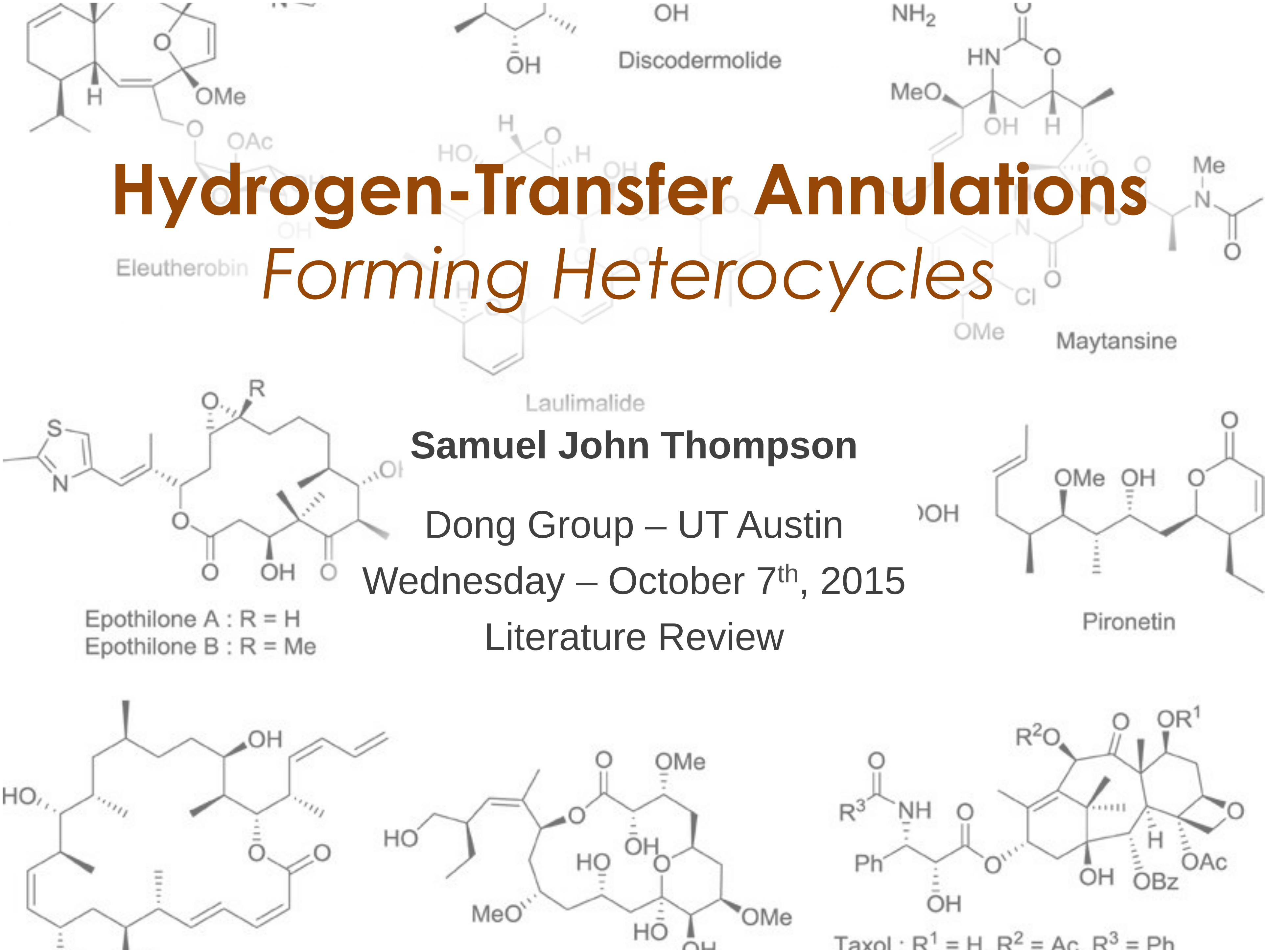

Hydrogen-Transfer Annulations

Forming Heterocycles

Samuel John Thompson

Dong Group – UT Austin

Wednesday – October 7th, 2015

Literature Review

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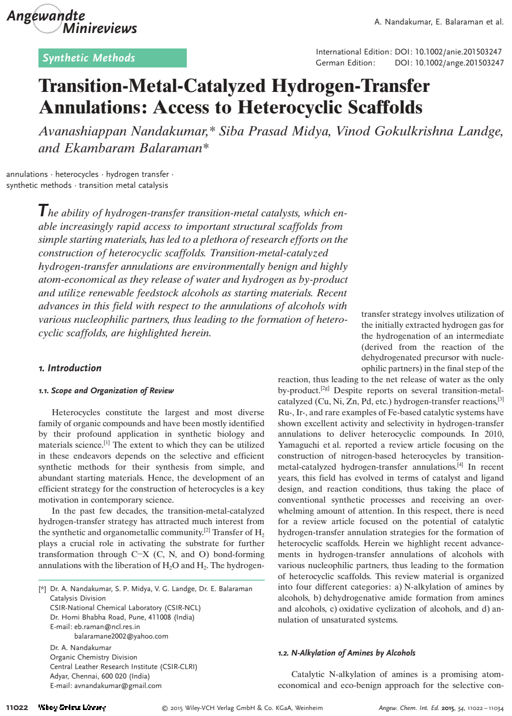

Synthetic Methods

International Edition: DOI: 10.1002/anie.201503247
German Edition: DOI: 10.1002/ange.201503247

Transition-Metal-Catalyzed Hydrogen-Transfer Annulations: Access to Heterocyclic Scaffolds

Avanashiappan Nandakumar, Siba Prasad Midya, Vinod Gokulkrishna Landge, and Ekambaram Balaraman**

annulations · heterocycles · hydrogen transfer · synthetic methods · transition metal catalysis

The ability of hydrogen-transfer transition-metal catalysts, which enable increasingly rapid access to important structural scaffolds from simple starting materials, has led to a plethora of research efforts on the construction of heterocyclic scaffolds. Transition-metal-catalyzed hydrogen-transfer annulations are environmentally benign and highly atom-economical as they release of water and hydrogen as by-product and utilize renewable feedstock alcohols as starting materials. Recent advances in this field with respect to the annulations of alcohols with various nucleophilic partners, thus leading to the formation of heterocyclic scaffolds, are highlighted herein.

1. Introduction

1.1. Scope and Organization of Review

Heterocycles constitute the largest and most diverse family of organic compounds and have been mostly identified by their profound application in synthetic biology and materials science.[1] The extent to which they can be utilized in these endeavors depends on the selective and efficient synthetic methods for their synthesis from simple, and abundant starting materials. Hence, the development of an efficient strategy for the construction of heterocycles is a key motivation in contemporary science.

In the past few decades, the transition-metal-catalyzed hydrogen-transfer strategy has attracted much interest from the synthetic and organometallic community.[2] Transfer of H_2 plays a crucial role in activating the substrate for further transformation through C−X (C, N, and O) bond-forming annulations with the liberation of H_2O and H_2. The hydrogen-transfer strategy involves utilization of the initially extracted hydrogen gas for the hydrogenation of an intermediate (derived from the reaction of the dehydrogenated precursor with nucleophilic partners) in the final step of the reaction, thus leading to the net release of water as the only by-product.[2g] Despite reports on several transition-metal-catalyzed (Cu, Ni, Zn, Pd, etc.) hydrogen-transfer reactions,[3] Ru-, Ir-, and rare examples of Fe-based catalytic systems have shown excellent activity and selectivity in hydrogen-transfer annulations to deliver heterocyclic compounds. In 2010, Yamaguchi et al. reported a review article focusing on the construction of nitrogen-based heterocycles by transition-metal-catalyzed hydrogen-transfer annulations.[4] In recent years, this field has evolved in terms of catalyst and ligand design, and reaction conditions, thus taking the place of conventional synthetic processes and receiving an overwhelming amount of attention. In this respect, there is need for a review article focused on the potential of catalytic hydrogen-transfer annulation strategies for the formation of heterocyclic scaffolds. Herein we highlight recent advancements in hydrogen-transfer annulations of alcohols with various nucleophilic partners, thus leading to the formation of heterocyclic scaffolds. This review material is organized into four different categories: a) N-alkylation of amines by alcohols, b) dehydrogenative amide formation from amines and alcohols, c) oxidative cyclization of alcohols, and d) annulation of unsaturated systems.

1.2. N-Alkylation of Amines by Alcohols

Catalytic N-alkylation of amines is a promising atom-economical and eco-benign approach for the selective con-

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Cp*Ir Complex-Catalyzed Hydrogen Transfer Reactions Directed toward Environmentally Benign Organic Synthesis

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Received 1 October 2004

Abstract: Catalytic activity of Cp*Ir complexes toward hydrogen transfer reactions are discussed. Three different types of reactions have been developed. The first is Oppenauer-type oxidation of alcohols. This reaction proceeds under quite mild conditions (room temperature in acetone) catalyzed by $[Cp^*IrCl_2]_2/K_2CO_3$, and both primary and secondary alcohols can be used as substrates. Introduction of a N-heterocyclic carbene ligand to the catalyst considerably enhances the catalytic activity, and a very high turnover number of 950 has been obtained in the oxidation of 1-phenylethanol. The second is the N-alkylation of amines with alcohols. A new effective catalytic system consisting of $[Cp^*IrCl_2]_2/K_2CO_3$ for the N-alkylation of primary amines with alcohols has been developed. Synthesis of indoles and 1,2,3,4-tetrahydroquinolines via intramolecular N-alkylation of amino alcohols and synthesis of nitrogen heterocycles via intermolecular N-alkylation of primary amines with diols catalyzed by a Cp*Ir complex have been also achieved. The third is the regio- and chemoselective transfer hydrogenation of quinolines. An efficient method for the transfer hydrogenation of quinolines catalyzed by $[Cp^*IrCl_2]_2/HClO_4$ using 2-propanol as a hydrogen source has been realized. A variety of 1,2,3,4-tetrahydroquinoline derivatives can be synthesized by this method. These results show that Cp*Ir complexes can be useful catalysts for hydrogen transfer reactions from the viewpoint of developing environmentally benign organic synthesis.

Key words: iridium, catalysis, hydrogen transfer, alcohols, amines

1 Introduction

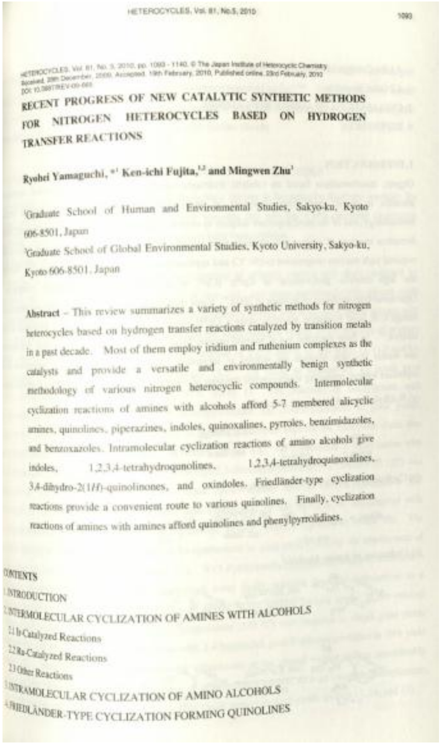
In the field of homogeneous catalytic organic synthesis, relatively little attention have been paid to the utilization of iridium as catalyst for a long time, while its family member, rhodium and cobalt, have seen extensive use as catalysts including industrial processes.1 This difference would be probably due to the scarcity of iridium as well as the preconceived idea that organoiridium complexes are too stable to be used as catalysts for organic synthesis. The stability of organoiridium complexes was advantageous for the studies on stoichiometric reactions in detail; thus the oxidative addition reaction, which is one of the most fundamental and important process in organometallic chemistry, has been studied using Vaska's complex $IrCl(CO)(PPh_3)_2$.2

The catalytic chemistry of iridium started with the discovery of a highly efficient catalyst, $[Ir(cod)(PCy_3)(py)]PF_6$, for hydrogenation of olefin by Crabtree et al. in 1977.3 Thereafter, a number of iridium-catalyzed hydrogenation systems including enantioselective reactions have been disclosed.4 In recent years, iridium complexes were found to be effective as catalysts for hydrosilylation,5 carbon-carbon6,7 and carbon-heteroatom8,9 bond formation, hydrogen transfer reaction,10 functionalization of C-H bonds,11–13 and the catalytic chemistry of iridium has been attracting quite a lot of interest. Most of these interesting reactions were achieved using low-valent iridium complexes coordinated with olefin, CO, halogen, or phosphorous ligands (e.g. $[IrCl(cod)]_2$) as a catalyst precursor.

On the other hand, a trivalent iridium complex bearing an η^5-pentamethylcyclopentadienyl (Cp*) ligand, $[Cp^*IrCl_2]_2$ (Figure 1), is another well-known stable complex of iridium. The first synthesis of $[Cp^*IrCl_2]_2$ was reported by Maitlis et al. in 1969.14 At first, $[Cp^*IrCl_2]_2$ was prepared by the reaction of $IrCl_3 \cdot xH_2O$ with hexamethyl Dewar benzene,14a,c however, a convenient preparation by the reaction of $IrCl_3 \cdot xH_2O$ with pentamethylcyclopentadiene was reported later.15 Now we can purchase it from the reagent market. The chemistry of Cp*Ir complex has been mainly focused on the stoichiometric reactions, and their ability toward C-H bond activation of hydrocarbon molecules was revealed by Bergman et al. and others.16,17 However, catalytic utilizations of Cp*Ir complexes have been relatively unexplored. Only a few examples of Cp*Ir complex-catalyzed reactions for organic synthesis other than simple hydrogenation reactions had been reported when we started our investigation in 1999.11a,18

Figure 1

SYNLETT 2005, No. 4, pp 0560–0571
Advanced online publication: 22.02.2005
DOI: 10.1055/s-2005-862381; Art ID: A36504ST



HETEROCYCLES, Vol. 81, No. 5, 2010, pp. 1093 - 1140. © The Japan Institute of Heterocyclic Chemistry
Received, 28th December, 2009, Accepted, 19th February, 2010, Published online, 23rd February, 2010
DOI: 10.3987/REV-09-665

RECENT PROGRESS OF NEW CATALYTIC SYNTHETIC METHODS FOR NITROGEN HETEROCYCLES BASED ON HYDROGEN TRANSFER REACTIONS

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Abstract – This review summarizes a variety of synthetic methods for nitrogen heterocycles based on hydrogen transfer reactions catalyzed by transition metals in a past decade. Most of them employ iridium and ruthenium complexes as the catalysts and provide a versatile and environmentally benign synthetic methodology of various nitrogen heterocyclic compounds. Intermolecular cyclization reactions of amines with alcohols afford 5-7 membered alicyclic amines, quinolines, piperazines, indoles, quinoxalines, pyrroles, benzimidazoles, and benzoxazoles. Intramolecular cyclization reactions of amino alcohols give indoles, 1,2,3,4-tetrahydroqunolines, 1,2,3,4-tetrahydroquinoxalines, 3,4-dihydro-2(1*H*)-quinolinones, and oxindoles. Friedländer-type cyclization reactions provide a convenient route to various quinolines. Finally, cyclization reactions of amines with amines afford quinolines and phenylpyrrolidines.

CONTENTS

Nandakumar & Balaraman *et al.*
Angew. Chem. Int. Ed. **2015**, *54*, 11022.

Fujita & Yamaguchi.
Synlett. **2005**, 560.

Fujita, Yamaguchi, & Zhu.
Heterocycles **2010**, 1093.

Two Major Catalyst Metals

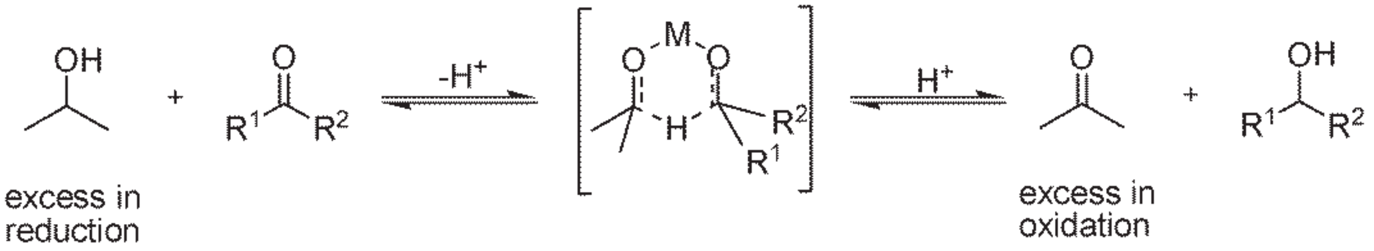
Other metals are used, but are not as widely explored

Cu, Ni, Zn, Pd, **Fe**, Rh, & more

Hydrogen-Transfer Reaction

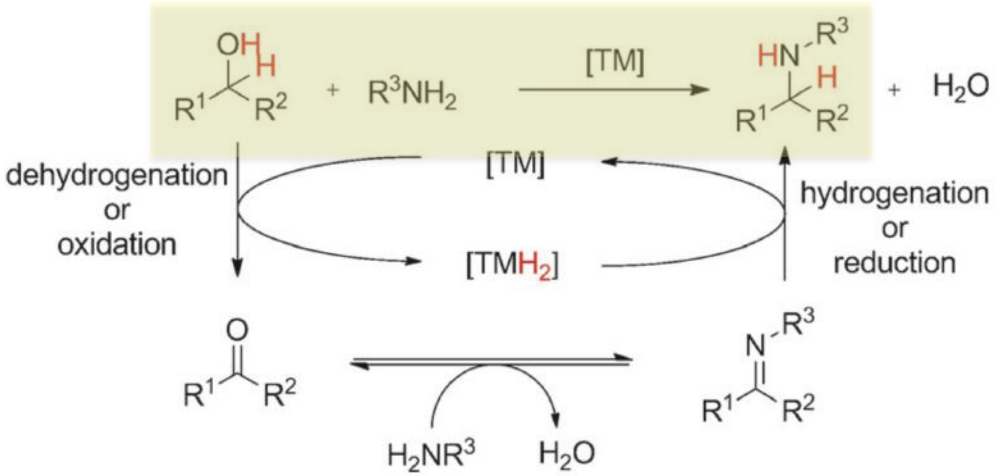
- Transfer of H_2 between a substrate (H-donor) to an H-acceptor:
  - Oxidation of alcohols or amines
  - Reduction of ketones or imines

- Inspiration comes from Oppenhauer Oxidation / Meerwein-Ponndorf-Verley Reduction (hydride transfer)



  - Used Industrially to make morphine, codeine, progesterone, etc
  - Ran on ton scales for production of chemicals

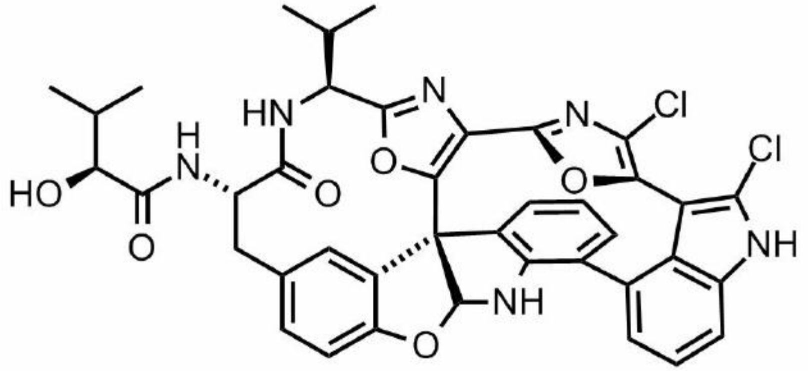
H-Transfer with Catalysis



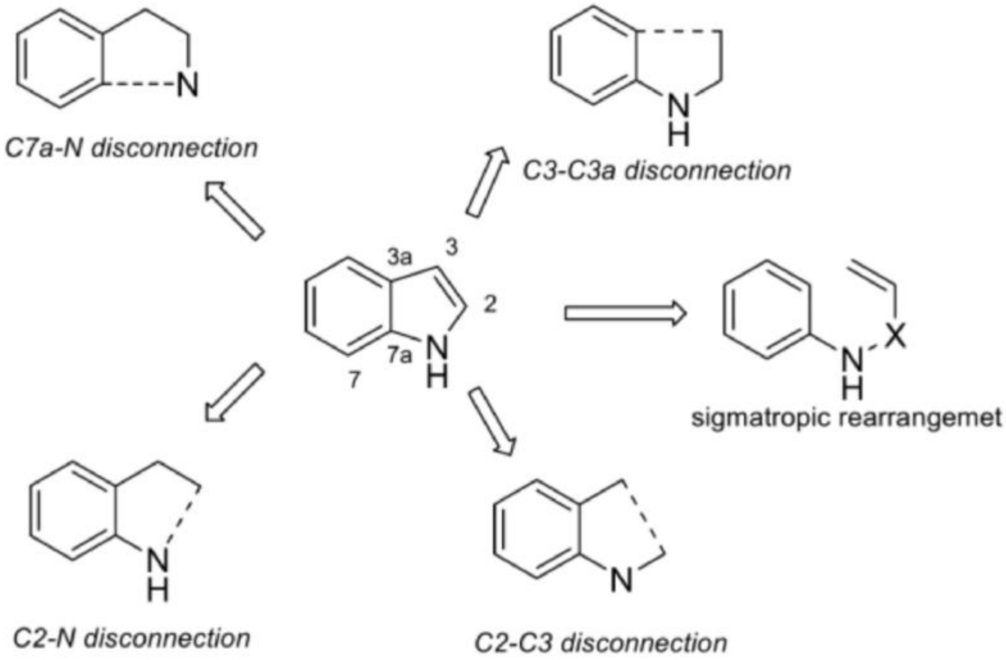
Traditional synthetic strategies

- Amine alkylation (halides)
- Reductive amination
- S_N2 displacement

Heterocylic Bond Disconnection



Diazonamide A



HETEROCYCLES IN ORGANIC CHEMISTRY

A HETEROCYCLE IN ORGANIC CHEMISTRY IS A RING OF CONNECTED ATOMS, WHERE ONE OR MORE OF THE ATOMS IN THE RING ARE ELEMENTS DIFFERENT FROM CARBON. HETEROCYCLES WITH OXYGEN, NITROGEN, AND SULFUR ARE THE MOST PREVALENT; SELENIUM, BORON, SILICON, ARSENIC & PHOSPHORUS CAN ALSO BE INCORPORATED.

● OXYGEN-BASED HETEROCYCLES ● NITROGEN-BASED HETEROCYCLES ● SULFUR-BASED HETEROCYCLES ● MULTIPLE HETEROATOM HETEROCYCLES

ETHYLENE OXIDE
Oxirane
C_2H_4O

TETRAHYDROFURAN
Oxolane
C_4H_8O

FURAN
Oxole
C_4H_4O

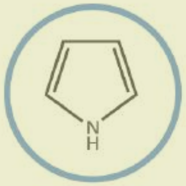
TETRAHYDROPYRAN
Oxane
$C_5H_{10}O$

4H-PYRAN
4H-Oxine
C_5H_6O

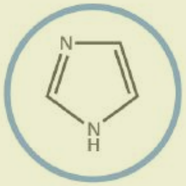
1,4-DIOXANE
p-Dioxane
$C_4H_8O_2$

ETHYLENE IMINE
Aziridine
C_2H_5N

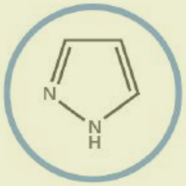
PYRROLIDINE
Azolidine
C_4H_9N



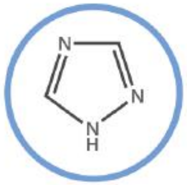
PYRROLE
Azole
C_4H_5N



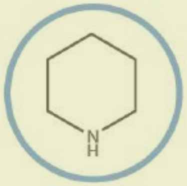
IMIDAZOLE
1,3-diazole
$C_3H_4N_2$



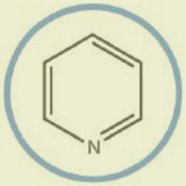
PYRAZOLE
1,2-diazole
$C_3H_4N_2$



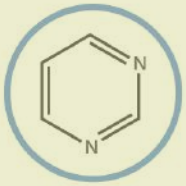
TRIAZOLE
1,2,4-triazole
$C_2H_3N_3$



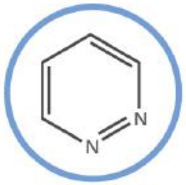
PIPERIDINE
Azinane
$C_5H_{11}N$



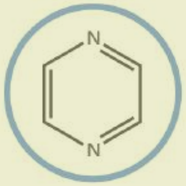
PYRIDINE
Azine
C_5H_5N



PYRIMIDINE
1,3-diazine
$C_4H_4N_2$



PYRIDAZINE
1,2-diazine
$C_4H_4N_2$

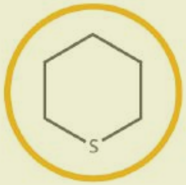


PYRAZINE
1,4-diazine
$C_4H_4N_2$

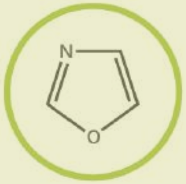
ETHYLENE SULFIDE
Thiirane
C_2H_4S

TETRAHYDROTHIOPHENE
Thiolane
C_4H_8S

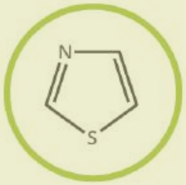
THIOPHENE
Thiole
C_4H_4S



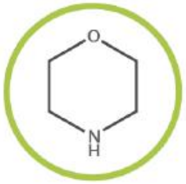
TETRAHYDROTHIOPYRAN
Thiane
$C_5H_{10}S$



OXAZOLE
1,3-oxazole
C_3H_3NO



THIAZOLE
1,3-thiazole
C_3H_3NS



MORPHOLINE
Tetrahydro-1,4-oxazine
C_4H_9NO

Key Players

- Ryohei Yamaguchi

  Kyoto University

- Robert Madsen

  University of Denmark

- David Milstein

Weizmann Institute of Science

- Krische

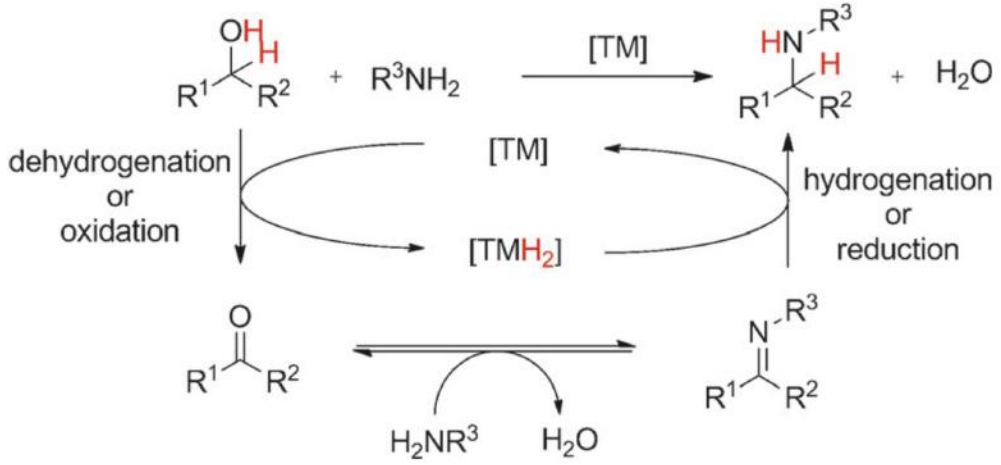
Overview

- Synthesis of *N*-Heterocycles
  1. N-alkylation of amines by alcohols
  2. Dehydrogenative amide formation from amines and alcohols
  3. Oxidative cyclization of alcohols
  4. Annulation of unsaturated systems (alkene/alkyne)

- Synthesis of *O*- / *S*-Heterocycles

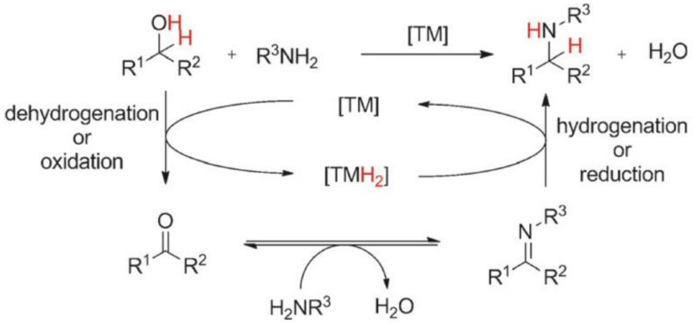
N-Alkylation of Amines

- Usually performed with alkyl halides
    - Difficult to control and predict reactivity
- Via amide reduction a
    - Toxic and expensive wastes

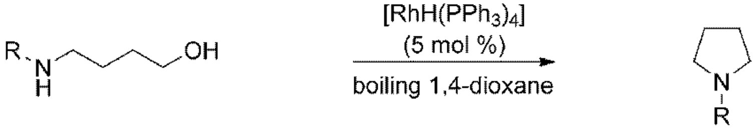


N-Alkylation of Amines

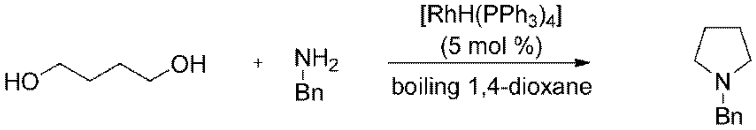
- Usually performed with alkyl halides
    - Difficult to control and predict reactivity
- Via amide reduction a
    - Toxic and expensive wastes



- First example of N-alkylation cyclization by Grigg in 1981



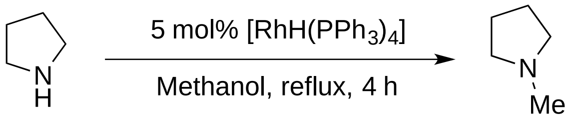
1a, R = *n*Bu (56 %)
1b, R = Bn (82 %)



10:1 ratio of diol/amine

1b (31 %)

Side: Methanol as alkylation reagent

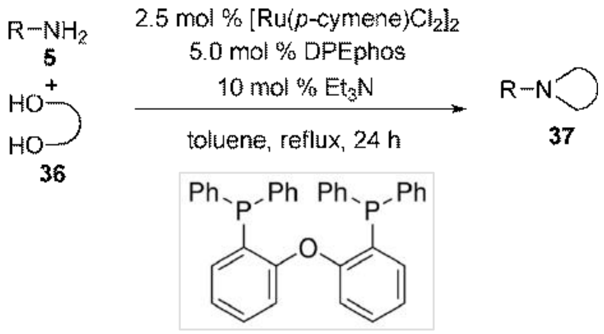


97% yield

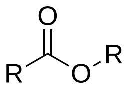
Grigg. *J. Chem. Soc. Chem. Commun.* 1981, 611.

Modern *N*-Alkylation through H-Transfer

- Jump ahead to 2009 – Williams et al. published very mild conditions

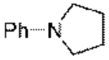
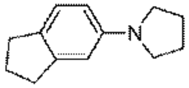
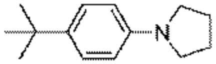
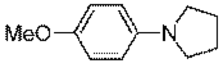
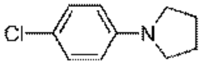
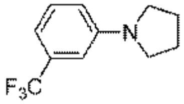
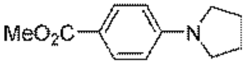
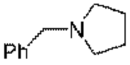
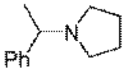
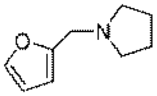
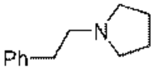
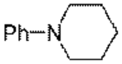
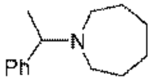


- Bidentate ligand suppresses ester formation



- Cyclic amine ring sizes = 5, 6, and 7

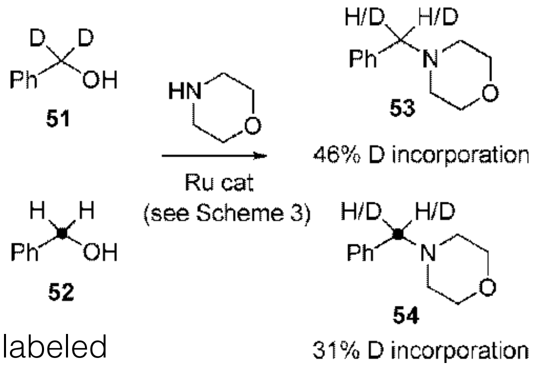
- Aryl and aliphatic amines

entry	product	conversion (%)^{a,b}
1		100 (78)
2		94 (74)
3		92 (85)
4		100 (70)
5		100 (87)
6		61 (60)
7		50 (33)
8		81 (72)
9		100 (82)
10		77 (63)
11		100 (69)
12		87 (72)
13		100 (65)

Watson *et al. JACS* 2009, *131*, 1766.

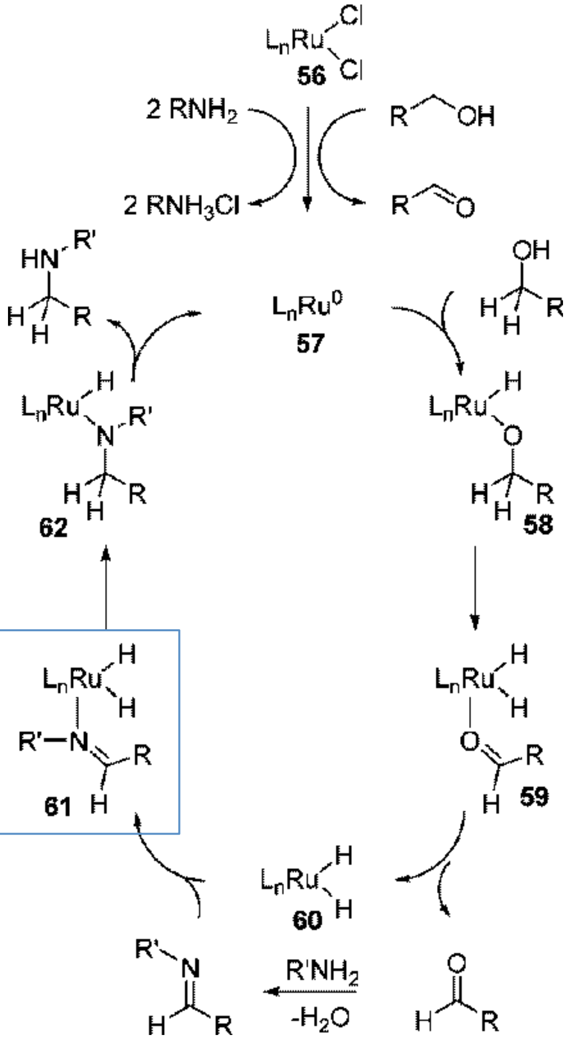
Modern *N*-Alkylation through H-Transfer

- Insight into mechanism
    - Does imine formation form at metal center?



C13 labeled

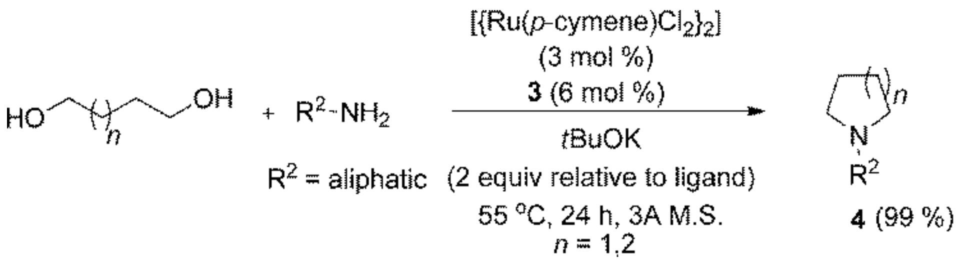
In our case,
This is η2 iminium complex
or via enamine



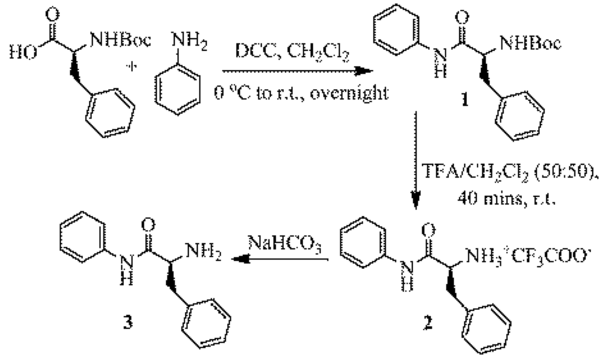
Watson *et al.* *JACS* **2009**, *131*, 1766.

Modern *N*-Alkylation through H-Transfer

- Enyong expaned in 2014 this reaction to lower temperatures

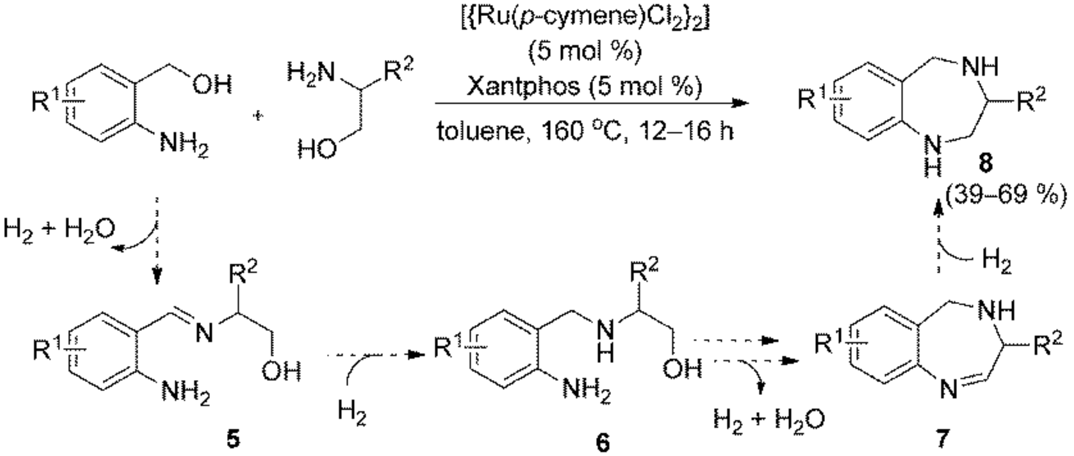


Enyong *et al*. *JOC* **2014**, *79*, 7553.



3 – decomposes above -20 °C

- Used for benzodiazepine core (show how normally made?)
  - Isolated intermediates 6 and 7

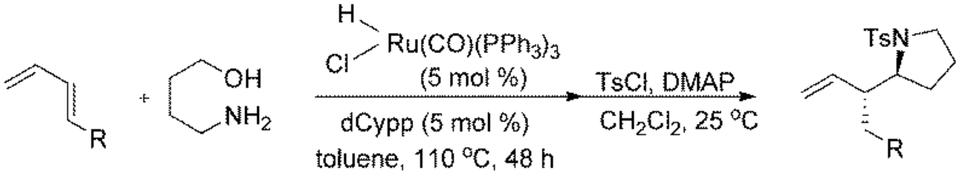


Cheap starting materials

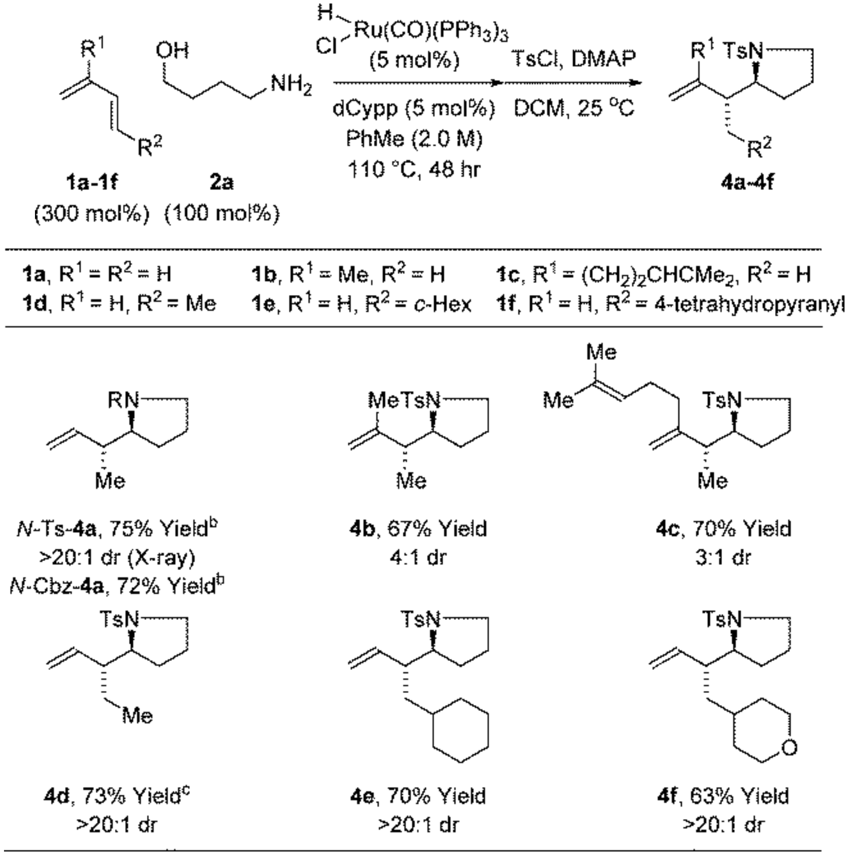
Taddei *et al*. *Eur. J. Org*. **2015**, *2015*, 1068.

Hydroaminoalkylation

- Krische – hydroaminoalkylation
  - Branch selective
  - Anti-diastereoselectivity



14 (63–75 %)



1a-1f (300 mol%) **2a** (100 mol%) **4a-4f**

1a, $R^1 = R^2 = H$ **1b**, $R^1 = Me$, $R^2 = H$ **1c**, $R^1 = (CH_2)_2CHCMe_2$, $R^2 = H$
1d, $R^1 = H$, $R^2 = Me$ **1e**, $R^1 = H$, $R^2 =$ *c*-Hex **1f**, $R^1 = H$, $R^2 =$ 4-tetrahydropyranyl

N-Ts-**4a**, 75% Yield[b]
>20:1 dr (X-ray)
N-Cbz-**4a**, 72% Yield[b]

4b, 67% Yield
4:1 dr

4c, 70% Yield
3:1 dr

4d, 73% Yield[c]
>20:1 dr

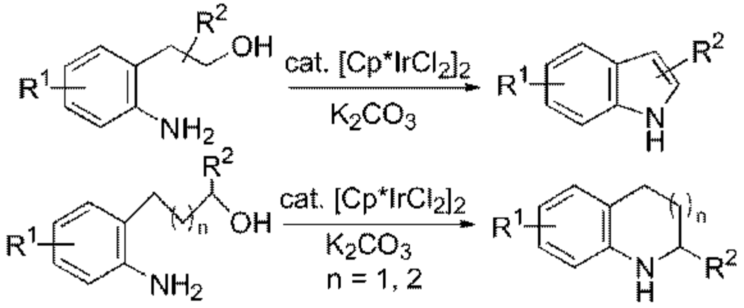
4e, 70% Yield
>20:1 dr

4f, 63% Yield
>20:1 dr

Krische *et al. JACS* 2015, *137*, 1798.

Modern *N*-Alkylation through H-Transfer

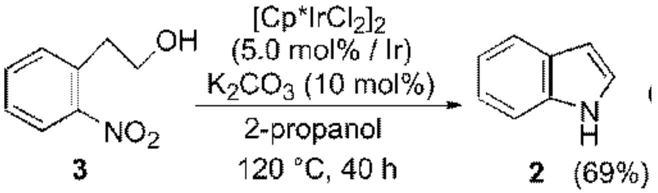
- Ir-catalyzed formation of indoles, tetrahydroquinolines, and benzapines



68-99% yield

58-96% yield

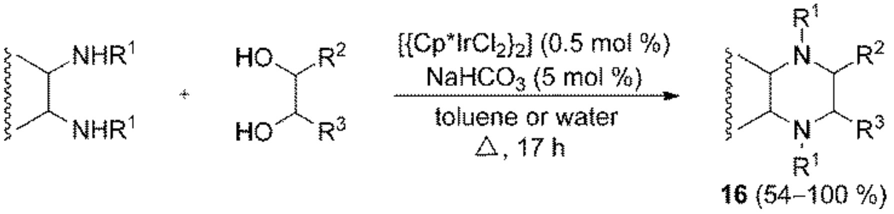
- They found that this catalyst with 2-propanol could be used to reduce nitrobenzene to analine (their own unpublished results)



Fujita & Yamaguchi. *Org. Lett.* 2002, *4*, 2691.

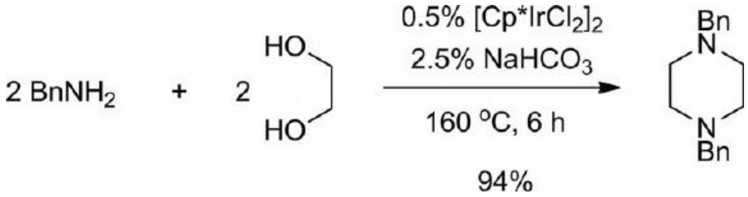
Modern *N*-Alkylation through H-Transfer

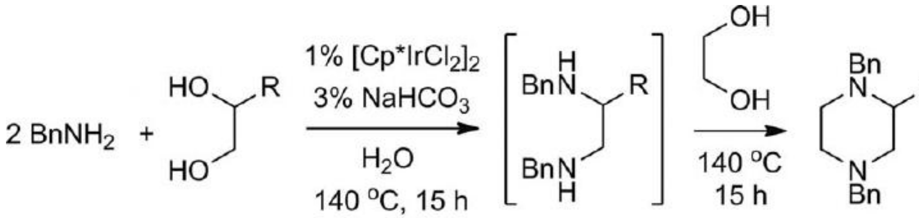
- Madsen used Cp*Ir complex to synthesize piperazines



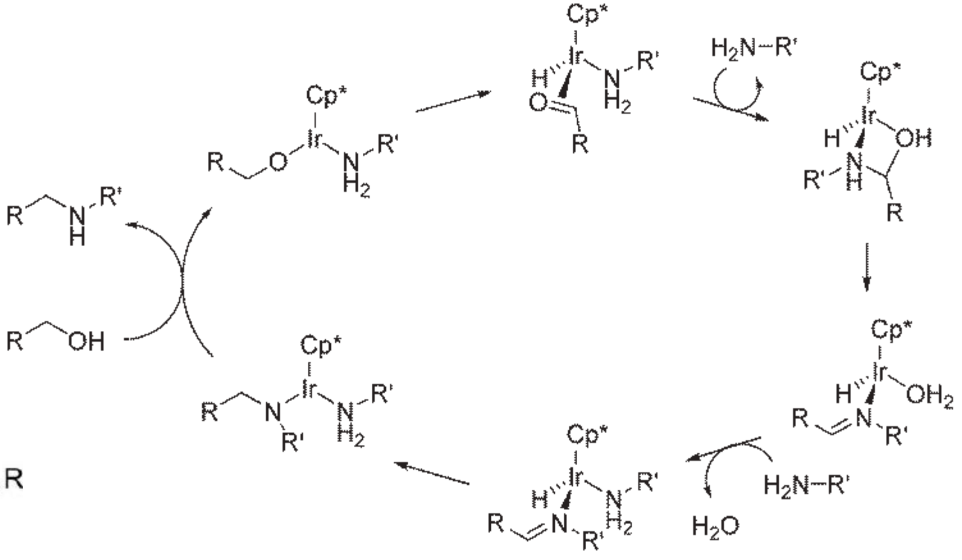
16 (54–100 %)

- Additionally, through 1,2-diols and a primary amine
  - 4 new C-N bonds, neat conditions





R = Me: 63%
R = Ph: 90%

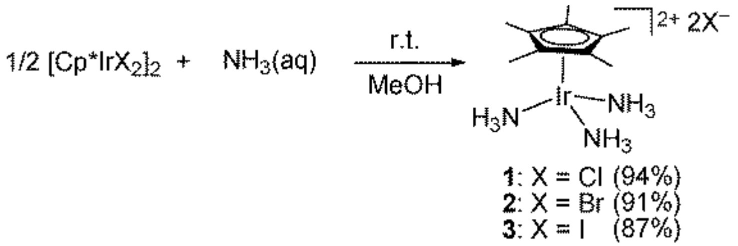


DFT Study
Aldehyde does not leave catalyst

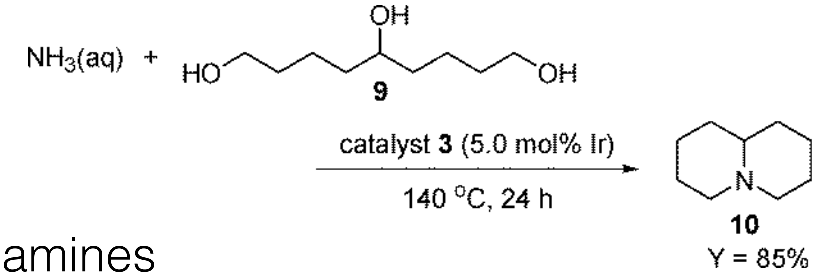
Madsen. *Eur. J. Org. Chem.* 2012, *2012*, 6752.

Creating better Ir catalysts

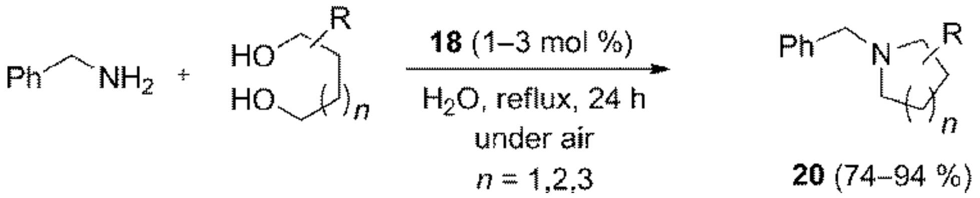
- Synthetic Challenge: use aqueous ammonia as N-source, however [Ru] and [Ir] catalysts have poor solubility in aqueous conditions



  - Sealed vessel
  - Works with stoichiometric NH_3 & scalable
  - Can be recycled

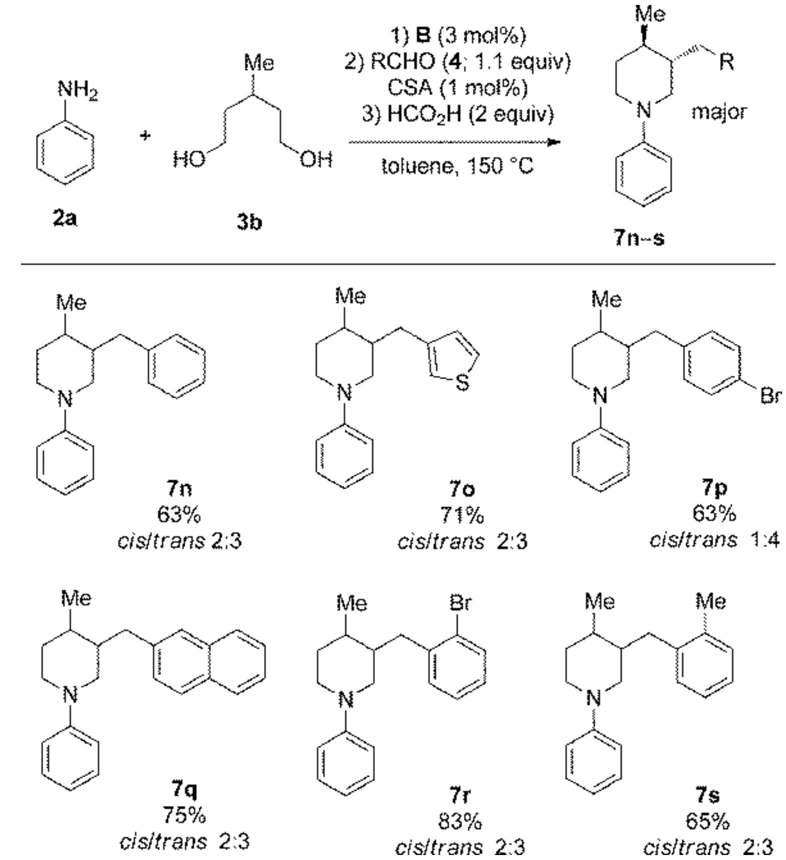


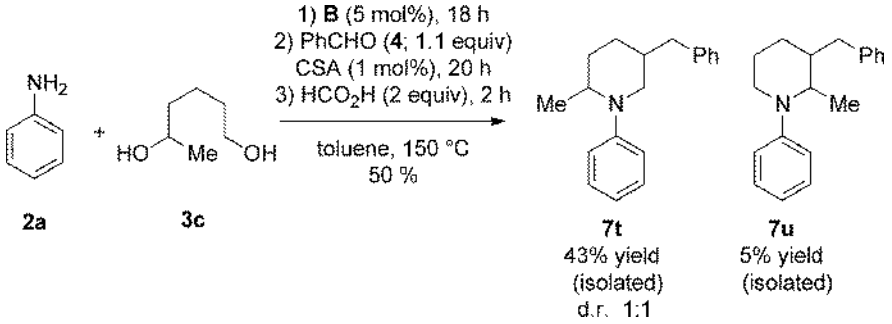
- Tolerated open air in later report for other amines

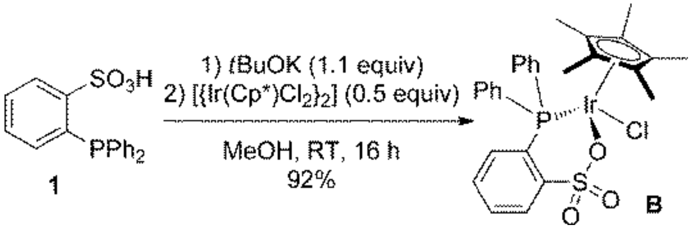


Fujita & Yamaguchi. *JACS* **2010**, *132*, 15108.
Adv. Synth. Catal. 2011, *353*, 1161.

Creating better Ir catalysts







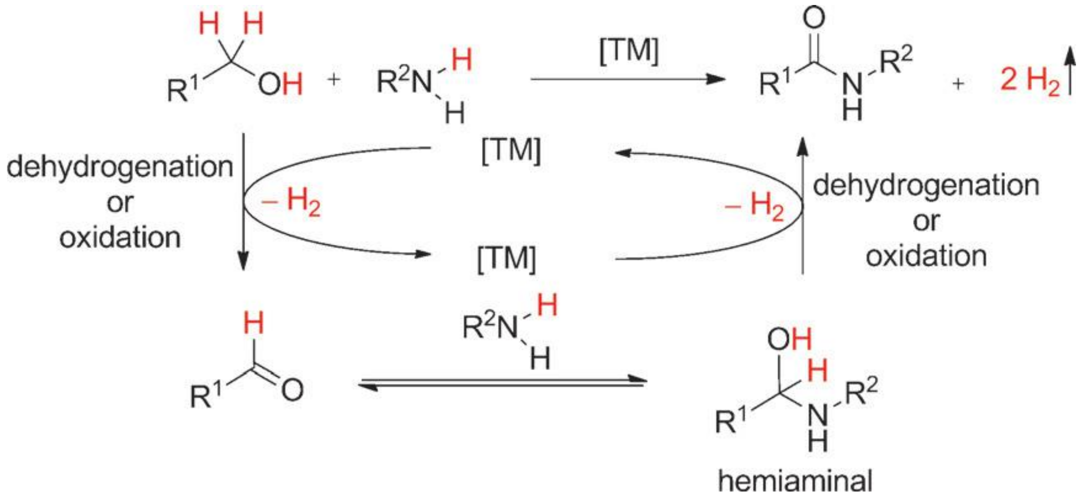
- P,O-ligand found to facilitate C3-alkylation of piperidines with Ir
  - Ru cat. Has no C3-alkylation
  - Ru(cymene) or Cp*Ir catalysts also failed
- Have much larger table with unsubstituted diols

Bruneau *et al. ACIE* 2012, *51*, 8876.

Dehydrogenative Amide Formation

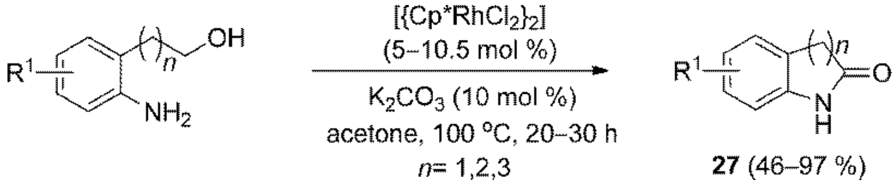
- Dehydrogenative amide formation from alcohols and amines
  - Applicable for Amide/peptide bonds
  - Usual formation occurs through activation of acid derivatives or acid/base rearrangement reactions

  - Development of acceptorless dehydrogenative amide formation with liberation of H_2 as byproduct → gas extrusion (capture) drives reaction



Dehydrogenative Amide Formation

- 2004 - Benzo-fused five, size, and seven membered lactams

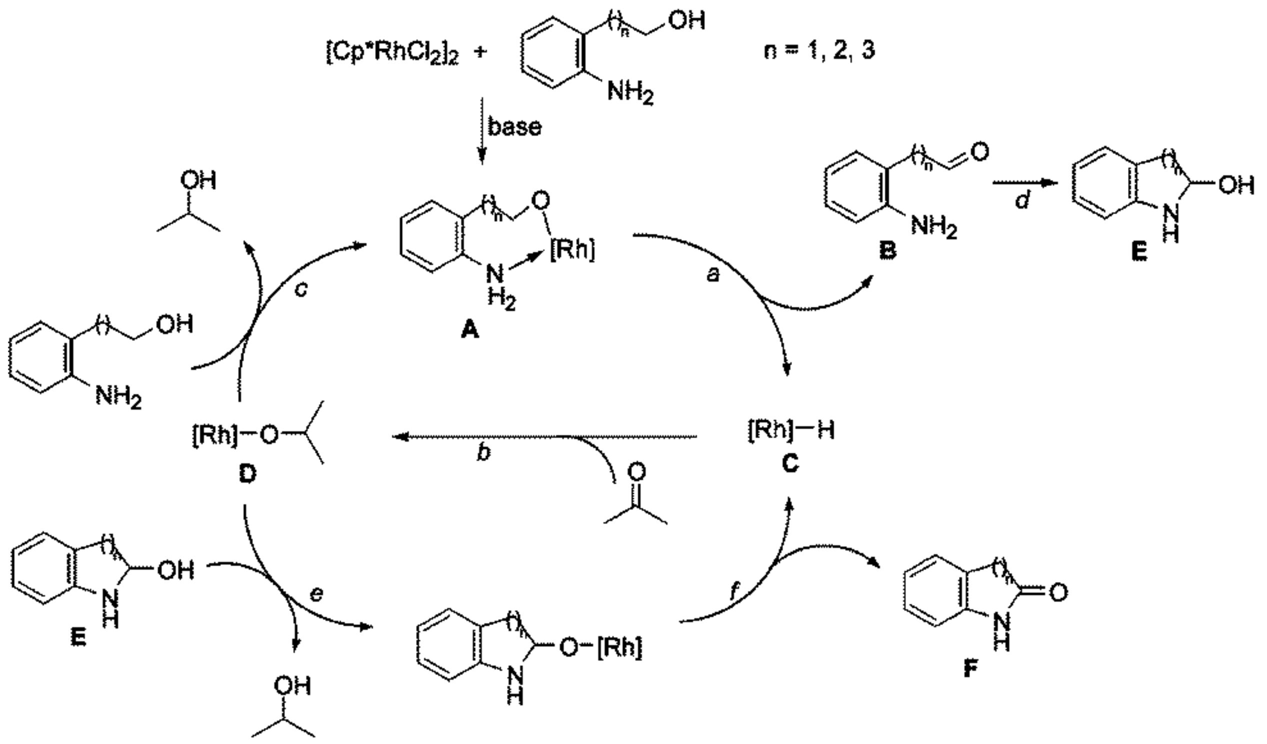


  - When using other solvents, major product is cyclized amines (not amide) – showing acetone is key for hydrogen accepting

Fujita & Yamaguchi. *Org. Lett.* 2004, *6,* 2785.

Dehydrogenative Amide Formation

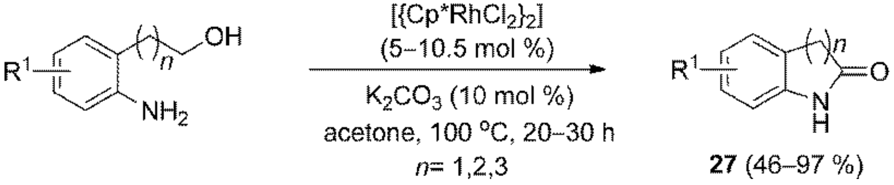
- Mechanism



Fujita & Yamaguchi. *Org. Lett.* 2004, *6,* 2785.

Dehydrogenative Amide Formation

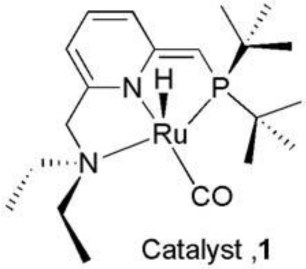
- 2004 - Benzo-fused five, size, and seven membered lactams



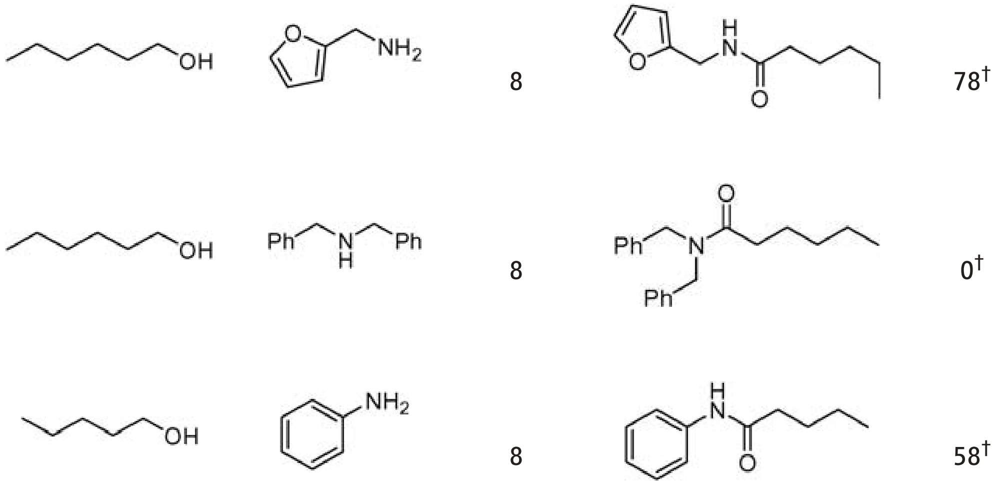
  - When using other solvents, major product is cyclized amines (not amide) – showing acetone is key for hydrogen accepting

Fujita & Yamaguchi. *Org. Lett.* 2004, *6,* 2785.

- 2007 – Milstein developed a general amidation strategy via a PNN pincer complex

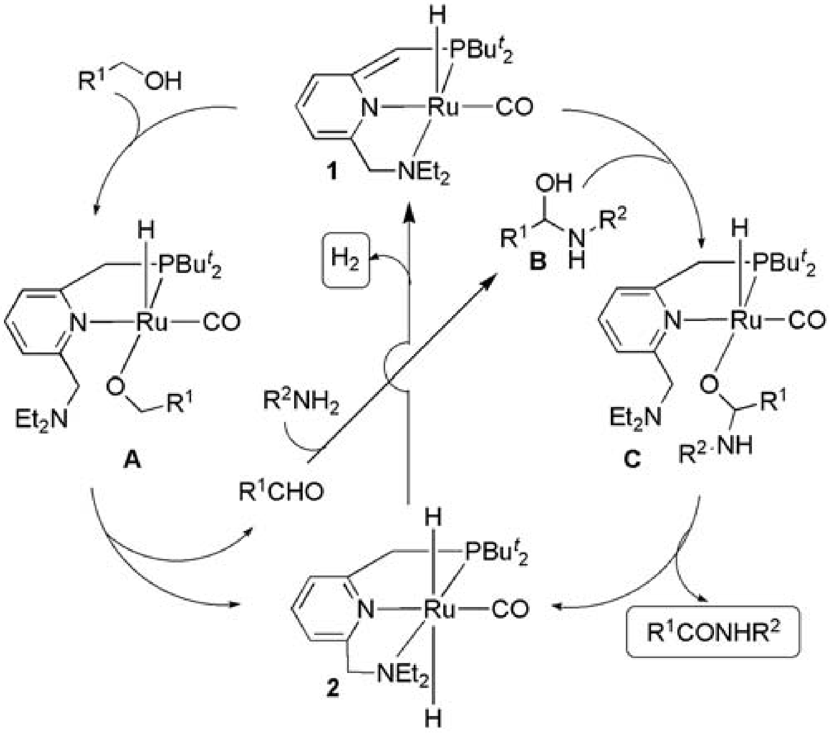


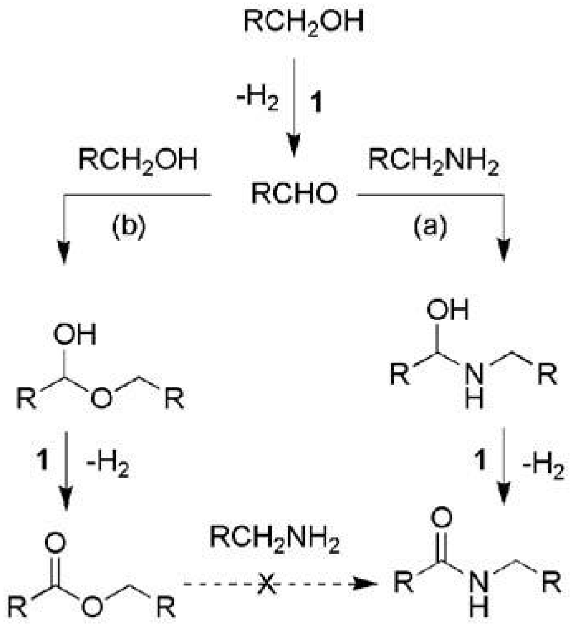
Catalyst ,**1**



Milstein *et al. Science* 2007, *317*, 790.

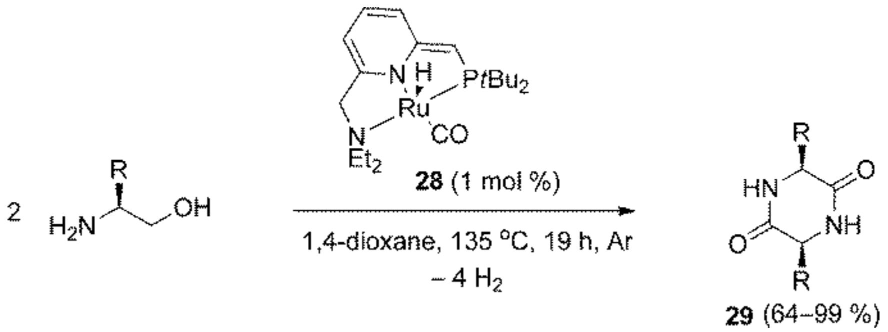
Dehydrogenative Amide Formation





Milstein *et al. Science* 2007*, 317,* 790.

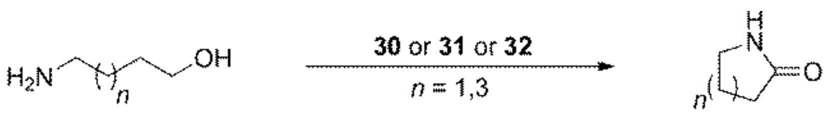
- Relevance for heterocycles, when β-amino alcohols with R ≠ H, Me → cyclic dipeptides



Milstein *et al. ACIE* 2011*, 50,* 12240.

Search of General Catalysts

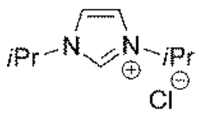
- Madsen - 2010
  - Wanted to find general stable catalysts for amide formation
  - Designed NHC-Ru complexes → all showed great reactivity



33

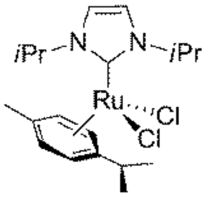
	n = 1	n = 3
30	65 %	49 %
31	68 %	53 %
32	60 %	48 %

[RuCl$_2$(cod)]



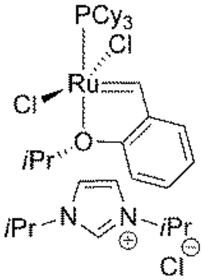
PCy$_3$ HBF$_4$, KO*t*Bu

30



PCy$_3$, KO*t*Bu

31

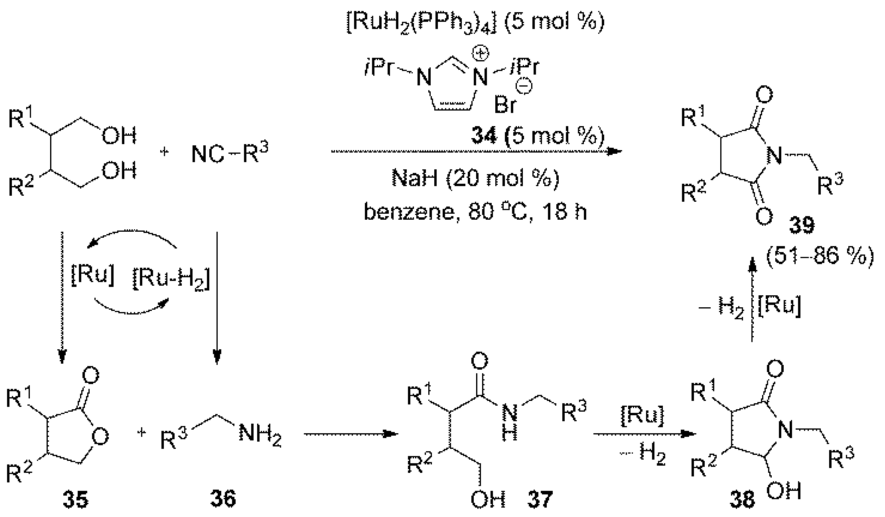


KO*t*Bu

32

Madsen *et al. Eur. J. Chem.* 2010, *16*, 6820.

- Hong – 2014 – Cyclic imide strategy

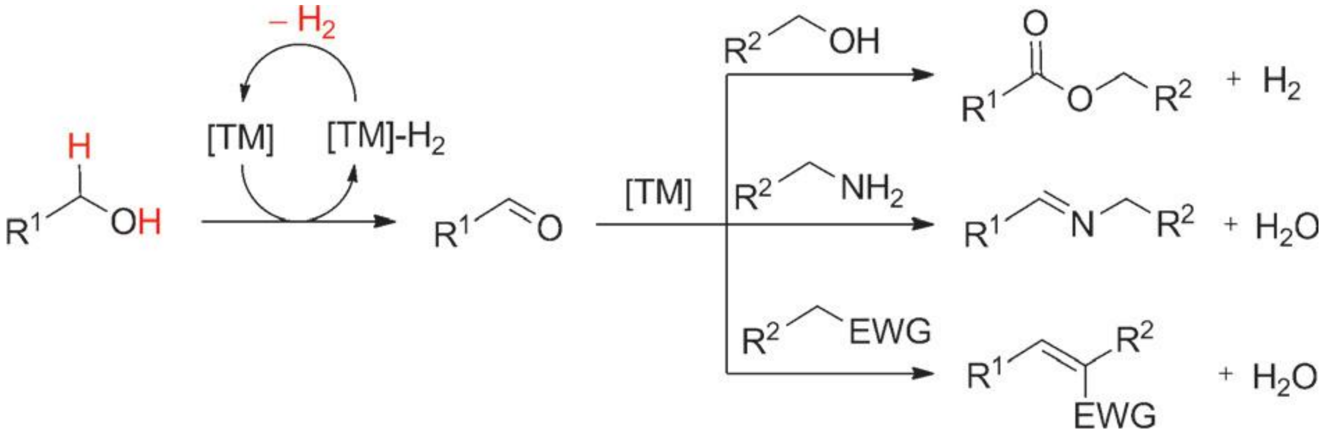


Nitrile acts as
N-source and H-acceptor

Hong *et al. Org. Lett.* 2014, *16*, 4404.

Oxidative Cyclization of Alcohols

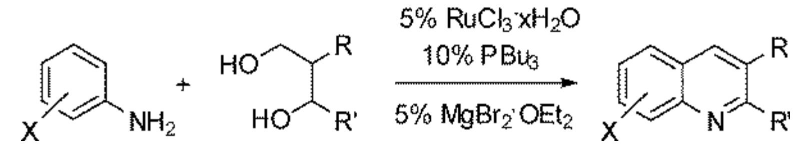
- Substrate does not accept hydrogen

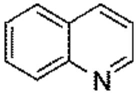
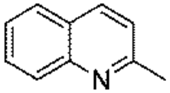
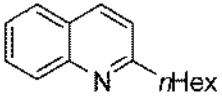
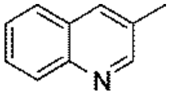
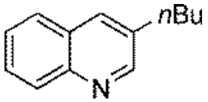
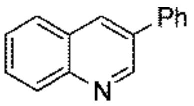
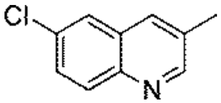


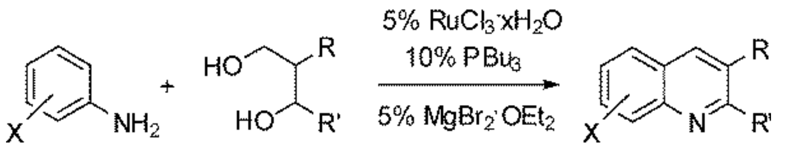
  - Great for quinoline, pyrrole, pyridine, etc…
  - Employing very general conditions, could be easy to synthesize new ligands using these procedures

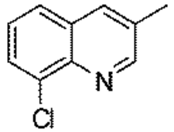
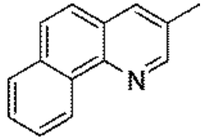
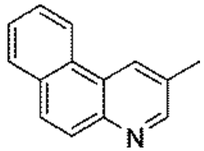
Annulation by Oxidative Cyclization

- Quinoline synthesis → One-pot procedure from 1,3 diols & analines
    - Screened Lewis Acids to help electrophilic cyclization



Entry	X	R	R′	Product	Yield[b]
1	H	H	H		20%
2	H	H	Me		32%[c]
3	H	H	*n*-Hex		30%[d]
4	H	Me	H		47%
5	H	*n*-Bu	H		48%
6	H	Ph	H		31%
7	*p*-Cl	Me	H		46%

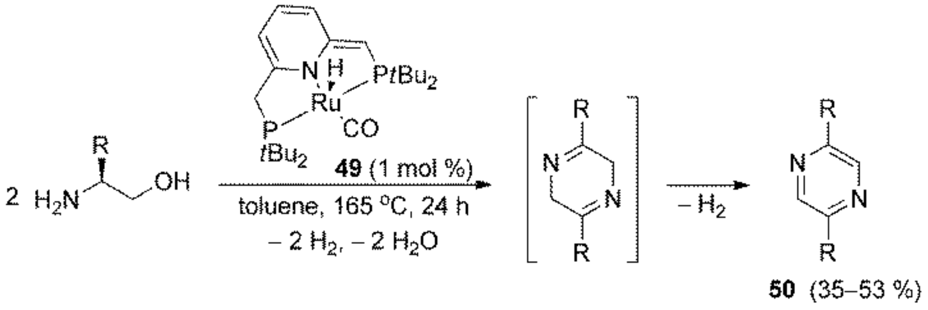


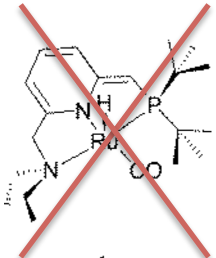
Entry	X	R	R′	Product	Yield[b]
16	*o*-Cl	Me	H		43%
17	—[h]	Me	H		54%
18	—[i]	Me	H		52%[j]

Madsen *et al. Org. Biomol. Chem.* 2011, *9*, 610.

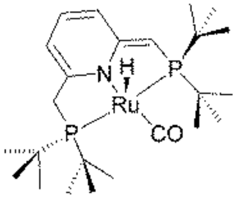
Pyrazine and Pyridine Synthesis

- Milstein pyrazine synthesis – using PNP ligands instead of PNN
  - Bulky PNP ligands release aldehyde which undergoes condensation with amine

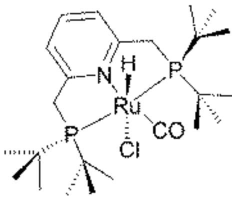




1



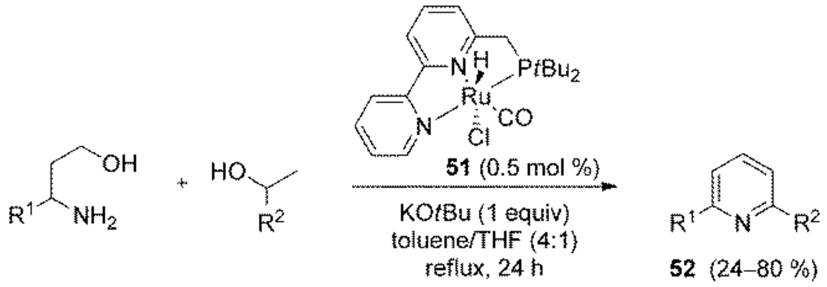
2



3

Milstein *et al. ACIE* 2011, *50,* 12240.

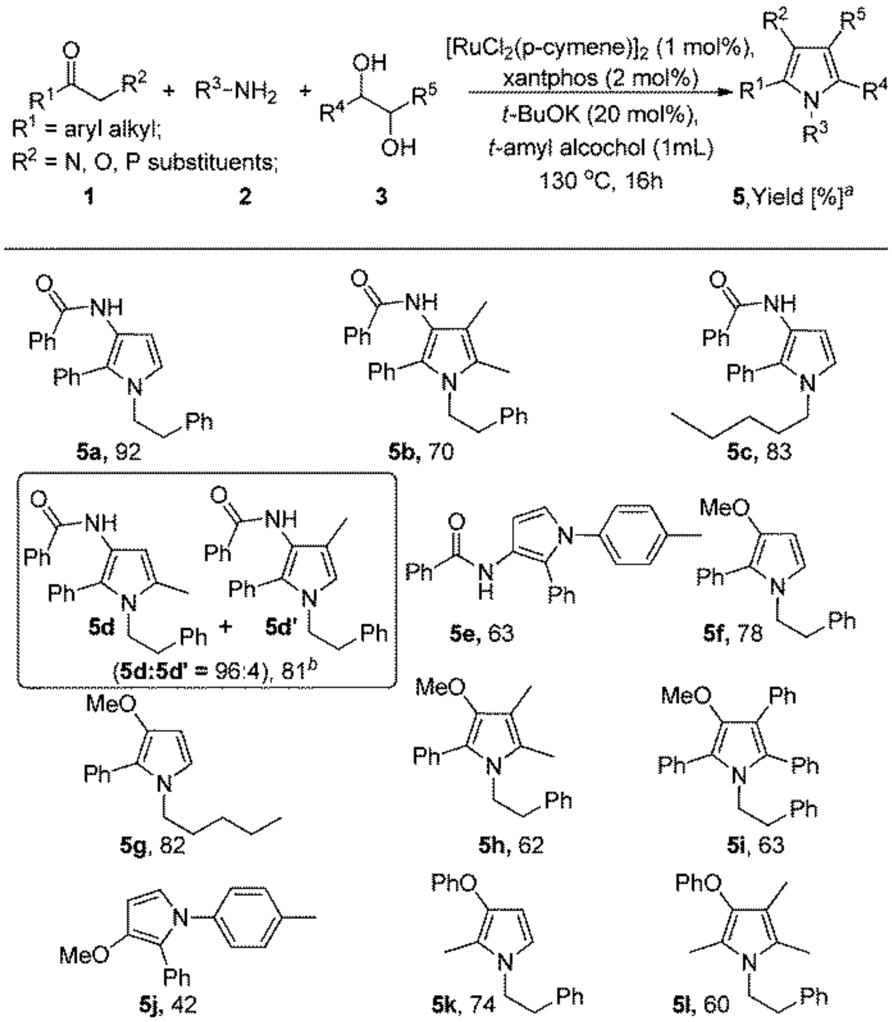
- Milstein pyridine synthesis
  - Cyclic and acyclic secondary alcohols could be used
  - C-N and C-C bond formation

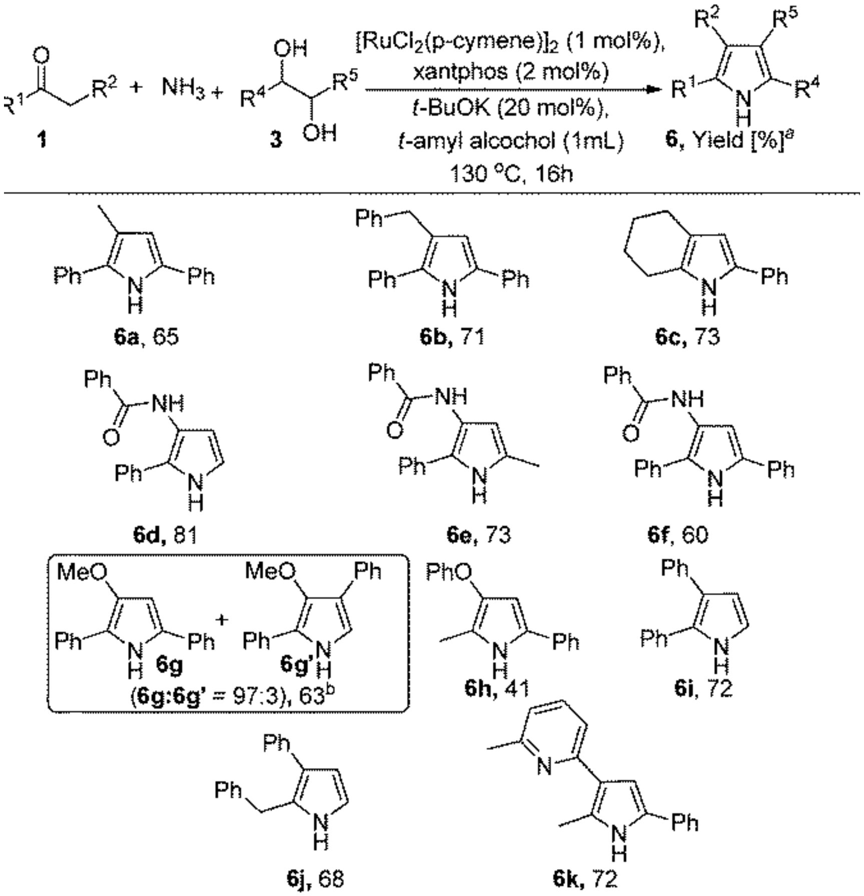


Milstein *et al. Chem. Commun.* 2013, *49,* 6632.

Pyrrole Synthesis

- Highly substituted pyrrole synthesis – 3-component annulation
  - Ketone / amine / vicinal diols

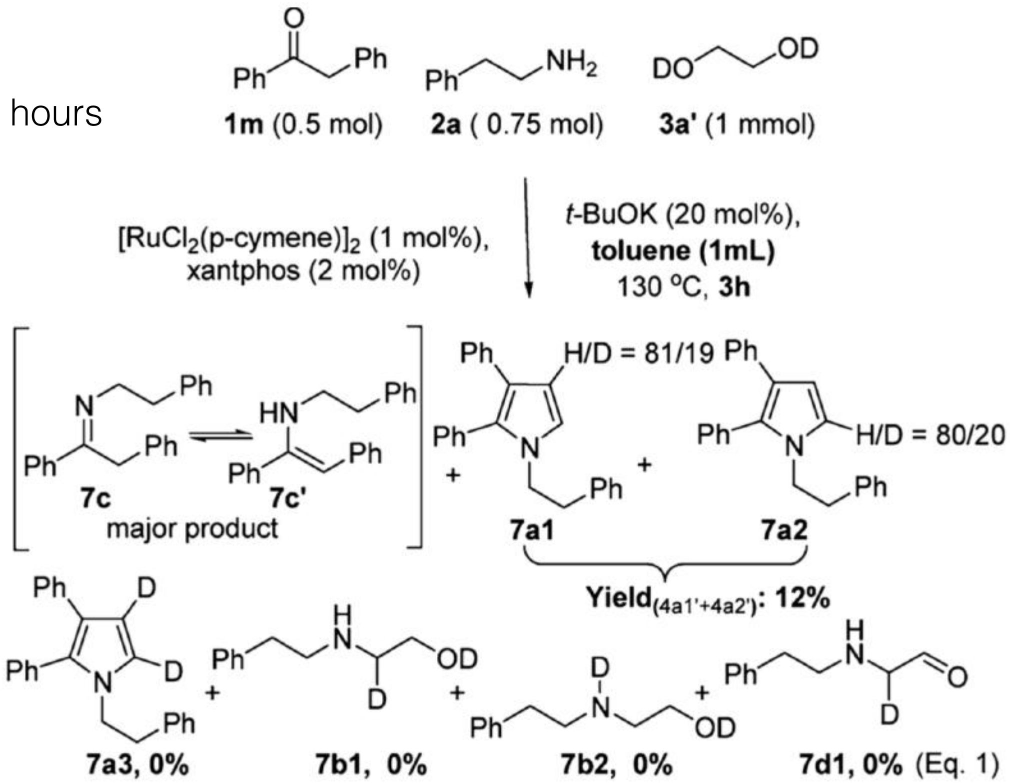


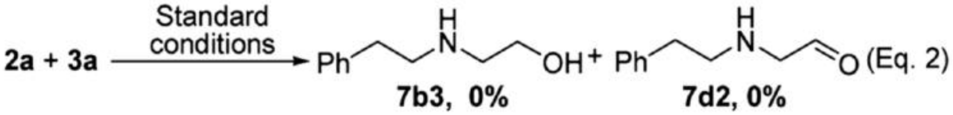


Beller *et al. JACS* 2013, *135,* 11384.

Pyrrole Synthesis

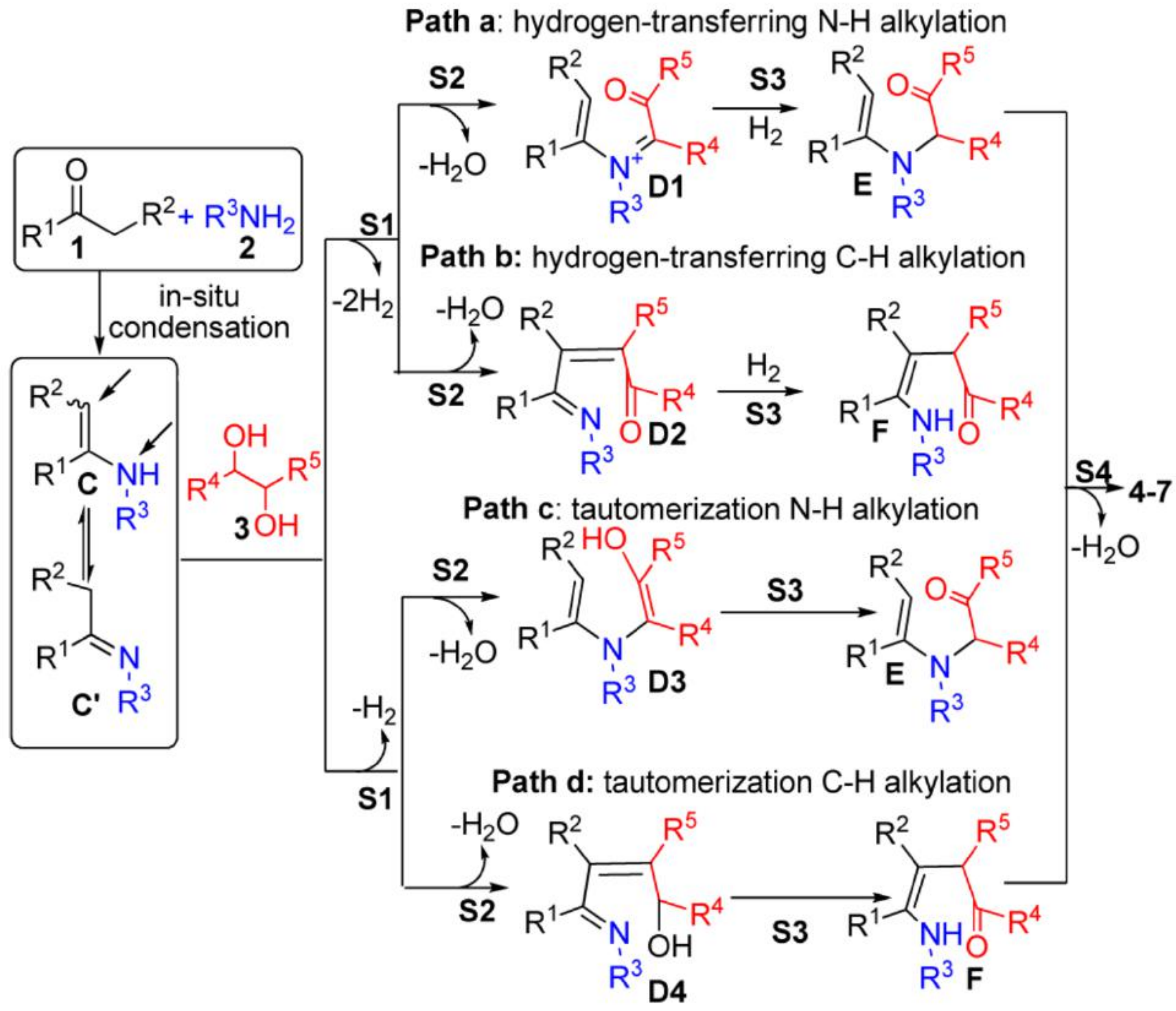
Stopped reaction after 3 hours





Beller *et al. JACS* 2013, *135*, 11384.

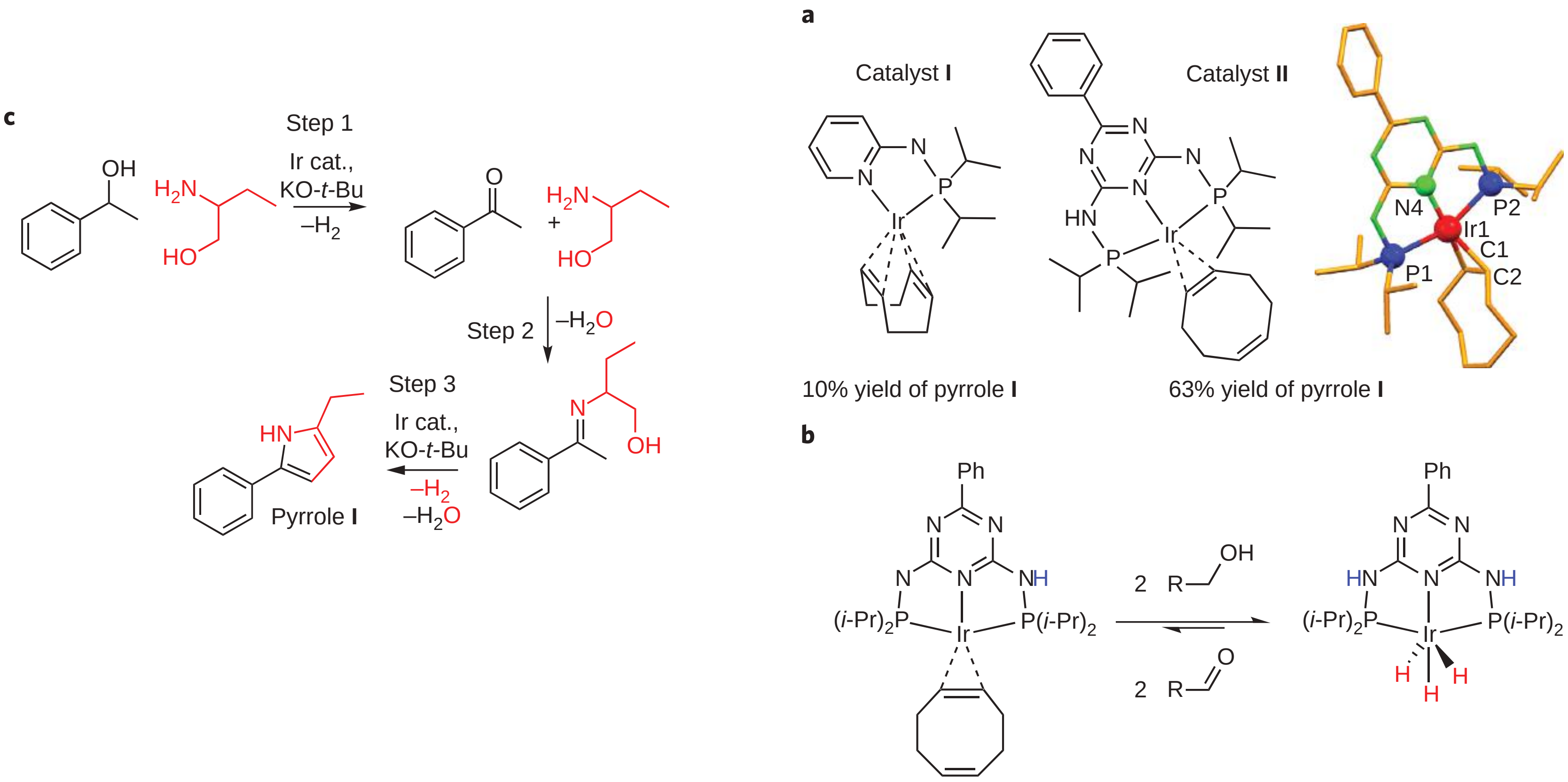
Pyrrole Synthesis



Beller *et al. JACS* 2013, *135*, 11384.

Pyrrole Synthesis

- Pyrrole synthesis
  - Renewable secondary alcohols -1,2-amino alcohols (from amino acids)
  - Water/air stable catalyst



Michlik & Kempe. *Nat. Chem.* 2013, *5,* 140.

Pyrrole Synthesis

- Pyrrole synthesis
  - Water/air stable catalyst – very low catalyst loadings

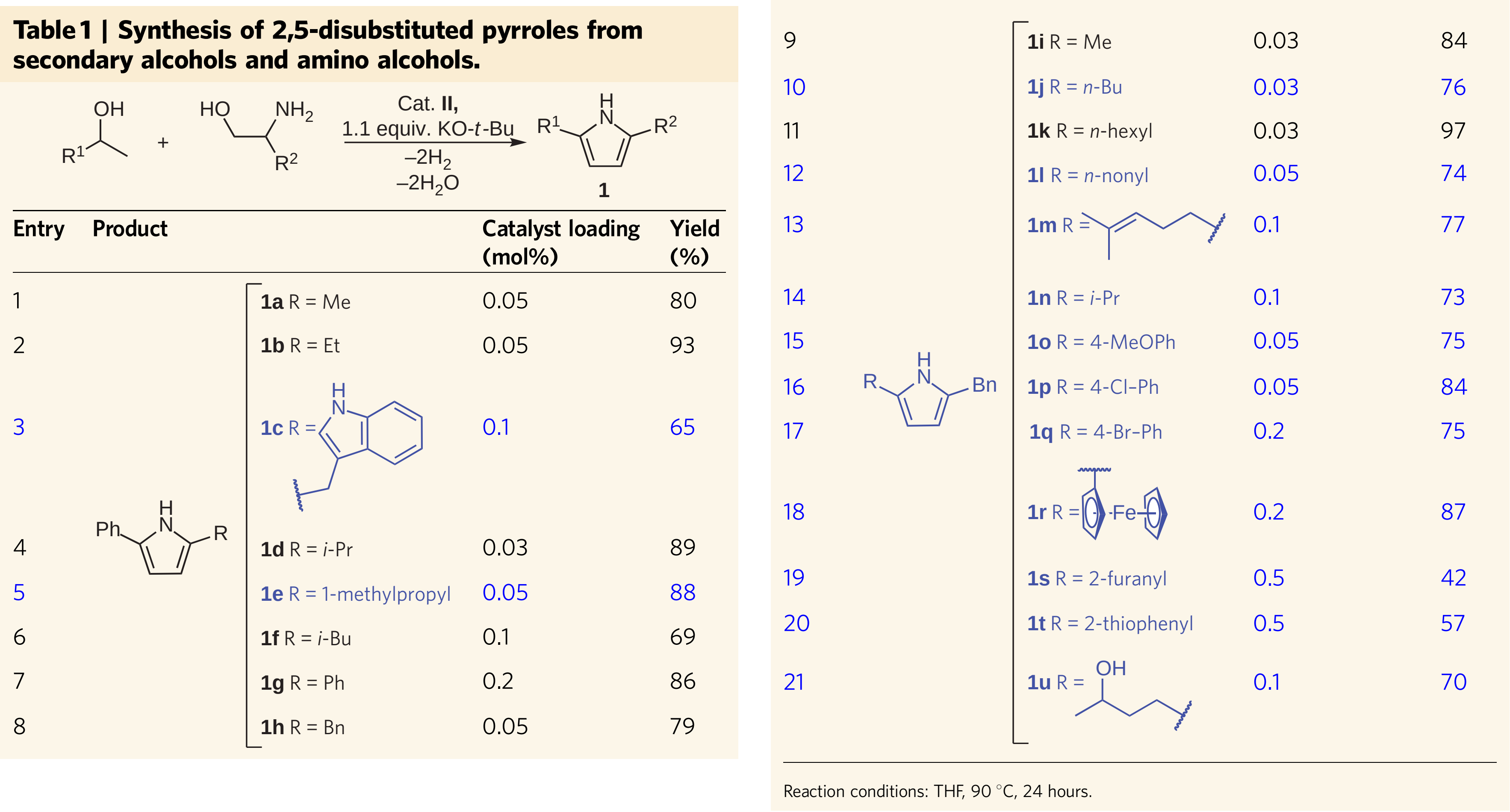


Table 1 | Synthesis of 2,5-disubstituted pyrroles from secondary alcohols and amino alcohols.

Entry	Product	Catalyst loading (mol%)	Yield (%)
1	**1a** R = Me	0.05	80
2	**1b** R = Et	0.05	93
3	**1c** R =	0.1	65
4	**1d** R = *i*-Pr	0.03	89
5	**1e** R = 1-methylpropyl	0.05	88
6	**1f** R = *i*-Bu	0.1	69
7	**1g** R = Ph	0.2	86
8	**1h** R = Bn	0.05	79
9	**1i** R = Me	0.03	84
10	**1j** R = *n*-Bu	0.03	76
11	**1k** R = *n*-hexyl	0.03	97
12	**1l** R = *n*-nonyl	0.05	74
13	**1m** R =	0.1	77
14	**1n** R = *i*-Pr	0.1	73
15	**1o** R = 4-MeOPh	0.05	75
16	**1p** R = 4-Cl-Ph	0.05	84
17	**1q** R = 4-Br-Ph	0.2	75
18	**1r** R =	0.2	87
19	**1s** R = 2-furanyl	0.5	42
20	**1t** R = 2-thiophenyl	0.5	57
21	**1u** R =	0.1	70

Reaction conditions: THF, 90 °C, 24 hours.

Michlik & Kempe. *Nat. Chem.* 2013, *5*, 140.

Pyrrole Synthesis

- 2,3,5-Pyrrole synthesis

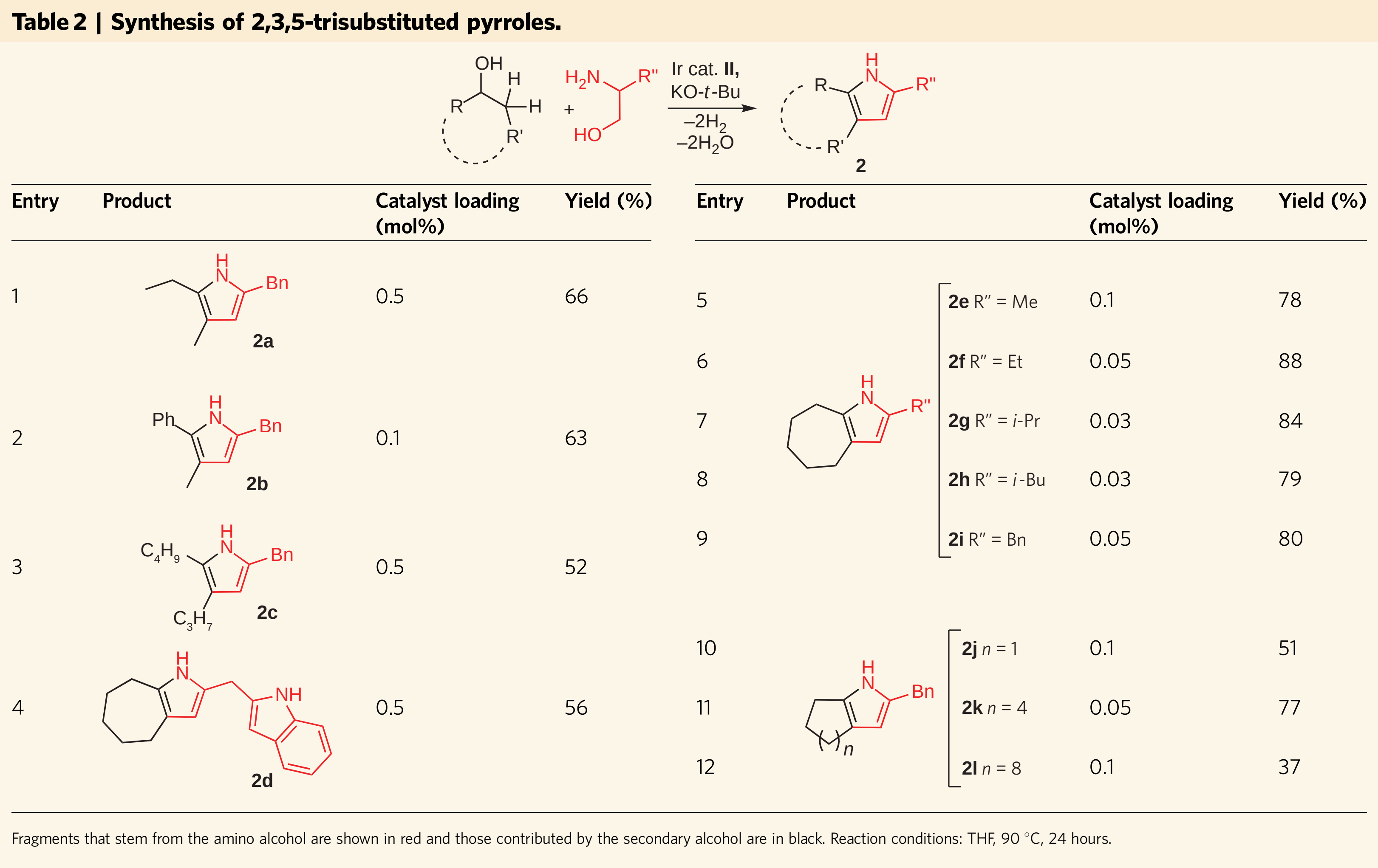


Table 2 | Synthesis of 2,3,5-trisubstituted pyrroles.

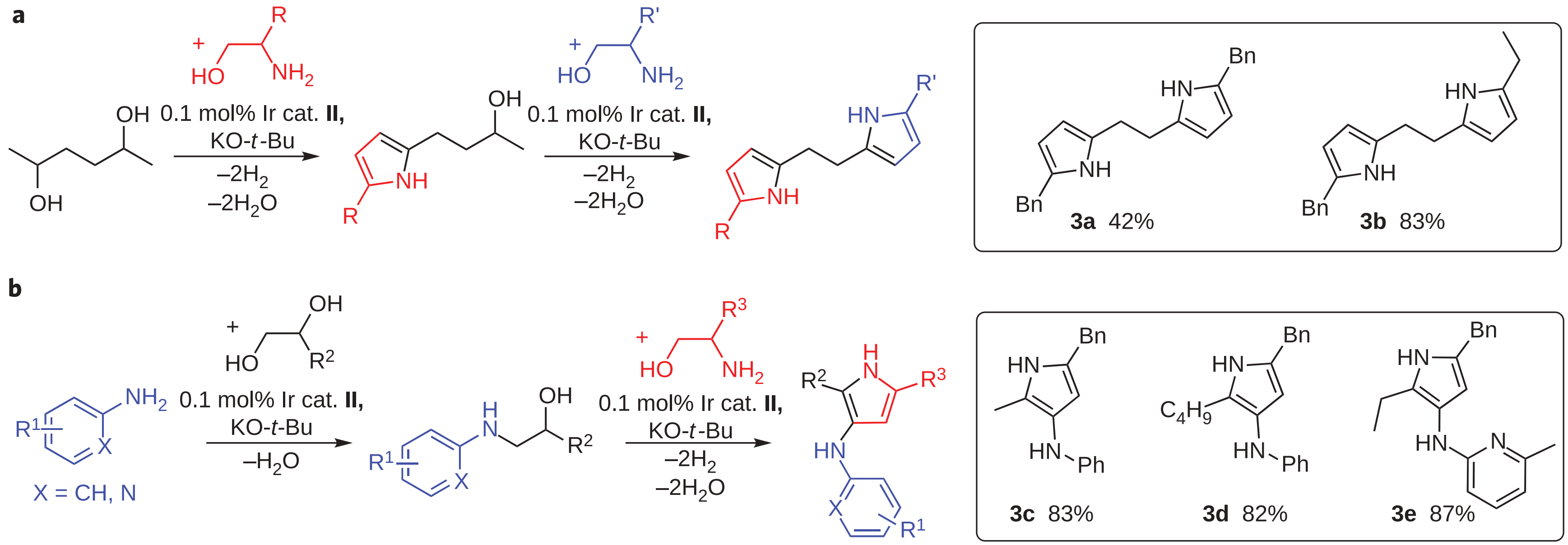
Entry	Product	Catalyst loading (mol%)	Yield (%)
1	**2a**	0.5	66
2	**2b**	0.1	63
3	**2c**	0.5	52
4	**2d**	0.5	56
5	**2e** R″ = Me	0.1	78
6	**2f** R″ = Et	0.05	88
7	**2g** R″ = *i*-Pr	0.03	84
8	**2h** R″ = *i*-Bu	0.03	79
9	**2i** R″ = Bn	0.05	80
10	**2j** *n* = 1	0.1	51
11	**2k** *n* = 4	0.05	77
12	**2l** *n* = 8	0.1	37

Fragments that stem from the amino alcohol are shown in red and those contributed by the secondary alcohol are in black. Reaction conditions: THF, 90 °C, 24 hours.

Michlik & Kempe. *Nat. Chem.* 2013, *5*, 140.

Pyrrole Synthesis

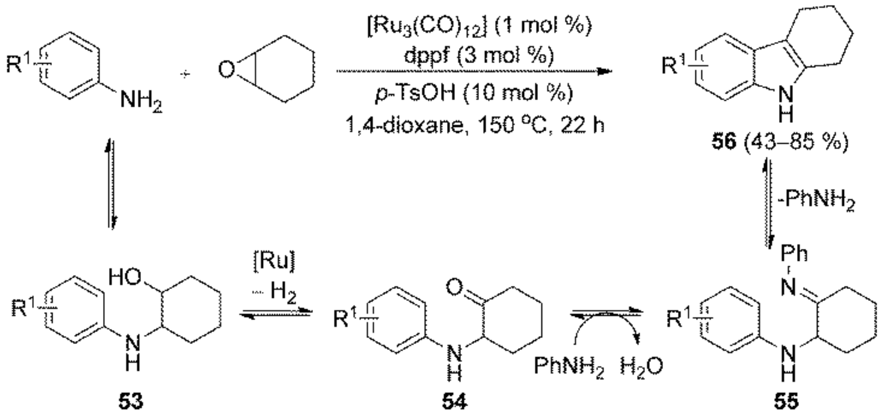
- Dipyrrole and aminopyrrole syntheses
  - High H_2 production
  - Useful for densely functionalized heterocycles



Michlik & Kempe. *Nat. Chem.* 2013, *5*, 140.

Indole Formation

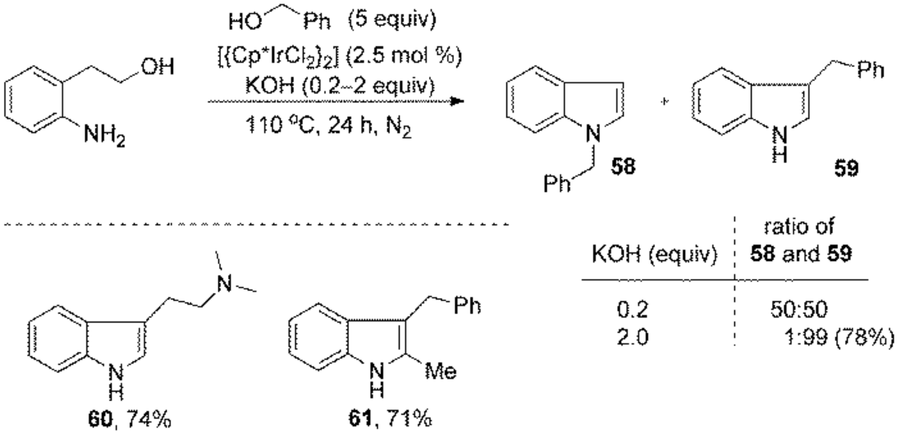
- Beller – Analine & epoxide
  - TsOH – necessary for epoxide opening and electrophilic cyclization



Amine must be unprotected
-indole anion important

Beller *et al. Chem. Eur. J.* 2014, *20,* 1818.

- Tethered amino/alcohol

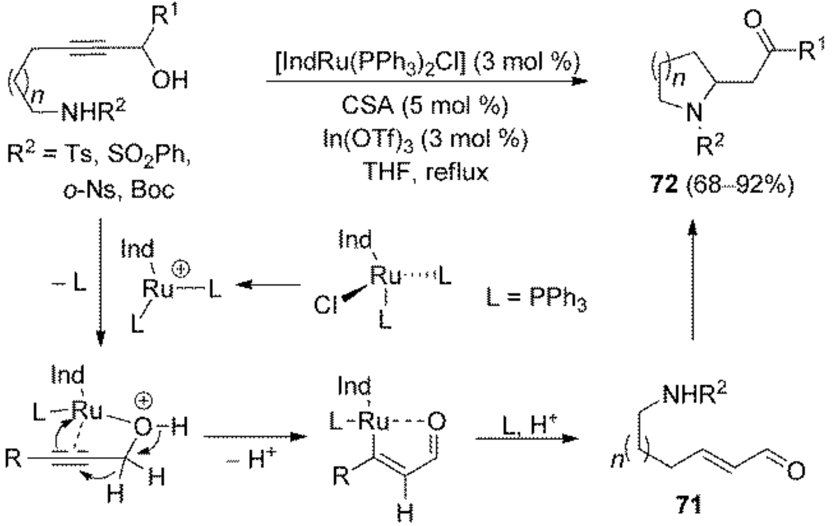


KOH (equiv)	ratio of **58** and **59**
0.2	50:50
2.0	1:99 (78%)

Keep *et al. Org. Lett.* 2007, *9,* 3299.

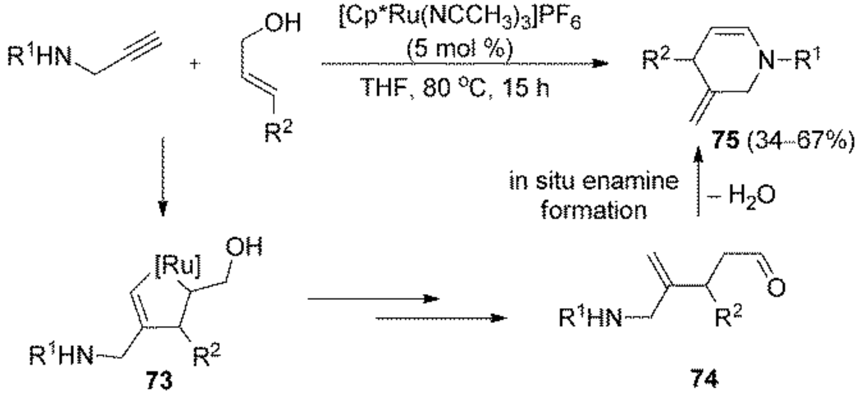
Unsaturated Systems in Annulations

- Redox isomerization of propargyl alcohols makes sensitive unsaturated carbonyl compounds



Trost *et al. JACS* 2008, *130*, 16502.

- Advanced piperidine intermediates
  - Cationic [Rh]



De´rien *et al. Chem. Commun.* 2012, *48*, 6589.

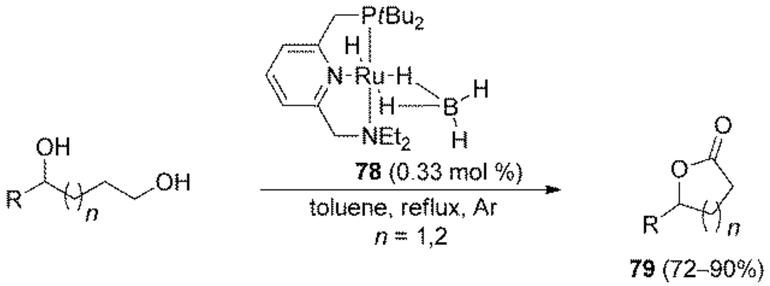
Overview

- Synthesis of *N*-Heterocycles
  1. N-alkylation of amines by alcohols
  2. Dehydrogenative amide formation from amines and alcohols
  3. Oxidative cyclization of alcohols
  4. Annulation of unsaturated systems (alkene/alkyne)

- Synthesis of *O*- / *S*-Heterocycles

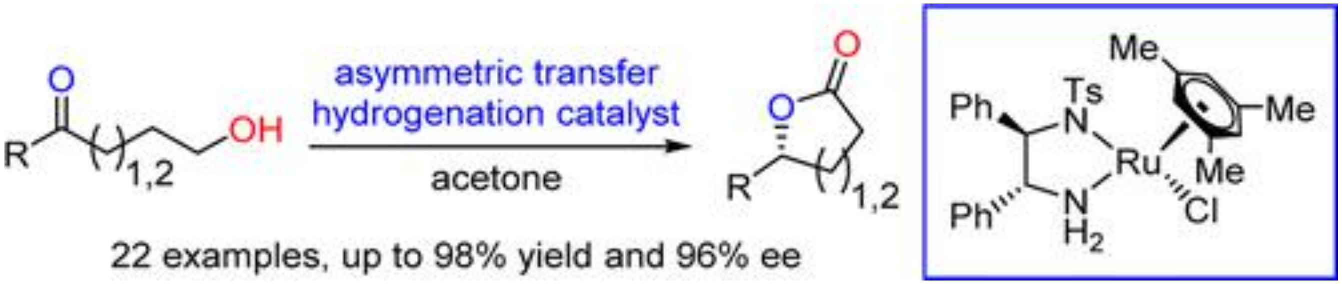
O/S-Heterocycle Formation

- Oxidative Cyclization of Alcohols to Lactones
  - Annulation of diols to lactones
  - H_2 as only byproduct



Milstein *et al. OM* 2011, *30,* 5716.

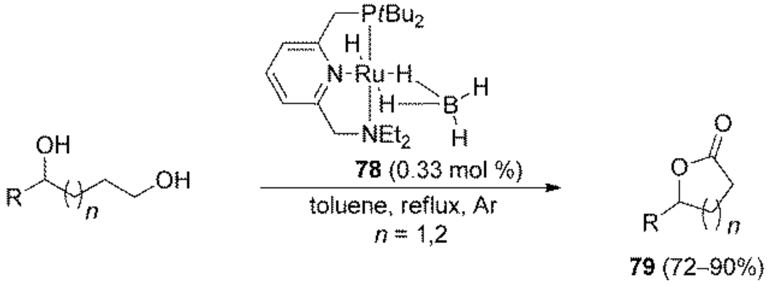
- Chemo- & Enantioselective Lactonization
  - Noyori H-transfer catalyst
  - Normal synthesis → keto aldehydes are very sensitive moieties



V Dong *et al. JACS* 2013, *135,* 5553.

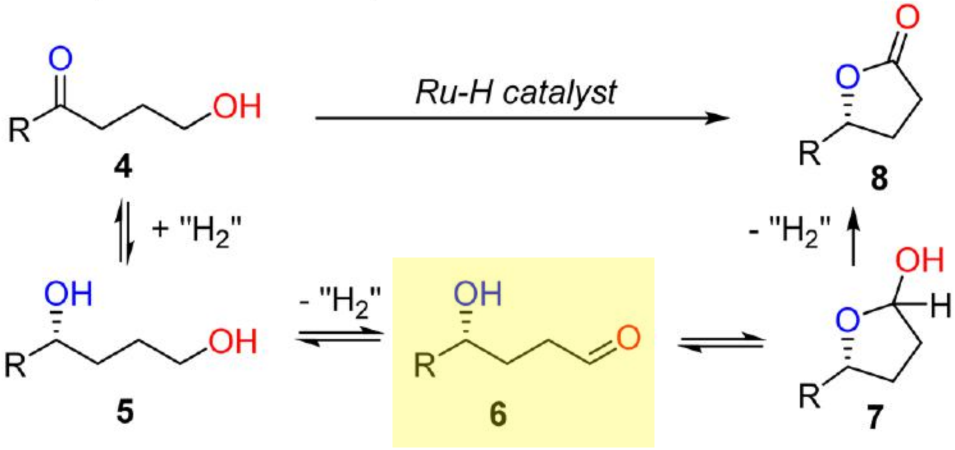
O/S-Heterocycle Formation

- Oxidative Cyclization of Alcohols to Lactones
  - Annulation of diols to lactones
  - H_2 as only byproduct



Milstein *et al. OM* 2011, *30,* 5716.

- Chemo- & Enantioselective Lactonization
  - Noyori H-transfer catalyst

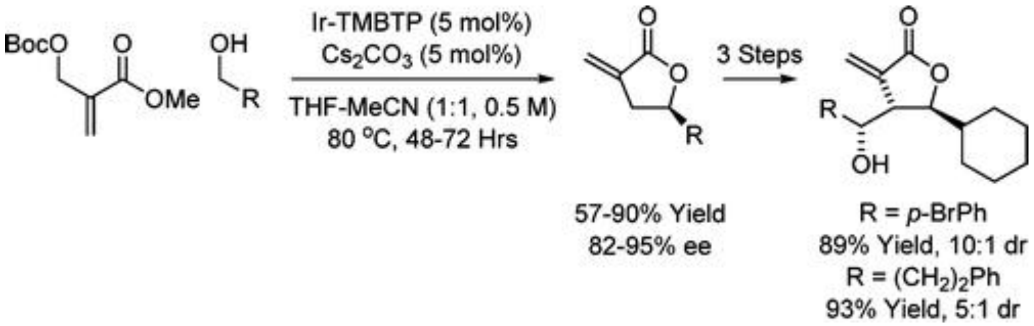


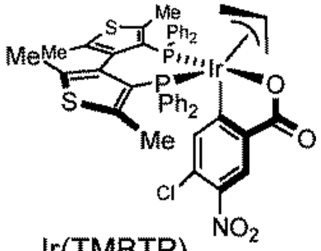
Compound 6 is prone to aldols, need in low concentration

V Dong *et al. JACS* 2013, *135,* 5553.

Chiral Lactones continued

- α-exo-Methylene γ-butyrolactones – present in 10% of natural products

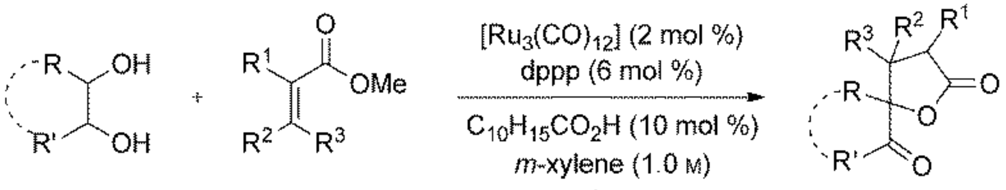




Ir(TMBTP)

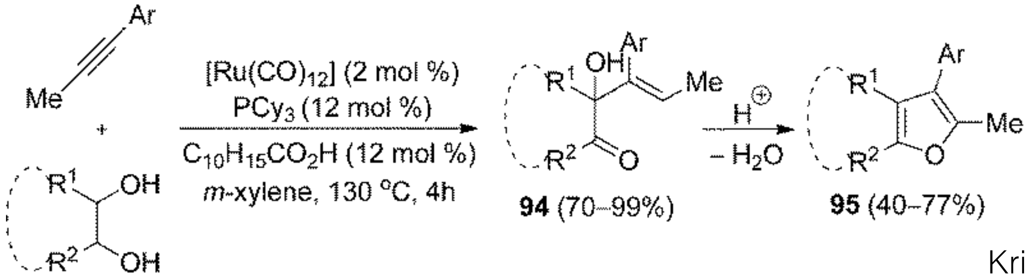
Krische *et al. JACS 134,* 11100.

- Spirolactones – from C-C coupling followed by lactonization



93 (51–99%)

- Furans – from redox-triggered C-C coupling of diols



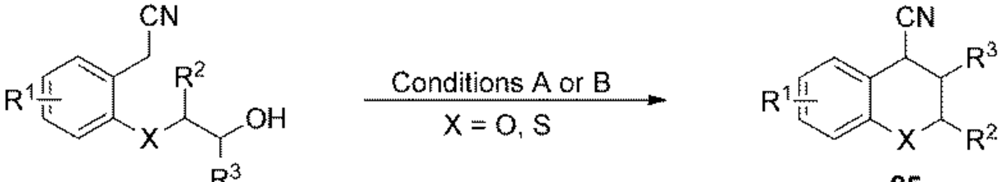
94 (70–99%)

95 (40–77%)

Krische *et al. ACIE 53,* 3232.

O/S-Heterocycle Formation

- Knoevenagel-type condensation to form chromanes & thiochromanes
  - Olefin intermediate captures [Ir]-H instead of nitrile



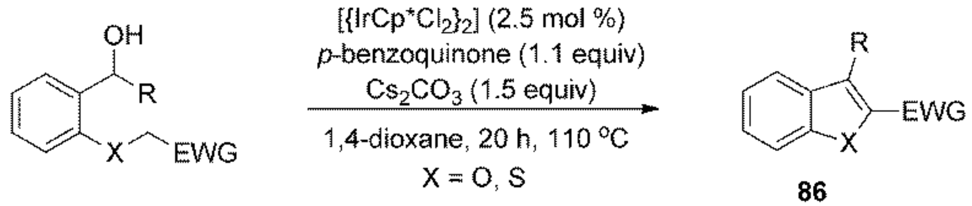
85

Conditions A:
[{IrCp*Cl$_2$}$_2$] (2.5 mol %)
Cs_2CO_3 (0.2 equiv)
1,4-dioxane, 110 °C, MW

Conditions B:
[{Ir(cod)Cl}$_2$] (2.5 mol %)
PPh_3 (10 mol %)
Cs_2CO_3 (0.2 equiv)
1,4-dioxane, 110 °C, MW

Cossy *et al. Eur. J. Org. Chem.* 2012, *2012,* 4453.

- Active methylene condensation
  - BQ is H-acceptor



EWG = CN, CO_2tBu, CON(Me)Ph,
C_6H_4*p*-NO_2

86
(40–98%)

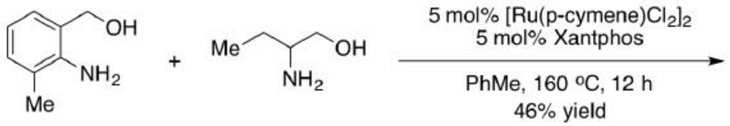
Cossy *et al. Org. Lett.* 2013, *15,* 3876.

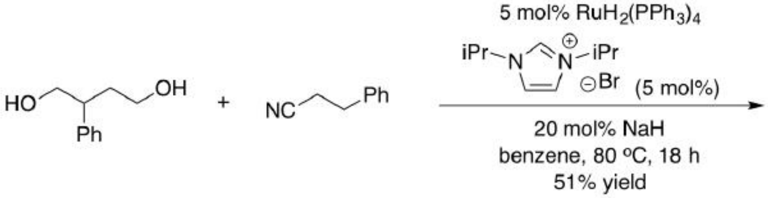
Final

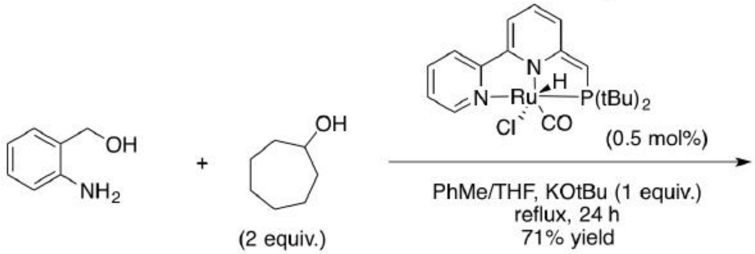
- H-Transfer annulations are a pretty mild way to synthesize heterocycles
- Although the substrates are not always the most trivial for these reactions, they can still be cheaper/easier to synthesize than trying to densely functionalize pyrroles, pyridines, etc
- I think this strategy is a great way to rethink organic synthesis and how to approach synthetic problems

Questions

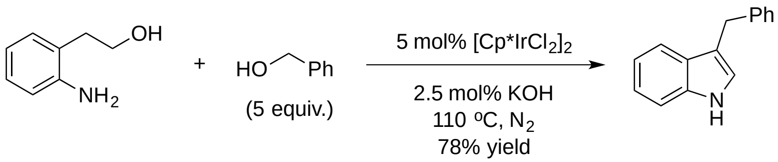
1. Predict the product.



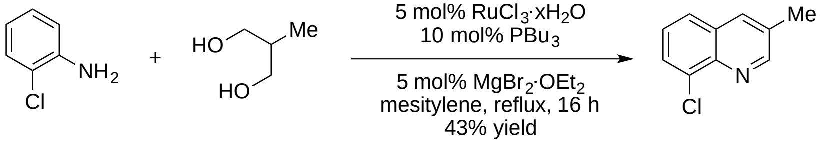




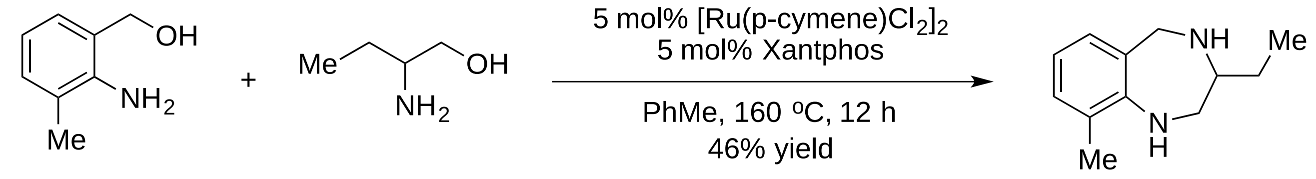
2. Predict the mechanism.

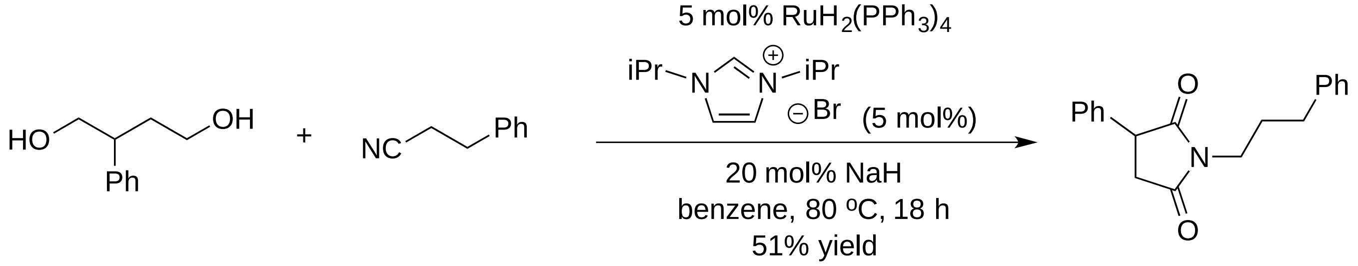


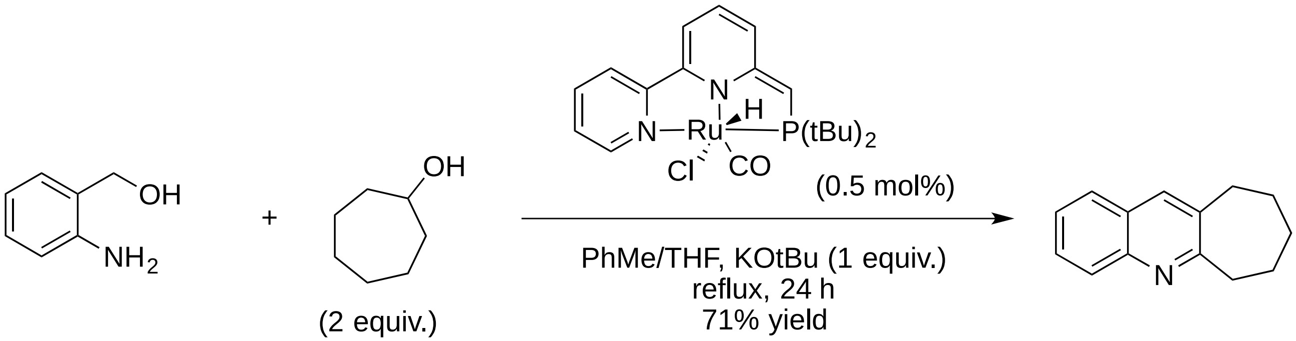
3. Predict the mechanism.



Questions 1

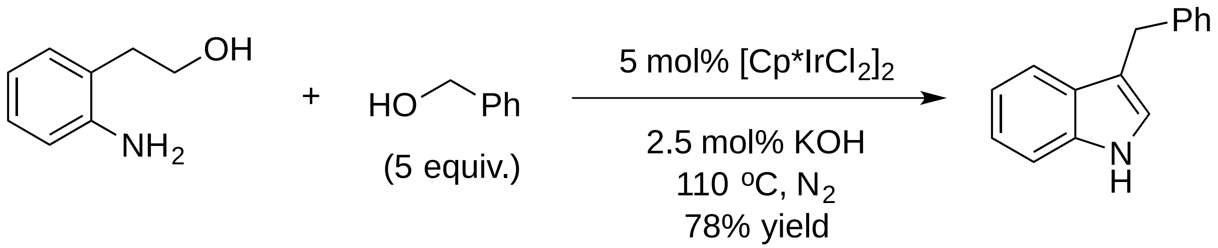

OH
NH2
Me
+
Me
OH
NH2
5 mol% [Ru(p-cymene)Cl2]2
5 mol% Xantphos
PhMe, 160 ºC, 12 h
46% yield
NH
Me
N
H
Me

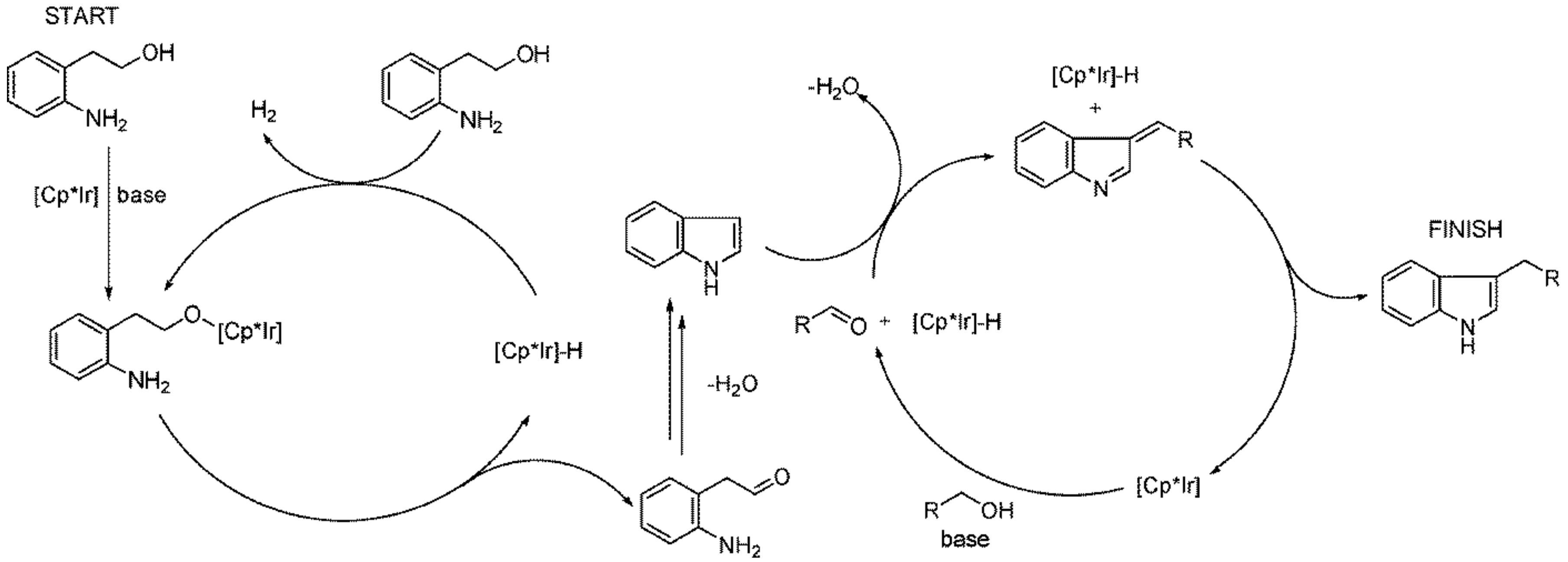

HO
OH
Ph
+
NC
Ph
5 mol% RuH2(PPh3)4
iPr
N
N
iPr
Br
(5 mol%)
20 mol% NaH
benzene, 80 ºC, 18 h
51% yield
Ph
O
N
O
Ph


OH
NH2
+
OH
(2 equiv.)
N
N
Ru
H
P(tBu)2
Cl
CO
(0.5 mol%)
PhMe/THF, KOtBu (1 equiv.)
reflux, 24 h
71% yield
N

Question 2

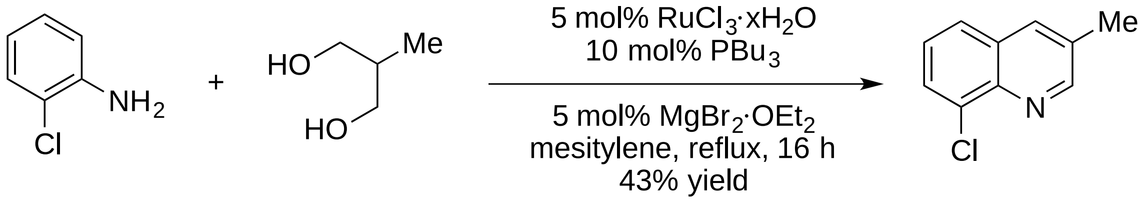
- d

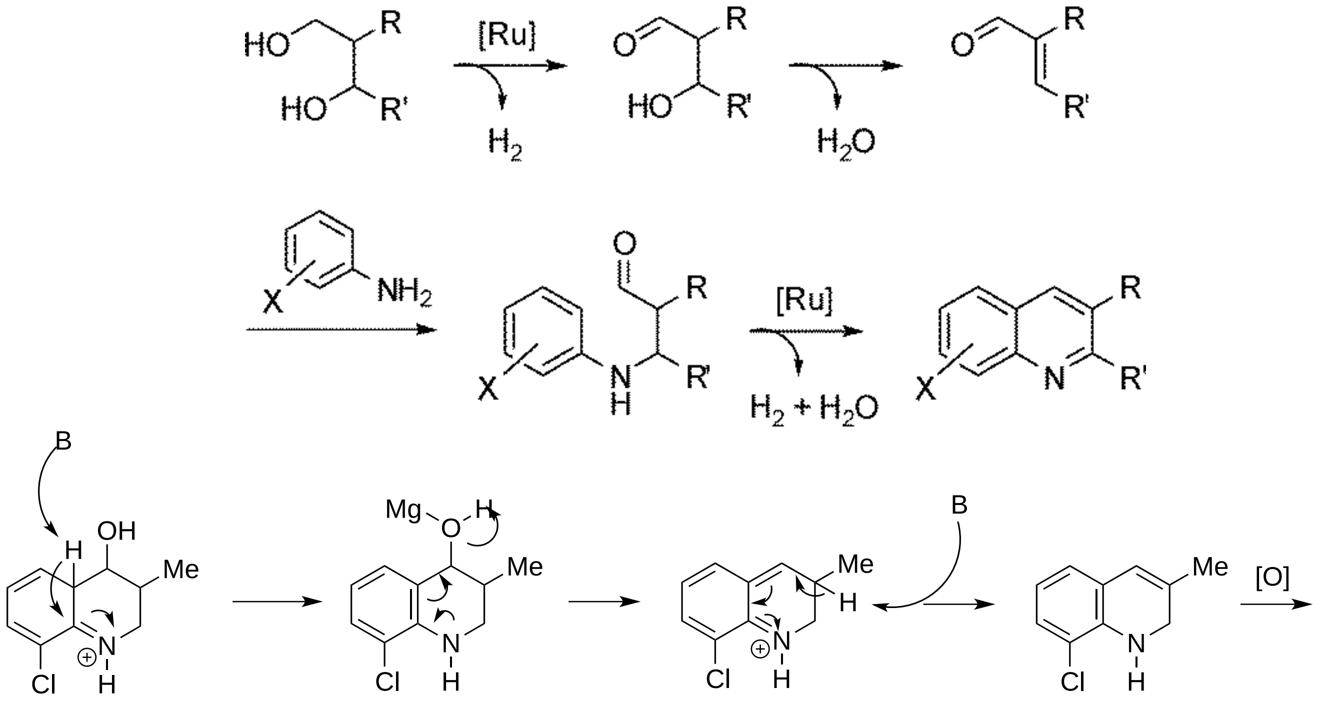

OH
NH$_2$
+
HO
Ph
(5 equiv.)
5 mol% [Cp*IrCl$_2$]$_2$
2.5 mol% KOH
110 °C, N$_2$
78% yield
Ph
N
H


START
OH
NH$_2$
[Cp*Ir]
base
H$_2$
OH
NH$_2$
O
[Cp*Ir]
NH$_2$
[Cp*Ir]-H
O
NH$_2$
-H$_2$O
N
H
-H$_2$O
[Cp*Ir]-H
+
N
R
R
O
+
[Cp*Ir]-H
R
OH
base
[Cp*Ir]
FINISH
R
N
H

Question 2

- Doebner–von Miller Quinoline Synthesis





Madsen *et al. Org. Biomol. Chem.* 2011, *9*, 610.