Transition Metal Mediated Saturated C-H Amination

Frontiers of Chemistry Seminar

Jingbo Xiao

September 18, 2004

Outline

1. ***Introduction***

2. ***C-H amination by Mangnaese (Mn) and Iron (Fe)***
3. ***C-H amination by Ruthenium (Ru)***
4. ***C-H amination by Cobalt (Co) and Rhodium (Rh)***
5. ***C-H amination by Copper (Cu) and Silver (Ag)***

6. ***Outlook***

Frontiers in This Field

Breslow, R. (Columbia University)

First example of transition metal C-H amination

Mansuy, D. (France)

Mn, Fe in porphyrin system (mechanism)

Che, C. -M. (Hong Kong University)

Mn, Ru and Rh in porphyrin system and asymmetric amination (mechanism)

Cenini, S. (Italy)

Co in porphyrin system

Muller, P. (Geneve University) and Du Bois, J. (Stanford University)

Rh-catalyzed C-H amination

Katsuki, T. (Japan), Taylor, P. C. (UK) and Perez, P. J. (Spain)

Cu-catalyzed C-H amination

He, C. (Chicago University)

Ag-catalyzed C-H amination

et al

Saturated C-H Amination: Introduction

Advantages:

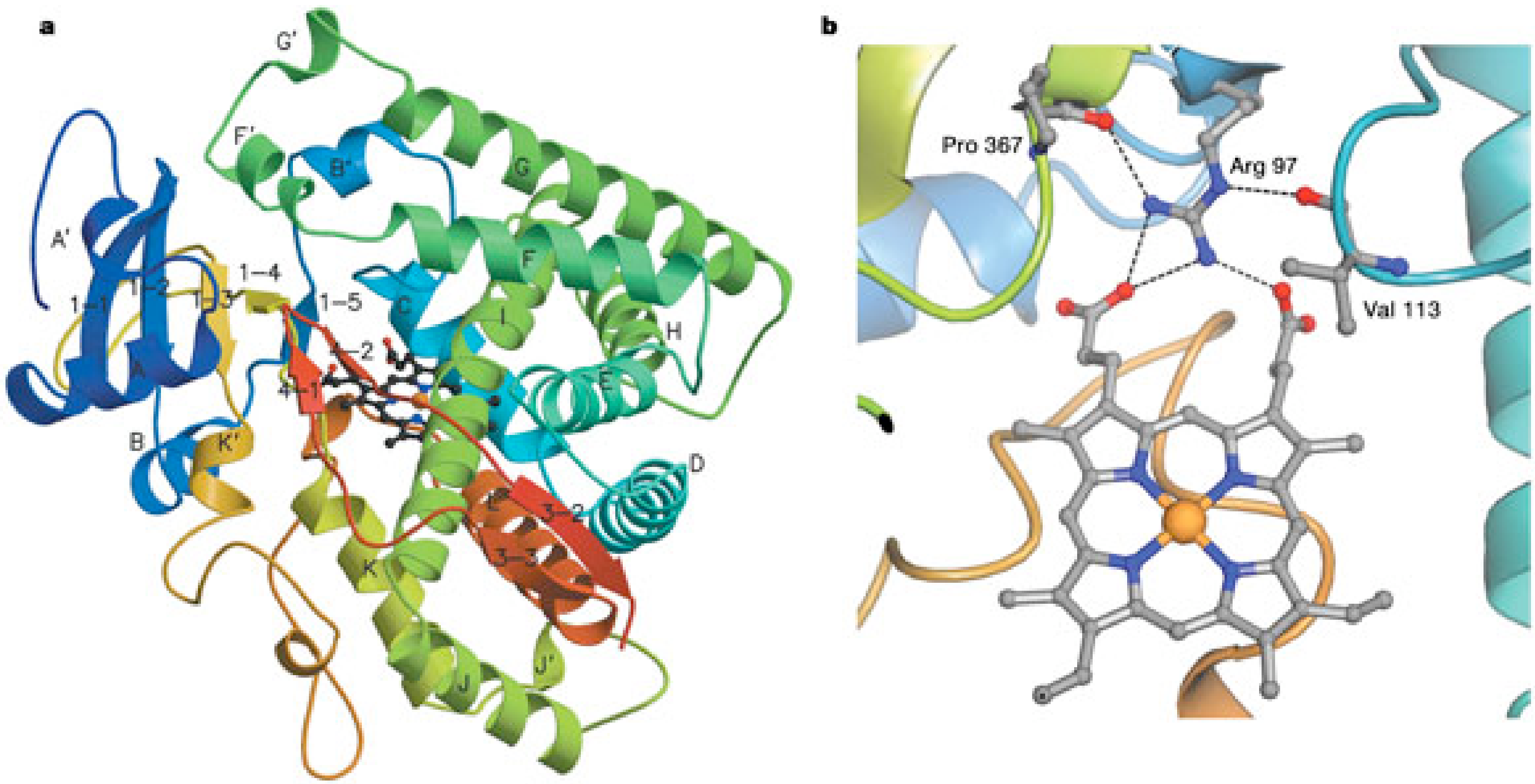
1. ***Saturated hydrocarbons which compose the majority of natural resources.***
2. ***Elucidation of the requirements for C-H amination will increase fundamental understanding of chemical reactivity.***

Disadvantages:

1. ***Lack of reactivity***
2. ***Poor of selectivity***
3. ***Mechanism is still unclear***

Inspiration of Saturated C-H Hydroxylation

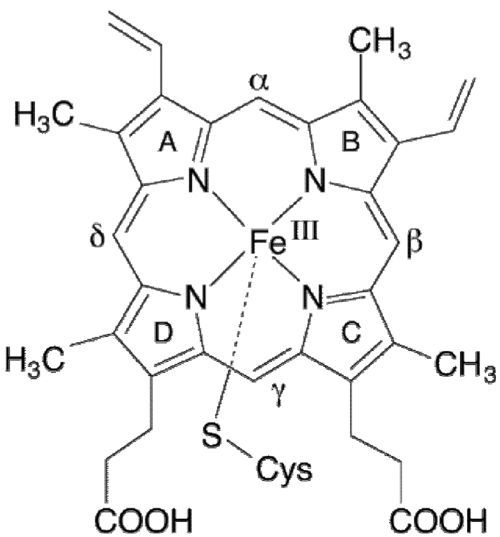
$$RC\text{-}H + O_2 + AH_2 \xrightarrow{P\text{-}450} RC\text{-}OH + H_2O + A$$



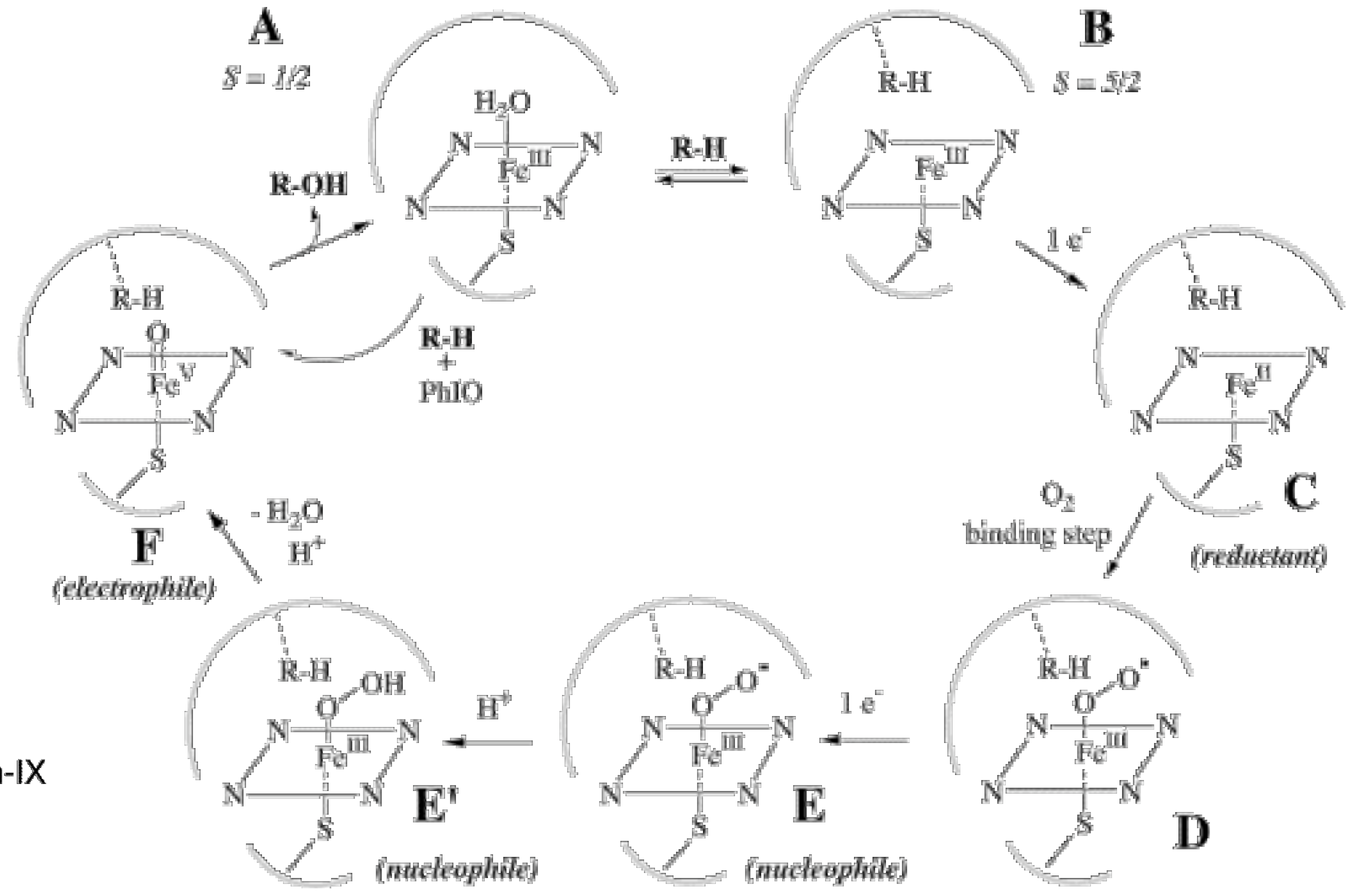
Structure of Cytochrome P-450 CYP2C9

Williams, P. A. et al, Nature, 2003, 424, 464.
Shaik, S. et al, Chem. Rev., 2004, 104, 3947.

Mechanism of Oxidation by Cytochrome P-450



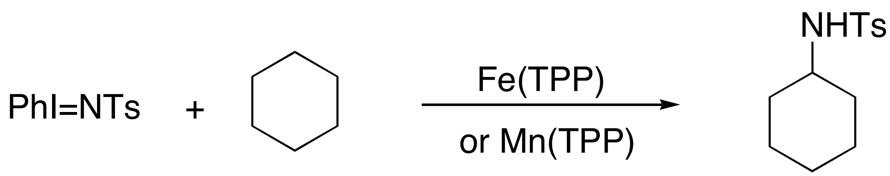
cysteinato-iron(III) protoporphyrin-IX



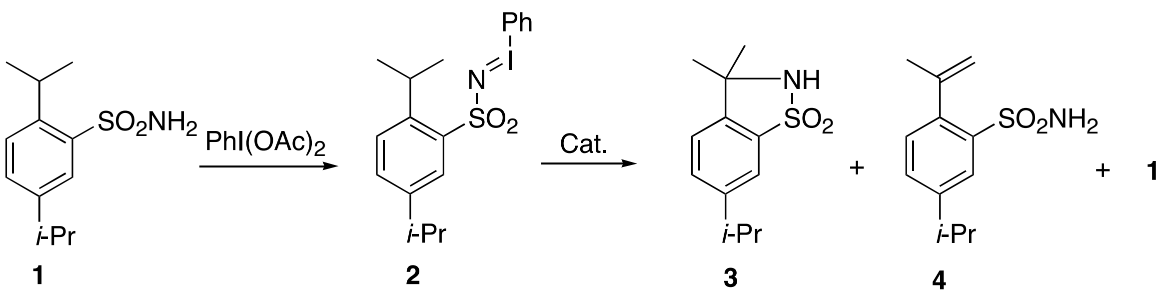
1. The oxenoid mechanism
2. The "rebound" radical mechanism

Shaik, S. et al, Chem. Rev., 2004, 104, 3947.
Shul'pin, G. et al, Chem. Rev., 1997, 97, 2879.

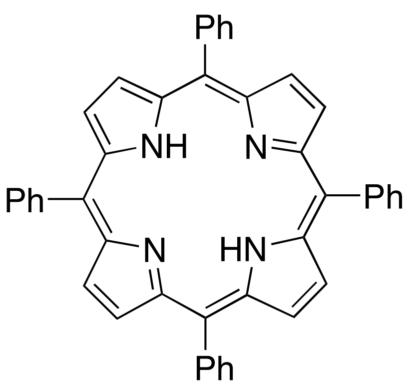
First Example of Saturated C-H Amination



Catalyst	*Yield (%)*
Fe(TPP)	*3.1*
Mn(TPP)	*6.5*



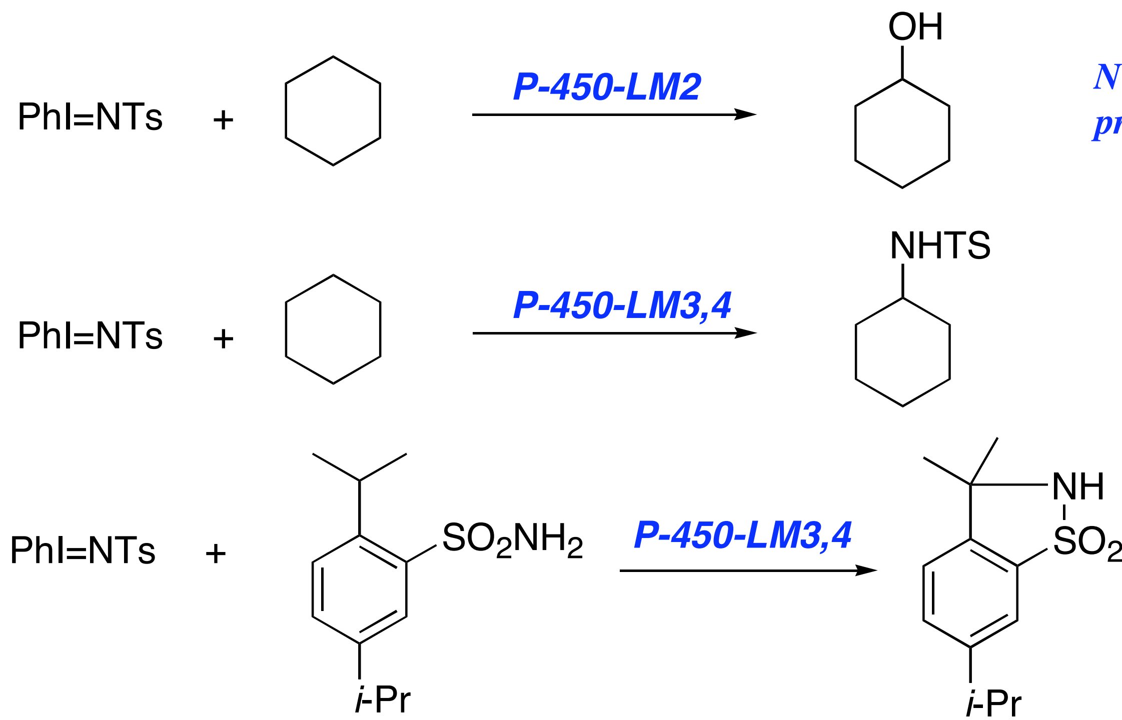
Catalyst	*Yields (%)*		
	3	*4*	*1*
Fe(TPP)	*77*	*1.4*	*12*
Mn(TPP)	*16*	*4.5*	*34*
$FeCl_3$	*16*	*0.2*	*23*
$Rh_2(OAc)_2$	*86*	*0.2*	*5.2*



Tetraphenylporphyrin (TPP)

Breslow, R. and Gellman, S. H., Chem. Commun., 1982, 1400.
Breslow, R. and Gellman, S. H., J. Am. Chem. Soc., 1983, 105, 6728.

Cytochrome P-450 Catalyzed C-H Amination



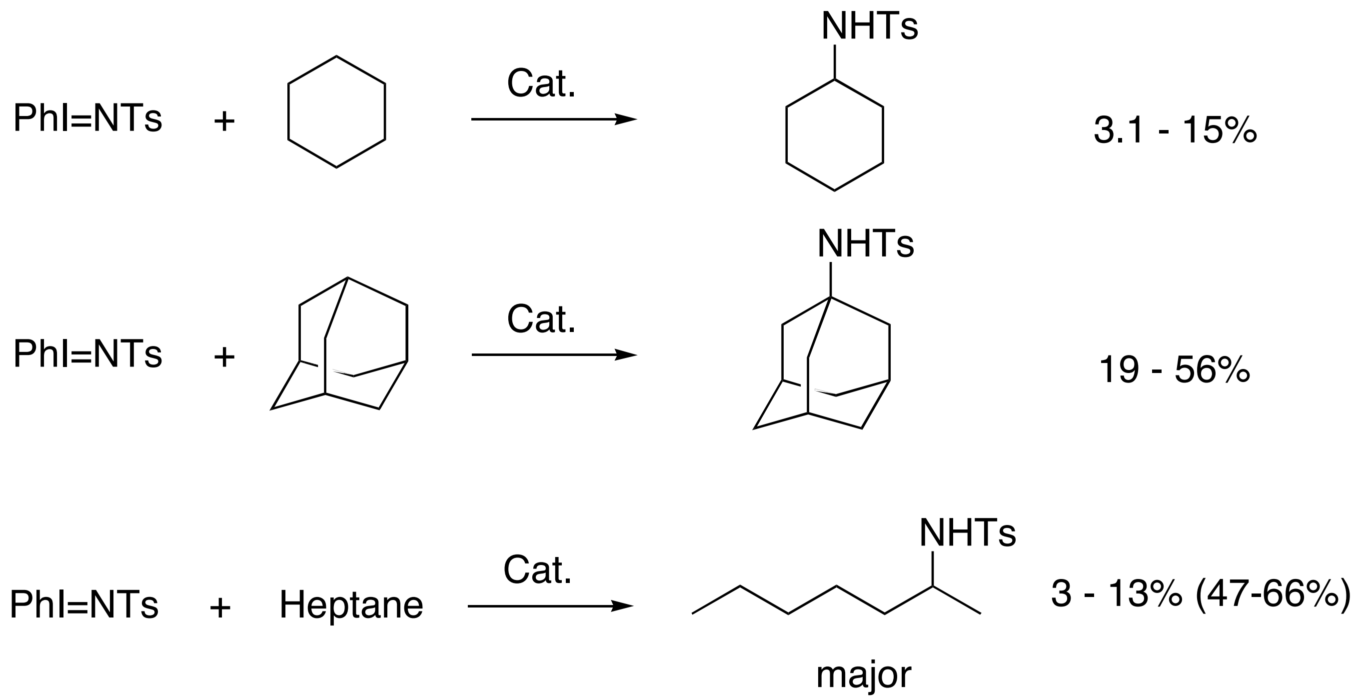
None of amindation product was detected.

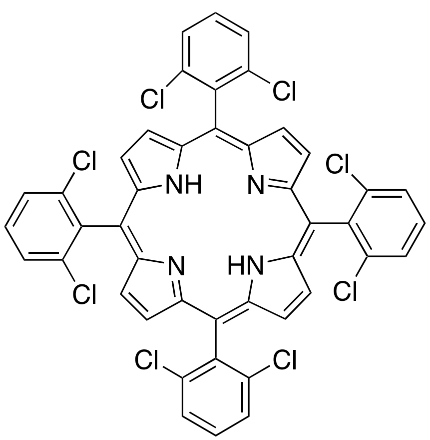
Amindation products were detected by GC-MS.

1. *Cytochrome P-450 catalyzed C-H amination is enzyme dependent.*
2. *Intramolecular nitrogen transfer proceeds more rapidly and yields greater of amination product than analogous intermolecular reaction.*
3. *The integrity of P-450 is crucial to its catalytic activity.*

Dawson, J. H. and Breslow, R., J. Am. Chem. Soc., 1985, 107, 6427.
White, R. E. et al, J. Am. Chem. Soc., 1984, 106, 4922.

Fe or Mn Catalyzed Saturated C-H Amination



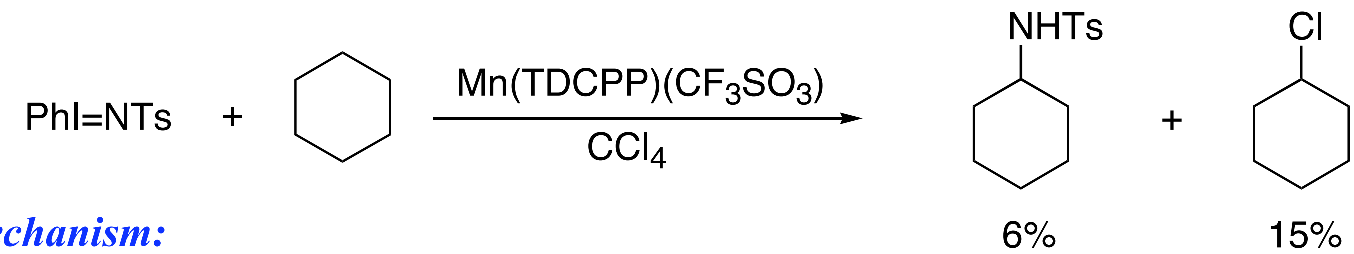


Tetra-2,6-dichorophenylporphyrin (TDCPP)

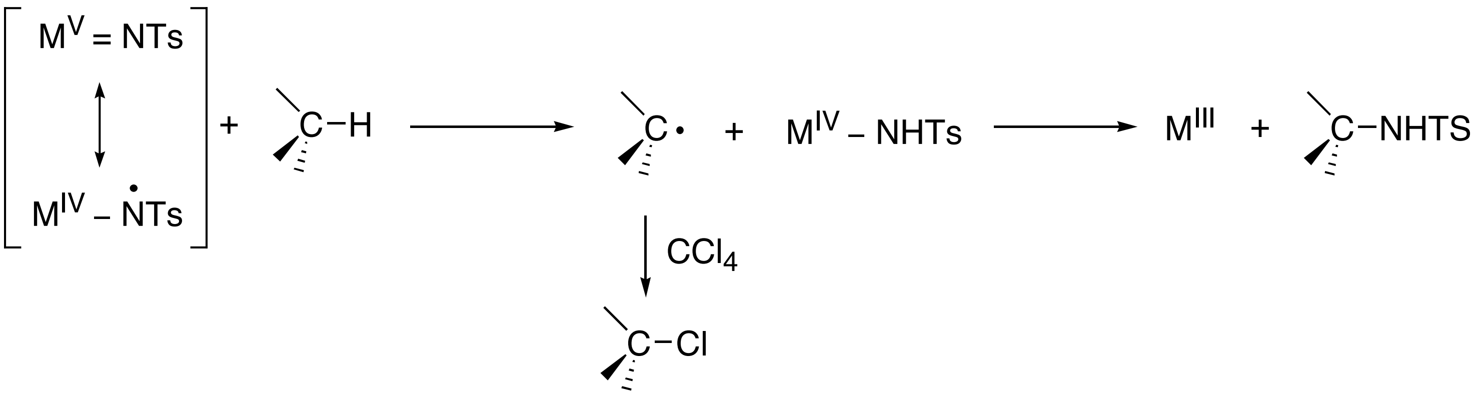
Catalysts: Mn(TPP)(Cl), Mn(TPP)(CF_3SO_3), Mn(TDCPP)(CF_3SO_3),*
Fe(TPP)(Cl), Fe(TPP)(CF_3SO_3), Fe(TDCPP)(CF_3SO_3)

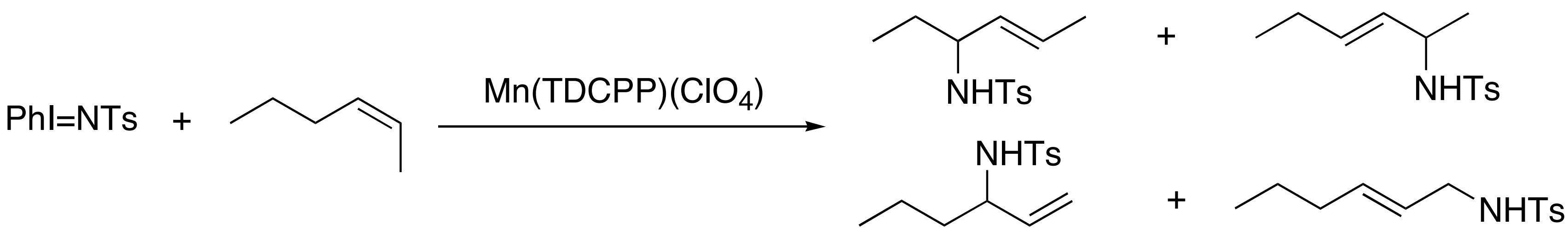
Mansuy, D. et al, New. J. Chem., 1989, 13, 651.

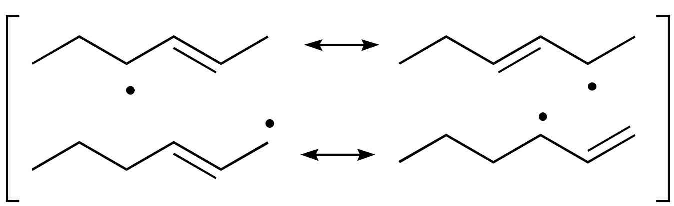
Mechanism Study



Proposed Mechanism:

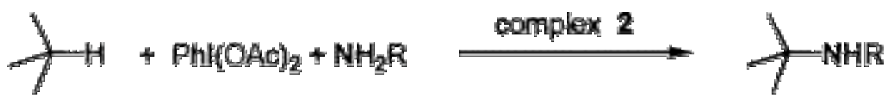


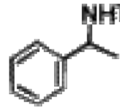
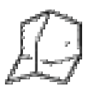
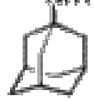
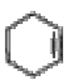
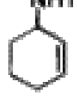


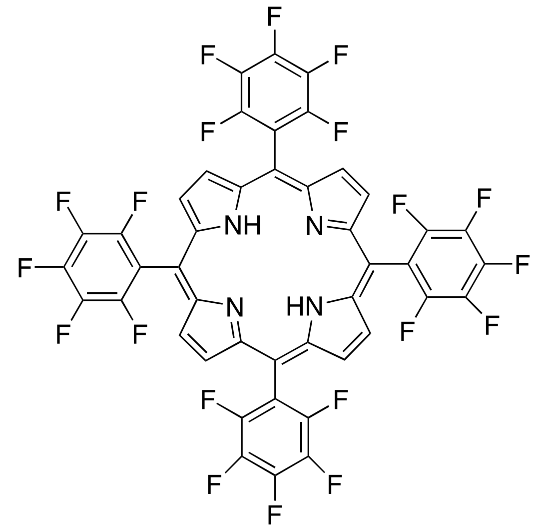


Mansuy, D. et al, New. J. Chem., 1989, 13, 651.
Mansuy, D. et al, Tetrahedron Lett., 1988, 29, 1927.

Mn-Catalyzed C-H Amination



entry	substrate	R	product	conversion (%)	isolated yield (%)[b]
1		Ts	 NHTs	58	81
2		Ts	 NHR	88	90
3		Ns		93	92
4		SO_2Me		94	81
5		Ts	 NHTs	36	72
6		Ts	 NHTs	86	83
7		Ts	 NHTs	91	85

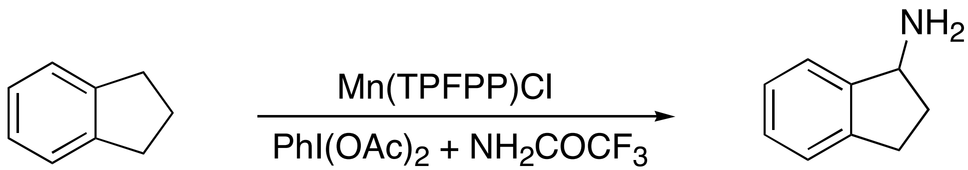


Tetrakis(pentafluorophenyl)porphyrin (TPFPP)

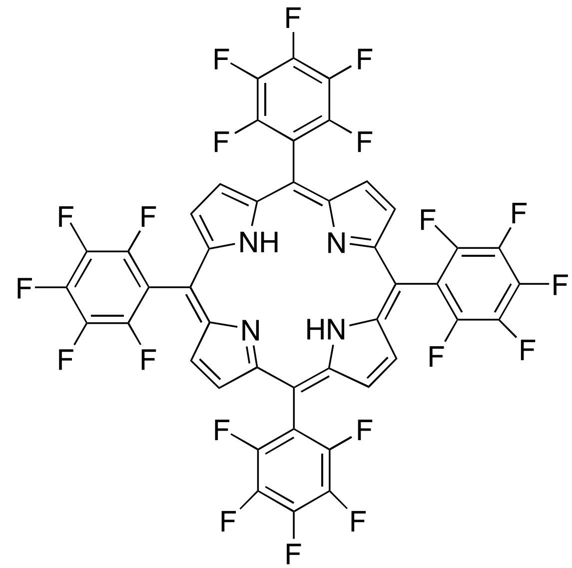
Electron-deficient Manganese porphyrine features high catalytic ability for nitrogen atom transfer process.

Che, C. -M. et al, Org. Lett., 2000, 2, 2233.

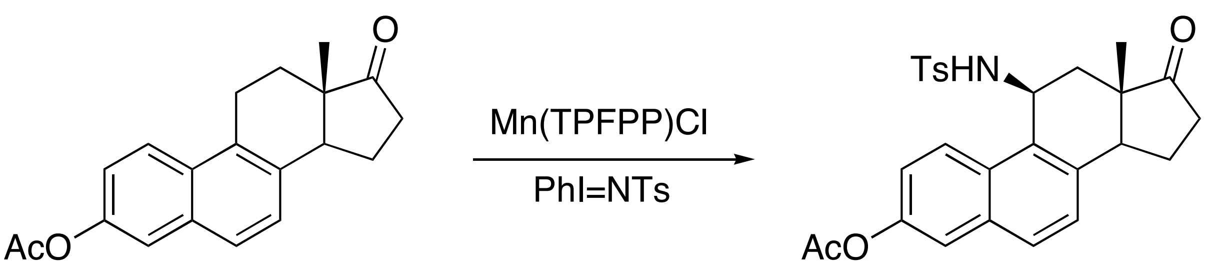
Mn-Catalyzed C-H Amination



entry	*additive*	*conversion*	*yield*
1	*none*	*55%*	*61%*
2	*Na_2CO_3*	*69%*	*88%*
3	*NaOH*	*73%*	*90%*



Tetrakis(pentafluorophenyl)porphyrin (TPFPP)

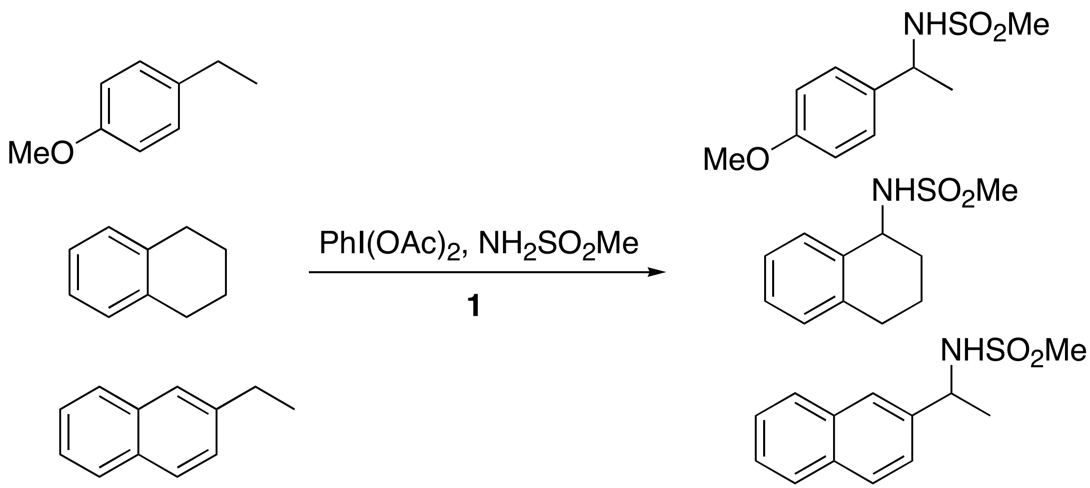


equilenin acetate

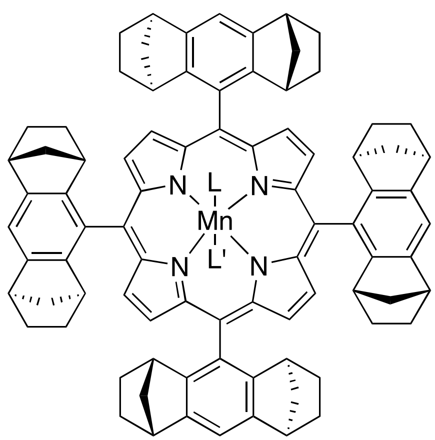
The only tosylamidation product
82% conversion
47% yield (HPLC) along with oxygenation products

Che, C. -M. et al, Org. Lett., 2000, 2, 2233.
Breslow, R. et al, Chem. Commun., 2000, 531.
Breslow, R. et al, Tetrahedron Lett., 2000, 41, 8063

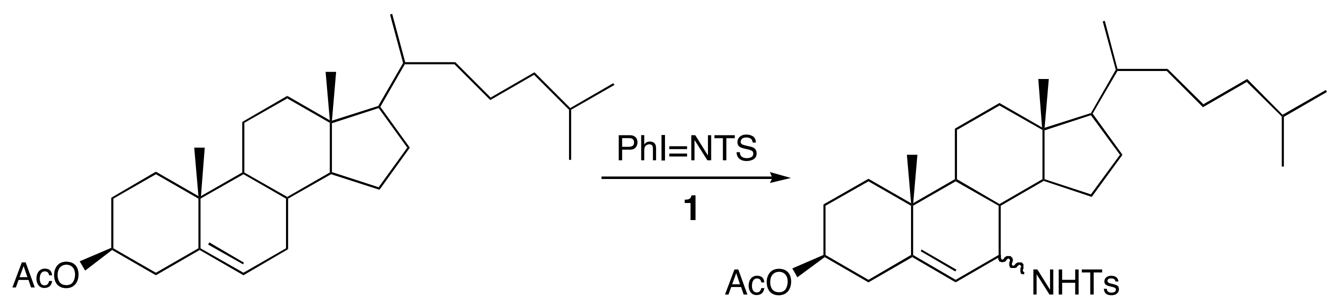
Mn-Catalyzed Asymmetric C-H Amination



Conversion	Yield	ee
26%	84%	50%
22%	84%	46%
21%	92%	56%



Mn(Por)(OH)(MeOH) 1*

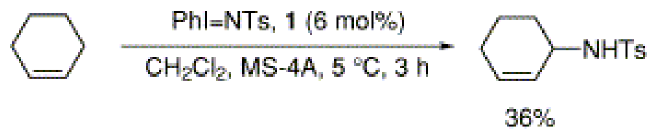


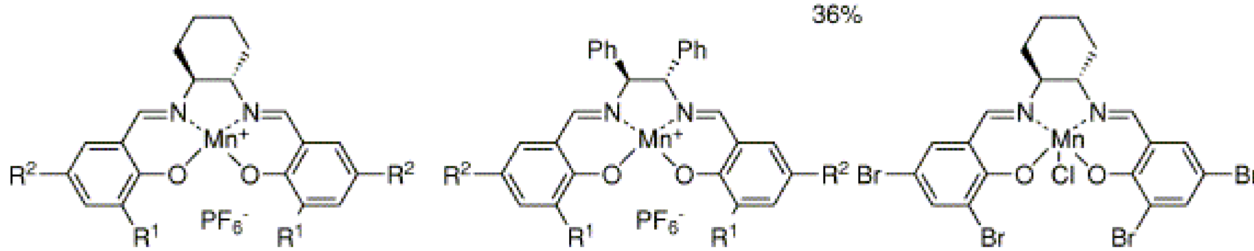
cholesteryl acetate

49% conversion
82% yield
4.2 : 1 = α : β

Che, C. -M. et al, Chem. Eur. J., 2002, 8, 1563.
Che, C. -M. et al, Chem. Commun., 1999, 2377.

Mn(salen)-Catalyzed Asymmetric C-H Amination

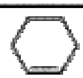
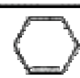
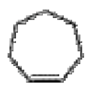
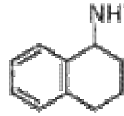
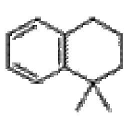
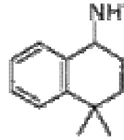
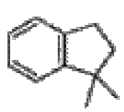
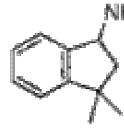




1: R^1, R^2= F **7**: R^1, R^2= H
2: R^1, R^2= Cl **8**: R^1= H, R^2= NO_2
3: R^1, R^2= Br **9**: R^1= *t*-Bu, R^2= NO_2
4: R^1, R^2= I

5: R^1, R^2= F
6: R^1, R^2= Br

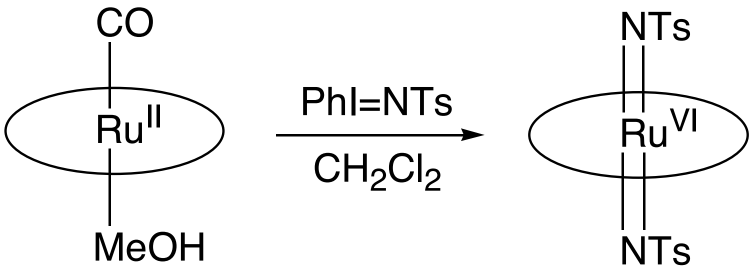
10

Entry	Substrate	Product	Yield (%)[b]	ee (%)	Configu.
1		 NHTs	44	67[c]	S[d]
2		 NHTs [c]	42	41[e]	S[f]
3		 NHTs	67	77[g]	S[h]
4		 NHTs	44	82[i]	–[j]
5		 NHTs	71	89[k]	–[j]

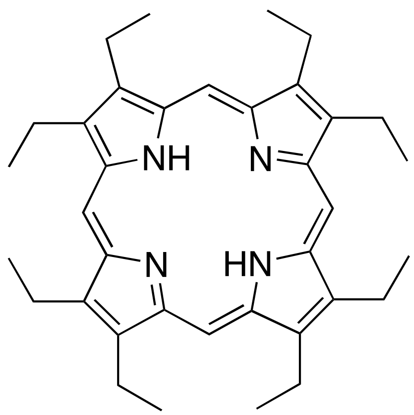
1. *Electron-deficient metalloporphyrin complex show high activity and selectivity.*
2. *C-H amination occurred in the coordination sphere.*
3. *Low temperature ~-40 °C give highest enantioselectivity*

Katsuki, T. et al, Tetrahedron Lett., 2001, 42, 3339.

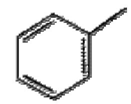
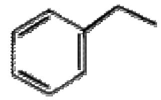
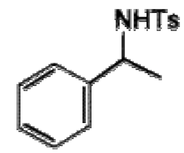
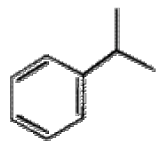
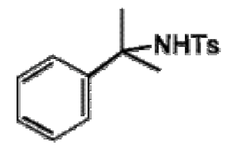
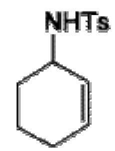
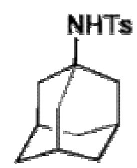
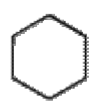
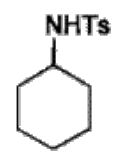
Ru-Mediated Saturated C-H Amination



reddish solid



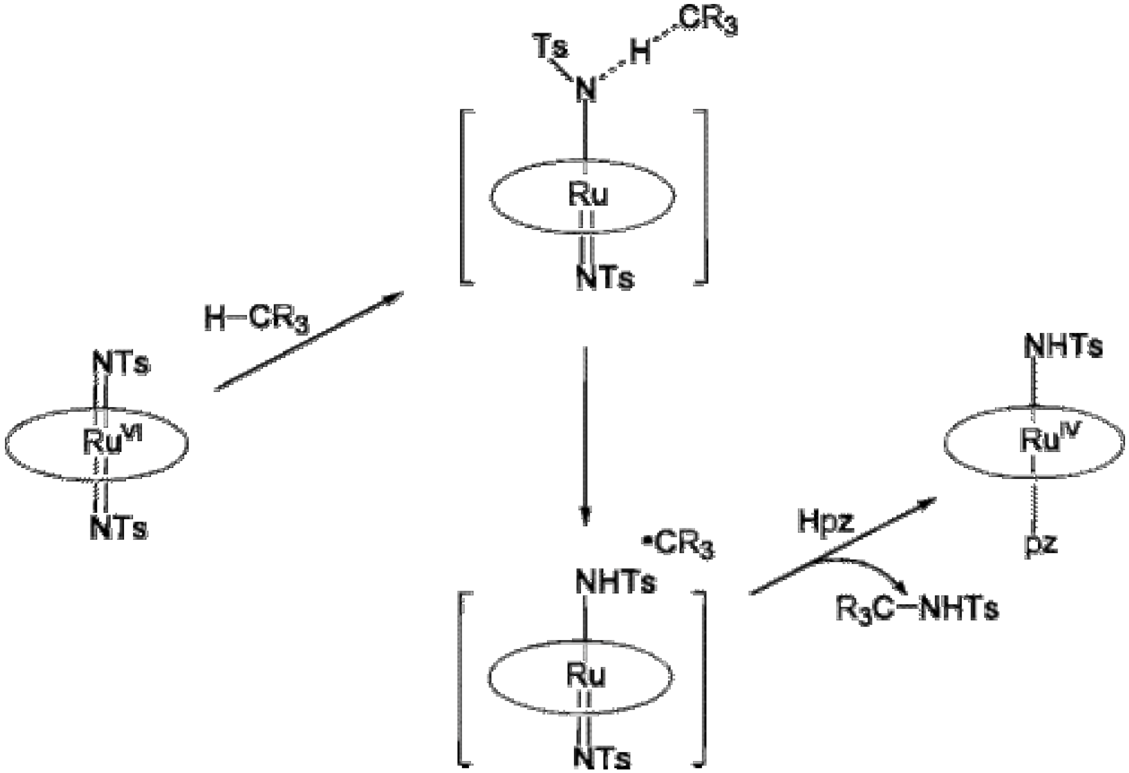
Octaethylporphyrin (OEP)

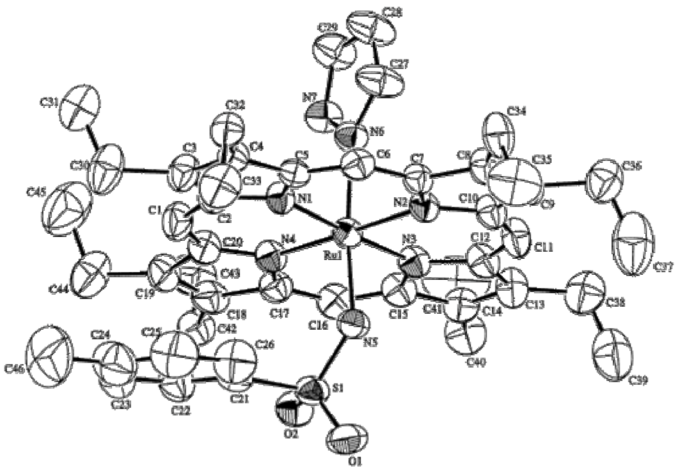
substrate	product	yield(%)^{a,b} 2a	2e
		9	11
		78	80
		71	77
		84	88
		52	60
		~ 10	

1. Stoichiometric Ru complex is necessary.
2. Very low yields for cyclohexane and toluene.
3. Completion with aziridination

Che, C. -M. et al, J. Am. Chem. Soc., 1999, 121, 9120.

Mechanism of Ru-Mediated C-H Amination

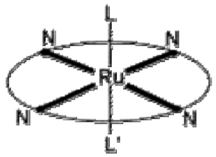




1. A Carboradical intermediate was proposed.
2. Electrophilic nature of the active ruthenium species.

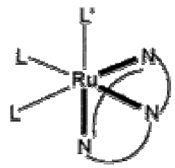
Che, C. -M. et al, J. Am. Chem. Soc., 1999, 121, 9120.

Ru-Catalyzed Amidation of Saturated C-H



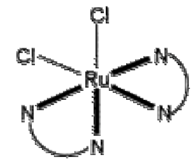
1

[Ru(Por)(L)(L')]



2

[Ru^{III}(Me_3tacn)$(L)_2$(L')]

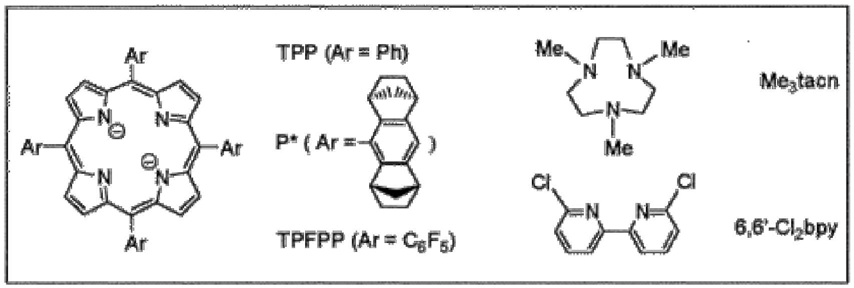


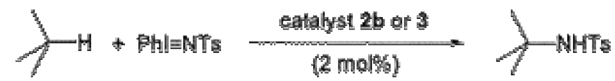
3

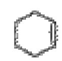
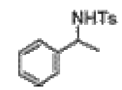
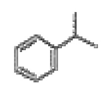
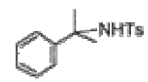
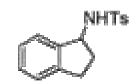
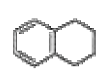
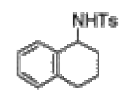
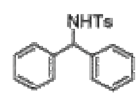
cis-[Ru^{II}(6,6'-Cl_2bpy)$_2Cl_2$]

1a: Por = TPP, L = L' = NTs
1b: Por = P*, L = L' = NTs
1c: Por = P*, L = CO, L' = EtOH
1d: Por = TPFPP, L = CO

2a: L = NHTs, L' = OH
2b: L = CF_3CO_2
L' = CF_3CO_2 or H_2O



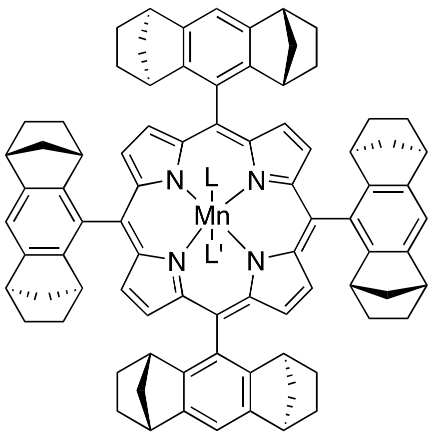


Entry	Substrate	Product	Catalyst	Conversion (%)	Yield (%)[b]
1 2			2b 3	57 52	87 86
3 4			2b 3	57 58	90 92
5 6			2b 3	79 70	93 90
7 8			2b 3	38 40	80 90
9 10			2b 3	53 49	85 81
11 12			2b 3	57 50	86 84
13 14			2b 3	61 58	90 89

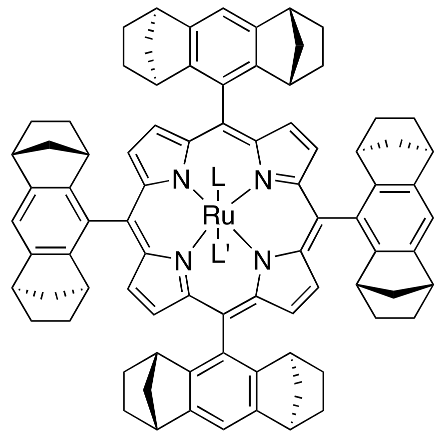
1. High selectivity of benzylic amidation.
2. Both electron-donating and-withdrawing substituents promote amidation process in para-substituted ethylbenzenes.
3. A hydrogen abstraction mechanism was proposed.

Che, C. -M. et al, Chem. Commun., 1998, 2677.
Che, C. -M. et al, J. Org. Chem., 2000, 65, 7858.

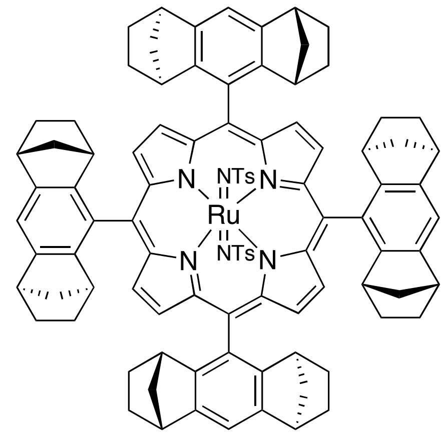
Ru-Mediated Asymmetric C-H Amination



Mn(Por)(OH)(MeOH) 1*

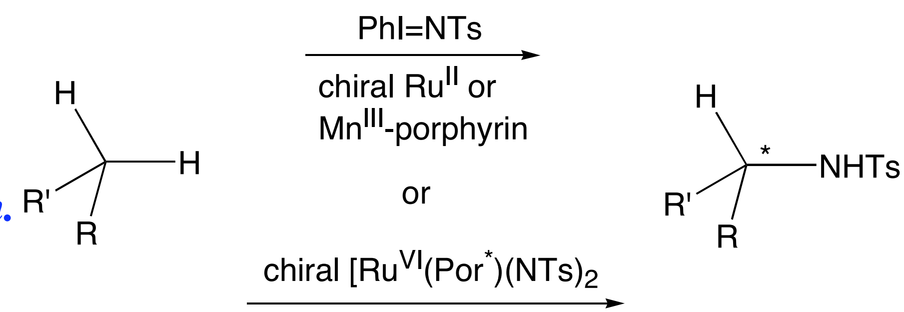


Ru(Por)(CO)(EtOH) 2*



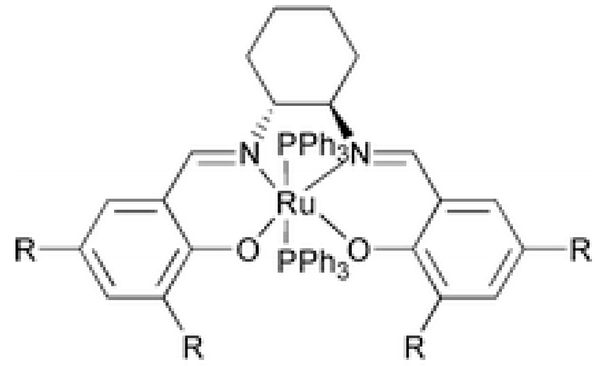
Ru(Por)$(NTs)_2$ 3*

1. *Low yields (16%-85% for benzylic amination).*
2. *Low enantioselectivity (5%-54% ee).*
3. *azirinatination and allylic amination competition.*
4. *Normally, Mn complex 1 was a slight high enantioselectivity than Ru complex 2.*
5. *Stoichiometric bis(tosylimido) Ru complex 3 gave the similar results.*

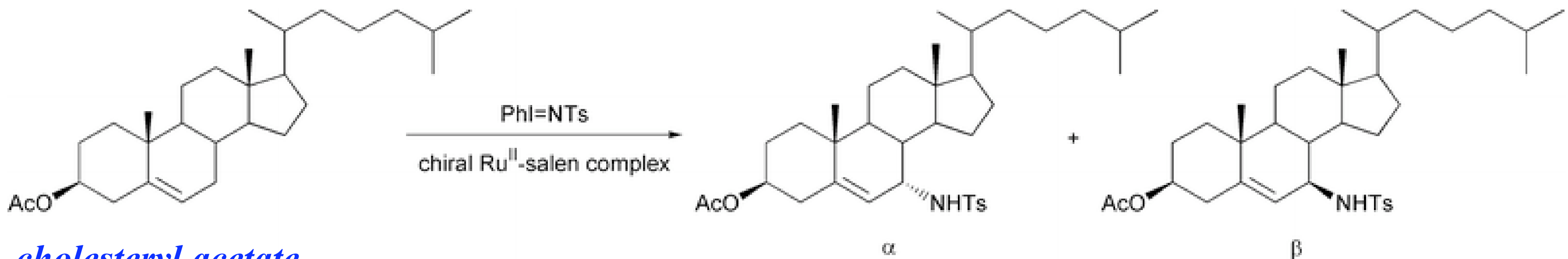


Che, C. -M. et al, Chem. Commun., 1999, 2377.
Che, C. -M. et al, Chem. Eur. J., 2002, 8, 1563.

Ru-Catalyzed Asymmetric C-H Amination



1 R = NO_2; **2** R = I; **3** R = Br



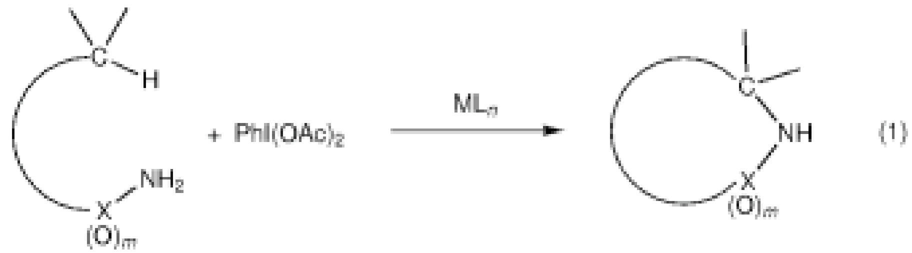
cholesteryl acetate

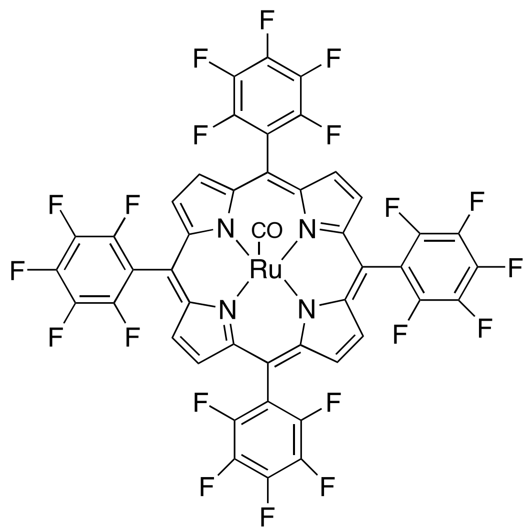
β : α *= 1.1 : 1 to 2.3 : 1*

1. 15-94% conversion of for silyl enol ethers and up to 97% ee.
2. Complex 3 gives the best results.
3. Good regioselectivity of amination of cholesteryl acetate but poor enantionselectivity with low conversion (24-28%).

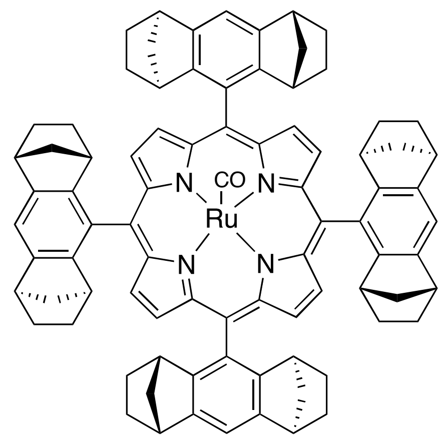
Che, C. -M. et al, Chem. Commun., 2002, 124.

Ru-Catalyzed Intramolecular Asymmetric C-H Amination





Ru(TPFPP)(CO) 1

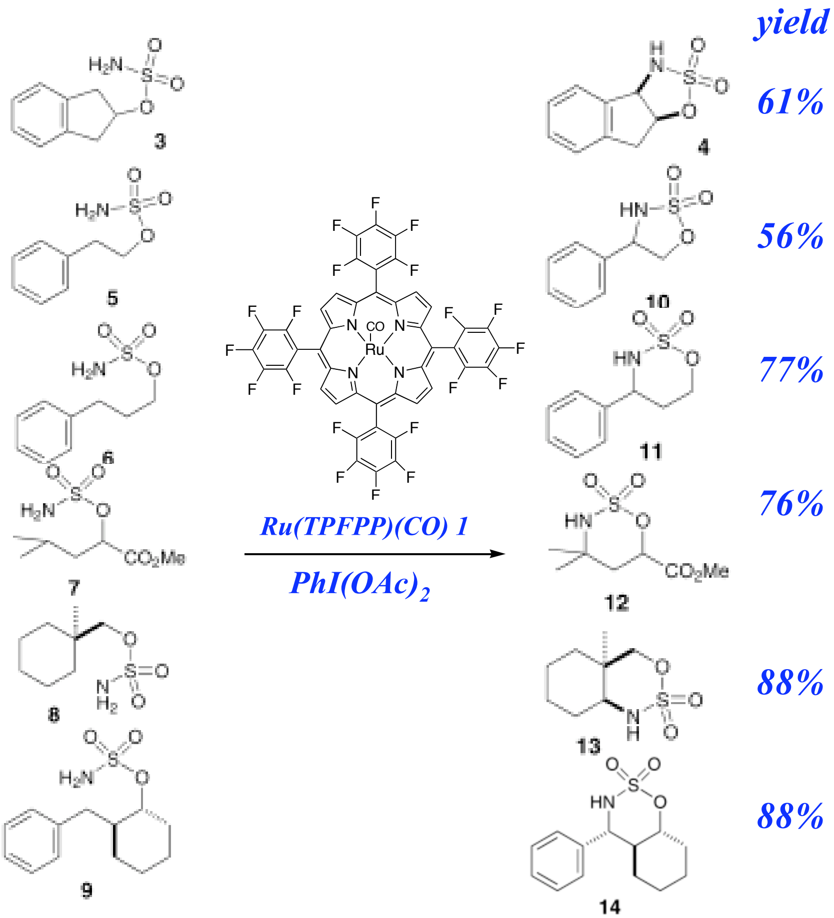


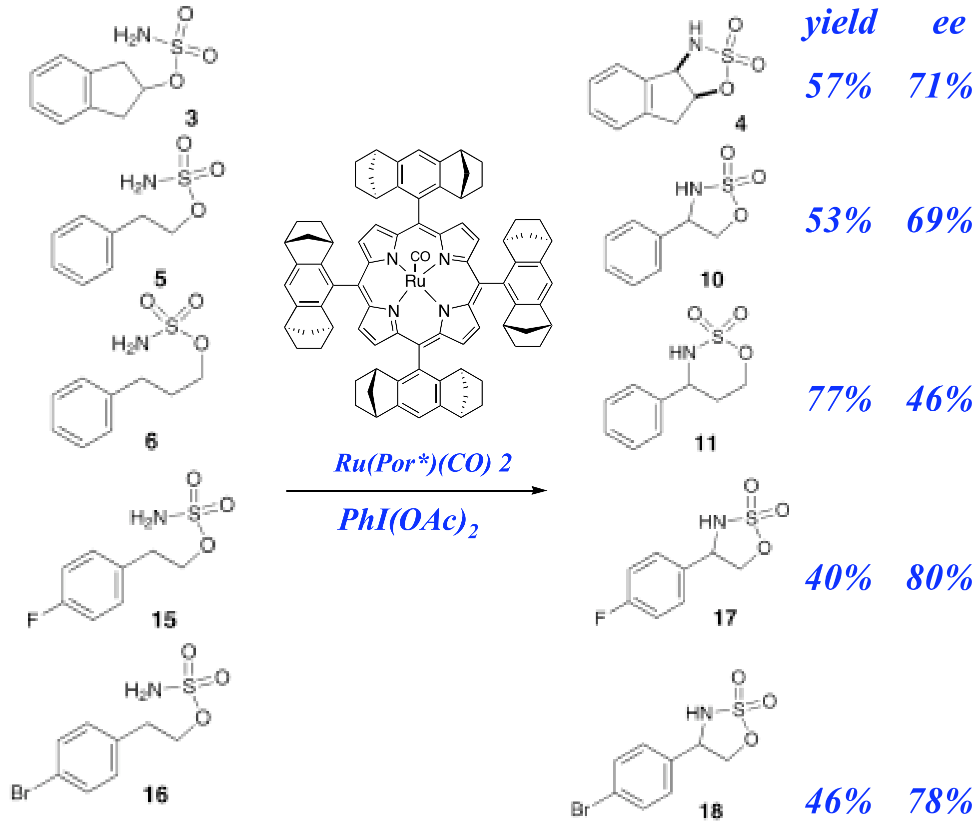
Ru(Por)(CO) 2*

1. *Electron-deficient ruthenium Ru(TPFPP)(CO) 1 gives high regioselectivity and diastereoselectivity.*
2. *Good enantionselectivity for Ru(Pro*)(CO) 2.*
3. *Yields are much higher than intermolecular amination.*
4. *Good regioselectivity of amination of cholesteryl acetate but with poor enantionselectivity.*

Che, C. -M. et al, Angew. Chem. Ed., 2002, 41, 3465.

Ru-Catalyzed Intramolecular Asymmetric C-H Amination

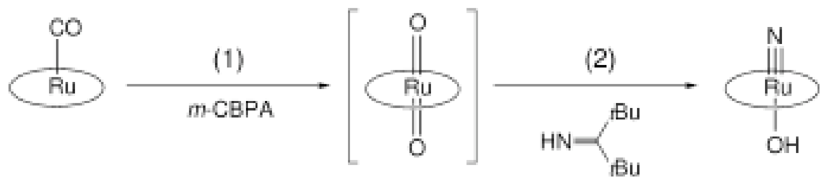




1. Electron-deficient ruthenium Ru(TPFPP)(CO) 1 gives high regioselectivity and diastereostereoselectivity.
2. Enantionselectivity of amination with ruthenium Ru(Por*)(CO) was solvents dependent (benzene is better).

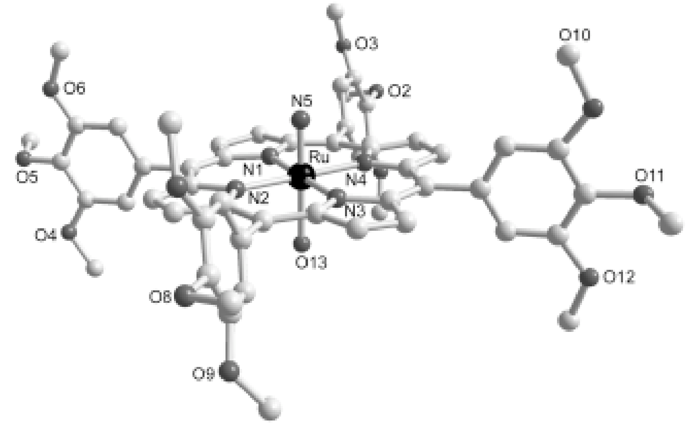
Che, C. -M. et al, Angew. Chem. Int. Ed., 2002, 41, 3465.

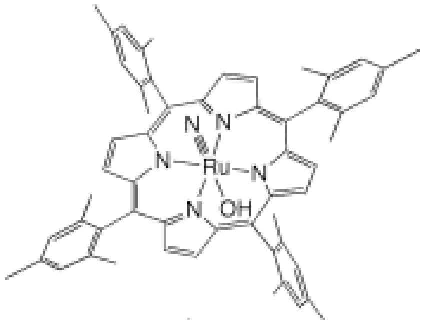
Ru-Mediated Saturated C-H Amination



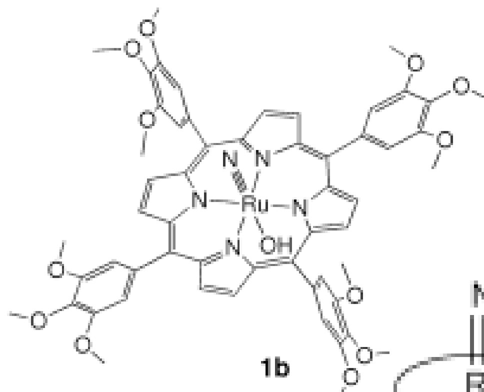
1

dark purple solid

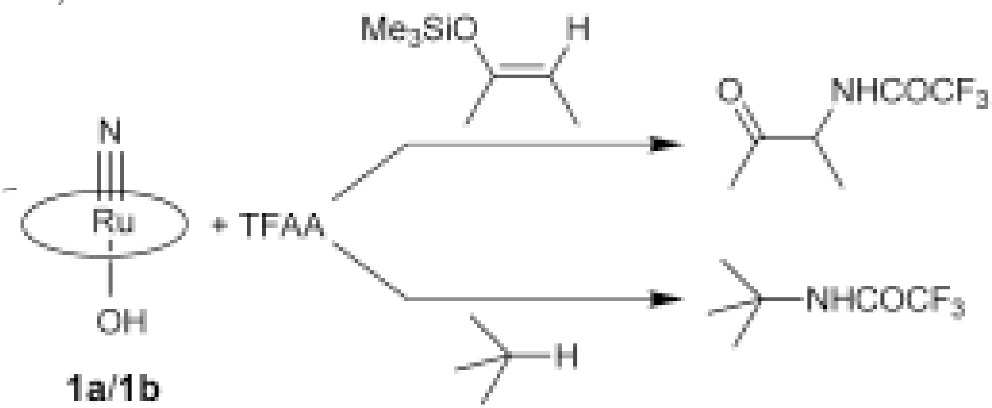




1a



1b



1a/1b

1. The first amination of saturated C-H bond with nitrido metal complex.
2. Ru-N(nitrido) distance: 1.656(5) A.
2. Obtained N-trifluoroacetyl amine from direct intermolecular amination.
3. Only Porphyrin ntrido ruthenium was reactive to hydrocarbons or silyl enol ehters.
4. Stoichiometric nitrido ruthenium was necessary.
5. Mechanism of reaction 2 was not clear yet.

Che, C. -M. et al, Angew. Chem. Int. Ed., 2003, 340.

Co-Catalyzed Saturated C-H Amination

$$ArR^1R^2CH + ArN_3 \xrightarrow{Co^{II}-porphyrin} ArR^1R^2C - NHAr + N_2$$

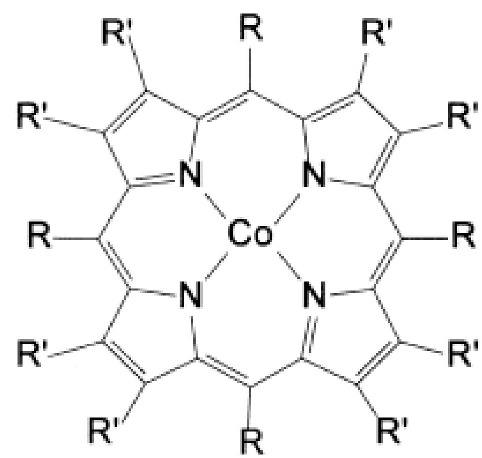
$$ArRHC - NHAr + ArN_3 \xrightarrow{Co^{II}-porphyrin} ArRC = NAr + ArNH_2 + N_2$$

[Co(tpp)] : R = Ph, R' = H

[Co(*p*-MeOtpp)]: R = *p*-MeOC_6H_4, R' = H

[Co(*p*-Cltpp)]: R = *p*-ClC_6H_4, R' = H

[Co(oep)]: R = H, R' = Et

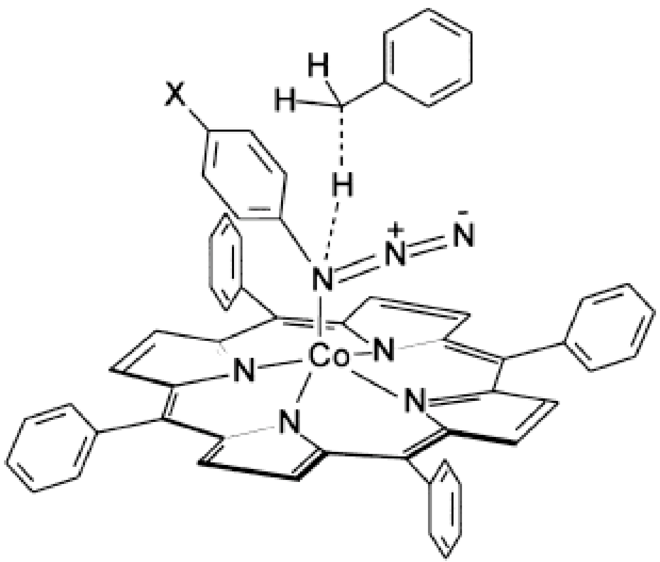


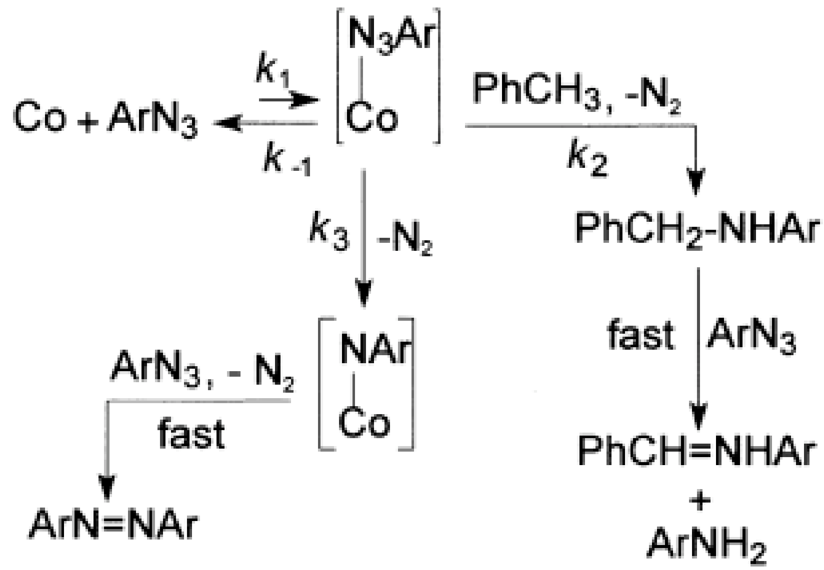
1. First porphyrin complex of cobalt catalyzed amination.
2. Para-nitrophenylazide gives the best results.

3. Only benzyl analogs were investigated.
4. Difficult to control to stop at amination step.
5. Yields are low with a lot of by-products (azide-derived aniline and the diarylazo compound).
6. Azido compounds are explosive.

Cenini, S. et al Chem. Eur. J., 2003, 9, 249.

Pathway of Co-Catalyzed C-H Amination



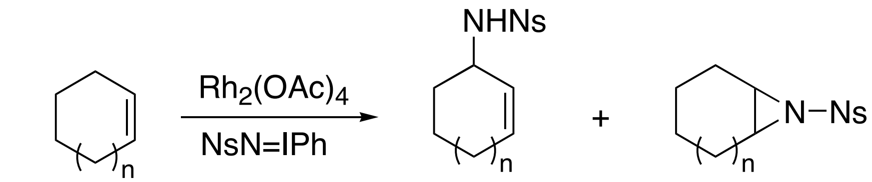


Co = [Co(tpp)]; Ar = *p*-$NO_2C_6H_4$

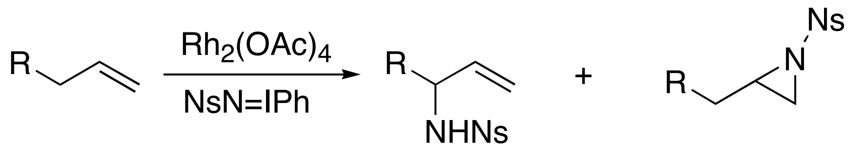
1. *Catalytic amount of Co(TPP) is necessary in the reaction.*
2. *Sterically bulky azides such as Ph_3CN_3, and adamantylazide give no reaction.*
3. *p-$CF_3C_6H_4N_3$ leads to fluorine loss to give Co(TPP)F (radical pathway?).*
4. *The reaction can be inhibitted by TEMPO (redical) .*
5. *The "pocket" conformation of arylazide makes steric hindrance for the incoming toluene molecule.*

Cenini, S. et al, Chem. Commun., 2000, 2265.
Cenini, S. et al, Chem. Eur. J., 2003, 9 249.

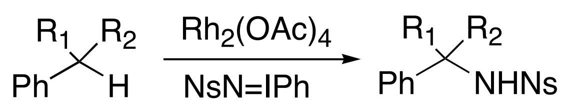
Rh-Catalyzed Saturated C-H Amination



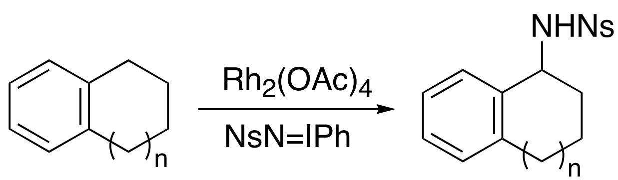
n = 0	44%	9%
n = 1	70%	4%
n = 2	17%	24%
n = 3	0%	54%



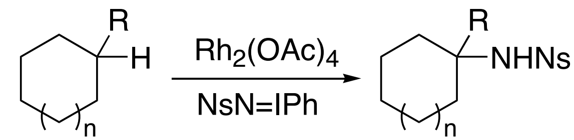
R = CH=CH$_2$	0%	40%
R = Ph	3%	32%



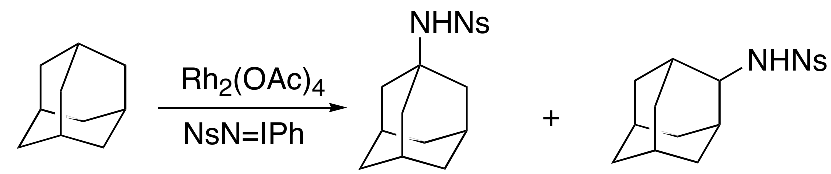
$R_1 = R_2$ = H	3%
R_1 = Me, R_2 = H	50%
$R_1 = R_2$ = Me	8%
R_1 = Ph, R_2 = H	13%



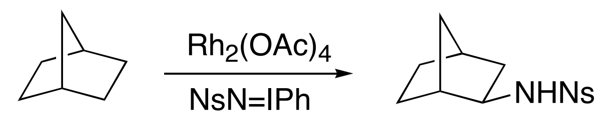
n = 0	69%
n = 1	51%



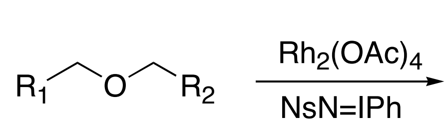
n = 0, R = Me,	16%
n = 1, R = Me,	18%
n = 1, R = H,	30%



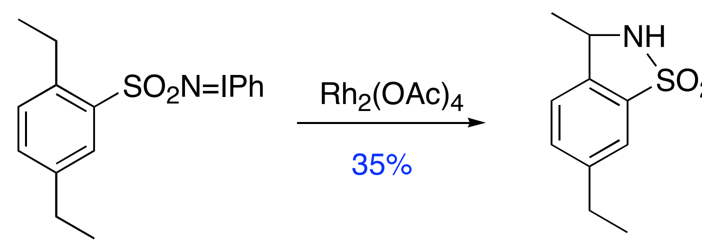
71% 5%



9%

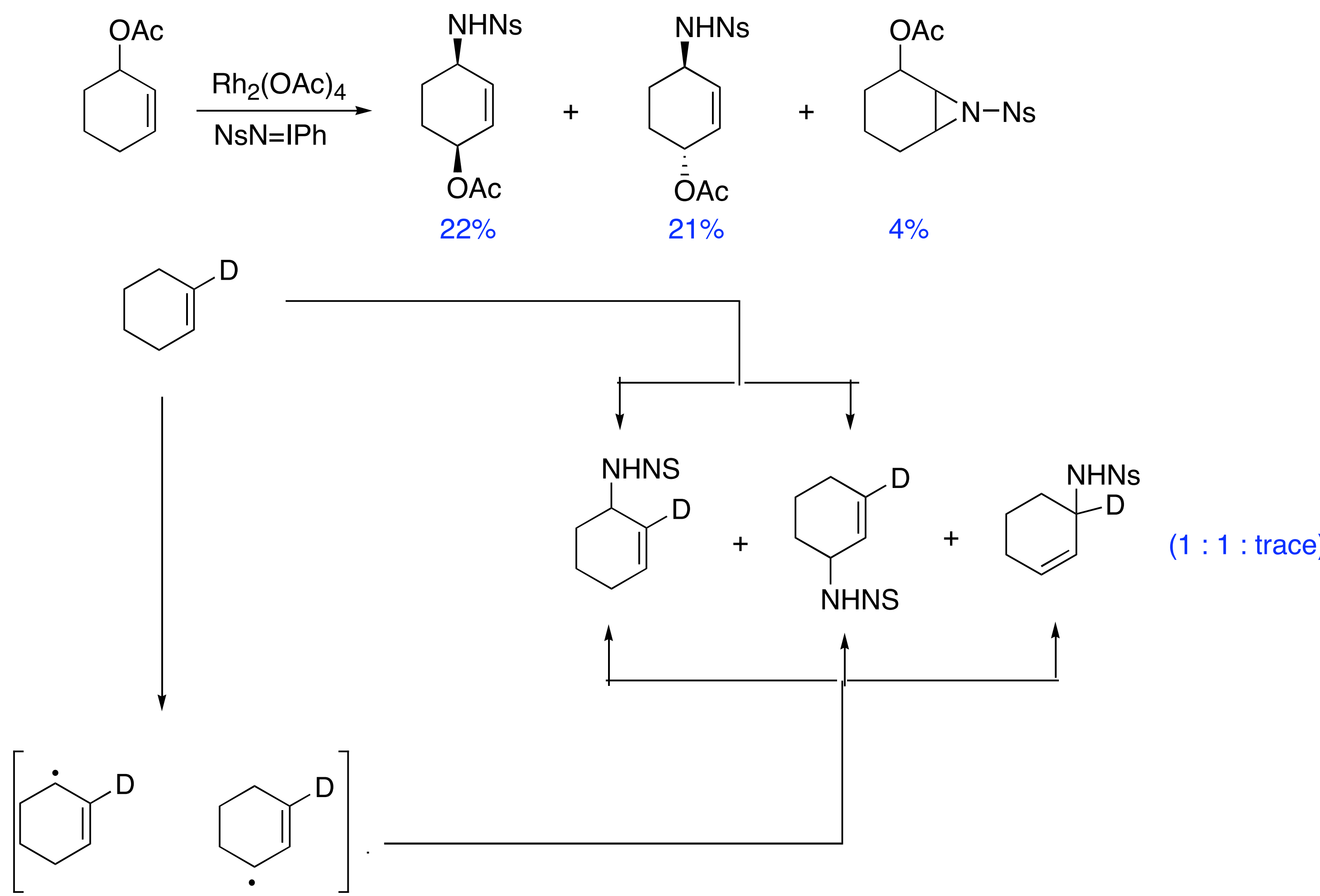


R_1-R_2 = CH$_2$CH$_2$	56%
R_1-R_2 = CH$_2$OCH$_2$	39%



Muller, P. et al, Helv. Chim. Acta., 1997, 80, 1087.

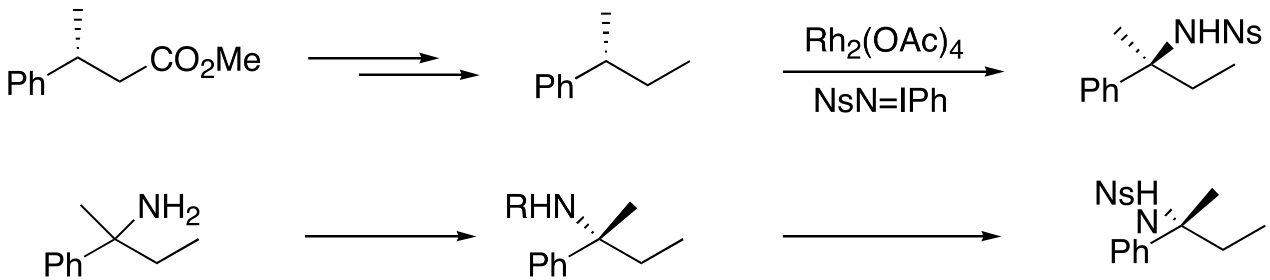
Mechanism of Rh-Catalyzed C-H Amination



A direct insertion mechanism is more possible.

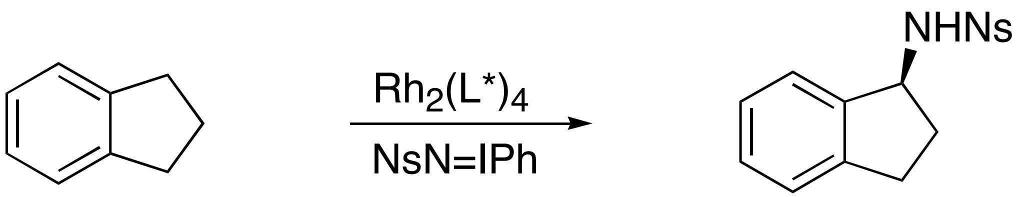
Muller, P. et al, Helv. Chim. Acta., 1997, 80, 1087.

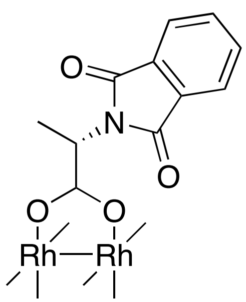
Rh-Catalyzed Asymmetric C-H Amination



[α] = -10.2

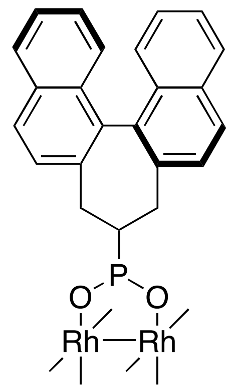
[α] = +8.8





$Rh_2\{(S)\text{-ptpa}\}_4$

77%, 7% ee

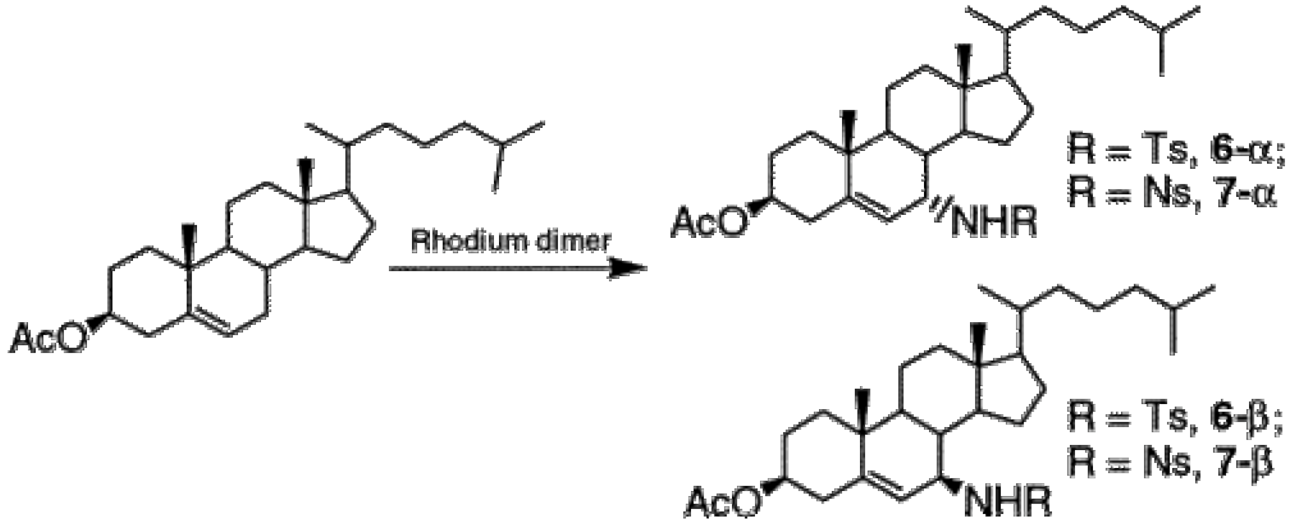


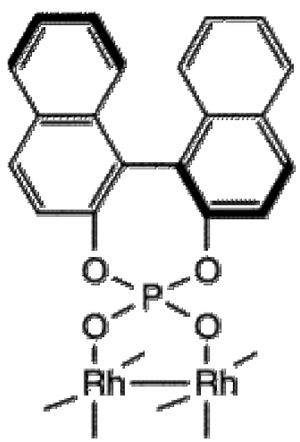
$Rh_2\{(R)\text{-bnp}\}_4$

71%, 31% ee

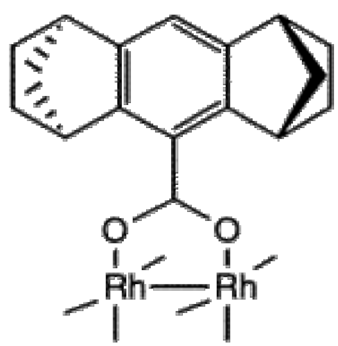
Muller, P. et al , Helv. Chim. Acta., 1997, 80, 1087.

Rh-Catalyzed Asymmetric C-H Amination

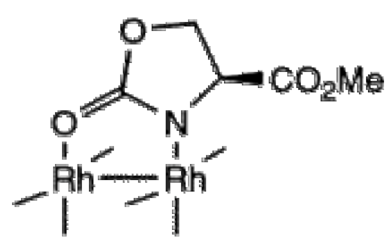




Rh_2(*R*-BNP)$_4$



Rh_2(*R*-ODACA)$_4$

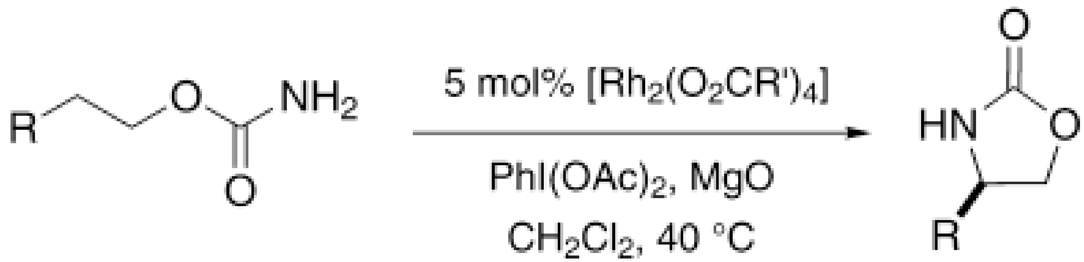


Rh_2(4*S*-MEOX)$_4$

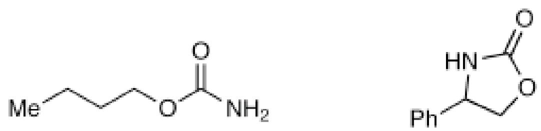
Rh_2(R-BNP)$_4$
PhINTs
Conversion: 21%
Yield: 73%
α : β ration: 9.0 (3.4-9.0)

Che, C. -M. et al, Org. Lett., 2002, 4, 4507.

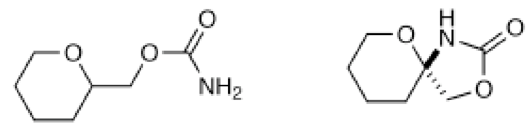
Rh-Catalyzed Intramolecular C-H Amination



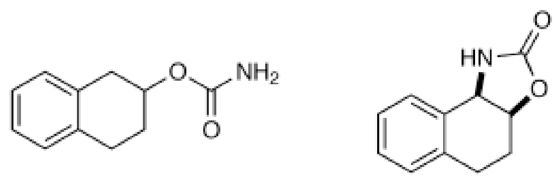
(1)



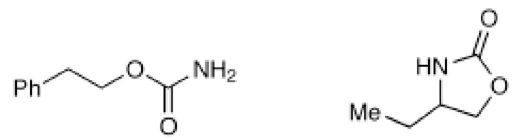
74%



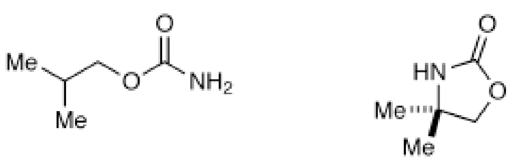
84%



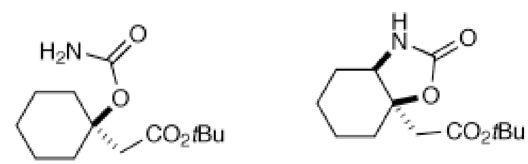
77%



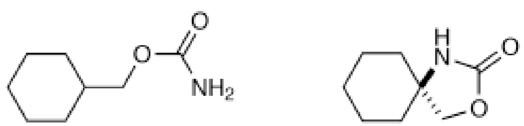
44%



83%



82%

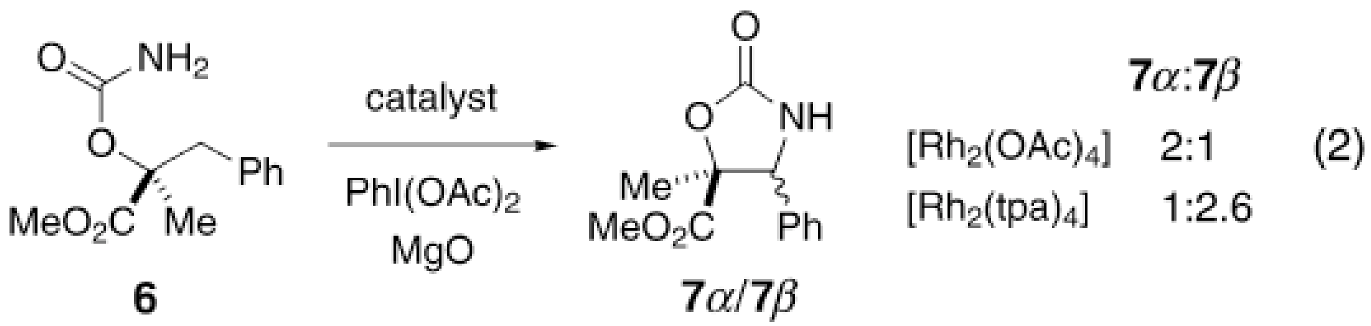


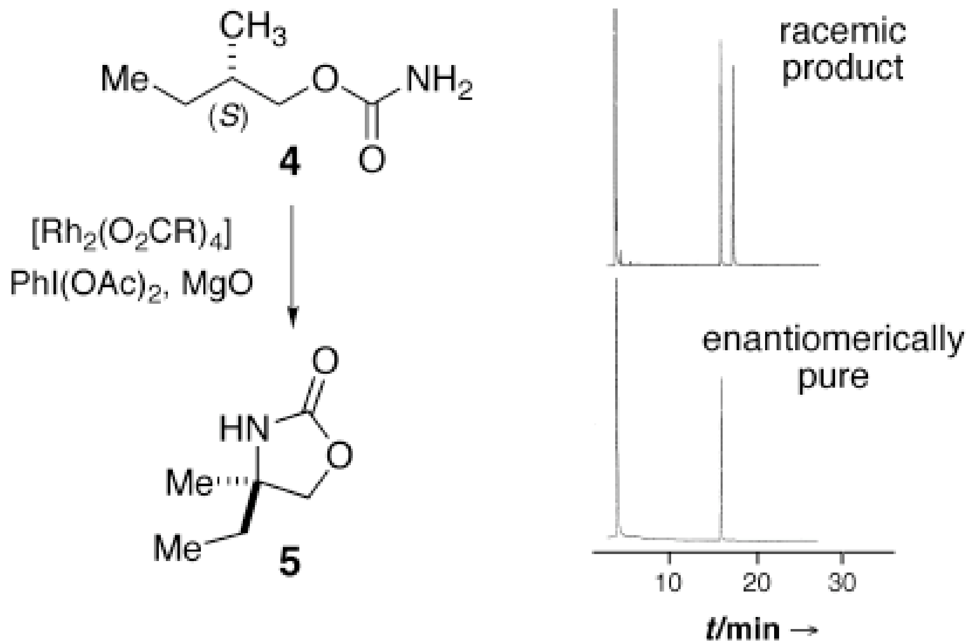
79%

83%

Du Bois, J. et al, Angew. Chem. Int. Ed. 2001, 40, 598.

Rh-Catalyzed Intramolecular C-H Amination

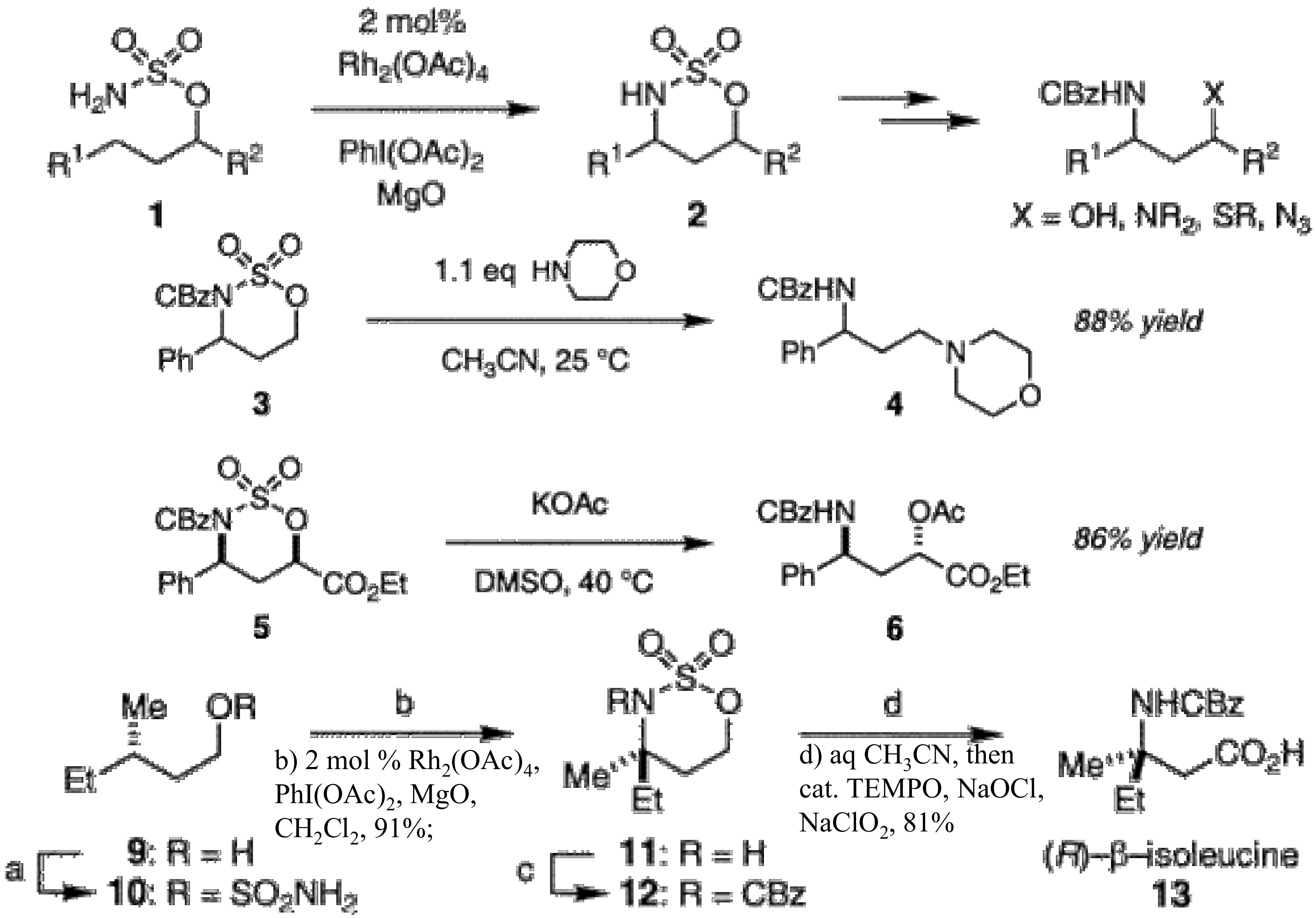




1. C-H insertion is stereospecific (retention configuration).
2. Not through free carbamoylnitrene intermediate.

Du Bois, J. et al, Angew. Chem. Int. Ed. 2001, 40, 598.

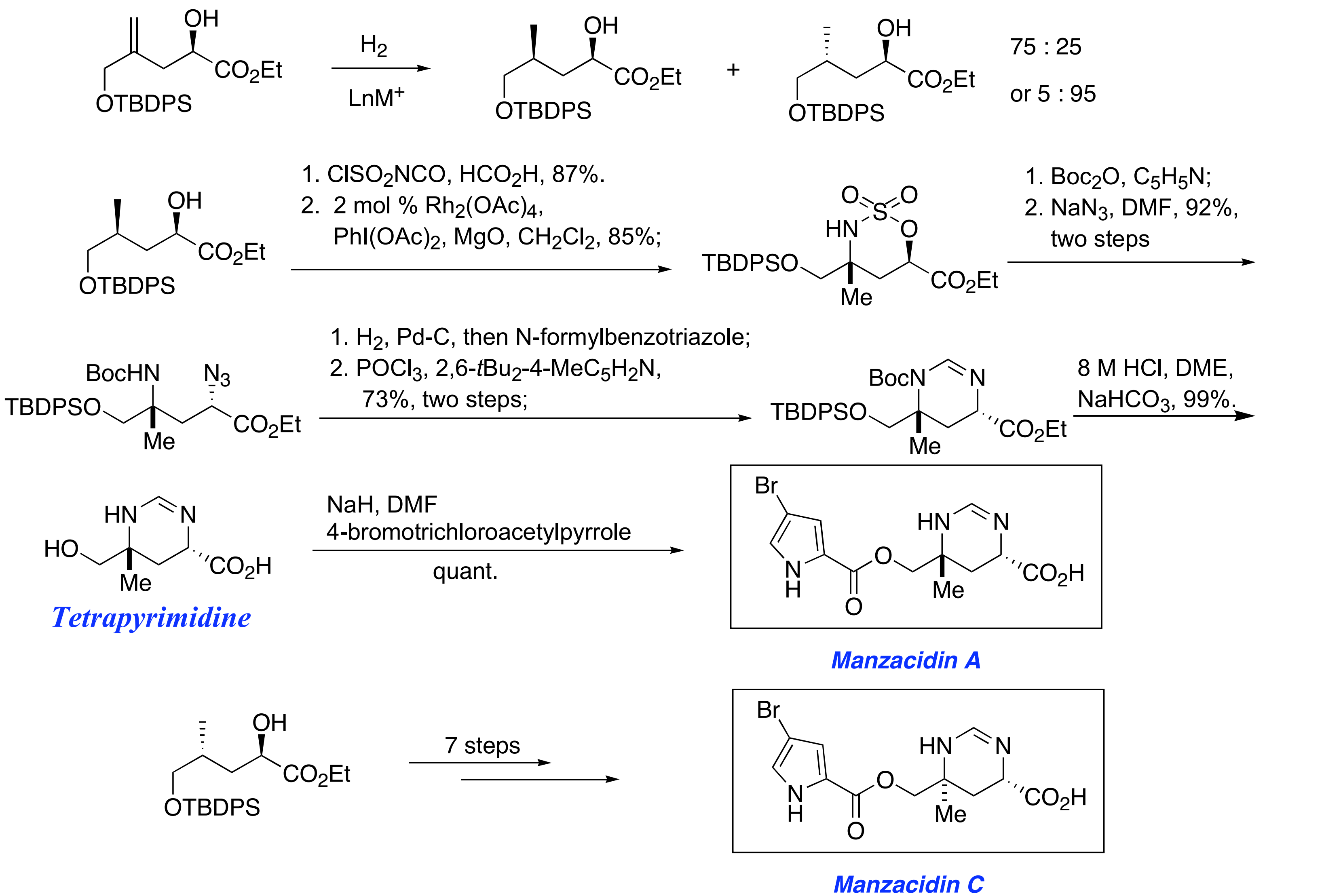
Rh-Catalyzed Intramolecular C-H Amination



A facial approach to 1, 3 amino alcohols or acids.

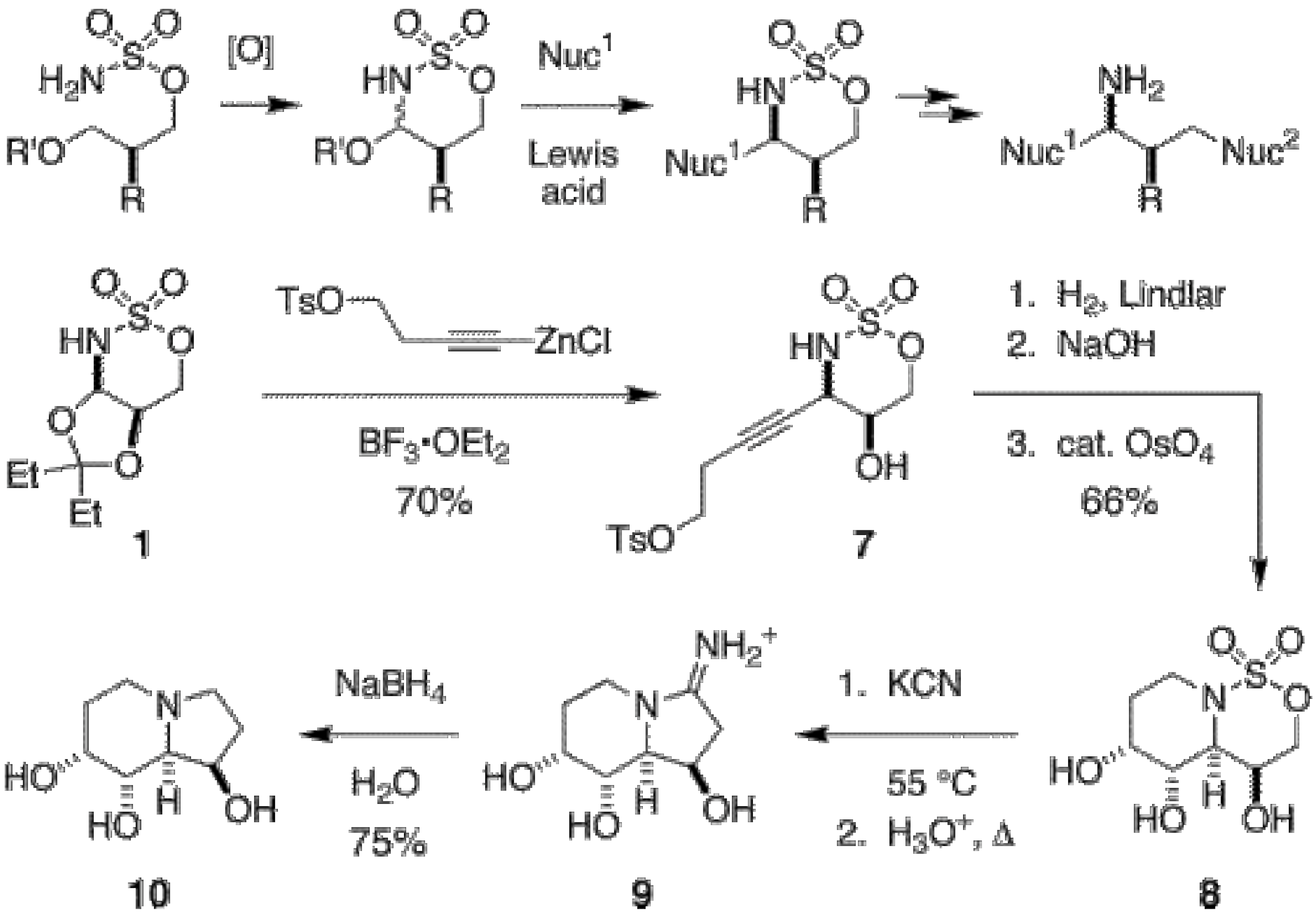
Du Bois, J. et al, J. Am. Chem. Soc., 2001, 123, 6935.
Du Bois, J. et al, Org. Lett., 2003, 5, 4823.

Rh-Catalyzed Intramolecular C-H Amination



Du Bois, J. et al, J. Am. Chem. Soc., 2002, 124, 12951.

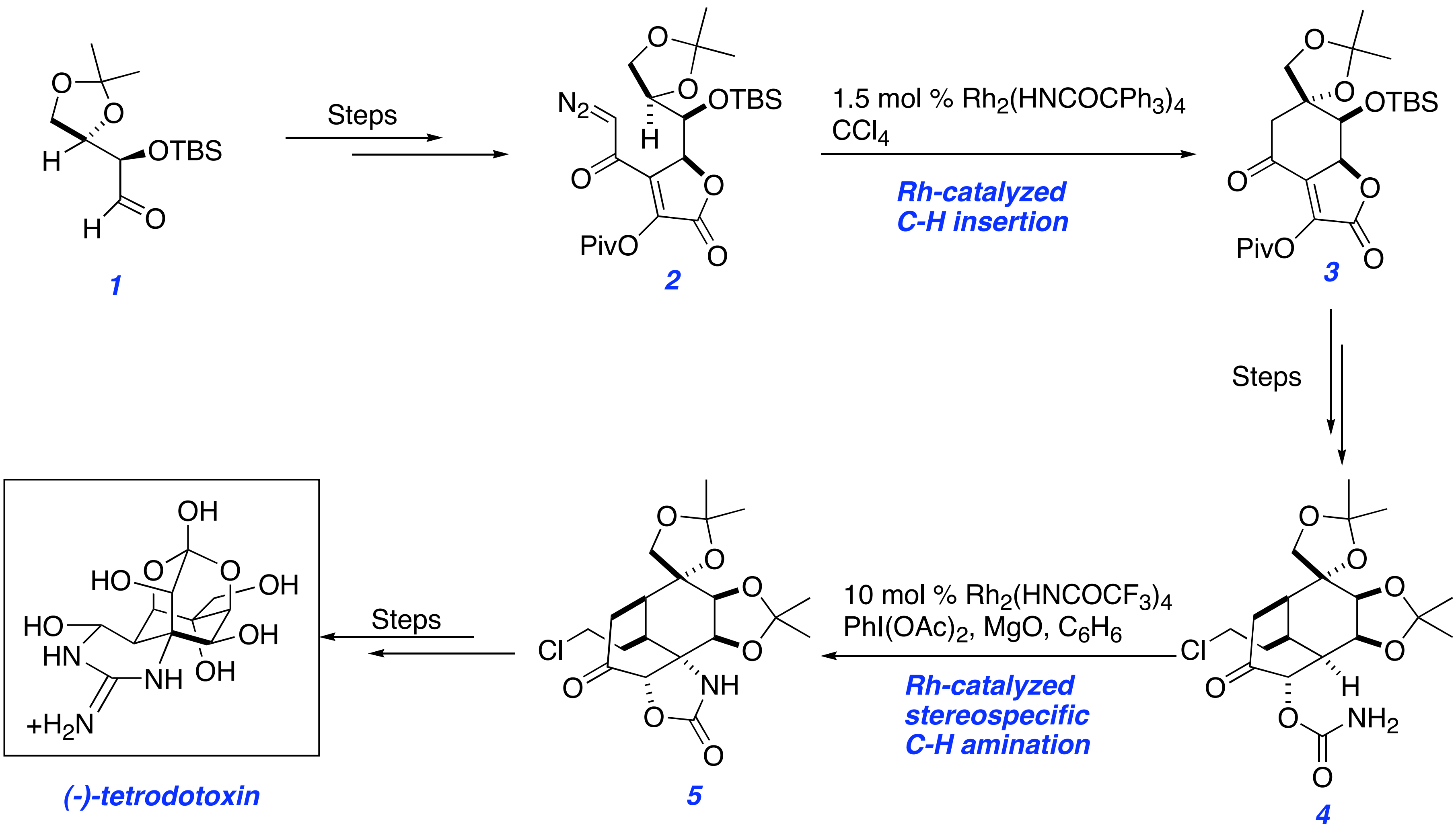
Rh-Catalyzed Intramolecular C-H Amination



Indolizidine

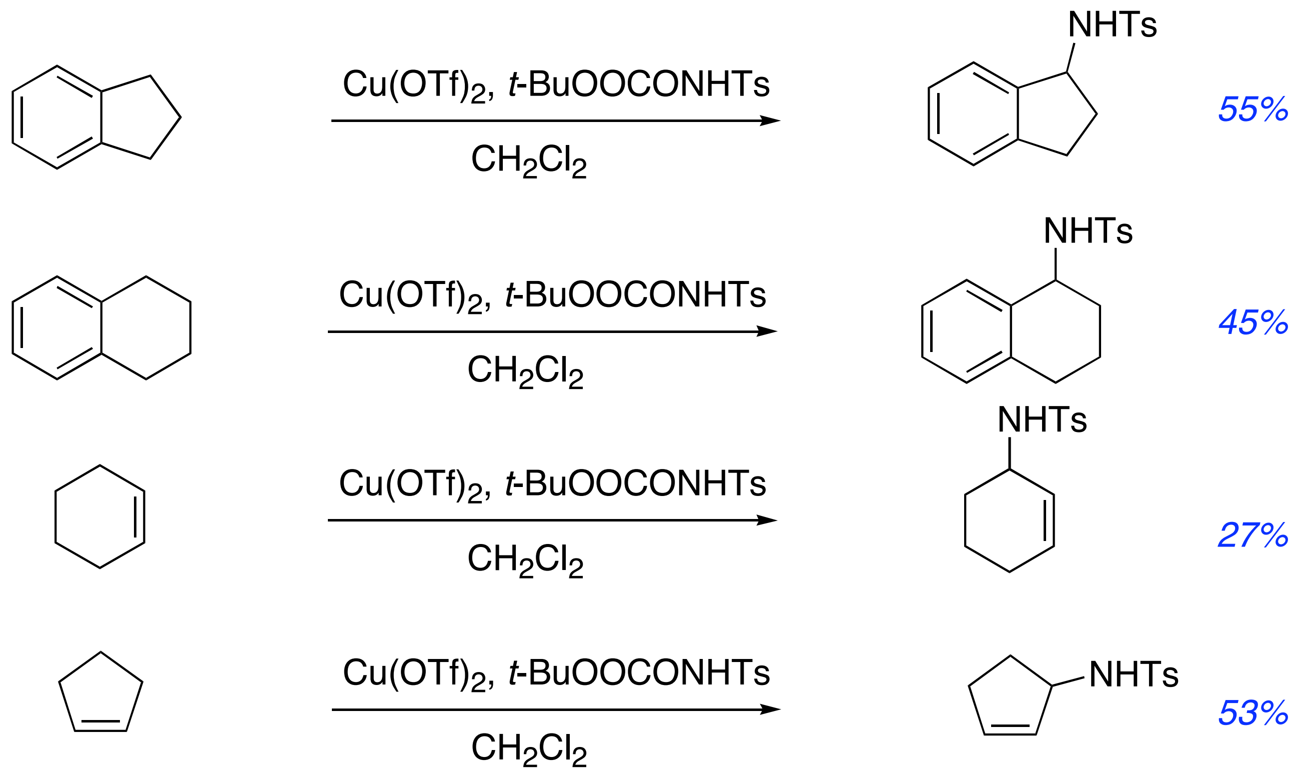
Du Bois, J. et al, J. Am. Chem. Soc., 2003, 125, 2028
Du Bois, J. et al, Angew. Chem. Int. Ed., 2004, 43, 4349.

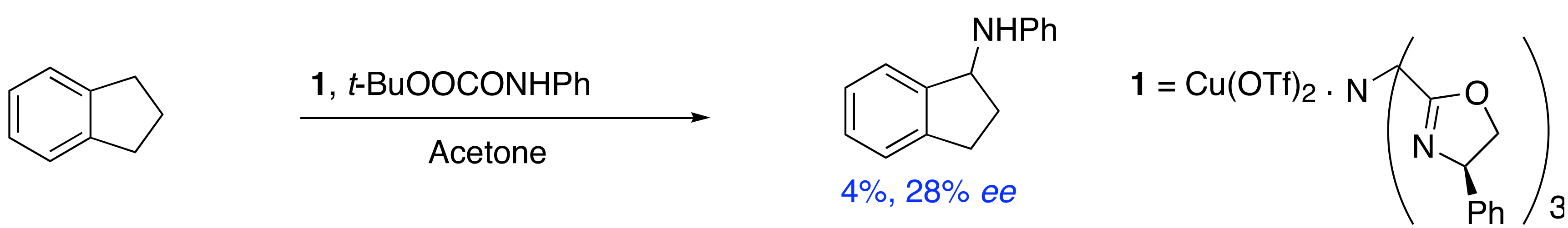
Rh-Catalyzed Intramolecular C-H Amination



Du Bois, J. et al, J. Am. Chem. Soc., 2003, 125, 11510.

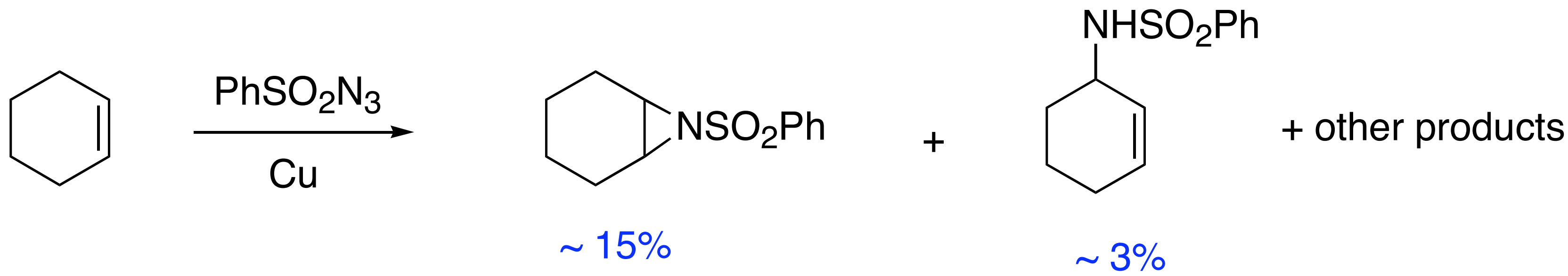
Cu-Catalyzed C-H Amination

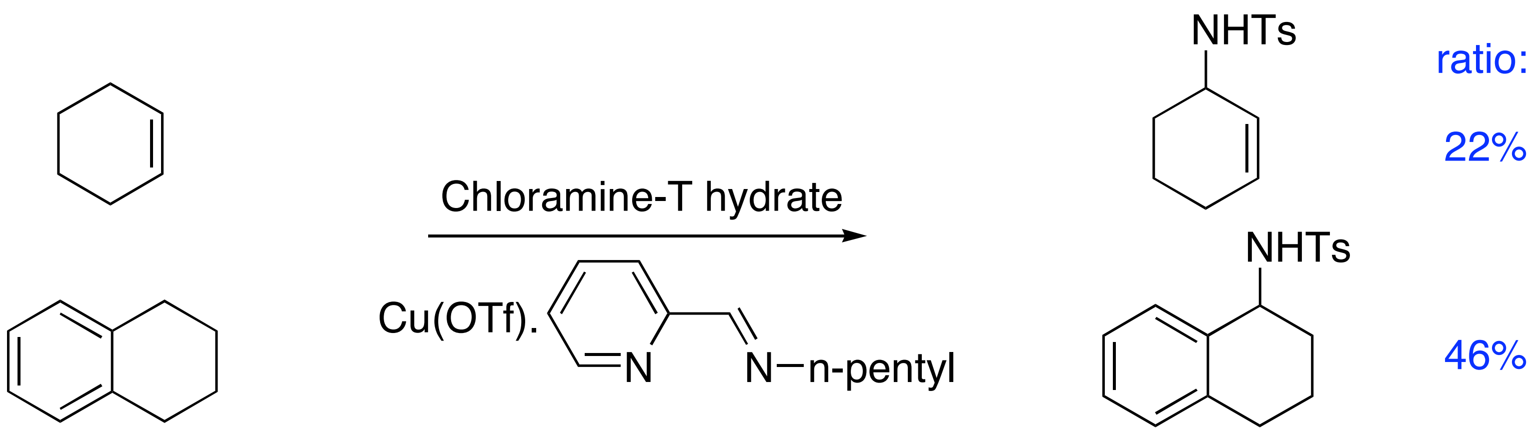


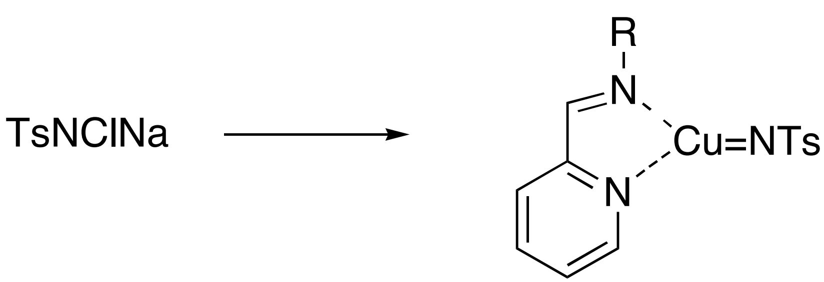


Katsuki, T. et al, Synlett, 1997, 1456.

Cu-Catalyzed C-H Amination



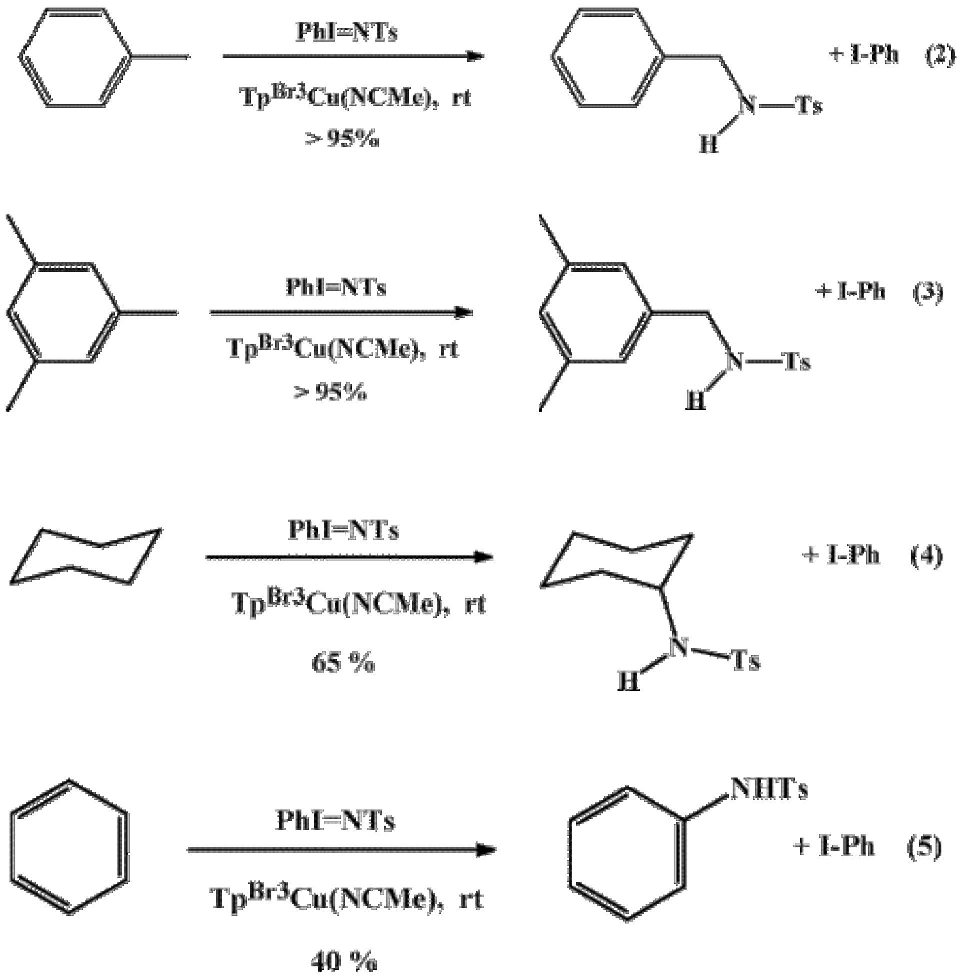


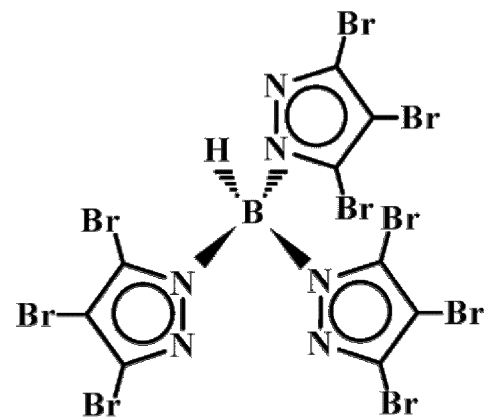


Chloramine-T hydrate
(TsNClNa.(H_2O)$_3$)

Khan, A. A. et al, J. Am. Chem. Soc, 1967, 89, 1951.
Taylor, P. C. et al, J. Org. Chem., 1998, 63, 9569

Cu-Catalyzed Intermolecular C-H Amination



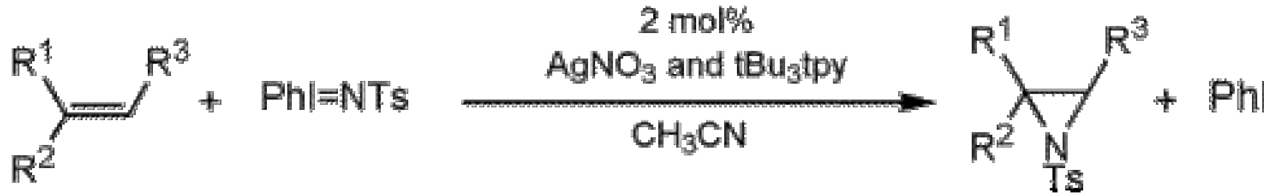


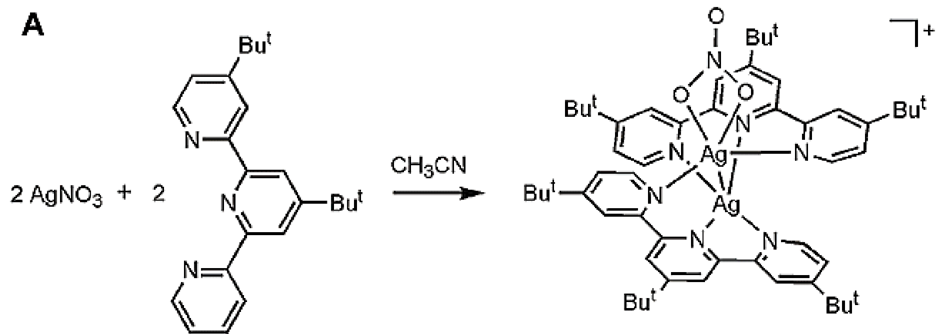
Tp^{Br_3}

homoscorpionate

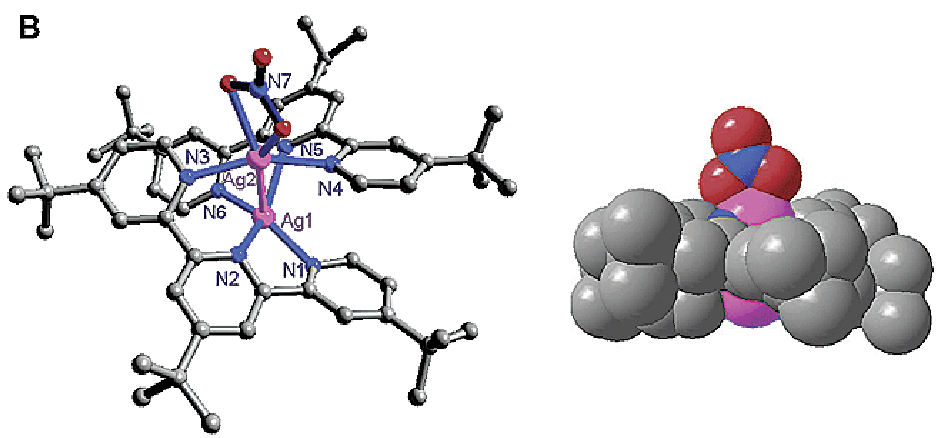
Perez, P. J. et al, J. Am. Chem. Soc, 2003, 125, 12078.

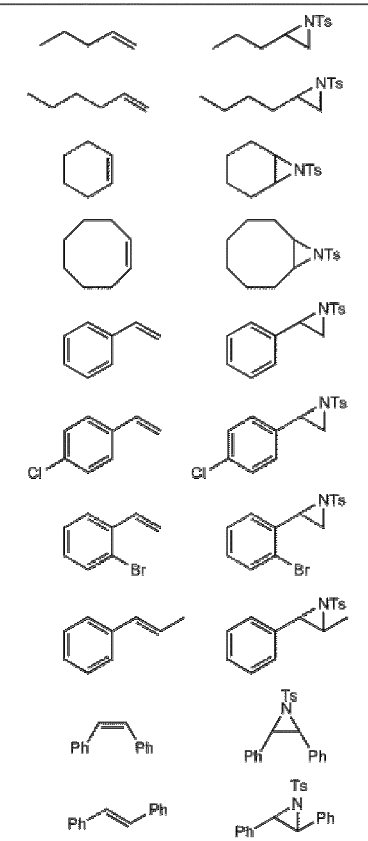
Ag-Catalyzed C-H Amination





[Ag_2(tBu$_3$tpy)$_3$(NO_3)](NO_3) (**1**)

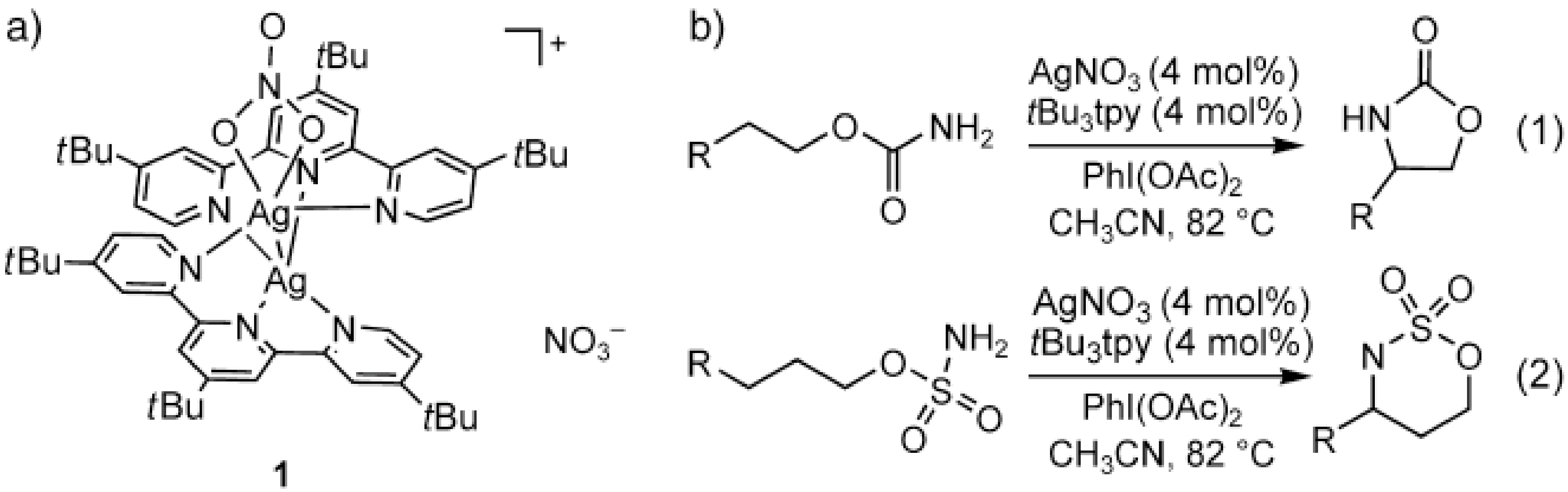




Entry	Substrate	Product	Yield[a]
1			66
2			71
3			81
4			88
5			91(89)[b]
6			74
7			80
8			90
9			86
10			88

He, C. et al, J. Am. Chem. Soc, 2003, 125, 16202.

Ag-Catalyzed Intramolecular C-H Amination



$[Ag_2(tBu_3tpy)_2NO_3]NO_3$ + PhI=NTS ⟶ Mass: 1188 $Ag_2(tBu_3tpy)_2$=NTS

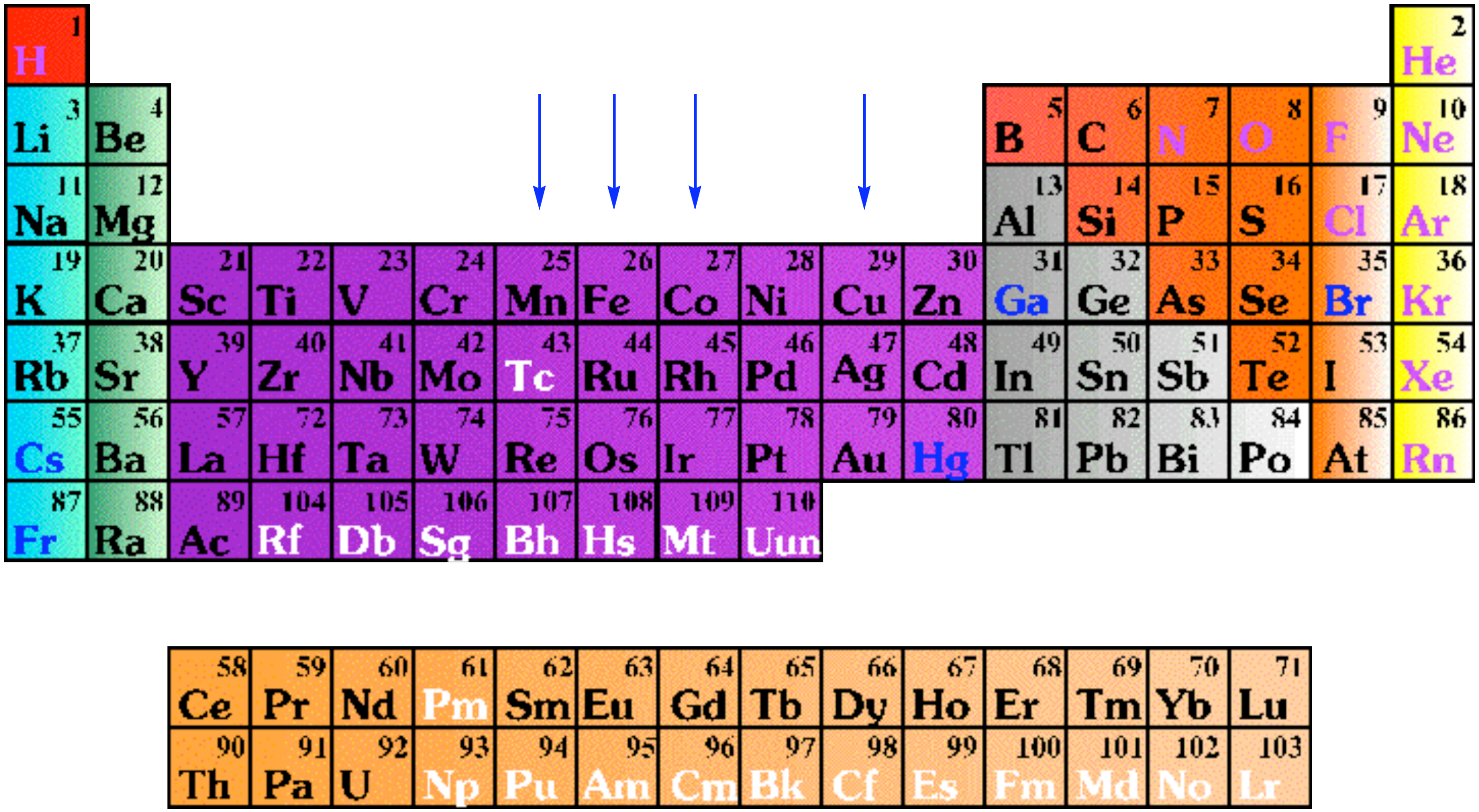
+ $PhI=NSO_2Ph$ ⟶ 1174 $Ag_2(tBu_3tpy)_2$=NPh

1. Very efficient intramolecular amination of saturated C-H bonds.
2. Silver-catalyzed reaction is stereospecific (nitrene intermediate).

3. Only t-Bu_3tpy gave the good results.
4. Amide doesn't work.

He, C. et al, Angew. Chem. Int. Ed., 2004, 43, 4210.

Transition Metal-Catalyzed C-H Amination



C-H Amination - What's next?

$$N_2$$