Ammonia in Transition Metal-catalyzed Reaction

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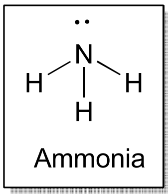
2011.4.20

Contents

Review: *Chem. Rev.* **1992**, *92*, 1.
Chem. Soc. Rev. **2010**, *39*, 2302.
Angew. Chem., Int. Ed. **2011**, *50*, 86.

1. Introduction

1-1. Ammonia As Nitrogen Source


Ammonia

- Colorles, irritating smelling gas.
- Bp. –33.4 °C, Mp. –77.7 °C
- pKa : 38 (H_2O), pK_{AH+} : 9.2 (H_2O)
- N-H bond strength : 107 kcal/mol
- Soluble in water, alcohol. and other polar organic solevents

Ammonia in Industry

Industrial Production: Haber-Bosch Process

$$3H_2 + N_2 \xrightleftharpoons{\text{Fe Catalyst}} 2NH_3$$

High Temperature : 400~500 °C
High Pressure : 10~35 MPa

•Ammonia was formed industrially around 100 million tonnes per year.
(almost the same amout by biological system)

•1~2% of the total global energy demand annually.

For recent advances in N_2 reduction and fixation
lit. Mr. Kimura 2010/4/21
lit. Dr. Yamaguchi 2009/2/21

Usage

- **Fertilizer (>80%)**
- Synthesis of amines

$$NH_3 + RX \longrightarrow NH_2R + NHR_2 + NR_3$$

- Synthesis of Inorganic acids and salts (nitric acid)

Most synthetic N-containing compounds can be derived back to ammonia.

1-2. Difficulty in Using Ammonia in Metal-catalyzed Reaction

Homogenios catalytic reactions using ammonia as a substrate are still limited.

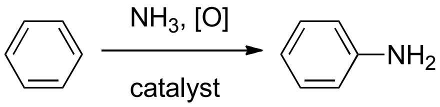
- Metals and ammonia tends to form stable Werner complexs.

  M——NH_3

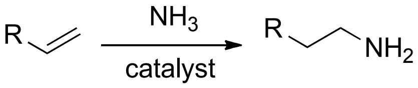
  Werner complex
- Low acidity and moderate basicity
- Strong N-H bond (107 kcal/mol) : Difficulty in N-H activation
- Ammonia is toxic gasous compound.
- Diffucult to supress over reactions.

Two reactions using ammonia are litsted as "The 10 challenges for catalysis"

Direct synthesis of anilines

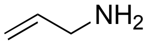


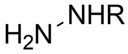
anti-Markovnikov selective hydroamination of unreactive olefin



C&EN, **1993**, 23

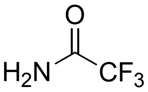
Ammonia Surrogates

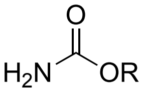


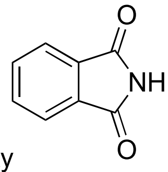


$BnNH_2$

increased nucleophilicity







increased acidity of N-H bond

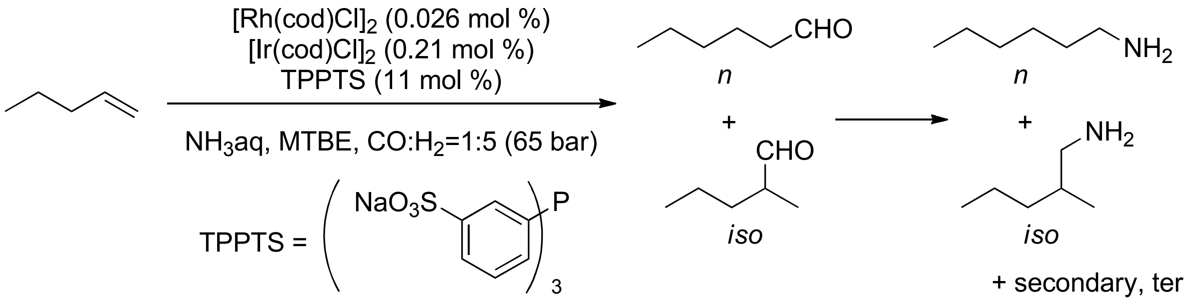
These protected ammonia equivalents are good substrates for several catalytic reactions. However, deprotection step is required.

2. Reactions Without Metal-Ammonia Coordination

2-1. Reductive Amination

Hydroaminomethylation in Biphasic System Using Water Soluble System

Herwig, J.; Beller, M. *et al. Angew. Chem., Int. Ed.* **1999**, *38*, 2372.



+ secondary, tertialy amines

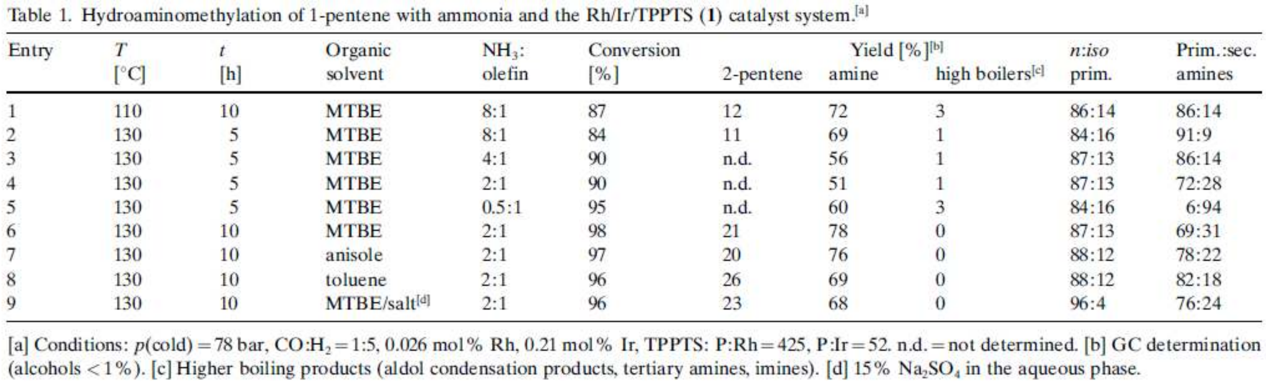
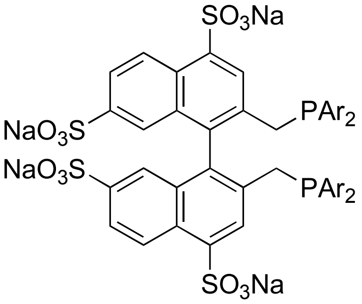


Table 1. Hydroaminomethylation of 1-pentene with ammonia and the Rh/Ir/TPPTS (**1**) catalyst system.[a]

Entry	*T* [°C]	*t* [h]	Organic solvent	NH$_3$: olefin	Conversion [%]	Yield [%][b] 2-pentene	amine	high boilers[c]	*n*:*iso* prim.	Prim.:sec. amines
1	110	10	MTBE	8:1	87	12	72	3	86:14	86:14
2	130	5	MTBE	8:1	84	11	69	1	84:16	91:9
3	130	5	MTBE	4:1	90	n.d.	56	1	87:13	86:14
4	130	5	MTBE	2:1	90	n.d.	51	1	87:13	72:28
5	130	5	MTBE	0.5:1	95	n.d.	60	3	84:16	6:94
6	130	10	MTBE	2:1	98	21	78	0	87:13	69:31
7	130	10	anisole	2:1	97	20	76	0	88:12	78:22
8	130	10	toluene	2:1	96	26	69	0	88:12	82:18
9	130	10	MTBE/salt[d]	2:1	96	23	68	0	96:4	76:24

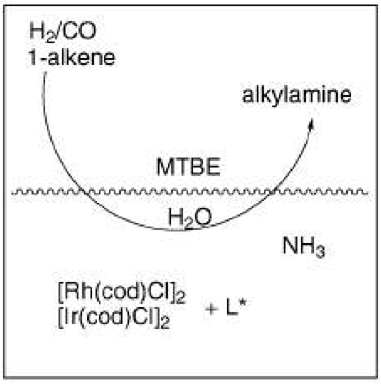
[a] Conditions: *p*(cold) = 78 bar, CO:H$_2$ = 1:5, 0.026 mol% Rh, 0.21 mol% Ir, TPPTS: P:Rh = 425, P:Ir = 52. n.d. = not determined. [b] GC determination (alcohols < 1%). [c] Higher boiling products (aldol condensation products, tertiary amines, imines). [d] 15% Na$_2$SO$_4$ in the aqueous phase.

n/*iso* Selectivity depends on ligand.



BINAS gave exclusively *n*-product.
(See the Table below)

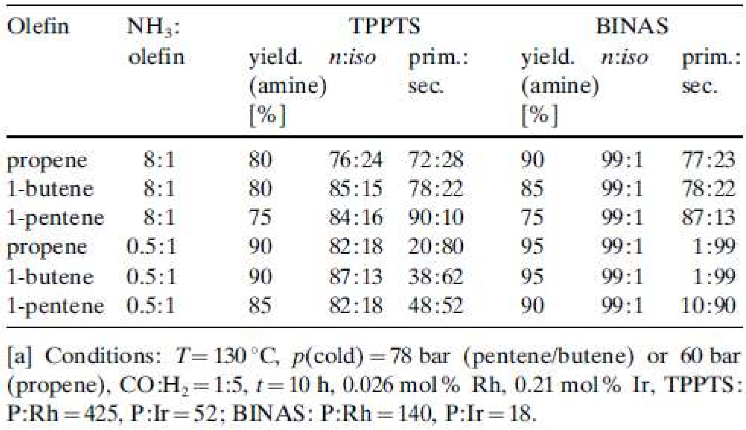
Extraction Effect



NH$_3$ << alkyl amine

NH$_3$ >> alkylamine
⇓
Prim. Selective

Reaction proceeds in water.

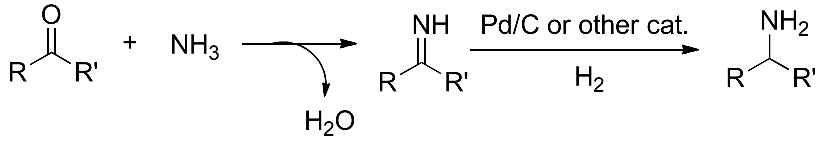


Olefin	NH$_3$: olefin	TPPTS yield. (amine) [%]	TPPTS *n*:*iso*	TPPTS prim.: sec.	BINAS yield. (amine) [%]	BINAS *n*:*iso*	BINAS prim.: sec.
propene	8:1	80	76:24	72:28	90	99:1	77:23
1-butene	8:1	80	85:15	78:22	85	99:1	78:22
1-pentene	8:1	75	84:16	90:10	75	99:1	87:13
propene	0.5:1	90	82:18	20:80	95	99:1	1:99
1-butene	0.5:1	90	87:13	38:62	95	99:1	1:99
1-pentene	0.5:1	85	82:18	48:52	90	99:1	10:90

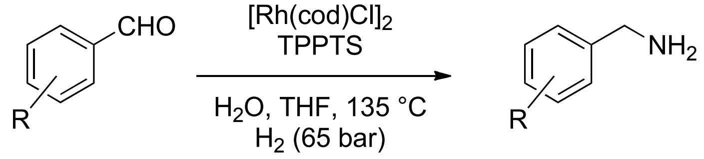
[a] Conditions: *T* = 130 °C, *p*(cold) = 78 bar (pentene/butene) or 60 bar (propene), CO:H$_2$ = 1:5, *t* = 10 h, 0.026 mol% Rh, 0.21 mol% Ir, TPPTS: P:Rh = 425, P:Ir = 52; BINAS: P:Rh = 140, P:Ir = 18.

Reductive Amination by Homogeneous Catalyst

Reductive amination using H_2 as reducing reagents are well known in the case of heterogeneous catalyst.



Reductive Amination of Aldehyde and Ammonia



Beller, M. *et al. Org. Lett.* **2002**, *4*, 2055.

Rh(I)-TPPTS catalyst is water soluble and could be recycled after phase seperation.

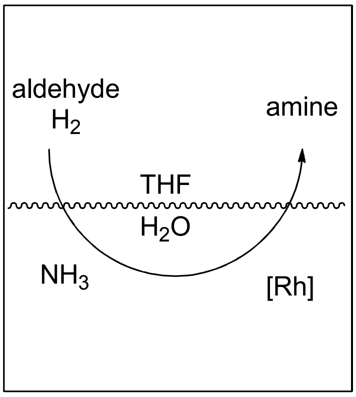
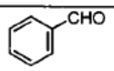
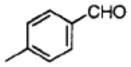
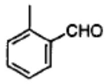
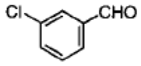
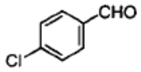
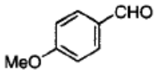
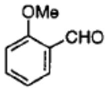
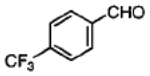
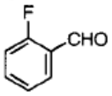
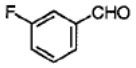
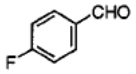
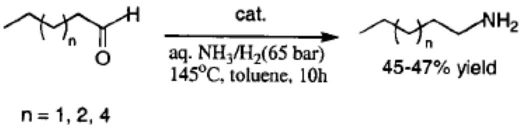


Table 2. Reductive Amination of Substituted Benzaldehydes[a]

substrate	yield **1** %	yield **2** %	Selectivity **1** vs. **2** alcohol, %
	86	3	97
	75	4	95
	65	7	90
	55	8	87
	78	9	90
	77	4	95
	85	3	97
	33	5	87
	58	9	87
	62	11	85
	62	14	82

[a] Reaction conditions: substrate (0.034 mol), $[Rh(cod)Cl]_2$ (0.05 mol %), TPPTS (1.3 mol %), NH_4OAc (50 mol %), THF (20 mL), 25% aqueous ammonia (20 mL), NH_3/substrate (8:1), org/aq (1:1), H_2 (65 bar) temperature (135 °C), time (2 h).

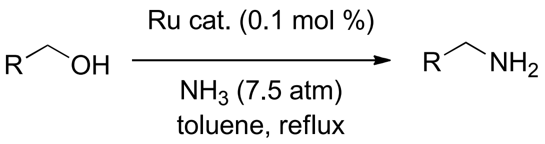
Scheme 3

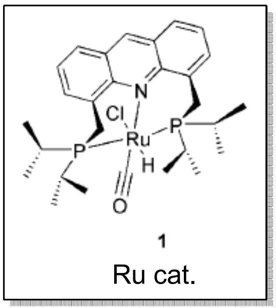


cat. = $[Rh(cod)Cl]_2$ / $[Ir(cod)Cl]_2$
or $[Rh(cod)Cl]_2$, TPPTS

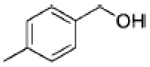
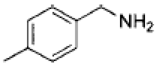
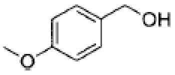
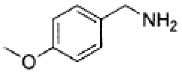
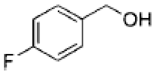
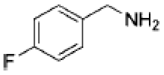
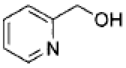
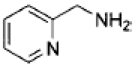
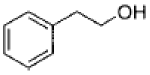
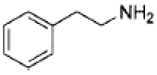
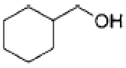
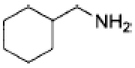
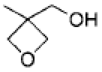
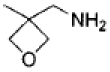
Synthesis of Amines from Alcohols

Milstein, D. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 8661.

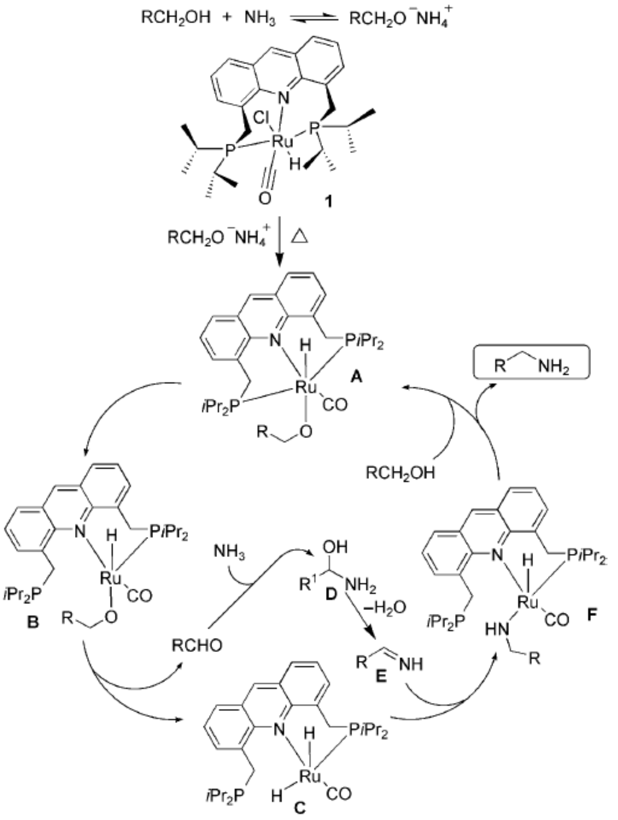




Ru cat.

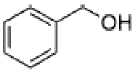
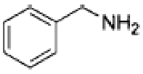
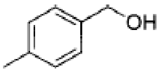
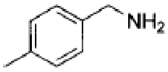
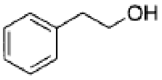
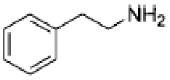
Entry	RCH_2OH	*t* [h]	Conv.	RCH_2NH_2	Yield [%][c]
1		12	100		83 (70)
2		14	100		78
3		24	100		91
4		30	100		96
5		12	100		94.8
6[b]		20	97		61 [34.6][d]
7		32	100		68.8
8		12	100		94.5
9[b]		18	93		67.7 (61)
10		25	95.5		82 (73)
11		25	96.4		90 (84)

[a] Complex **1** (0.01 mmol), alcohol (10 mmol), ammonia (7.5 atm), and toluene (3 mL) were heated in a Fischer–Porter reactor.[23] Conversion of alcohols and yield of products were analyzed by GC. Yield in parenthesis represents the yield of isolated product. [b] Neat reaction. Yield of isolated product is an average of two experiments. [c] The corresponding imine is the major byproduct in all reactions (analyzed by GC-MS and MS(ESI)); its yield was not determined. [d] Yield of dipentylamine.



Reaction in water gave good results.

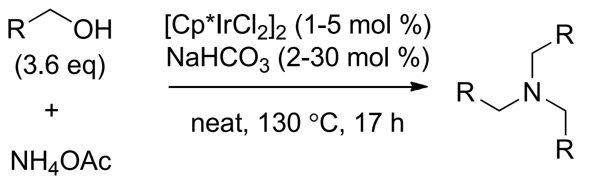
$$RCH_2OH + NH_3 \xrightarrow[\text{Water, 135 °C}]{\mathbf{1}\ (0.1\ \text{mol}\ \%),\ \Delta} RCH_2NH_2 + RCH{=}NCH_2R$$

Entry	RCH_2OH	*t* [h]	Conv.	RCH_2NH_2	Yield [%][b]
1		18	100		95.4 (86)
2		18	100		91.7
3		36	100		80.4[c]
4		24	92.4		54.8[d]
5[e]		28	89.4		74.3
6[f]		30	99		79.7
7[f]		30	98.7		70.0

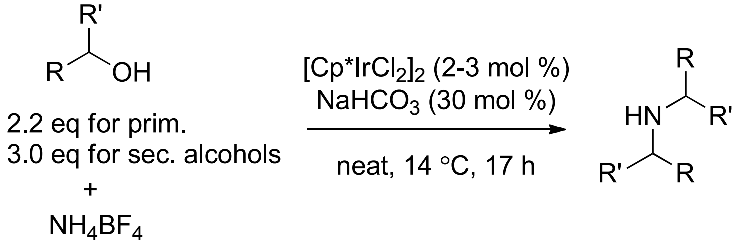
[a] Complex **1** (0.01 mmol), alcohol (10 mmol), ammonia (7.5 atm), and water (3 mL) were heated at reflux in a Fischer–Porter reactor.[23] Conversion of alcohols and yield of products were analyzed by GC; yield of isolated product in parenthesis. [b] Corresponding imine was the major byproduct in entries 1–3; corresponding acid was the byproduct in entries 5–7. [c] Corresponding acids were found in aqueous layer. [d] Hexamide was found in aqueous layer. [e] Mixture of 2 mL water and 2 mL toluene was used as solvent. [f] Mixture of 1 mL water and 2 mL dioxane was used as solvent.

Synthesis of Secondary and Tertiary Amines

Yamaguchi, R.; Fujita, K. *et al. Org. Lett.* **2008**, *10*, 181.



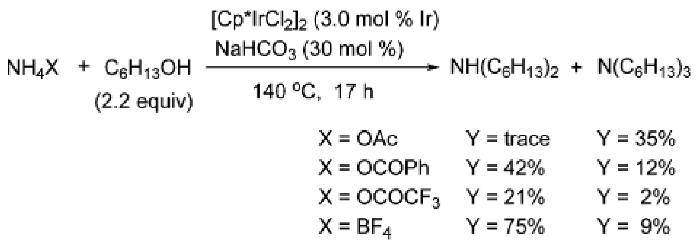
55-92% yield
R = aromatic and aliphatic



primary and secondary alcohols were used.
54-98% yield

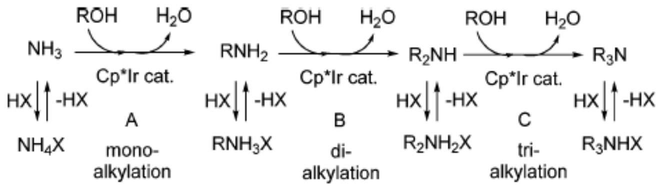
Selectivity depends on acidity of ammonium salts.
Stronger acidic salts gave secondary amines. However, the reason for selectivity was unclear.

Scheme 2

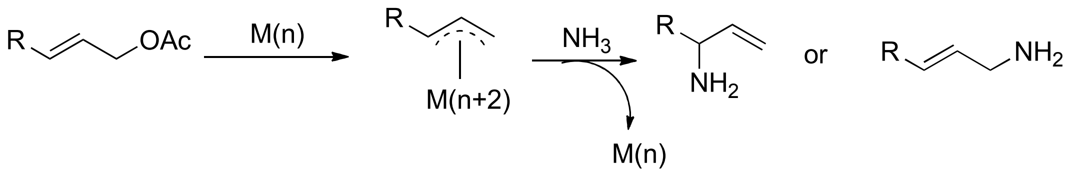


X	Y	Y
X = OAc	Y = trace	Y = 35%
X = OCOPh	Y = 42%	Y = 12%
X = $OCOCF_3$	Y = 21%	Y = 2%
X = BF_4	Y = 75%	Y = 9%

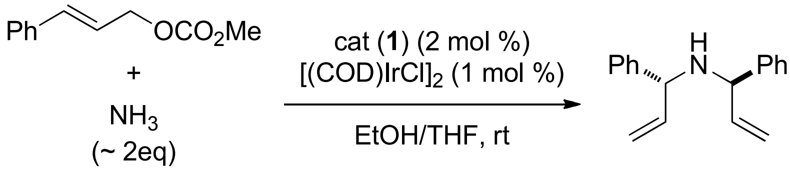
Scheme 4



2-2. Allylic Substitution

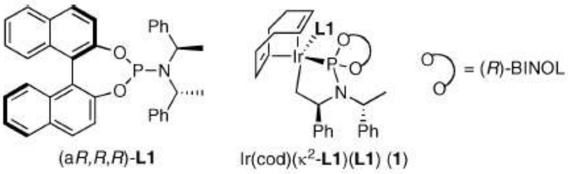


Ir-catalyzed Asymmetric Allylic Amination



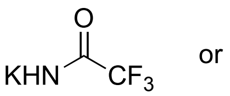
93% yield
94/6 dr
99% ee

No primary amine was obtained.



Formed primary amine showed higher reactivity than ammonia itself.

To obtain primary amine, they used ammonia surrogates.

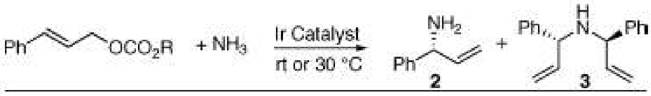


or Boc_2NLi

Hartwig, J. F. *et al. Org. Lett.* **2007**, *9*, 3949.

Ir-catalyzed Asymmetric Allylic Amination to Primary Amines Using Ammonia

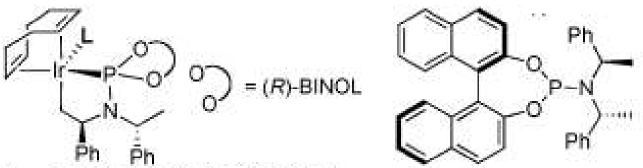
Hartwig, J. F. *et al.* *J. Am. Chem. Soc.* **2009**, *131,* 11312.



entry	R	Ir cat. (mol %)	equiv of NH_3	T (°C)	time (h)	yield (%)[b]	2:3[b]
1	Et	**1a** (2) + $[Ir(COD)Cl]_2$ (1)	100	30	15	45	94:6
2	Me	**1b** (4)	16	rt	24	59	65:35
3	Me	**1b** (4)	100	rt	24	63	90:10
4	Et	**1b** (4)	100	rt	48	66	91:9
5[c]	Et	**1b** (4)	100	30	15	81	92:8

---

[a] Reactions were conducted in 1:1 THF-d_8/ethanol-d_6 in a medium-wall NMR tube with 4.0 mol % Ir catalyst, 0.15 mmol of cinnamyl carbonate, and hexamethylbenzene or mesitylene as an internal standard. [b] Determined by ^{1}H NMR spectroscopy of the reaction mixture. [c] Performed in THF-d_8.

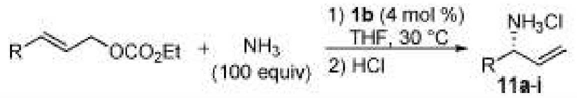


L = κ^1-**L1**: [Ir(COD)(κ^2-**L1**)(**L1**)] (**1a**)

L = ethylene: [Ir(COD)(κ^2-**L1**)(ethylene)] (**1b**)

(R_a,R_c,R_c)-**L1**

- Large excess NH_3 was necessary to obtain primary amine.
- Additional Ir source was not tolerant with large amout of NH_3. (entry 1)
  This additional Ir captures ligand from catalyst to give active 16 electron complex.

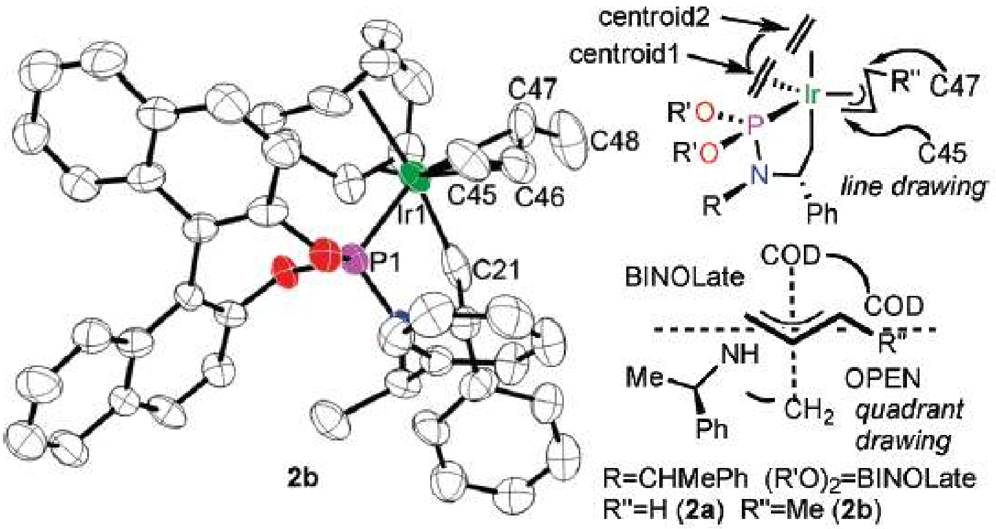


entry	R	11	yield (%)[b]	time (h)	ee (%)[c]
1	C_6H_5	**11a**	73	4	97
2	p-MeC_6H_4	**11b**	63	4	99
3	p-$MeOC_6H_4$	**11c**	58	14	98
4	p-BrC_6H_4	**11d**	57	12	99
5	p-$CF_3C_6H_4$	**11e**	51	12	99
6	m-$MeOC_6H_4$	**11f**	66	12	98
7[d]	n-heptyl	**11g**	49	24	96
8[e]	$TrOCH_2$	**11h**	53	5	97
9[f]	1-cyclohexenyl	**11i**	57	12	99

---

[a] Reactions were conducted on a 0.5 mmol scale in THF (0.5 mL) in a 10 mL pressure vessel with a vacuum side arm. Yields and enantioselectivities are averages from two independent runs. Products were characterized as their HCl salts. [b] Isolated yields of branched monoallylation products **11**. [c] Determined by chiral HPLC. [d] Conducted at room temperature. [e] Isolated as the free amine. [f] Conducted with 5 mol % **1b**.

X-ray Structure of π-allyl Ir Complex



2b

R=CHMePh $(R'O)_2$=BINOLate
R''=H (**2a**) R''=Me (**2b**)

Ir-C47 : 2.377 Å $\Longrightarrow$ Nucleophilic Attack on C47 is favorable.
Ir-C45 : 2.240 Å
(trans effect of P ligand)

Hartwig, J. F. *et al.* *J. Am. Chem. Soc.* **2009**, *131*, 7228.

Pd-catalyzed Allylic Amination Using aqueous NH_3

Kobayashi, S. *et al. J. Am. Chem. Soc.* **2009,** *131*, 4201.

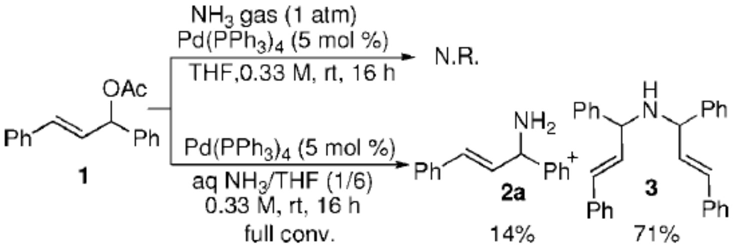


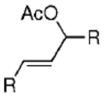
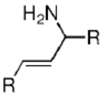
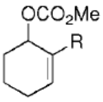
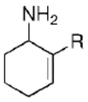
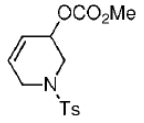
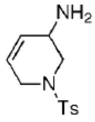
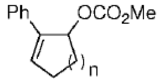
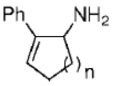
Table 1. Optimization of Reaction Conditions

$$\mathbf{1} \xrightarrow[\text{aq. } NH_3\text{/solvent, rt}]{Pd(PPh_3)_4 \text{ cat.}} \mathbf{2a} + \mathbf{3}$$

entry	solvent	NH_3(aq)/ solvent	conc. (M)	cat. (mol%)	time (h)	selectivity (2a/3)[a]	yield (%)[b] 2a	3
1	THF	1:6	0.33	5	16	26:74	14	71
2	THF	1:2	0.33	5	6	28:72	20	66
3	THF	1:2	0.17	5	10	47:53	34	55
4[c]	THF	1:2	0.11	5	23	59:41	40	42
5	THF	1:2	0.11	10	12	62:36	44	39
6	toluene	1:2	0.11	10	12	–	trace	trace
7	DMF	1:2	0.11	10	12	68:32	48	37
8	acetonitrile	1:2	0.11	10	12	58:42	39	46
9	1,4-dioxane	1:2	0.11	10	12	77:23	61	29
10	1,4-dioxane	1:2	0.06	10	18	83:17	66	22
11	1,4-dioxane	1:2	0.04	10	18	89:11	71	16
12	1,4-dioxane	1:2	0.03	10	18	–	0	0
13[d]	1,4-dioxane	1:2	0.03	10	18	91:9	73	13

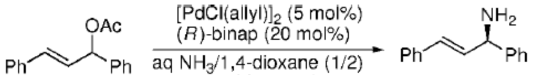
[a] The **2a**/**3** molar ratio was determined by ^{1}H NMR spectroscopic analysis of the crude material. [b] Isolated yield after chromatography (**2a** and **3** were separated). Yield of **3** was based on half the amount of **1**. [c] 12% of **1** was recovered. [d] 13 mol % of external PPh_3 was added.

Table 2. Allylic Amination Using Aqueous Ammonia

Entry	Substrate	Product (**2**)		Cond-itions[a]	Select-ivity[b]	Yield (%)[c]
1			**a**: R = Ph	A	89/11	71
2			**b**: R = -$(CH_2)_2$Ph	A	93/7	79
3			**c**: R = Ph	B	96/4	81
4			**d**: R = *p*-$MeOC_6H_4$-	B	94/6	80
5			**e**: R = *m*-$NO_2C_6H_4$-	B	95/5	80
6			**f**: R = 3,5-$CF_3C_6H_3$-	A	97/3	82
7			**g**: R = -$(CH_2)_3$Ph	B	>99/<1	82
8			**h**	B	94/6[d]	85
9			**i**: n = 1	B	94/6	82
10			**j**: n = 3	B	93/7	76

[a] A: Table 1, entry 11. B: Table 1, entry 9. [b] The primary/secondary amine molar ratio was determined by ^{1}H NMR spectroscopic analysis of the crude material. [c] Isolated yield of **2** after chromatography. [d] Calculated on the basis of isolated products.

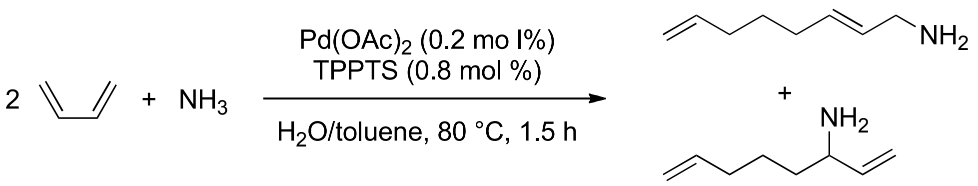
Scheme 2. Preliminary Investigation of Asymmetric Allylic Amination Using Aqueous Ammonia



71% yield
87% ee

Telomerization of Butadinene and Ammonia

Driessen-Hölscher, B. *et al. Angew. Chem., Int. Ed.* **1996**, *35*, 1708.
Driessen-Hölscher, B. et *al. Chem. Eur. J.* **1999,** *5,* 2069.



+ secondary
tartiary amines

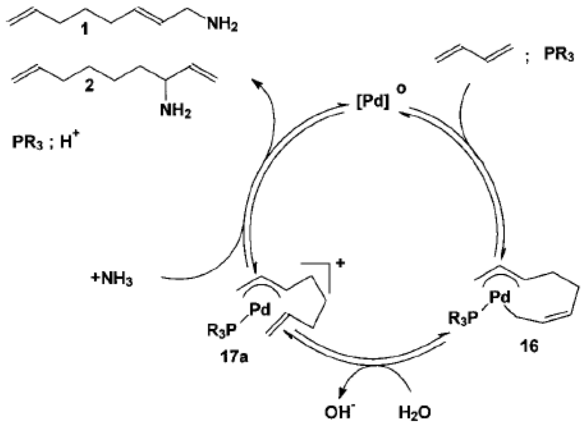
One pahse reaction mainly gave tertiary amines.

Table 2. Influence of the organic solvent on the catalytic two-phase telomerization of butadiene and ammonia [a].

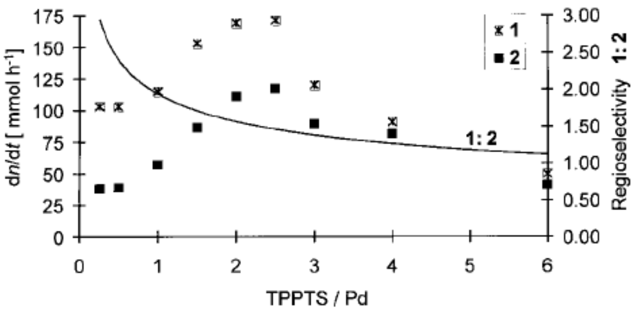
Entry	Second phase	Selectivity [%] 1+2	3	4	Total yield [%] [b]
1	–	60.5	30	-	41
2	toluene	88	6	-	55
3	pentane	79	16	-	61
4	ethyl acetate	53	18	-	40

[a] Reaction conditions: $Pd(OAc)_2$ (0.15 mmol), tppts (0.6 mmol), H_2O (20 mL), organic solvent (12.5 mL), ammonia (300 mmol), butadiene (75 mmol). T = 80 °C, t = 1.5 h. [b] Total yield based on butadiene.

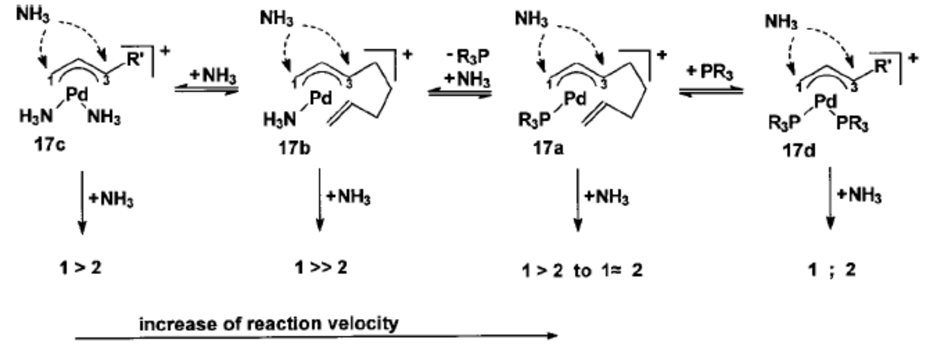
Proposed Reaction Mechanism



Relation between Ligand/Pd Ratio and Reactivity or Selectivity



Selectivity and Reactivity of Several Intermediates



NH_3 : σ-donor ligand : deaccelerate the nucleophilic attack.
olefin, PR_3 : σ-donor and π-acceptor ligand : accelerate the nucleophilic attack.

These effects are larger at *trans* position to the ligand.

Summary of Reductive Amination and Allylic Substitution

In these reactions, ammonia reacts with substrates without participation of catalysts.
Main problem is the selectivity between primary, secondary and tertiary amines.
Biphasic reaction systems or use of large excess amount of NH_3 could solve this problem.

3. Amination of Aryl Halides

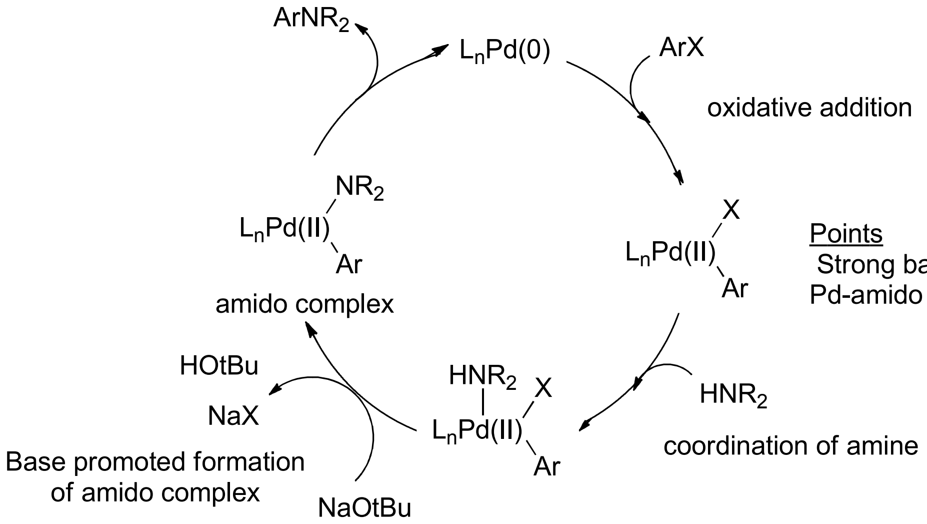
3-1. Pd-catalyzed Reactions

Buchwald-Hartwig Amination Using Amines

$$ArX + R^1R^2NH \xrightarrow[\text{base (stoich)}]{\text{Pd source, phosphine ligand}} ArNR_1R_2$$

Typical conditions
Pd: $Pd(OAc)_2$, Pd_2dba_3
ligand: P(*o*-tol)$_3$, BINAP, dppf
base: NaO*t*Bu, K_2CO_3, $CsCO_3$

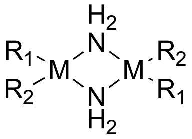
Catalytic Cycle



Points
Strong base was necessary for formation of Pd-amido complex.

Problems of Aniline Syntesis by Ammonia

- Ligands tends to be kicked out by the coordination of ammonia.
- Metal-amido complexes often favor the bridging structure and reductive elimination is difficult.



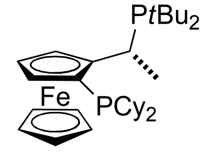
- Produced anilines are generally more reactive than ammonia.

Bulky, electron-rich, strongly coordinating ligands are suitable to overcome these problems.
- Ammonia would not kick out the ligands.
- Ligands could Inhibit the formation of dimer and promote reductive elimination.
- Sterically unhindered ammonia would react faster than produced anilines.

The First Report of Buchwald-Hartwig Amination Using NH_3

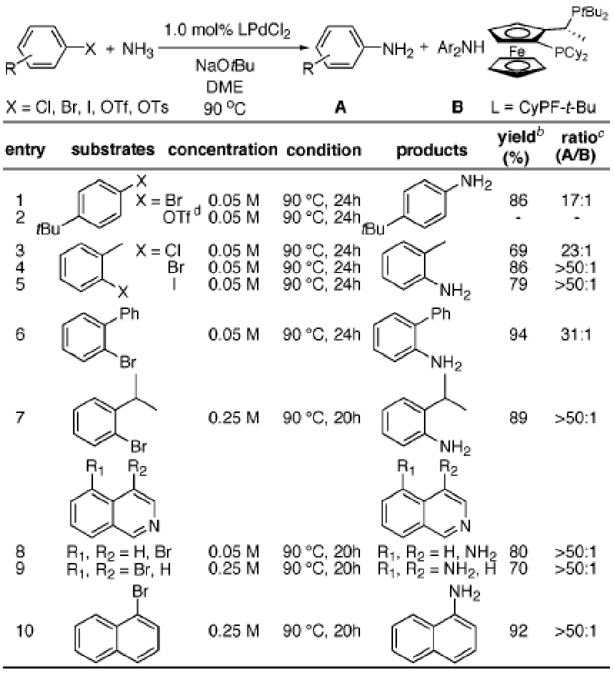
Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2006**, *128*, 10028.

$$\underset{X=Cl,\ Br,\ I}{ArX} + \underset{(200\ psi;\ ca.\ 14\ atm)}{NH_3} \xrightarrow[\text{DME, 90 °C}]{LPdCl_2\ (1.0\ mol\ \%)} ArNH_2 + Ar_2NH$$

L =


Josiphos

Table 1. Coupling of Aryl Halides with Ammonia, Catalyzed by CyPF-*t*-BuPdCl$_2$[a]

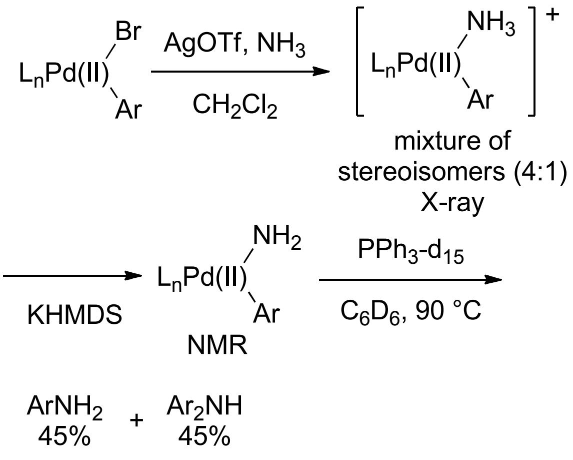


entry	substrates	concentration	condition	products	yield[b] (%)	ratio[c] (A/B)
1	X = Br	0.05 M	90 °C, 24h		86	17:1
2	OTf[d]	0.05 M	90 °C, 24h		-	-
3	X = Cl	0.05 M	90 °C, 24h		69	23:1
4	Br	0.05 M	90 °C, 24h		86	>50:1
5	I	0.05 M	90 °C, 24h		79	>50:1
6		0.05 M	90 °C, 24h		94	31:1
7		0.25 M	90 °C, 20h		89	>50:1
8	R$_1$, R$_2$ = H, Br	0.05 M	90 °C, 20h	R$_1$, R$_2$ = H, NH$_2$	80	>50:1
9	R$_1$, R$_2$ = Br, H	0.25 M	90 °C, 20h	R$_1$, R$_2$ = NH$_2$, H	70	>50:1
10		0.25 M	90 °C, 20h		92	>50:1

[a] Reactions conducted in a Parr bomb with 1.0 mol % of Pd(CyPF*t*-Bu)Cl$_2$, 1 mmol of ArBr, and 2.0 equiv of NaO*t*-Bu at 90 °C in DME (20.0 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude product. [d] No product; only the phenol was observed.

- •Other ligands (P*t*Bu$_3$, Q-Phos, X-Phos, IPr, dppf, BINAP etc) did not promote reactions.
- •Lower NH$_3$ pressure gave lower conversion and lower A/B ratio.
- •This condition also applicable reactions using LiNH$_2$ as N source.

Identification of Intermediates

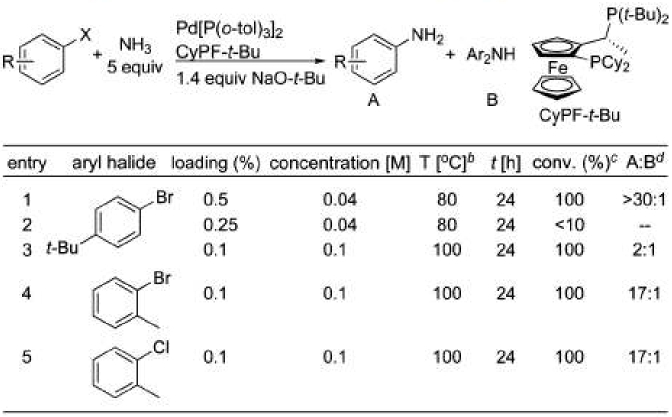


Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2009**, *131*, 11049.

Improved Reaction Conditions

They screened several catalyst precursors and found the combination of Pd[P(*o*-tol)$_3$] and CyPF-*t*Bu (Josiphos) in dioxane was the best conditions.

Table 2. Determination of the Catalyst Loading Required for the Coupling of Ammonia with *ortho*-Substituted Aryl Halides[a]

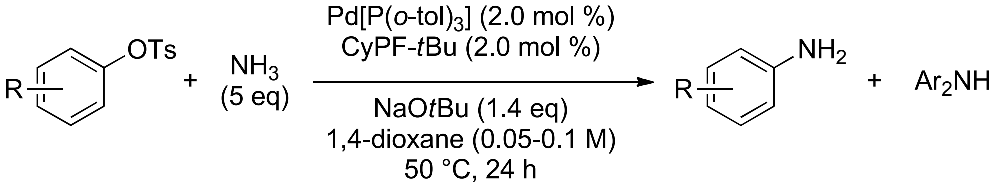


entry	aryl halide	loading (%)	concentration [M]	T [°C][b]	*t* [h]	conv. (%)[c]	A:B[d]
1		0.5	0.04	80	24	100	>30:1
2		0.25	0.04	80	24	<10	--
3		0.1	0.1	100	24	100	2:1
4		0.1	0.1	100	24	100	17:1
5		0.1	0.1	100	24	100	17:1

[a] Reactions conducted with 1:1 ratio of metal to ligand, 0.5 mmol aryl bromide, 5 mL of 0.5 M ammonia solution, and 1.4 equiv of NaO-*t*-Bu in 1,4-dioxane. [b] Temperature of bath. [c] Determined by GC analysis. [d] Determined by ^{1}H NMR spectroscopy.

- •No need to use excess amout of gasous ammonia.
- •Results were sensitive to concentration.
- •0.1 mol % catalyst gave excellent results.
- •These conditions showed wide substrate scope with ArX (Cl, Br, I) by using 0.1-2.0 mol % catalyst.
- •When Pd(II) compounds were used as Pd sources, Pd(0) generation seemed not efficient.
- •Ester, ketone, nitrile are tolerant by changing the base to K$_3$PO$_4$ and decreasing temp. to 70 °C.

Reaction using tosylates proceeded in mild conditions to give good results.

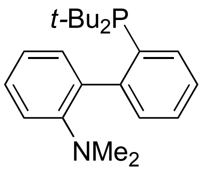


55-86% yield
17:1- >50:1 selectivity

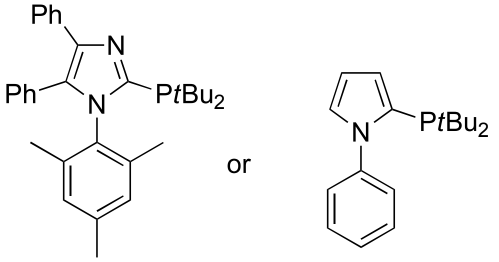
(Higher temp. promoted decomp. of tosyltes by base.)

Other Reported Reactions

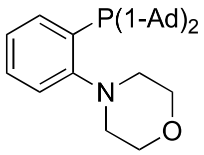
Buchwald, S. L. *et al. J. Am. Chem. Soc.* **2007**, *129*, 10354.
Beller, M. *et al. Chem. Eur. J.* **2009**, *15*, 4528.
Stradiotto, M. *et al. Angew. Chem., Int. Ed.* **2010**, *49*, 4071.



Buchwald *et al.*



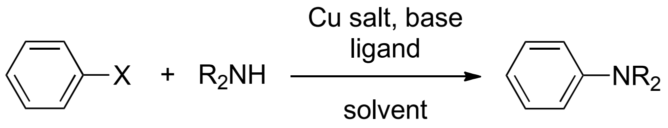
Beller *et al.*



Stradiotto *et al.*

3-2. Cu-catalyzed Reactions

Ullmann Reaction

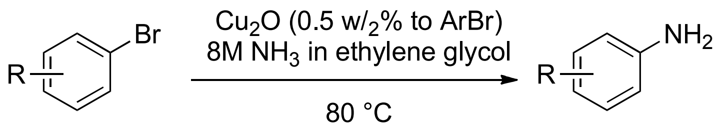


Similiar mechanism to Pd is proposed (Cu(**III**),Cu(**I**) cycle)

Several reaction of halopyridines with ammonia were repoted from early 20th century.
However, high temperature (150-250 °C) were necessary.

First Mild and Practical Copper-catalyzed Amination

Lang, F. *et al. Tetrahedron Lett. 2001*, *42*, 3251.



- Substrate scope was limited to electron-deficient aryl bromide or iodide.
(pyridine or benzene with electron-withdrawing groups)

- Small amount of addition of ethylene glycol proceeded.

Neither secondary nor tertiary amines were observed, which is common in Cu-catalyzed amination.

Using Aqueous Ammonia

Taillefer, M. *et al. Angew. Chem.* **2009**, *121*, 343.

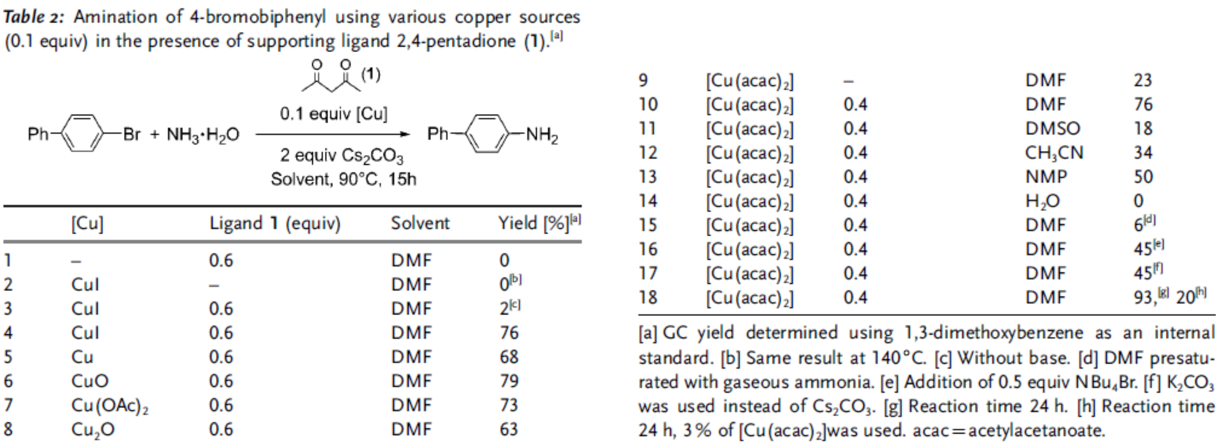
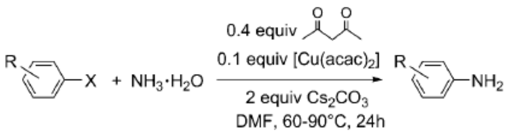


Table 2: Amination of 4-bromobiphenyl using various copper sources (0.1 equiv) in the presence of supporting ligand 2,4-pentadione (**1**).[a]

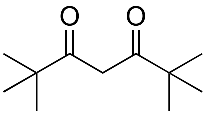
$$\text{Ph-C}_6\text{H}_4\text{-Br} + NH_3\cdot H_2O \xrightarrow[\text{2 equiv } Cs_2CO_3,\ \text{Solvent, 90°C, 15h}]{\text{(1)},\ \text{0.1 equiv [Cu]}} \text{Ph-C}_6\text{H}_4\text{-NH}_2$$

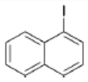
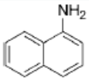
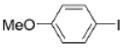
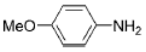
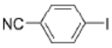
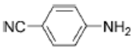
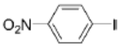
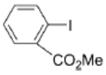
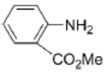
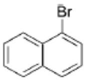
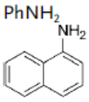
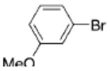
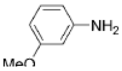
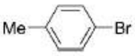
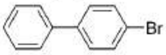
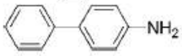
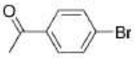
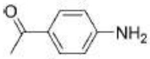
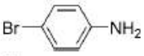
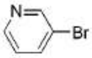
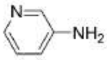
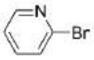
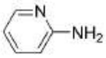
	[Cu]	Ligand **1** (equiv)	Solvent	Yield [%][a]
1	–	0.6	DMF	0
2	CuI	–	DMF	0[b]
3	CuI	0.6	DMF	2[c]
4	CuI	0.6	DMF	76
5	Cu	0.6	DMF	68
6	CuO	0.6	DMF	79
7	$Cu(OAc)_2$	0.6	DMF	73
8	Cu_2O	0.6	DMF	63
9	$[Cu(acac)_2]$	–	DMF	23
10	$[Cu(acac)_2]$	0.4	DMF	76
11	$[Cu(acac)_2]$	0.4	DMSO	18
12	$[Cu(acac)_2]$	0.4	CH_3CN	34
13	$[Cu(acac)_2]$	0.4	NMP	50
14	$[Cu(acac)_2]$	0.4	H_2O	0
15	$[Cu(acac)_2]$	0.4	DMF	6[d]
16	$[Cu(acac)_2]$	0.4	DMF	45[e]
17	$[Cu(acac)_2]$	0.4	DMF	45[f]
18	$[Cu(acac)_2]$	0.4	DMF	93,[g] 20[h]

[a] GC yield determined using 1,3-dimethoxybenzene as an internal standard. [b] Same result at 140°C. [c] Without base. [d] DMF presaturated with gaseous ammonia. [e] Addition of 0.5 equiv NBu_4Br. [f] K_2CO_3 was used instead of Cs_2CO_3. [g] Reaction time 24 h. [h] Reaction time 24 h, 3% of $[Cu(acac)_2]$was used. acac = acetylacetanoate.



ligand **6**
(entry 3)



	ArX	$ArNH_2$	Yield [%][a]
1			90
2			80
3			94,93[b] 99[c]
4			63
5			23
6	PhBr	$PhNH_2$	78
7			88
8			85
9			65, 79[d]
10			90,98[c]
11			92, 82[b]
12			92, 84[b]
13			41
14			84
15			82

[a] At 90°C (general case). [b] At 60°C. [c] At 90°C with ligand **6**. [d] Reaction time, 36 h.

For other examples, see review:*Angew. Chem., Int. Ed.* **2011**, *50*, 86.

Summary of Arylation

Pd-catalyzed Reactions

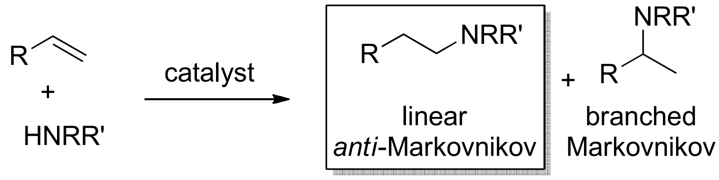
- Bulky, electron-rich, phosphine ligands are essential to obtain desired product.
- Selectivity between primary and secondary amines are main problem.
  Use of large excess amount of ammonia is effective for primary selective reaction.
- Wide substrate scope has been obtained. Even ArCl and ArOTs gave good results with low catalyst loading.

Cu-catalyzed Reactions

- In most cases, primary amines are only product.
- Relatively high catalyst loading is necessary and substrate scope is limited.
  Sensitive to steric hiderance. Reaction with ArCl is difficult.

4. Hydroamination

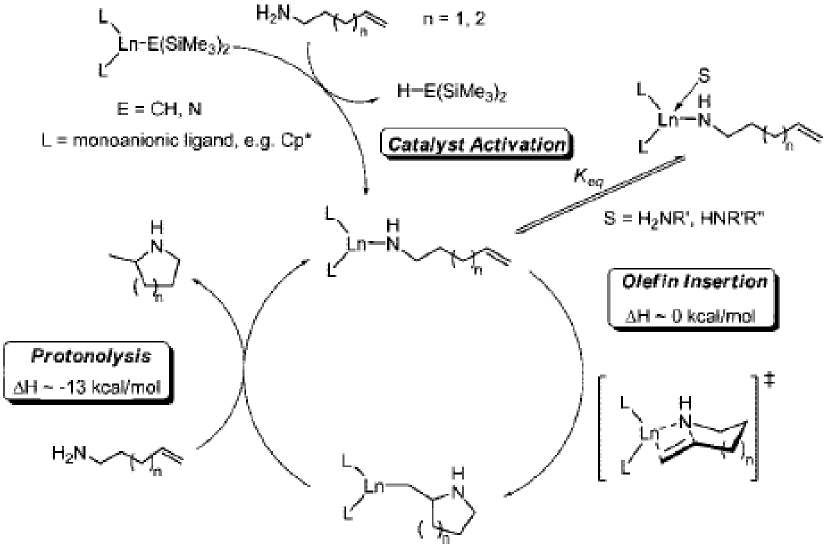
4-1. Hydroamination With Amines



anti-Markovnikov selective intermolecular hydroamination of olefin to give linear amines is highly imortant and formidable challeng.

Rare-Earth Metal-catalyzed Hydroamination

Scheme 3. Simplified Mechanism for Rare-Earth Metal Catalyzed Hydroamination/Cyclization of Aminoalkenes



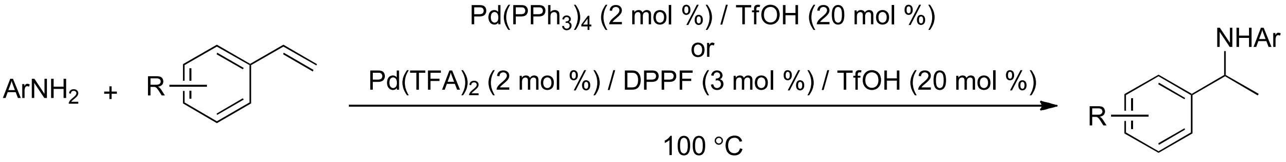
This type reactions were well studied using rare-earth metal-Cp* amido complexs or related complexs.

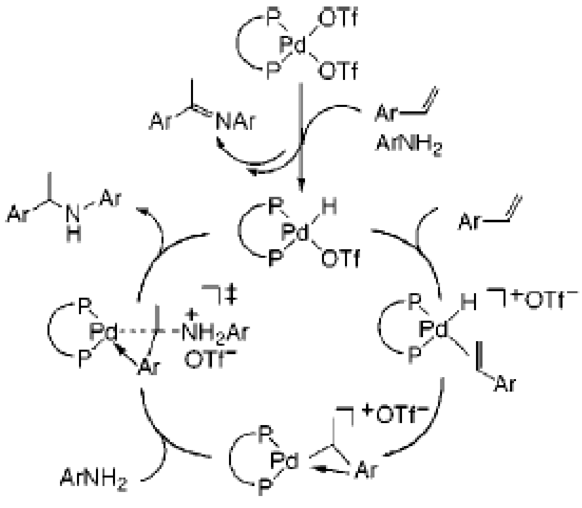
Also alkaline-earth metal amido complex are known to catalyze hydroamination.

However those reactions show Markovnikov-selectivity.

For detail, see review:
Chem. Rev. **2008**, *108*, 3795.

Late Transition Metal Catalyzed Markovnikov Selective Reactions

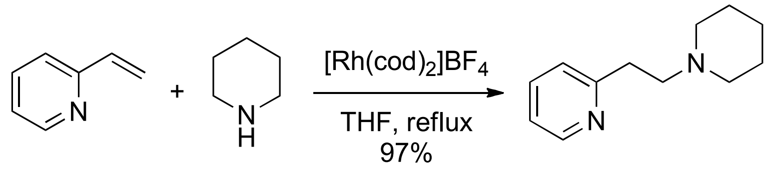




- Markovnikov Selectivity
- Pd π-benzyl complex is major species in reaction mixture (isolated and characterized by NMR and X-ray)
- Addition of amines proceed via stereo inversion.

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2000**, *122*, 9546.
Mechanistic Study: *J. Am. Chem. Soc.* **2002**, *124*, 1167.

Substrate Induced anti-Markovnikov Selectivity

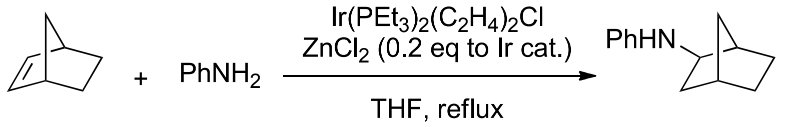


Reaction seemed to proceed via cooridation of pyridine to Rh.

Beller, M. *et al. Eur. J. Inorg. Chem.* **1999**, 1121.

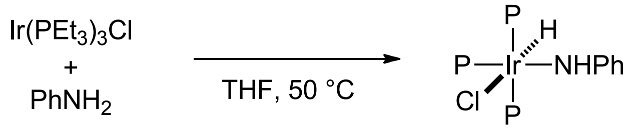
Hydroamination via N-H Activation

Milstein, D. *et al. J. Am. Chem. Soc.* **1988**, *110*, 6738.

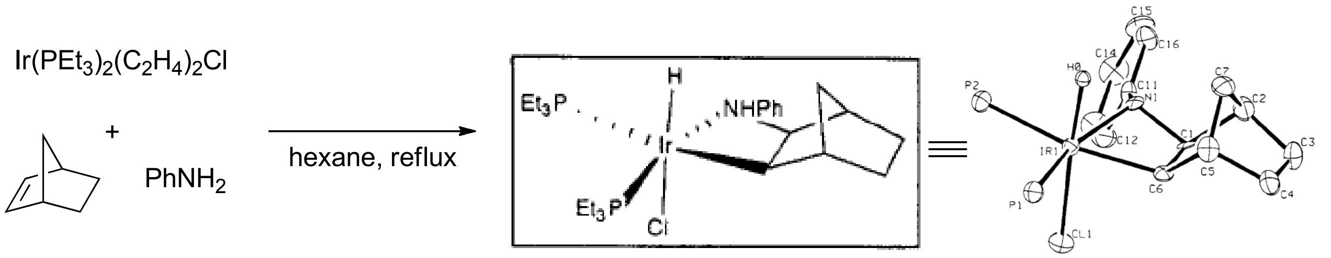


up to 7.0 TON

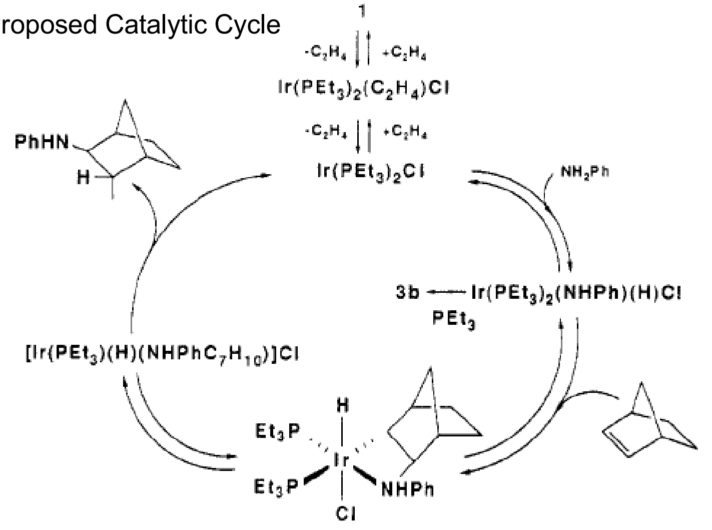
Stoichiometric Reactions Affording Intermediates



Determined by NMR
(Ir-^{1}H : –21.47, coupled with P)



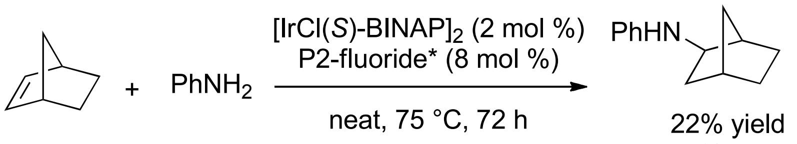
Proposed Catalytic Cycle



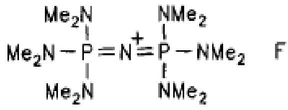
$ZnCl_2$ would promote reductive elimination by facilitating the dissociation of Cl anion and generation of 16 electton cationic complex.

Aysmmetric Version

Togni, A. *et al. J. Am. Chem. Soc.* **1997**, *119*, 10857.



22% yield
95% ee

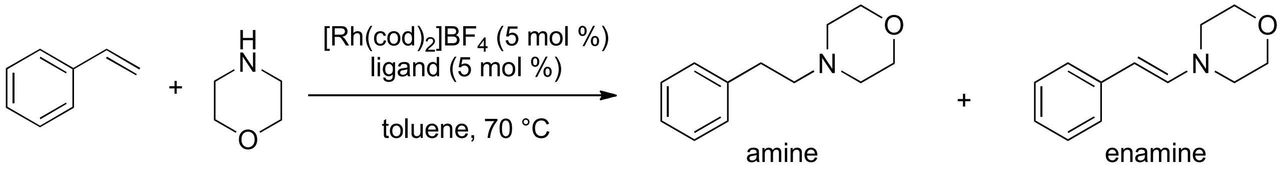


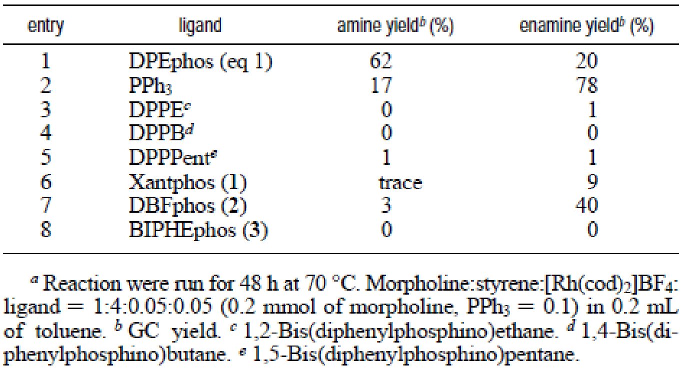
P2-fluoride

P2-fluoride as "naked" F^- source might coordinate to Ir and promote oxidative addition.

Rh-catalyzed *Anti*-Markovnikov-selective Hydroamination

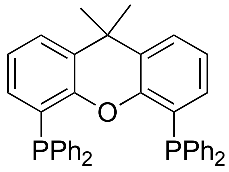
Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2003**, *125*, 5608.



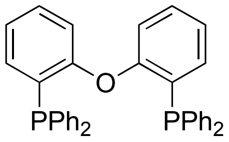


entry	ligand	amine yield[b] (%)	enamine yield[b] (%)
1	DPEphos (eq 1)	62	20
2	PPh_3	17	78
3	DPPE[c]	0	1
4	DPPB[d]	0	0
5	DPPPent[e]	1	1
6	Xantphos (1)	trace	9
7	DBFphos (2)	3	40
8	BIPHEphos (3)	0	0

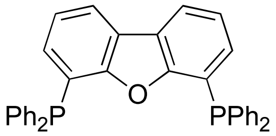
[a] Reaction were run for 48 h at 70 °C. Morpholine:styrene:[Rh(cod)$_2$]BF$_4$:ligand = 1:4:0.05:0.05 (0.2 mmol of morpholine, PPh_3 = 0.1) in 0.2 mL of toluene. [b] GC yield. [c] 1,2-Bis(diphenylphosphino)ethane. [d] 1,4-Bis(diphenylphosphino)butane. [e] 1,5-Bis(diphenylphosphino)pentane.



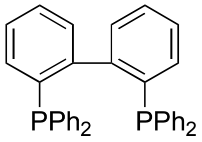
Xantphos



DPEphos

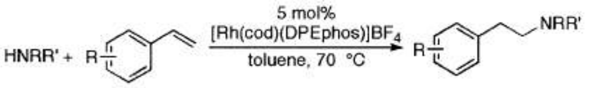


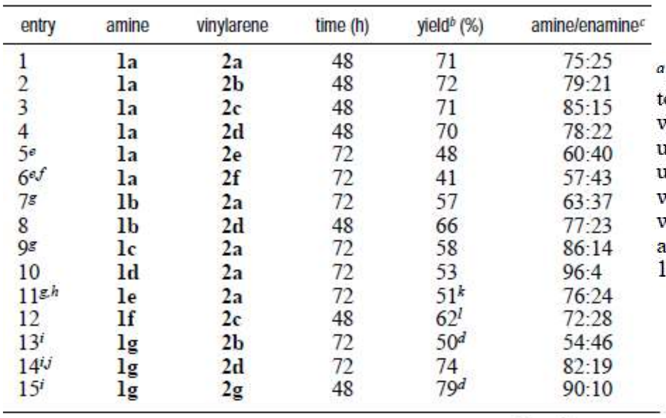
DBFphos



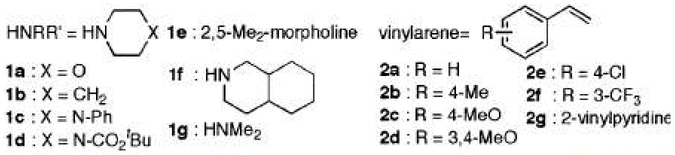
BIPHEphos

Only DPEphos gave hydroamination product in moderate selectivity.





entry	amine	vinylarene	time (h)	yield[b] (%)	amine/enamine[c]
1	1a	2a	48	71	75:25
2	1a	2b	48	72	79:21
3	1a	2c	48	71	85:15
4	1a	2d	48	70	78:22
5[e]	1a	2e	72	48	60:40
6[e,f]	1a	2f	72	41	57:43
7[g]	1b	2a	72	57	63:37
8	1b	2d	48	66	77:23
9[g]	1c	2a	72	58	86:14
10	1d	2a	72	53	96:4
11[g,h]	1e	2a	72	51[k]	76:24
12	1f	2c	48	62[l]	72:28
13[i]	1g	2b	72	50[d]	54:46
14[i,j]	1g	2d	72	74	82:19
15[i]	1g	2g	48	79[d]	90:10



1a : X = O
1b : X = CH_2
1c : X = N-Ph
1d : X = N-$CO_2{}^tBu$
1e : 2,5-Me_2-morpholine
1g : $HNMe_2$
2a : R = H
2b : R = 4-Me
2c : R = 4-MeO
2d : R = 3,4-MeO
2e : R = 4-Cl
2f : R = 3-CF_3
2g : 2-vinylpyridine

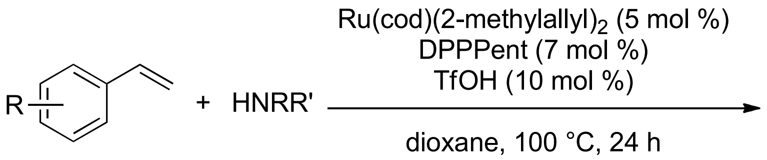
[a] Amine:vinylarene:Rh catalyst = 1:4:0.05 (1 mmol of amine) in 1 mL of toluene. [b] Isolated yield by silica gel column chromatography. [c] Selectivity was calculated from the GC area. [d] GC yield. [e] 10 mol % Rh catalyst was used. [f] 2.0 equiv of vinylarene was used. [g] 75 °C. [h] 0.5 mL of toluene was used. [i] Dimethylamine 2.0 M in THF solution (0.5 mL) and 0.5 mL toluene was used. [j] No toluene was added. [k] Diastereomer ratio of starting amine was 74:26, ratio of products was 82:18. The ratio was determined by GC area. [l] Diastereomer ratio of starting amine was 7:93, ratio of products was 17:83. The ratio was determined by GC area.

Primary amines gave no reactions.

Reason for selectivity have not been repoted.

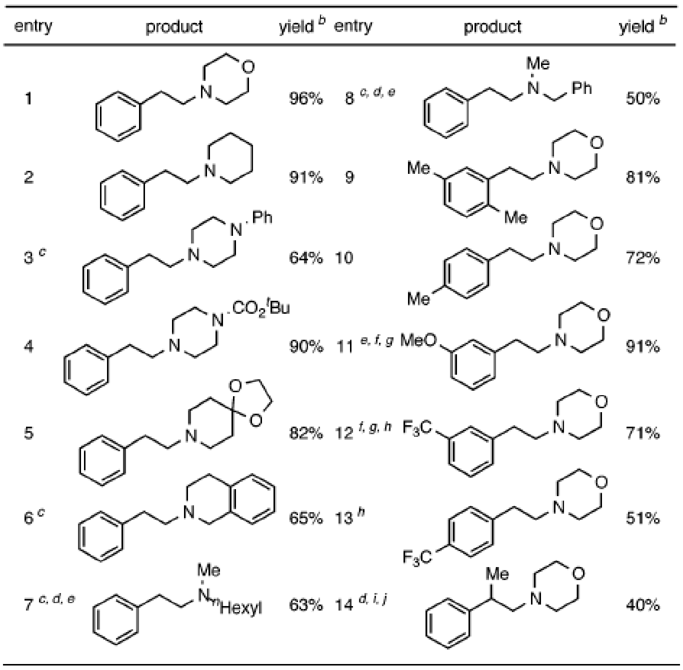
Ru-catalyzed Highly Selective Hydroamination

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2004**, *126*, 2702.
J. Am. Chem. Soc. **2005**, *127*, 5756.



- No enamine was observed.
- Only trace amout of branched product was observed under optimized conditions.
- No reaction occured in the absense TfOH or Ru cat.

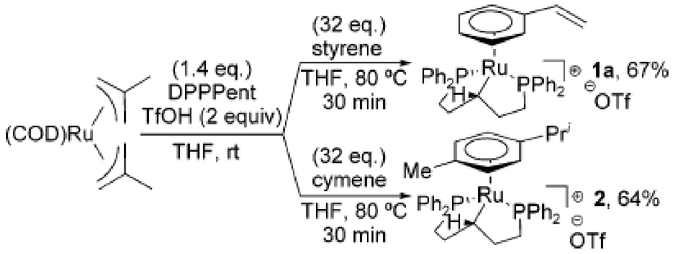
Substrate Scope



entry	product	yield[b]	entry	product	yield[b]
1		96%	8[c, d, e]		50%
2		91%	9		81%
3[c]		64%	10		72%
4		90%	11[e, f, g]		91%
5		82%	12[f, g, h]		71%
6[c]		65%	13[h]		51%
7[c, d, e]		63%	14[d, i, j]		40%

[a] Amine/vinylarene/Ru/DPPPent/TfOH = 1:2:0.05:0.07:0.10 (1 mmol of amine) in 0.50 mL of dioxane. [b] Isolated yield. [c] 4 mmol of vinylarene was used. [d] 80 °C. [e] 48 h. [f] 0.25 mL of dioxane. [g] 110 °C. [h] D*i*PPF was used as ligand. [i] 1.5 mmol of vinylarene was used. [j] 72 h.

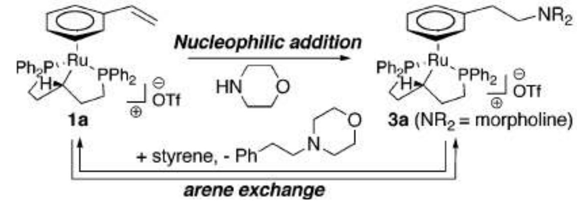
Ru-arene complexes as Intermediates

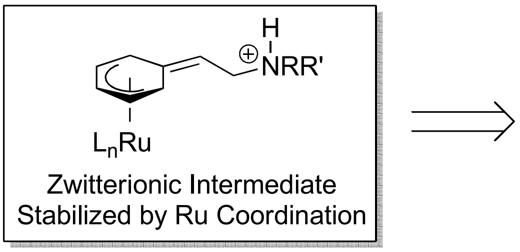


These complexs showed slightly higher reactivity when used as catalyst.

Proposed Reaction Mechanism

Scheme 5

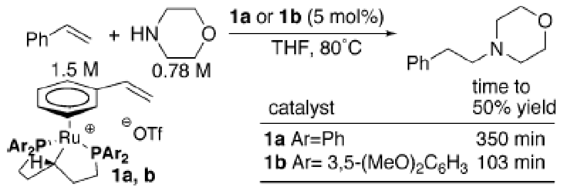




Zwitterionic Intermediate Stabilized by Ru Coordination

Electron deficient ligand showed higher reactivity.

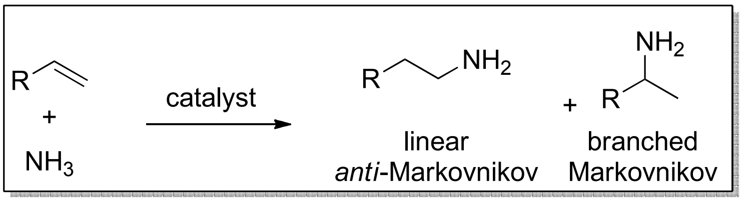
Scheme 6



catalyst	time to 50% yield
1a Ar=Ph	350 min
1b Ar= 3,5-$(MeO)_2C_6H_3$	103 min

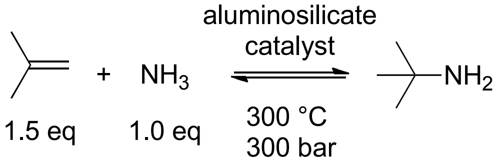
Problem: The reaction of this type mechanism can be applied to only aryl-vinyl substrates in principle.

4-2. Hydroamination With Ammonia



So far, there has been no report of selective homogeneous metal catalyst for this process.

Heterogeneous Catalyst

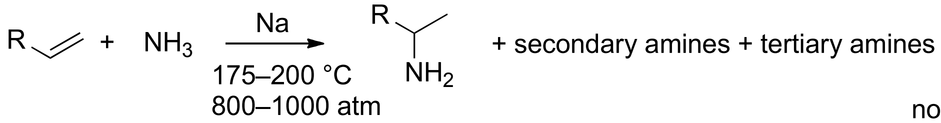


9-17% conversion
>95% selectivity

This process was commercialized by BASF.
Hayes, K. S. *Applied Catalysis A: General* **2001**, *221*, 187.

Alkali Metal-catalyzed Hydromination

Reactions between NH_3 and olefin under extremely harsh conditions were reported.

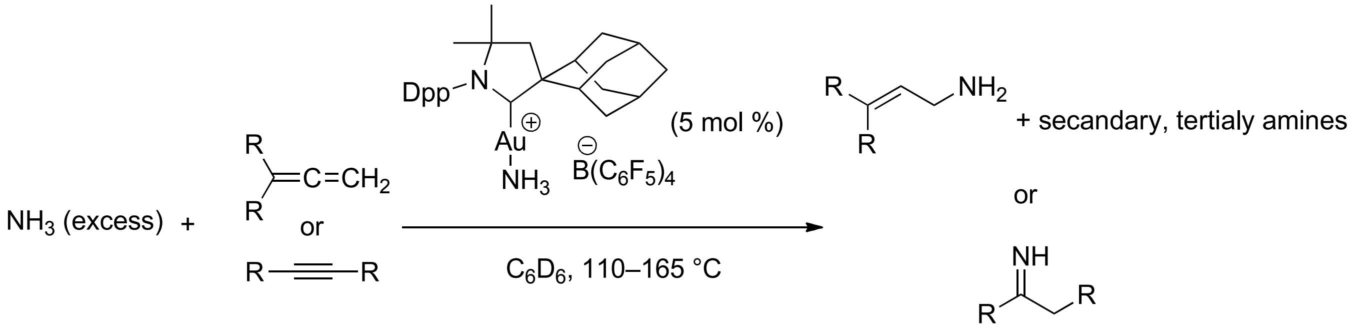


not selective, not high yield

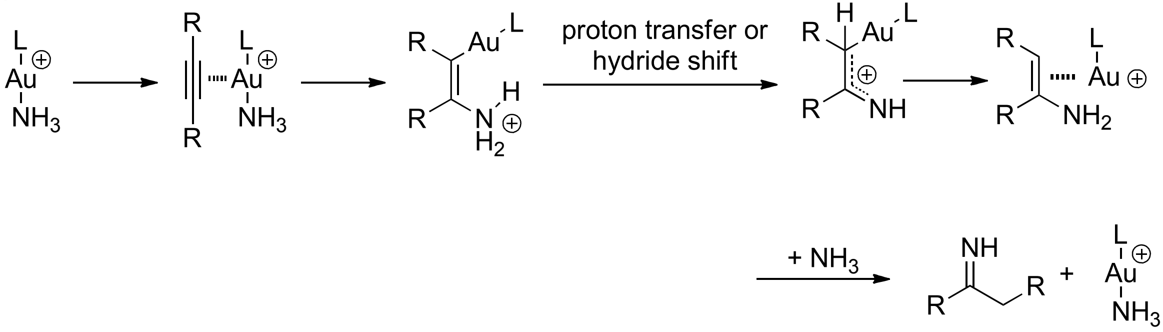
Howk, B. W. *et al. J. Am. Chem. Soc.* **1954**, *76*, 1899.

Gold-catalyzed Hydroamination of Alkynes and Allenes with Ammonia

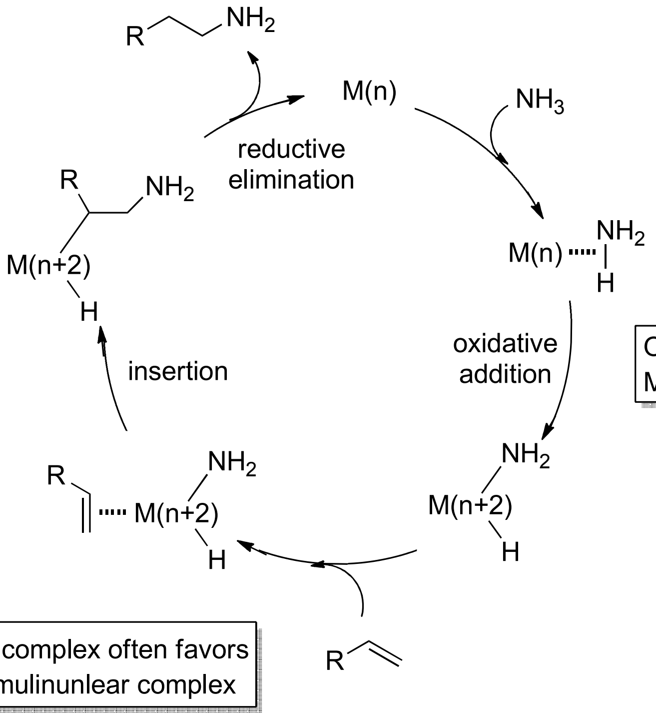
Bertrand, G. *et al. Angew. Chem., Int. Ed.* **2008**, *47*, 5224.



Proposed Reaction Mechanism



One of The Hypothetical Mechanism of Hydroamination with Ammonia



Oxidative addition to form M-NH_2 complex is difficult.

- Strong bonding energy
- Stable Werner complex

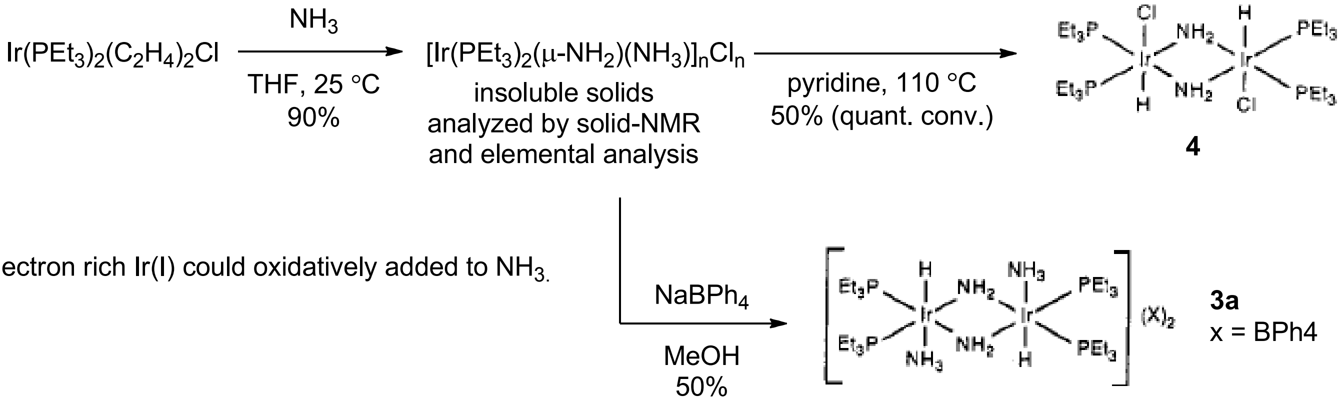
M-NH_2 complex often favors stable mulinunlear complex

5. N-H Activation of Ammonia

5-1. Multimetallic Activation

Oxidative Addition of Ir(I)

Casalnuovo, A. L.; Milstein, D. *et al. Inorg. Chem.* **1987**.*26*. 971.



$Ir(PEt_3)_2(C_2H_4)_2Cl \xrightarrow[\text{THF, 25 °C, 90\%}]{NH_3} [Ir(PEt_3)_2(\mu\text{-}NH_2)(NH_3)]_nCl_n$

insoluble solids
analyzed by solid-NMR
and elemental analysis

pyridine, 110 °C
50% (quant. conv.)

4

$NaBPh_4$
MeOH
50%

3a
x = BPh4

Electron rich Ir(I) could oxidatively added to NH_3.

X-ray Structures of **3a** and **4**

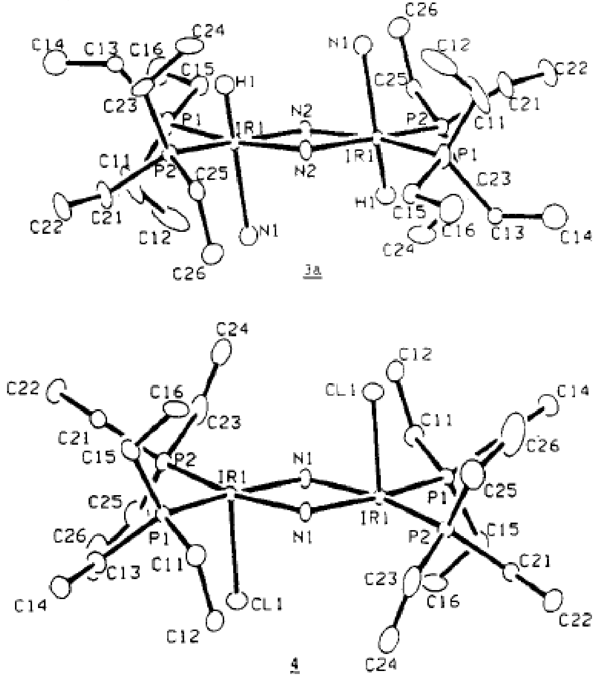
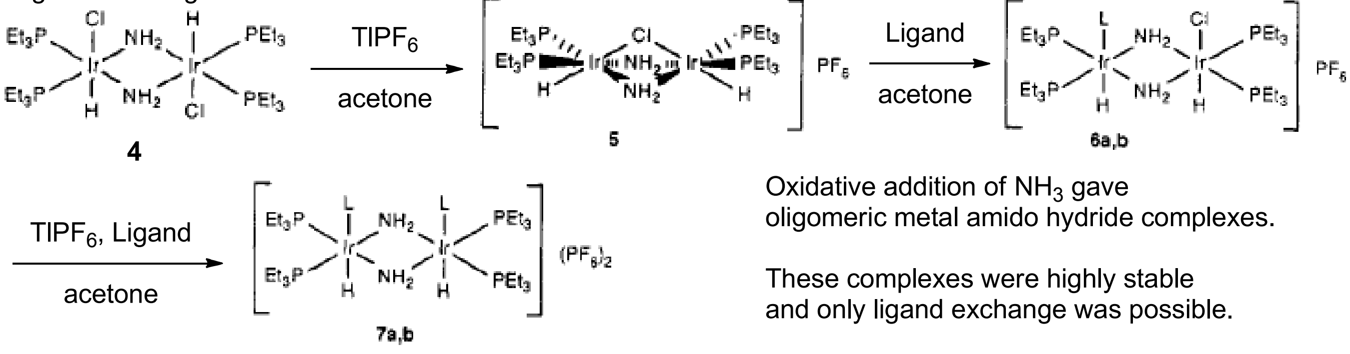


Figure 1. ORTEP drawings of **3a** (cation only) and **4** showing thermal ellipsoids at 20% probability level. Selected bond distances (Å) and angles (deg) are as follows. For **3a**: Ir–N_1, 2.244 (4); Ir_1–N_2, 2.128 (3); Ir_1–N_2, 2.127 (3); Ir_1–H_1, 1.61 (5); Ir_1–P_1, 2.274 (1); Ir_1–P_2, 2.280 (1); N_2–Ir_1–N_2, 77.0 (1); N_1–Ir_1–N_2, 84.3 (1); N_1–Ir_1–N_2, 84.5 (1); P_1–Ir_1–N_2, 170.1 (1); P_2–Ir_1–N_2, 169.9 (1); H_1–Ir_1–N_1, 157 (2). For **4**: Ir_1–N_1, 2.10 (1); Ir_1–N_1, 2.13 (1); Ir_1–P_1, 2.264 (4); Ir_1–P_2, 2.264 (4); Ir_1–Cl_1, 2.504 (4); Cl_1–Ir_1–P_1, 96.4 (1); Cl_1–Ir_1–P_2, 94.3 (1); Cl_1–Ir_1–N_1, 87.8 (3); Cl_1–Ir_1–N_1, 84.4 (3); P_1–Ir_1–N_1, 168.6 (3); P_2–Ir_1–N_1, 168.7 (3); N_1–Ir_1–N_1, 75.3 (5).[10]

Ligand exchanges



4

$TlPF_6$
acetone

5

Ligand
acetone

6a,b

$TlPF_6$, Ligand
acetone

7a,b

Ligand = CO gas or *t*BuNC

Oxidative addition of NH_3 gave
oligomeric metal amido hydride complexes.

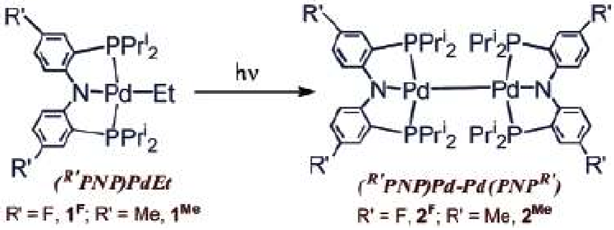
These complexes were highly stable
and only ligand exchange was possible.

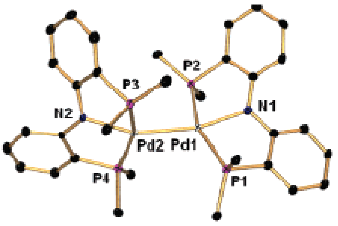
Oxidative addition also occured without σ-donating ligands.
See: Milstein, D. *et al. Angew. Chem., Int. Ed.* **1991**, *30*, 707.

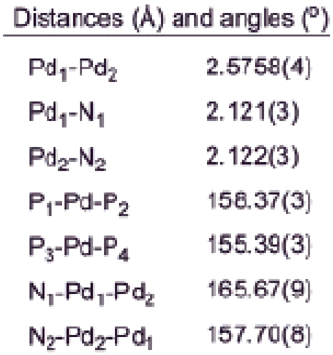
Oxidative Addition of Pd(I) Dimer Comlex

Ozerov. O. V. *et al. J. Am. Chem. Soc.* **2007**, *129*, 10318.

Photolytic Generation of Pd(I)-Dimer



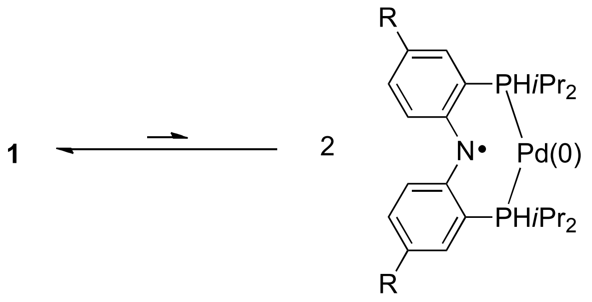




Distances (Å) and angles (°)	
Pd$_1$-Pd$_2$	2.5758(4)
Pd$_1$-N$_1$	2.121(3)
Pd$_2$-N$_2$	2.122(3)
P$_1$-Pd-P$_2$	156.37(3)
P$_3$-Pd-P$_4$	155.39(3)
N$_1$-Pd$_1$-Pd$_2$	165.67(9)
N$_2$-Pd$_2$-Pd$_1$	157.70(8)

Pd has distorted square-planar.
Pd-Pd length indicates existence of Pd-Pd bond.

Equilibrium betweem Monomer and Dimer



NMR analysis shows the Pd-dimer is almost diamangnetic.

But EPR spectrum indicates existence of *"organic radicals"*.

Bimetallic Oxidative Addition of Ammonia

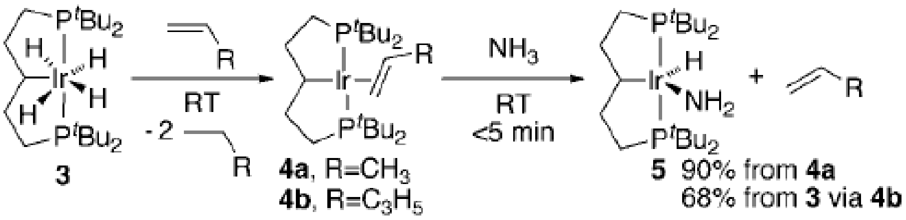
$$(^{R'}\text{PNP})\text{Pd-Pd}(\text{PNP}^{R'}) \xrightarrow[C_6D_6,\ 85\ ^\circ C]{H\text{-}NH_2} \underset{5^F \text{ or } 5^{Me}}{(^{R'}\text{PNP})\text{PdH}} + \underset{7^F \text{ or } 7^{Me}}{(^{R'}\text{PNP})\text{PdNH}_2}$$

Reaction mechanism was unrevealed.

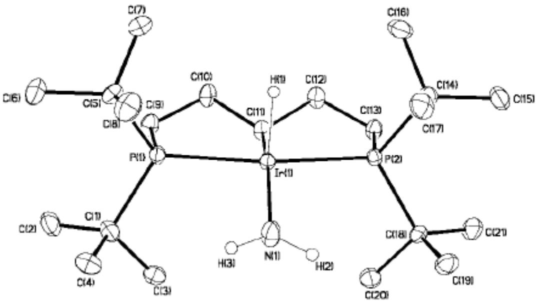
5-2. Monometallic Activation

Oxidative Addition of NH_3 to Form Monomeric Ir Complex

Hartwig, J. F. *et al. Science* **2005**, *307*, 1080.



X-ray Structure of **5**

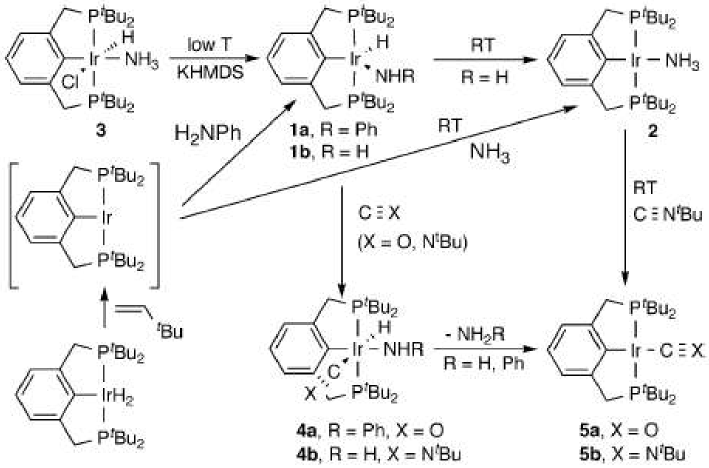


ORTEP diagram of **5**

Geometry between trigonal bipyramidal and square pyramidal indicated π-donation from amido p orbital to Ir center.

Mechanistic studies, reaction using ND_3 and kinetic experimetns, supported the path of direct oxidative addition after ligand dissociation, Electron-donating alkyl backbone is essential.

Hartwig, J. F. *et al. J. Am. Chem. Soc.* **2003**, *125*, 13644.

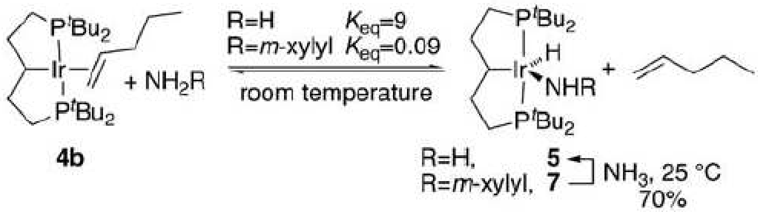


Amido hydride complex rapidly gave ammonia (Werner) complex at rt.
(stable < –30 °C)

Oxidative additon of anilines is thermodyamically favorable.

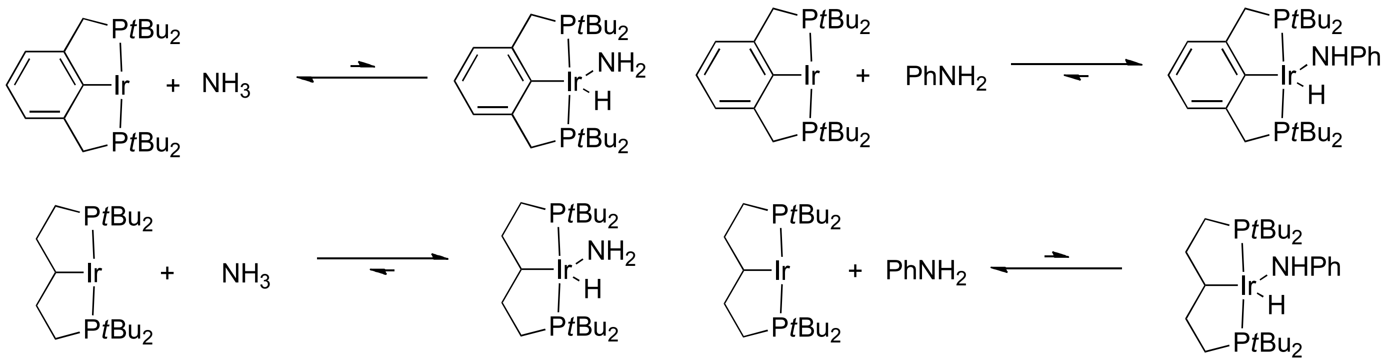
$$(\mathrm{PCP})\mathrm{IrH(Ph)} + \mathrm{PhNH_2} \xrightleftharpoons{K = 105} (\mathrm{PCP})\mathrm{IrH(NHPh)} + \mathrm{PhH}$$

Thermodyanmics with Alkyl Backbone Ligand



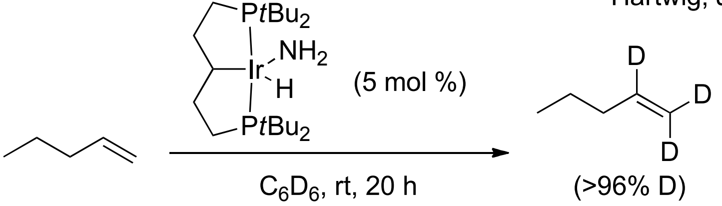
Surprisingly, anilido complex is less favorable than parent amido complex.
They said this is due to the steric factor or stronger π-donation of NH$_3$.
(But neither of them can explain the differece between aryl and alkyl backbone ligands.)

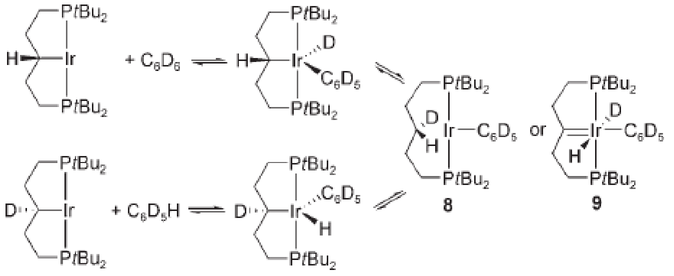
If the coodination of olefin (good π-acceptor) does not affect the equilibrium,..



This [PCP]Ir(H)NH$_2$ was not so kinetically stable.

Hartwig, J. F. *et al. Angew. Chem., Int. Ed.* **2008**, *47*, 5785.

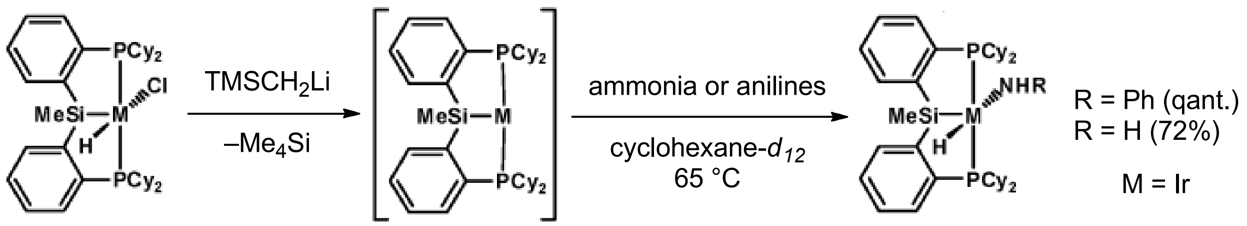




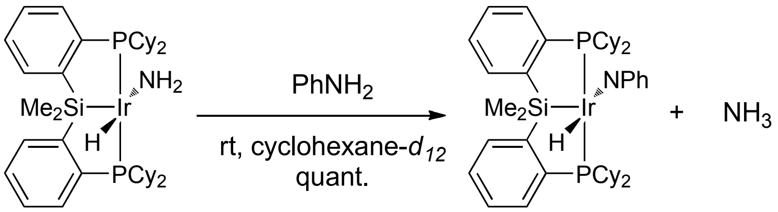
Scheme 1. Proposed pathways for the iridium-catalyzed H/D exchange in C$_6$D$_6$.

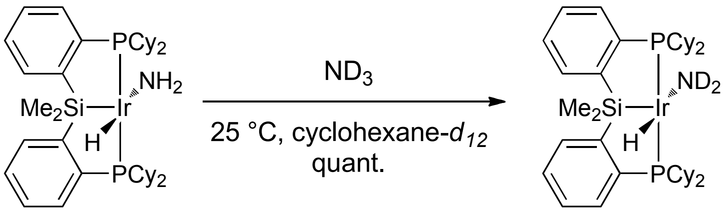
More Stable [PSiP]Ir(H)NH_2 Complex

Turculet, L. *et al. J. Am. Chem. Soc.* **2009**, *131*, 14234.



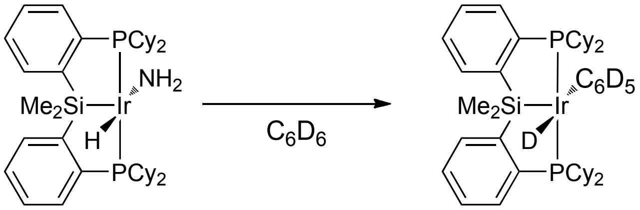
Amido Exchange by Unrevealed Mechanism





Simple reductive elimination/oxidative addition mechanism cannot explain.

Reductive Elimination



This reaction proceeded at only higher temp (>100 °C).

6. Summary

Recently, several transitionmetal-catalyzed reactions using NH_3 has been achieved.

Reactions which don't require formation of M-NH_2 ,reductive amination, allylic substitutions, could be achieved by relatively small modification of reaction conditions to inhibit over reactions.

Excellent reaction conditions for Buchwald-Hartwig amination and Ullmann amination were also achieved. Key for the former is using bulky, electron rich ligand, which is recent standard strategy used in several transitionmetal catalyzed reactions.

Hydroamination is one of the most important but challenging reaction and has not been achieved.

To discover and develop new catalytic reactions, several groups are challenging oxidative addition of NH_3. So far, only stoichiometric processes have been reported.