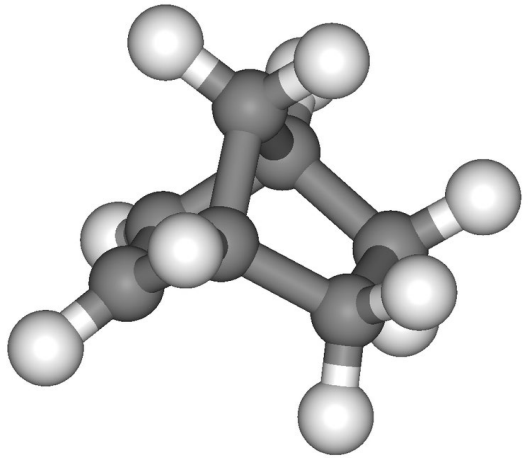
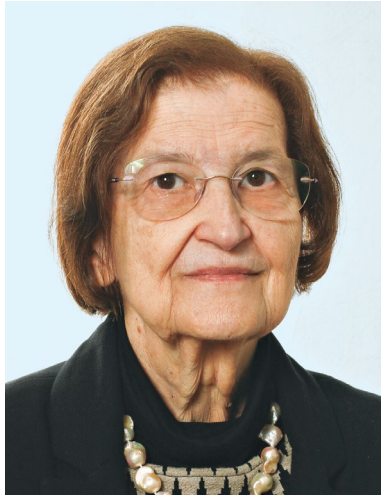
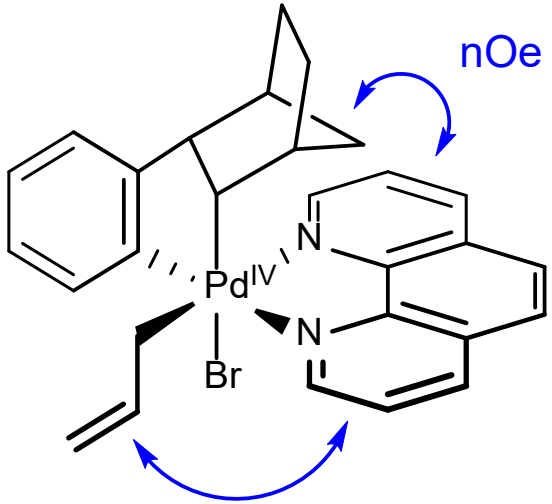
Catellani Reaction:
Mechanistic Investigations and Structurally Modified Norbornene Co-Catalysts



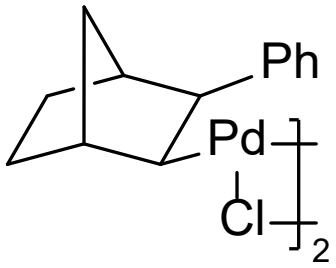




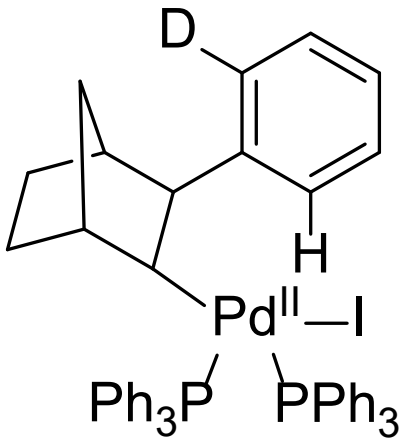
Nick Wade
Denmark Group Meeting
April 25th, 2023

Presentation Overview

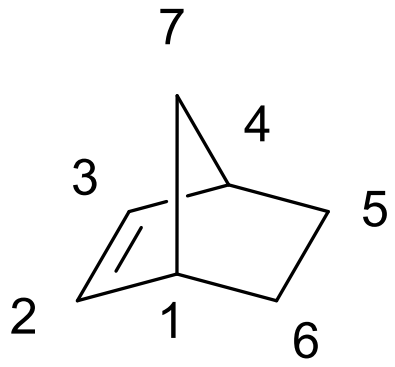
Initial investigations, stoichiometric studies and first report



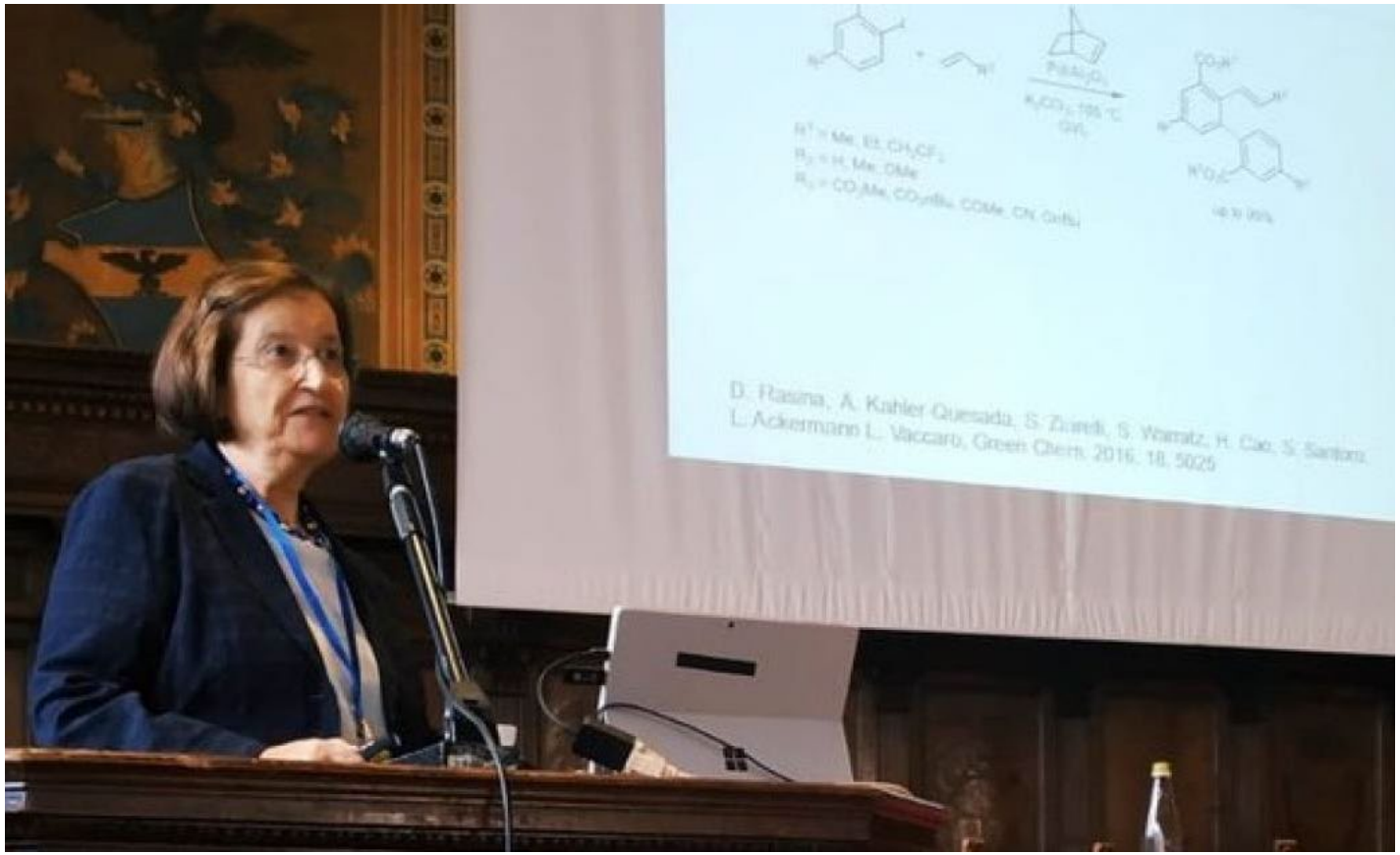
In-Depth look the proposed mechanism



Reaction limitations solved by Structurally Modified Norbornene Co-Catalysts (smNBEs)



Professor Marta Catellani: Biography

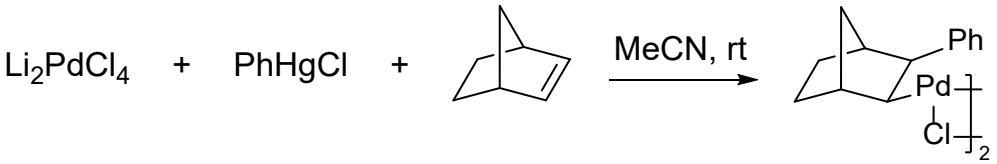


Professor Marta Catellani, 2022

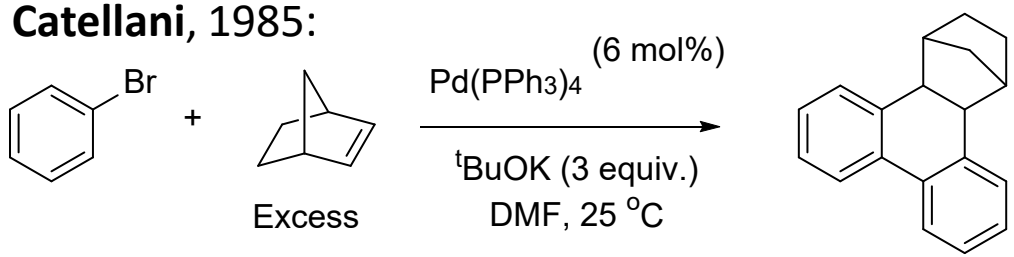
- PhD from University of Parma in 1971
- Post-Doc under Jack Halpern at the University of Chicago
- Returned to University of Parma as a research faculty member in 1974
- As of 2019, Professor Catellani was appointed Chair of the Chemistry department

Stoichiometric Studies and Early Reports

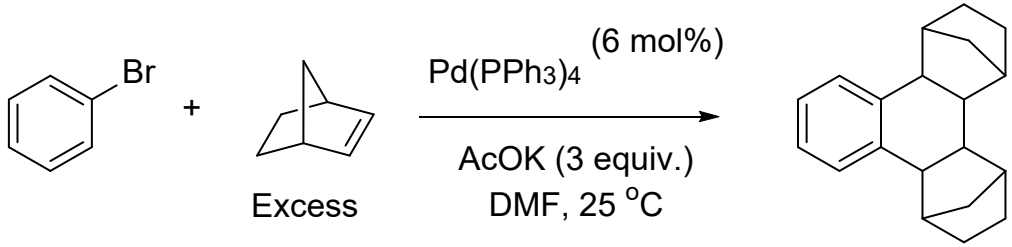
Horino, 1974:



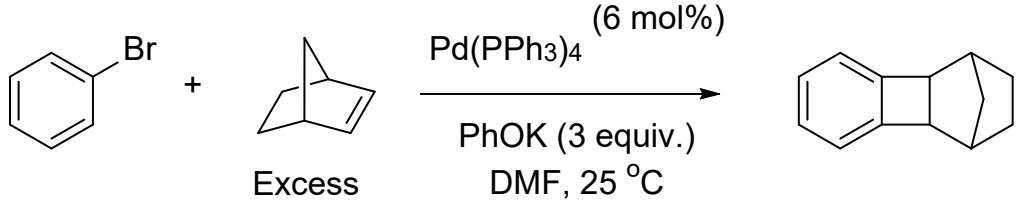
Catellani, 1985:



Catellani, 1982:



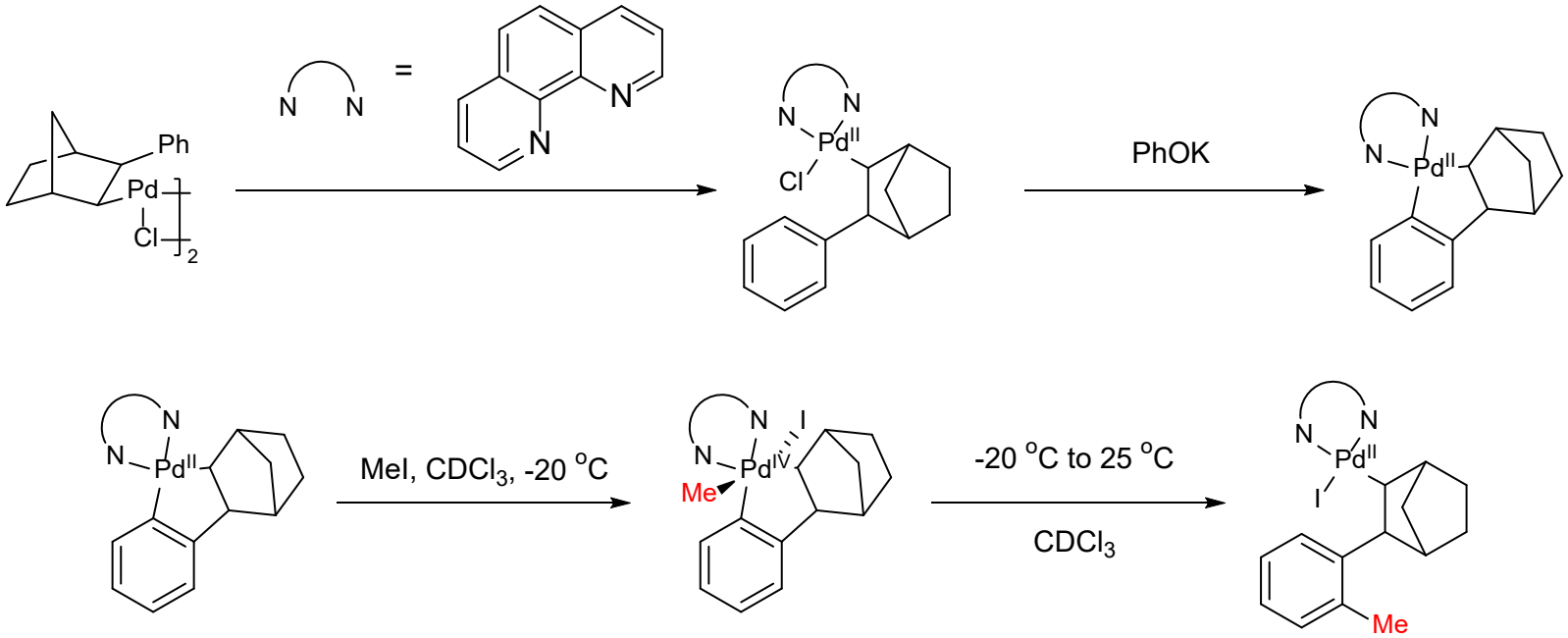
Catellani, 1985:



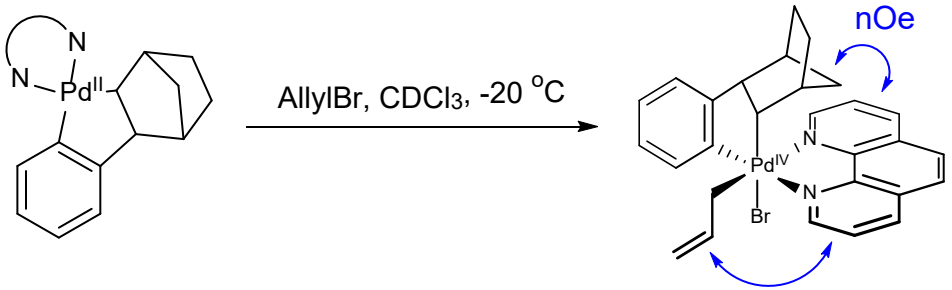
Tetrahedron Lett. **1974**, 15, 647−650; *J. Organomet. Chem.* **1982**, 239, C35−C37; *J. Organomet. Chem.* **1985**, 286, C13−C16.

Stoichiometric Studies and Early Reports

Catellani, 1988:



Catellani, 1990:

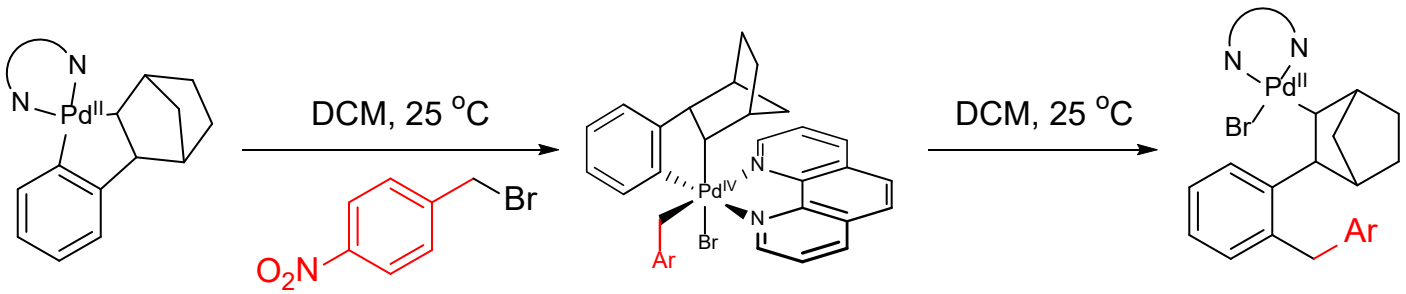


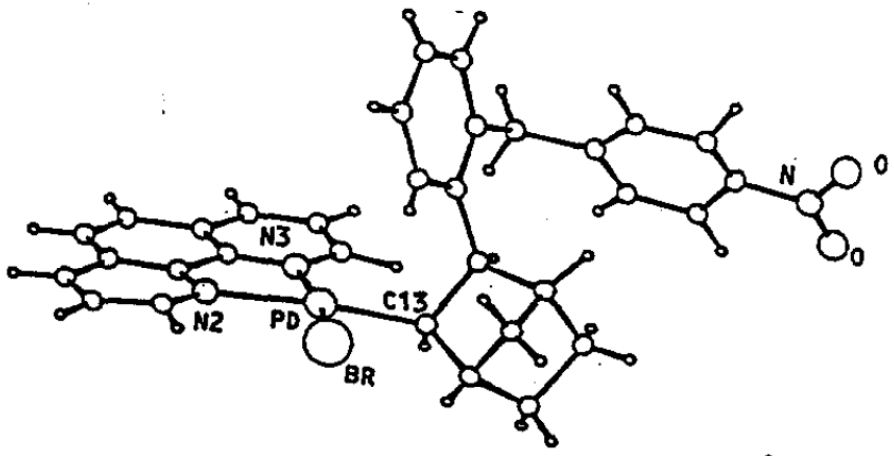
Relative stereochemistry determined by nOe

J. Organomet. Chem. **1988**, 346, C27–C30; *J. Organomet. Chem.* **1990**, 390, 251–255

Stoichiometric Studies and Early Reports

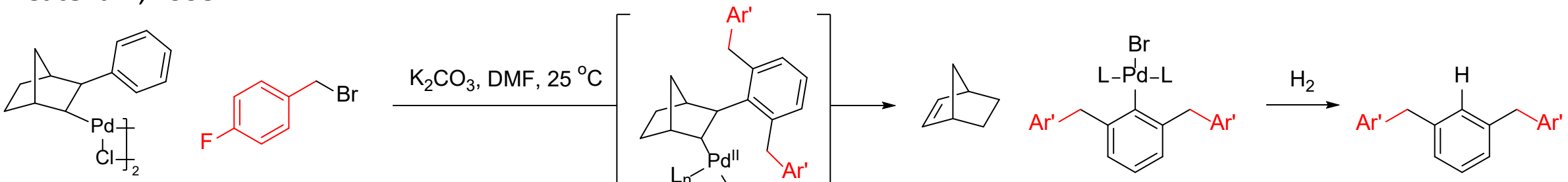
Catellani, 1993:





X-Ray structure of Norbornene-Pd species

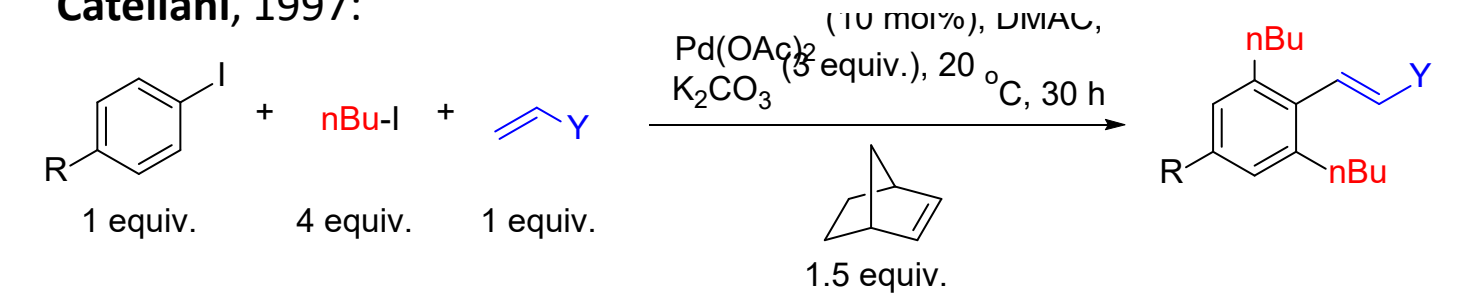
Catellani, 1995:

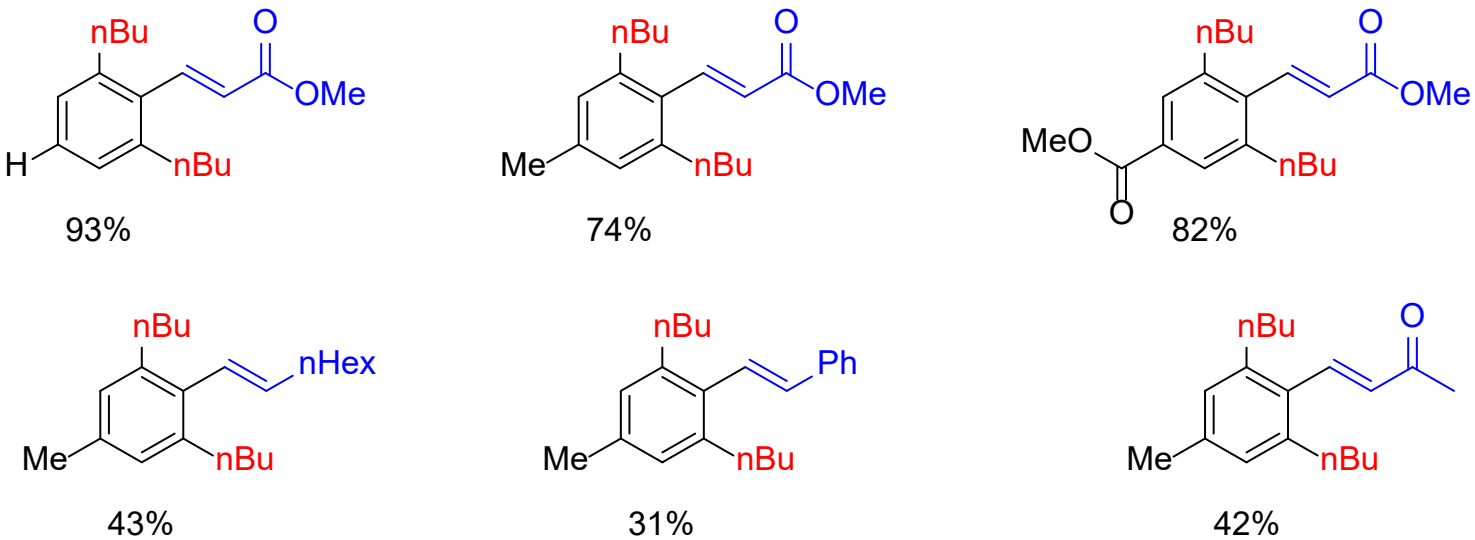


J. Organomet. Chem. **1993**, 458, C12–C15; *Angew Chem Int Ed.* **1995**, 33, 2421-2424

Stoichiometric Studies and Early Reports

Catellani, 1997:



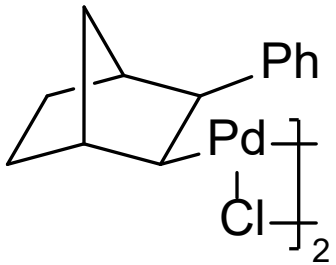


>90% selectivity for 1,3-dialkylation over mono-alkylation

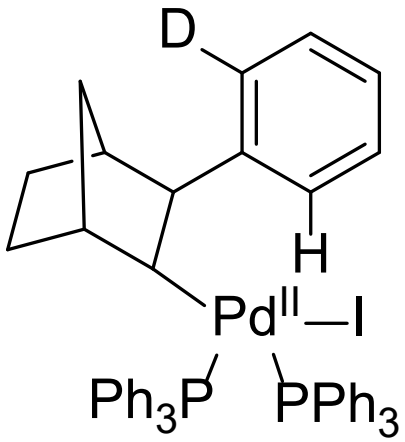
Angew. Chem., Int. Ed. **1997**, 36, 119–122

Presentation Overview

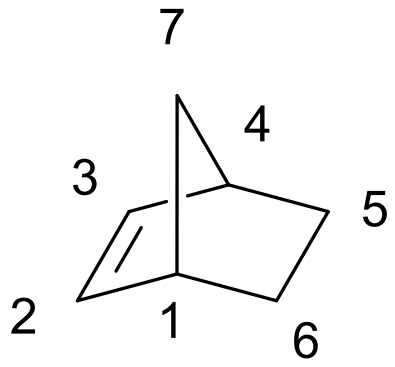
Initial investigations, stoichiometric studies and first report



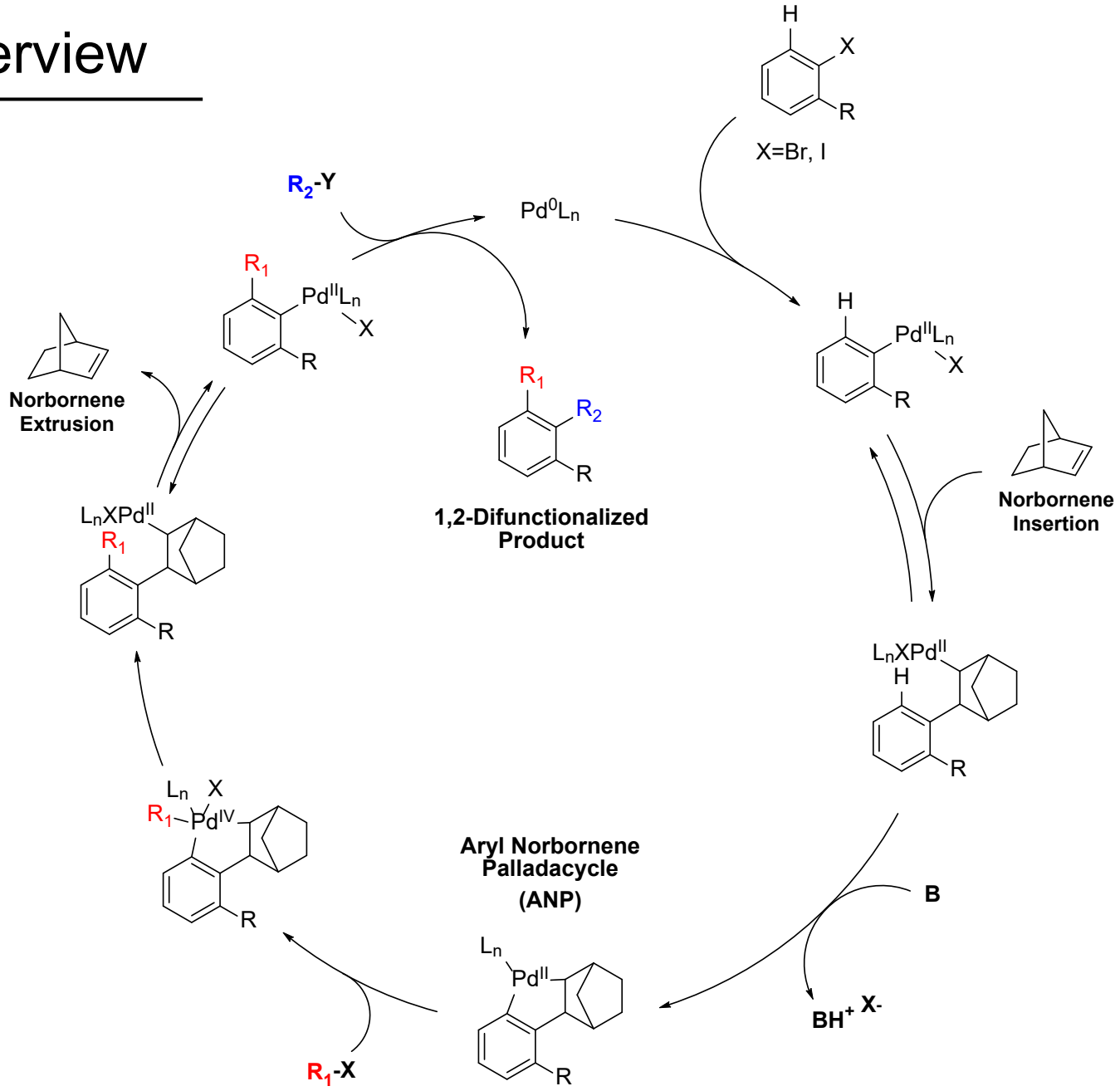
In-Depth look the proposed mechanism



Reaction limitations solved by Structurally Modified Norbornene Co-Catalysts (smNBEs)

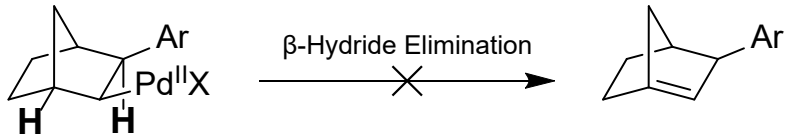


Mechanism: Overview

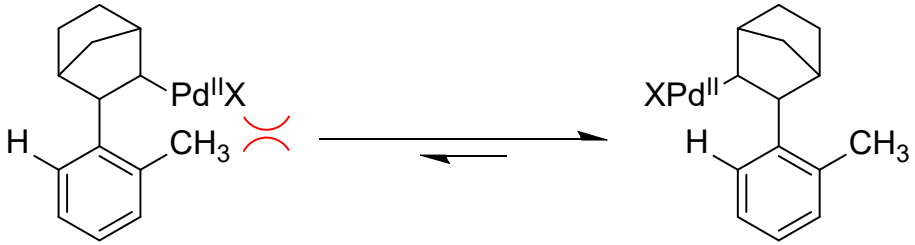


Mechanism: Why Norbornene?

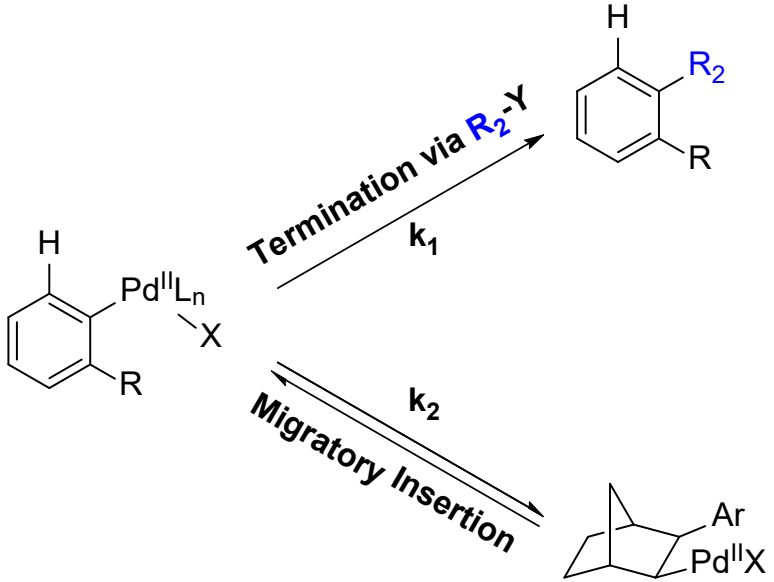
Bicyclic geometry precludes β-Hydride elimination



Norbornene as an *ortho* directing group and an *ipso* protecting group

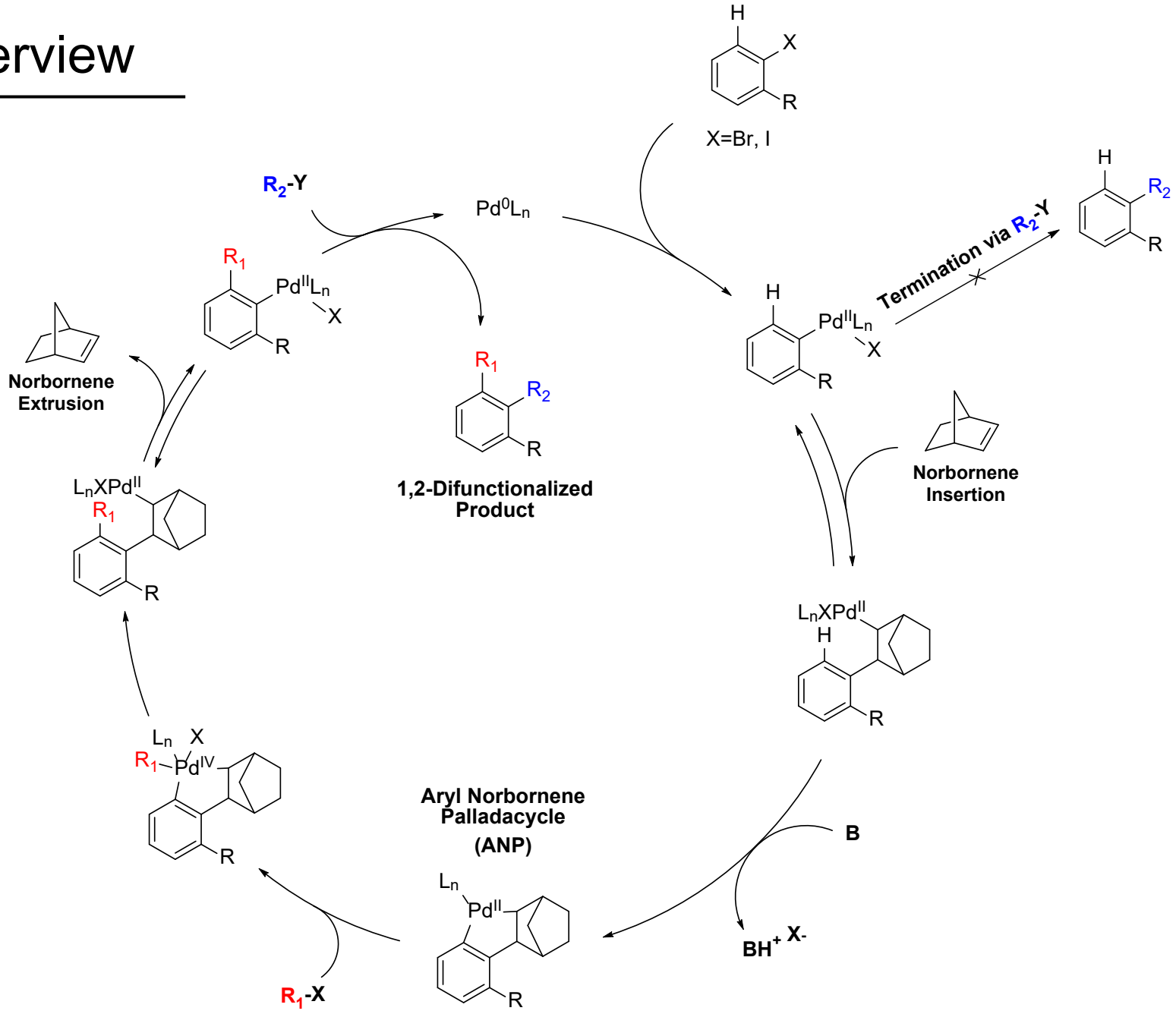


Migratory Insertion is fast but reversible



Chem. Eur. J. **2011**, 17, 8175 – 8188

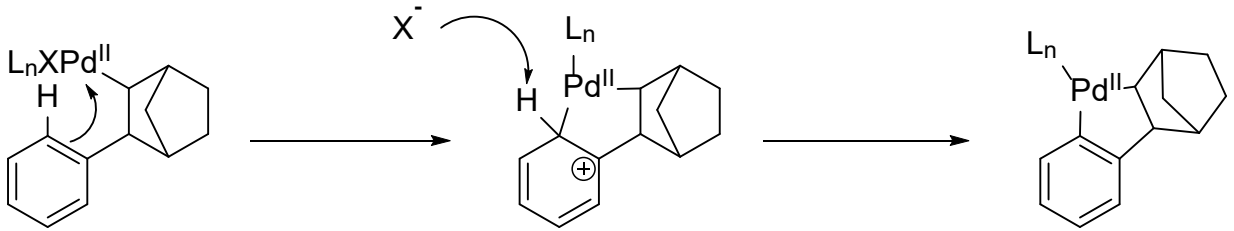
Mechanism: Overview



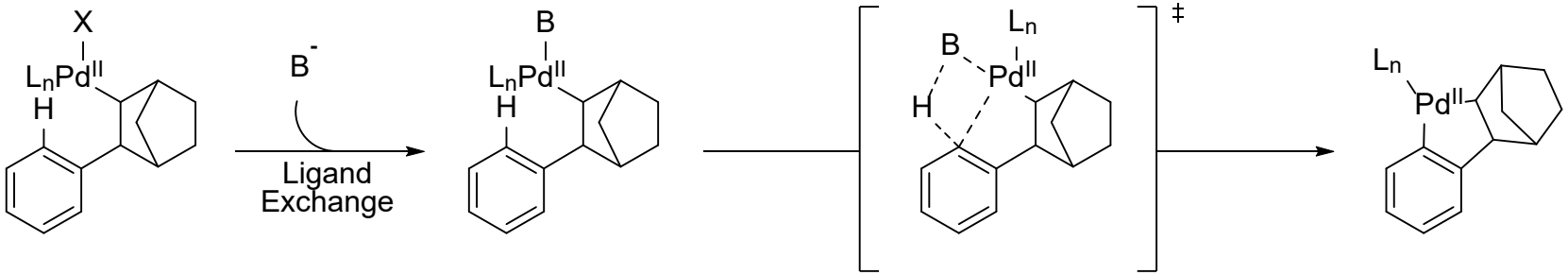
Mechanism: C-H Activation vs. Electrophilic Aromatic Substitution

Two plausible mechanisms:

Electrophilic Aromatic Substitution (EAS):



Concerted Metalation-Deprotonation (CMD):

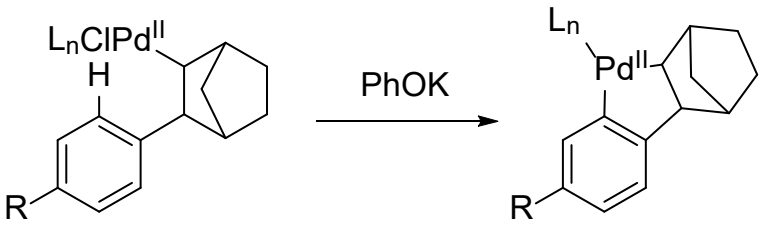


Chem. Eur. J. **2011**, 17, 8175 – 8188

Mechanism: C-H Activation vs. Electrophilic Aromatic Substitution

Early Mechanistic Evidence:

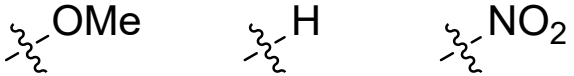
Catellani, 1992:



L_n=Py

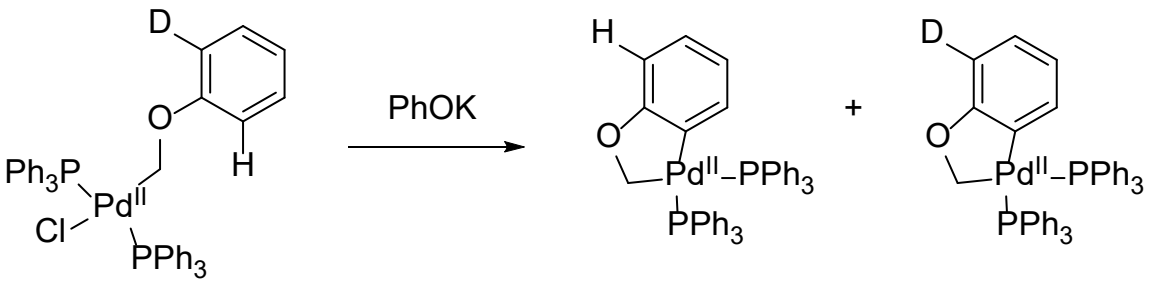
Electronic effects of the *para*-R group significantly impacted rates

Time to 50% conversion:



10 min 100 min 240 min

Echavarren, 2001:



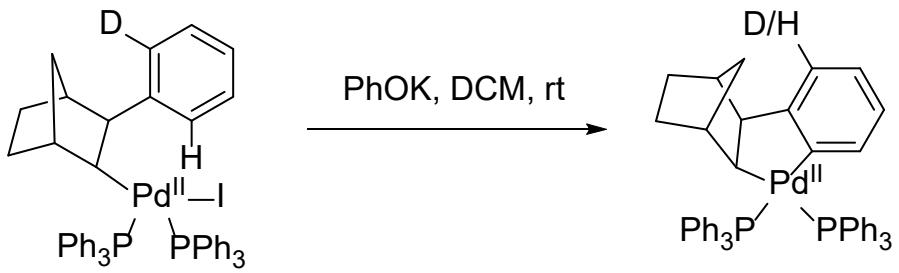
1:1 Ratio of H/D products formed

J. Organomet. Chem. **1992**, 425, 151–154; *Chem. Eur. J.* **2001**, 7, 11-17

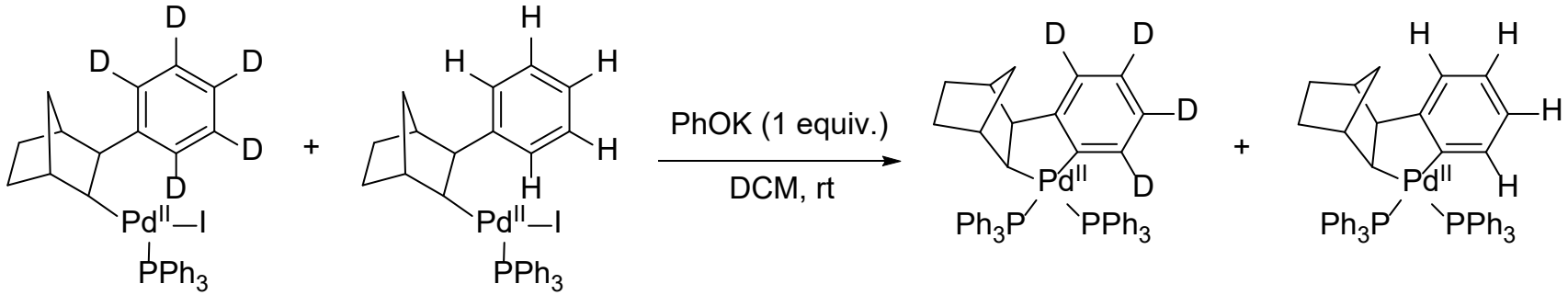
Mechanism: C-H Activation vs. Electrophilic Aromatic Substitution

Reinvestigation:

Lautens, 2011:



Intramolecular KIE:
K_H/K_D=4.2



1 equiv.

1 equiv.

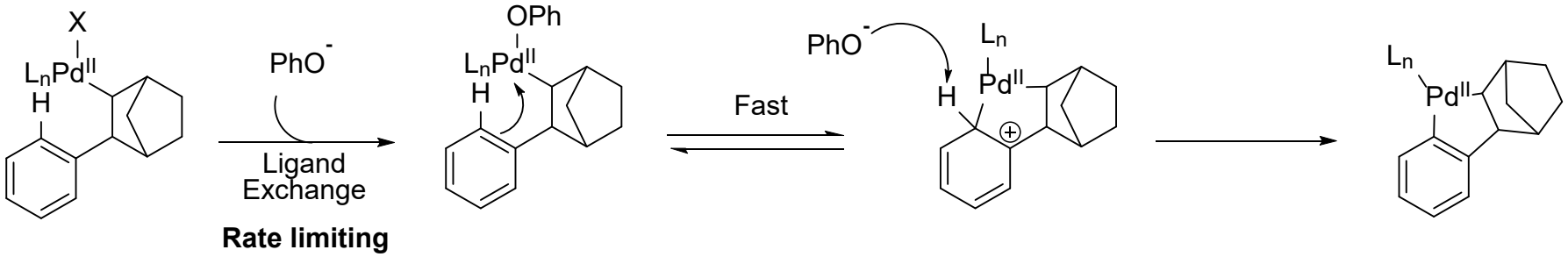
Competitive
KIE: K_H/K_D=1.0

Chem. Eur. J. **2011**, 17, 8175 – 8188

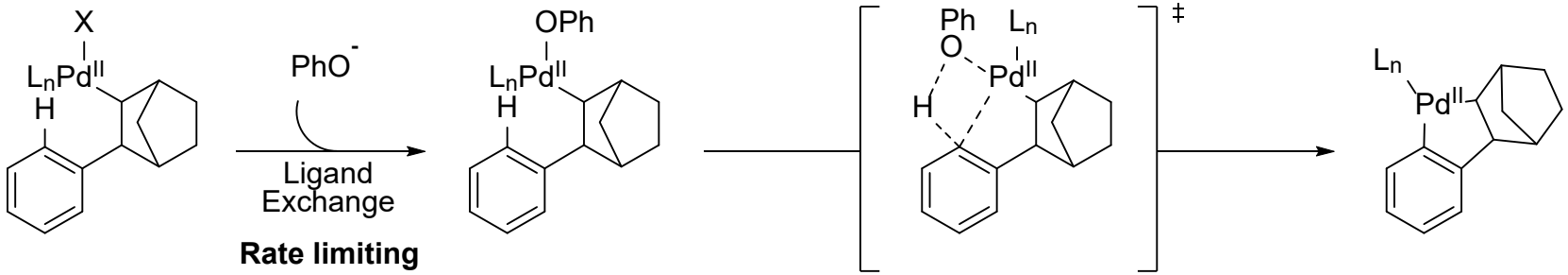
Mechanism: C-H Activation vs. Electrophilic Aromatic Substitution

Lautens' Proposal:

Electrophilic Aromatic Substitution (EAS):

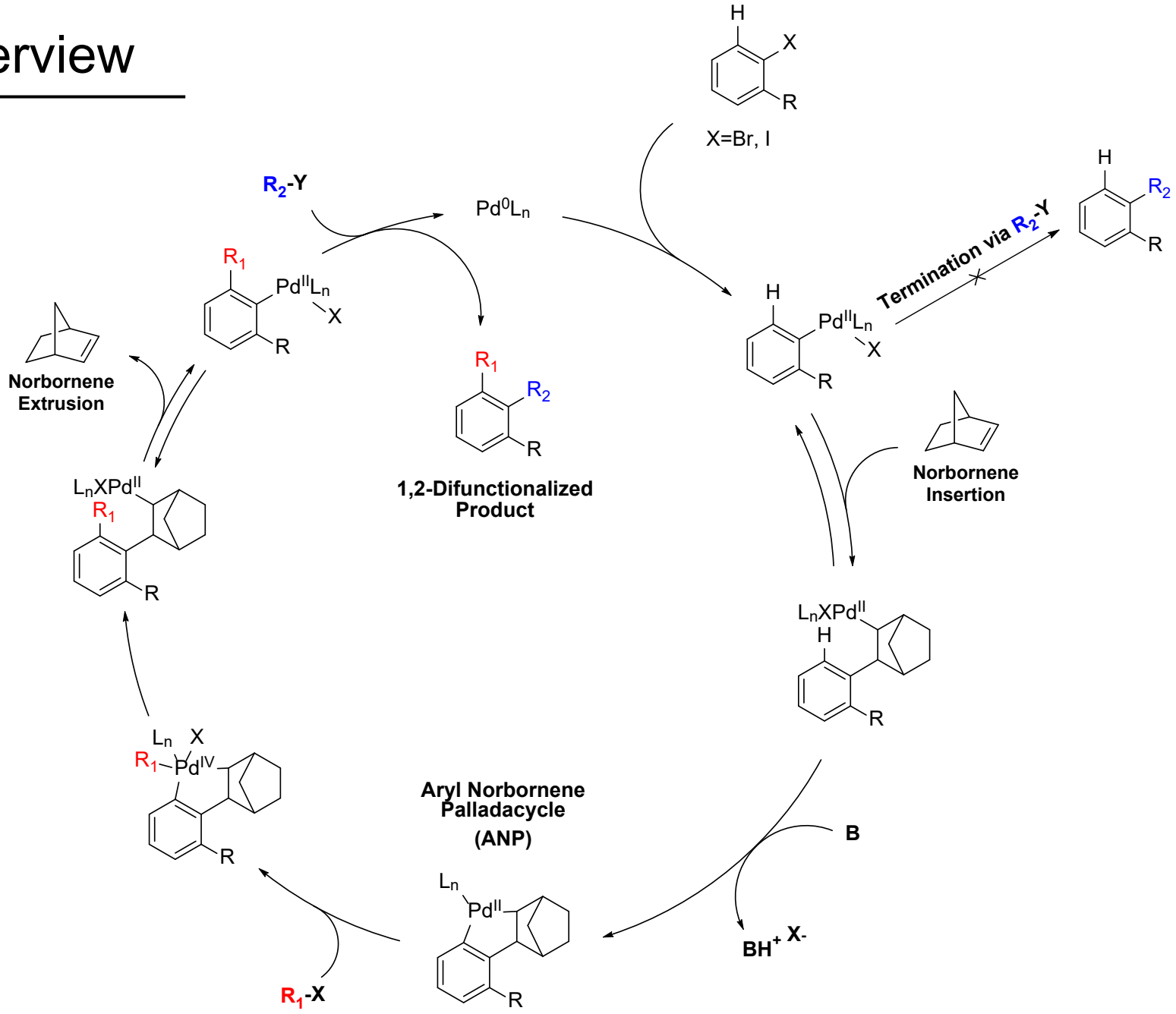


Concerted Metalation-Deprotonation (CMD):



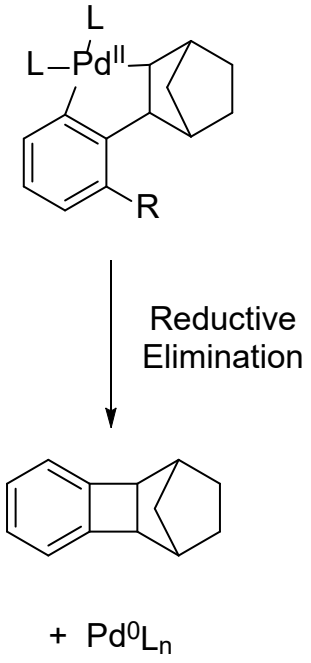
Chem. Eur. J. **2011**, 17, 8175 – 8188

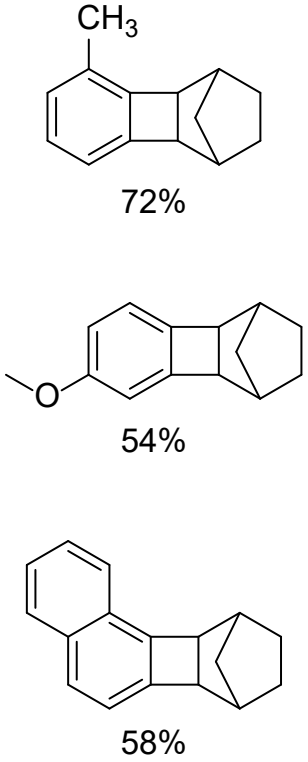
Mechanism: Overview



Mechanism: Aryl Norbornene Palladacycle (ANP)

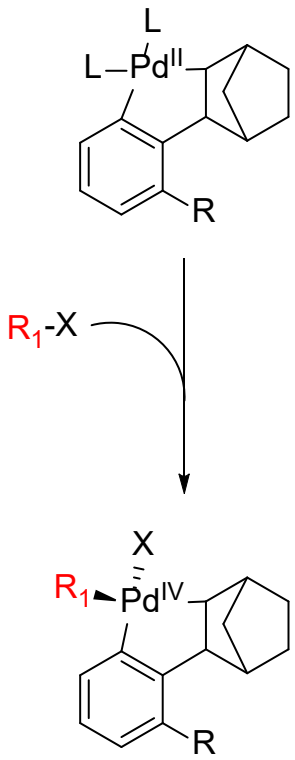
Unproductive Pathway: ANP reductive elimination



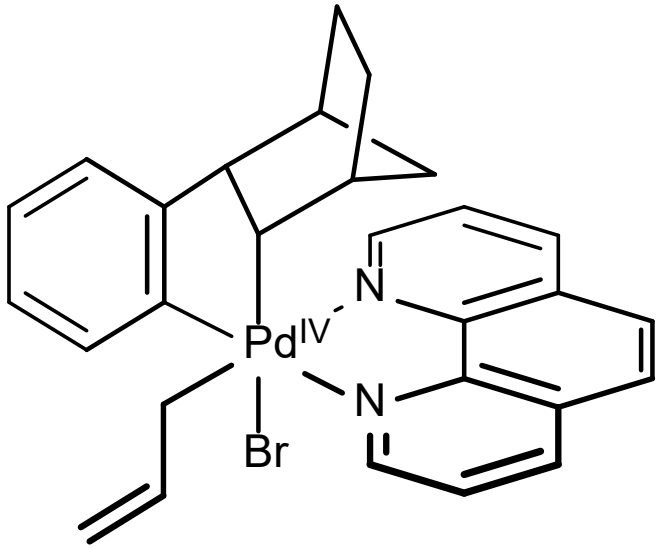


Catellani,
1996, *Synthesis*

Productive Pathway: ANP Oxidative Addition to Pd^{IV}



Ligands omitted for clarity*

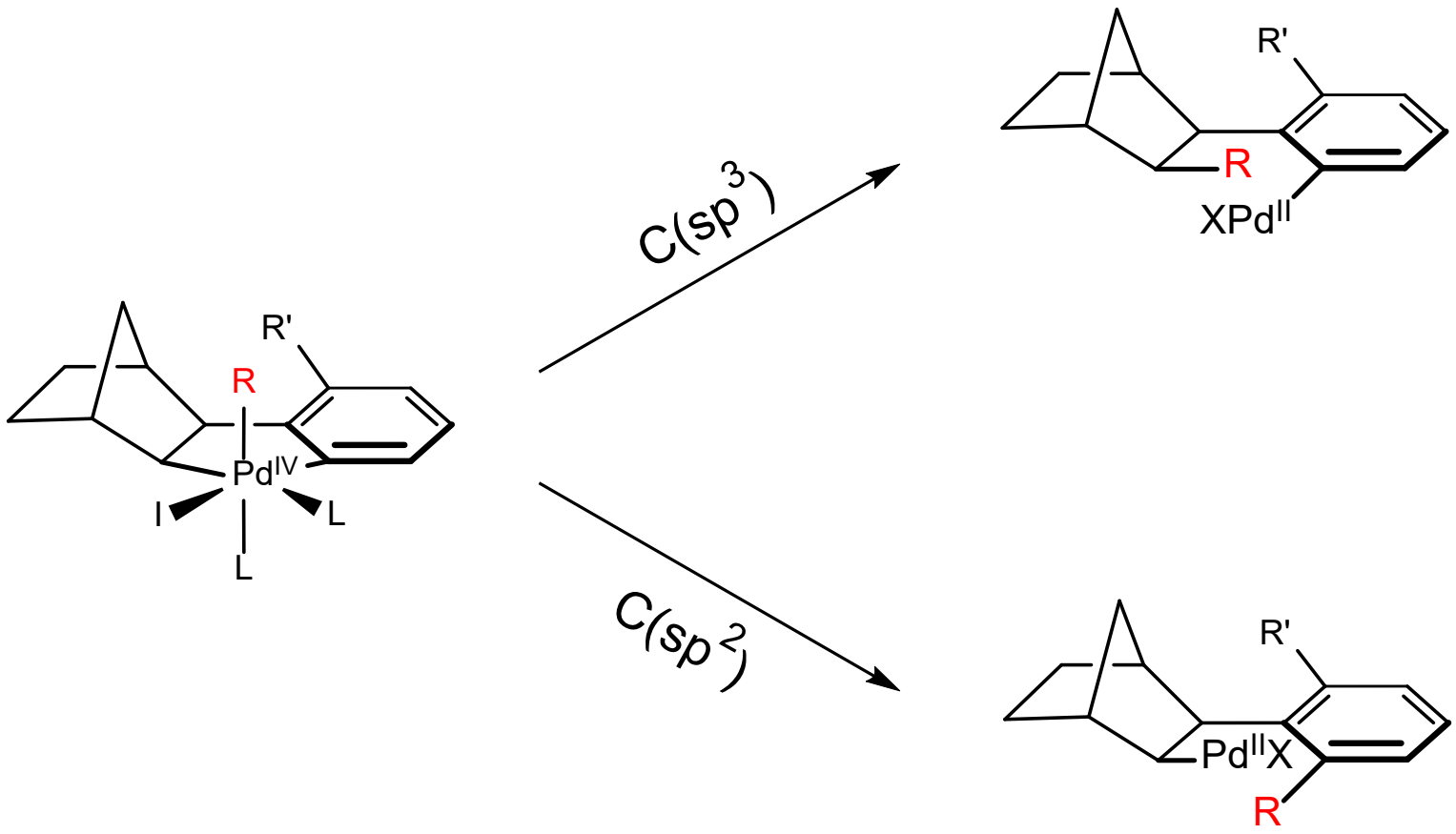


Stable up to -20 °C

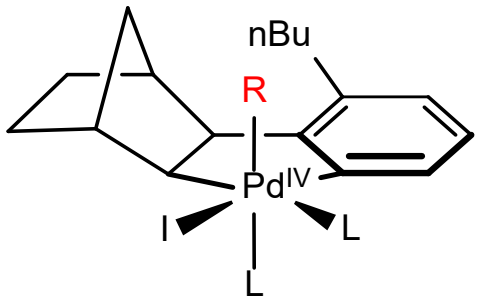
J. Organomet. Chem. **1990**, 390, 251–255; *Synthesis* **1996**, 6, 769-772

Mechanism: Aryl Norbornene Palladacycle (ANP)

Productive Pathway: ANP Oxidative Addition to Pd^{IV}

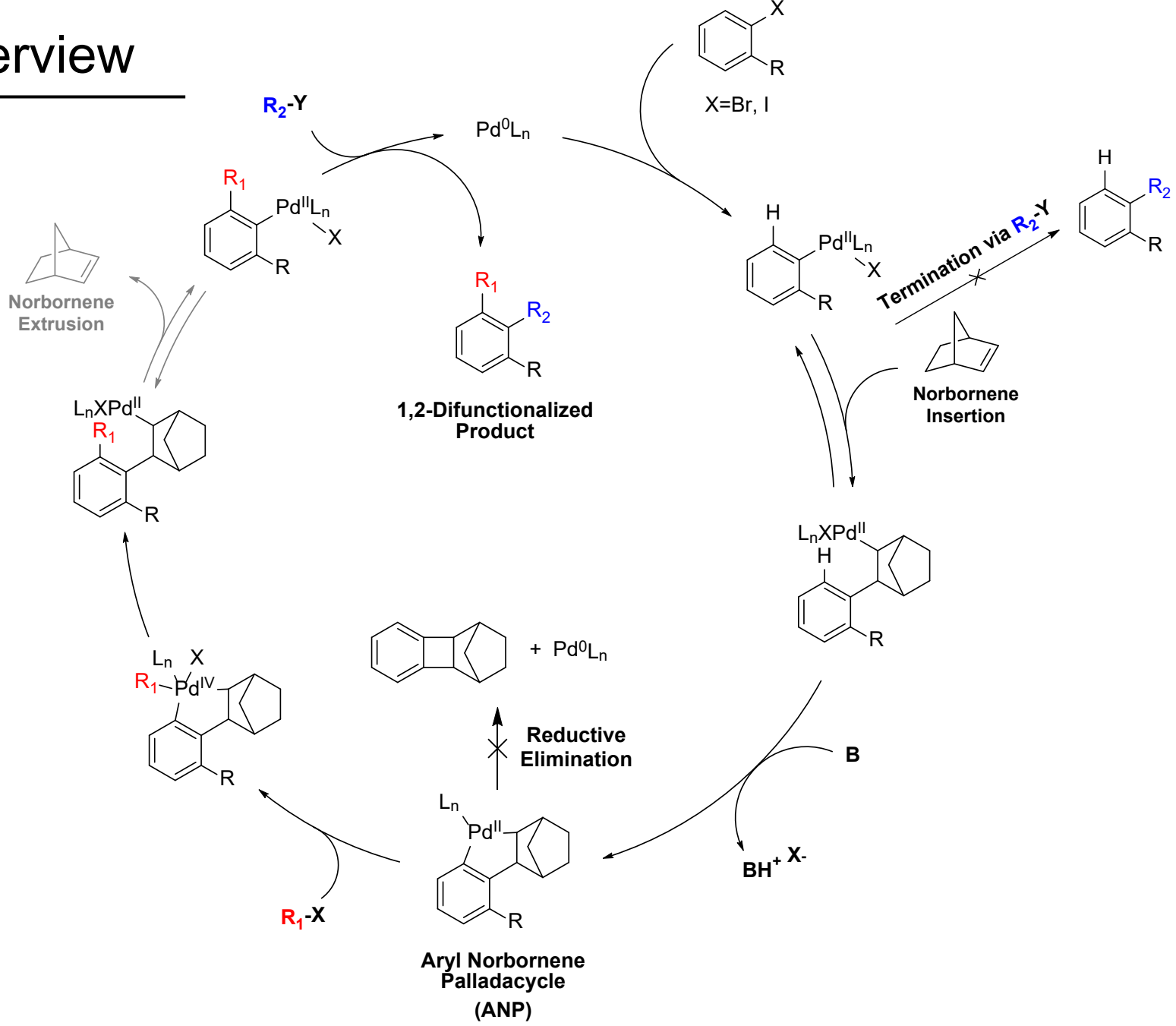


Catellani, 1998:
"The *Ortho* Effect"



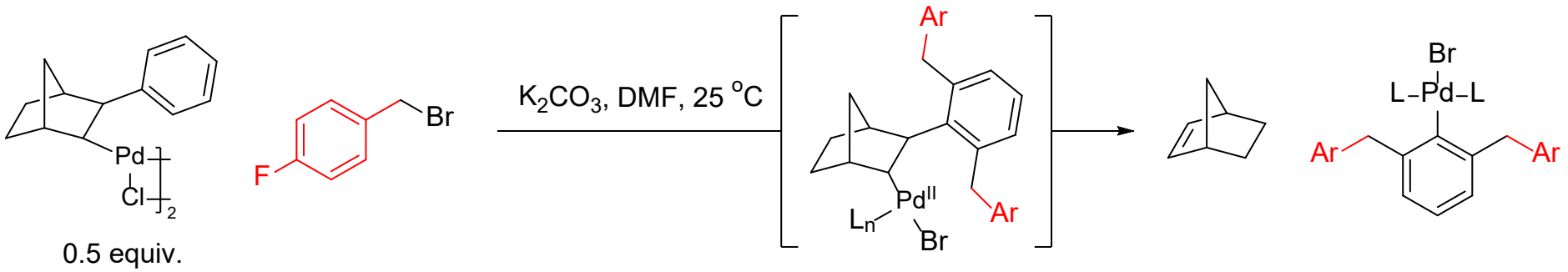
New J. Chem. **1998**, 22, 759–761.

Mechanism: Overview

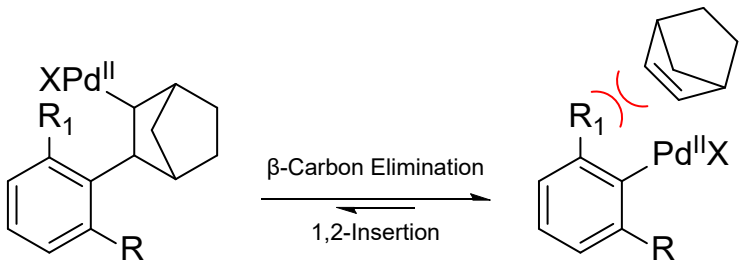


Mechanism: Norbornene Extrusion

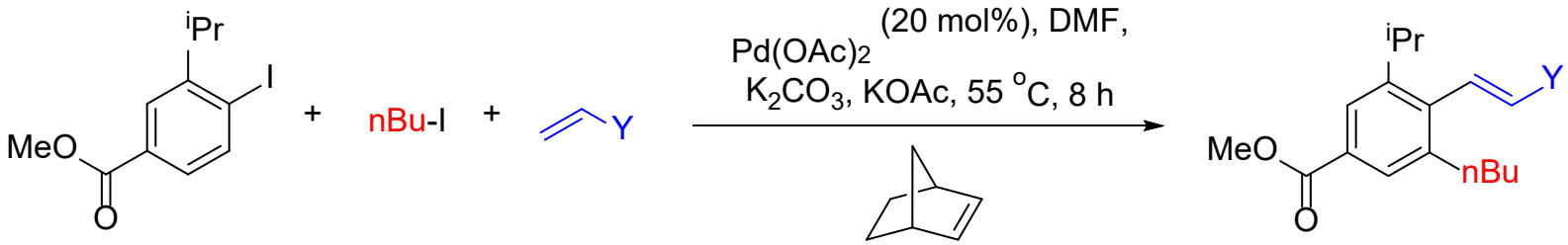
Catellani, 1995: Disubstitution without an *ortho* substituent



Proposed Equilibrium:

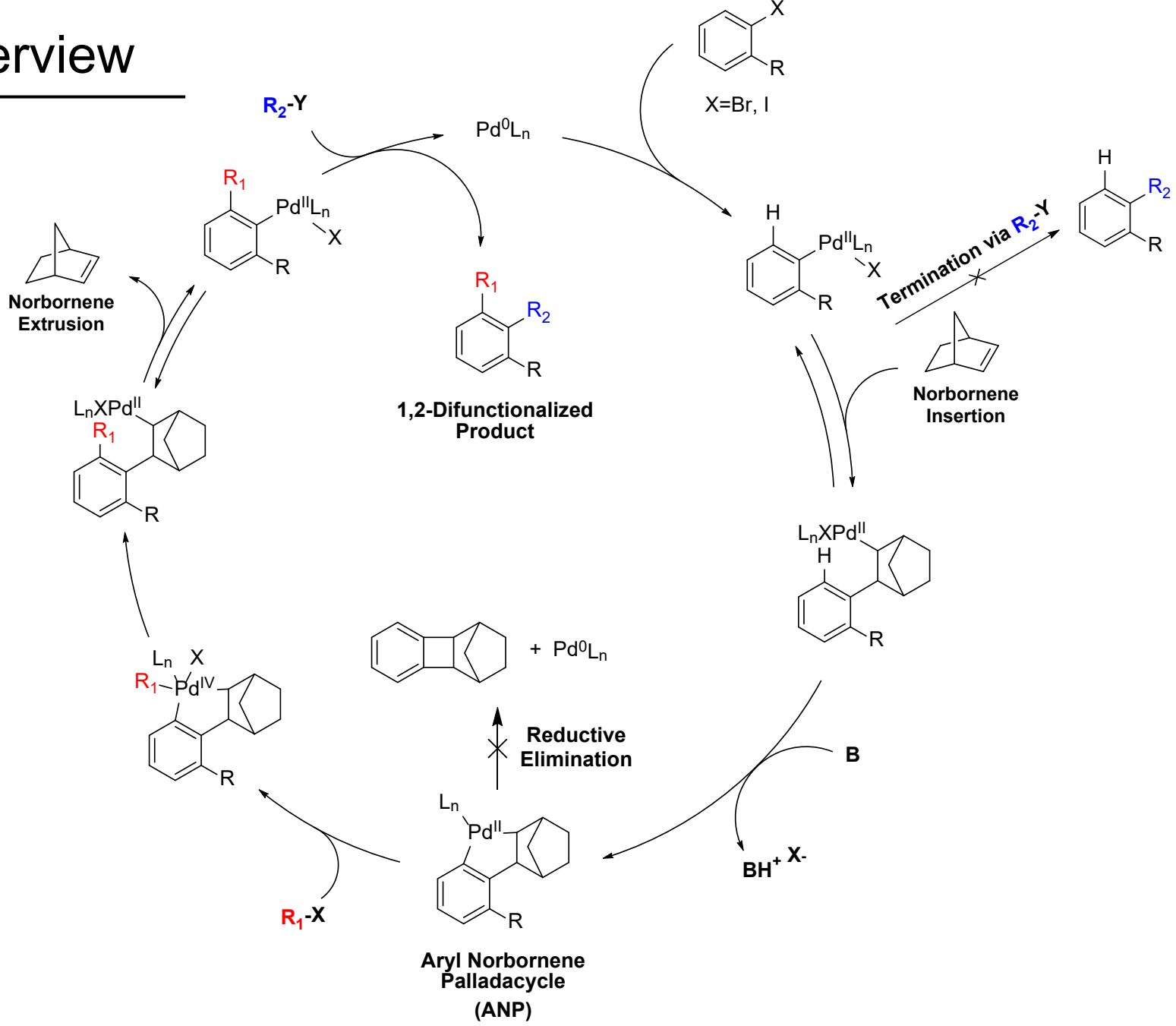


Catellani, 1999: Mono-substitution with an aliphatic *ortho* substituent

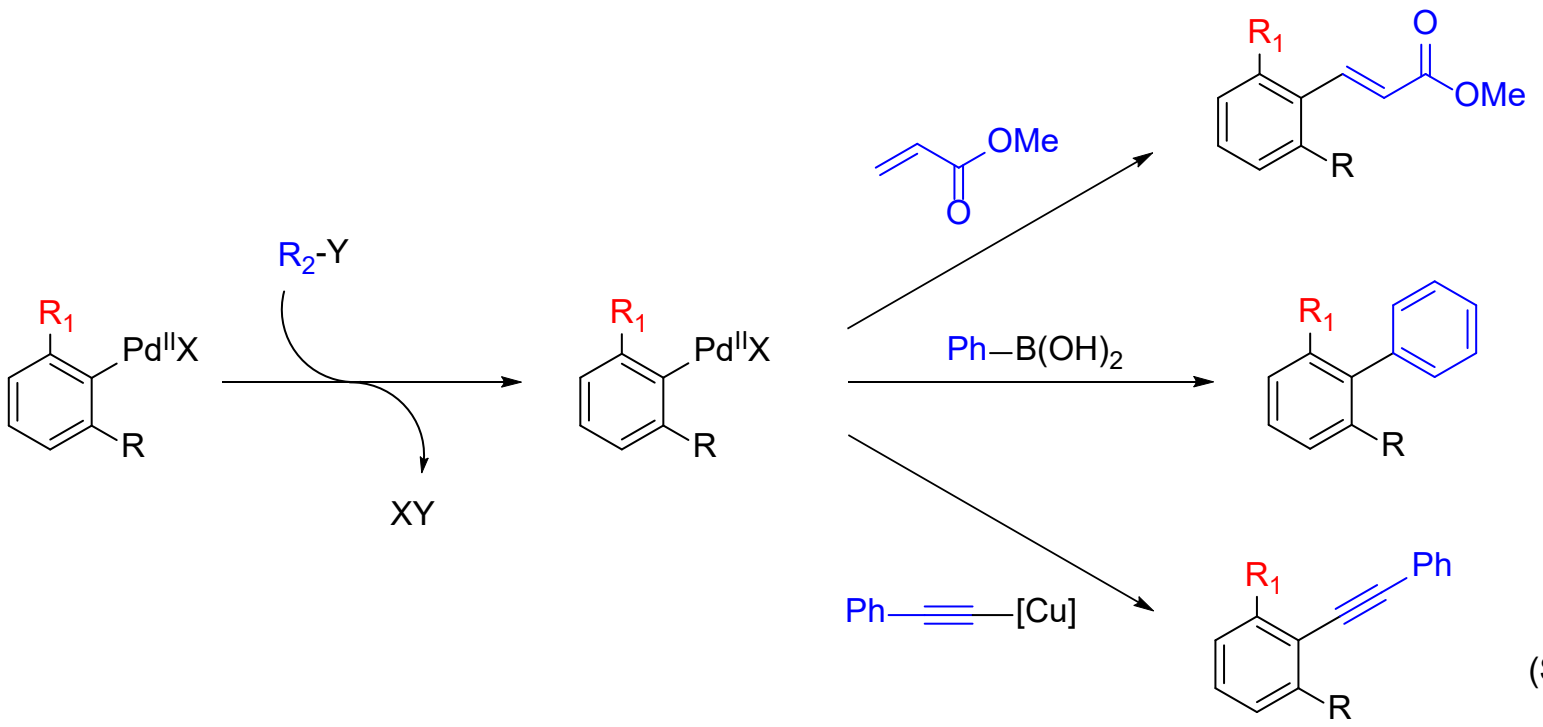


Angew. Chem., Int. Ed. **1995**, 33, 2421–2422; *Tetrahedron* **1999**, 55, 6595–6602

Mechanism: Overview



Mechanism: Termination of Aryl Palladium



Catellani, 1997
(Heck termination)

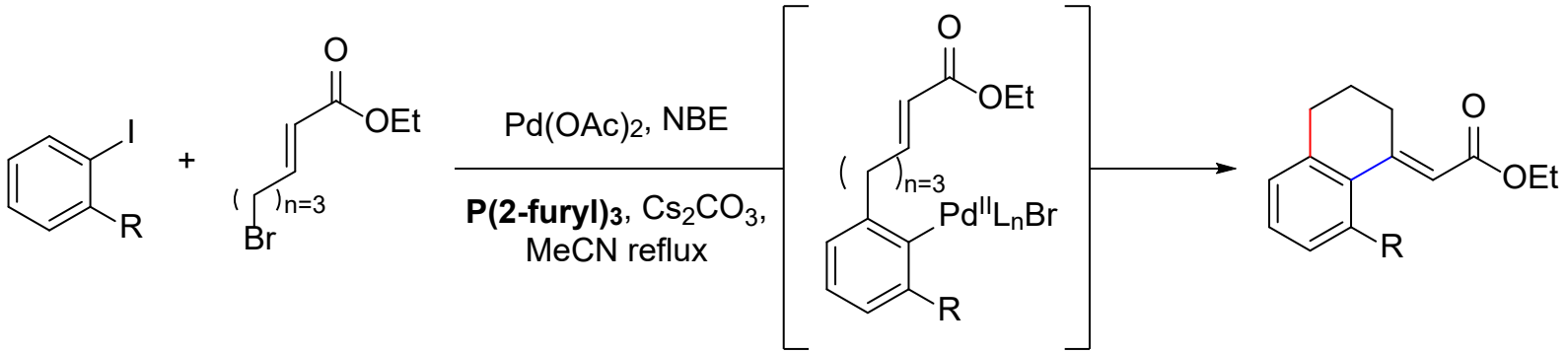
Catellani, 2000
(Suzuki termination)

Catellani, 2004
(Sonagoshira termination)

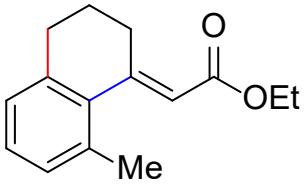
Angew. Chem., Int. Ed. Engl. **1997**, 36, 119–122; *Chem. Commun.* **2000**, 157–158; *J. Organomet. Chem.* **2004**, 689, 3741–3749.

Termination of Aryl Palladium: Scope and Examples

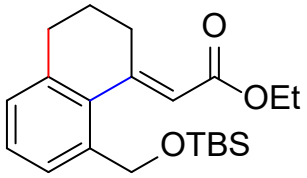
Lautens, 2000:



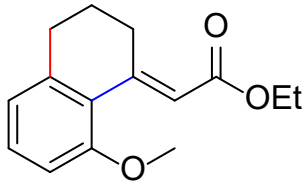
Abridged Scope:



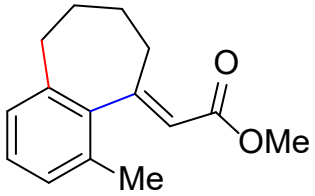
90%



60%



29%

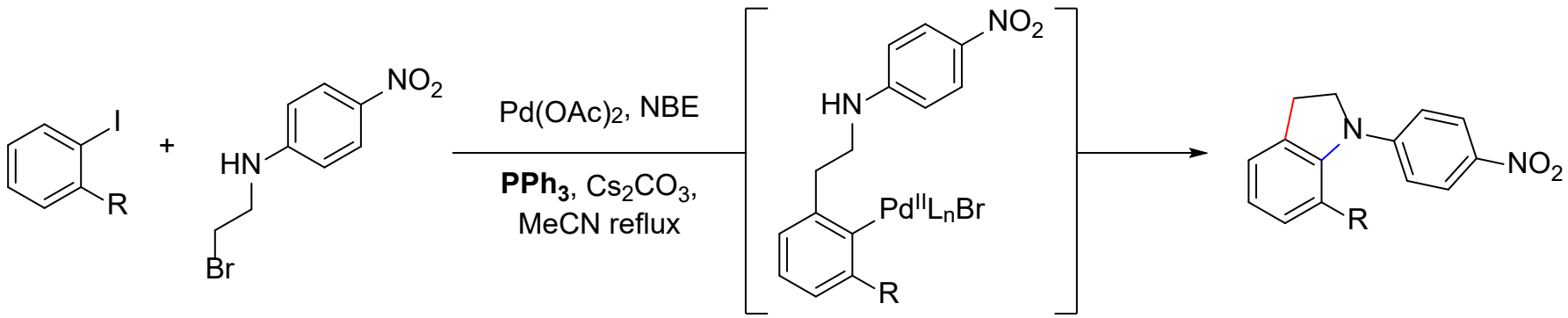


83%

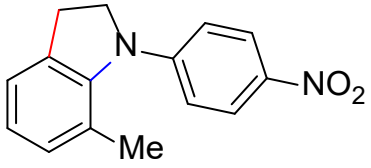
Angew. Chem., Int. Ed. **2000**, 39, 1045−1046

Termination of Aryl Palladium: Scope and Examples

Lautens, 2007:



Abridged Scope:



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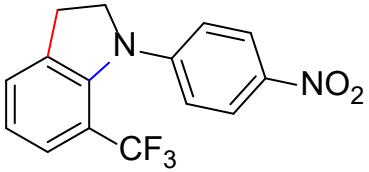

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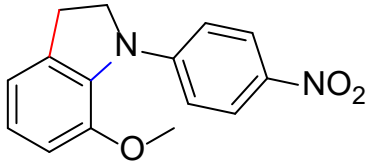

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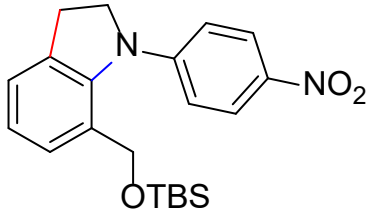
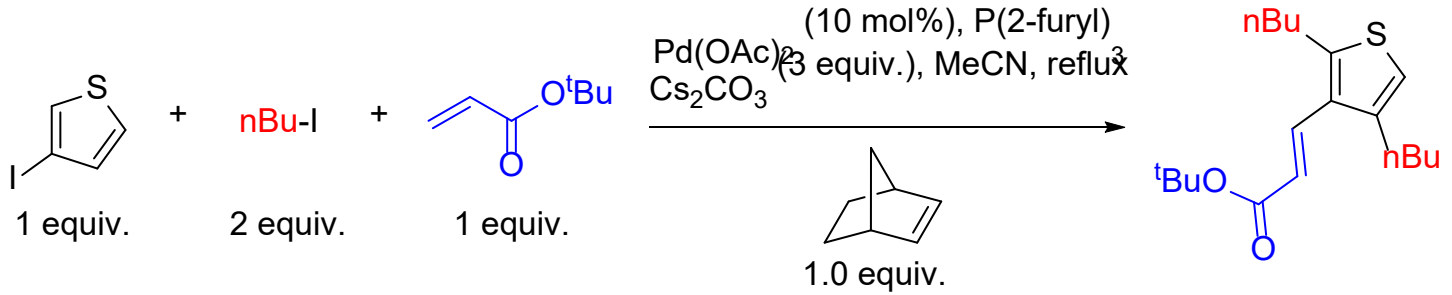


30%

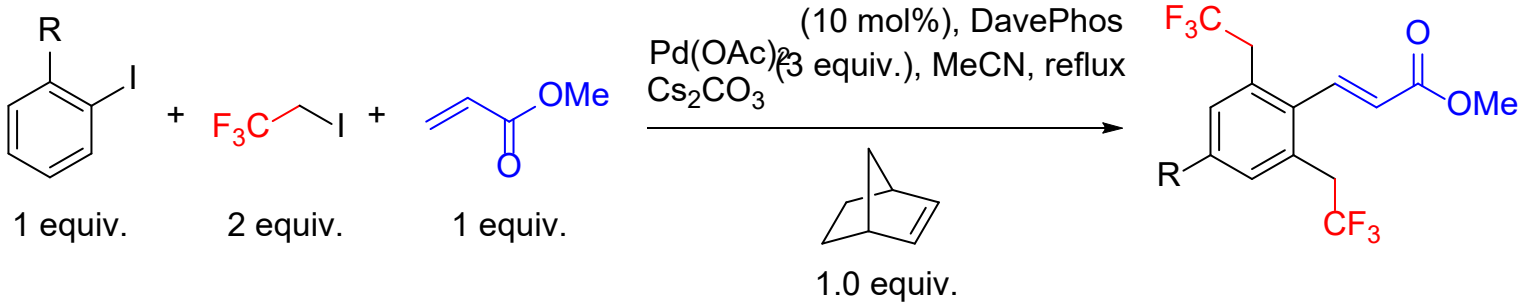
Org. Lett. **2007**, 9, 5255– 5258

Termination of Aryl Palladium: Scope and Examples

Lautens, 2006:



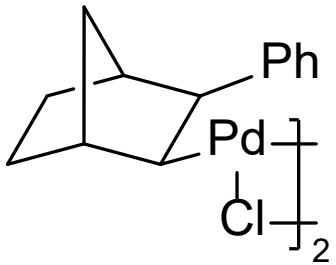
Liu, 2014:



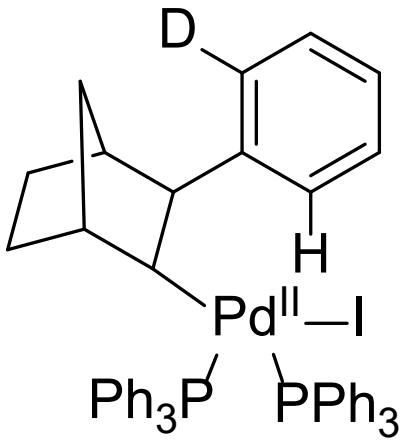
Org. Lett. **2006**, 8, 3939−3942; *Angew. Chem., Int. Ed.* **2014**, 53, 10174−10178

Presentation Overview

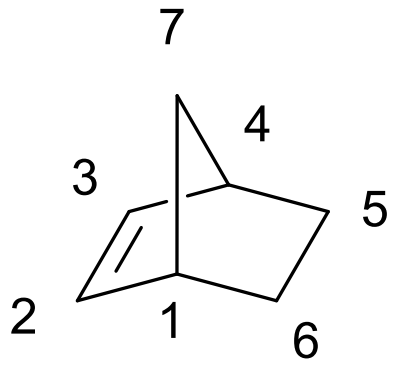
Initial investigations, stoichiometric studies and first report



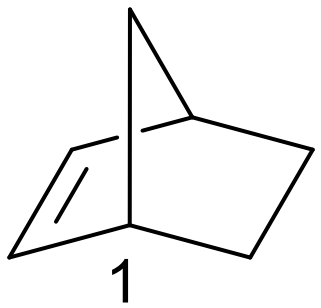
In-Depth look the proposed mechanism



Reaction limitations solved by Structurally Modified Norbornene Co-Catalysts (smNBEs)

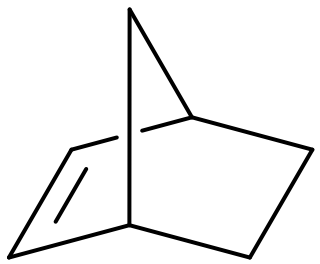


Structurally Modified Norbornenes (smNBEs)



1

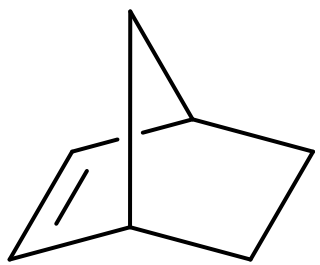
Ortho Constraint



2

Meta Constraint
and C-H Activation

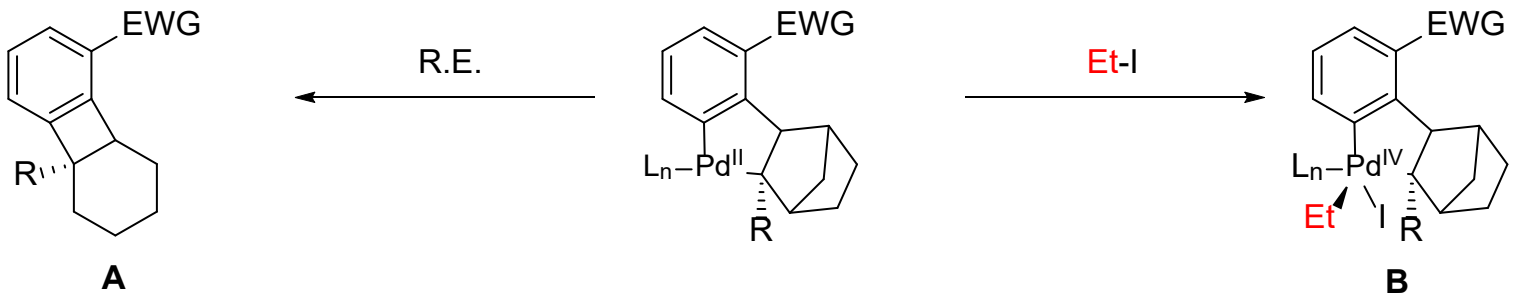
7



L-Type Ligand?
Future directions

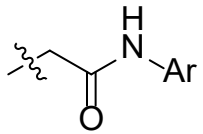
Problem: Cyclobutane Formation

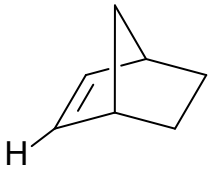
Slow Oxidative Addition to form Pd^{IV} leads to deleterious cyclobutane formation:



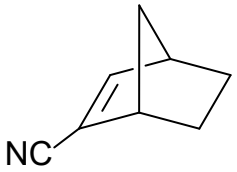
Yu, 2015: Turning a difficult substrate class into a new preparative method

EWG =

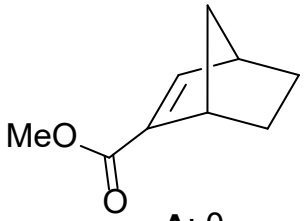




A: 85%
B: 10%



A: 0%
B: 29%

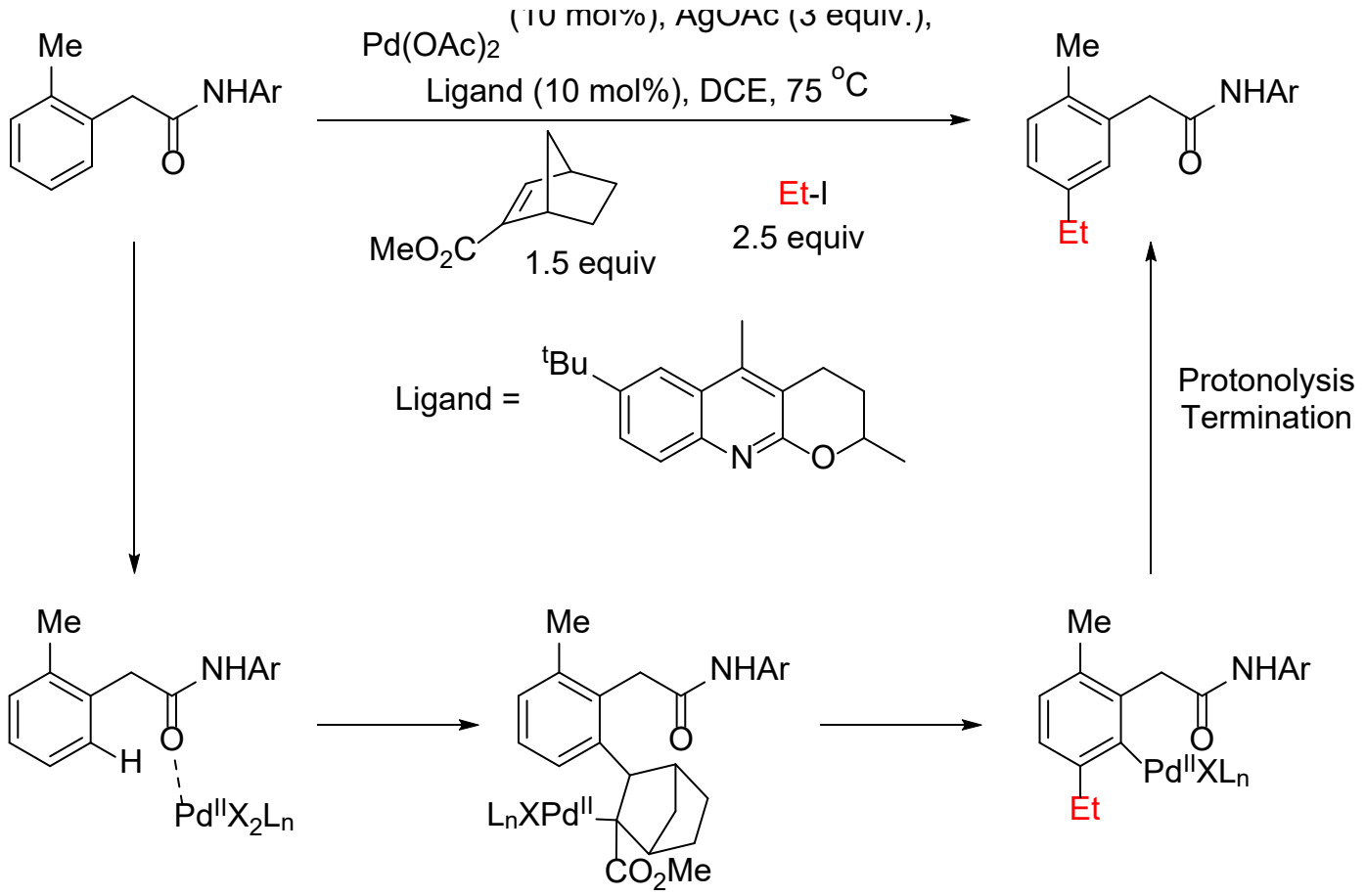


A: 0
B: 97%

J. Am. Chem. Soc. **2015**, 137, 11574–11577.

Solution: Sterically Hindered Norbornenes

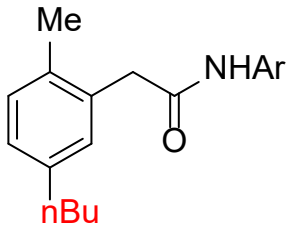
Yu, 2015: Bulky ligand and 2-substituted NBE block reductive elimination



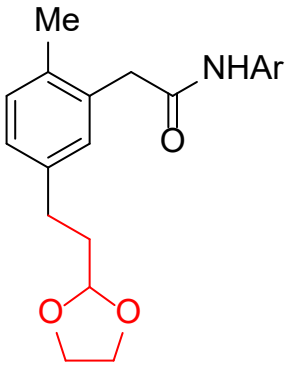
J. Am. Chem. Soc. **2015**, 137, 11574–11577.

Meta Functionalization

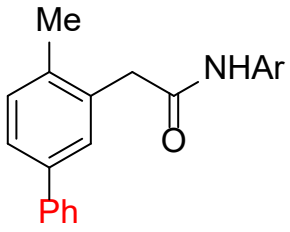
Yu, 2015: Meta Alkylation and Arylation



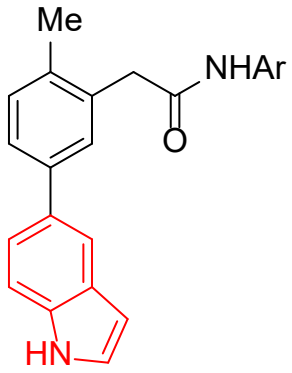
85%



90%

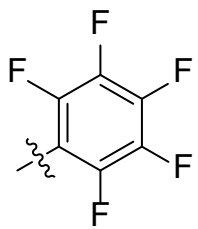


57%

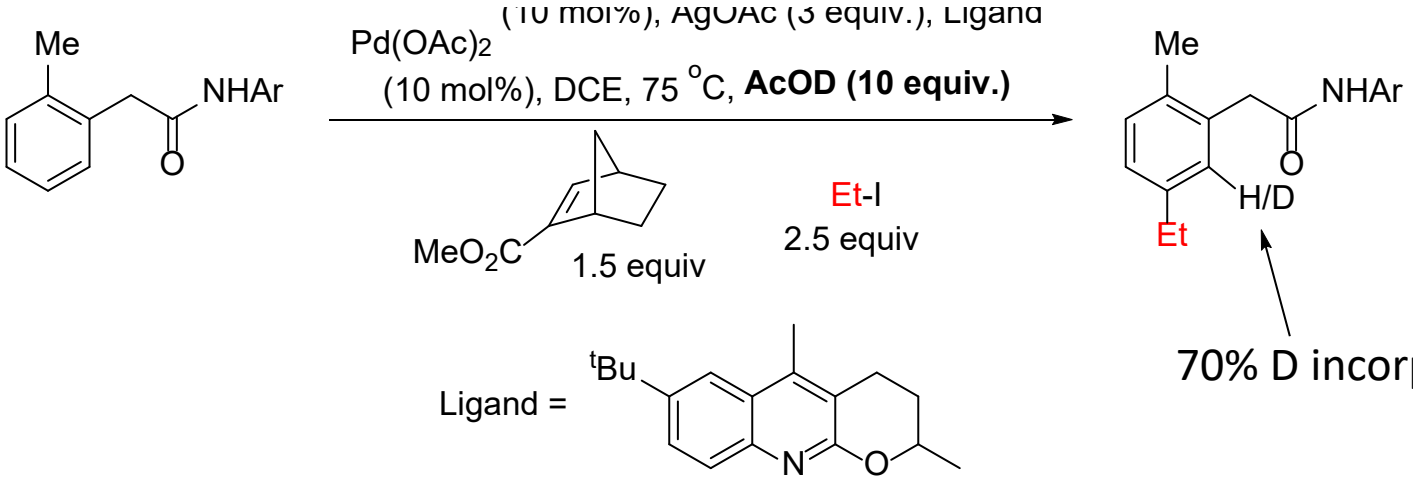


52%

Ar =



Yu, 2015: Protonolysis termination supported by AcOD study

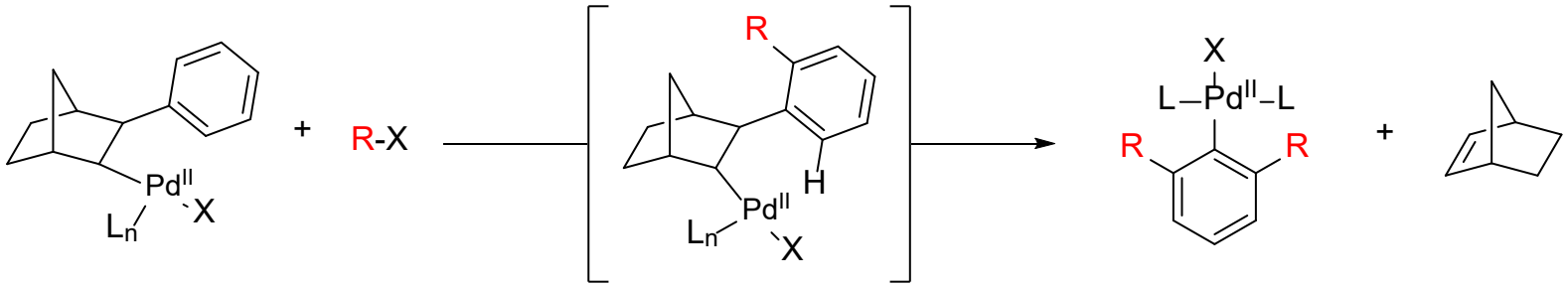


70% D incorporation

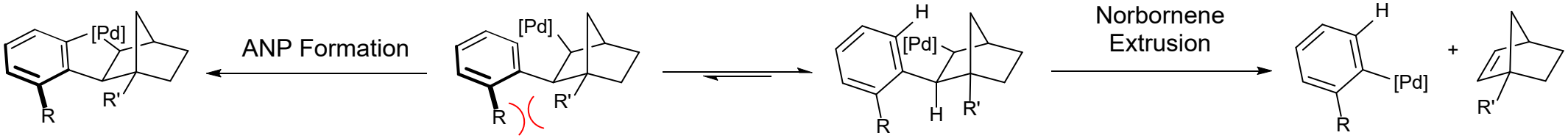
J. Am. Chem. Soc. **2015**, 137, 11574–11577.

Problem: “The *Ortho* Constraint”

Disubstitution without an *ortho* substituent:

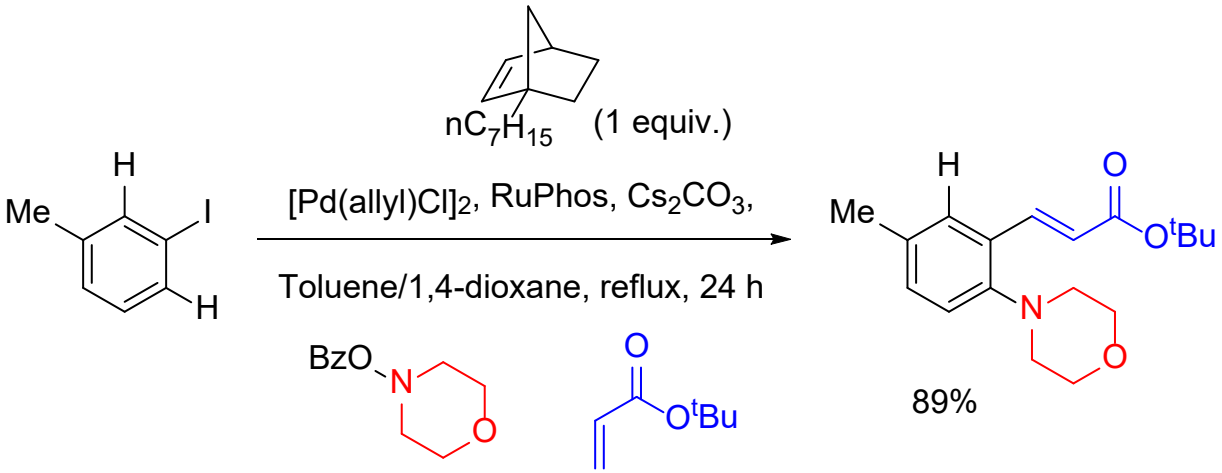


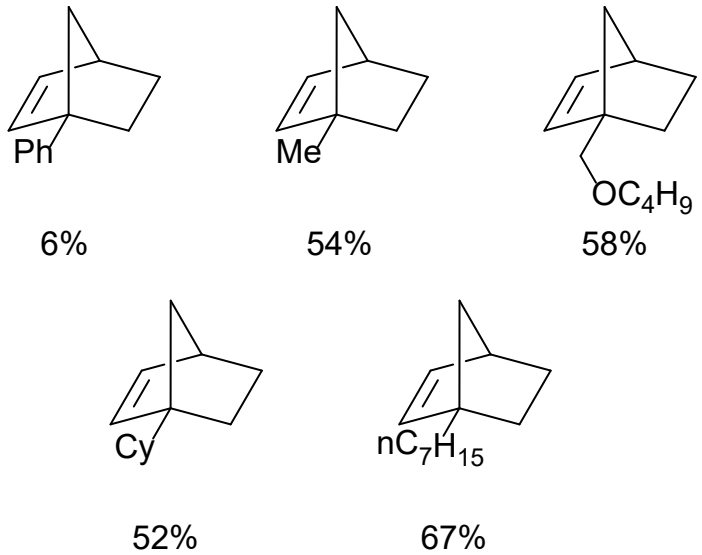
1-Substitued Norbornenes block difunctionalization:

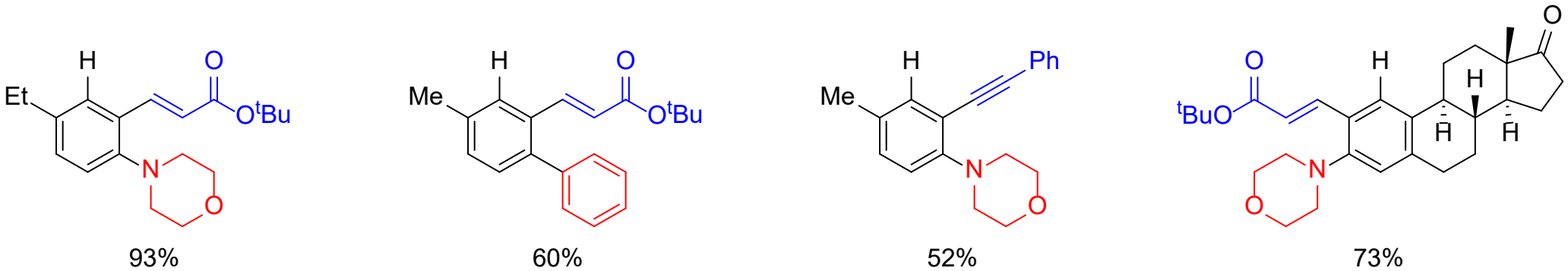


Solution: 1-Substituted NBEs

Dong, 2018: Preparative method for mono-substitution



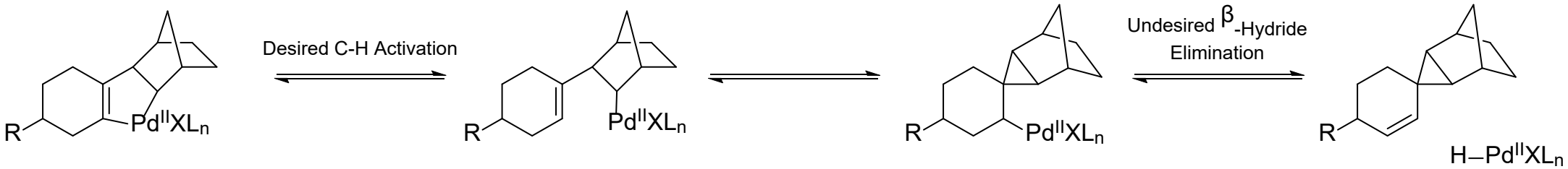




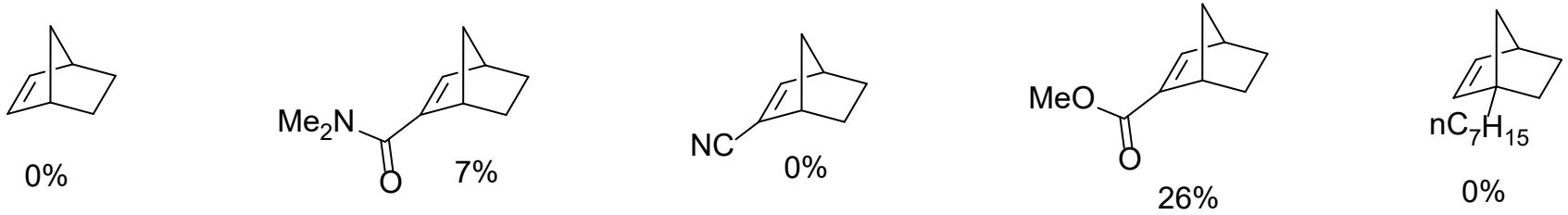
Nat. Chem. **2018**, 10, 866–872.

Expansion into Olefinic C-H Activation

Problem: Olefin reactivity and activated allylic C-H bonds



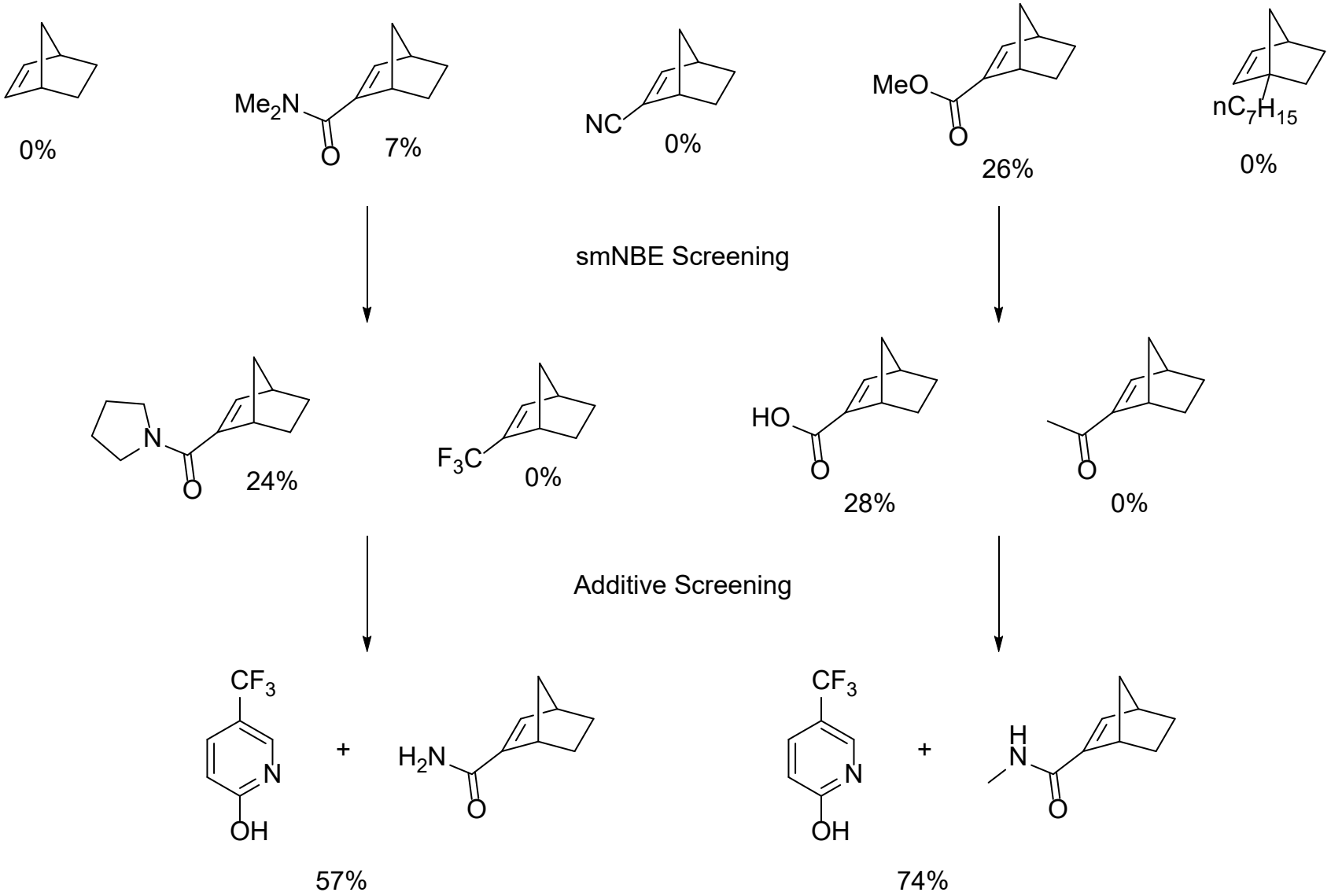
Dong, 2019: Initial smNBEs screened



Nat. Chem. **2019**, 11, 1106–1112.

Expansion into Olefinic C-H Activation

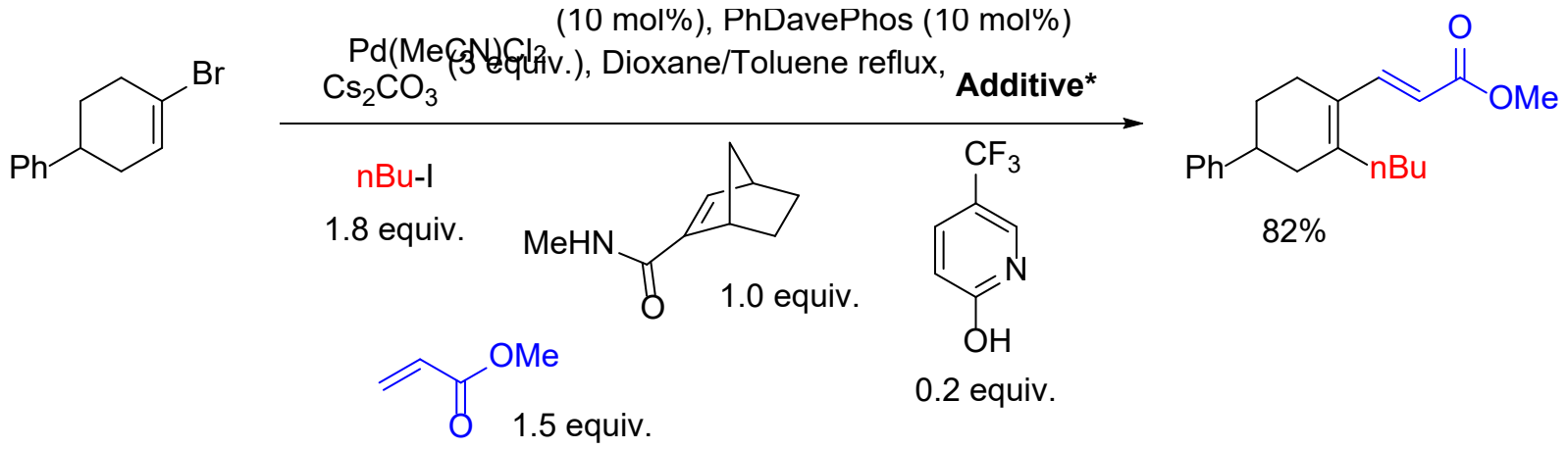
Dong, 2019: Initial smNBEs screened

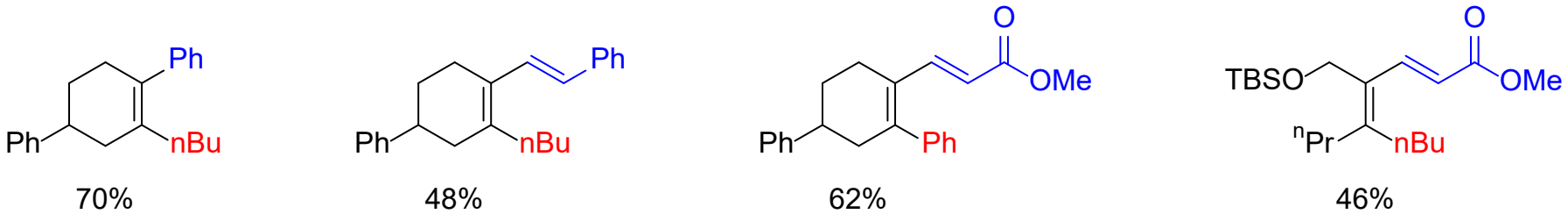


Nat. Chem. **2019**, 11, 1106–1112.

Expansion into Olefinic C-H Activation

Dong, 2019: C-H Activation becomes facile enough to functionalize internal olefins

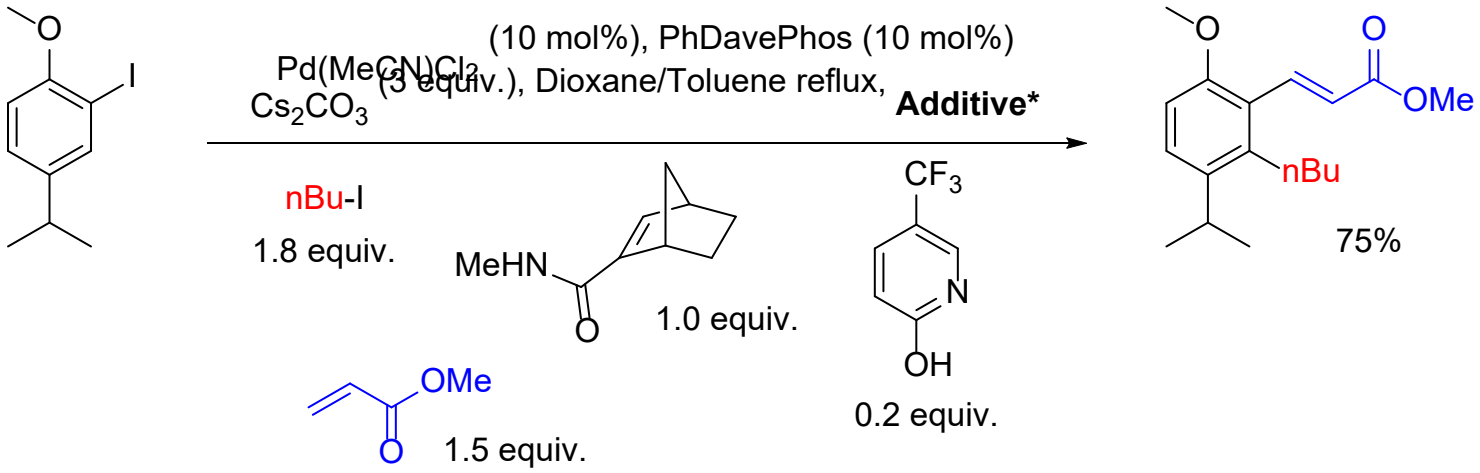


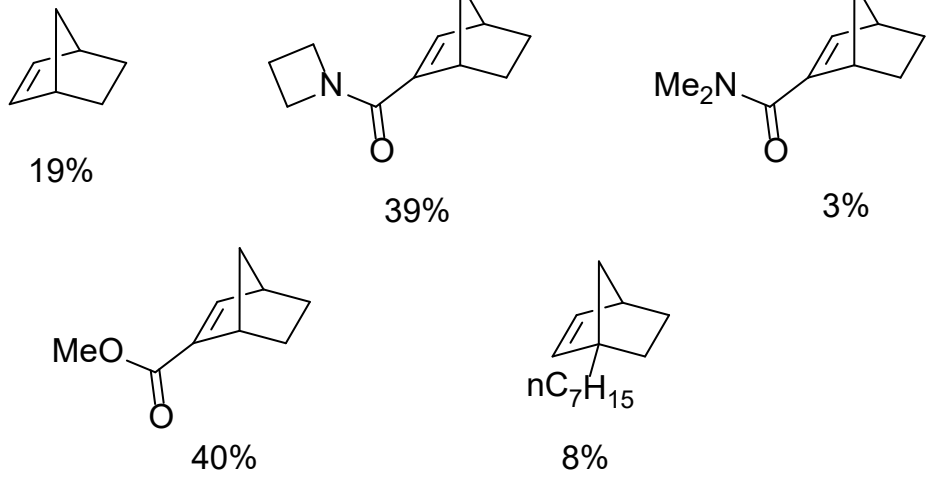


Nat. Chem. **2019**, 11, 1106–1112.

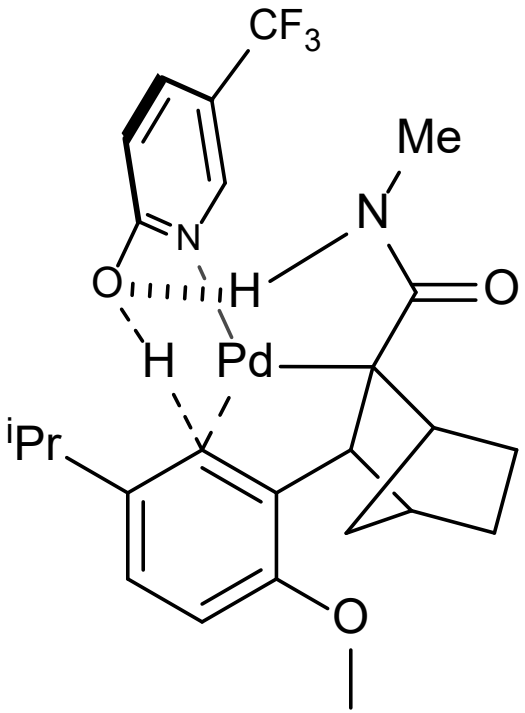
Application to Sterically Challenging Arene Systems

Dong, 2020: Carry-over to congested aryl rings





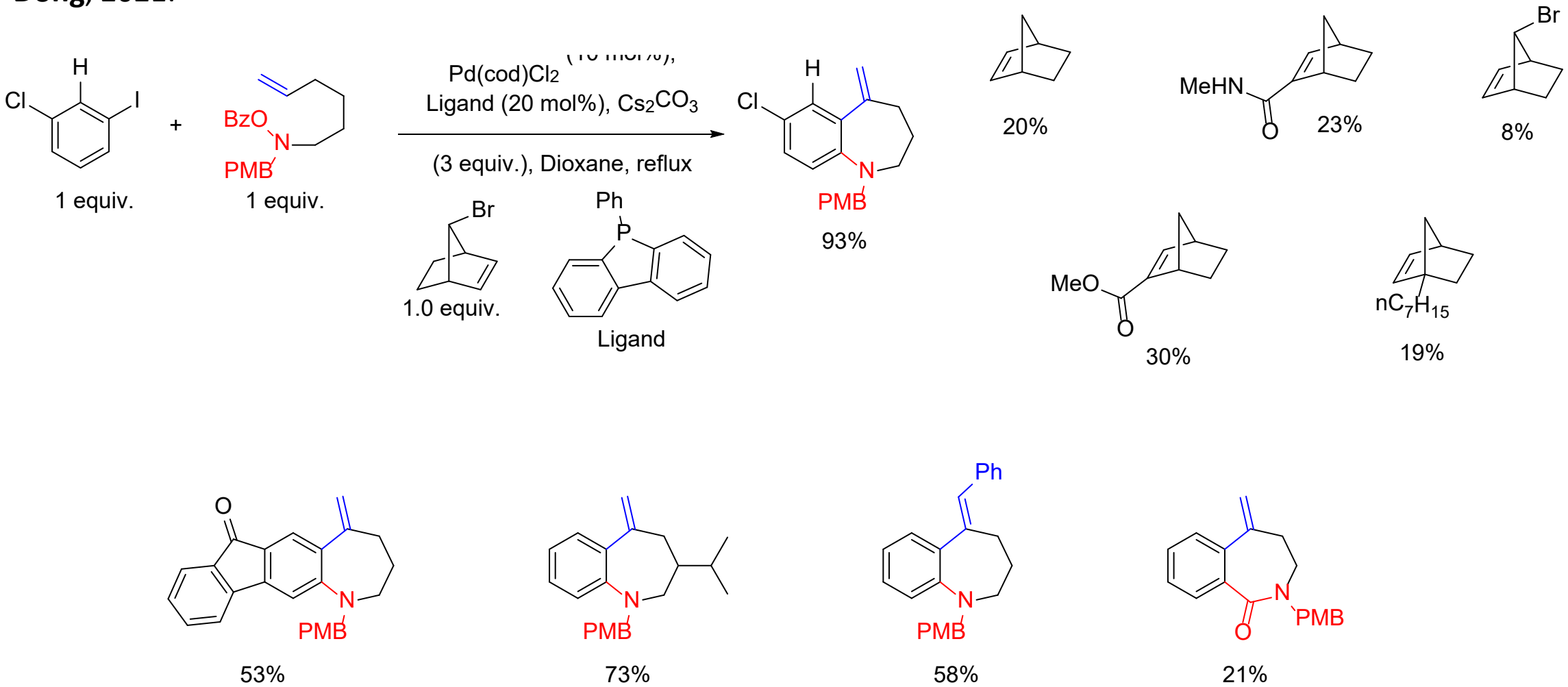
Proposed H-bonding:



J. Am. Chem. Soc. **2020**, 142, 3050–3059.

Future Directions: 7-Substituted NBEs

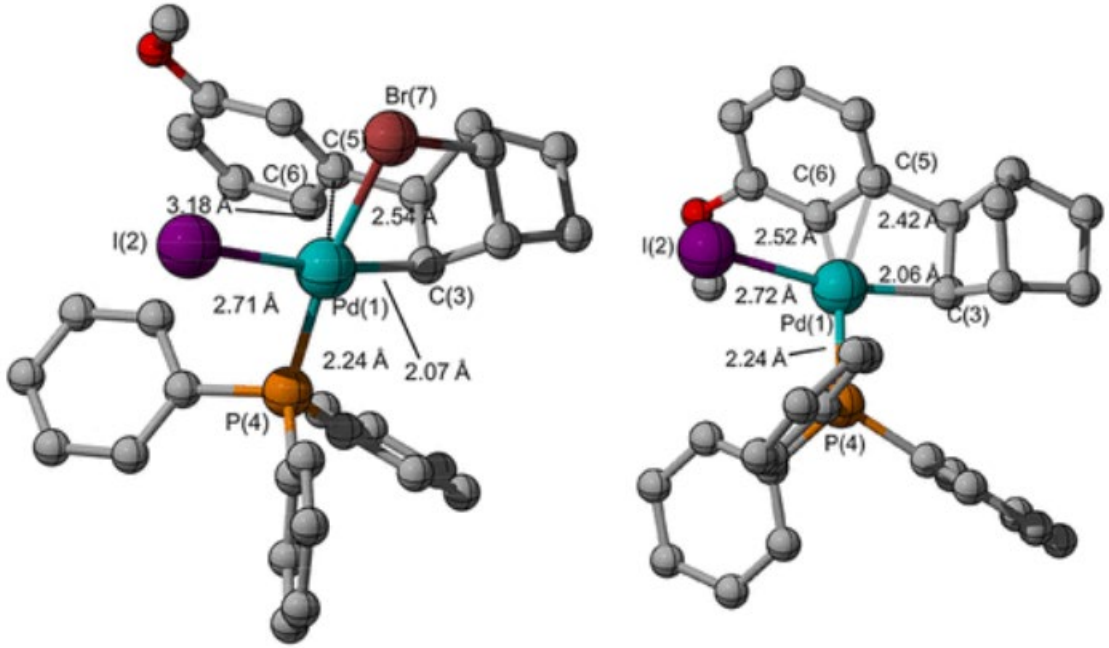
Dong, 2021:



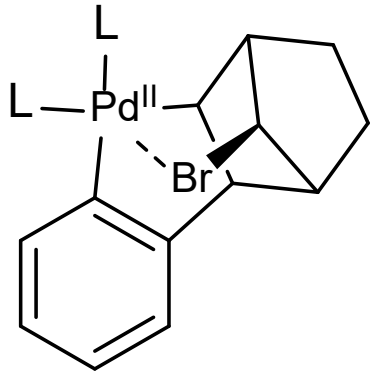
J. Am. Chem. Soc. **2021**, 143, 26, 9991–10004

Future Directions: 7-Substituted NBEs

Dong, 2021: Versatile role of 7-bromo group:



Suppress cyclobutane formation



Calculated 5.1 kcal/mol difference in $\Delta G^{\ddagger}$ between 7-bromo and 7-H NBEs.

J. Am. Chem. Soc. **2021**, 143, 26, 9991–10004

Questions?

Additional Readings

"Structurally Modified Norbornenes: A Key Factor to Modulate Reaction Selectivity in the Palladium/Norbornene Cooperative Catalysis"

J. Am. Chem. Soc. **2020**, 142, 42, 17859–17875

"Palladium/Norbornene Cooperative Catalysis"

Chem. Rev. **2019**, 119, 12, 7478–7528

"Synthesis in the Key of Catellani: Norbornene-Mediated ortho C–H Functionalization" (book chapter)

Martins, A., Mariampillai, B., Lautens, M. (**2009**). Synthesis in the Key of Catellani: Norbornene-Mediated ortho C–H Functionalization. In: Yu, JQ., Shi, Z. (eds) C-H Activation. Topics in Current Chemistry, vol 292.

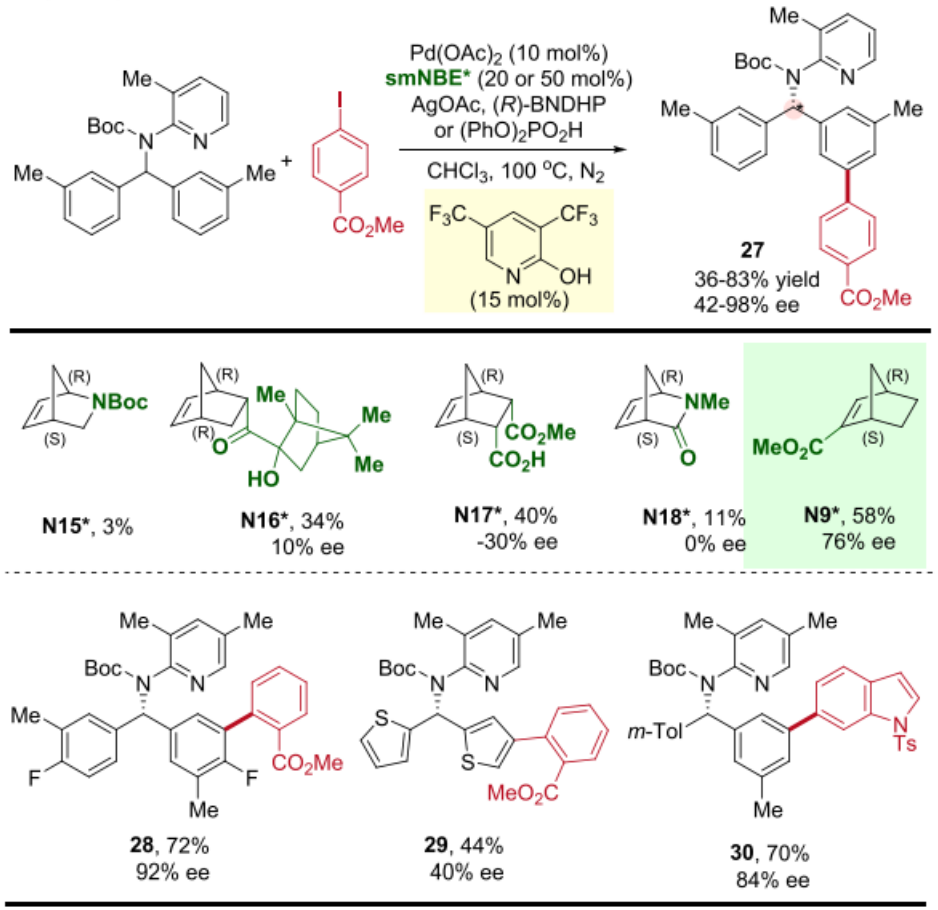
"Pd/Norbornene: A Winning Combination for Selective Aromatic Functionalization via C–H Bond Activation"

Acc. Chem. Res. **2016**, 49, 7, 1389–1400

Backup Slide

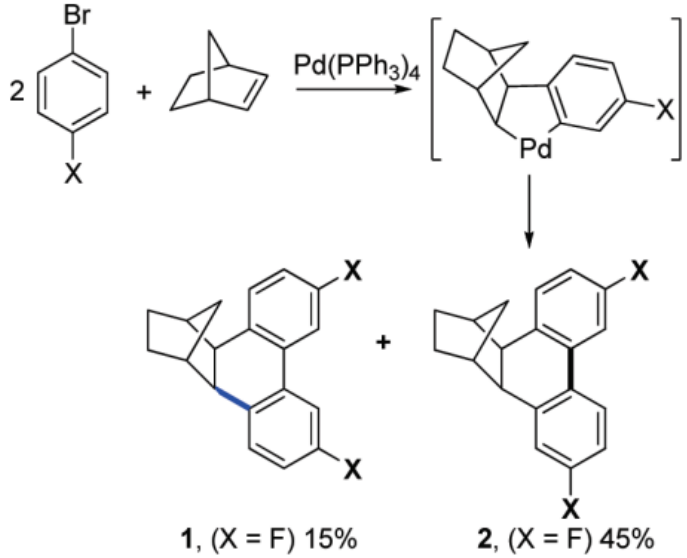
Scheme 7. Enantioselective *Meta* C–H Arylation and Alkylation Enabled by a Chiral smNBE

a. diarylmethylamine substrates



Backup Slide

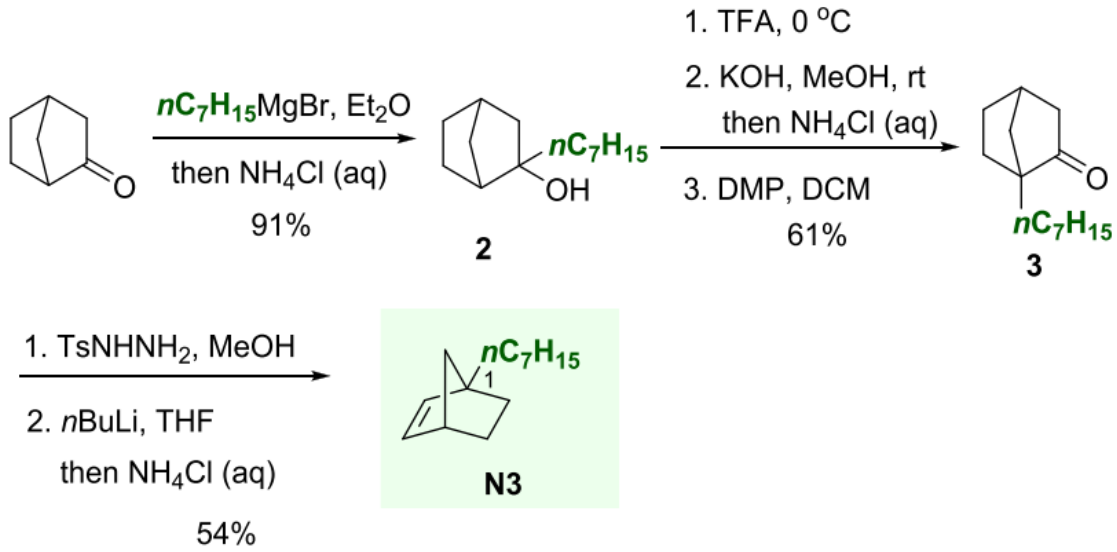
Scheme 2. Unselective Aryl–Alkyl (1, *blue*) and Aryl–Aryl (2, *black*) and Coupling by Catalytic Reaction of a 4-Substituted Bromobenzene Derivative and Norbornene



the same reaction, however, the outcome has been quite different. A mixture of two products is obtained, which derive from aryl attack on the norbornyl or the aryl sites of the metallacycle followed by ring closure. In the presence of a para substituent, two positional isomers of hexahydromethanotriphenylene are formed. For example, 4-bromofluorobenzene gives a mixture of 45 and 15% of the two products (Scheme 2, X = F). Compound **1** comes from initial $C(sp^2)-C(sp^3)$ bond formation while compound **2** results from an initial $C(sp^2)-C(sp^2)$ coupling.[12]

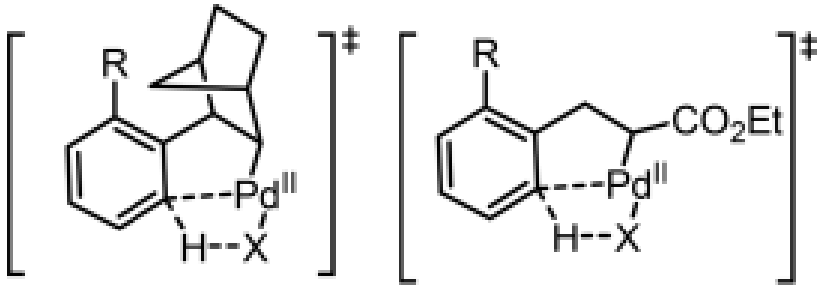
Backup Slide

d. preparation of N3



Backup Slide

Scheme 17. Activation Barrier of NBE or Acrylate Directed C–H Metalation



21.1 kcal/mol 34.5 kcal/mol

Backup Slide