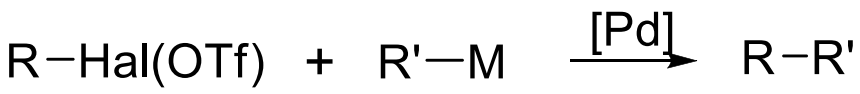
MODERN CROSS-COUPLING

I.P.Beletskaya

WSOC-2017, Krasnovidovo, 13-18 Jan. 2017

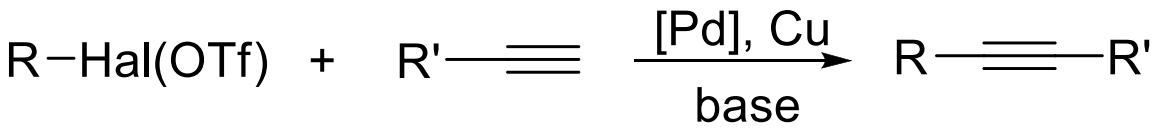
Cross-coupling reactions



R=Ar, Vinyl; R'=Ar, Vinyl, Alk

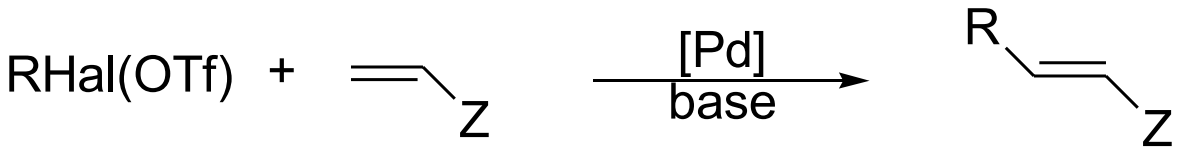
M = MgX (Tamao - Kumada)
= SnR_3 (Migita - Kosugi - Stille)
= ZnX (Negishi)
= $B(OH)_2$ (Suzuki - Miyaura)
= SiR_3 (Hiyama)

Sonogashira - Hagihara



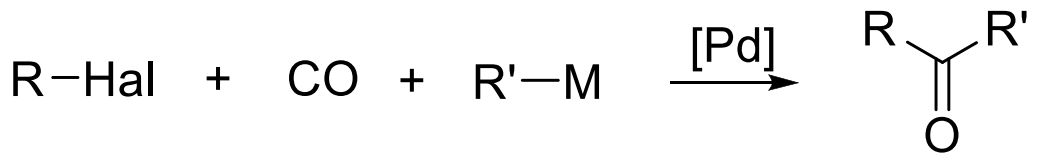
R=Ar, Vinyl; R'=Ar, Alk

Mizoroki-Heck reaction



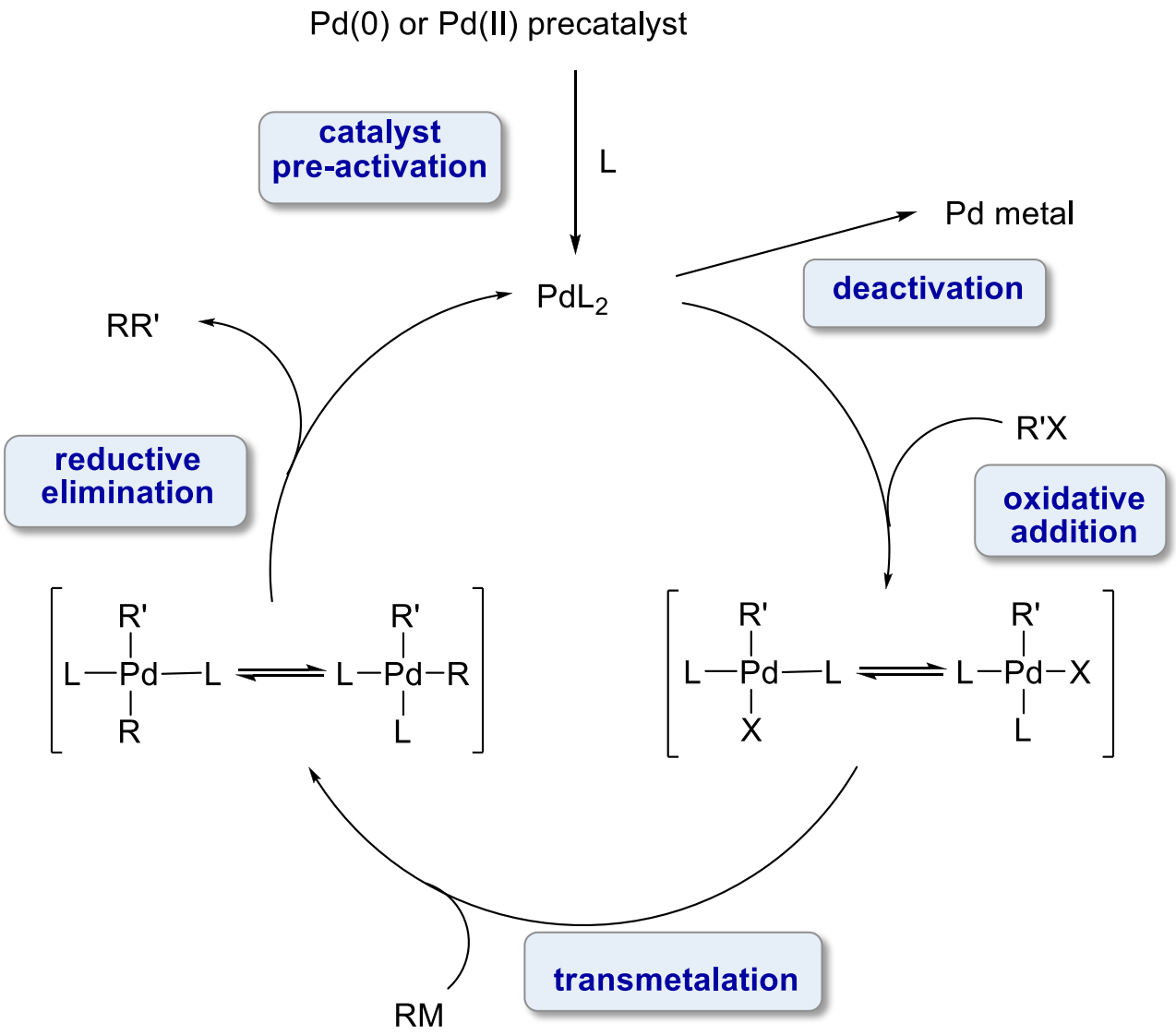
R = Ar, vinyl
Z = Ar, COOH, COOR, CN

Carbonylation

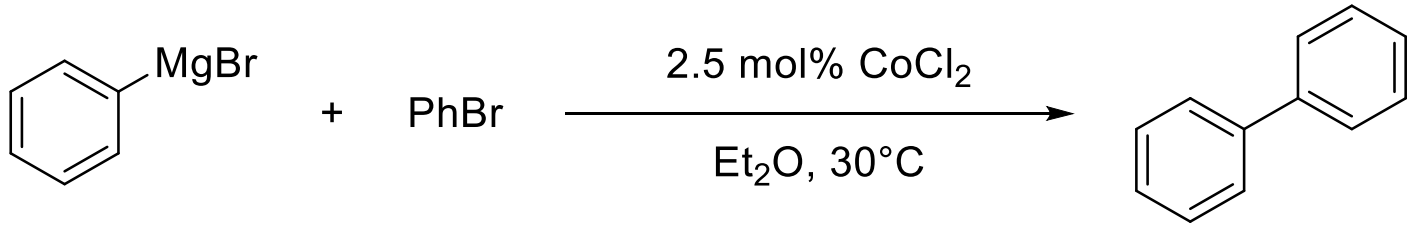


R=Ar, Vinyl;
HNu = H_2O, ROH, RNH_2, R_2NH, RSH

Catalytic cycle of Pd-catalyzed reactions

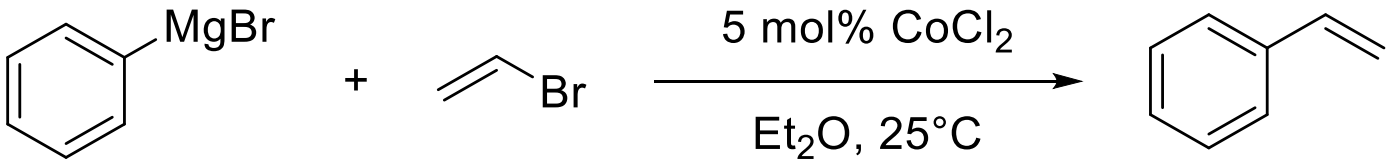


Co-catalyzed cross-coupling



86%

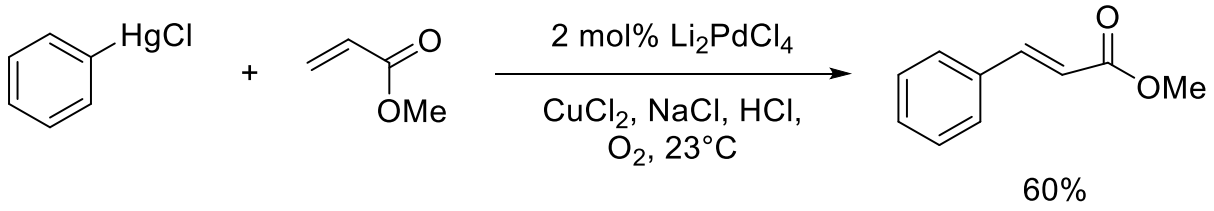
Kharasch 1941



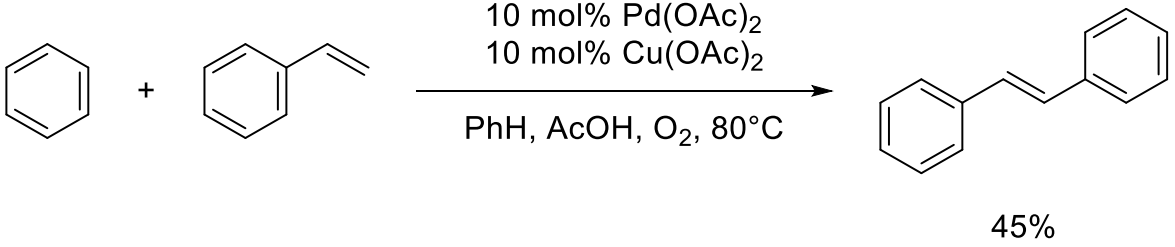
56%

1943

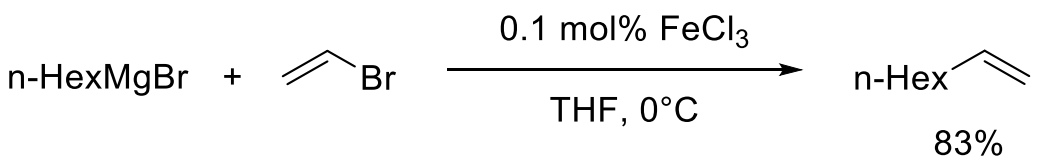
Pd-catalyzed Heck-reaction



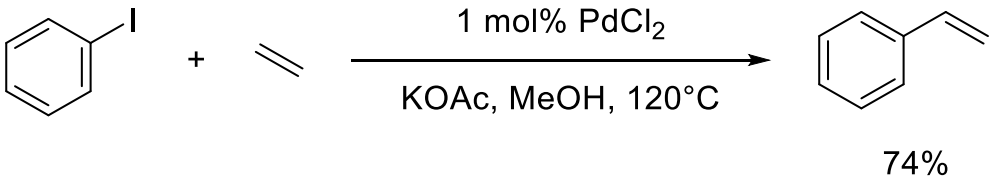
Heck, 1968



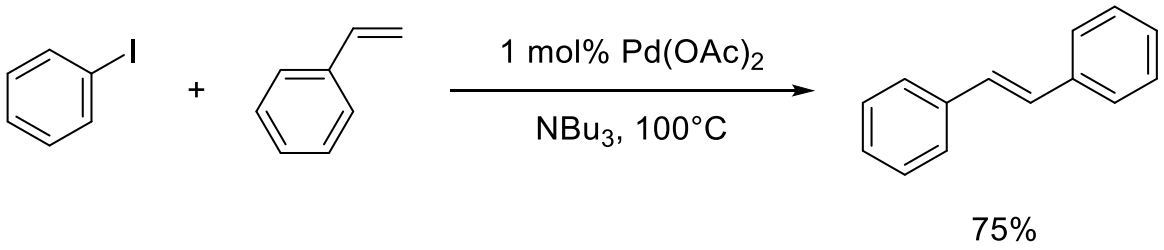
Fujiwara, Moritani 1969



1971

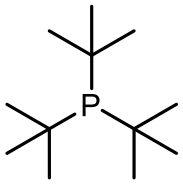


Mizoroki, 1971

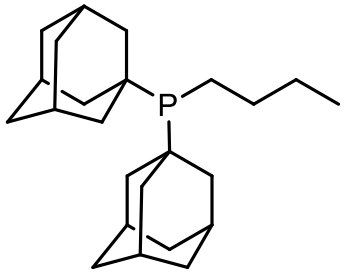


Heck, 1972

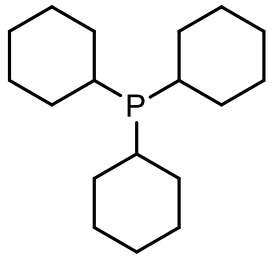
Electron-rich bulky monodentate phosphine ligands



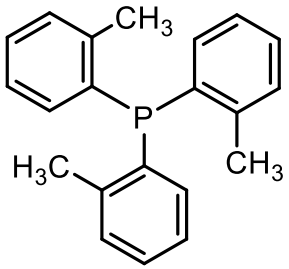
t-Bu$_3$P



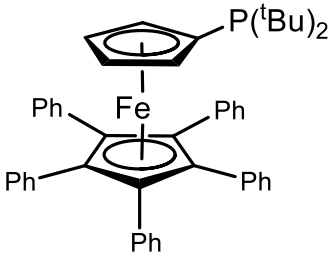
Ad$_2$(n-Bu)P



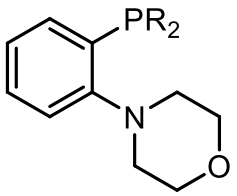
Cy$_3$P



(o-tolyl)$_3$P

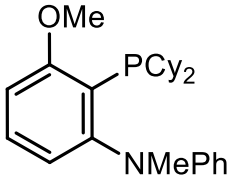


Q-Phos



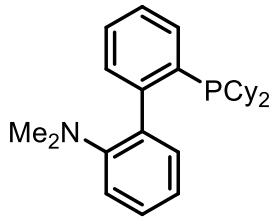
Mor-DalPhos (1-Ad)

R=2-tolyl

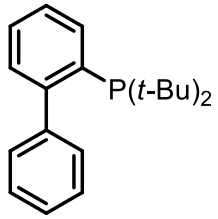


Zheda-Phos

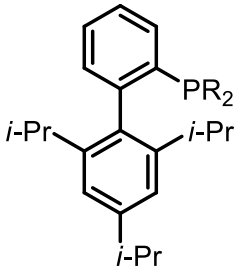
Monodentate biaryl phosphine ligands



DavePhos

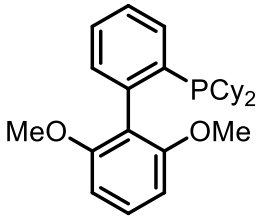


JohnPhos

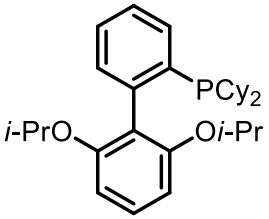


XPhos **R=Cy**

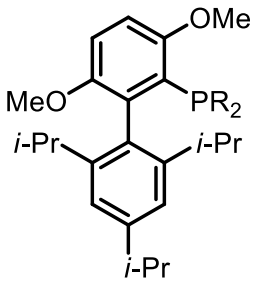
***t*-BuXPhos** **R=Bu^t**



SPhos



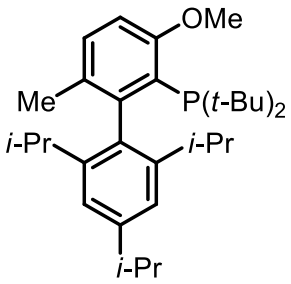
RuPhos



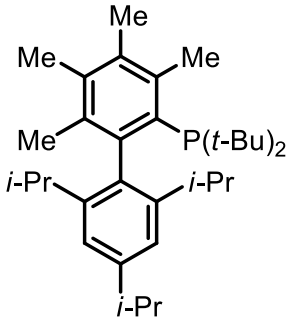
BrettPhos **R=Cy**

***t*-BuBrettPhos** **R=Bu^t**

R=AdBrettPhos

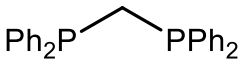


RockPhos

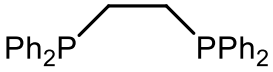


Me$_4$*t*-BuXPhos

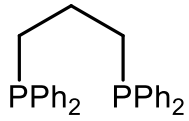
Chelating ligands



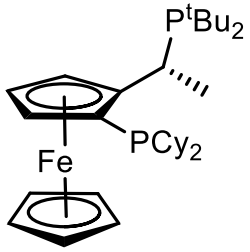
dppm
73°



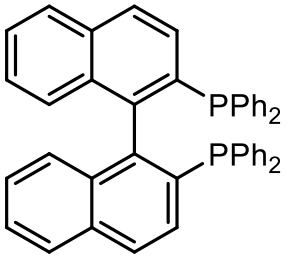
dppe
86°



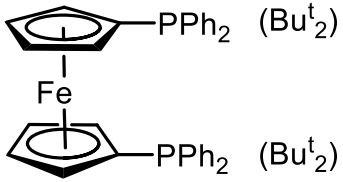
dppp
91°



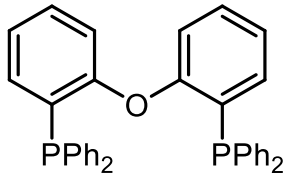
JosPhos



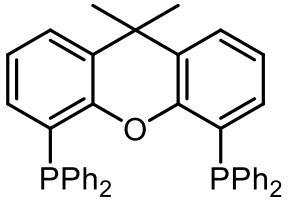
Binap
93°



dppf 99°
dtbpf 104°

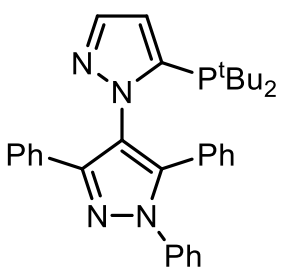


DPEPhos
104°



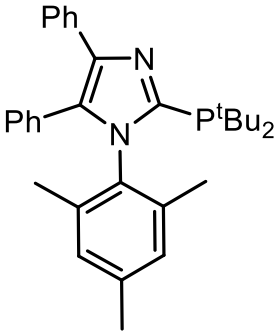
XantPhos
108°

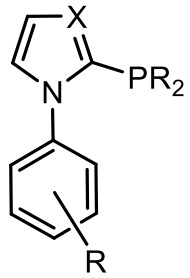
Heterobiarylphosphine ligands



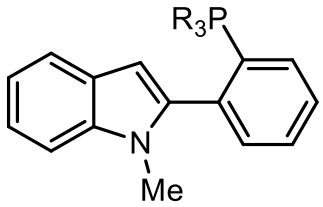
BippyPhos

Singer





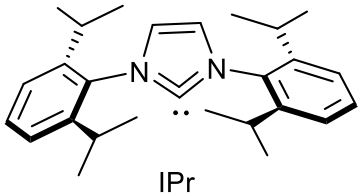
Beller



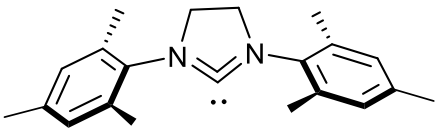
Kwong

N-heterocyclic carbenes

Первое поколение нагруженных NHC



IPr



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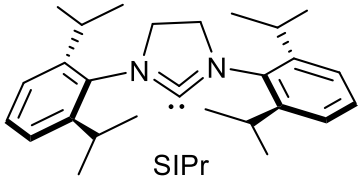
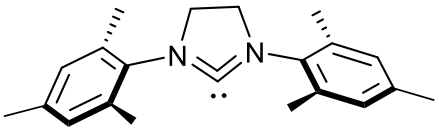
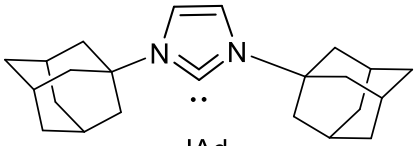


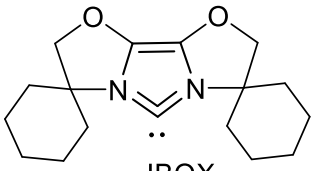
SIPr



SIMes

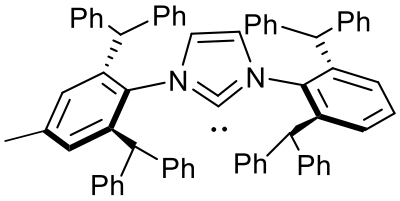


IAd

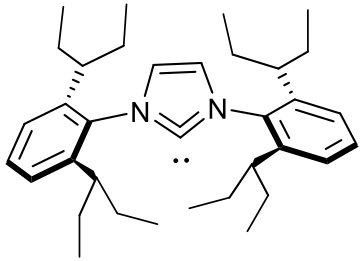


IBOX

Второе поколение нагруженных NHC

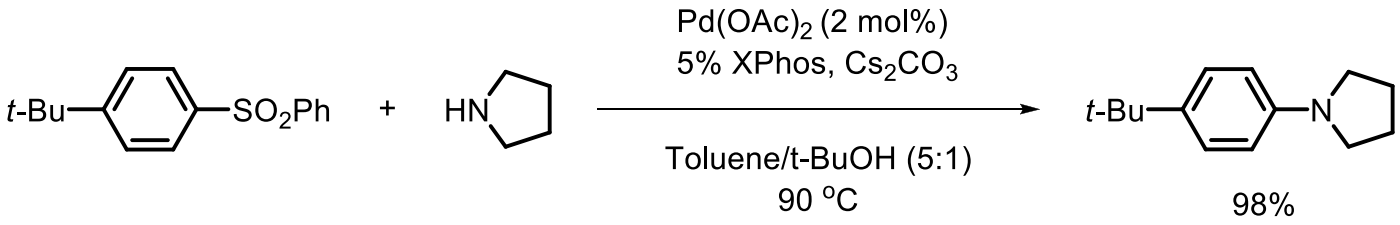


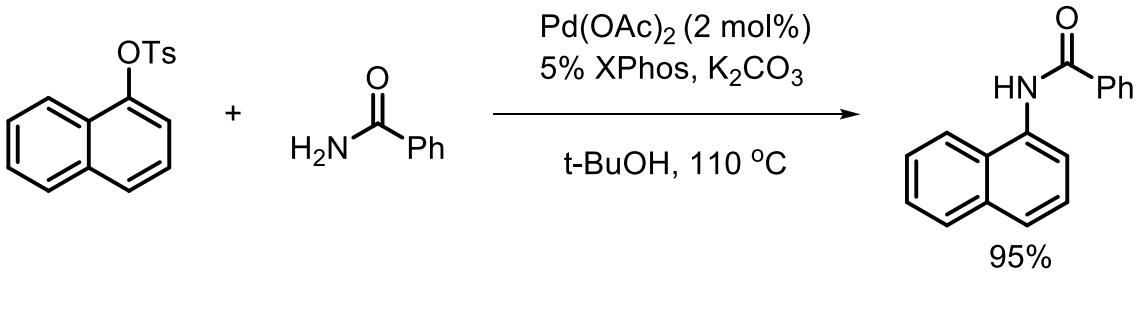
IPr*

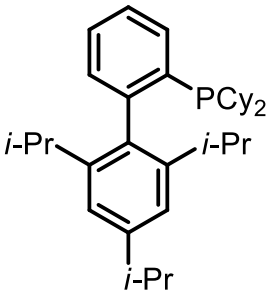


IPent

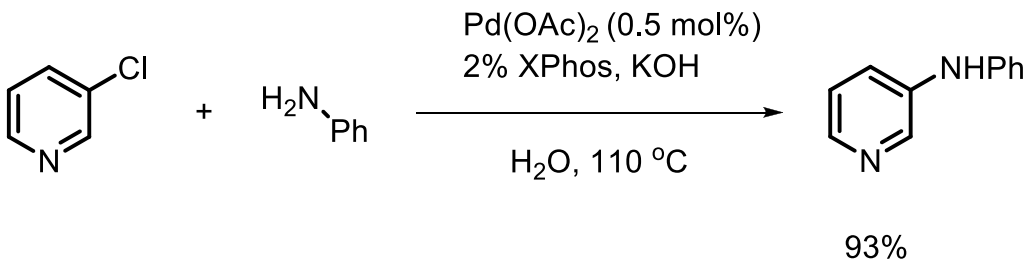
“Проблемные” реакции C-N кросс-сочетания, решенные с помощью Pd/XPhos



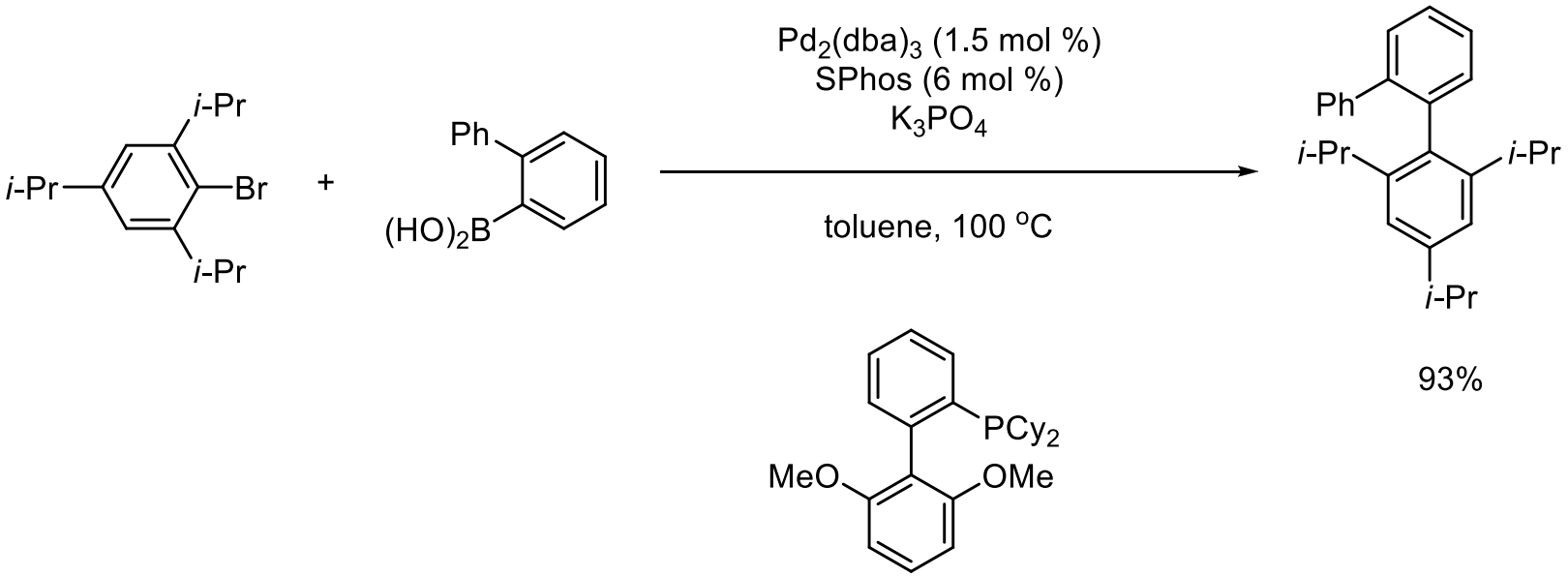




XPhos

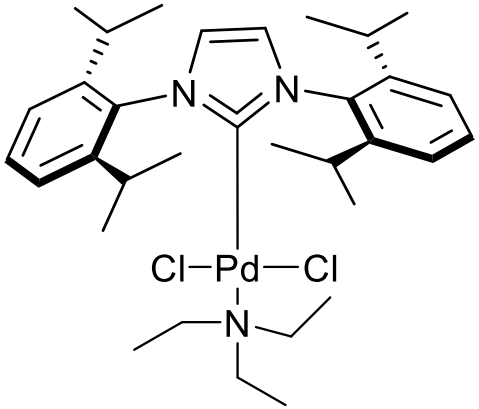


Formation of highly hindered biaryls via S-M coupling



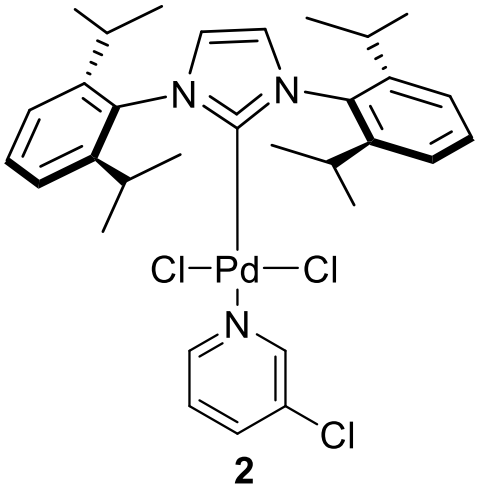
SPhos

Precatalysts in S-M reaction



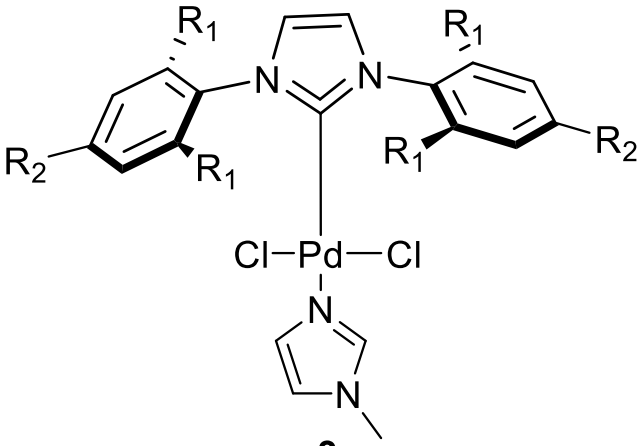
1

$[Pd(IPr)(Et_3N)Cl_2]$



2

[Pd(IPr)(PEPPSI)]



3

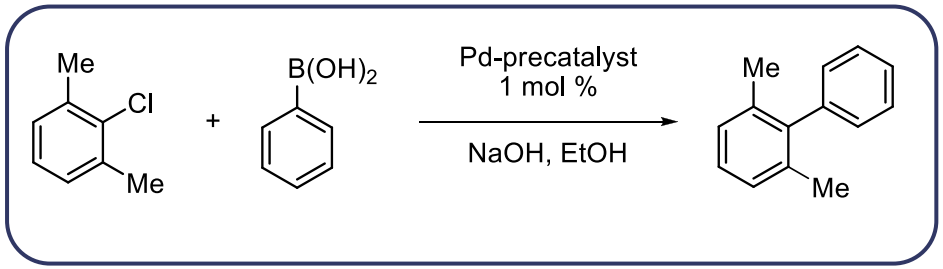
$[Pd(NHC)(Im)Cl_2$

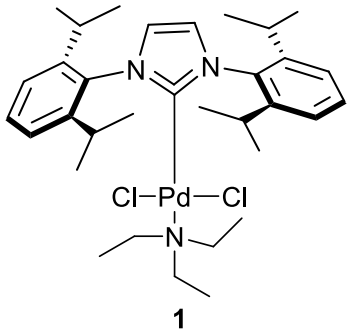
NHC=IPr, IMes

Navarro

Organ

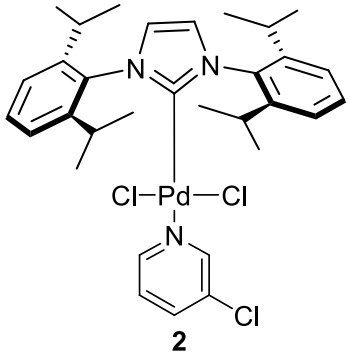
S-M reaction catalyzed by Pd-NHC





1

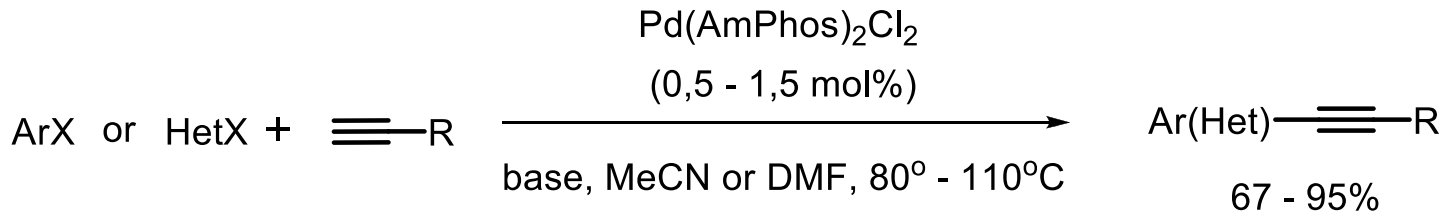
[Pd(IPr)(Et$_3$N)Cl$_2$]

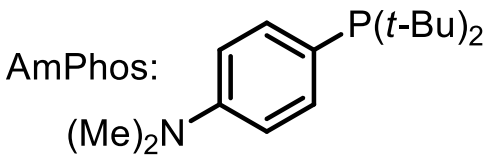


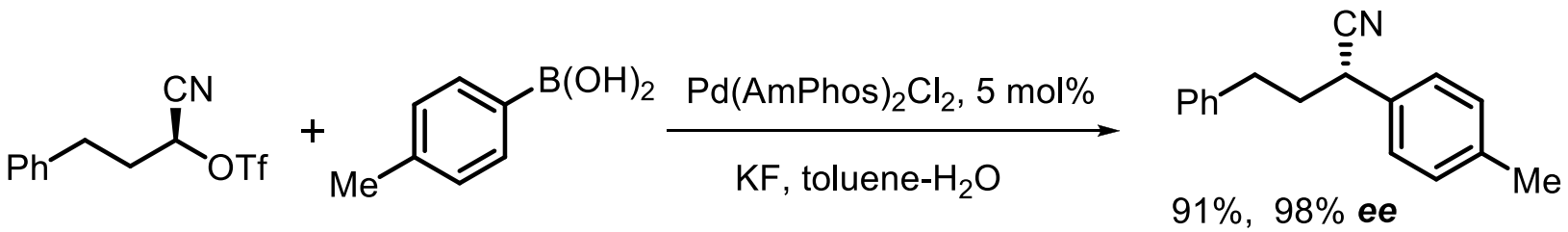
2

[Pd(IPr)(PEPPSI)]

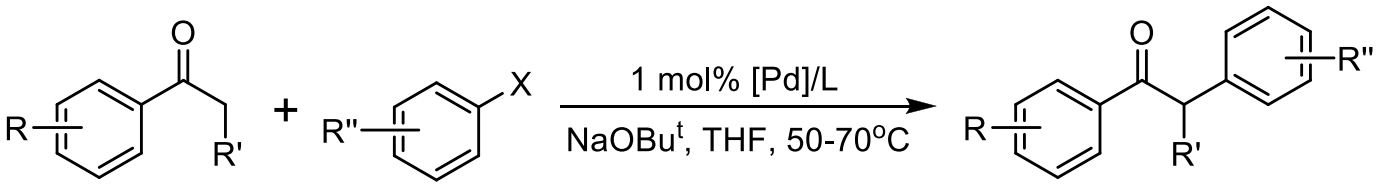
Entry	Catalyst	T (°C)	Time	Yield (%) ,GC
1	1	25	3 ч	37
2	2	25	1.5 ч	96
3	1	40	2 ч	98
4	2	40	20 мин	98


ArX or HetX +
R
Pd(AmPhos)2Cl2
(0,5 - 1,5 mol%)
base, MeCN or DMF, 80° - 110°C
Ar(Het)
R
67 - 95%


AmPhos:
P(t-Bu)2
(Me)2N

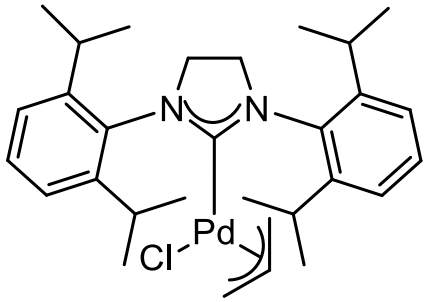

CN
Ph
OTf
+
B(OH)2
Me
Pd(AmPhos)2Cl2, 5 mol%
KF, toluene-H2O
CN
Ph
Me
91%, 98% ee

α-Arylation of ketones



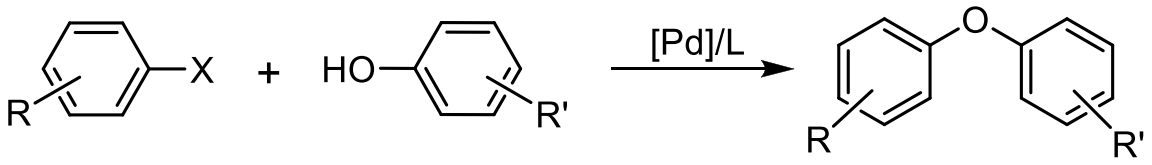
X = Cl, Br, OTf

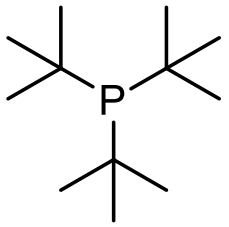
R' = H, R" = CF_3, X = Cl 81%
R' = H, R" = OMe; X = Cl 78%
X = OTf 87%

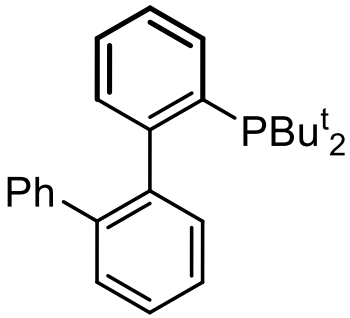
L = 

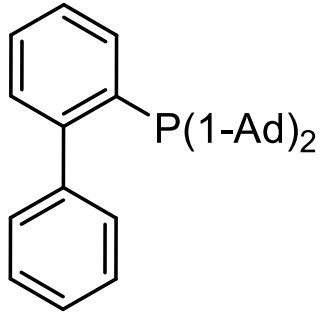
[Pd(SIPr)(allyl)Cl] = cat

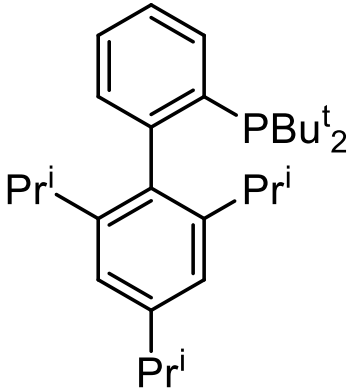
C-O bond formation

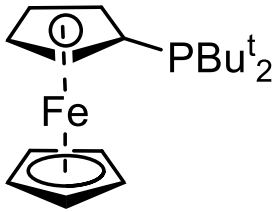


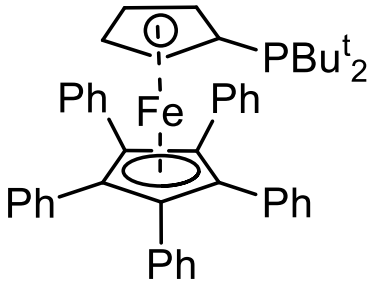


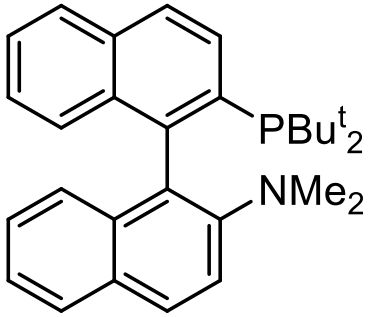


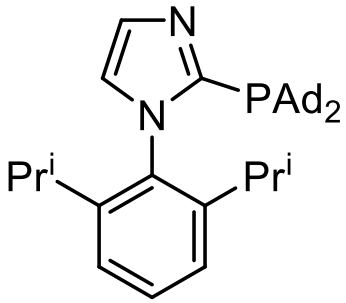




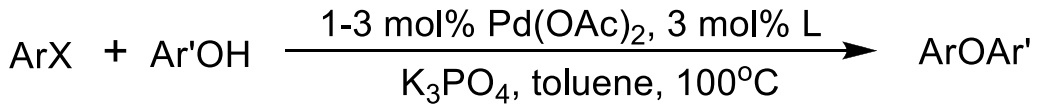






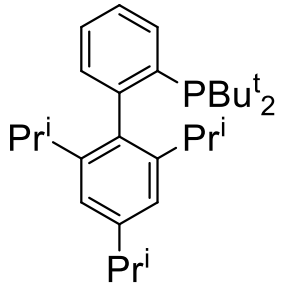


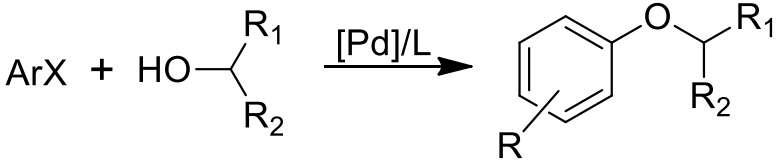
C-O bond formation



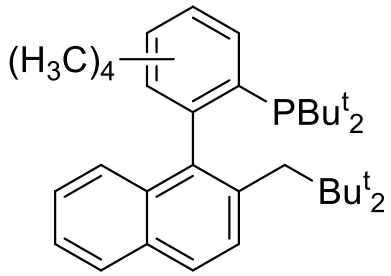
EWG EDG

X = Cl, Br



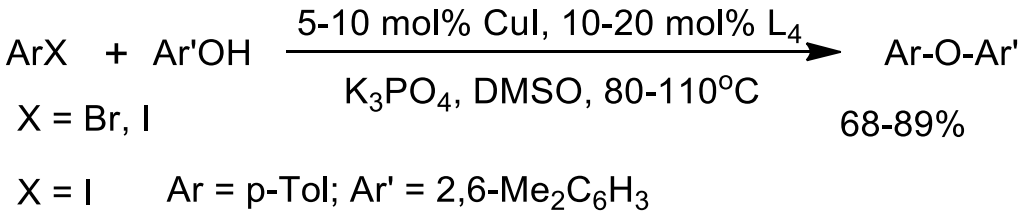


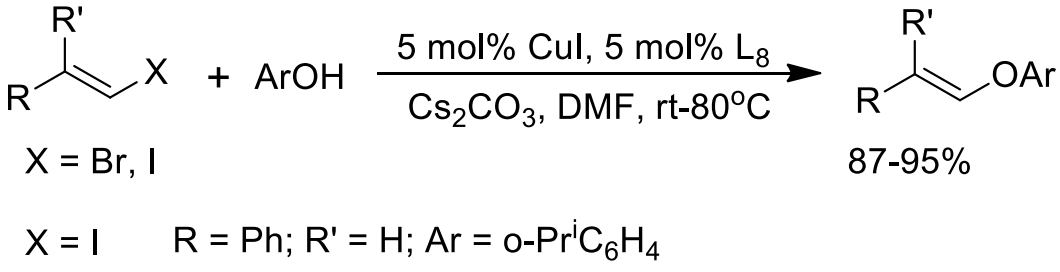
Pd(OAc)$_2$

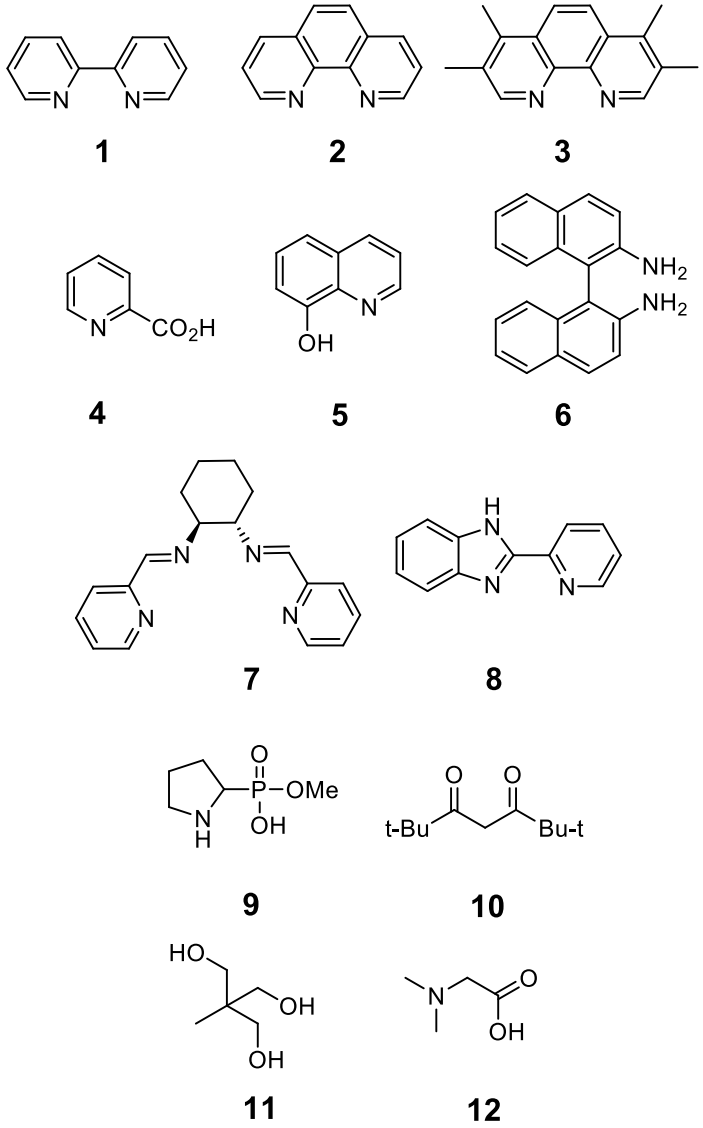


63-80%

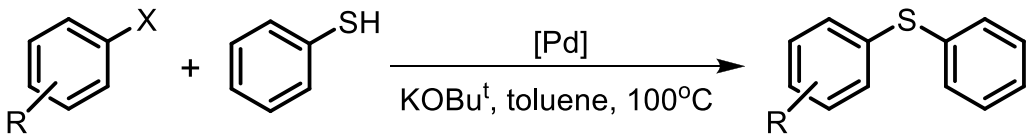
Cu-catalyzed C-O bond formation



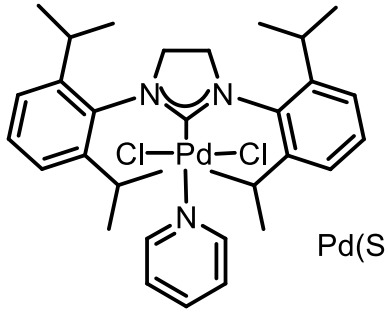




Pd- and Cu-catalyzed C-S bond formation



X = Cl, Br



Pd(SIP)(Py)Cl_2

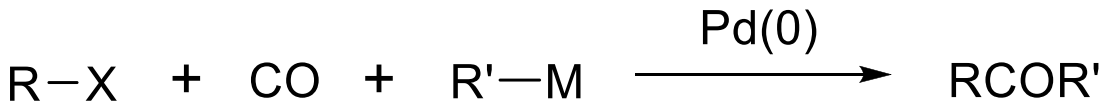
ArI + RSH $\xrightarrow[K_2CO_3,\ i\text{-}PrOH,\ 80^oC]{5\ mol\%\ CuI,\ 2\ eq\ HO(CH_2)_2OH}$ ArSR

71-93%

Ar = o-$NH_2CH_2C_6H_4$; R = p-$CH_3OC_6H_4$ 95%

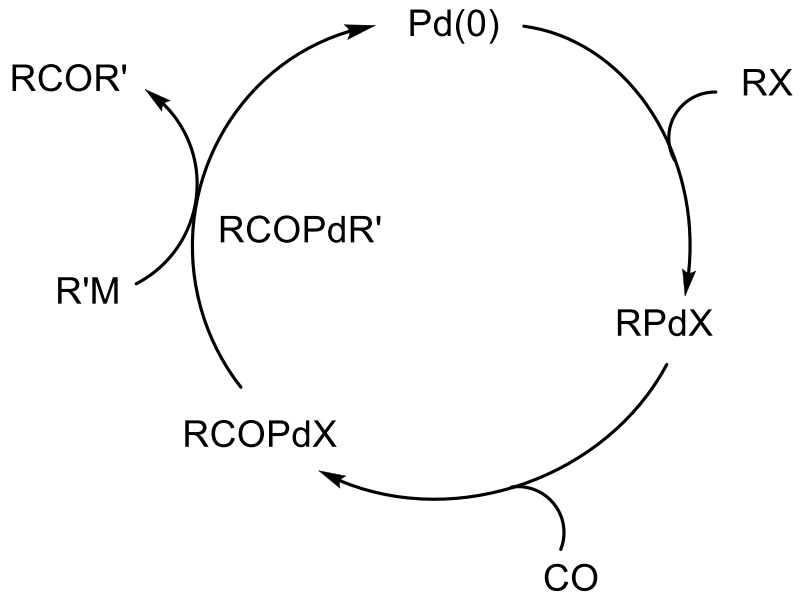
Ar = p-$CH_3OC_6H_4$; R = Br 91%

Carbonylative cross-coupling



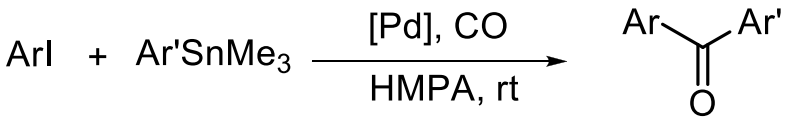
R = Ar, Het, Alkenyl, Alkynyl

X = I, Br, OTf, N_2^+



Carbonylative cross-coupling

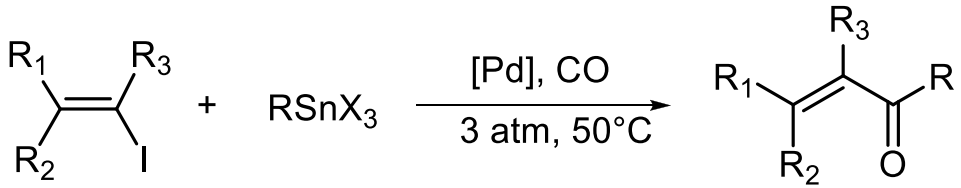
Sn



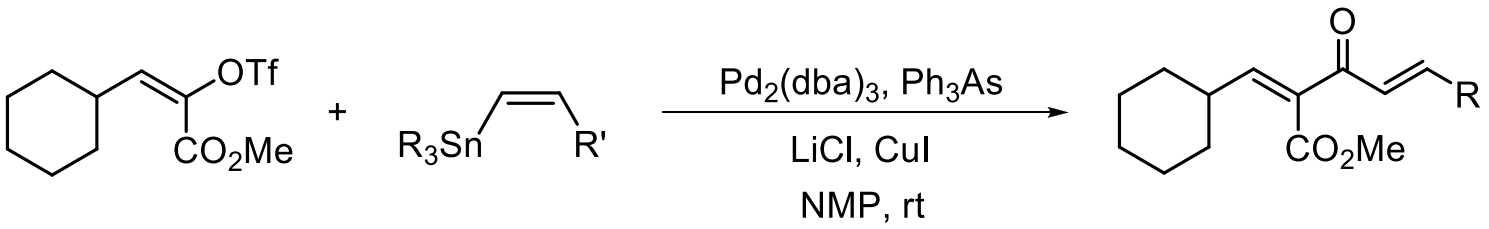
ArN_2BF_4
RI^+PhX^-

($PdCl_2$ 0.2 mol%, DME-H_2O 4:1, rt)

J. Organometal. Chem., 1983, 250, 551

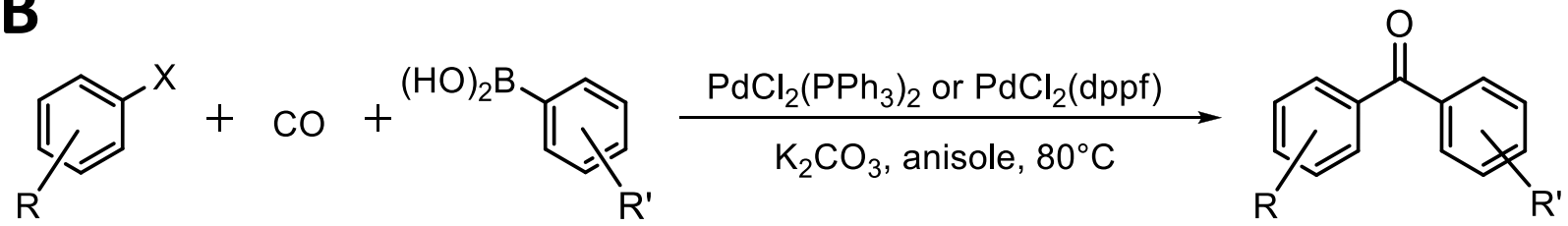


LiCl, CuI

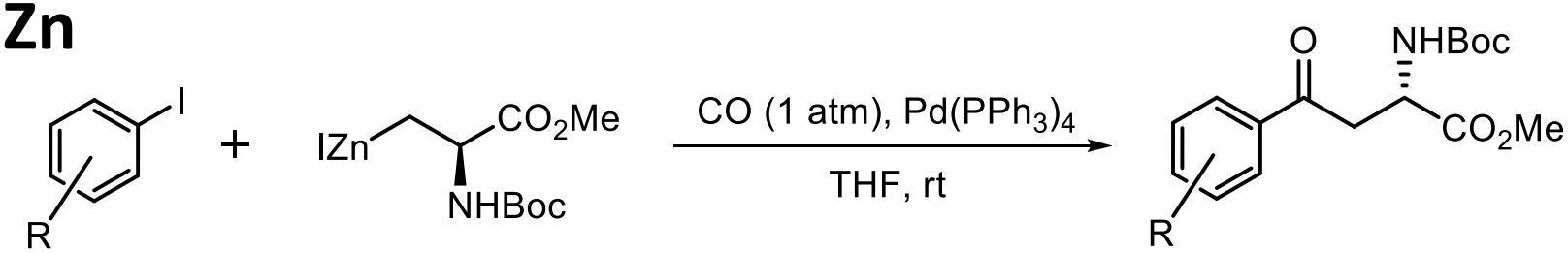


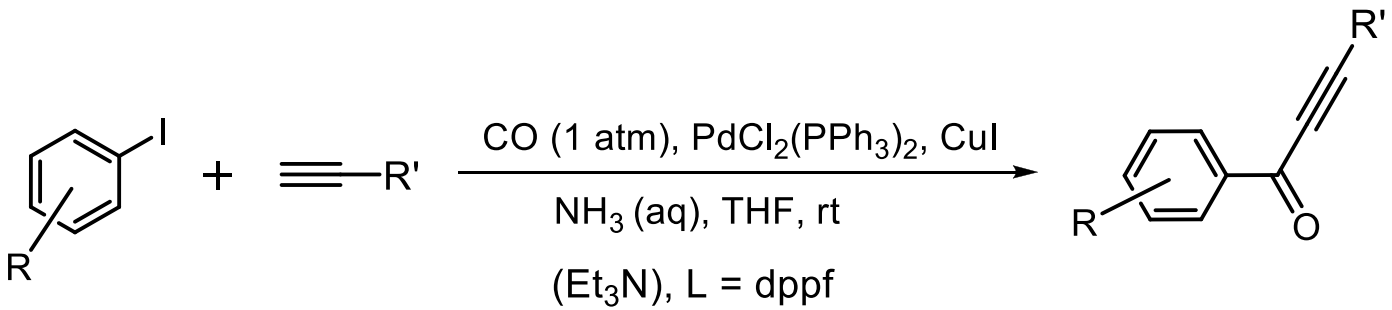
Carbonylative cross-coupling

B

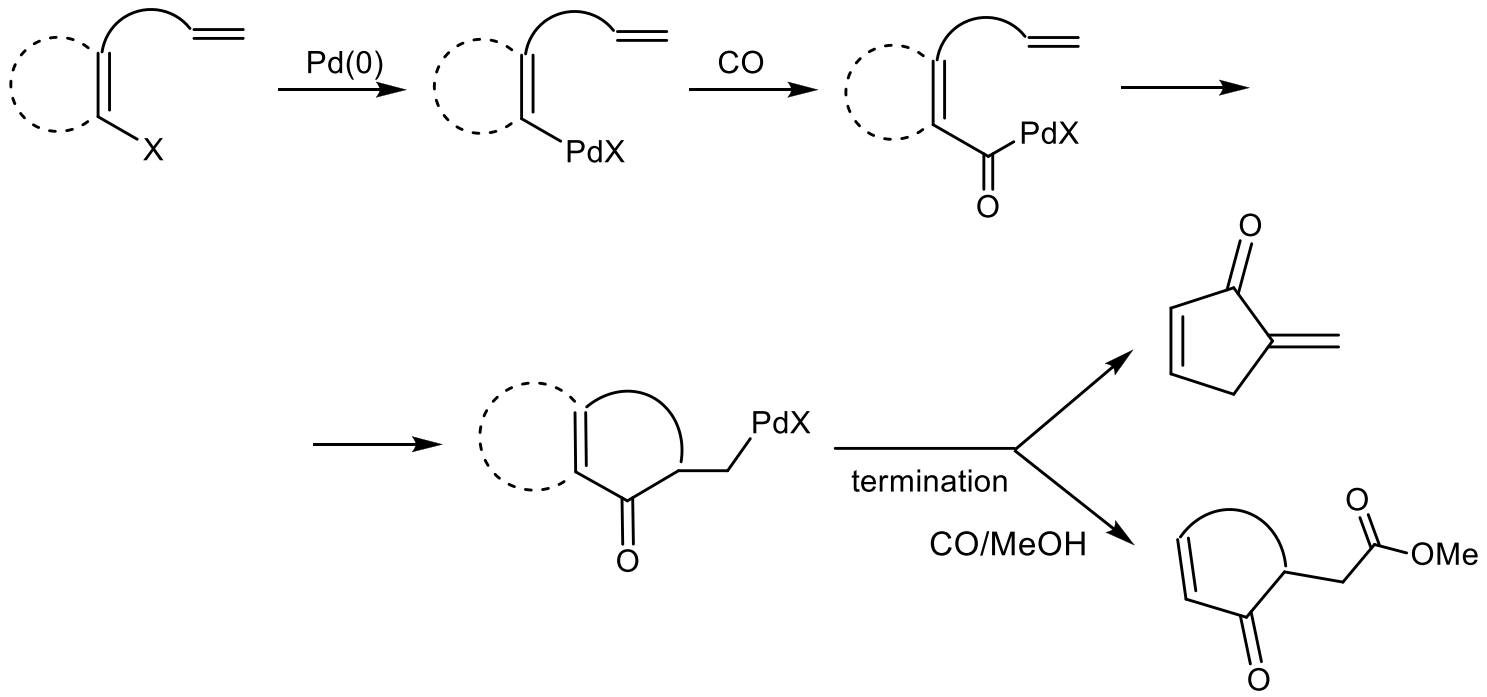


Zn

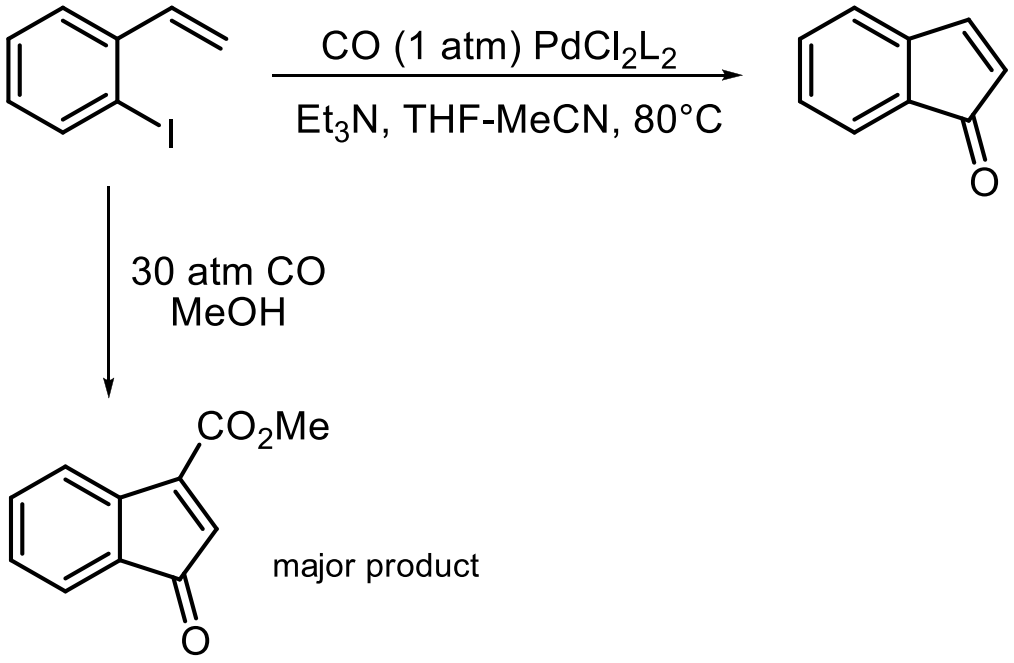




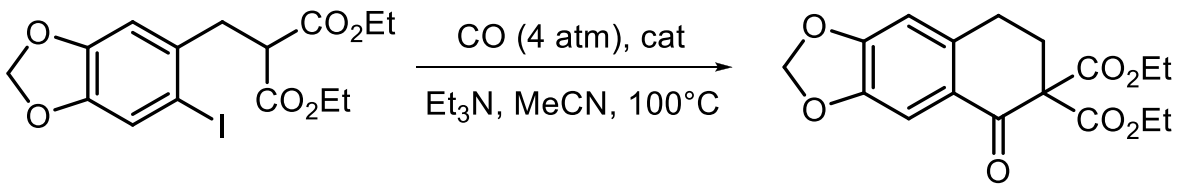
Double carbonylation



Carbonylative cross-coupling

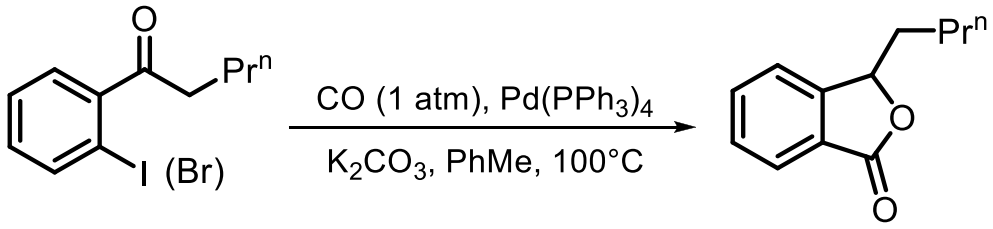


Intramolecular reaction



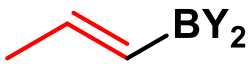
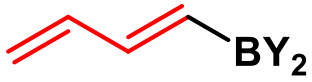
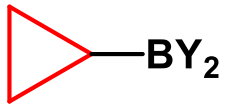
cat $NiCl_2(PPh_3)_2$ 92%

Li_2CuCl_4 98%

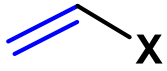


Stereoselective S-M reactions

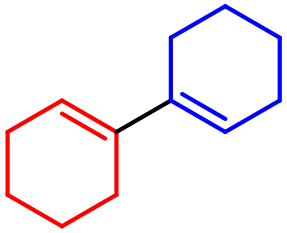
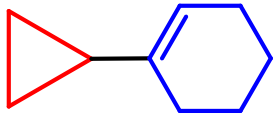
nucleophiles

Ar-BY_2   Alk-BY_2 

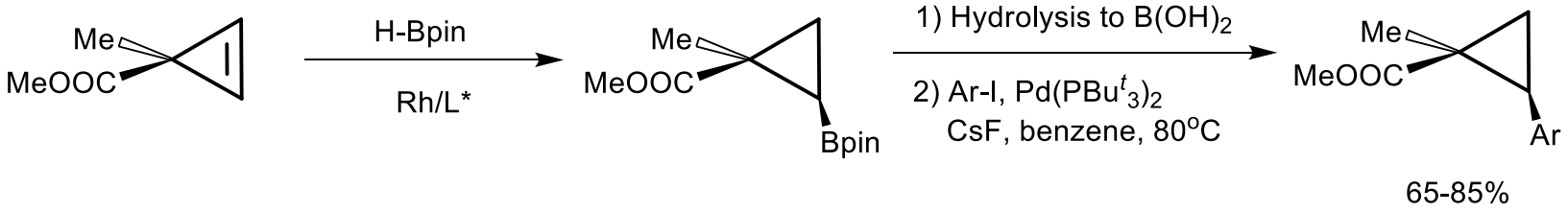
electrophiles

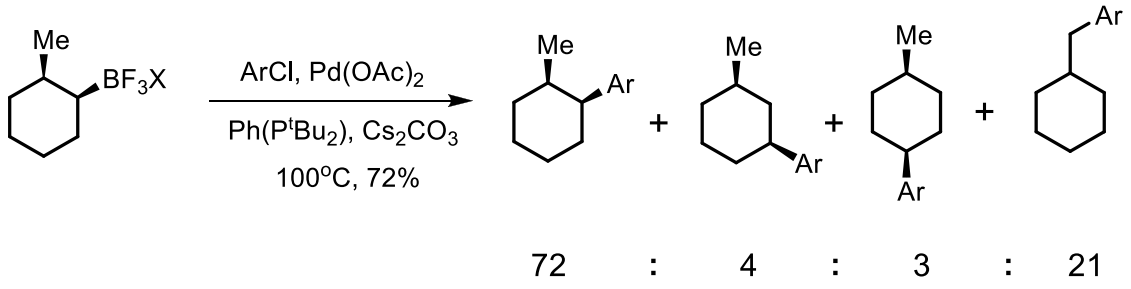
Ar-X  Alk-X

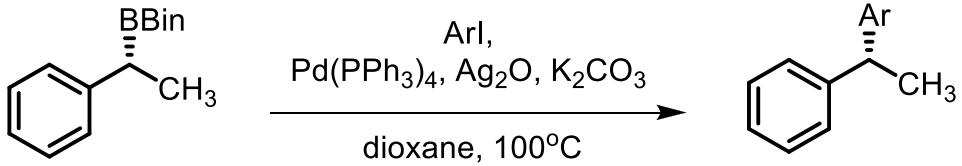
products

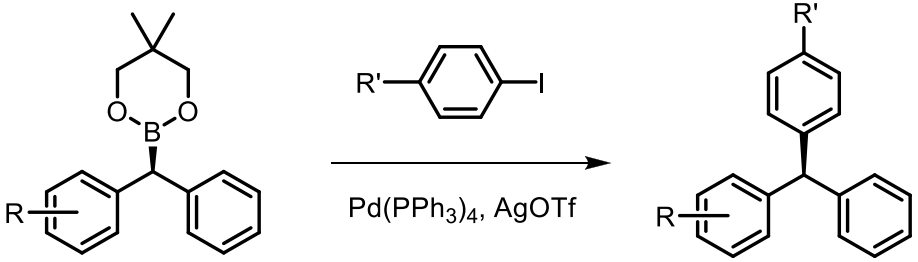
 

Chiral nucleophiles

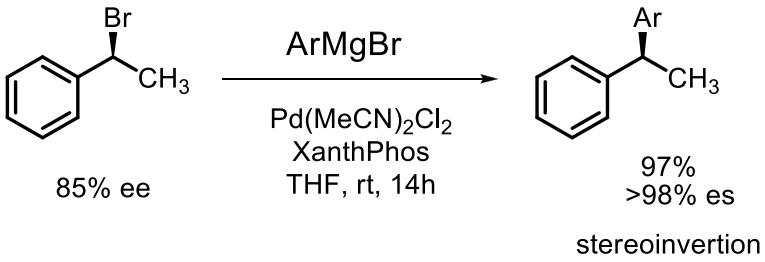


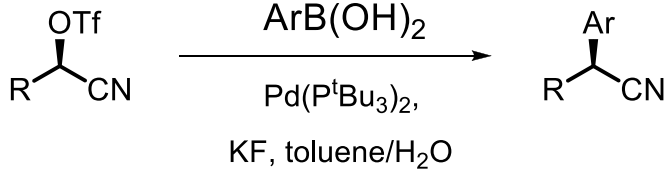


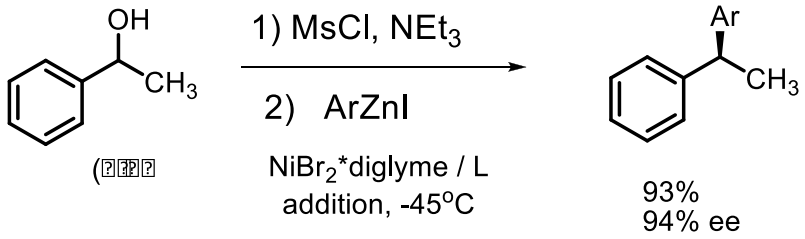




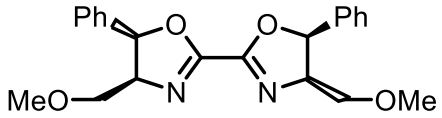
Enantioselective S-M reaction



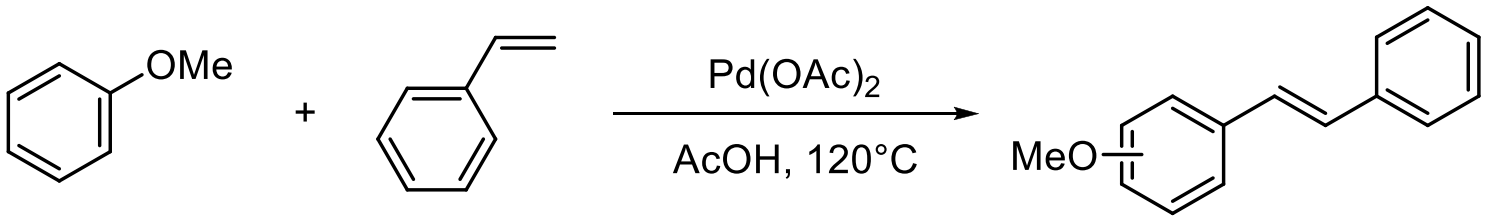




L =

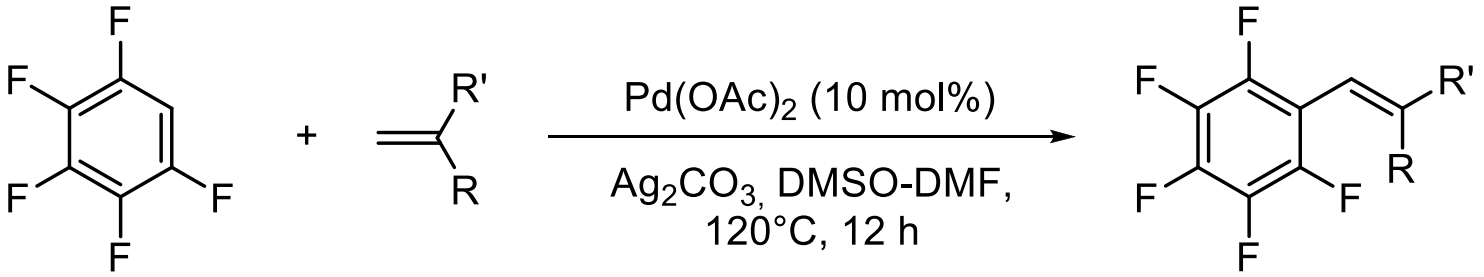


The Fujiwara – Moritani Reaction



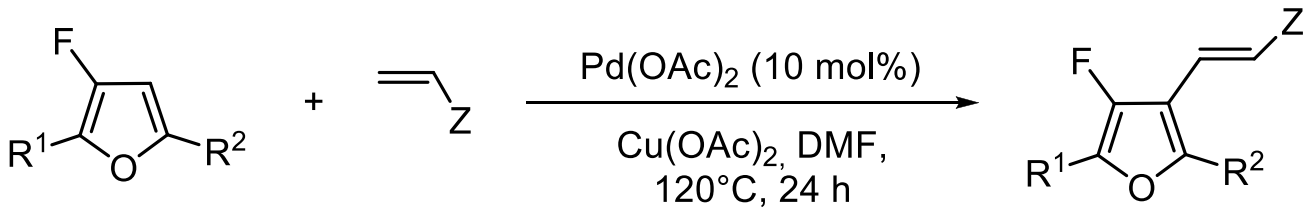
o: m: p = 30: 5: 48

[Pd] - stoichiometry

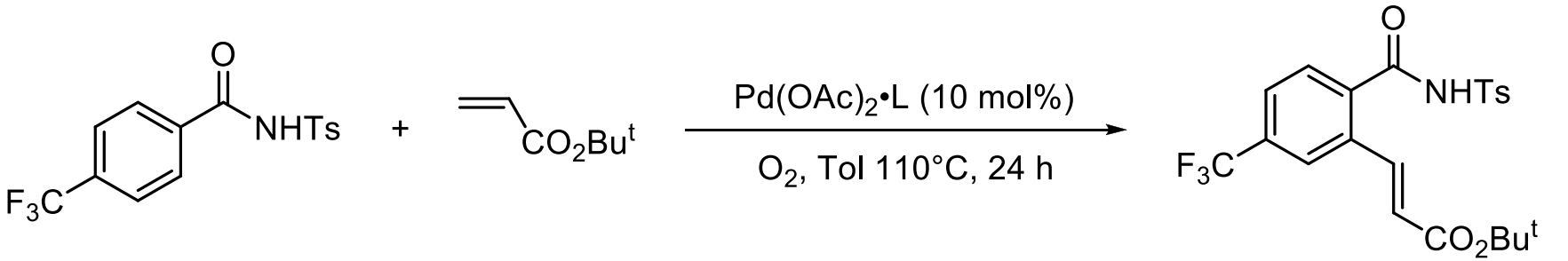


R' = H; R = CO_2Me, CO_2Bu, CO_2NMe_2, CN, COEt, COPh, Ph
R' = Me; R = CO_2Me, Ph

F-M C-H-activation



R^1, R^2 = Alk, Ar; Z = CO_2R, Ar



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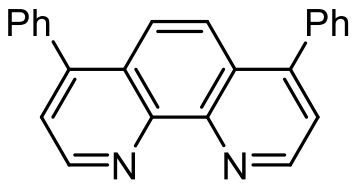
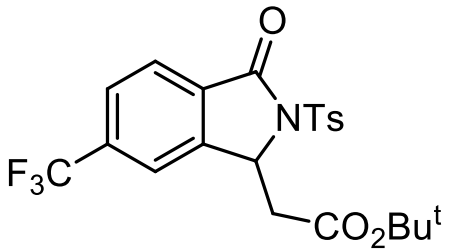
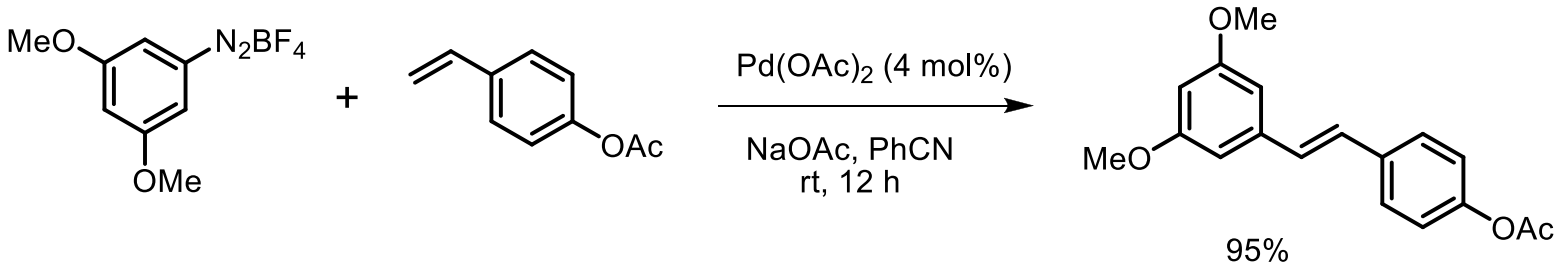
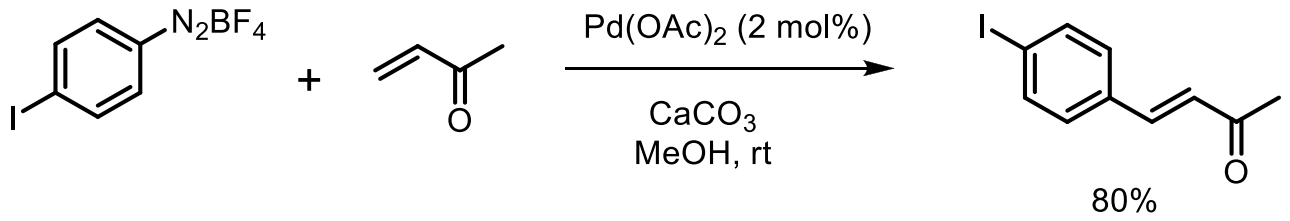


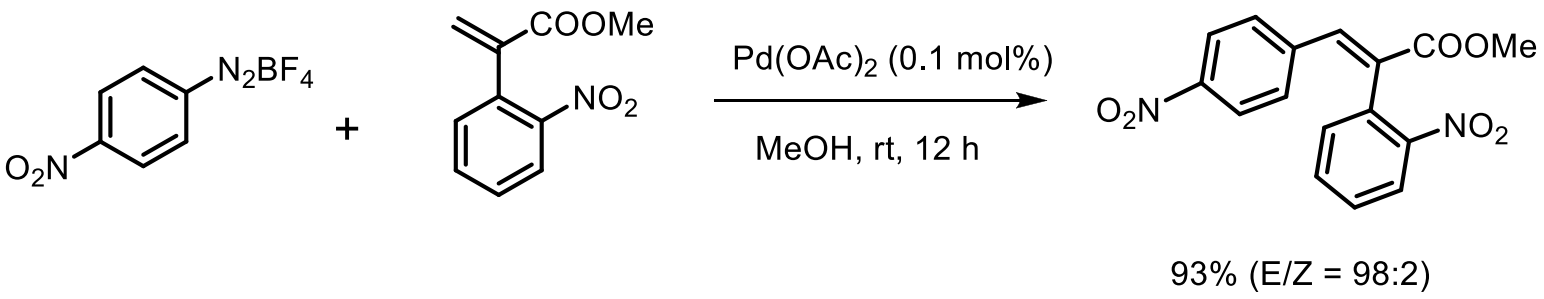


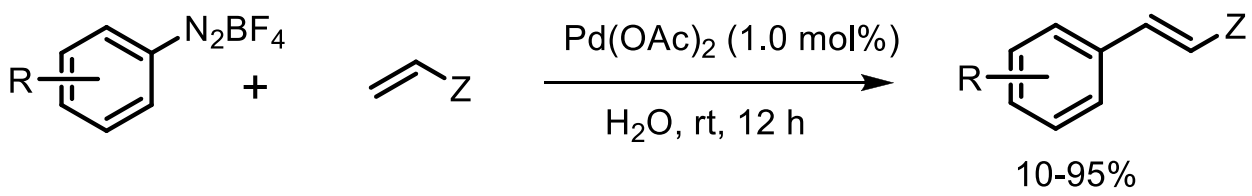
64%

Matsuda-Heck reaction



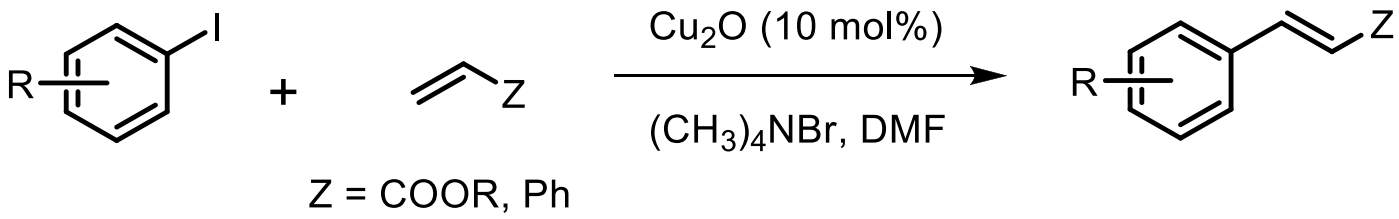


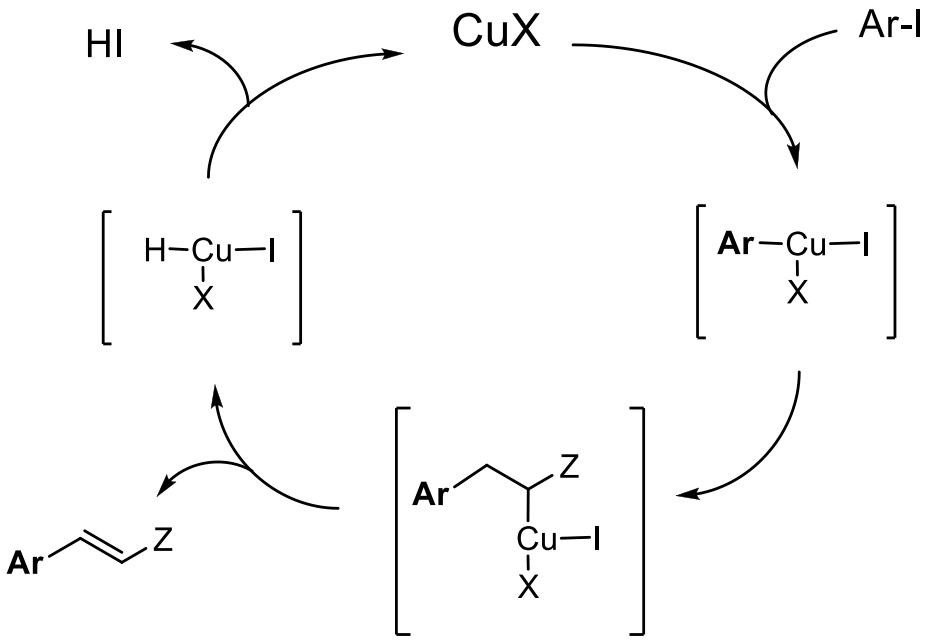




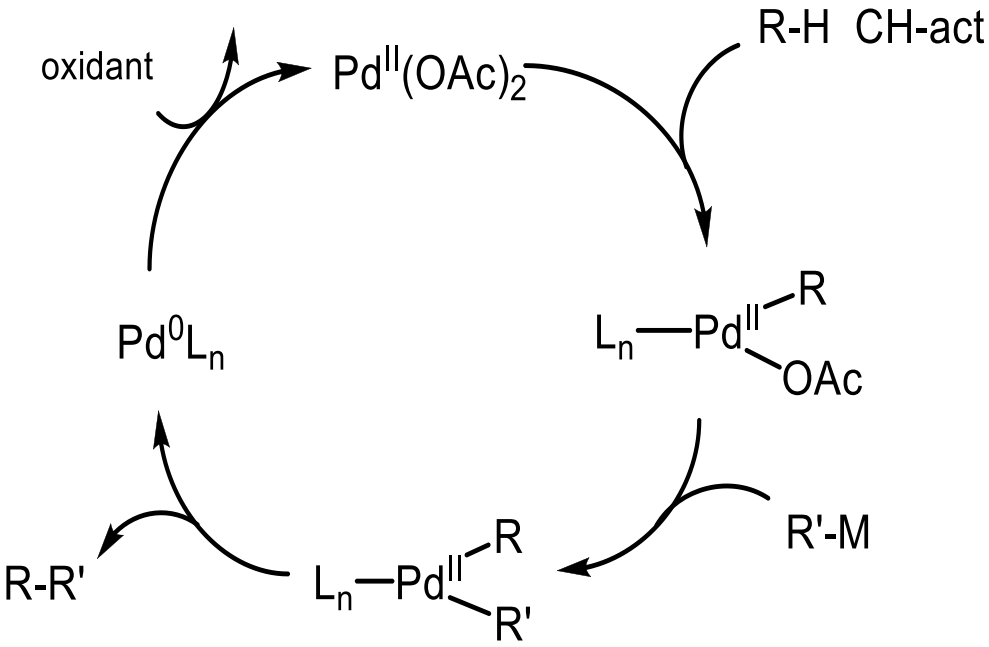
Z = COOR, PCOOH, C(O)Et, Ar,
CH_2Ph, CH_2OAc, CH(OH)Me

Ru, Rh, Cu, Ni, Fe

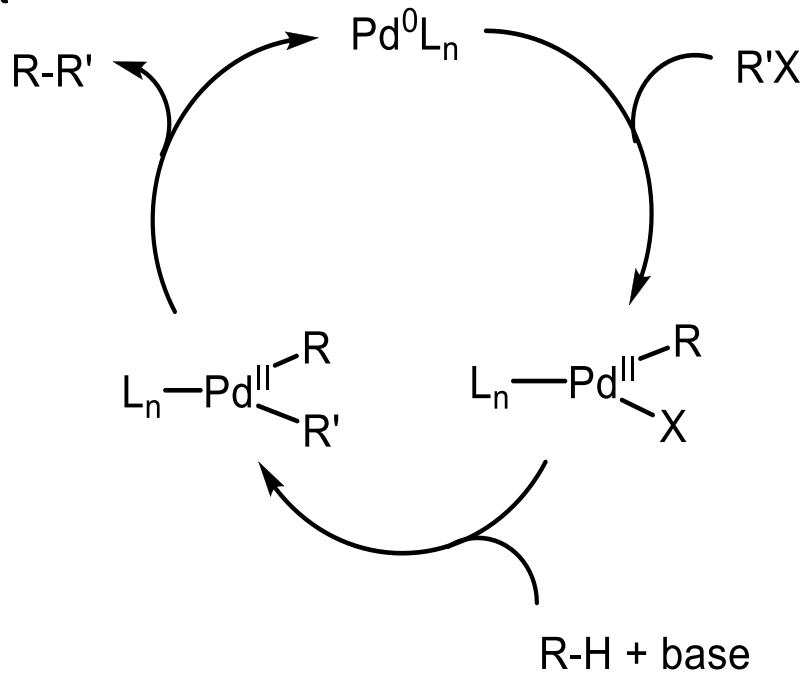

R
I
+
Z
Cu2O (10 mol%)
(CH3)4NBr, DMF
R
Z
Z = COOR, Ph


HI
CuX
Ar-I
H–Cu–I
X
Ar–Cu–I
X
Ar
Z
Cu–I
X
Ar
Z

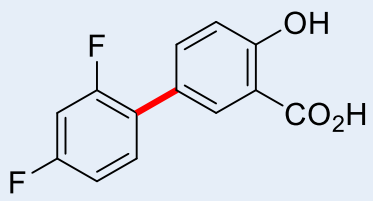
RH + R'M


oxidant
$Pd^{II}(OAc)_2$
R-H CH-act
$L_n—Pd^{II}(R)(OAc)$
R'-M
$L_n—Pd^{II}(R)(R')$
R-R'
Pd^0L_n

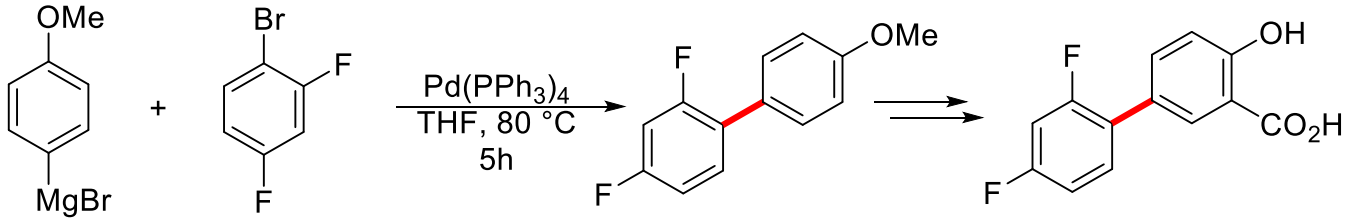
RH + R'X

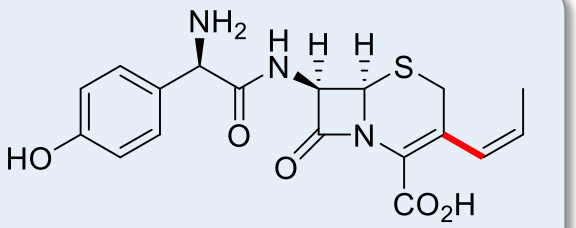

Pd^0L_n
R'X
$L_n—Pd^{II}(R)(X)$
R-H + base
$L_n—Pd^{II}(R)(R')$
R-R'

Application in drug synthesis

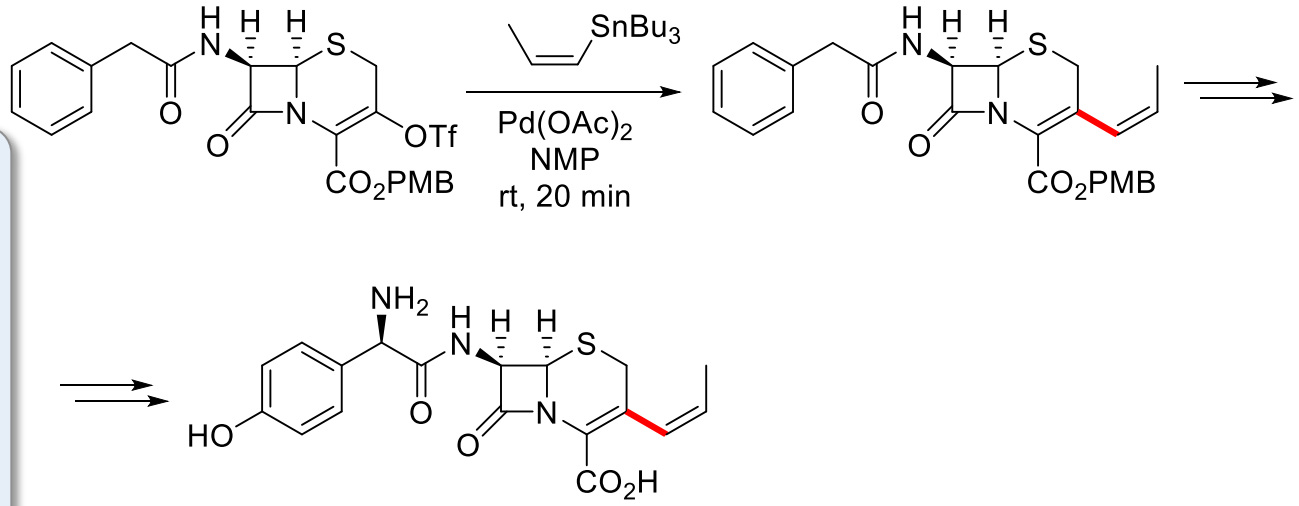


Diflunisal (Merck)
anti-inflammatory

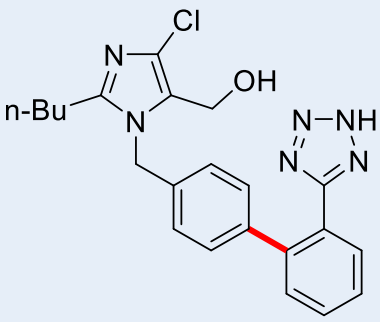




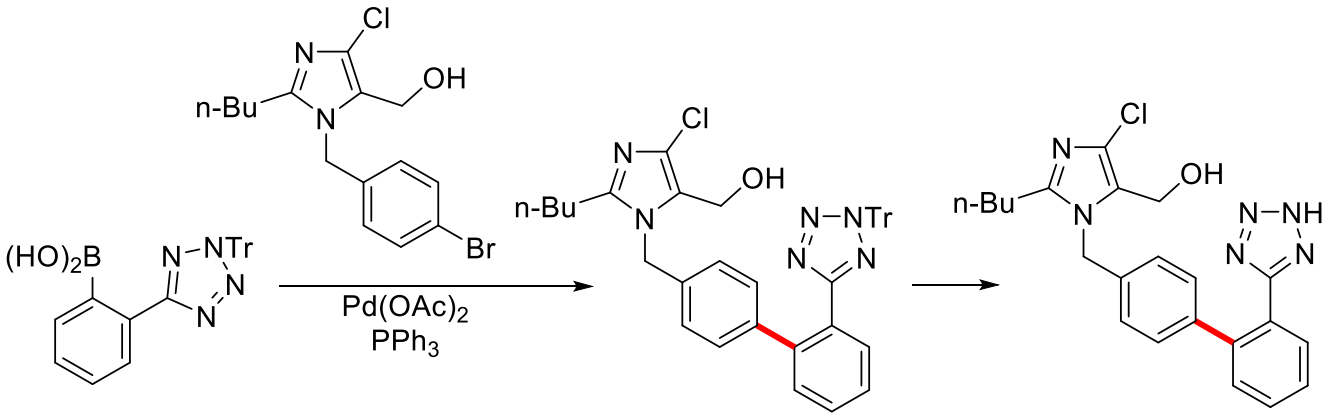
cis-Cefprozil
(Bristol-Meyers Squibb)
antibiotic

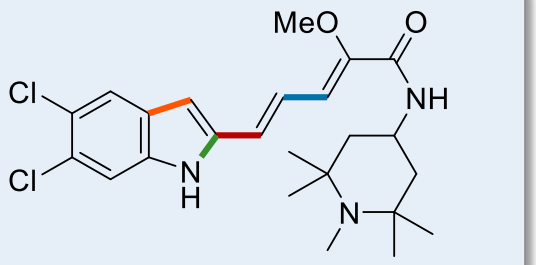


Application in drug synthesis

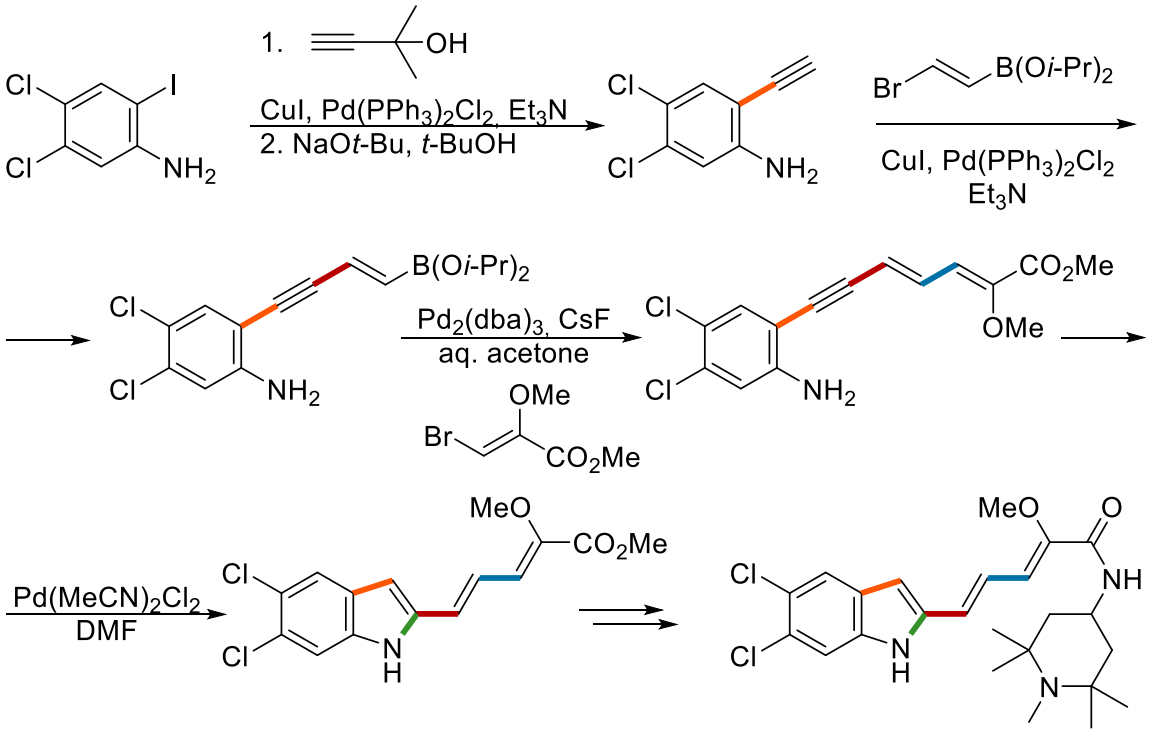


Losartan (Merck/DuPont)
antihypertensive

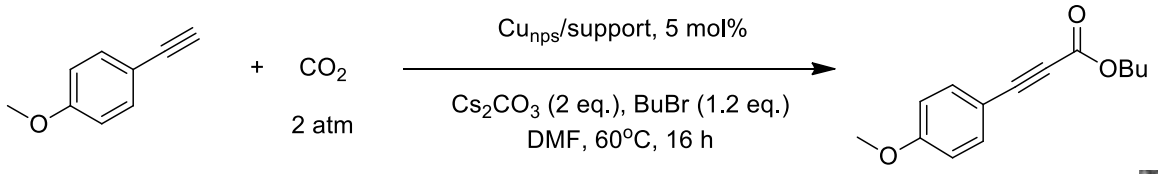


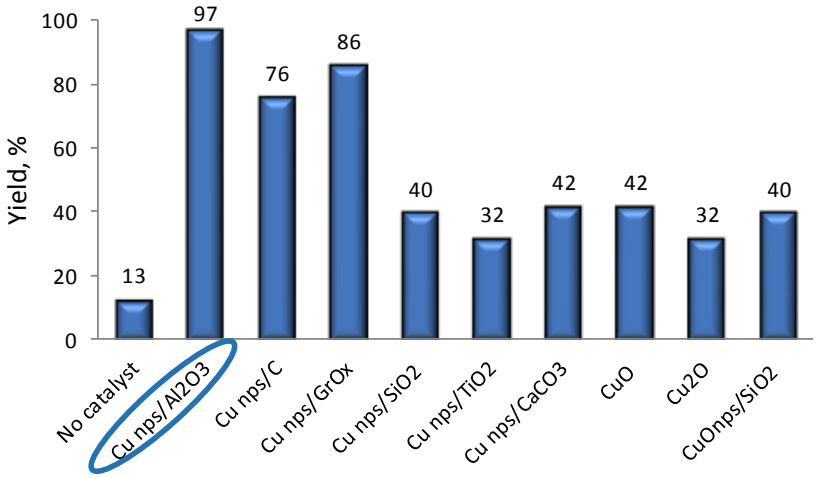


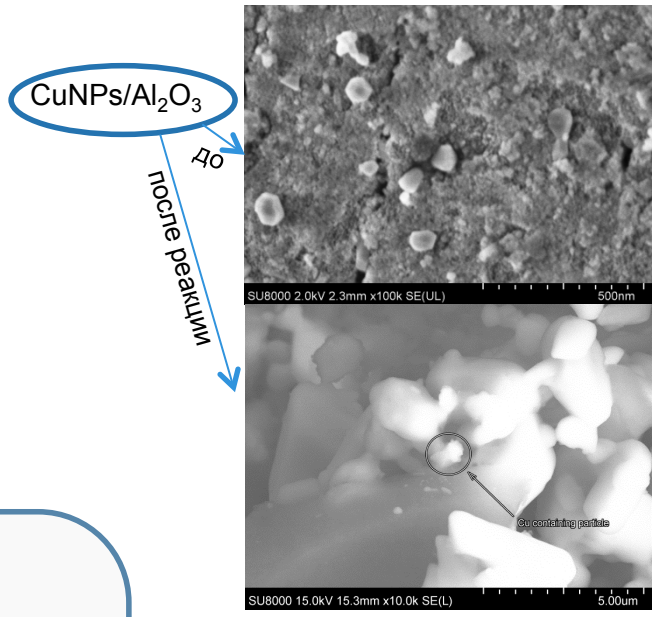
SB 242784 (SmithKline Beecham)
antihypertensive

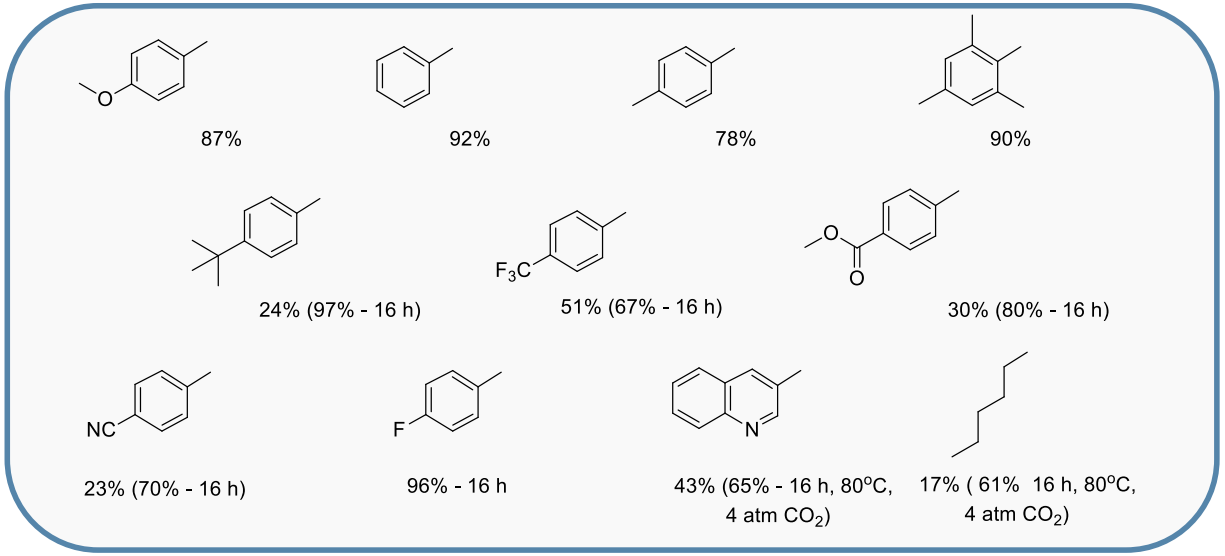


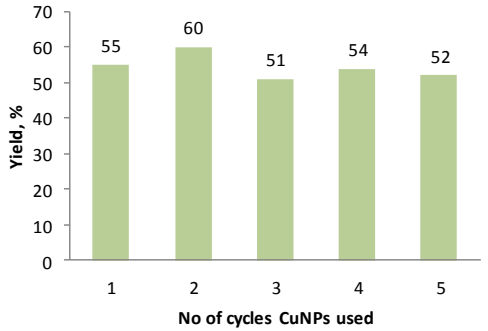
Карбоксилирование терминальных алкинов



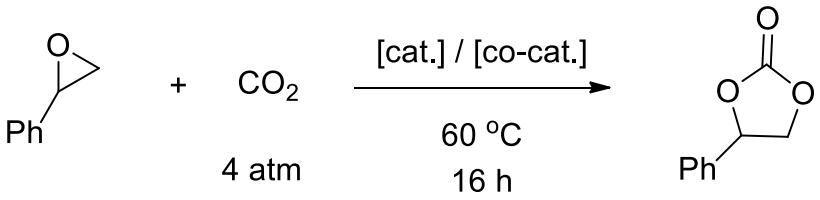








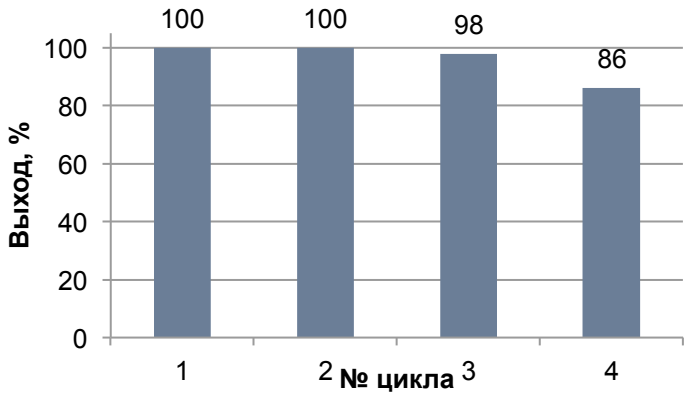
Карбоксилирование эпоксидов



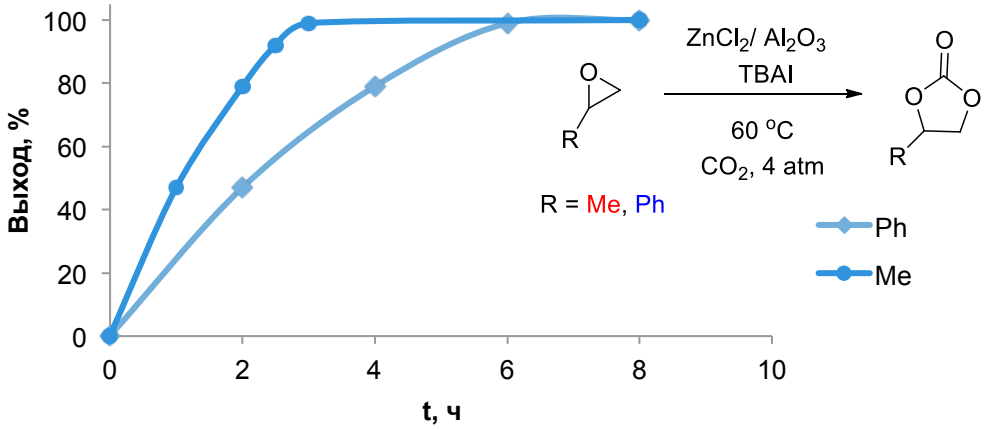
Cat. (mol %)	Co-cat. (mol %)	Conv., %
SiO_2 (2.5)	TBAI (0.8)	50
Al_2O_3 (2.5)	TBAI (0.4)	28
TiO_2 (2.5)	TBAI (0.4)	5
$ZnCl_2/SiO_2$ (0.8)	TBAI (0.8)	100
$ZnCl_2/Al_2O_3$ (0.6)	TBAI (0.8)	96
$ZnCl_2/TiO_2$ (0.6) *	TBAI (1.6)	100
$ZnCl_2/Al_2O_3$ (0.6)	**TBAI (1.6)**	**100**

*- отделение хуже, чем $ZnCl_2/Al_2O_3$

Рециклизация $ZnCl_2/Al_2O_3$ в карбоксилировании оксида стирола

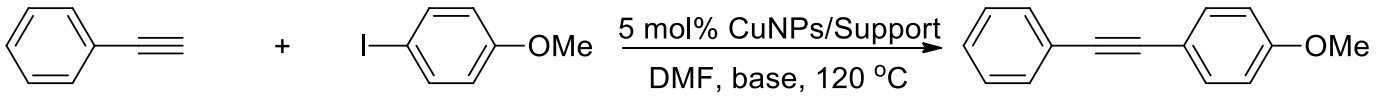


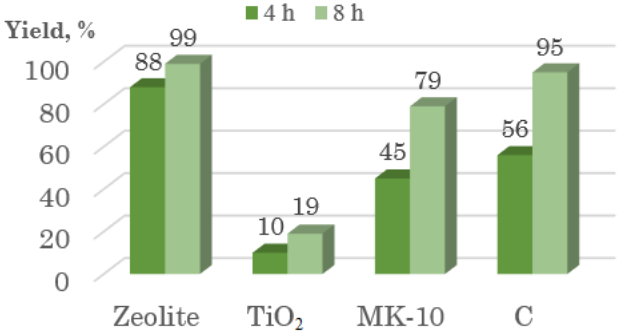
Кинетическая зависимость карбоксилирования пропилен- и стирол оксида, катализируемого $ZnCl_2/Al_2O_3$ и TBAI

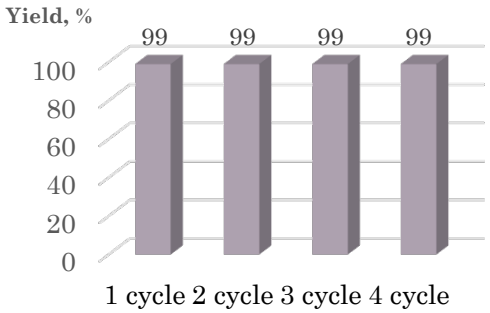


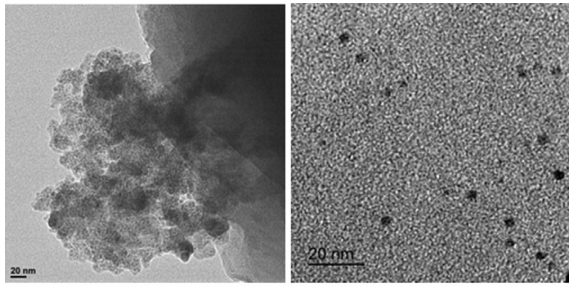
Supported copper nanoparticles in cross-coupling*

Sonogashira reaction



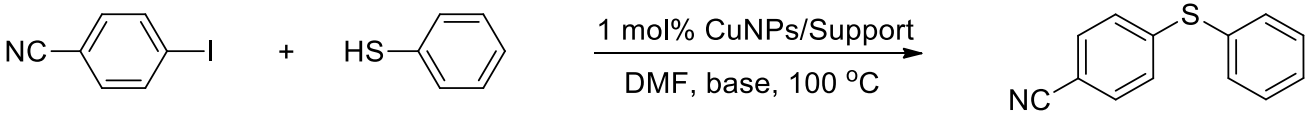


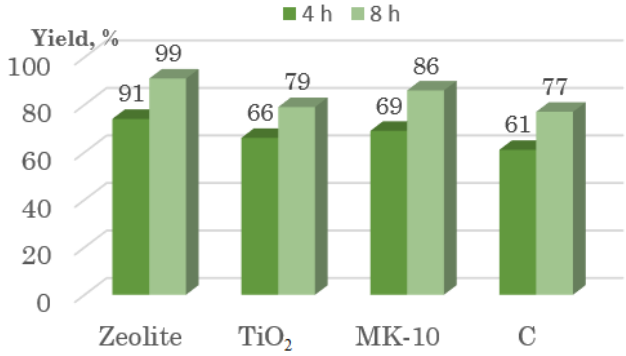


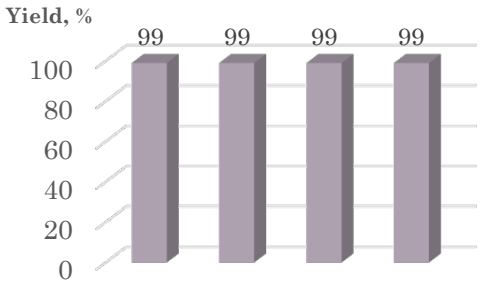


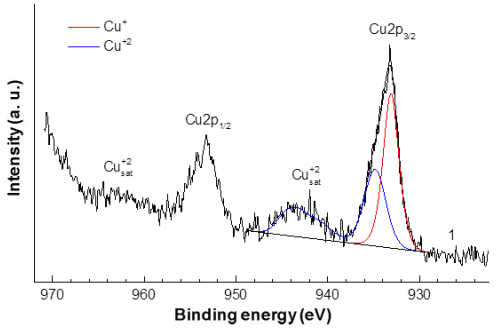
TEM micrograph of **CuNPs/ZY**
d(CuNPs = 2.0±0,9 nm)

Thiol arylation





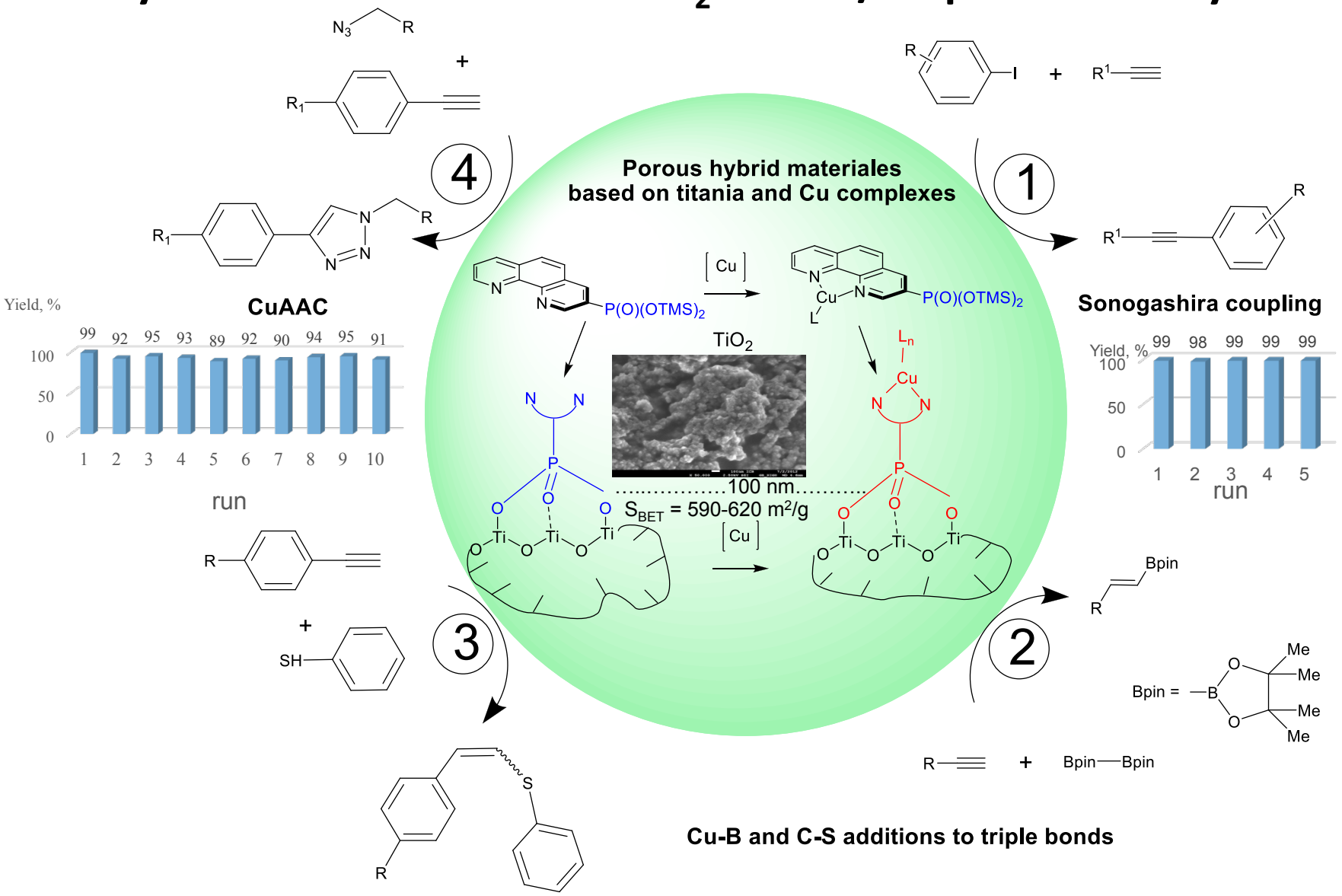




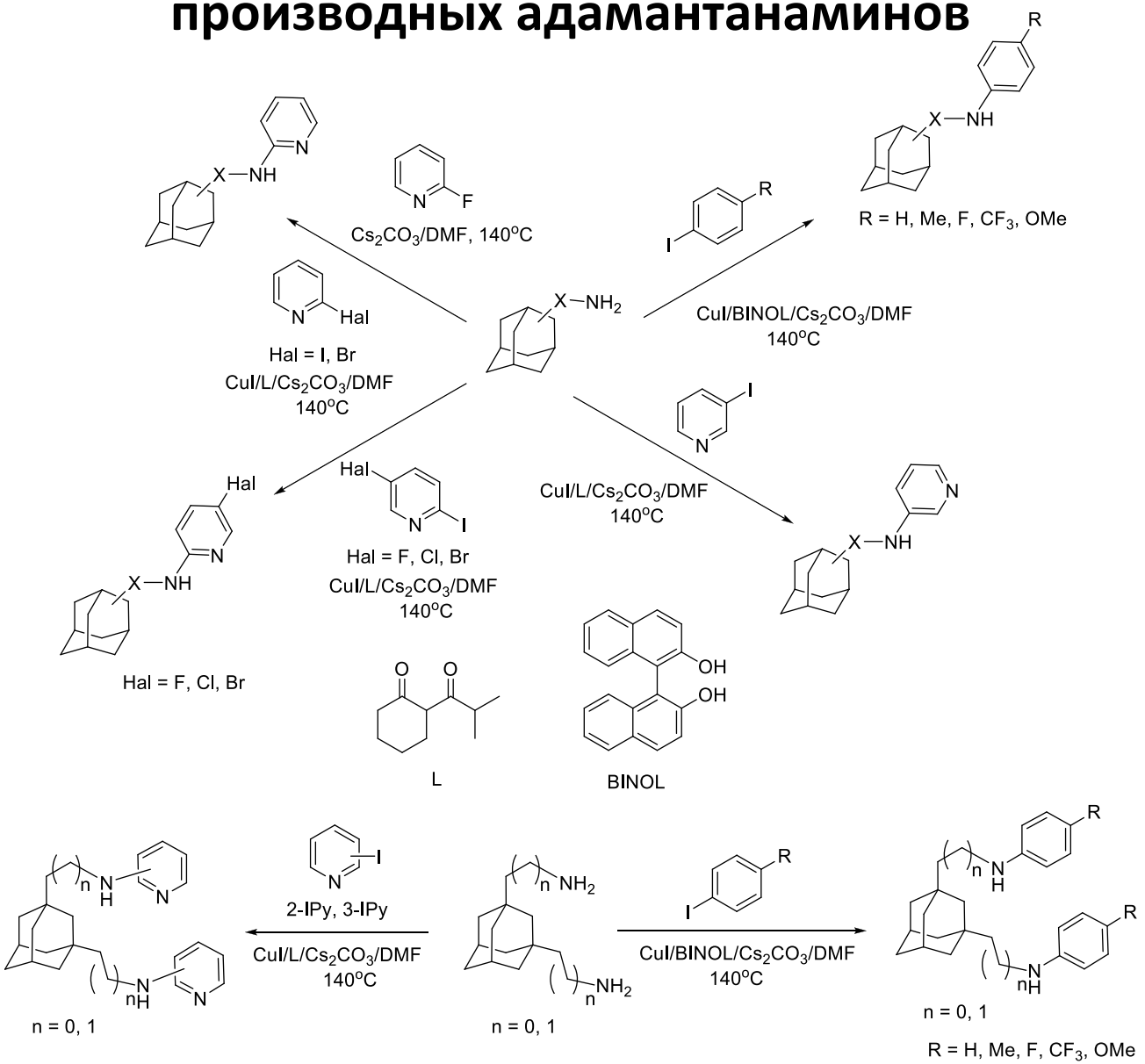
XPS spectrum of **CuNPs/ZY**

***In collaboration with prof. F. Alonso, Alicante, Spain**

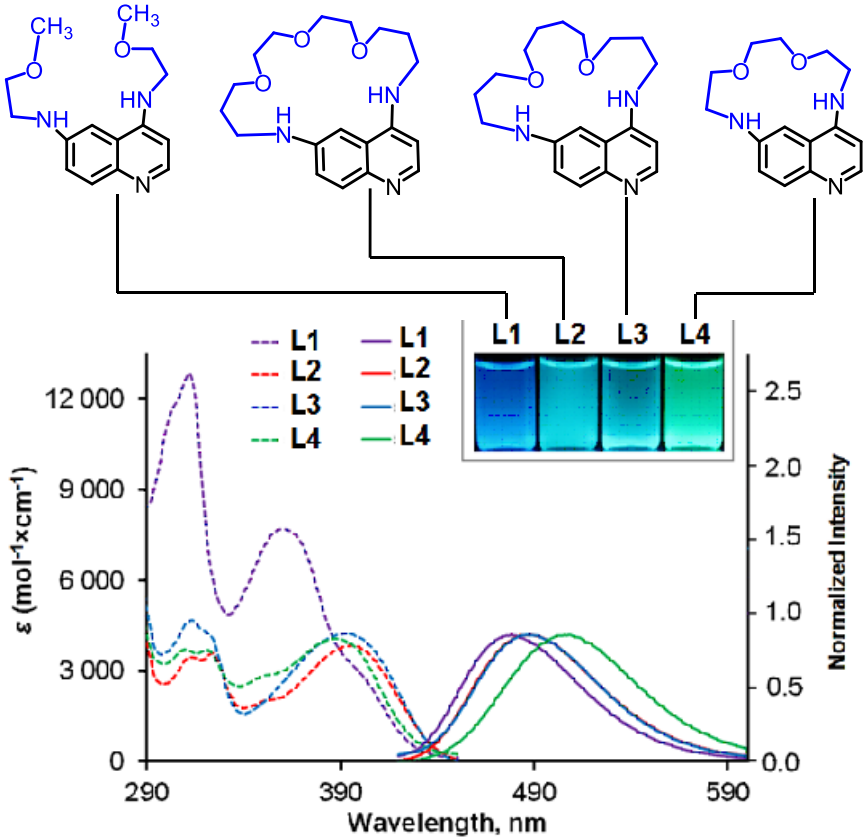
Hybrid material based on TiO_2 and Cu/3-Pphen in catalysis

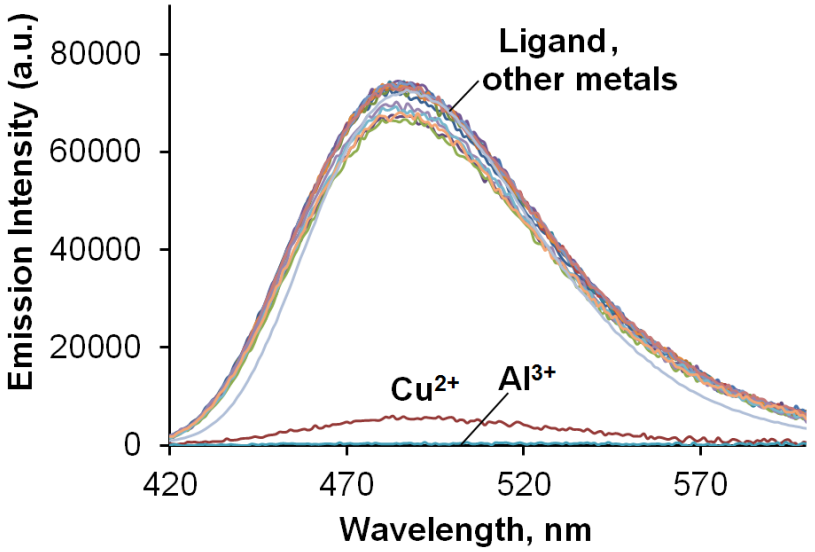


Cu(I)-катализируемое аминирование в синтезе производных адамантанаминов



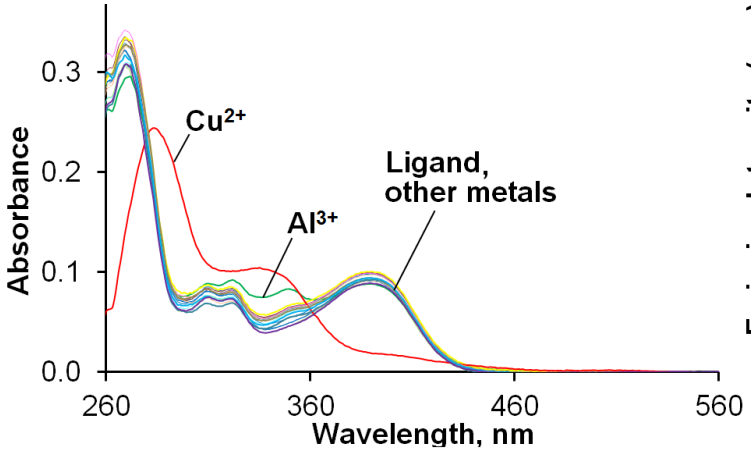
Макроциклы на основе 4,6-диаминохинолина

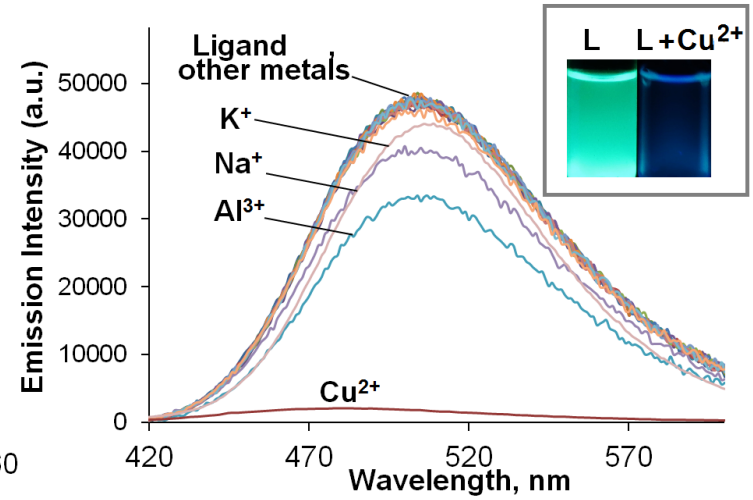




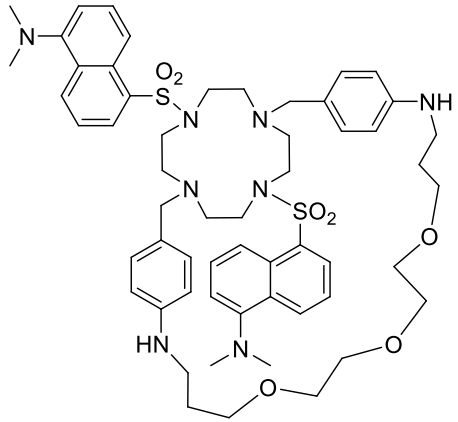
CH_3CN

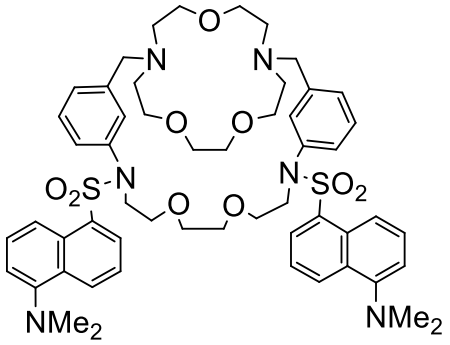
λ_{ex} = 385 нм

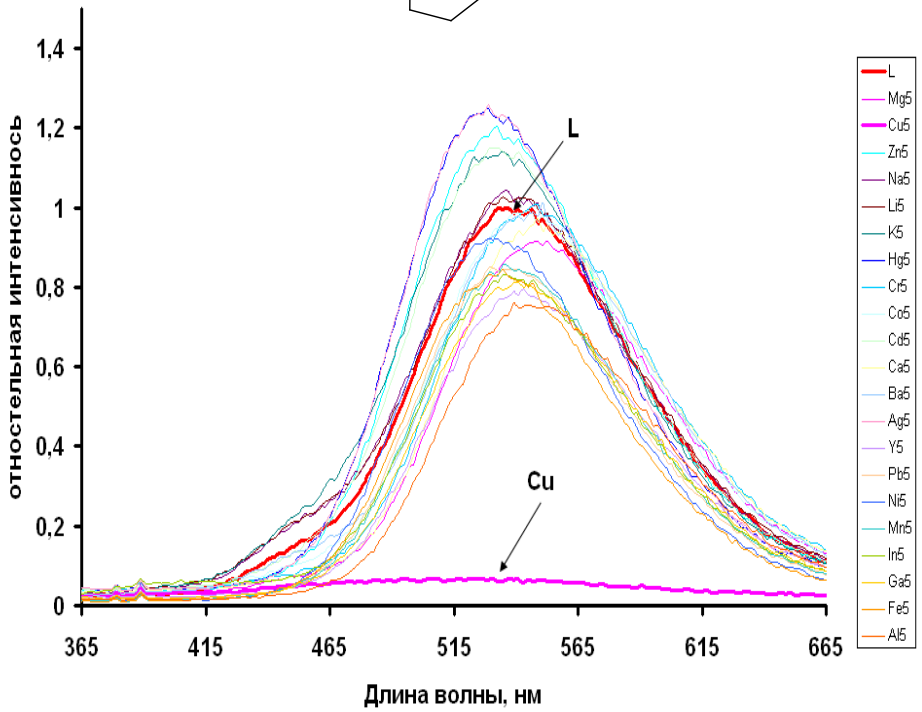


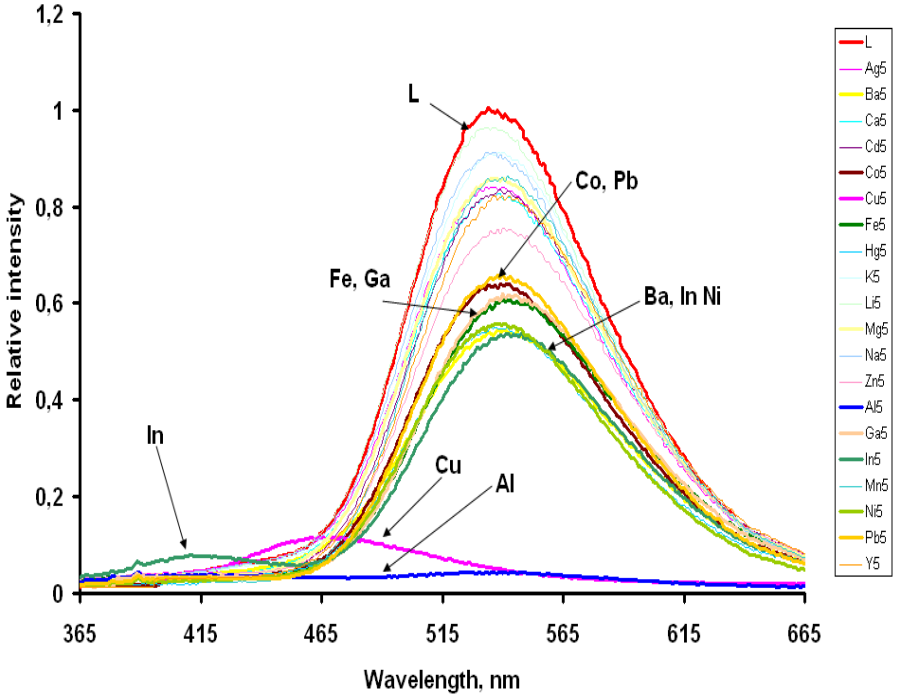


Макробициклы с флуорофорными группами-детекторы катионов металлов

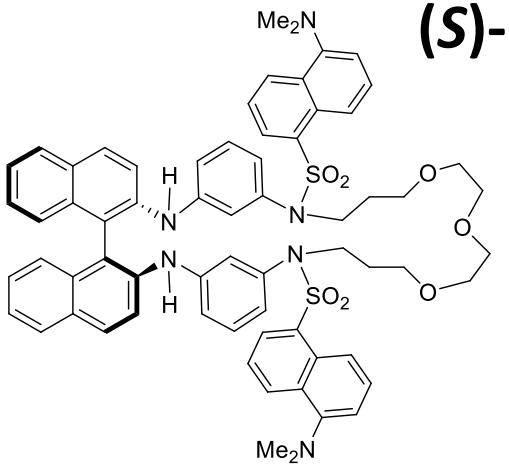


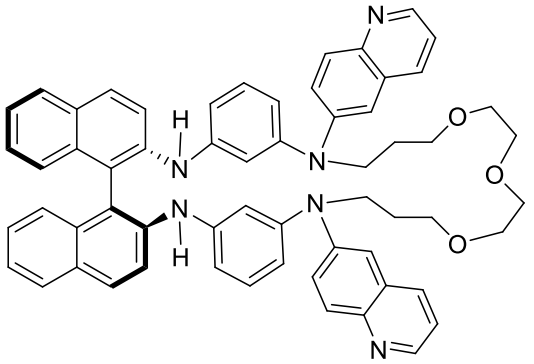


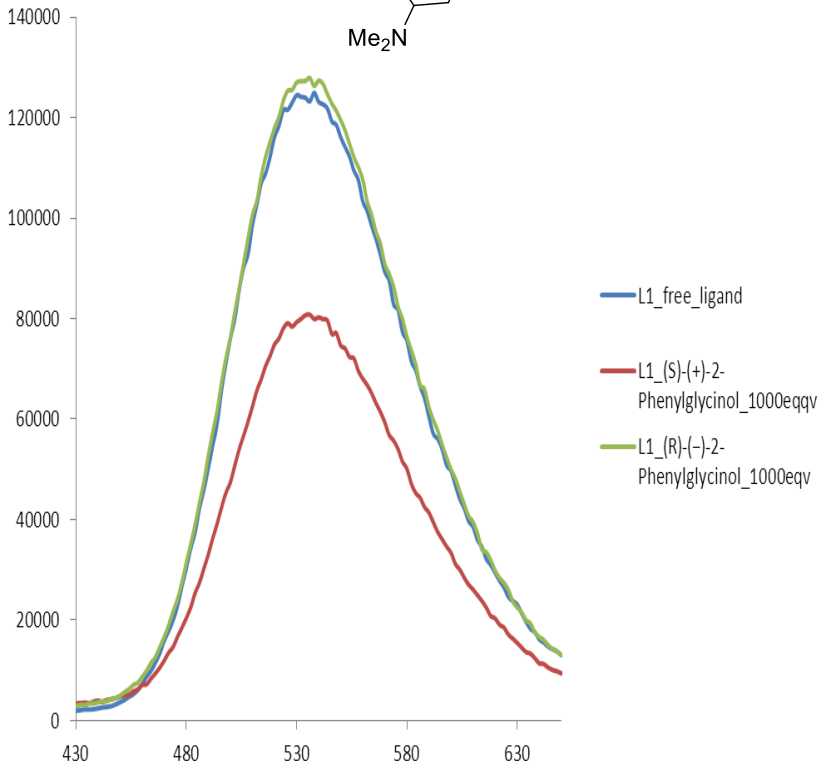


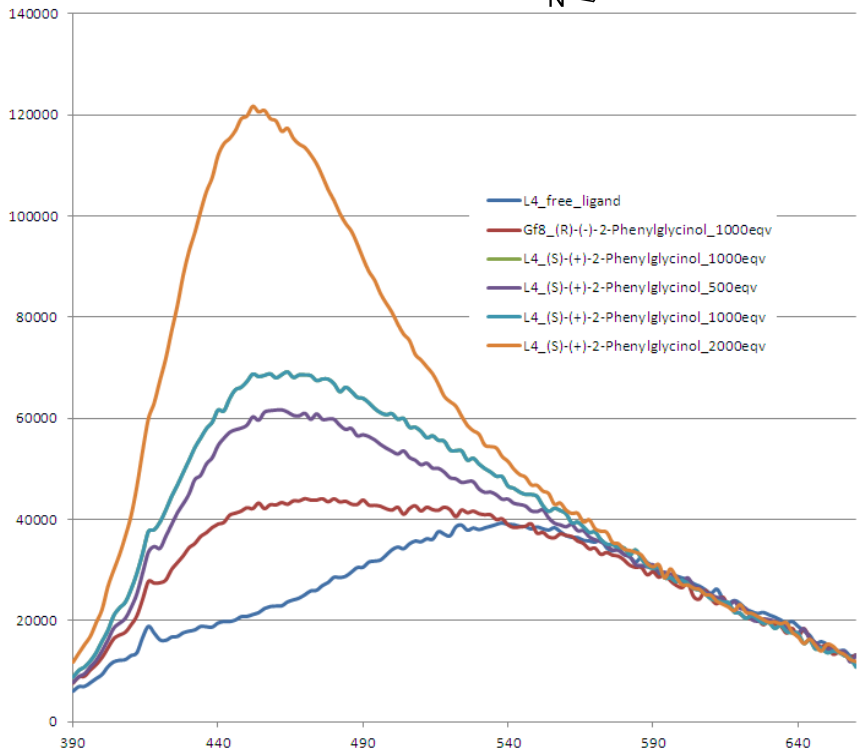


Хиральные макроциклы – флуоресцентные детекторы (*S*)-(+)-2-фенилглицинола

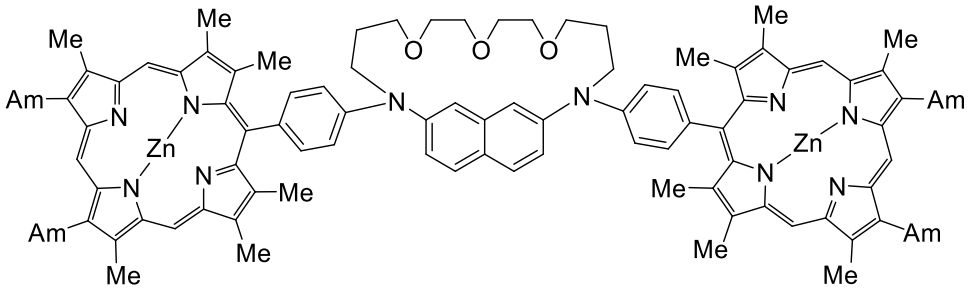




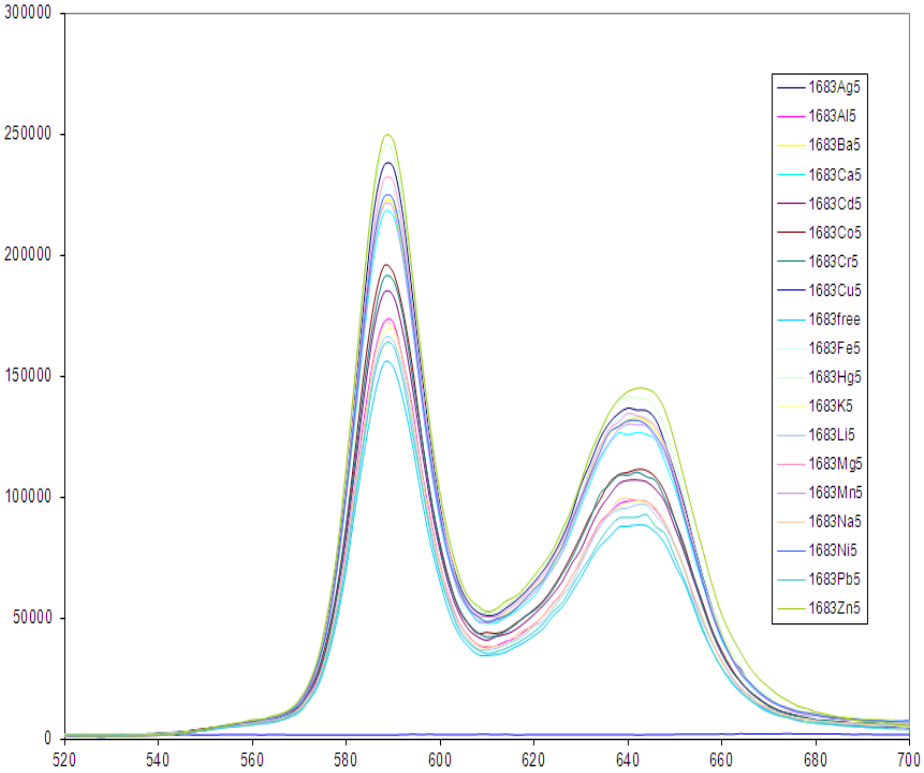


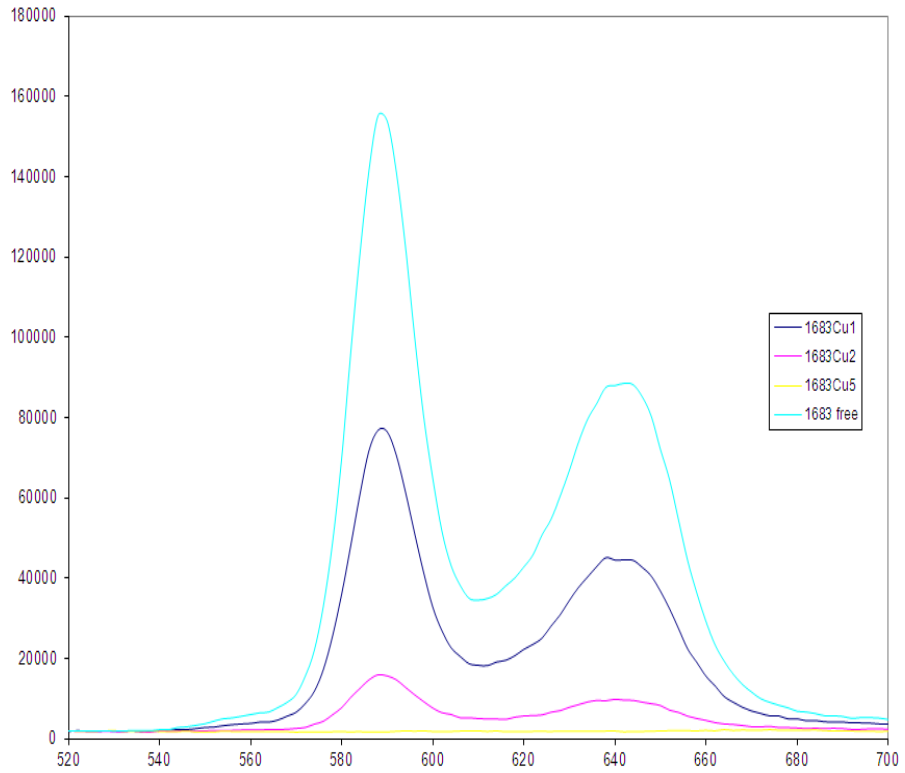


Биспорфириновое производное диазатриоксамакроцикла – флуоресцентный сенсор на Cu(II)



Предел обнаружения
0.14 mM





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