

# 1,4-MIGRATION OF PALLADIUM IN ORGANIC SYNTHESIS

**GROUP SEMINAR - 17/04/2020**

**EPFL - ISIC - LSPN**

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**LSPN**

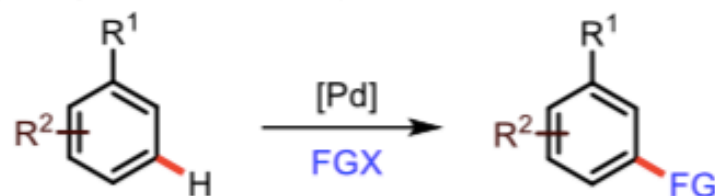
LABORATOIRE DE SYNTHÈSE  
ET PRODUITS NATURELS

# TABLE ON CONTENTS

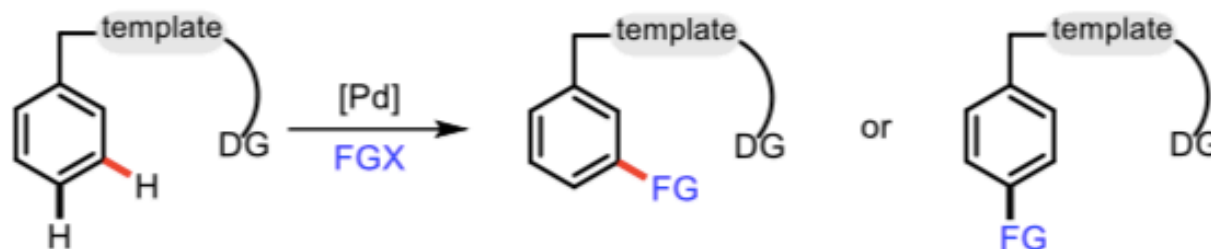
1. Introduction
2. Aryl to aryl 1,4 migration
3. Aryl to alkyl 1,4 migration
4. Aryl to vinyl 1,4 migration
5. Aryl to imidoyl 1,4 migration
6. Vinylic to Aryl 1,4 migration
7. Alkyl to aryl 1,4 migration
8. Conclusion

# C-H ACTIVATION

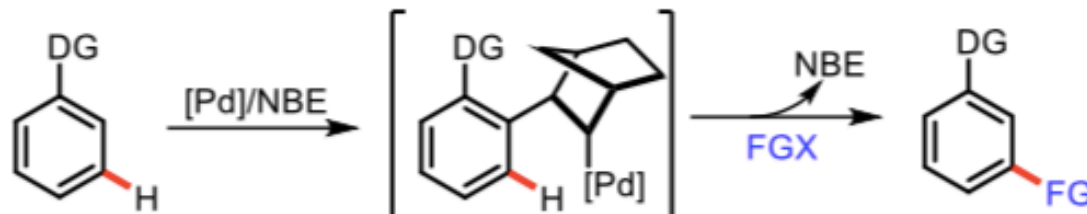
a) **Previous work:** Steric/electronic effects for *meta*-C-H functionalization



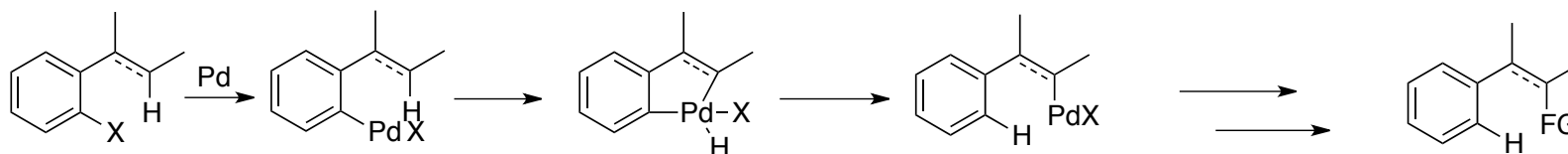
b) **Previous work:** U or D-shaped template for *meta*- or *para*-C-H functionalization



c) **Previous work:** Norbornene as a transient mediator for *meta*-C-H functionalization

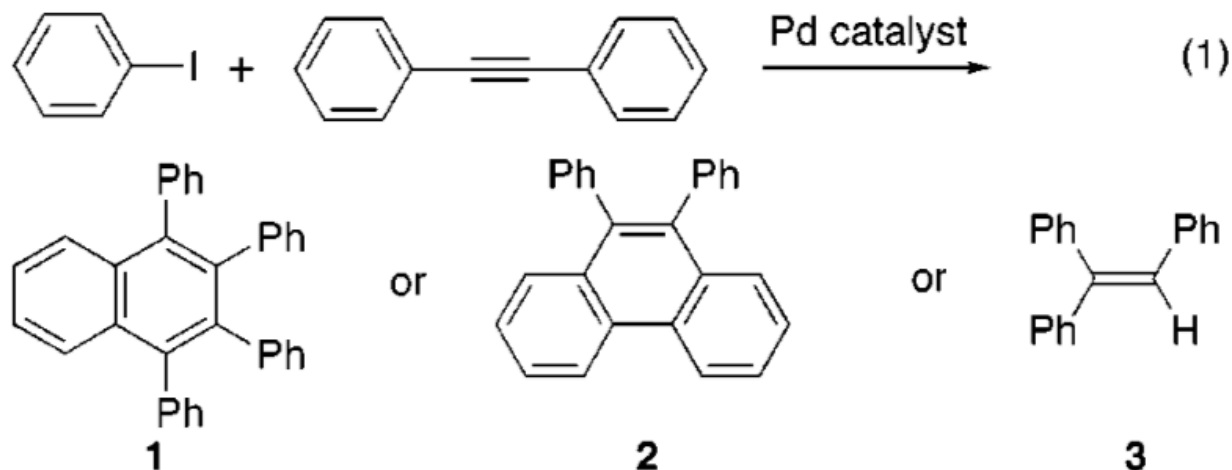


# C-H ACTIVATION – 1,4-MIGRATION



- no directing group;
- Introduction of palladium moiety to a remote site where direct introduction of palladium may be difficult
- C–H bond that is four or five bonds away from palladium

## LITERATURE DATA



2% Pd(OAc)<sub>2</sub>  
4% PPh<sub>3</sub>  
Et<sub>3</sub>N, MeNO<sub>2</sub>,  
100 C, 3d  
47%  
Heck

5% Pd(OAc)<sub>2</sub>  
K<sub>2</sub>CO<sub>3</sub>  
N-Bu<sub>4</sub>NBr, DMF,  
100 C, 3d  
69%  
Dyker

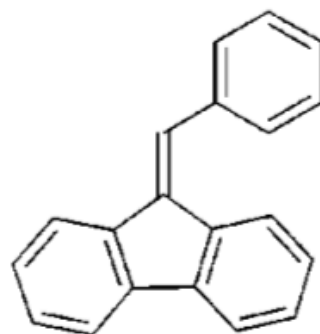
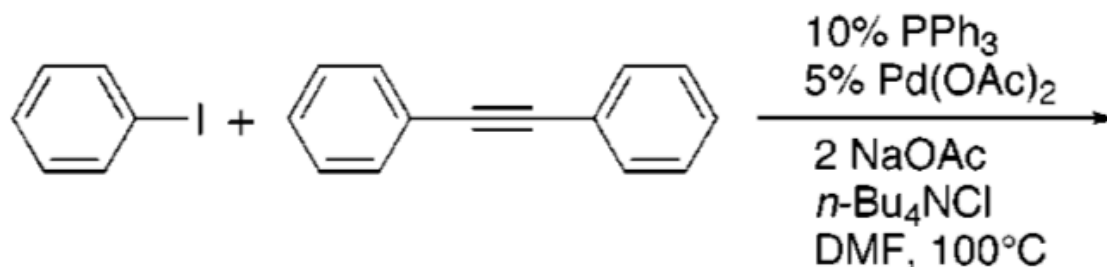
0.5% Pd(OAc)<sub>2</sub>(PPh<sub>3</sub>)  
HCOOH, Et<sub>3</sub>N  
MeCN  
80 C, 6.5 h  
87%  
Cacchi

Conditions

# SYNTHESIS OF FLUORENES

LSPN

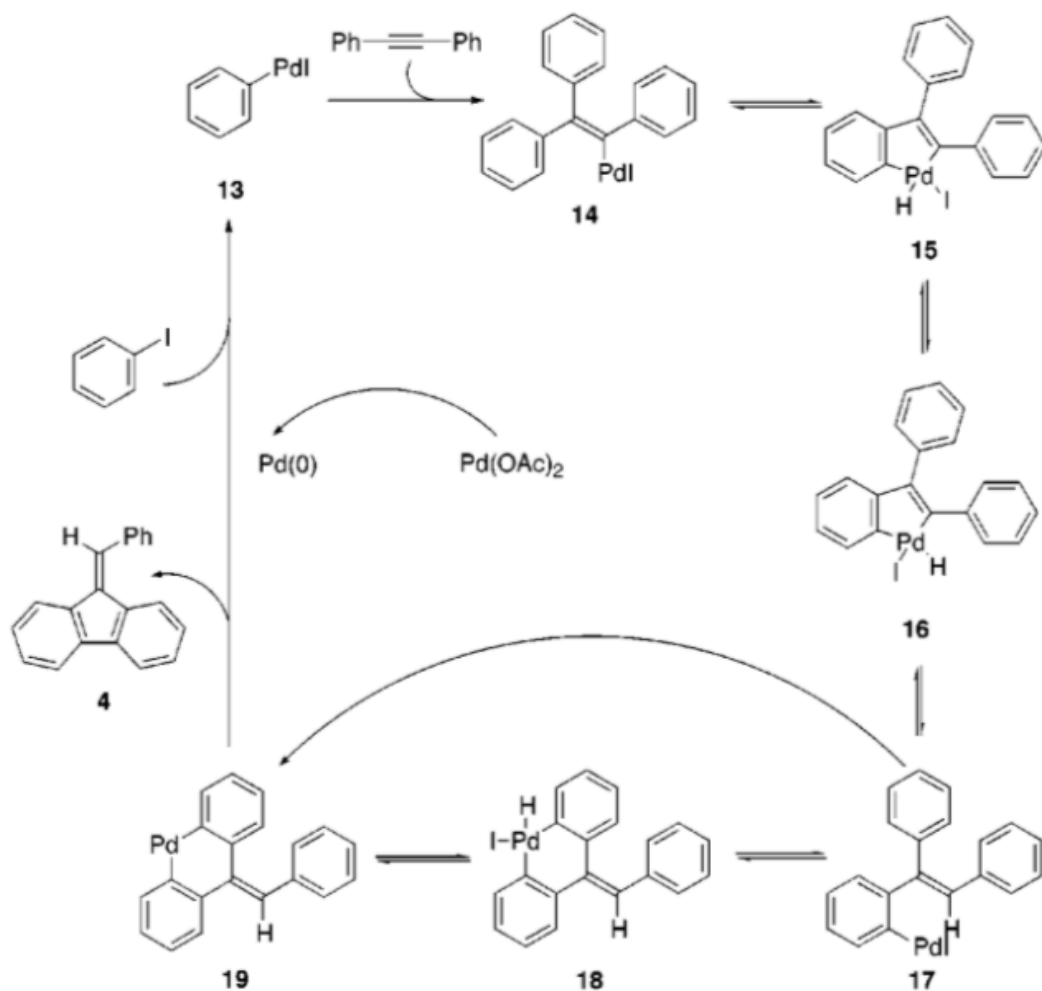
LABORATOIRE DE SYNTHÈSE  
ET PRODUITS NATURELS



4 62%

- 14 examples with good to moderate yield
- Aryl iodides with EDG and EWG;
  - Heteroatomic halides

# MECHANISM

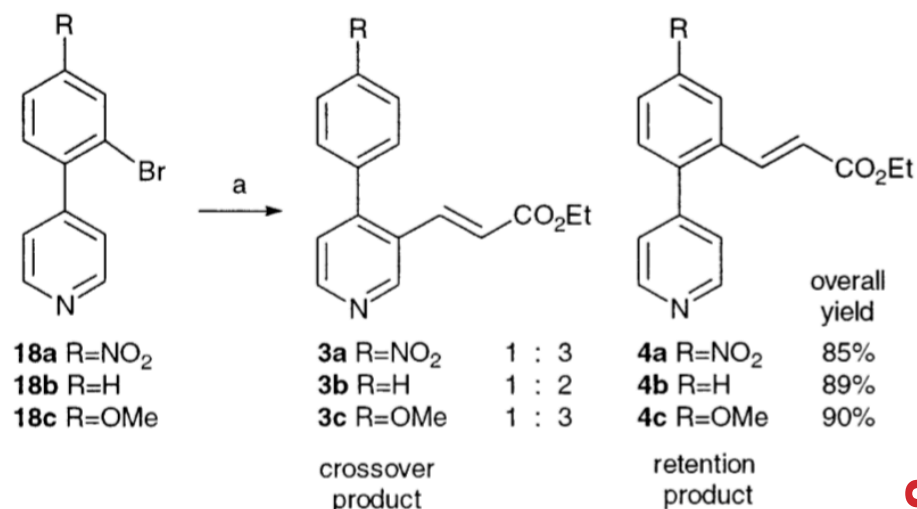
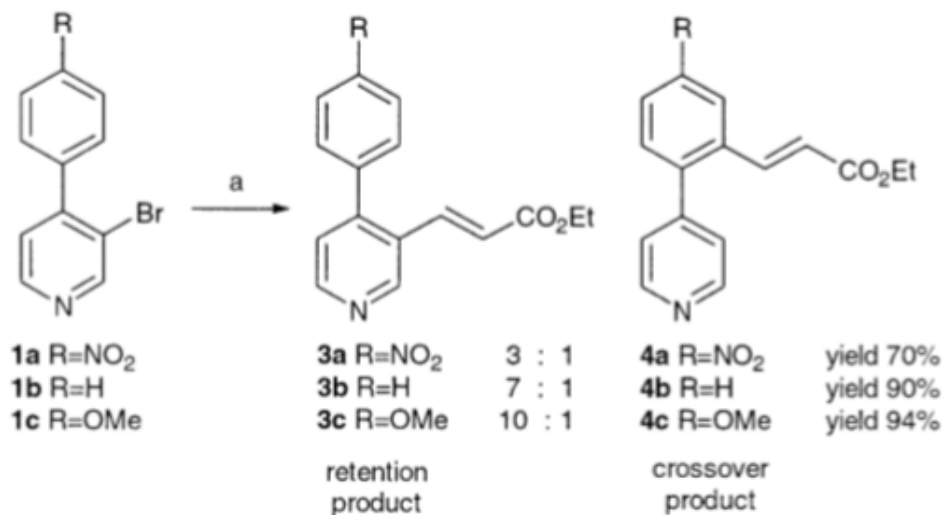


This process appears to involve  
(1) oxidative addition,  
(2) alkyne insertion,  
(3) 1,4-Pd migration, and  
(4) aryl-aryl coupling.

# ARYL TO ARYL MIGRATION

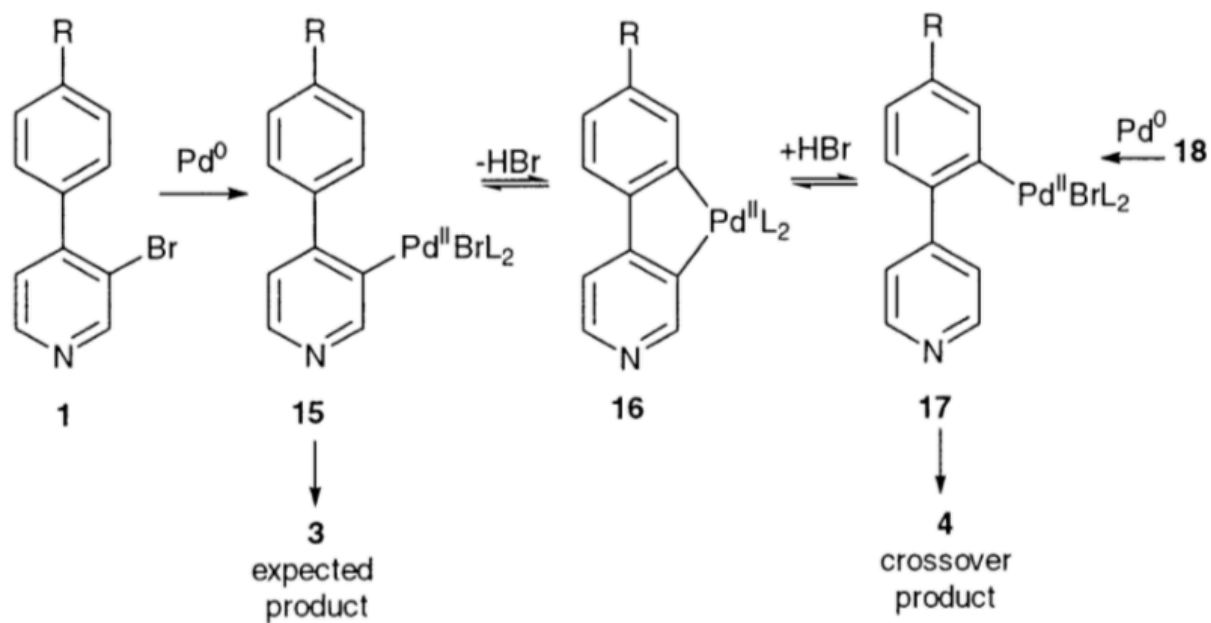
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LABORATOIRE DE SYNTHÈSE  
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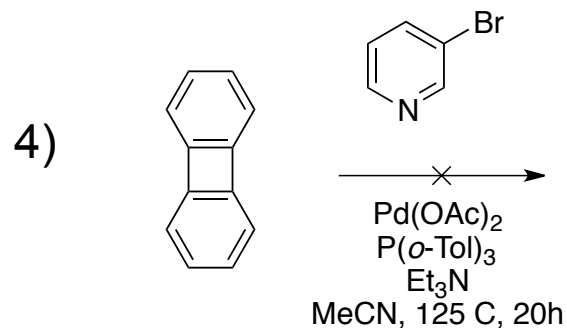
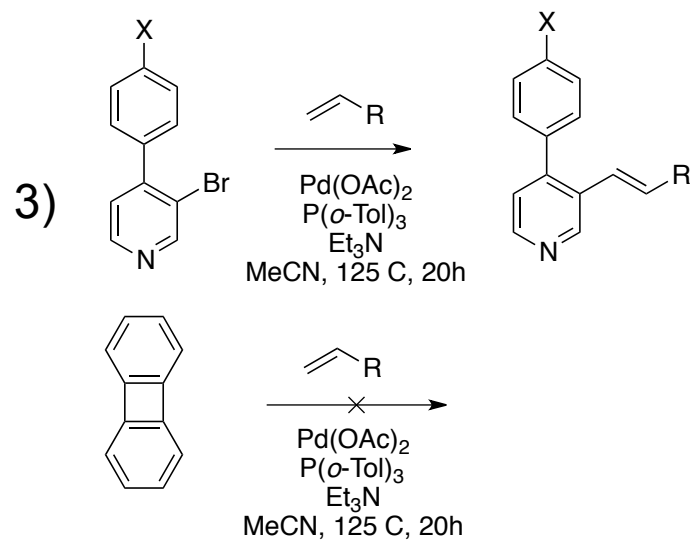
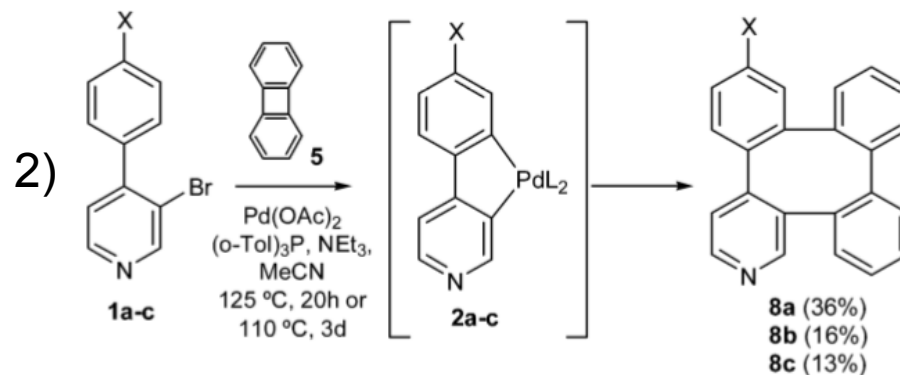
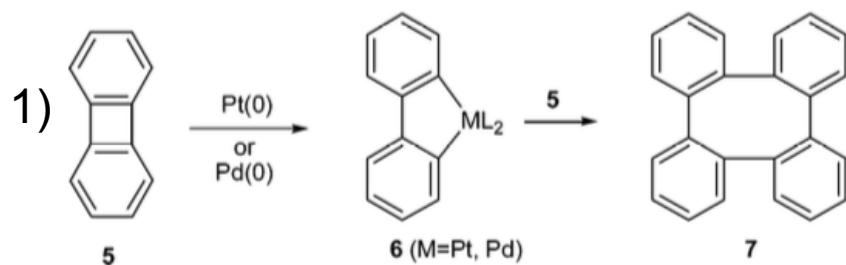




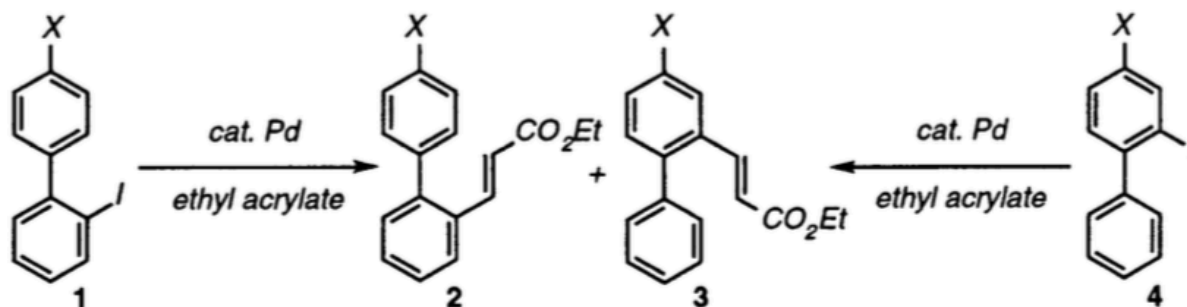
# MECHANISM



# PROOF OF MECHANISM

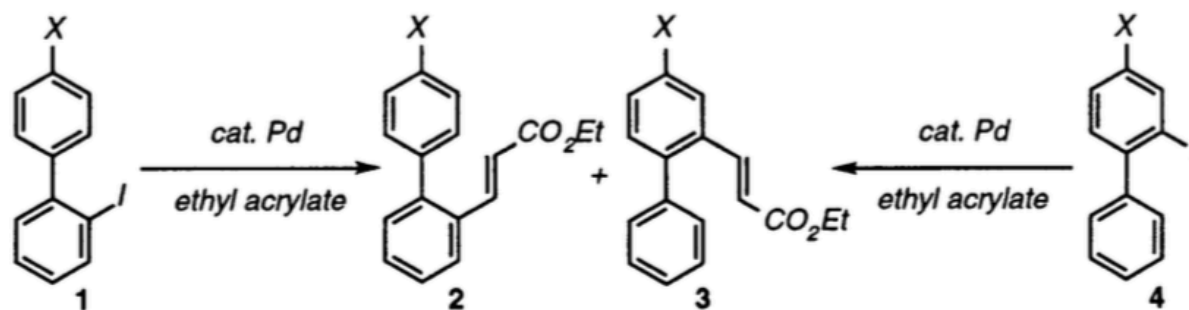


# ARYL TO ARYL PALLADIUM MIGRATION

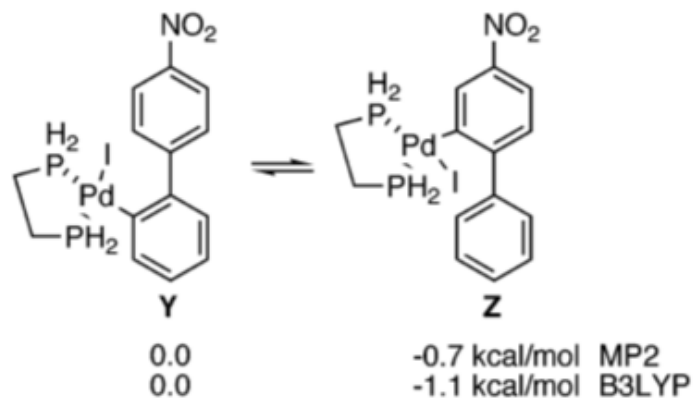
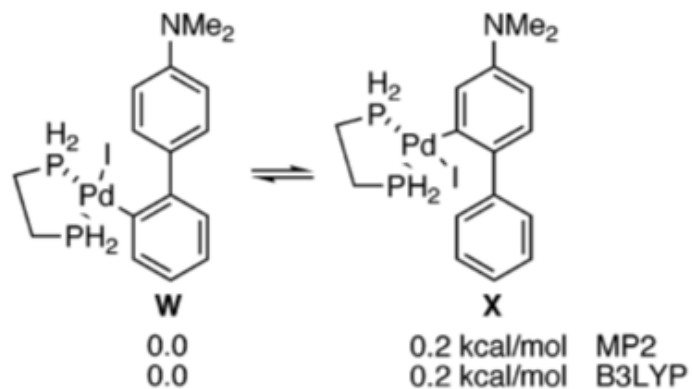


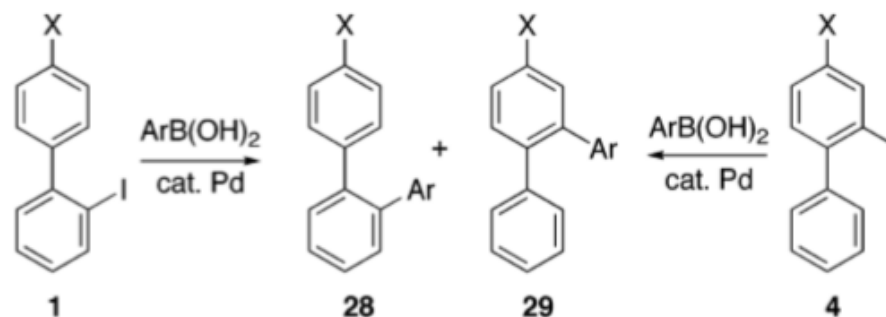
**Table 1.** Pd-Catalyzed Reaction of 2-Iodo-4'-methylbiphenyl (**1a**) and Ethyl Acrylate (EA)<sup>a</sup>

entry	EA equiv	conditions	time (d)	mol ratio		%yield
				<b>2a</b>	<b>3a<sup>b</sup></b>	
1	4	TBAC, NaHCO <sub>3</sub> <sup>c</sup>	1.0	100:0		100
2	4	TBAC, NaHCO <sub>3</sub>	1.0	95:5		100
3	1	TBAC, NaHCO <sub>3</sub>	1.0	77:23		92
4	1	CsPiv	1.5	54:46		93
5	1	5% dppm, CsPiv	1.5	50:50		88
6	1	10% PPh <sub>3</sub> , CsPiv	1.5	50:50		87



entry	substrate	X	procedure <sup>a</sup>	time (d)	% yield	mole ratio 2:3 <sup>b</sup>
1	<b>1a</b>	Me	A	1.0	100	100:0
2			C	1.5	88	50:50
3	<b>4a</b>	Me	A	1.0	93	0:100
4			C	1.5	86	49:51
5	<b>1b</b>	NMe <sub>2</sub>	A	1.0	80	100:0
6			C	1.0	90	55:45
7	<b>4b</b>	NMe <sub>2</sub>	A	1.0	100	0:100
8			C	1.5	93	49:51
9	<b>1c</b>	OMe	A	2.0	100	100:0
10			C	2.0	93	52:48
11	<b>4c</b>	OMe	A	2.0	99	0:100
12			C	2.0	92	48:52
13	<b>1d</b>	CO <sub>2</sub> Et	A	2.0	72	100:0
14			D	1.0	86	48:52
15	<b>4d</b>	CO <sub>2</sub> Et	A	1.0	99	0:100
16			D	1.0	83	42:58
17	<b>1e</b>	NO <sub>2</sub>	B	1.0	85	100:0
18			D	2.5	46 (40) <sup>c</sup>	39:61
19	<b>4e</b>	NO <sub>2</sub>	B	1.0	89	0:100
20			D	2.5	37 (50) <sup>c</sup>	33:67





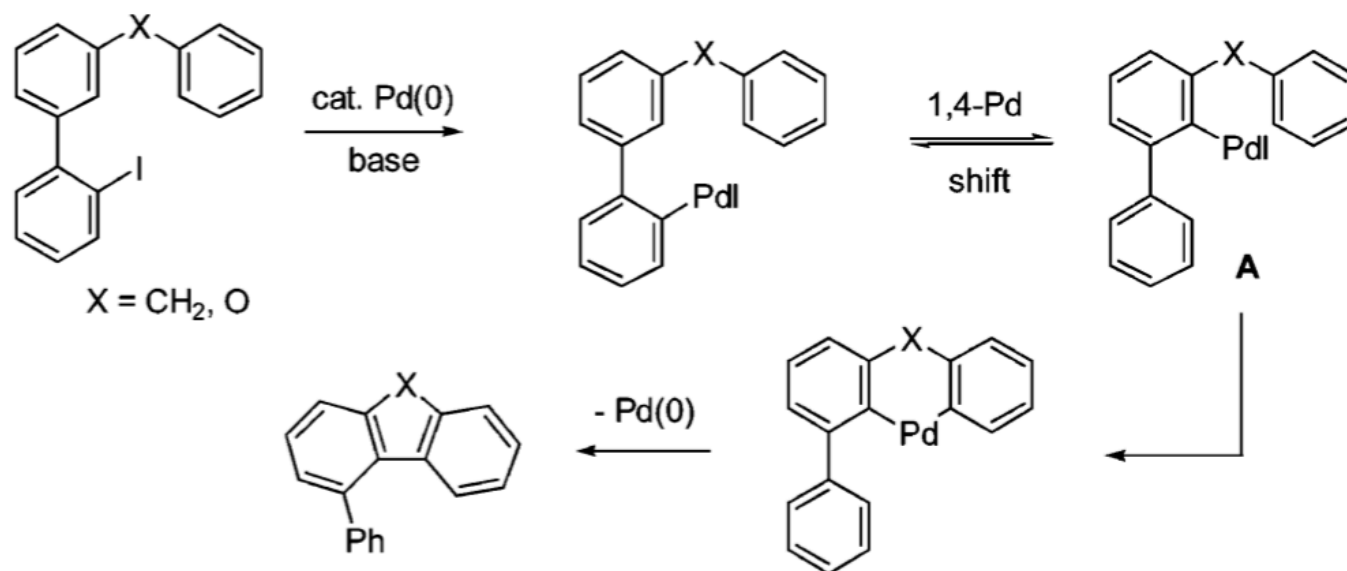
entry	biphenyl, X =	ArB(OH) <sub>2</sub> , Ar =	time (h)	mole ratio 28:29 <sup>b</sup>	% yield
1	1a, Me	<i>p</i> -MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> (27a)	4	51:49	78
2	4a, Me	(27a)	6	49:51	83
3	1a, Me	Ph (27b)	3	52:48	79
4	4a, Me	(27b)	10	50:50	69
5	1a, Me	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> (27c)	3	52:48	93
6	4a, Me	(27c)	6	49:51	90
7	1b, MeO	(27a)	4	42:58	85
8	4b, MeO	(27a)	9	39:61	75
9	1c, CO <sub>2</sub> Et	(27a)	10	40:60	84
10	4c, CO <sub>2</sub> Et	(27a)	10	34:66	68
11	1d, NO <sub>2</sub>	(27a)	25	23:77	61
12	4d, NO <sub>2</sub>	(27a)	10	16:84	75

Conditions: 1.4 equiv of arylboronic acid, 5 mol% Pd(OAc)<sub>2</sub>, 5 mol% dppm, 2.0 equiv. CsPiv, 2.0 equiv of PA, and 20 equiv of H<sub>2</sub>O in 4 mL of DMF at 100 °C

# ARYL TO ARYL PALLADIUM MIGRATION – SYNTHESIS OF FUSED POLYCYCLES

LSPN

LABORATOIRE DE SYNTHÈSE  
ET PRODUITS NATURELS

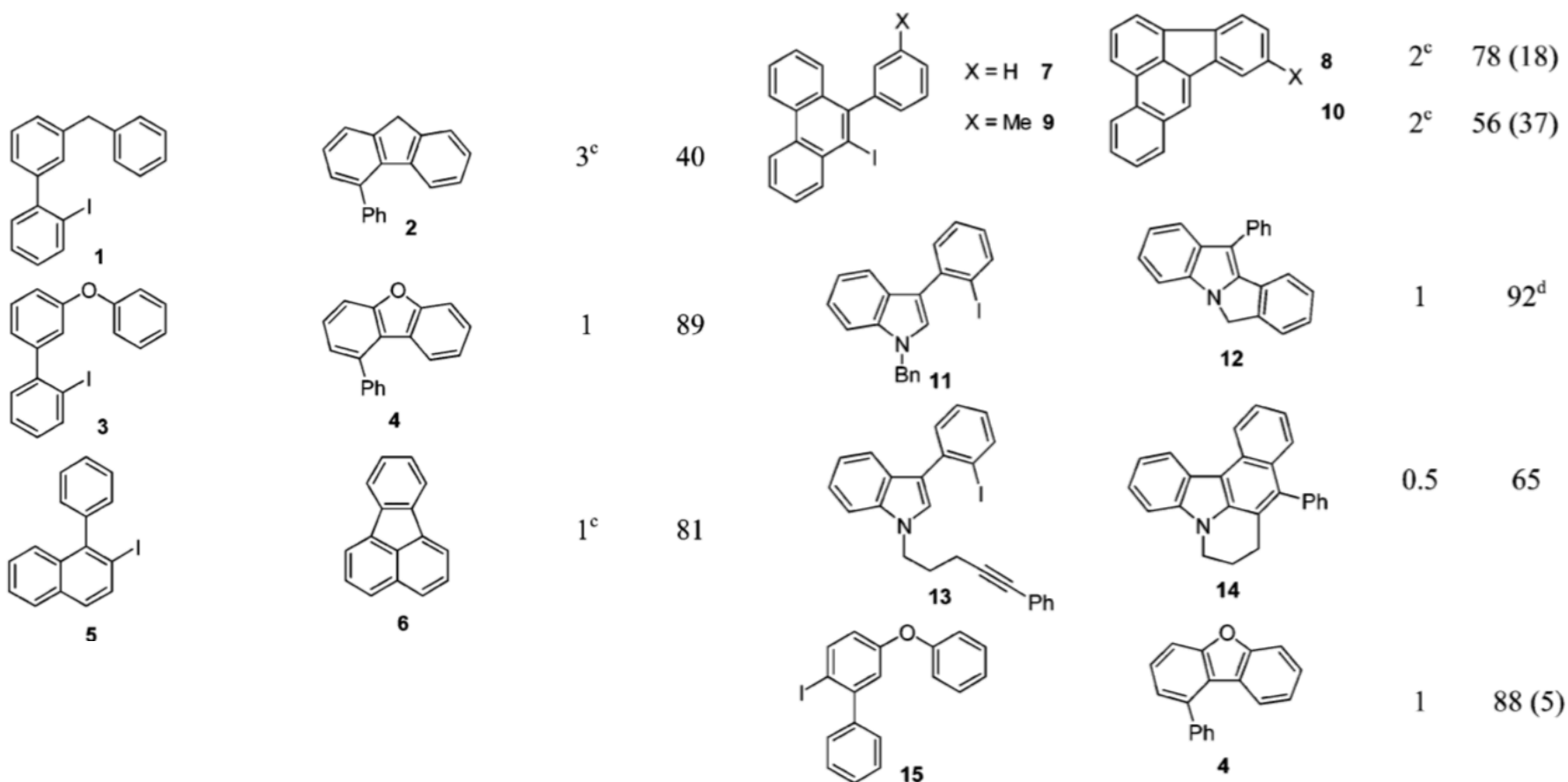


Conditions: 5 mol% Pd(OAc)<sub>2</sub>, 5 mol% dppm, 2 equiv. of CsPiv  
in DMF, at 100 °C

# ARYL TO ARYL PALLADIUM MIGRATION – SYNTHESIS OF FUSED POLYCYCLES

LSPN

LABORATOIRE DE SYNTHÈSE  
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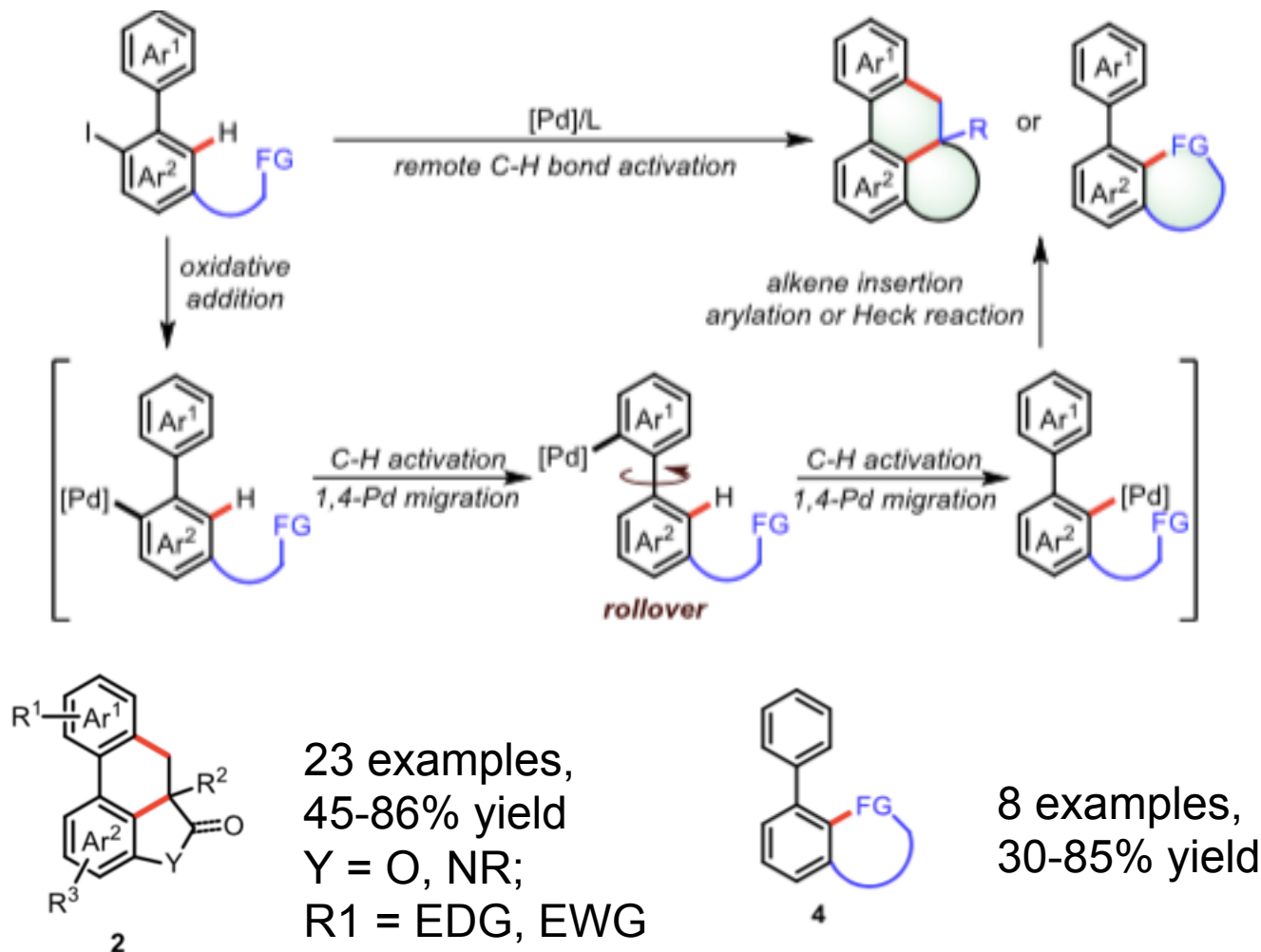




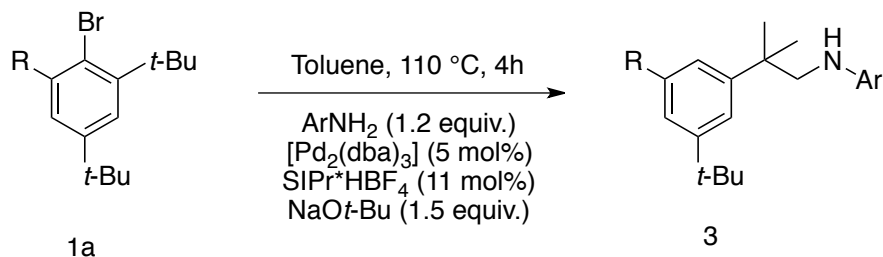
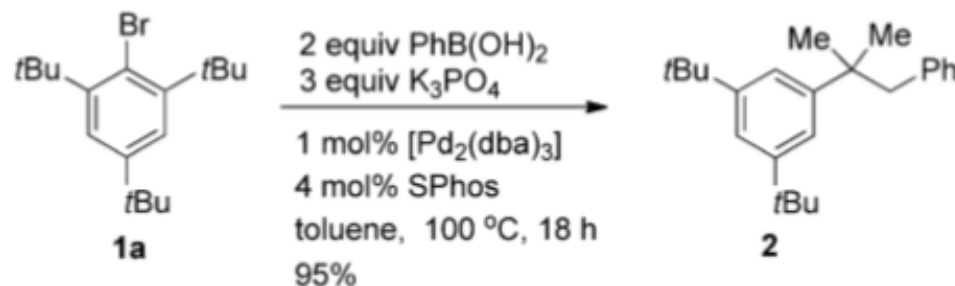
# ARYL TO ARYL PALLADIUM MIGRATION – SYNTHESIS OF FUSED POLYCYCLES

LSPN

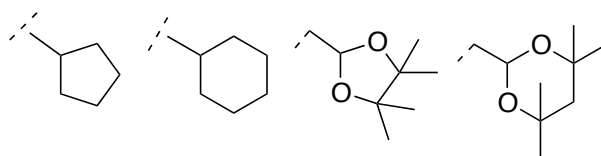
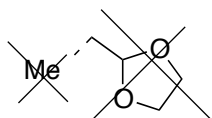
LABORATOIRE DE SYNTHÈSE  
ET PRODUITS NATURELS



# ARYL TO ALKYL MIGRATION



R = iPr, OTMS, TMS

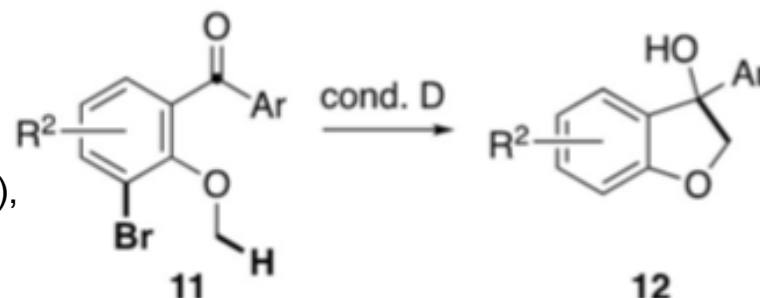
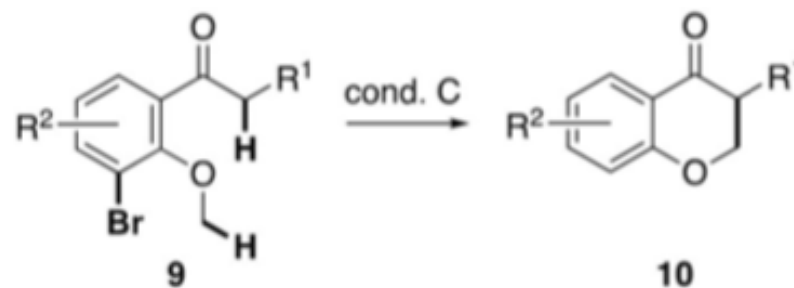
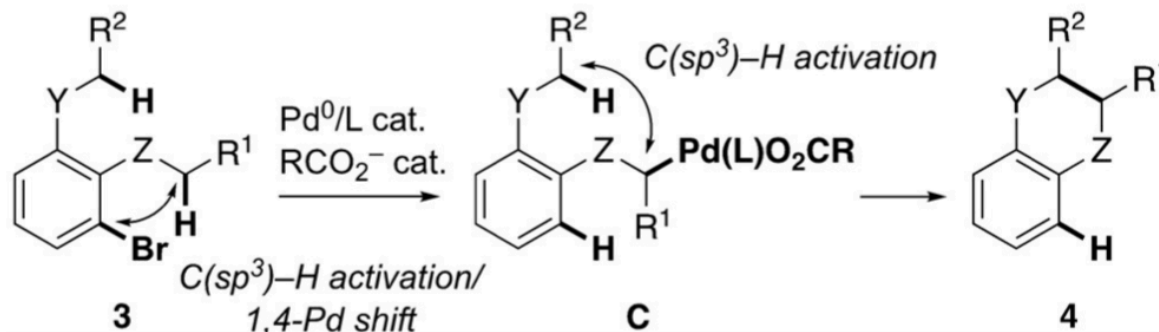


16 examples with good to moderate yields  
- Anilines with EDG and EWG;

# ARYL TO ALKYL PALLADIUM MIGRATION - SYNTHESIS OF FUSED POLYCYCLES

LSPN

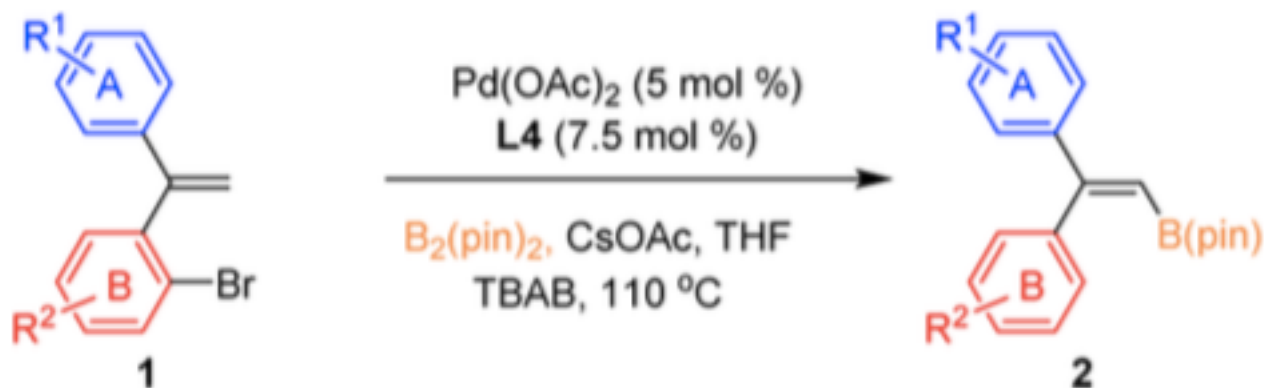
LABORATOIRE DE SYNTHÈSE  
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30 examples,  
38-90% yield

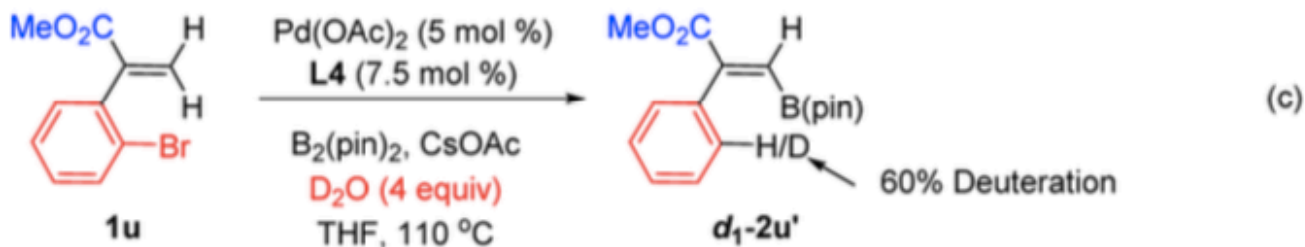
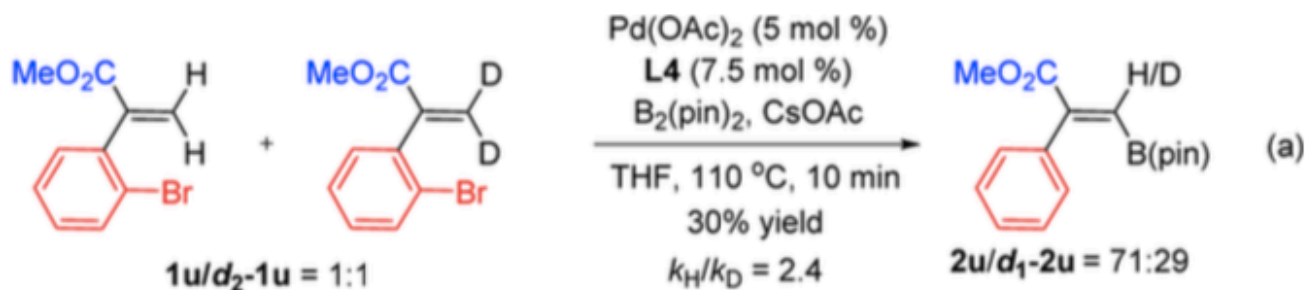
Conditions A:  $\text{Pd}(\text{PCy}_3)_2$  (10 mol%),  $\text{CsOPiv}$  (1.0 equiv),  
toluene, 140 C (sealed tube)

# ARYL TO VINYL PALLADIUM MIGRATION



17 examples,  
57-83% yield

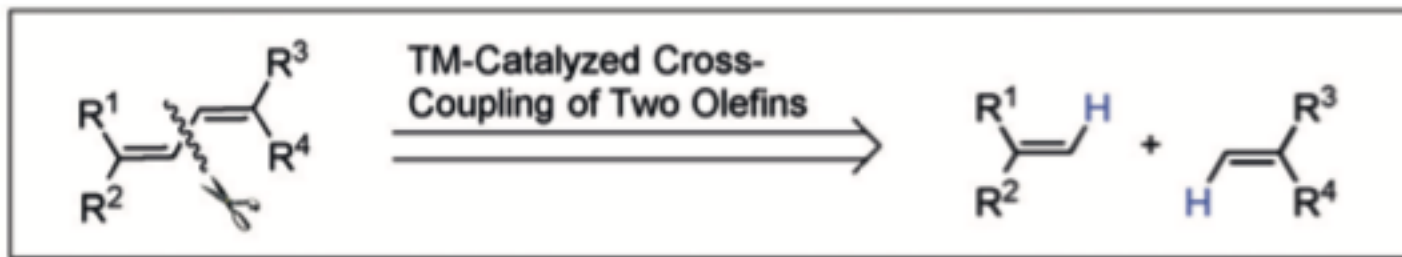
# DEUTERIUM-LABELING EXPERIMENTS



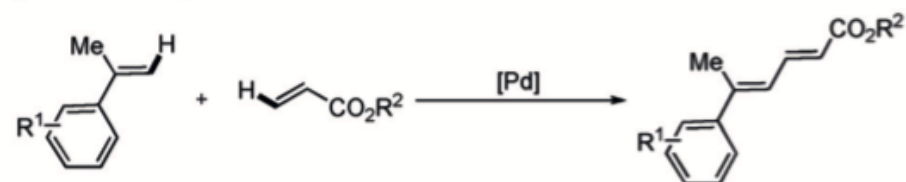
# ARYL TO VINYL PALLADIUM MIGRATION – SYNTHESIS OF 1,3-DIENES

LSPN

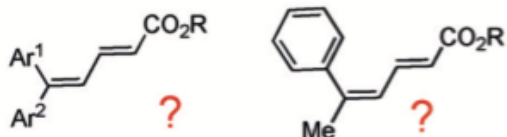
LABORATOIRE DE SYNTHÈSE  
ET PRODUITS NATURELS



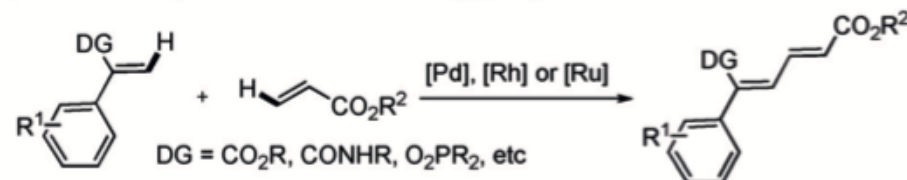
a) Controlled by the inherent steric difference of substituents



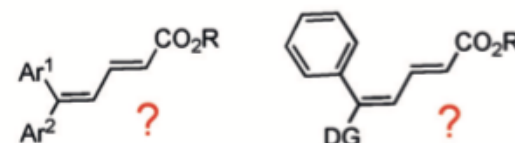
Problematic selectivities for:



b) Controlled by a hetero-atom directing group



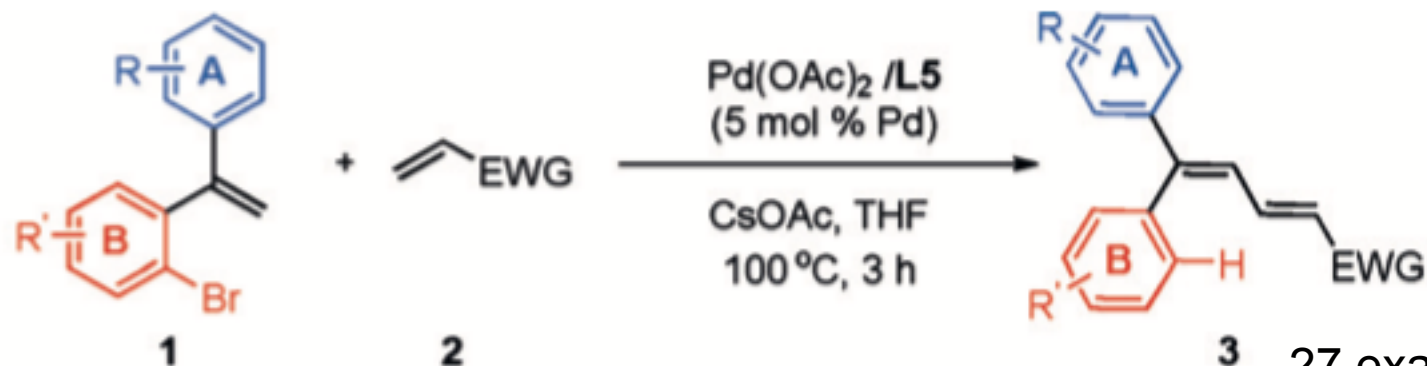
Problematic selectivities for:



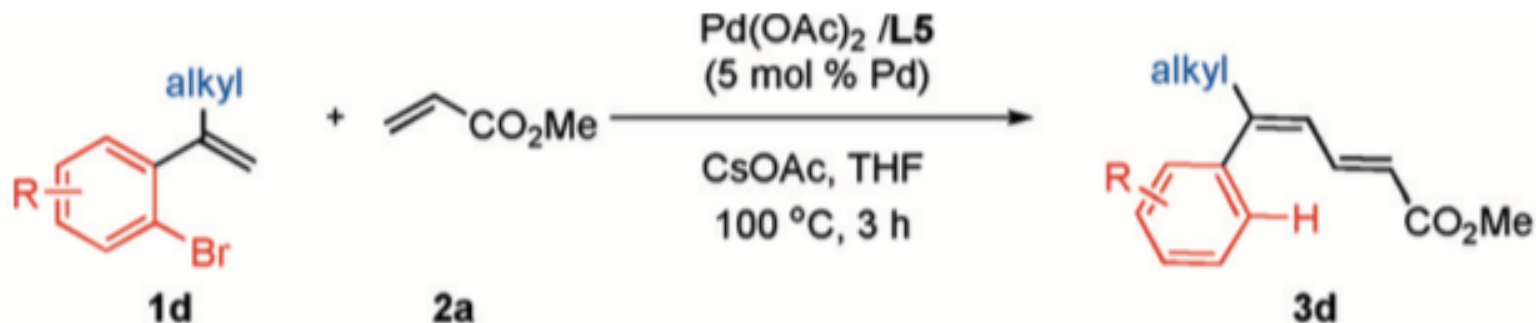
# ARYL TO VINYL PALLADIUM MIGRATION – SYNTHESIS OF 1,3-DIENES

LSPN

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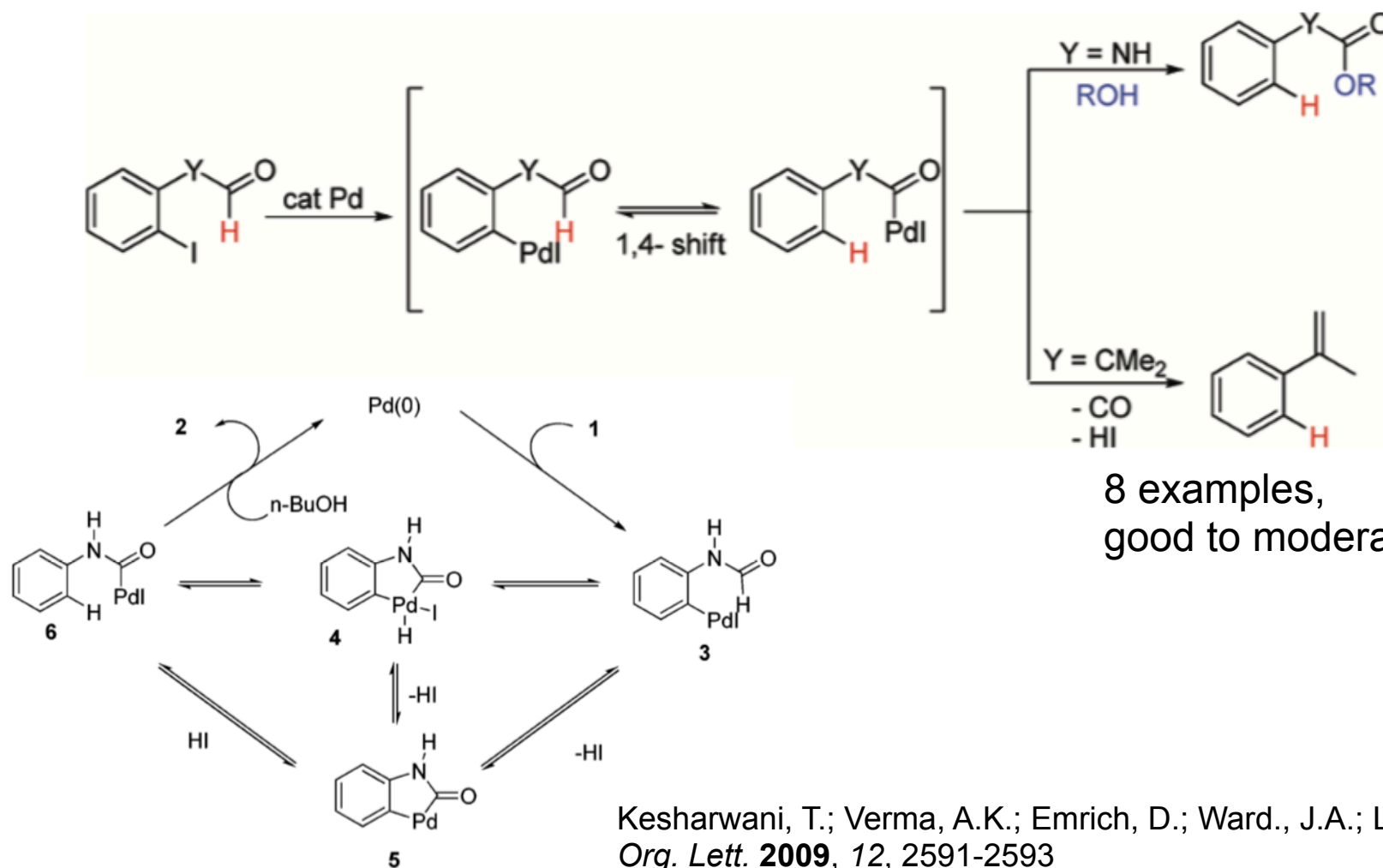


27 examples,  
34-86% yield (>90:10)



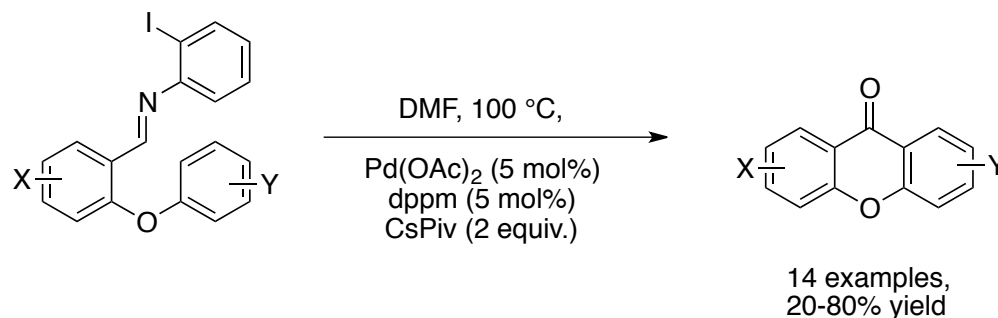
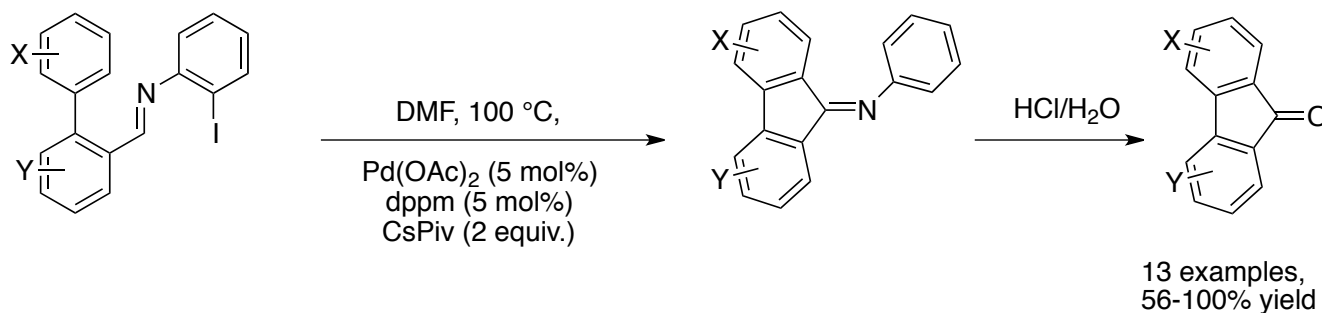
6 examples,  
57-78% yield (>90:10)

# ARYL TO ACYL PALLADIUM MIGRATION

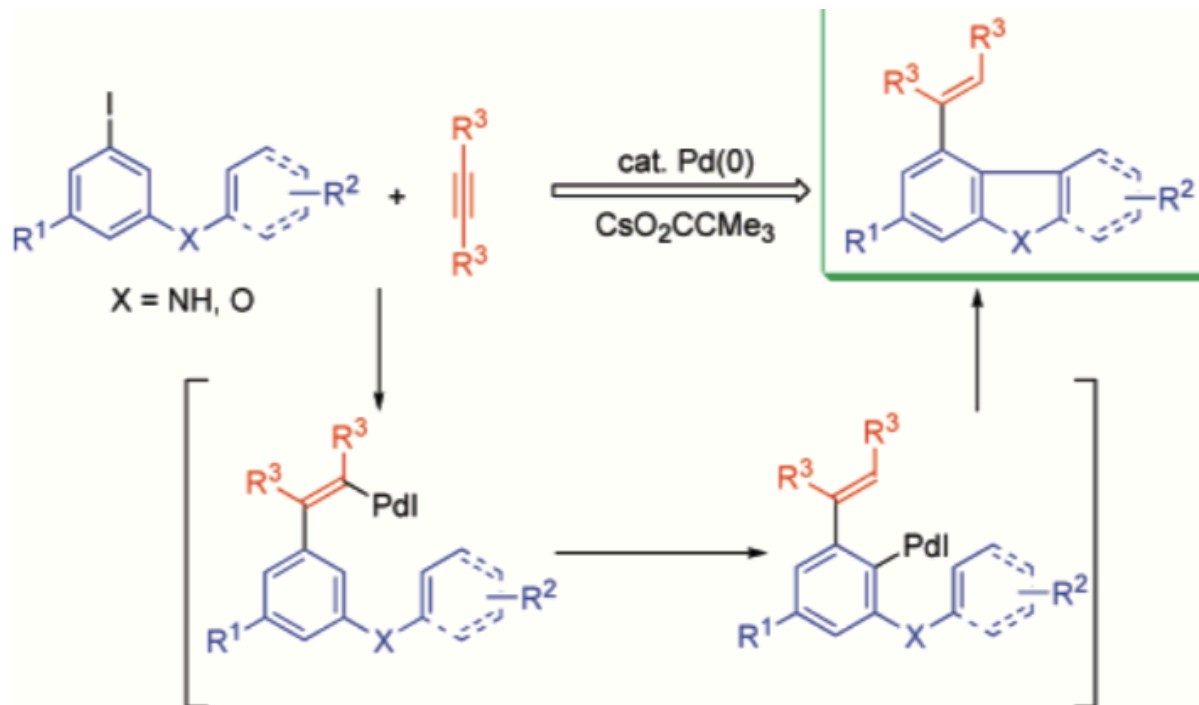




# ARYL TO IMIDOYL PALLADIUM MIGRATION



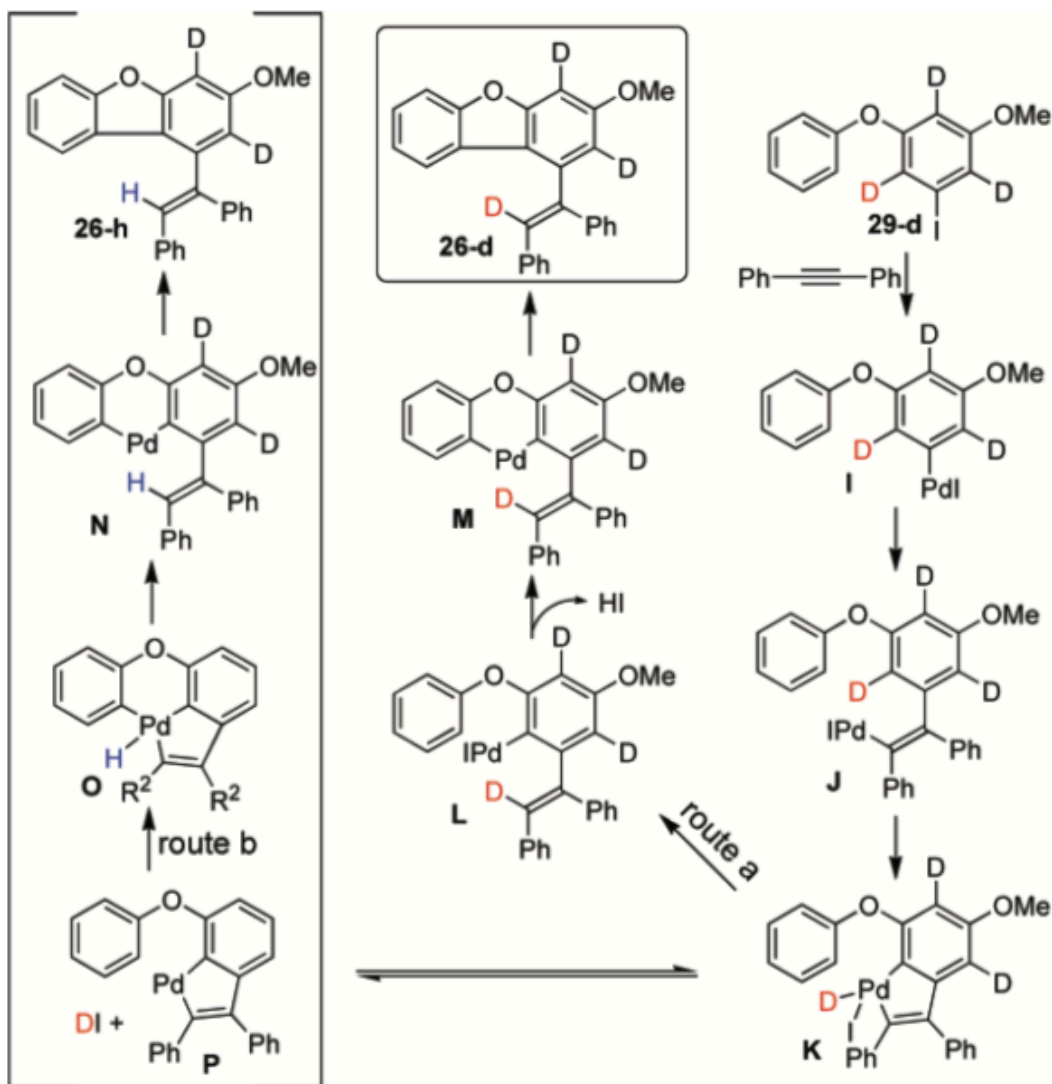
# VINYLIC TO ARYL PALLADIUM MIGRATION



28 examples with good to moderate yields  
- Aryl iodides with EDG and EWG;

Conditions: 5 mol%  $\text{Pd(OAc)}_2$ ,  
5 mol%  $\text{dppm}$ , 2 equiv.  $\text{CsPiv}$  in  $\text{DMF}$ ,  $100^\circ\text{C}$

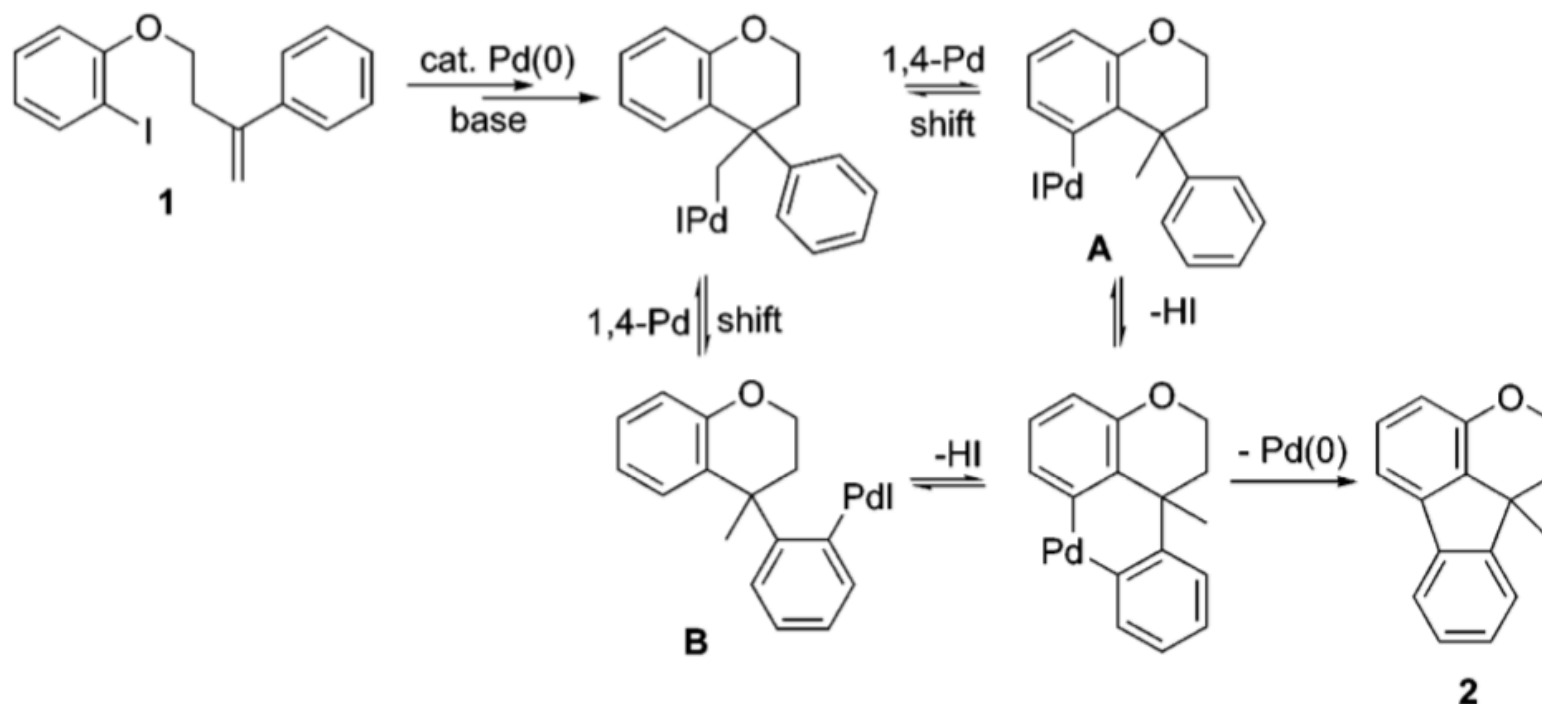
# DEUTERIUM LABELING EXPERIMENTS



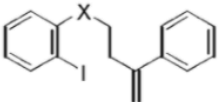
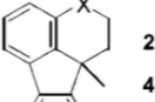
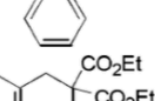
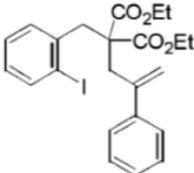
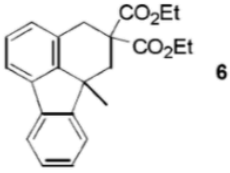
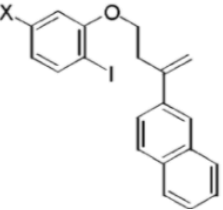
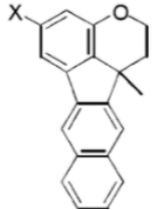
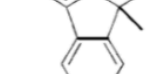
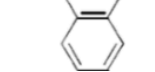
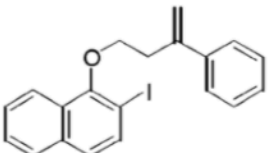
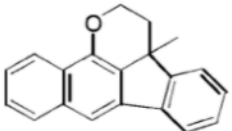
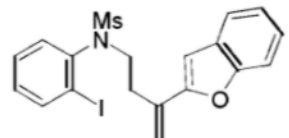
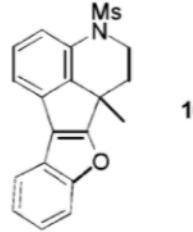
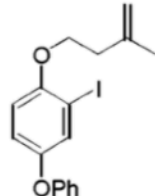
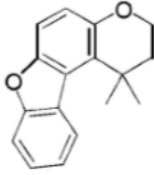
# ALKYL TO ARYL MIGRATION

LSPN

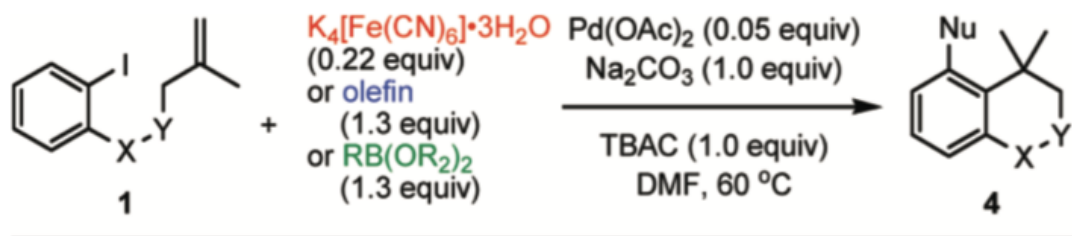
LABORATOIRE DE SYNTHÈSE  
ET PRODUITS NATURELS



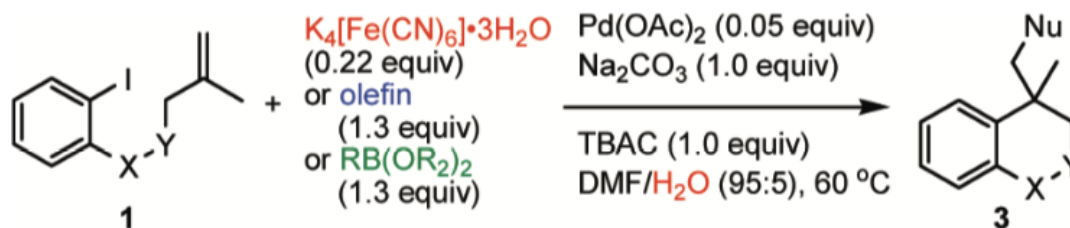
## SCOPE

substrate	product	time (h)	% yield <sup>b</sup>
 X = O 1 X = NMs 3	 2  4	4 1	88 95
 5	 6	5	82 <sup>c</sup>
 X = H 7 X = OMe 9 X = NO <sub>2</sub> 11	 8  10  12	4 3 4	84 91 21
 13	 14	2	95
 15	 16	4	76
 17	 18	4	83 <sup>d</sup>

# ALKYL TO ARYL PALLADIUM MIGRATION

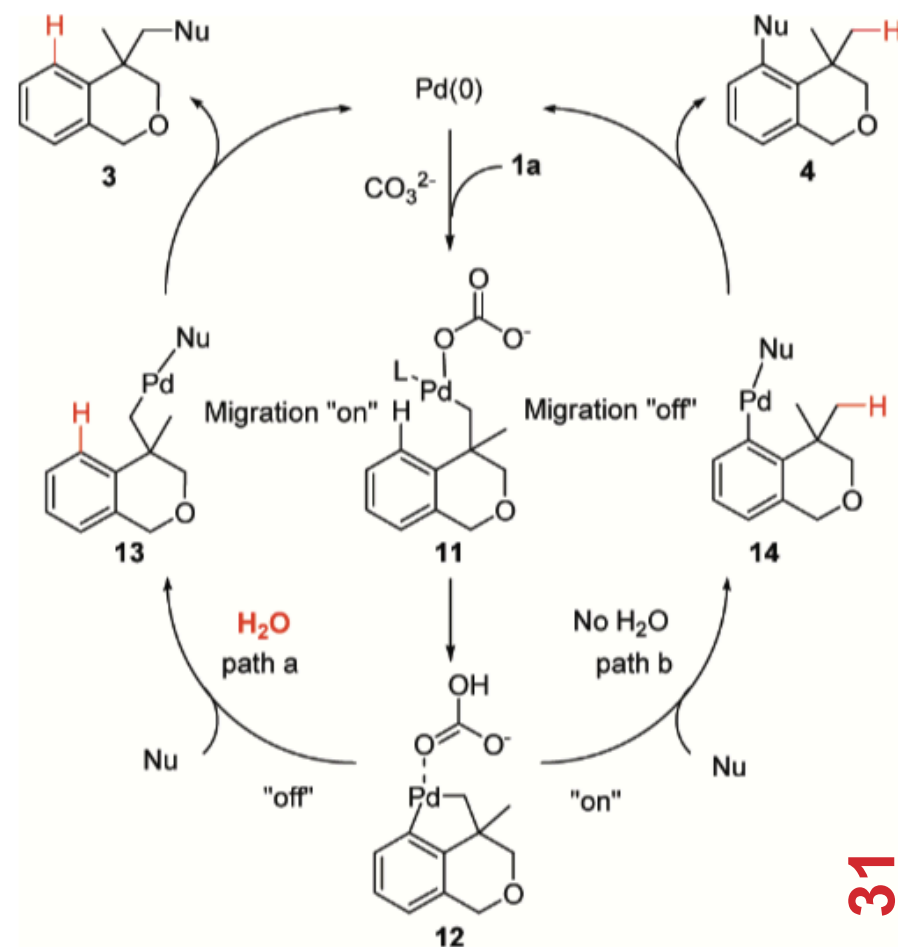
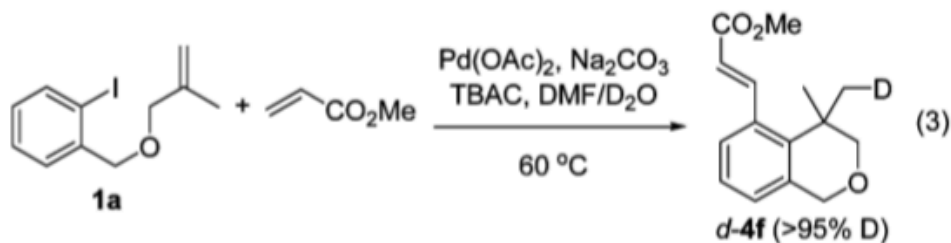
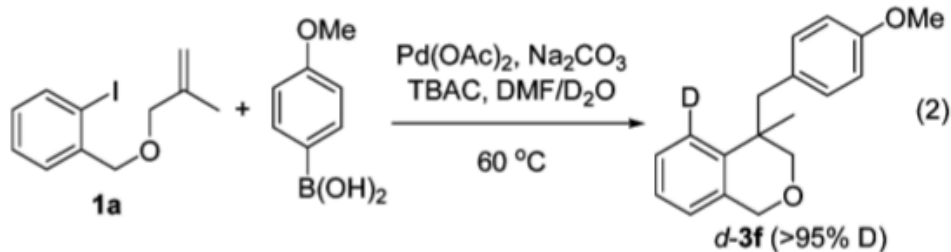
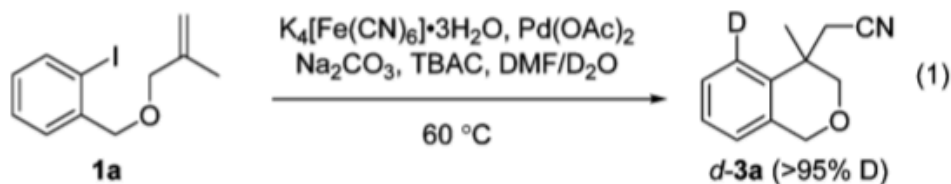


16 examples,  
47-95% yields



9 examples,  
60-95% yields

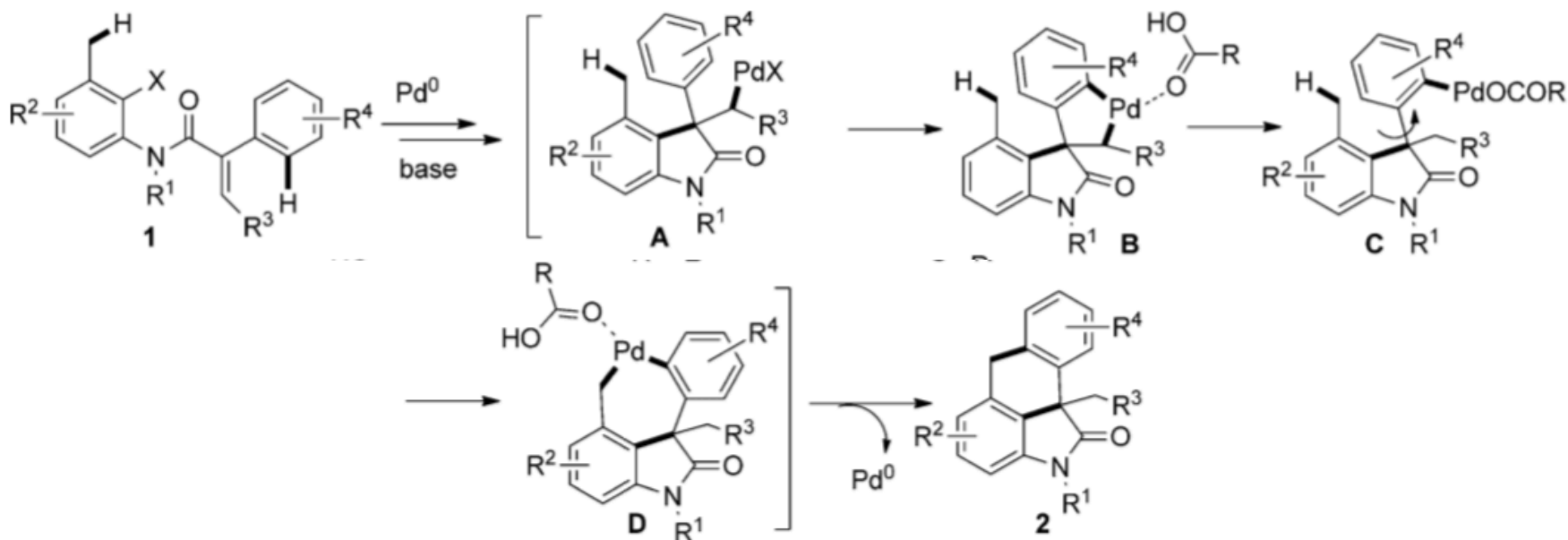
# DEUTERIUM LABELING EXPERIMENTS



# ALKYL TO ARYL MIGRATION

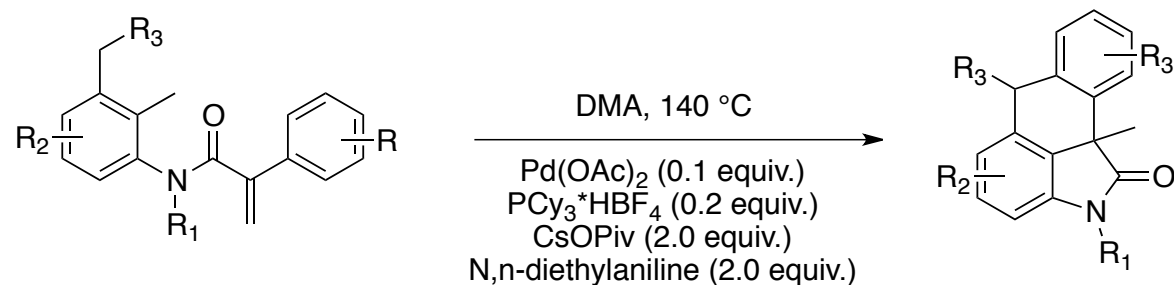
LSPN

LABORATOIRE DE SYNTHÈSE  
ET PRODUITS NATURELS





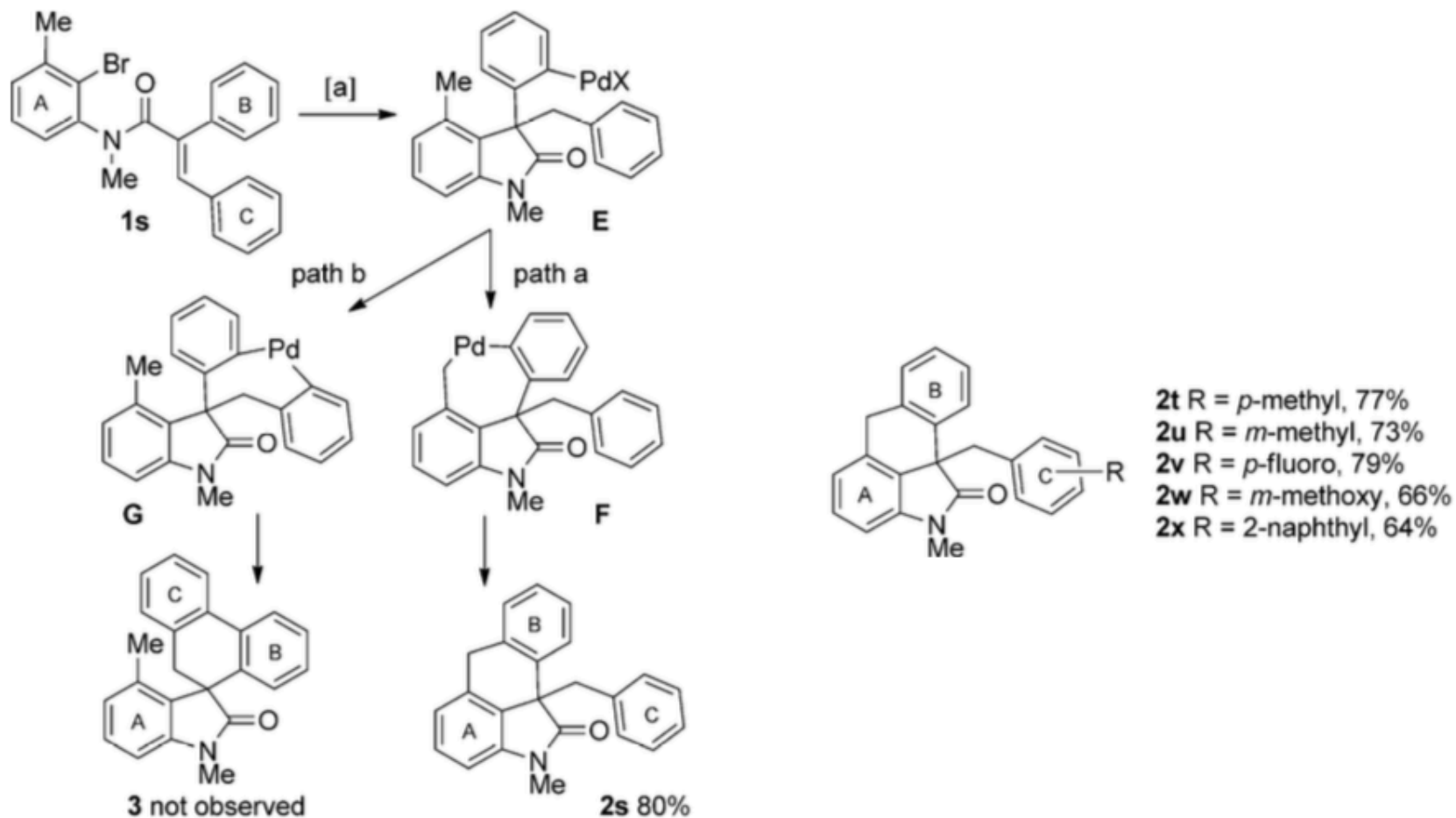
## SCOPE



16 examples,  
25-97% yield

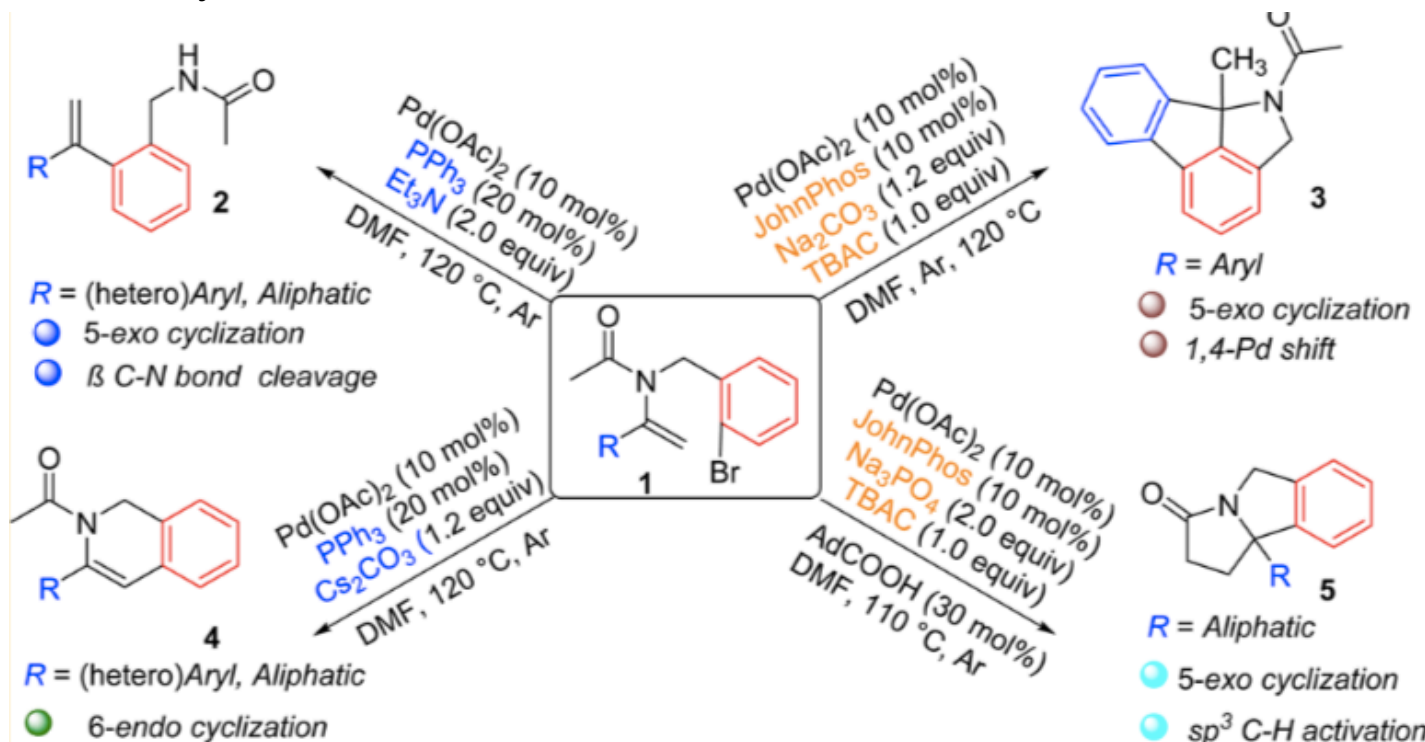
R1 = Bn, PMB, Ph, SEM, Me;  
R2 = H, OMe, Me, CN;  
R3 = H;  
R = Me, Ph, OMe, F

## SCOPE

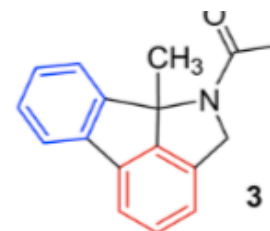


# ALKYL TO ARYL MIGRATION

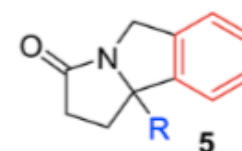
25 examples,  
31-87% yields



12 examples,  
36-75% yields



R = Aryl  
 ● 5-exo cyclization  
 ● 1,4-Pd shift



R = Aliphatic  
 ● 5-exo cyclization  
 ● sp<sup>3</sup> C-H activation

17 examples,  
35-82% yields

25 examples,  
31-87% yields

# CONCLUSION

**Remote C–H activation via through-space palladium migration shows to be an efficient method to introduce a palladium moiety into a position where direct palladium introduction may not be straightforward.**

**To force the 1,4 migration we can:**

- Use monodentate ligands;**
- Dilute the reaction mixture;**
- Use pivalates and acetates as bases;**
- Create steric hindrance around Pd atom to avoid direct cross-coupling reaction;**
- Stabilize the Pd-intermediate.**

**THANK YOU FOR  
YOUR  
ATTENTION**