New frontiers in catalytic C-H activation

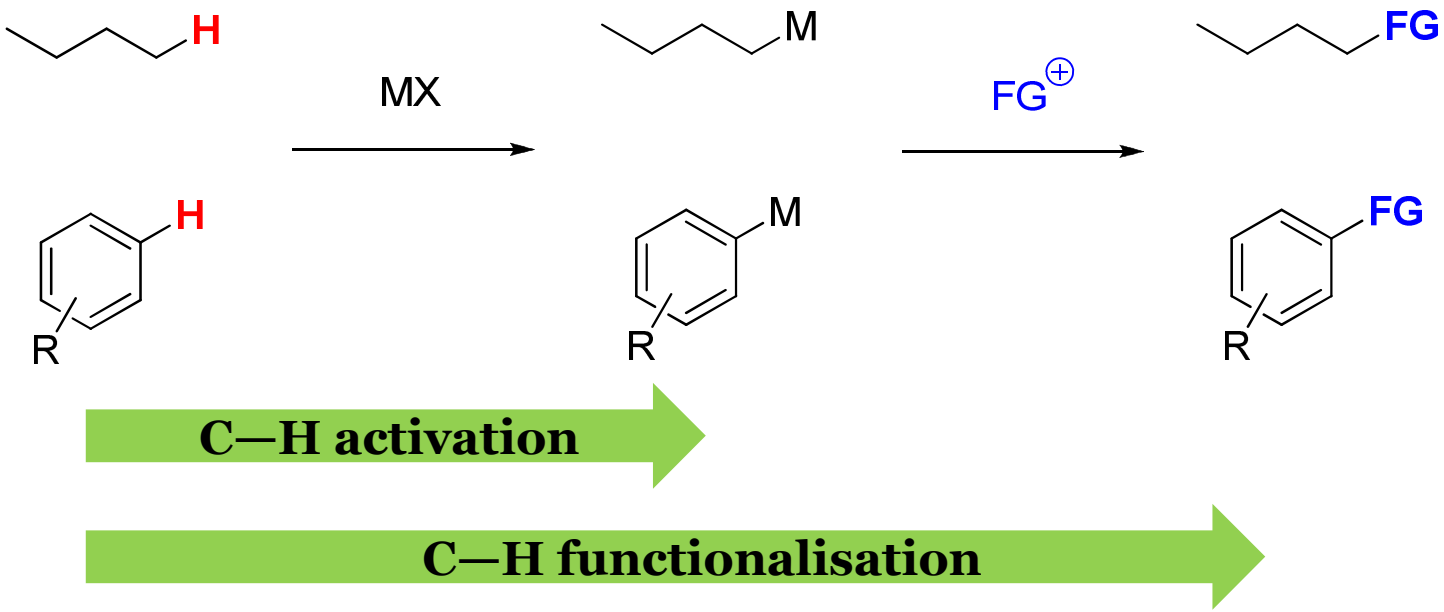
Dr. Igor Larrosa

School of biological and chemical sciences

Queen Mary
University of London

SCI (London) – November 2010

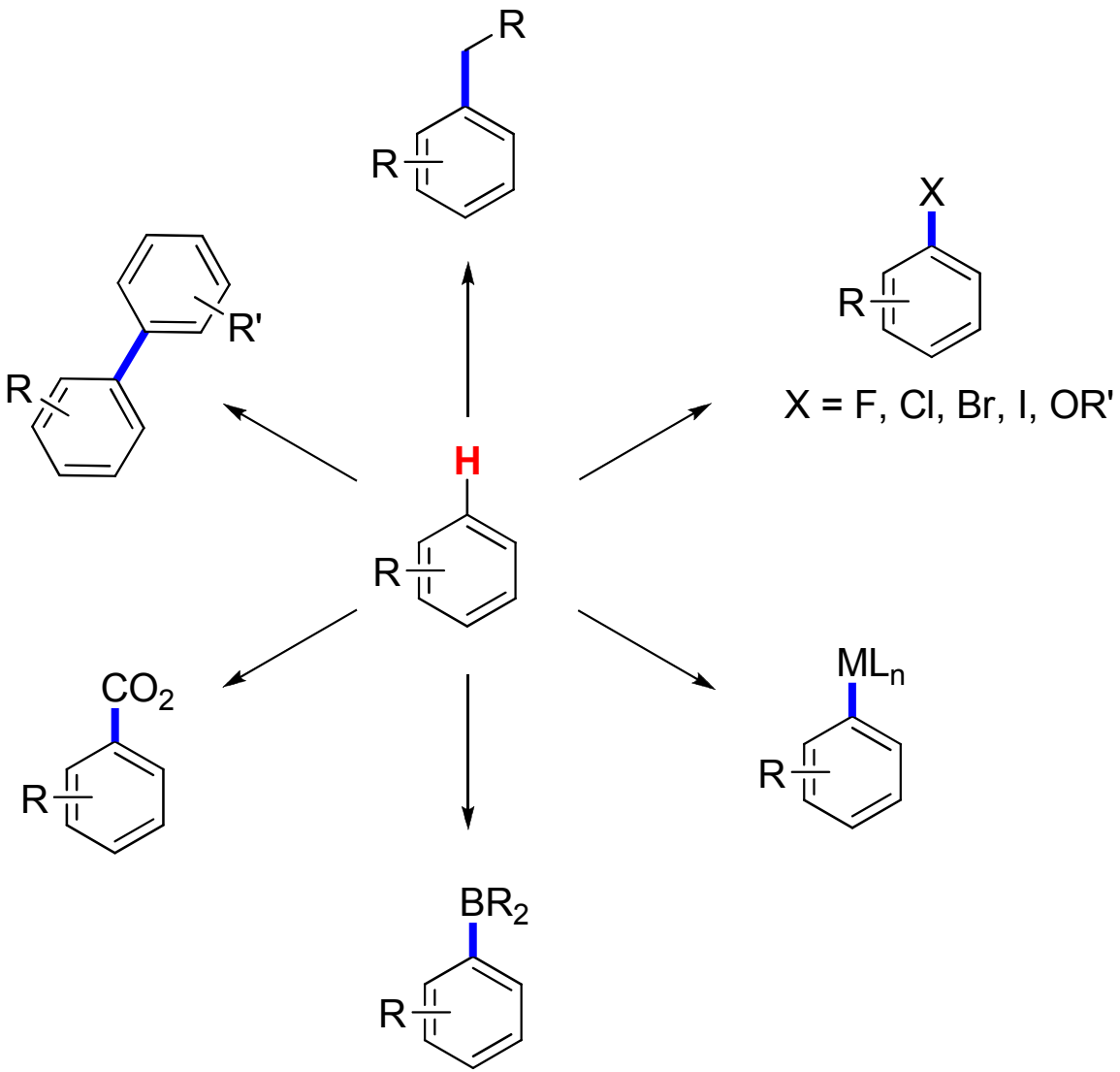
C—H activation: definitions



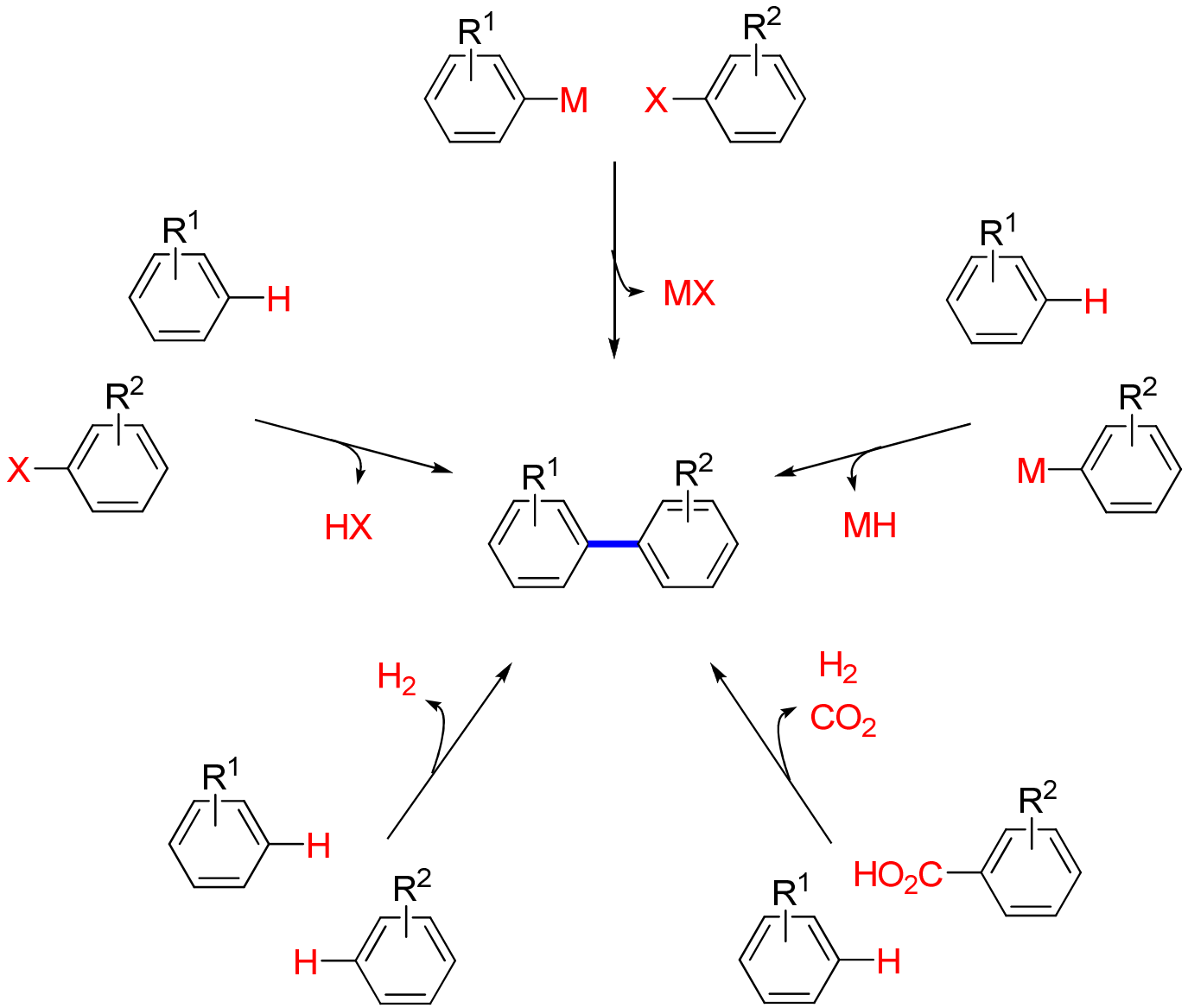
C—H activation results in the formation of a C—M bond

C—H functionalisation represents the overall process where H is replaced with a functional group (FG)

C—H activation: scope

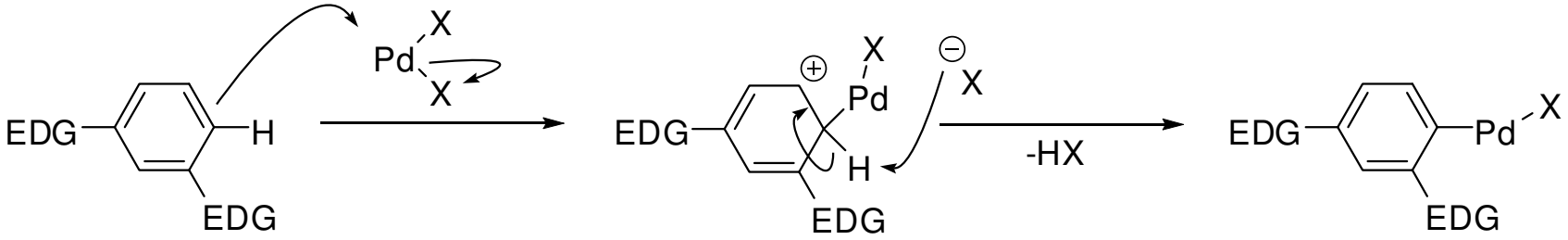


Cross-coupling strategies

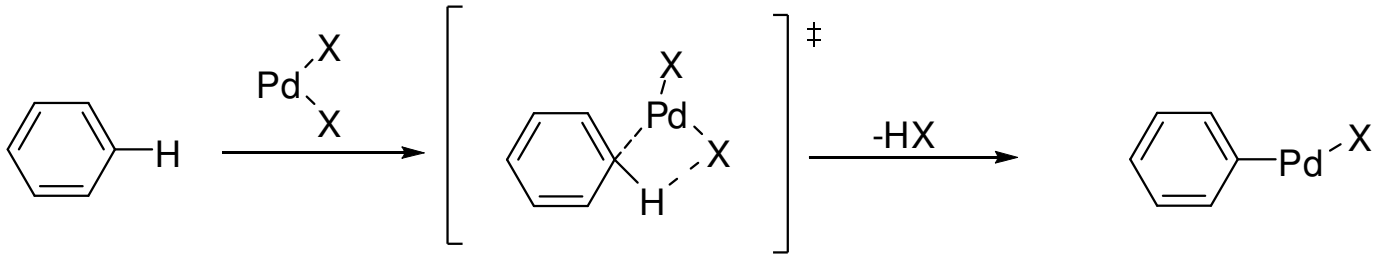


Mechanisms for arene C—H activation with Pd catalysts

Electrophilic aromatic substitution:

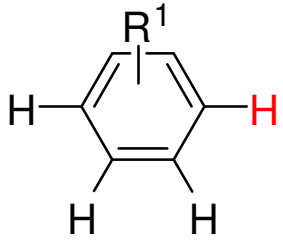


Concerted metalation/proton abstraction:



C—H arylation: challenges

C—H bonds are ubiquitous and diverse… How to activate the desired one?



Regioselectivity

High bond strength of an aryl C—H bond

(about 110 kcal/mol, versus for example 51 kcal/mol for C—I)

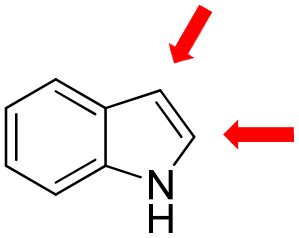
Reactivity

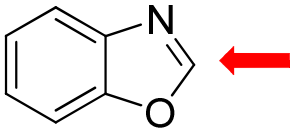
How to protect sensitive functional groups?

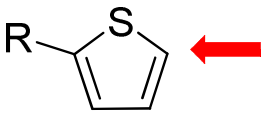
Chemoselectivity

Control of regioselectivity

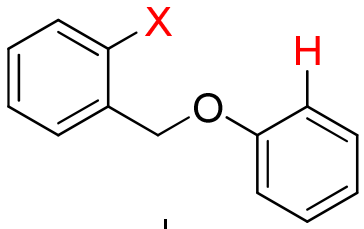
Intrinsic

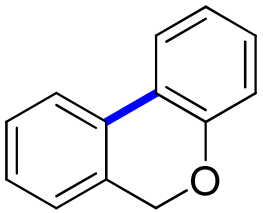




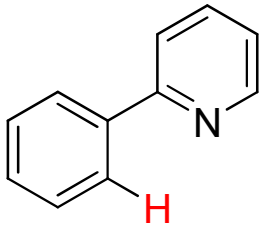


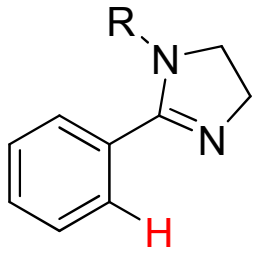
Intramolecular



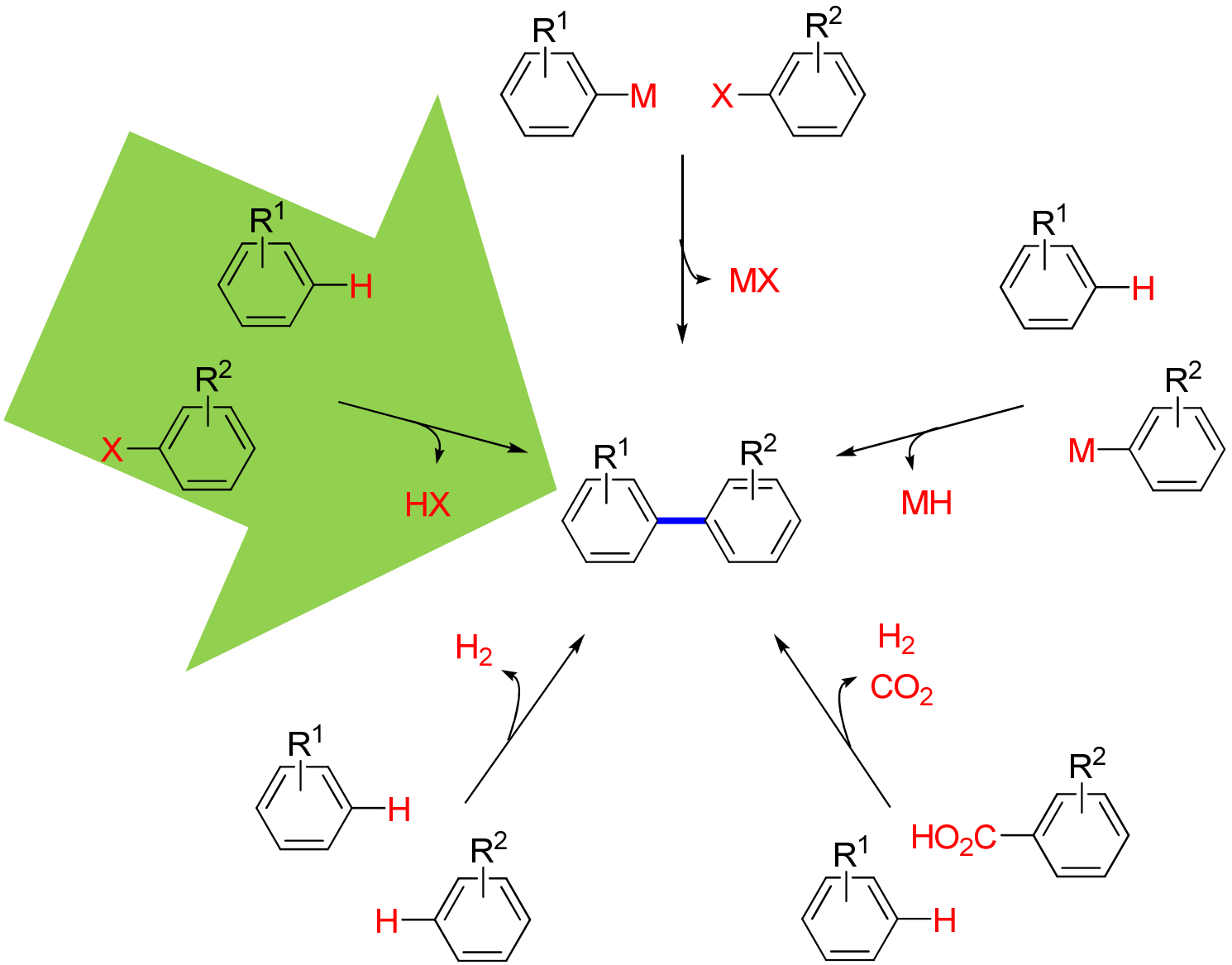


Directing groups



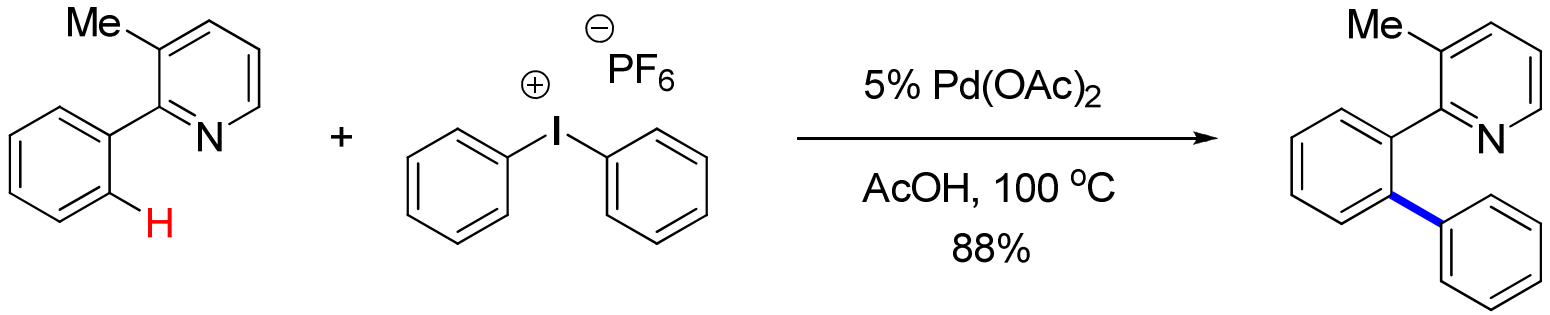


Cross-coupling strategies



Use of directing groups 1: pyridine

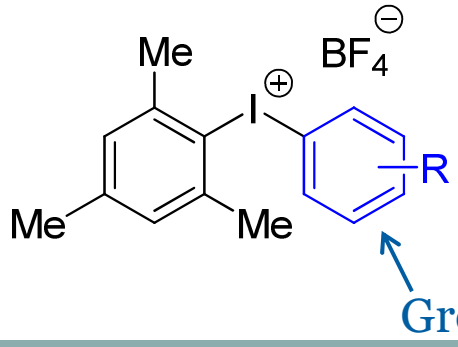
C—H + C—X



Me substitutent required to prevent bis-arylation

Requires special arylating agents

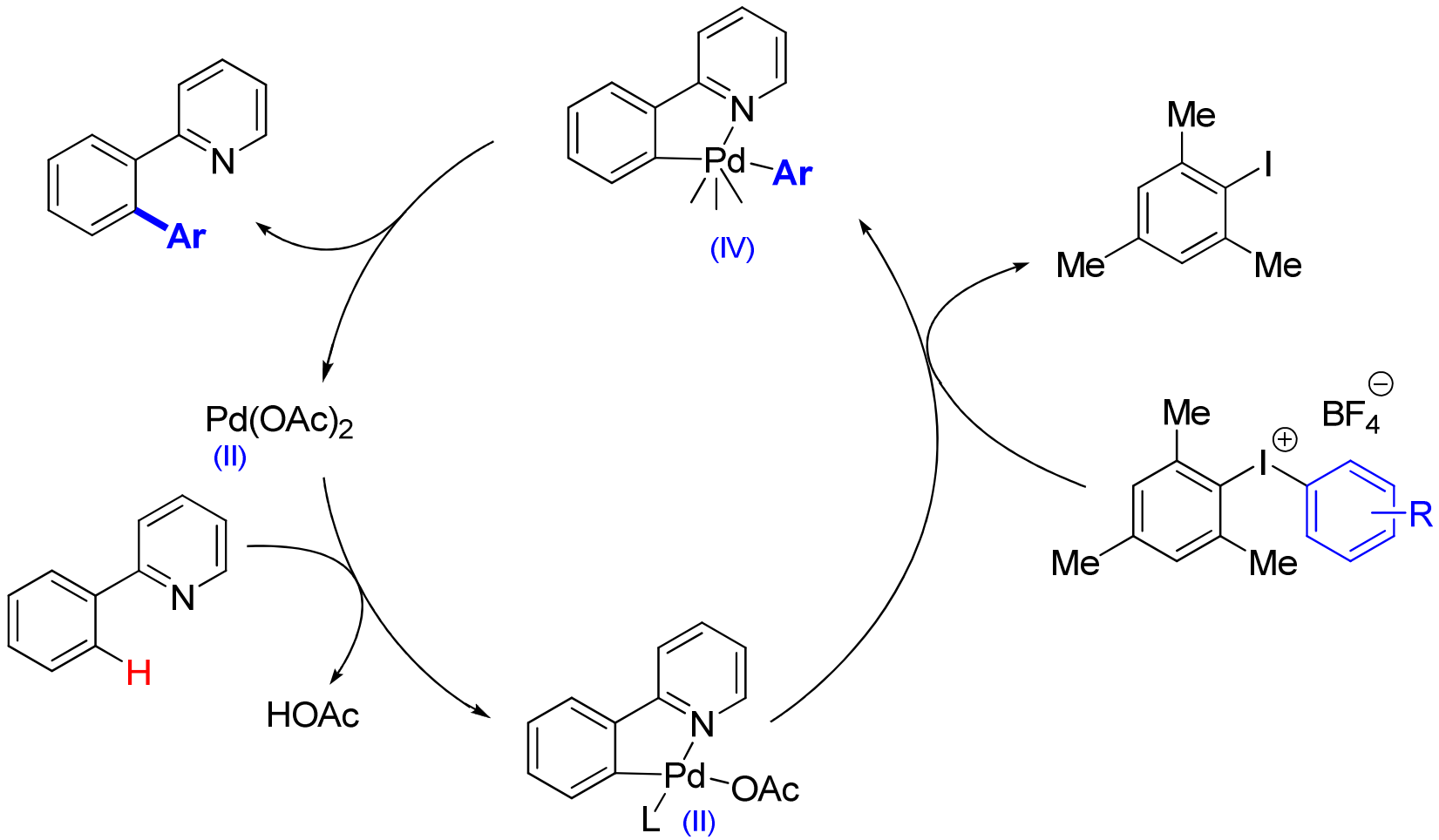
Only one arene group is transferred: the use of mesitylene as the second arene allows selective transfers



R = 4-F, 4-Cl, 4-Me, 4-OMe

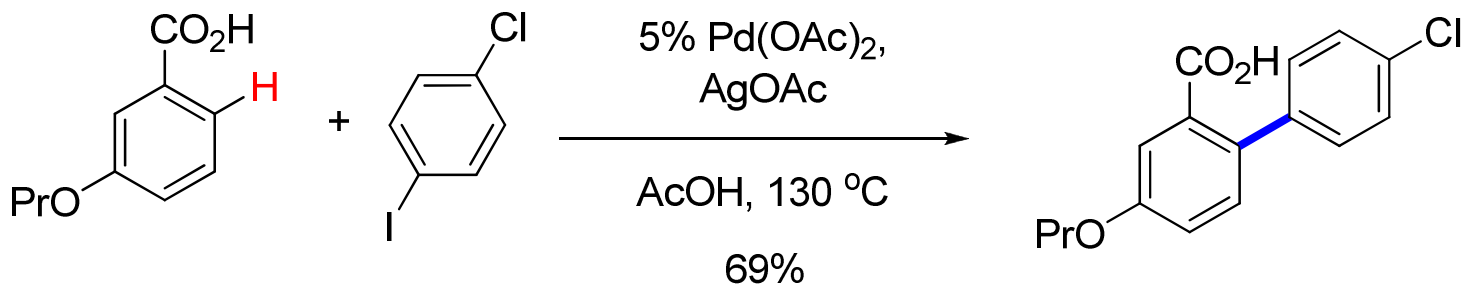
Sanford, *JACS*, **2005**, 7330; *JACS*, **2009**, 11234

Proposed mechanism: a $Pd^{II/IV}$ catalytic cycle



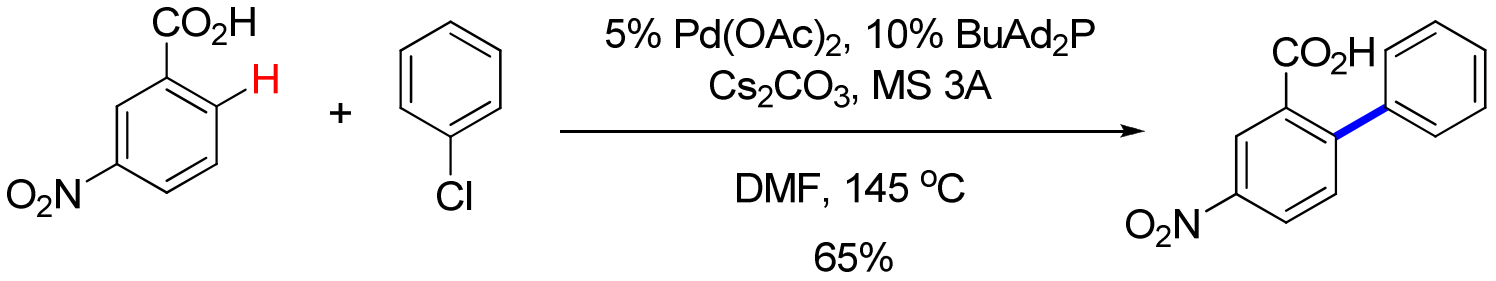
More recently, a bimetallic intermediate Pd^{IV}/Pd^{II} or Pd^{III}/Pd^{III} has been proposed

Use of directing groups 2: carboxylic acids



Operationally simple

A $Pd^{II/IV}$ type mechanism is proposed

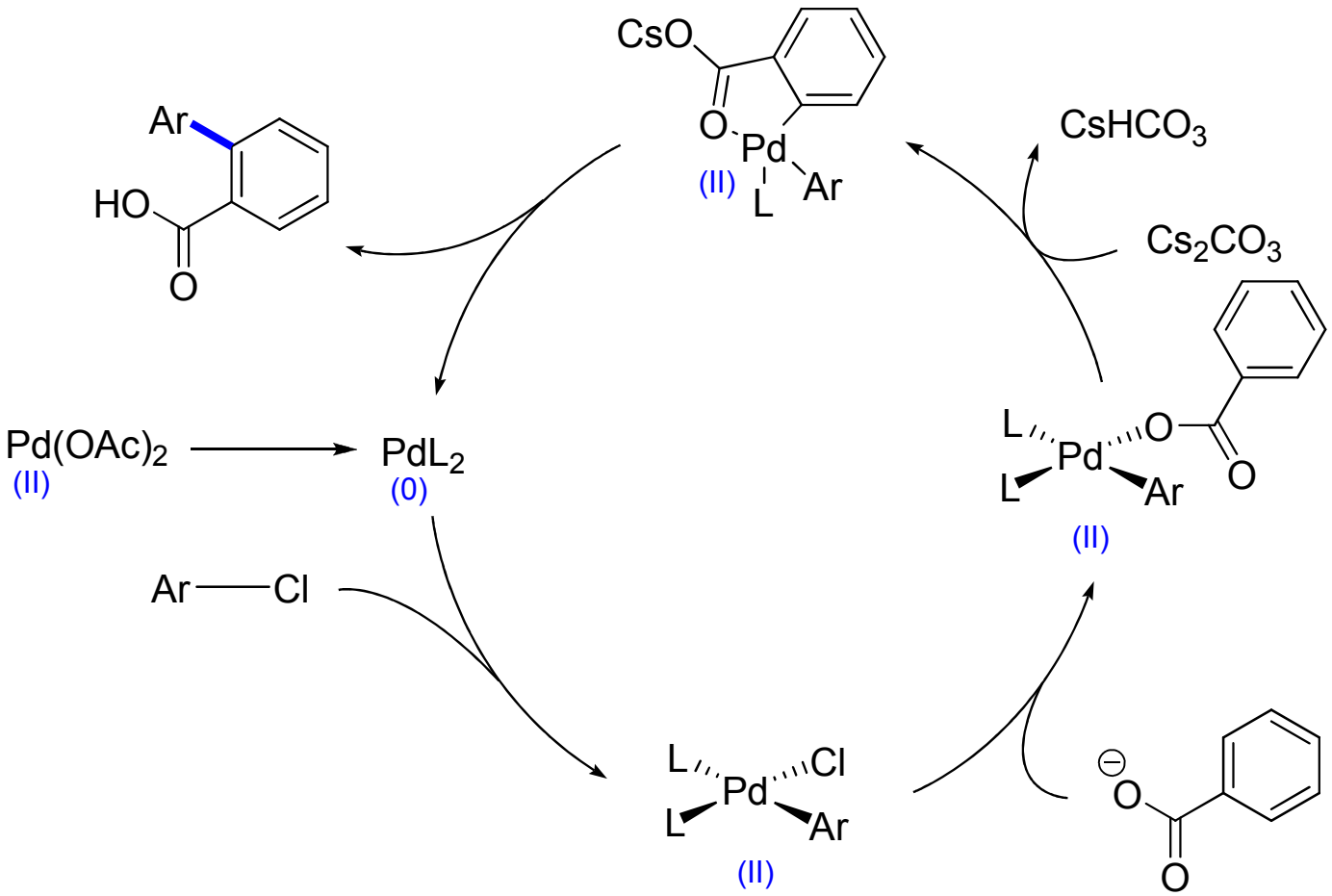


Requires the use of glovebox

A $Pd^{O/II}$ type mechanism also proposed

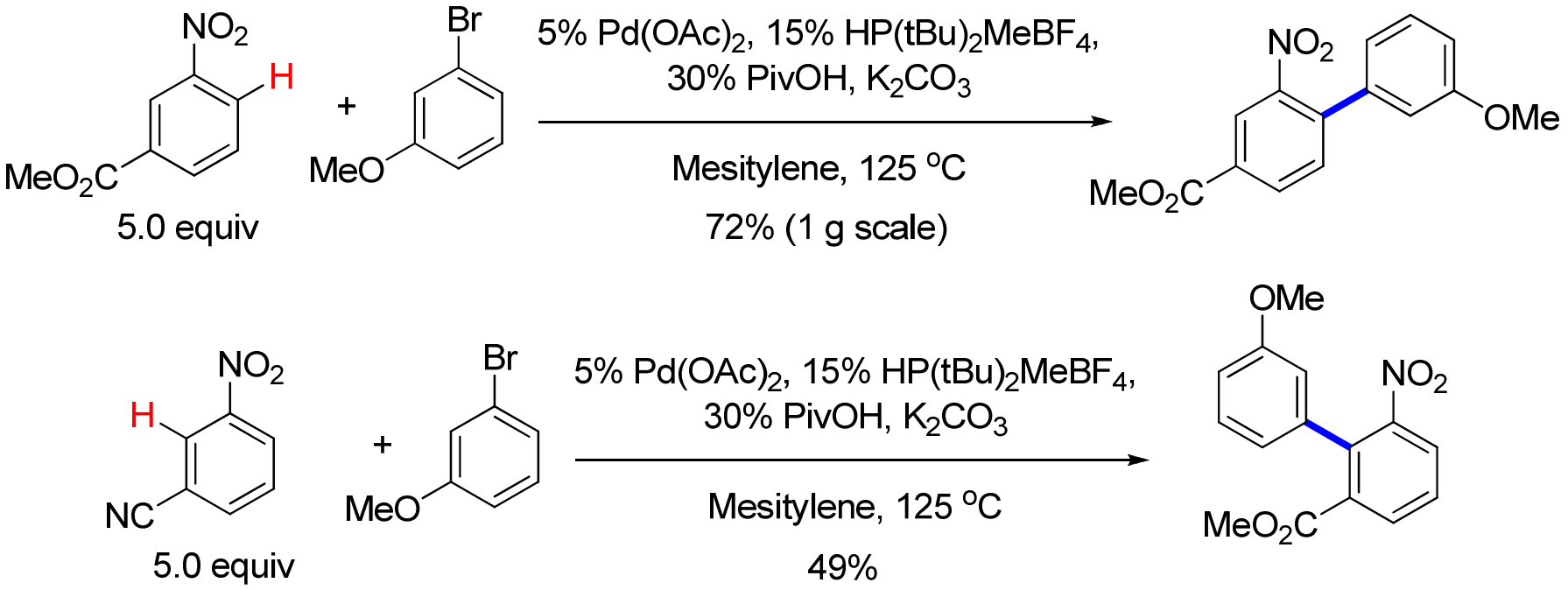
Daugulis, *JACS*, **2007**, 9879

Proposed mechanism: a $Pd^{0/II}$ catalytic cycle



Use of directing groups 3: nitro group

C—H + C—X



Taking advantage of the strong inductive effect of nitro groups

Regioselectivity dictated by nitro group, sterics and electronics

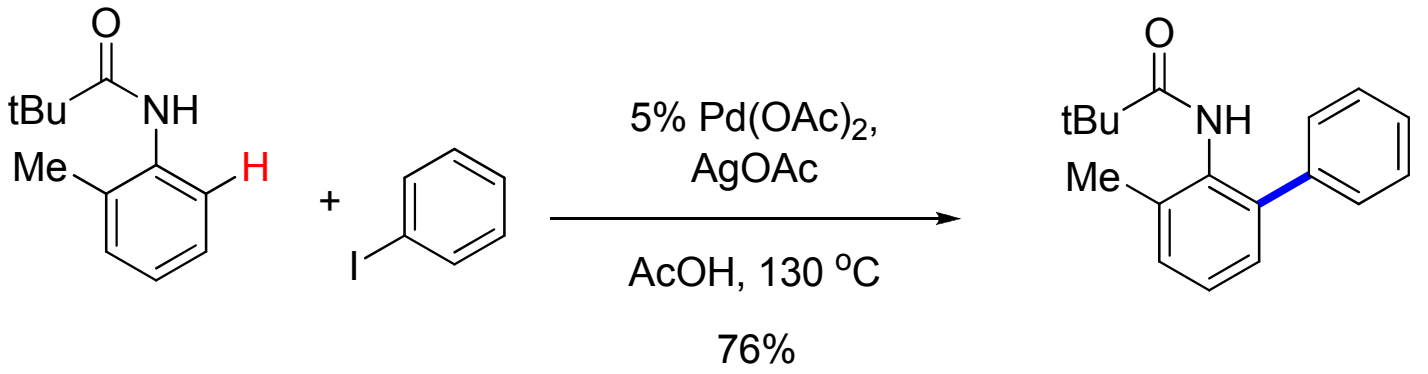
Good selectivity mono- versus bis-arylation

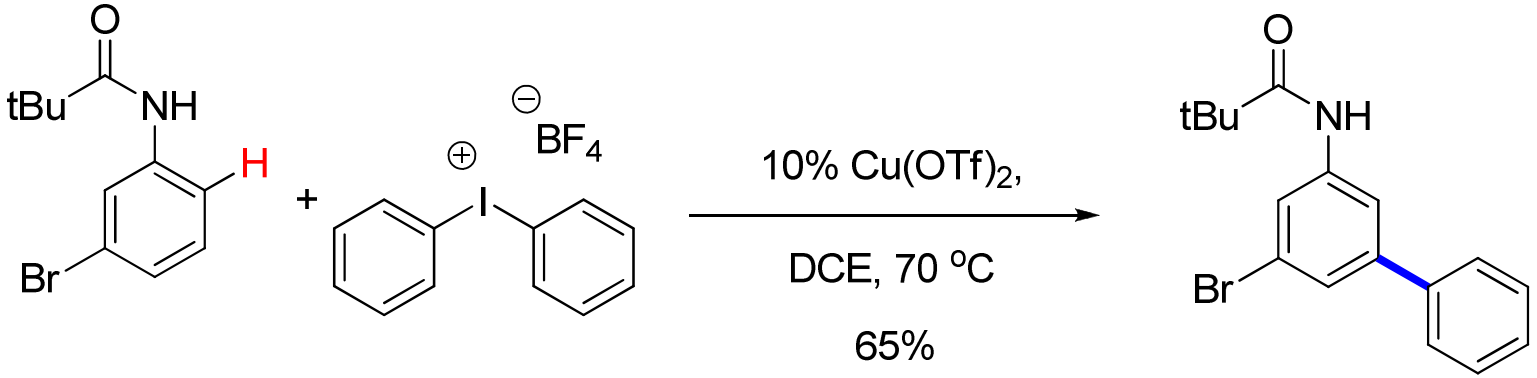
Vital role of PivOH (*vide infra*)

Fagnou, *OrgLett*, **2008**, 4533

Use of directing groups 4: anilides

C—H + C—X

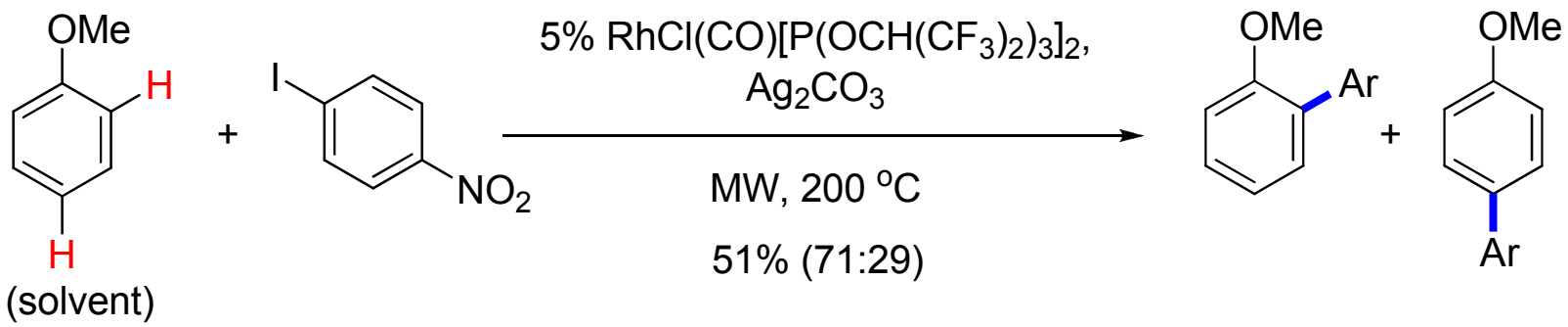




Meta selectivity is observed with this Cu-mediated system

Daugulis, *ACIE*, **2005**, 4046; Gaunt, *Science*, **2009**, 323, 1593

Use of directing groups 5: methoxy

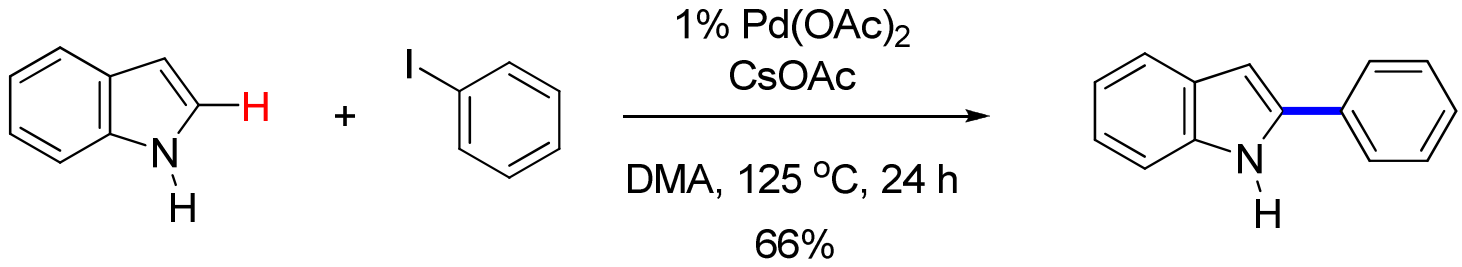


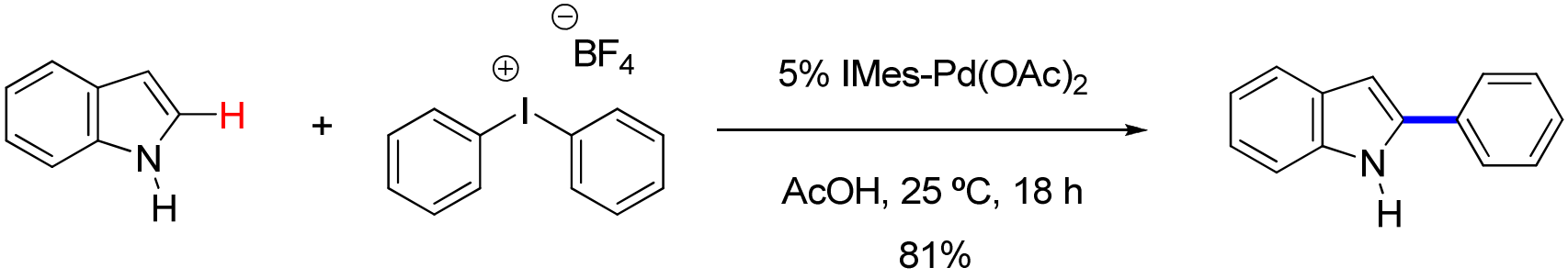
ortho – para regioselectivity is consistent with an electrophilic aromatic substitution-type mechanism

Itami, *JACS*, **2006**, 11748

Heteroaromatics 1: indole

C—H + C—X





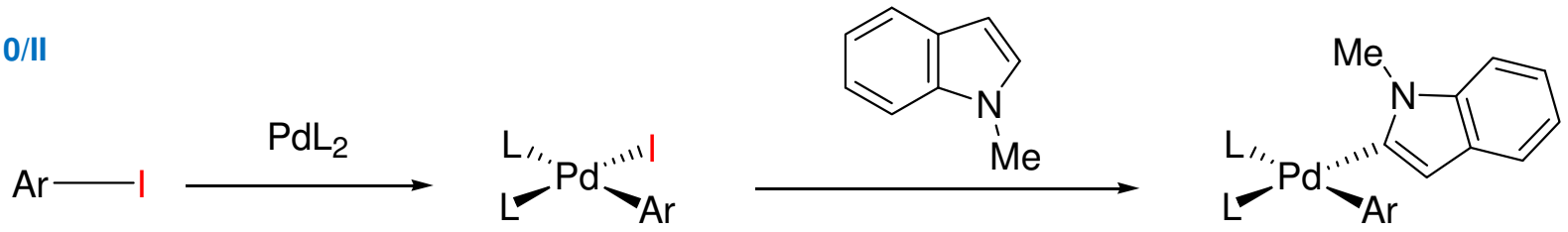
Remarkable increase in reactivity when using I^{III} species

Sames, *JACS*, **2005**, 8050; Sanford, *JACS*, **2006**, 4972

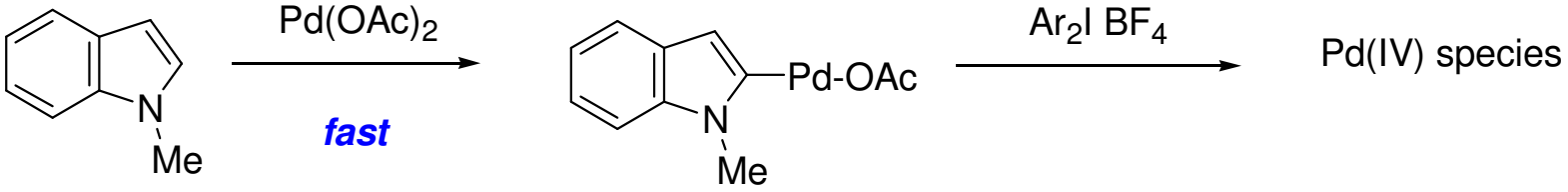
Heteroaromatics 1: indole

C—H + C—X

$Pd^{0/II}$

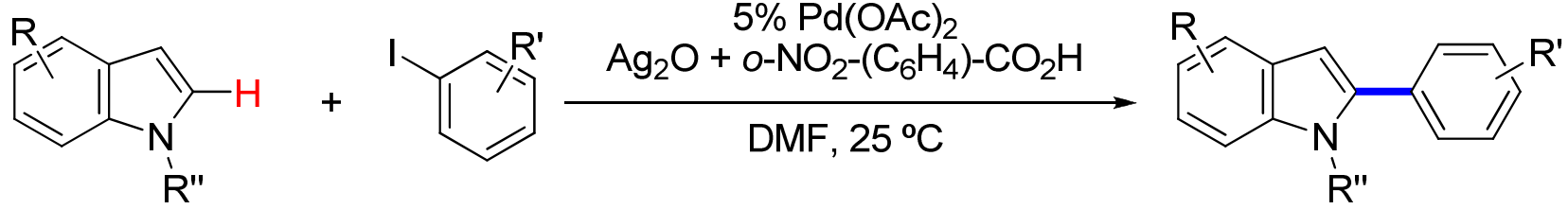


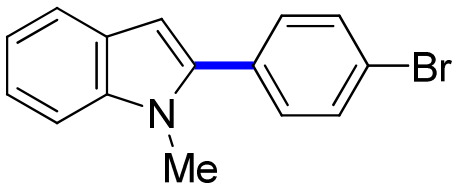
$Pd^{II/IV}$



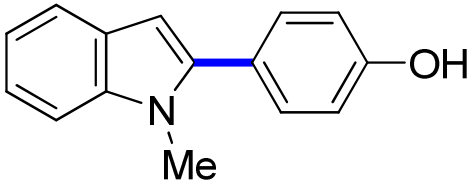
Heteroaromatics 1: indole

C—H + C—X

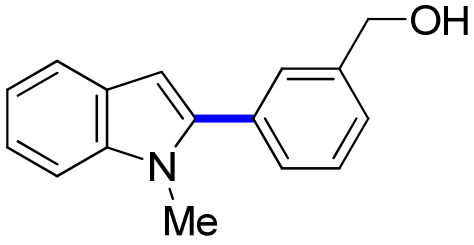




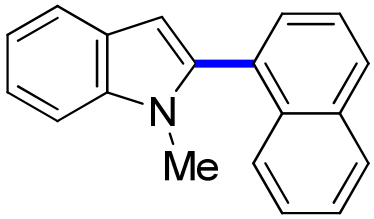
99%



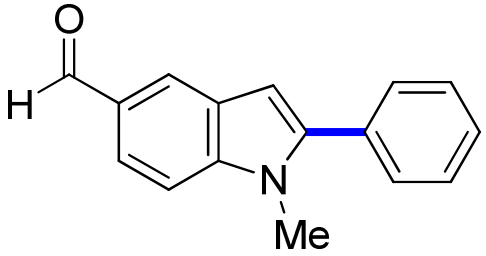
82%



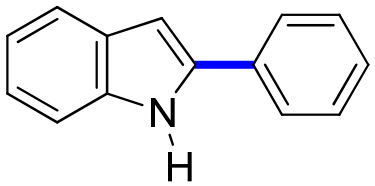
87%



76%



88%

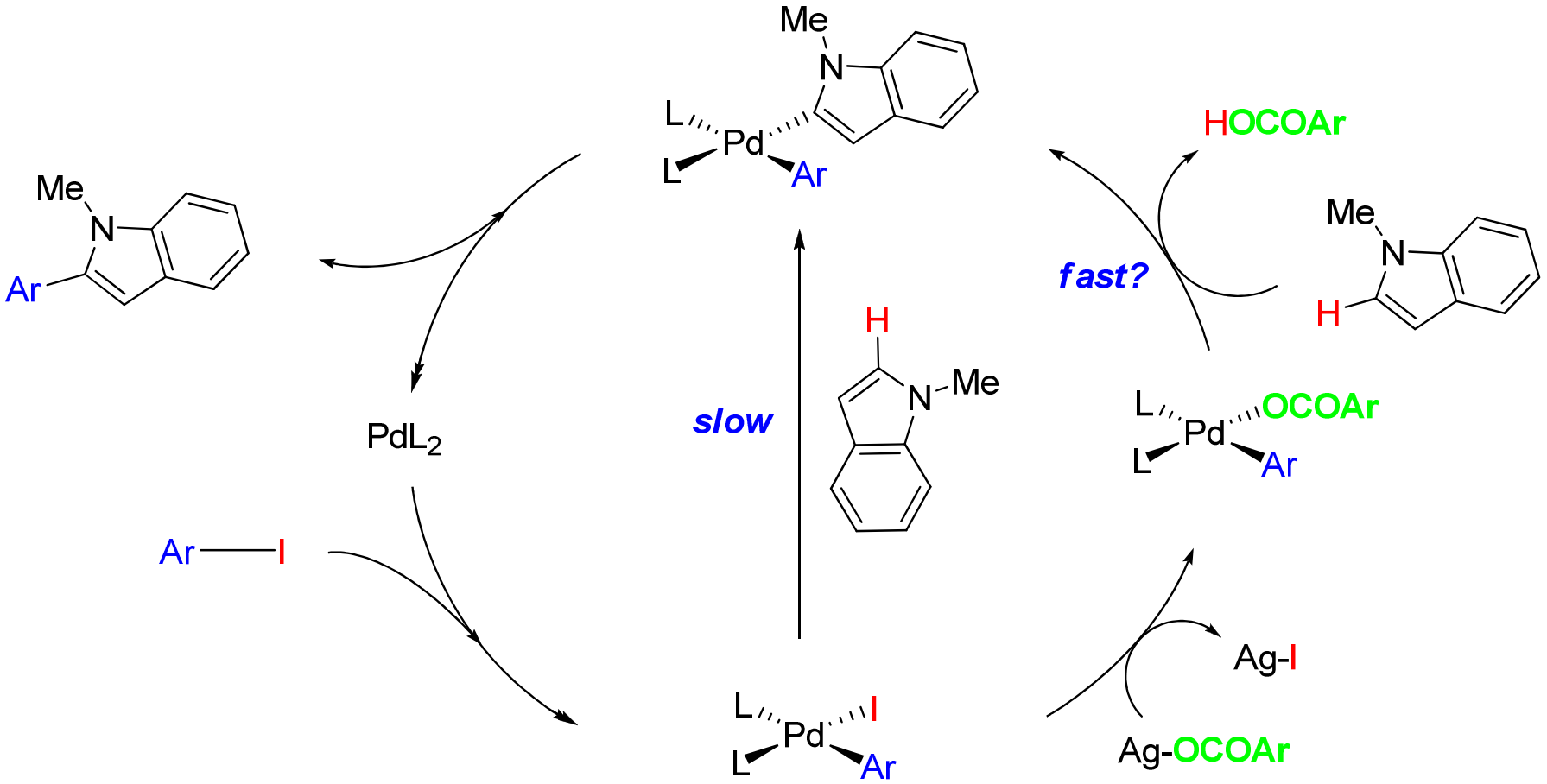


61% (50 ºC)

Larrosa, *JACS*, **2008**, 2926

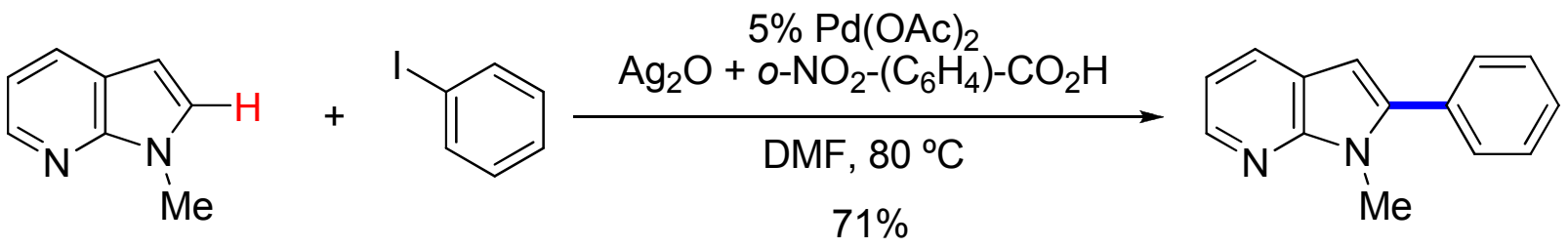
Heteroaromatics 1: indole

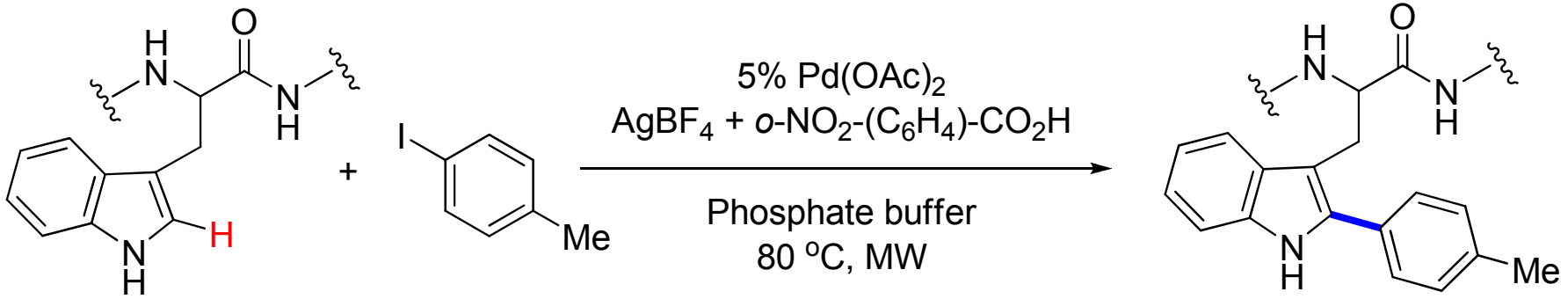
C—H + C—X



Heteroaromatics 1: indole

C—H + C—X



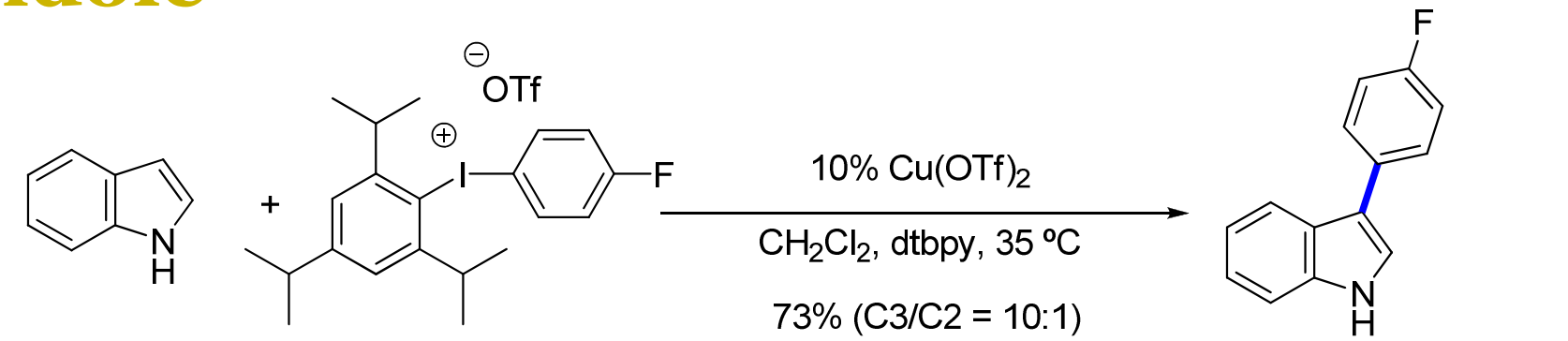


Ac-Lys-Gly-**Trp**-Ala-OH 95%

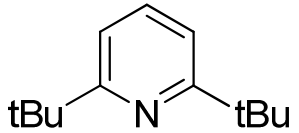
Fagnou, *OrgLett*, **2009**, 1357; Albericio & Lavilla, *Chem. Eur. J.*, **2010**, 1124

Heteroaromatics 1: indole

C—H + C—X

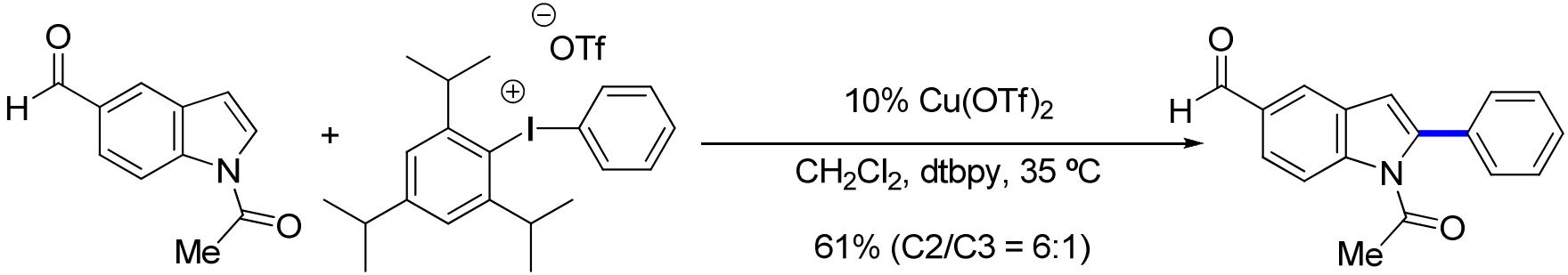


Regioselectivity is controlled via the substituent at N



dtbpy

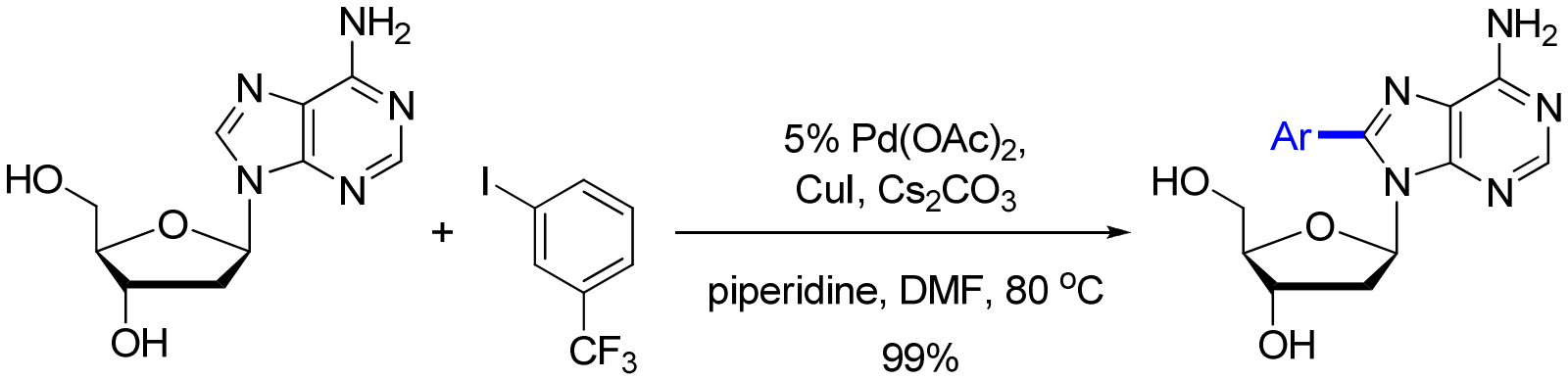
A $Cu^{I/III}$ catalytic cycle is proposed



Gaunt, *JACS*, **2008**, 8172

Heteroaromatics 2: 2'-deoxiadenosin

C—H + C—X



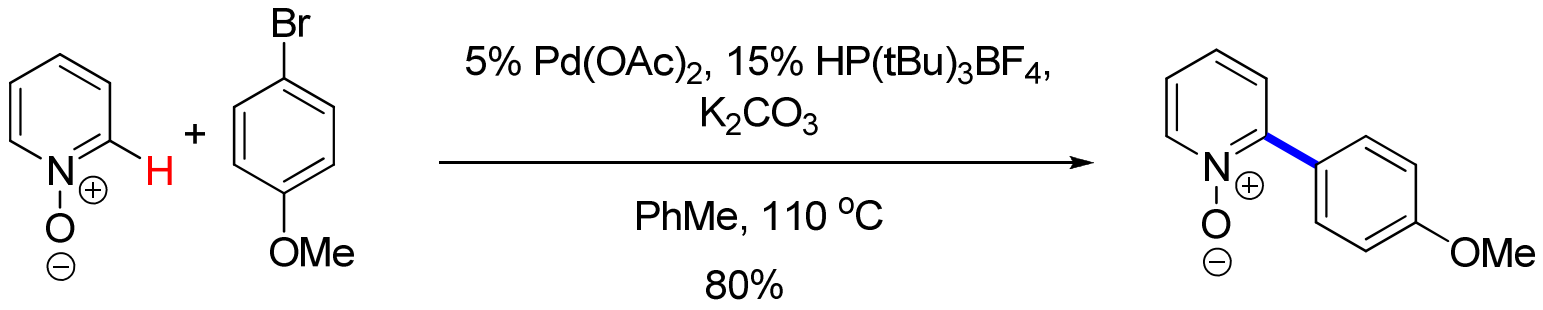
It is proposed that CuI/Cs_2CO_3 mediates the C—H activation step, which subsequently transmetallates to Pd

Higher temperatures result in deglycosylation

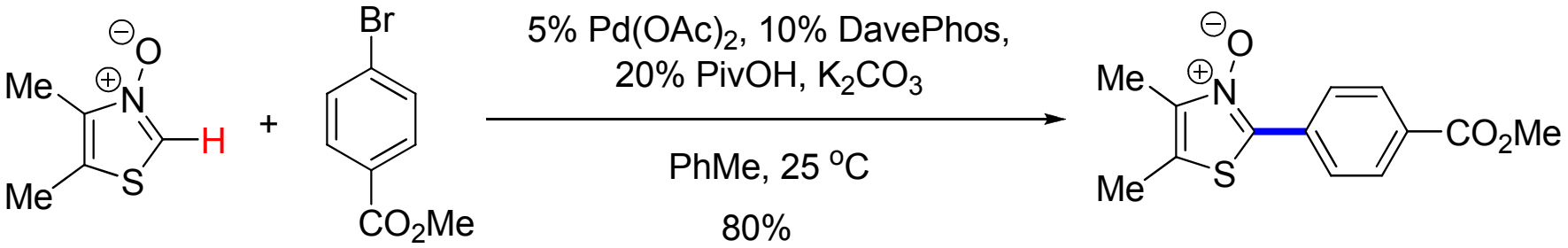
Fairlamb, *JOC*, **2009**, 5810

Heteroaromatics 3: *N*-oxides

C—H + C—X



Pyridines are difficult substrates in traditional cross-couplings

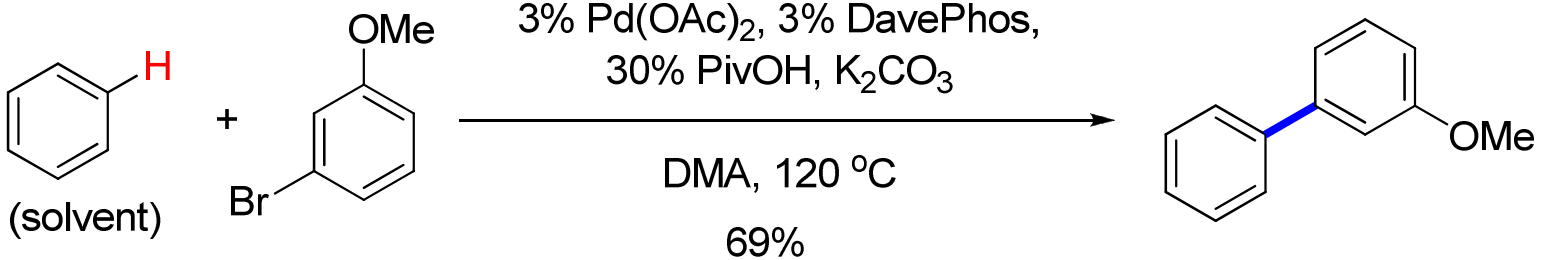


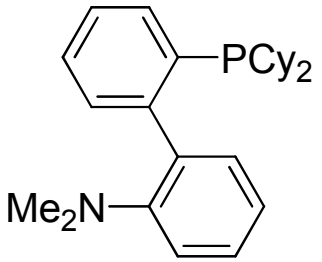
N-Oxides easily cleaved with a reducing agent (H_2, Pd/C or Zn powder)

Fagnou, *JACS*, **2005**, 18020; *JACS*, **2008**, 3276

Use of 'simple' arenes

C—H + C—X





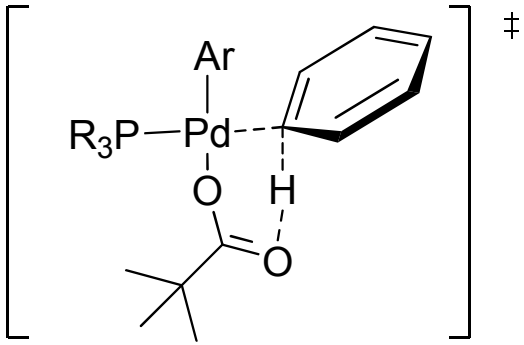
DAVEPhos

KIE of 5.5 indicates C—H cleavage in rds

Anisole is less reactive than benzene (no S_EAr)

A concerted metallation deprotonation mechanism (CMD) is proposed

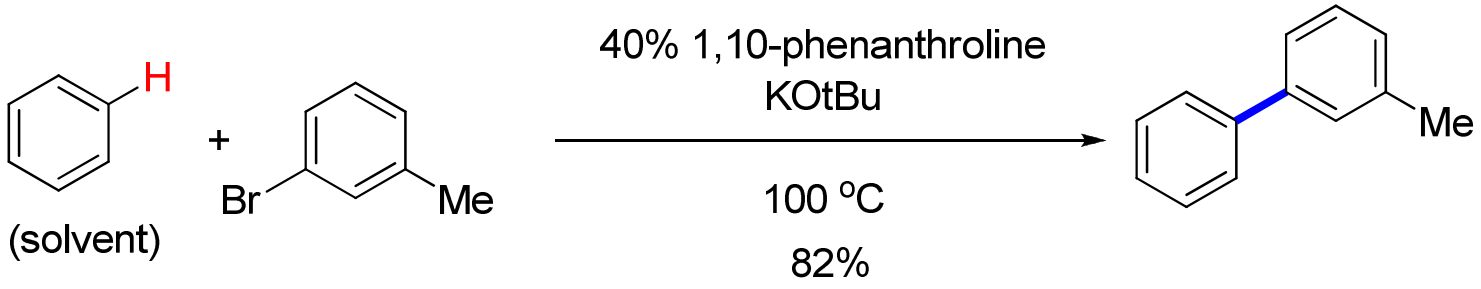
Hindered pivalic acid is proposed to prevent competitive occupation of vacant sites



Fagnou, *JACS*, **2006**, 16496

Transition metal free arylations

C—H + C—X

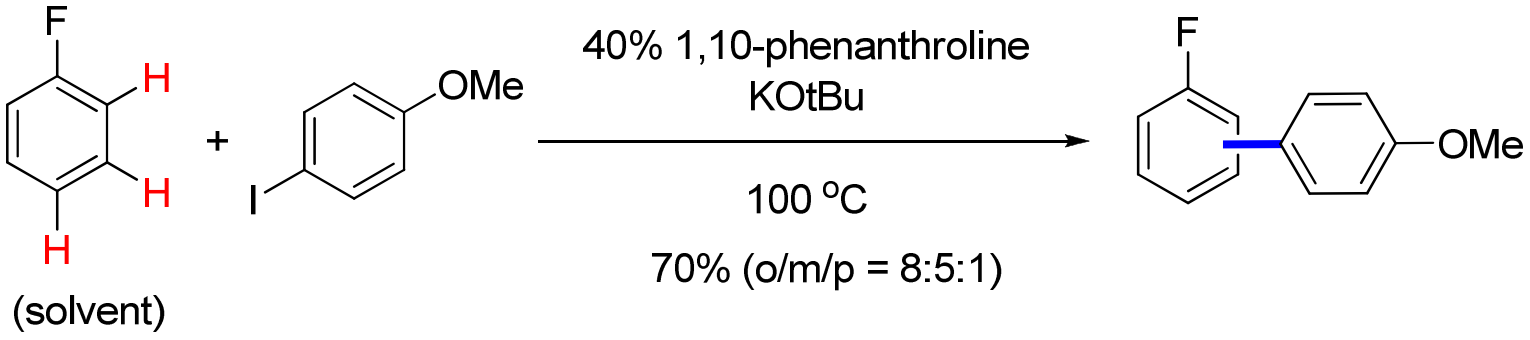


1,10-phenanthroline

Transition metal free C—H arylation

Radical mechanism suspected

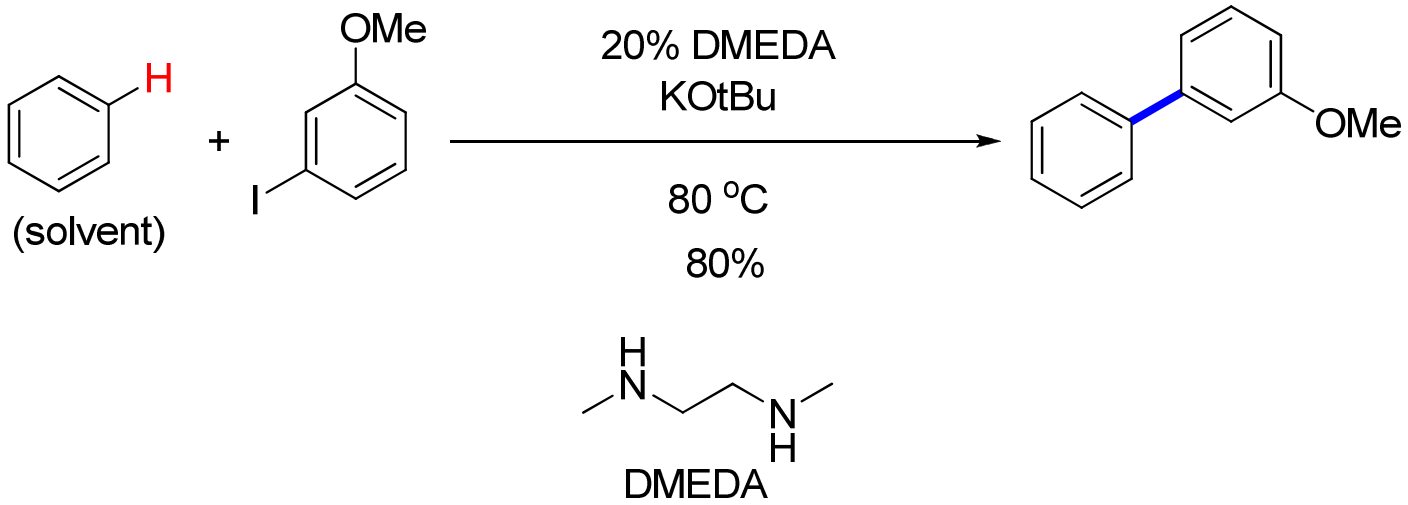
Addition of traces of TM does not affect the reaction



Shi, *Nature Chem.*, **2010**, doi:10.1038/nchem.862

Transition metal free arylations

C—H + C—X



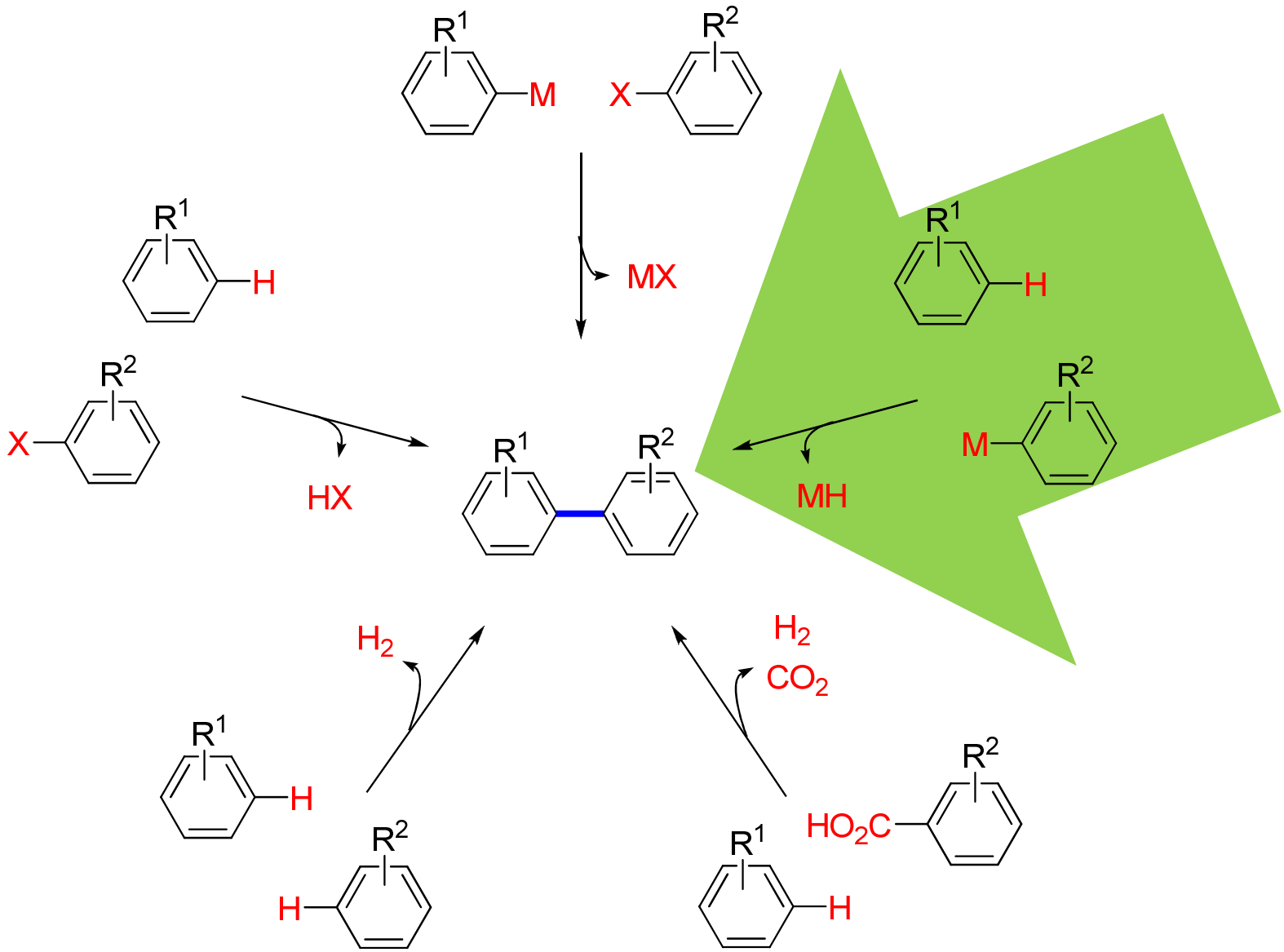
Single regioisomers rule out benzyne-type mechanism

KIE of 1.29 suggests C—H cleavage is not rate determining

Addition of TEMPO switches off the reaction – radical mechanism

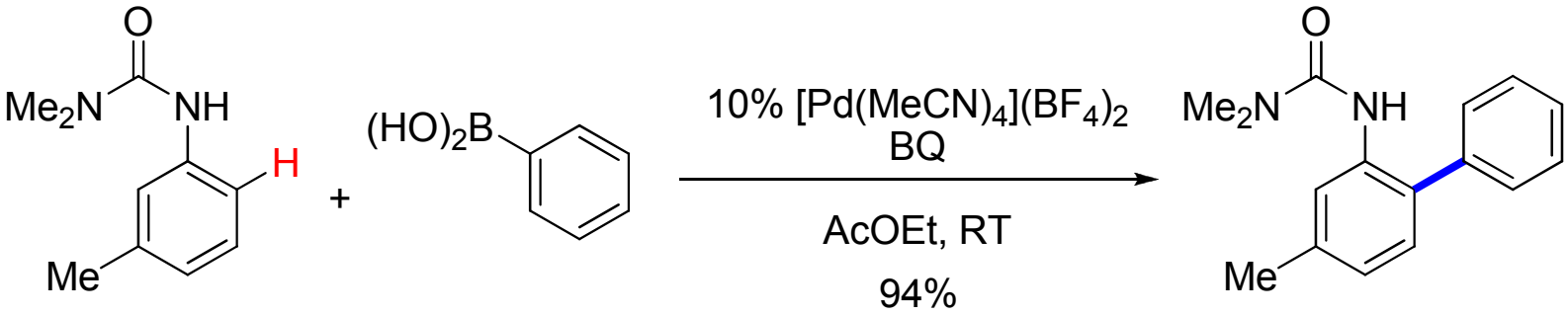
Lei, *JACS*, **2010**, doi:10.1021/ja103050x

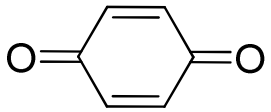
Cross-coupling strategies



Boronic acids

C—H + C—M





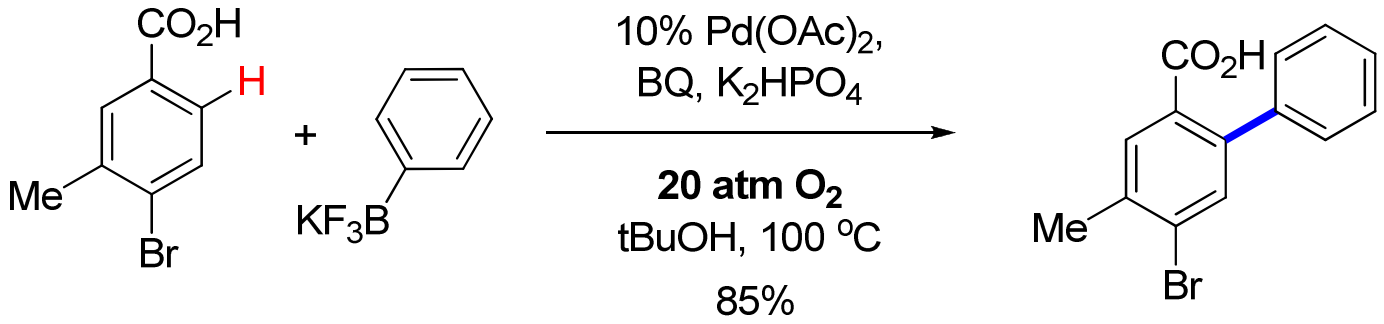
Benzoquinone (BQ)

Highly reactive cationic Pd catalyst used
(with Pd(OAc)2 <1% yield obtained)

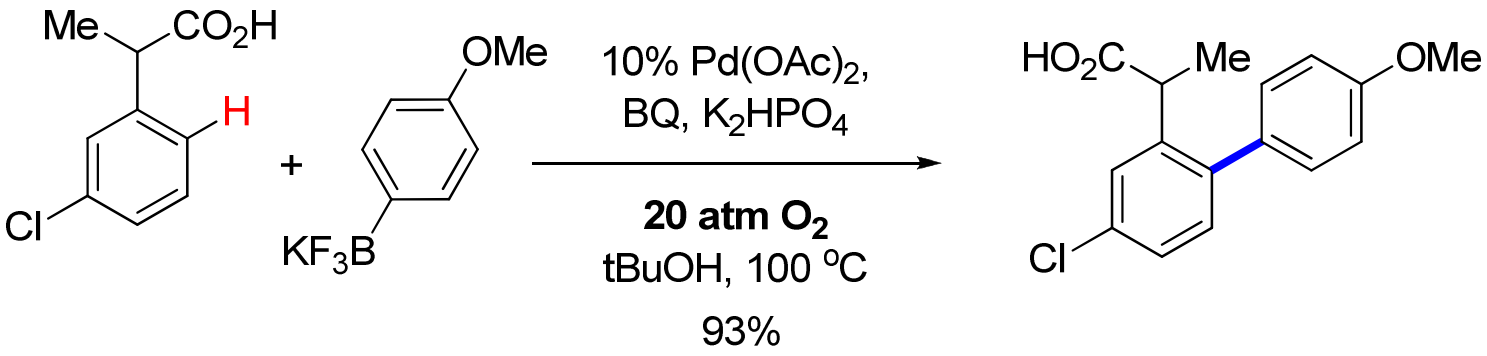
Lipshultz, *JACS*, **2010**, 4978

Boronic acids

C—H + C—M



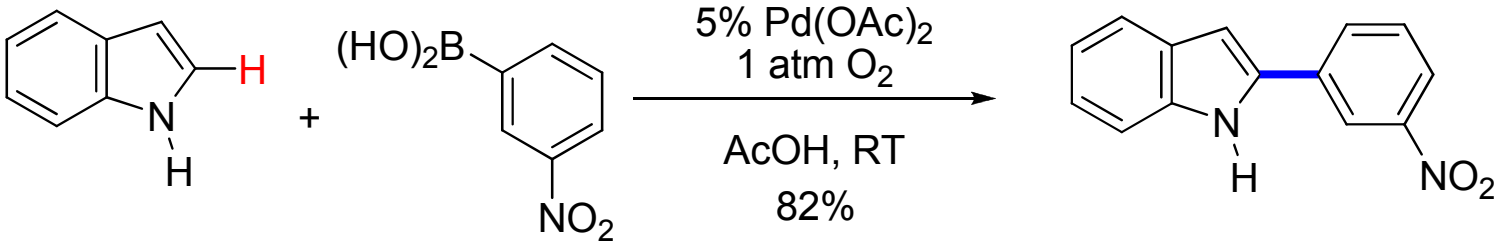
O_2 is used as the oxidant but 20 atm are required



Yu, *JACS*, **2008**, 17676

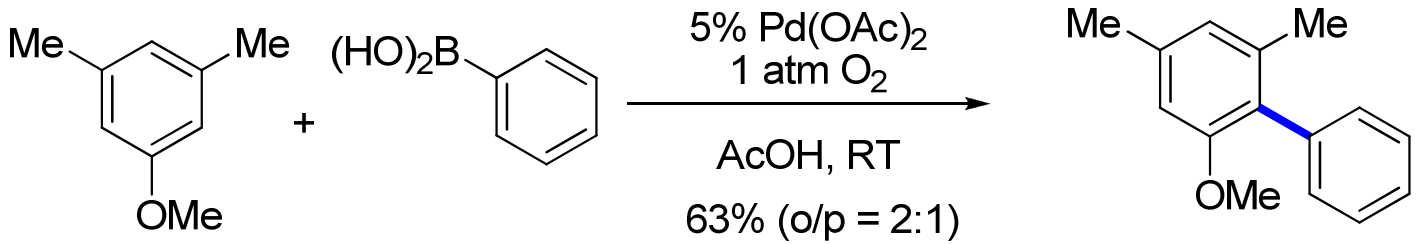
Boronic acids

C—H + C—M



O_2 is used as the oxidant

Reactions occur at room temperature

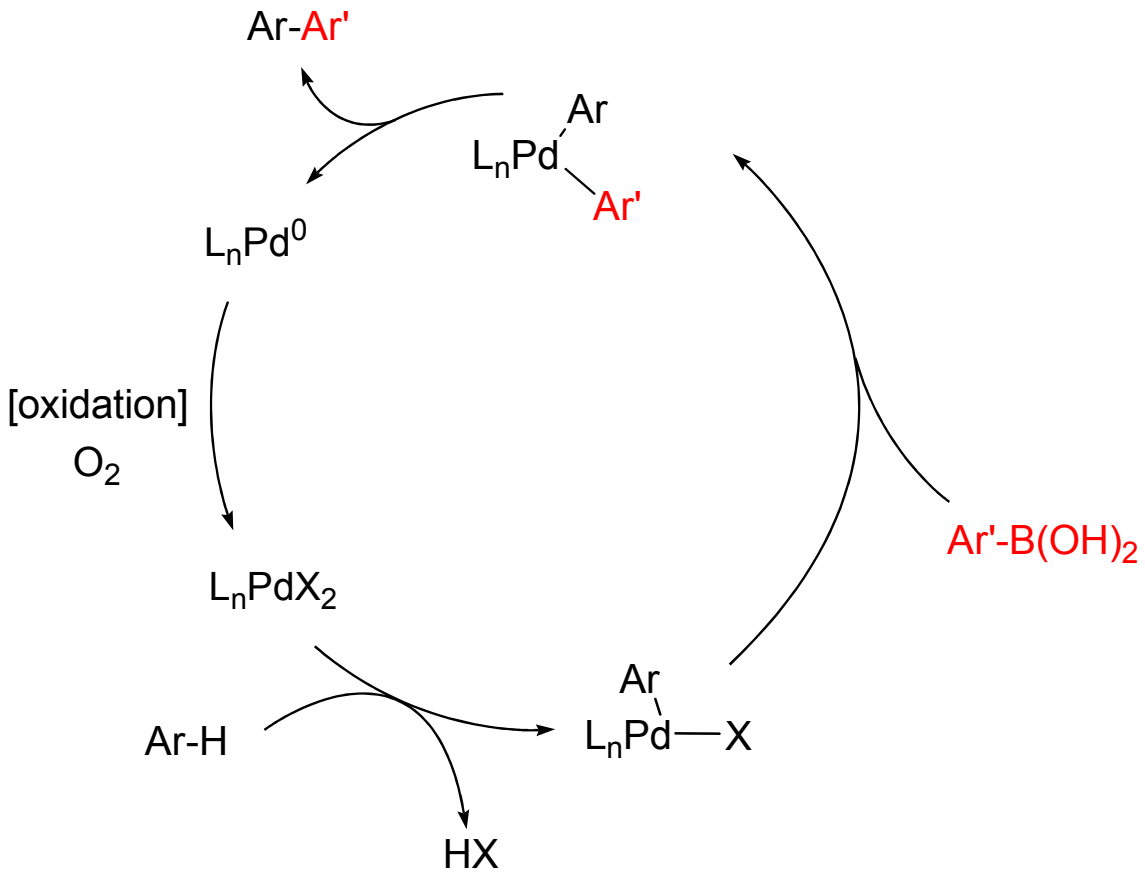


Regioselectivity control is difficult in substituted arenes

Shi, *ACIE*, **2008**, 1473

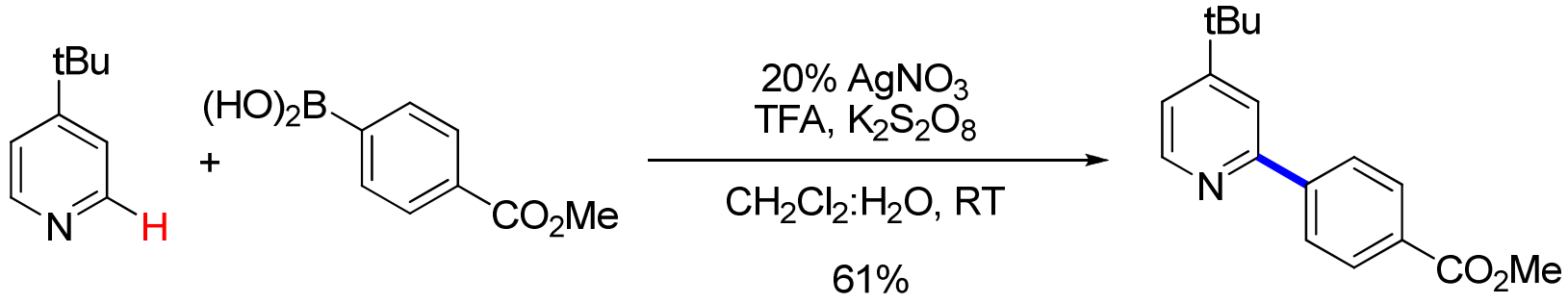
Boronic acids

Proposed mechanism:

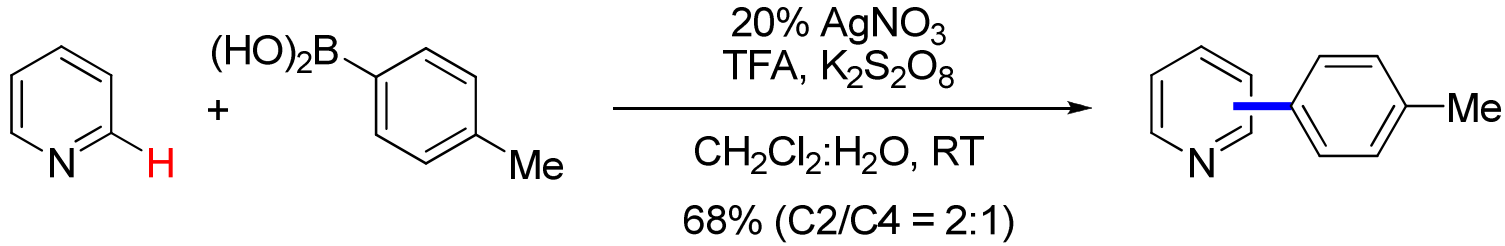


Boronic acids

C—H + C—M



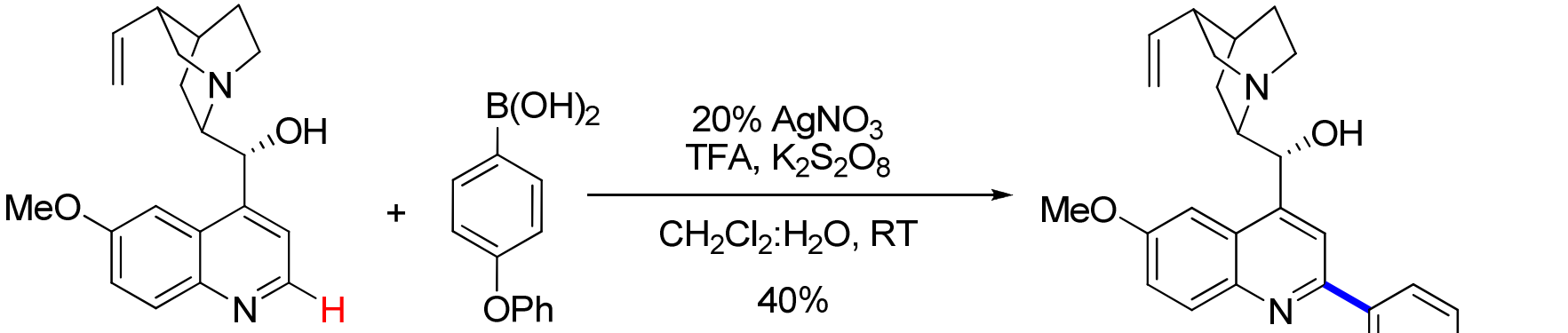
Also works with other electron-poor heteroarenes but low regioselectivity



A substituent in C4 is necessary to control the regioselectivity

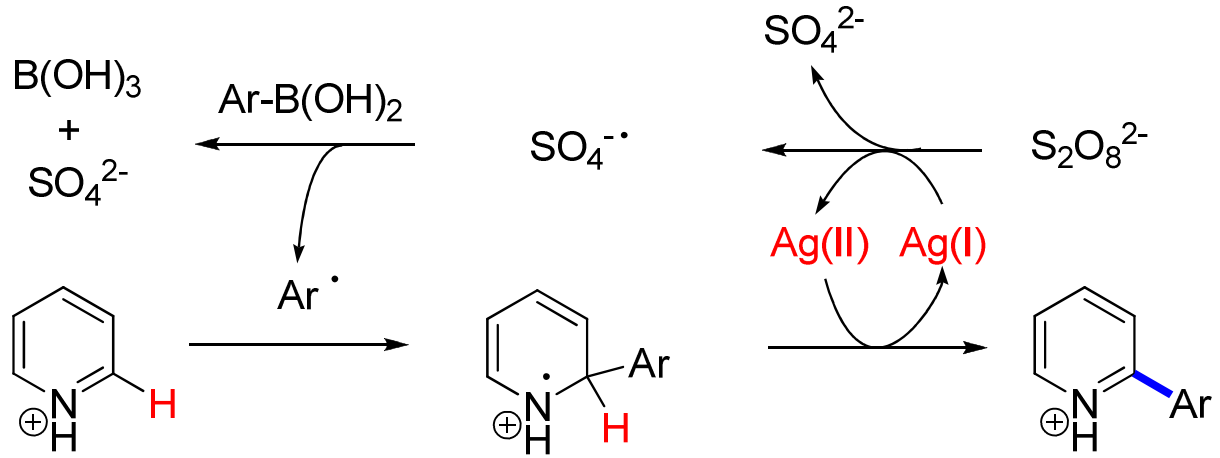
Boronic acids

C—H + C—M



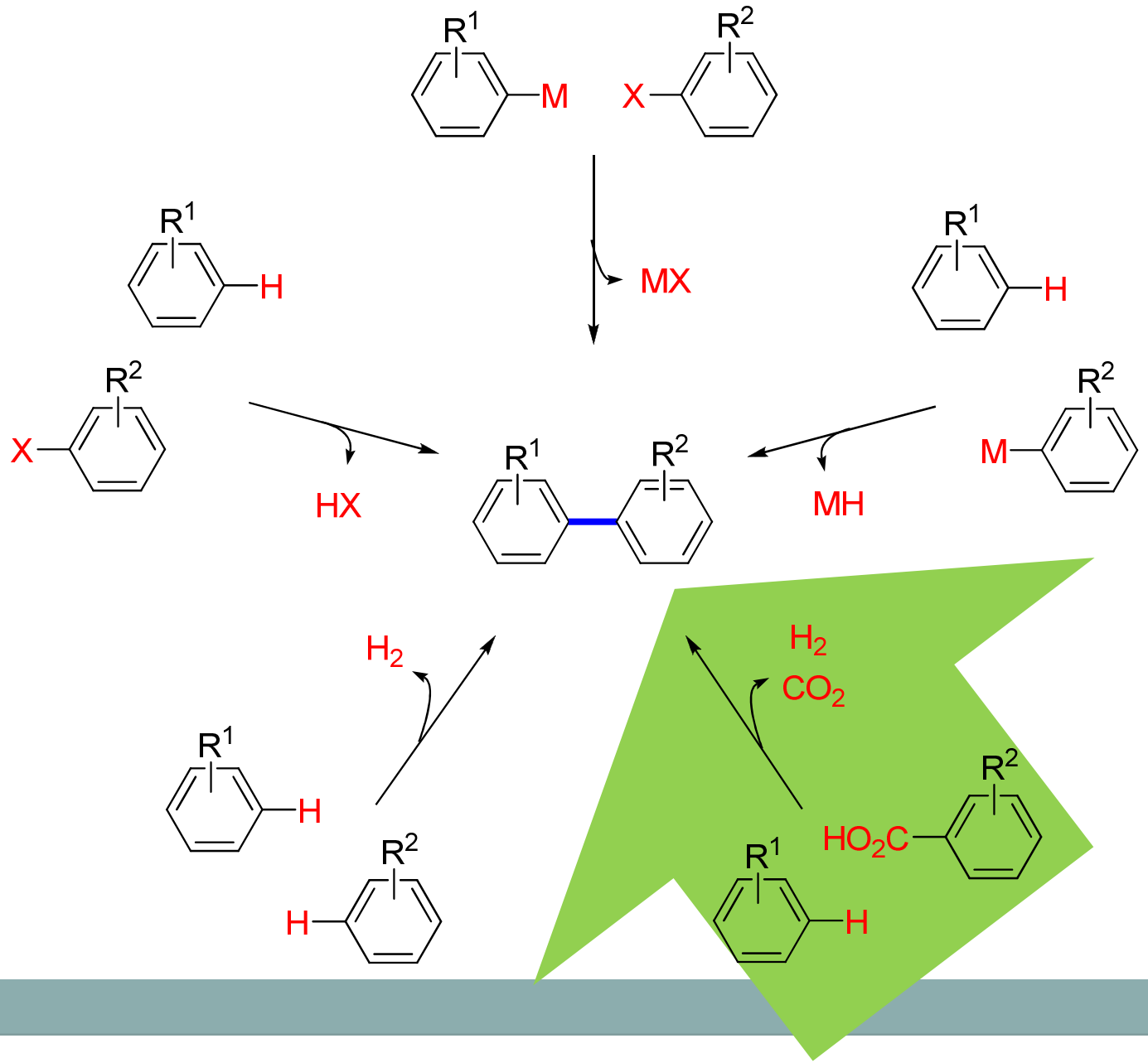
Direct arylation of quinine

Proposed mechanism:



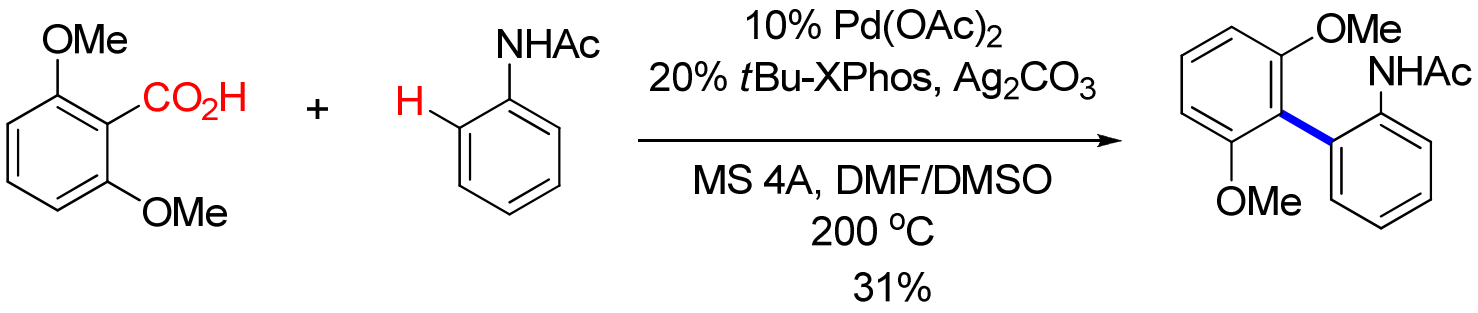
Baran, *JACS*, **2010**, 13194

Cross-coupling strategies



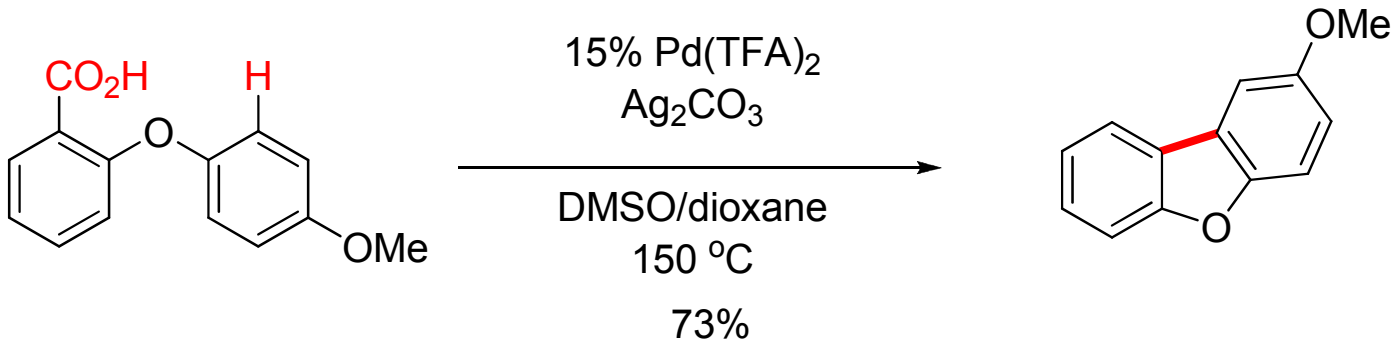
Decarboxylative activation

C—H + C—CO_2H



Three different arenes used in low to moderate yields

Main side reaction is protodecarboxylation

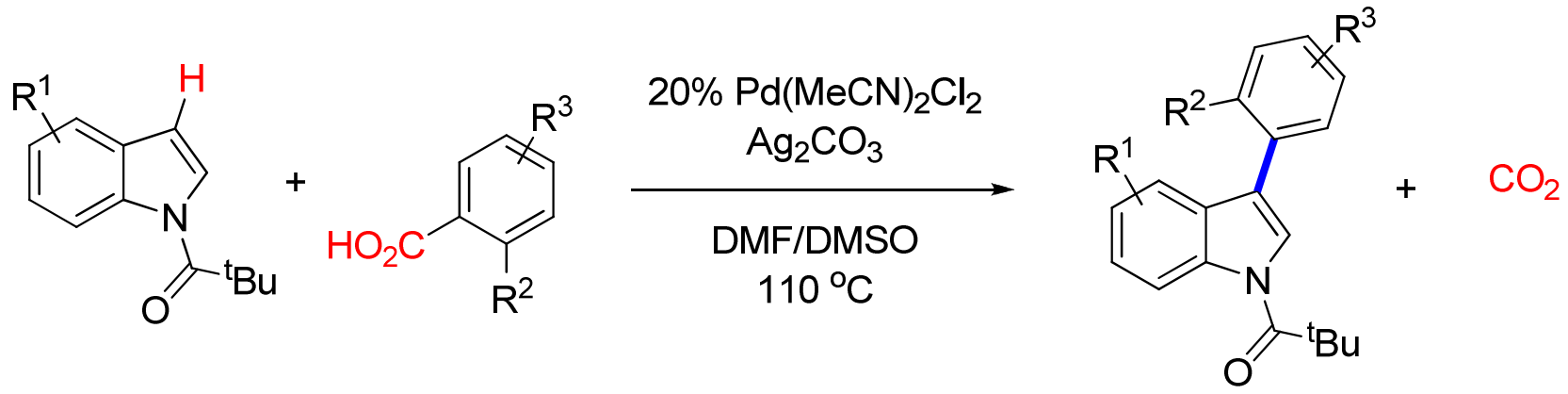


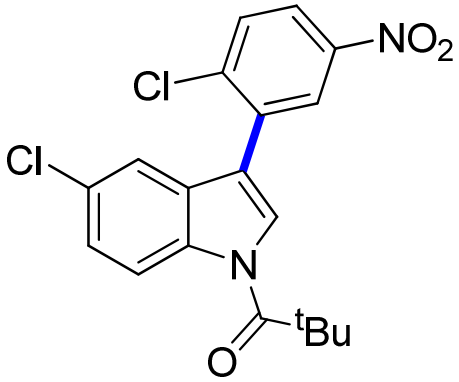
Substitution in the 'arene' part is explored

Crabtree, *ChemComm*, **2008**, 6312; Glorius, *JACS*, **2009**, 4194

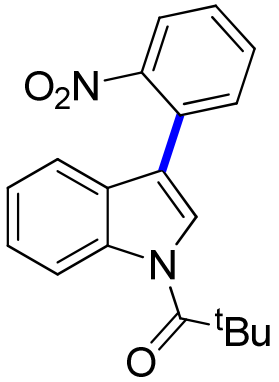
Decarboxylative activation

C—H + C—CO_2H

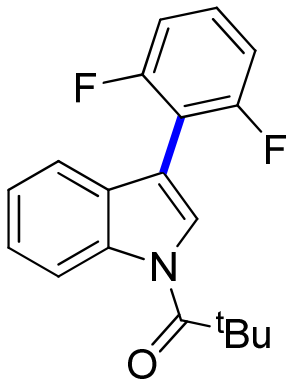




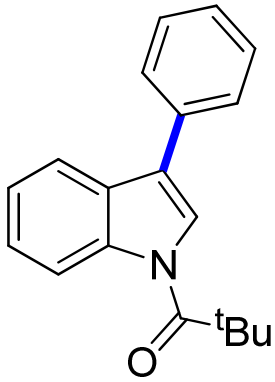
71%



63%



70%



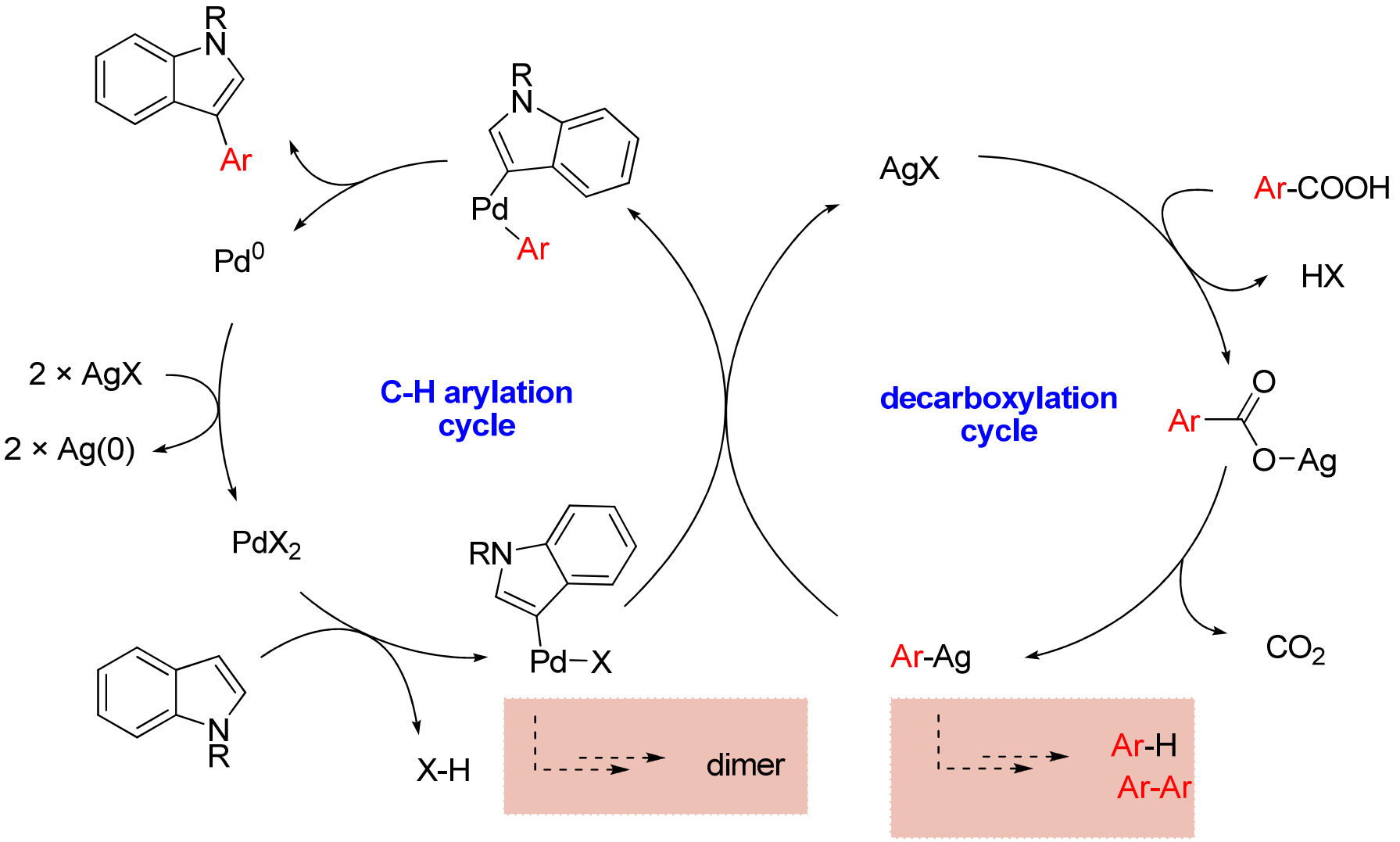
0%

An EWG is required *ortho* to the CO2H

Larrosa, *OrgLett*, **2009**, 5506

Decarboxylative activation

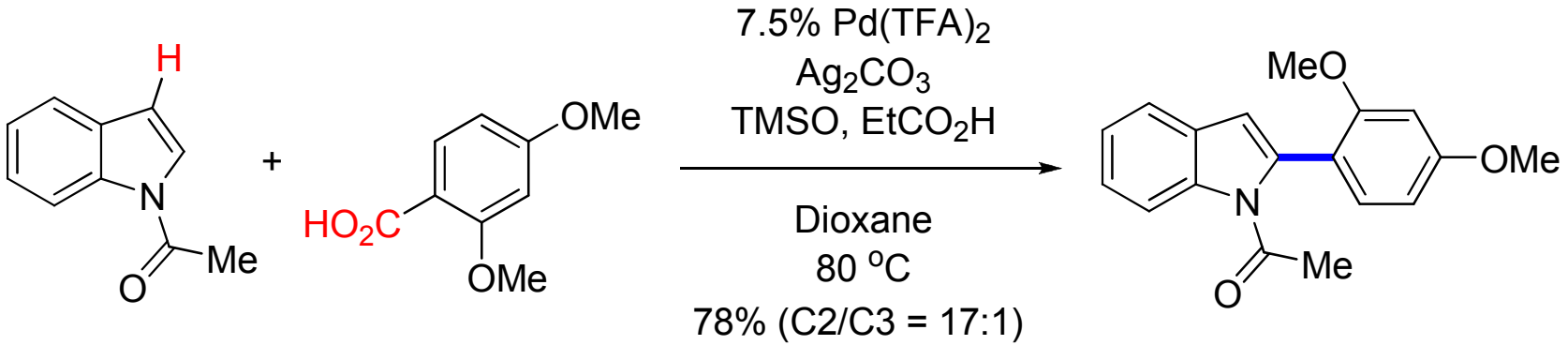
C—H + C—CO_2H



Larrosa, *OrgLett*, **2009**, 5506

Decarboxylative activation

C—H + C—CO_2H

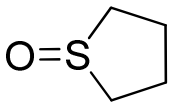


Ortho electron-donating substituents can also be used, but regioselectivity changes from C3 to C2

TMSO is added as a ligand to facilitate the decarboxylation step

Pd is proposed to mediate the decarboxylation in this case

Stoichiometric silver still used as the oxidant

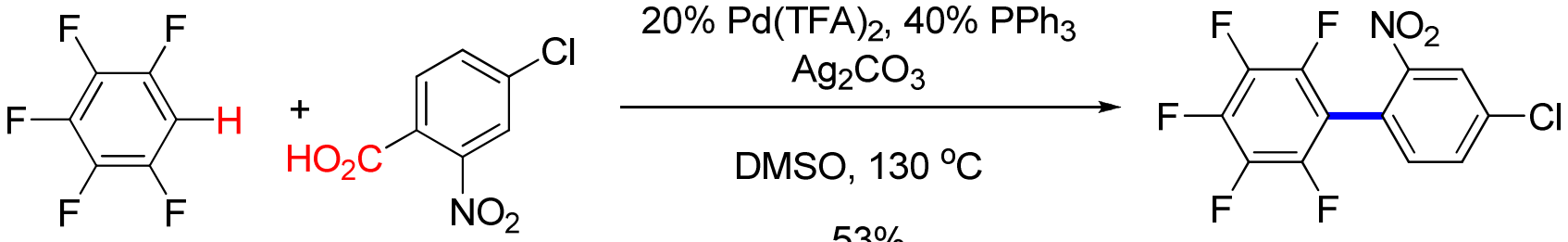


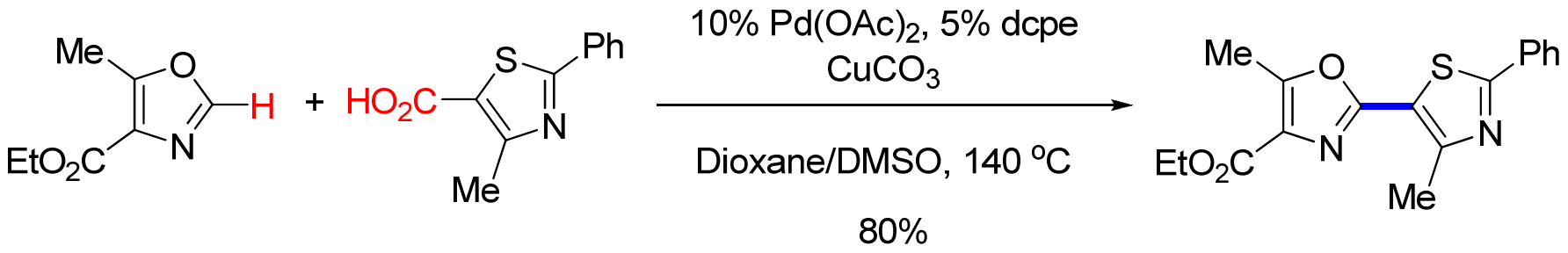
TMSO

Su, *ChemComm*, **2010**, 5876

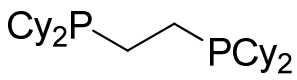
Decarboxylative activation

C—H + C—CO_2H





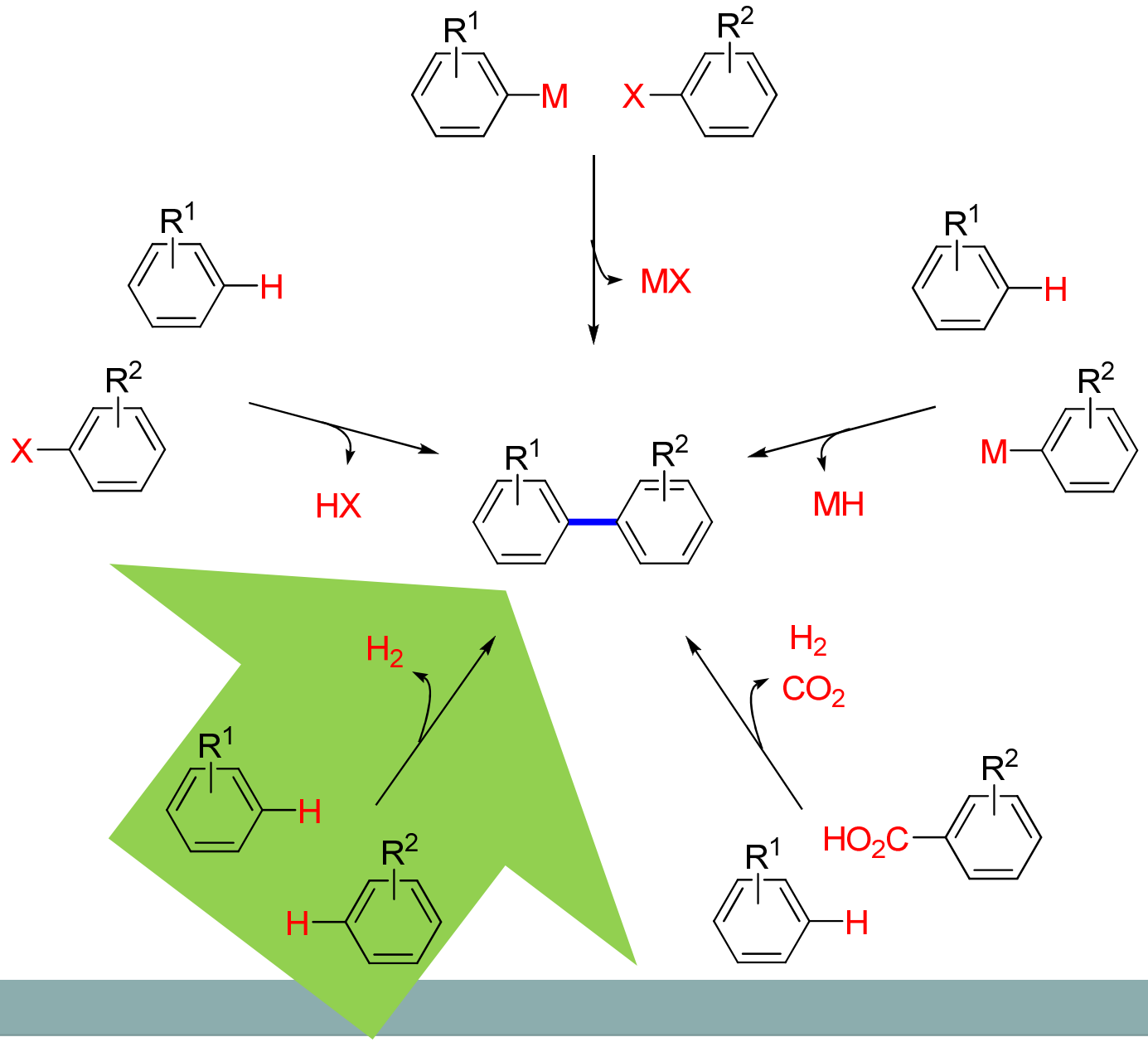
Uses $CuCO_3$ as the terminal oxidant



dcpe

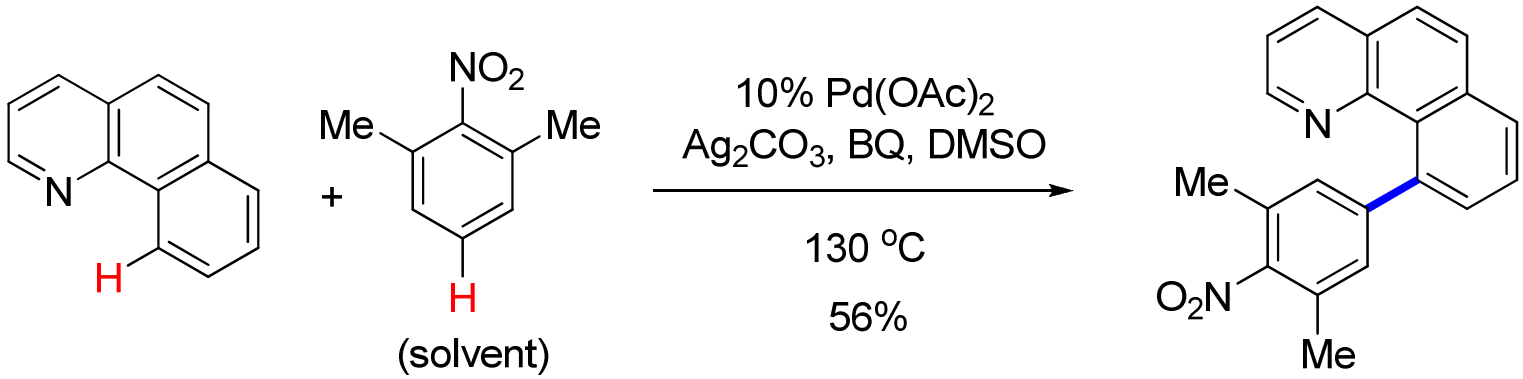
Tan, *OrgLett*, **2010**, 1565; Greaney, *ACIE*, **2010**, 2768

Cross-coupling strategies



Oxidative couplings

C—H + C—H



Steric based selectivity

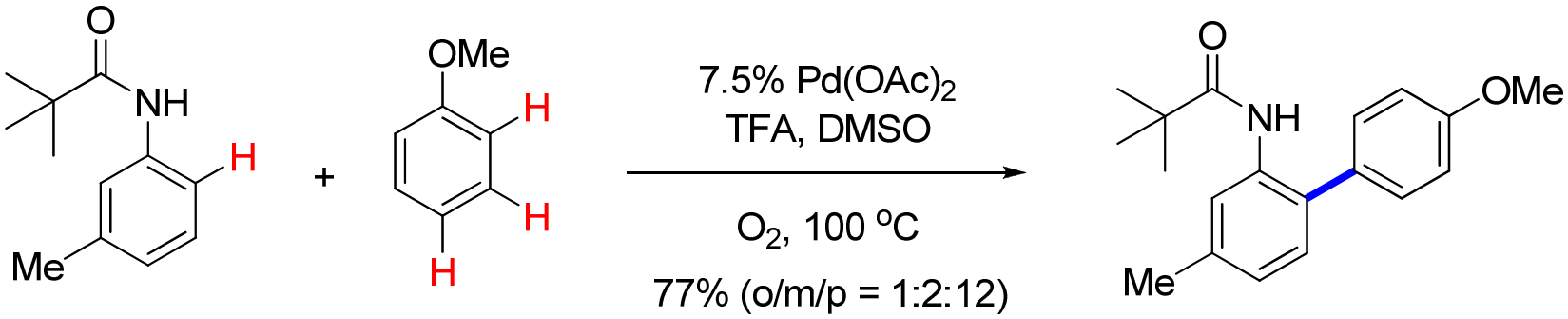
Benzoquinone is ligated to the Pd during the C—H activation step, and influences regioselectivity

KIE of 3.4 (in second arene) suggest a sigma bond metathesis C—H activation step

Sanford, *JACS*, **2007**, 11904; *JACS*, **2009**, 9651

Oxidative couplings

C—H + C—H



Similar to Sanford's, the C—H activation on the second arene is directed by sterics

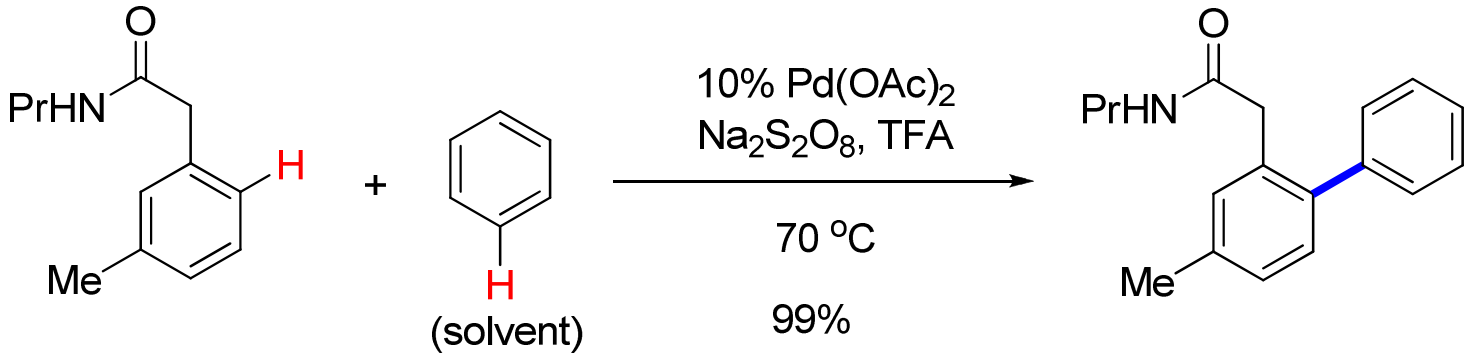
Acidic arenes, such as pentafluorobenzene react sluggishly

O2 is used as the terminal oxidant

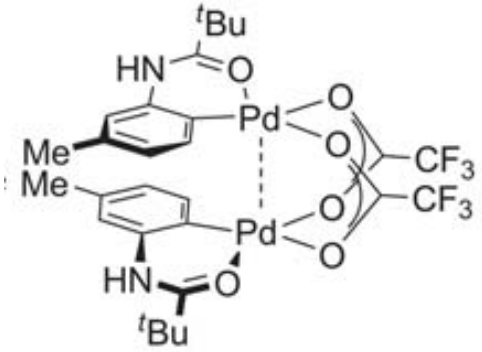
Buchwald, *OrgLett*, **2008**, 2207

Oxidative couplings

C—H + C—H



C—H activation on the second arene is directed by sterics

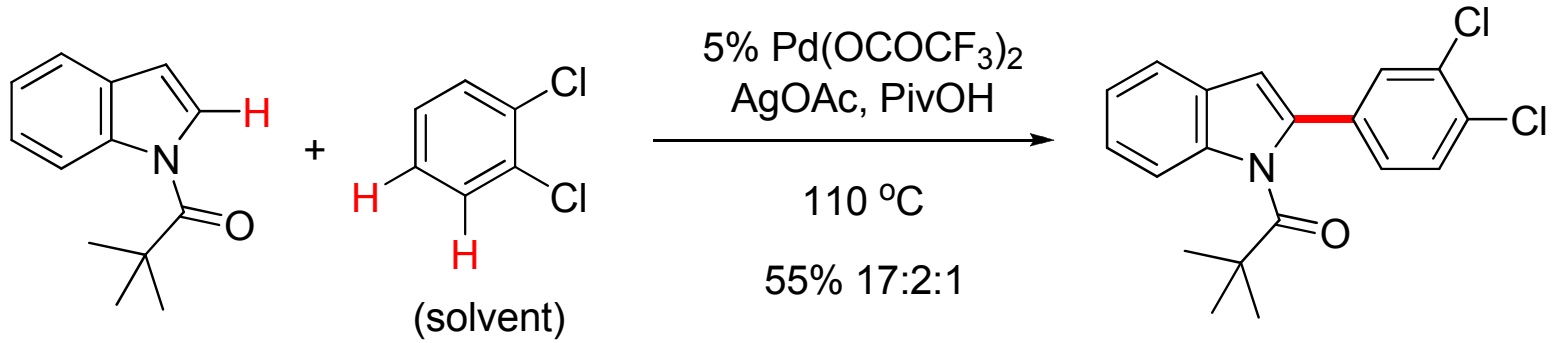


Persulfate mediated oxidation of cyclopalladated bimetallic species to Pd^{III} or Pd^{IV} is suggested

Dong, *ChemSci*, **2010**, 331

Oxidative couplings

C—H + C—H



Use of $Cu(OAc)_2$ as the oxidant leads to C3 arylation

It is suggested that Pd cluster formation and breaking are responsible for the switch in selectivity

Fagnou, *JACS*, **2007**, 12072; *Science*, **2007**, 317, 1172

Future developments

Development of new catalytic systems allowing milder conditions

Exploitation of new directing groups for C—H activation

Development of more robust oxidative couplings using O_2 as the terminal oxidant

Methodologies that do not require the use of glovebox or Schlenk techniques

Organocatalysis?

More reading

General reviews on C—H functionalisation:

Thematic issue in *Chem Rev*: **2010**, issue 2.
C-H activation in the *Topics in Current Chemistry series*, Eds. Yu and Shi, **2010**, Springer
Upcoming thematic issue in Chem Soc Rev: mid-2011

Recent reviews on C-H arylation:

Doucet, *ChemCatChem*, **2010**, 20;
Ashenhurst, *Chem Soc Rev*, **2010**, 540;
Ackerman, *ACIE*, **2009**, 9792;
Yu, *ACIE*, **2009**, 5094;
Bellina, Rossi, *Tetrahedron*, **2009**, 10269;
Lautens, *Chem Rev*, **2007**, 174

Other reviews:

Bergman, Ellman, *Chem Rev*, **2010**, 624; use of rhodium catalysts
Marder, Hartwig, *Chem Rev*, **2010**, 890; C-B bond formation
Eisenstein, *Chem Rev*, **2010**, 749; mechanisms