

The Development of Radical-Based Palladium Chemistry

1 IA																			18 VIIA		
1 H Hydrogen 1.008	2 IIA																		2 He Helium 4.002602		
3 Li Lithium 6.94	4 Be Beryllium 9.0121831																		10 Ne Neon 20.1797		
11 Na Sodium 22.98976928	12 Mg Magnesium 24.305	3 IIIB	4 IVB	5 VB	6 VIB	7 VIIIB	8 VIIIB	9 VIIIB	10 VIIIB	11 IB	12 IIB	13 IIIa	14 IVA	15 VA	16 VIA	17 VIIA	18 VIIA				
19 K Potassium 39.0983	20 Ca Calcium 40.078	21 Sc Scandium 44.955908	22 Ti Titanium 47.867	23 V Vanadium 50.9415	24 Cr Chromium 51.9961	25 Mn Manganese 54.938044	26 Fe Iron 55.845	27 Co Cobalt 58.933194	28 Ni Nickel 58.6934	29 Cu Copper 63.546	30 Zn Zinc 65.38	31 Ga Gallium 69.723	32 Ge Germanium 72.630	33 As Arsenic 74.921595	34 Se Selenium 78.971	35 Br Bromine 79.904	36 Kr Krypton 83.798				
37 Rb Rubidium 85.4678	38 Sr Strontium 87.62	39 Y Yttrium 88.90584	40 Zr Zirconium 91.224	41 Nb Niobium 92.90637	42 Mo Molybdenum 95.95	43 Tc Technetium (98)	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.90550	46 Pd Palladium 106.42	47 Ag Silver 107.8682	48 Cd Cadmium 112.414	49 In Indium 114.818	50 Sn Tin 118.710	51 Sb Antimony 121.760	52 Te Tellurium 127.60	53 I Iodine 126.90447	54 Xe Xenon 131.293				
55 Cs Caesium 132.90545196	56 Ba Barium 137.327	57 - 71 Lanthanoids	72 Hf Hafnium 178.49	73 Ta Tantalum 180.94788	74 W Tungsten 183.84	75 Re Rhenium 186.207	76 Os Osmium 190.23	77 Ir Iridium 192.217	78 Pt Platinum 195.084	79 Au Gold 196.966569	80 Hg Mercury 200.592	81 Tl Thallium 204.38	82 Pb Lead 207.2	83 Bi Bismuth 208.98040	84 Po Polonium (209)	85 At Astatine (210)	86 Rn Radon (222)				
87 Fr Francium (223)	88 Ra Radium (226)	89 - 103 Actinoids	104 Rf Rutherfordium (267)	105 Db Dubnium (268)	106 Sg Seaborgium (269)	107 Bh Bohrium (270)	108 Hs Hassium (269)	109 Mt Meitnerium (278)	110 Ds Darmstadtium (281)	111 Rg Roentgenium (282)	112 Cn Copernicium (285)	113 Nh Nihonium (286)	114 Fl Flerovium (289)	115 Mc Moscovium (289)	116 Lv Livermorium (293)	117 Ts Tennessine (294)	118 Og Oganesson (294)				

57 La Lanthanum 138.90547	58 Ce Cerium 140.016	59 Pr Praseodymium 140.90766	60 Nd Neodymium 144.242	61 Pm Promethium (145)	62 Sm Samarium 150.36	63 Eu Europium 151.964	64 Gd Gadolinium 157.25	65 Tb Terbium 158.92535	66 Dy Dysprosium 162.500	67 Ho Holmium 164.93033	68 Er Erbium 167.259	69 Tm Thulium 168.93422	70 Yb Ytterbium 173.045	71 Lu Lutetium 174.9668	
89 Ac Actinium (227)	90 Th Thorium 232.0377	91 Pa Protactinium 231.03588	92 U Uranium 238.02891	93 Np Neptunium (237)	94 Pu Plutonium (244)	95 Am Americium (243)	96 Cm Curium (247)	97 Bk Berkelium (247)	98 Cf Californium (251)	99 Es Einsteinium (252)	100 Fm Fermium (257)	101 Md Mendelevium (258)	102 No Nobelium (259)	103 Lr Lawrencium (266)	

Andria Pace

MacMillan Group Meeting

Literature Talk

April 12, 2022

Palladium: a versatile element

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H Hydrogen 1.008		He Helium 4.002602
Li Lithium 6.94	Be Beryllium 9.0121831	
Na Sodium 22.98976928	Mg Magnesium 24.305	
	3 IIIB	13 IIIA
	4 IVB	14 IVA
	5 VB	15 VA
	6 VIB	16 VIA
	7 VIIIB	17 VIIA
	8 VIIIB	
	9 VIIIB	
	10 VIIIB	
	11 IB	
	12 IIB	
K Potassium 39.0983	Ca Calcium 40.078	5 Boron
	Sc Scandium 44.955908	6 Carbon
	Ti Titanium 47.867	7 Nitrogen
	V Vanadium 50.9415	8 Oxygen
	Cr Chromium 51.9961	9 Fluorine
	Mn Manganese 54.938044	10 Neon
	Fe Iron 55.845	11 Aluminum
	Co Cobalt 58.933194	12 Silicon
	Ni Nickel 58.6934	13 Phosphorus
	Cu Copper 63.546	14 Sulfur
	Zn Zinc 65.38	15 Chlorine
	Ga Gallium 69.723	16 Argon
	Ge Germanium 72.630	17 Krypton
	As Arsenic 74.921595	18 Kr
	Se Selenium 78.971	
	Br Bromine 79.904	
Rb Rubidium 85.4678	Sr Strontium 87.62	37 Antimony
	Y Yttrium 88.90584	38 Tellurium
	Zr Zirconium 91.224	39 Iodine
	Nb Niobium 92.90637	40 Xenon
	Mo Molybdenum 95.95	41 131.293
	Tc Technetium (98)	
	Ru Ruthenium 101.07	
	Rh Rhodium 102.90550	
	Pd Palladium 106.42	
	Ag Silver 107.8682	
	Cd Cadmium 112.414	
	In Indium 118.710	
	Sn Tin 121.760	
	Sb Antimony 126.90447	
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		75 Re Rhenium 186.207
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Fr Francium (223)	Ra Radium (226)	87 Actinoids
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		104 Rf Dubnium (268)
		105 Db Seaborgium (269)
		106 Sg Bohrium (270)
		107 Bh Hassium (269)
		108 Hs Meitnerium (278)
		109 Mt Darmstadtium (281)
		110 Ds Roentgenium (282)
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interconversion between diverse oxidation states

versatile and widely used in cross coupling

utilized in natural product synthesis, agrochemistry, and pharmaceutical production

Palladium: a versatile element

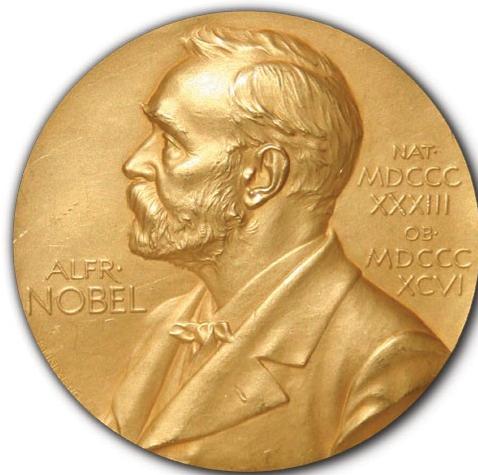
*accessed via
1e-pathways*

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interconversion between diverse oxidation states

versatile and widely used in cross coupling

Palladium: a versatile element



**2010 Nobel Prize
in chemistry**

Heck

Negishi

Suzuki

"For palladium-catalyzed cross-coupling in organic synthesis"

Stille

Sonogashira

Tsuji-Trost

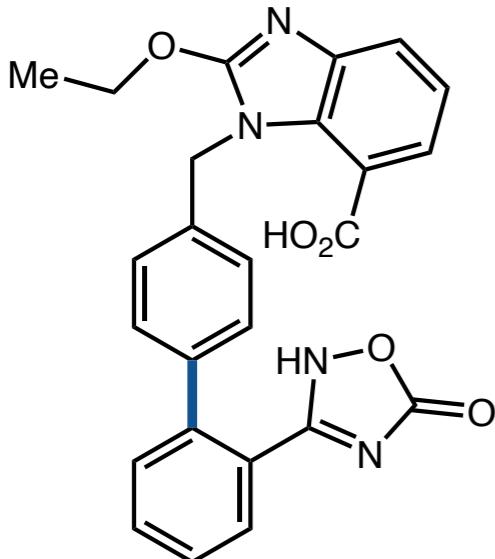
Hiyama-Denmark Buchwald-Hartwig

interconversion between diverse oxidation states

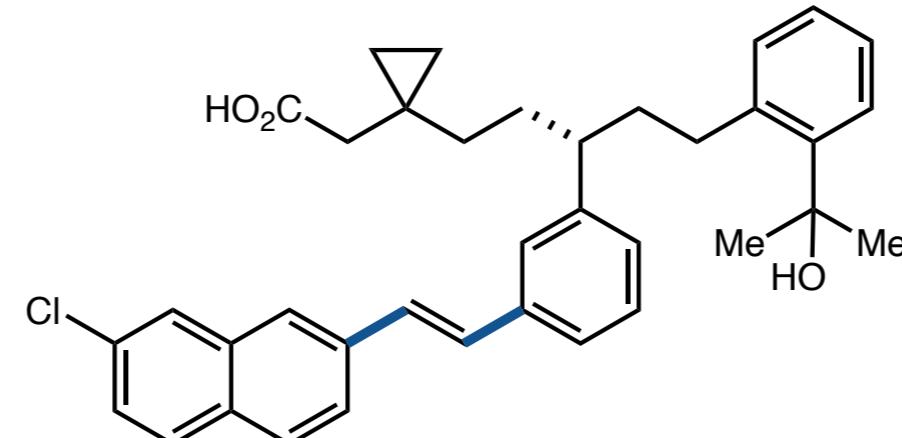
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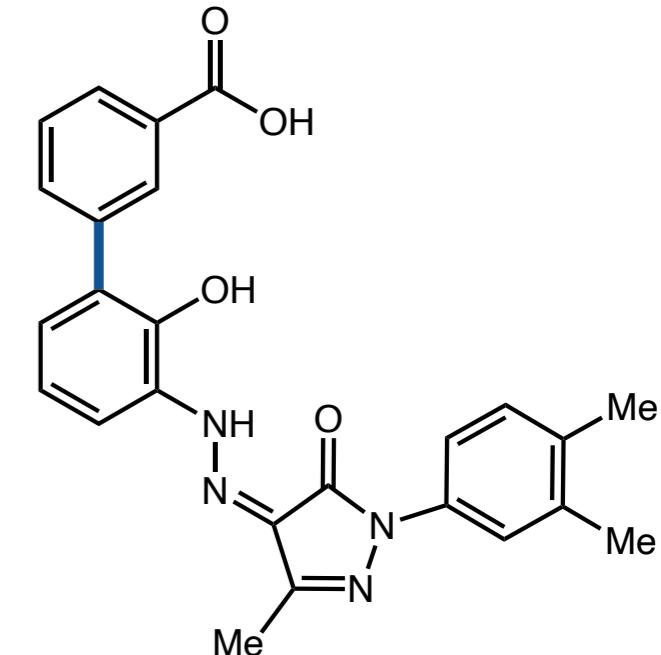
Palladium: a versatile element



Azilva
\$764 Million
cardiovascular



Singulair
\$462 Million
respiratory



Promacta
\$1.7 Billion
oncology

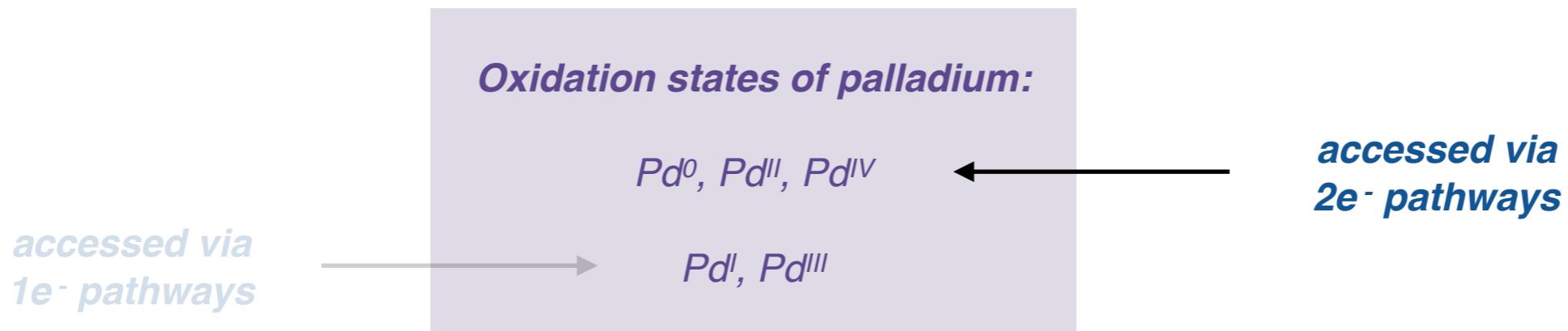
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Qureshi, M.; Njardarson, J. "Top 200 Small Molecule Pharmaceuticals by Retail Sales in 2020."
Bollikonda, S.; Mohanarangam, S.; Jinna, R.; Kandirelli, V.; Makthala, L.; Sen, S.; Chaplin, D.;
Lloyd, R.; Mahoney, T.; Dahanukar, V.; Oruganti, S.; Fox, M. *J. Org. Chem.* **2015**, *80*, 3891.

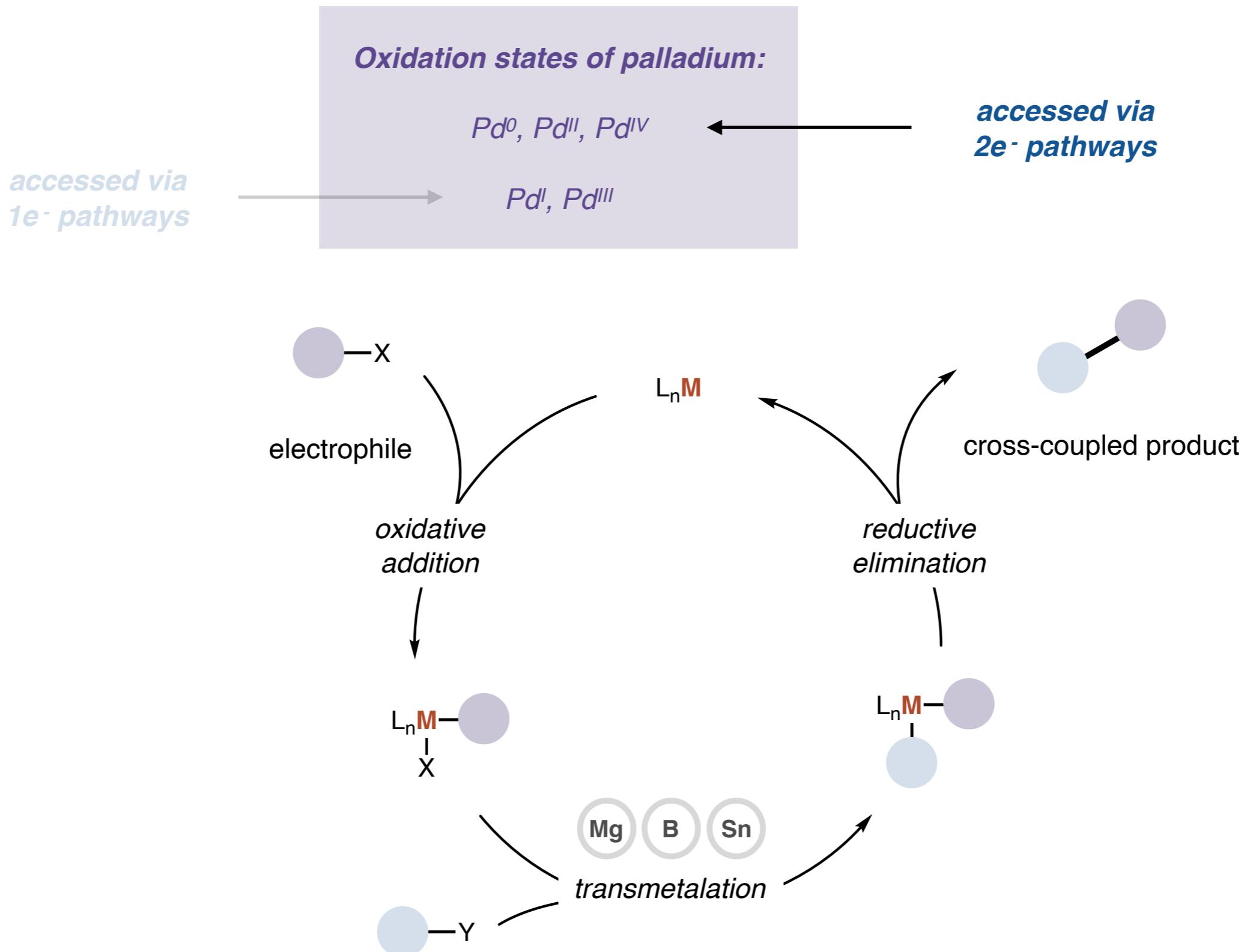
Radical-Based Palladium Chemistry



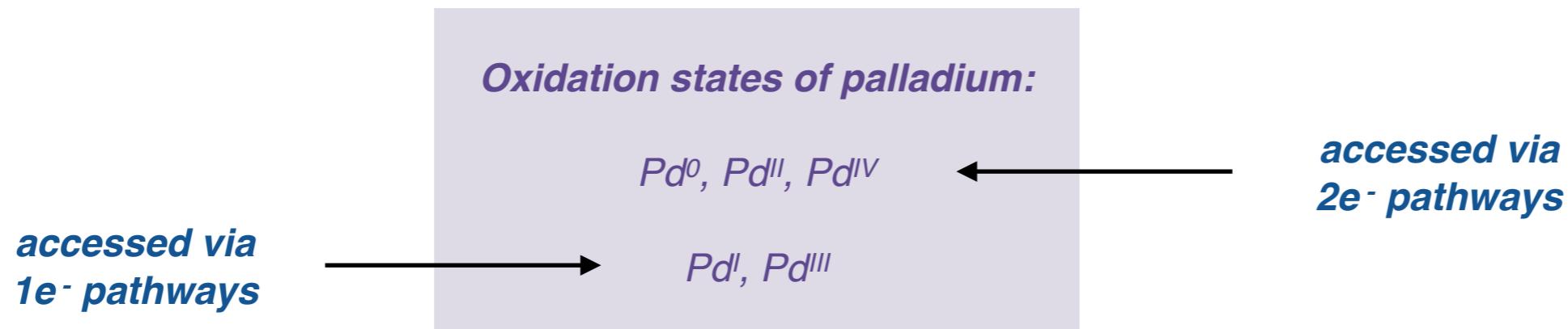
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Radical-Based Palladium Chemistry



Radical-Based Palladium Chemistry



New elementary steps can provide alternative mechanistic pathways to access key intermediates or activate typically inert coupling partners

Radical-Based Palladium Chemistry

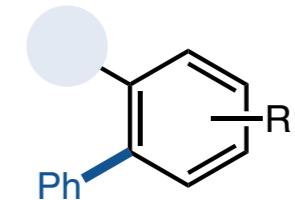
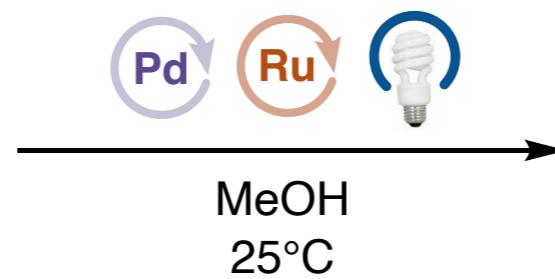
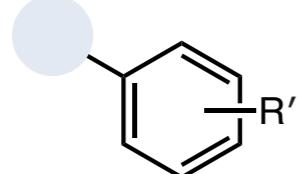
What is radical-based palladium chemistry?

Radical-Based Palladium Chemistry

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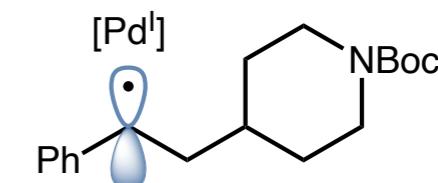
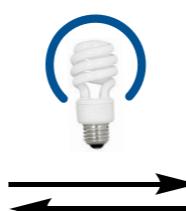
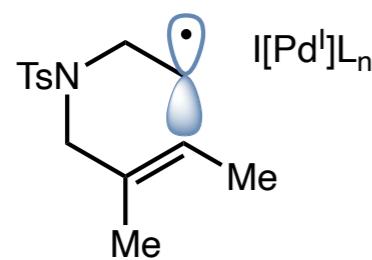
Photoredox Catalysis

Photoredox using Pd as a cross-coupling catalyst



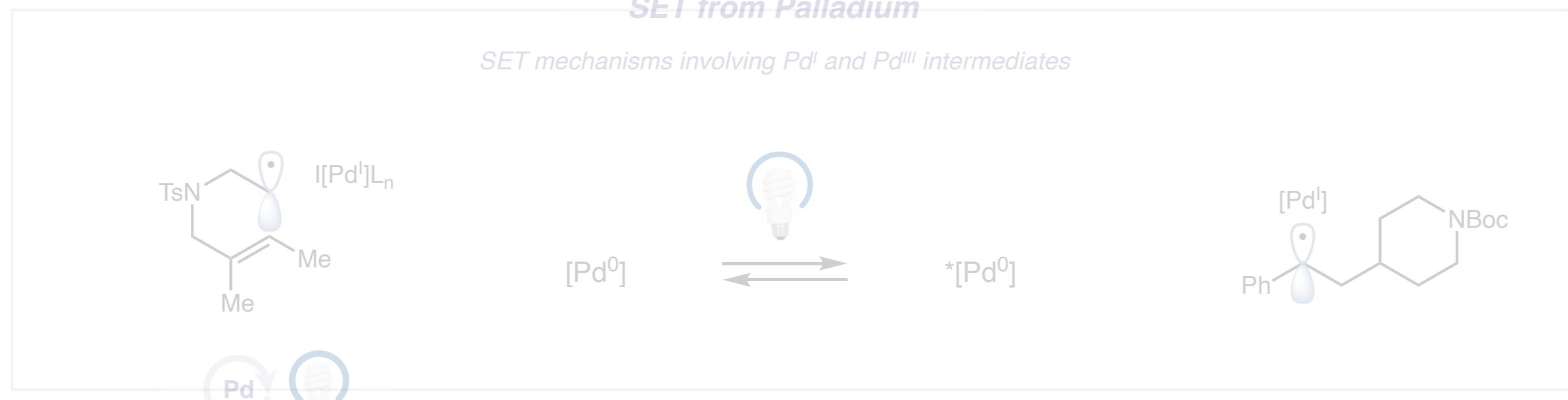
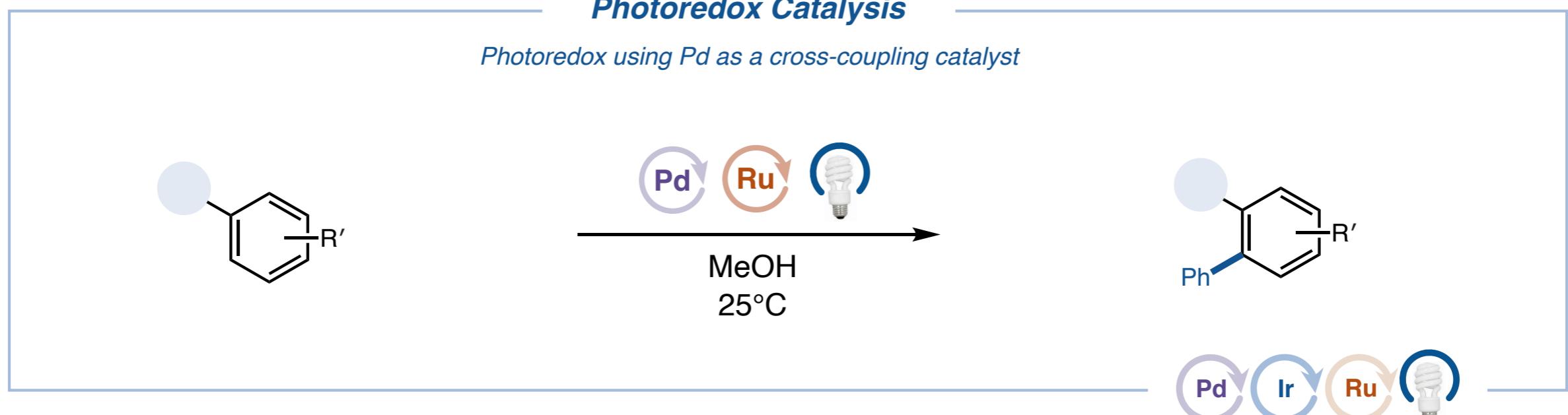
SET from Palladium

SET mechanisms involving Pd^{II} and Pd^{III} intermediates



Radical-Based Palladium Chemistry

What is radical-based palladium chemistry?



Liu, Q.; Dong, X.; Li, J.; Dong, Y.; Liu, H. *ACS Catal.* **2015**, 5, 6111.

Radical-Based Palladium Chemistry

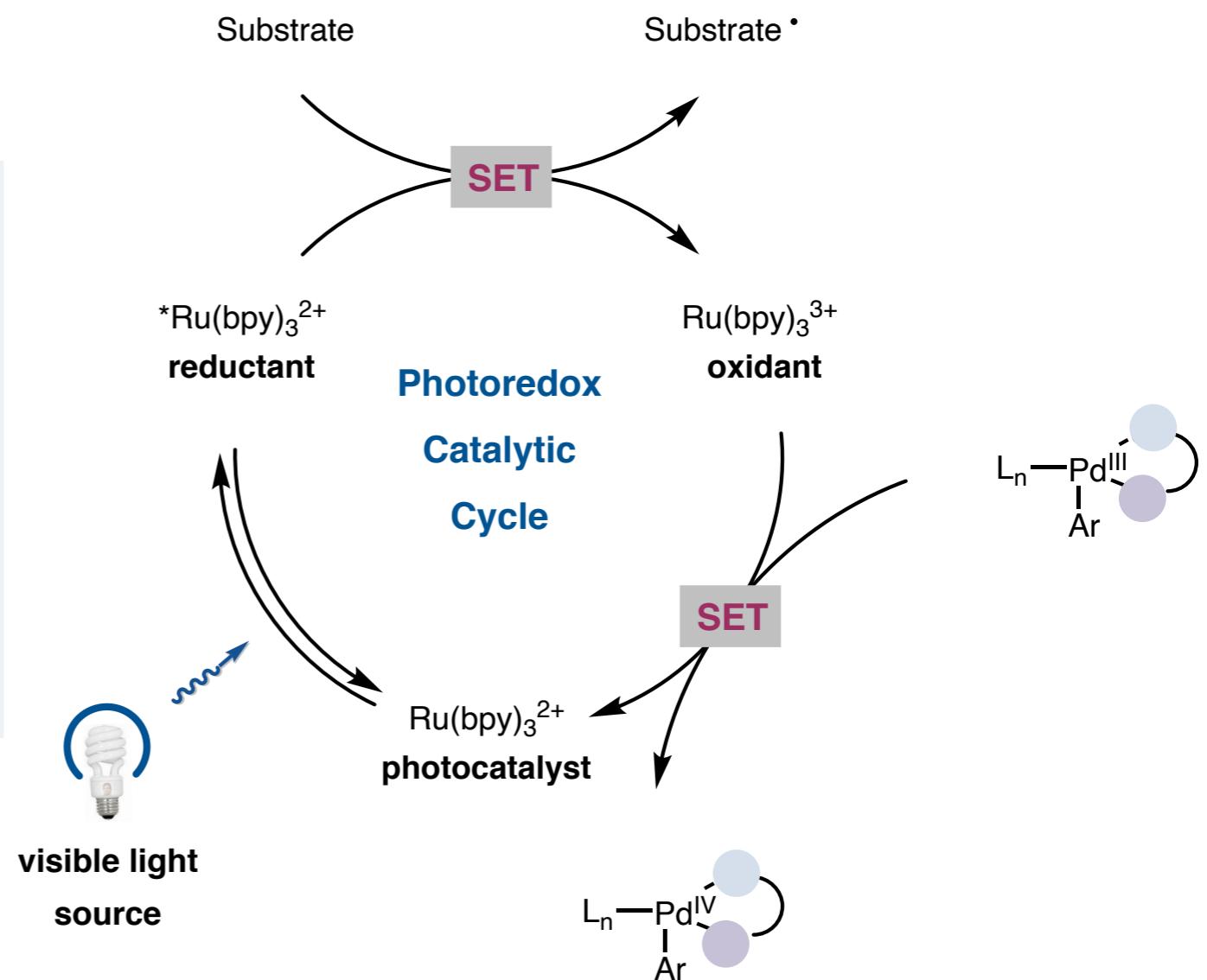
accessed via
1e⁻ pathways

Oxidation states of palladium:

Pd⁰, Pd^{II}, Pd^{IV}

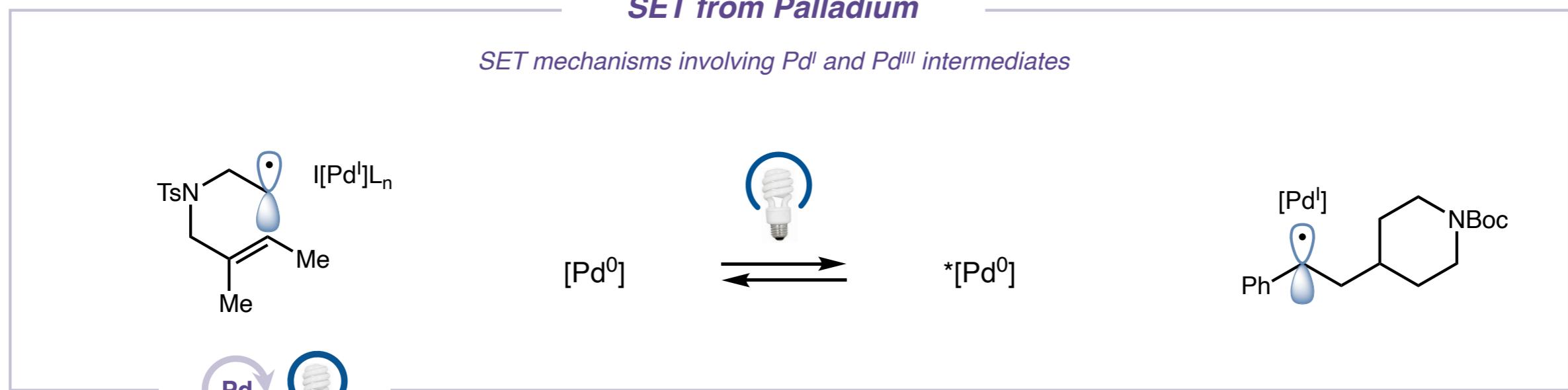
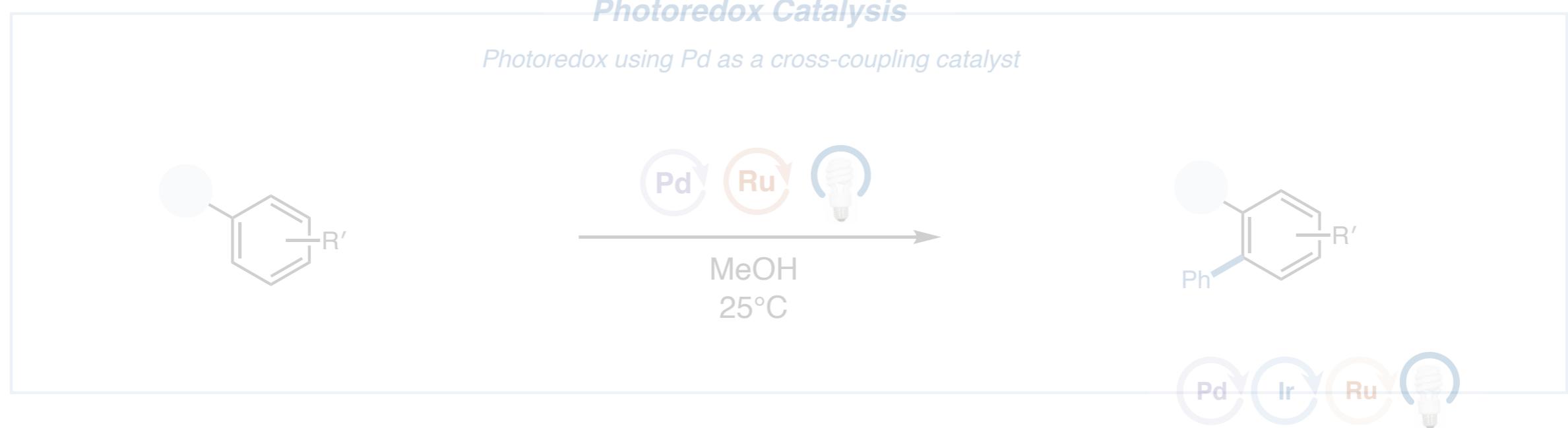
Pd^I, Pd^{III}

- Radical-based reactivity of Pd**
Type 1
- Palladium can be oxidized by a photocatalyst
 - Palladium itself is not being excited



Radical-Based Palladium Chemistry

What is radical-based palladium chemistry?



Radical-Based Palladium Chemistry

Oxidation states of palladium:

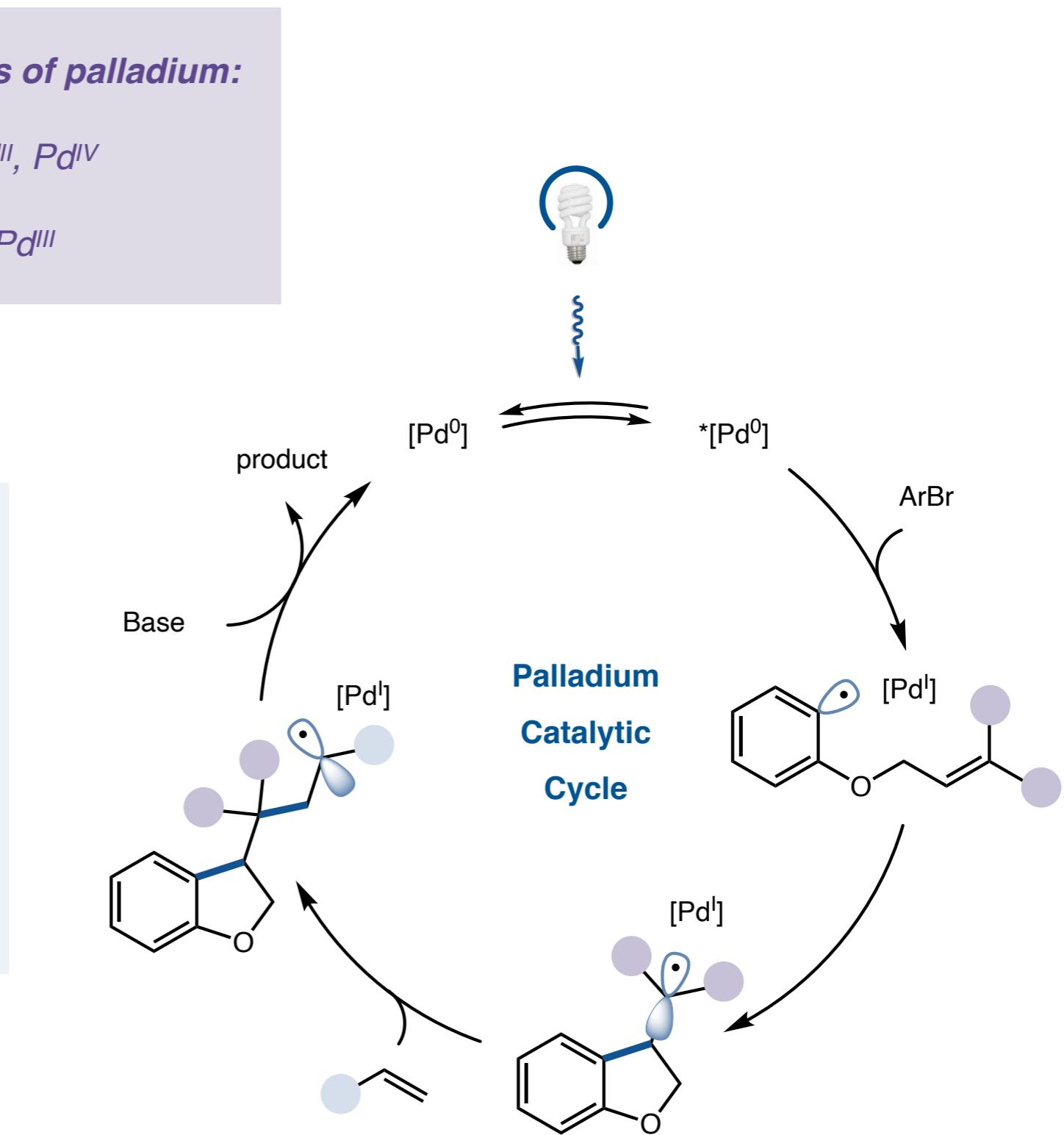
accessed via 1e⁻ pathways

Pd^0, Pd^{II}, Pd^{IV}

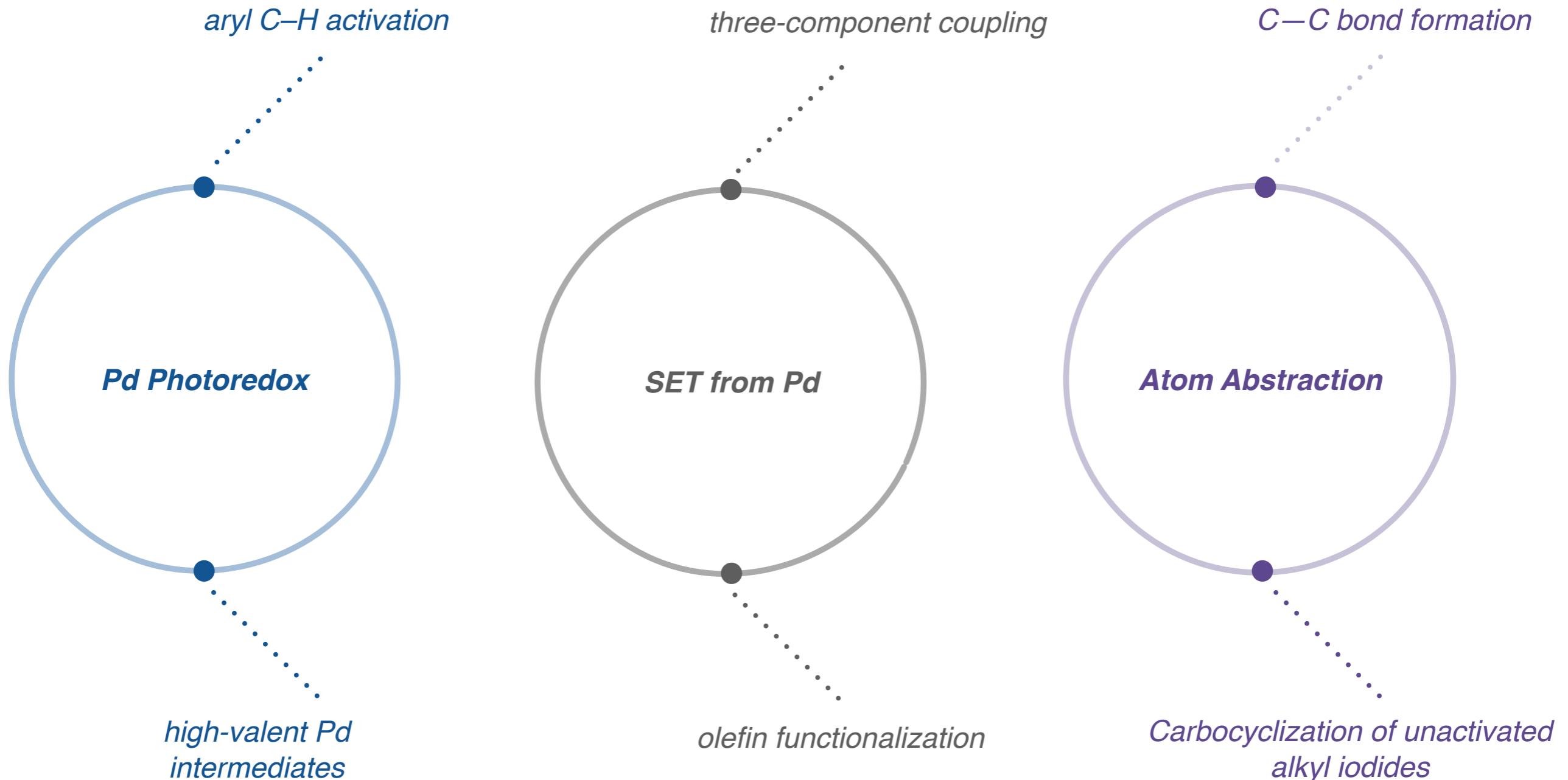
Pd^I, Pd^{III}

Radical-based reactivity of Pd Type 2

- Palladium can be directly excited
- Can perform SET chemistry for halide abstraction and olefin addition



Three main areas of radical-based palladium chemistry



This is a broad and active field of interest!

Three main areas of radical-based palladium chemistry

Pd Photoredox:
aryl C–H activation

SET from Pd:
olefin functionalization

Atom Abstraction:
C–C bond formation



Melanie Sanford
University of Michigan



Frank Glorius
WWU Münster



Erik Alexanian
University of North Carolina-
Chapel Hill

Three main areas of radical-based palladium chemistry

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Melanie Sanford
University of Michigan



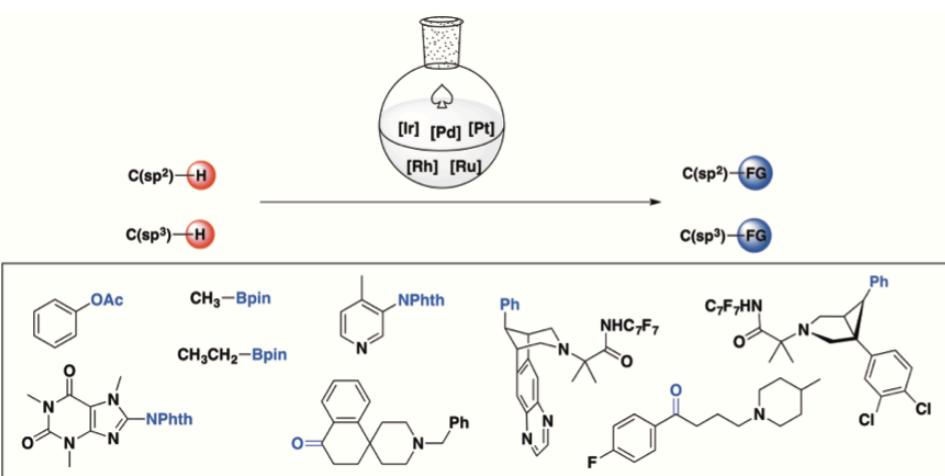
Frank Glorius
WWU Münster



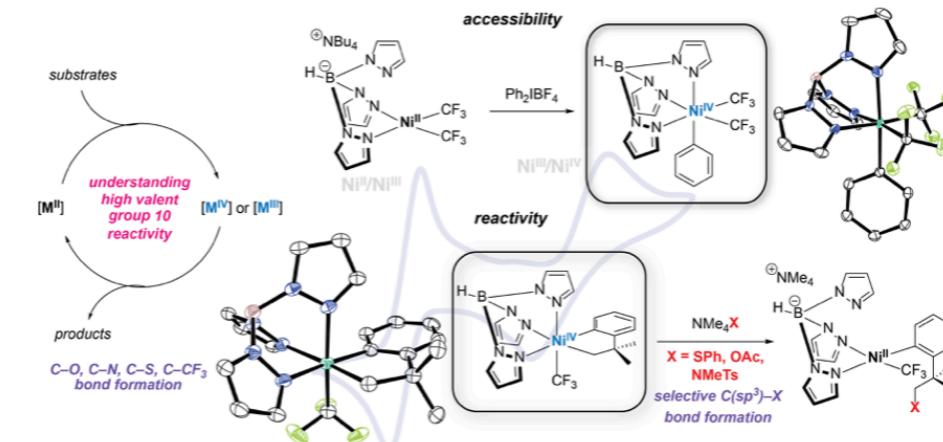
Erik Alexanian
University of North Carolina-
Chapel Hill

Research in the Sanford group

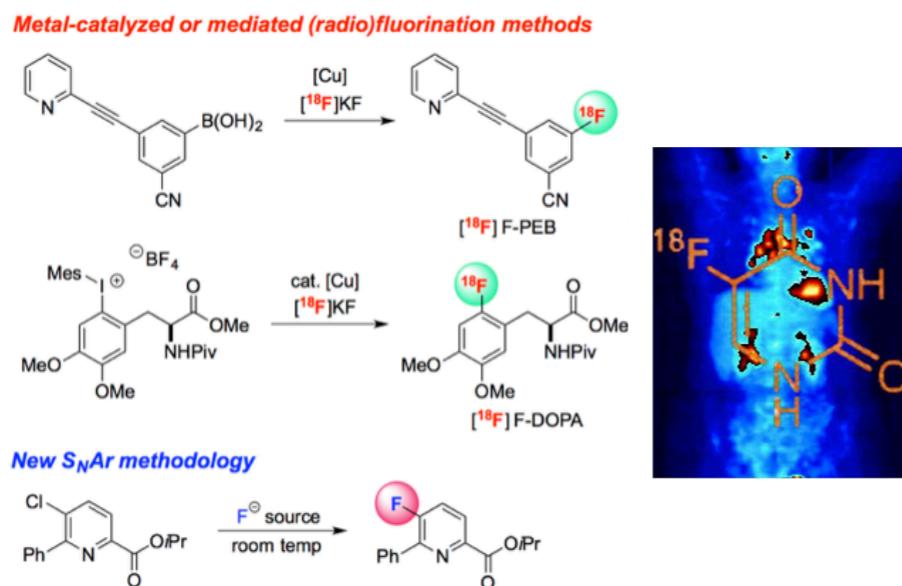
C—H Functionalization



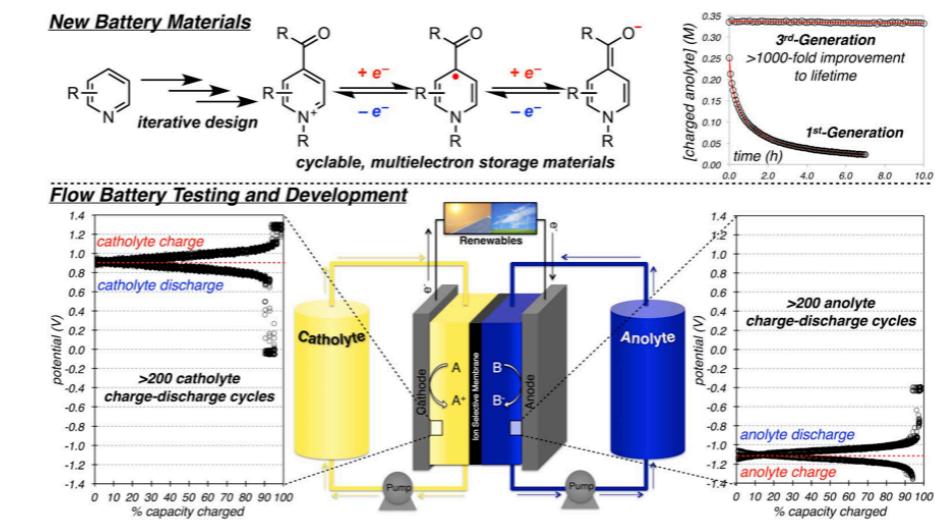
Organometallics



Fluorination



Flow Batteries



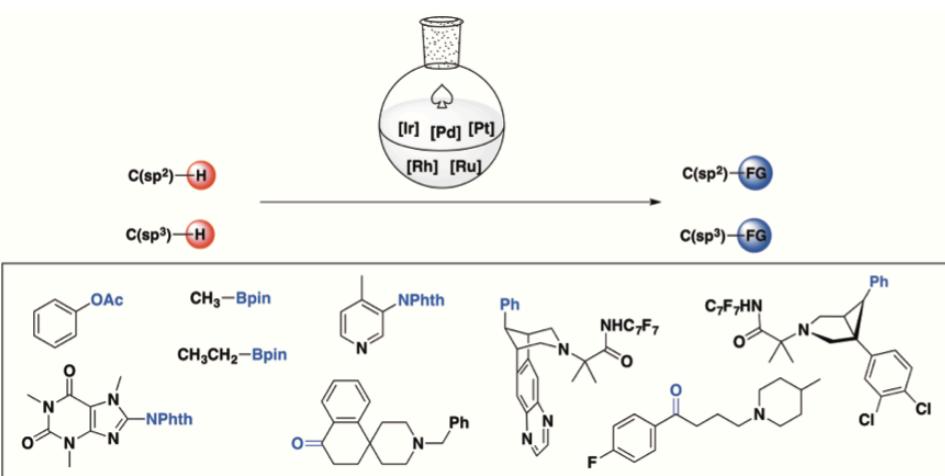
Bourm J.; Camasso, N.; Sanford, M. *J. Am. Chem. Soc.* **2015**, *137*, 8034.

Mossine, A.; Brooks, A.; Makaravage, K.; Miller, J.; Ichiiishi, N.; Sanford, M. *Org. Lett.* **2015**, *17*, 5780.

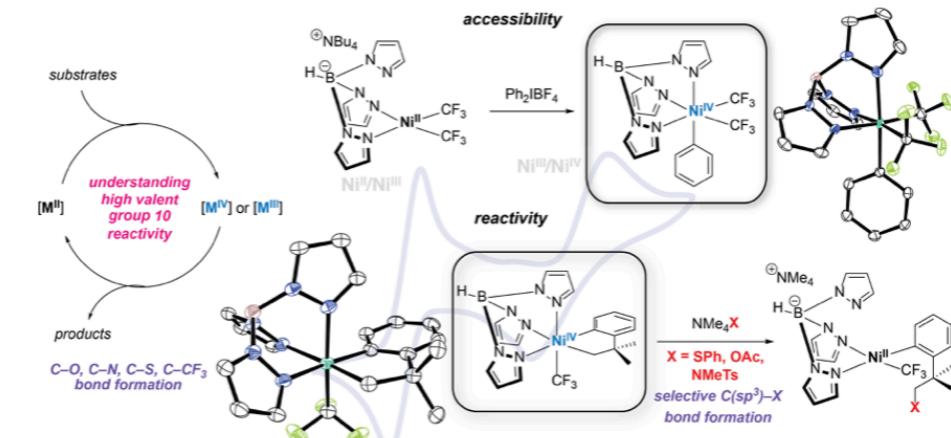
Sevov, C.; Brooner, R.; Chenard, E.; Assary, R.; Moore, J.; Rodriguez-Lopez, J.; Sanford, M. *J. Am. Chem. Soc.* **2015**, *137*, 14465.

Research in the Sanford group

C—H Functionalization



Organometallics



A.B. Chemistry: Yale University,
1996 (Bob Crabtree)

PhD. Chemistry: Caltech,
2001 (Bob Grubbs)

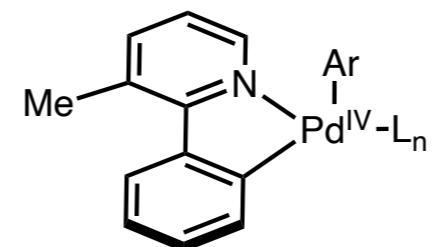
Postdoc: Princeton University,
2008 (Jay Groves)



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High valent palladium reactivity

Why would we want to access high valent palladium?



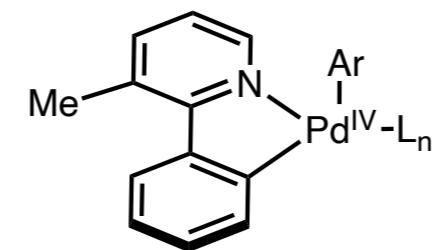
■ ***facile reductive elimination***

■ ***unique reactivity***

■ ***catalytically competent***

High valent palladium reactivity

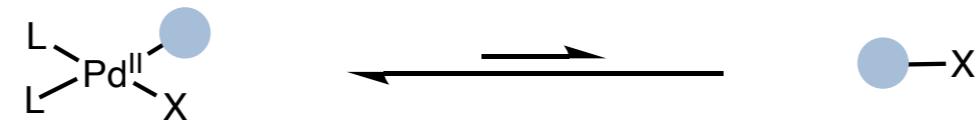
Why would we want to access high valent palladium?



■ *unique reactivity*

High valent palladium reactivity

Why would we want to access high valent palladium?

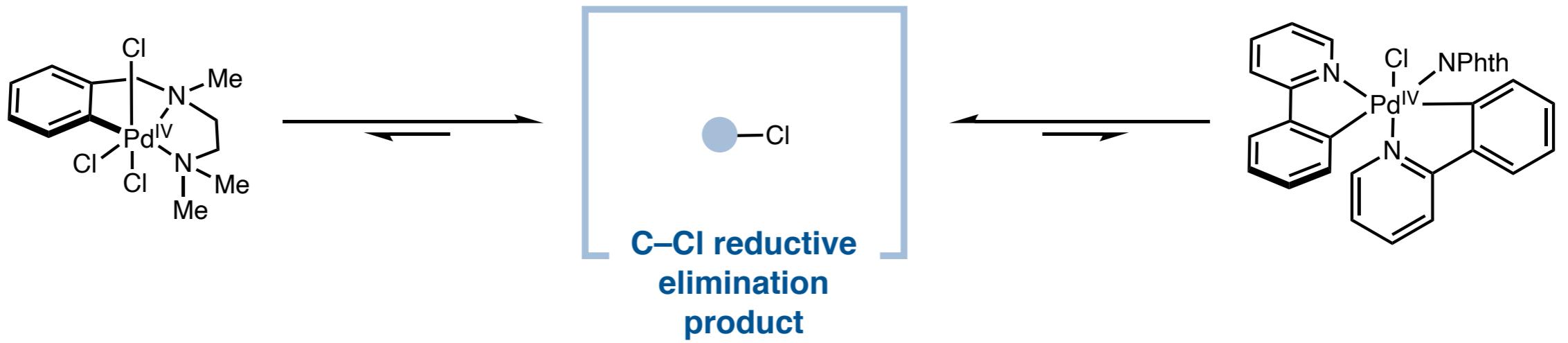


C–X reductive elimination is unfavorable for most Pd^{II}

- C–X and C–CF₃ reductive elimination are challenging from low-valent Pd

High valent palladium reactivity

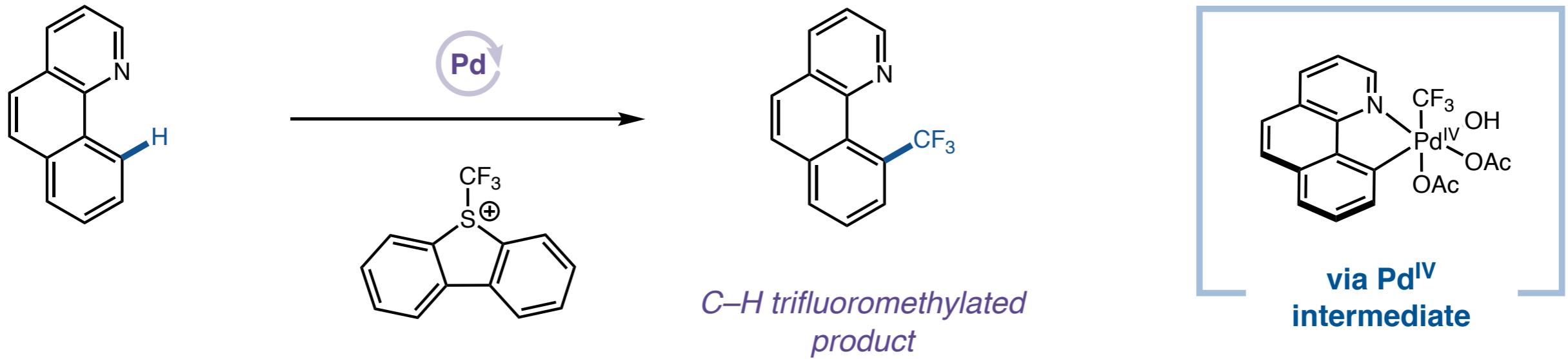
Why would we want to access high valent palladium?



- C-X and C-CF₃ reductive elimination are challenging from low-valent Pd
- Most Pd⁰/Pd^{II} transformations involve C-X bond breaking, not forming

High valent palladium reactivity

Why would we want to access high valent palladium?

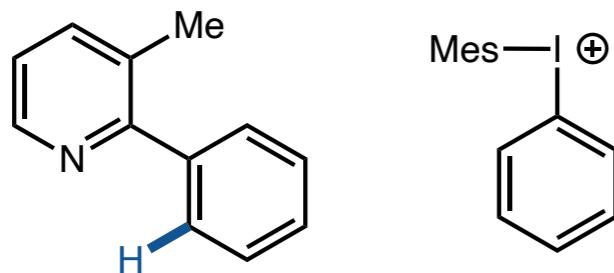


- C–X and C–CF₃ reductive elimination are challenging from low-valent Pd
- Most Pd⁰/Pd^{II} transformations involve C–X bond breaking, not forming

Therefore, if we want to make halogenated or CF₃-containing products, we need high-valent Pd

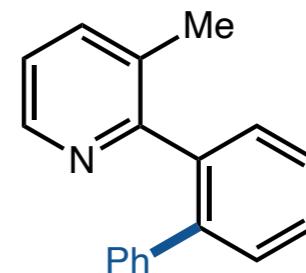
C—H arylation: a model reaction

C—H Arylation



10 mol% Pd(OAc)₂

AcOH, 100°C



- ✗ high temperature
- ✗ acidic solvent

- *high functional group tolerance*
- *no pre-activation of C—H substrate*

Design elements

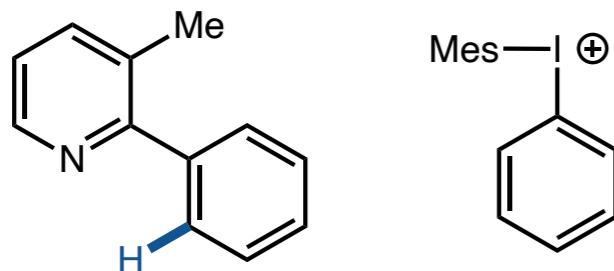
room temperature

non-acidic solvent

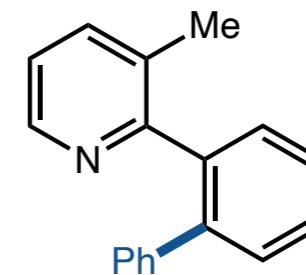
no stoichiometric oxidant

C–H arylation: a model reaction

C–H Arylation



10 mol% Pd(OAc)₂
AcOH, 100°C



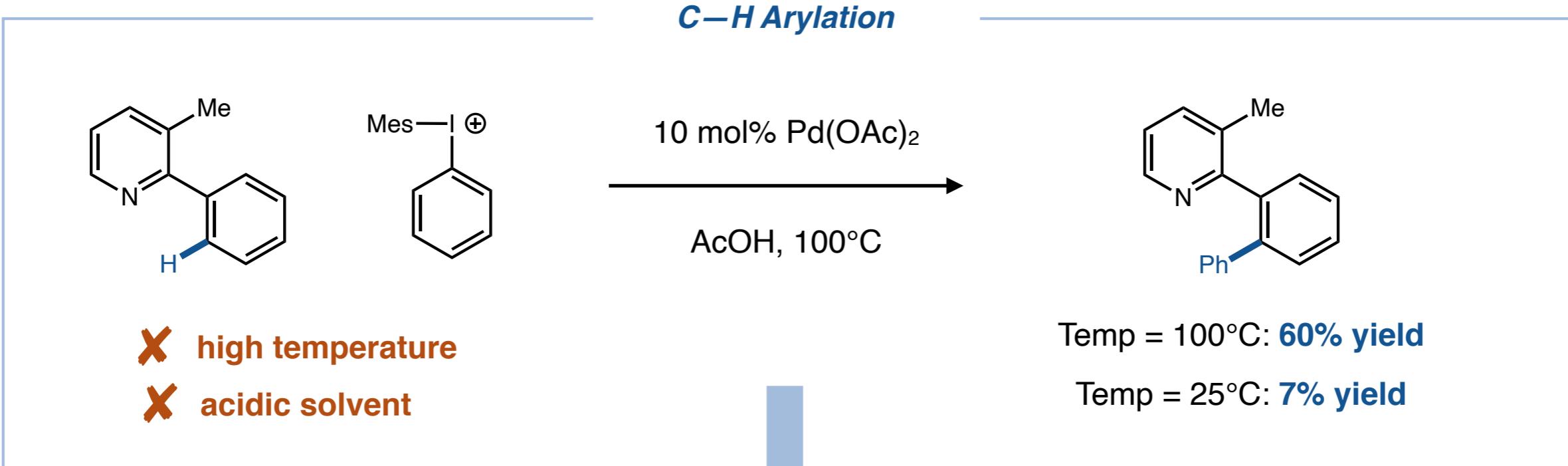
✗ **high temperature**
✗ **acidic solvent**

Temp = 100°C: **60% yield**
Temp = 25°C: **7% yield**

Kalyani, D.; Deprez, N.; Desai, L.; Sanford, M. *J. Am. Chem. Soc.* **2005**, 127, 7330.

Kalyani, D.; McMurtrey, K.; Neufeldt, S.; Sanford, M. *J. Am. Chem. Soc.* **2011**, 133, 18566.

C—H arylation: a model reaction

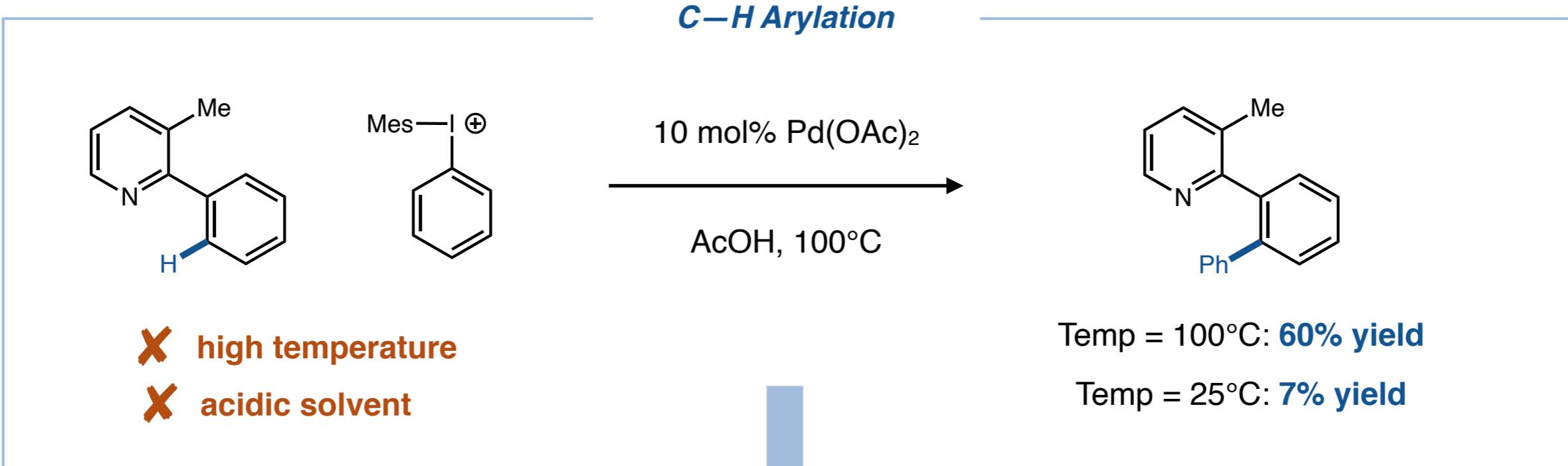


- mechanistic studies revealed that oxidation of dimer is rate-limiting
- rate of reaction could be increased with more reactive arylating reagents

Kalyani, D.; Deprez, N.; Desai, L.; Sanford, M. *J. Am. Chem. Soc.* **2005**, *127*, 7330.

Kalyani, D.; McMurtrey, K.; Neufeldt, S.; Sanford, M. *J. Am. Chem. Soc.* **2011**, *133*, 18566.

C–H arylation: a model reaction

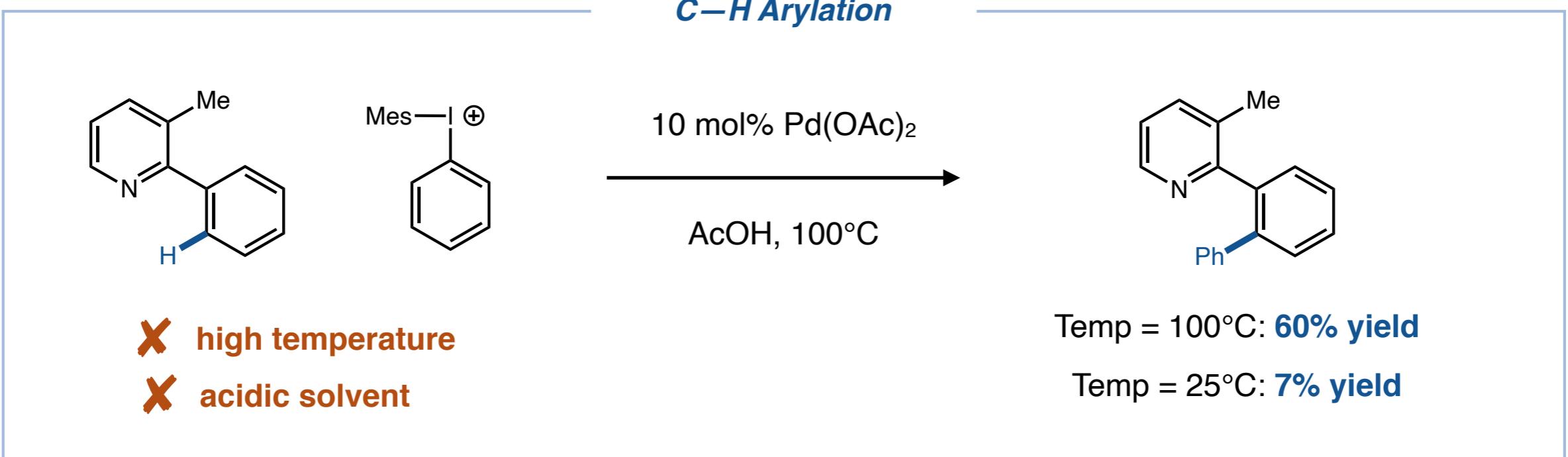


- mechanistic studies revealed that oxidation of dimer is rate-limiting
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Kalyani, D.; Deprez, N.; Desai, L.; Sanford, M. *J. Am. Chem. Soc.* **2005**, *127*, 7330.

Kalyani, D.; McMurtrey, K.; Neufeldt, S.; Sanford, M. *J. Am. Chem. Soc.* **2011**, *133*, 18566.

C–H arylation: a model reaction



Literature precedent:
aryl diazonium reagents

room temperature activation

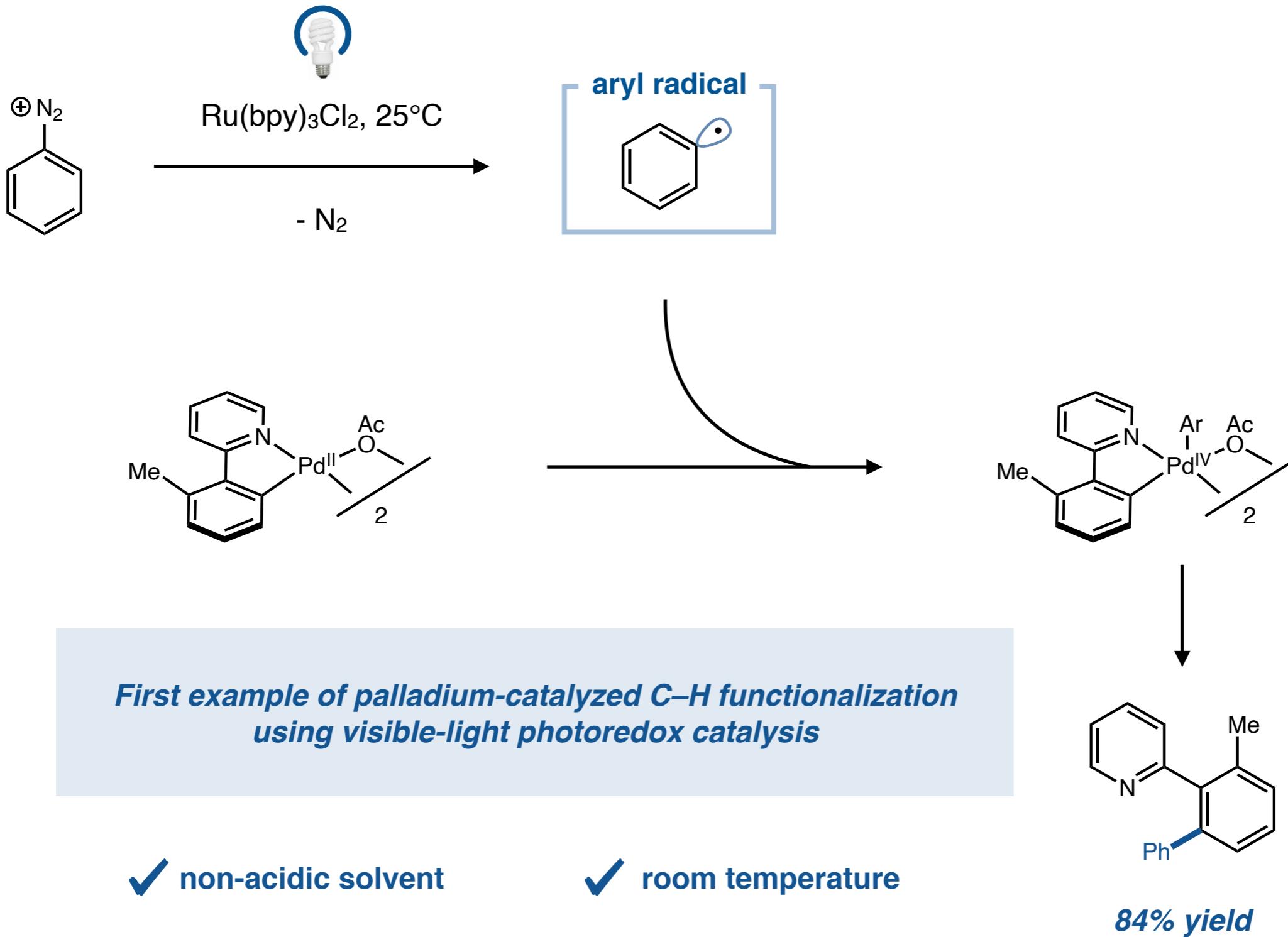
aryl radical generation

nitrogen as byproduct

Kalyani, D.; Deprez, N.; Desai, L.; Sanford, M. *J. Am. Chem. Soc.* **2005**, *127*, 7330.

Kalyani, D.; McMurtrey, K.; Neufeldt, S.; Sanford, M. *J. Am. Chem. Soc.* **2011**, *133*, 18566.

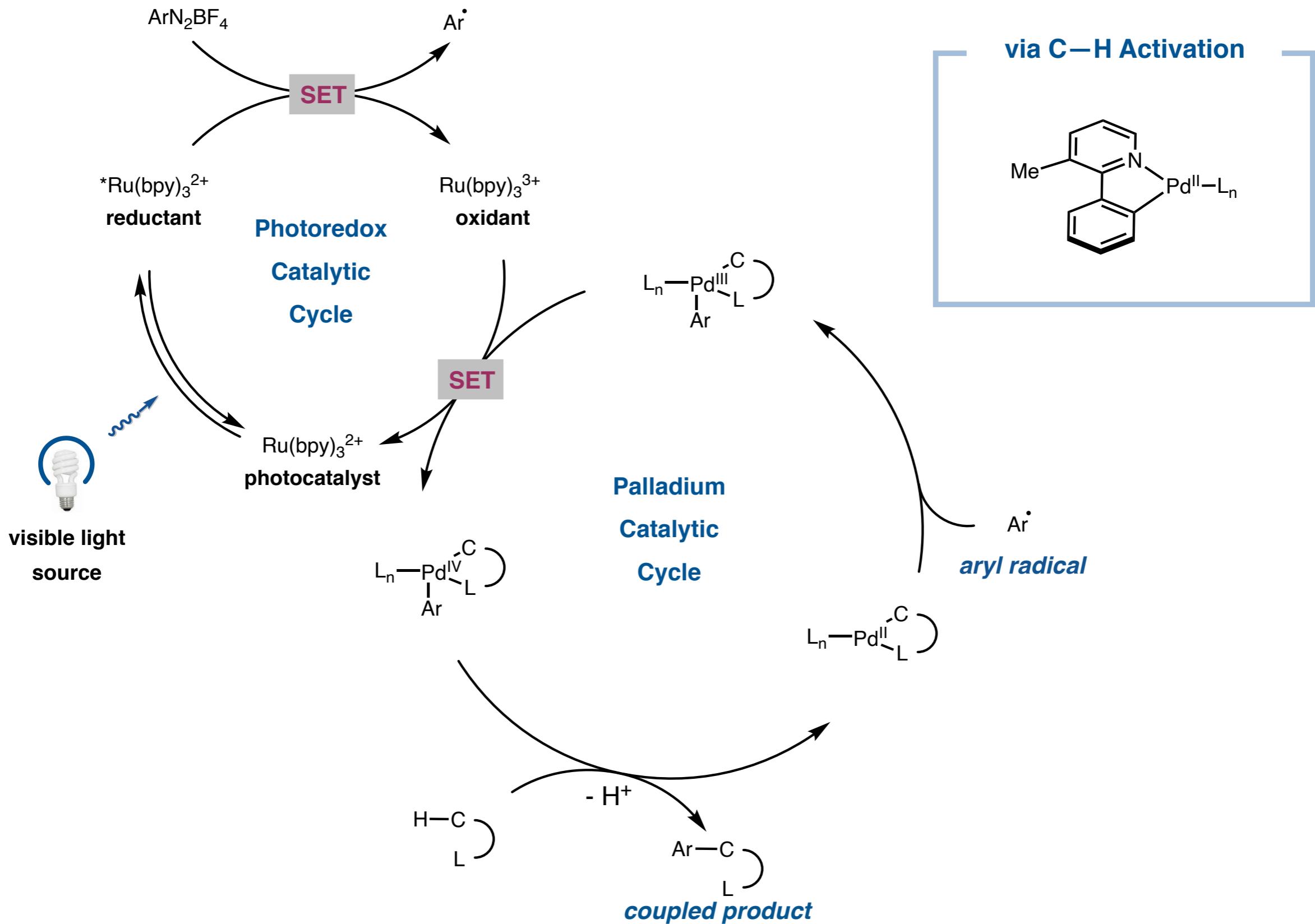
C–H arylation: a model reaction



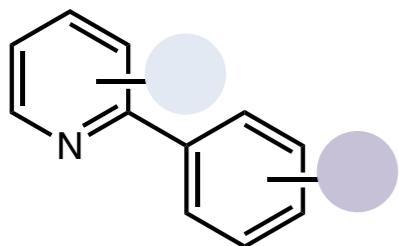
Kalyani, D.; Deprez, N.; Desai, L.; Sanford, M. *J. Am. Chem. Soc.* **2005**, *127*, 7330.

Kalyani, D.; McMurtrey, K.; Neufeldt, S.; Sanford, M. *J. Am. Chem. Soc.* **2011**, *133*, 18566.

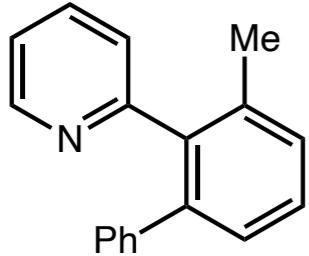
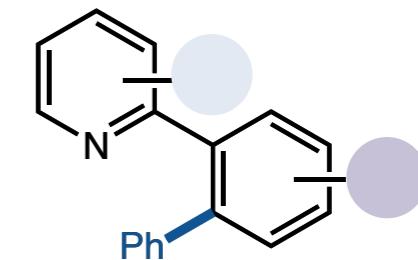
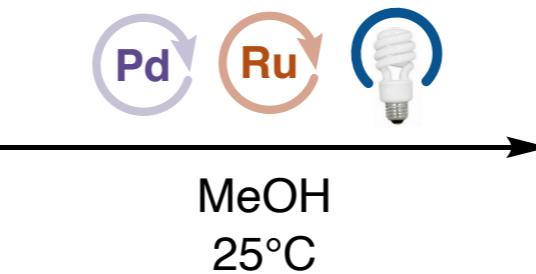
Proposed mechanism



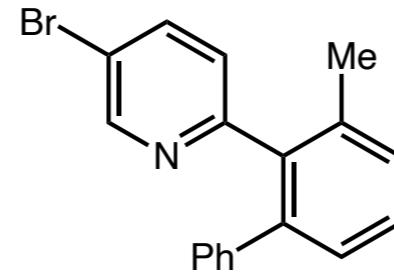
Scope of arylpyridine



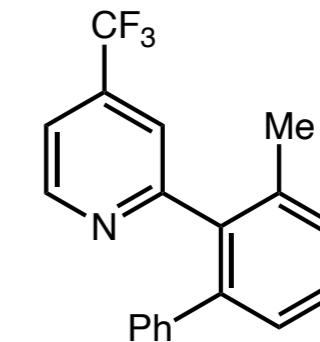
[ArN₂]⁺



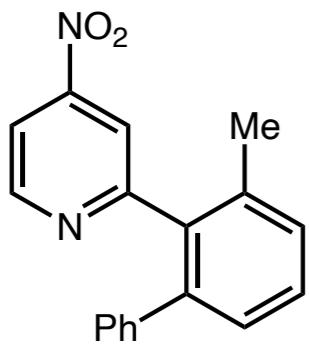
76% yield



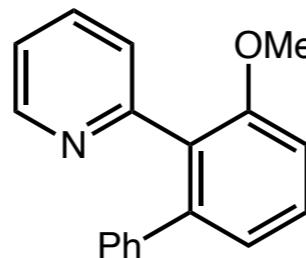
63% yield



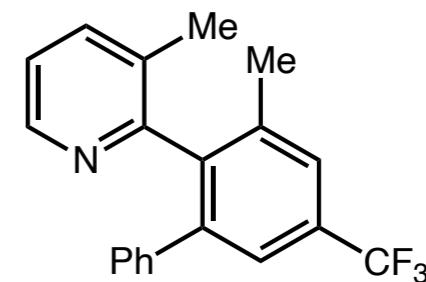
59% yield



47% yield

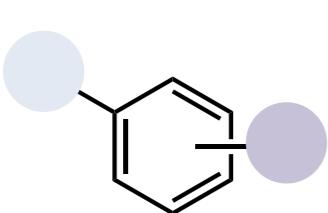


69% yield

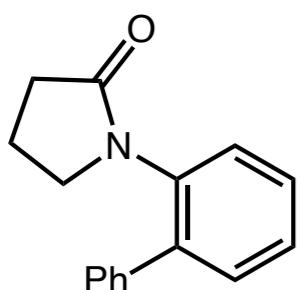
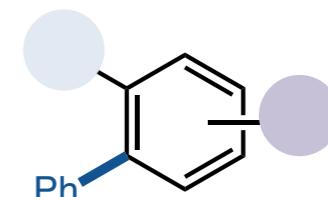
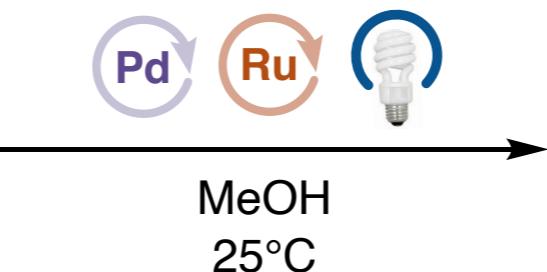


60% yield

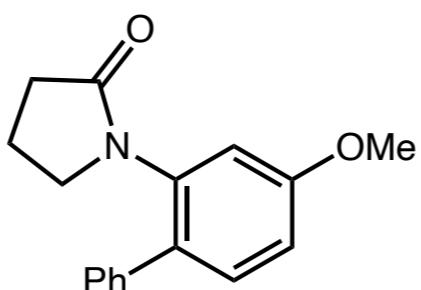
Scope of directing group



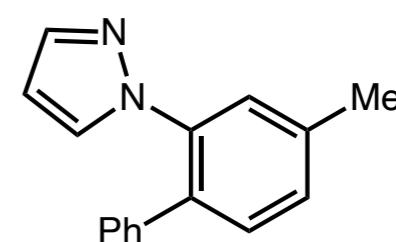
$[\text{ArN}_2]^+$



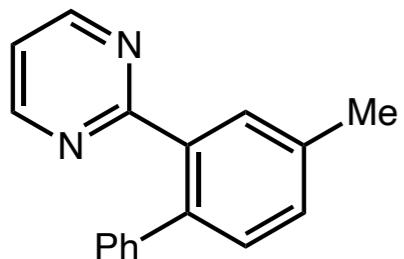
72% yield



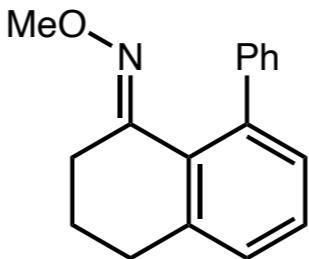
79% yield



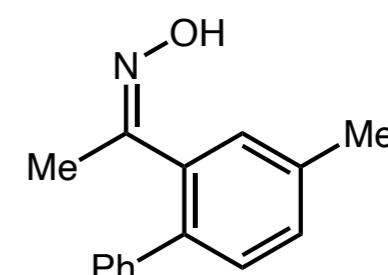
53% yield



44% yield

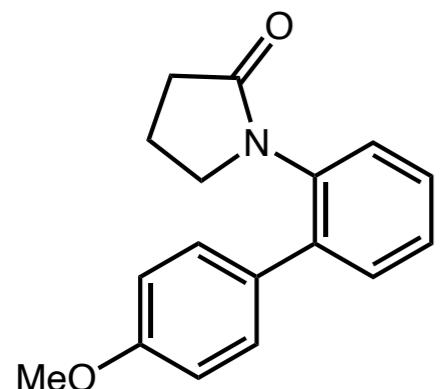
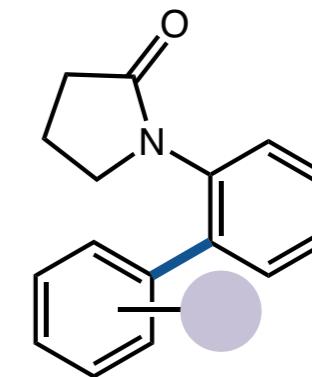
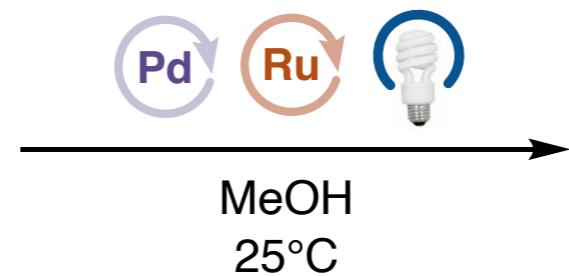
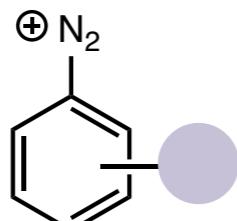
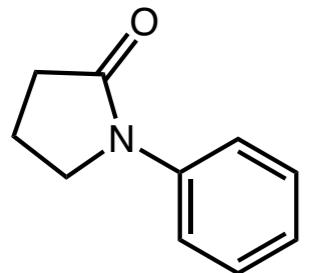


49% yield

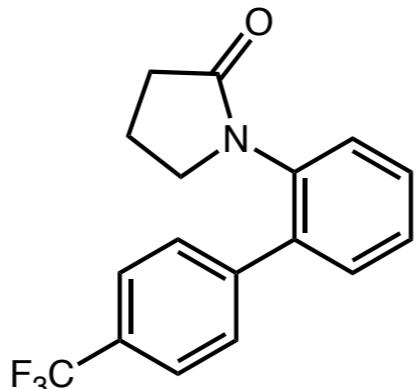


50% yield

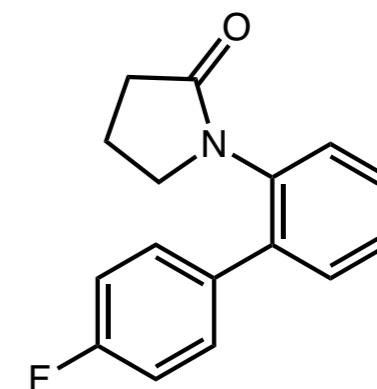
Scope of aryl diazonium



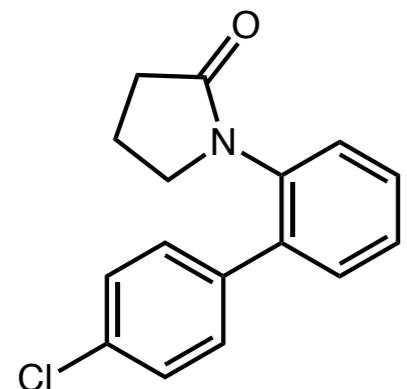
76% yield



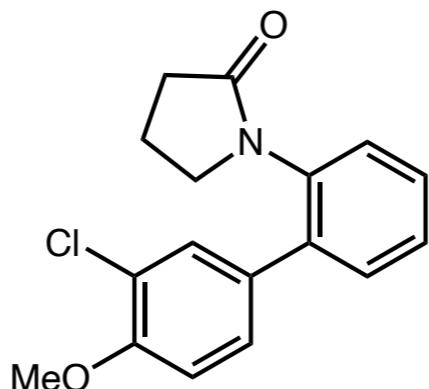
87% yield



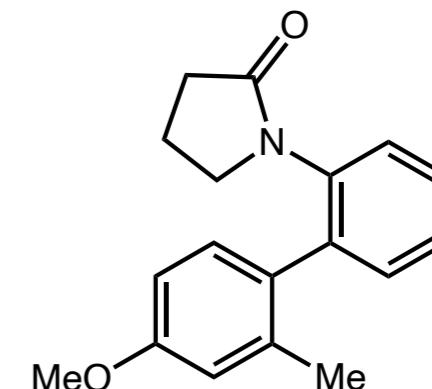
76% yield



78% yield

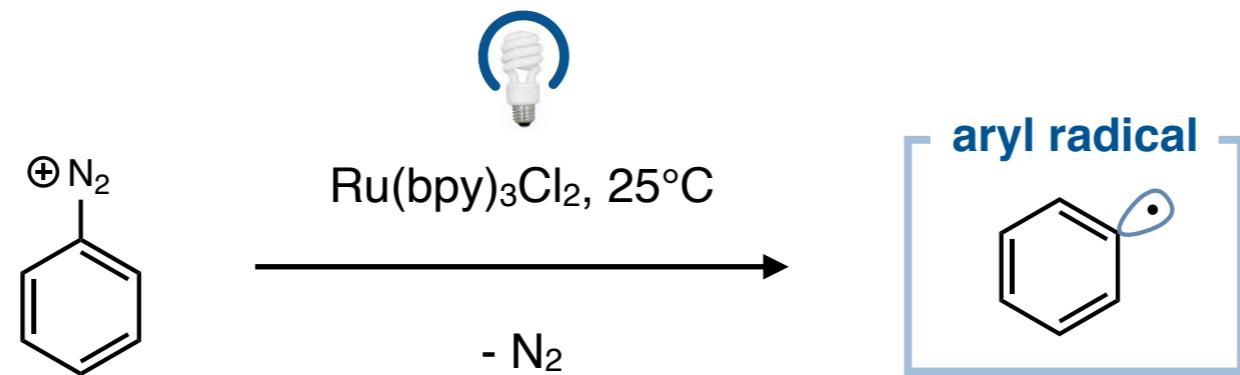


79% yield



57% yield

C–H activation with diaryliodonium reagents



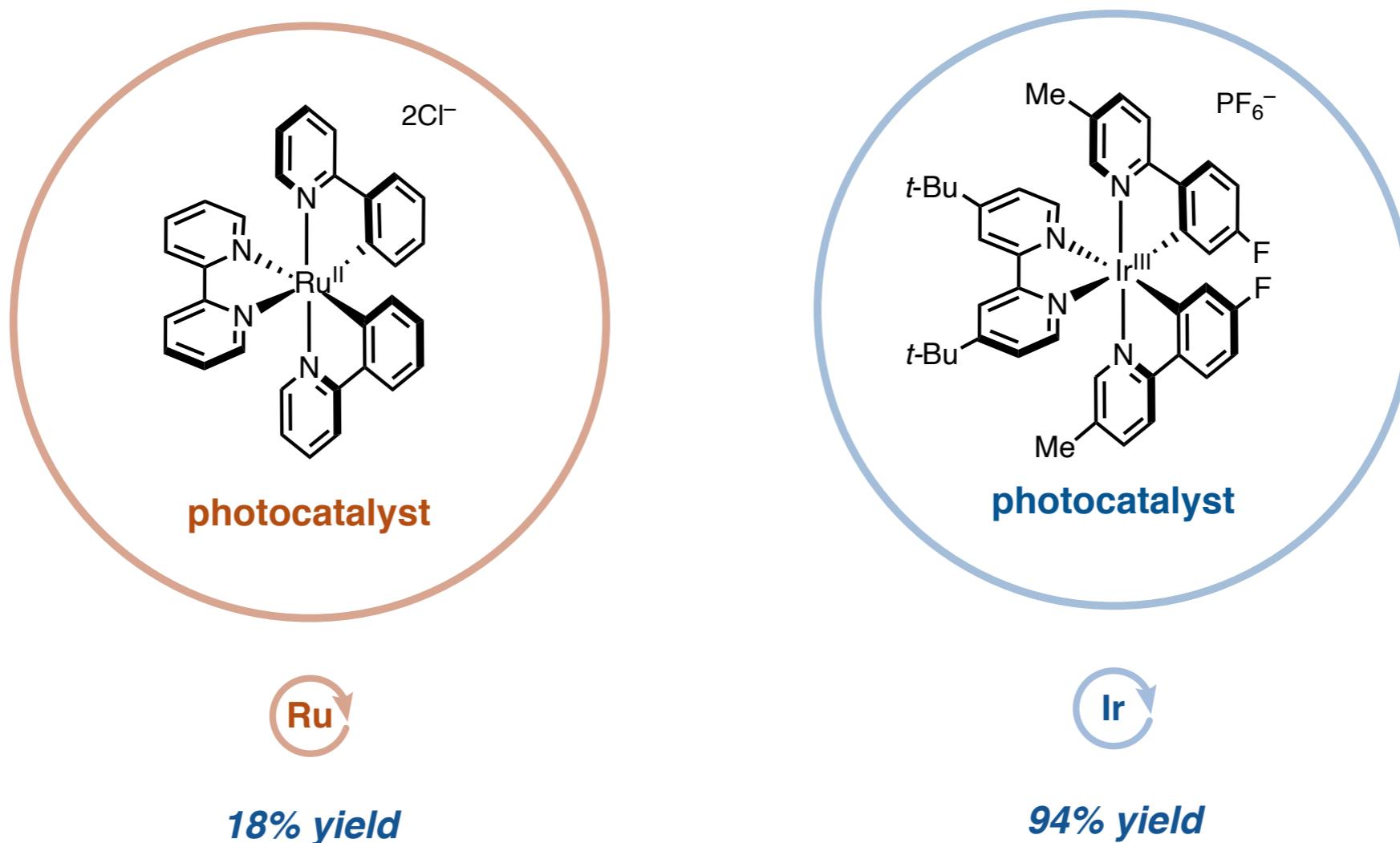
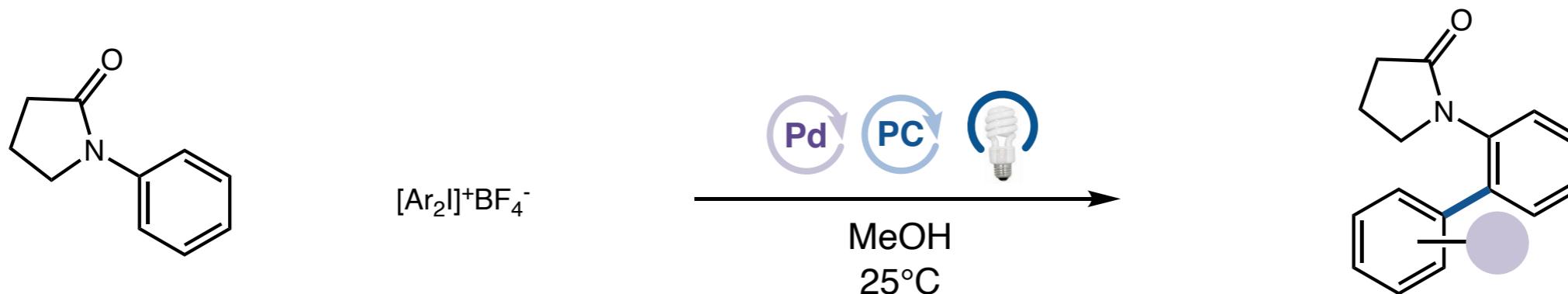
Can we apply these principles towards C–H activation with diaryliodonium reagents?

Neufeldt, S.; Sanford, M. *Adv. Synth. Catal.* **2012**, 354, 3517.

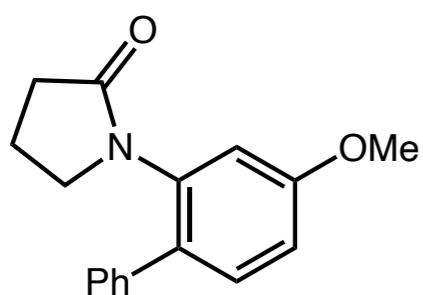
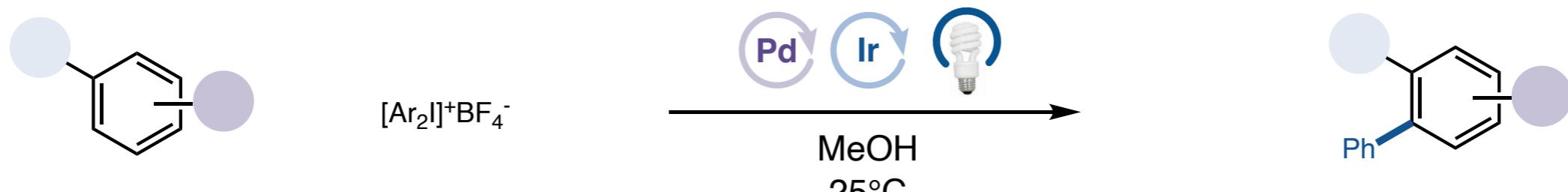
Kalyani, D.; Deprez, N.; Desai, L.; Sanford, M. *J. Am. Chem. Soc.* **2005**, 127, 7330.

Kalyani, D.; McMurtrey, K.; Neufeldt, S.; Sanford, M. *J. Am. Chem. Soc.* **2011**, 133, 18566.

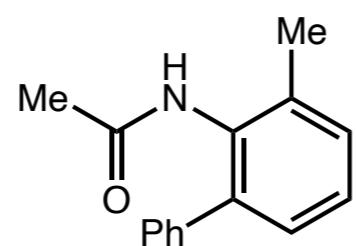
C—H activation with diaryliodonium reagents



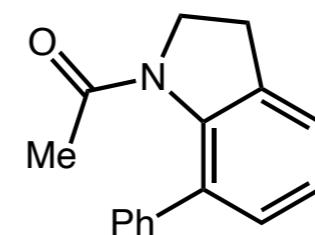
Scope of directing group



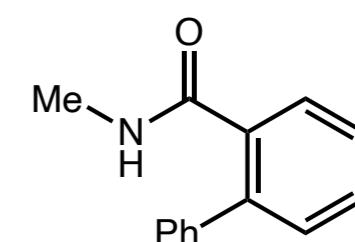
94% yield



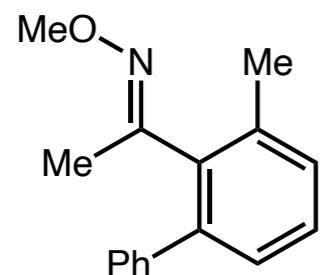
72% yield



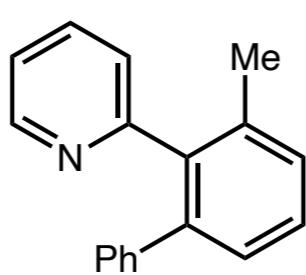
44% yield



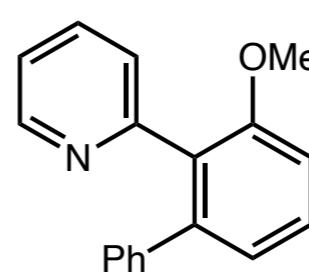
54% yield



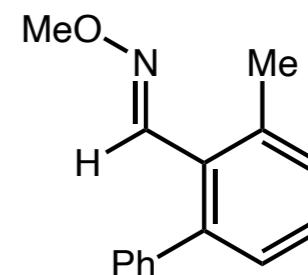
60% yield



62% yield

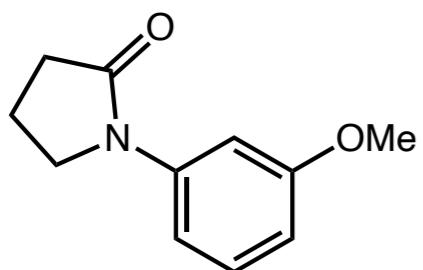


67% yield

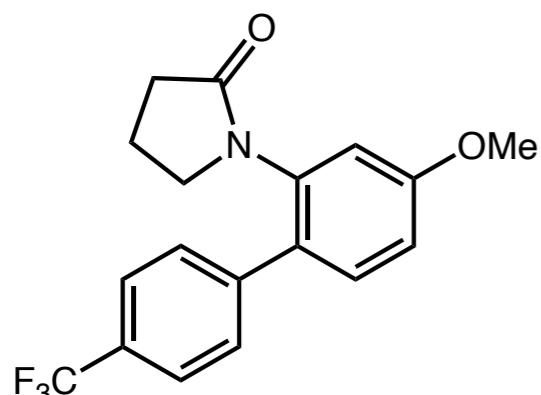
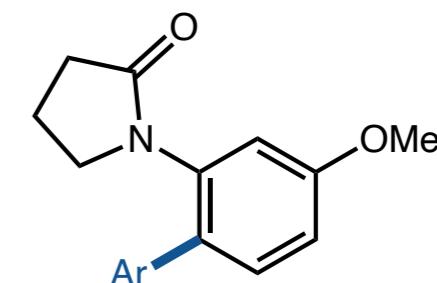
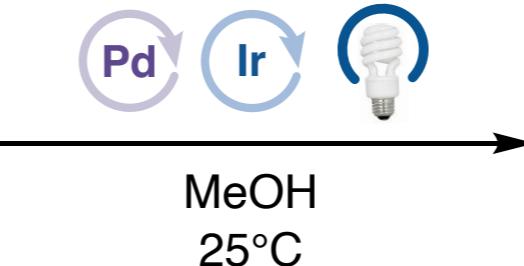


57% yield

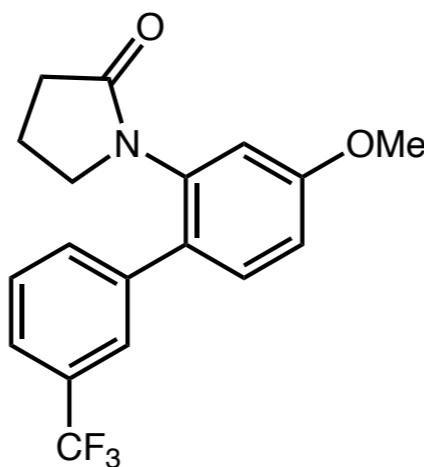
Scope of diaryliodonium reagents



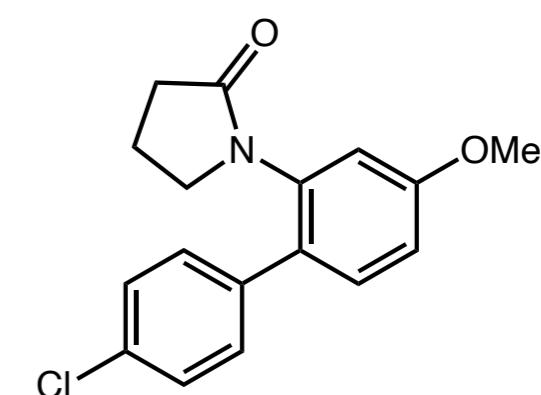
$[\text{Ar}_2\text{I}]^+\text{BF}_4^-$



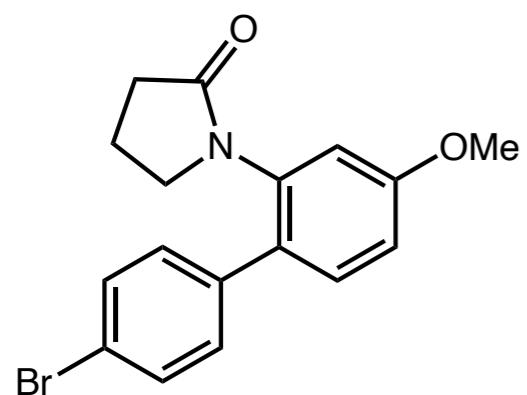
69% yield



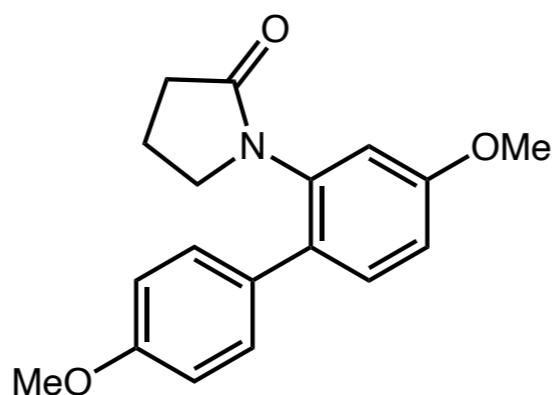
56% yield



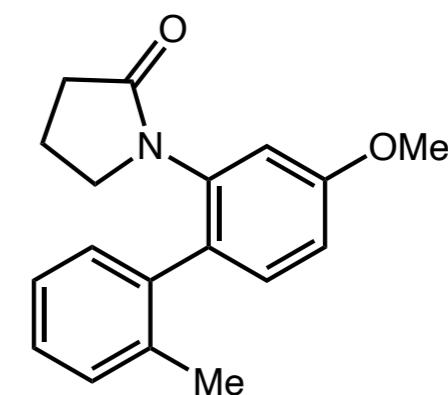
77% yield



79% yield

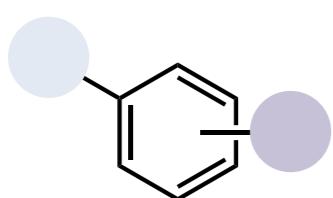


41% yield

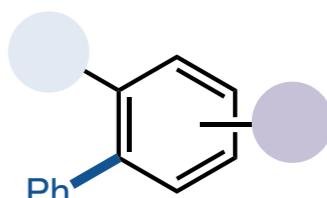


85% yield

Comparison of C–H arylation scopes



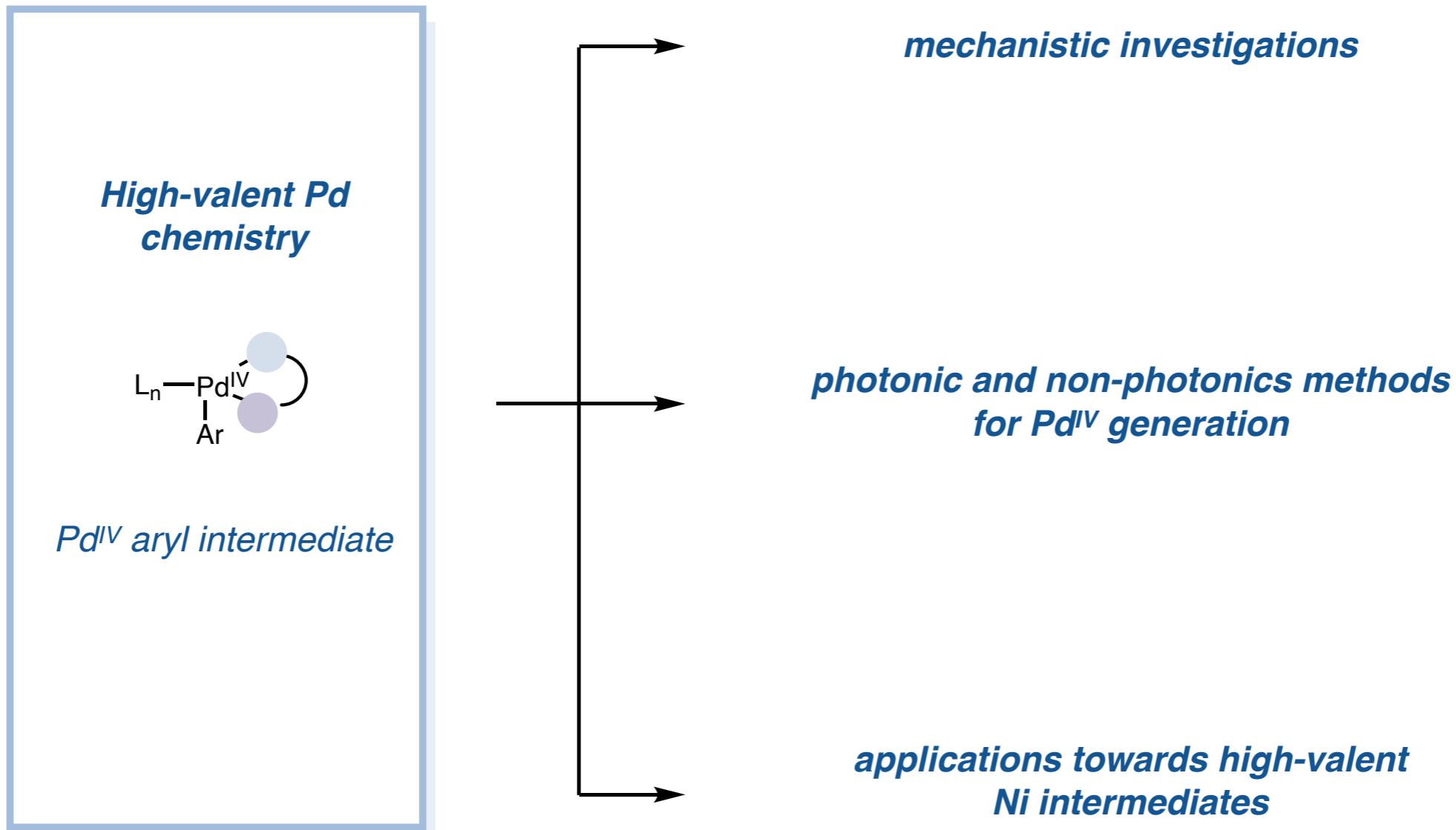
Pd Ir
MeOH
25°C



91% yield	25% yield	38% yield	23% yield	66% yield
89% yield	54% yield	52% yield	52% yield	<1% yield

orthogonal and complementary scopes

Further directions in the Sanford group



Three main areas of radical-based palladium chemistry

Pd Photoredox:
aryl C–H activation

SET from Pd:
olefin functionalization

Atom Abstraction:
C–C bond formation



Melanie Sanford
University of Michigan



Frank Glorius
WWU Münster



Erik Alexanian
University of North Carolina-
Chapel Hill

Three main areas of radical-based palladium chemistry

Pd Photoredox:
aryl C–H activation

SET from Pd:
olefin functionalization

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C–C bond formation



Melanie Sanford
University of Michigan



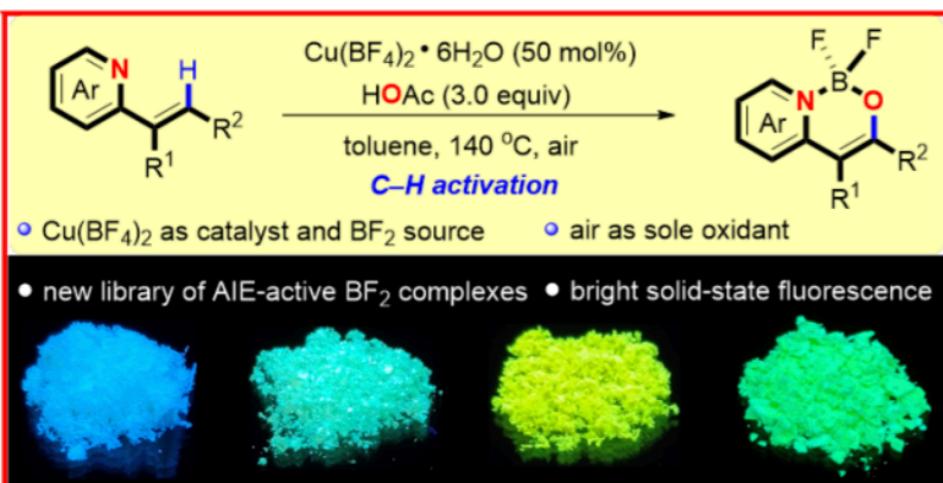
Frank Glorius
WWU Münster



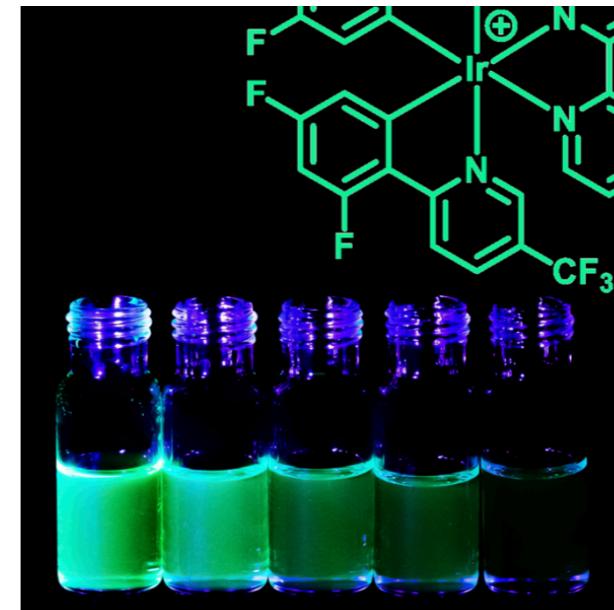
Erik Alexanian
University of North Carolina-
Chapel Hill

Research in the Glorius group

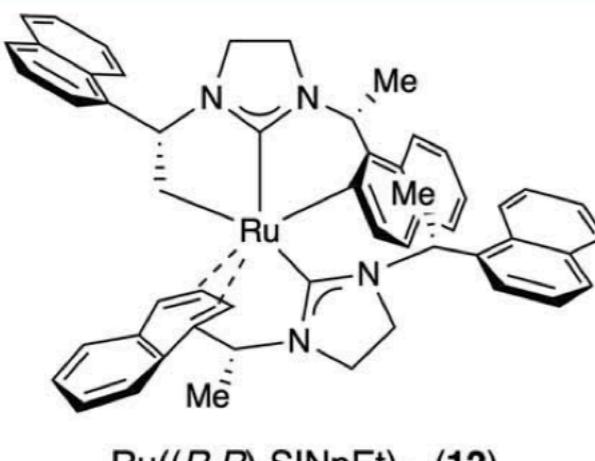
C—H Activation



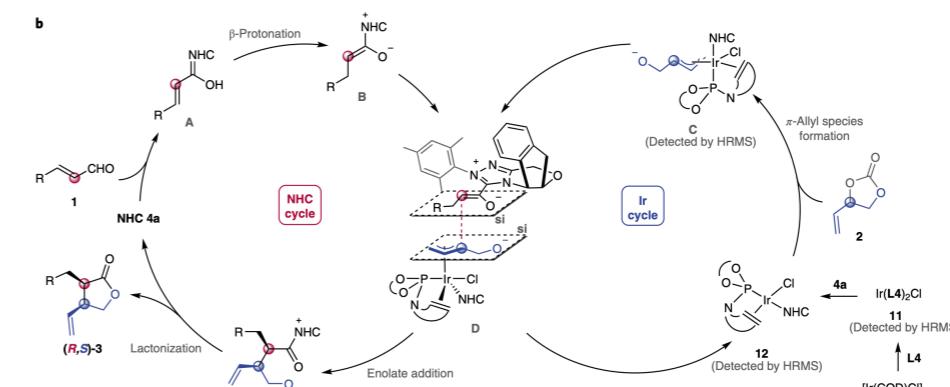
Photocatalysis



Arene Hydrogenation



Organocatalysis



Pinkert, T.; Das, M.; Schrader, M.; Glorius, F. *J. Am. Chem. Soc.* **2021**, *143*, 7648.

Huang, H.; Bellotti, P.; Chen, P.; Houk, K.; Glorius, F. *Nature Synth.* **2022**, *1*, 59.

Singha, S.; Serrano, E.; Mondal, S.; Daniliuc, C.; Glorius, F. *Nature Cat.* **2020**, *3*, 48.

Wiesenfeldt, M.; Moock, D.; Paul, D.; Glorius, F. *Chem. Sci.* **2021**, *12*, 5611.

Research in the Glorius group

Photocatalysis



A.B. Chemistry: University of Hannover,
1997 (H. M. R. Hoffmann)

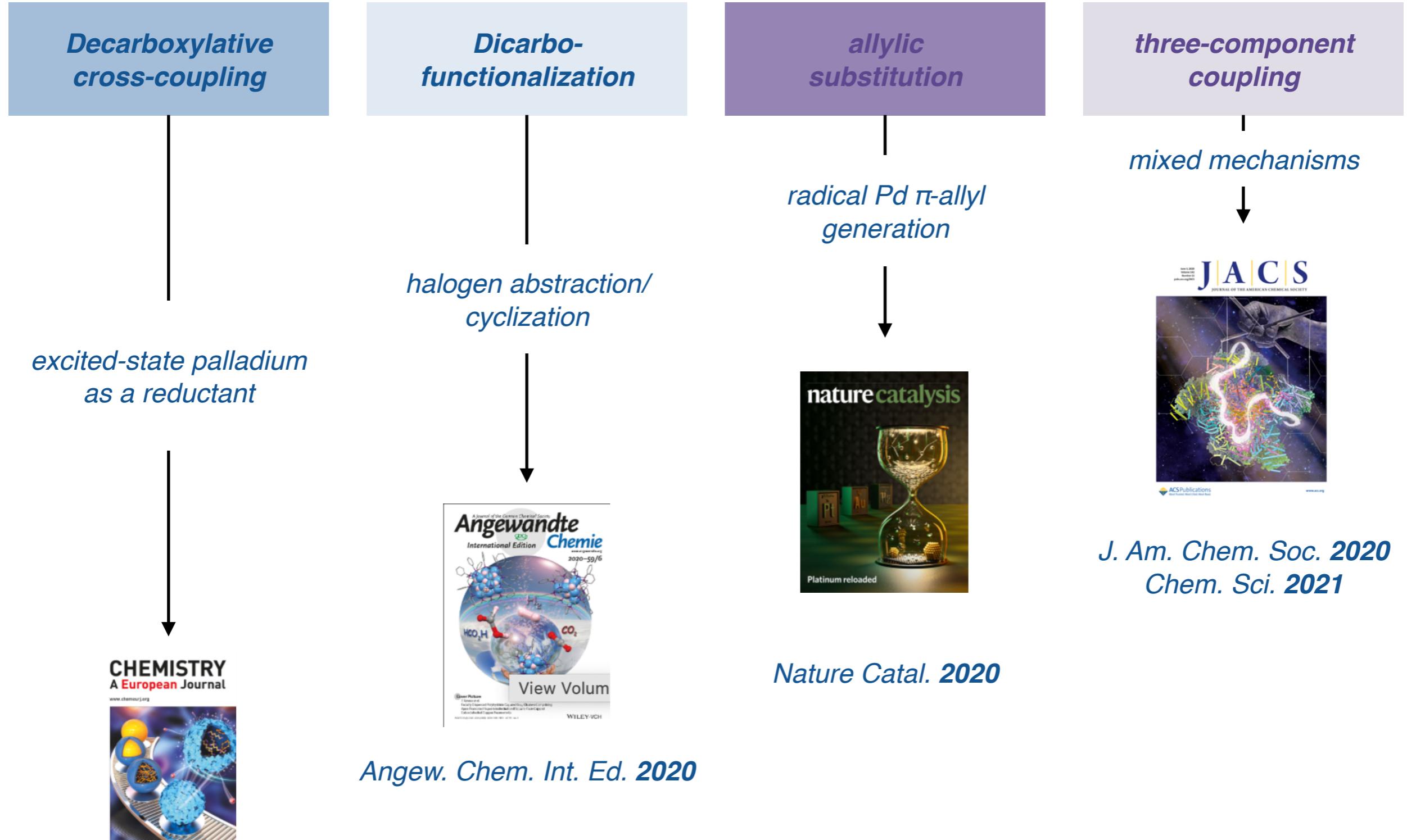
PhD. Chemistry: University of Basel,
2000 (Andreas Pfaltz)

Postdoc: Harvard University,
2001 (David Evans)



- Pinkert, T.; Das, M.; Schrader, M.; Glorius, F. *J. Am. Chem. Soc.* **2021**, *143*, 7648.
Huang, H.; Bellotti, P.; Chen, P.; Houk, K.; Glorius, F. *Nature Synth.* **2022**, *1*, 59.
Singha, S.; Serrano, E.; Mondal, S.; Daniliuc, C.; Glorius, F. *Nature Cat.* **2020**, *3*, 48.
Wiesenfeldt, M.; Moock, D.; Paul, D.; Glorius, F. *Chem. Sci.* **2021**, *12*, 5611.

Glorius group contribution to radical palladium chemistry

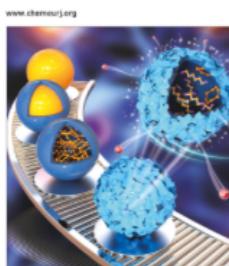


Decarboxylative cross-coupling

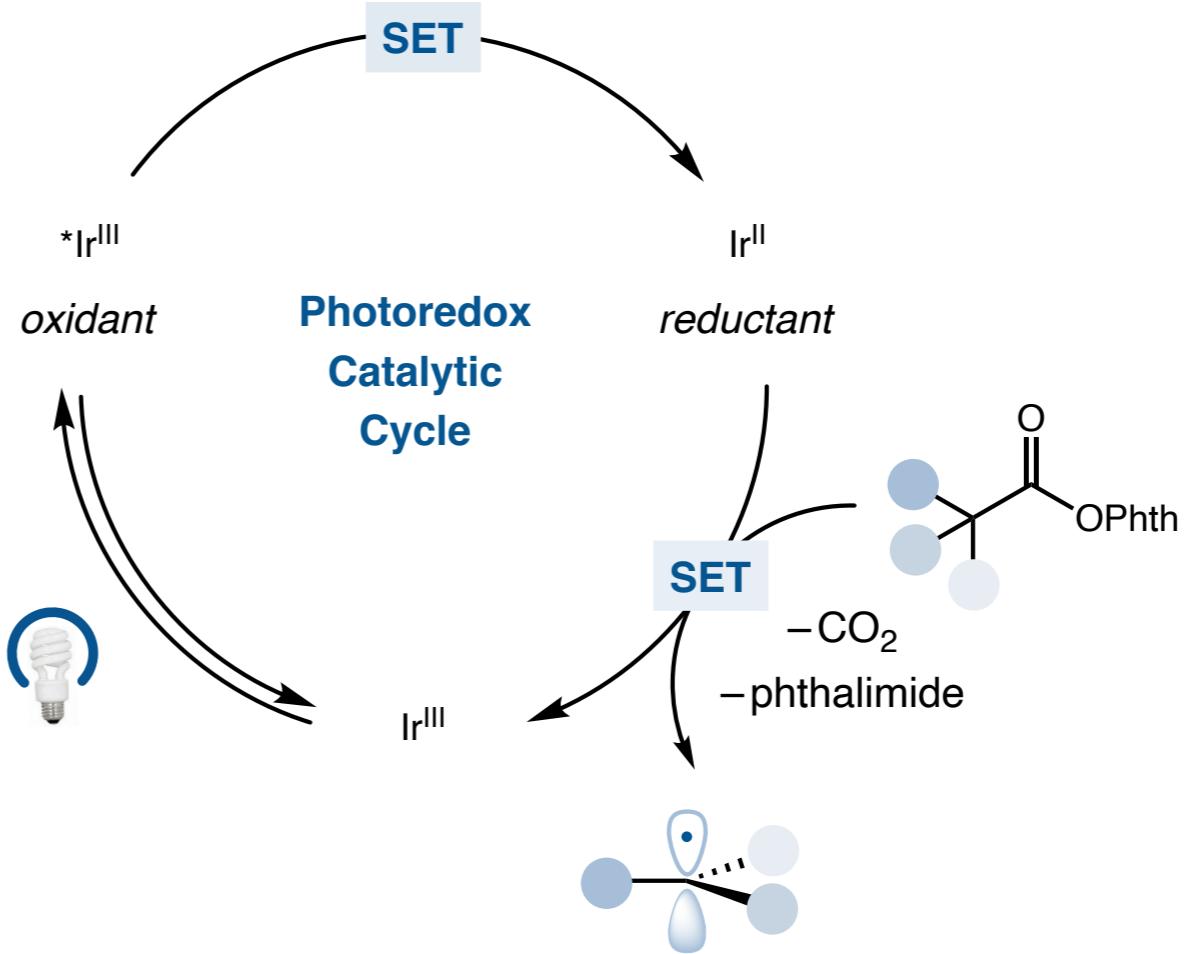
Decarboxylative cross-coupling

excited-state palladium
as a reductant

CHEMISTRY
A European Journal



Reminiscent of our Ir photocatalytic cycles!



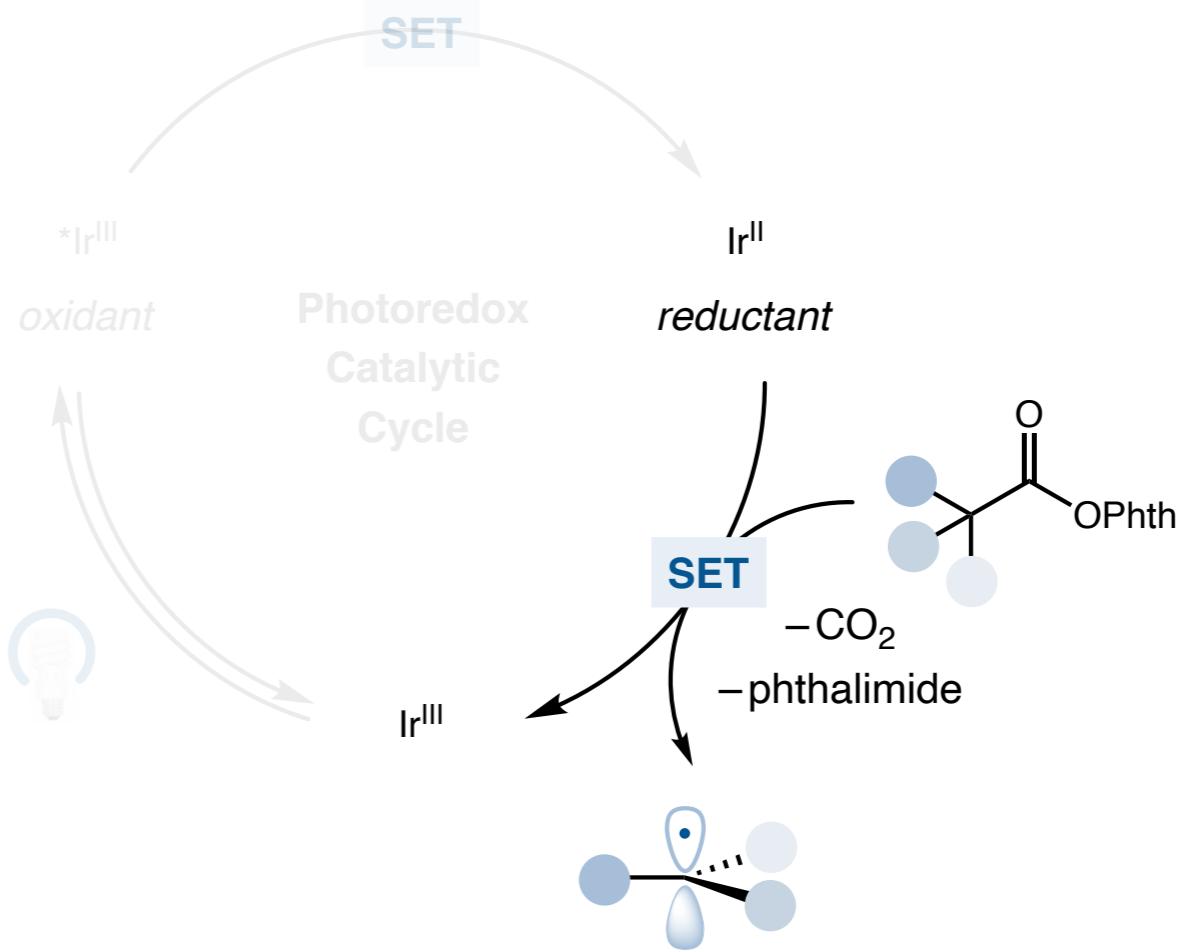
Decarboxylative cross-coupling

Decarboxylative
cross-coupling

excited-state palladium
as a reductant



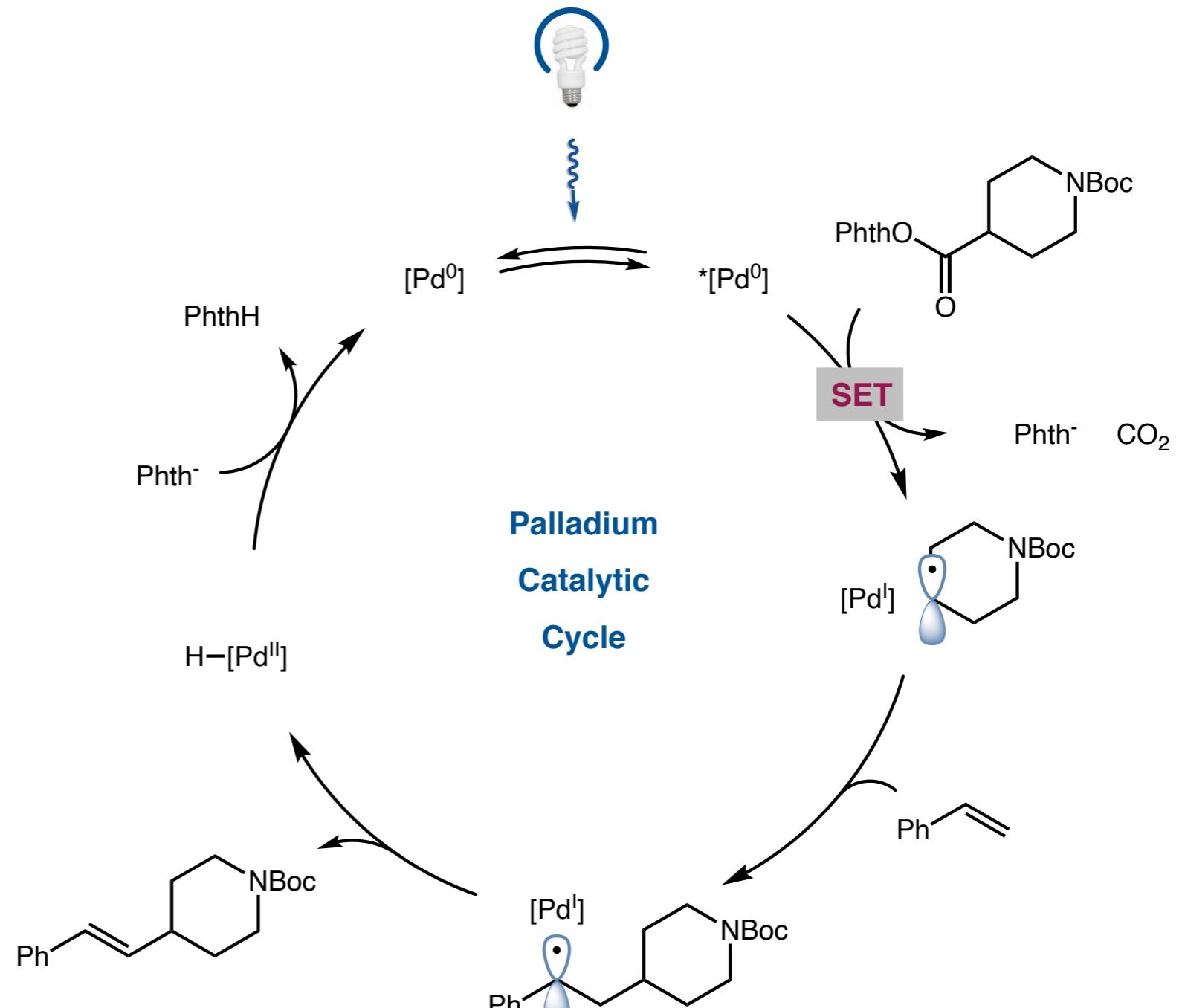
Reminiscent of our Ir photocatalytic cycles!



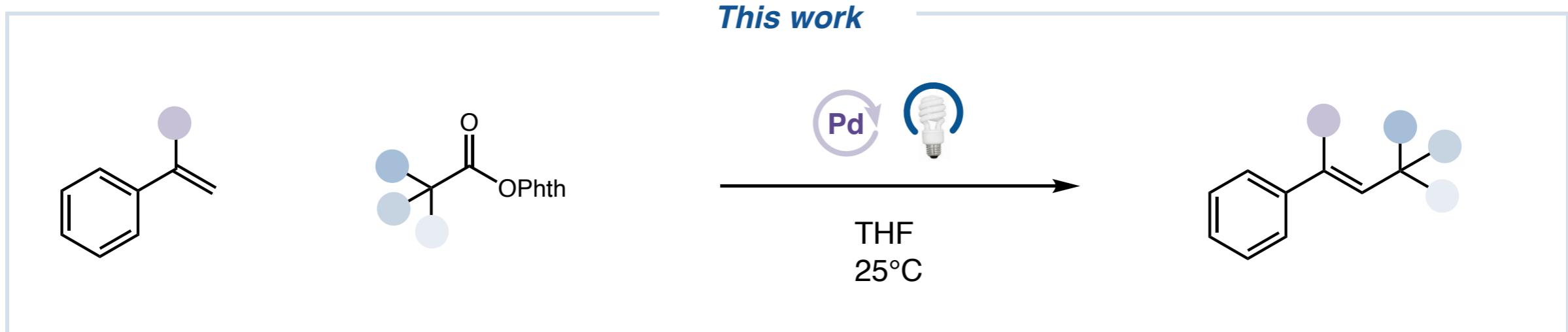
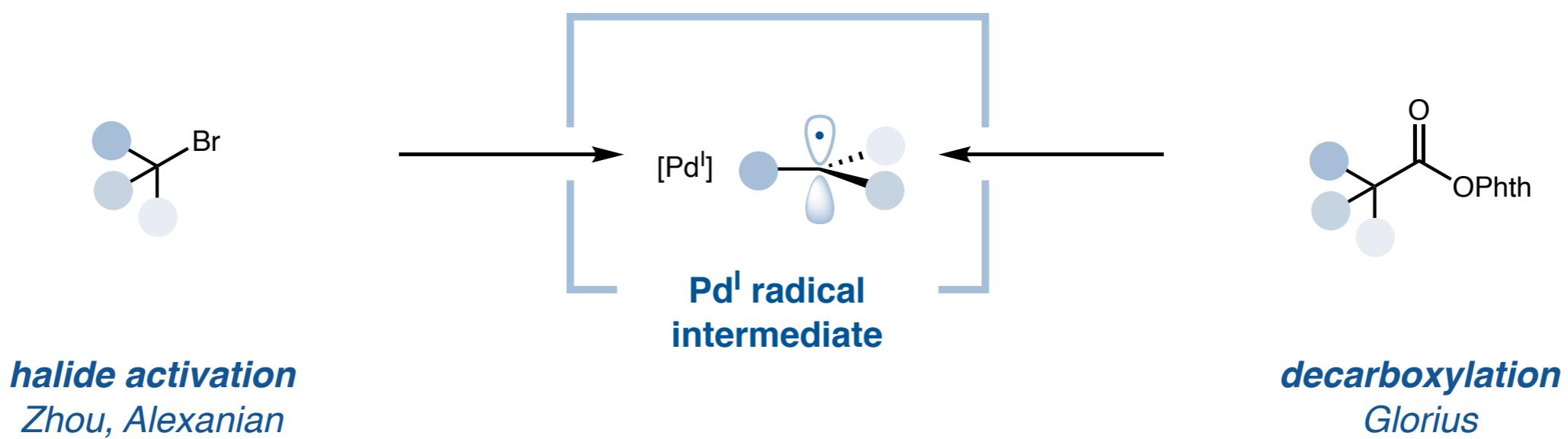
Decarboxylative cross-coupling

Decarboxylative cross-coupling

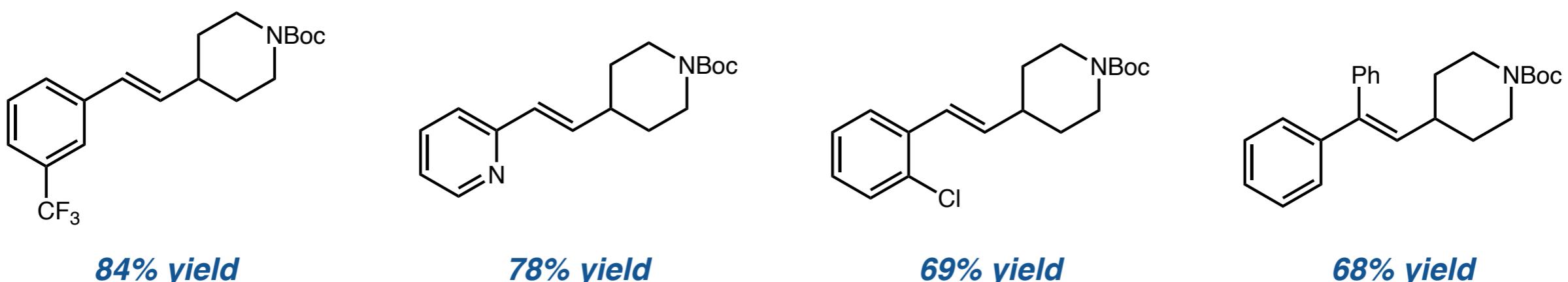
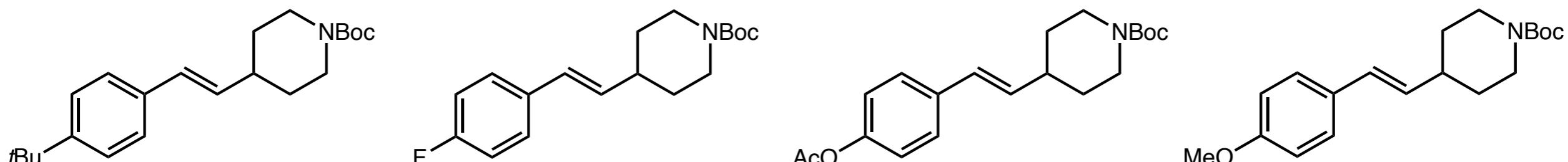
excited-state palladium
as a reductant



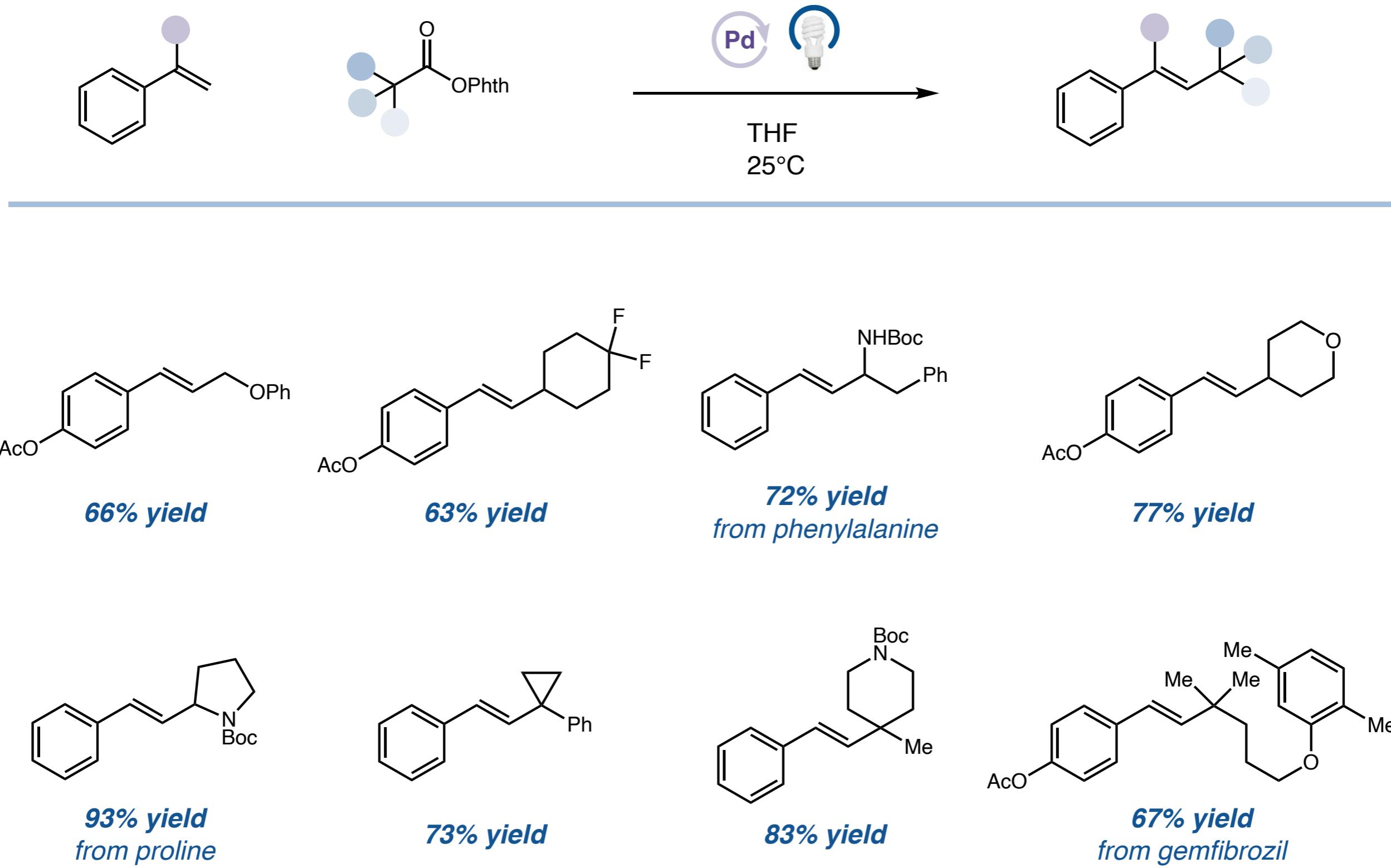
Decarboxylative cross-coupling



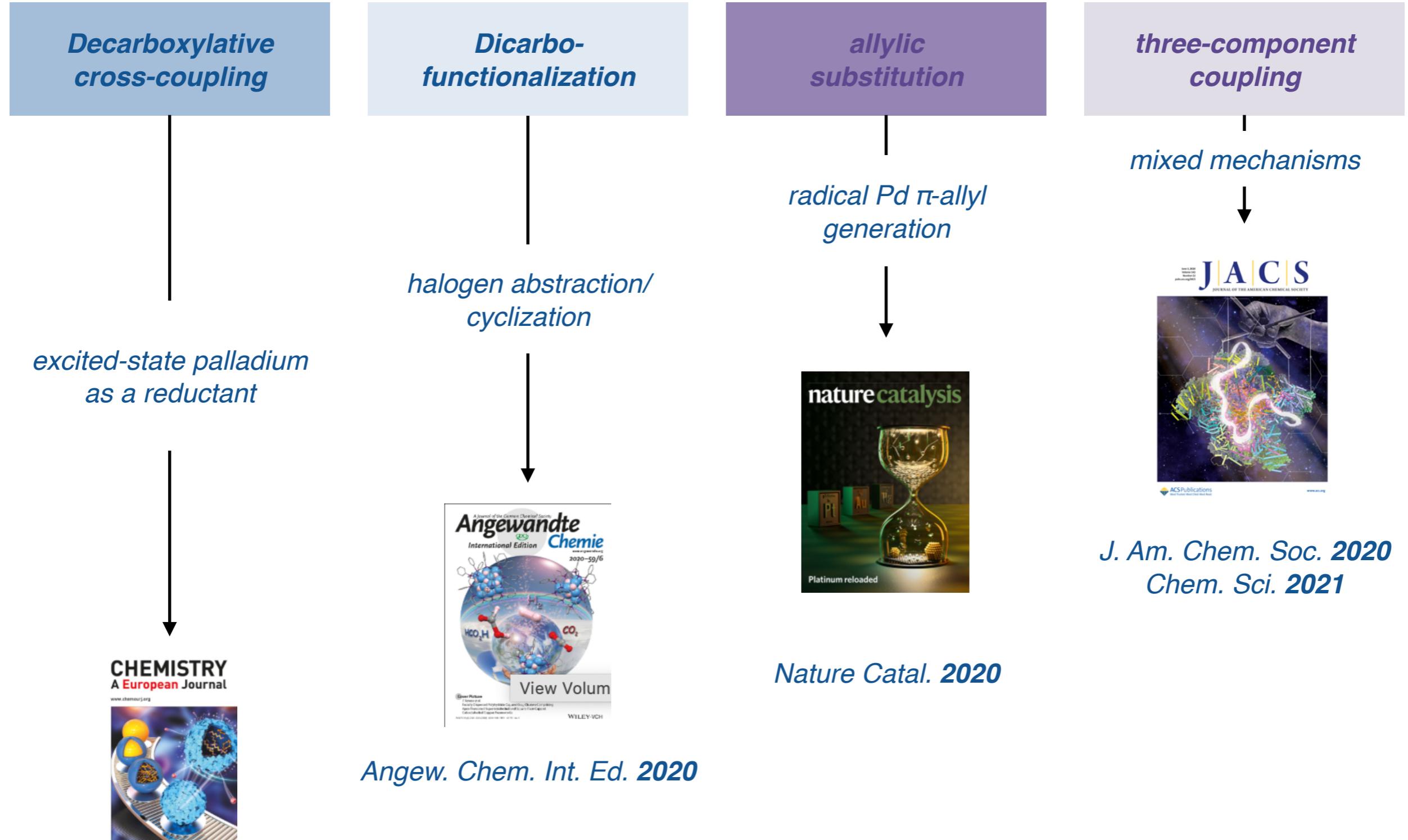
Scope of decarboxylative cross-coupling



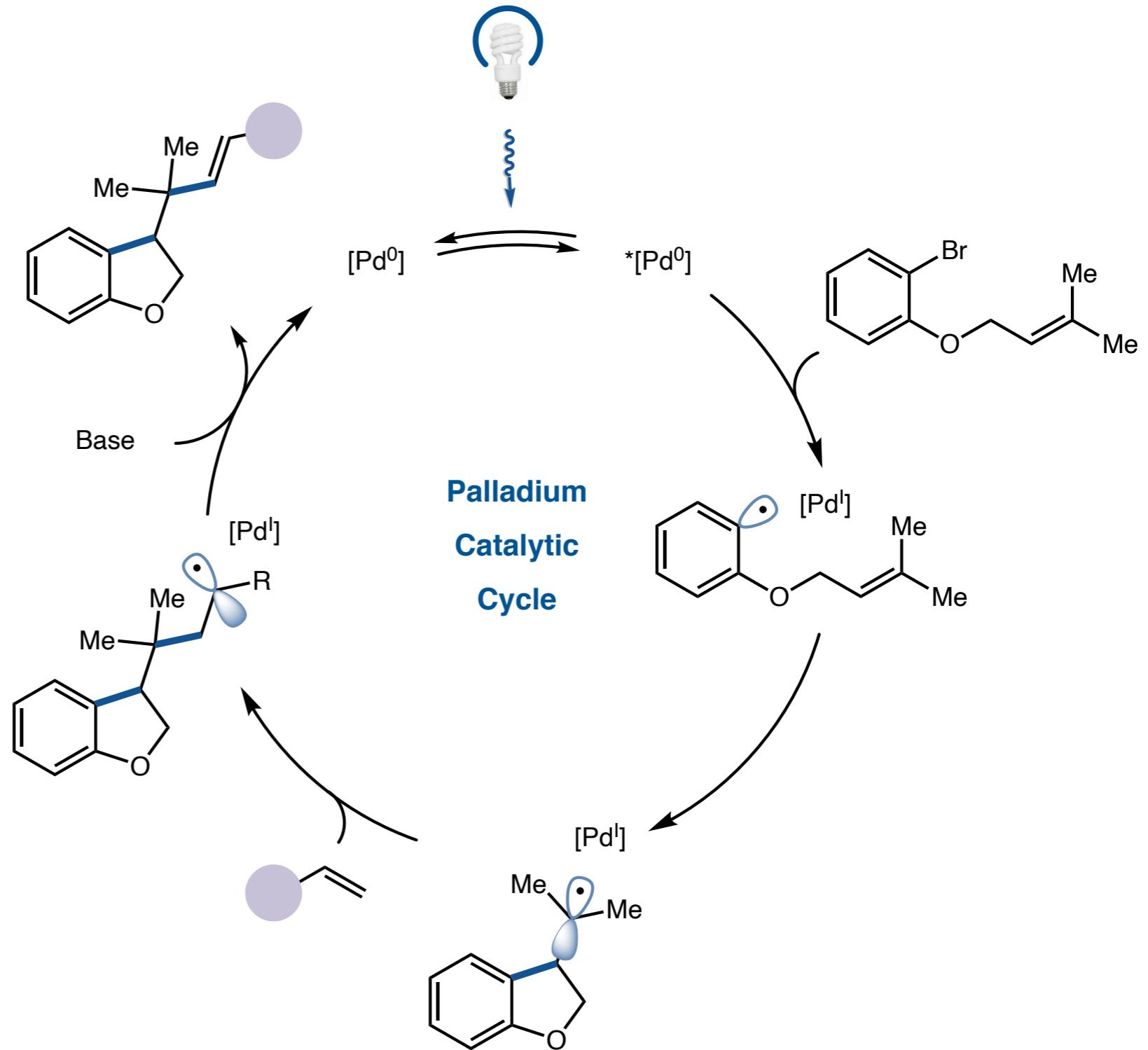
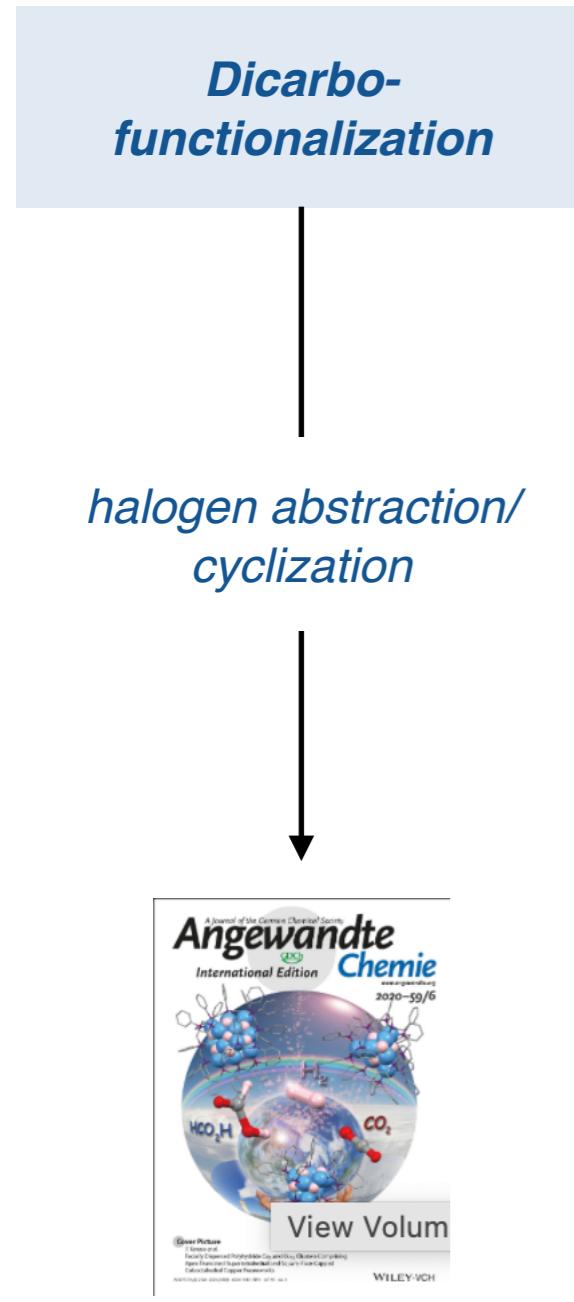
Scope of decarboxylative cross-coupling



Glorius group contribution to radical palladium chemistry

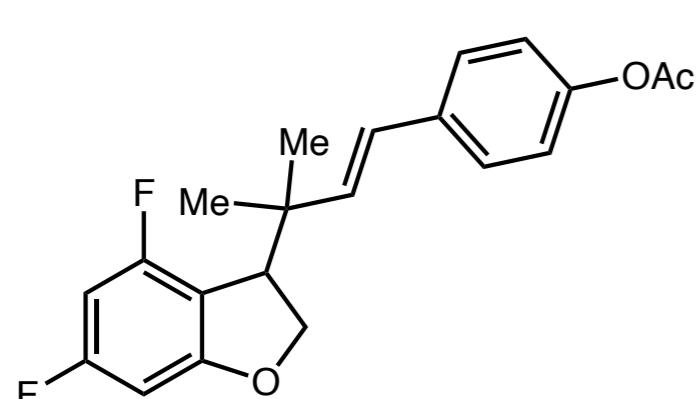


Glorius group contribution to radical palladium chemistry

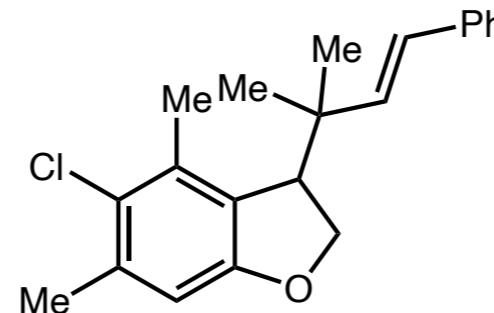


Angew. Chem. Int. Ed. **2020**

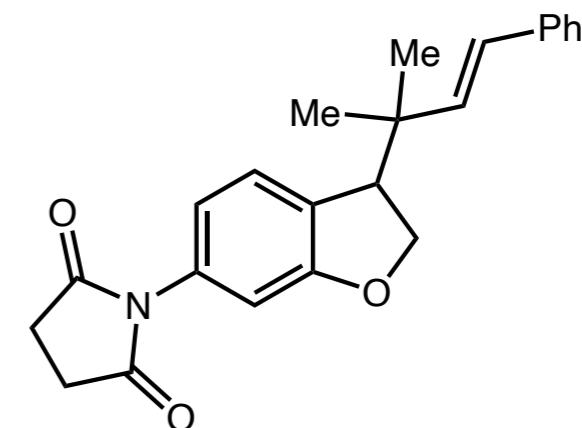
Tethered olefin scope of dicarbofunctionalization



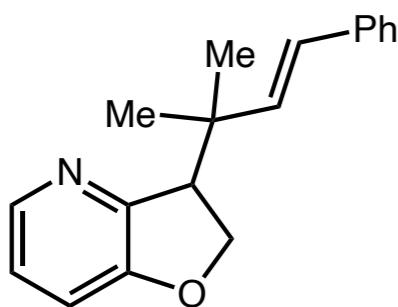
37% yield



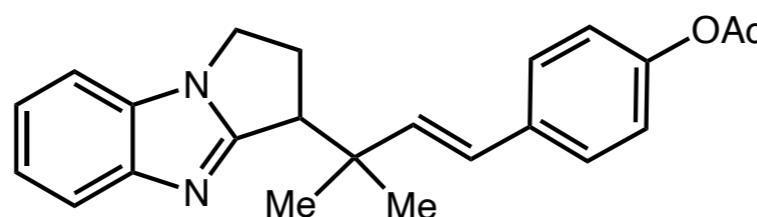
40% yield



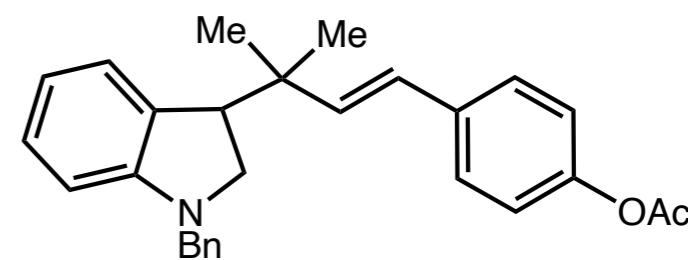
80% yield



61% yield

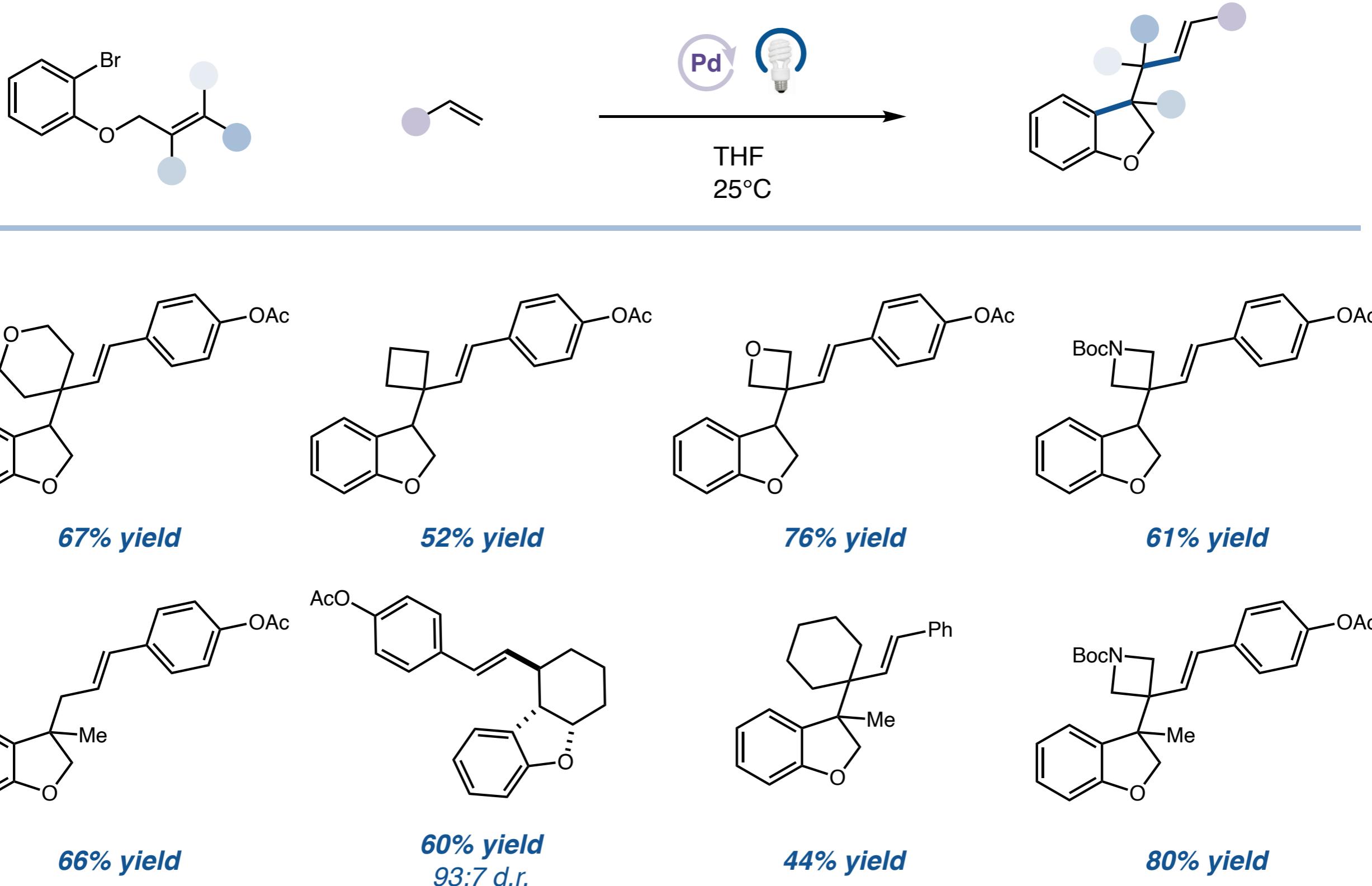


97% yield

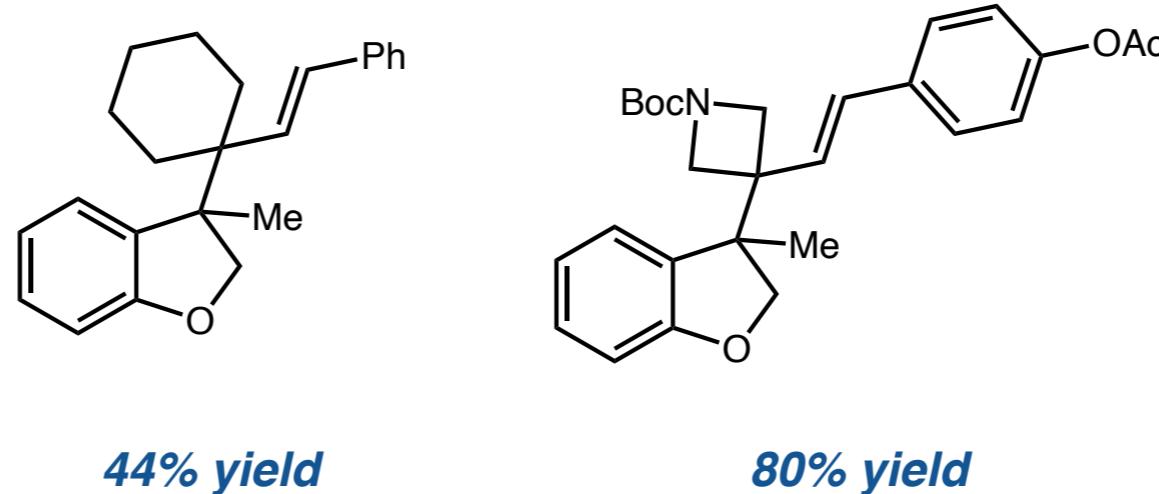
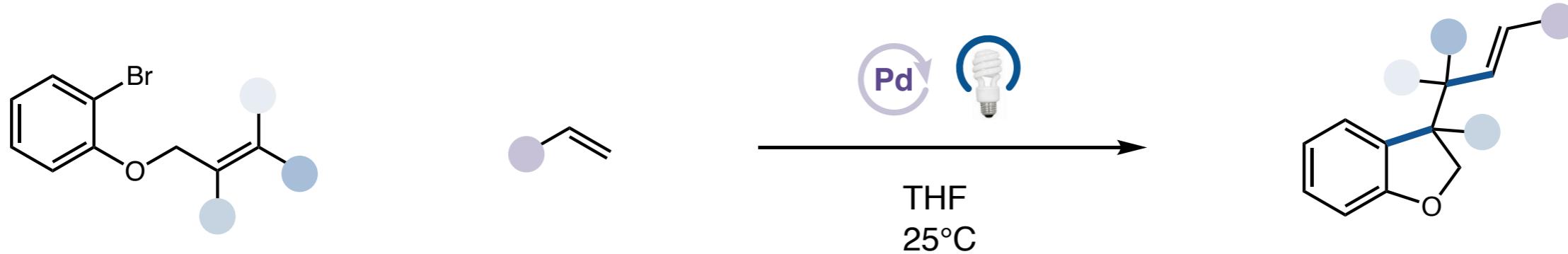


70% yield

Tethered olefin scope of dicarbofunctionalization



Tethered olefin scope of dicarbofunctionalization

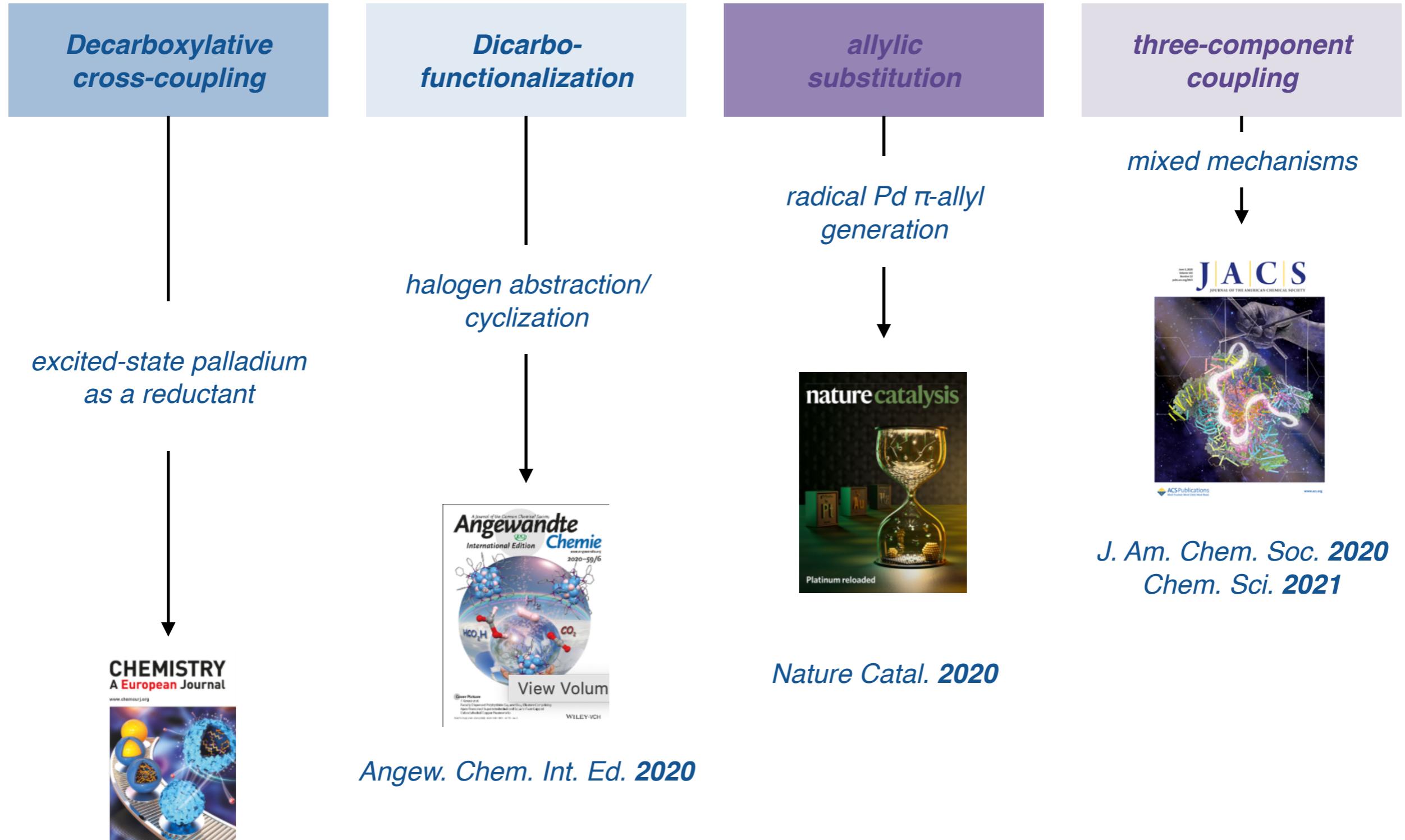


44% yield

80% yield

*This method can form two adjacent, all-carbon
quaternary centers in good yields!*

Glorius group contribution to radical palladium chemistry



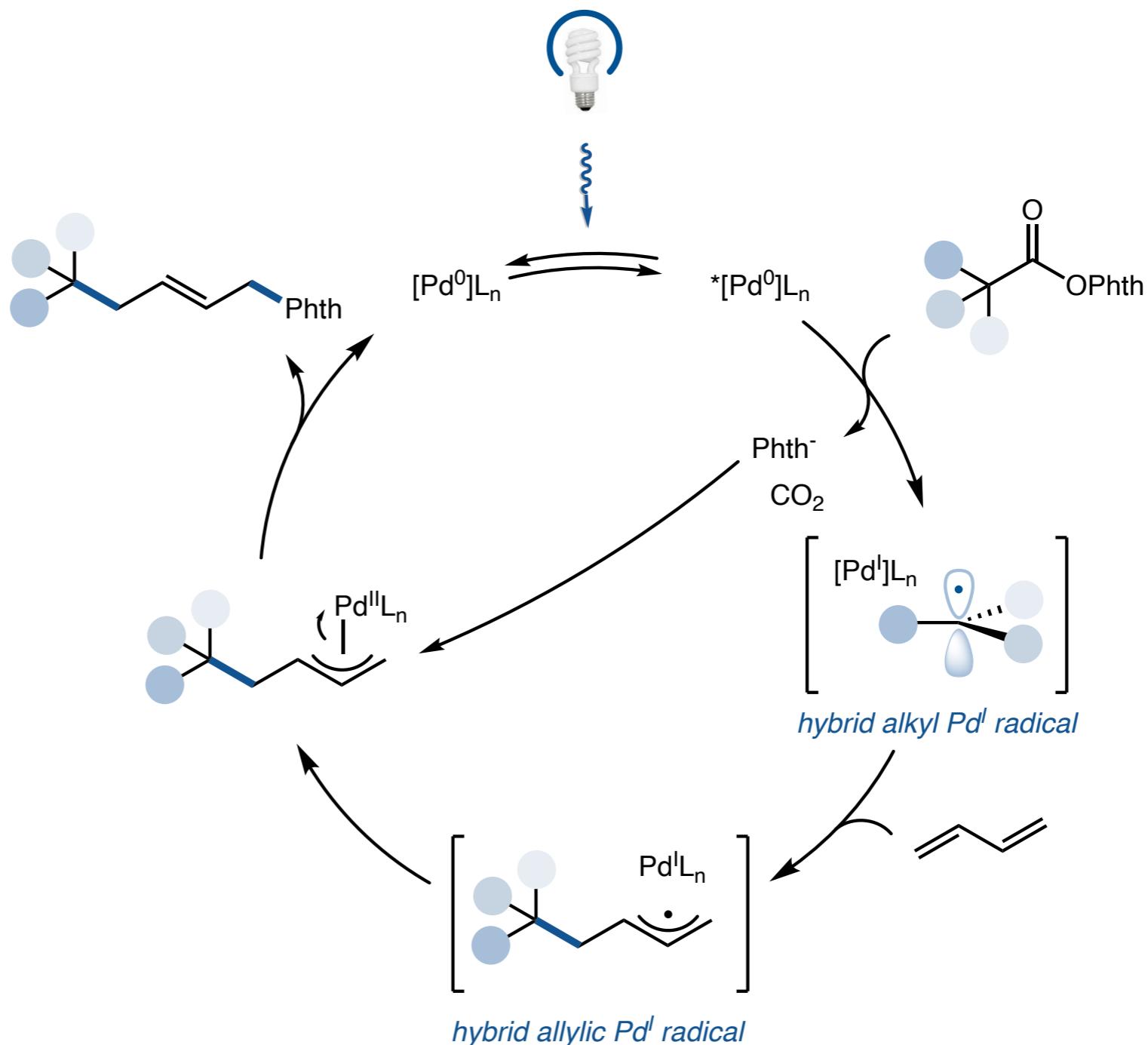
Glorius group contribution to radical palladium chemistry

allylic
substitution

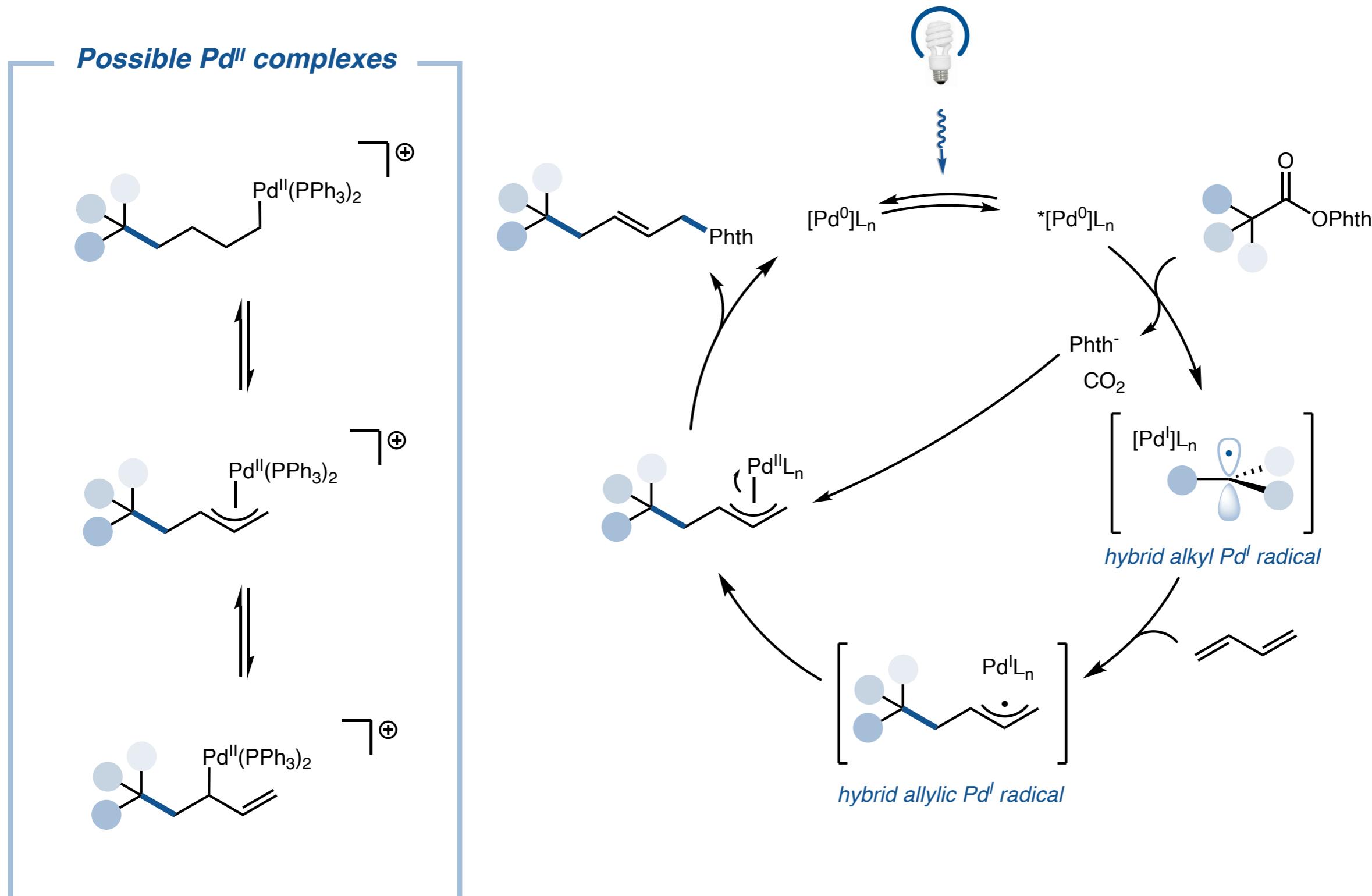
radical Pd π -allyl
generation



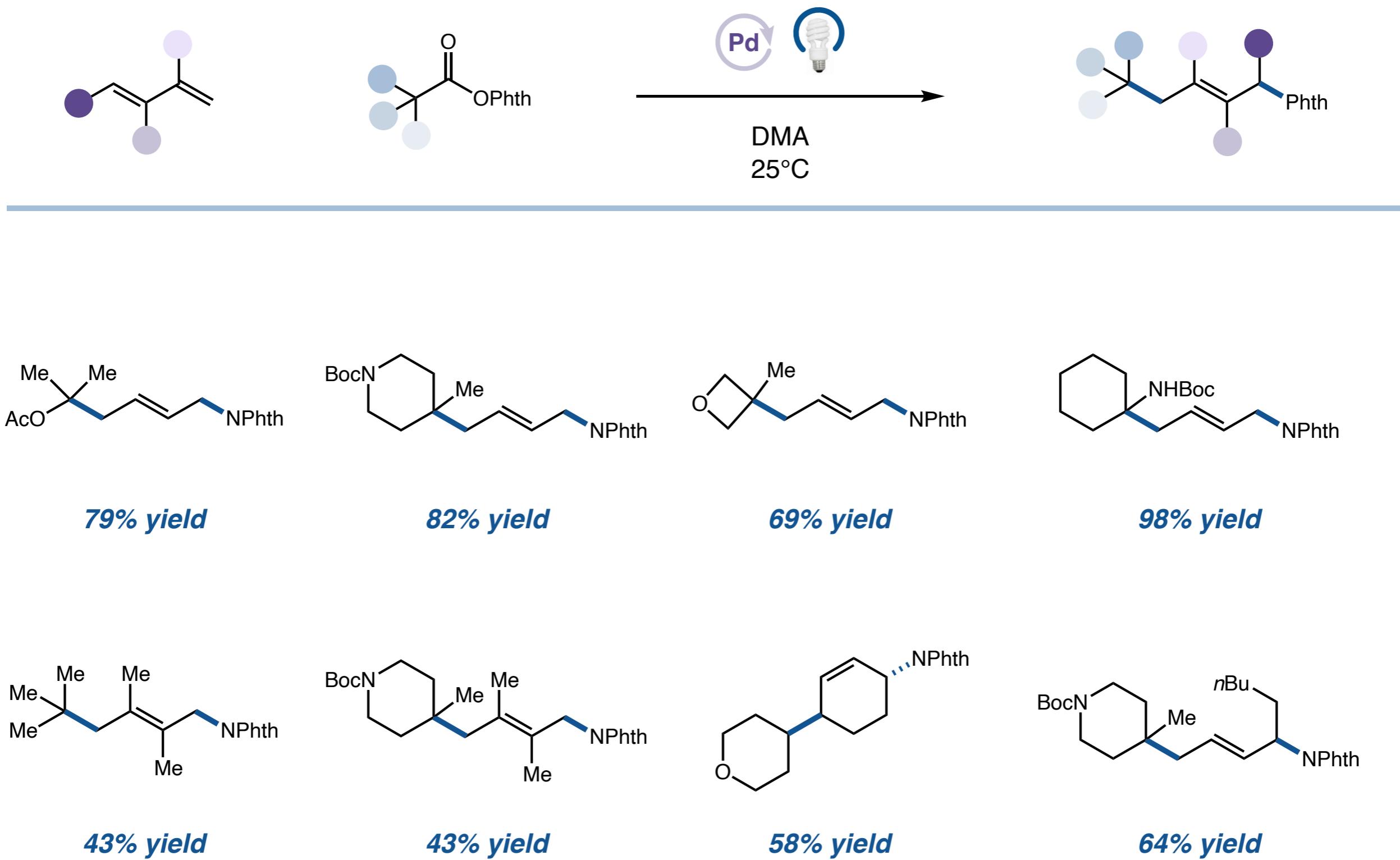
Nature Catal. 2020



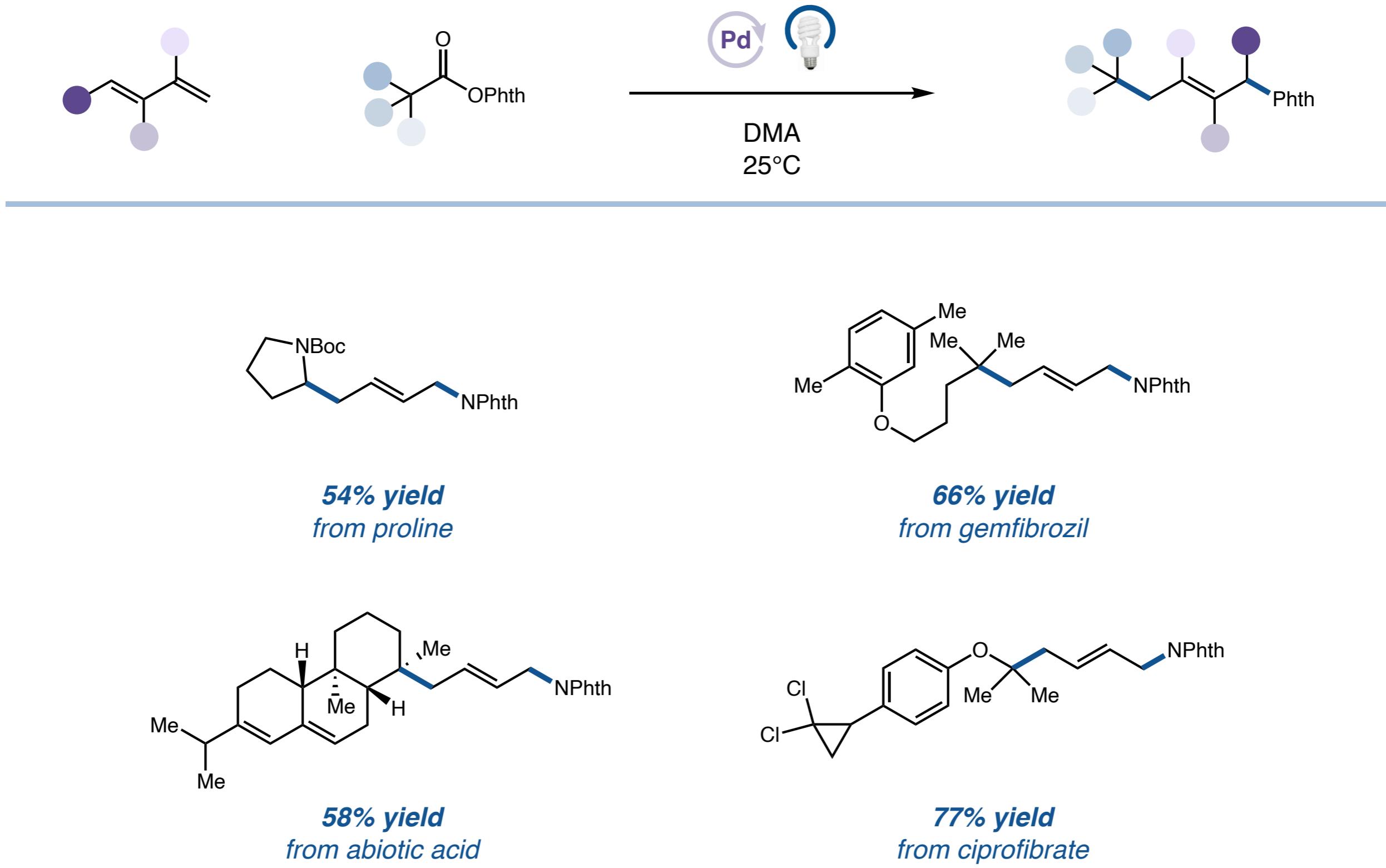
Radical allylic substitution



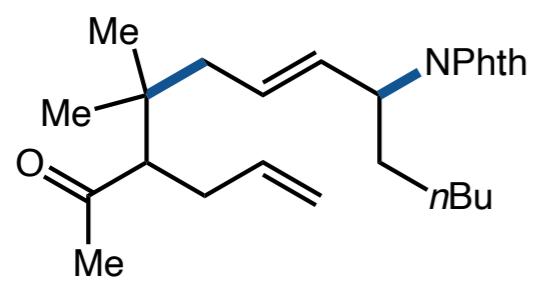
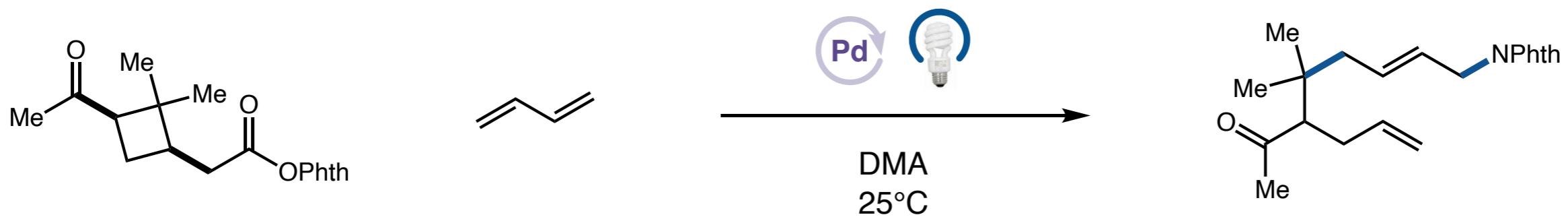
Scope of allylic substitution



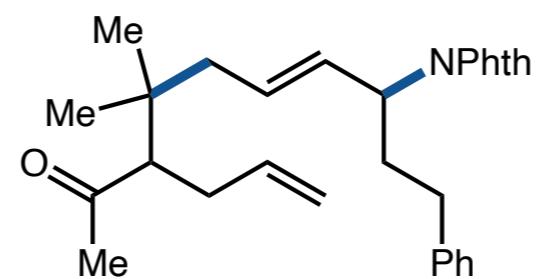
Scope of allylic substitution: complex examples



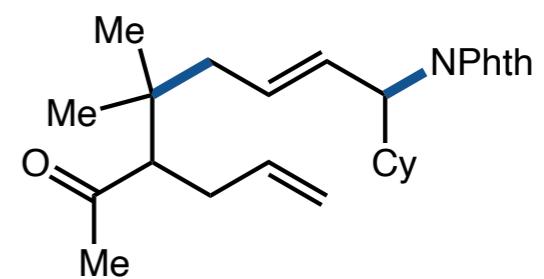
Scope of allylic substitution: cascade reactions



48% yield

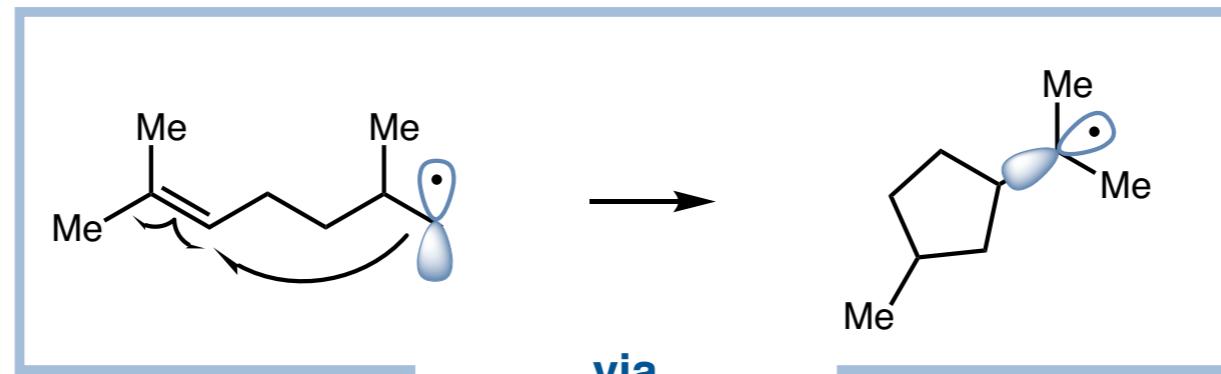
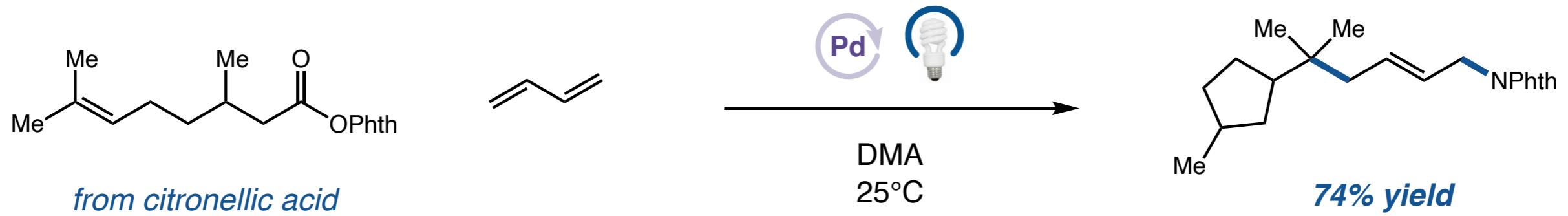


47% yield



52% yield

Scope of allylic substitution: cascade reactions



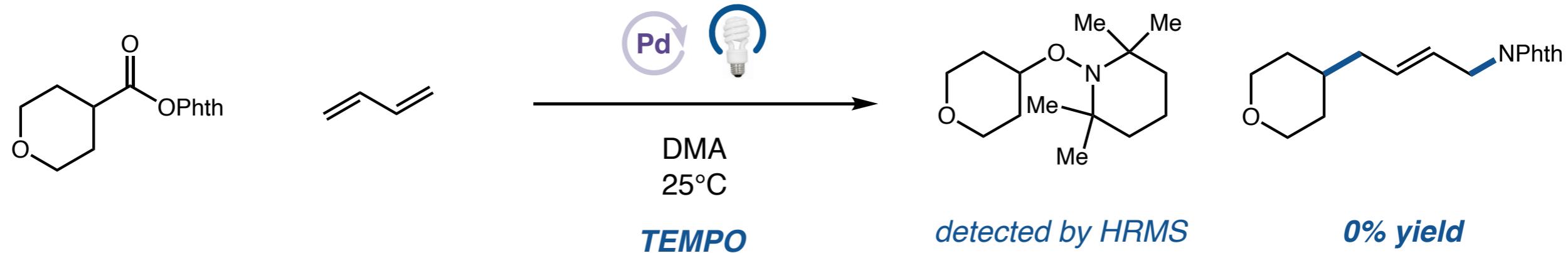
■ overall 59 examples

■ late stage functionalization

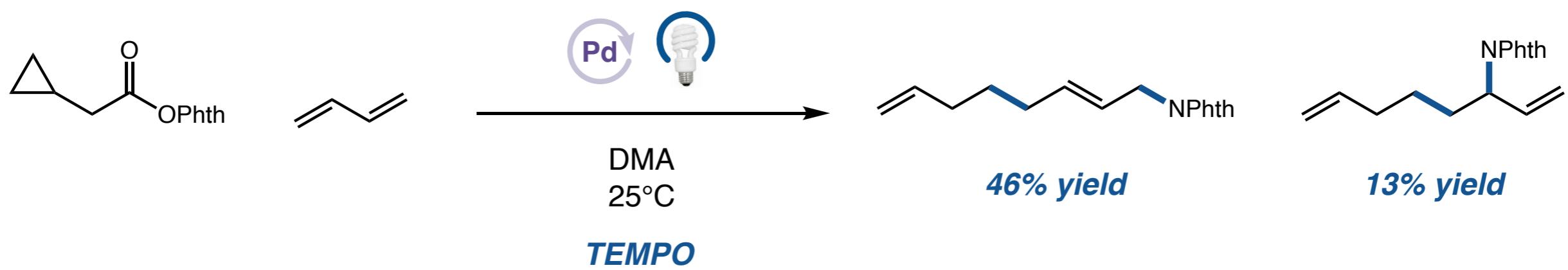
■ cascade reactions

Mechanistic considerations

■ radical inhibitor



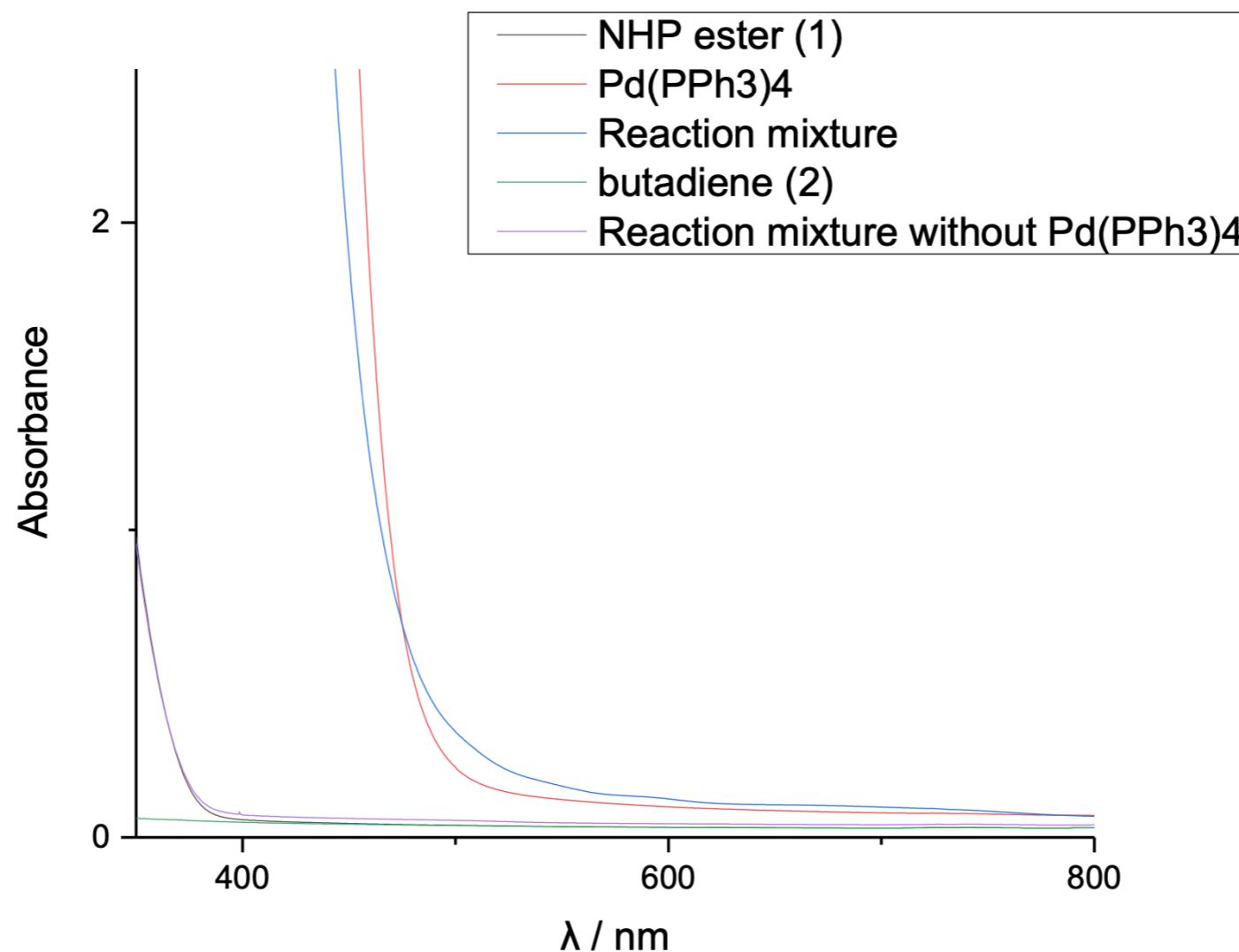
■ radical clock



Mechanistic considerations



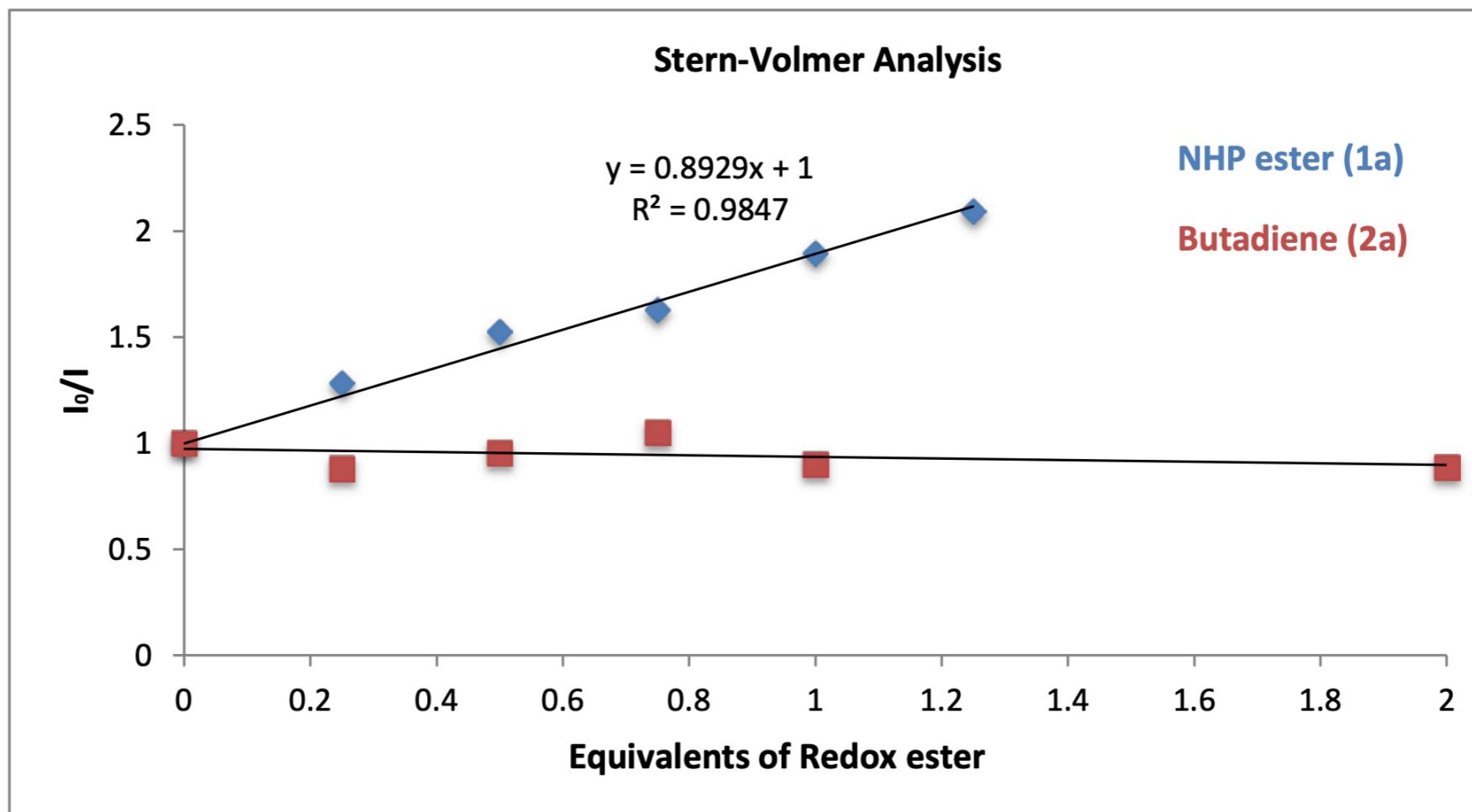
UV-vis



Of the reactants, $\text{Pd}(\text{PPh}_3)_4$ is the only light absorbing species

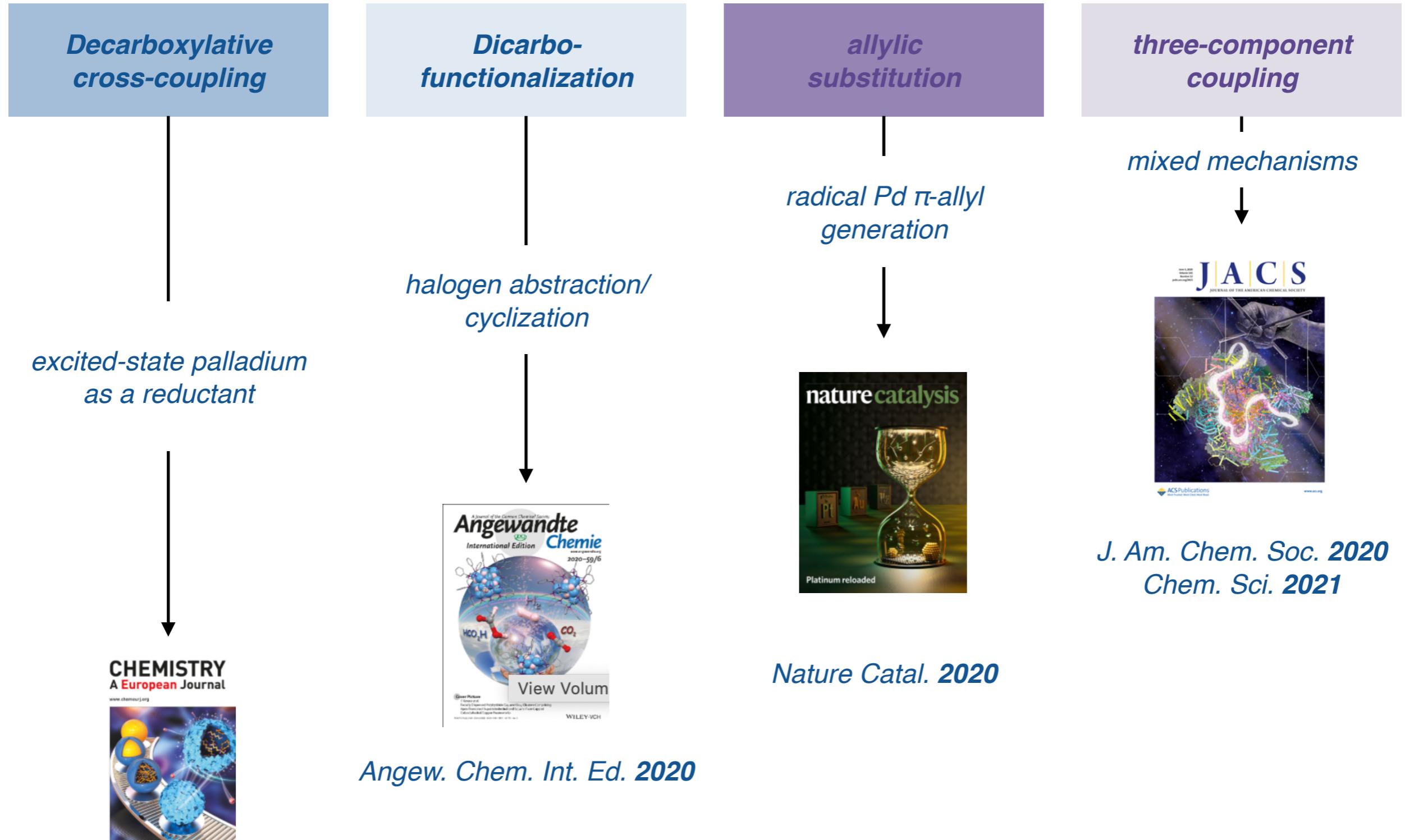
Mechanistic considerations

Stern-Volmer



Photoexcited Pd⁰ can reduce the redox active ester through SET

Glorius group contribution to radical palladium chemistry



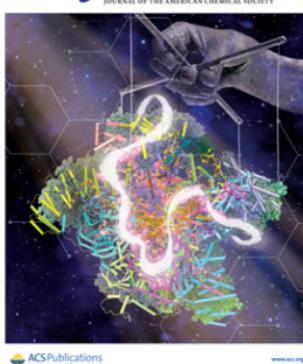
Glorius group contribution to radical palladium chemistry

*three-component
coupling*

mixed mechanisms

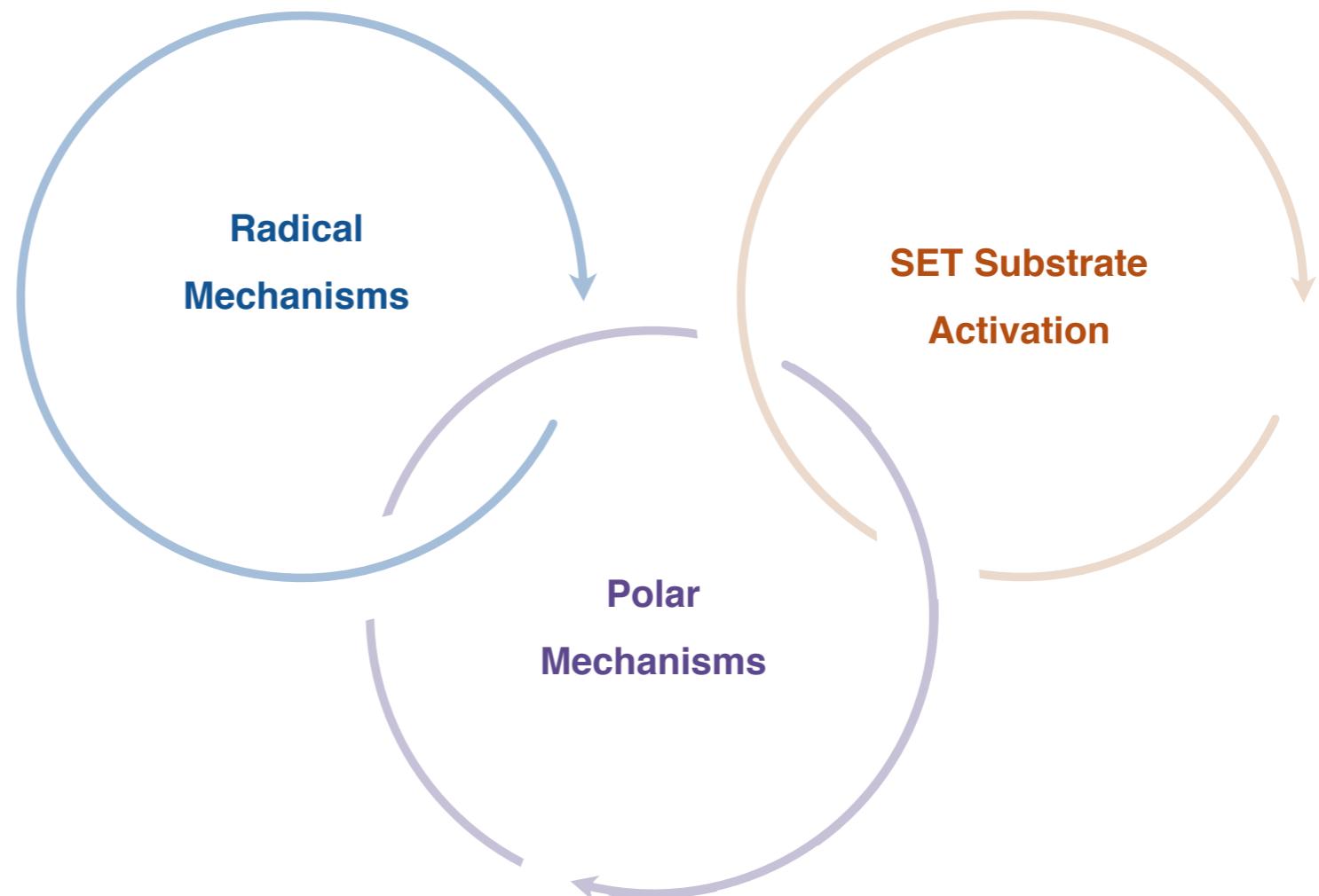


J|A|C|S



ACS Publications

J. Am. Chem. Soc. **2020**
Chem. Sci. **2021**

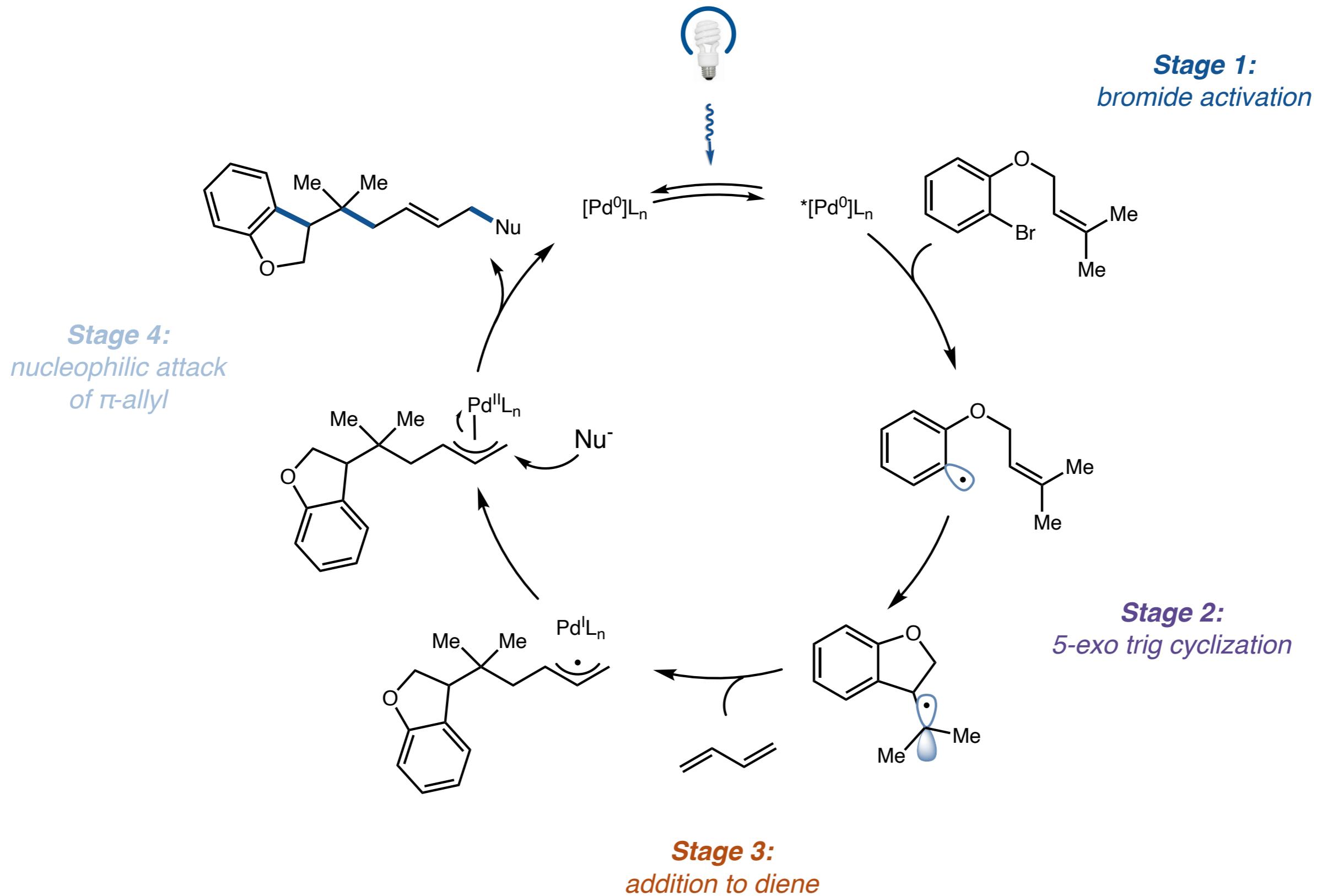


*combining a variety of the mechanisms we've discussed thus far
allows for unique three-component reactions*

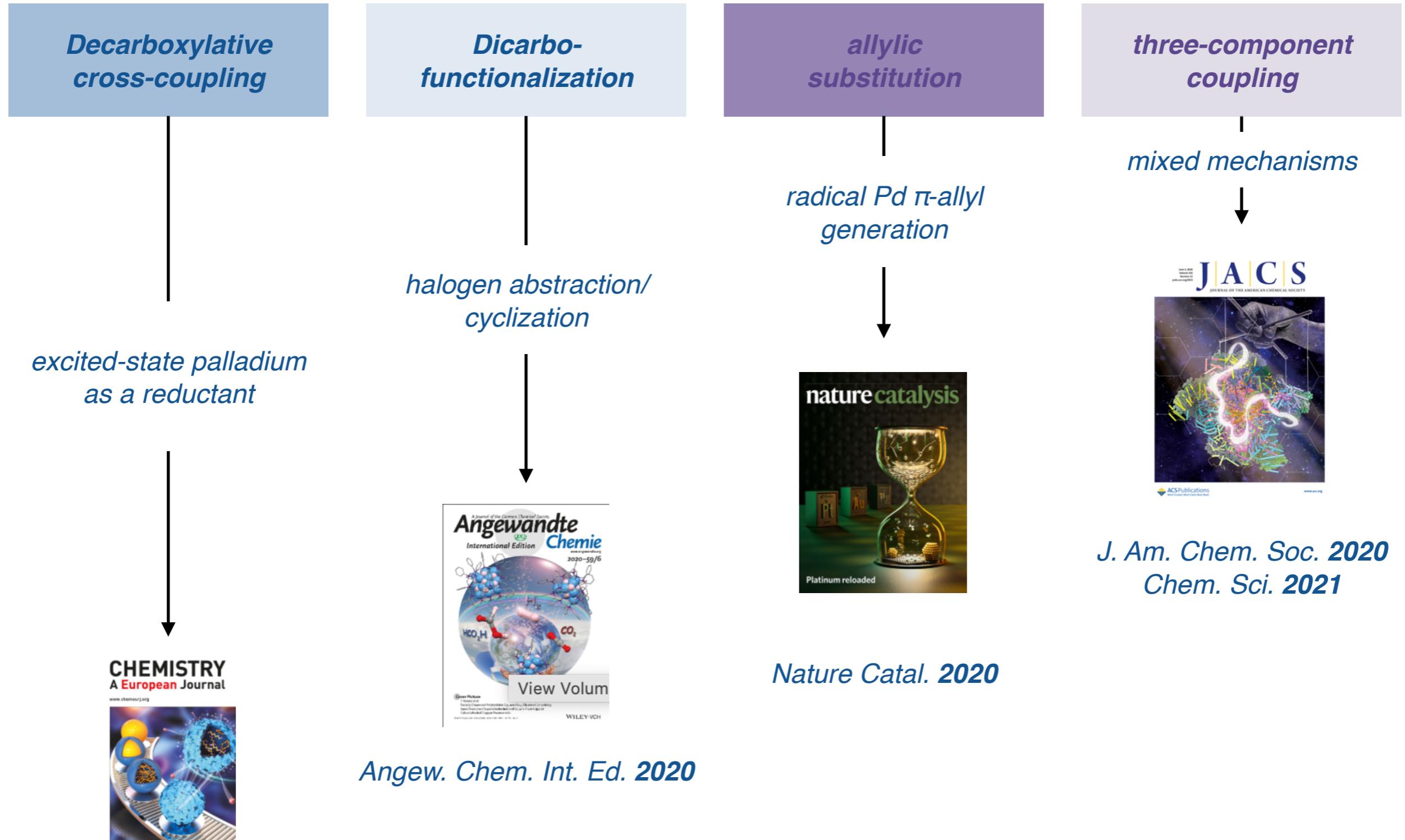
Huang, H.; Bellotti, P.; Pfluger, P.; Schwarz, J.; Heidrich, B.; Glorius, F. *J. Am. Chem. Soc.* **2020**, *142*, 10173.

Bellotti, P.; Koy, M.; Gutheil, C.; Heuvel, S.; Glorius, F. *Chem. Sci.* **2021**, *12*, 1810.

Three-component coupling



Glorius group contribution to radical palladium chemistry



Three main areas of radical-based palladium chemistry

Pd Photoredox:
aryl C–H activation

SET from Pd:
olefin functionalization

Atom Abstraction:
C–C bond formation



Melanie Sanford
University of Michigan



Frank Glorius
WWU Münster



Erik Alexanian
University of North Carolina-
Chapel Hill

Three main areas of radical-based palladium chemistry

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University of Michigan



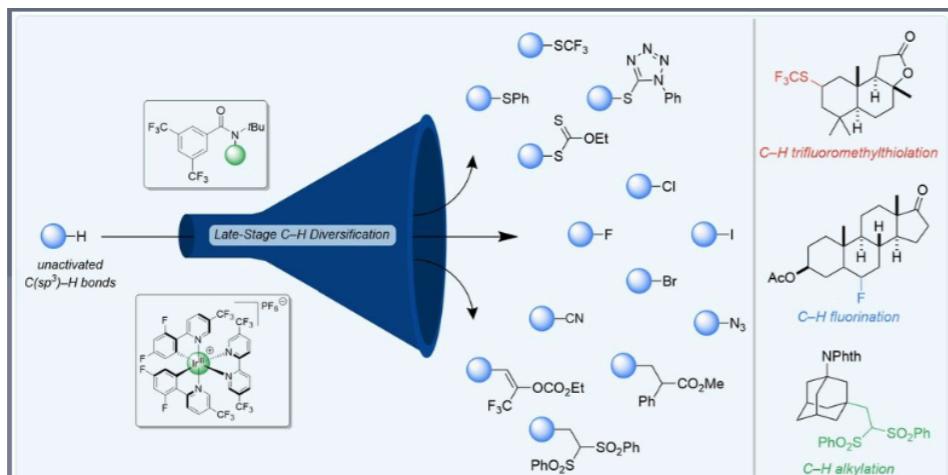
Frank Glorius
WWU Münster



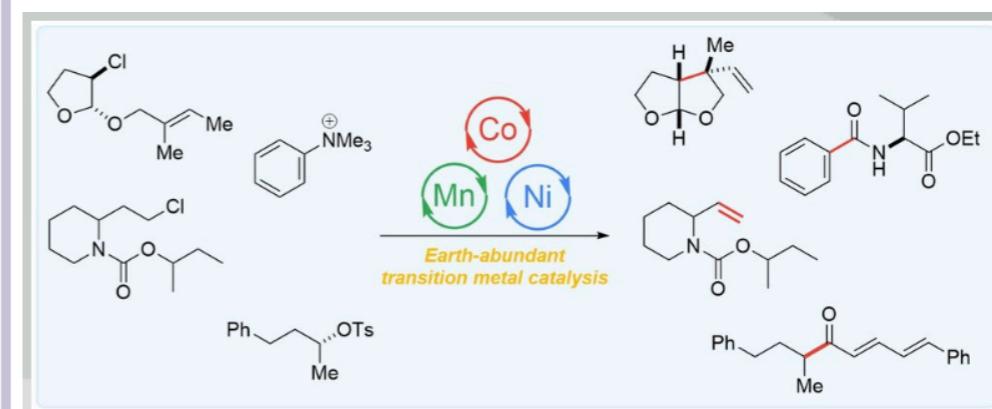
Erik Alexanian
University of North Carolina-
Chapel Hill

Research in the Alexanian group

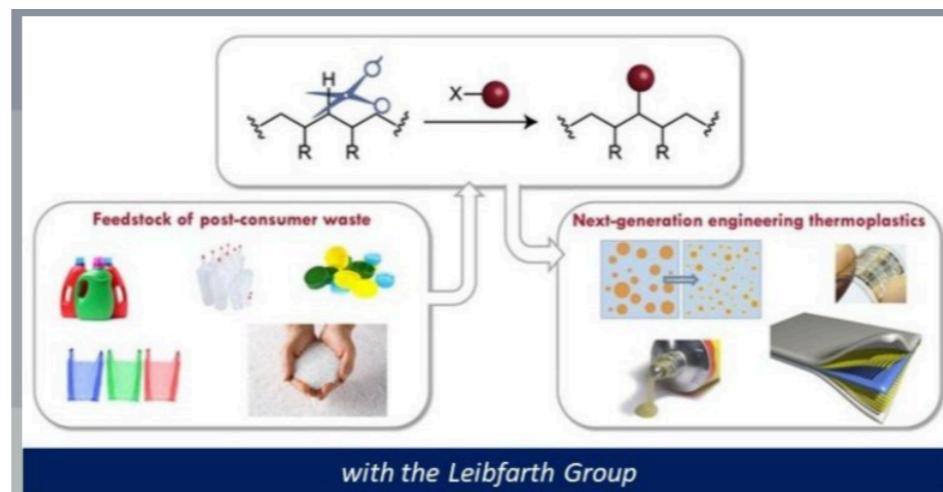
Radical-Mediated C—H Functionalization



Catalytic C—C Bond Formations



Polymer C—H Functionalization

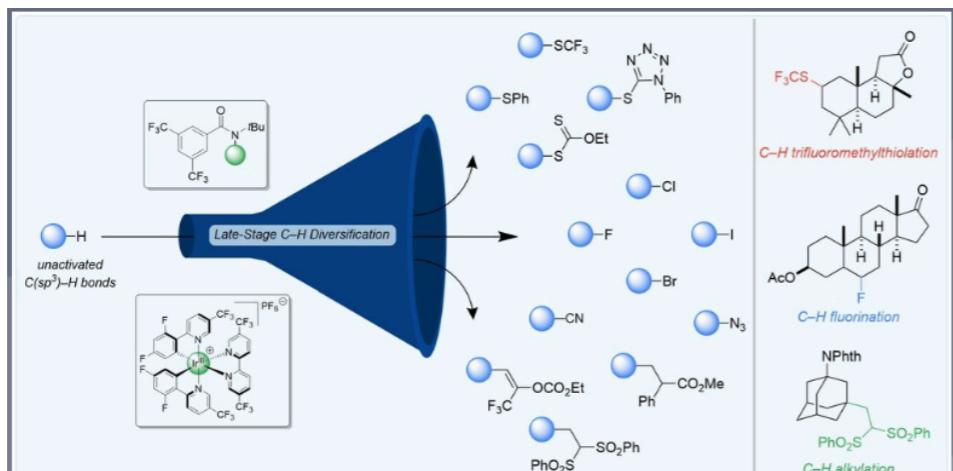


with the Leibfarth Group

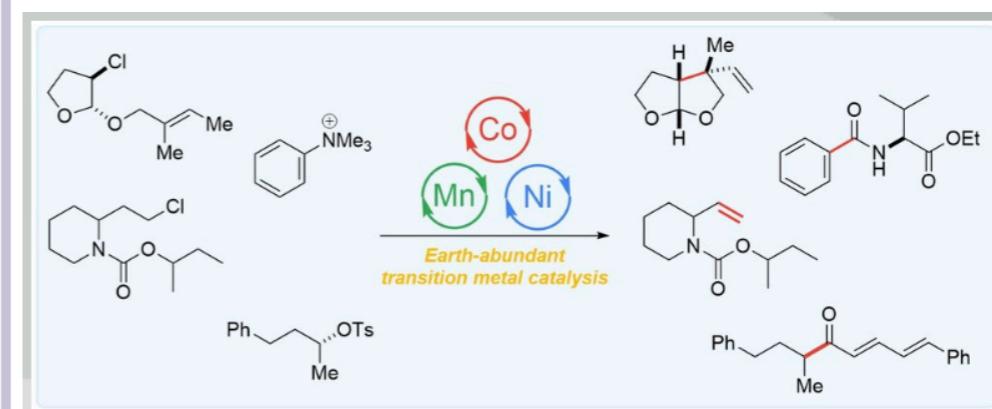
- Na, C.; Ravelli, D.; Alexanian, E. *J. Am. Chem. Soc.* **2020**, *142*, 44.
Williamson, J.; Na, C.; Johnson, R.; Daniel, W.; Alexanian, E.; Leibfarth, F. *J. Am. Chem. Soc.* **2019**, *141*, 12815.
Tercenio, Q.; Alexanian, E. *Org. Lett.* **2021**, *23*, 7215.

Research in the Alexanian group

Radical-Mediated C—H Functionalization



Catalytic C—C Bond Formations



A.B. Chemistry: *Harvard University,*
2001 (Amir Hoveyda)

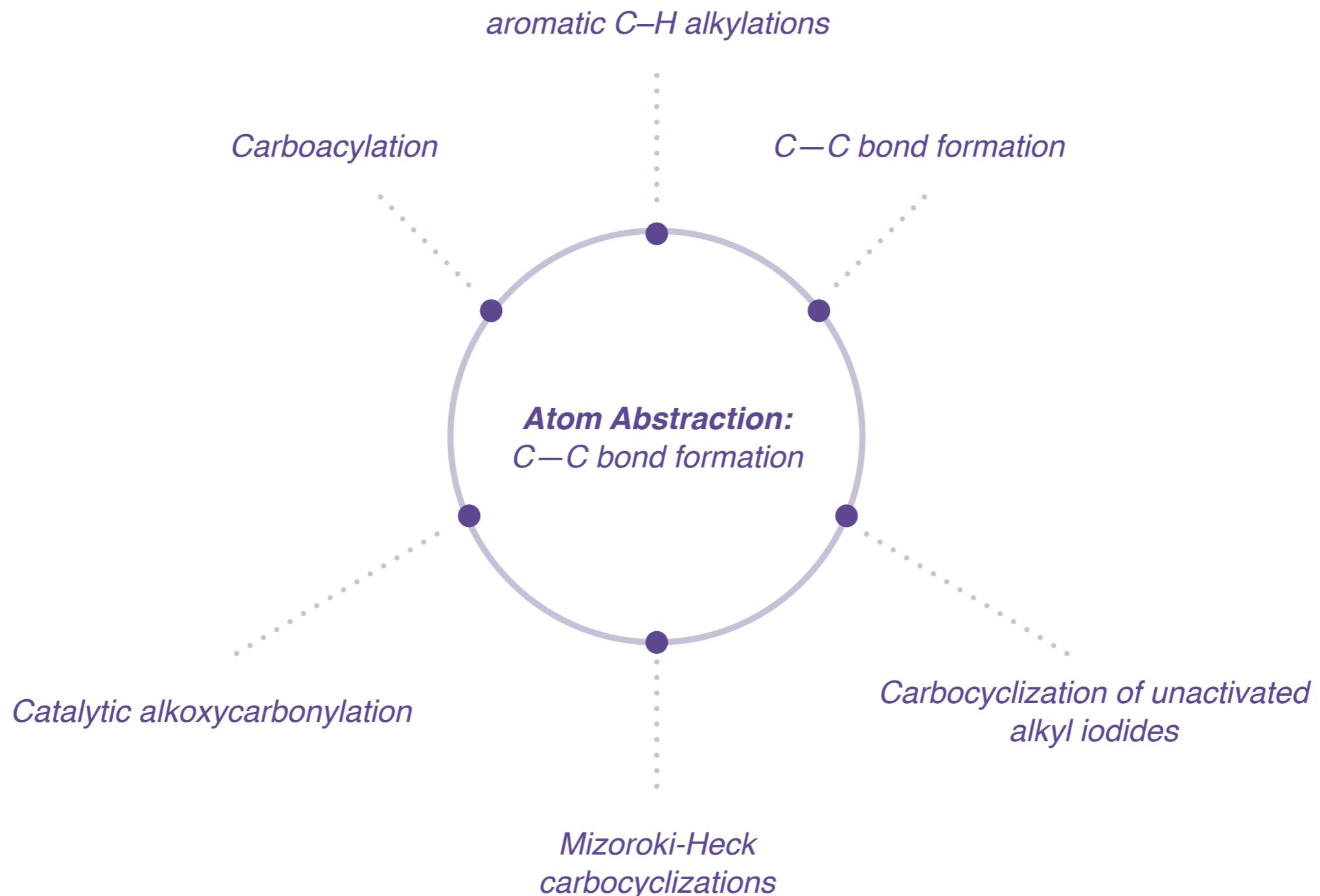
PhD. Chemistry: *Princeton University,*
2006 (Erik Sorensen)

Postdoc: *Yale and University of Illinois,*
2008 (John Hartwig)



**THE UNIVERSITY
of NORTH CAROLINA
at CHAPEL HILL**

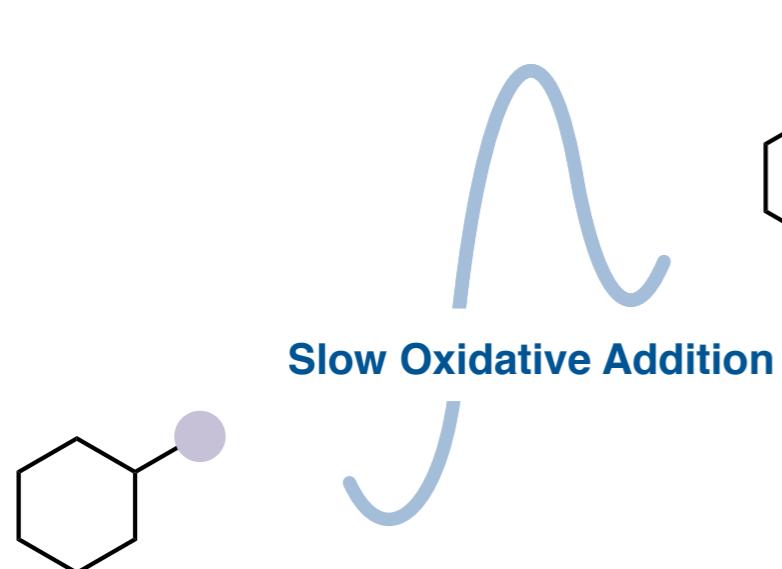
Research in the Alexanian group



Na, C.; Ravelli, D.; Alexanian, E. *J. Am. Chem. Soc.* **2020**, *142*, 44.
Williamson, J.; Na, C.; Johnson, R.; Daniel, W.; Alexanian, E.; Leibfarth, F. *J. Am. Chem. Soc.* **2019**, *141*, 12815.
Tercenio, Q.; Alexanian, E. *Org. Lett.* **2021**, *23*, 7215.

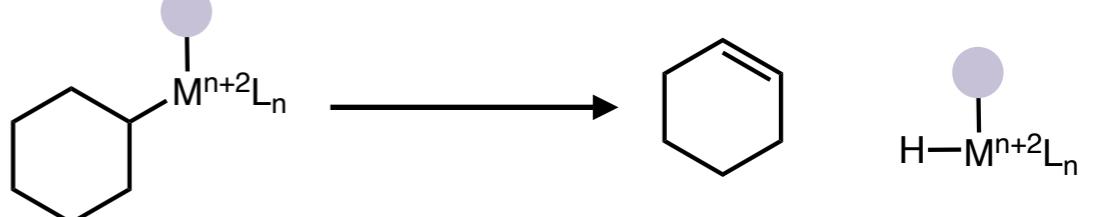
Challenges of 2e⁻ activation of alkyl electrophiles

Oxidative Addition

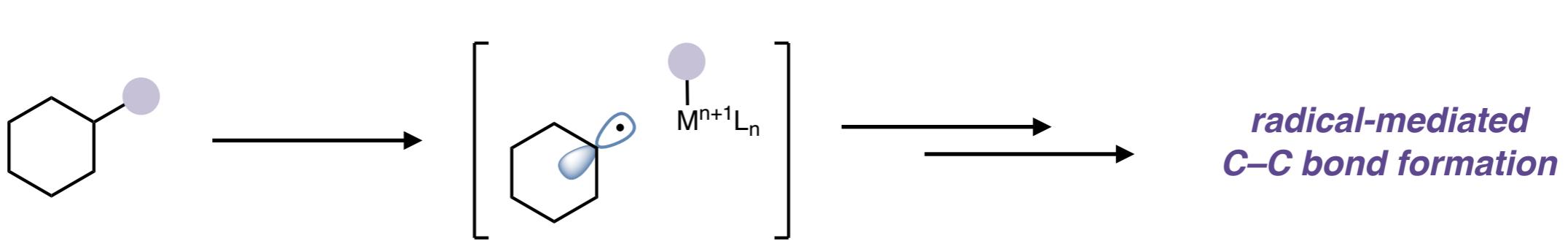


● = I, Br, Cl

Competitive β -hydride elimination



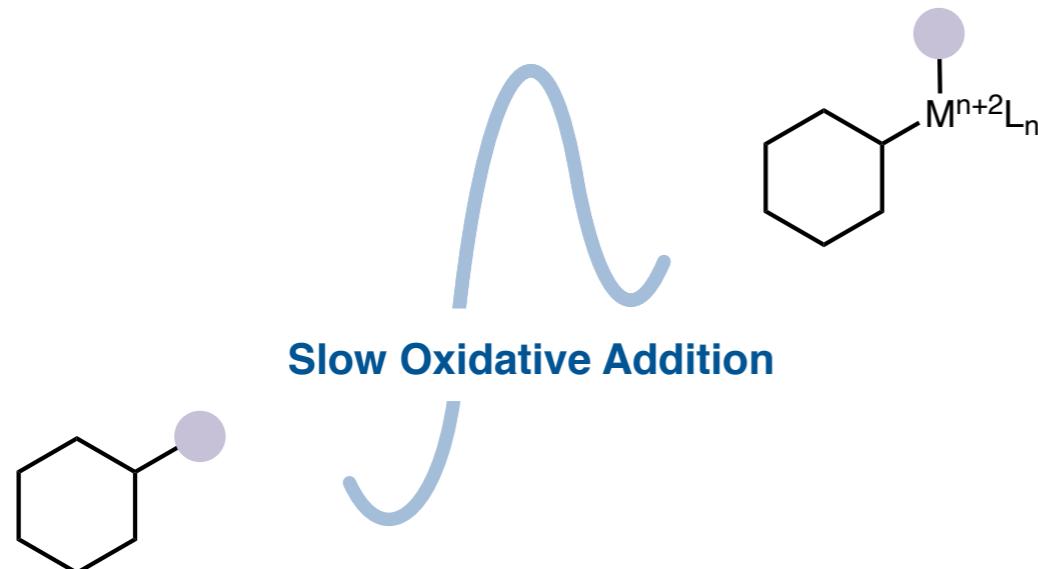
Alternative Mechanism



*radical-mediated
C–C bond formation*

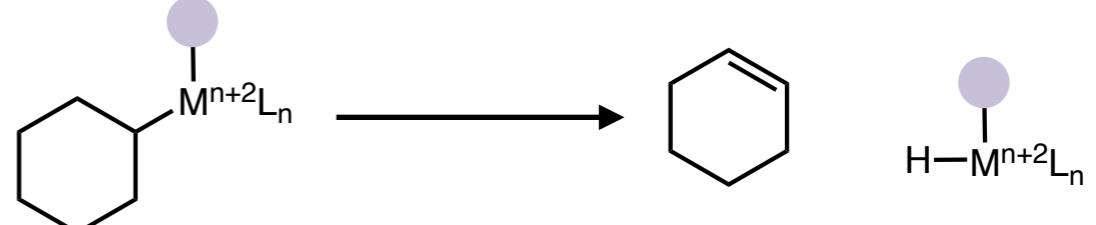
Challenges of $2e^-$ activation of alkyl electrophiles

Oxidative Addition



● = I, Br, Cl

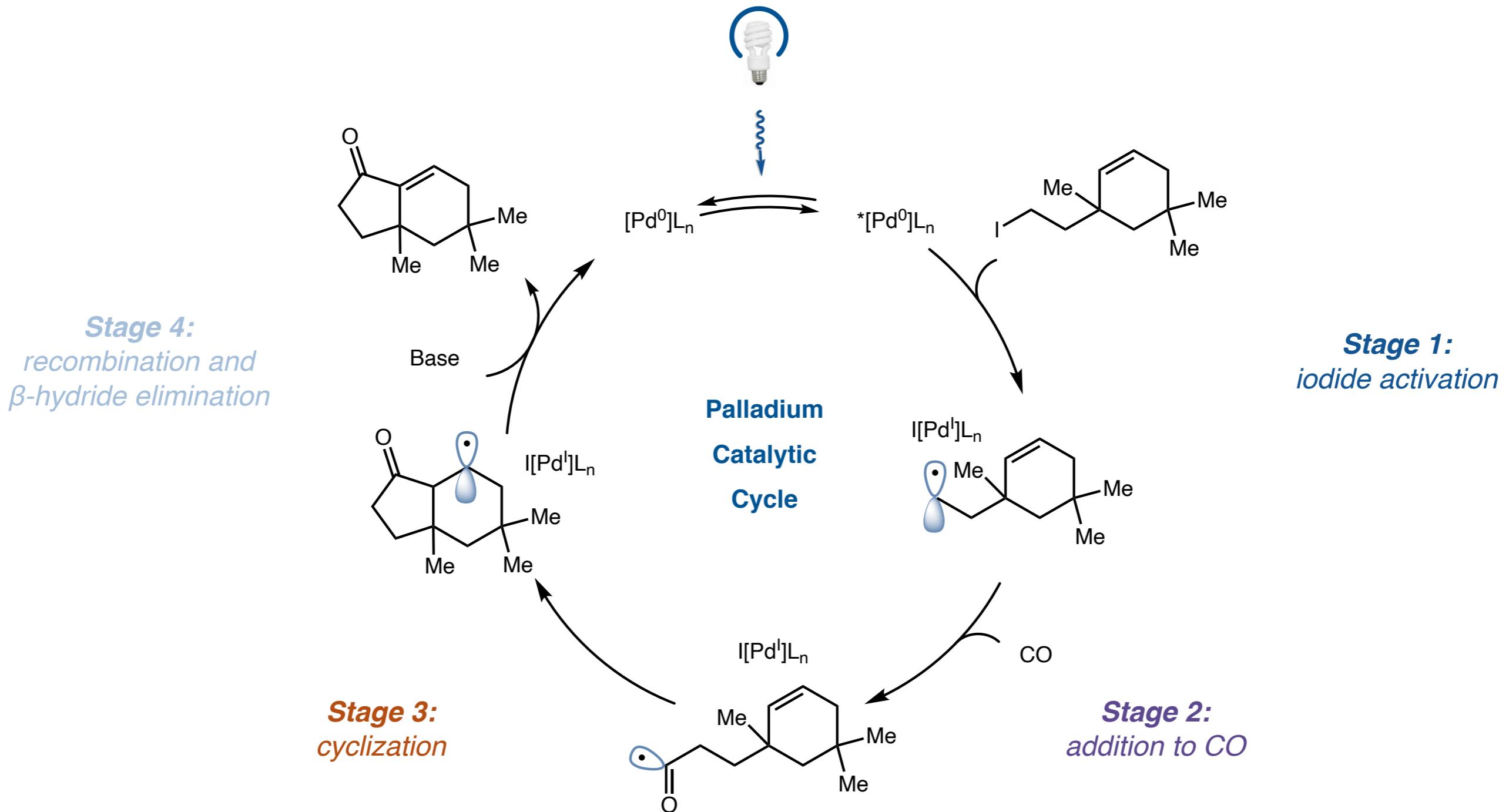
Competitive β -hydride elimination



Alternative Mechanism



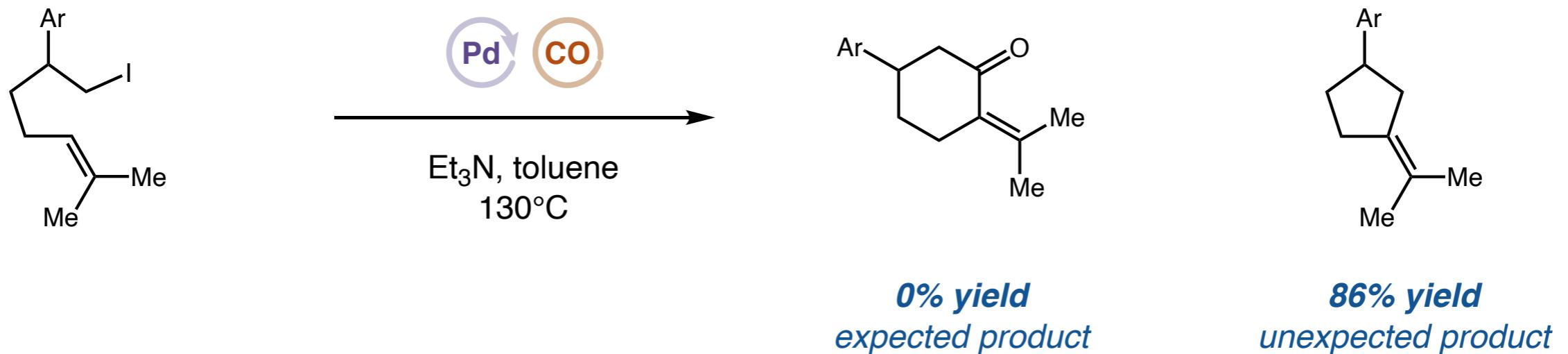
Carbonylative cyclization Mechanism



Bloome, K.; Alexanian, E. J. Am. Chem. Soc. **2010**, 132, 12823.

Bloome, K.; McMahan, R.; Alexanian, E. J. Am. Chem. Soc. **2011**, 133, 20146.

Carbocyclization: an unexpected result

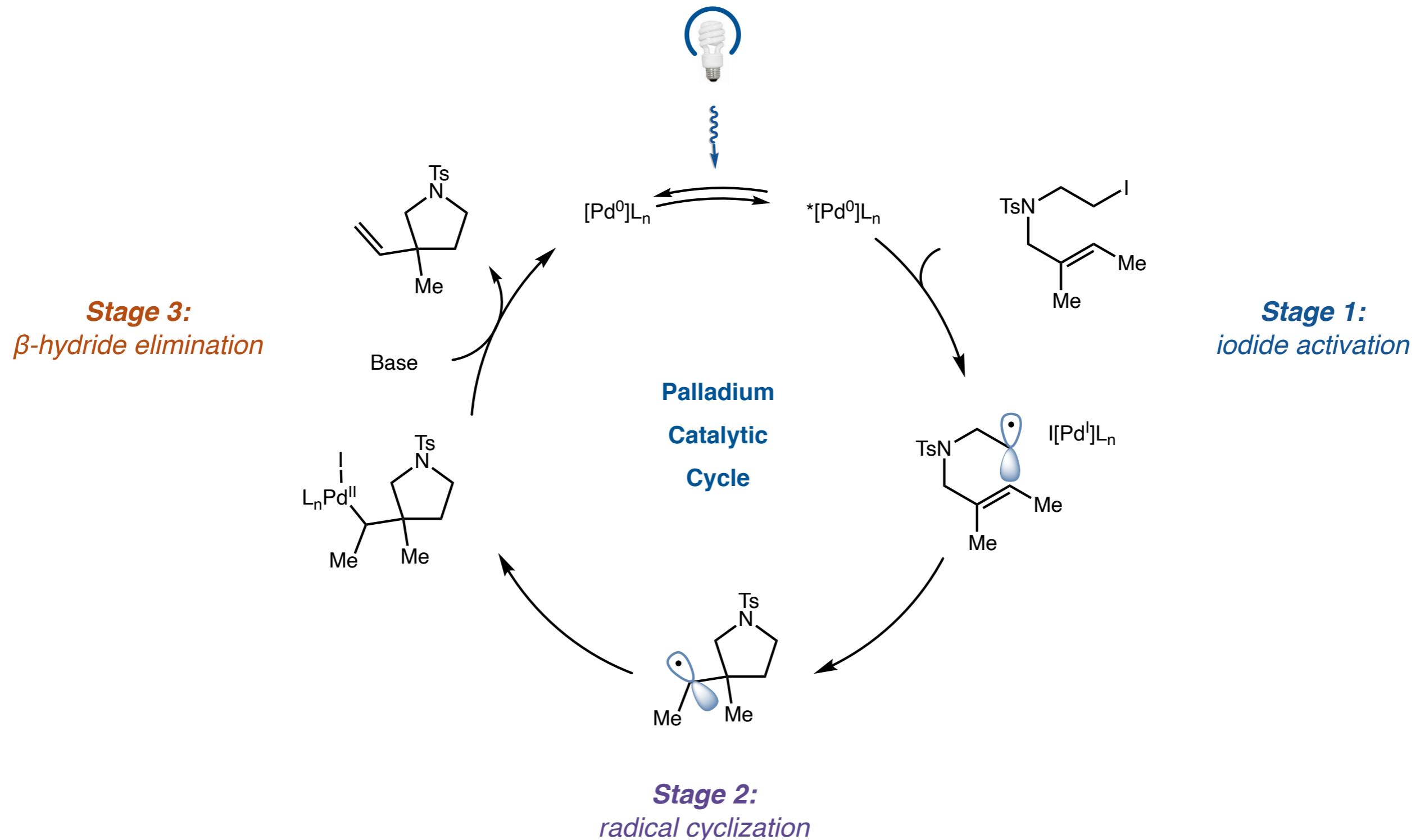


This result shows the feasibility of Heck-type carbocyclizations using radical-based Pd chemistry

Bloome, K.; Alexanian, E. J. Am. Chem. Soc. **2010**, 132, 12823.

Bloome, K.; McMahan, R.; Alexanian, E. J. Am. Chem. Soc. **2011**, 133, 20146.

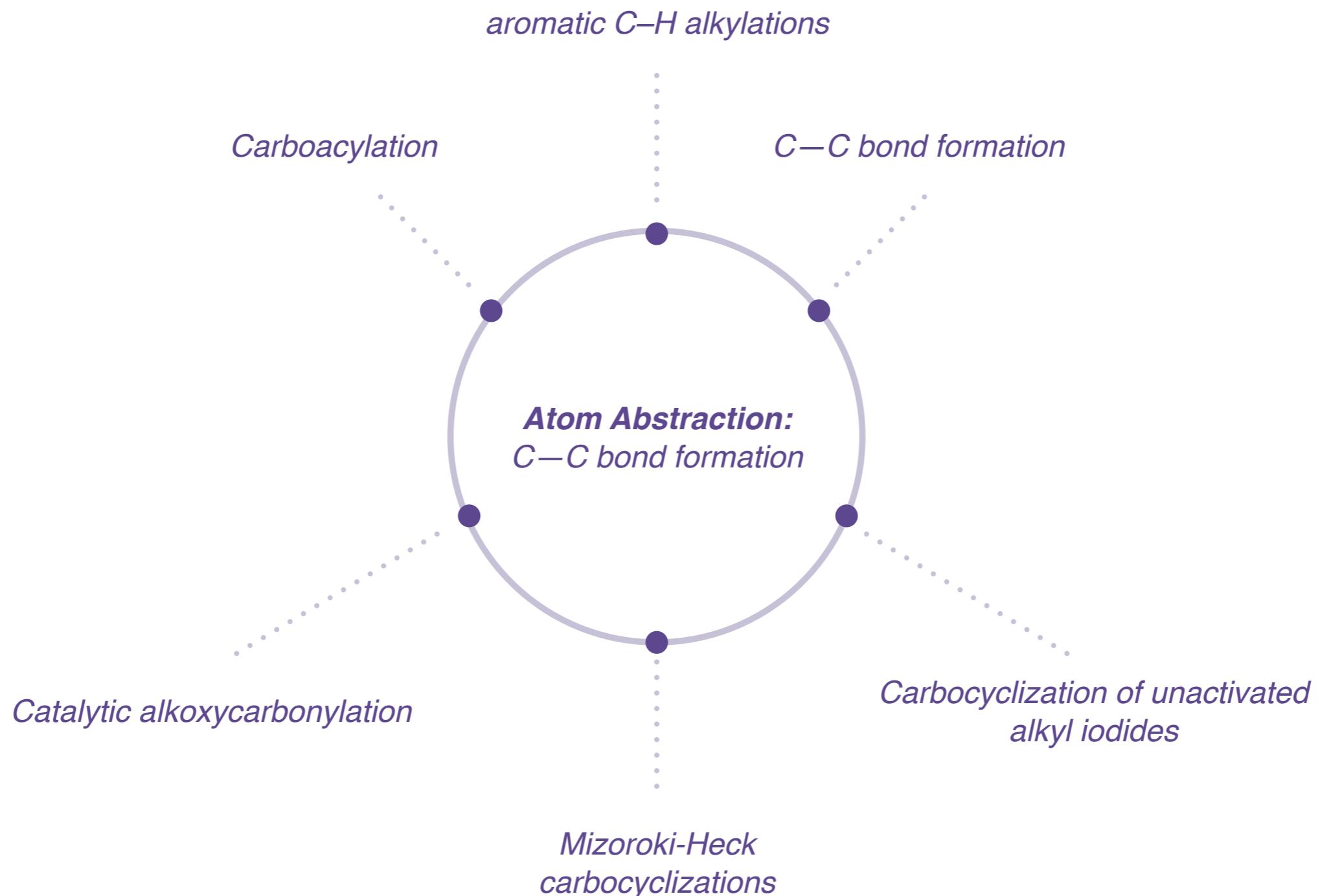
Carbocyclization



Bloome, K.; Alexanian, E. J. Am. Chem. Soc. **2010**, 132, 12823.

Bloome, K.; McMahan, R.; Alexanian, E. J. Am. Chem. Soc. **2011**, 133, 20146.

Research in the Alexanian group



Na, C.; Ravelli, D.; Alexanian, E. *J. Am. Chem. Soc.* **2020**, *142*, 44.
Williamson, J.; Na, C.; Johnson, R.; Daniel, W.; Alexanian, E.; Leibfarth, F. *J. Am. Chem. Soc.* **2019**, *141*, 12815.
Tercenio, Q.; Alexanian, E. *Org. Lett.* **2021**, *23*, 7215.

Palladium: a versatile element

Oxidation states of palladium:

Pd⁰, Pd^{II}, Pd^{IV}

Pd^I, Pd^{III}

1 H Hydrogen 1.008	2 He Helium 4.002602
3 Li Lithium 6.94	4 Be Beryllium 9.0121831
11 Na Sodium 22.98976928	12 Mg Magnesium 24.305
19 K Potassium 39.0983	20 Ca Calcium 40.078
37 Rb Rubidium 85.4678	38 Sr Strontium 87.62
55 Cs Caesium 132.90545196	56 Ba Barium 137.327
87 Fr Francium (223)	88 Ra Radium (226)
21 Sc Scandium 44.955908	22 Ti Titanium 47.867
23 V Vanadium 50.9415	24 Cr Chromium 51.9961
25 Mn Manganese 54.938044	26 Fe Iron 55.845
27 Co Cobalt 58.93194	28 Ni Nickel 58.6934
29 Cu Copper 63.546	30 Zn Zinc 65.38
31 Ga Gallium 69.723	32 Ge Germanium 72.630
33 As Arsenic 74.921995	34 Se Selenium 78.971
35 Br Bromine 79.904	36 Kr Krypton 83.798
37 Rb Rubidium 85.4678	38 Sr Strontium 87.62
39 Y Yttrium 88.90584	40 Zr Zirconium 91.224
41 Nb Niobium 92.90637	42 Mo Molybdenum 95.95
43 Tc Technetium (98)	44 Ru Ruthenium 101.07
45 Rh Rhodium 102.90550	46 Pd Palladium 106.42
47 Ag Silver 107.8682	48 Cd Cadmium 112.414
49 In Indium 118.710	50 Sn Tin 121.760
51 Sb Antimony 126.90447	52 Te Tellurium 127.60
53 I Iodine 126.90447	54 Xe Xenon 131.293
55 Cs Caesium 132.90545196	56 Ba Barium 137.327
57 - 71 Lanthanoids	72 Hf Hafnium 178.49
73 Ta Tantalum 180.94788	74 W Tungsten 183.84
75 Re Rhenium 186.207	76 Os Osmium 190.23
77 Ir Iridium 192.217	78 Pt Platinum 195.084
79 Au Gold 196.966569	80 Hg Mercury 200.592
81 Tl Thallium 204.38	82 Pb Lead 207.2
83 Bi Bismuth 208.98040	84 Po Polonium (209)
85 At Astatine (210)	86 Rn Radon (222)
87 Fr Francium (223)	88 Ra Radium (226)
89 - 103 Actinoids	104 Rf Rutherfordium (267)
105 Db Dubnium (268)	106 Sg Seaborgium (269)
107 Bh Bohrium (270)	108 Hs Hassium (269)
109 Mt Meitnerium (278)	110 Ds Darmstadtium (281)
111 Rg Roentgenium (282)	112 Cn Copernicium (285)
113 Nh Nihonium (286)	114 Fl Flerovium (289)
115 Mc Moscovium (289)	116 Lv Livermorium (293)
117 Ts Tennessine (294)	118 Og Oganesson (294)

57 La Lanthanum 138.90547	58 Ce Cerium 140.016	59 Pr Praseodymium 140.90766	60 Nd Neodymium 144.242	61 Pm Promethium (145)	62 Sm Samarium 150.36	63 Eu Europium 151.964	64 Gd Gadolinium 157.25	65 Tb Terbium 158.92535	66 Dy Dysprosium 162.500	67 Ho Holmium 164.93033	68 Er Erbium 167.259	69 Tm Thulium 168.93422	70 Yb Ytterbium 173.045	71 Lu Lutetium 174.9668
89 Ac Actinium (227)	90 Th Thorium 232.0377	91 Pa Protactinium 231.03588	92 U Uranium 238.02891	93 Np Neptunium (237)	94 Pu Plutonium (244)	95 Am Americium (243)	96 Cm Curium (247)	97 Bk Berkelium (247)	98 Cf Californium (251)	99 Es Einsteinium (252)	100 Fm Fermium (257)	101 Md Mendelevium (258)	102 No Nobelium (259)	103 Lr Lawrencium (266)

interconversion between diverse oxidation states

versatile and widely used in cross coupling

utilized in natural product synthesis, agrochemistry, and pharmaceutical production

Questions?

1 IA															18 VIIIA		
1 H Hydrogen 1.008	2 Be Beryllium 9.0121631														2 He Helium 4.002602		
3 Li Lithium 6.94	4 Be Beryllium 9.0121631																
11 Na Sodium 22.98976928	12 Mg Magnesium 24.305																
19 K Potassium 39.0983	20 Ca Calcium 40.078	21 Sc Scandium 44.955908	22 Ti Titanium 47.867	23 V Vanadium 50.9415	24 Cr Chromium 51.9961	25 Mn Manganese 54.938044	26 Fe Iron 55.845	27 Co Cobalt 58.93194	28 Ni Nickel 58.6934	29 Cu Copper 63.546	30 Zn Zinc 65.38	31 Ga Gallium 69.723	32 Ge Germanium 72.630	33 As Arsenic 74.921996	34 Se Selenium 78.971	35 Br Bromine 79.904	36 Kr Krypton 83.798
37 Rb Rubidium 85.4678	38 Sr Strontium 87.62	39 Y Yttrium 88.90584	40 Zr Zirconium 91.224	41 Nb Niobium 92.90637	42 Mo Molybdenum 95.95	43 Tc Technetium (98)	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.90550	46 Pd Palladium 106.42	47 Ag Silver 107.8682	48 Cd Cadmium 114.818	49 In Indium 115.710	50 Sn Tin 118.710	51 Sb Antimony 123.760	52 Te Tellurium 127.60	53 I Iodine 126.90447	54 Xe Xenon 131.293
55 Cs Caesium 132.90545196	56 Ba Barium 137.327	57 - 71 Lanthanoids	72 Hf Hafnium 178.49	73 Ta Tantalum 180.54788	74 W Tungsten 183.84	75 Re Rhenium 186.207	76 Os Osmium 190.23	77 Ir Iridium 192.217	78 Pt Platinum 195.084	79 Au Gold 196.9665	80 Hg Mercury 200.592	81 Tl Thallium 204.38	82 Pb Lead 207.2	83 Bi Bismuth 208.98040	84 Po Polonium (209)	85 At Astatine (210)	86 Rn Radon (222)
87 Fr Francium (223)	88 Ra Radium (226)	89 - 103 Actinoids	104 Rf Rutherfordium (267)	105 Db Dubnium (268)	106 Sg Seaborgium (269)	107 Bh Bohrium (270)	108 Hs Hassium (269)	109 Mt Meitnerium (278)	110 Ds Darmstadtium (281)	111 Rg Roentgenium (282)	112 Cn Copernicium (285)	113 Nh Nhonium (286)	114 Fl Flerovium (289)	115 Mc Moscovium (289)	116 Lv Livermorium (293)	117 Ts Tennessine (294)	118 Og Oganesson (294)

57 La Lanthanum 138.90547	58 Ce Cerium 140.116	59 Pr Praseodymium 140.90766	60 Nd Neodymium 144.242	61 Pm Promethium (145)	62 Sm Samarium 150.30	63 Eu Europium 151.964	64 Gd Gadolinium 157.9402	65 Tb Terbium 158.92535	66 Dy Dysprosium 162.500	67 Ho Holmium 164.93033	68 Er Erbium 167.259	69 Tm Thulium 169.93422	70 Yb Ytterbium 173.045	71 Lu Lutetium 174.96668	
89 Ac Actinium (227)	90 Th Thorium 232.0377	91 Pa Protactinium 231.03588	92 U Uranium 238.02891	93 Np Neptunium (237)	94 Pu Plutonium (244)	95 Am Americium (243)	96 Bk Berkelium (247)	97 Cf Californium (251)	98 Es Einsteinium (252)	99 Fm Fermium (257)	100 Md Mendelevium (258)	101 No Nobelium (259)	102 Lr Lawrencium (266)		

