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Palladium-Catalyzed Highly Diastereoselective Oxidative Cascade Cyclization Reactions

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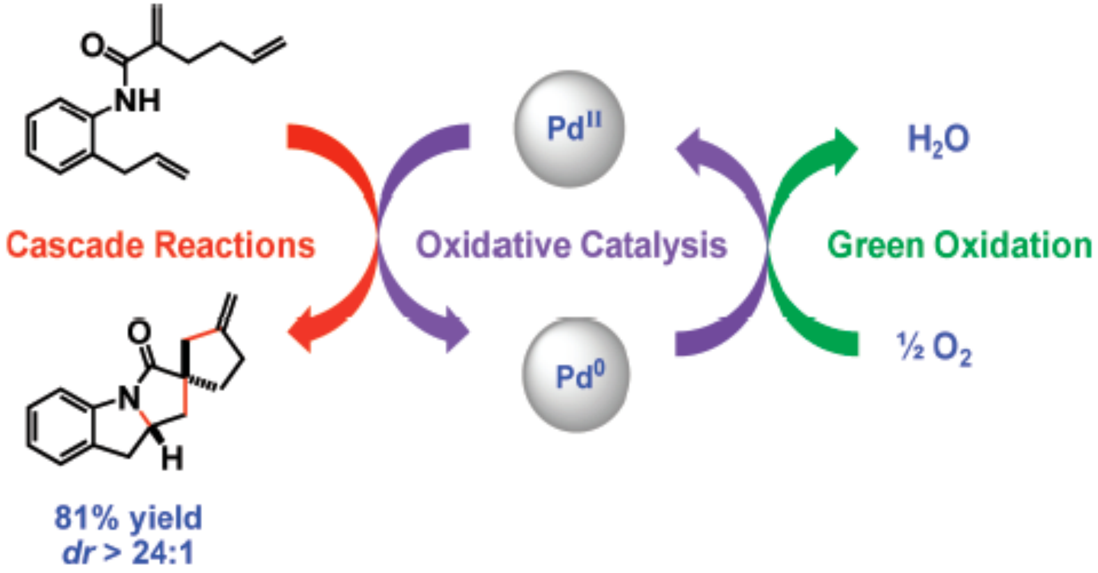
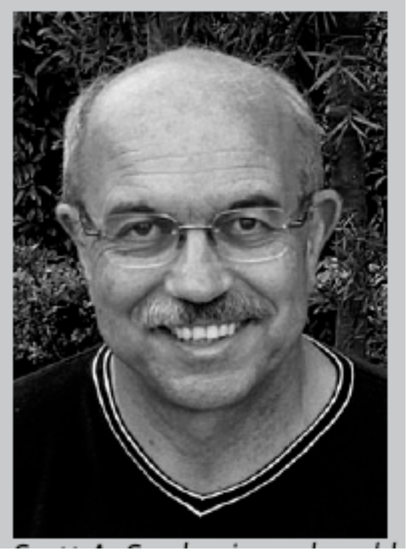


• Cascade Cyclization Reactions

> • “The design and implementation of cascade reactions is a challenging facet of organic chemistry, yet one that can impart striking novelty, elegance, and efficiency to synthetic strategies.”
>
> ***K. C. Nicolaou***



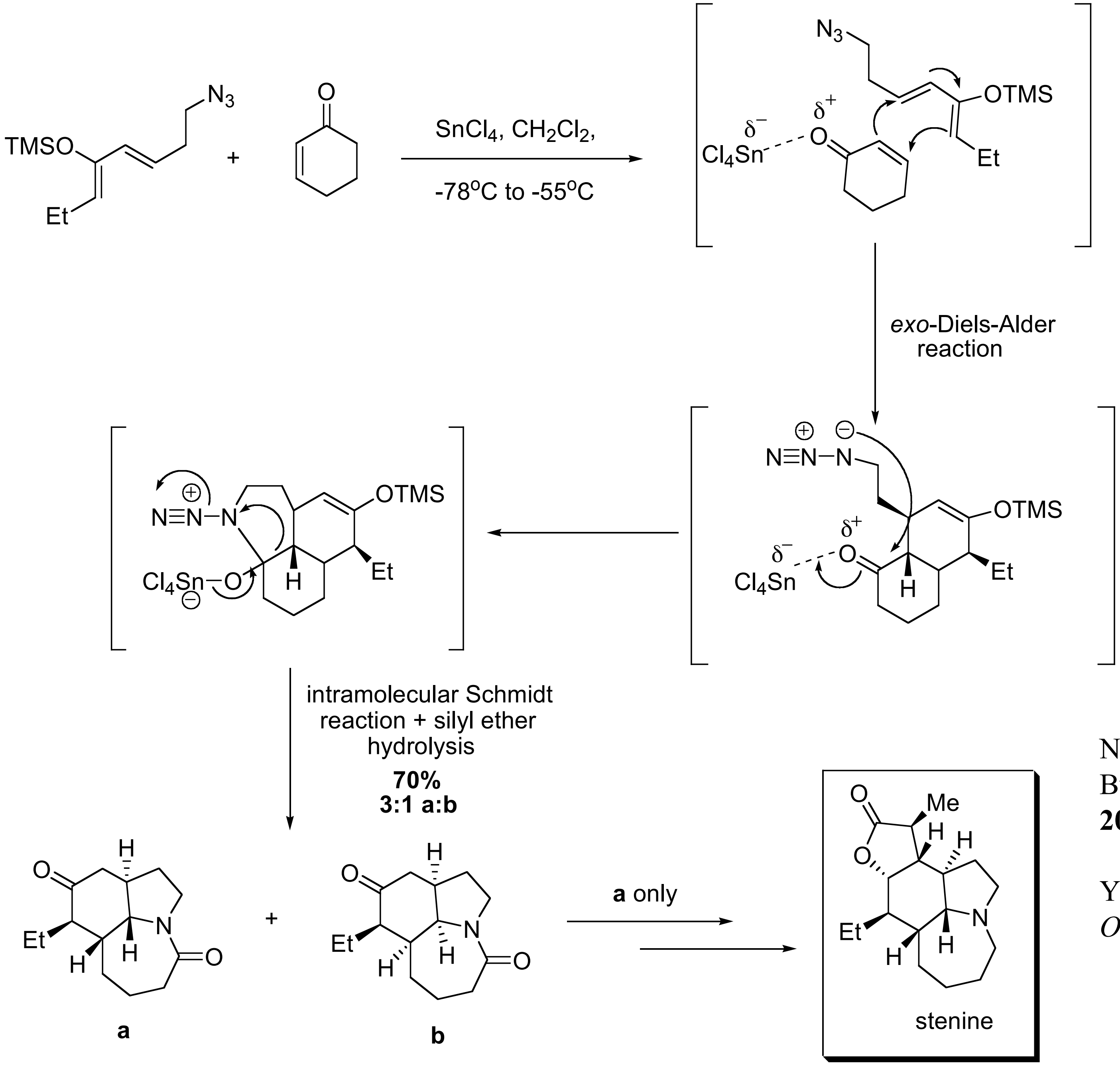
Five Classifications of Cascade Cyclization Reactions:

1. **Nucleophilic Cascades**
2. **Electrophilic Cascades**
3. **Radical Cascades**
4. **Pericyclic Cascades**
5. **Transition-Metal-Catalyzed Cascades**

- **generates molecular complexity enantioselectively**
- **catalytic**
- **bond construction unparalleled by nature**
- **Pd—blossomed into powerful tool over the past 25 years**
- **Heck is most popular Pd-catalyzed cascade reaction**

Nicolaou, K.C.; Edmonds, D.J.; Bulger, P.G. *Angew. Chem. Int. Ed*. **2006**, *45*, 7134-7186.

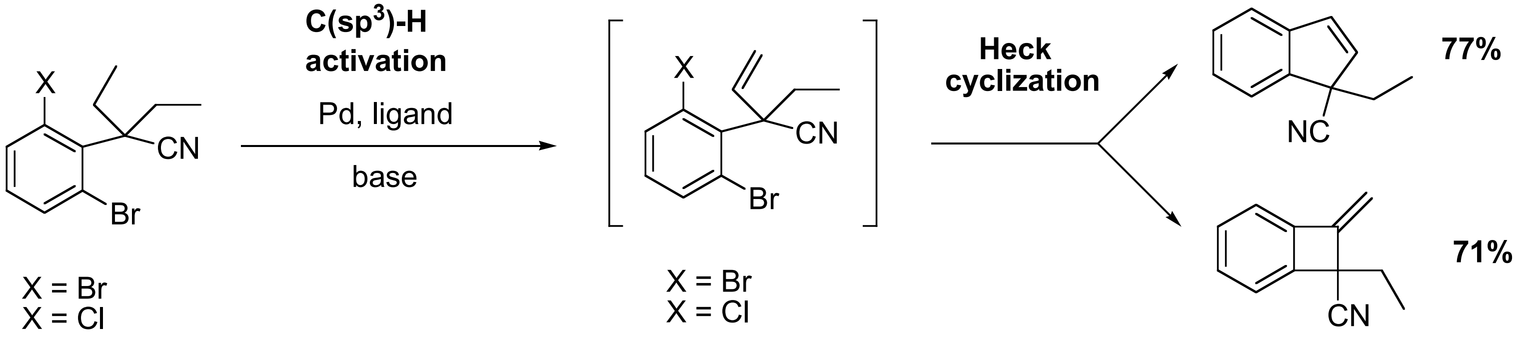
• Pericyclic Diels-Alder/Schmidt cascade to stenine:



Nicolaou, K.C.; Edmonds, D.J.; Bulger, P.G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186.

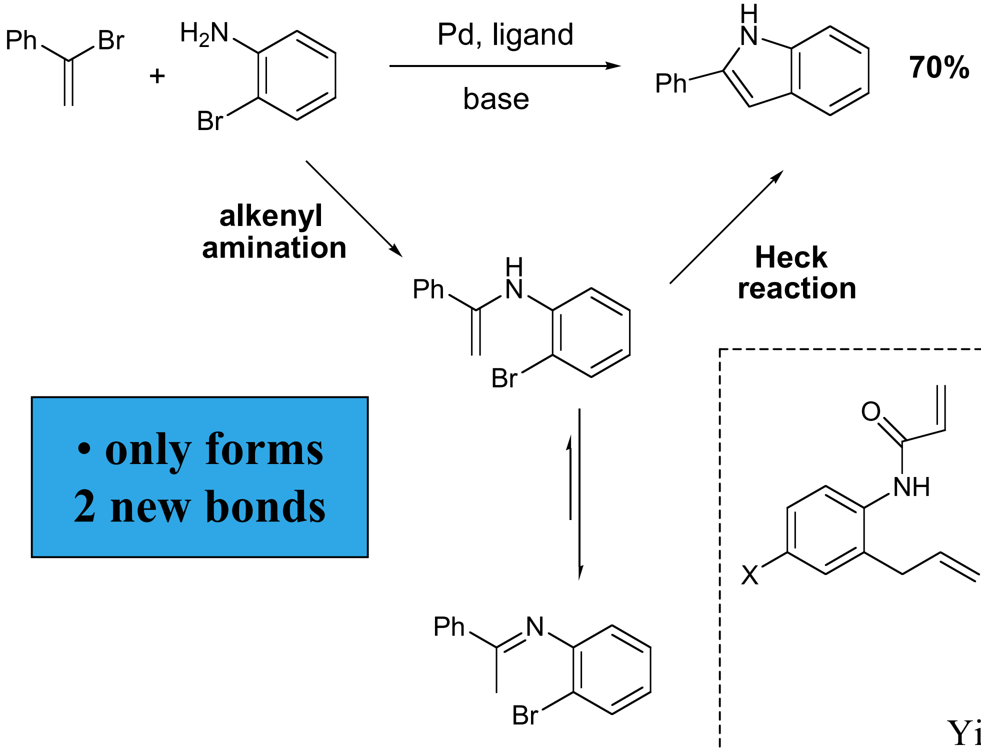
Y. Zeng, S. Reddy, E. Hirt, J. Aubé, *Org. Lett.* **2004, *6*,** 4993-4995.

• Sample of Heck cyclization cascades and their weaknesses:



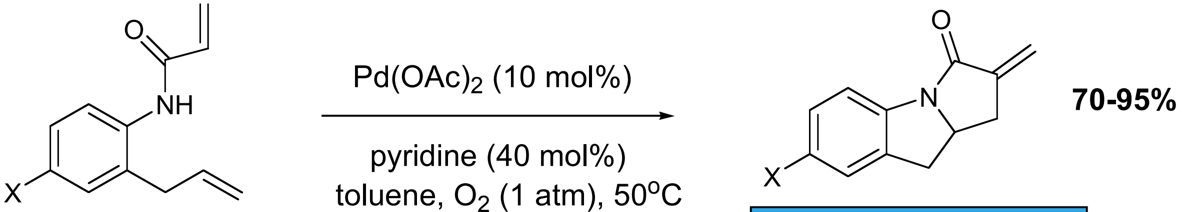
• needs activation

Hitce, J.; Baudoin, O. *Adv. Synth. Catal.* **2007**, *349*, 2054-2060.



• only forms 2 new bonds

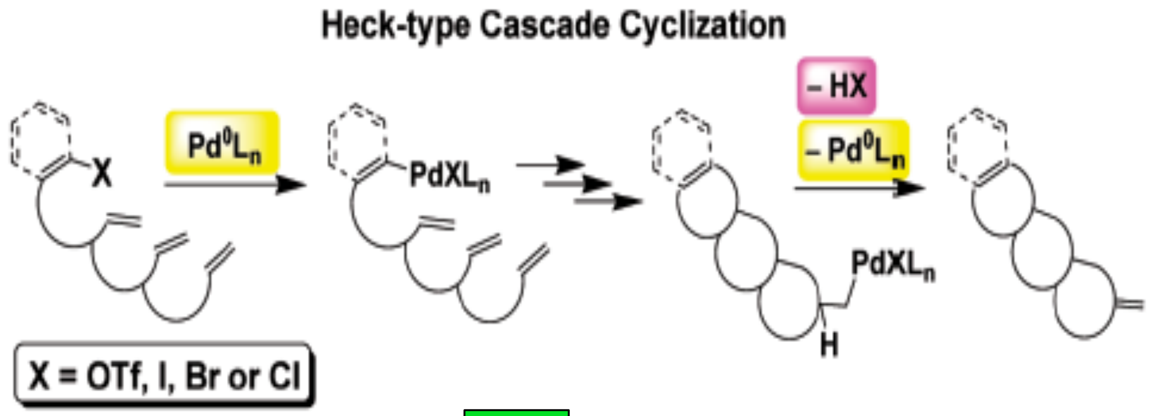
Barluenga, J.; Fernández, M.A.; Aznar, F.; Valdés, C. *Chem. Eur. J.* **2005**, *11*, 2276-2283.



• only forms 2 new bonds

Yip, K.; Zhu, N.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130-3131.

• Heck-type cascade cyclization popularity



…not without drawbacks

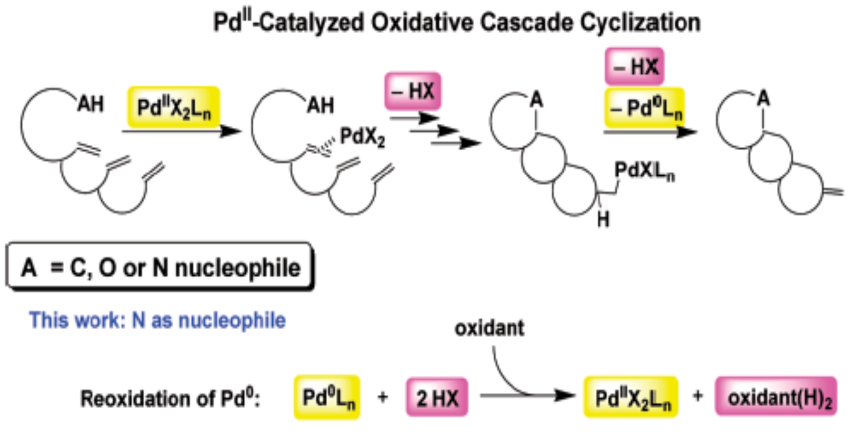
1. **preactivation of precursors leads to stoichiometric amounts of hydrohalic or triflic acids**
2. **palladium complexes usually contain air-sensitive phosphine ligands**
3. **reaction scope limited to carbon-carbon bond formation**

Goal:

to refine methodology toward cascade cyclization reactions that are more atom-economical and applicable to carbon-heteroatom bond formation

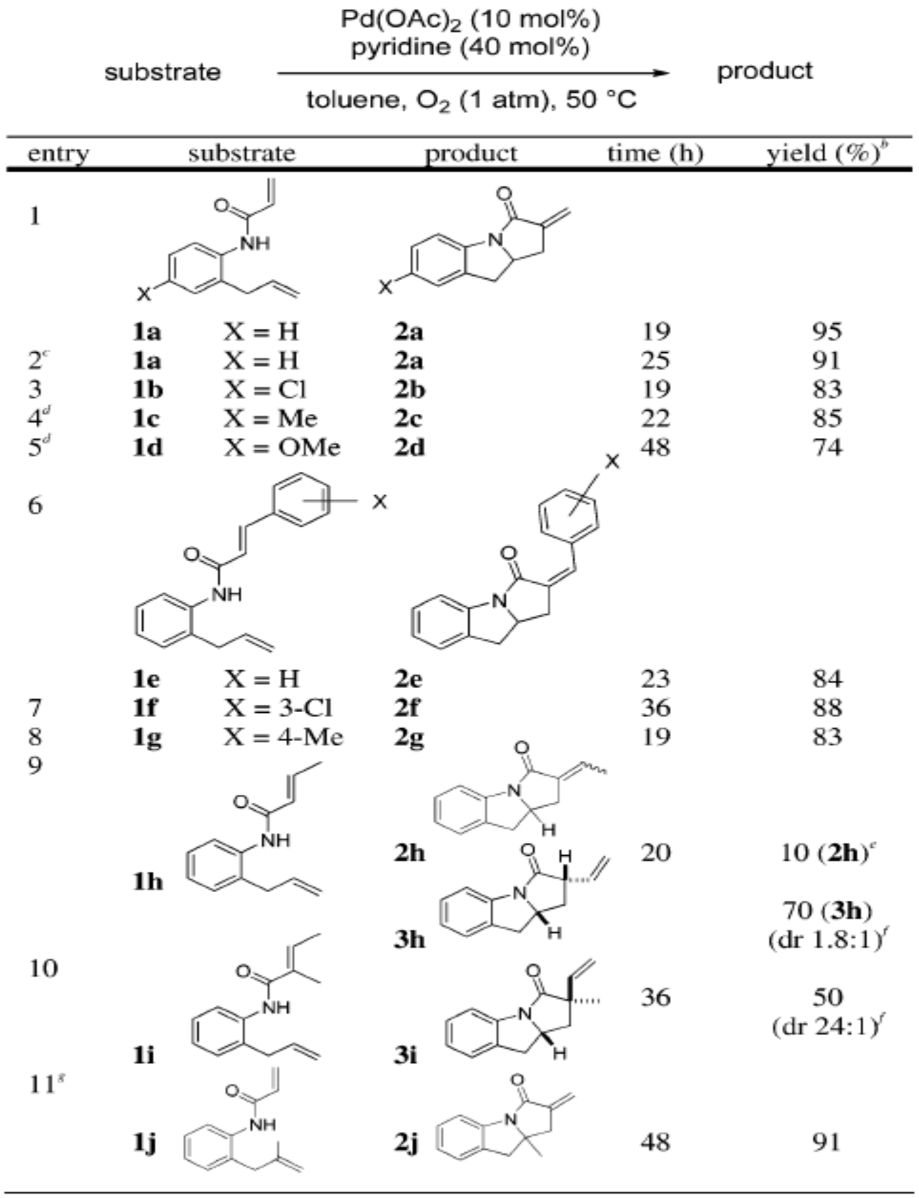
Yip, K.; Zhu, N.; Yang, D. *Org*. *Lett*. **2009**, *11*, 1911-1914.

• Previous work…..



- used $Pd(OAc)_2$/pyridine and $Pd(TFA)_2$/(-)-sparteine as the catalyst systems
- obtain racemic and enantioenriched indoline derivatives
- free of any undesired monocyclization products even in the absence of tandem relays

Yip, K.; Zhu, N.; Yang, D. *Org. Lett.* **2009**, *11*, 1911-1914.
Yip, K.; Zhu, N.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130-3131.



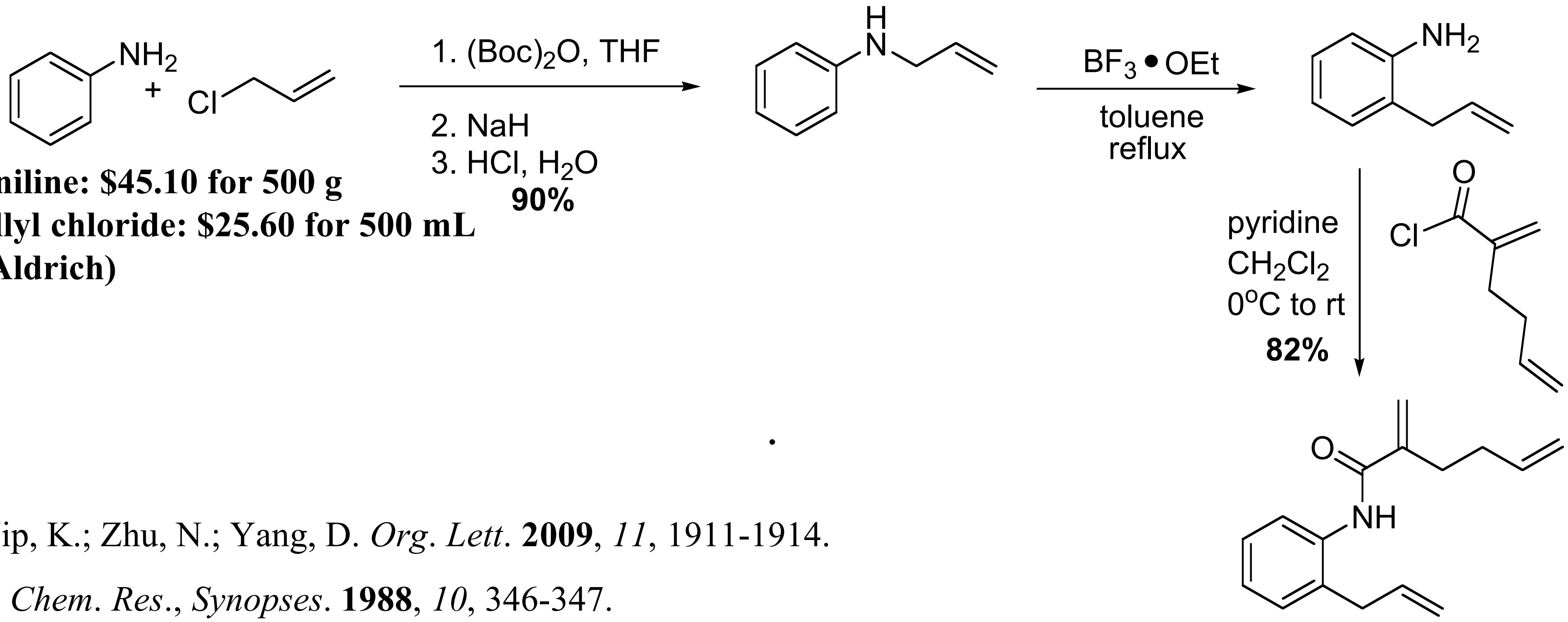
$$\text{substrate} \xrightarrow[\text{toluene, } O_2 \text{ (1 atm), 50 °C}]{Pd(OAc)_2 \text{ (10 mol\%)}\ \text{pyridine (40 mol\%)}} \text{product}$$

entry	substrate		product	time (h)	yield (%)[b]
1	**1a**	X = H	**2a**	19	95
2[c]	**1a**	X = H	**2a**	25	91
3	**1b**	X = Cl	**2b**	19	83
4[d]	**1c**	X = Me	**2c**	22	85
5[d]	**1d**	X = OMe	**2d**	48	74
6	**1e**	X = H	**2e**	23	84
7	**1f**	X = 3-Cl	**2f**	36	88
8	**1g**	X = 4-Me	**2g**	19	83
9	**1h**		**2h** **3h**	20	10 (**2h**)[e] 70 (**3h**) (dr 1.8:1)[f]
10	**1i**		**3i**	36	50 (dr 24:1)[f]
11[g]	**1j**		**2j**	48	91

• Title Paper: Palladium Catalyzed Highly Diastereoselective Oxidative Cascade Cyclization Reactions

- isoquinoline and quinoline as ligands *instead* of pyridine and (-)-sparteine
- $Pd(OAc)_2$/isoquinoline or quinoline as the catalyst system
- unsaturated anilides cyclize under an oxygen atmosphere (1 atm)
- furnish structurally versatile indoline derivatives
- good yields (~80%)
- make 1 C-N bond and 2 C-C bonds in a single step (one of which is a *quaternary* center)
- excellent diastereoselectivity (dr > 24:1)

• Synthesis of starting material (1a)

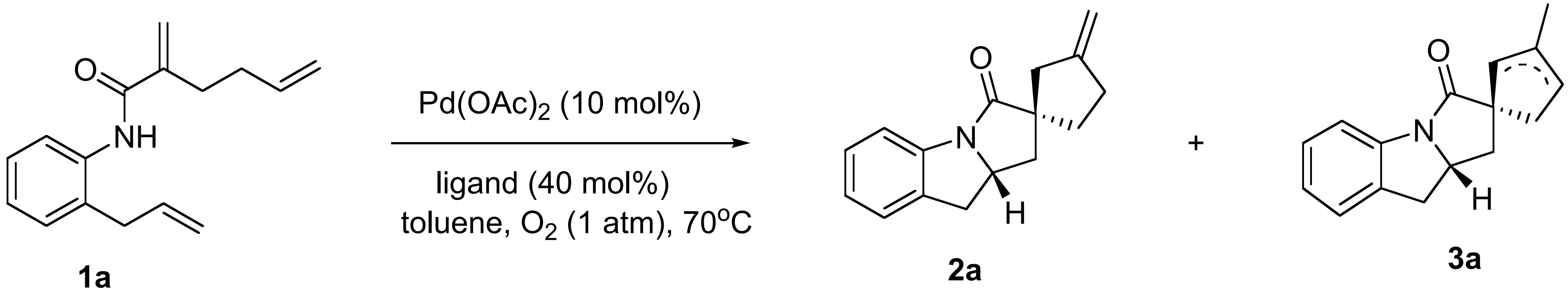


aniline: $45.10 for 500 g
allyl chloride: $25.60 for 500 mL
(Aldrich)

Yip, K.; Zhu, N.; Yang, D. *Org. Lett.* **2009**, *11*, 1911-1914.

J. Chem. Res., Synopses. **1988**, *10*, 346-347.

• Ligand screening


Pd(OAc)$_2$ (10 mol%)

ligand (40 mol%)
toluene, O$_2$ (1 atm), 70°C

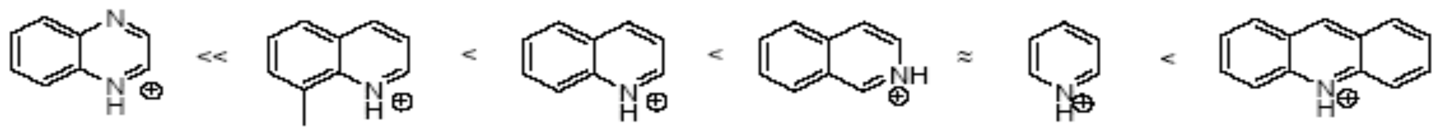
1a **2a** **3a**

entry	ligand	conversion (%)	yield (%) 2a+3a	product ratio (2a:3a)
1	6-methoxyquinoline	43	39	1:8.3
2	acridine	65	24	1:6.3
3	8-methylquinoline	42	26	1:3.2
4	quinoxaline	52	39	1:1.4
5	pyridine	73	56	1.5:1
6	quinoline	86	70	4.2:1
7	isoquinoline	89	76	5.6:1

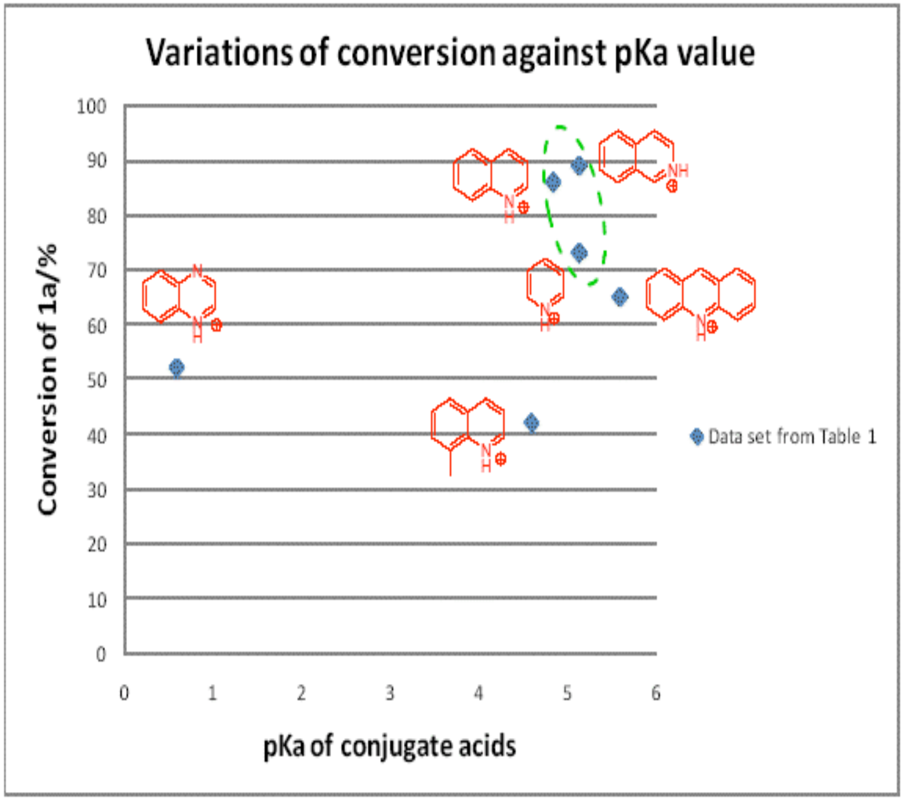
Yip, K.; Zhu, N.; Yang, D. *Org. Lett.* **2009**, *11*, 1911-1914.

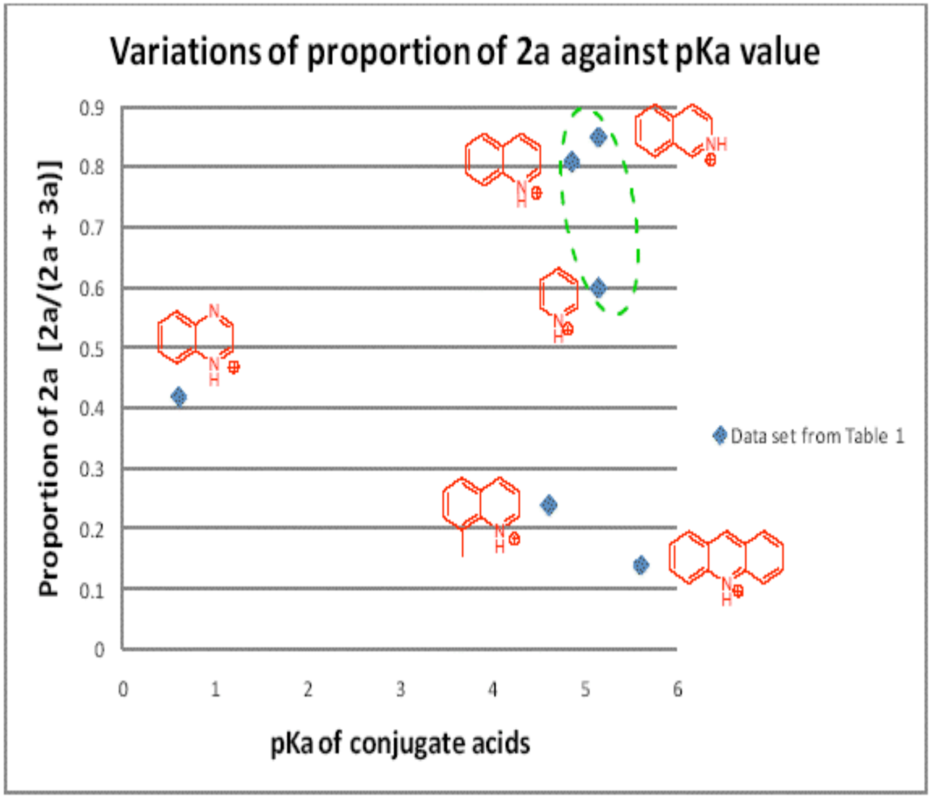
- **Basicity correlation with reaction conversion and product ratio**

Conjugate acids:



pK_a (in H_2O):	0.6	4.60	4.85	5.14	5.14	5.60
N-heteroaromatics:	Quinoxaline	8-Methylquinoline	Quinoline	Isoquinoline	Pyridine	Acridine

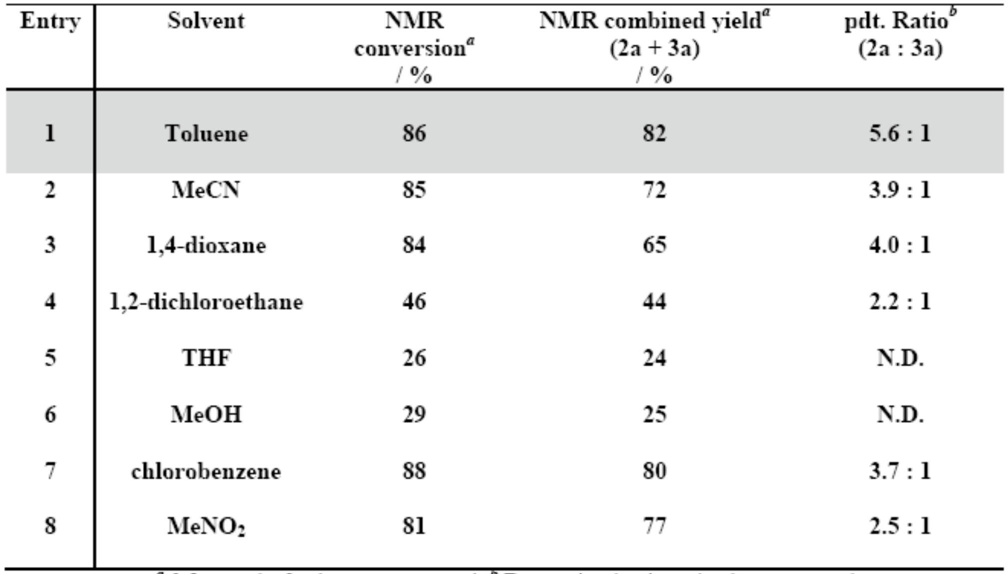




- **hypothesized that the basicities played a major role in suppressing olefin isomerization**

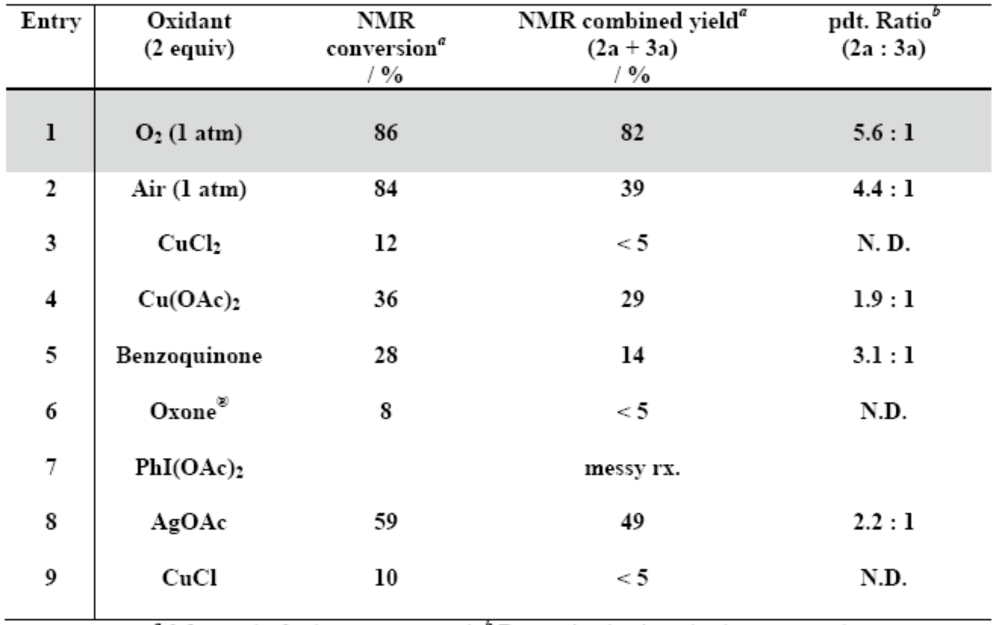
Yip, K.; Zhu, N.; Yang, D. *Org. Lett.* **2009**, *11*, 1911-1914.

• Solvent effect and oxidant screening



Entry	Solvent	NMR conversion[a] / %	NMR combined yield[a] (2a + 3a) / %	pdt. Ratio[b] (2a : 3a)
1	Toluene	86	82	5.6 : 1
2	MeCN	85	72	3.9 : 1
3	1,4-dioxane	84	65	4.0 : 1
4	1,2-dichloroethane	46	44	2.2 : 1
5	THF	26	24	N.D.
6	MeOH	29	25	N.D.
7	chlorobenzene	88	80	3.7 : 1
8	$MeNO_2$	81	77	2.5 : 1

[a] 0.2 mmol of substrate was used. [b] Determined using nitrobenzene as the internal standard.



Entry	Oxidant (2 equiv)	NMR conversion[a] / %	NMR combined yield[a] (2a + 3a) / %	pdt. Ratio[b] (2a : 3a)
1	O_2 (1 atm)	86	82	5.6 : 1
2	Air (1 atm)	84	39	4.4 : 1
3	$CuCl_2$	12	< 5	N. D.
4	$Cu(OAc)_2$	36	29	1.9 : 1
5	Benzoquinone	28	14	3.1 : 1
6	Oxone®	8	< 5	N.D.
7	$PhI(OAc)_2$		messy rx.	
8	AgOAc	59	49	2.2 : 1
9	CuCl	10	< 5	N.D.

[a] 0.2 mmol of substrate was used. [b] Determined using nitrobenzene as the internal standard.

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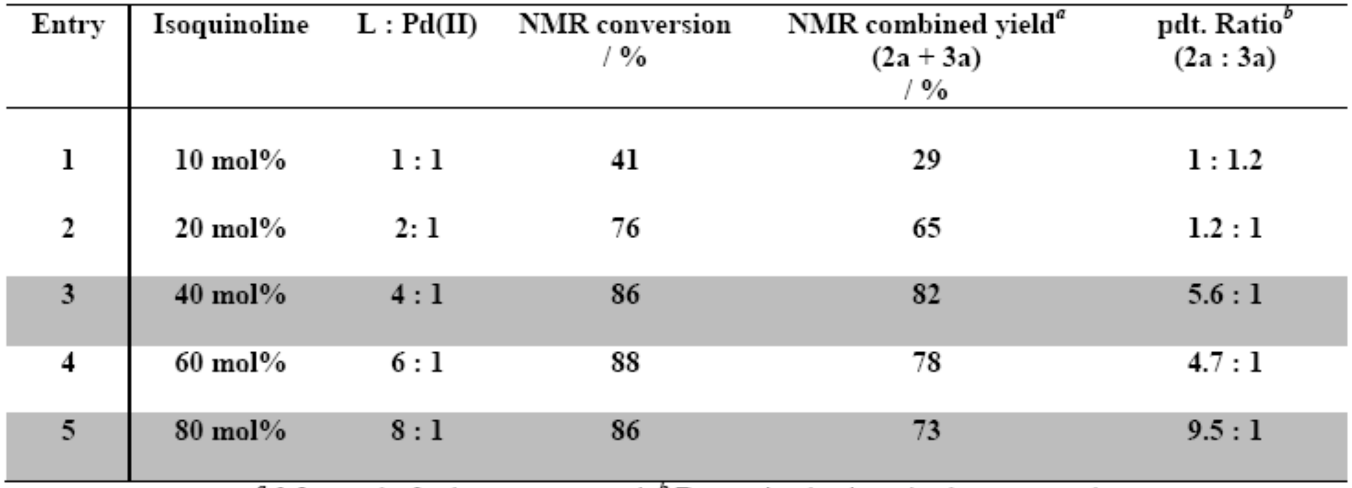
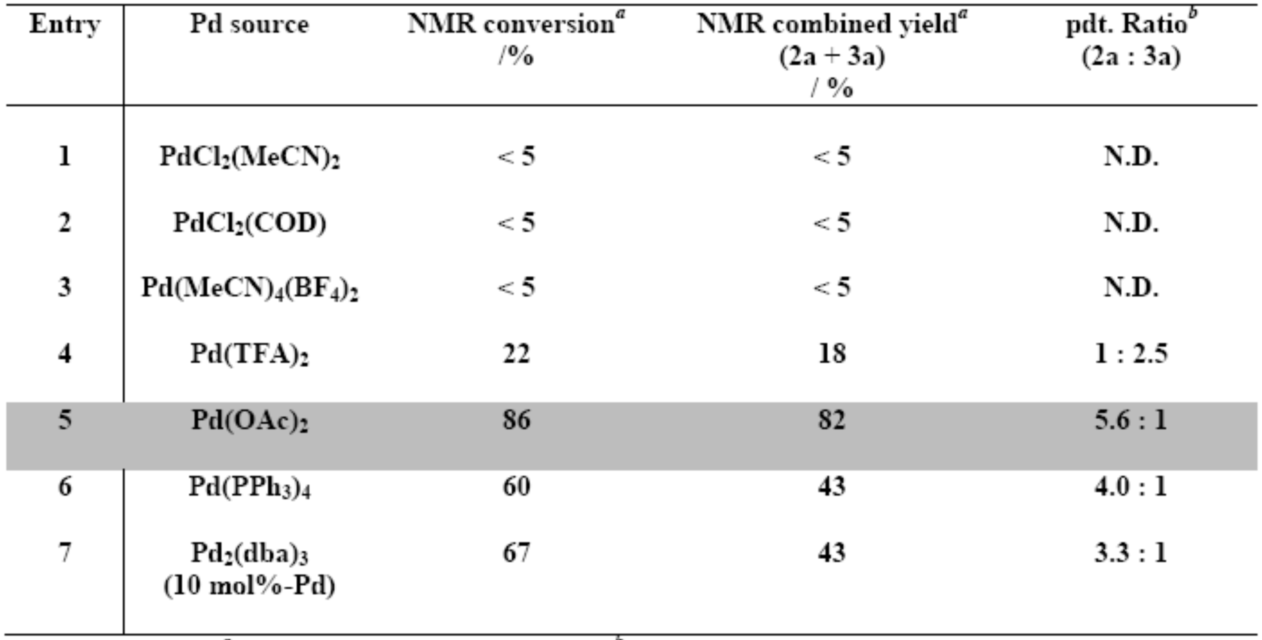
• Ligand to Pd (II) ratio and effect of Pd source



Entry	Isoquinoline	L : Pd(II)	NMR conversion / %	NMR combined yield[a] (2a + 3a) / %	pdt. Ratio[b] (2a : 3a)
1	10 mol%	1 : 1	41	29	1 : 1.2
2	20 mol%	2: 1	76	65	1.2 : 1
3	40 mol%	4 : 1	86	82	5.6 : 1
4	60 mol%	6 : 1	88	78	4.7 : 1
5	80 mol%	8 : 1	86	73	9.5 : 1

[a] 0.2 mmol of substrate was used. [b] Determined using nitrobenzene as the internal standard.

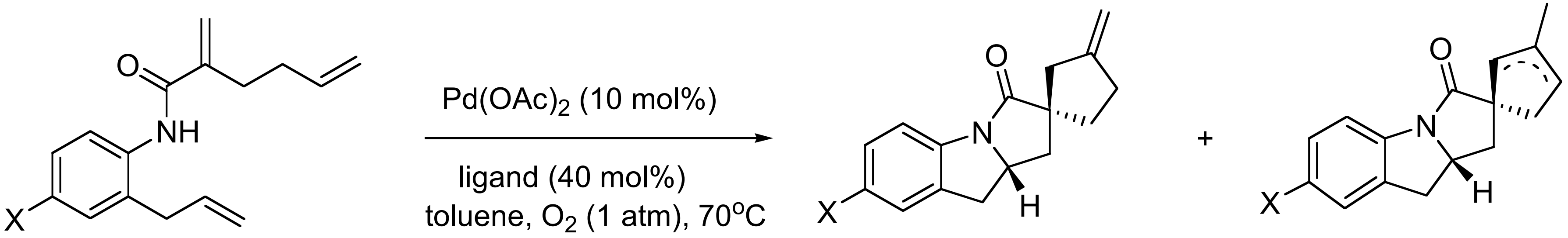


Entry	Pd source	NMR conversion[a] /%	NMR combined yield[a] (2a + 3a) / %	pdt. Ratio[b] (2a : 3a)
1	$PdCl_2(MeCN)_2$	< 5	< 5	N.D.
2	$PdCl_2(COD)$	< 5	< 5	N.D.
3	$Pd(MeCN)_4(BF_4)_2$	< 5	< 5	N.D.
4	$Pd(TFA)_2$	22	18	1 : 2.5
5	$Pd(OAc)_2$	86	82	5.6 : 1
6	$Pd(PPh_3)_4$	60	43	4.0 : 1
7	$Pd_2(dba)_3$ (10 mol%-Pd)	67	43	3.3 : 1

[a] 0.2 mmol of substrate was used. [b] Determined using nitrobenzene as the internal standard.

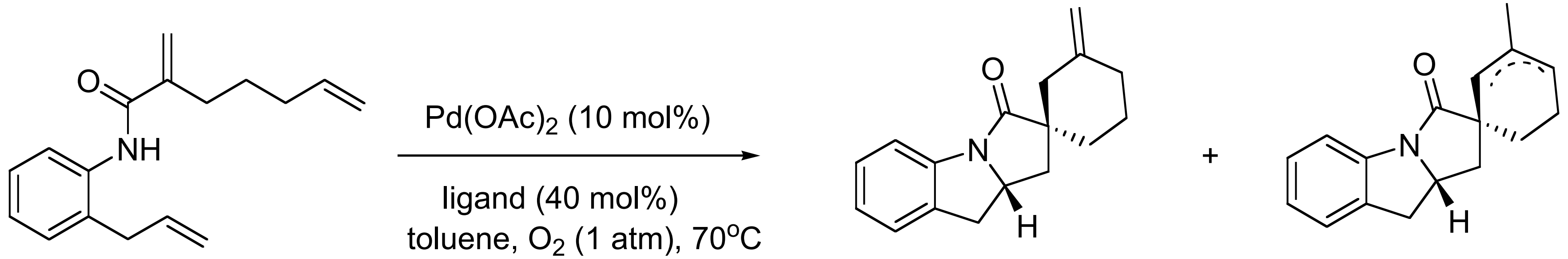
Yip, K.; Zhu, N.; Yang, D. *Org*. *Lett*. **2009**, *11*, 1911-1914.

• Scope of the cascade cyclization using quinoline and isoquinoline as ligands



1a **2a** **3a**

X	quinoline (2a:3a %yield)	isoquinoline (2a:3a % yield)
H	60:9	81:3
F	55:7	70:3
OMe	34:29	55:5

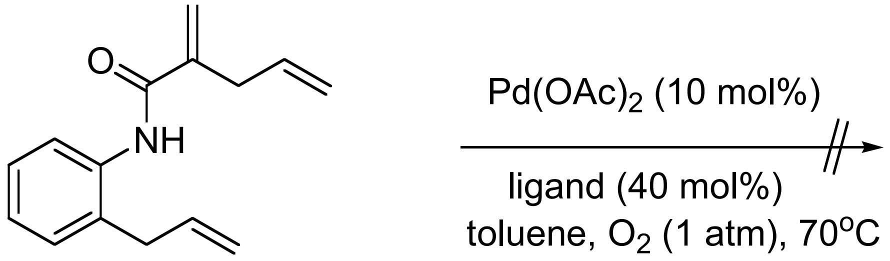


1d **2d** **3d**

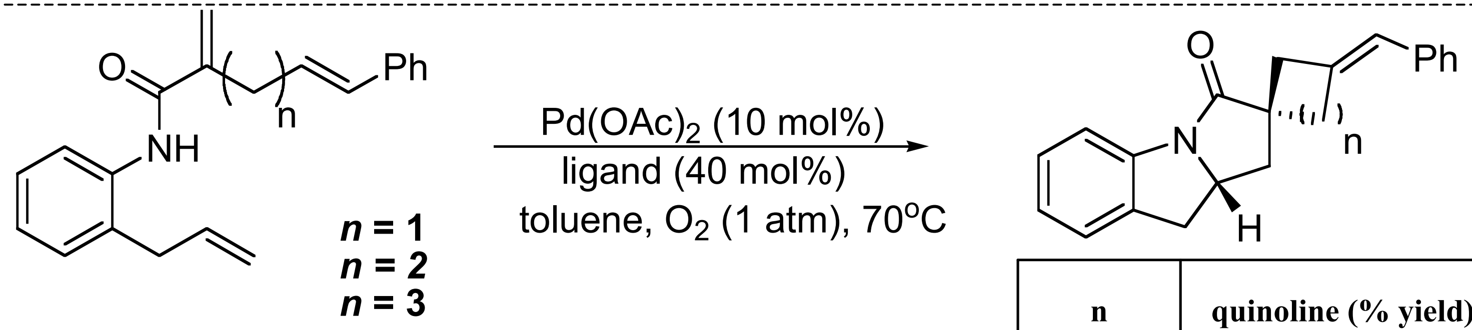
	quinoline (% yield)	isoquinoline (% yield)
exo	59	45
endo	5	2

Yip, K.; Zhu, N.; Yang, D. *Org*. *Lett*. **2009**, *11*, 1911-1914.

• Scope of the cascade cyclization using quinoline and isoquinoline as ligands, continued



1e



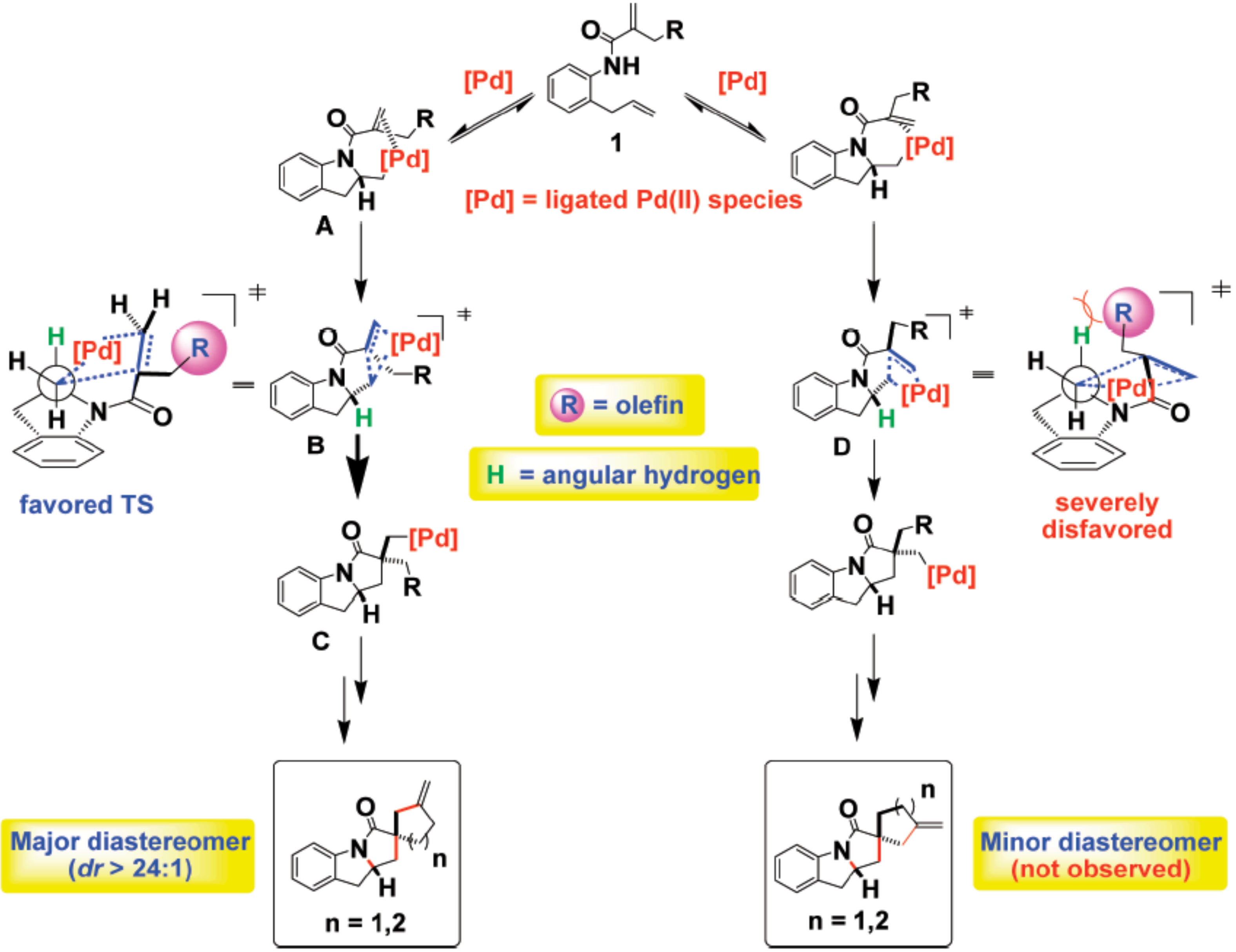
n	quinoline (% yield)	isoquinoline (% yield)
1	33	N/A
2	N/A	77
3	55	N/A

key scope points:

- **quinoline and isoquinoline have similar rxn times**
- **Pd/(OAc)$_2$/isoquinoline resulted in better yields**
- **cyclization not correlate with substrate's electronic properties**
- ***endo*-olefinic products form by secondary addition of palladium hydride to the *exo* moiety**

Yip, K.; Zhu, N.; Yang, D. *Org*. *Lett*. **2009**, *11*, 1911-1914.

• Transition State Model



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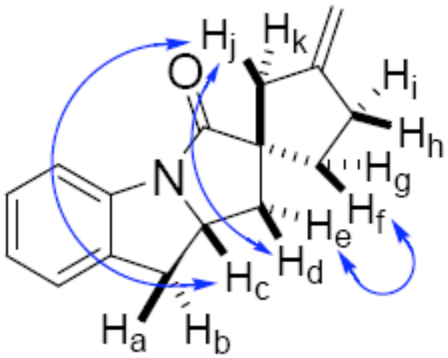
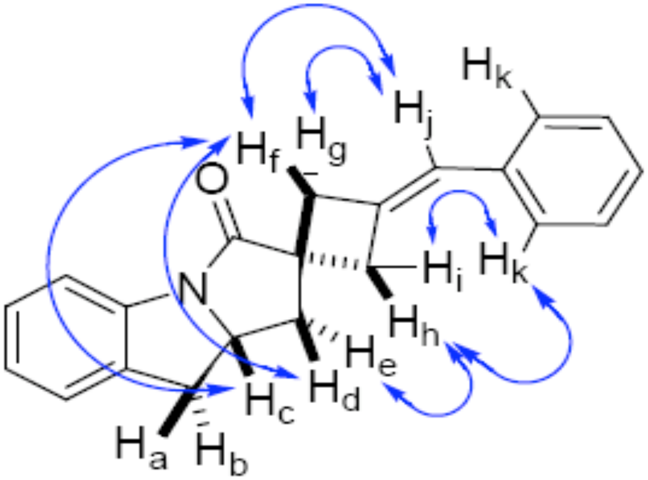
- **Key nOe interactions**



2a

H_c–H_j : strong nOe
H_d–H_j : strong nOe
H_d–H_f : weak nOe
H_e–H_f : strong nOe
H_e–H_j : weak nOe



2f

H_c–H_f : strong nOe
H_d–H_f : strong nOe
H_e–H_h : strong nOe
H_f–H_j : strong nOe
H_g–H_j : strong nOe
H_h–H_j : weak nOe
H_i–H_j : weak nOe
H_h–H_k : strong nOe
H_i–H_k : strong nOe

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• Conclusions:

- **new palladium-catalyzed oxidative cyclization reactions**
- **highly diastereoselective**
- **construct three new bonds and two chiral centers in a single step (one of which is a quaternary center)**
- **$Pd(OAc)_2$/isoquinoline and $Pd(OAc)_2$/quinoline systems are an extension of the well documented $Pd(OAc)_2$/pyridine system**
- **pushes past the previous reaction scope to include formation of a carbon-nitrogen bond**
- **overall more atom-economical and applicable in pursuit of green chemistry**

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