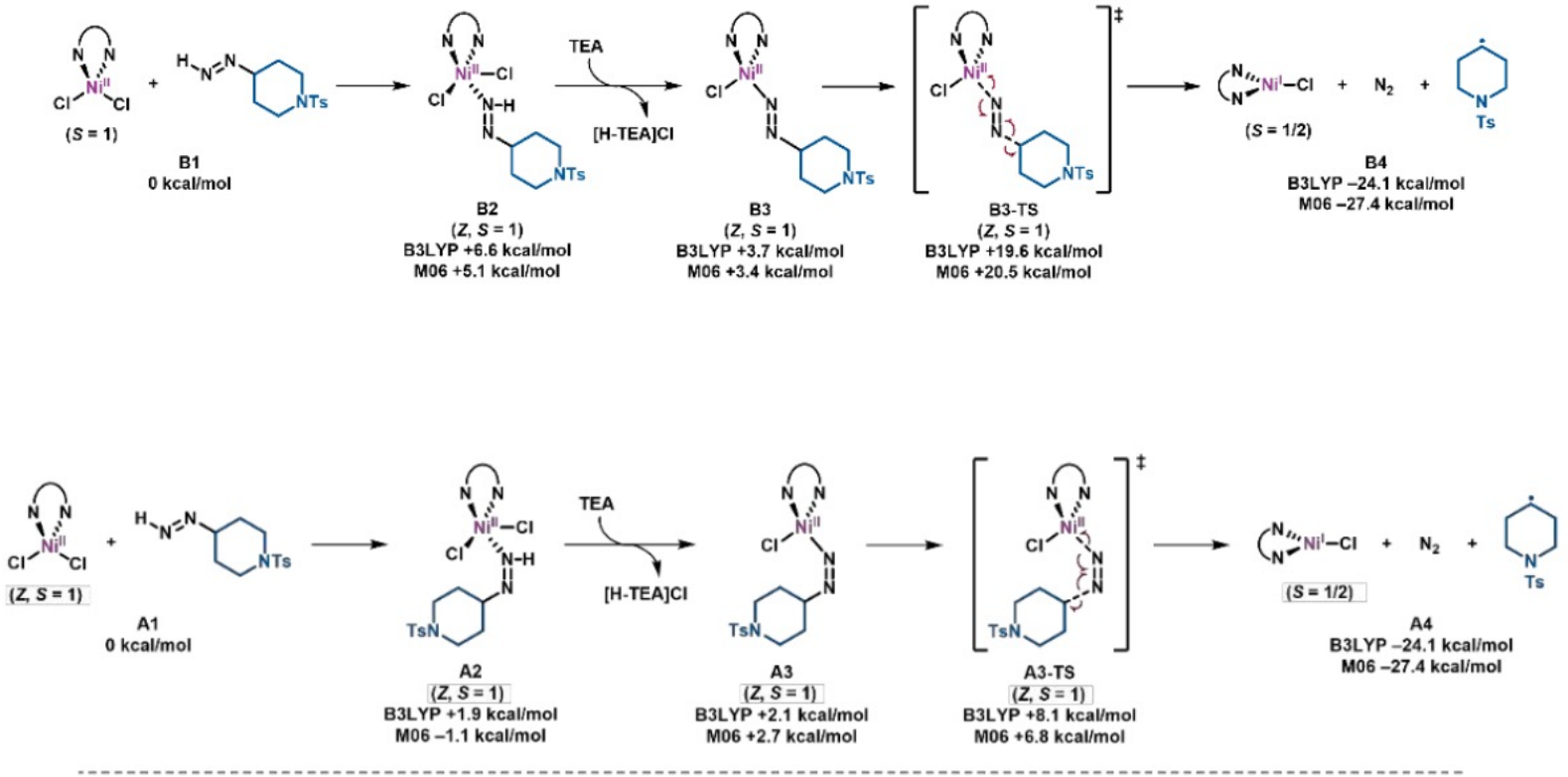
Appendix

Electron Density / Alkyl Radical capture



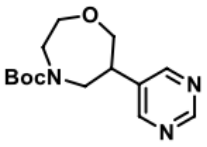
1) Sun, J.; et al. *Science* **2025**, *387*, 1377.

E versus Z coordinated Structure

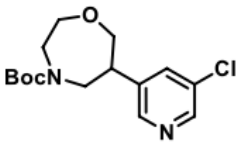


1) Sun, J.; et al. *Science* **2025**, *387*, 1377.

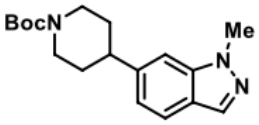
Extended Reaction Scope



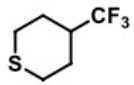
16% (X = Br)



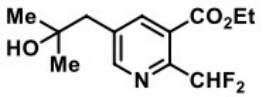
11% (X = Br)



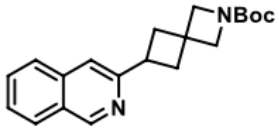
52% (NMR yield, X = Br)



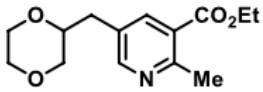
64% NMR yield
(average of 2 runs)



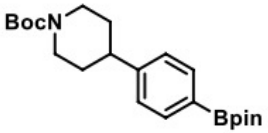
synthetically useful quantities
for med. chem. obtained
(X = Br)



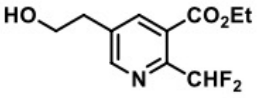
synthetically useful quantities
for med. chem. obtained
(X = Br)



synthetically useful quantities
for med. chem. obtained
(X = Br)



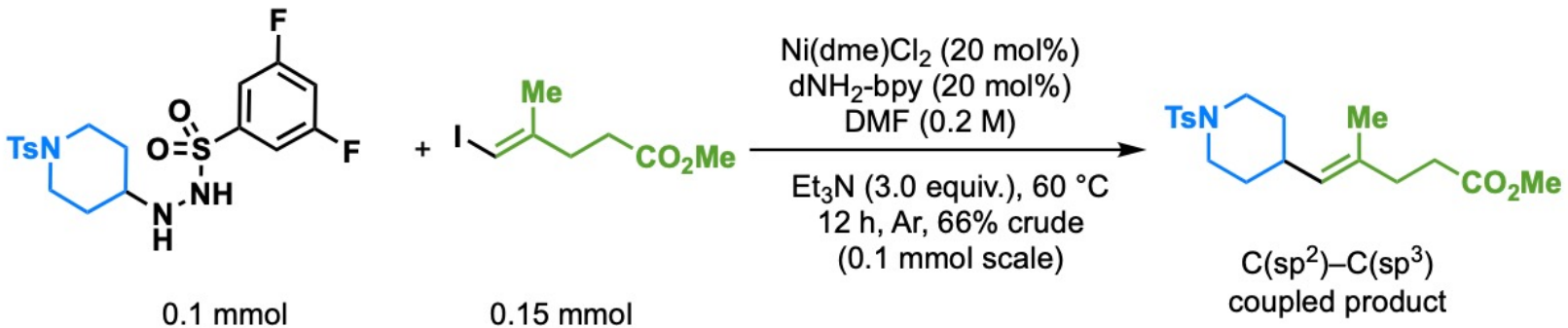
55%



47% (X = Br)
using dF hydrazide regioisomeric mix

1) Sun, J.; et al. *Science* **2025**, *387*, 1377.

Optimization

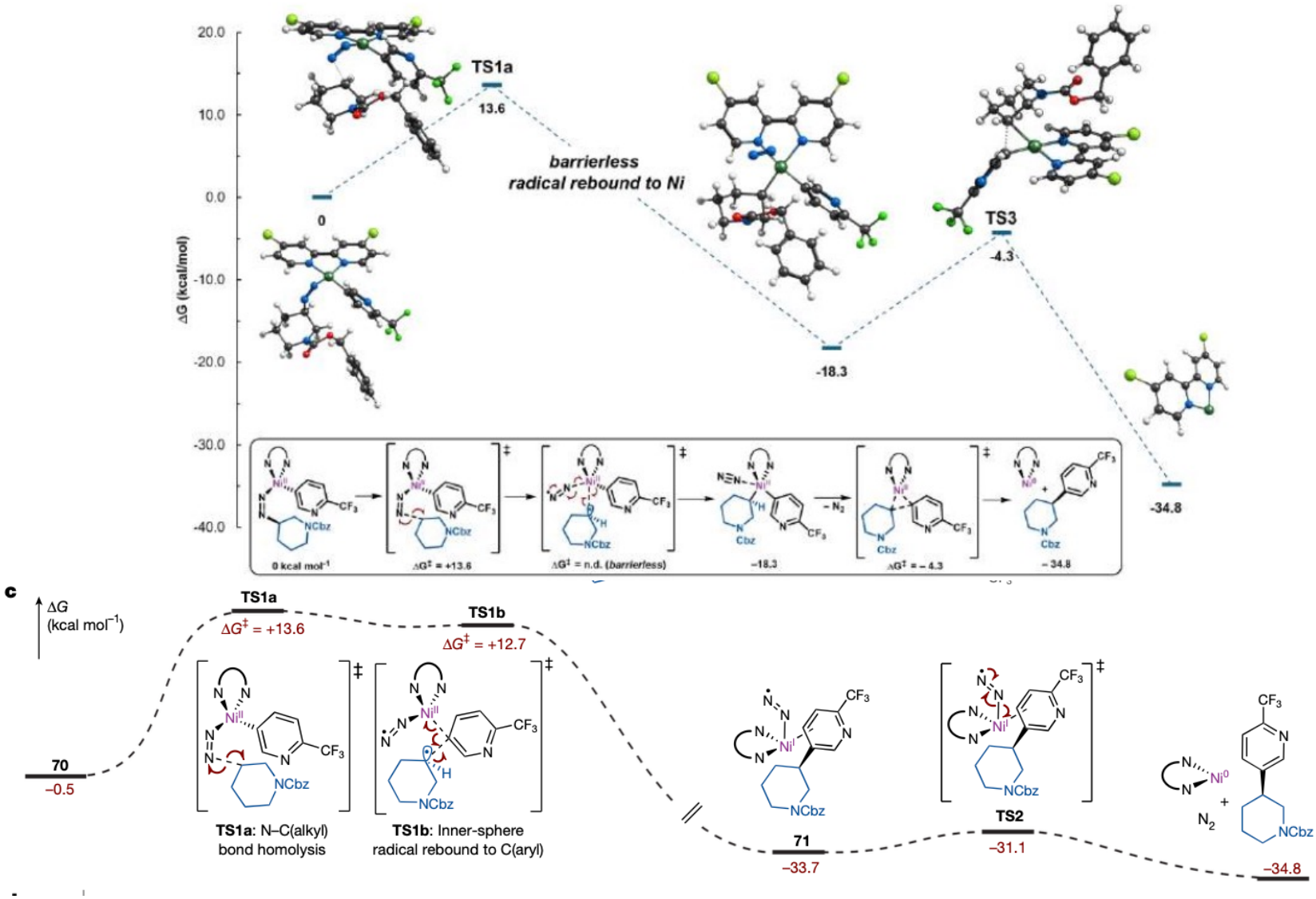


Derivation	crude yield/%[a]
standard	66% (65% isolated)
pimperidine, 75 °C	56% (55% isolated)
pimperidine instead of Et_3N (60 °C)	57%
bpy instead of dNH_2-bpy	51%
dMeO-bipy instead of dNH_2-bipy	53%
Bathophenoroline instead of dNH_2-bipy	48%
2,6-di(1-pyrazolyl)pyridine instead of dNH_2-bipy	21%
Ts instead of SO_2Ar (3,5-dF-Ph)	34%
r.t. instead of 60 °C	29%
vinyl iodide (1.0 eq.), hydrazide (1.5 eq.)	61%
Ts instead of SO_2Ar (75 °C)	18%

a. Crude yield determined by 1H NMR analysis with dibromomethane as internal standard.

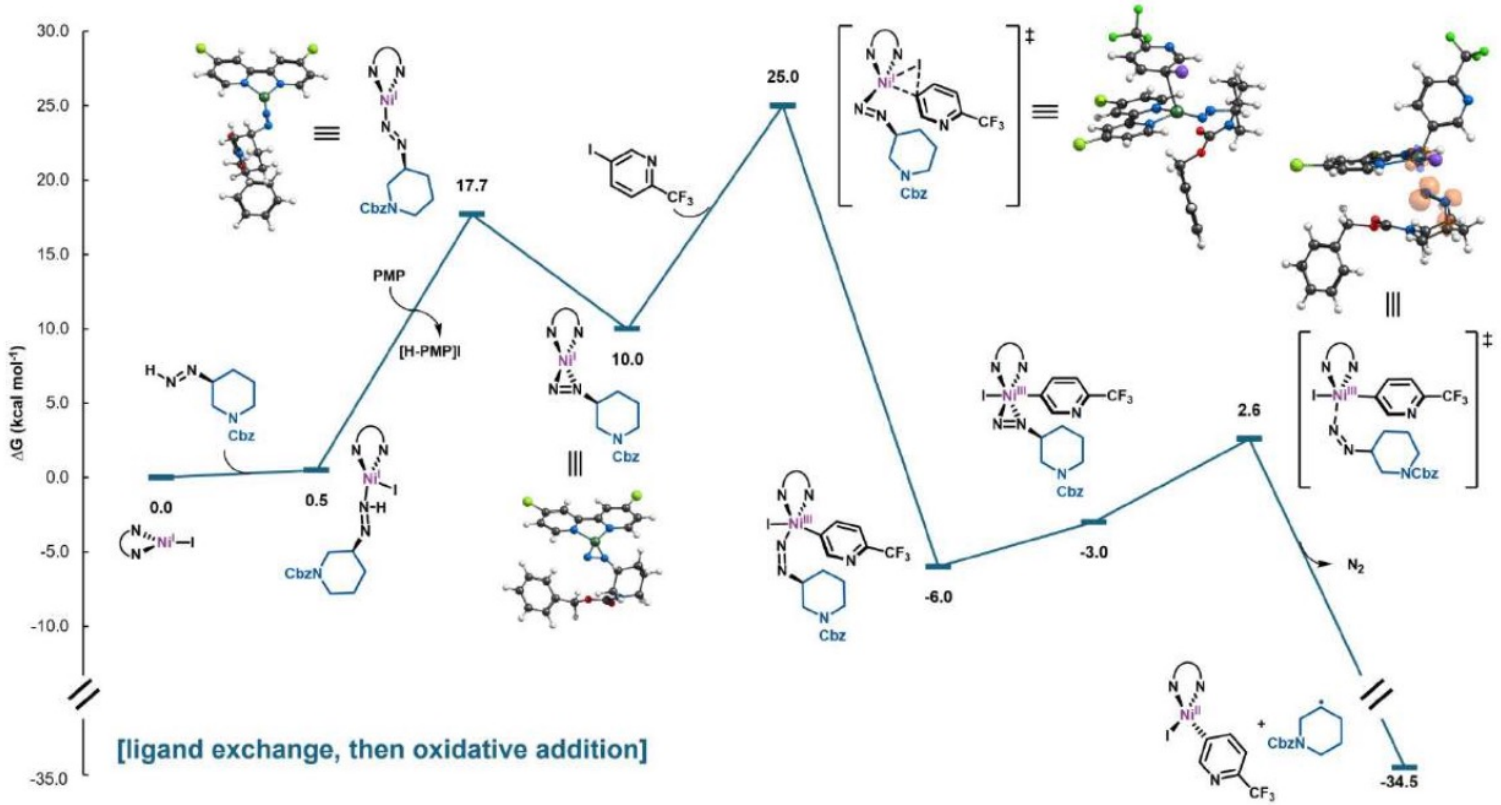
1) Sun, J.; et al. *Science* **2025**, *387*, 1377.

Vs Inner Sphere



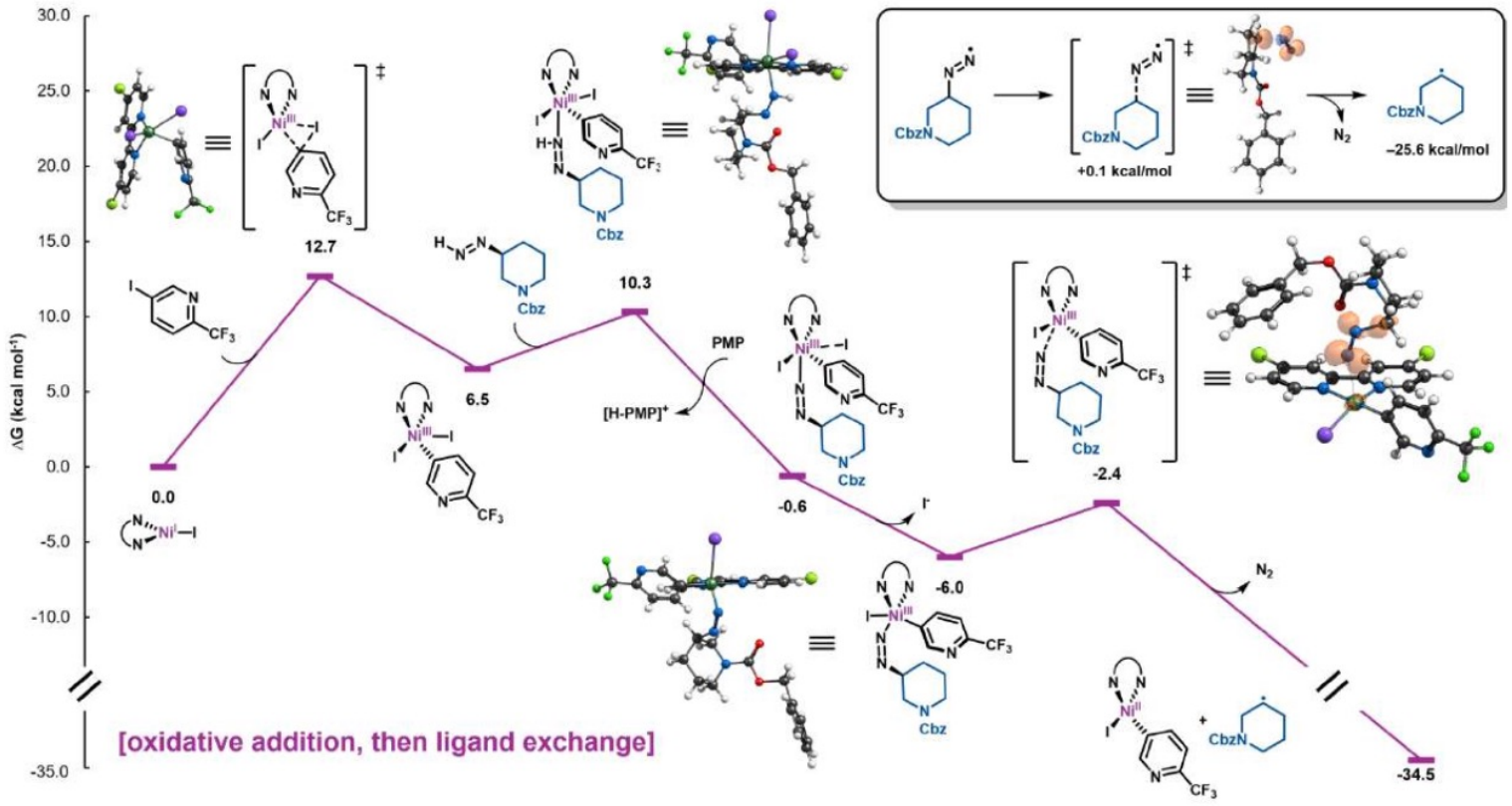
1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

Ligand exchange then Oxidative addition



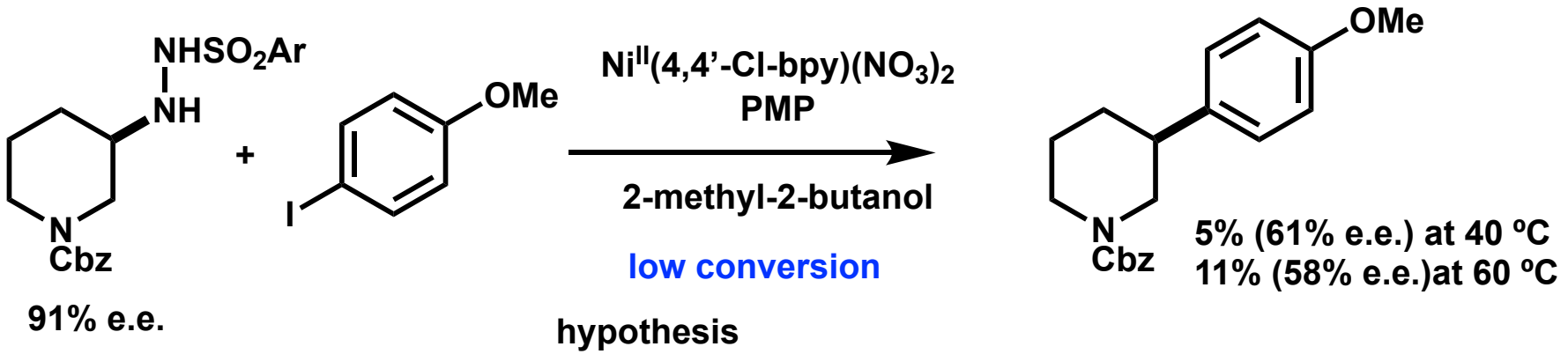
1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

Oxidative addition then Ligand Exchange



1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

Effect of para-substituent

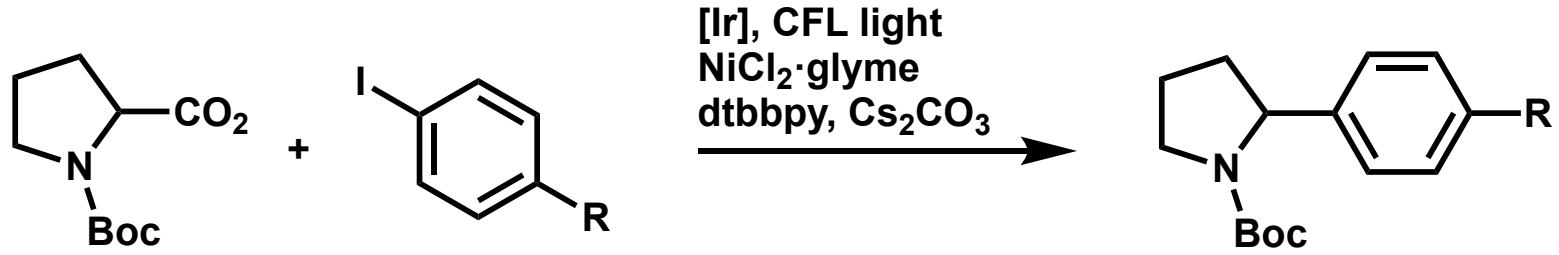


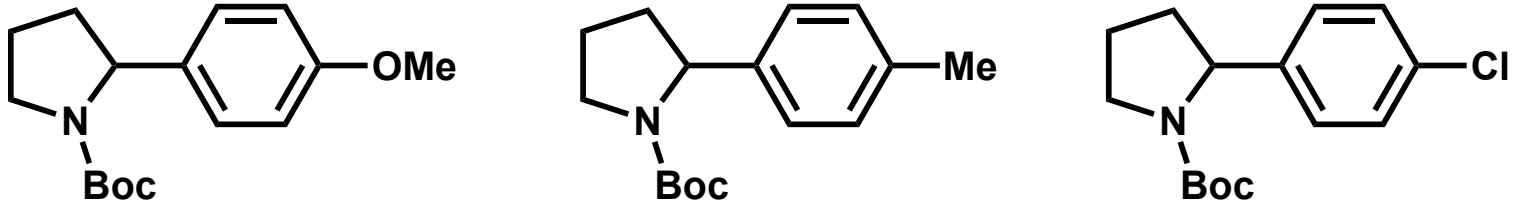
91% e.e.

hypothesis

· discourage diazene coordination to Ni by increasing the electron density of the Ni center

· suppress inner-sphere radical capture mechanism by raising the energy of the acceptor orbital.



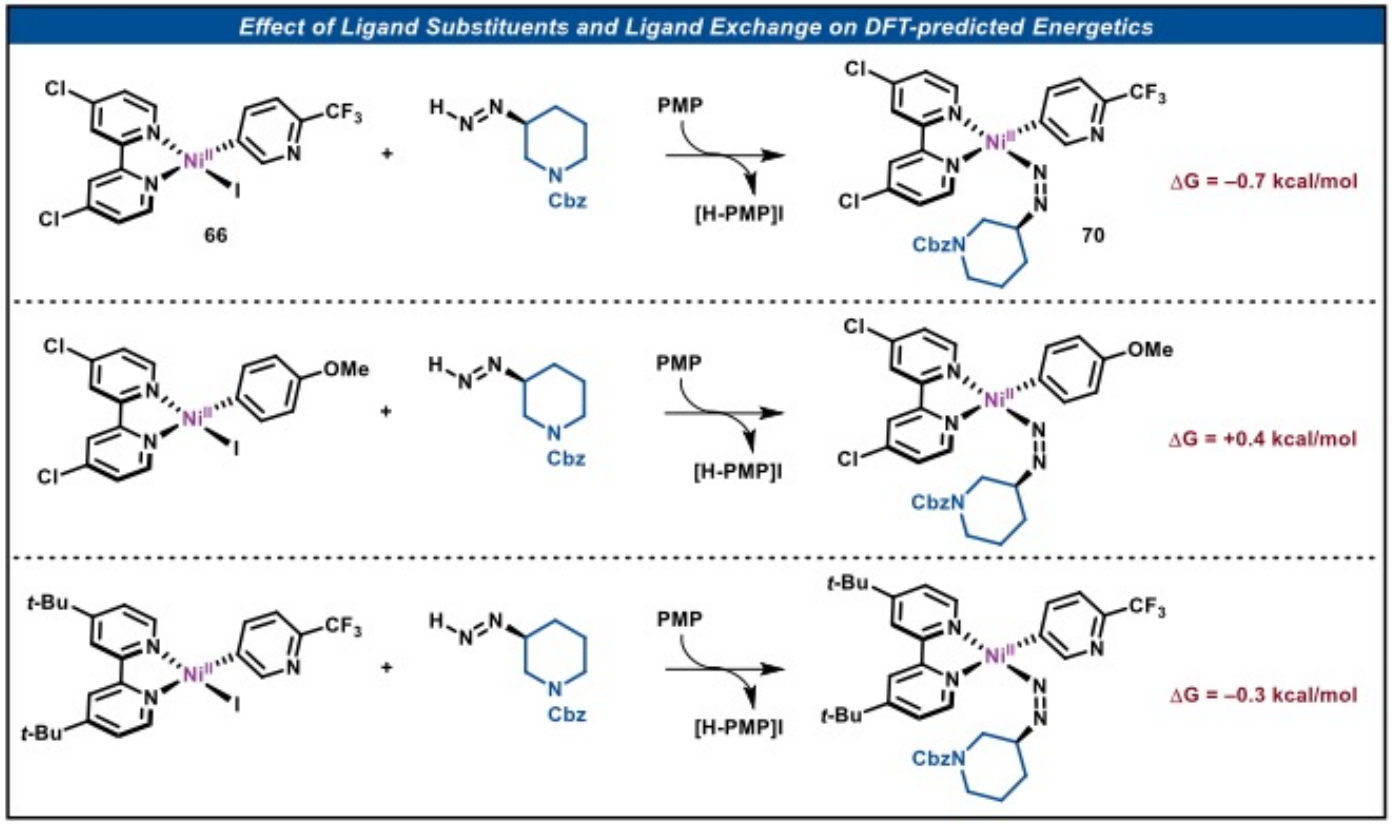


74% 78% 77%

1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

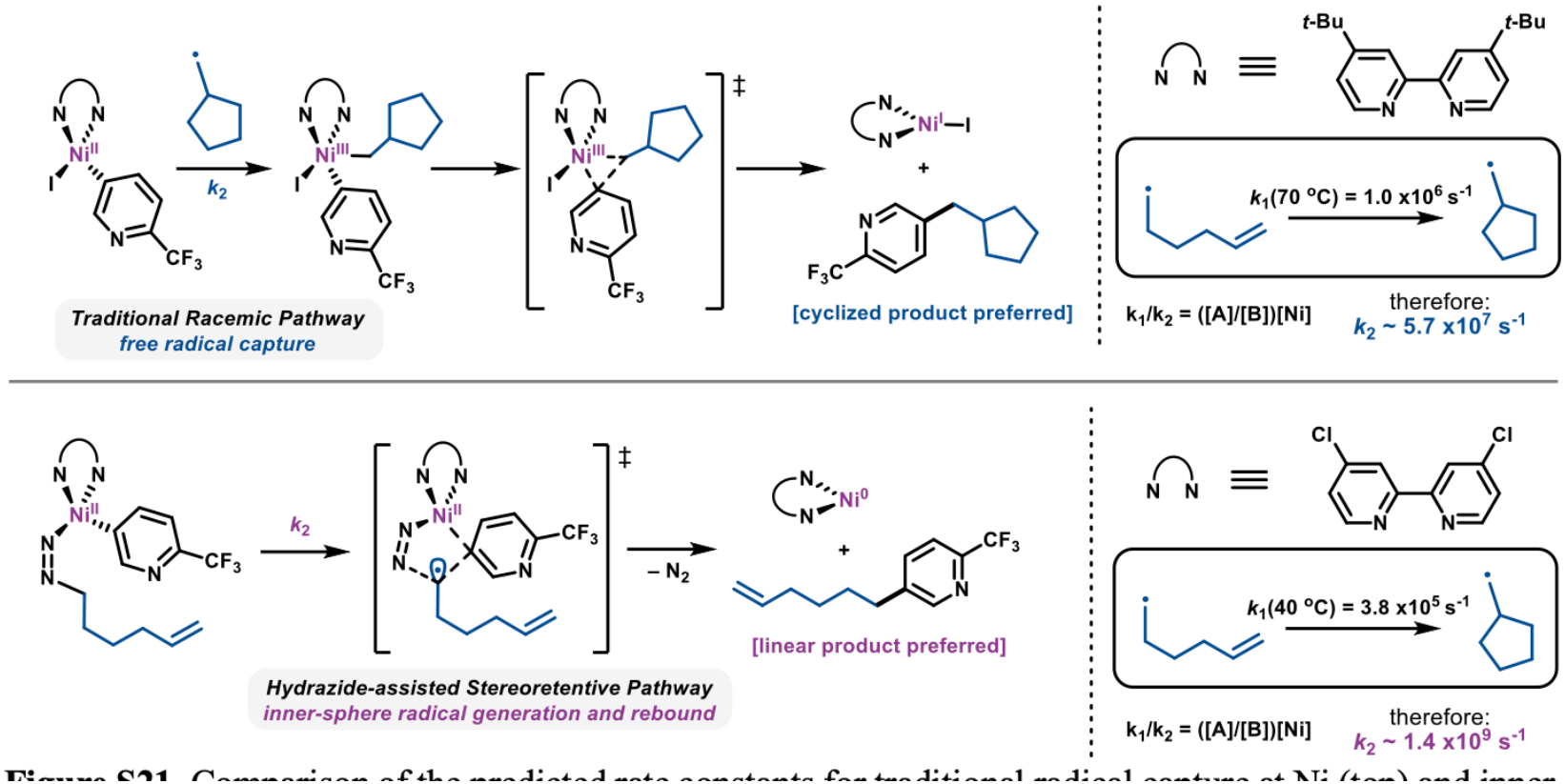
2) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437.

Effect of para-substituent



1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.

Ni capture vs 5-*exo*-cyclization



1) Sun, J.; He, J.; Massaro, L.; Cagan, D. A.; Tsien, J.; Wang, Y.; Attard, F. C.; Smith, J. E.; Lee, J. S.; Kawamata, Y.; Baran, P. S. *Nature* **2025**, *642*, 85.