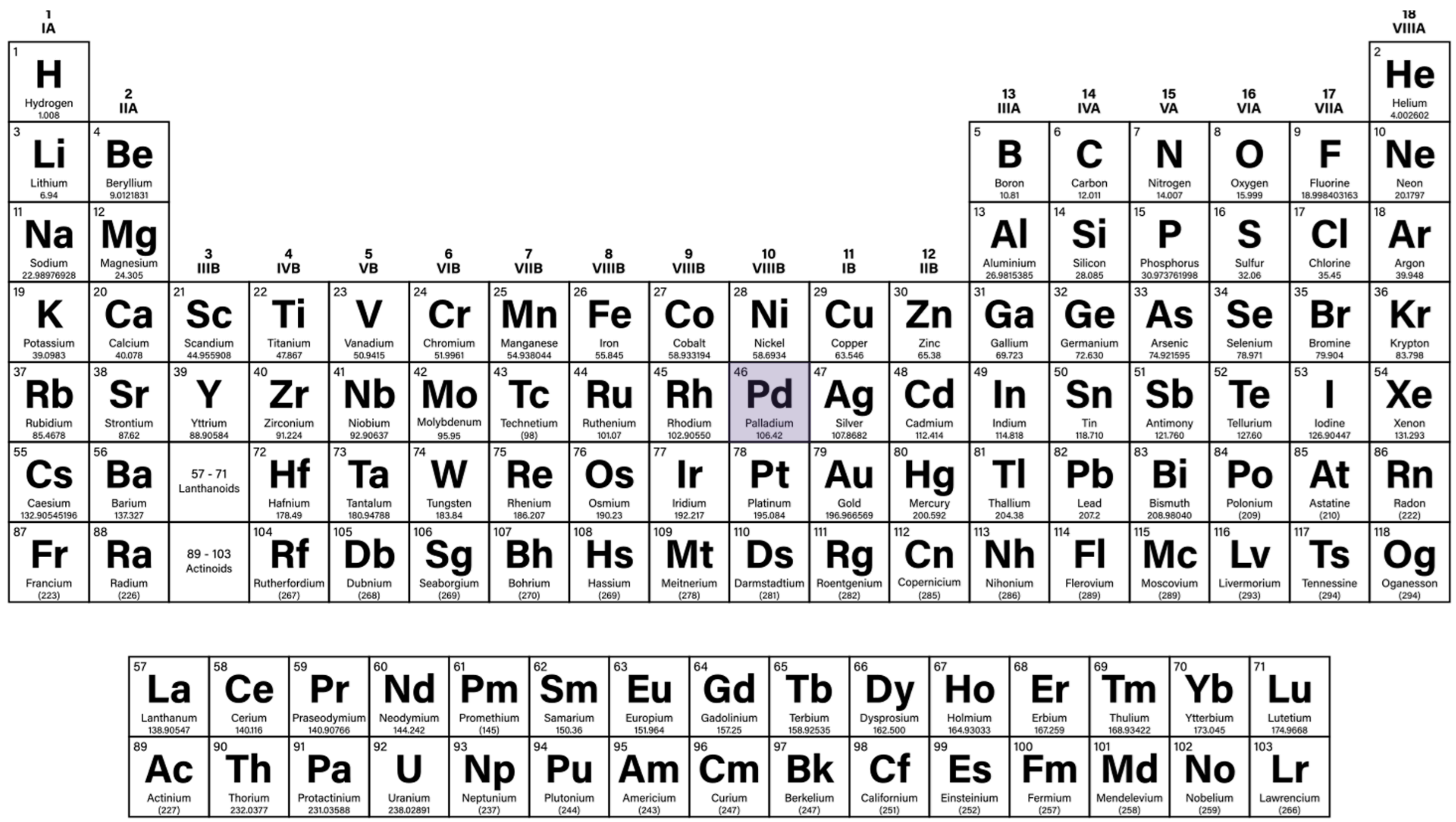
The Development of Radical-Based Palladium Chemistry



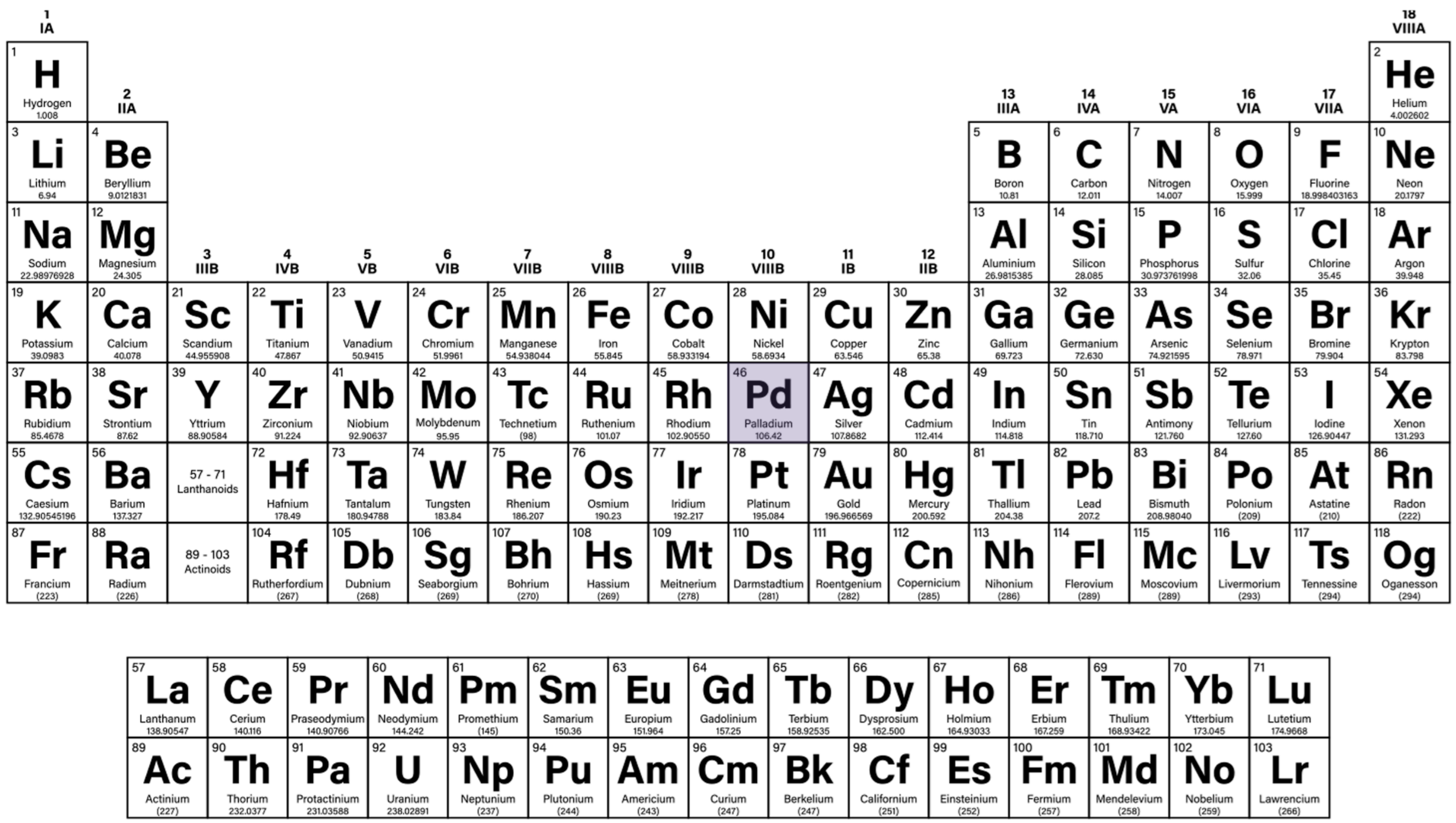
Andria Pace

MacMillan Group Meeting

Literature Talk

April 12, 2022

Palladium: a versatile element



interconversion between diverse oxidation states

versatile and widely used in cross coupling

utilized in natural product synthesis, agrochemistry, and pharmaceutical production

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

Palladium: a versatile element

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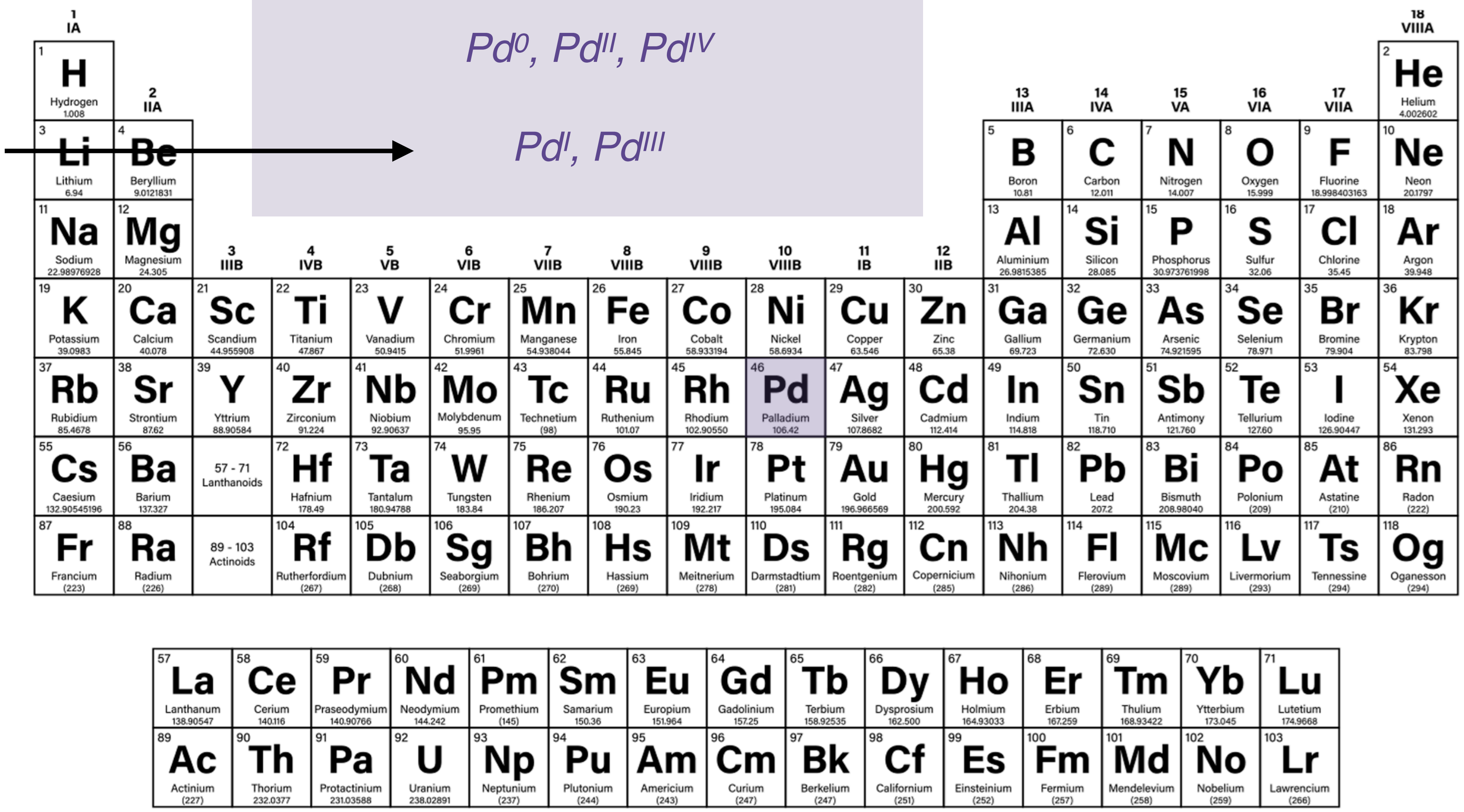
accessed via $1e^-$ pathways → *Pd^I, Pd^{III}*



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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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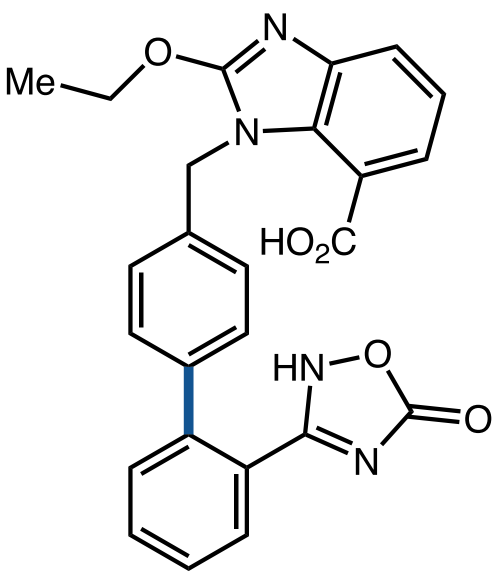
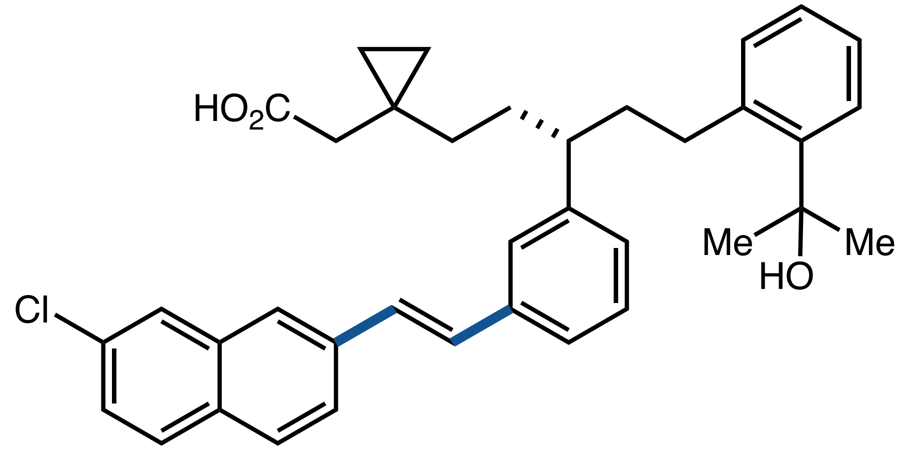
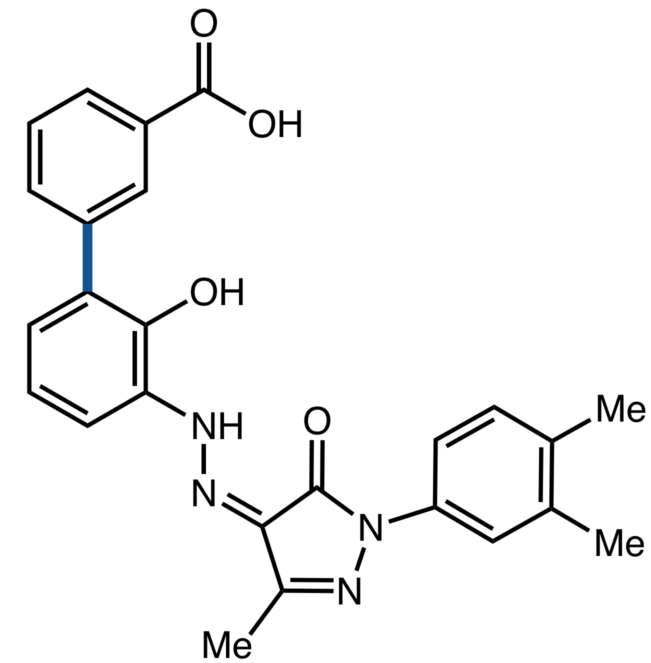


Azilva
$764 Million
cardiovascular



Singulair
$462 Million
respiratory



Promacta
$1.7 Billion
oncology

interconversion between diverse oxidation states

versatile and widely used in cross coupling

utilized in natural product synthesis, agrochemistry, and pharmaceutical production

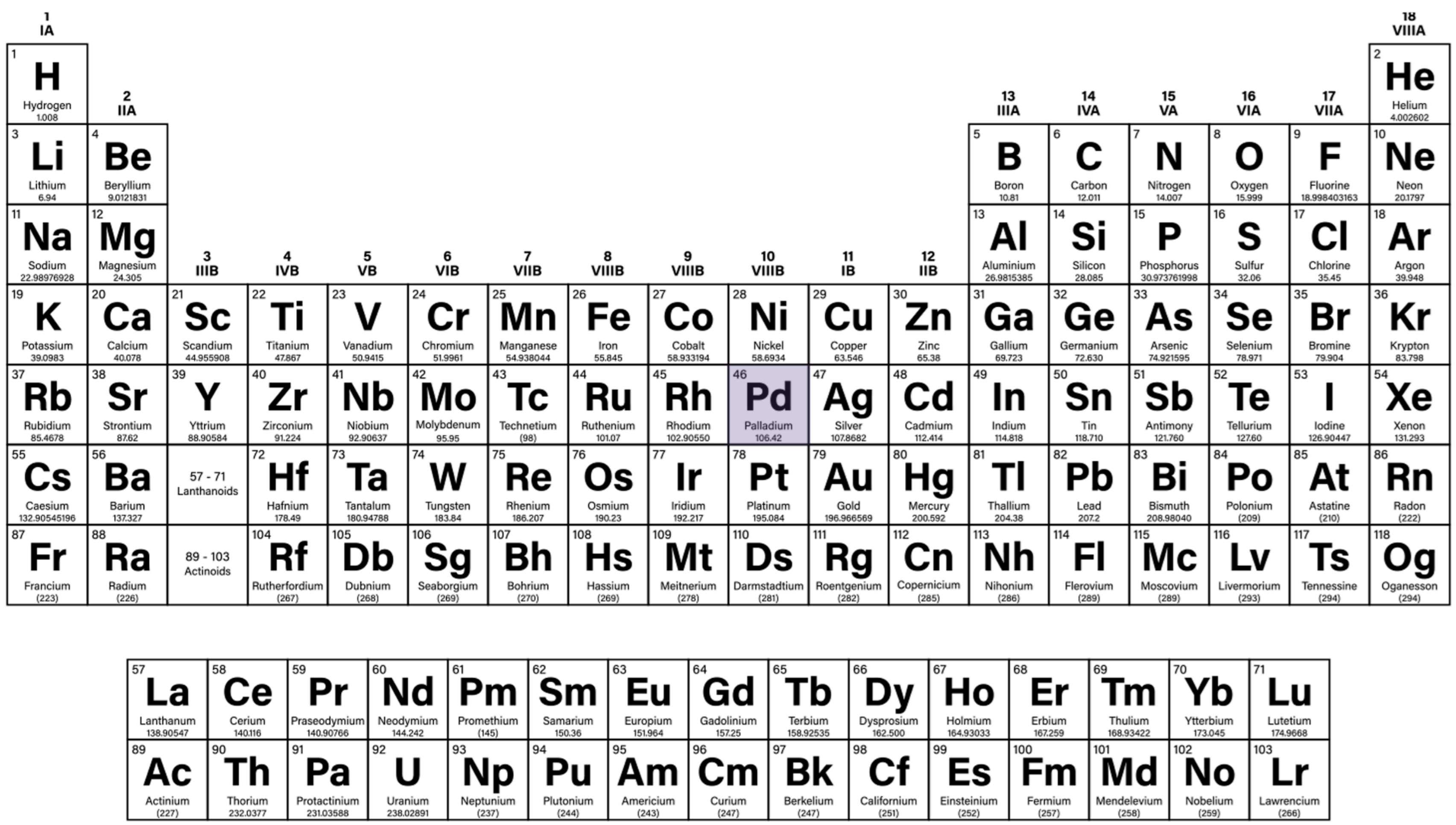
Qureshi, M.; Njardarson, J. “Top 200 Small Molecule Pharmaceuticals by Retail Sales in 2020.”
Bollikonda, S.; Mohanarangam, S.; Jinna, R.; Kandirelli, V.; Makthala, L.; Sen, S.; Chaplin, D.; Lloyd, R.; Mahoney, T.; Dahanukar, V.; Oruganti, S.; Fox, M. *J. Org. Chem.* **2015**, *80*, 3891.

Radical-Based Palladium Chemistry

Oxidation states of palladium:

Pd^0, Pd^{II}, Pd^{IV} ← **accessed via $2e^-$ pathways**

accessed via $1e^-$ pathways → Pd^I, Pd^{III}



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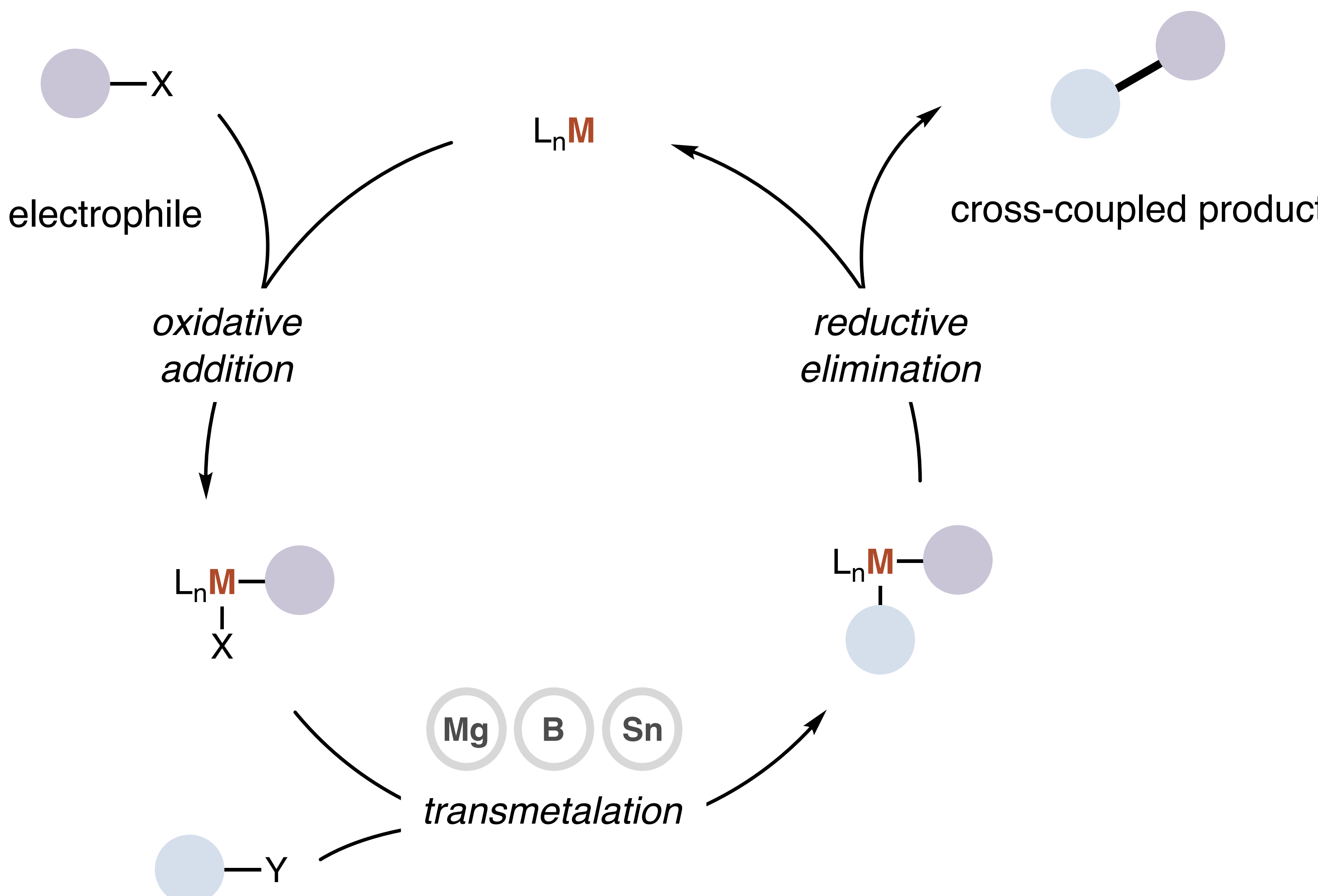

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New elementary steps can provide alternative mechanistic pathways to access key intermediates or activate typically inert coupling partners

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

Radical-Based Palladium Chemistry

What is radical-based palladium chemistry?

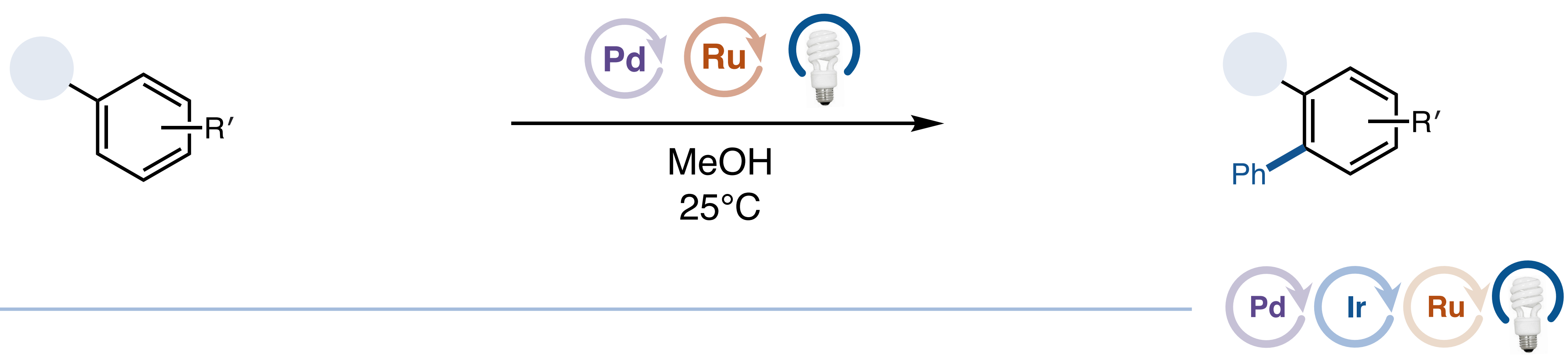
Liu, Q.; Dong, X.; Li, J.; Dong, Y.; Liu, H. *ACS Catal.* **2015**, *5*, 6111.

Radical-Based Palladium Chemistry

What is radical-based palladium chemistry?

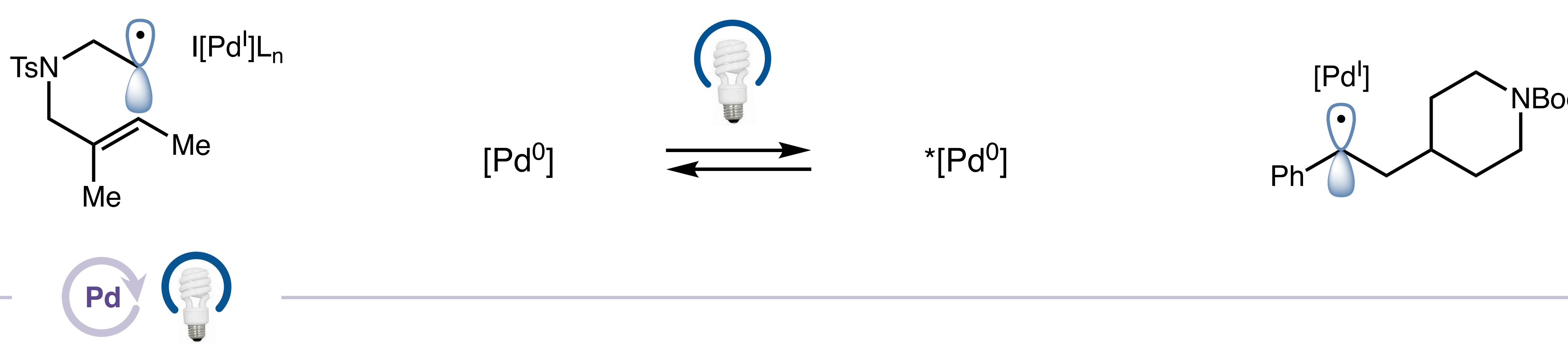
Photoredox Catalysis

Photoredox using Pd as a cross-coupling catalyst



SET from Palladium

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



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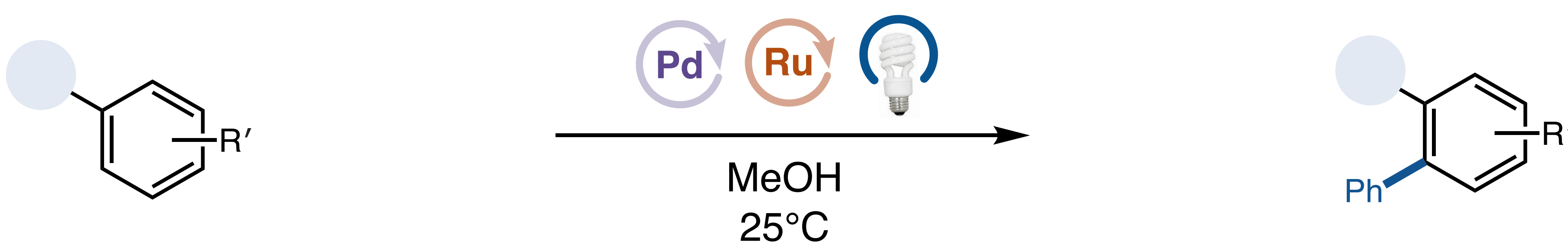

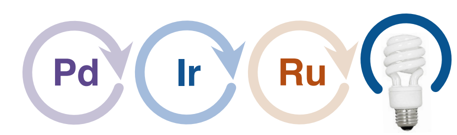

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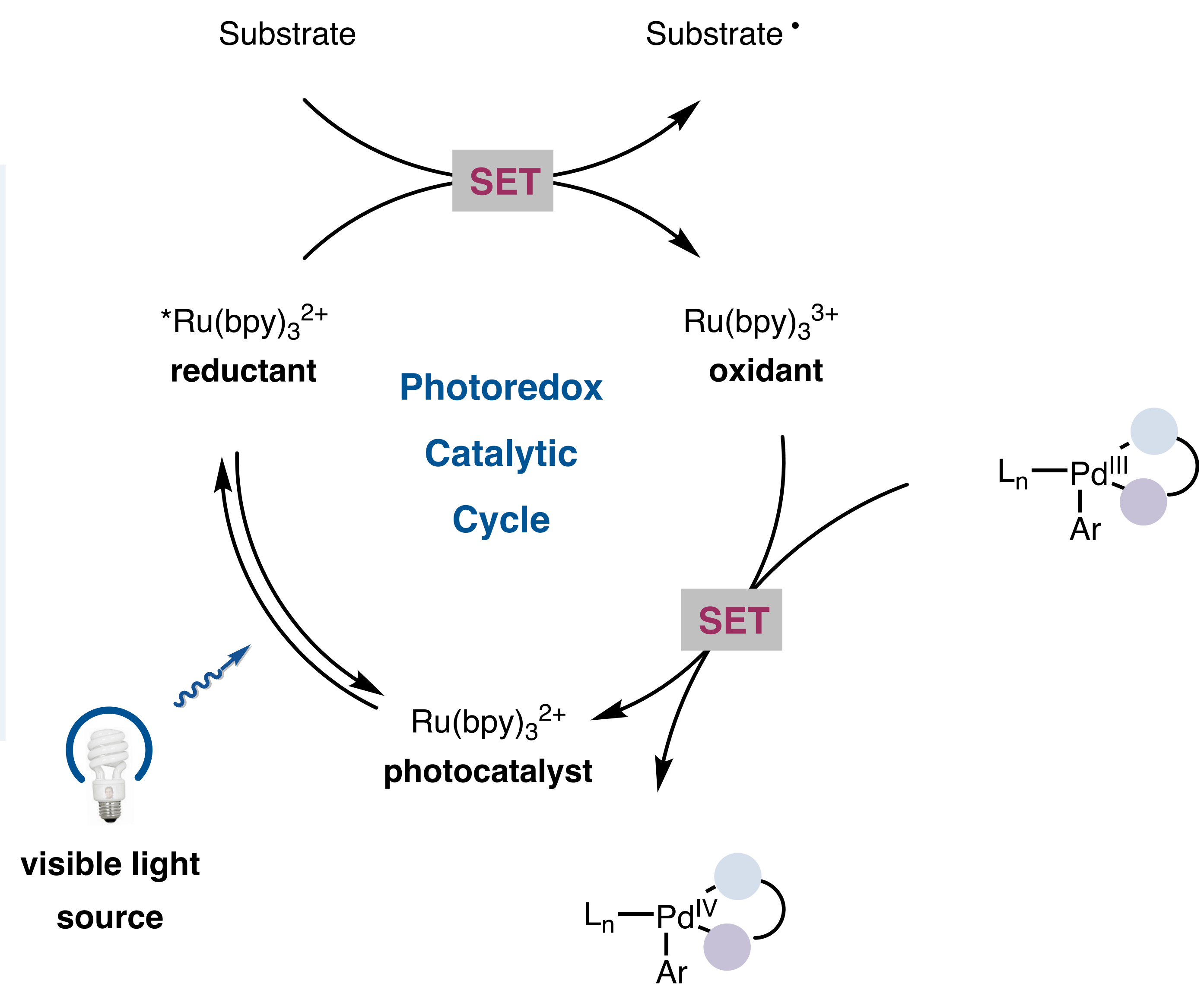
Radical-based reactivity of Pd
Type 1

- ***Palladium can be oxidized by a photocatalyst***
- ***Palladium itself is not being excited***



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What is radical-based palladium chemistry?

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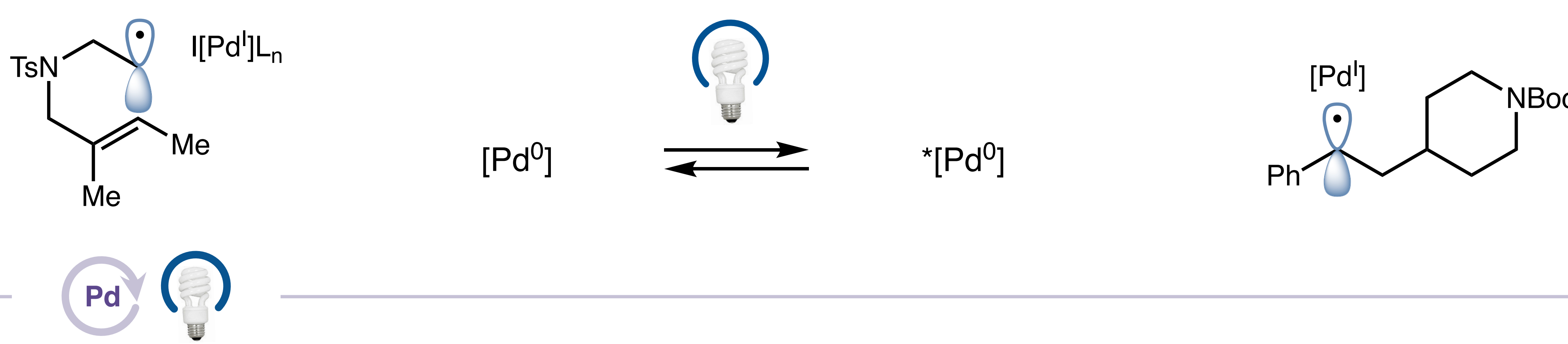


Liu, Q.; Dong, X.; Li, J.; Dong, Y.; Liu, H. *ACS Catal.* **2015**, *5*, 6111.

Radical-Based Palladium Chemistry

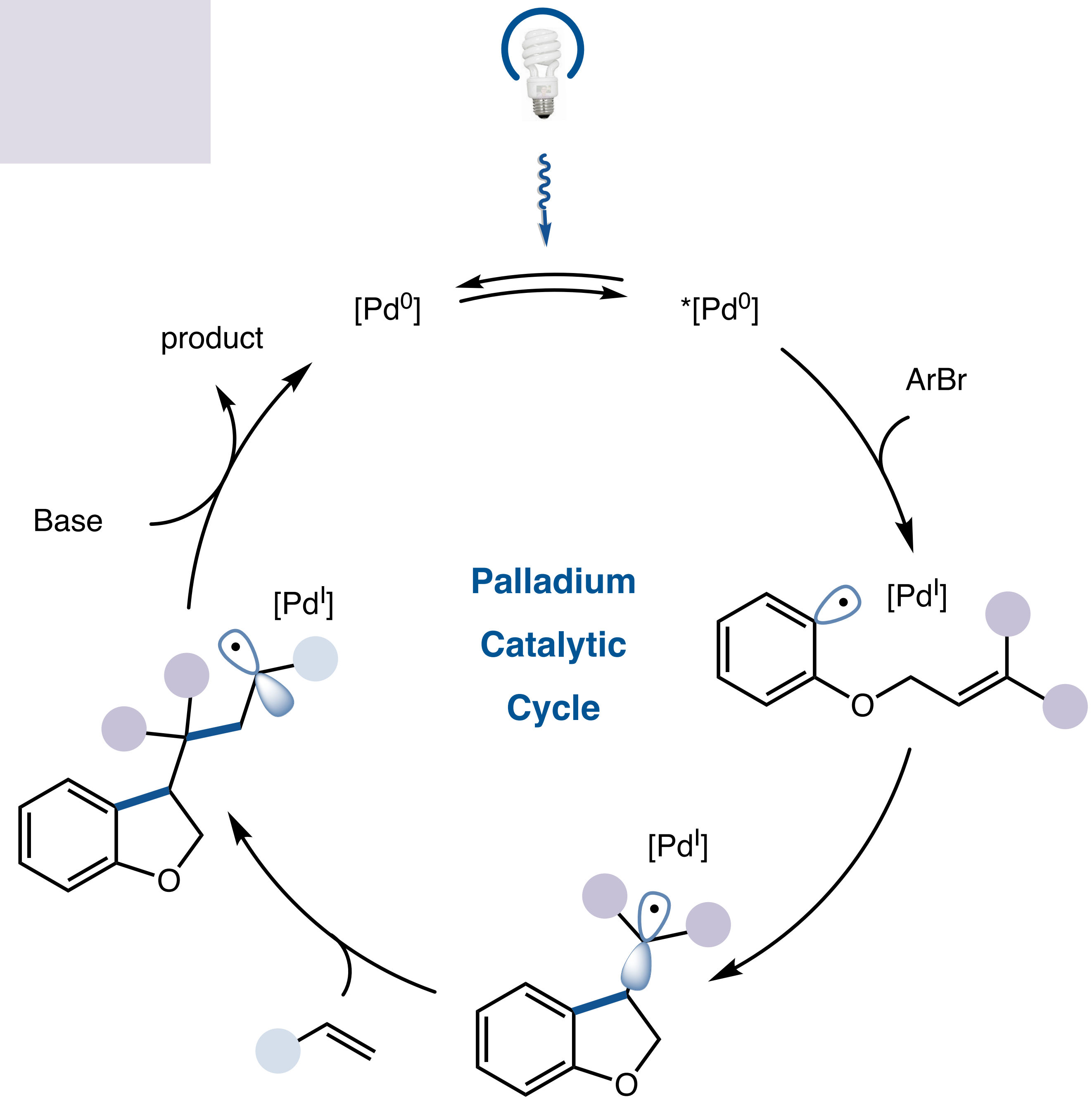
Oxidation states of palladium:

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

accessed via 1e⁻ pathways → *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***



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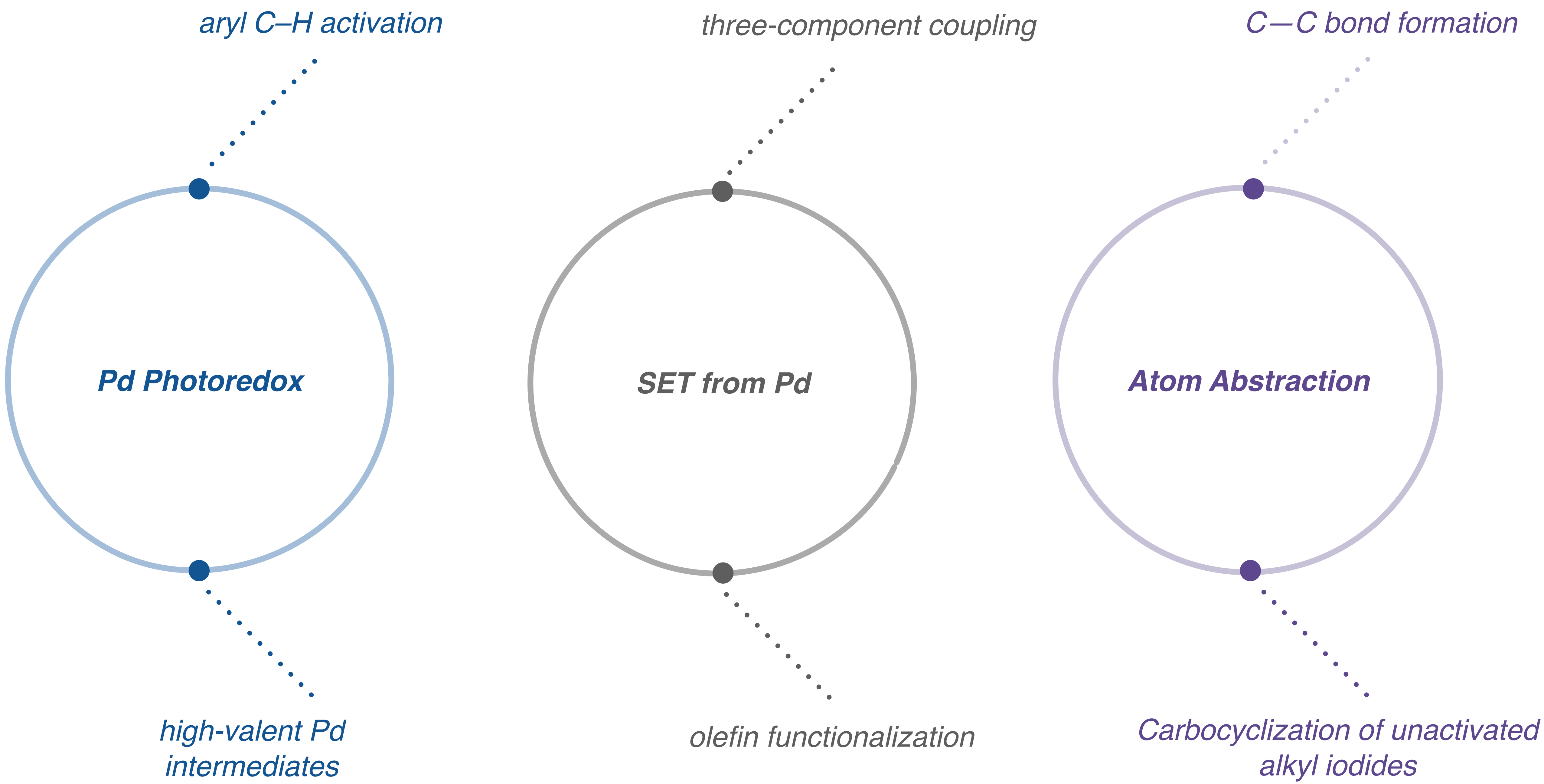
Three main areas of radical-based palladium chemistry



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

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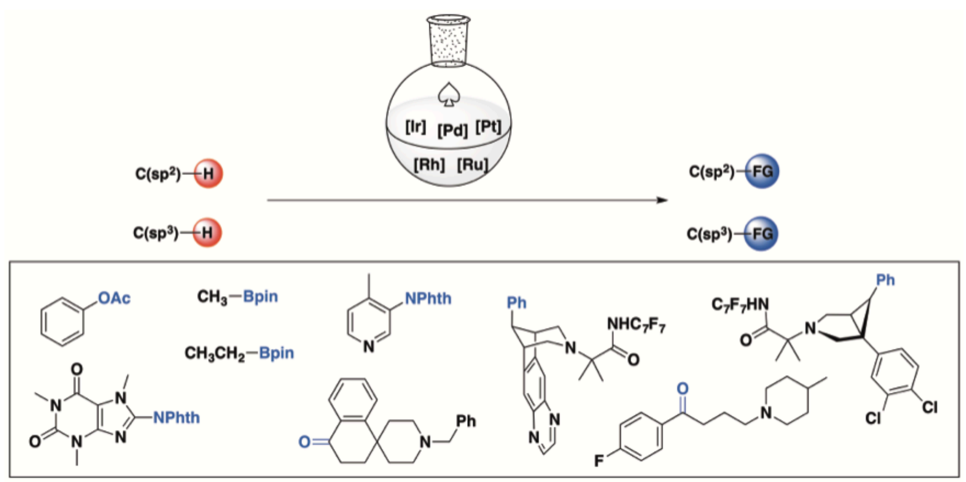
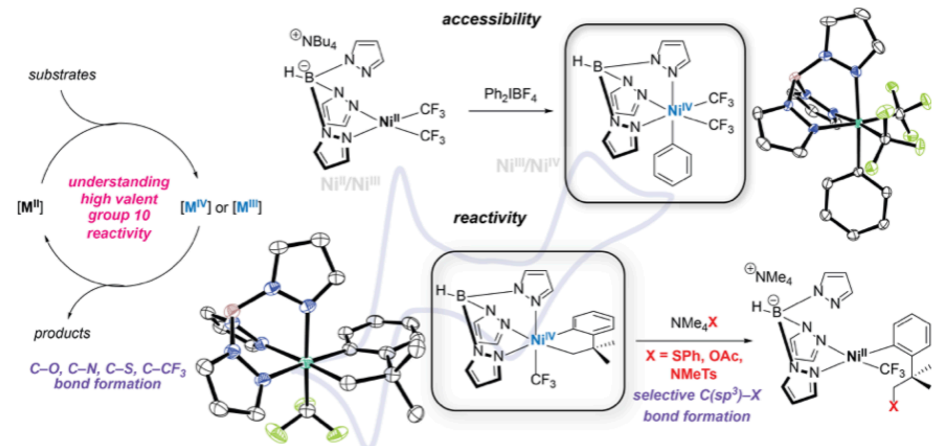
Research in the Sanford group

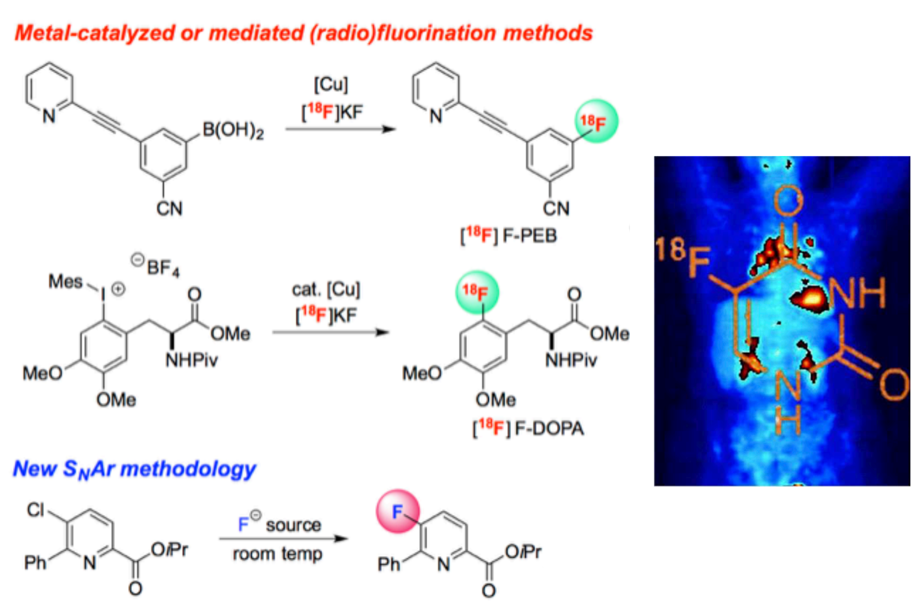
C—H Functionalization



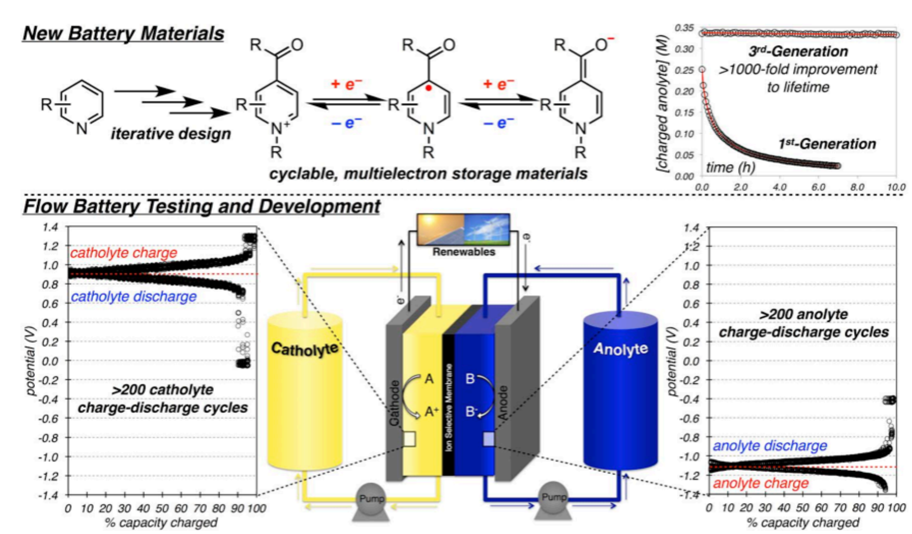
Organometallics



Fluorination



Flow Batteries



Bourm J.; Camasso, N.; Sanford, M. *J. Am. Chem. Soc.* **2015**, *137*, 8034.
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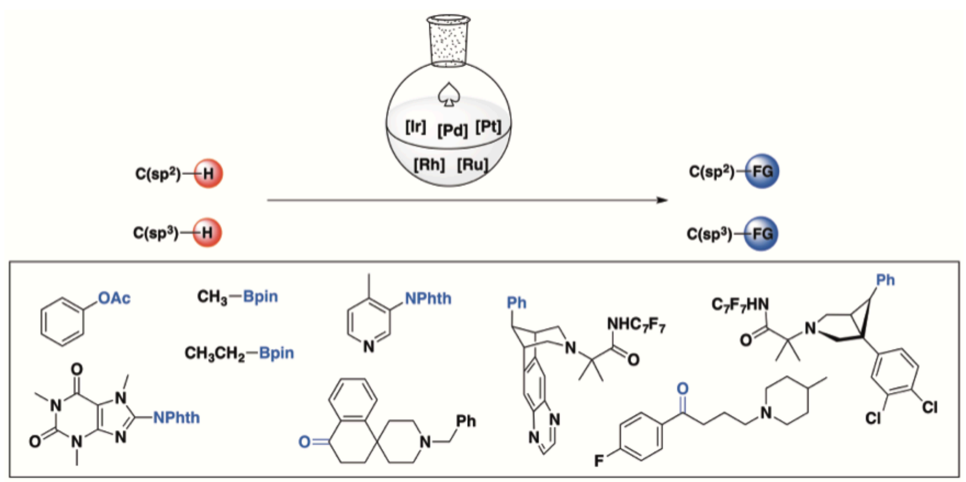
Sevov, C.; Brooner, R.; Chenard, E.; Assary, R.; Moore, J.; Rodriguez-Lopez, J.; Sanford, M. *J. Am. Chem. Soc.* **2015**, *137*, 14465.

Research in the Sanford group

C—H Functionalization



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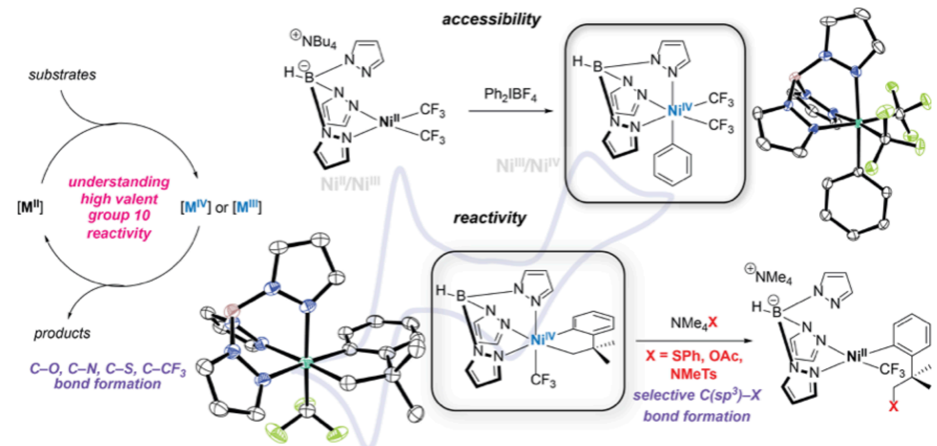

A.B. Chemistry: *Yale University, 1996 (Bob Crabtree)*

PhD. Chemistry: *Caltech, 2001 (Bob Grubbs)*

Postdoc: *Princeton University, 2008 (Jay Groves)*

UNIVERSITY OF MICHIGAN

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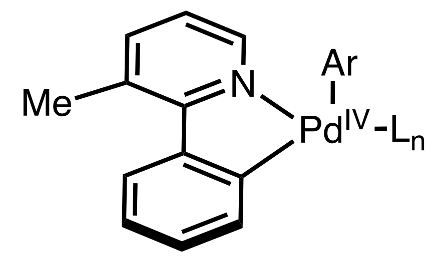
High valent palladium reactivity

Why would we want to access high valent palladium?



- ***facile reductive elimination***
- ***unique reactivity***
- ***catalytically competent***

Hickman, A.; Sanford, M. *Nature,* **2012**, *484*, 177.

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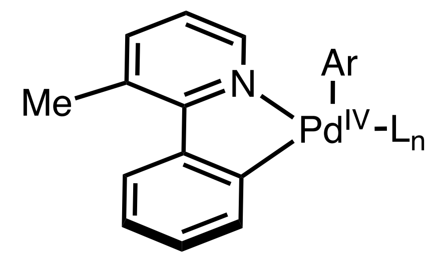

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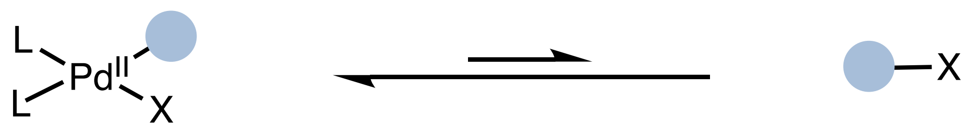

C–X reductive elimination is unfavorable for most Pd[II]

- **C–X and C–CF_3 reductive elimination are challenging from low-valent Pd**

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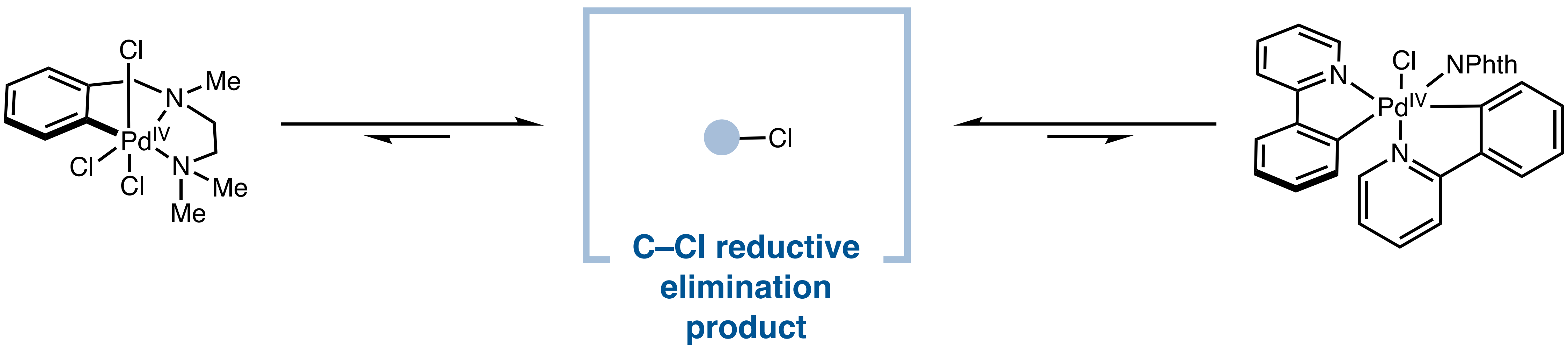

- **C–X and C–CF_3 reductive elimination are challenging from low-valent Pd**
- **Most Pd^0/Pd^{II} transformations involve C–X bond breaking, not forming**

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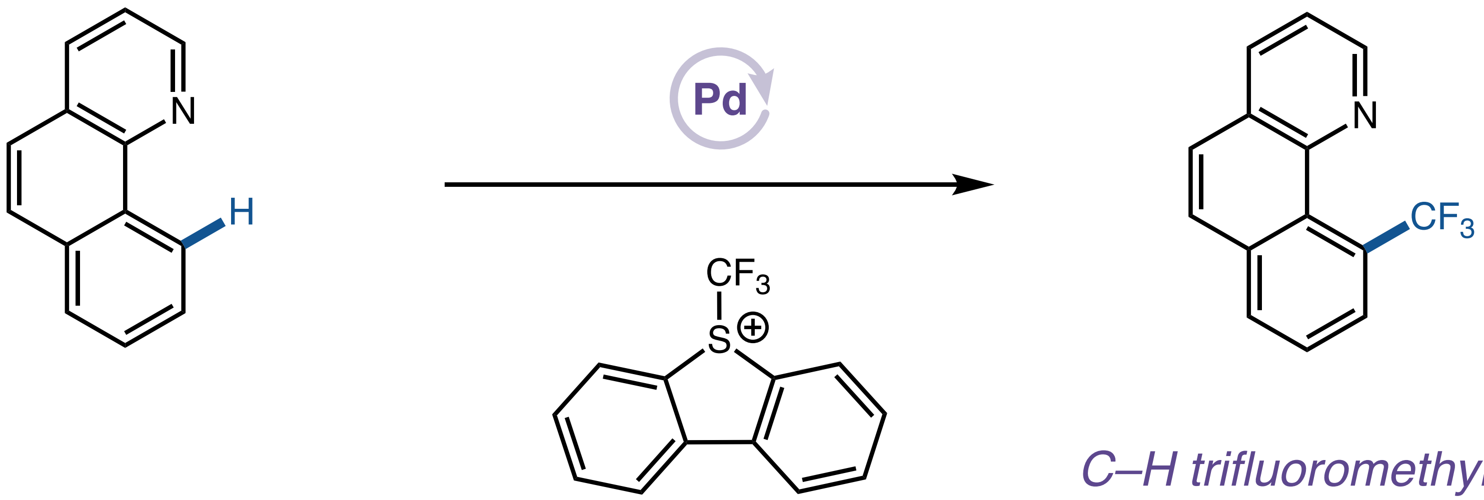
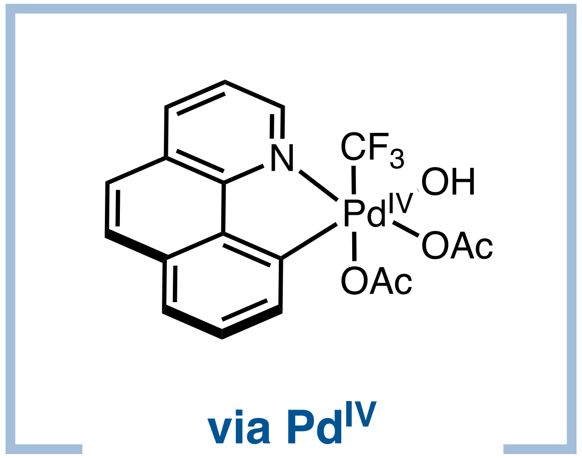


C–H trifluoromethylated product



via Pd^{IV} intermediate

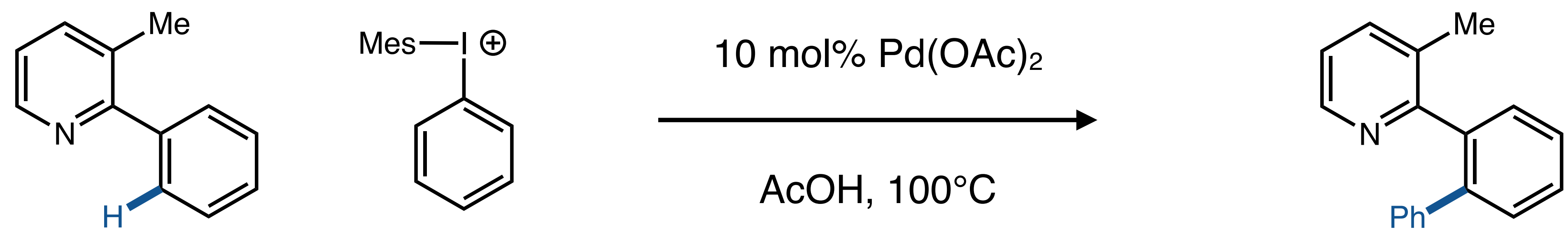
- **C–X and C–CF_3 reductive elimination are challenging from low-valent Pd**
- **Most Pd^0/Pd^{II} transformations involve C–X bond breaking, not forming**

Therefore, if we want to make halogenated or CF_3-containing products, we need high-valent Pd

Hickman, A.; Sanford, M. *Nature,* **2012**, *484*, 177.

C—H arylation: a model reaction

C—H Arylation



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

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

Design elements

room temperature

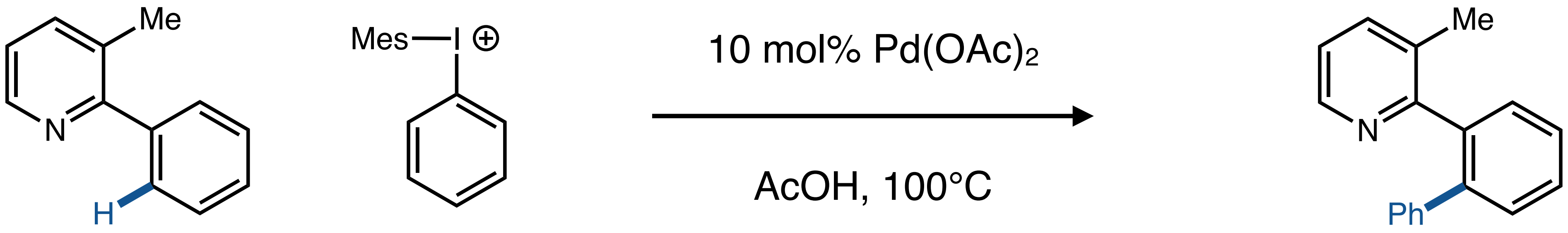
non-acidic solvent

no stoichiometric oxidant

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

C—H arylation: a model reaction

C—H Arylation



✗ **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.

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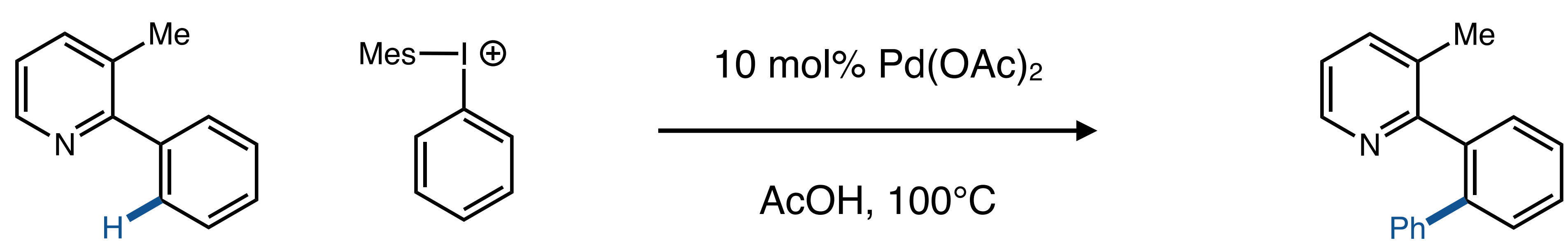

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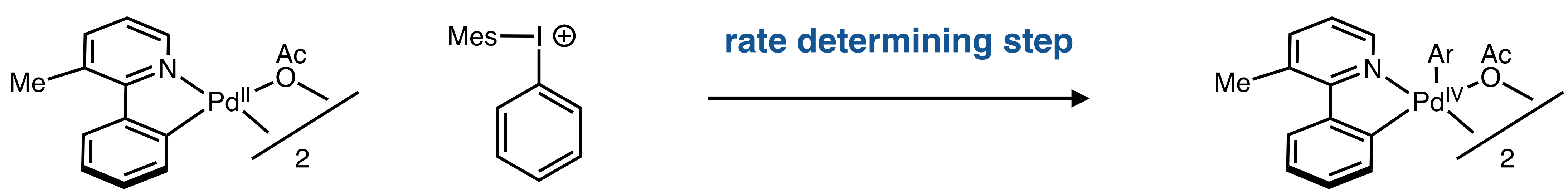

- **mechanistic studies revealed that oxidation of dimer is rate-limiting**
- **rate of reaction could be increased with more reactive arylating reagents**

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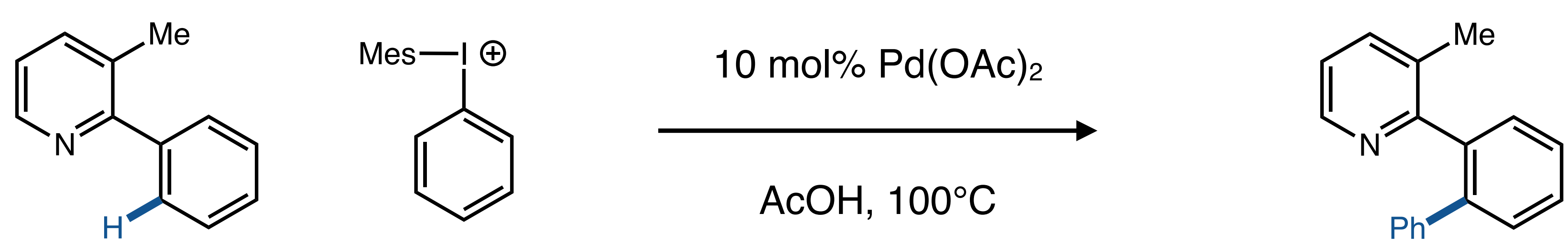

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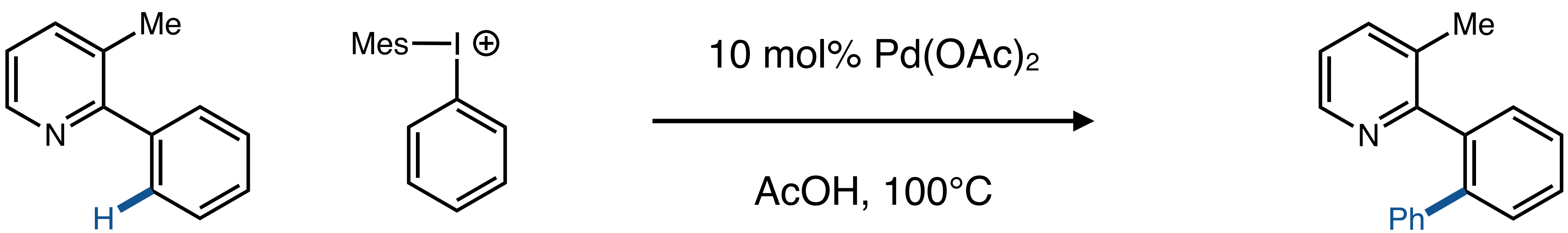

✗ **high temperature**

✗ **acidic solvent**

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Literature precedent:
aryl diazonium reagents

room temperature activation

aryl radical generation

nitrogen as byproduct

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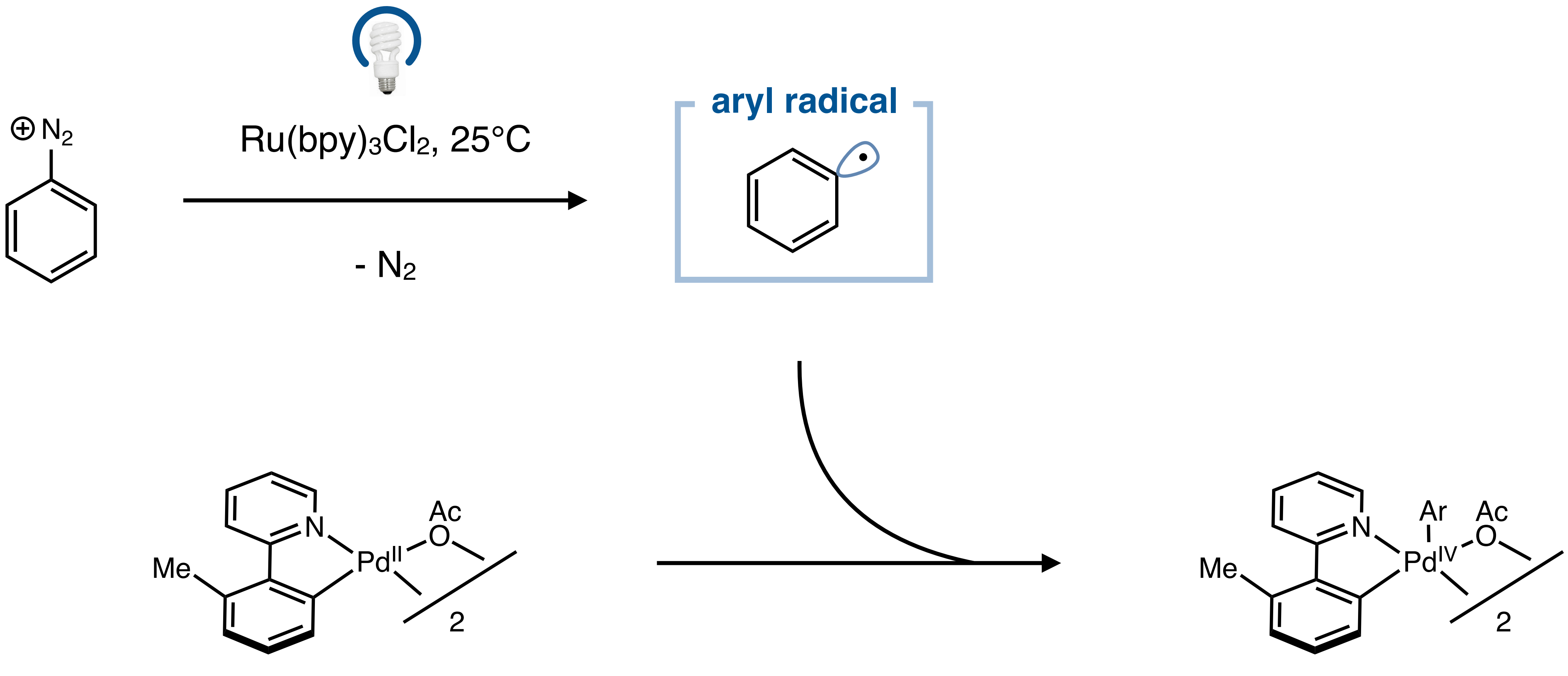
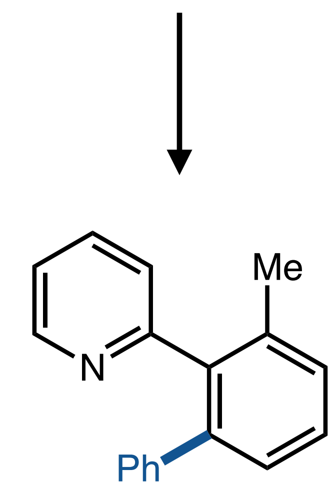


First example of palladium-catalyzed C–H functionalization using visible-light photoredox catalysis



✔ **non-acidic solvent** ✔ **room temperature**

84% yield

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

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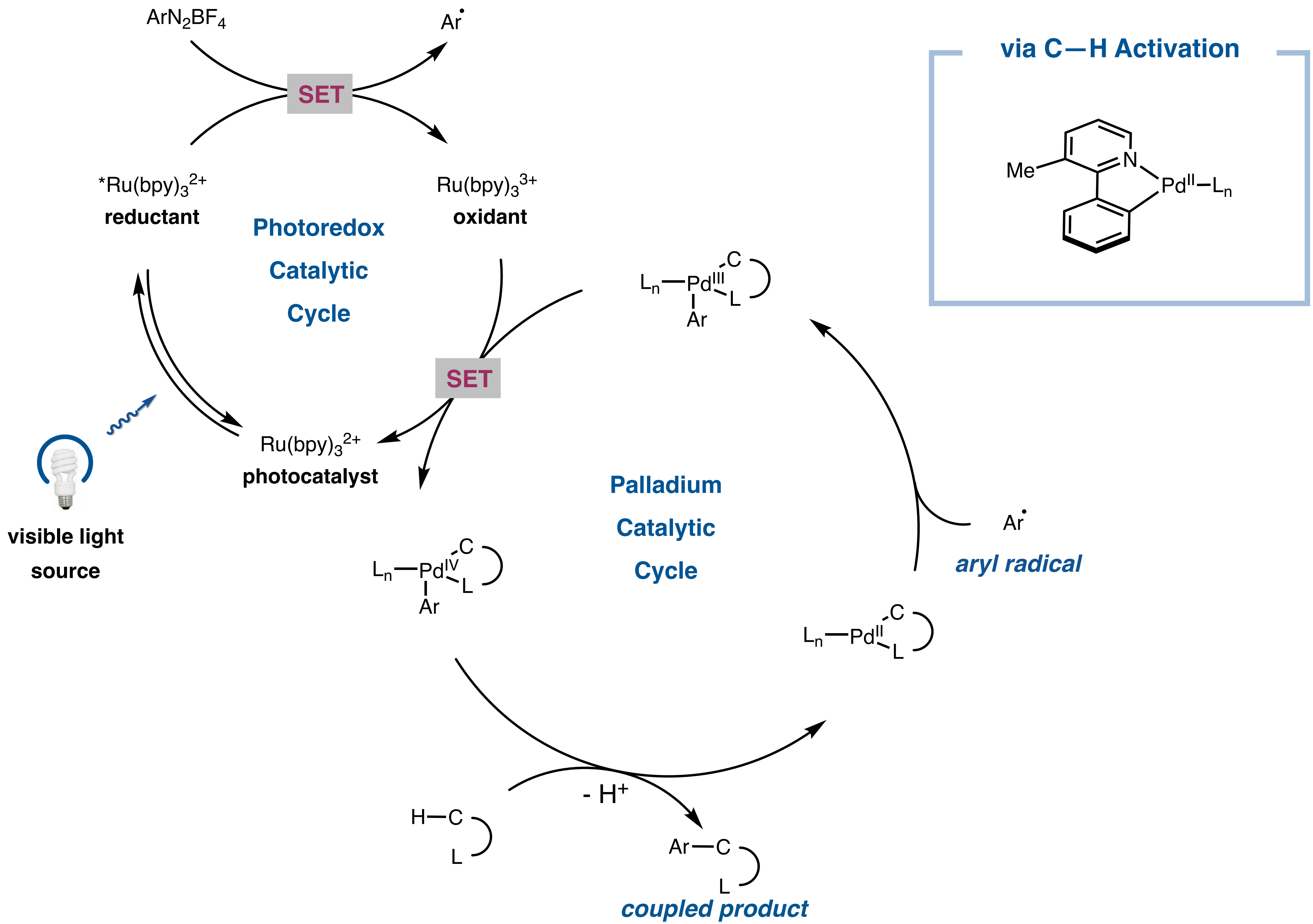
Proposed mechanism



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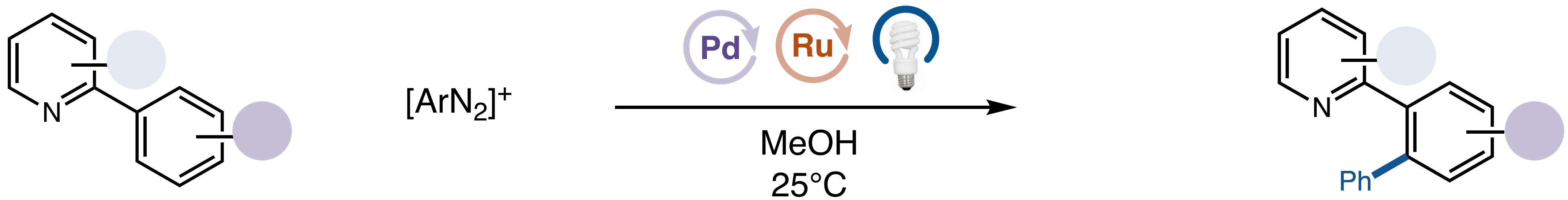
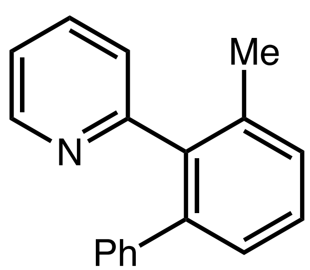
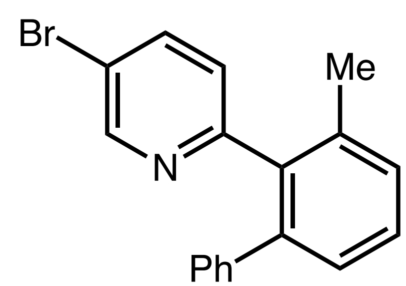
Scope of arylpyridine

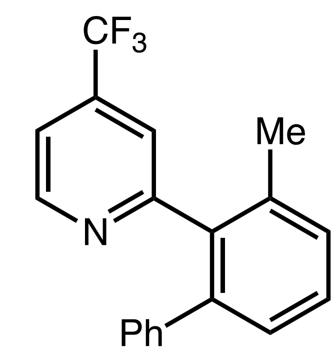




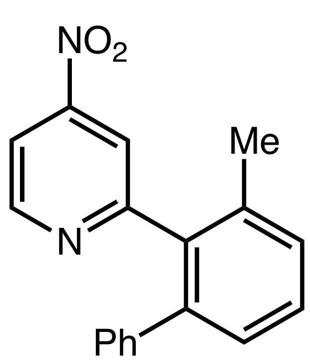
76% yield



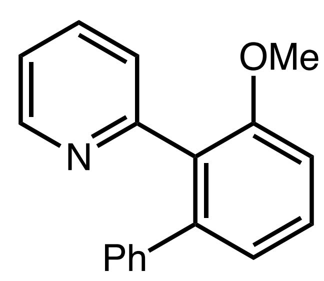
63% yield



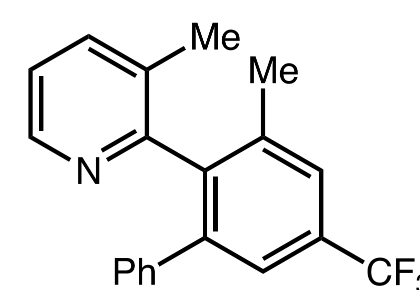
59% yield



47% yield



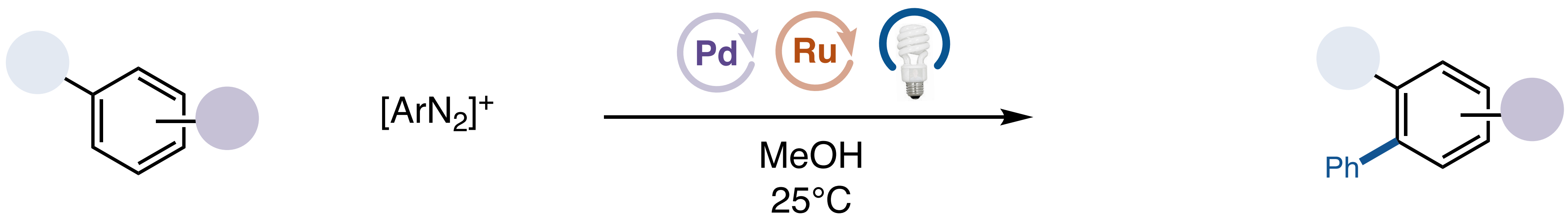
69% yield

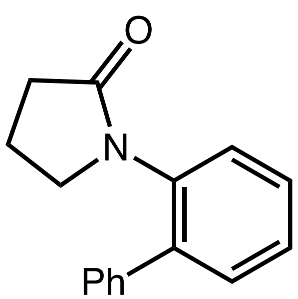


60% yield

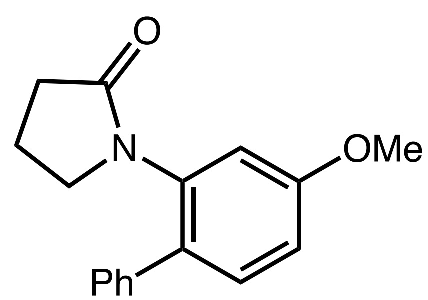
Kalyani, D.; McMurtrey, K.; Neufeldt, S.; Sanford, M. *J. Am. Chem. Soc.* **2011**, *133*, 18566.

Scope of directing group

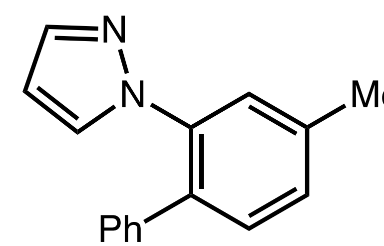




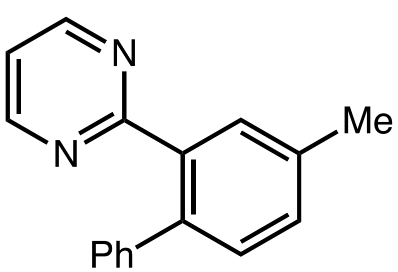
72% yield



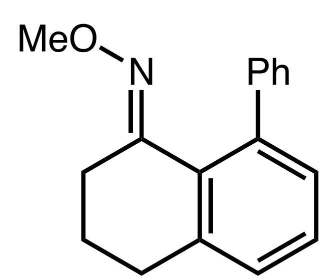
79% yield



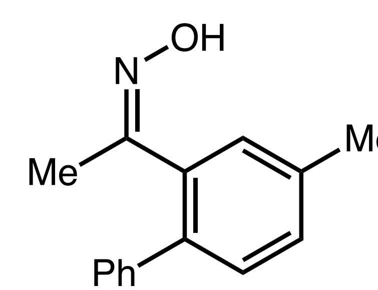
53% yield



44% yield



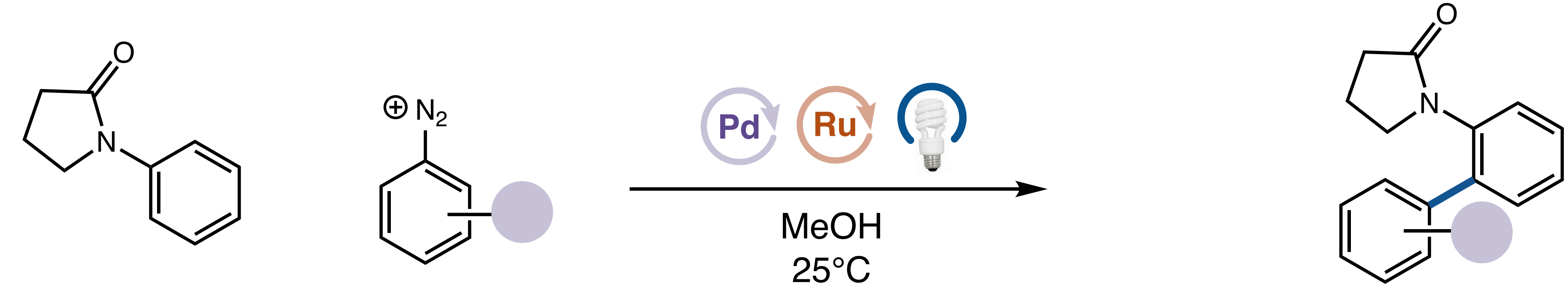
49% yield

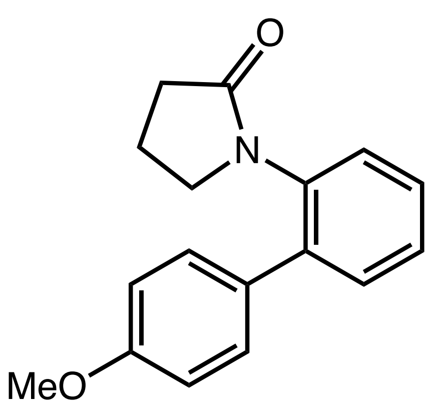


50% yield

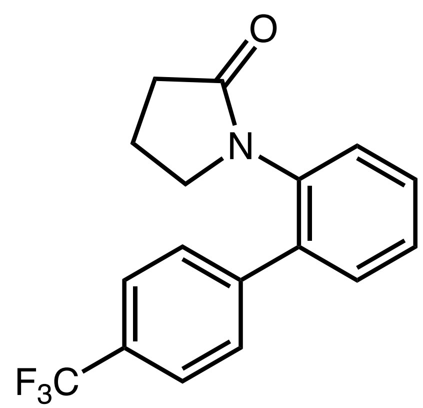
Kalyani, D.; McMurtrey, K.; Neufeldt, S.; Sanford, M. *J. Am. Chem. Soc.* **2011**, *133*, 18566.

Scope of aryldiazonium

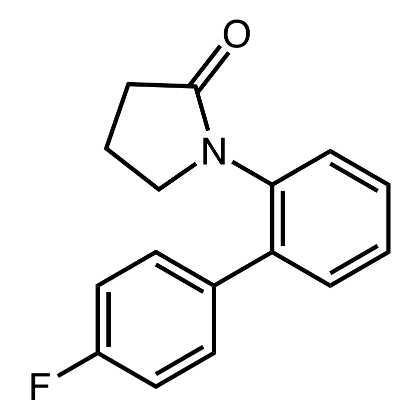




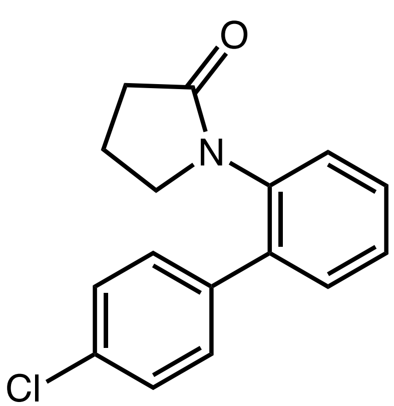
76% yield



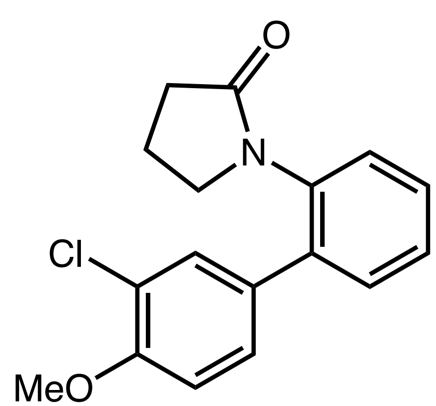
87% yield



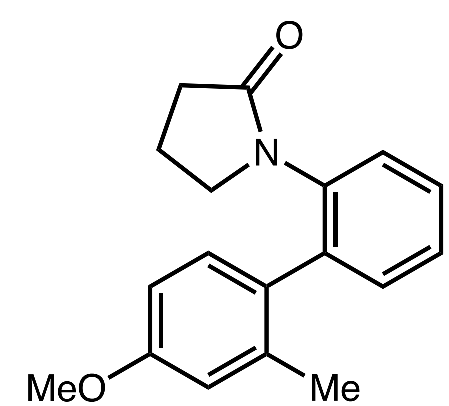
76% yield



78% yield



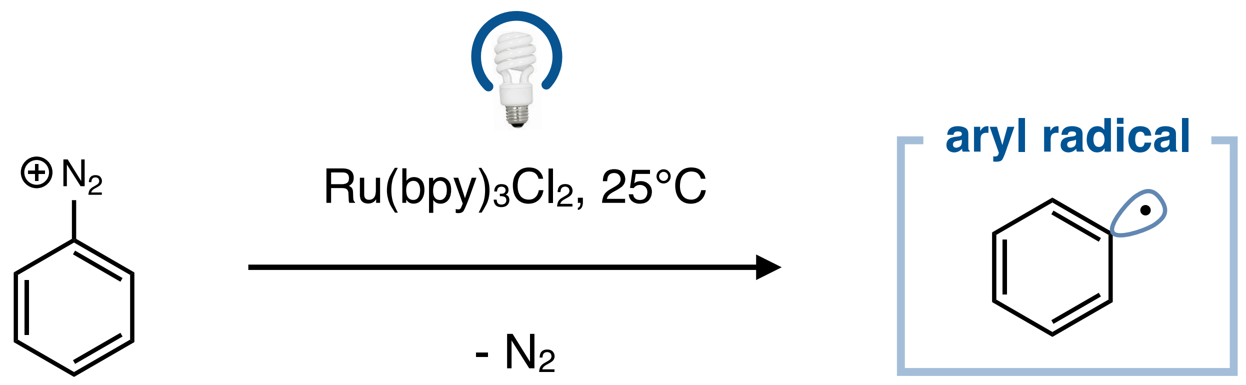
79% yield



57% yield

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

C—H activation with diaryliodonium reagents



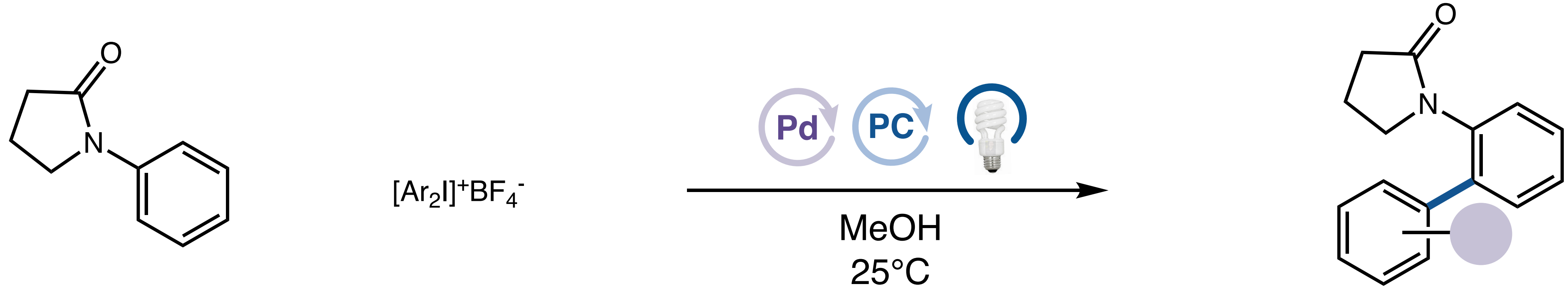
Can we apply these principles towards C–H activation with diaryliodonium reagents?

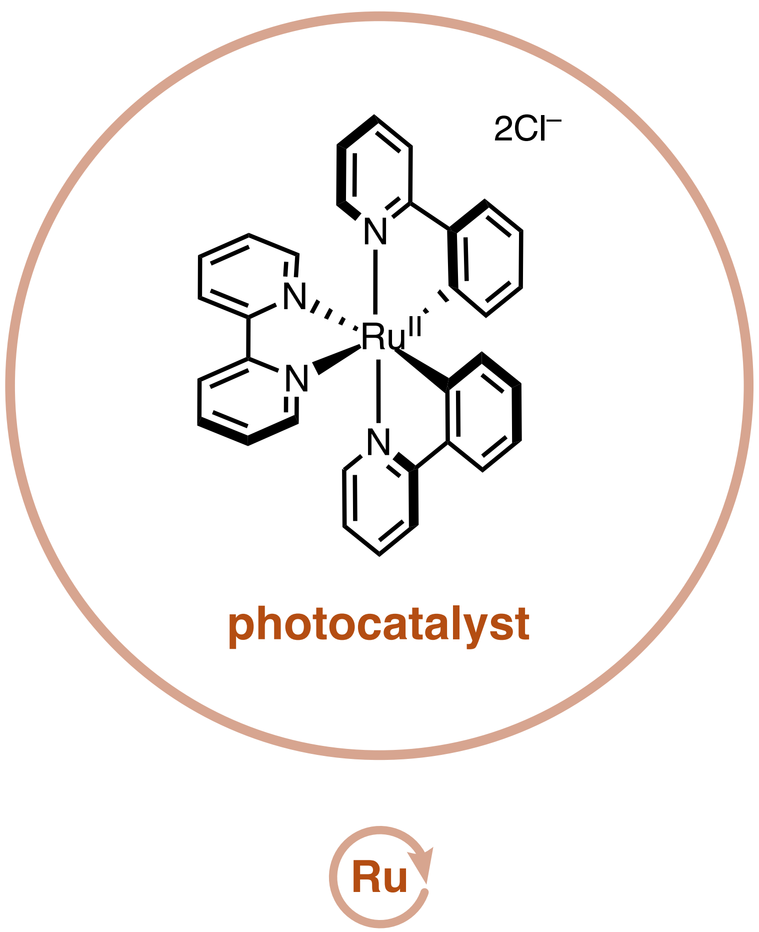
Neufeldt, S.; Sanford, M. *Adv. Synth. Catal.* **2012**, *354*, 3517.

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

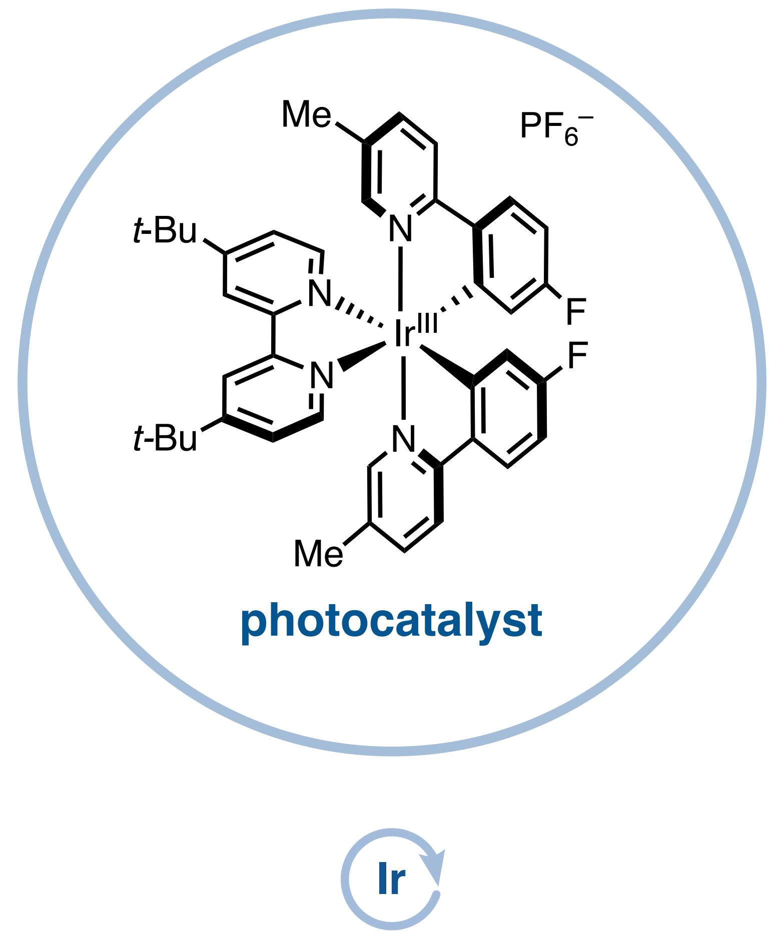
Kalyani, D.; McMurtrey, K.; Neufeldt, S.; Sanford, M. *J. Am. Chem. Soc.* **2011**, *133*, 18566.

C—H activation with diaryliodonium reagents





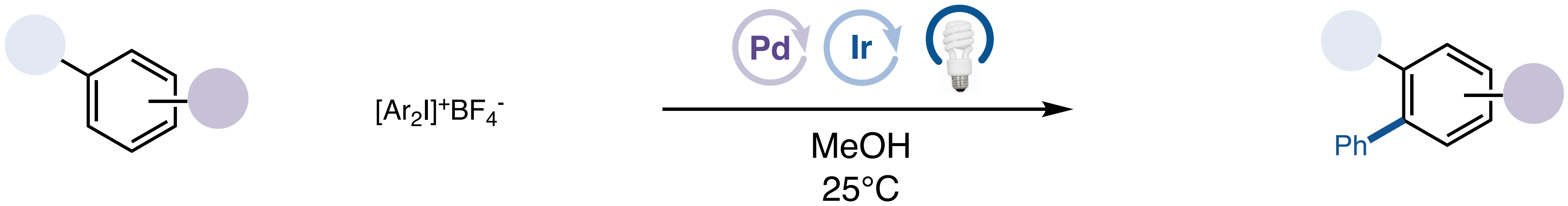
18% yield

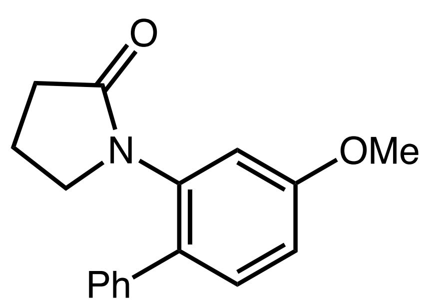


94% yield

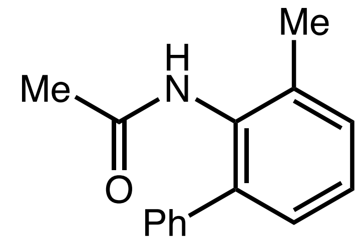
Neufeldt, S.; Sanford, M. *Adv. Synth. Catal.* **2012**, *354*, 3517.

Scope of directing group

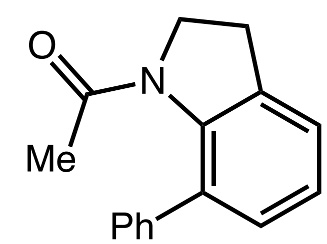




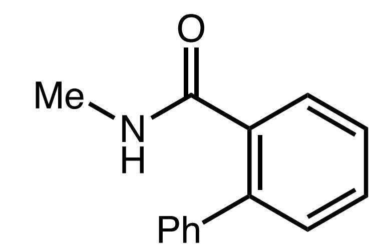
94% yield



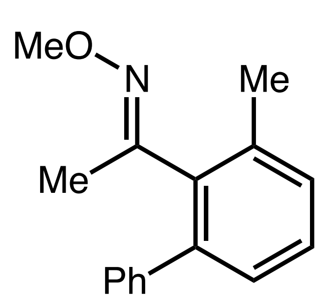
72% yield



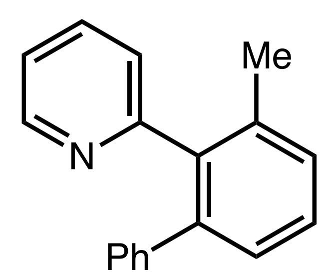
44% yield



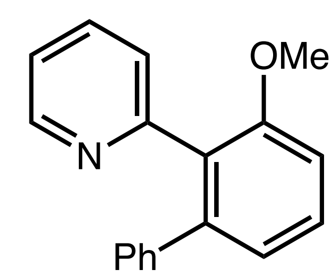
54% yield



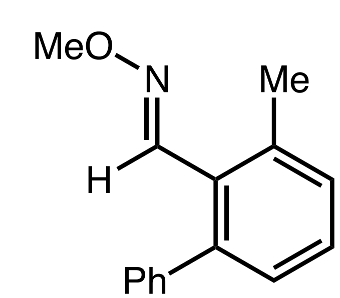
60% yield



62% yield



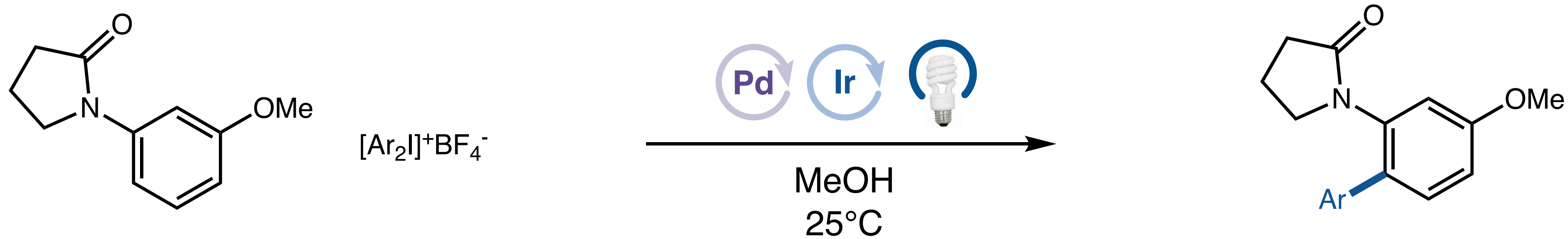
67% yield

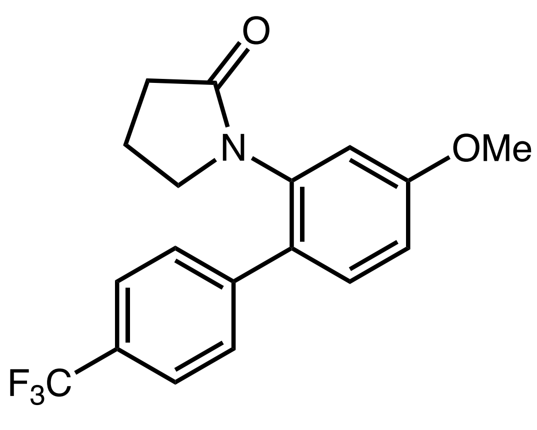


57% yield

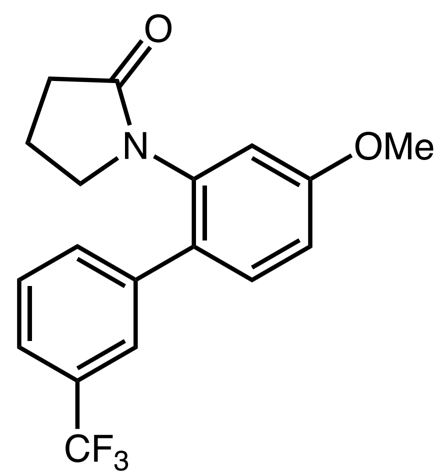
Neufeldt, S.; Sanford, M. *Adv. Synth. Catal.* **2012**, *354*, 3517.

Scope of diaryliodonium reagents

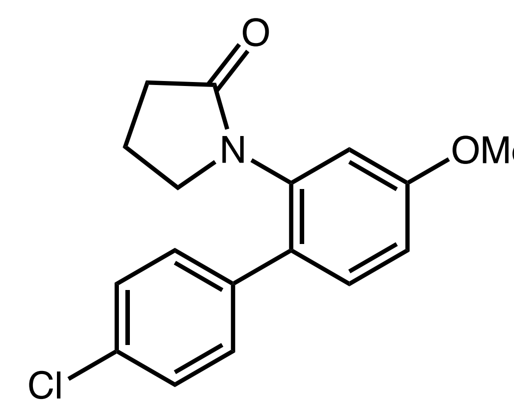




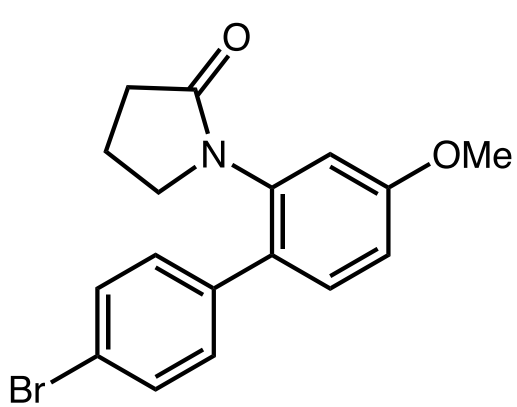
69% yield



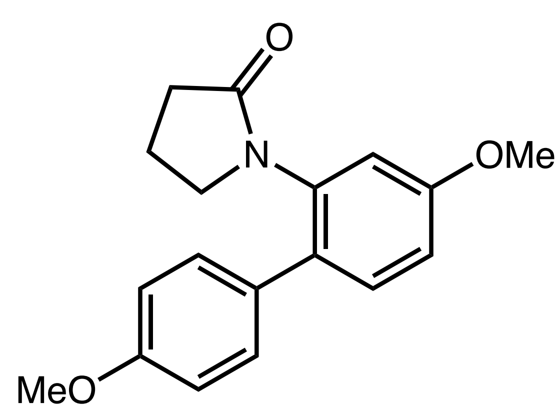
56% yield



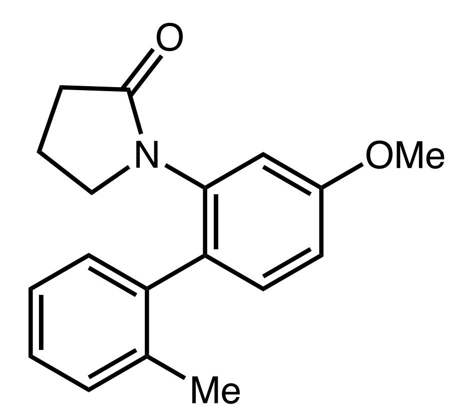
77% yield



79% yield



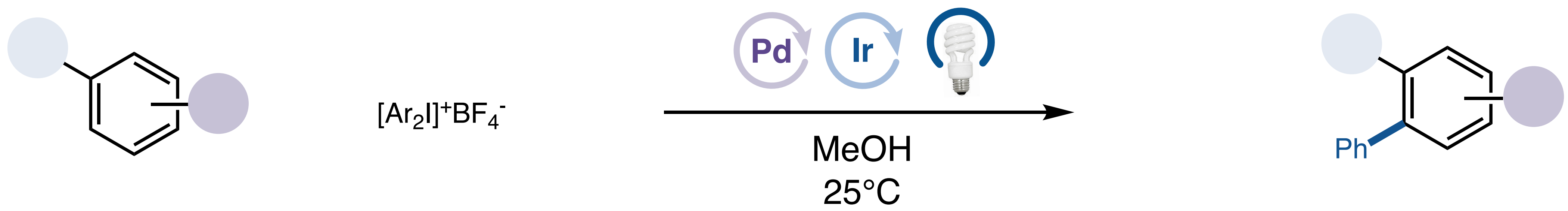
41% yield

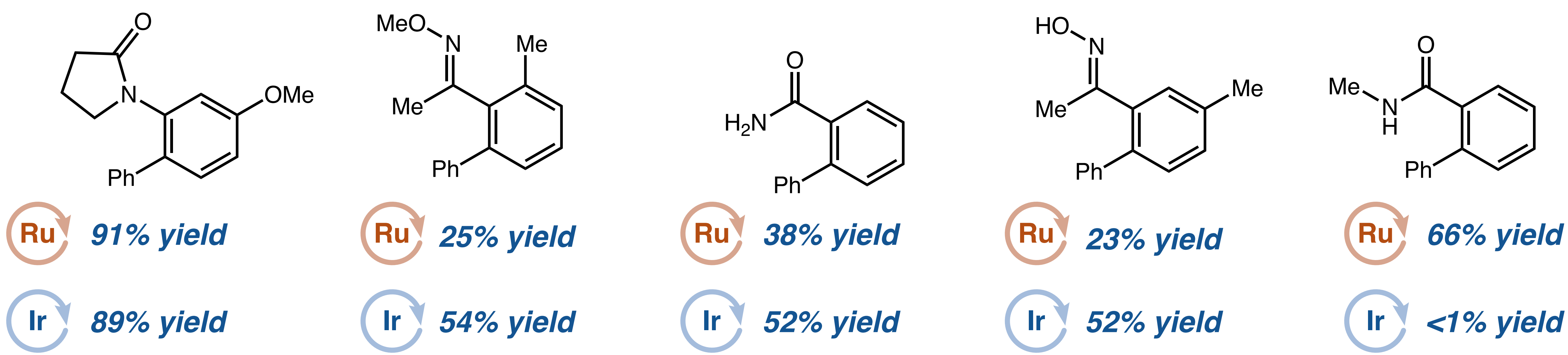


85% yield

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

Comparison of C–H arylation scopes



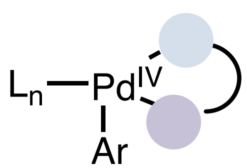


orthogonal and complementary scopes

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

Further directions in the Sanford group

High-valent Pd chemistry



Pd^{IV} aryl intermediate

mechanistic investigations

photonic and non-photonics methods for Pd^{IV} generation

applications towards high-valent Ni intermediates

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

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

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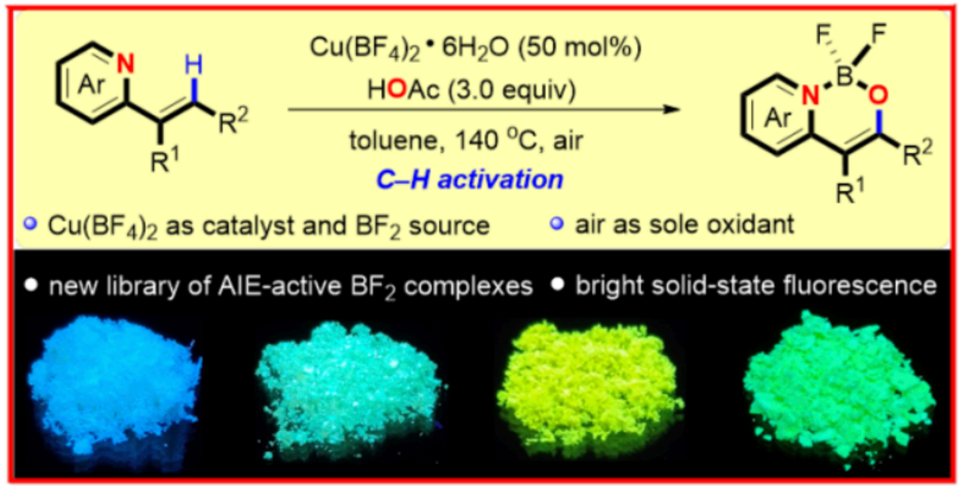
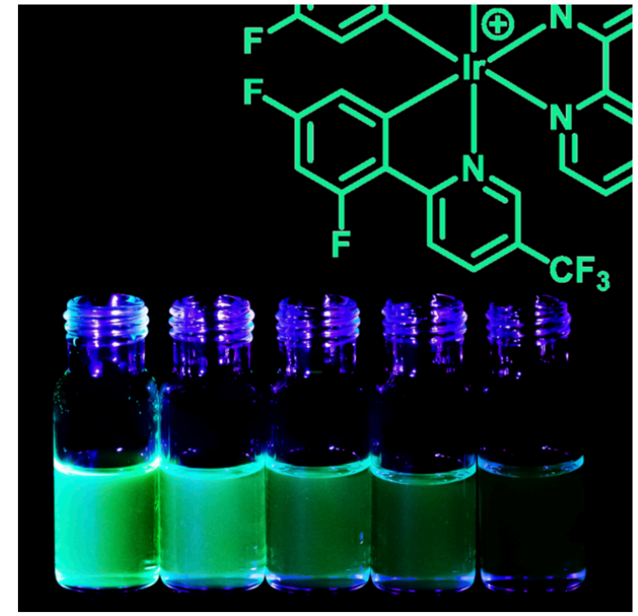
University of North Carolina-Chapel Hill

Research in the Glorius group

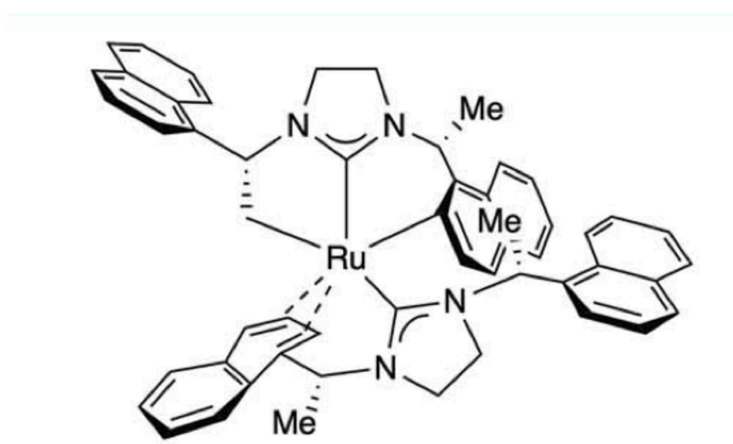
C—H Activation



Photocatalysis

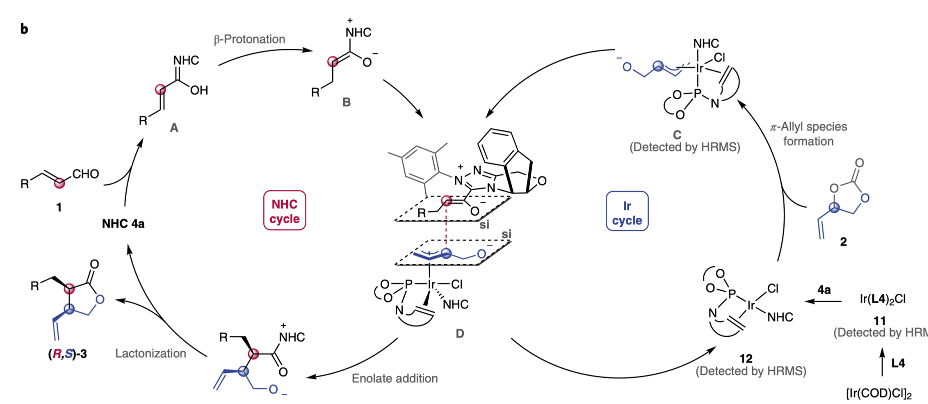


Arene Hydrogenation



Ru((*R*,*R*)-SINpEt)$_2$, (**12**)

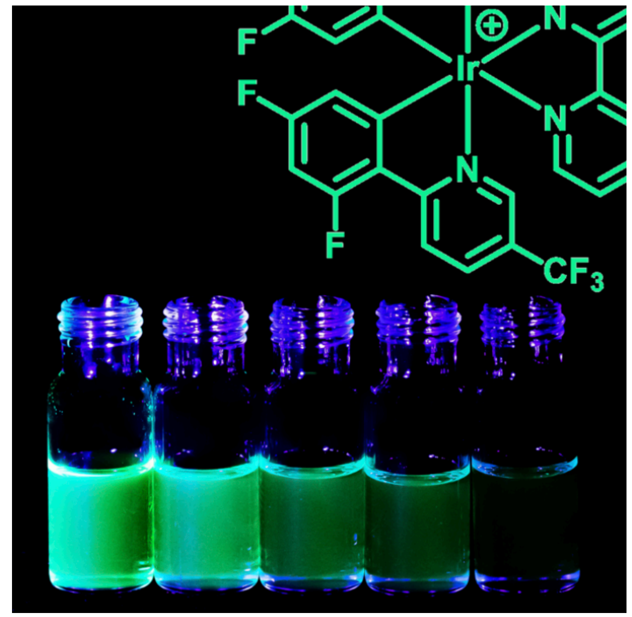
Organocatalysis



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)*

WWU MÜNSTER

Pinkert, T.; Das, M.; Schrader, M.; Glorius, F. *J. Am. Chem. Soc.* **2021**, *143*, 7648.
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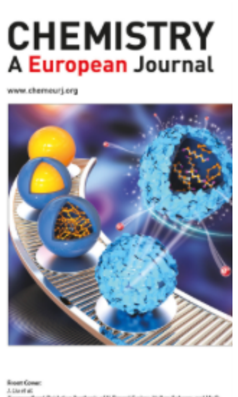
Singha, S.; Serrano, E.; Mondal, S.; Daniliuc, C.; Glorius, F. *Nature Cat.* **2020**, *3*, 48.
Wiesenfeldt, M.; Moock, D.; Paul, D.; Glorius, F. *Chem. Sci.* **2021**, *12*, 5611.

Glorius group contribution to radical palladium chemistry

Decarboxylative cross-coupling

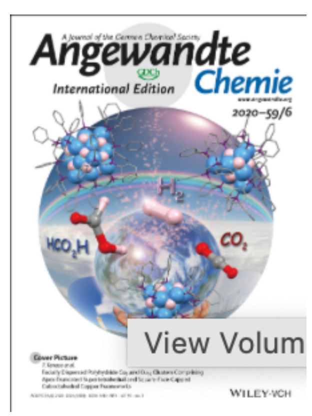
excited-state palladium as a reductant



Chem. Eur. J. ***2018***

Dicarbo-functionalization

halogen abstraction/ cyclization



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

allylic substitution

radical Pd π-allyl generation

Nature Catal. ***2020***

three-component coupling

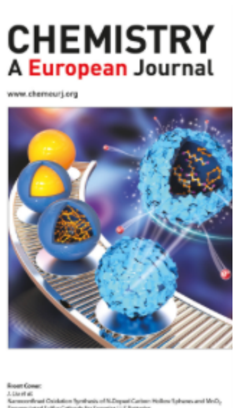
mixed mechanisms

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

Decarboxylative cross-coupling

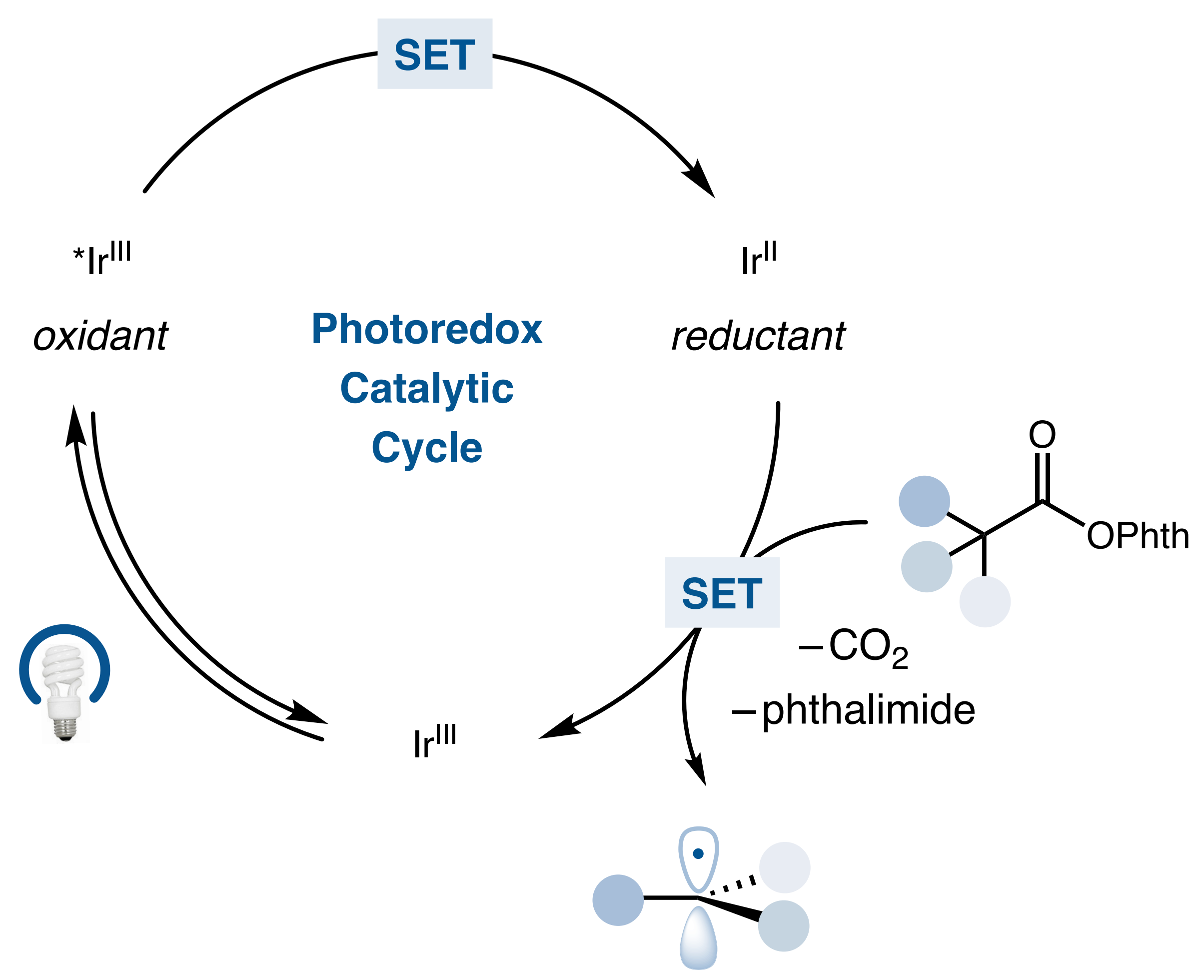
Decarboxylative cross-coupling

excited-state palladium as a reductant



Chem. Eur. J. ***2018***

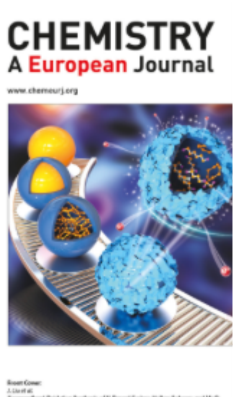
Reminiscent of our Ir photocatalytic cycles!



Decarboxylative cross-coupling

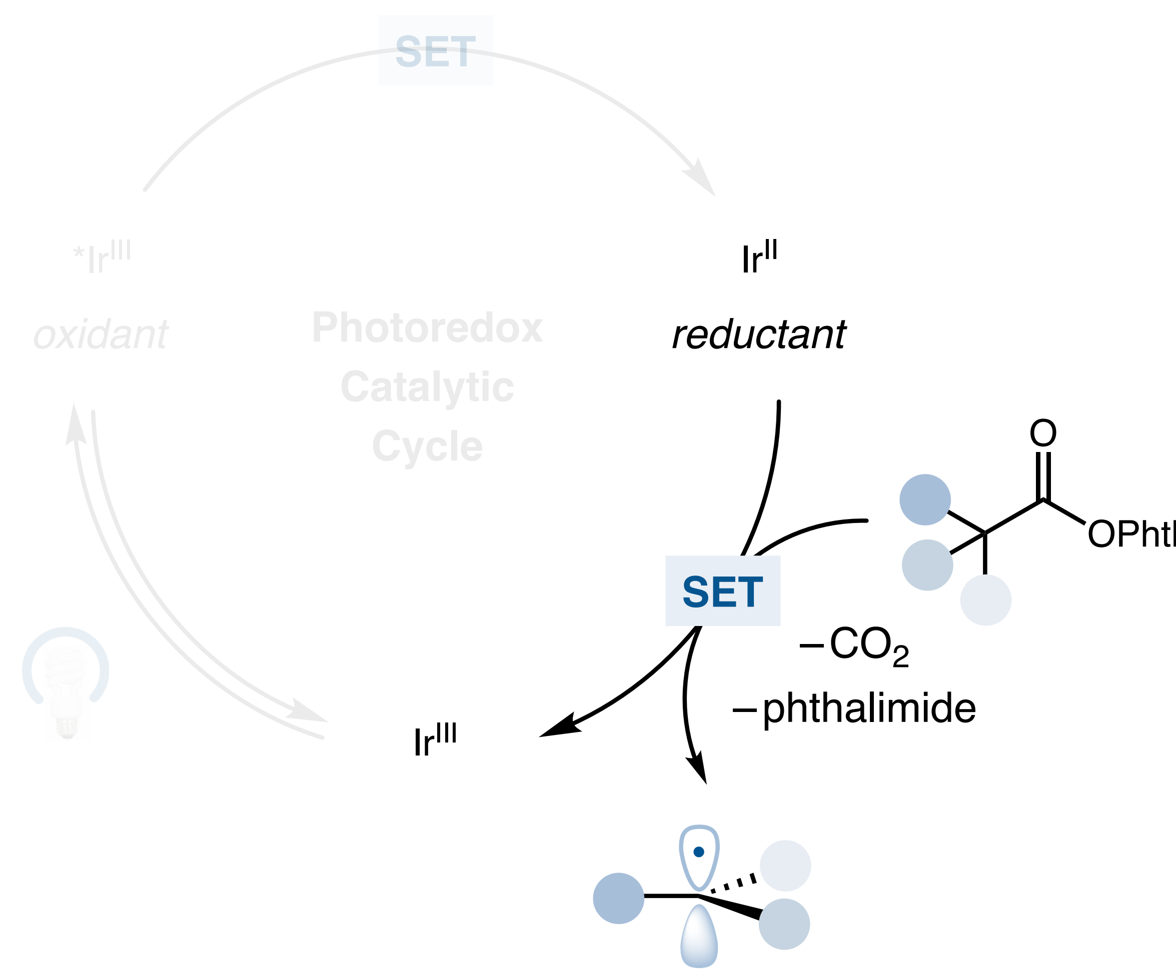
Decarboxylative cross-coupling

excited-state palladium as a reductant



Chem. Eur. J. ***2018***

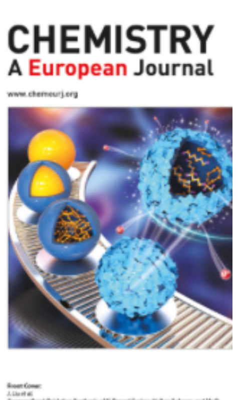
Reminiscent of our Ir photocatalytic cycles!



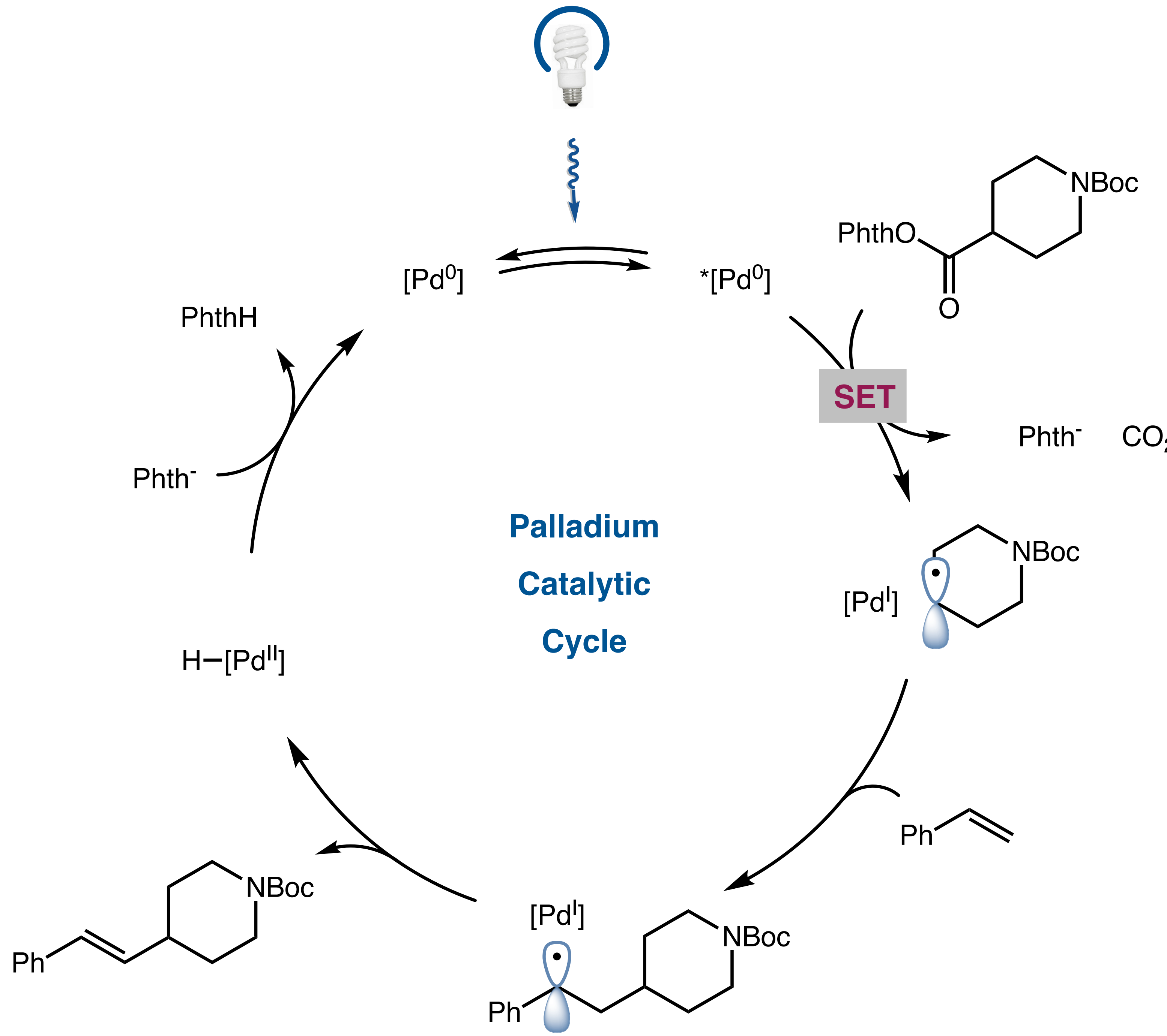
Decarboxylative cross-coupling

Decarboxylative cross-coupling

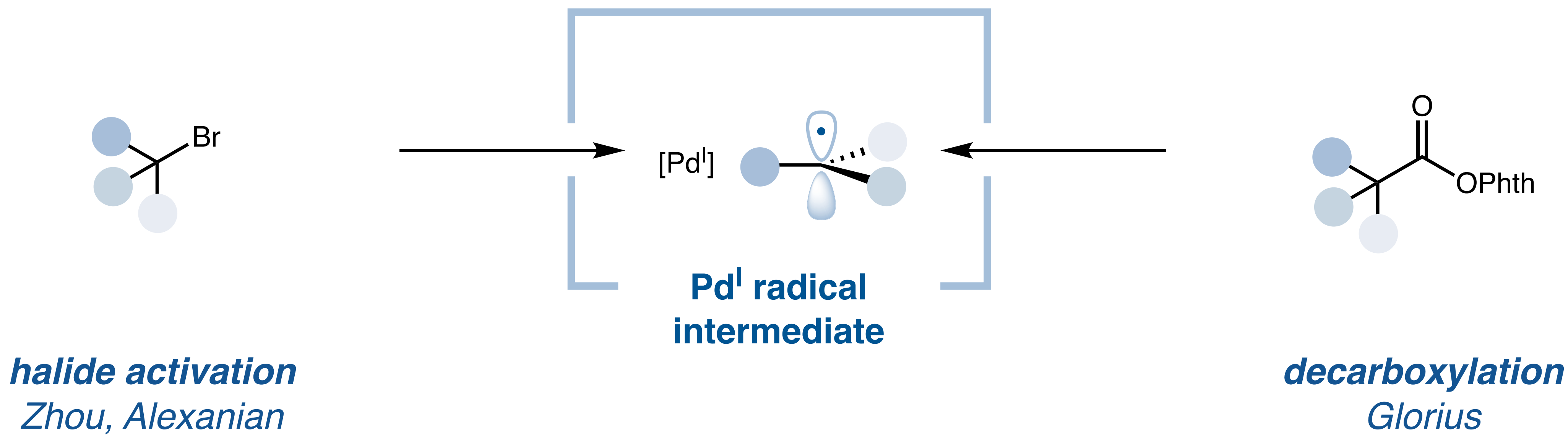
excited-state palladium as a reductant

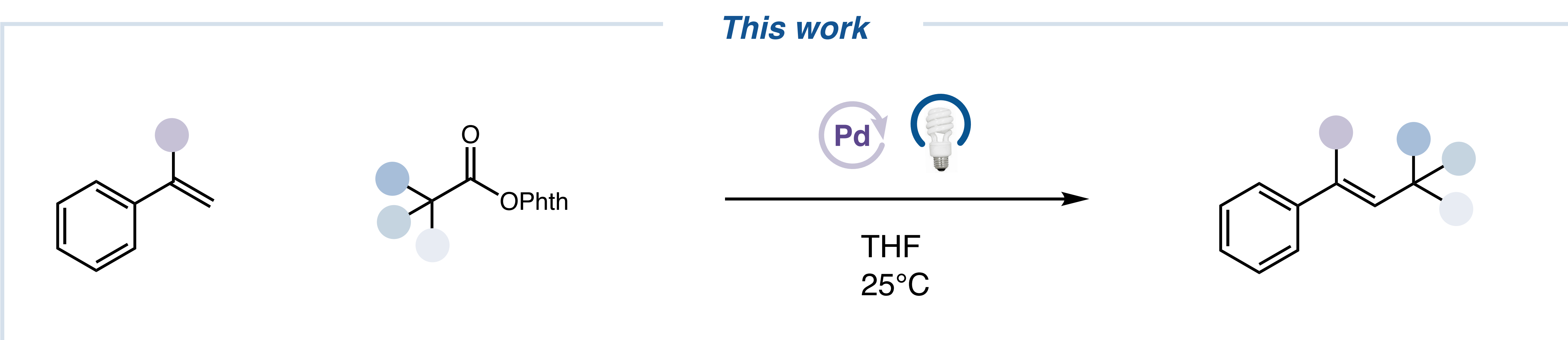


Chem. Eur. J. ***2018***



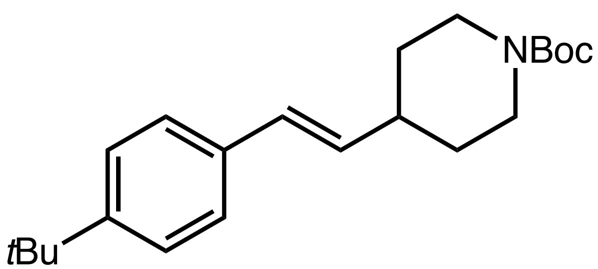
Decarboxylative cross-coupling



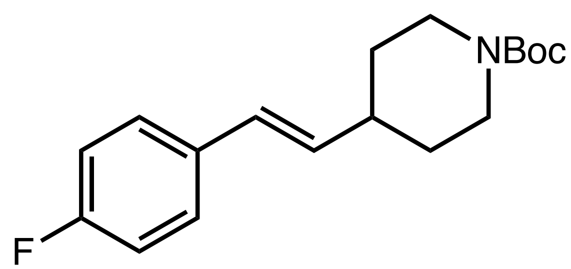


Koy, M.; Sandfort, F.; Tlahuext-Aca, A.; Quak, L.; Daniliuc, C.; Glorius, F. *Chem. Eur. J.* **2018**, *24*, 4552.

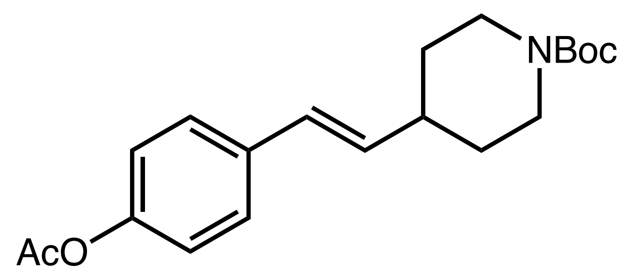
Scope of decarboxylative cross-coupling



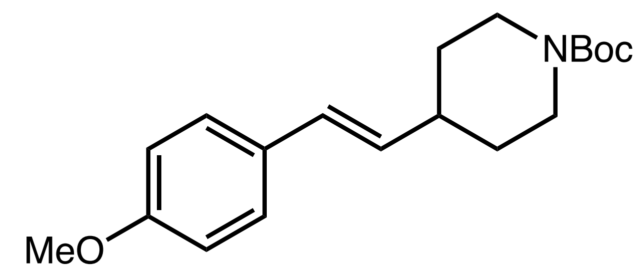
77% yield



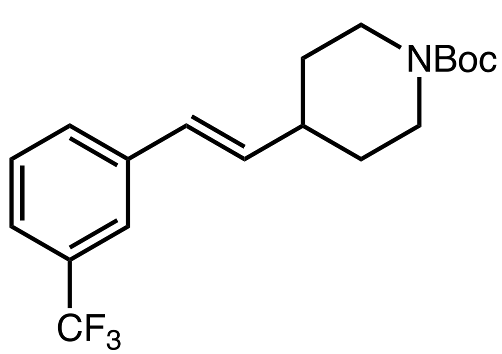
77% yield



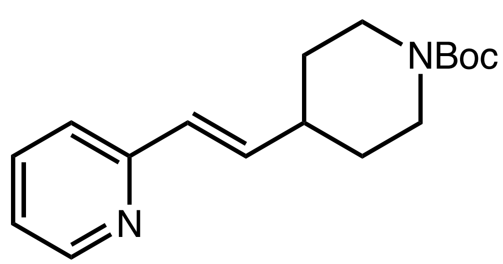
76% yield



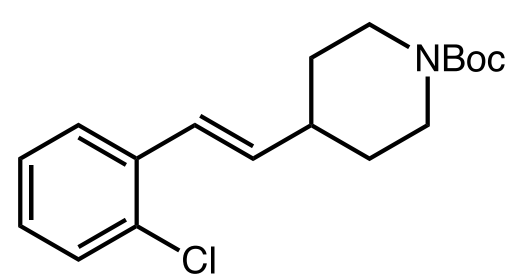
80% yield



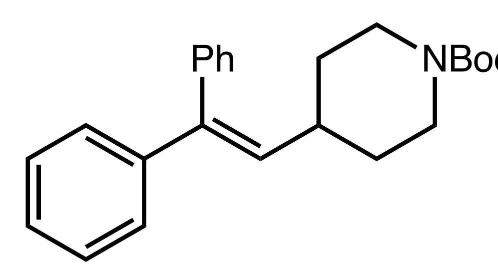
84% yield



78% yield



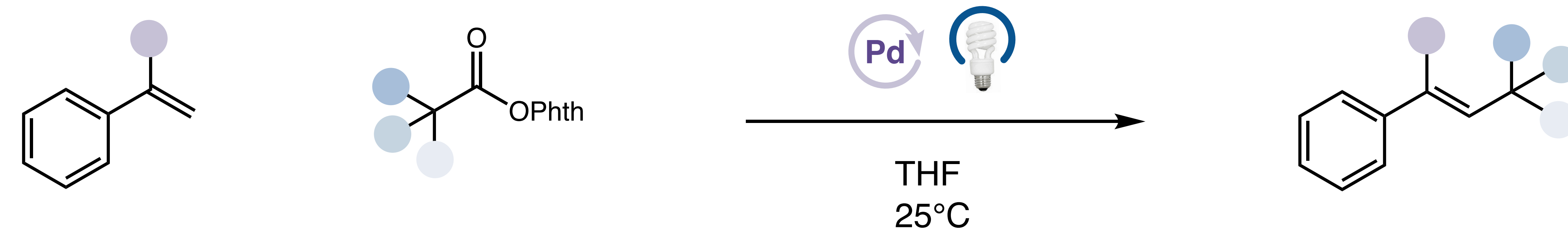
69% yield

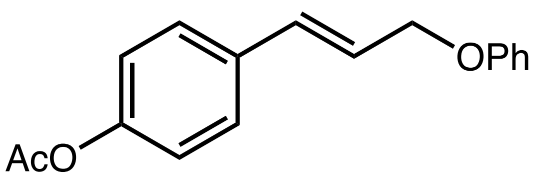


68% yield

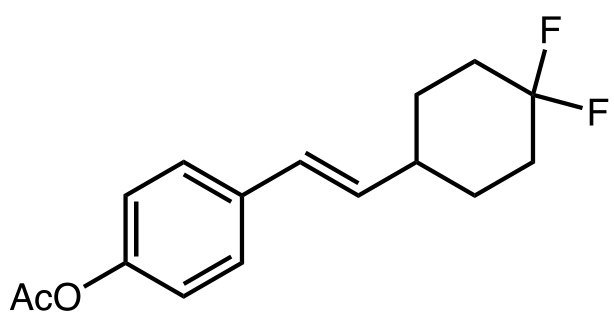
Koy, M.; Sandfort, F.; Tlahuext-Aca, A.; Quak, L.; Daniliuc, C.; Glorius, F. *Chem. Eur. J.* **2018**, *24*, 4552.

Scope of decarboxylative cross-coupling

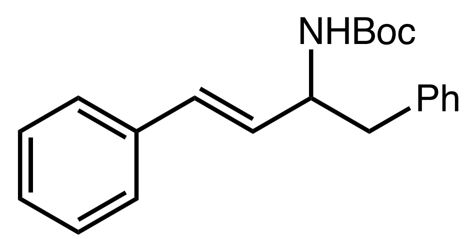




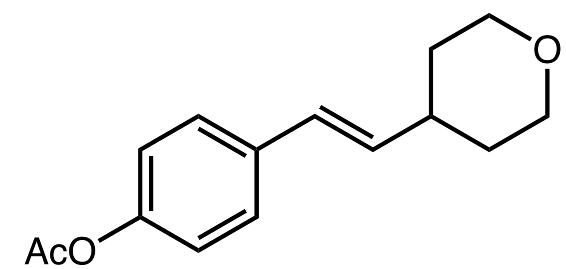
66% yield



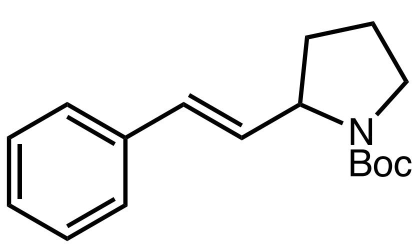
63% yield



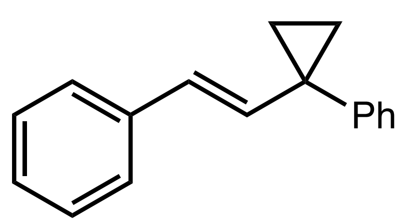
72% yield
from phenylalanine



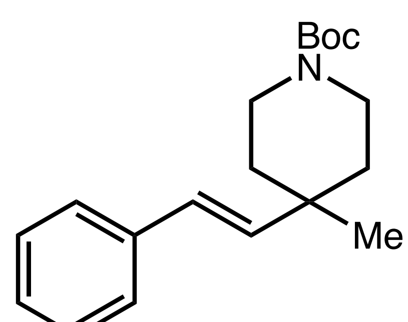
77% yield



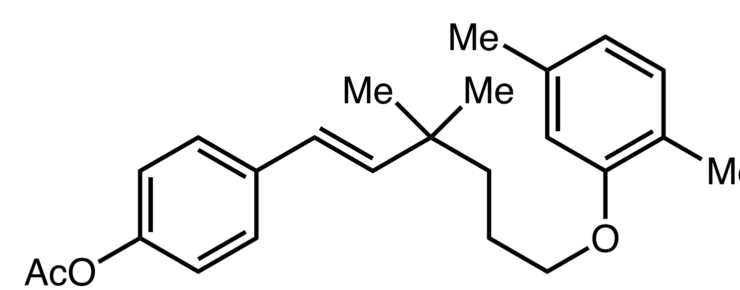
93% yield
from proline



73% yield



83% yield



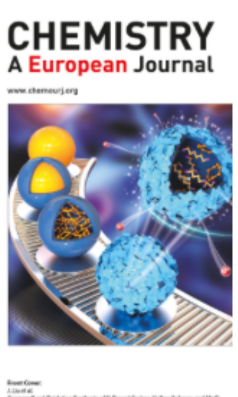
67% yield
from gemfibrozil

Koy, M.; Sandfort, F.; Tlahuext-Aca, A.; Quak, L.; Daniliuc, C.; Glorius, F. *Chem. Eur. J.* **2018**, *24*, 4552.

Glorius group contribution to radical palladium chemistry

Decarboxylative cross-coupling

excited-state palladium as a reductant



Chem. Eur. J. ***2018***

Dicarbo-functionalization

halogen abstraction/ cyclization

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

allylic substitution

radical Pd π-allyl generation

Nature Catal. ***2020***

three-component coupling

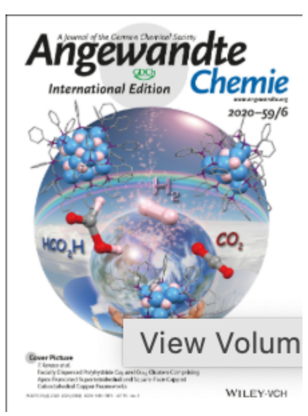
mixed mechanisms

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

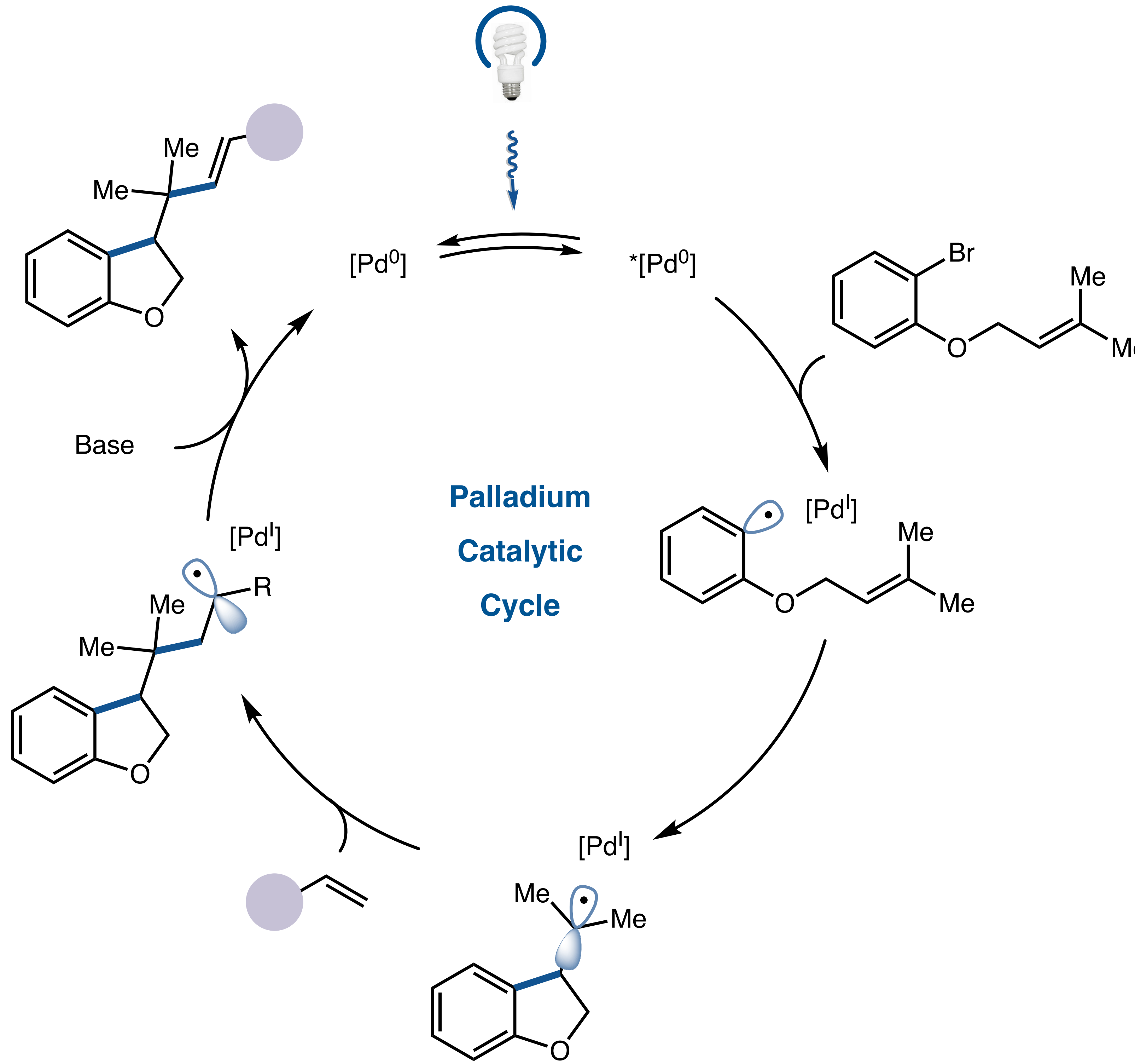
Glorius group contribution to radical palladium chemistry

Dicarbo-functionalization

halogen abstraction/ cyclization

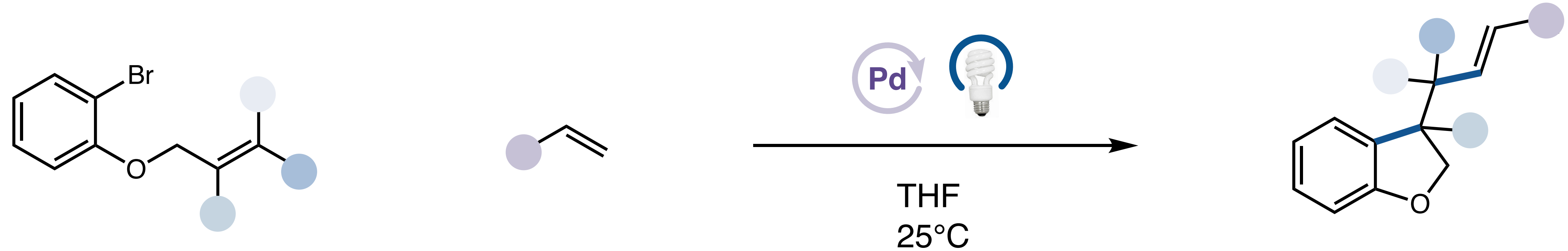


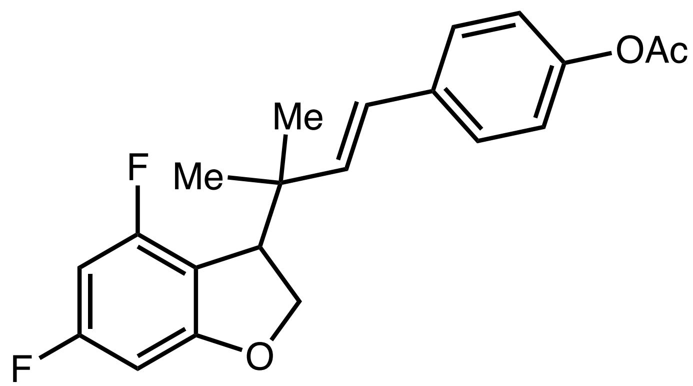
Angew. Chem. Int. Ed. ***2020***



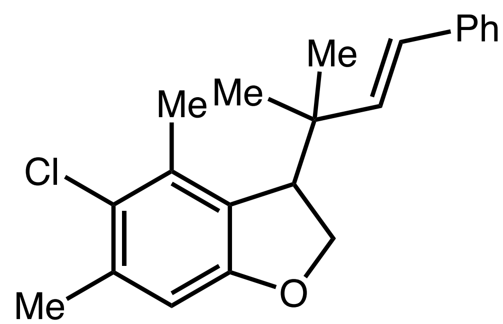
Koy, M.; Bellotti, P.; Katzenburg, F.; Daniliuc, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2020**, *59*, 2375.

Tethered olefin scope of dicarbofunctionalization

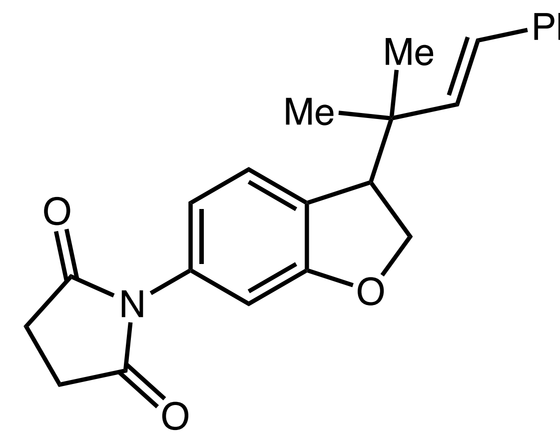




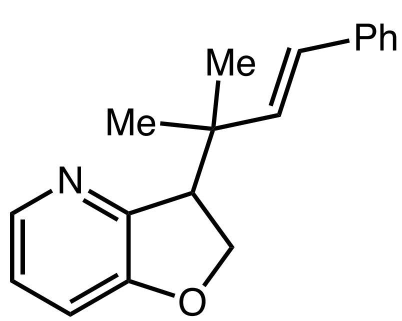
37% yield



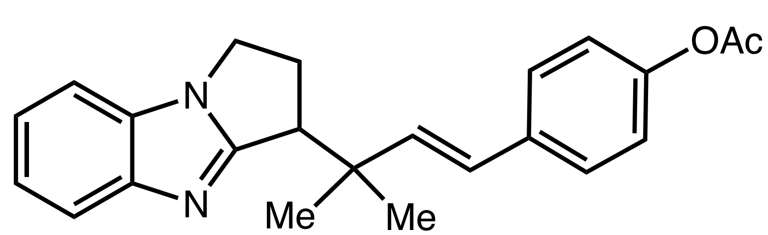
40% yield



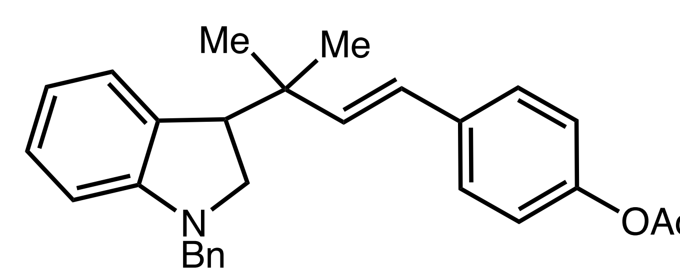
80% yield



61% yield



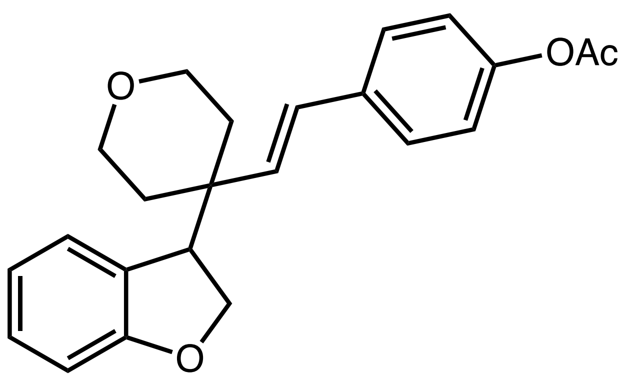
97% yield



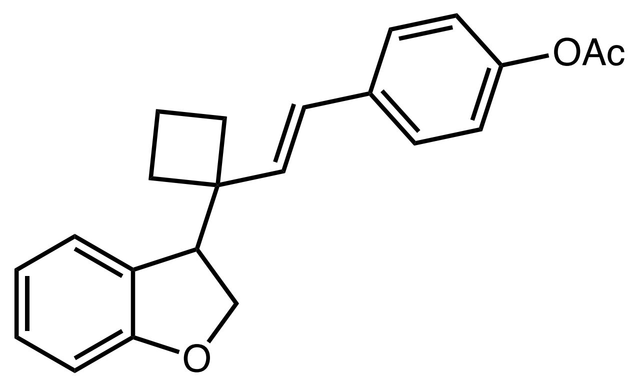
70% yield

Koy, M.; Bellotti, P.; Katzenburg, F.; Daniliuc, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2020**, *59*, 2375.

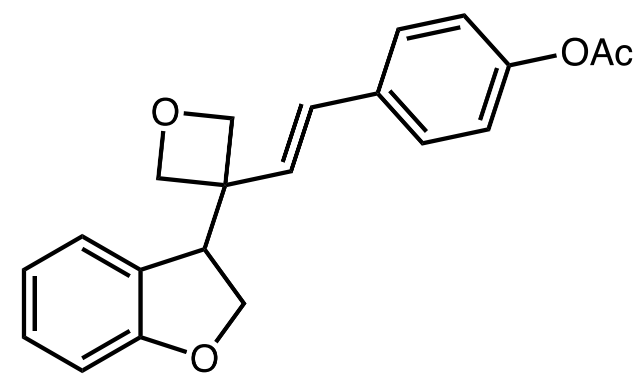
Tethered olefin scope of dicarbofunctionalization



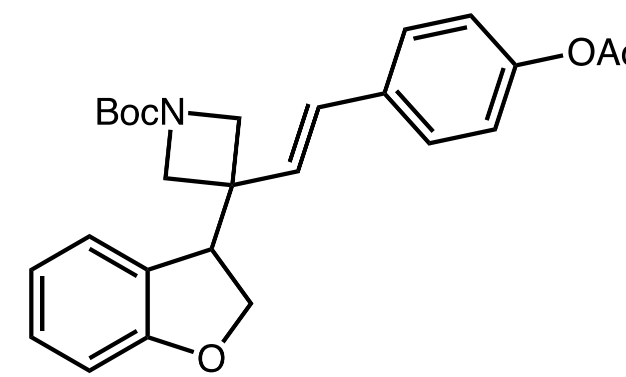
67% yield



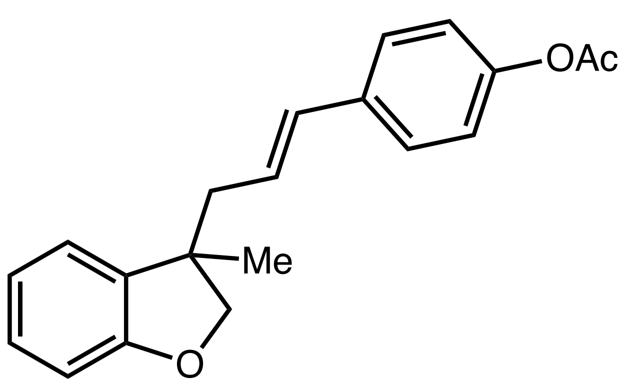
52% yield



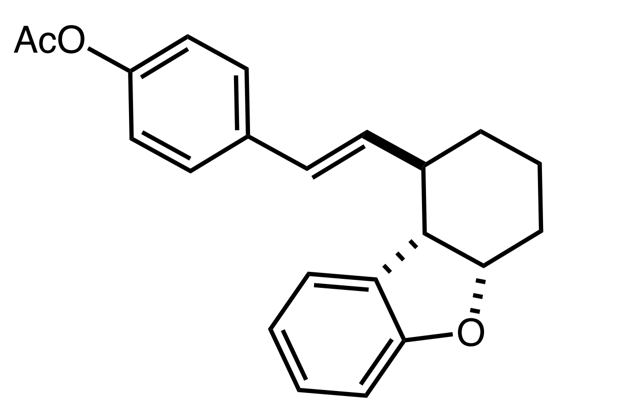
76% yield



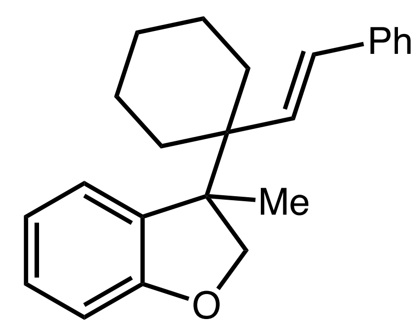
61% yield



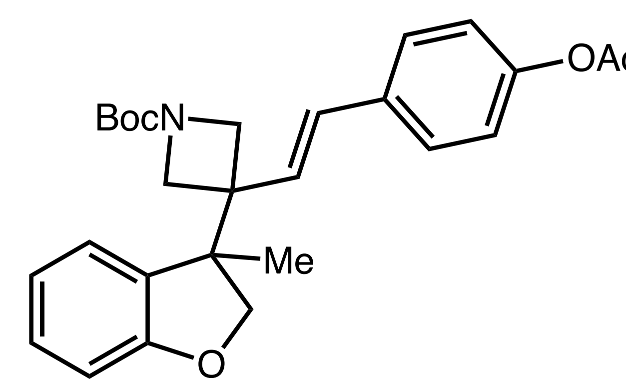
66% yield



60% yield
93:7 d.r.



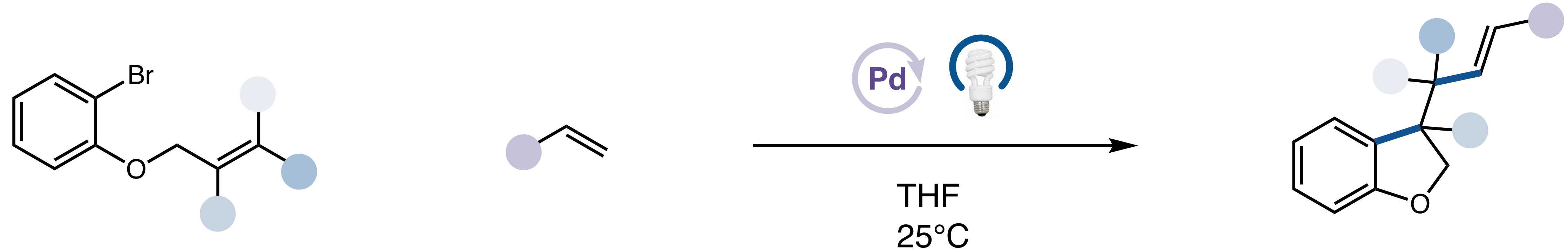
44% yield

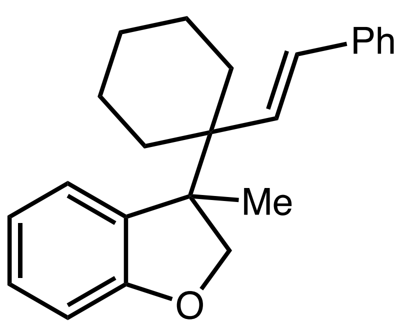


80% yield

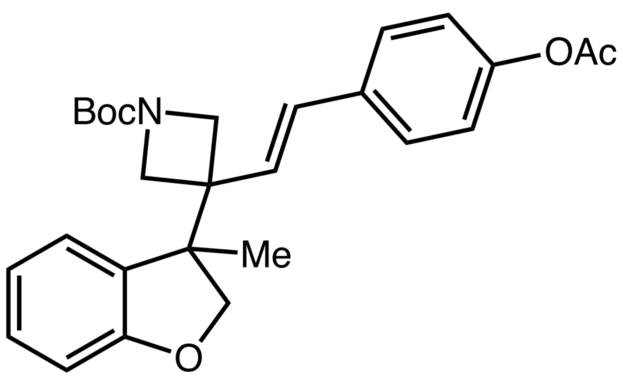
Koy, M.; Bellotti, P.; Katzenburg, F.; Daniliuc, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2020**, *59*, 2375.

Tethered olefin scope of dicarbofunctionalization





44% yield



80% yield

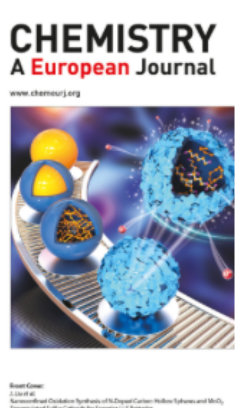
This method can form two adjacent, all-carbon quaternary centers in good yields!

Koy, M.; Bellotti, P.; Katzenburg, F.; Daniliuc, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2020**, *59*, 2375.

Glorius group contribution to radical palladium chemistry

Decarboxylative cross-coupling

excited-state palladium as a reductant



Chem. Eur. J. ***2018***

Dicarbo-functionalization

halogen abstraction/ cyclization

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

allylic substitution

radical Pd π-allyl generation

Nature Catal. ***2020***

three-component coupling

mixed mechanisms

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

Glorius group contribution to radical palladium chemistry

allylic substitution

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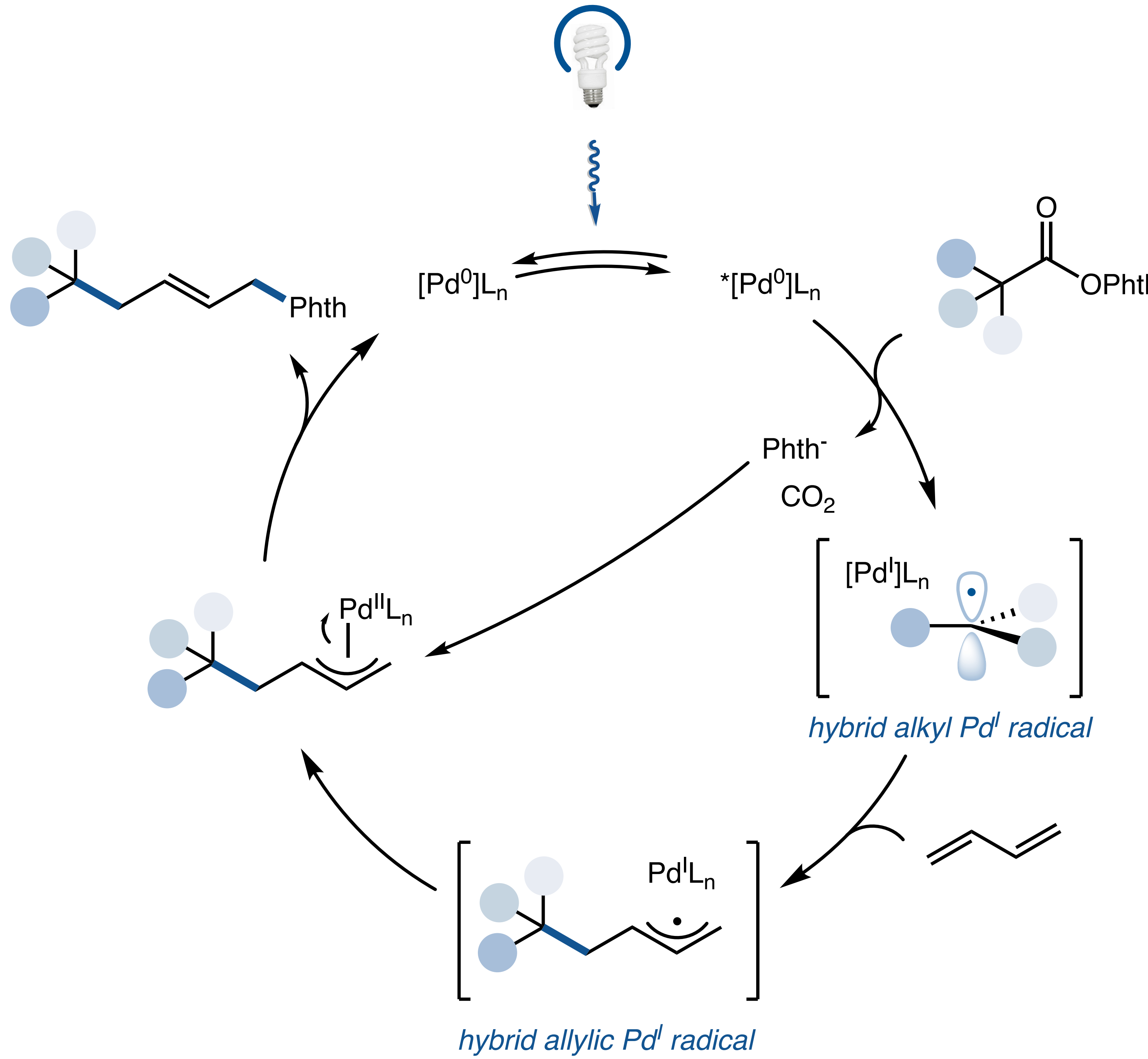
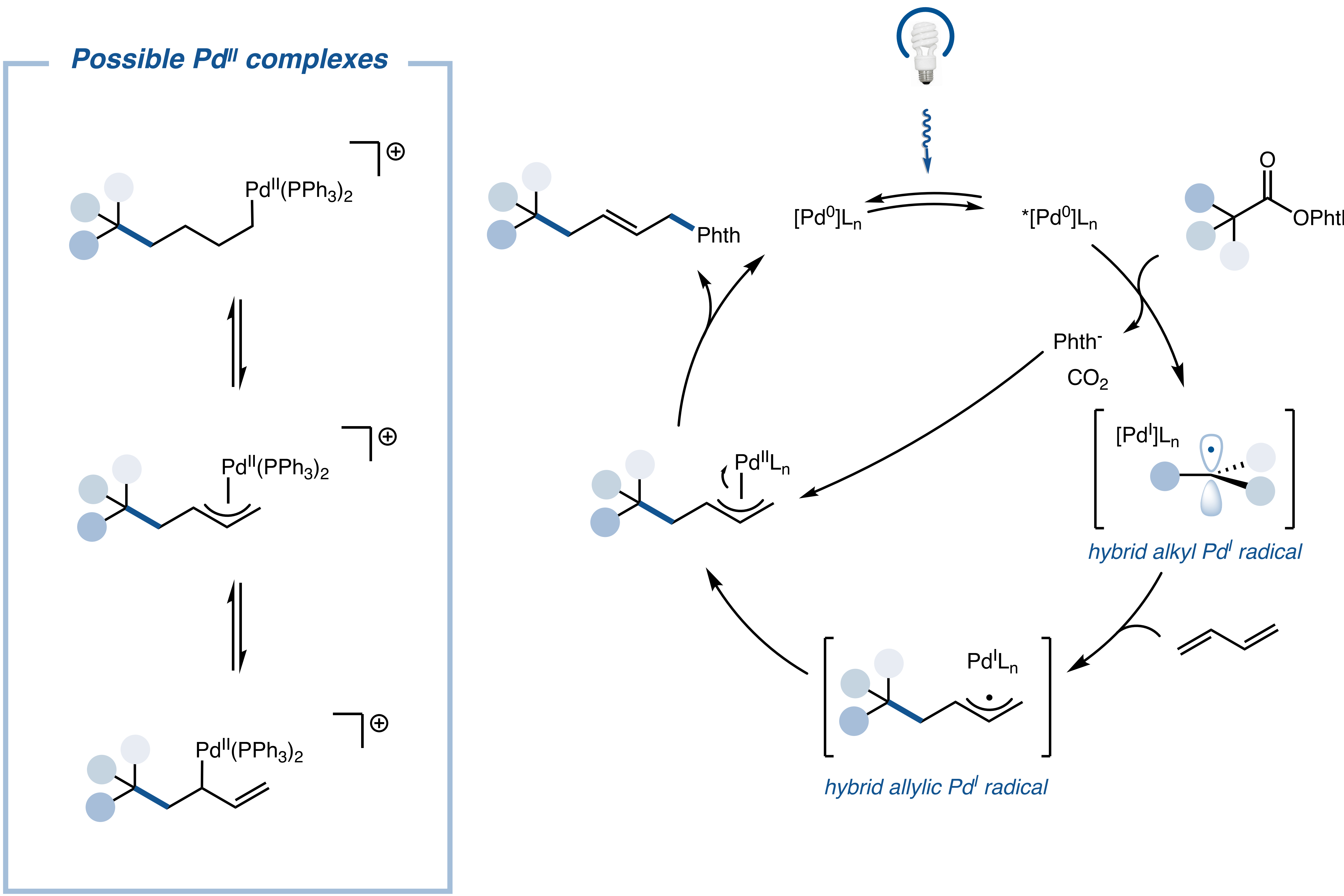
Nature Catal. ***2020***



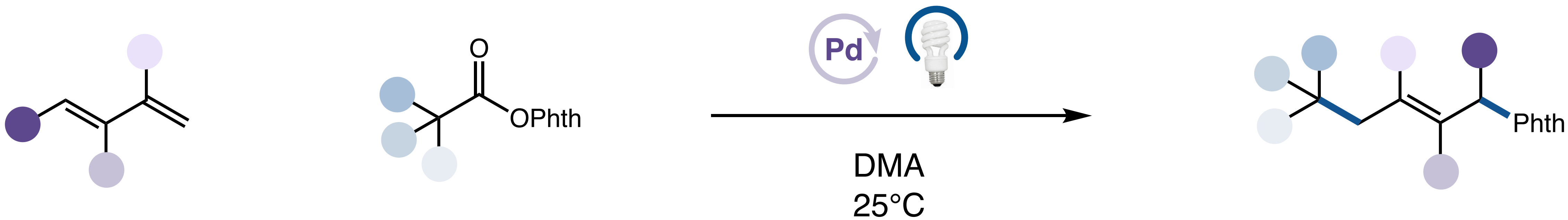
Huang, H.; Koy, M.; Serrano, E.; Pfluger, P.; Schwarz, J.; Glorius, F. *Nature Catal.* **2020**, *3*, 393.

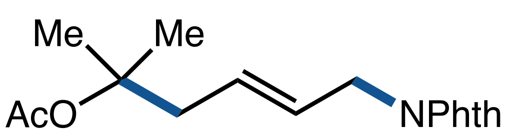
Radical allylic substitution



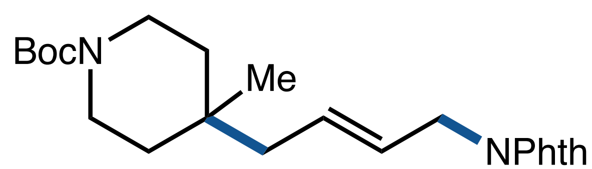
Huang, H.; Koy, M.; Serrano, E.; Pfluger, P.; Schwarz, J.; Glorius, F. *Nature Catal.* **2020**, *3*, 393.

Scope of allylic substitution

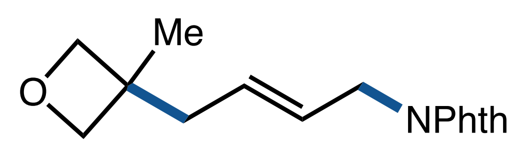




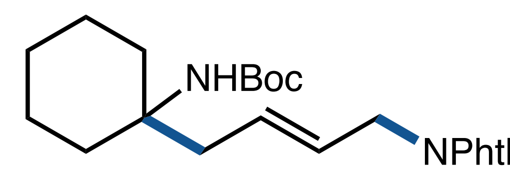
79% yield



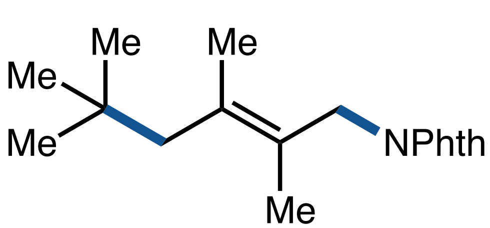
82% yield



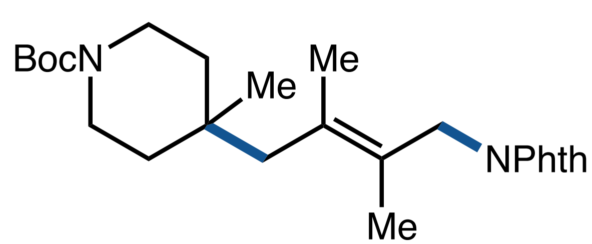
69% yield



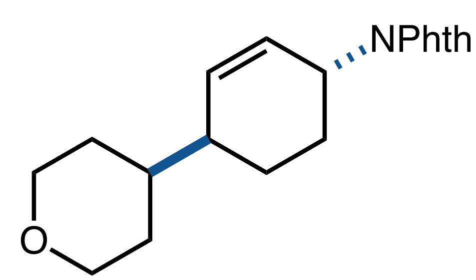
98% yield



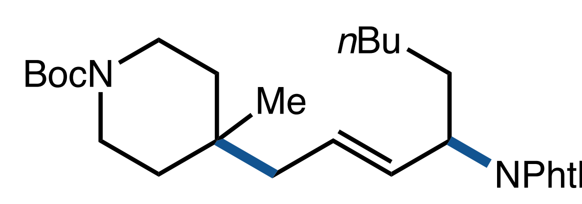
43% yield



43% yield



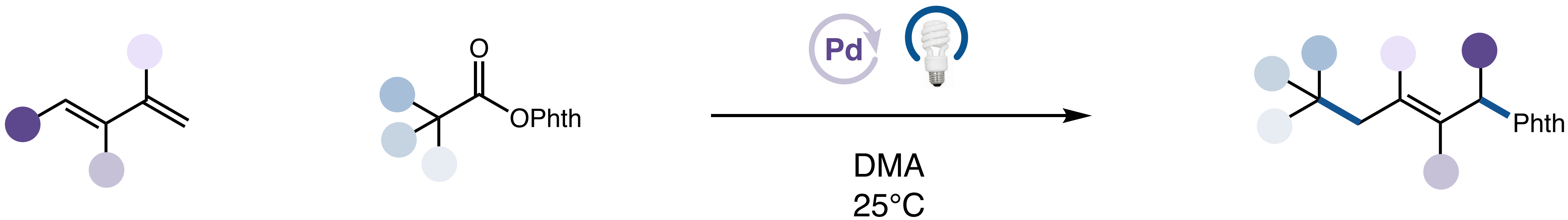
58% yield

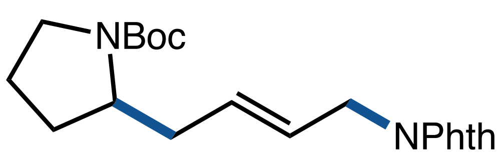


64% yield

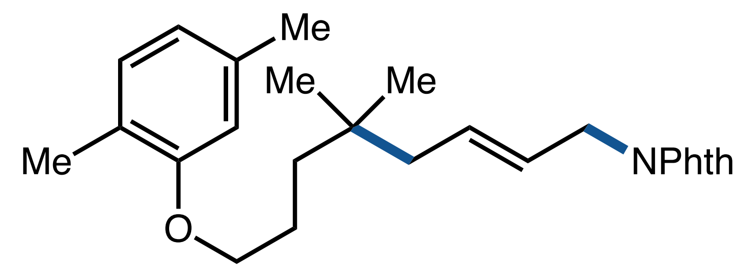
Huang, H.; Koy, M.; Serrano, E.; Pfluger, P.; Schwarz, J.; Glorius, F. *Nature Catal.* **2020**, *3*, 393.

Scope of allylic substitution: complex examples

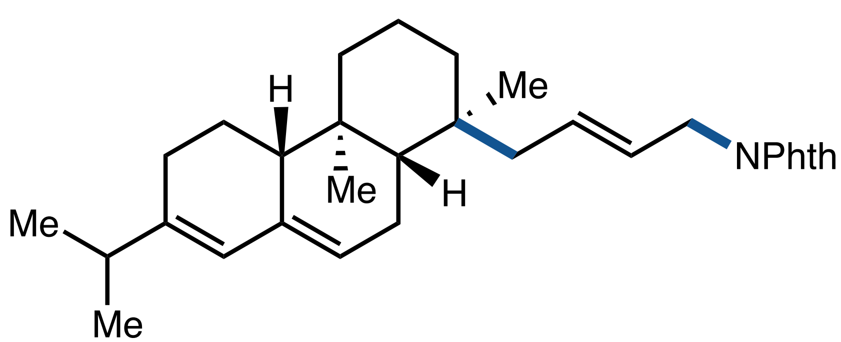




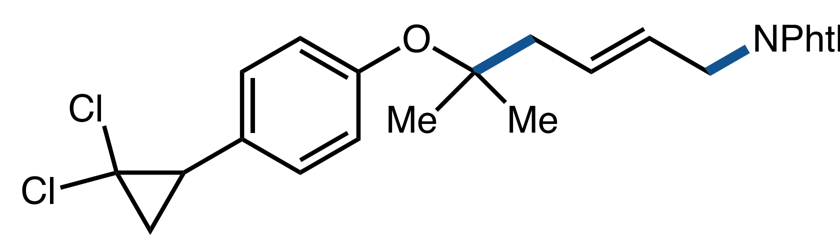
54% yield
from proline



66% yield
from gemfibrozil



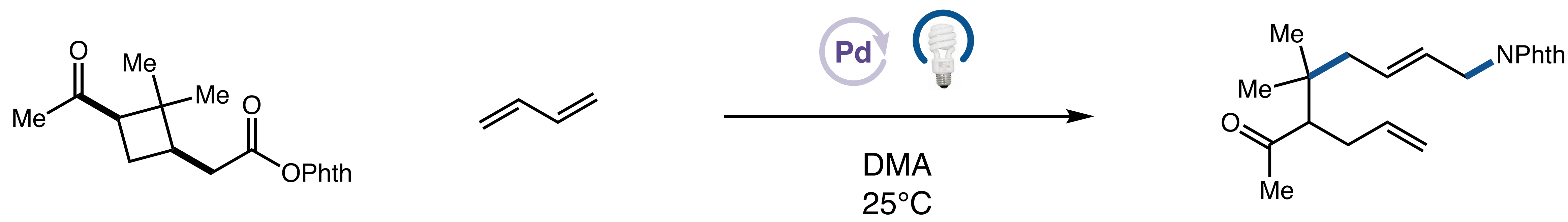
58% yield
from abiotic acid



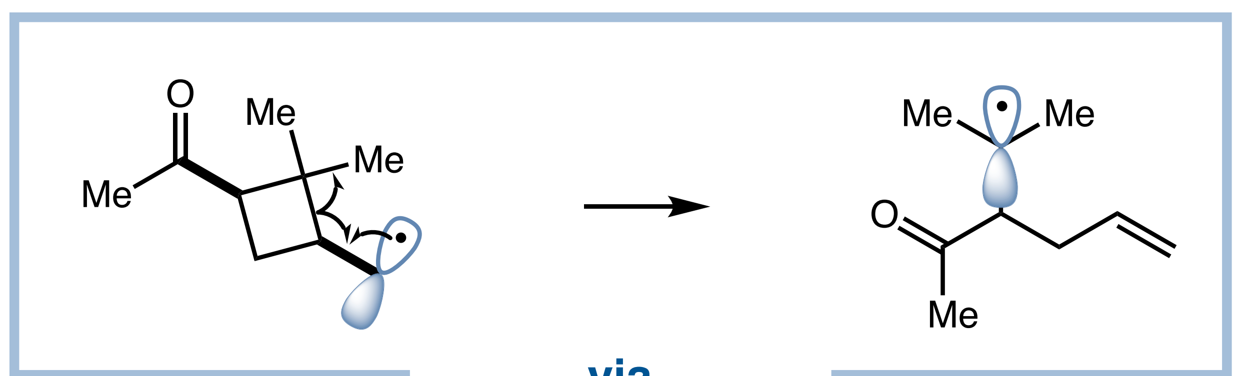
77% yield
from ciprofibrate

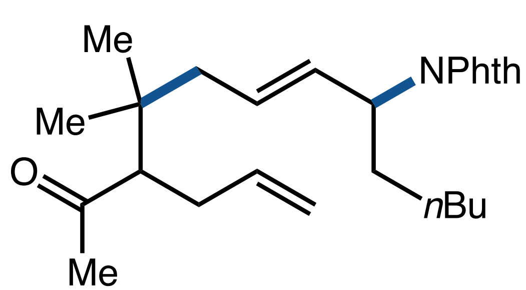
Huang, H.; Koy, M.; Serrano, E.; Pfluger, P.; Schwarz, J.; Glorius, F. *Nature Catal.* **2020**, *3*, 393.

Scope of allylic substitution: cascade reactions

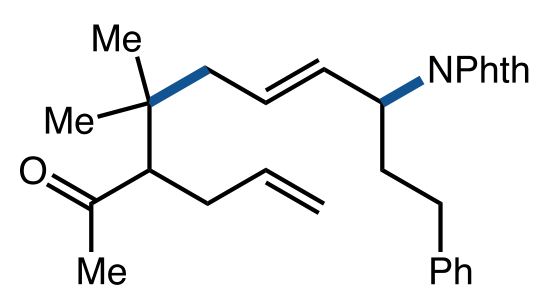


via

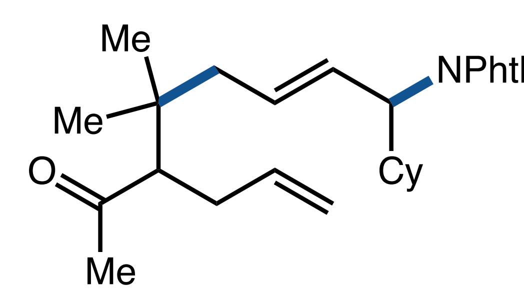




48% yield



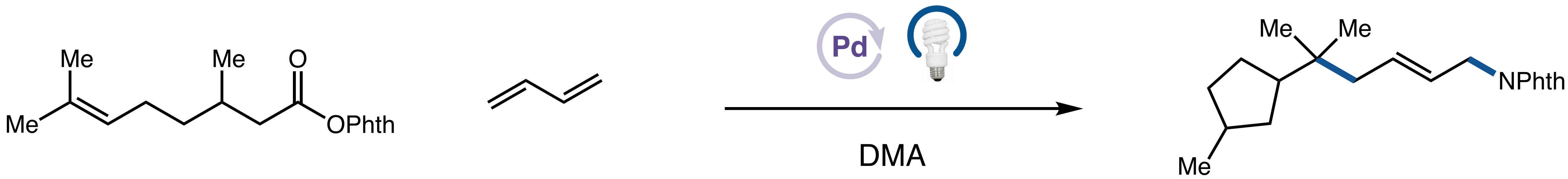
47% yield



52% yield

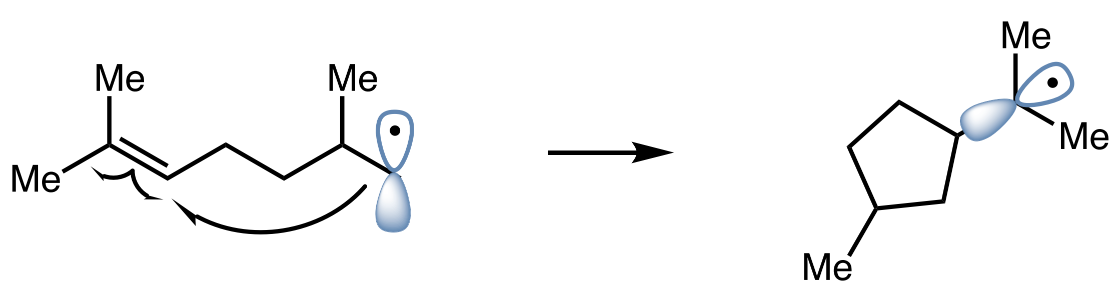
Huang, H.; Koy, M.; Serrano, E.; Pfluger, P.; Schwarz, J.; Glorius, F. *Nature Catal.* **2020**, *3*, 393.

Scope of allylic substitution: cascade reactions



from citronellic acid

74% yield



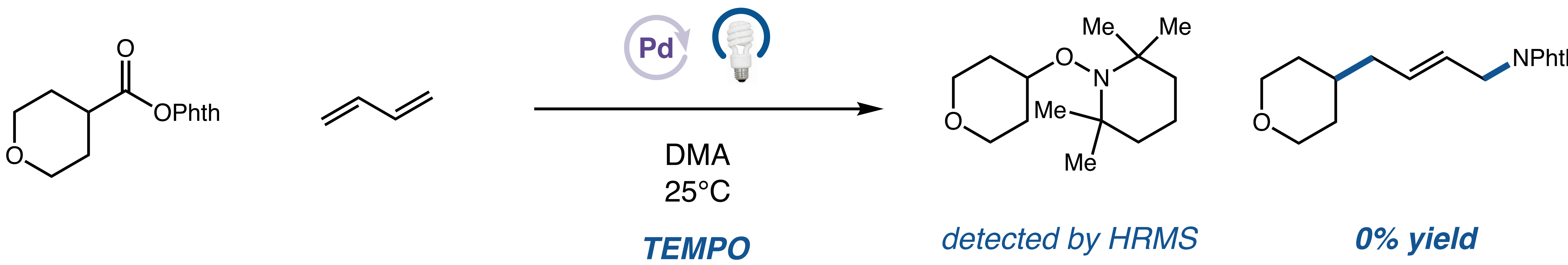
via

- ***overall 59 examples***
- ***late stage functionalization***
- ***cascade reactions***

Huang, H.; Koy, M.; Serrano, E.; Pfluger, P.; Schwarz, J.; Glorius, F. *Nature Catal.* **2020**, *3*, 393.

Mechanistic considerations

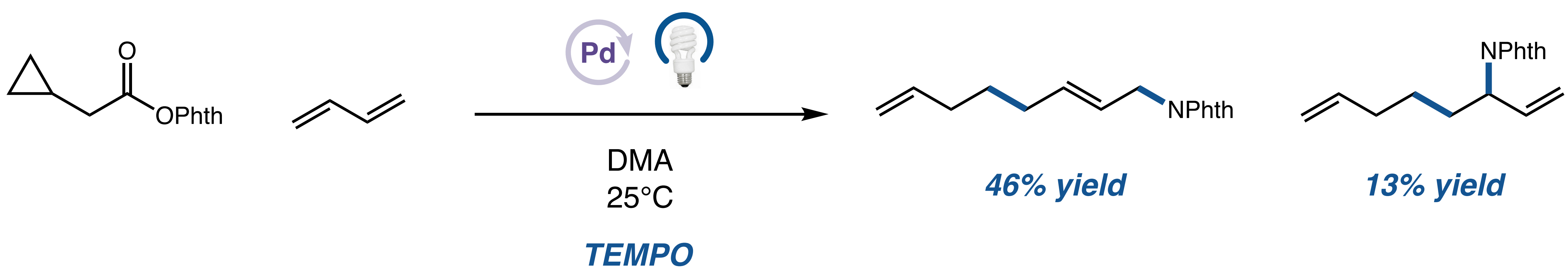
radical inhibitor



detected by HRMS

0% yield

radical clock



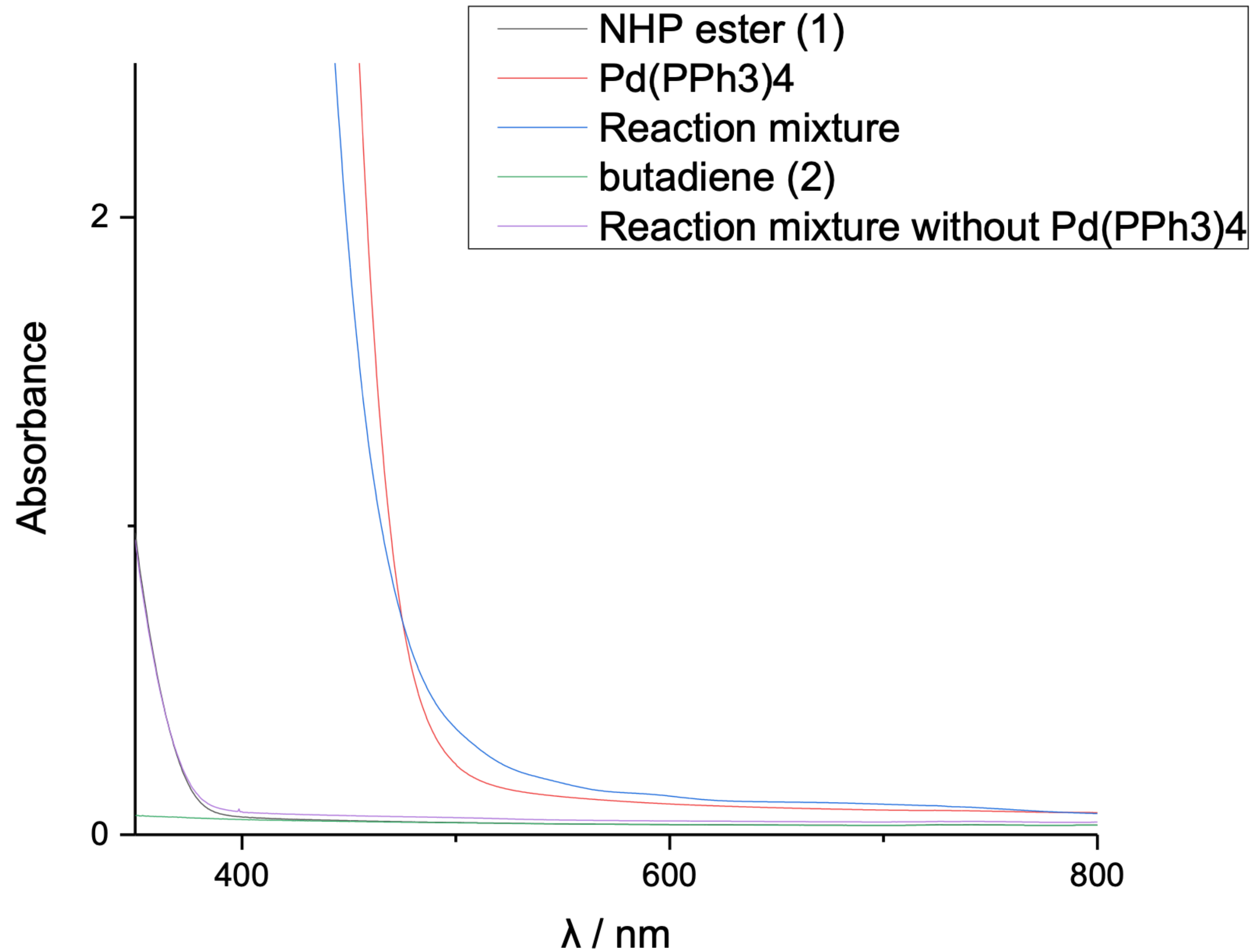
46% yield

13% yield

Huang, H.; Koy, M.; Serrano, E.; Pfluger, P.; Schwarz, J.; Glorius, F. *Nature Catal.* **2020**, *3*, 393.

Mechanistic considerations

- ***UV-vis***

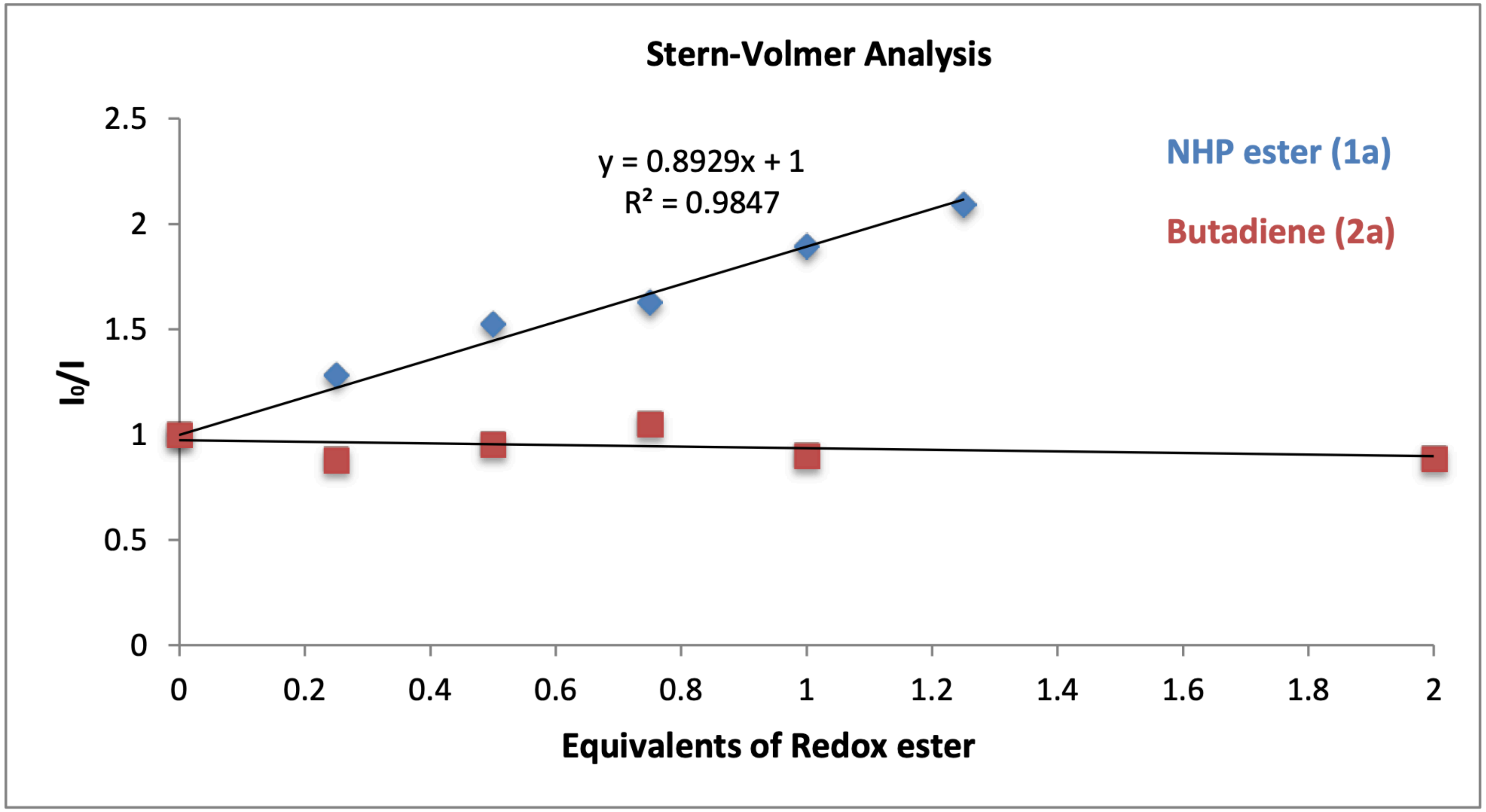


Of the reactants, Pd(PPh_3) is the only light absorbing species

Huang, H.; Koy, M.; Serrano, E.; Pfluger, P.; Schwarz, J.; Glorius, F. *Nature Catal.* **2020**, *3*, 393.

Mechanistic considerations

Stern-Volmer

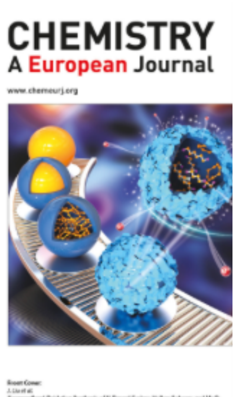


Photoexcited Pd^0 can reduce the redox active ester through SET

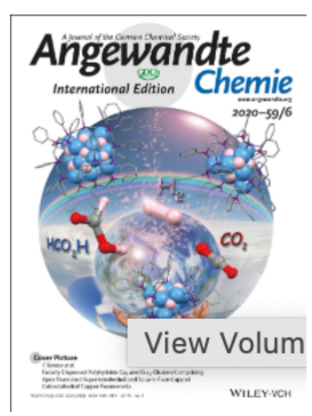
Huang, H.; Koy, M.; Serrano, E.; Pfluger, P.; Schwarz, J.; Glorius, F. *Nature Catal.* **2020**, *3*, 393.

Glorius group contribution to radical palladium chemistry

Decarboxylative cross-coupling	***Dicarbo-functionalization***	***allylic substitution***	***three-component coupling***
excited-state palladium as a reductant	*halogen abstraction/ cyclization*	*radical Pd π-allyl generation*	*mixed mechanisms*



Chem. Eur. J. ***2018***



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

Nature Catal. ***2020***

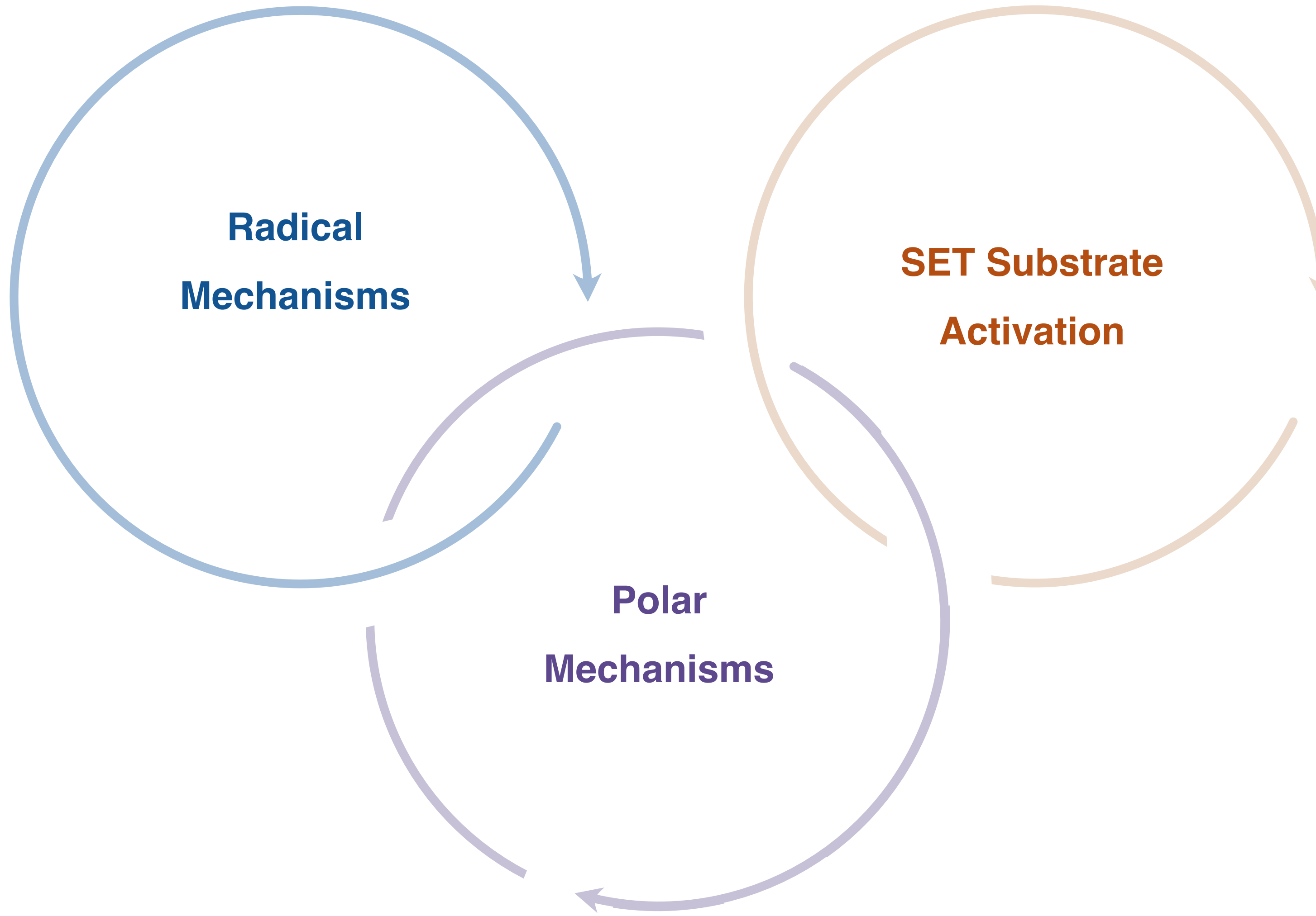
J. Am. Chem. Soc. ***2020***
Chem. Sci. ***2021***

Glorius group contribution to radical palladium chemistry

three-component coupling

mixed mechanisms

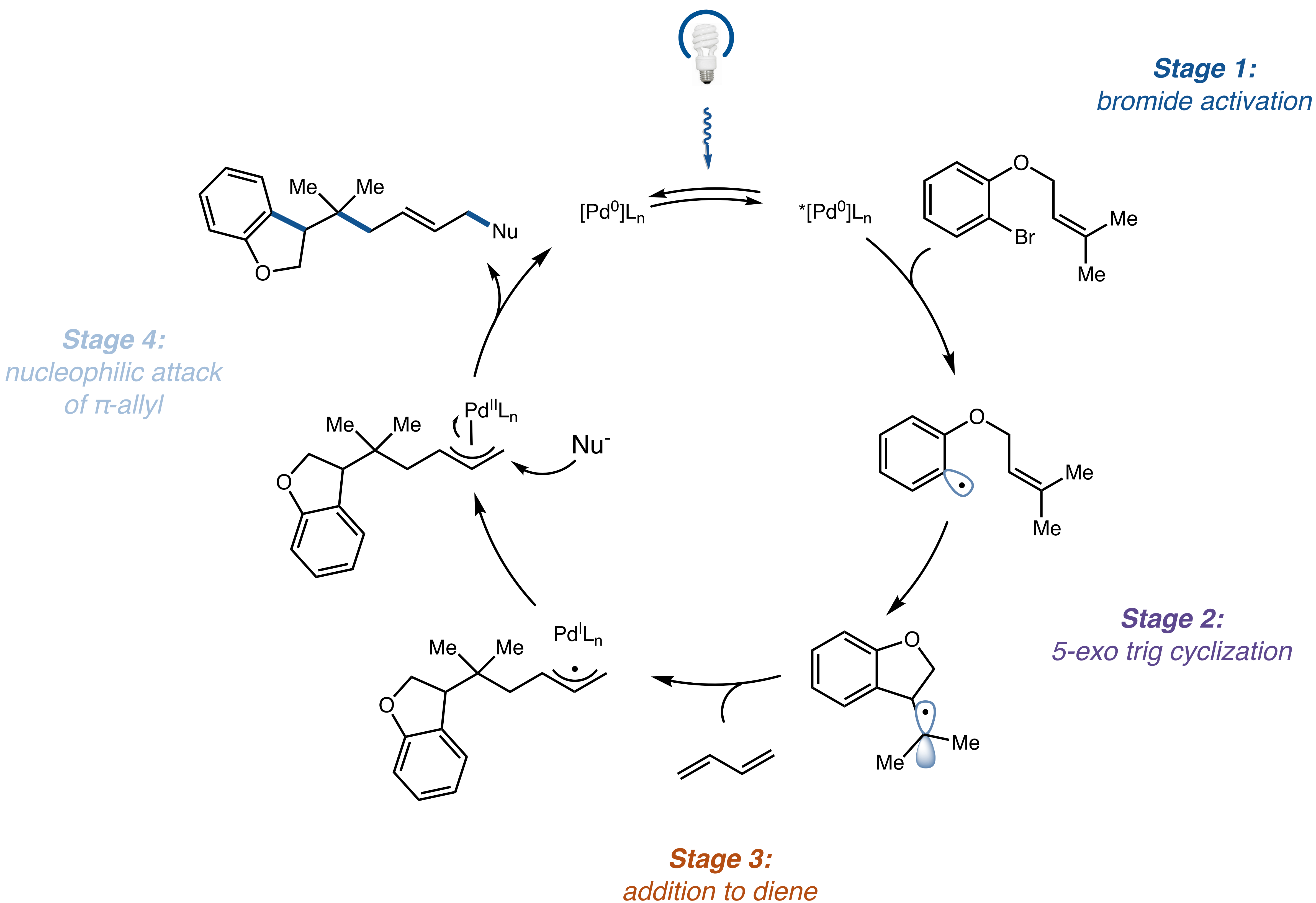
J. Am. Chem. Soc. ***2020***
Chem. Sci. ***2021***



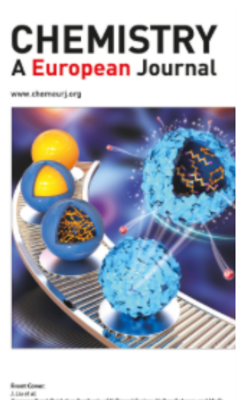
combining a variety of the mechanisms we've discussed thus far allows for unique three-component reactions

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

Decarboxylative cross-coupling	Dicarbo-functionalization	allylic substitution	three-component coupling
excited-state palladium as a reductant	halogen abstraction/ cyclization	radical Pd π-allyl generation	mixed mechanisms
			
Chem. Eur. J. ***2018***	*Angew. Chem. Int. Ed.* ***2020***	*Nature Catal.* ***2020***	*J. Am. Chem. Soc.* ***2020*** *Chem. Sci.* ***2021***

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

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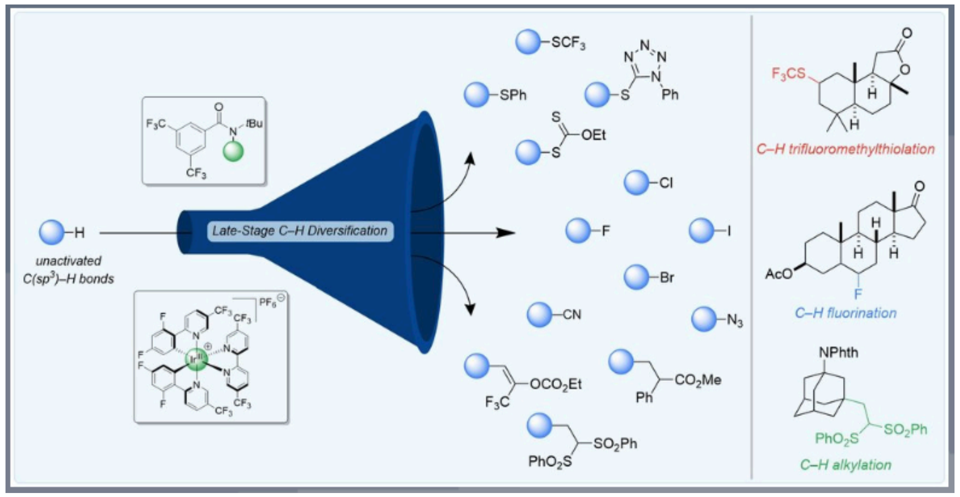
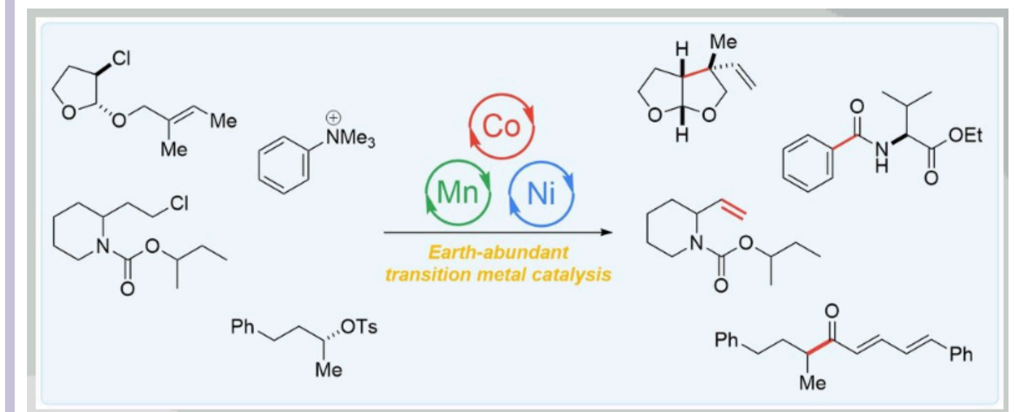
Research in the Alexanian group

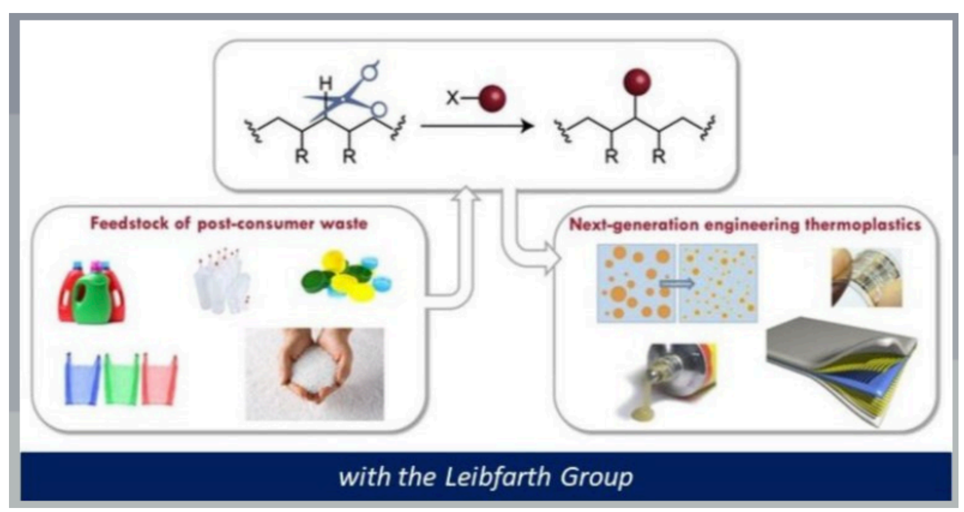
Radical-Mediated C—H Functionalization



Catalytic C—C Bond Formations



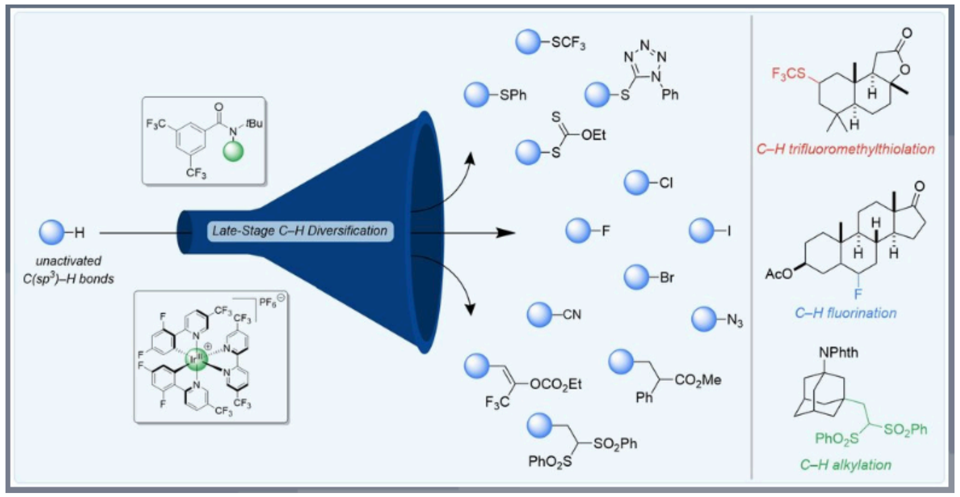
Polymer C—H Functionalization



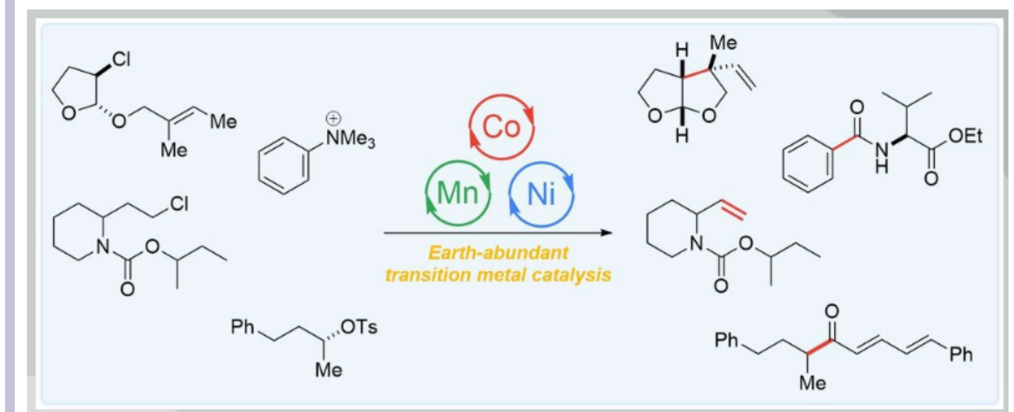
Na, C.; Ravelli, D.; Alexanian, E. *J. Am. Chem. Soc.* **2020**, *142*, 44.
Williamson, J.; Na, C.; Johnson, R.; Daniel, W.; Alexanian, E.; Leibfarth, F. *J. Am. Chem. Soc.* **2019**, *141*, 12815.
Tercenio, Q.; Alexanian, E. *Org. Lett.* **2021**, *23*, 7215.

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

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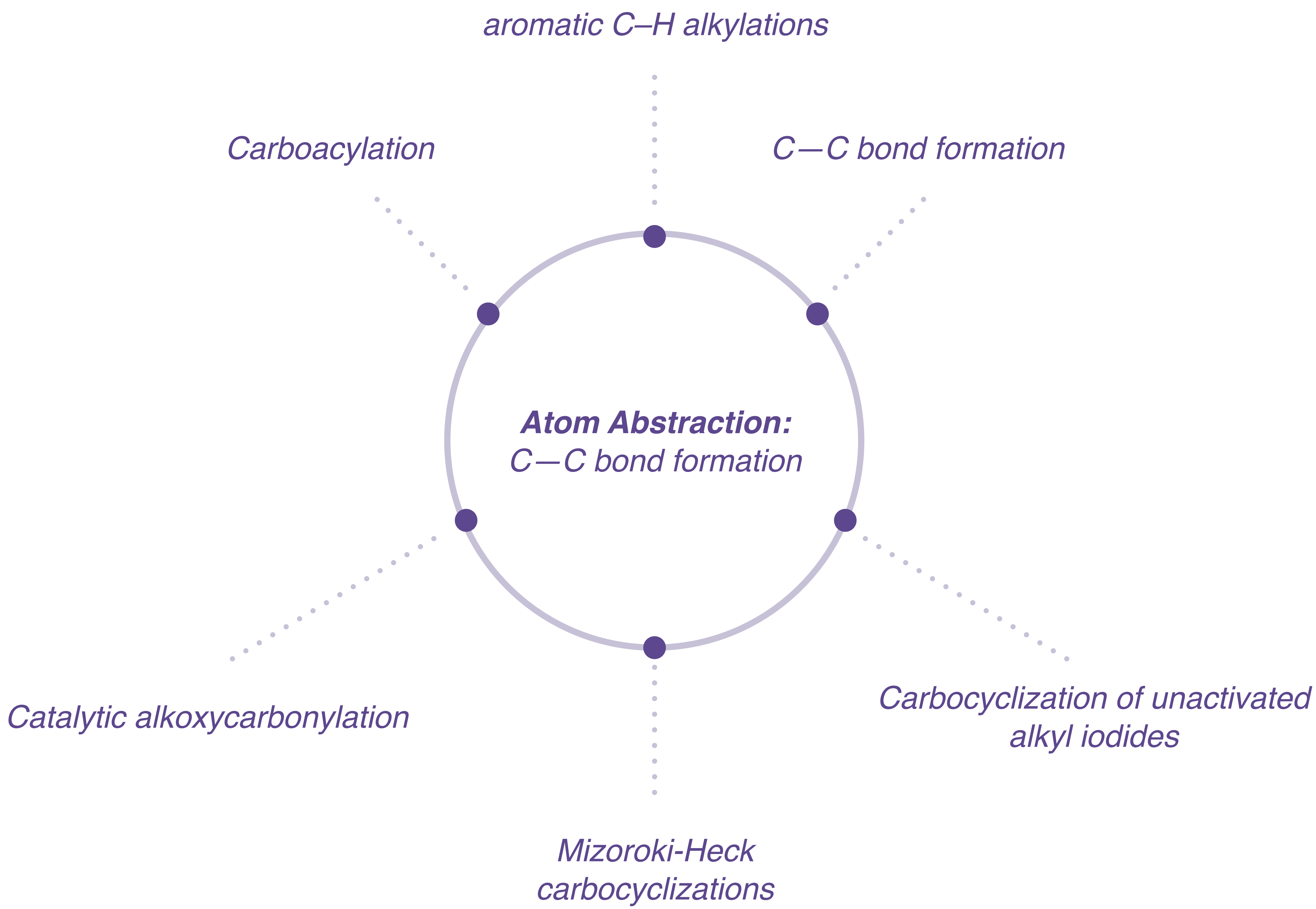

Na, C.; Ravelli, D.; Alexanian, E. *J. Am. Chem. Soc.* **2020**, *142*, 44.
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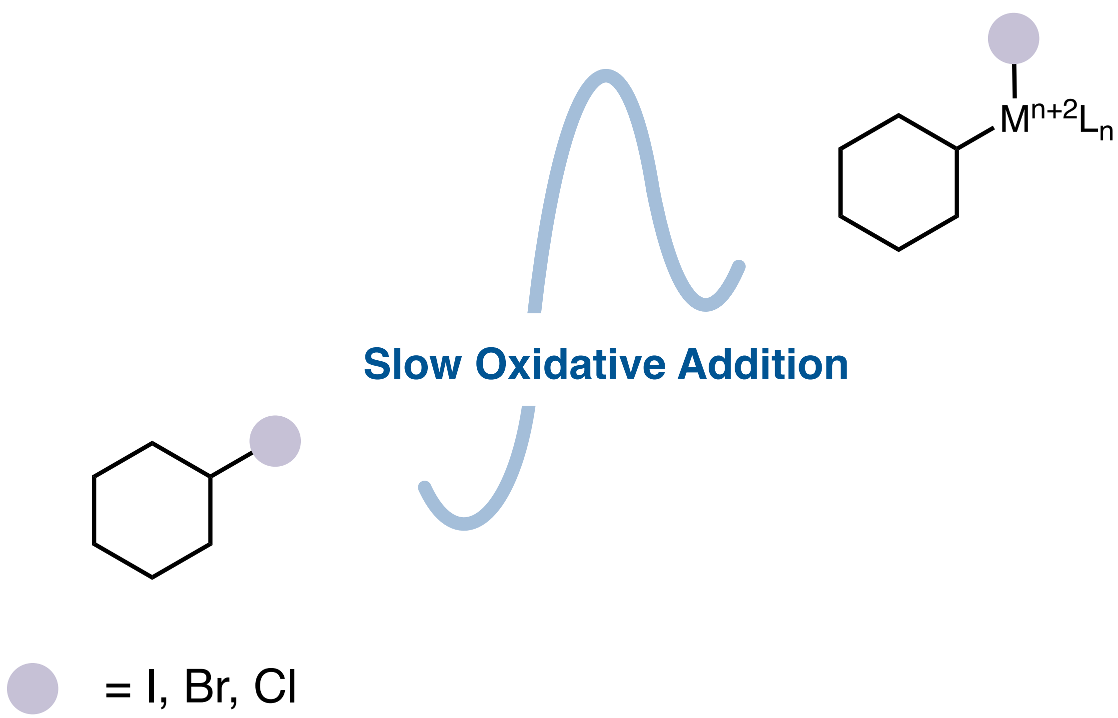
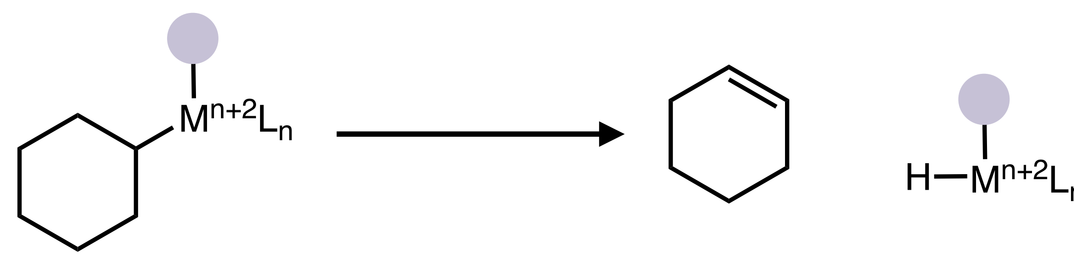
Challenges of 2e⁻ activation of alkyl electrophiles

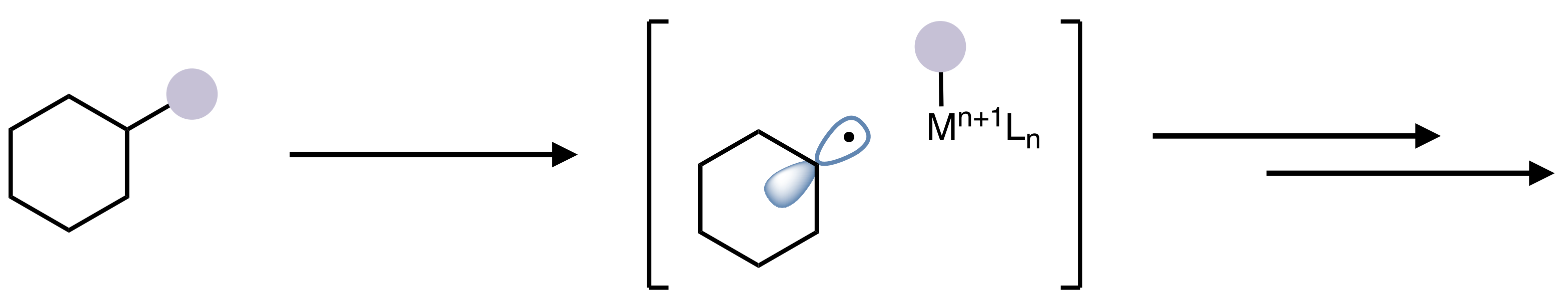
Oxidative Addition



Competitive β-hydride elimination



Alternative Mechanism

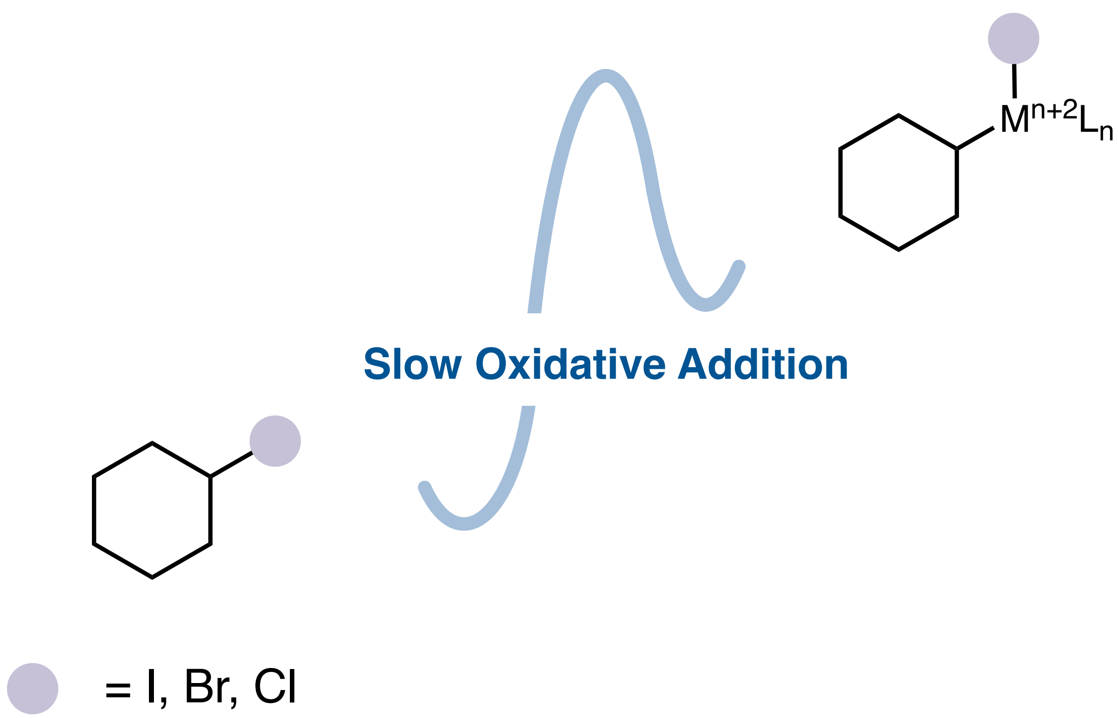


radical-mediated C–C bond formation

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

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

Oxidative Addition



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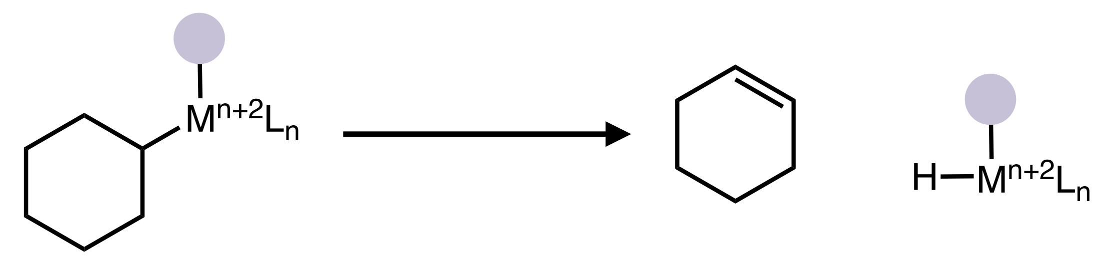

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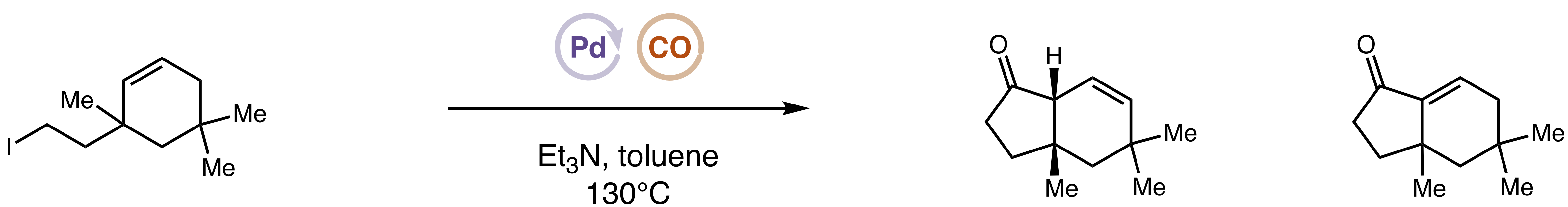
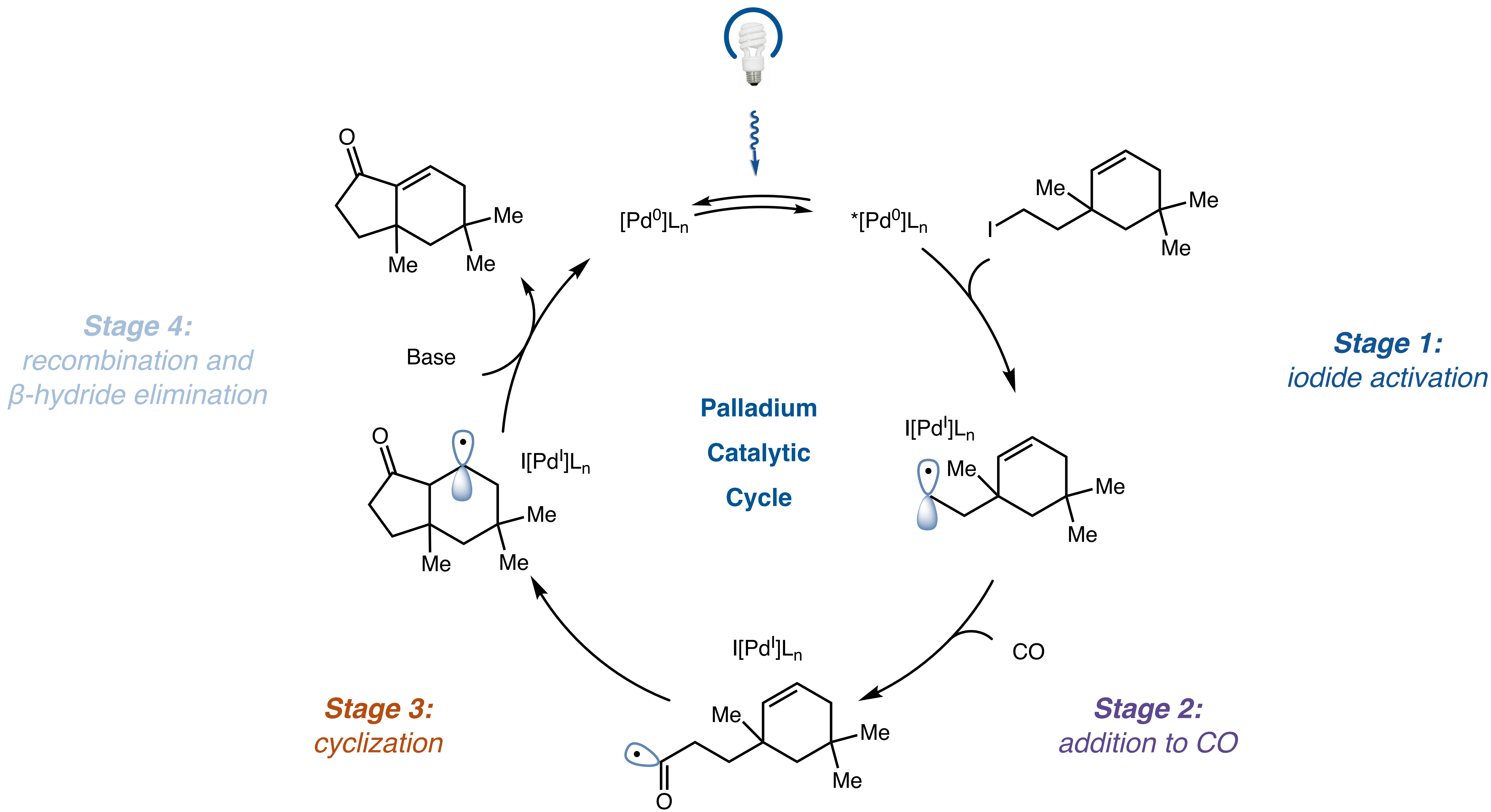


Bloome, K.; Alexanian, E. J. Am. Chem. Soc. **2010**, *132*, 12823.

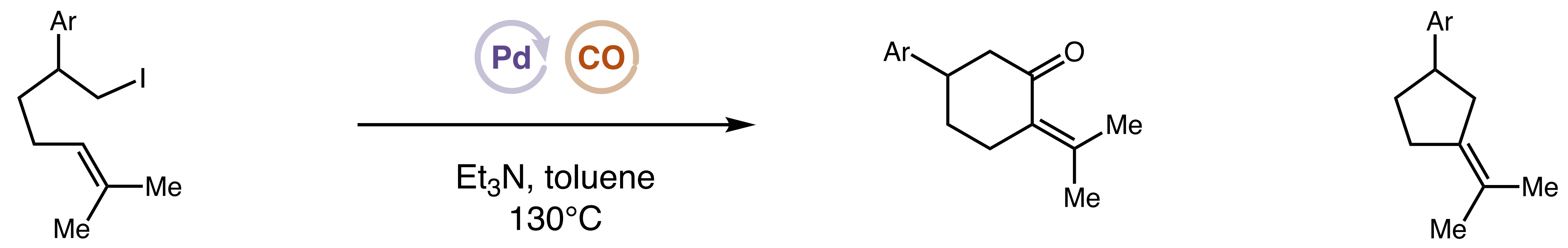
Carbonylative cyclization Mechanism



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

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

Carbocyclization: an unexpected result



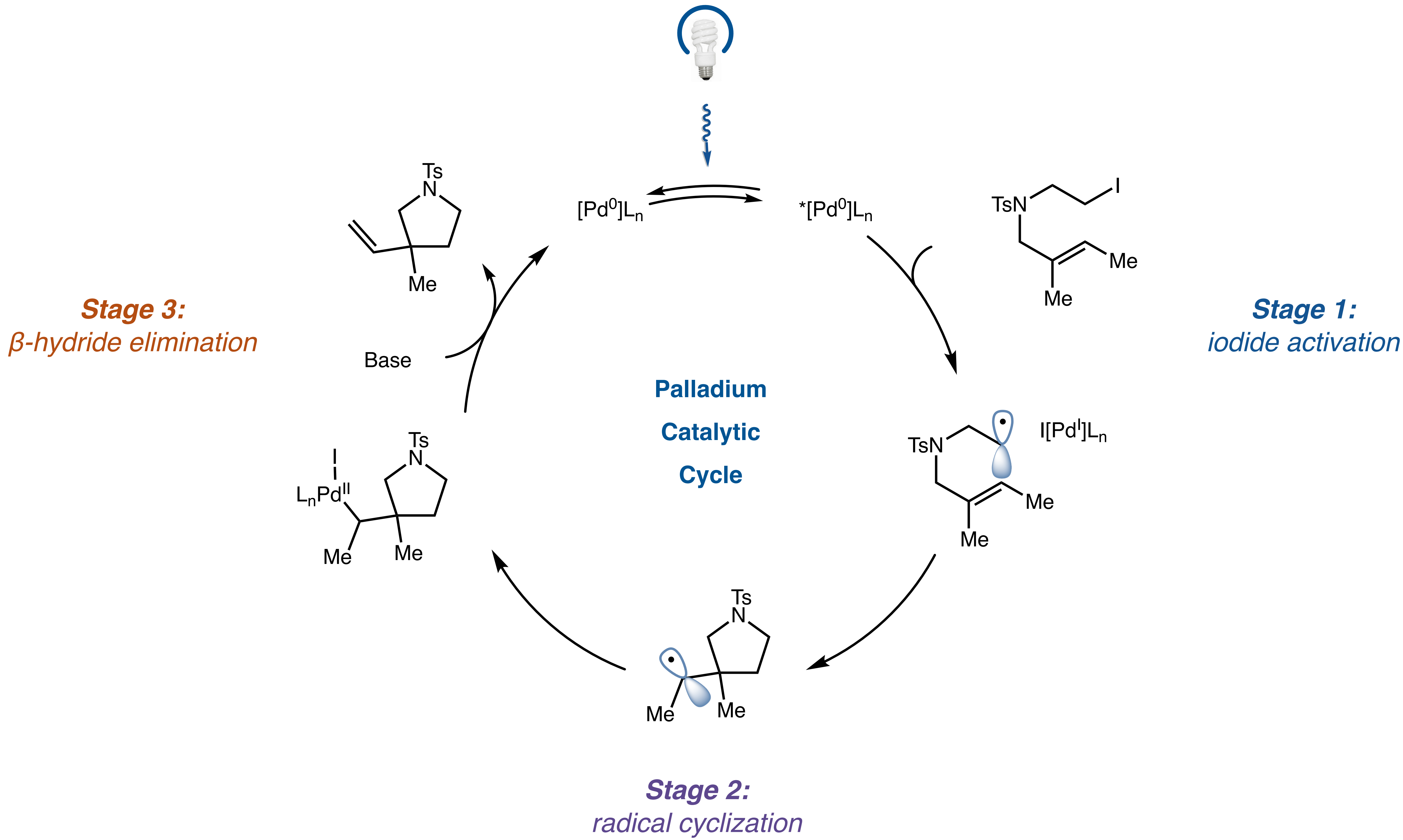
0% yield
expected product

86% yield
unexpected product

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.; McMahen, R.; Alexanian, E. J. Am. Chem. Soc. **2011**, *133*, 20146.

Carbocyclization



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

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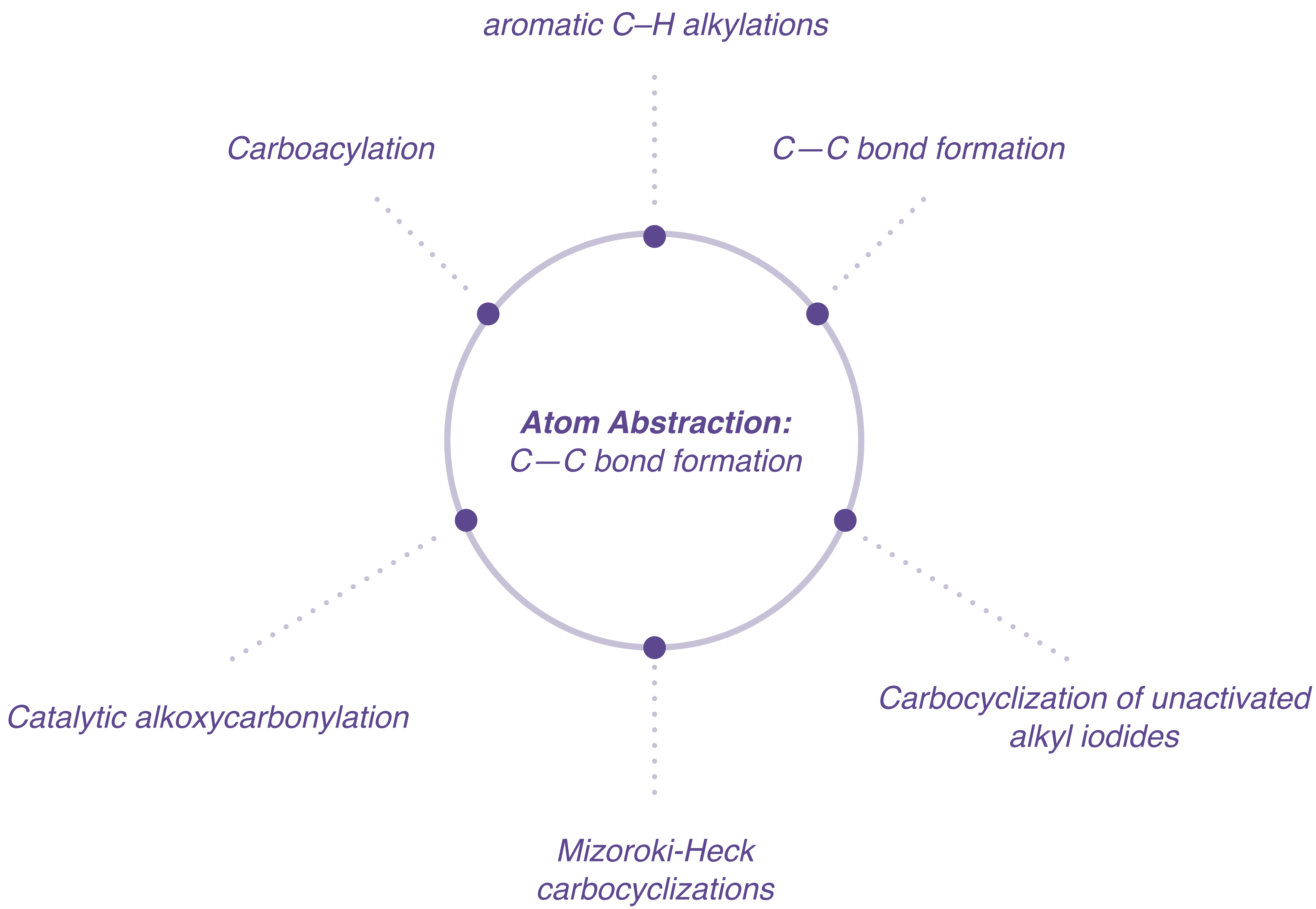
Research in the Alexanian group



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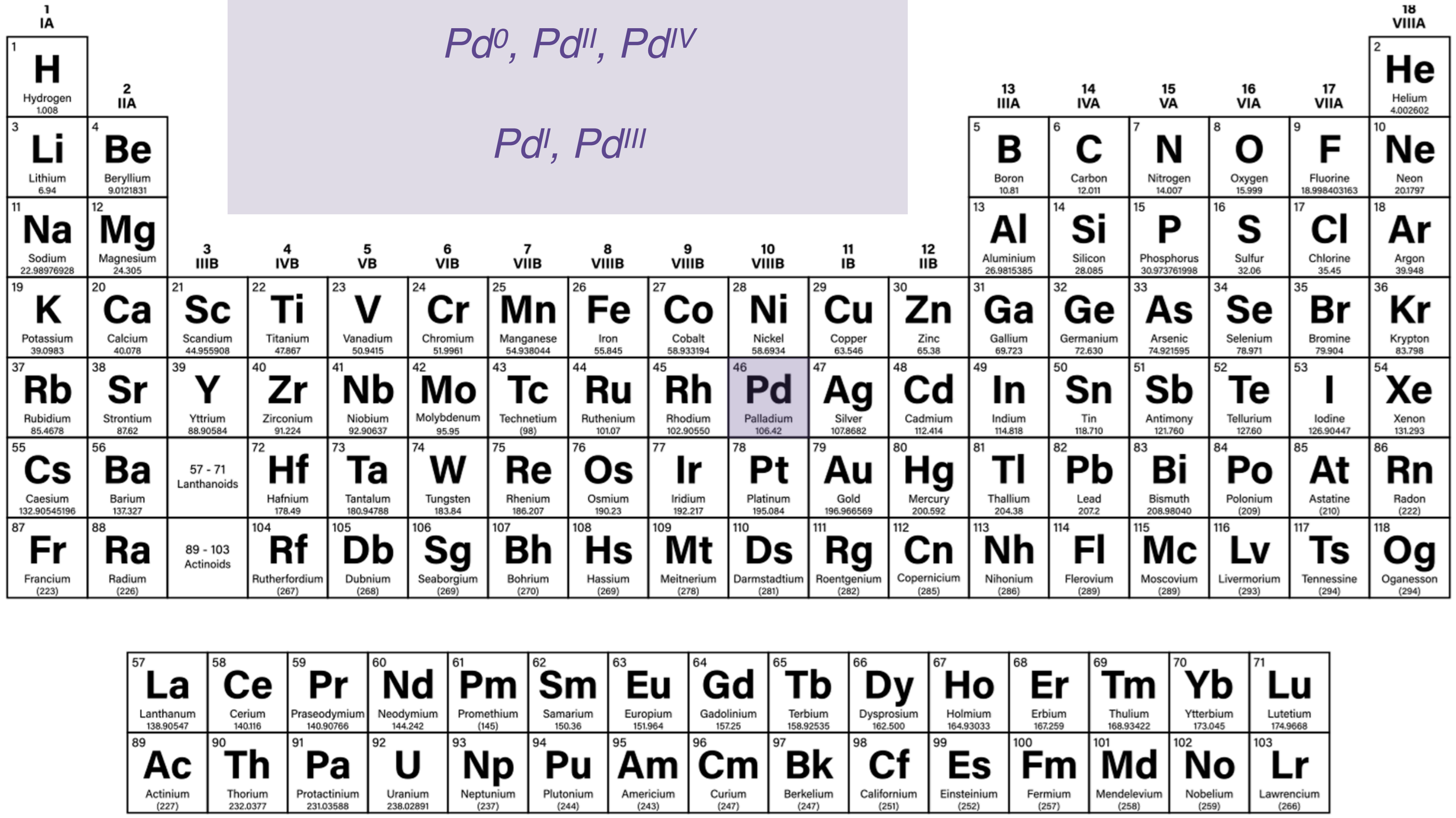
Tercenio, Q.; Alexanian, E. *Org. Lett.* **2021**, *23*, 7215.

Palladium: a versatile element

Oxidation states of palladium:

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

Pd^I, Pd^{III}



interconversion between diverse oxidation states

versatile and widely used in cross coupling

utilized in natural product synthesis, agrochemistry, and pharmaceutical production

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

Questions?