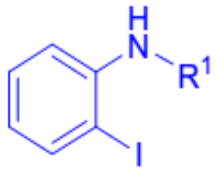
LAROCK INDOLE SYNTHESIS

Larock indole synthesis (1991):



o-iodoaniline

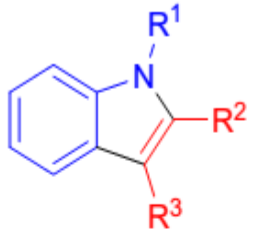
+

(1.5-2.0 equiv.)

disubstituted alkyne

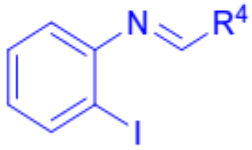
$Pd^{(0)}$ or $Pd^{(II)}$ complexes (cat.)
ligand (catalytic) / solvent

MCl (1 equivalent)
base (5 equivalents)
$R^2 > R^3$



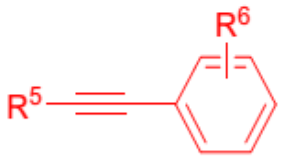
Substituted indole

Modified Larock indole synthesis for fused systems (1999):



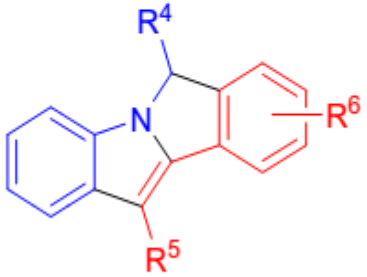
o-iodoaniline-derived imine

+



$Pd^{(0)}$ or $Pd^{(II)}$ complexes (cat.)
ligand (catalytic) / solvent / heat

$(n\text{-Bu})_4NCl$ (1 equivalent)
base (1-2 equivalents)

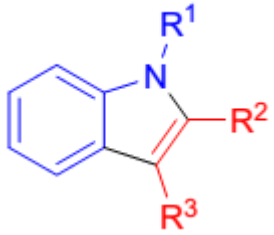


Isoindolo[2,1-*a*]indoles

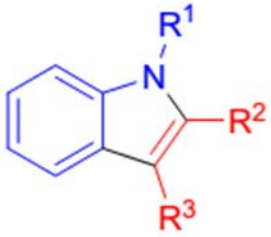
R^1 = alkyl, acyl, SO_2Ar; $R^{2\text{-}3}$ = 1°, 2°, 3° alkyl, aryl, alkenyl, CH_2OH, SiR_3; M = $(n\text{-Bu})_4N^+$, Li; base = Na_2CO_3, K_2CO_3, KOAc
R^4 = alkyl, aryl; R^5 = 1°, 2°, 3° alkyl, aryl, CH_2OH, CO_2R; R^6 = EWG or EDG; base = Na_2CO_3, *i*-Pr_2NEt

Main features

- Regioselectivity



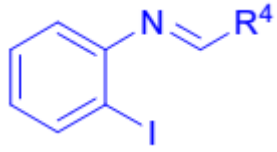
R2 is larger!

- R2=SiR3, 

product can be protodesilylated halogenated or coupled with alkene via Pd-catalyzed reaction

- Equivalent of LiCl and excess base
- Typically DMF is used as solvent

Modifications:

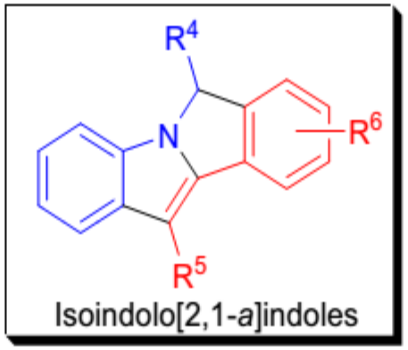


can be used.

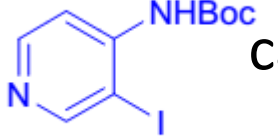
Modified Larock indole synthesis for fused systems (1999):

o-iodoaniline-derived imine

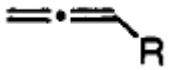
$Pd^{(0)}$ or $Pd^{(II)}$ complexes (cat.)
ligand (catalytic) / solvent / heat
$(n\text{-Bu})_4NCl$ (1 equivalent)
base (1-2 equivalents)

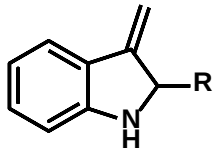


Isoindolo[2,1-*a*]indoles

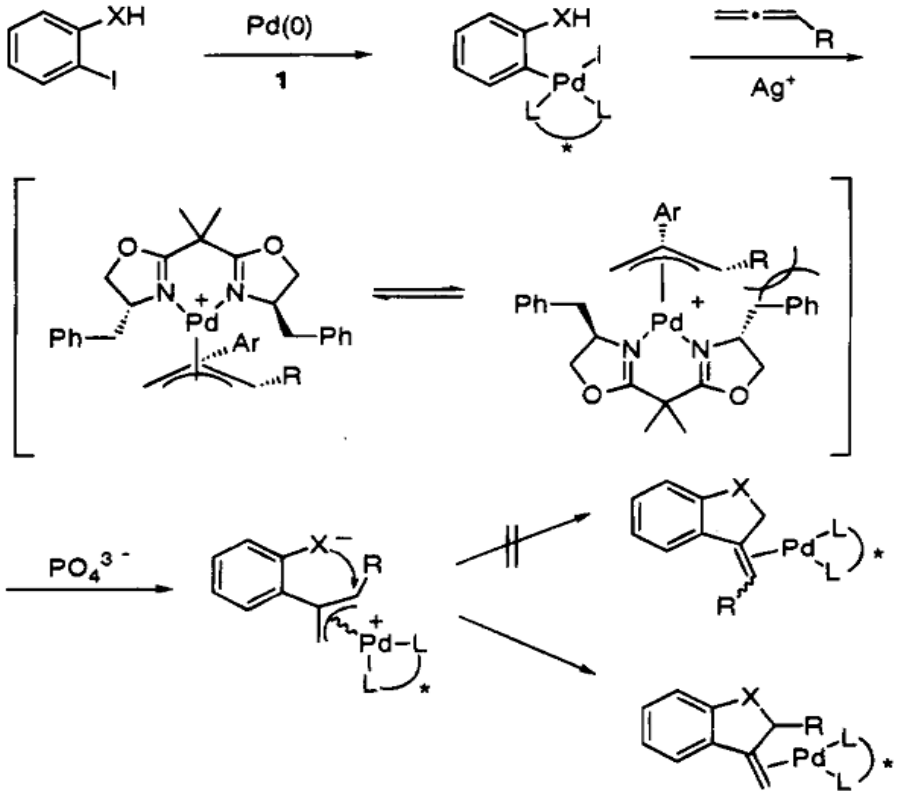


can be used as substrates

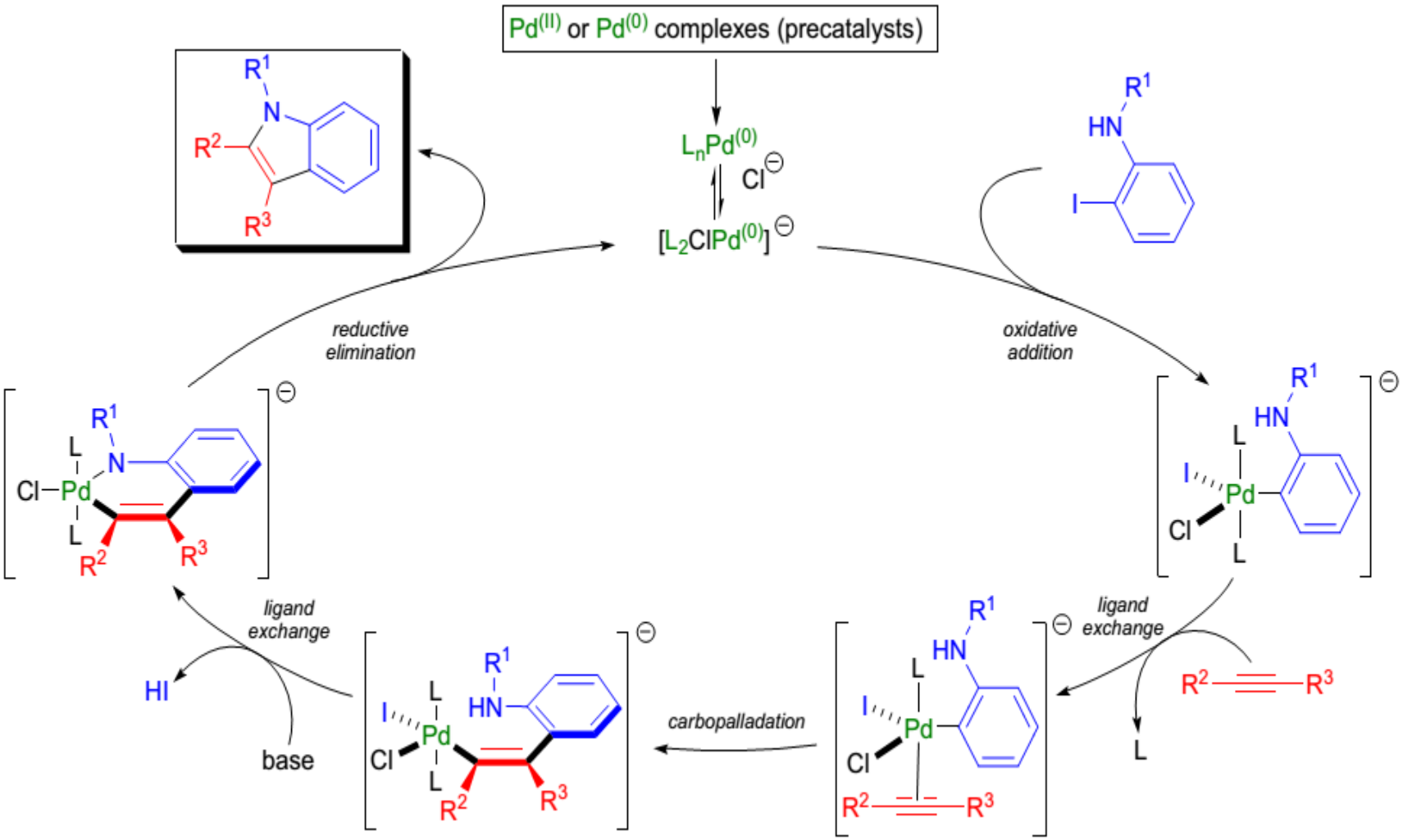
Alkyne can be replaced with allenes 

product 

Mechanism

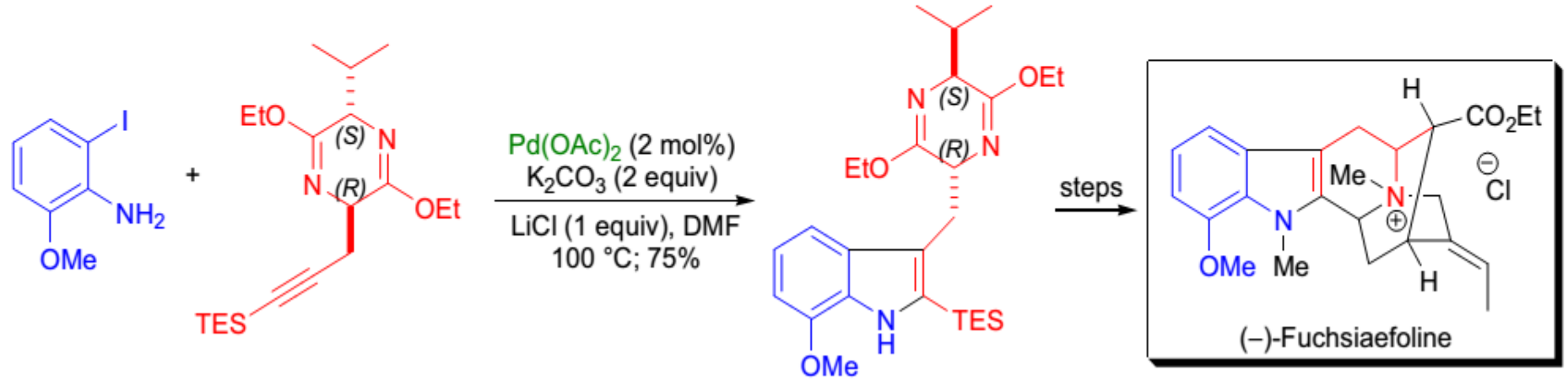


Mechanism

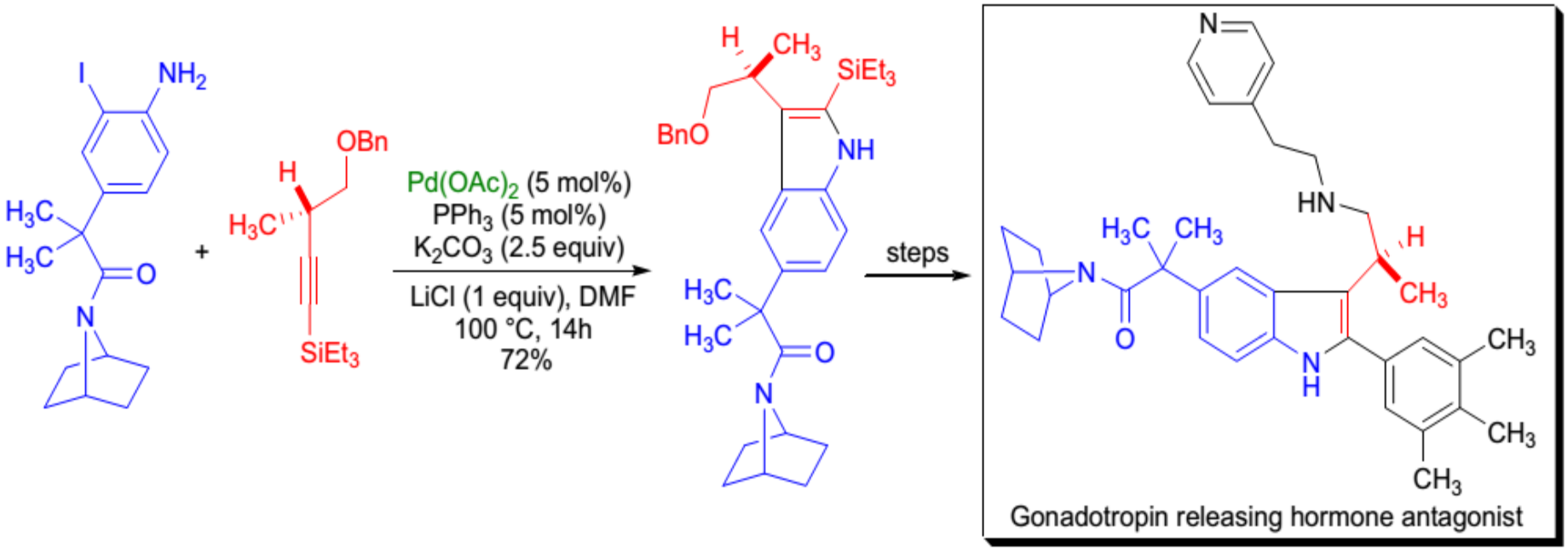

Pd(II) or Pd(0) complexes (precatalysts)
LnPd(0)
Cl
[L2ClPd(0)]
oxidative addition
ligand exchange
R2
R3
carbopalladation
ligand exchange
L
base
HI
reductive elimination

Applications

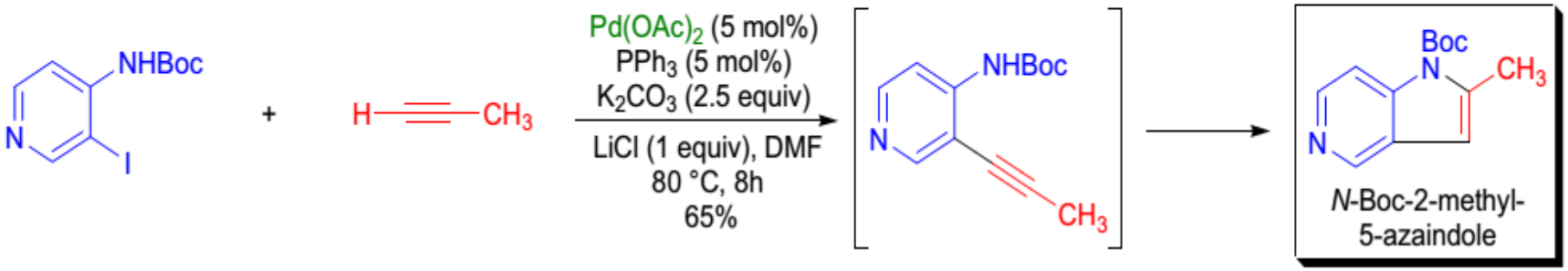
The total synthesis of (–)-fuchsiaefoline was accomplished in the laboratory of J.M. Cook using the *Larock indole synthesis* to prepare the key precursor 7-methoxy-D-tryptophan in enantiopure form.[22] The propargyl-substituted Schöllkopf chiral auxiliary was reacted with 2-iodo-6-methoxyaniline in the presence of 2 mol% $Pd(OAc)_2$ to give the expected indole in good yield. Interestingly, the *Bartoli indole synthesis* gives 7-substituted indoles only in moderate yield.



T.F. Walsh and co-workers synthesized two (*S*)-β-methyl-2-aryltryptamine based gonadotropin hormone antagonists *via* a consecutive *Larock indole synthesis* and *Suzuki cross-coupling*. The required (*S*)-β-methyltryptophol derivatives were prepared by coupling 4-substituted *o*-iodoanilines with optically active internal alkynes under standard conditions. The resulting 2-trialkylsilyl substituted indoles were then subjected to a *silver-assisted iododesilylation reaction* to afford the 2-iodo-substituted indoles that served as coupling partners for the *Suzuki cross-coupling* step.



The preparation of diversely substituted azaindoles is fairly difficult, and there are no generally applicable strategies in the literature. Research by L. Xu et al. showed that 2-substituted-5-azaindoles could be synthesized by the Pd-catalyzed coupling of aminopyridyl iodides with terminal alkynes.[13] The coupling reaction proceeded in good yield under the conditions originally developed by Larock. Therefore, this example can be considered an extension of the *Larock indole synthesis*. By stopping the reaction early it was shown that the intermediate was an internal alkyne.



A complete reversal of regioselectivity was observed by M. Isobe and co-workers during the *Larock heteroannulation* of *o*-iodoaniline with α-C-glucosylpropargyl glycine in an attempt to prepare *C*-glycosyltryptophan.[14]