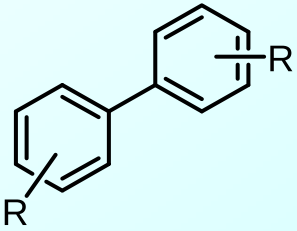
StéRéO

Institut des Sciences Moléculaires de Marseille
iSm2
www.ism2.univ-cezanne.fr
UMR 6263

Aryl-Aryl bond formation by transition-metal-catalyzed direct arylation



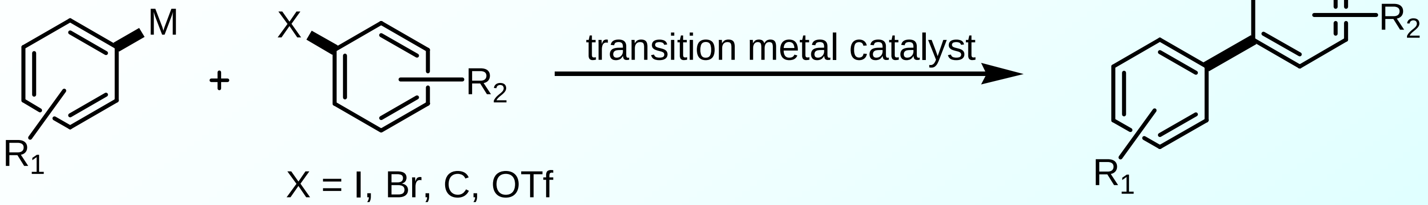
Christophe ALLAIS

Bibliographic group-meeting

10.01.2008

Introduction

Routes for the construction of aryl-aryl bonds



X = I, Br, C, OTf

1972 : Kumada-Corriu coupling : M = Mg cat = Ni or Pd

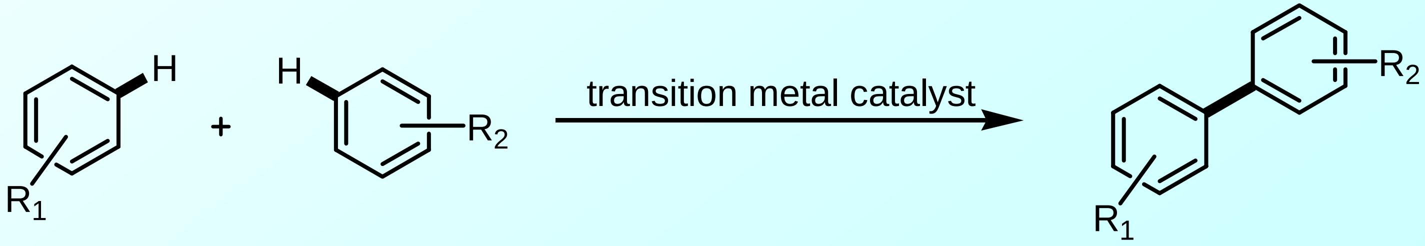
1977 : Negishi coupling : M = Zn cat = Ni or Pd

1977 : Stille coupling : M = Sn cat = Pd

1979 : Suzuki coupling : M = B cat = Pd

1988 : Hiyama coupling : M = Si cat = Pd

Prefunctionalization required
Waste



G. Bringmann et *al. Angew. Chem. Int. Ed*. **2005**, *44*, 5384.

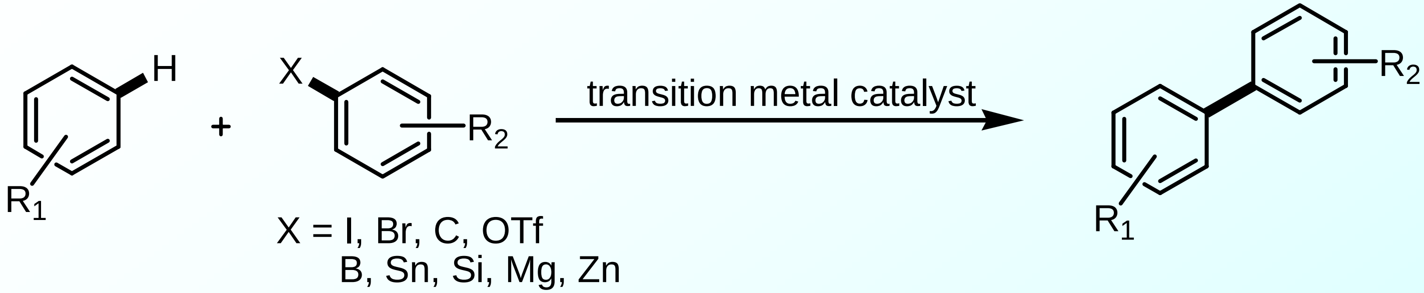
Contents

Introduction

1. Direct arylation of aryl C-H bonds
2. Intermolecular aryl-aryl bond formation
    2.1. Cascade reactions involving alkenes and alkynes
    2.2. Directing-group-assisted arylation of aromatic hydrocarbons
    2.3. Direct arylation without directing-group
3. Intramolecular aryl-aryl bond formation
4. Applications in synthesis of natural products
5. Direct arylation of heteroaryl C-H bonds
6. The challenging reaction

Conclusion

1. Direct arylation of aryl C-H bonds



Coupling of an aryl halide with an organometallic : cross-coupling reaction

Coupling of two simple arenes : oxidative coupling reaction

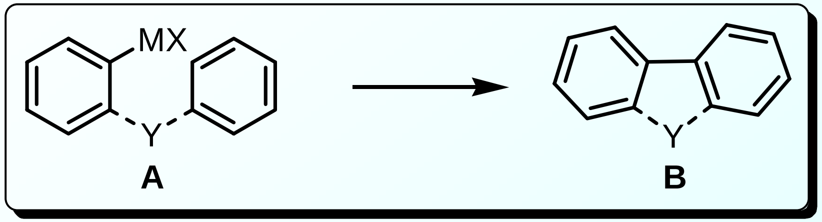
Coupling of an aryl halide with a simple arene : ???

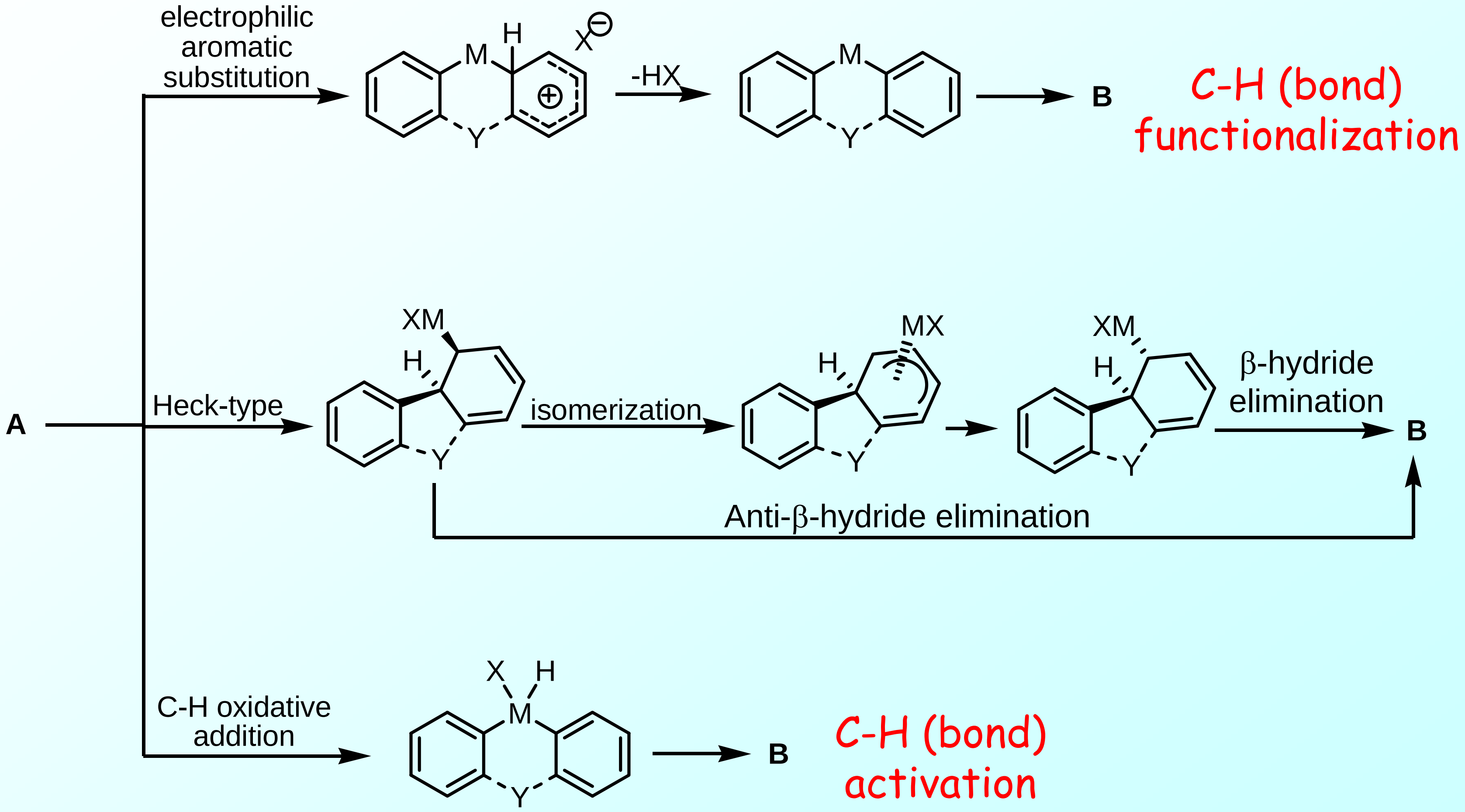
- C-H (bond) activation
- C-H (bond) functionalization
- Cross-dehalogenative coupling
- Direct arylation

Interests : limitation or absence of prefunctionalization
prevention of waste

D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174.

1. Direct arylation of aryl C-H bonds (mechanisms)





electrophilic aromatic substitution

-HX

C-H (bond) functionalization

Heck-type

isomerization

β-hydride elimination

Anti-β-hydride elimination

C-H oxidative addition

C-H (bond) activation

D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174.

1. Direct arylation of aryl C-H bonds (reaction conditions)

Transition-metal used : Pd, Ru, Rh

Ligands depend on the nature of the aryl halide

Aryl iodides : monodentate phosphines such as PPh_3

Aryl bromides : PPh_3 or more sterically bulky and electron-rich trialkylphosphines

Aryl chlorides : Electron-rich and sterically-hindered trialkylphosphines,
Buchwald's biphenylphosphines
N-heterocyclic carbenes

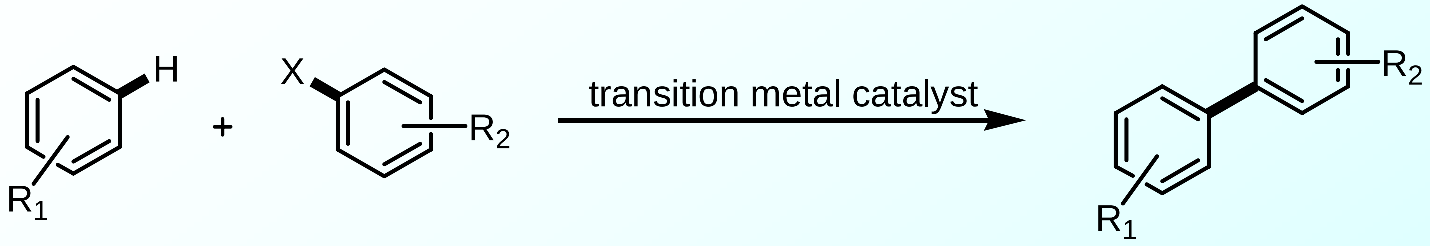
Base : inorganic bases such as K_2CO_3, Cs_2CO_3, KOAc, *t*-BuOK, CsOPiv

Solvent : aprotic and polar such as DMF, DMA, CH_3CN, NMP, DMSO
or non polar such as toluene and xylene

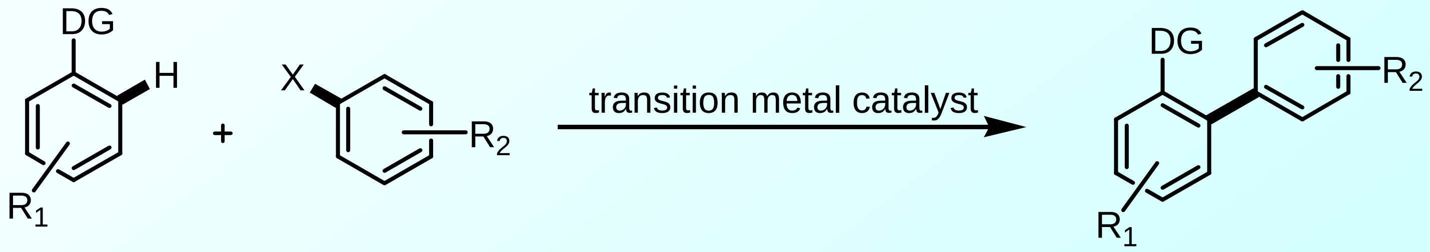
Temperature : >100°C for several hours to days

Contents

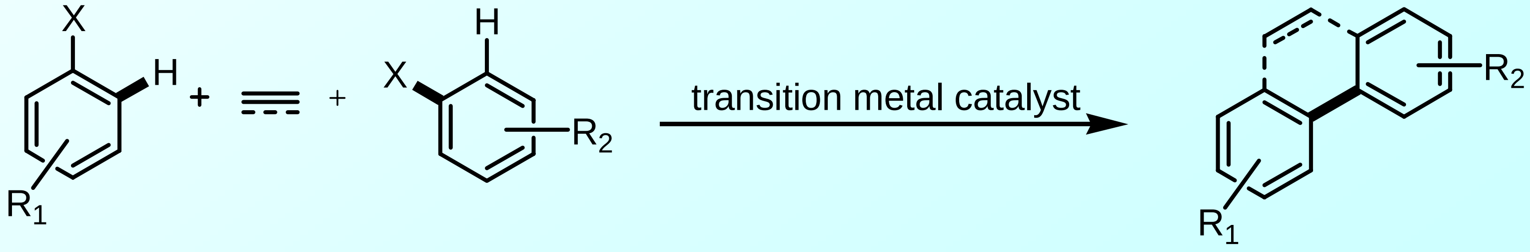
2. Intermolecular aryl-aryl bond formation



R_1 = electron-donating or electron-withdrawing group



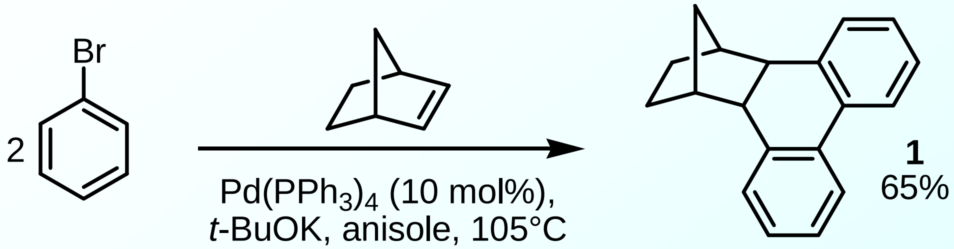
DG = directing group

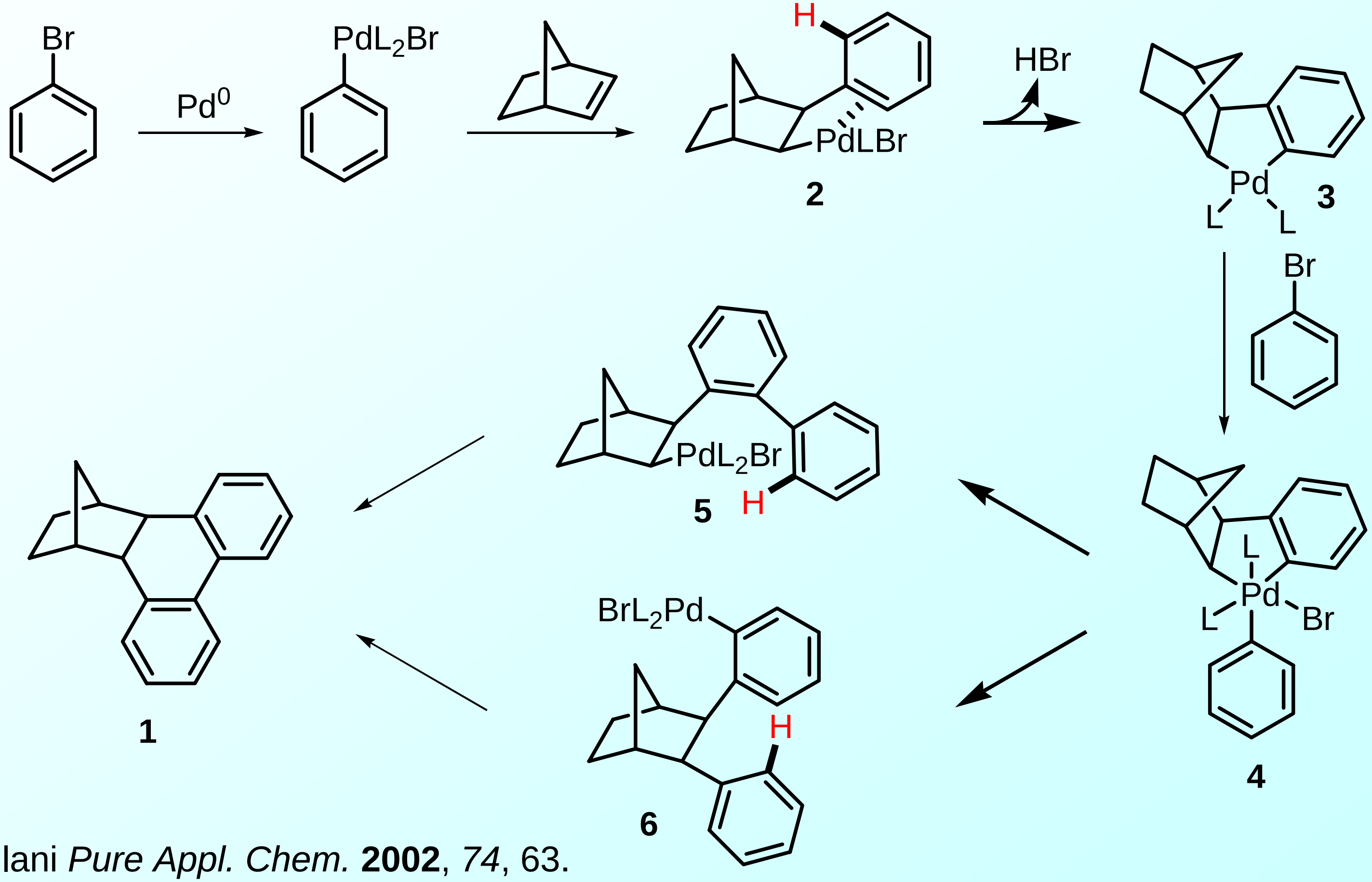


Contents

2.1. Cascade reactions involving alkenes and alkynes

Alkenes

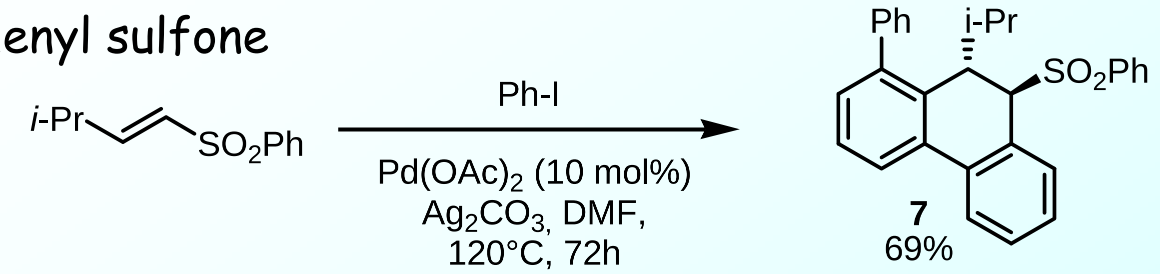


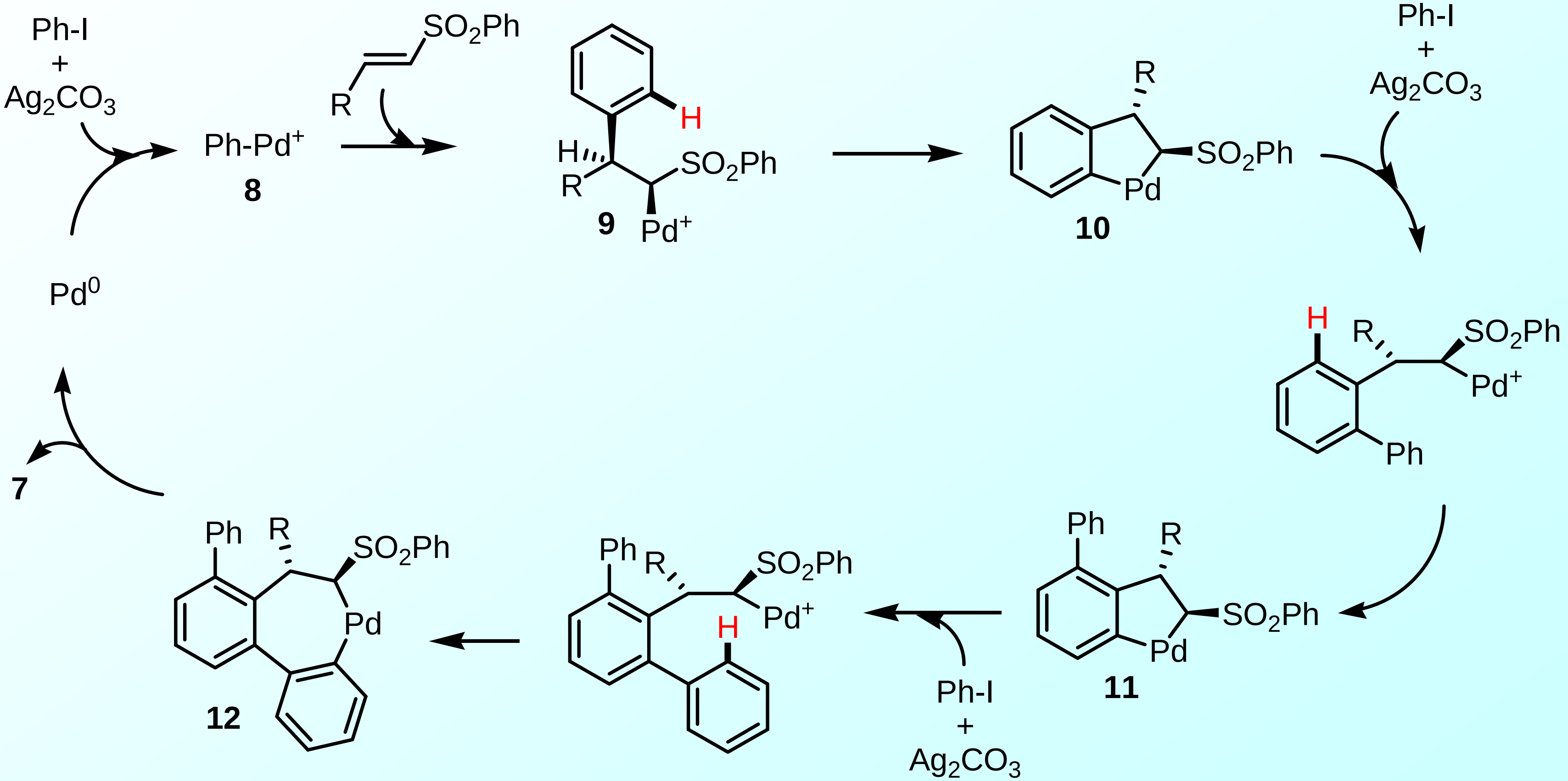


M. Catellani *Pure Appl. Chem.* **2002**, *74*, 63.
M. Catellani *Synlett* **2003**, 298.

2.1. Cascade reactions involving alkenes and alkynes

α,β-unsatured phenyl sulfone

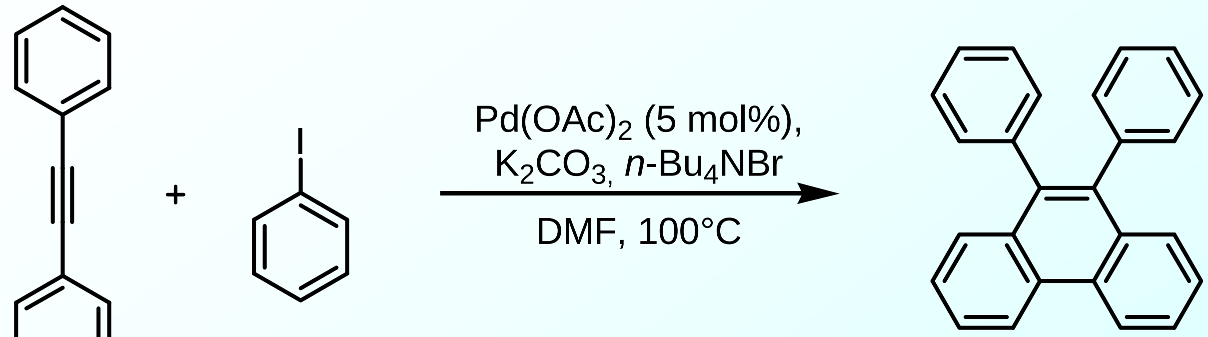




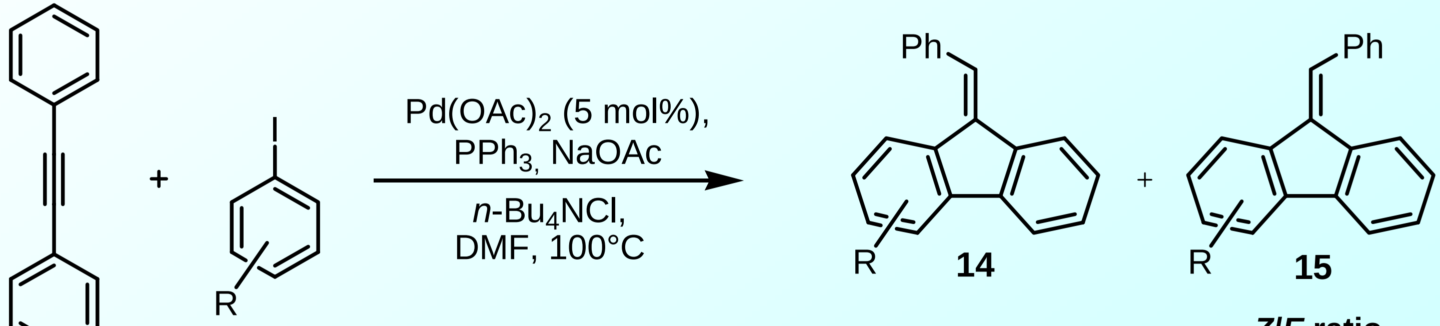
J. C. Carretero et *al. Angew. Chem. Int. Ed.* **2001**, *40*, 1291.
J. C. Carretero et *al. Chem. Eur. J.* **2006**, *12*, 4576.

2.1. Cascade reactions involving alkenes and alkynes

Alkynes



13
77%



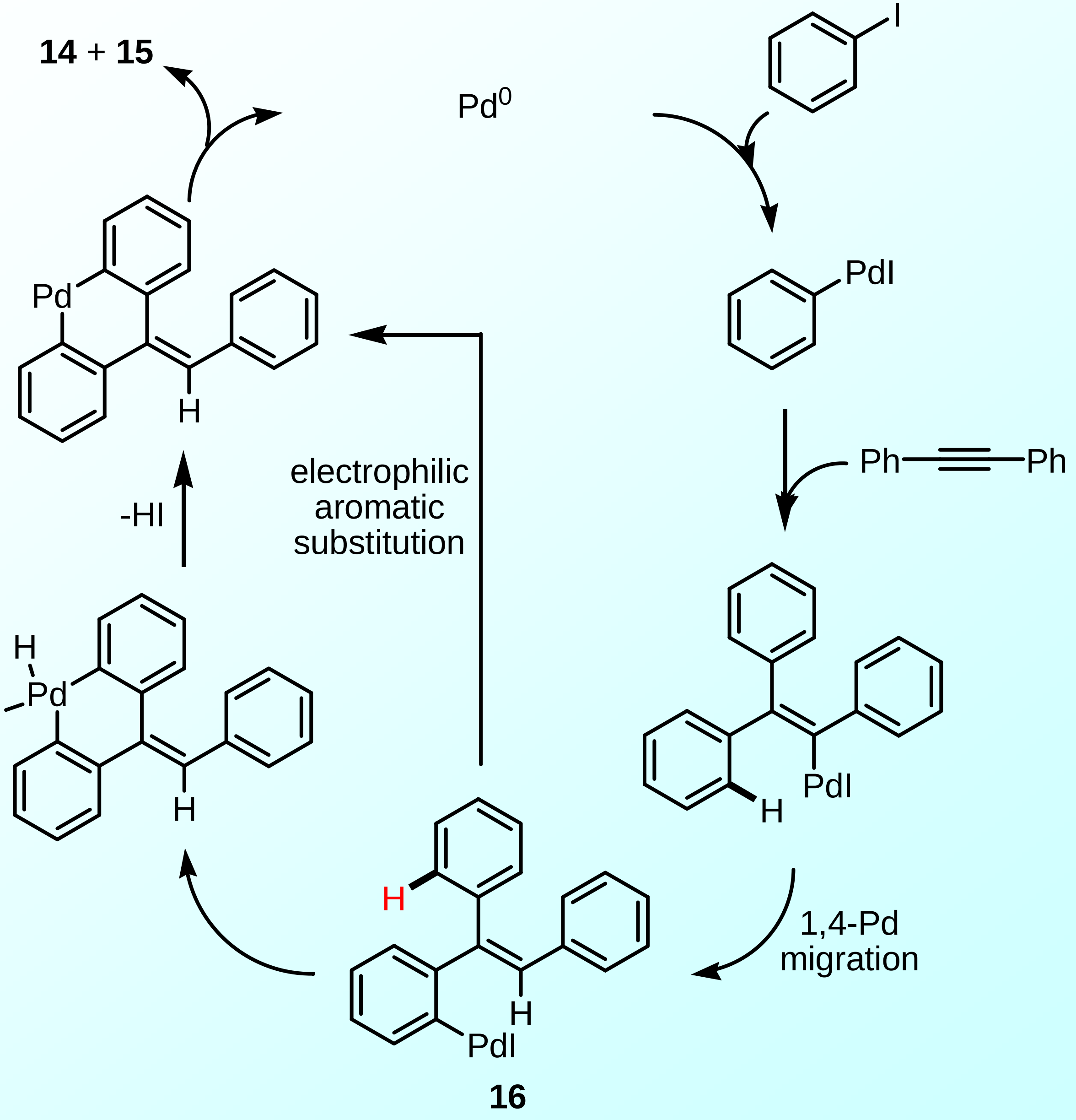
14 **15**

			***Z*/*E* ratio**
R =	**H**	**62%**	
	2-CF$_3$	**75%**	**only *E***
	2-*t*-Bu	**35%**	**only *E***
	2-Me	**61%**	**40/60**
	2-OMe	**25%**	**42/58**
	4-Me	**60%**	**40/60**
	4-OMe	**45%**	**40/60**
	4-CO$_2$Et	**45%**	**40/60**

G. Dyker et *al. Tetrahedron Lett.* **1994**, *35*, 7633.
R. C. Larock et *al. Org. Lett.* **2000**, *2*, 3329.
R. C. Larock et *al. J. Org. Chem.* **2001**, *66*, 7372.

2.1. Cascade reactions involving alkenes and alkynes

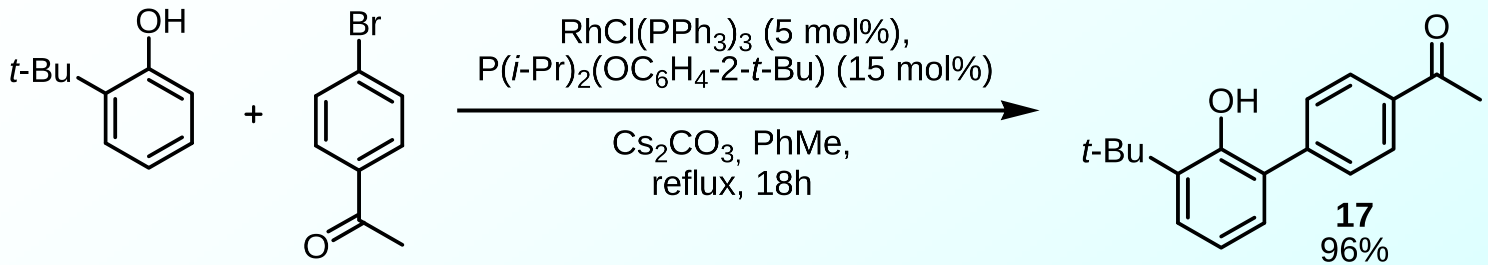
Alkynes

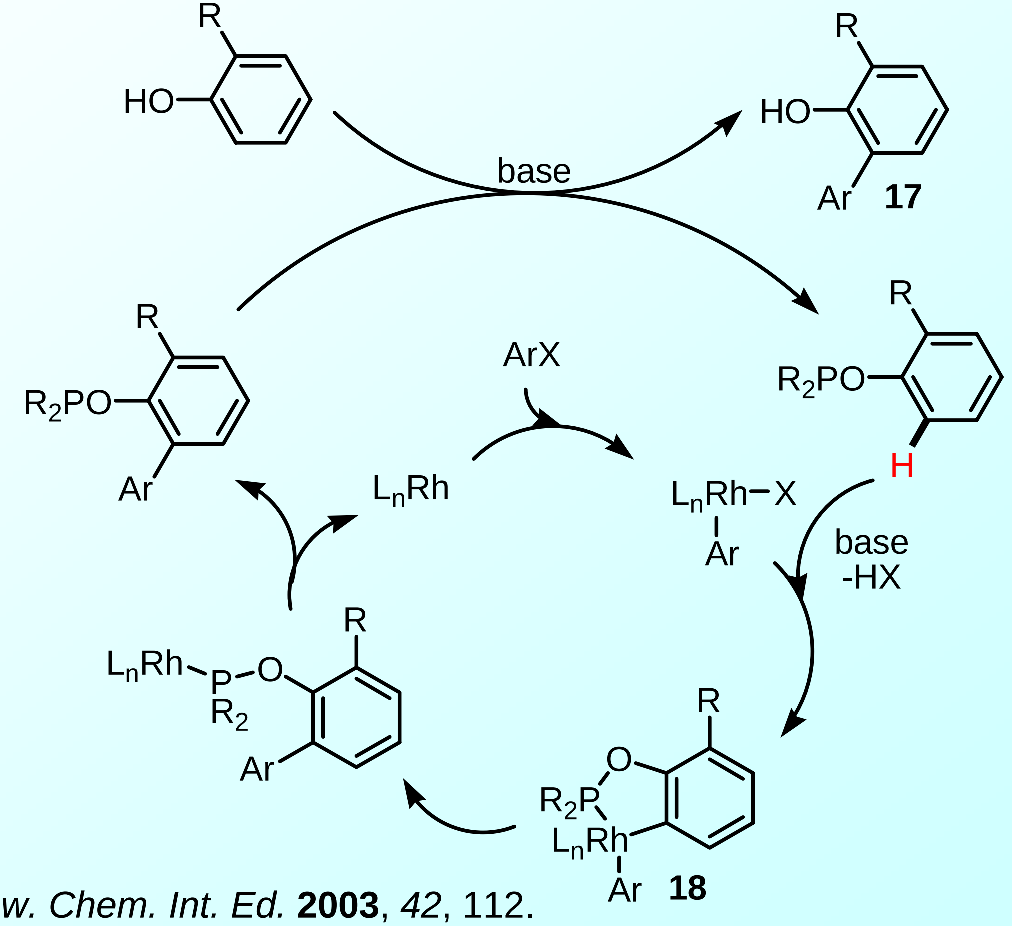


Contents

2.2. DG-assisted arylation of aromatic hydrocarbons

Phenols

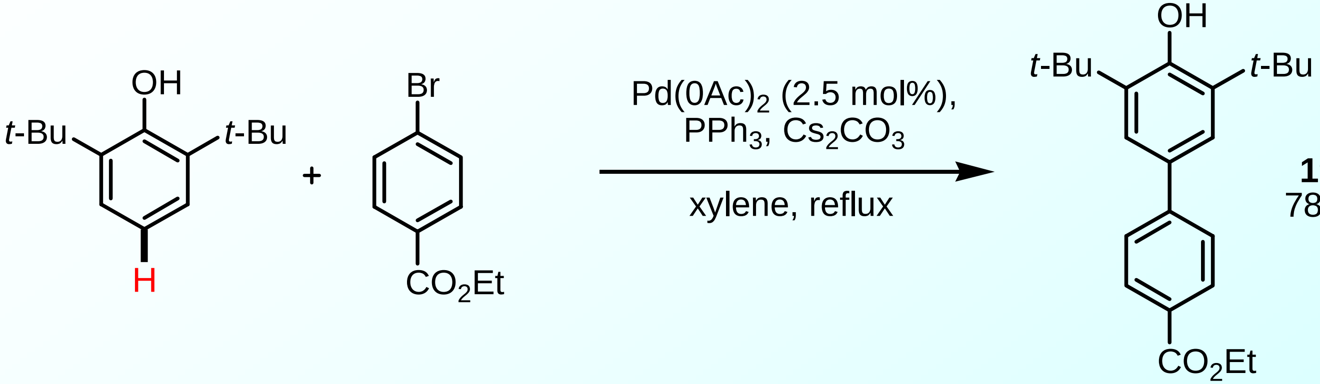




R. B. Bedford et *al. Angew. Chem. Int. Ed.* **2003**, *42*, 112.
R. B. Bedford et *al. J. Org. Chem.* **2003**, *68*, 8669.

2.2. DG-assisted arylation of aromatic hydrocarbons

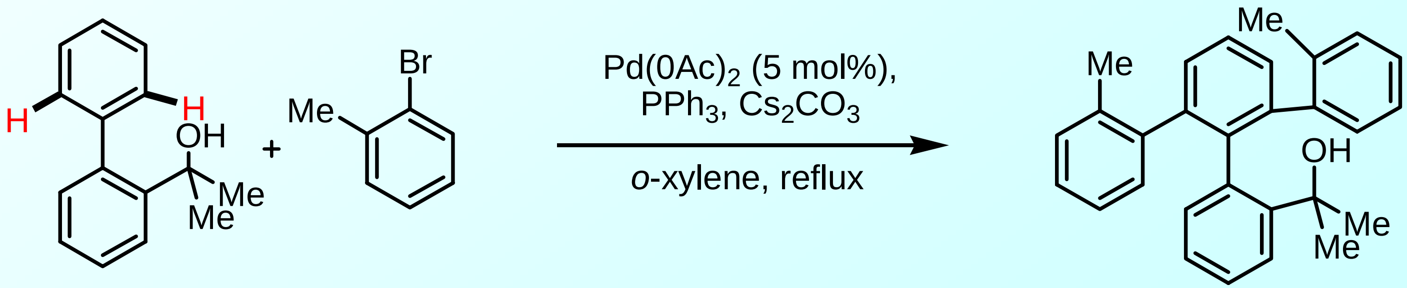
Phenols



19
78%

M. Miura et *al. Chem. Lett.* **1998**, 931.

Arylmethanols

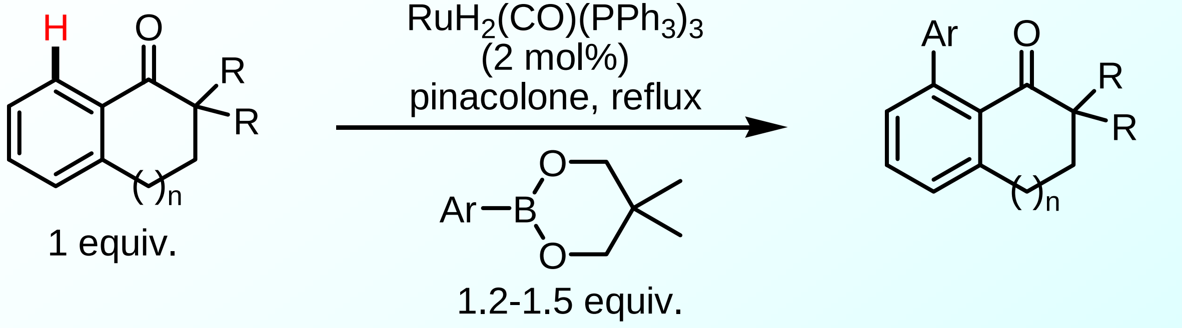


20
55%

M. Miura et *al. J. Am. Chem. Soc.* **2001**, *123*, 10407.
M. Miura et *al. J. Am. Chem. Soc.* **2004**, *126*, 8658.

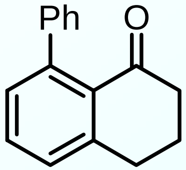
2.2. DG-assisted arylation of aromatic hydrocarbons

Ketones

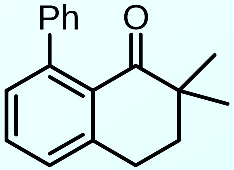


1 equiv.

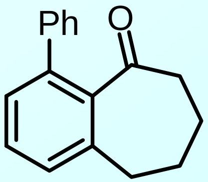
1.2-1.5 equiv.



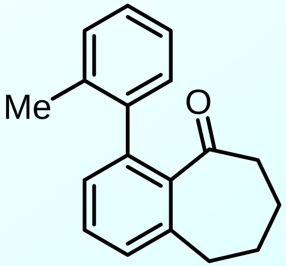
21
92%



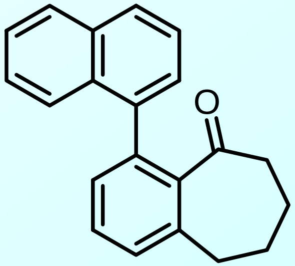
22
98%



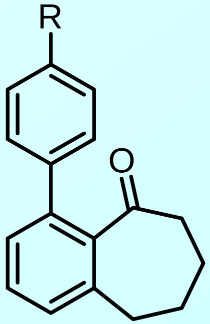
23
91%



24
96%



25
92%



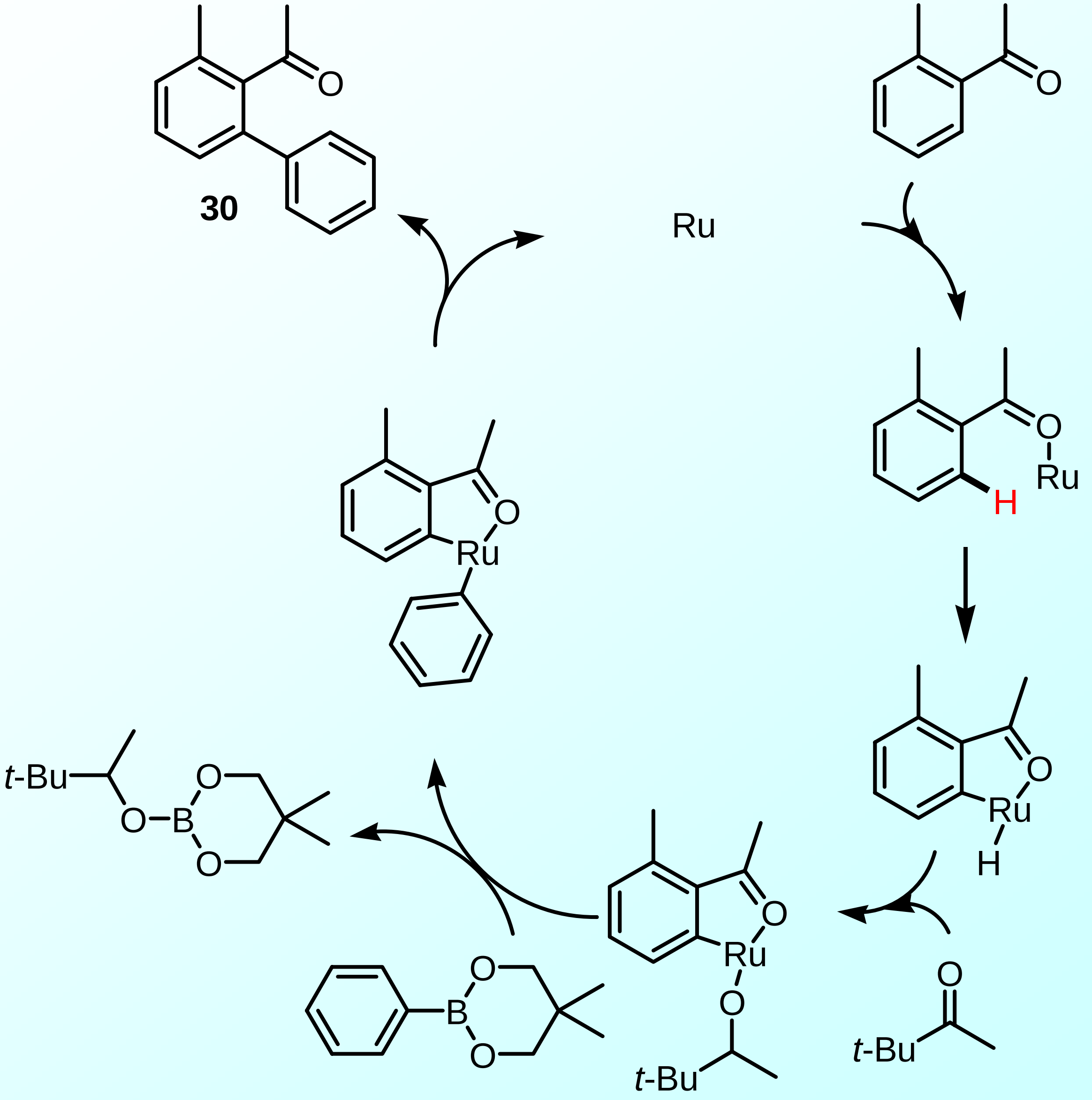
26-29

			Cpd
R =	**OMe**	**88%**	**26**
	NMe_2	**84%**	**27**
	F	**75%**	**28**
	CF_3	**84%**	**29**

F. Kakiuchi et *al. J. Am. Chem. Soc.* **2005**, *127*, 5936.

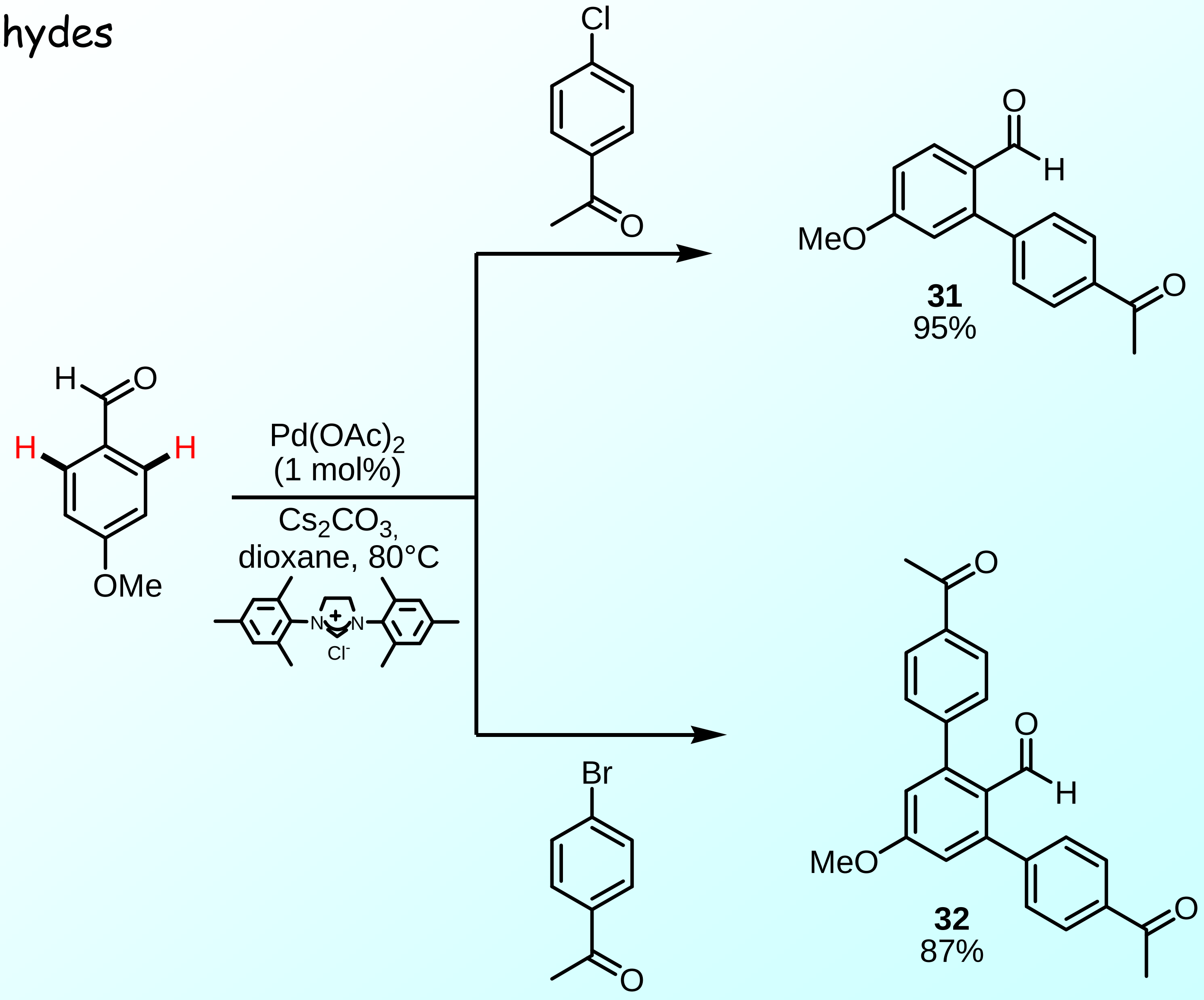
2.2. DG-assisted arylation of aromatic hydrocarbons

Ketones



2.2. DG-assisted arylation of aromatic hydrocarbons

Benzaldehydes



$Pd(OAc)_2$ (1 mol%)

Cs_2CO_3, dioxane, 80°C

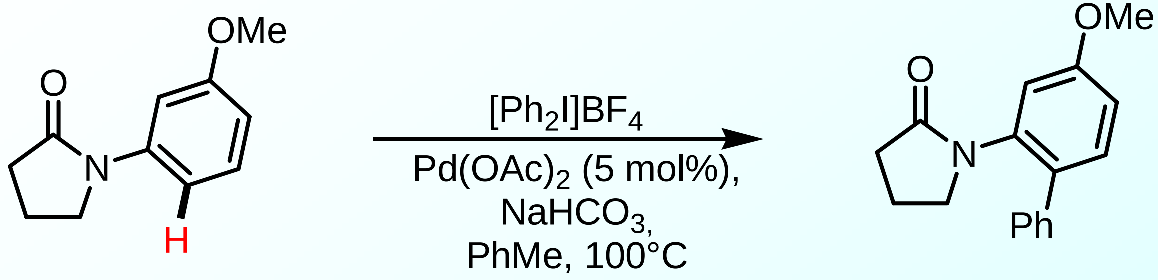
31 95%

32 87%

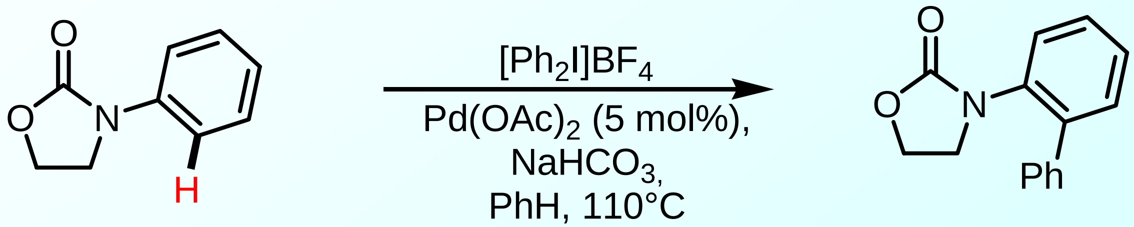
N. Gürbüz et *al. Tetrahedron Lett.* **2005**, *46*, 2273.

2.2. DG-assisted arylation of aromatic hydrocarbons

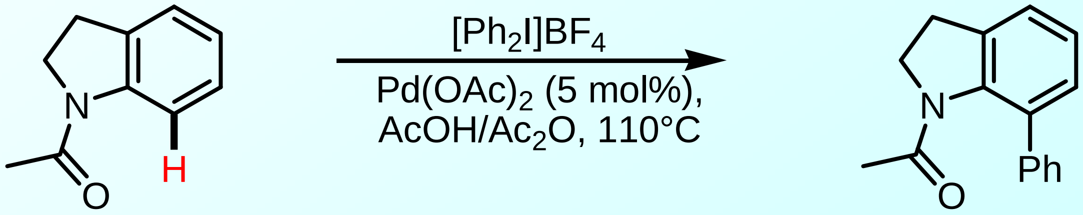
Amides



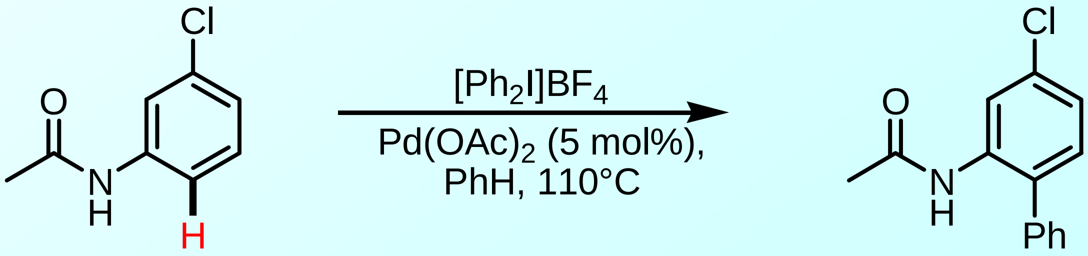
33
84%



34
83%



35
49%

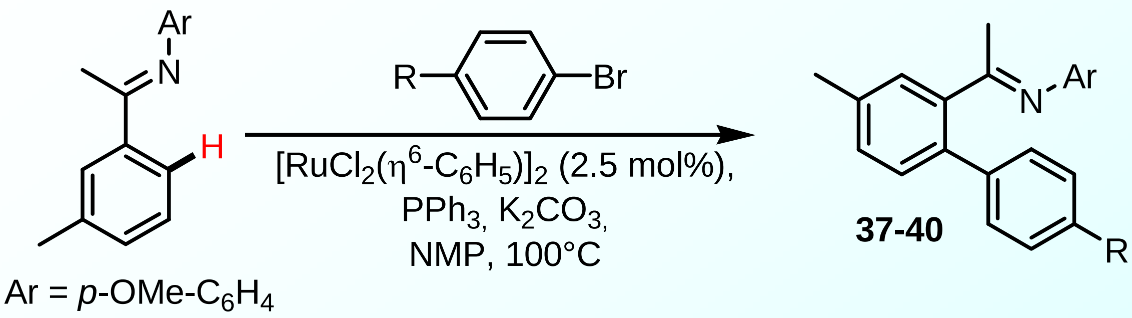


36
67%

M. S. Sanford et *al. J. Am. Chem. Soc.* **2005**, *127*, 7330.

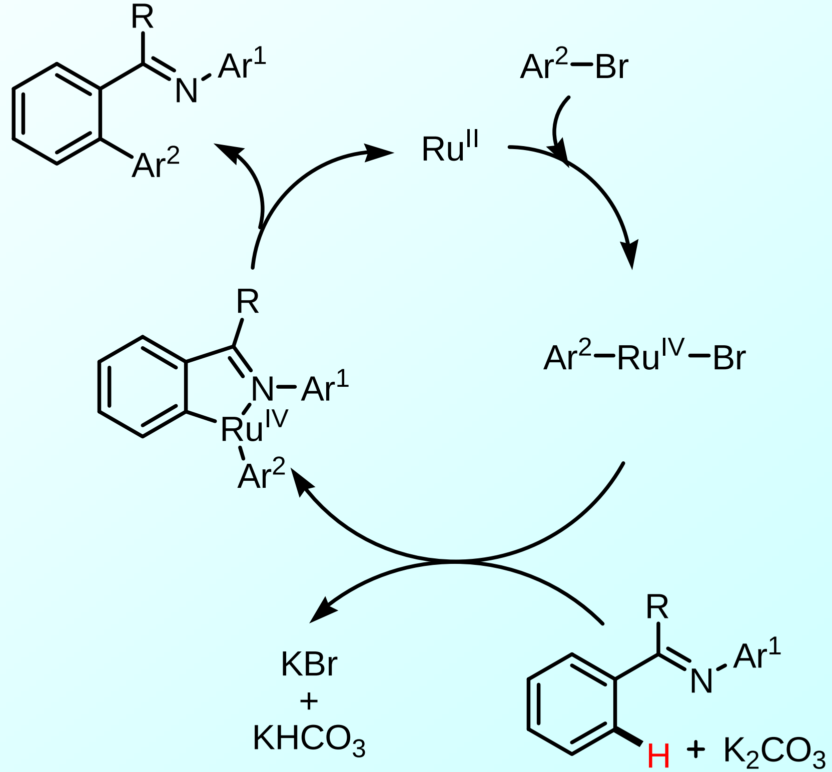
2.2. DG-assisted arylation of aromatic hydrocarbons

Imines



37-40

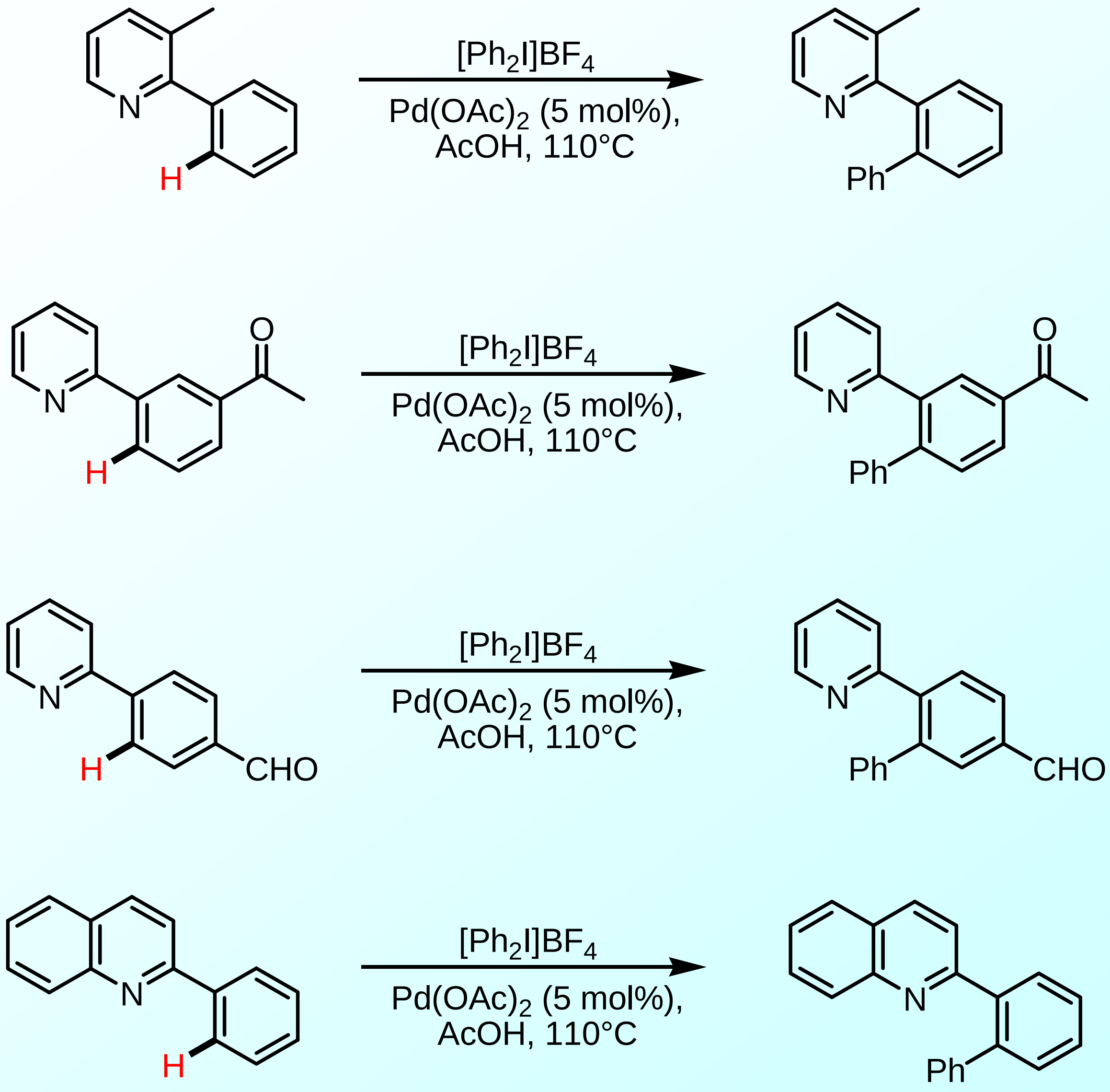
R =	
H	**83%**
F	**85%**
Me	**74%**
OMe	**88%**



S. Oi et *al. Org. Lett.* **2002**, *4*, 1783.

2.2. DG-assisted arylation of aromatic hydrocarbons

Pyridines



44
88%

45
91%

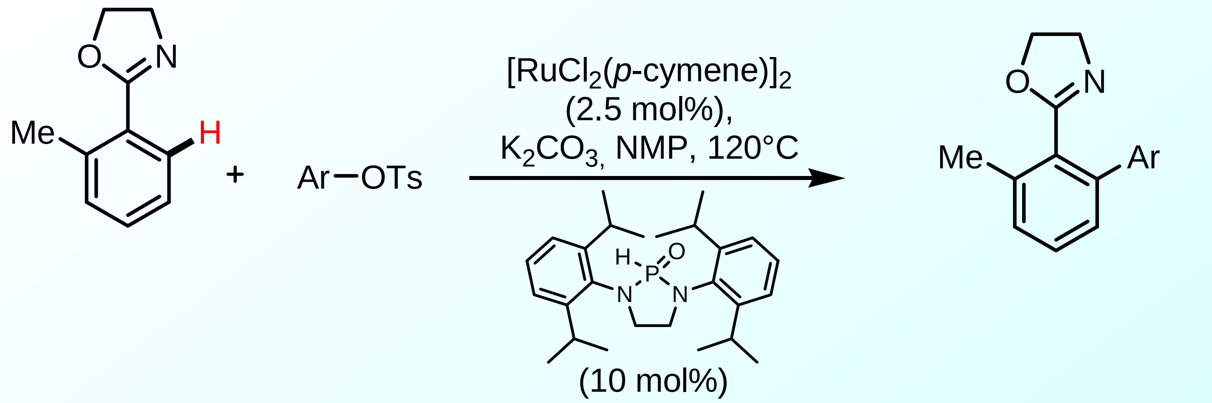
46
51%

47
58%

M. S. Sanford et *al. J. Am. Chem. Soc.* **2005**, *127*, 7330.

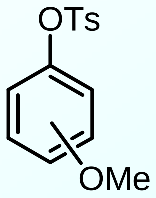
2.2. DG-assisted arylation of aromatic hydrocarbons

Oxazolines, Imidazolines

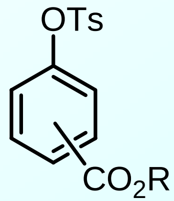


$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), K_2CO_3, NMP, 120°C

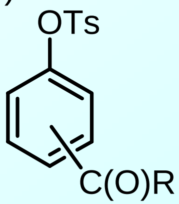
(10 mol%)



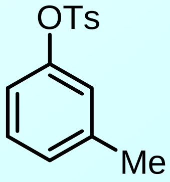
4-OMe 71%
3,5-OMe 51%
2-OMe 50%



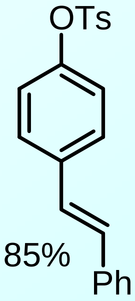
4-CO_2Me 93%
3-CO_2Et 73%



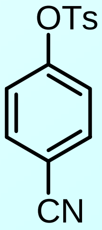
4-C(O)Ph 94%
4-C(O)Me 93%



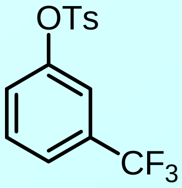
81%



85%



59%

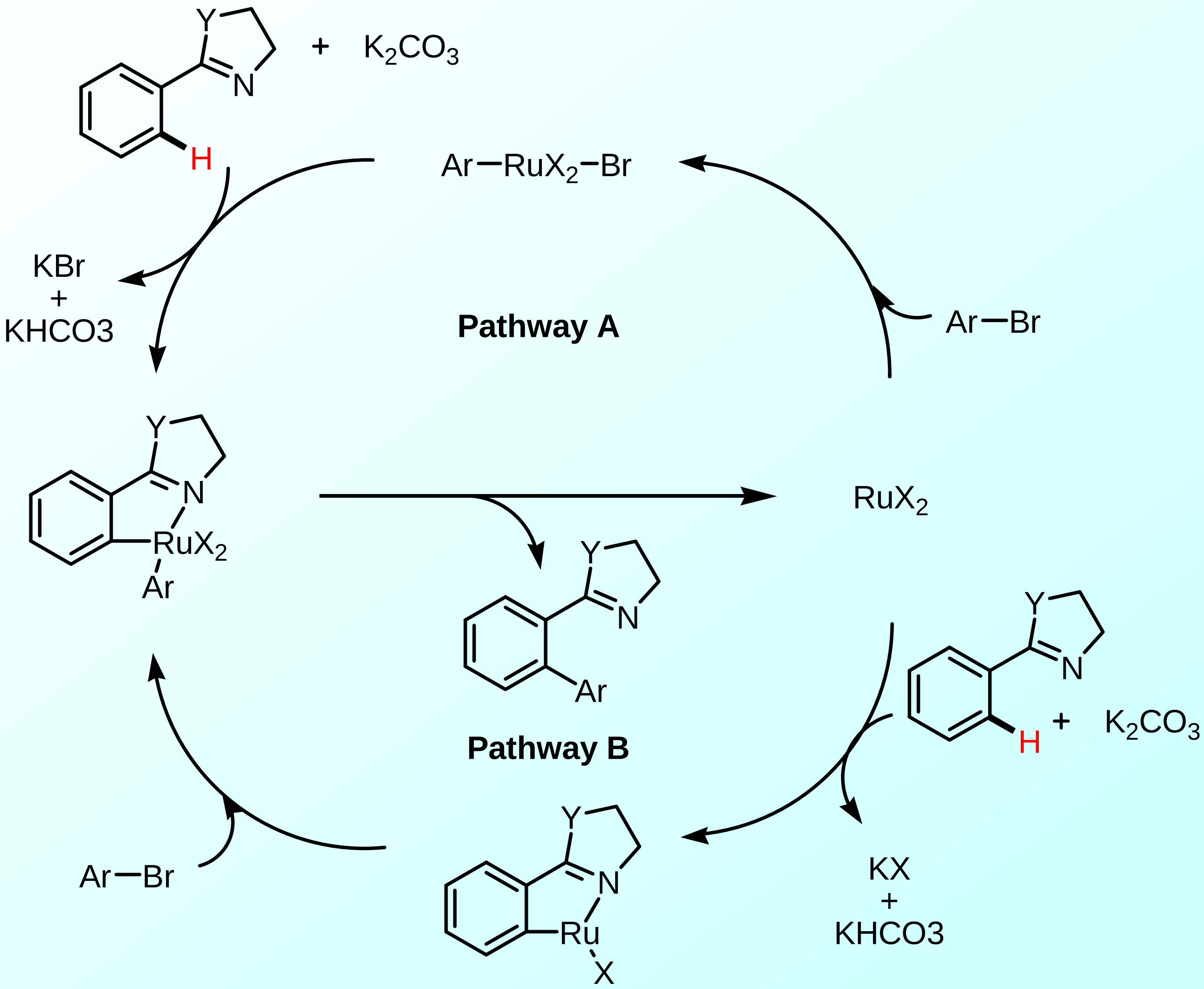


96%

L. Ackermann et *al. Angew. Chem. Int. Ed.* **2006**, *45*, 2619.

2.2. DG-assisted arylation of aromatic hydrocarbons

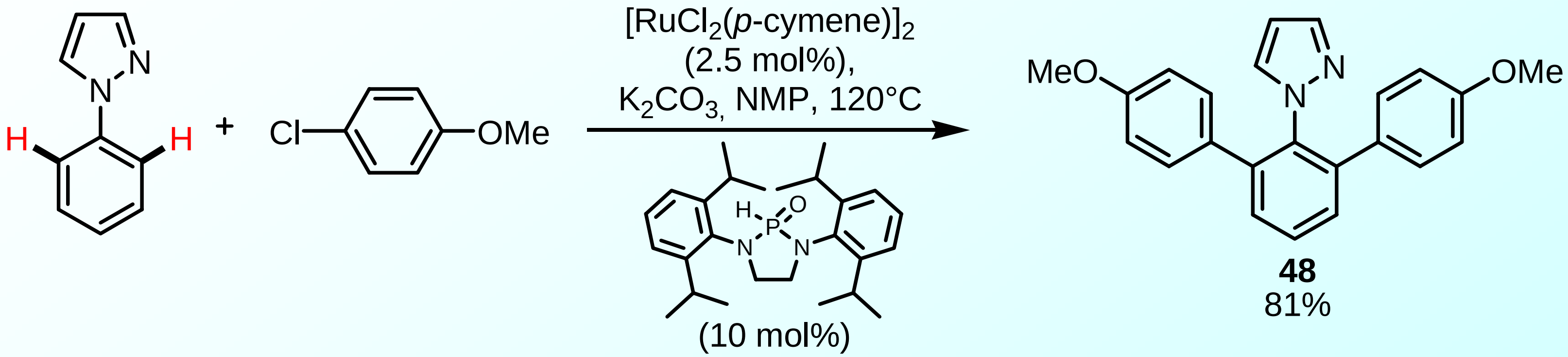
Oxazolines, Imidazolines



S. Oi et *al. J. Org. Chem.* **2005**, *70*, 3113.

2.2. DG-assisted arylation of aromatic hydrocarbons

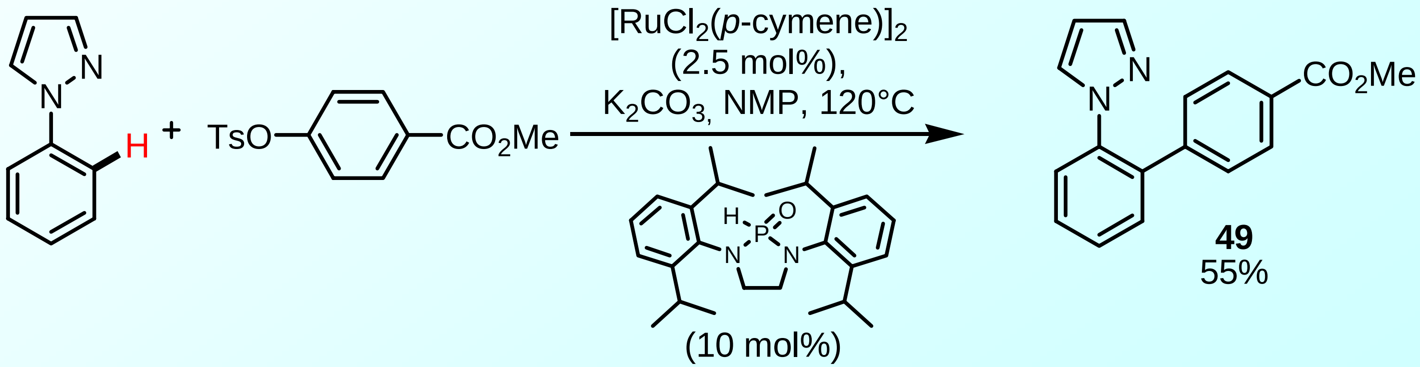
Pyrazoles



$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), K_2CO_3, NMP, 120°C

(10 mol%)

48
81%



$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%), K_2CO_3, NMP, 120°C

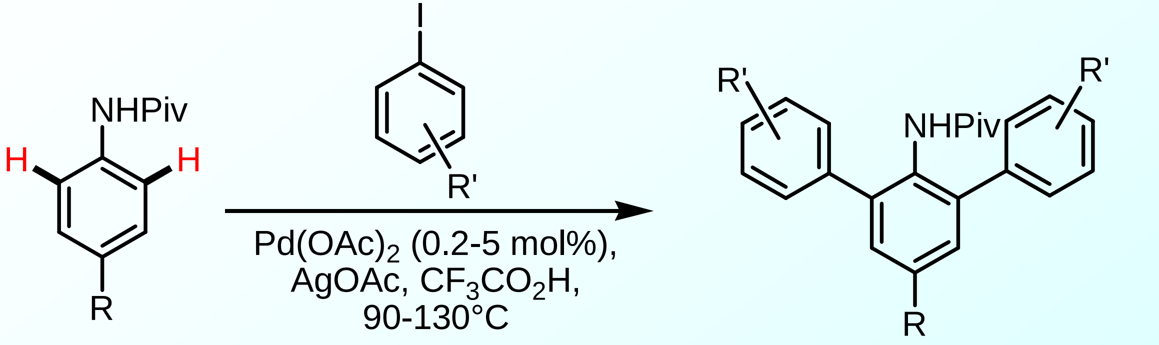
(10 mol%)

49
55%

L. Ackermann et *al. Angew. Chem. Int. Ed.* **2006**, *45*, 2619.

2.2. DG-assisted arylation of aromatic hydrocarbons

Anilides

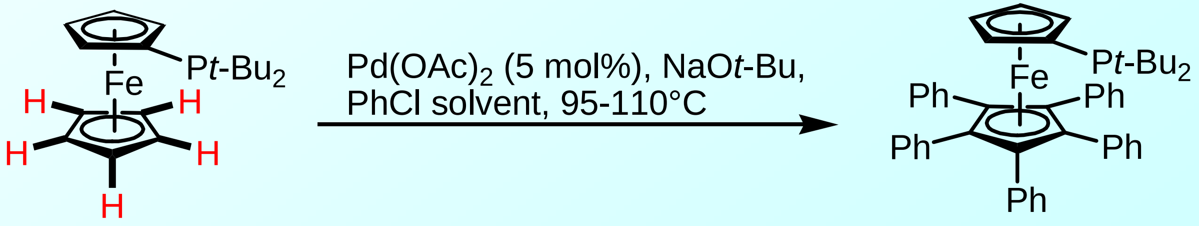


R = H, Br, I, Me
R' = H, 3-Br, 4-Me, 4-OMe, 4-CO_2Me

55-96%

O. Daugulis et *al. Angew. Chem. Int. Ed.* **2005**, *44*, 4046.

Phosphines

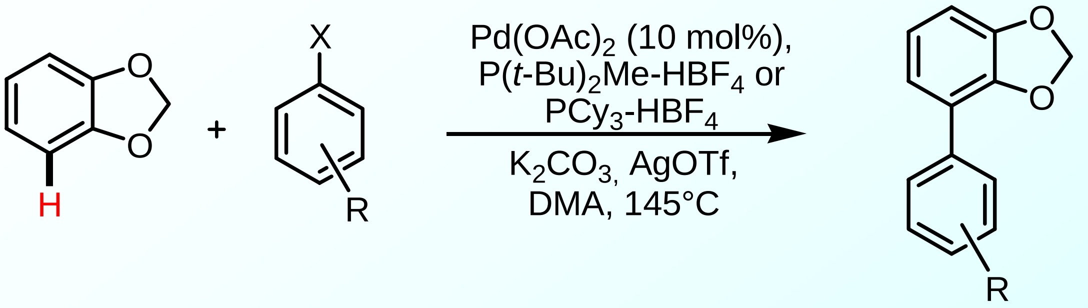


50
90%

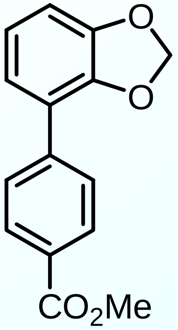
J. F. Hartwig et *al. J. Am. Chem. Soc.* **2002**, *67*, 5553.

2.2. DG-assisted arylation of aromatic hydrocarbons

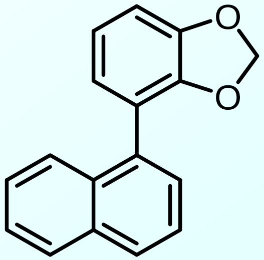
Ethers



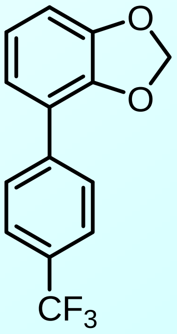
$Pd(OAc)_2$ (10 mol%),
$P(t\text{-}Bu)_2Me\text{-}HBF_4$ or
$PCy_3\text{-}HBF_4$
K_2CO_3, AgOTf,
DMA, 145°C



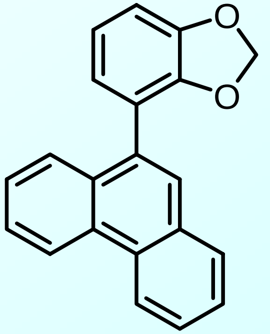
62%
(X = Cl)



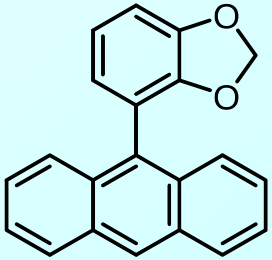
78% (X = Cl)
83% (X = Br)



86%
(X = Br)



81%
(X = Br)

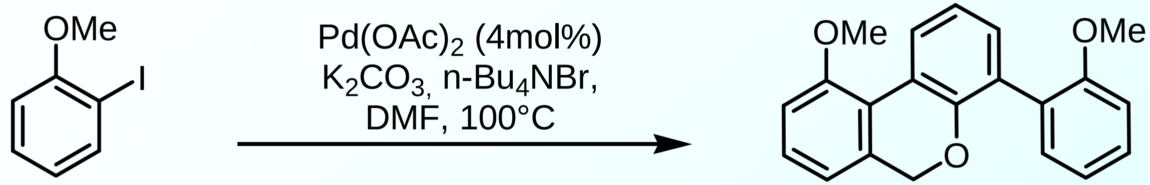


80%
(X = Br)

K. Fagnou et *al. J. Am. Chem. Soc.* **2006**, *128*, 581.

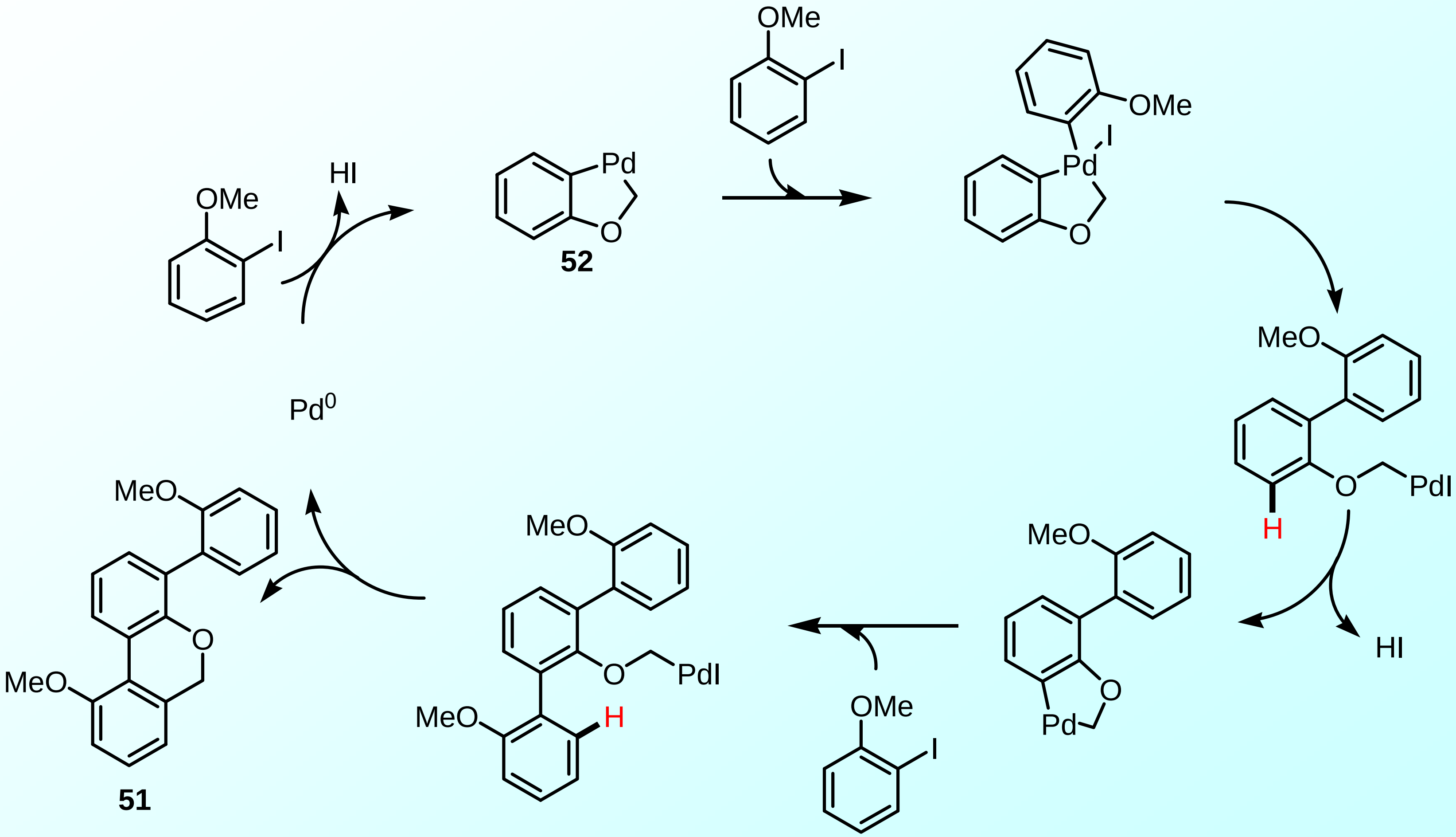
2.2. DG-assisted arylation of aromatic hydrocarbons

Alkyls



$Pd(OAc)_2$ (4mol%)
K_2CO_3, n-Bu_4NBr,
DMF, 100°C

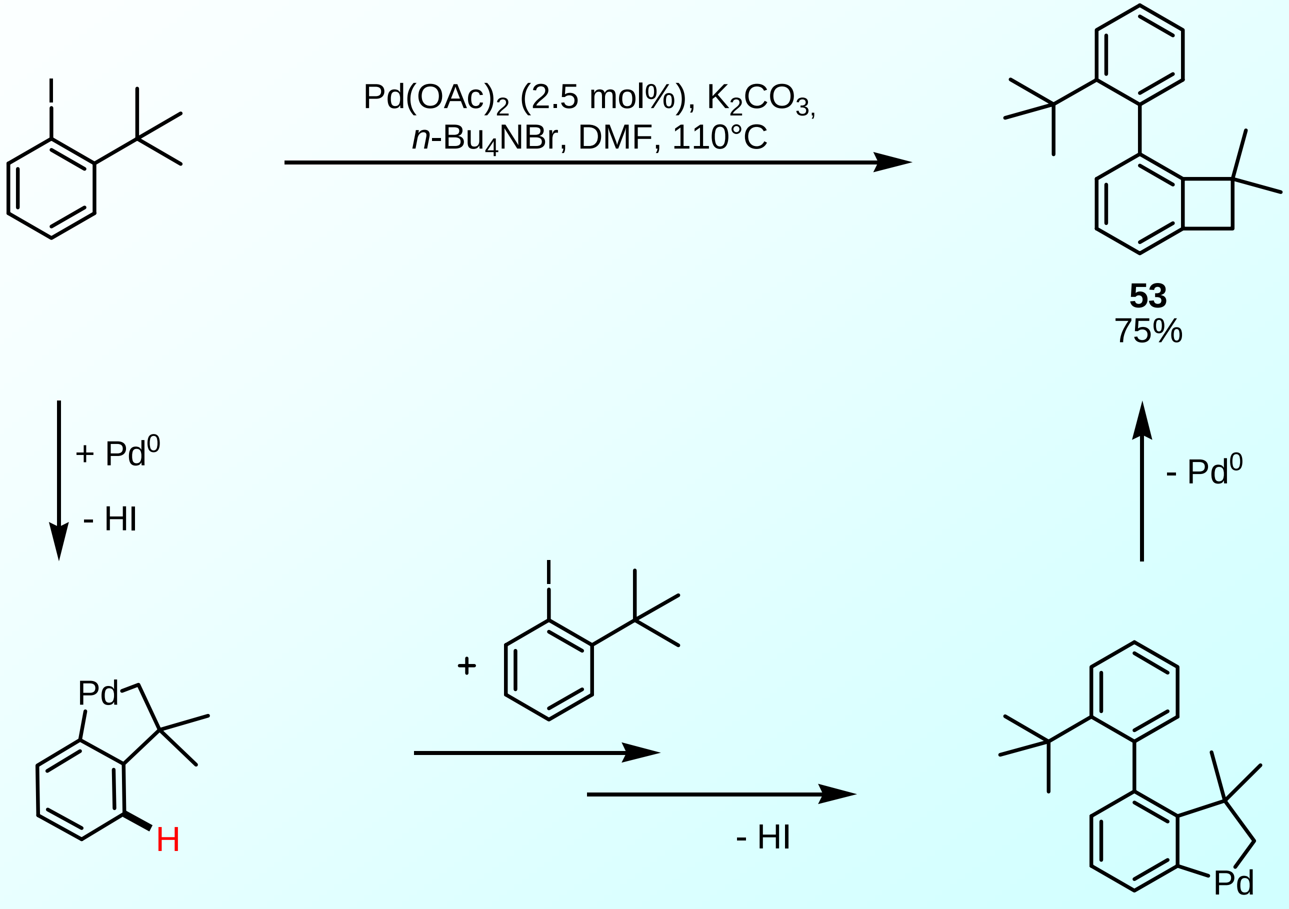
51
90%



G. Dyker et *al. J. Organomet. Chem.* **1998**, *555*, 141.

2.2. DG-assisted arylation of aromatic hydrocarbons

Alkyls



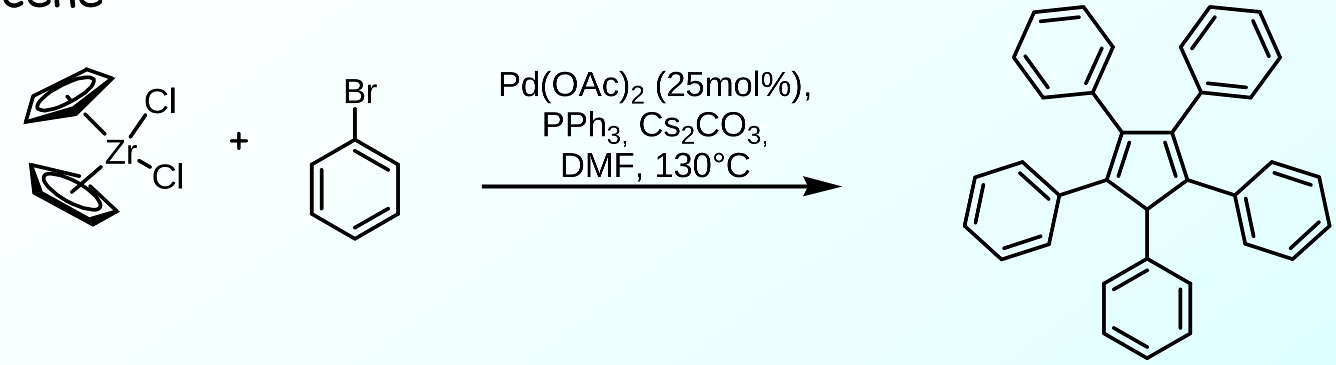
53
75%

G. Dyker et *al. Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 103.
For a paper on related process, see : O. Baudoin et *al. Angew. Chem. Int. Ed.* **2003**, *42*, 5736.

Contents

2.3. Direct arylation without directing-group

Metallocene

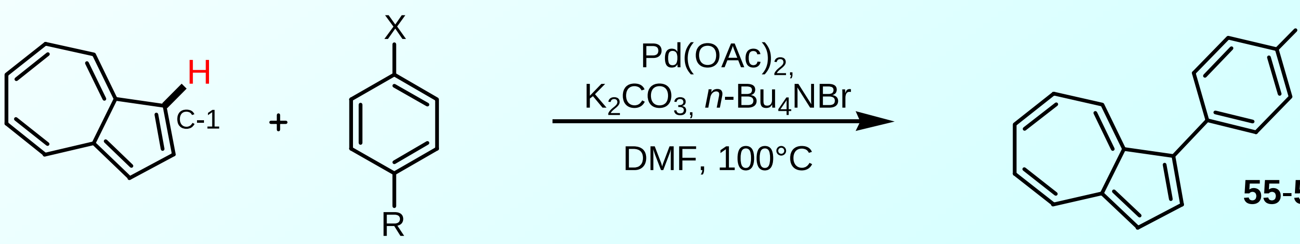


$Pd(OAc)_2$ (25mol%), PPh_3, Cs_2CO_3, DMF, 130°C

54
70%

G. Dyker, M. Miura, *Adv. Synth. Catal.* **2003**, *345*, 1127.

Azulene



$Pd(OAc)_2$, K_2CO_3, n-Bu_4NBr

DMF, 100°C

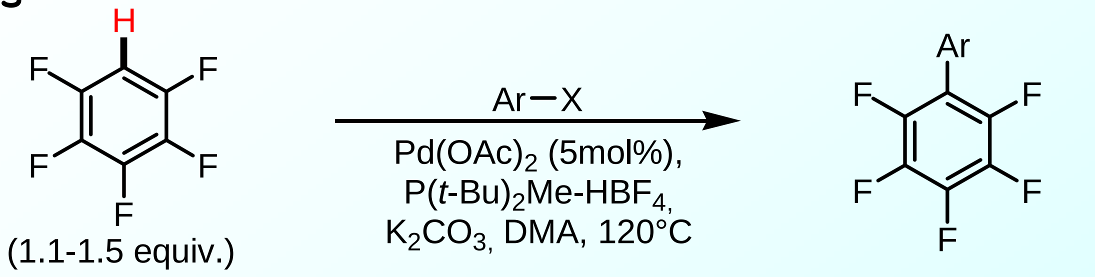
55-58

X	R	Equiv. Of ArX	$Pd(OAc)_2$	Yield
I	**H**	**5**	**5 mol%**	**5%**
I	**H**	**30**	**5 mol%**	**13%**
Cl	NO_2	**5**	**5 mol%**	**16%**
Cl	NO_2	**5**	**15 mol%**	**28%**

G. Dyker et *al. J. Organomet. Chem.* **2000**, *606*, 108.

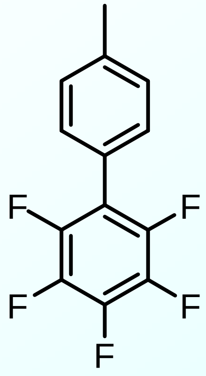
2.3. Direct arylation without directing-group

Perfluorobenzenes

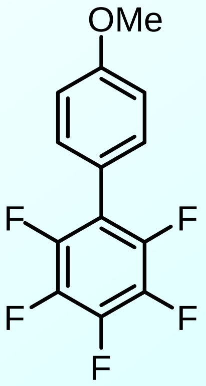


$Pd(OAc)_2$ (5mol%),
$P(t\text{-}Bu)_2Me\text{-}HBF_4$,
K_2CO_3, DMA, 120°C

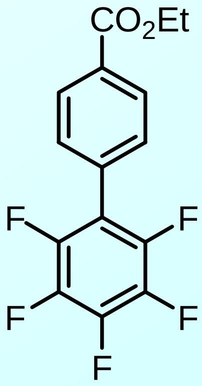
(1.1-1.5 equiv.)



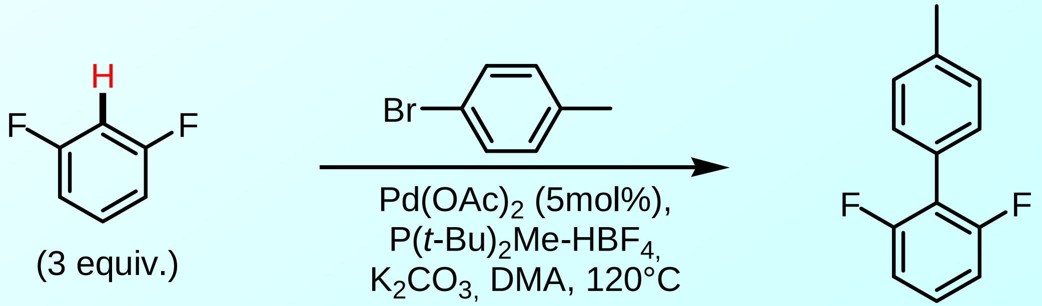
59
98%



60
76%



61
83%



(3 equiv.)

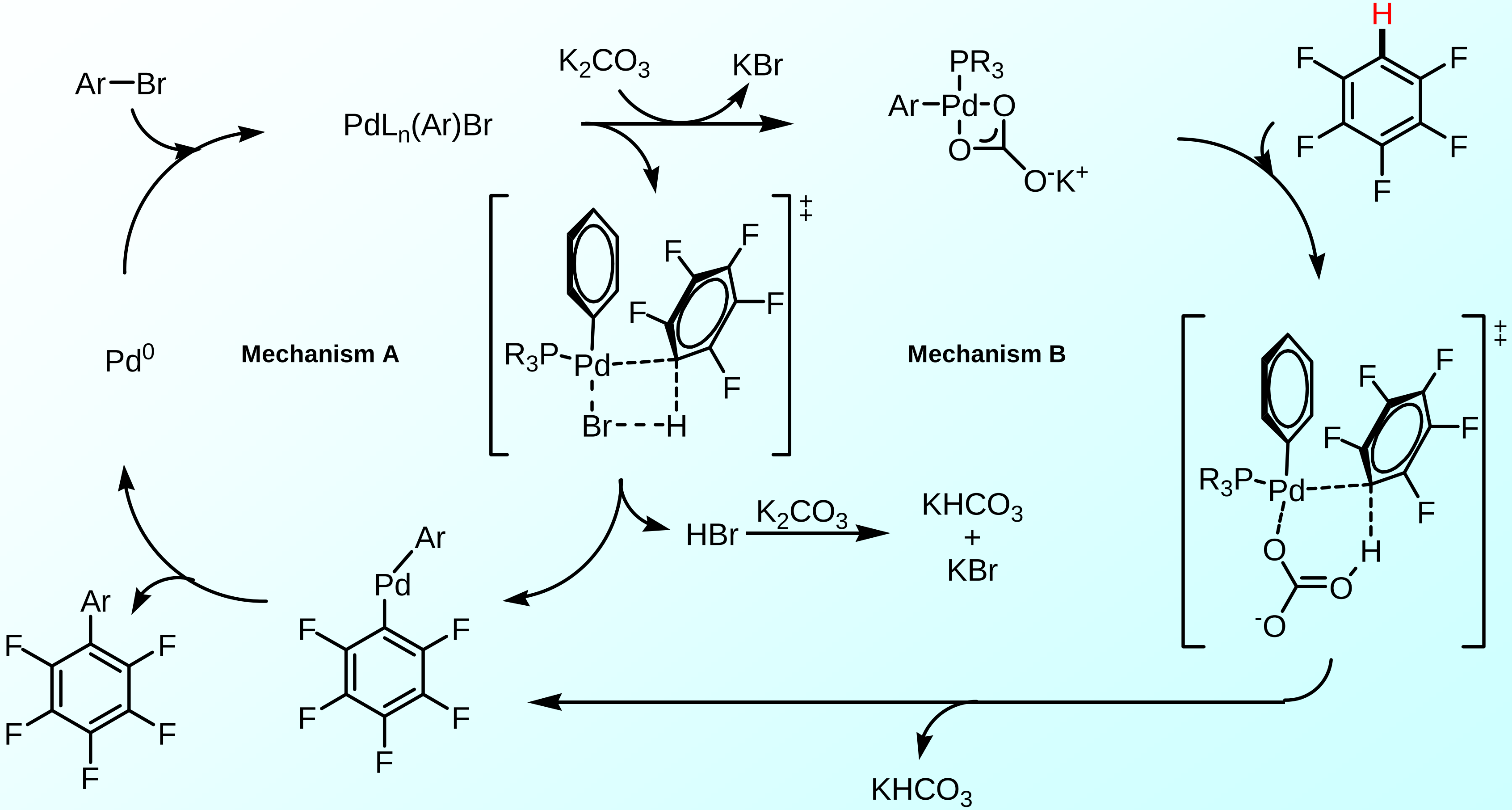
$Pd(OAc)_2$ (5mol%),
$P(t\text{-}Bu)_2Me\text{-}HBF_4$,
K_2CO_3, DMA, 120°C

62
85%
(plus 9% di-)

K. Fagnou et *al. J. Am. Chem. Soc.* **2006**, *128*, 8754.

2.3. Direct arylation without directing-group

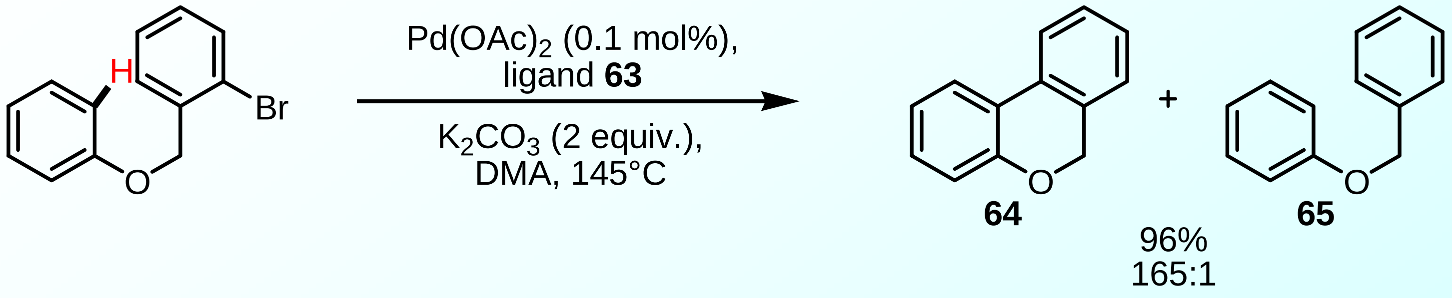
Perfluorobenzenes



Contents

3. Intramolecular aryl-aryl bond formation

Direct arylation

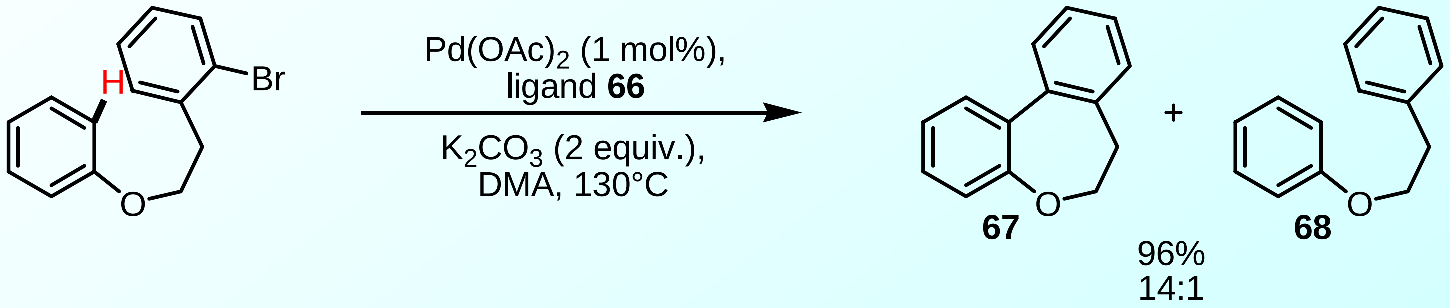


Pd(OAc)$_2$ (0.1 mol%),
ligand **63**

K$_2$CO$_3$ (2 equiv.),
DMA, 145°C

64 + **65**

96%
165:1

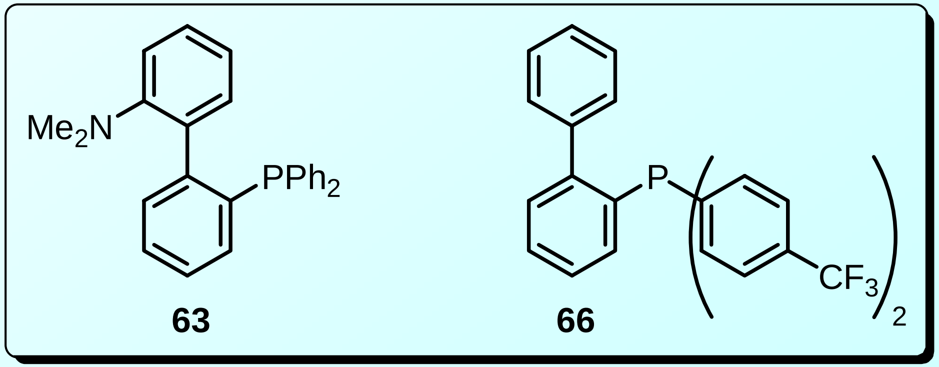


Pd(OAc)$_2$ (1 mol%),
ligand **66**

K$_2$CO$_3$ (2 equiv.),
DMA, 130°C

67 + **68**

96%
14:1

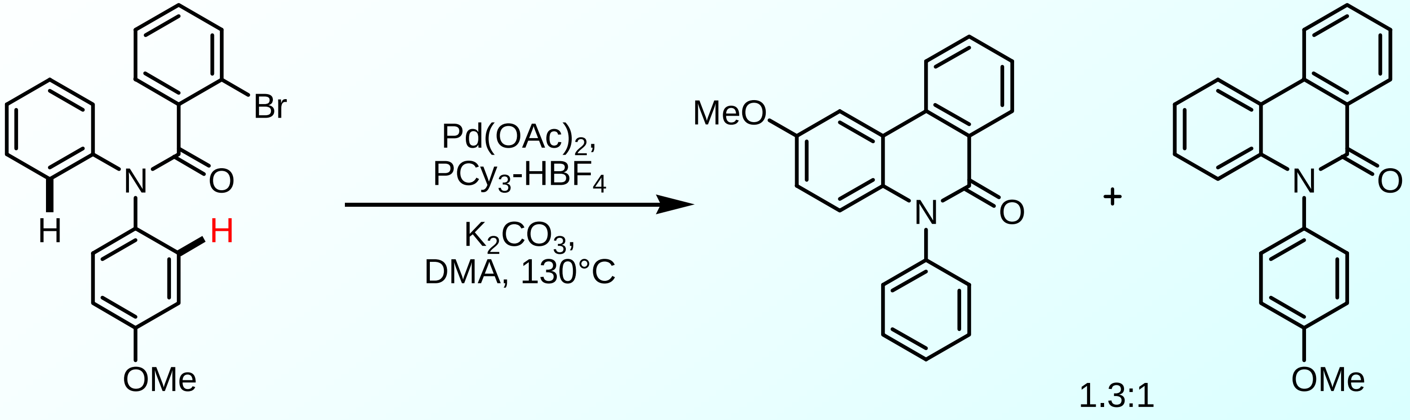


63 **66**

K. Fagnou et *al. J. Am. Chem. Soc.* **2004**, *126*, 9186.

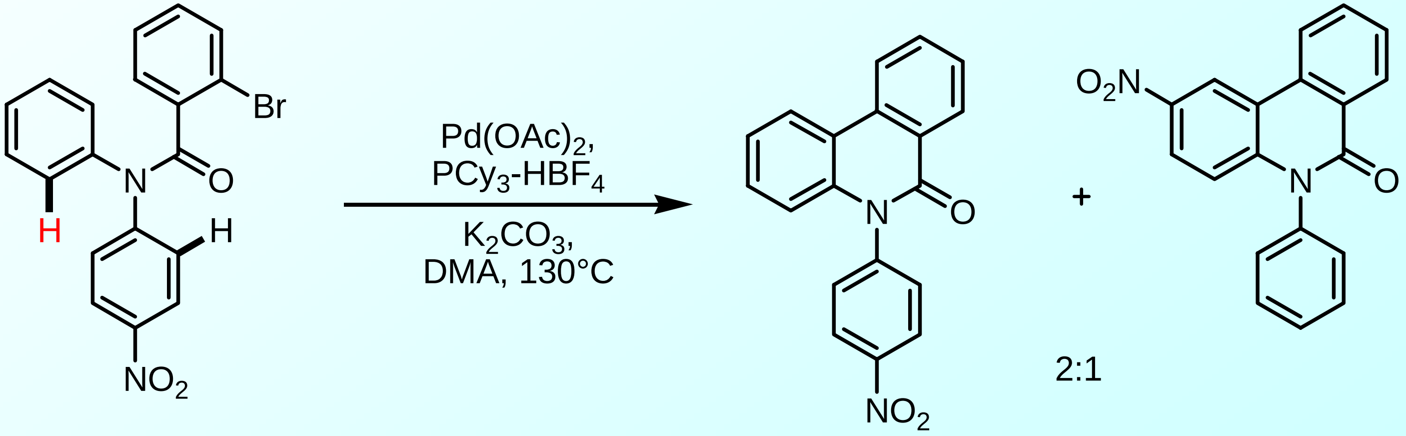
3. Intramolecular aryl-aryl bond formation

Electron-poor vs. Electron-rich arene



1.3:1

69 **70**



2:1

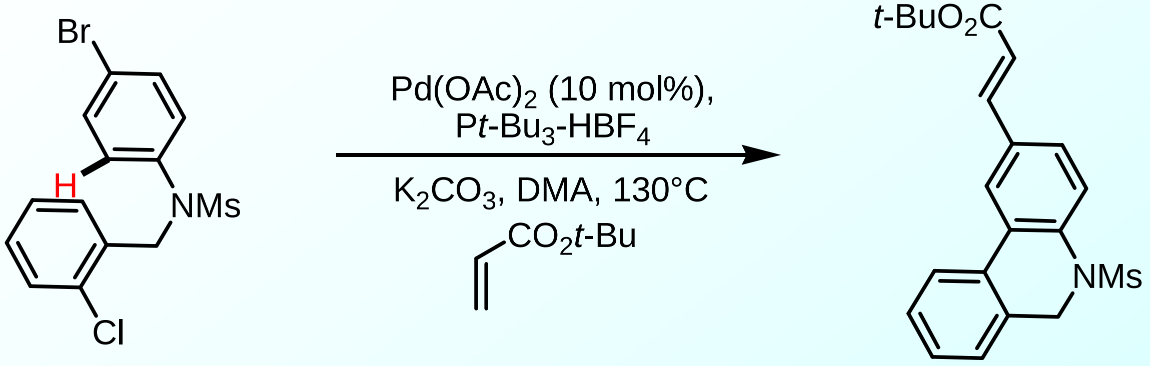
71 **72**

⇨ Electron-rich arenes

K. Fagnou et *al. J. Am. Chem. Soc.* **2006**, *128*, 581.

3. Intramolecular aryl-aryl bond formation

Tandem Heck/direct arylation sequence

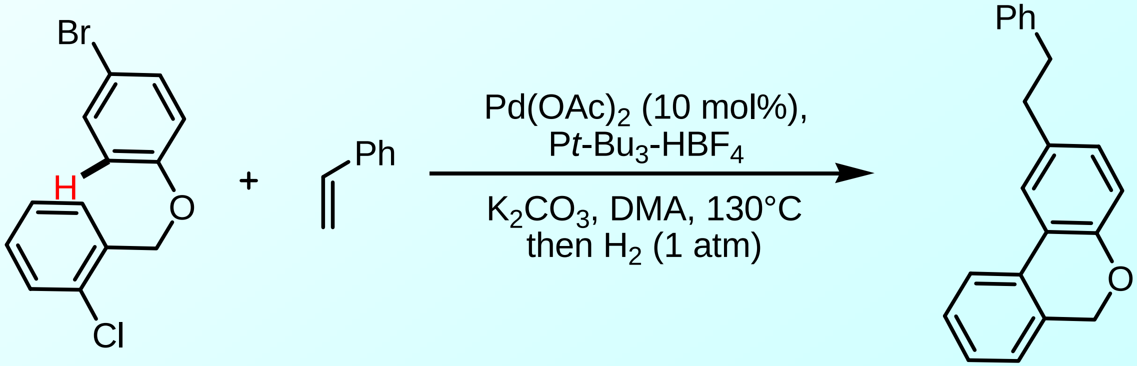


Pd(OAc)$_2$ (10 mol%),
Pt-Bu$_3$-HBF$_4$
K$_2$CO$_3$, DMA, 130°C

73
71%

K. Fagnou et *al. J. Org. Chem.* **2006**, *71*, 1711.

Tandem Heck/direct arylation/hydrogenation sequence



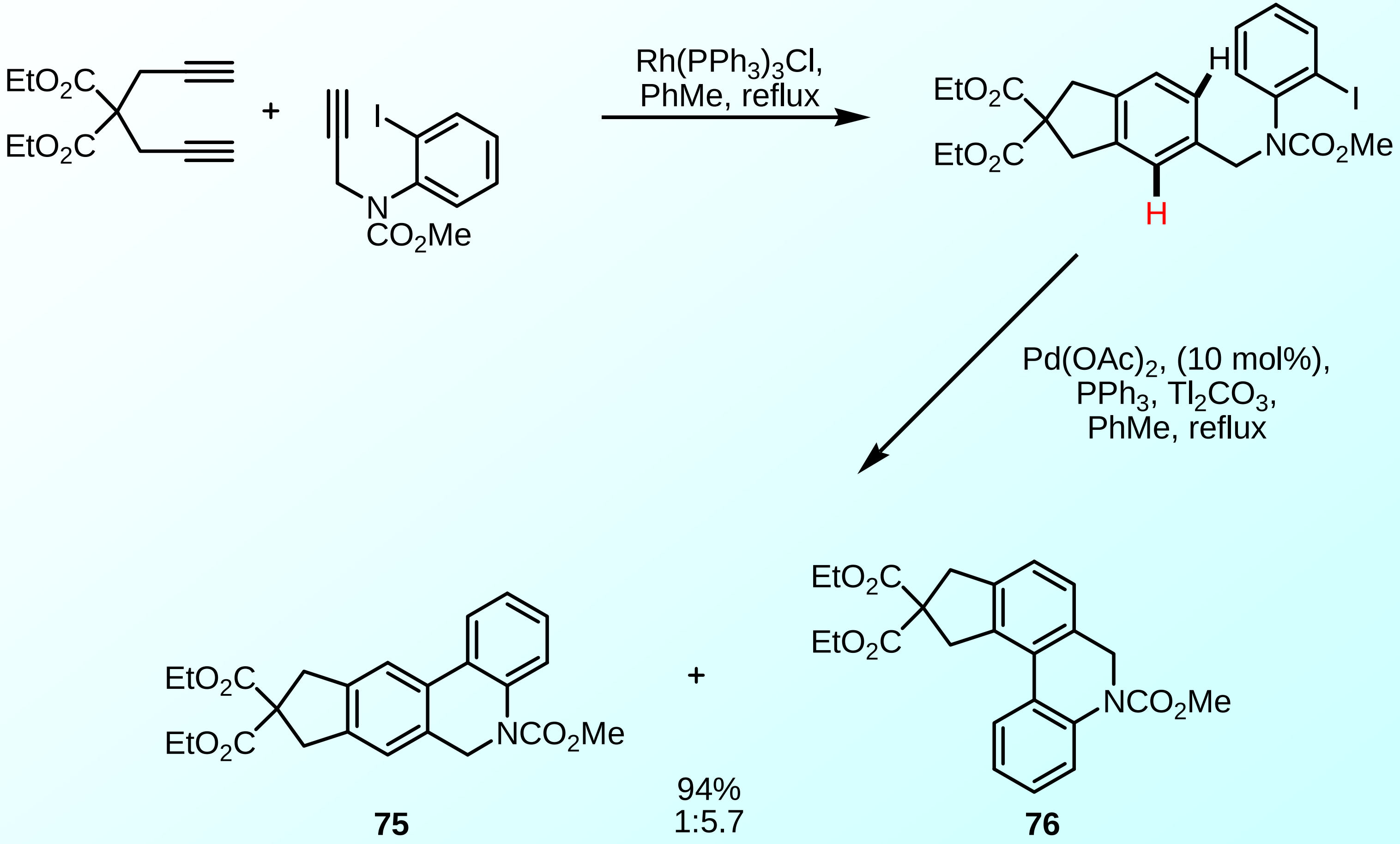
Pd(OAc)$_2$ (10 mol%),
Pt-Bu$_3$-HBF$_4$
K$_2$CO$_3$, DMA, 130°C
then H$_2$ (1 atm)

74
69%

K. Fagnou et *al. J. Org. Chem.* **2006**, *71*, 1711.

3. Intramolecular aryl-aryl bond formation

[2+2+2] cycloaddition followed by direct arylation



$Rh(PPh_3)_3Cl$, PhMe, reflux

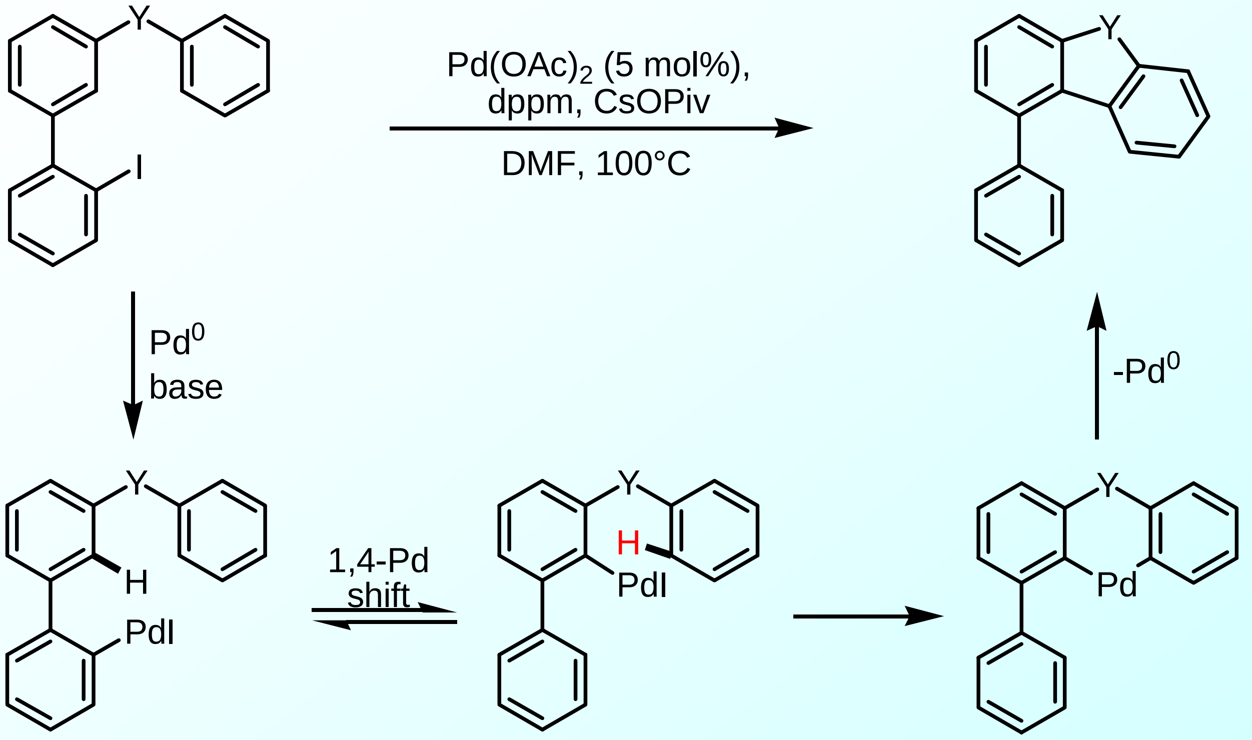
$Pd(OAc)_2$, (10 mol%), PPh_3, Tl_2CO_3, PhMe, reflux

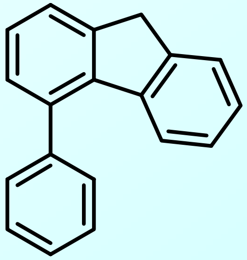
94%
1:5.7

R. Grigg et *al. Tetrahedron Lett.* **2000**, *41*, 3003.

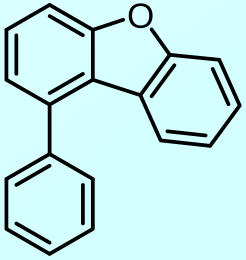
3. Intramolecular aryl-aryl bond formation

Palladium migration





77
40%



78
89%

R. C. Larock et *al. J. Am. Chem. Soc.* **2003**, *125*, 11506.
R. C. Larock et *al. J. Org. Chem.* **2004**, *69*, 8251.

Contents

Introduction

1. Direct arylation of aryl C-H bonds

2. Intermolecular aryl-aryl bond formation

   2.1. Cascade reactions involving alkenes and alkynes

   2.2. Directing-group-assisted arylation of aromatic hydrocarbons

   2.3. Direct arylation without directing-group

3. Intramolecular aryl-aryl bond formation

4. Applications in synthesis of natural products

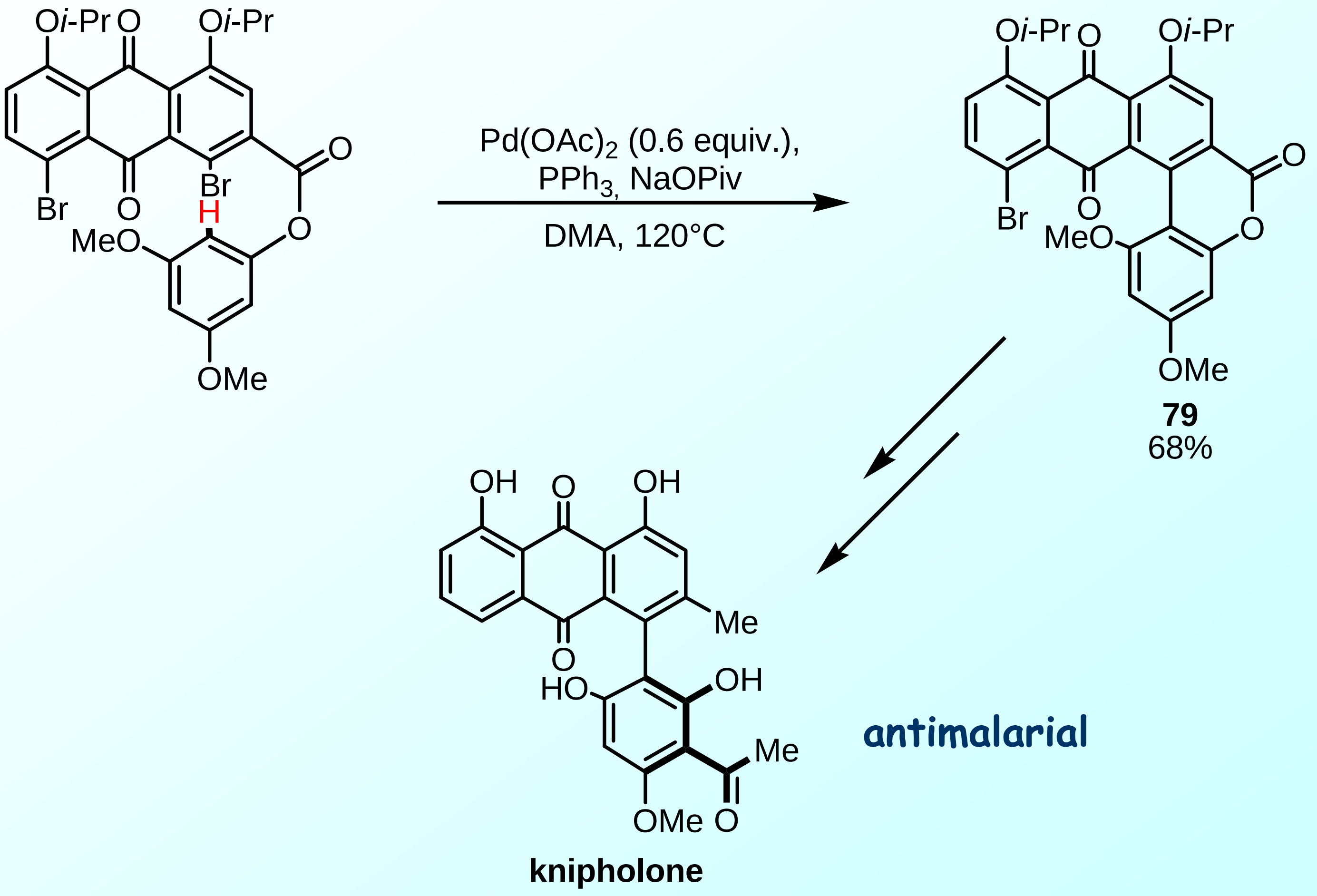
5. Direct arylation of heteroaryl C-H bonds

6. The challenging reaction

Conclusion

4. Application in synthesis of natural products

Lactone method for atropoenantioselective synthesis of knipholone



$Pd(OAc)_2$ (0.6 equiv.), PPh_3, NaOPiv

DMA, 120°C

79
68%

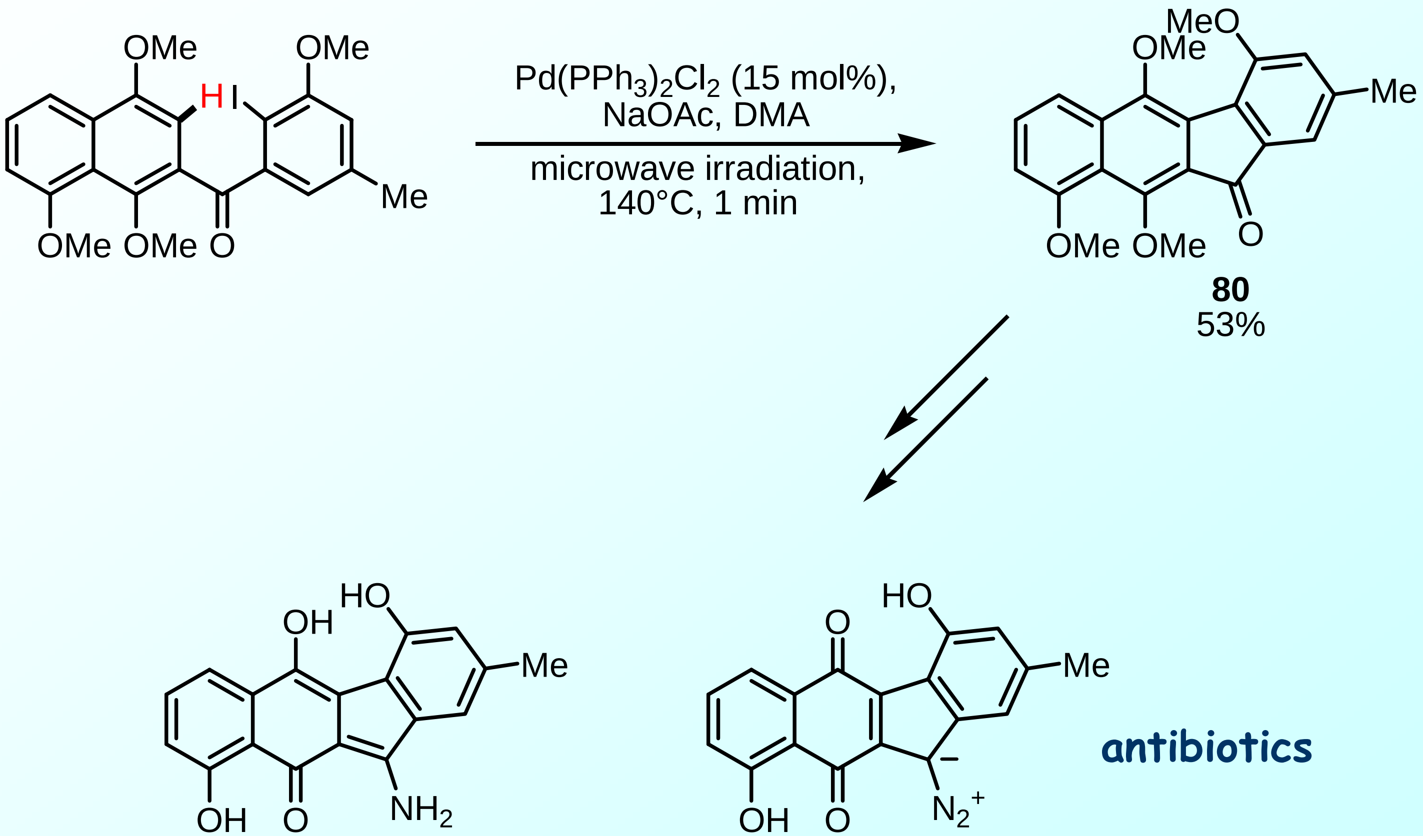
knipholone

antimalarial

G. Bringmann et *al. Angew. Chem. Int. Ed.* **2001**, *40*, 1687.
G. Bringmann et *al. J. Org. Chem.* **2002**, *67*, 5595.
For enantioselective ring-opening, see Bringmann, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 761.

4. Application in synthesis of natural products

Rare microwave heating for access to benzo[*b*]fluorenone



80
53%

stealthin C

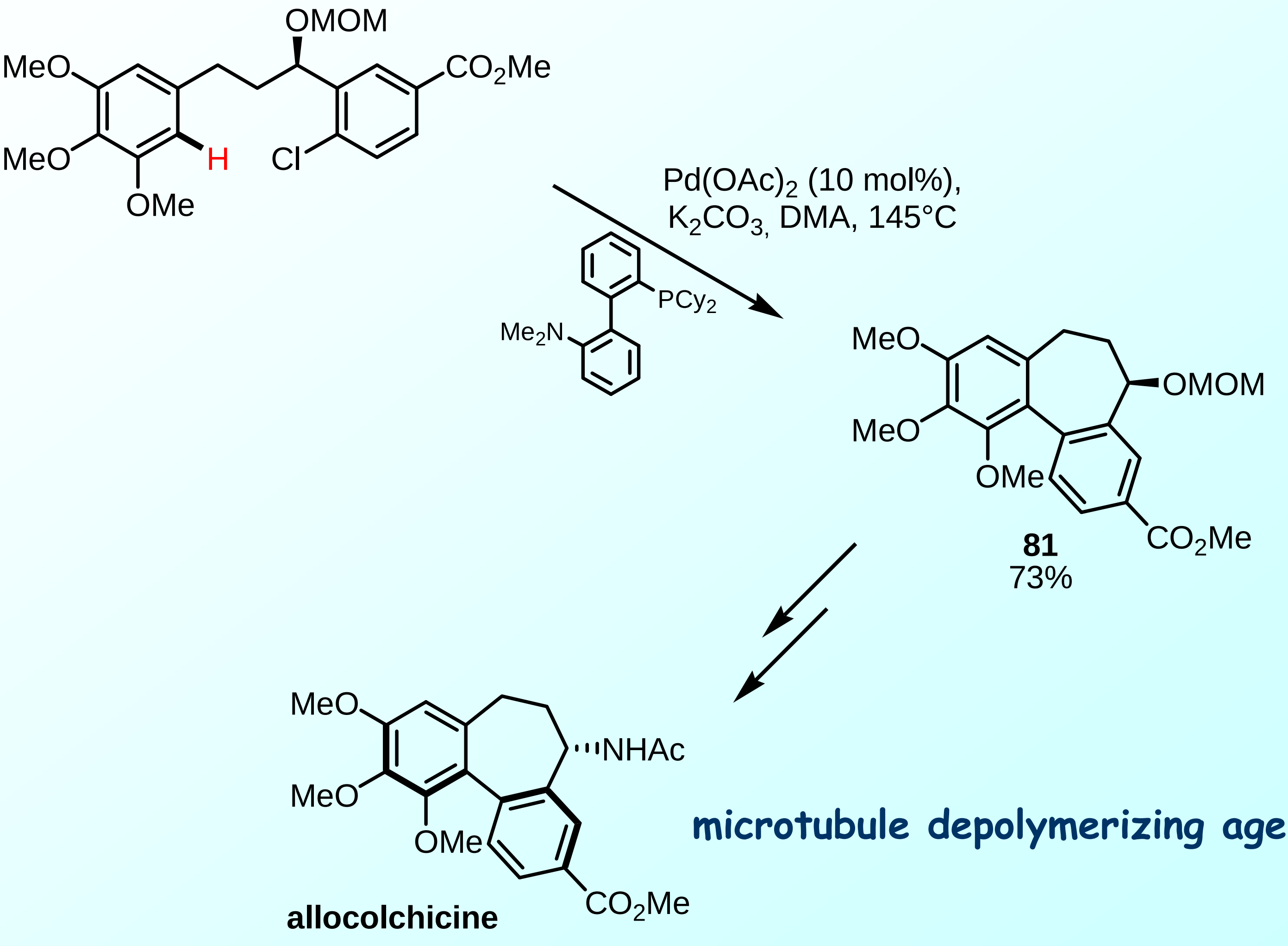
prekinamycin

antibiotics

G. Qabaja, G. B. Jones, *J. Org. Chem*. **2000**, *65*, 7187
G. Qabaja, G. B. Jones*, Tetrahedron Lett.* **2000**, *41*, 5317.

4. Application in synthesis of natural products

Enantioselective synthesis of allocolchicine



$Pd(OAc)_2$ (10 mol%), K_2CO_3, DMA, 145°C

81
73%

allocolchicine

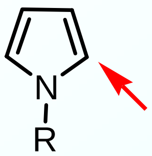
microtubule depolymerizing agent

K. Fagnou, M. Leblanc, *Org. Lett.* **2005**, *7*, 2849.

Contents

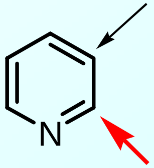
5. Direct arylation of heteroaryl C-H bonds

Pyrroles



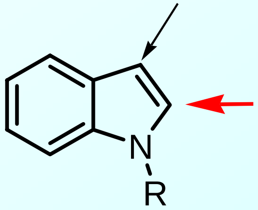
Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996.

Pyridines



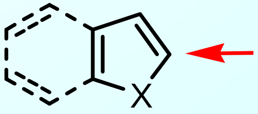
Sasson, *J. Chem. Soc., Perkin Trans.* **2000**, *2*, 1809.

Indoles



Sames, *J. Am. Chem. Soc.* **2005**, *127*, 7171.

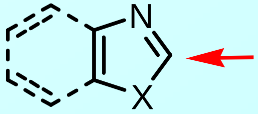
Benzofuranes
Benzothiophène



X = O, S

Ohta, *Heterocycles* **1992**, *33*, 257.

Benzimidazoles
Benzoxazoles
Benzothiazole



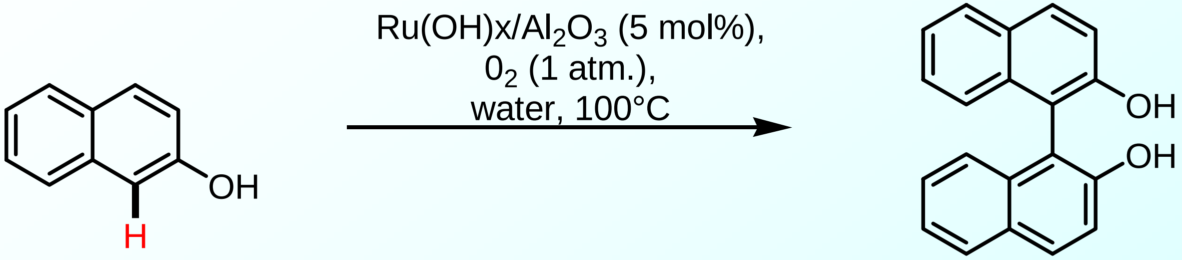
X = N, O, S

Bellina *Eur. J. Org. Chem.* **2006**, 1379.

Contents

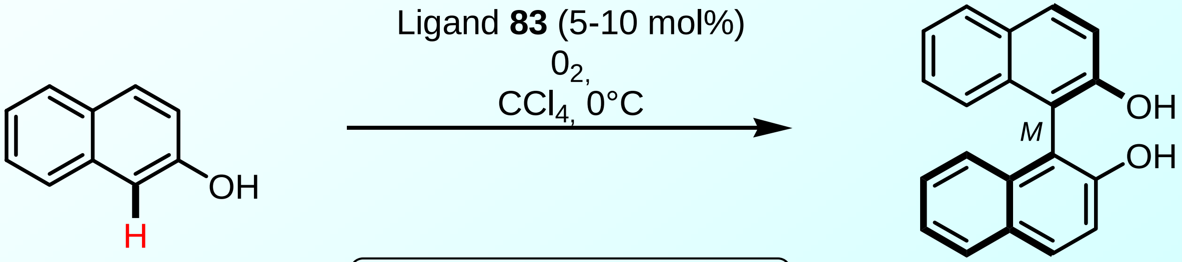
6. The challenging reaction

Oxidative coupling reaction : binaphtols



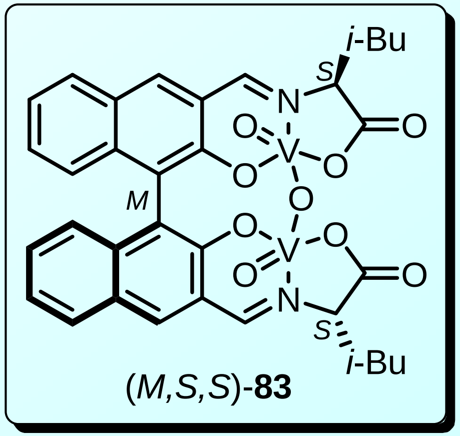
$Ru(OH)x/Al_2O_3$ (5 mol%),
O_2 (1 atm.),
water, 100°C

82
98%



Ligand **83** (5-10 mol%)
O_2,
CCl_4, 0°C

82
95%
ee = 83%

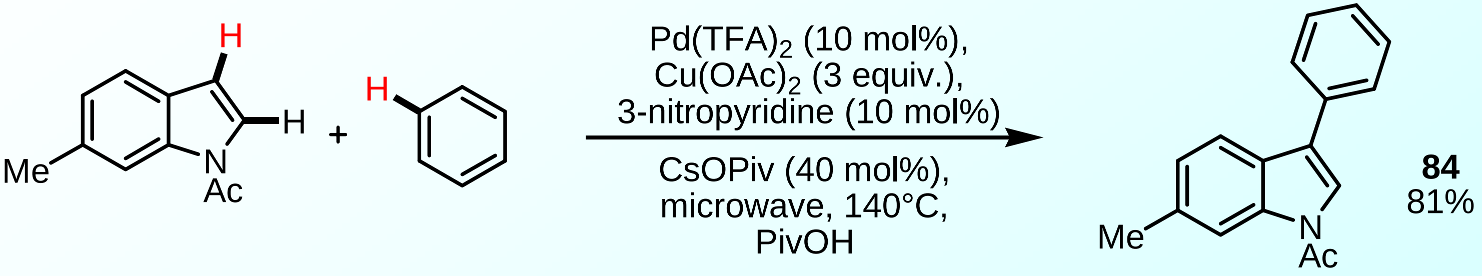


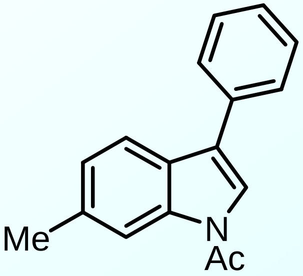
(*M*,*S*,*S*)-**83**

N. Mizuno et *al. J. Am. Chem. Soc.* **2005**, *127*, 6632.
L. Gong et *al. Angew. Chem. Int. Ed.* **2002**, *41*, 4532.

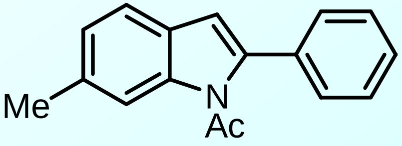
6. The challenging reaction

Oxidative coupling reaction : indole-benzene

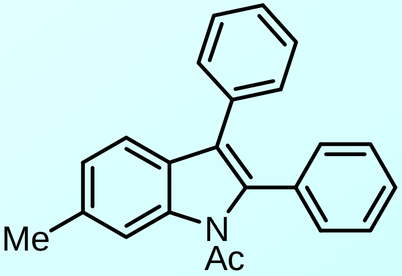




84



85



86

ratio : 10:1:0.6

Regioselective
No prefunctionalization of arenes required
Limitation of waste

K. Fagnou, D. R. Stuart, *Science* **2007**, *316*, 1172.

Conclusion

Direct arylation

Versatile method (different systems of bases, ligands, metal…)

⇨ Make direct arylation more and more regio- and chimioselective

Formation of a wide range of aryl-aryl bonds

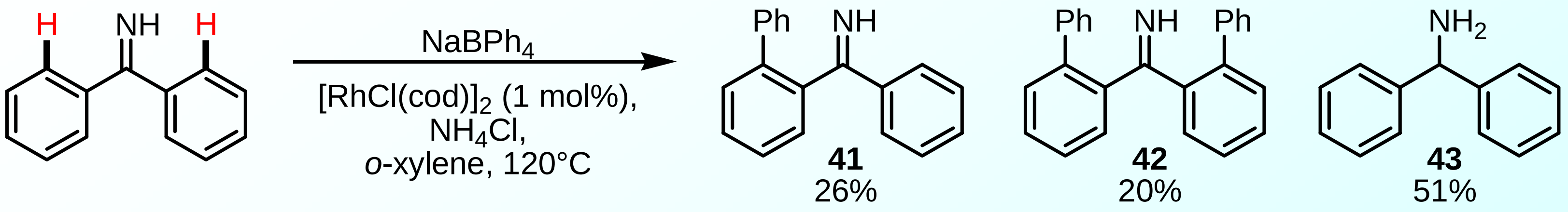
Formation of a wide range of heteroaryl-heteroaryl bonds

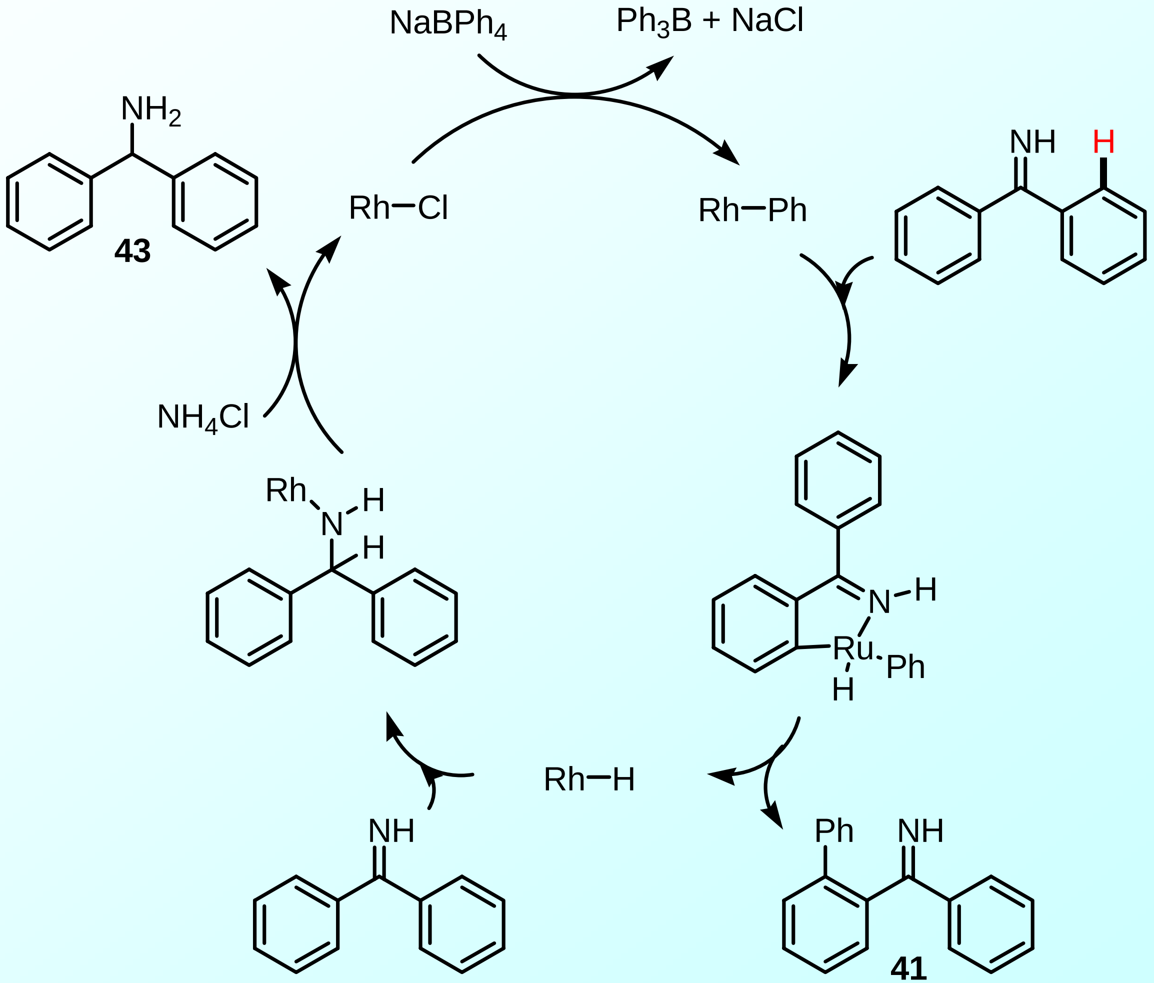
Development of milder, lower temperature systems, catalyst systems, use of aryl chlorides, preventing waste…

⇨ Make direct arylation more and more industrially attractive

2.2. DG-assisted arylation of aromatic hydrocarbons

Imines





M. Miura et *al. Org. Lett.* **2005**, *7*, 2229.