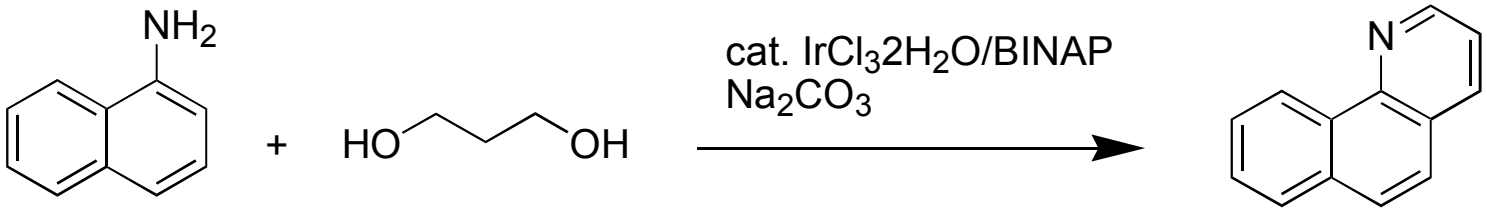
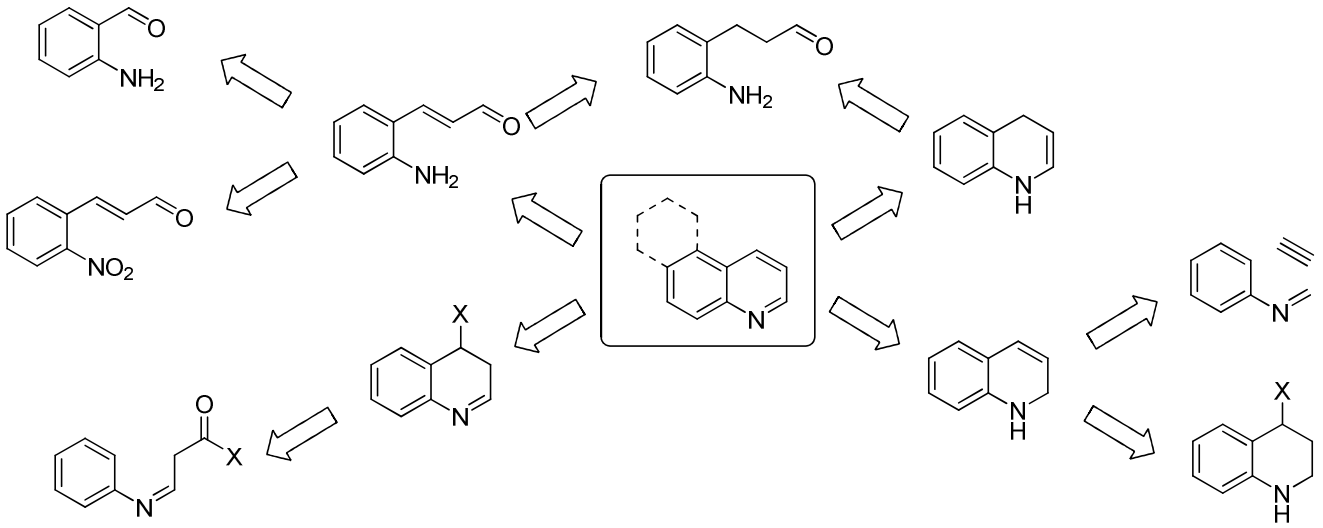
N-Heterocyclization of Naphthylamines with 1,2- and1,3-Diols Catalyzed by an Iridium Chloride/BINAP System



Hiroomi Aramoto, Yasushi Obora, and Yasutaka Ishii
J. Org. Chem. **2009**, *74*, 628.

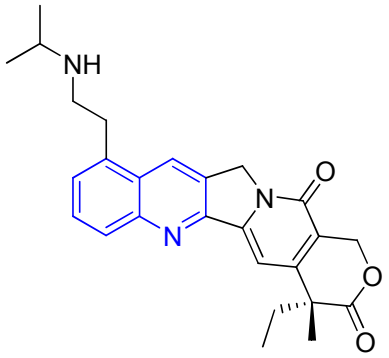
Current literature
12/20/08 → 01/17/09
Akira Nakamura

Classic Quinoline Synthesis



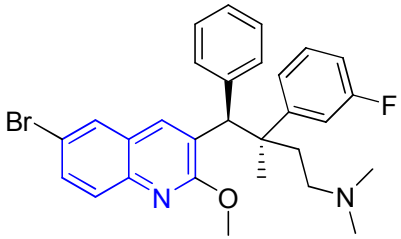
Camps Synthesis
Combes Synthesis
Conrad-Limpach Reaction
Diels-Reese Reaction
Doebner reaction
Doebner Miller Reaction
Friedlander Synthesis
Gould-Jacobs Reaction
Knorr Synthesis
Niementowski Synthesis
Pfitzinger Synthesis
Povarov reaction
Riehm Synthesis
Skraup Reaction

Quinoline-bearing compounds



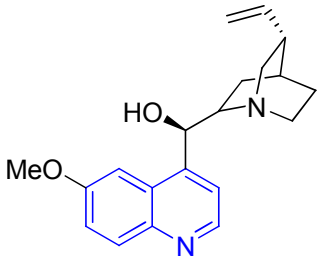
Belotecan

anti-tumor activity

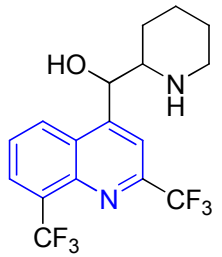


R207910

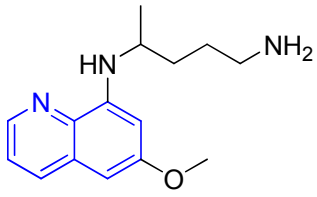
anti-tuberculosis activity



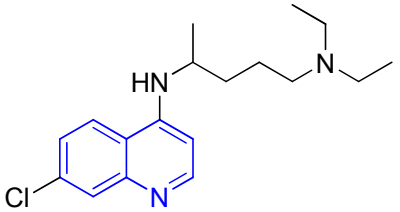
Quinine



Mefloquine



Primaquine



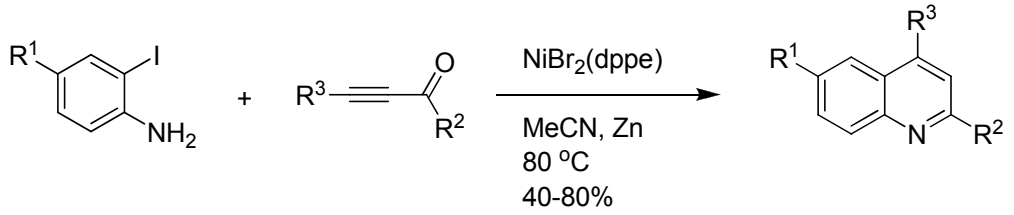
Chloroquine

anti-malaria activity

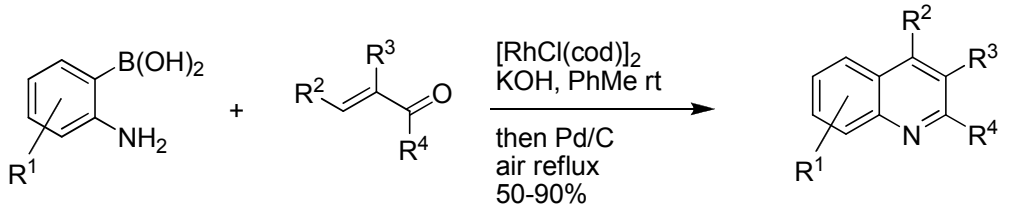
Quinoline Alkaloids Review:

Natural Product Reports **2005**, *22*, 627-646.

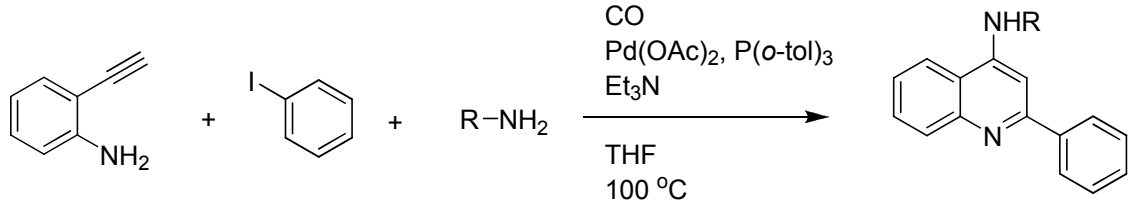
Metal-catalyzed Recent Quinoline Synthesis



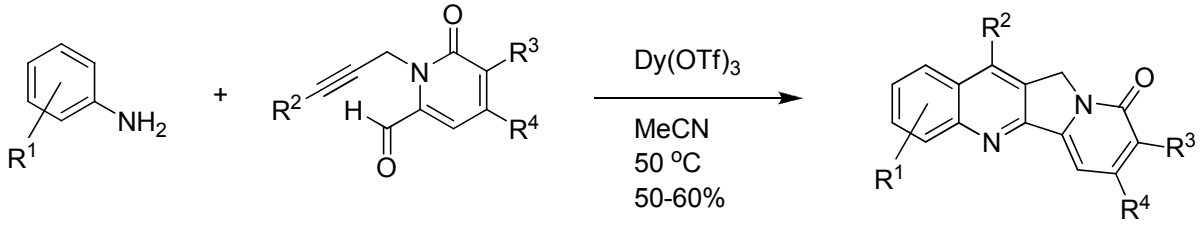
J. Org. Chem. **2006**, *71*, 7079



Org. Lett. **2008**, *10*, 4117.



J. Org. Chem. **2005**, *70*, 6454.

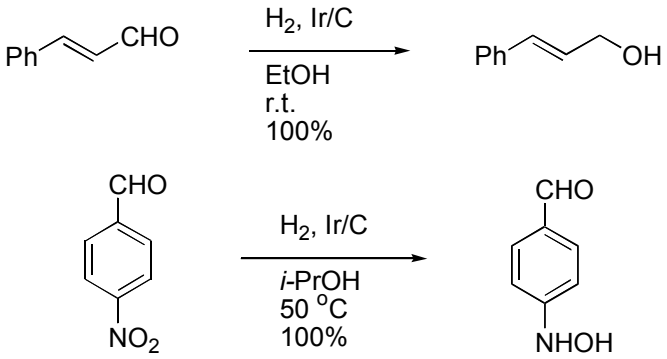


Org. Lett. **2004**, *6*, 4913.

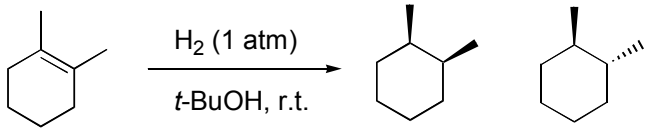
Ir catalyst

Iridium catalysts are well known as moderately active hydrogenation catalysts

Chemoselective Hydrogenation



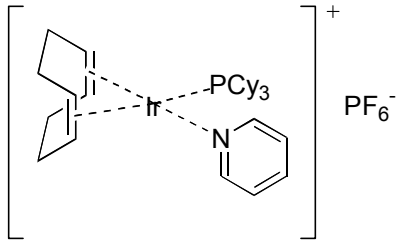
Stereoselective Hydrogenation



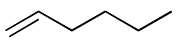
Catalyst	
Ru	93.5 : 6.5
Rh	87.6 : 12.4
Pd	26.4 : 73.6
Os	98.7 : 1.3
Ir	99.2 : 0.8
Pt	79.1 : 20.9

Chem. Lett. **1984**, 1625.

Crabtree' catalyst

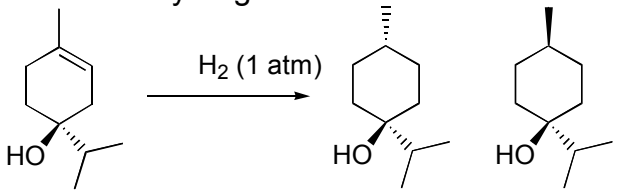


Hydrogenation of hindered olefin

		
Crabtree's	6400	4000
Wilkinson's	9000	0

Acc. Chem. Res. **1979**, *12*, 331.

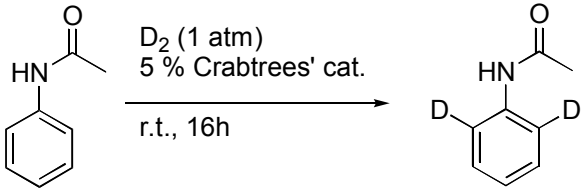
Stereoselective Hydrogenation



5% Pd/C / EtOH	20	:	80
5% Pd/C / c-Hex	53	:	47
2.5% Crabtree's cat.	99.9	:	0.1

J. Am. Chem. Soc. **1983**, *105*, 1072.

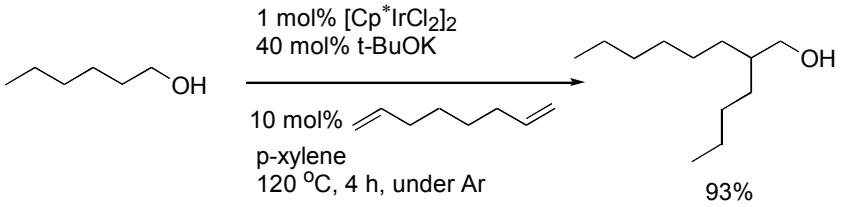
Hydrogen Isotope Exchange



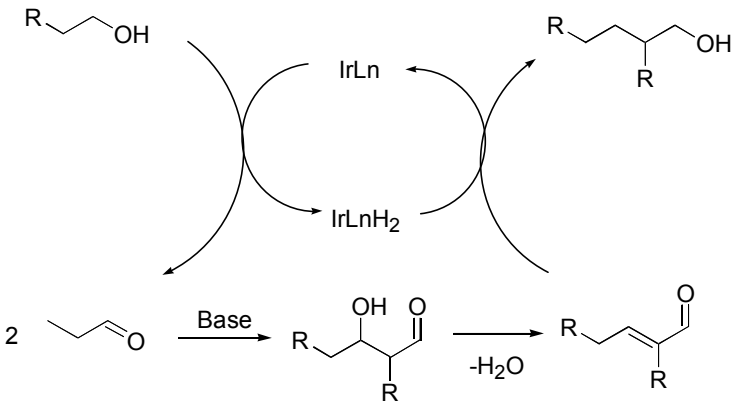
Label. Compd. Radiopharm. **1995**, *36*, 497.

Ir catalyzed reactions

Guerbet reaction



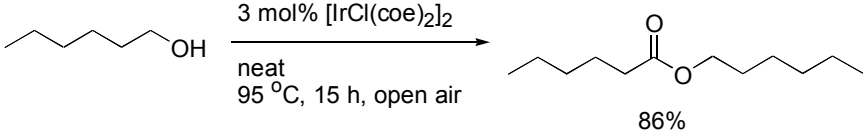
Plausible reaction mechanism



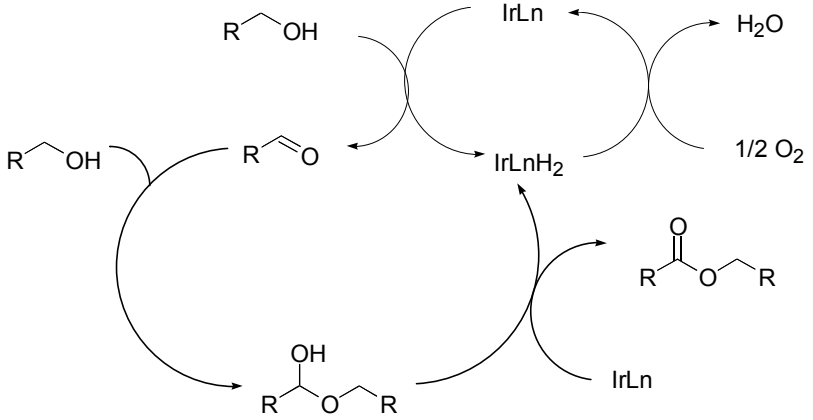
In the presence of base, primary alcohols are converted to β–alkylated dimer alcohols.

Ishii, Y. *J. Org. Chem.* **2006**, *71*, 8306.

Oxidative dimerization to ester



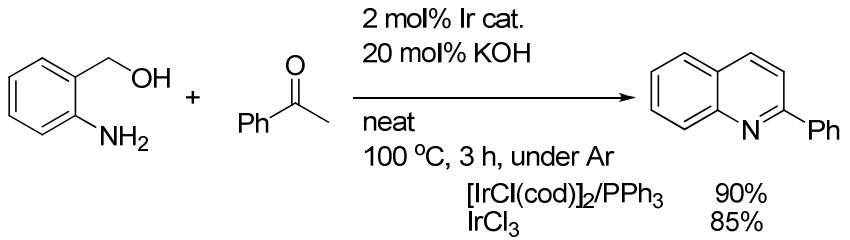
Proposed mechanism

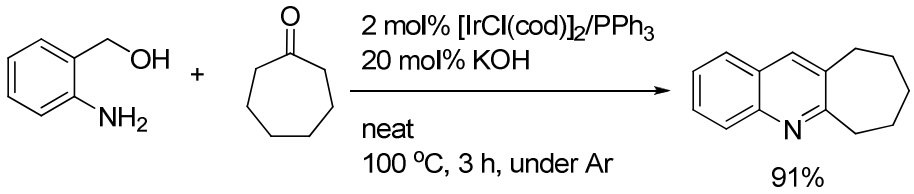


In the absence of base, primary alcohols are converted to esters at moderate temperature.

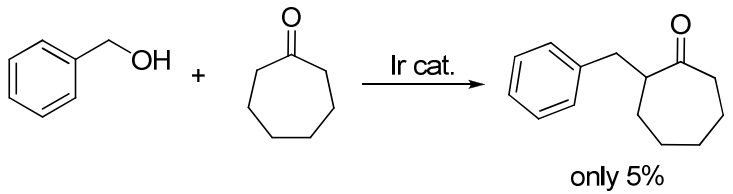
Ishii, Y. *Tetrahedron Lett.* **2006**, *47*, 9199.

Ir catalyzed quinoline synthesis



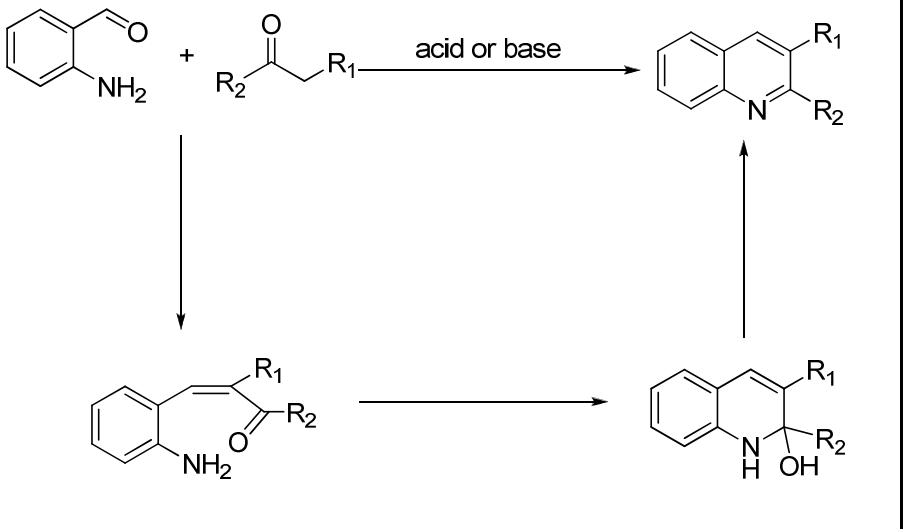


Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 4539

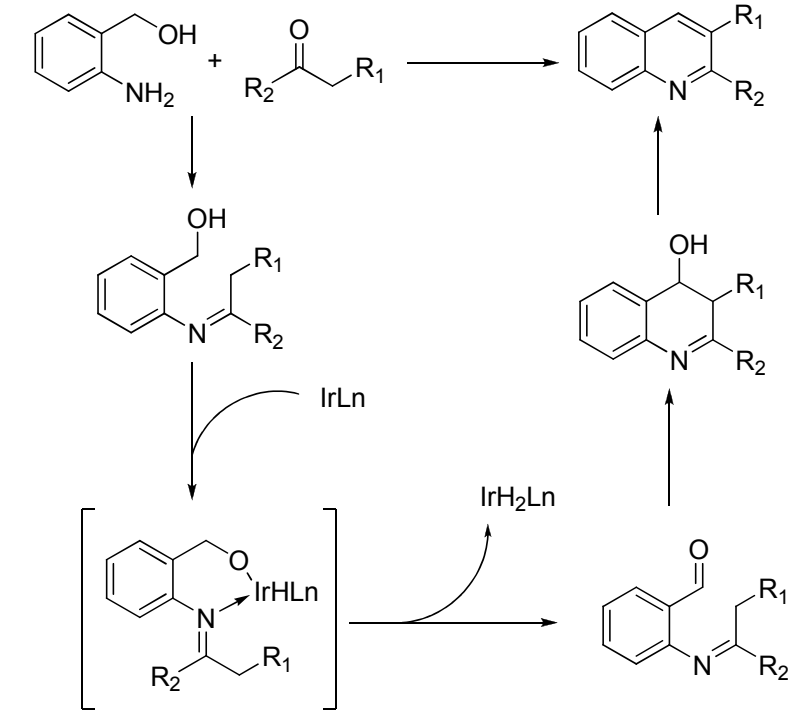


First intermediate would not come from Aldol cross coupling

Friedlander synthesis

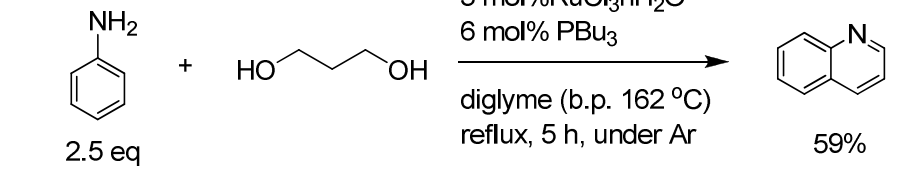


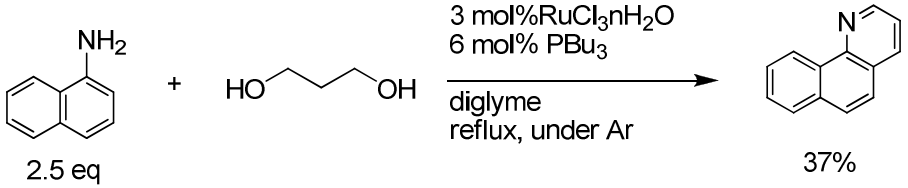
Proposed mechanism



Title paper work

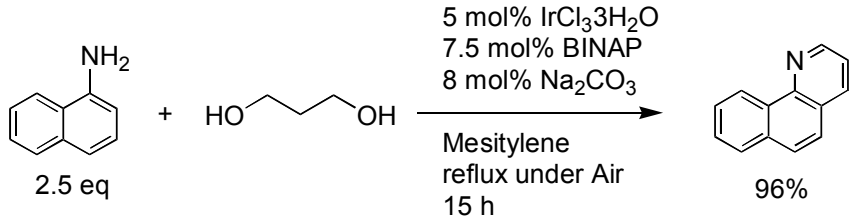
First precedent



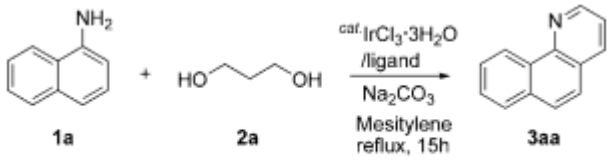


Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 1673.

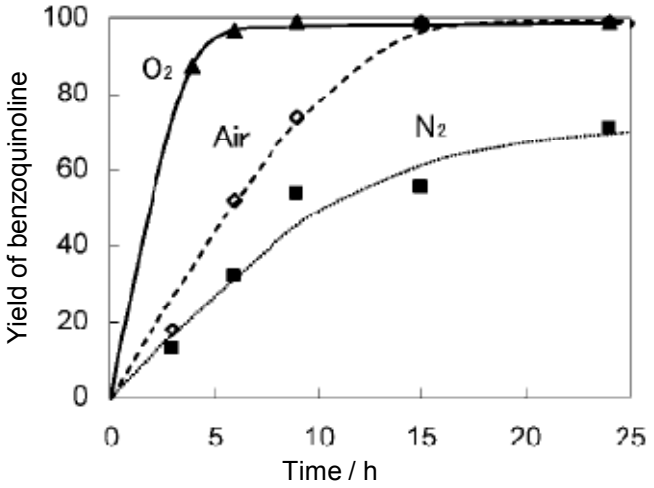
Title paper



Optimization

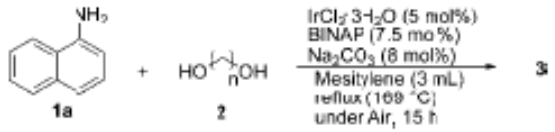


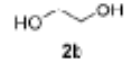
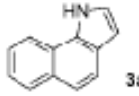
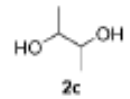
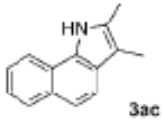
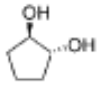
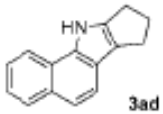
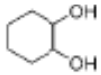
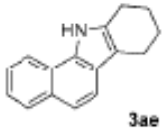
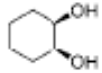
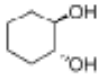
entry	ligand	temp/°C	yield of **3aa**/%[b]
1	–	169	–
2	PPh_3	169	44
3	$P(^nOct)_3$	169	66
4	dppe	169	14
5	dppp	169	13
6	BINAP	169	99 (96)
7[c]	BINAP	169	58
8	BINAP	150	3
9[d]	BINAP	169	79
10[e]	BINAP	169	55
11[f]	BINAP	169	–



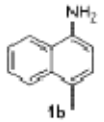
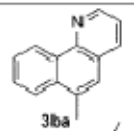
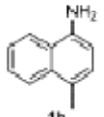
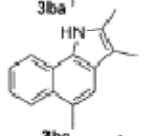
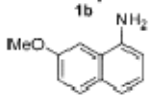
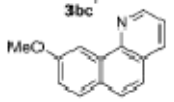
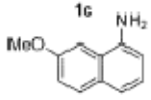
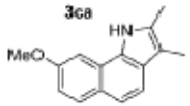
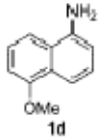
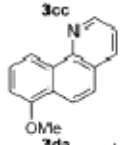
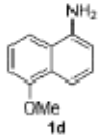
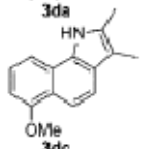
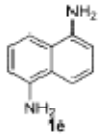
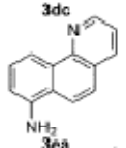
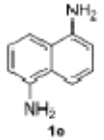
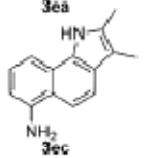
Oxidation step is involved as an important step

Substrate scope



Entry	2	Product (3)	Yield (%)[a]
1	 2b	 3ab	56 (47)
2	 2c	 3ac	99 (96)
3[c,d]	 2d	 3ad	80 (84)
4[c,d]	 2e (*cis*/*trans* = 64/36)	 3ae	99 (88)
5[c,e]	 *cis*-2e	3ae	98 (90)
6[c,d]	 *trans*-2e	3ae	96 (88)

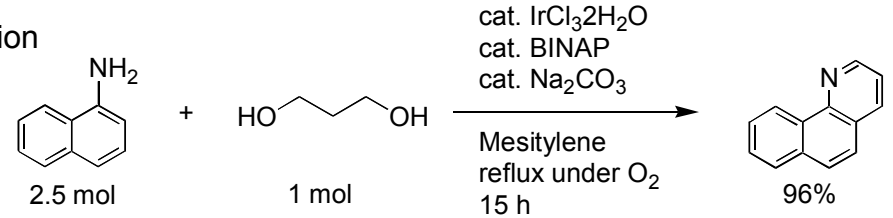
[a] 1a (5 mmol) was allowed to react with 2 (2 mmol) in the presence of $IrCl_3 \cdot 3H_2O$ (0.1 mmol, 5 mol % based on 2), ligand (0.15 mmol, 7.5 mol %), and Na_2CO_3 (0.16 mmol, 8 mol %) under air at refluxing temperature (169 °C) in mesitylene (3 mL) for 15 h. [b] GLC yields based on 2 used. The numbers in parentheses show isolated yields. [c] 1a (10 mmol) was used. [d] PPh_3 (0.2 mmol, 10 mol % based on 2) was used instead of BINAP.

Entry	1	2	Product (3)	Yield (%)[b]
1	 1b	2a	 3ba	95 (90)
2	 1b	2c	 3bc	90 (88)
3	 1c	2a	 3ca	78 (72)
4	 1c	2c	 3cc	80(78)
5	 1d	2a	 3da	76 (72)
6	 1d	2c	 3dc	79(76)
7	 1e	2a	 3ea	66 (59)
8	 1e	2c	 3ec	58 (52)

[a] 1a (5 mmol) was allowed to react with 2 (2 mmol) in the presence of $IrCl_3 \cdot 3H_2O$ (0.1 mmol, 5 mol % based on 2), BINAP (0.15 mmol, 7.5 mol %), and Na_2CO_3 (0.16 mmol, 8 mol %) under O_2 (1 atm) at refluxing temperature (169 °C) in mesitylene (3 mL) for 15 h. [b] GLC yields based on 2 used. The numbers in parentheses show isolated yields.

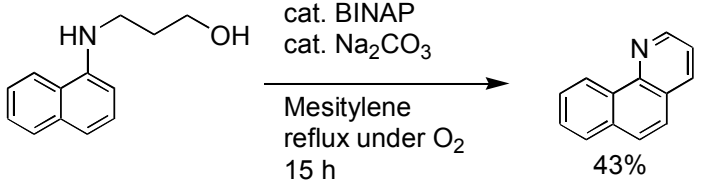
Mechanistic investigation

Optimized condition



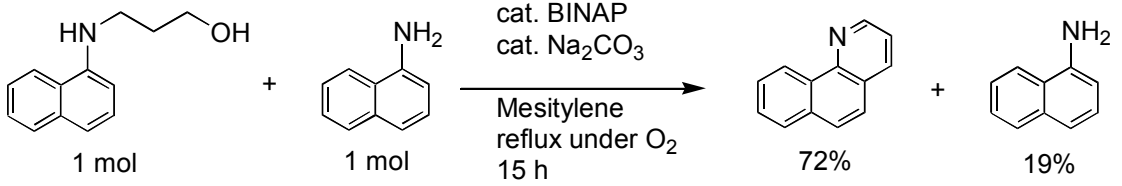
2.5 mol + 1 mol → 96%

First intermediate?



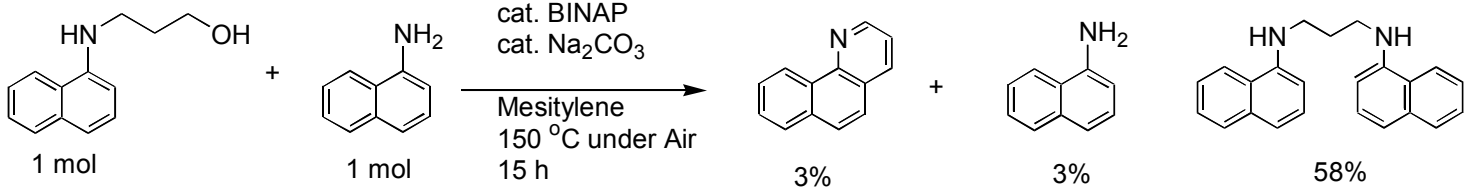
43%

Additional amine

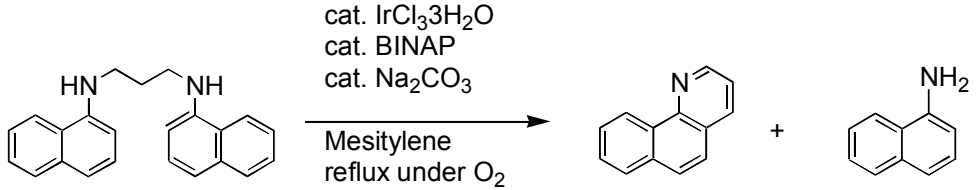


1 mol + 1 mol → 72% + 19%

A litte bit low temp.



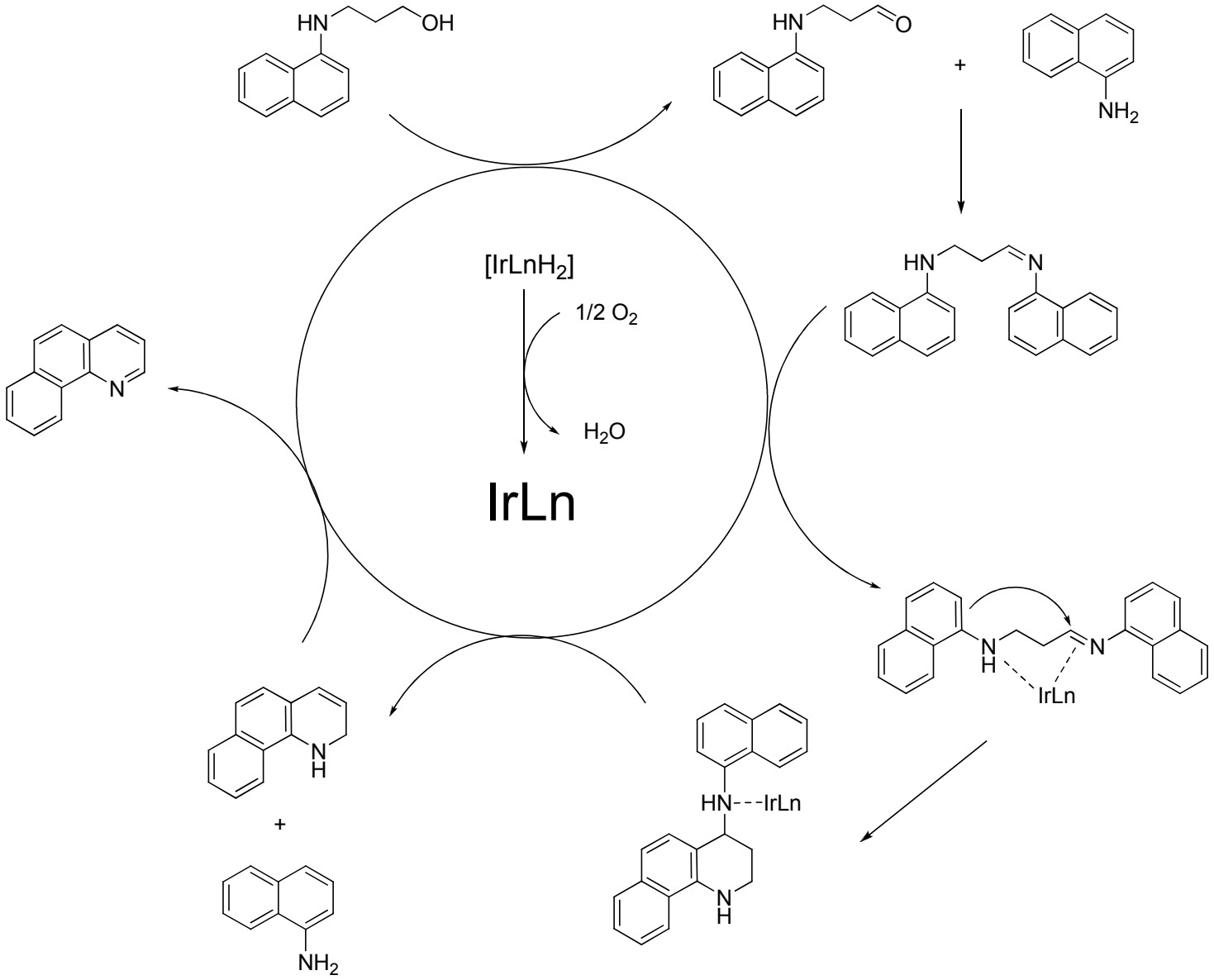
1 mol + 1 mol → 3% + 3% + 58%



76% + 83%

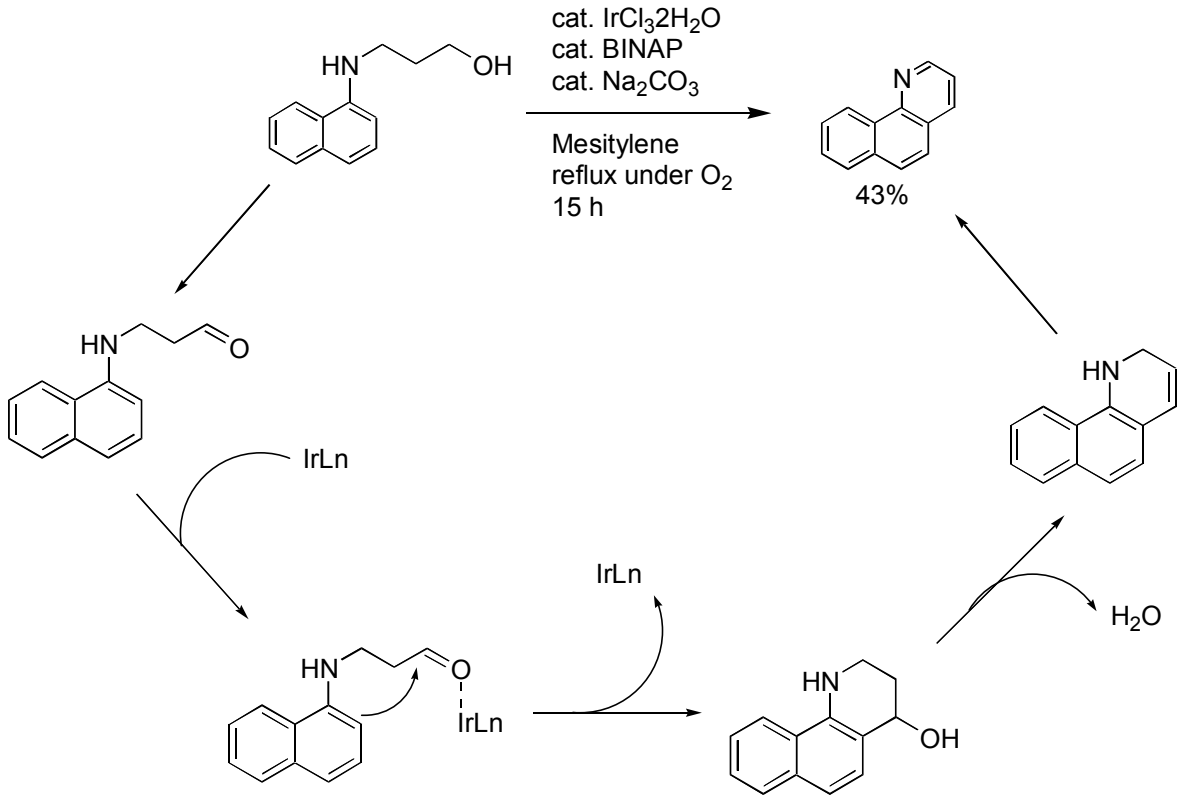
Proposed Mechanism

In the presence of excess amine



Another Plausible Mechanism

In the absence of excess amine



Conclusions

- $IrCl_3$ / BINAP system provides benzoquinolines and benzoindoles in good yield.
- Oxygen play an important role to improve the yield of Ir-cat. *N*-Heterocyclization.