Catellani Reaction

(Pd-Catalyzed Sequential Reaction)

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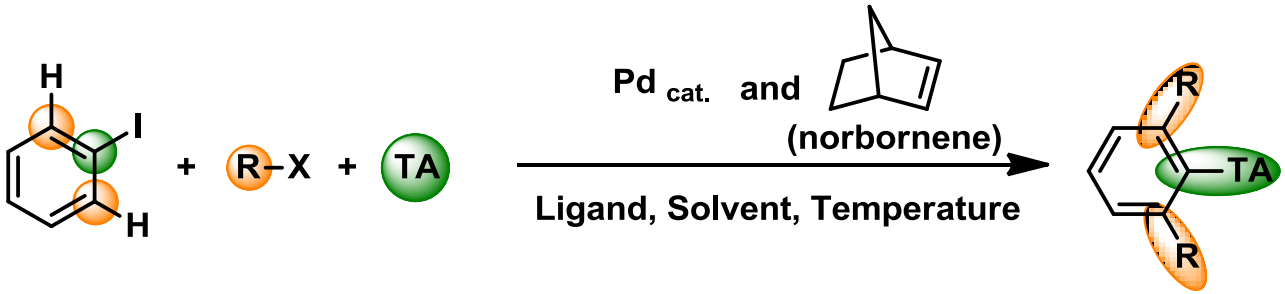
Introduction

Typical Catellani Reaction

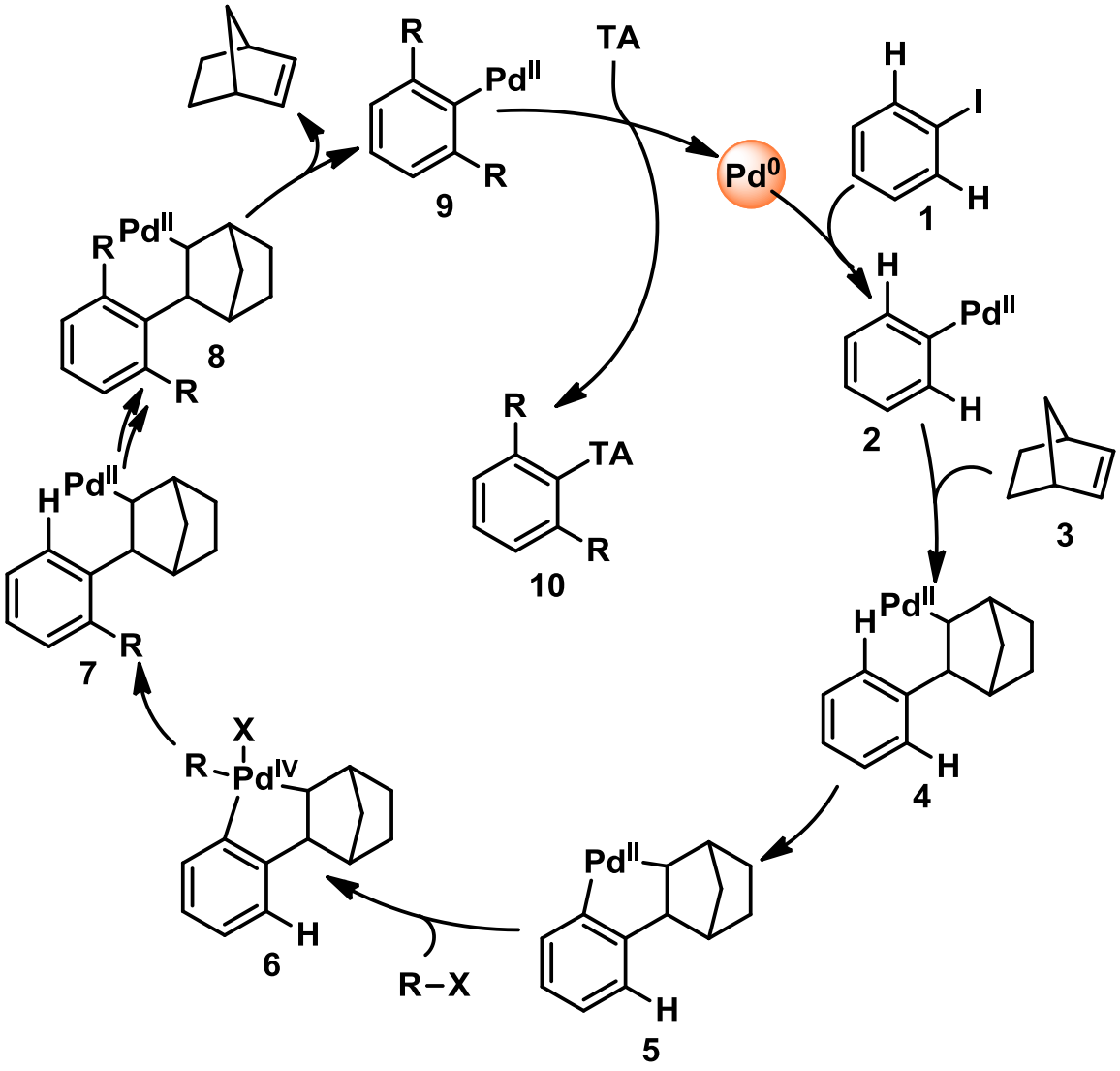


R: Alkyl, Aryl
X: I, Br, Cl
TA: Terminating Agents (H_2, Olifen, Arylboronic Acid, Alkye, etc.)

Main characters of Catellani Reaction

- Versatile method for C–C coupling
- Selective *ortho* C–H functionalization
- Co-catalytic system (Pd and norbornene)

General Mechanism



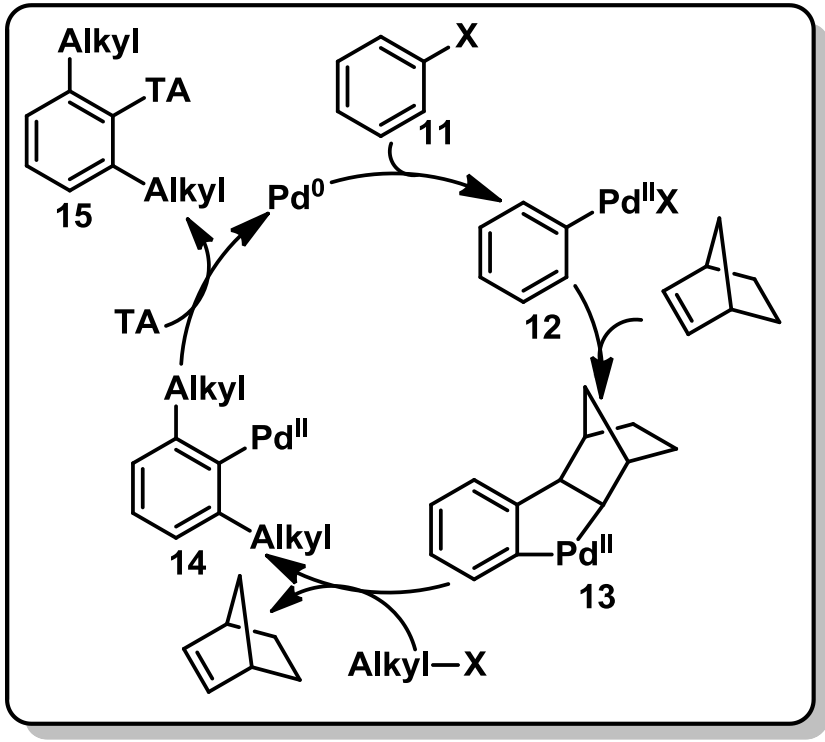
o-Alkylation

Challenges:

How to control selective oxidative addition of **Pd^0** with iodobenzene?

How to control selective oxidative addition of **Pd^{II}(13)** with alkyl iodide?

How to control selective reaction of **TA** with **Pd^{II}(14)**?



Solutions:

At room temperature:
To **Pd^0**: **Aryl-X** > **Alkyl-X**
To **Pd^{II}**: **Aryl-X** < **Alkyl-X**

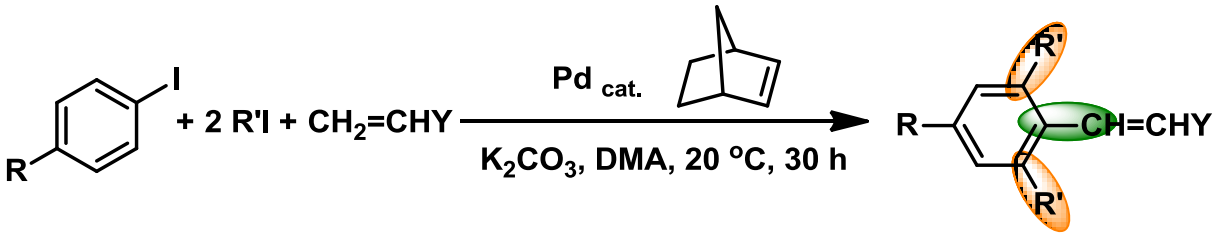
Increase the use of **Norbornene** and **Alkyl-X**

Choose a suitable **Terminating Agent (TA)**

Good terminating events

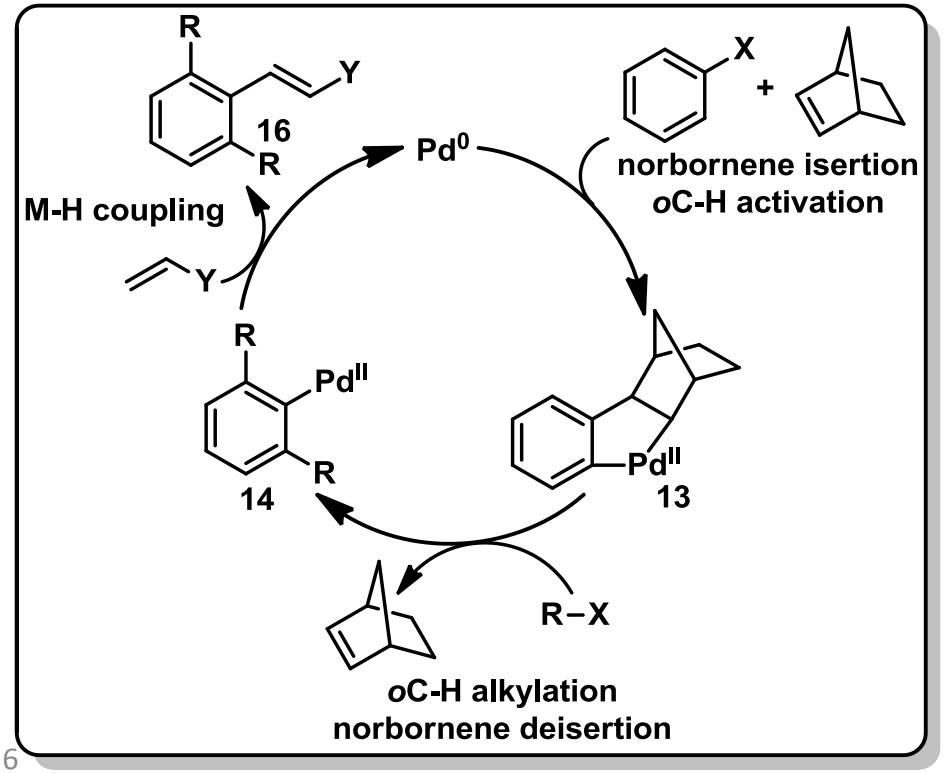
Mizoroki-Heck Coupling, Suzuki-Miyaura Coupling, Cassar-Sonogashira Coupling, Cyanation, Direct Arylation, Amination, Hydrogenolysis, etc.

o-Alkylation and Application



R: H, Me, CO_2Me
R': *n*Bu, *n*Oct, CH_2CH_2Ph
Y: CO_2Me, COMe, Ph, *n*Hex

33-100 %, conversion



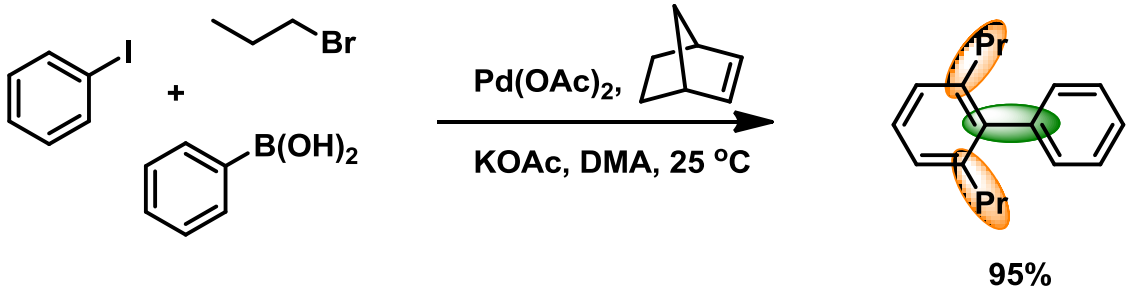
The first example of Catellani Reaction

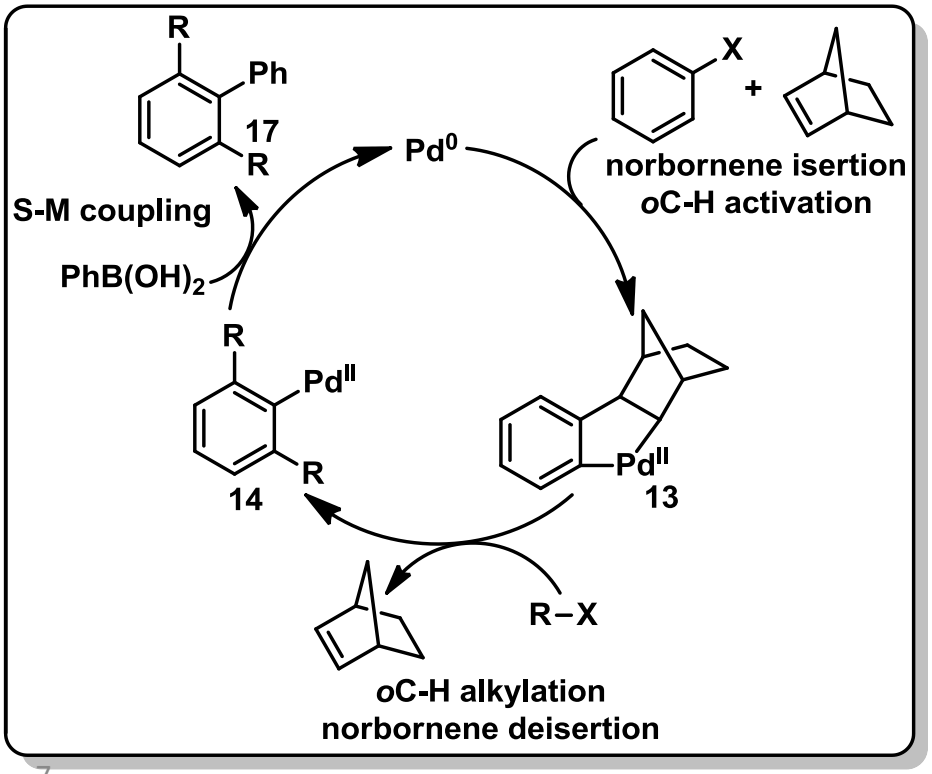
Proposed a suitable reaction mechanism

Terminating event is **Mizoroki-Heck Coupling**

Catellani, M. etc. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 119.

o-Alkylation and Application





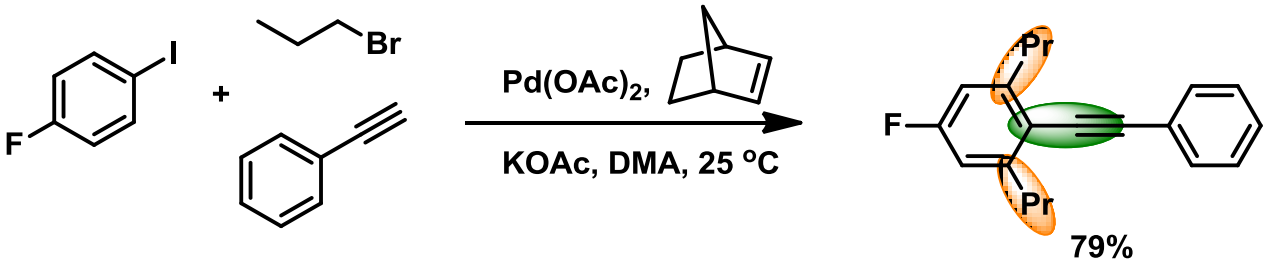
Terminating event is **Suzuki-Miyaura Coupling.**

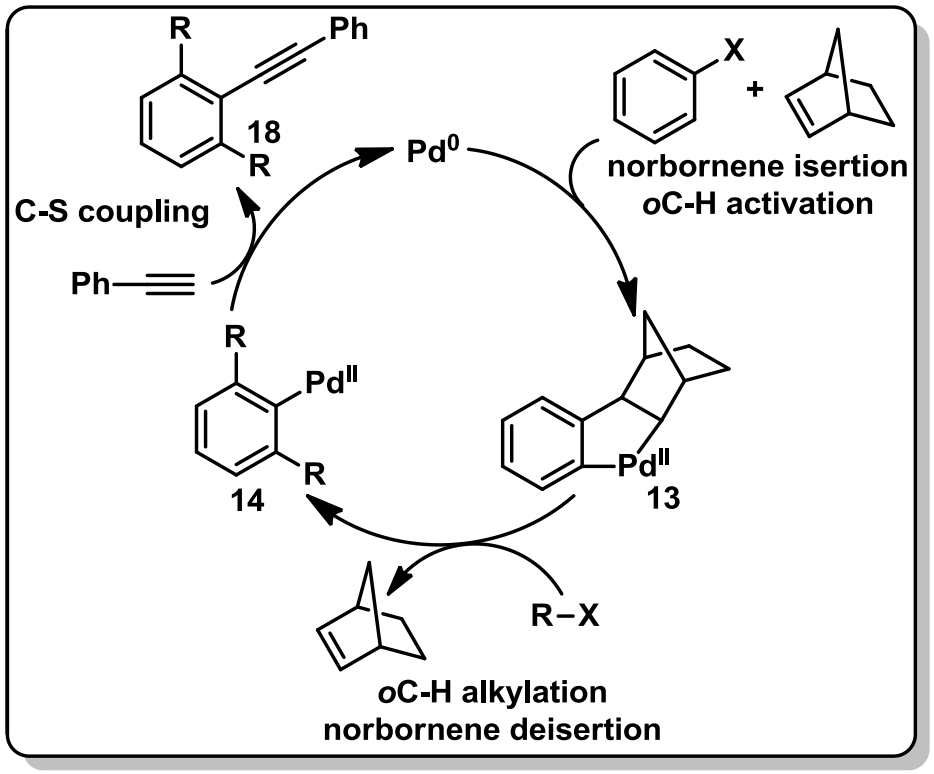
Efficient way to synthesize 2,6-disubstituted biphenyls.

2,6-disubstituted biphenyls can be used as ligand.

Catellani, M. etc. *J. Chem. Soc. Chem. Commun.* **2000**, *157.*

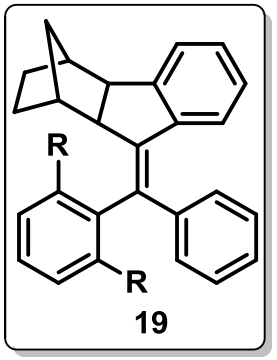
o-Alkylation and Application





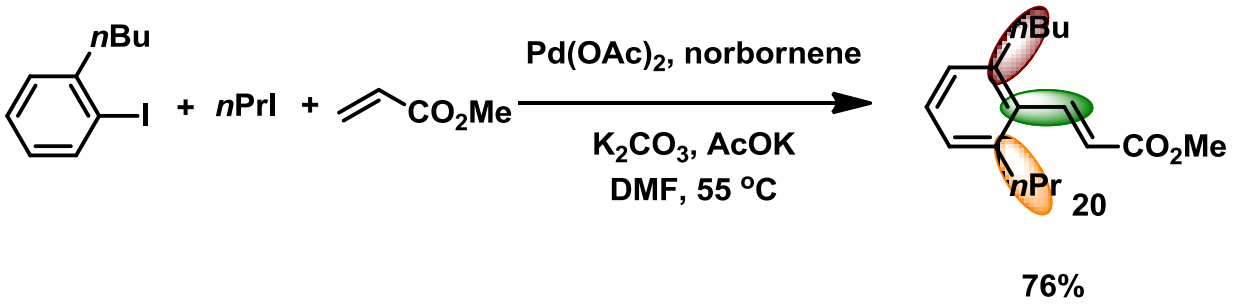
Terminating event is **Cassar-Sonogashira Coupling**

Diphenylacetylene is not suitable for the reaction.



Catellani, M. etc. *J. Organomet. Chem.* **2004**, *689*, 3741.

o-Alkylation and Application

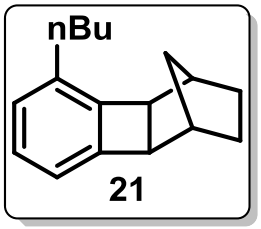


The first time to synthesize *o,o'*-differently substituted vinylarenes.

Problems

Using different alkyl iodides leads to all the possible combinations of the *ortho* substituents.

Using pre-substituted aryl iodide leads to competed elimination byproduct.



Solutions

Increasing the use of **Alkyl iodide**.

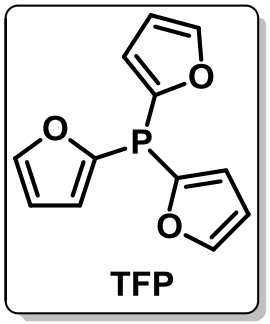
Adding **KOAc** could lead good result.

Catellani, M. etc. *Tetrahedron* **1999**, *55*, 6595.

o-Alkylation and Application

22 23

Entry	R	*n*	K_2CO_3 Yield [%][b]	Cs_2CO_3 Yield [%][b]
1	Me	1	85	90
		2	62	83
2	CH_2OTBS	1	41	60
		2	33	47
3	CH_2OMe	1	20	35
		2	6	25
4	OMe	1	29	26
		2	41	93
5	CO_2Me	1	–[c]	–[c]
		2	–[c]	–[c]



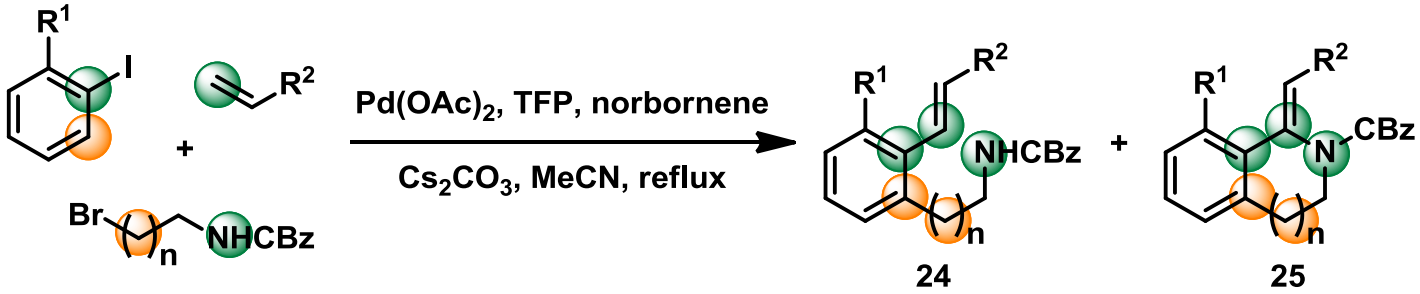
Achievements

Using TFP as ligand can efficiently promote o-alkylation.

Applying Catellani Reaction to synthesize condensed ring.

Lautens, M. etc. *Angew. Chem. Int. Ed. Engl.* ***2000****, 39,* 1045; *J. Org. Chem.* **2001**, *66*, 8127.

o-Alkylation and Application



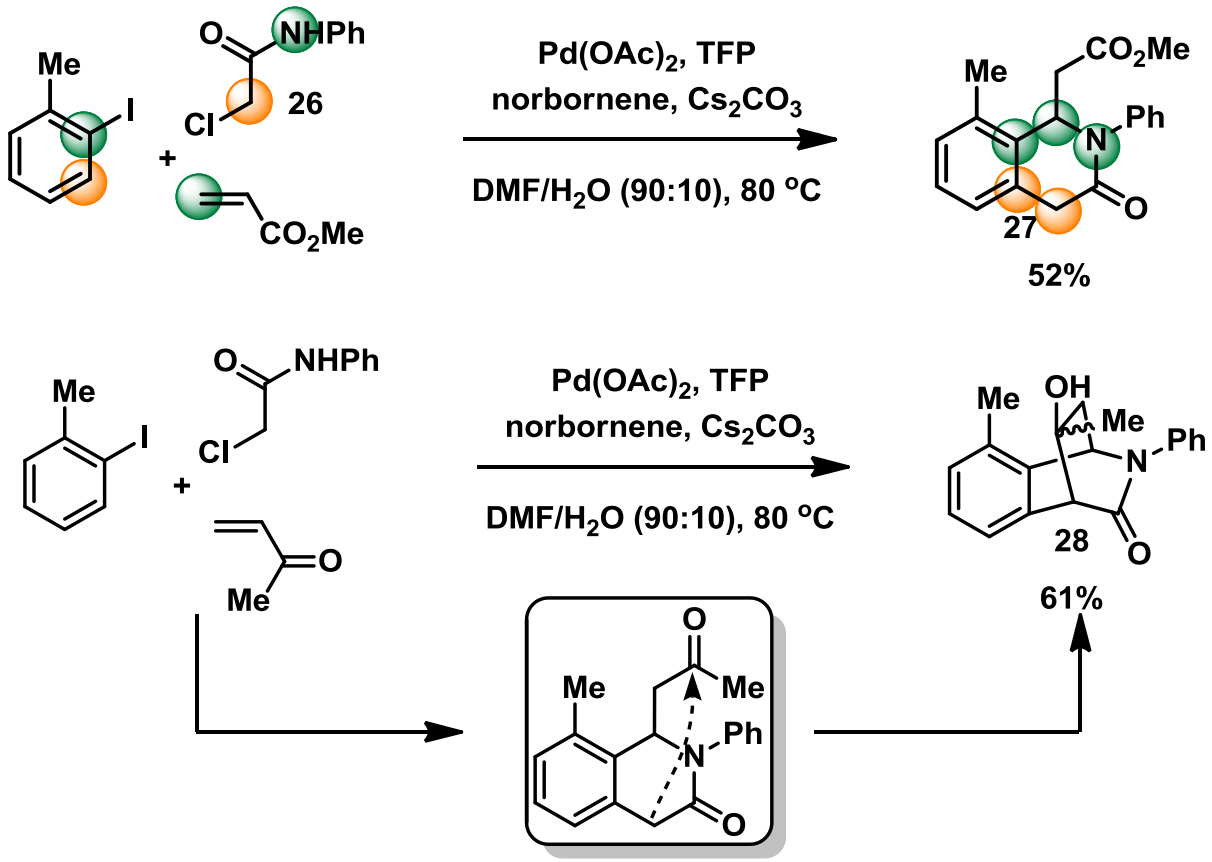
Entry	*n*	R_1	R_2	Time (h)	Molar ratio[b] **25/24**	Yield (%)[c]	
						25	**24**
1	1	Me	CO_2Me	20	1/0	65	—
2	1	Me	CO_2Me	3	1/9	5	68
3	1	Et	CO_2Me	20	1/0	40	—
4	1	*i*-Pr	CO_2Me	20	1/0	62	—
5	1	Me	CO_2t-Bu	20	1/0	68	—
6	1	Me	COMe	4	1/0	60[d]	—
7	2	Me	CO_2Me	20	0/1	—	70
8	2	Me	CO_2t-Bu	20	0/1	—	65
9	2	Me	CO_2Me	3.5[e]	7/3	34	16
10	2	Me	CO_2t-Bu	4[e]	7.5/2.5	43	11

Achievements

Combining the Catellani Reaction with an aza-Michael addition reaction to synthesize condensed rings.

Catellani, M. etc. *Tetrahedron Lett.* **2004**, *45*, 6903.

o-Alkylation and Application

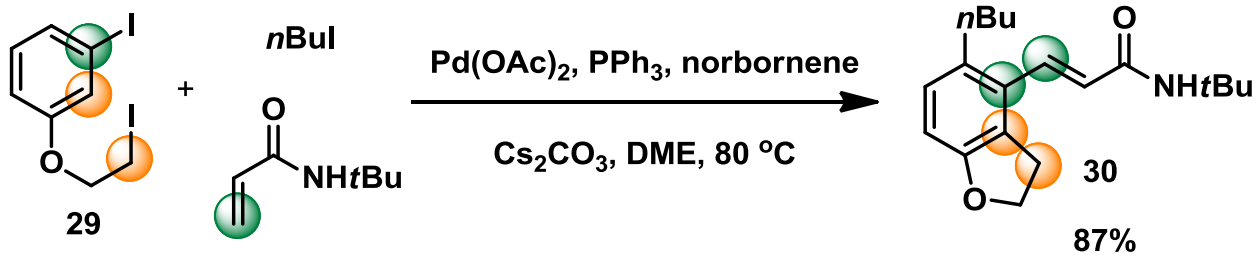


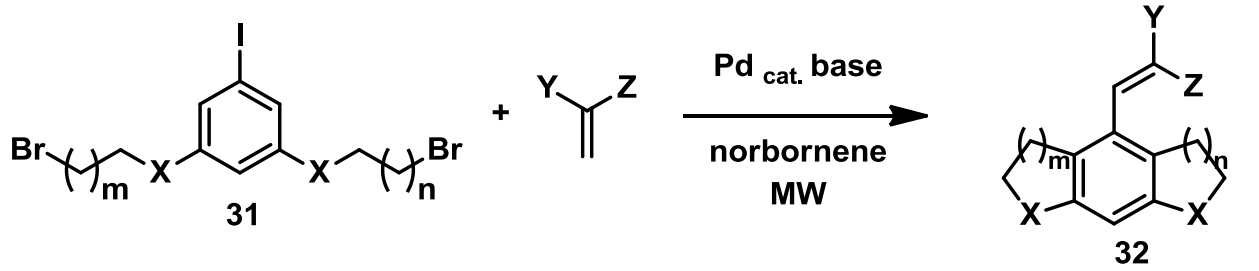
Achievements

First example of using alkyl chloride as alkylation source.

Ferraccioli, R. etc. *Eur. J. Org. Chem.* **2009**, 3161.

o-Alkylation and Application





X: O, S, NTs, -$OCH_2Si(Me_2)$-
m, n: 1, 2, 3
Y, Z: ester, amide etc.

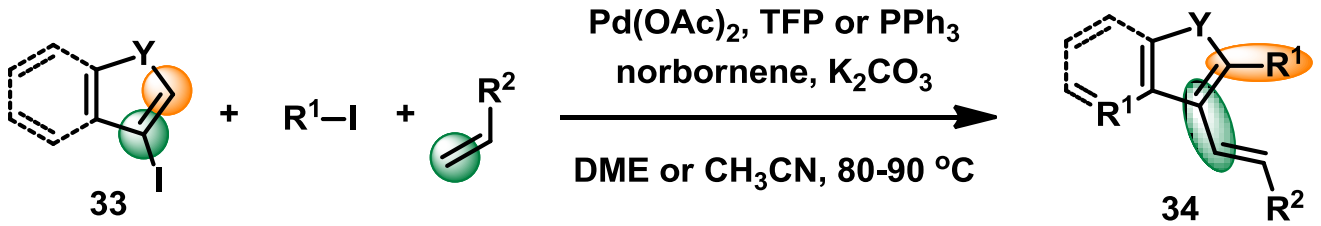
up to 85%

Achievements

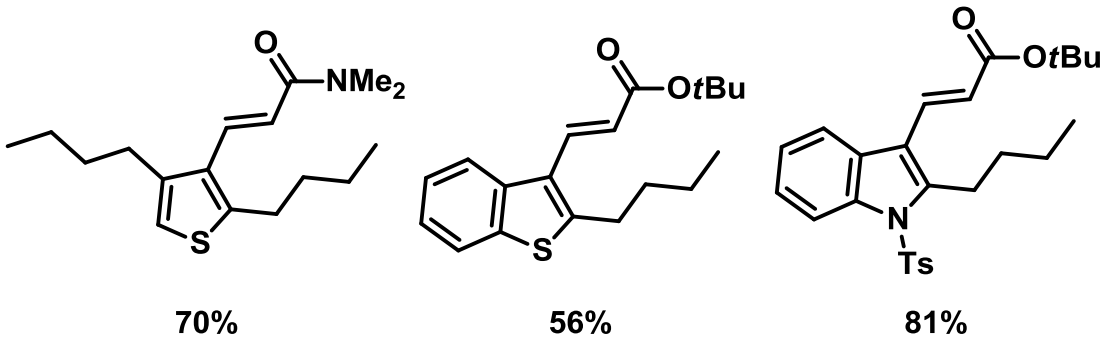
Exploring ways of synthesizing polycycles.

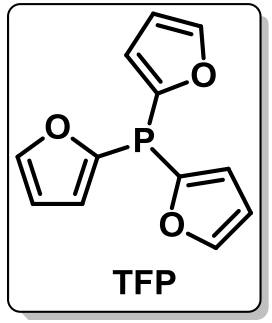
Lautens, M. etc. *Org. Lett.* **2003**, *5*, 4827; *J. Org. Chem.* **2007**, *72*, 775.

o-Alkylation and Application



Selected Examples:



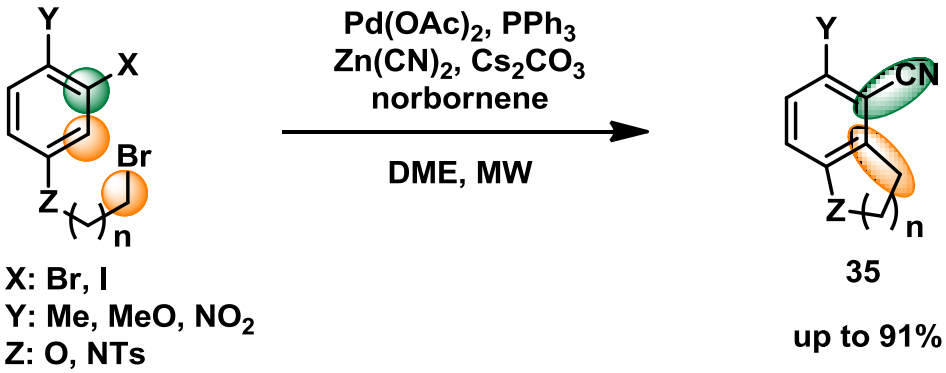


Achievements

Expanding the Catellani Reaction to **hereroaryl iodides**.

Lautens, M. etc. *Org. Lett.* **2006**, *8*, 3939.

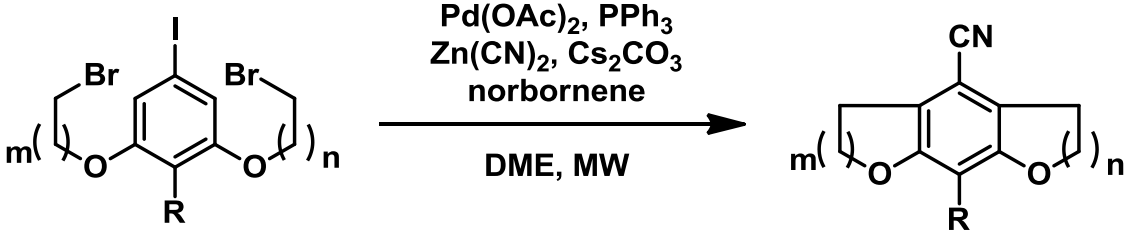
o-Alkylation and Application



X: Br, I
Y: Me, MeO, NO_2
Z: O, NTs

35

up to 91%



R: H, MeO
m, n: 1, 2

36

up to 88%

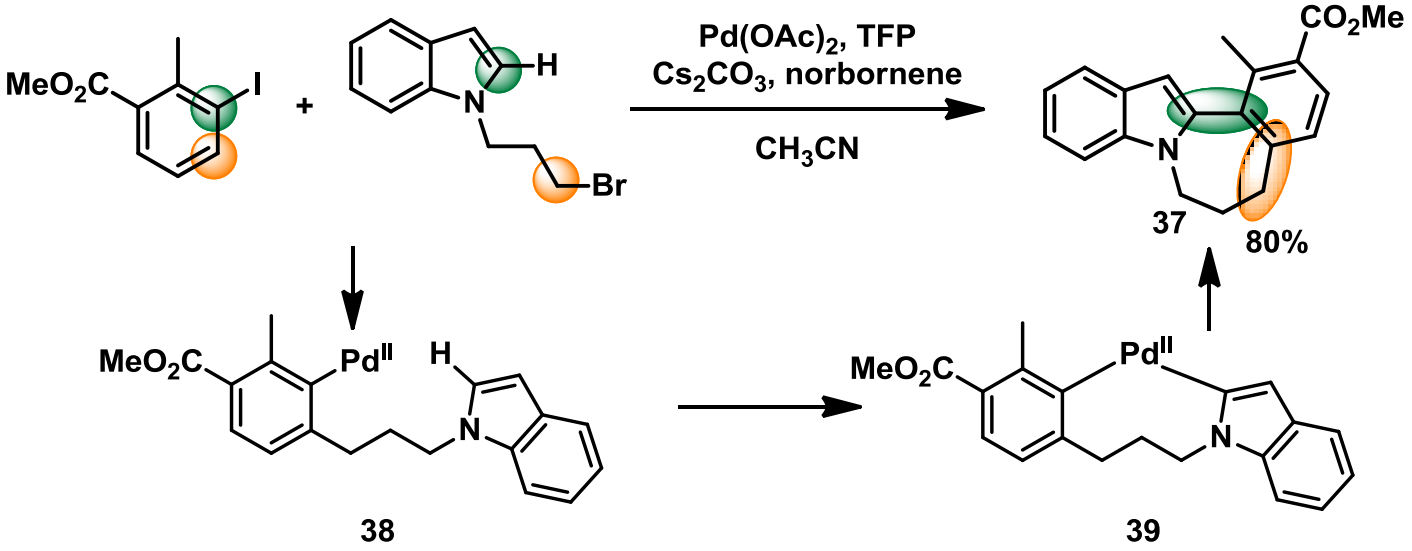
Achievements

The first example of terminating Catellani reaction with **Cyanation**.

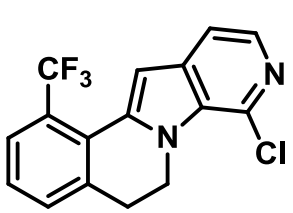
-CN can be transformed into -COOH, $-CONH_2$, $-CH_2NH_2$, etc.

Lautens, M. etc. *J. Am. Chem. Soc.* **2006**, *128*, 14436.

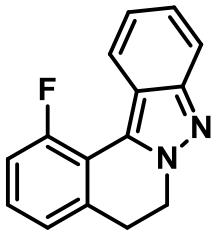
o-Alkylation and Application



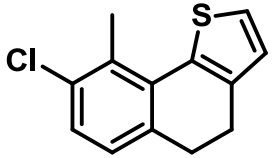
Selected Examples:



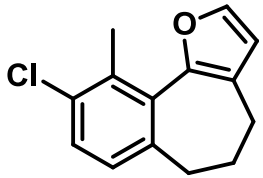
66%



95%



77%



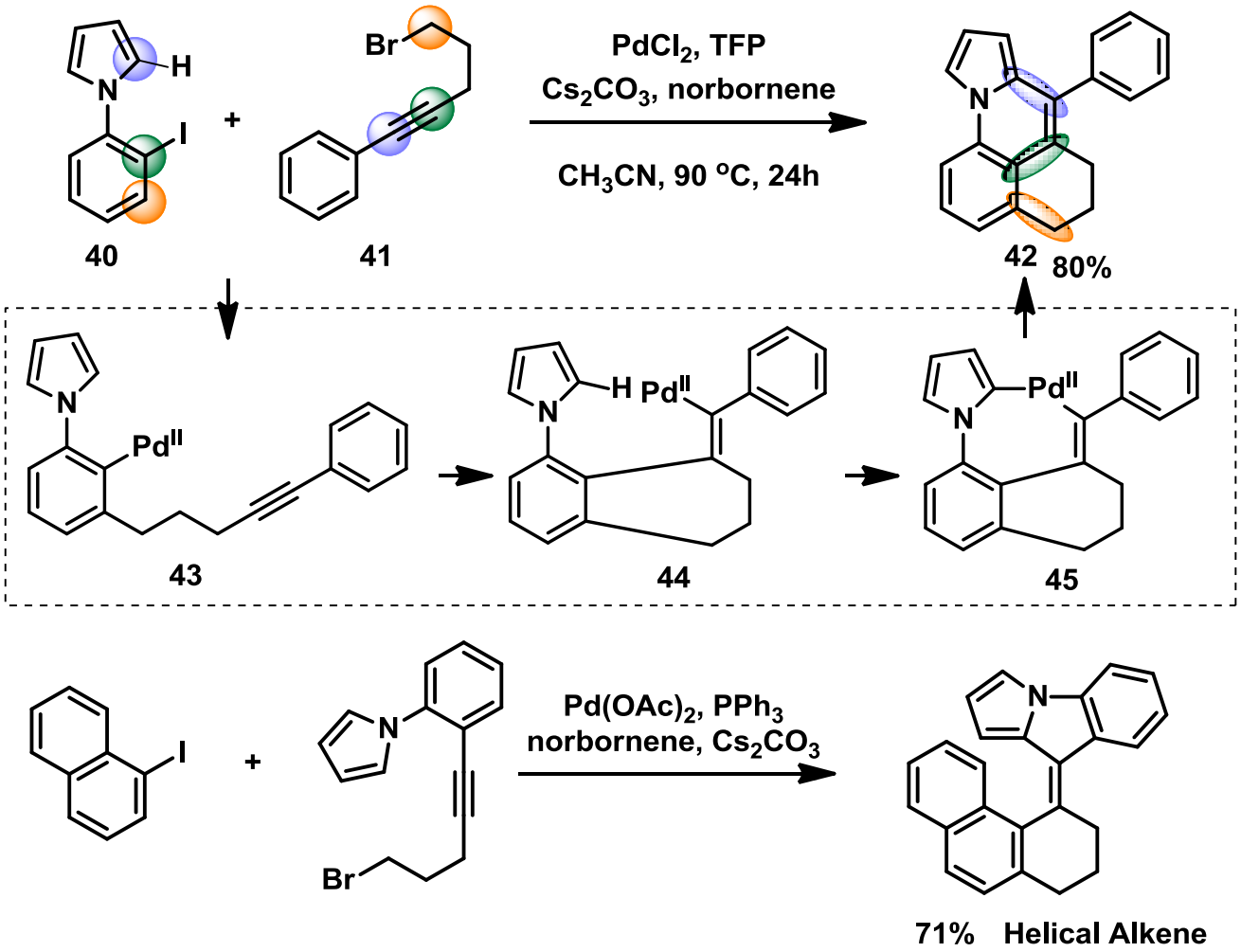
53%

Achievement

Examples of terminating Catellani reaction with **Direct Arylation**.

Lautens, M. etc. *J. Am. Chem. Soc.* **2005**, *127*, 13148; *Org. Lett.* **2006**, *8*, 2043; *Org. Lett.* **2006**, *8*, 3601; *Org. Lett.* **2006**, *8*, 4827; *J. Org. Chem.* **2008**, *73*, 1888. *J. Org. Chem.* **2008**, *73*, 8705; *J. Org. Chem.* **2008**, *73*, 9164.

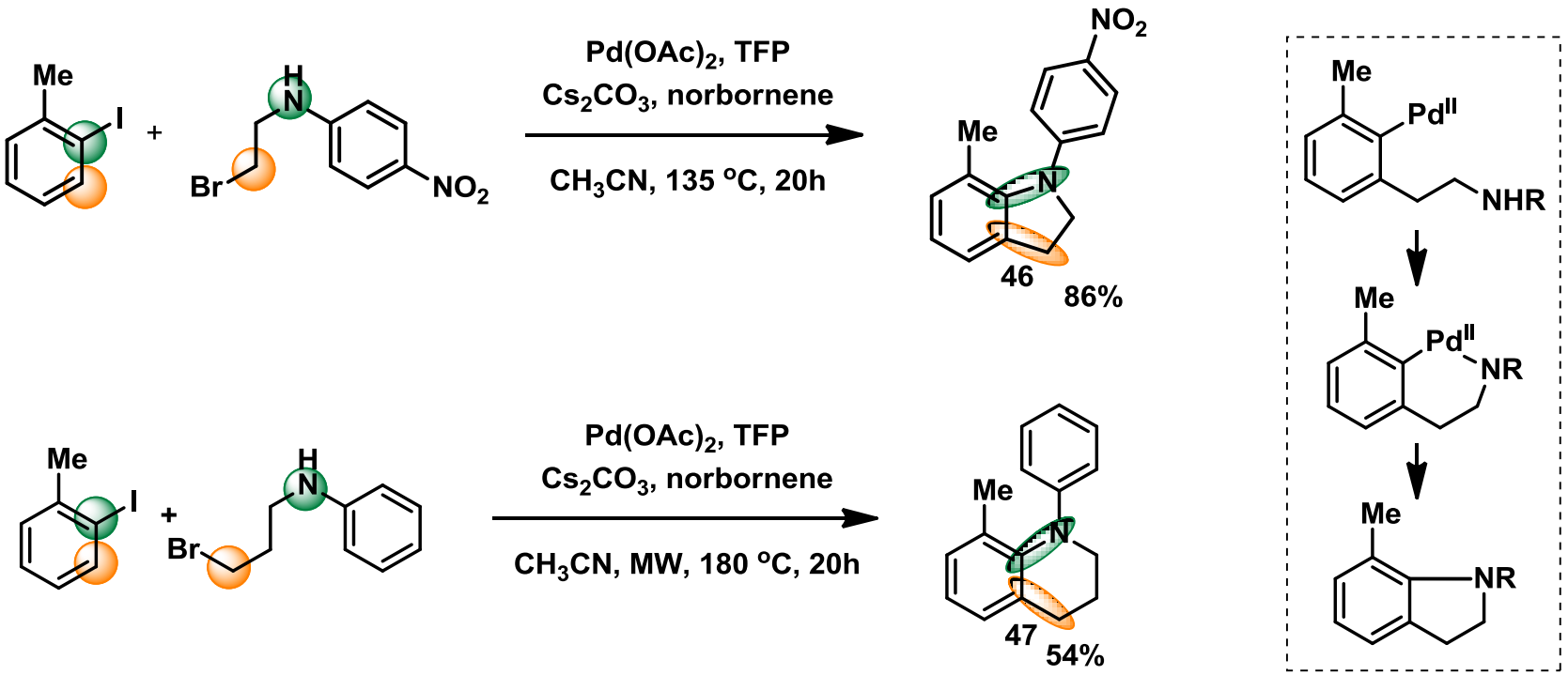
o-Alkylation and Application



Helical Alkenes are widely used in **material science**.

Lautens, M. etc. *Tetrahedron* **2008**, *64*, 6002; *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 9846.

o-Alkylation and Application



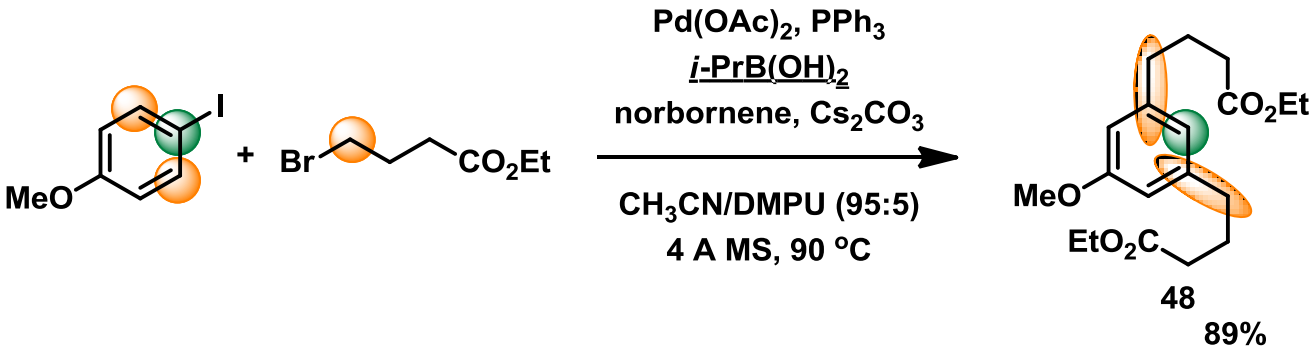
Achievements

The first example of terminating Catellani reaction with **Amination**.

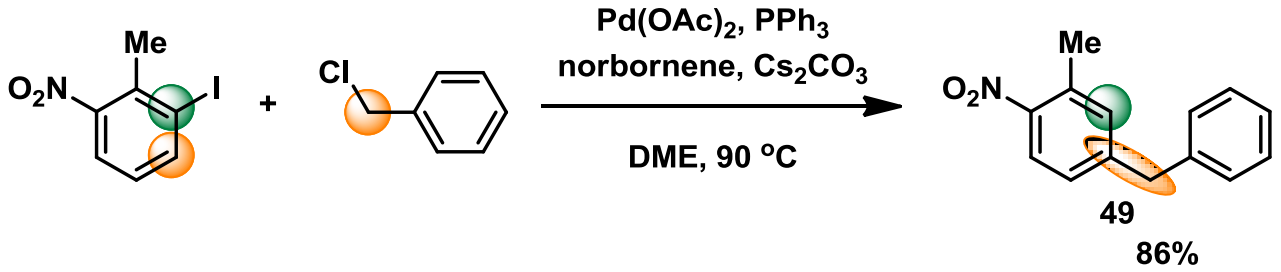
Creating another way of synthesizing condensed hetero-rings.

Lautens, M. etc. *Org. Lett.* **2007**, *9*, 5255.

o-Alkylation and Application



H-donor: alkyl halide, alkylboronic acid, benzyl alcohol.



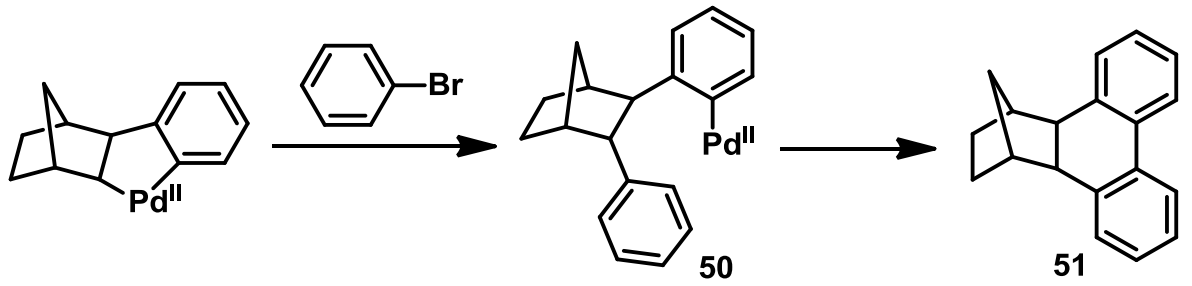
Achievement

Terminating event is **Hydrogenolysis**.

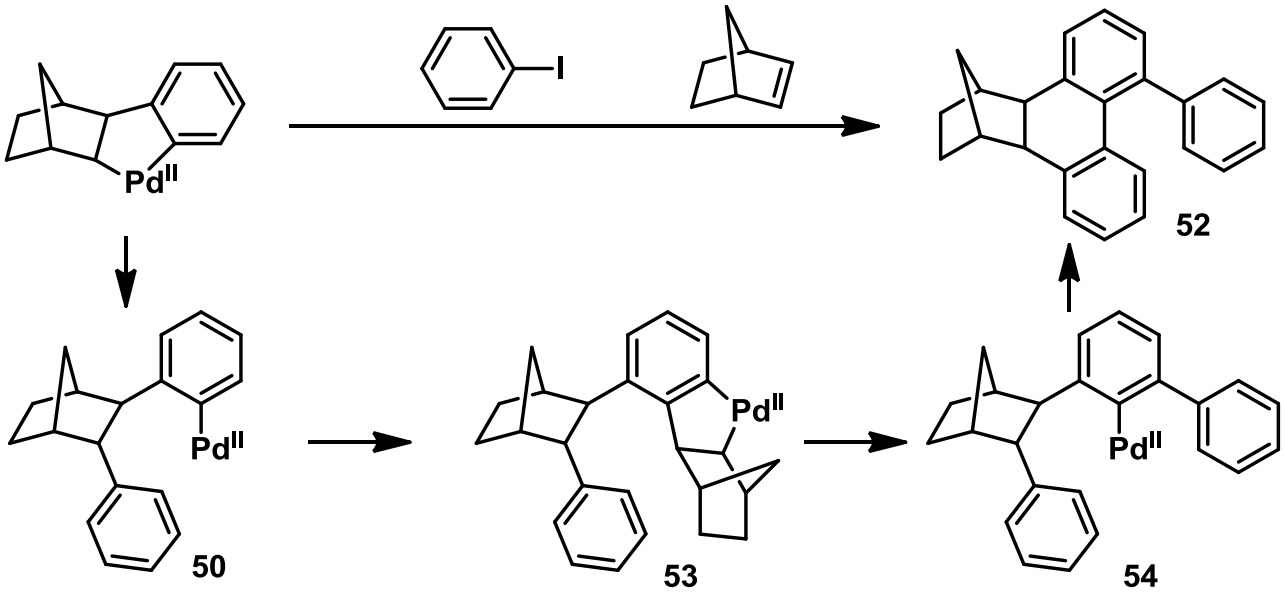
Lautens, M. etc. *Org. Lett.* **2005**, *7*, 4053; *Org. Lett.* **2008**, *10*, 5095.

The beginning of *o*-Arylation

In the absence of norbornene

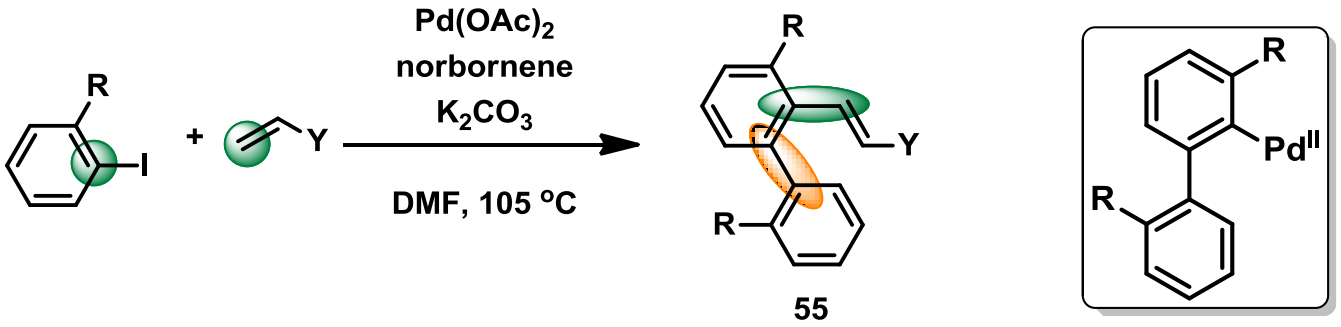


In the presence of norbornene



Catellani, M. etc. *J. Organomet. Chem.* **1985**, *286*, C13; *J. Organomet. Chem.* **1998**, *584*, 63.

o-Arylation and Application



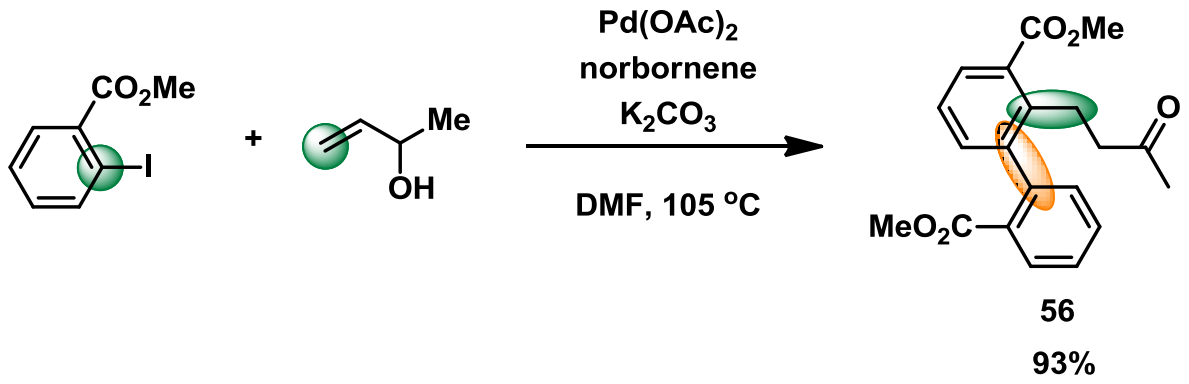
R	Y	yield (%)
Me	CO_2Me	79
Et	CO_2Me	79
i-Pr	CO_2Me	84
OMe	CO_2Me	88
CO_2Me	CO_2Me	98
Me	SOPh	81
Et	COMe	79
Et	Ph	87

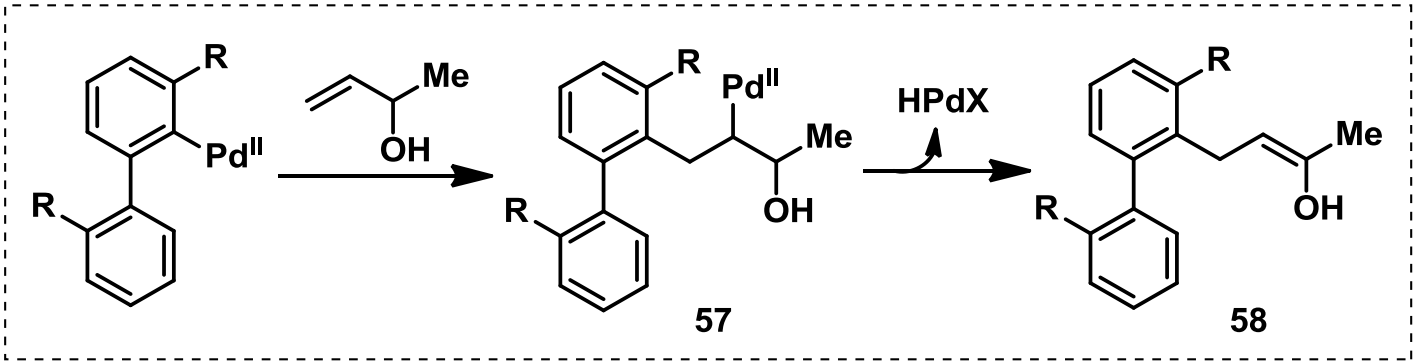
Achievement

Terminating event is **Heck Coupling**.

Catellani, M. etc. *Synthesis.* **2003**, 2671.

o-Arylation and Application



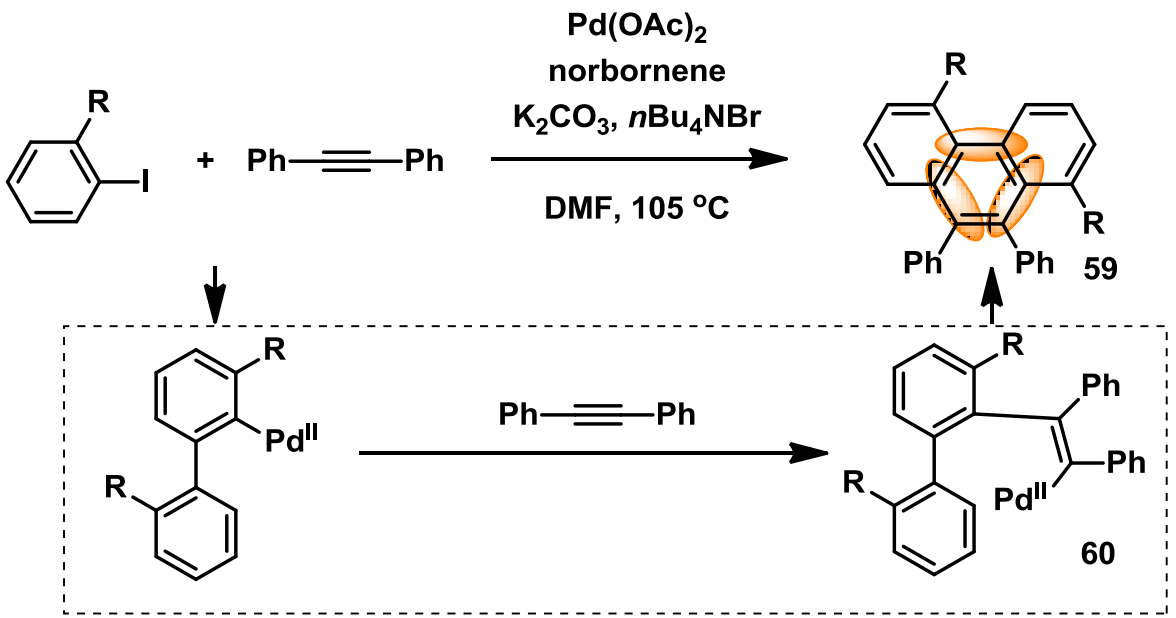


Achievement

The first time to introduce an alkyl chain containing carbonyl group.

Catellani, M. etc. *J. Organomet. Chem*. **2003**, *687*, 473.

o-Arylation and Application

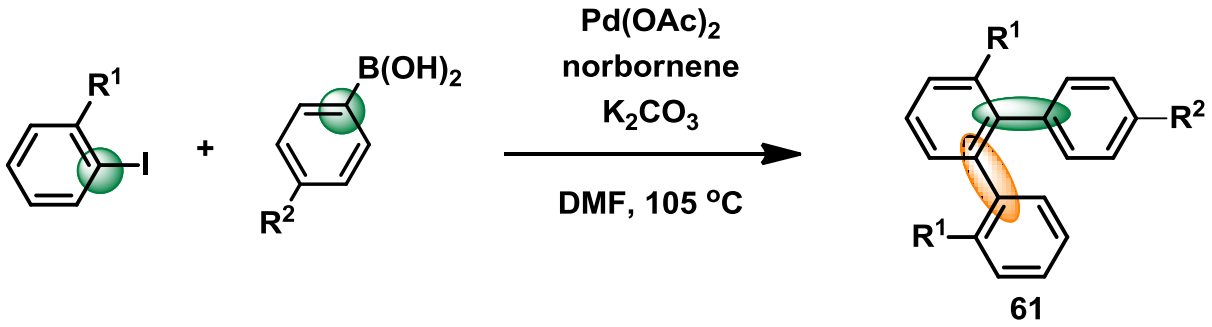


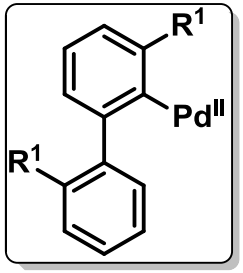
R	yield (%)
Me	82
Et	85
n-Pr	83
i-Pr	93
n-Bu	84
OMe	64

Incorporation of diphenylacetylene, formation of condensed arenes.

Catellani, M. etc. *Org. Lett.* **2001**, *3*, 3611.

o-Arylation and Application





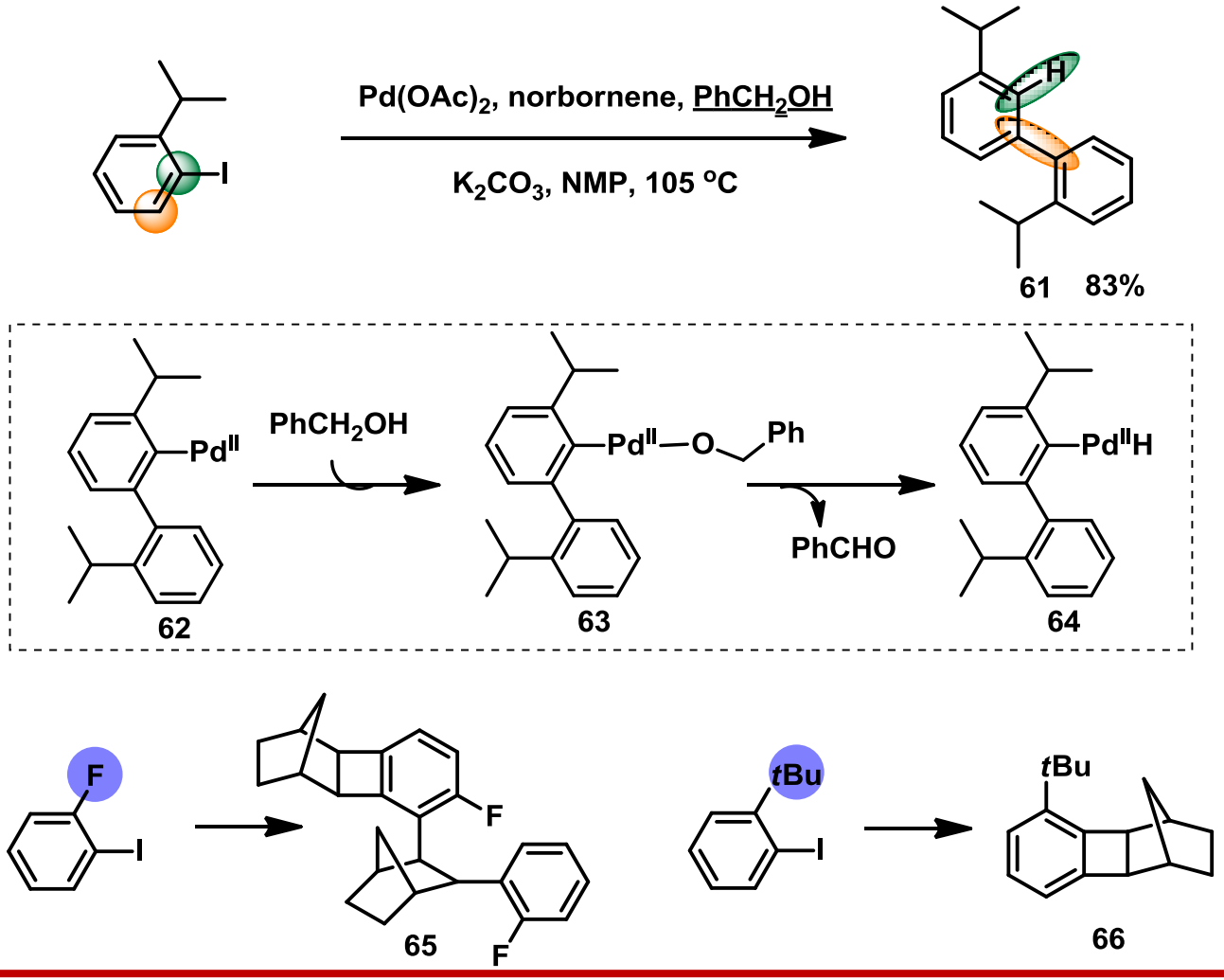
R^1	R^2	yield (%)
Me	H	88
Et	H	77
i-Pr	H	93
n-Bu	H	73
OMe	H	82
CO_2Me	H	89
n-Bu	4-Me	72
n-Bu	4-F	71
n-Pr	2-Me	73

Achievement

Terminating event is **Suzuki Coupling**.

Catellani, M. etc. *J. Mol. Catal. A: Chem.* **2003**, 204-205, 115.

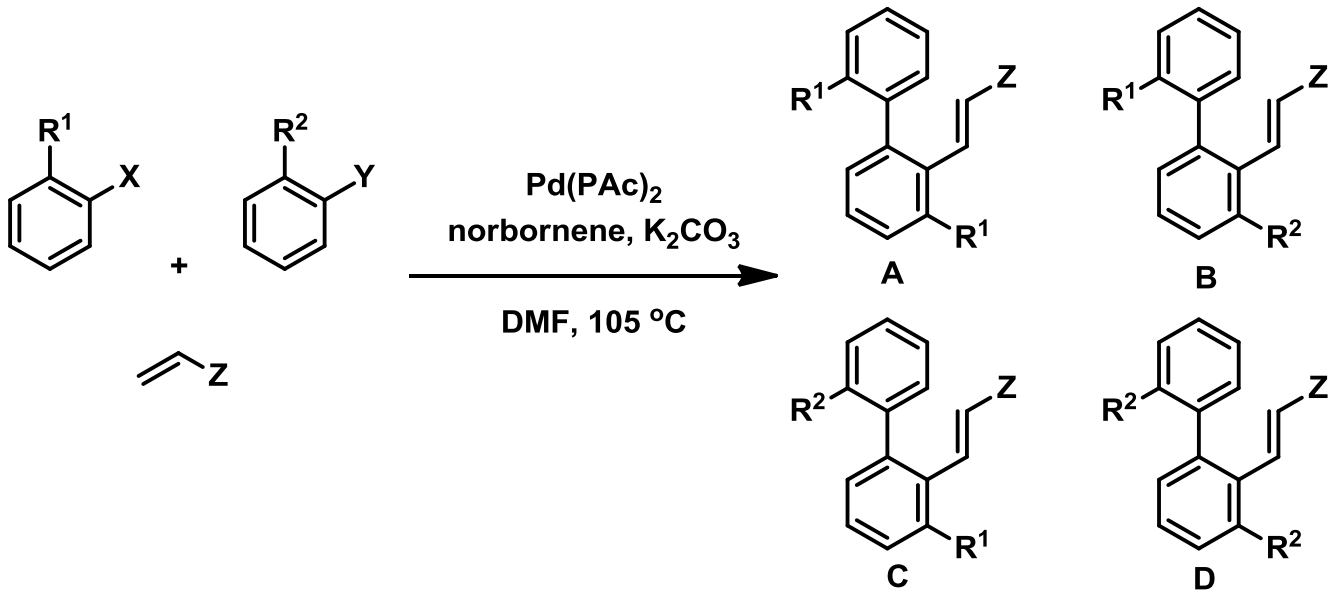
o-Arylation and Application

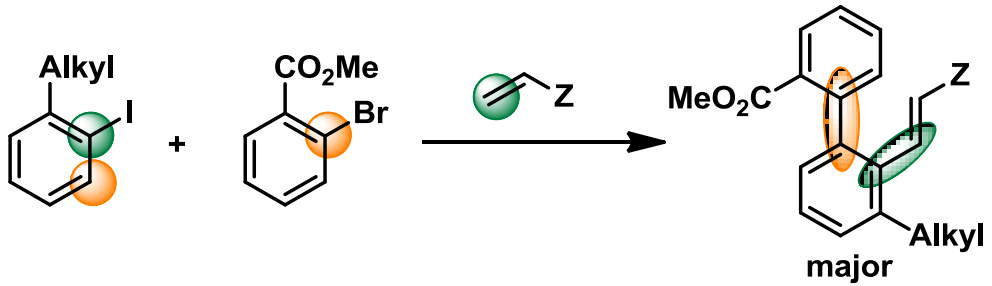


Terminating event is **Hydrogenolysis**.

Catellani, M. etc. *Can. J. Chem.* **2005**, *83*, 741.

o-Arylation and Application



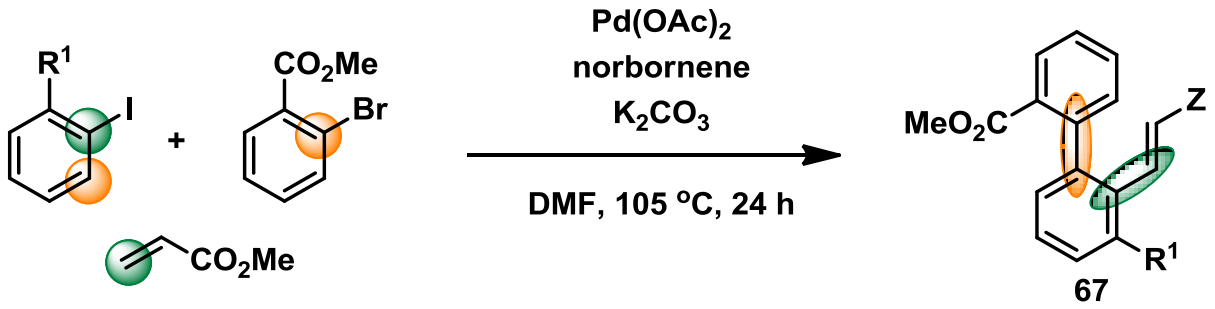


To **Pd^0**: **Aryl-I > Aryl-Br**
To **Pd^{II}**: **Aryl-I < Aryl-Br**

Big Progress

Coupling with two different aryl halide (**Cross Coupling**).

o-Arylation and Application



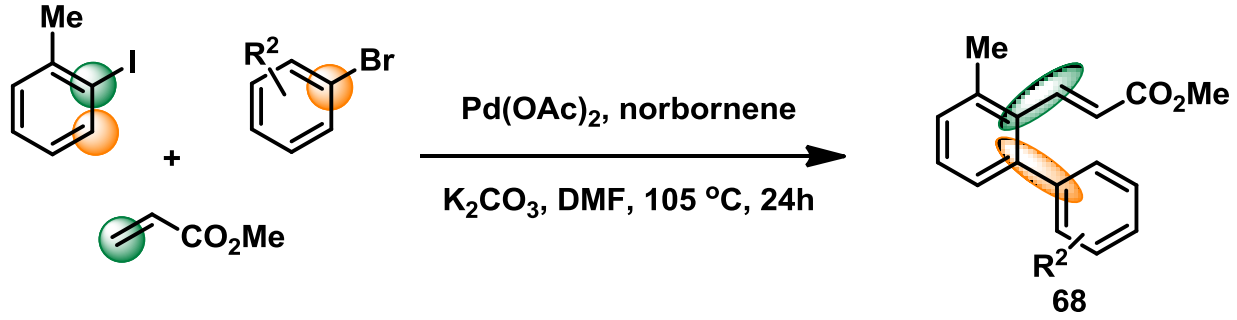
R^1	yield (%)
Me	80
i-Pr	74
t-Bu	37
Ph	73
OMe	83
OCH_2Ph	80
NMe_2	82
CF_3	77

Achievement

The first example of Cross Coupling. Terminating event is **Heck Coupling**.

Catellani, M. etc. *J. Am. Chem. Soc.* **2004**, *126*, 78.

o-Arylation and Application

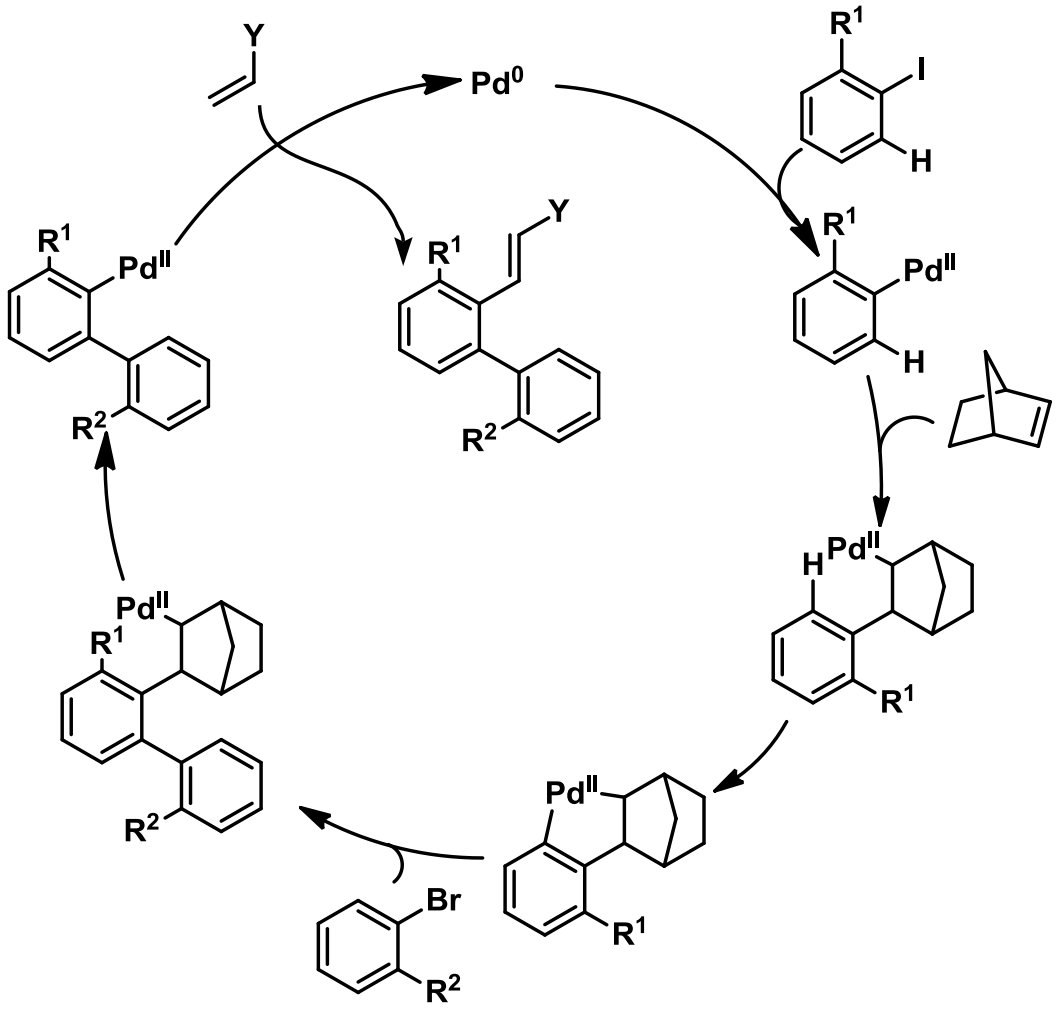


68

R^2	yield (%)
o-NO_2	72
m-NO_2	76
p-NO_2	83
o-CF_3	
m-CF_3	71
p-CF_3	80
o-CN	13
m-CN	62
p-CN	79
o-CO_2Me	80
m-CO_2Me	37
p-CO_2Me	71

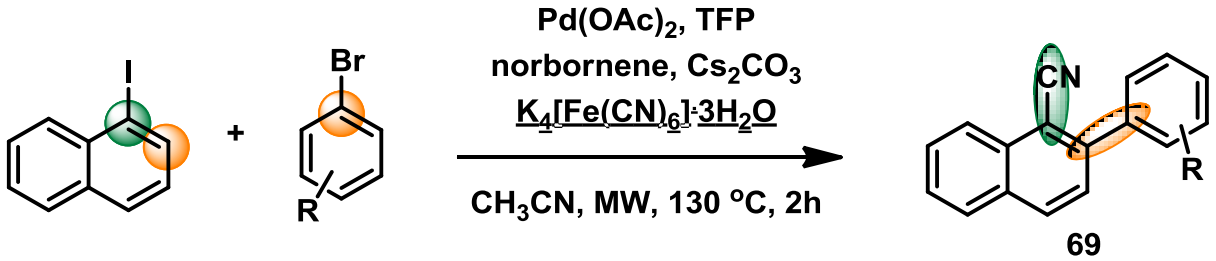
Catellani, M. etc. *J. Am. Chem. Soc.* **2004**, *126*, 78.

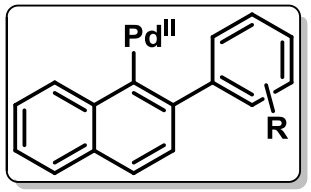
o-Arylation and Application



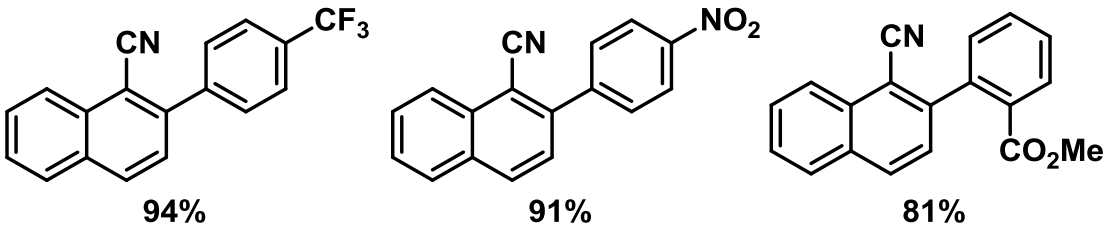
Mechanism of **Cross Coupling**

o-Arylation and Application





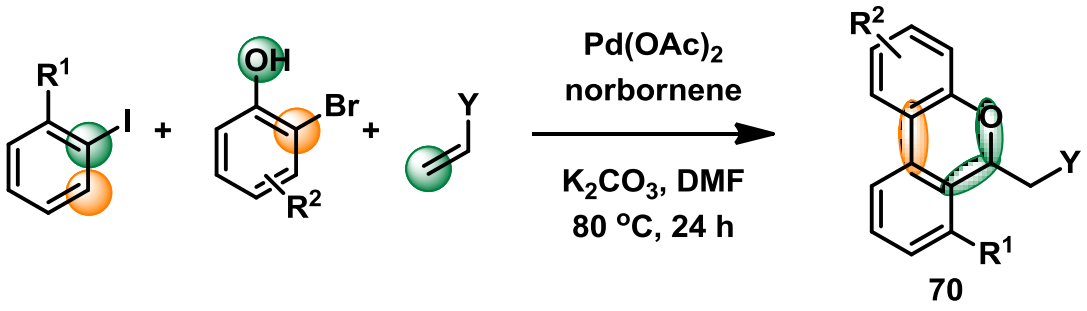
Selected Examples:



Terminating event is **Cyanation**.

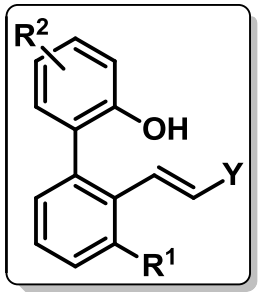
Lautens, M. etc. *J. Am. Chem. Soc.* **2007**, *129*, 15372.

o-Arylation and Application



70

R^1	R^2	Y	yield (%)
Me	H	CO_2Me	83
Et	H	CO_2Me	64
CF_3	H	CO_2Me	92
2,4-Me	H	CO_2Me	88
Me	5-Me	CO_2Me	52
Me	5-CO_2Me	CO_2Me	72
Me	5-NO_2	CO_2Me	83
Me	H	CO_2Me	93
Me	H	COMe	73



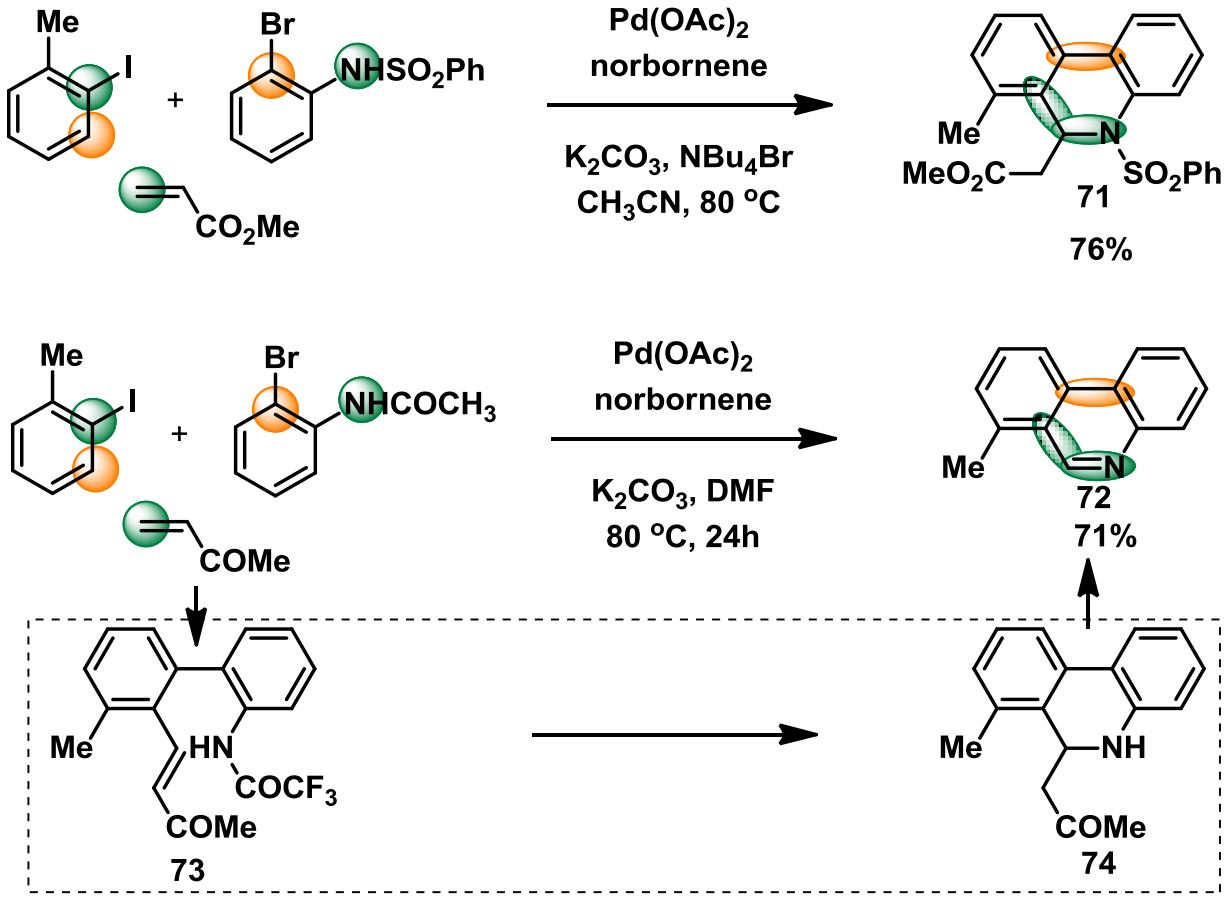
Achievements

Combining Catellani Reaction with Michael-Type Addition.

Efficient way to synthesize condensed hetero-ring.

Catellani, M. etc. *Org. Lett.* **2006**, *8*, 3967.

o-Arylation and Application

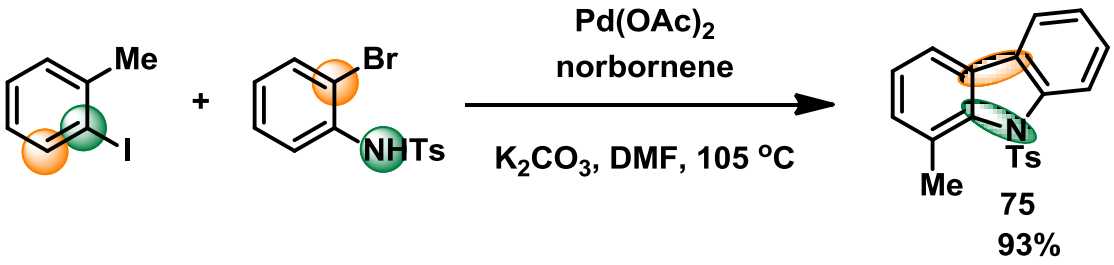


Achievements

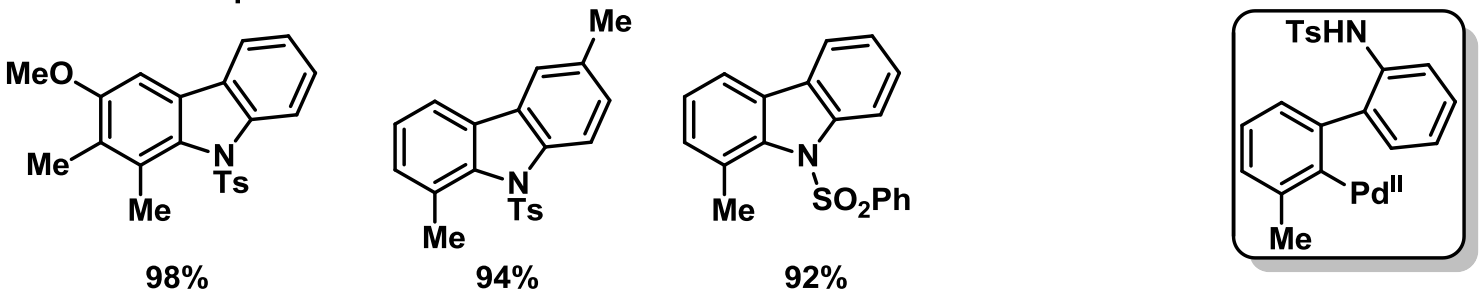
Combining Catellani Reaction with aza-Michael Addition.

Catellani, M. etc. *Adv. Synth. Catal.* **2008**, 350, 2513; *Adv. Synth. Catal.* **2010**, 352, 1451.

o-Arylation and Application



Selected Examples:



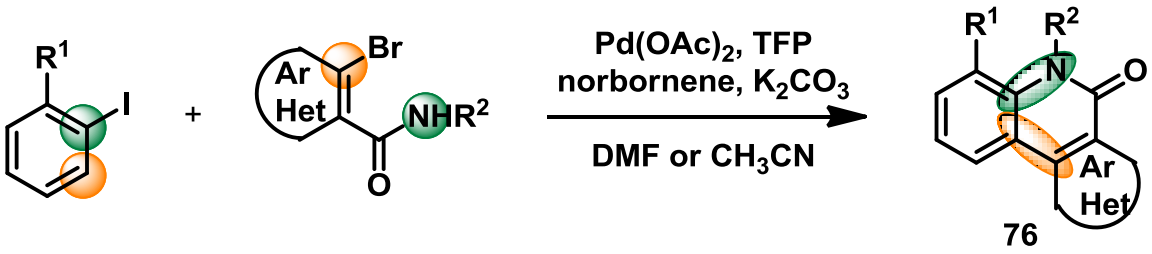
Achievements

Terminating Catellani Reaction with **C-N Coupling**.

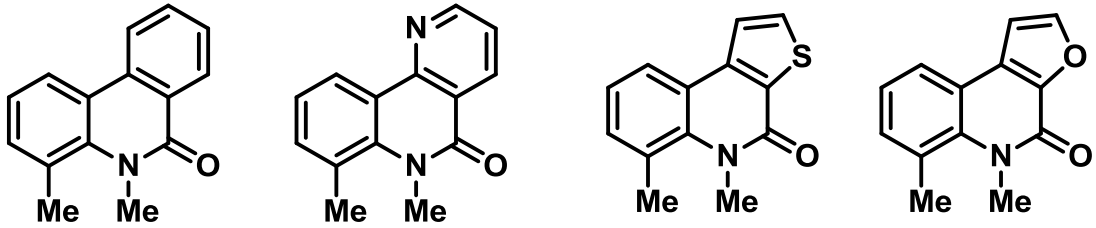
Exploring way of synthesizing hetero-aromatic ring.

Catellani, M. etc. *Adv. Synth. Catal.* **2008**, 350, 2179.

o-Arylation and Application



Selected Examples:



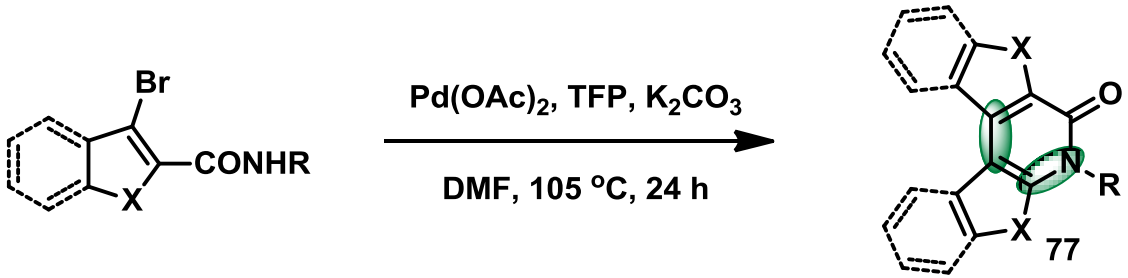
87% 55% 80% 82%

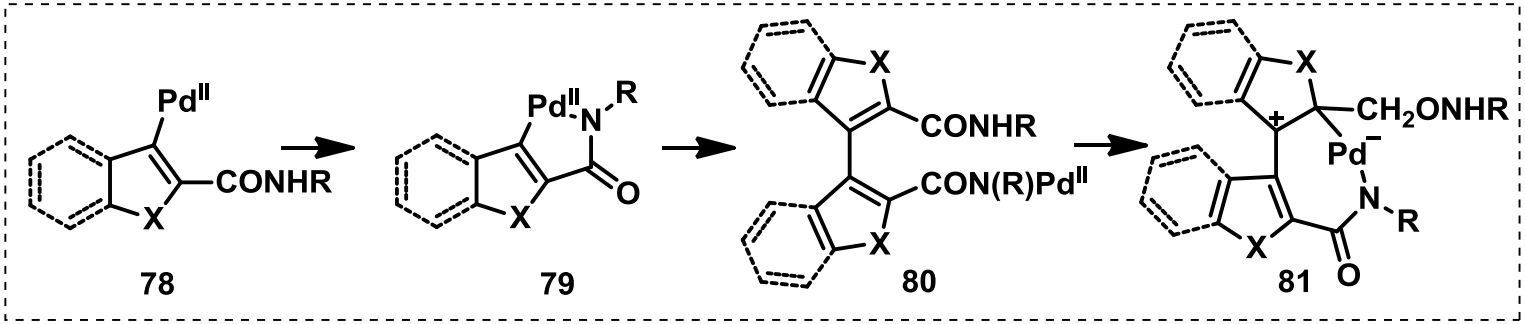
Achievements

Expanding reaction to **heteroaryl bromide**.

Catellani, M. etc. *Org. Lett.* **2004**, *6*, 4759.

o-Arylation and Application





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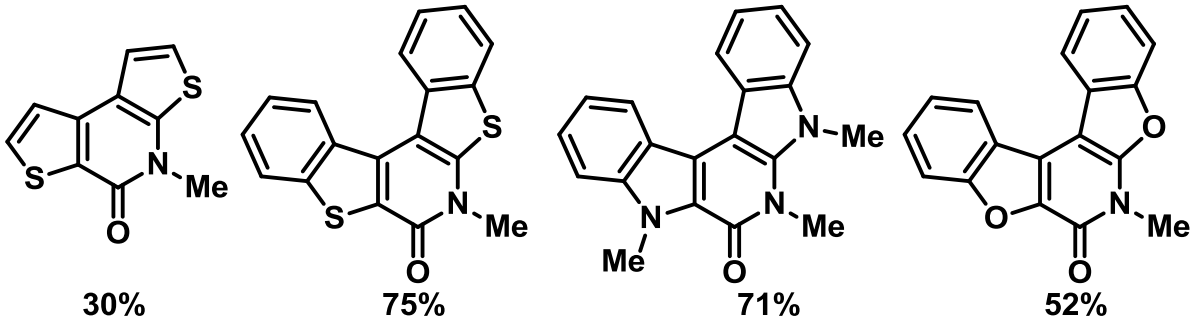
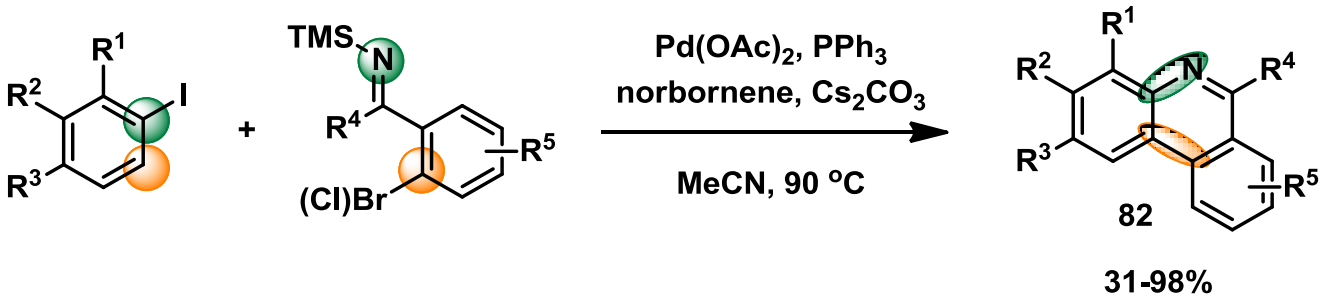
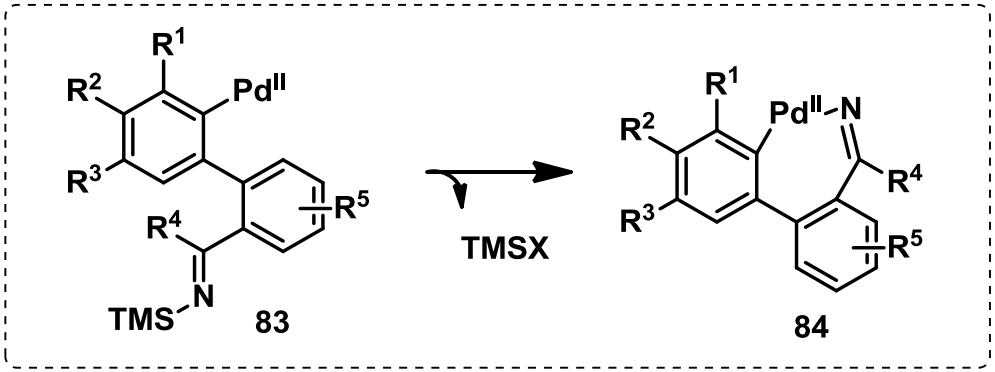


These polycyclic condensed heteroaryl rings are good candidates for pharmaceutics.

Catellani, M. etc. *J. Am. Chem. Soc.* **2006**, *128*, 722.

o-Arylation and Application

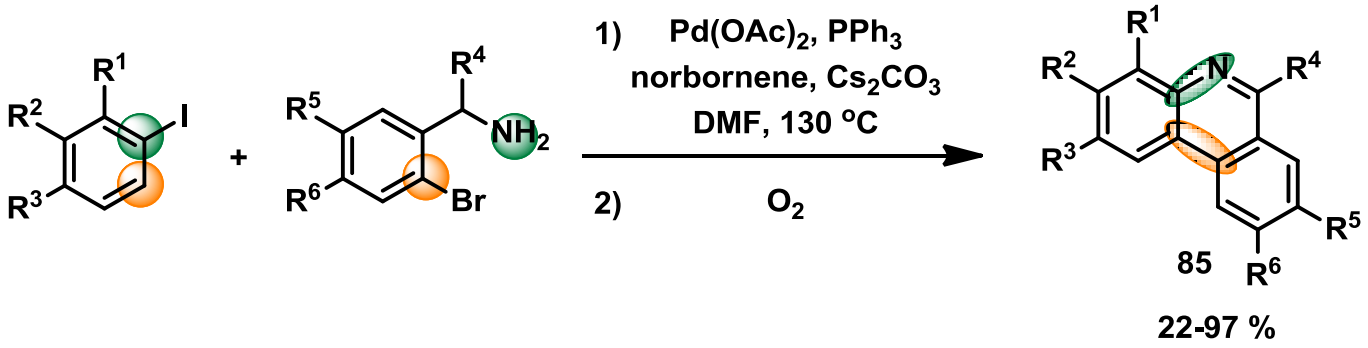




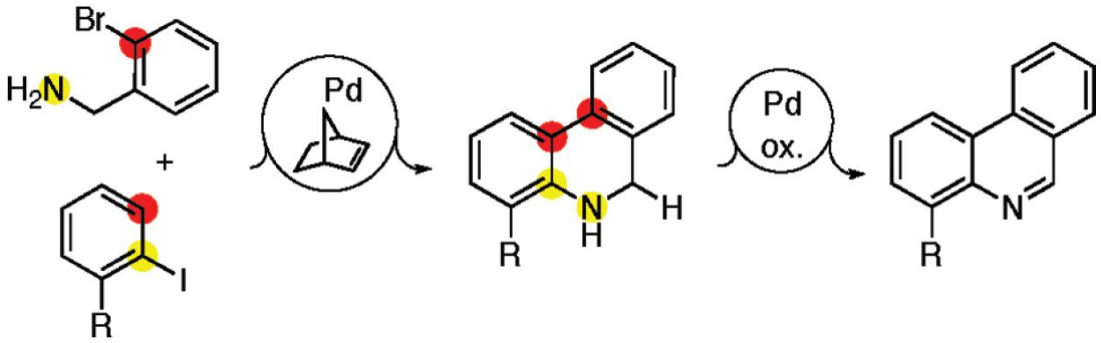
Using **imine** as reagent to directly synthesize polycyclic condensed heteroaryl rings.

Lautens, M. etc. Angew. Chem. Int. Ed. Engl. **2009**, *48*, 6713.

o-Arylation and Application



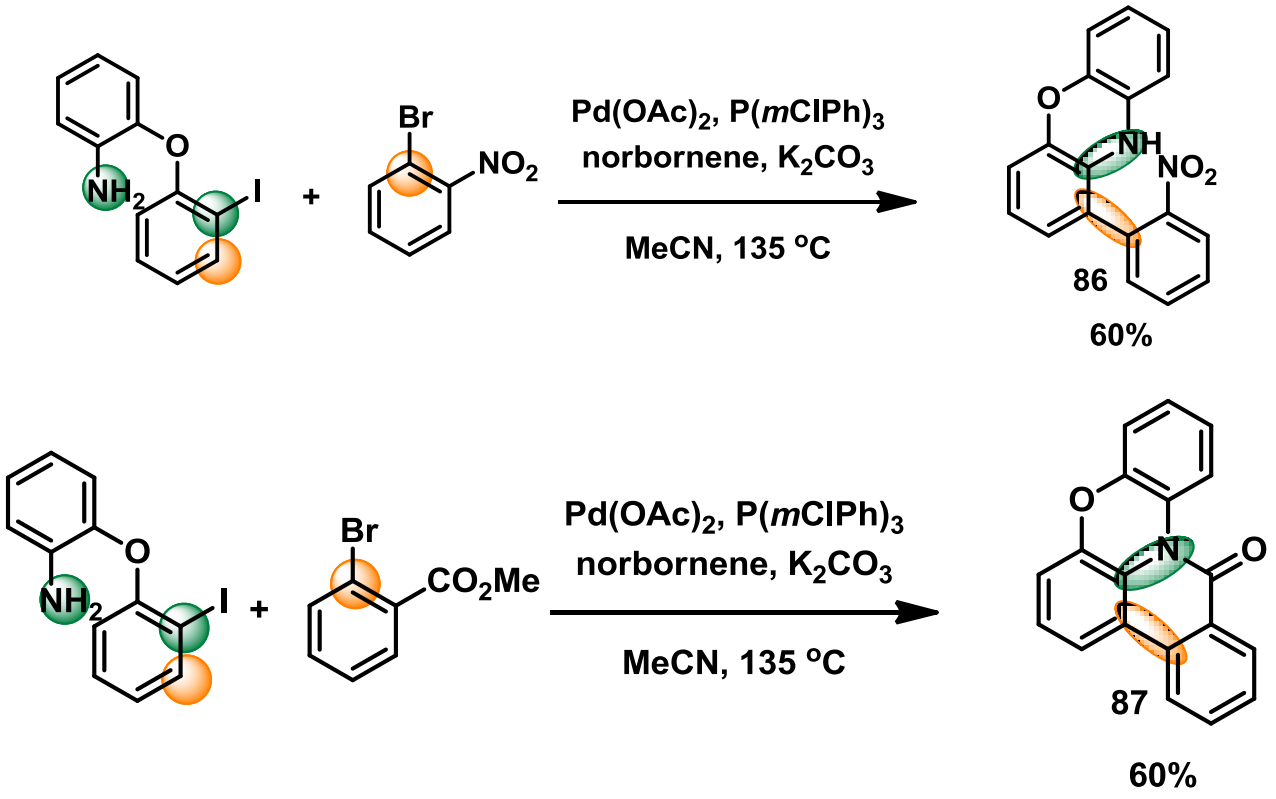
Strategy



A new way of synthesizing polycyclic condensed heteroaryl rings.

Malacria, M. etc. *Org. Lett.* **2010**, 12, 5692.

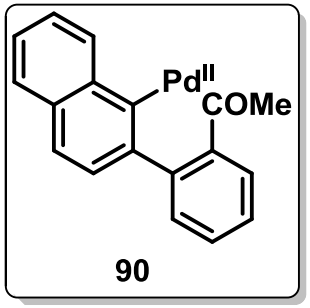
o-Arylation and Application



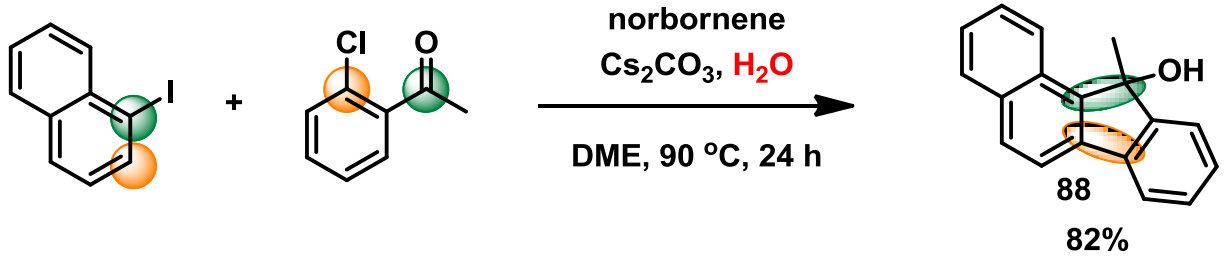
Putting the amine group at a proper position can lead to form a new cycle.

Lautens, M. etc. *J. Org. Chem.* **2010**, 75, 3495.

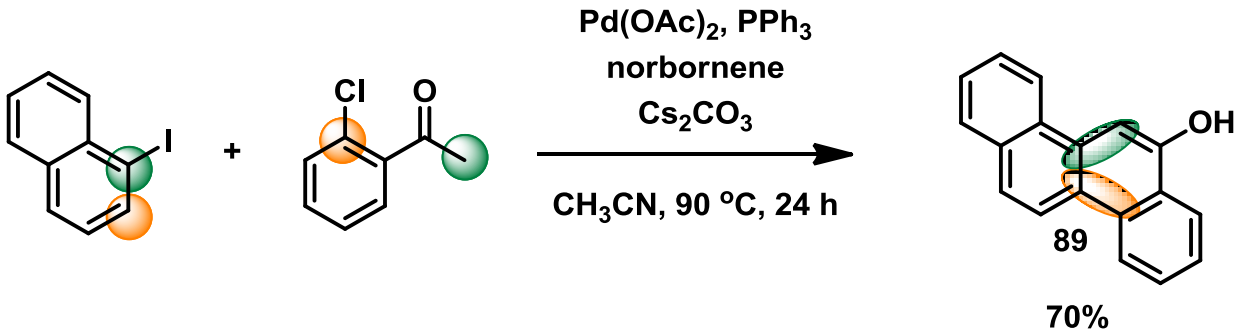
o-Arylation and Application



90: Nucleophile



90: Electrophile

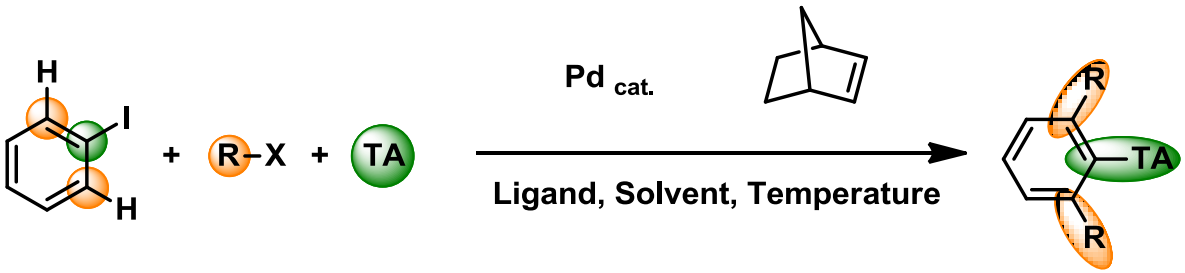


Switching the reactivity of **Pd^{II}** by changing the reaction condition.

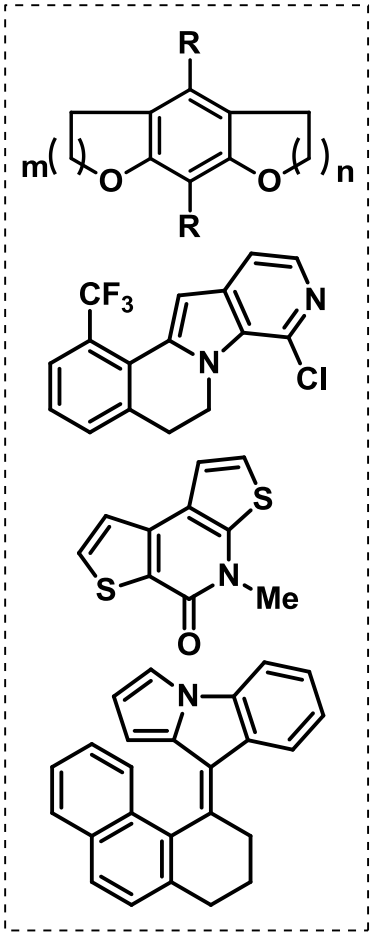
Lautens, M. etc. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 1849.

Summary and Outlook

Summary



R: Alkyl, Aryl
X: I, Br, Cl
TA: Terminating Agents (H_2, Olifen, Arylboronic Acid, Alkye, etc.)



Outlook

Exploring ways of *ortho* C-H funtionalization.

Exploring ways of initial step.

Recent Achievement: *J. Am. Chem. Soc.* **2011**, *133*, 12990; *J. Am. Chem. Soc.* **2012**, *134*, 14563; *J. Am. Chem. Soc.* **2013**, *135*, 9318; *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 6080; *J. Am. Chem. Soc.* **2013**, DOI:ja410823e.
Important Reviews: *Synthesis* **2013**, *45*, 581; *Top. Curr. Chem.* **2010**, *292*, 1. *Acc. Chem. Res.* **2008**, *41*, 1512. *Top. Organomet. Chem.* **2005**, *14*, 21.

Thanks for your attentions!