2008.9.3 (Wed.)
Hiroyuki Morimoto (D3)

Current and Future Challenges in Catalysis

—C–H Amination and Chemo-/Regioselective Reaction as Model Cases—

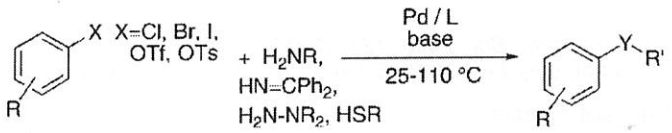
Contents

I. Introduction

1.1 State-of-the-Art Catalysis Methods

1.1.1 Catalytic Amination Reactions–Buchwald-Hartwig Amination

A summary of recent progress: Hatwig, J. F. *Acc. Chem. Res.* **2008**, *41*, *ASAP*.



First-generation catalyst: Pd/P(*o*-tolyl)$_3$
Second-generation catalyst: Pd/chelating aromatic phosphines
Third-generation catalysts: Pd/Hindered alkylphosphines and carbenes •••for 2°-/1°-amines
Fourth-generation catalysts: Pd/Hindered alkyl bisphosphines •••for 1°-amines and thiols

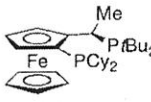
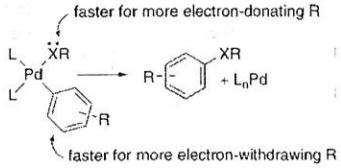
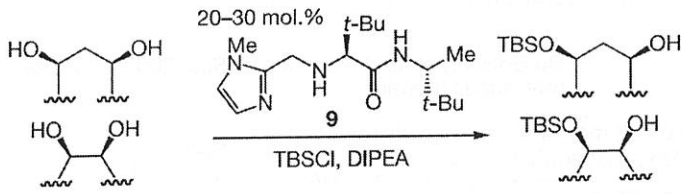


FIGURE 1. Josiphos ligand CyPF*t*Bu in the fourth-generation catalyst.



1.1.2 Regioselective Reactions–Desymmetrization of Diols

A recent example: Hoveyda, A. H.; Snapper, M. L.; et al. *Nature* **2006**, *443*, 67.



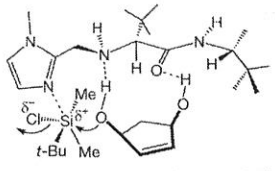
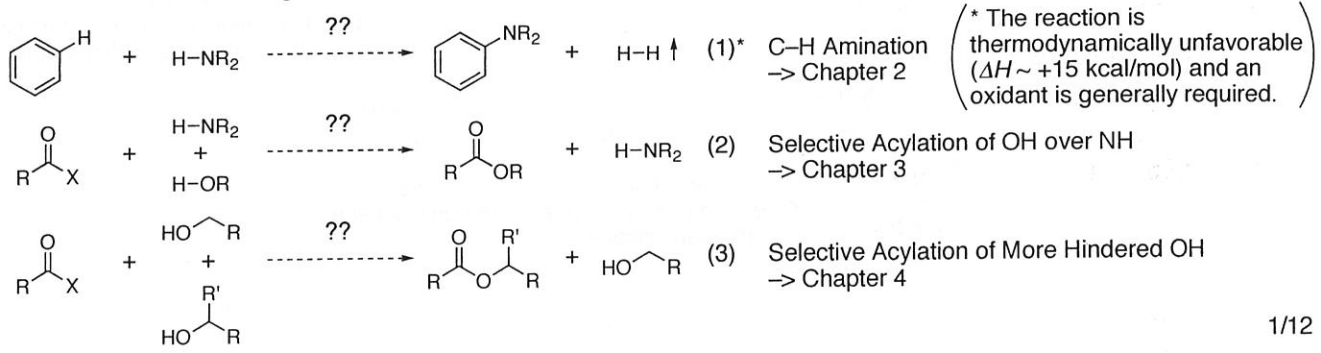


Figure 3 | Proposed transition state model for catalytic enantioselective silylation of diol 1.

1.2 Current Challenges in Catalysis



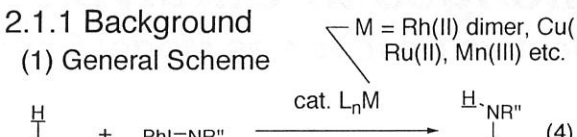
2. C–H Amination

Review: Davies, H. M. L.; et al. *Nature* **2008**, *451*, 417; Sanford, M. S.; et al. *Tetrahedron* **2006**, *62*, 2439; and references therein. See also: Suzuki Lit. Seminar 2008.08.02 (Fe-catalyzed C–H oxidation); Noda Lit. Seminar 2007.10.20 (oxidative C–C bond formation); **Dr. Kuramochi Lit. Seminar 2007.09.12 (Du Bois' total synthesis of Saxitoxin)**; Itano Lit. Seminar 2007.05.23 (Sanford's C–H oxidation); **Tanaka Lit. Seminar 2007.02.07 (Du Bois' total synthesis of Tetrodotoxin)**; Yamaguchi Lit. Seminar 2006.09.09 (C–H insertion of carbenoids); Handa Lit. Seminar 2006.07.15 (oxidative amination of olefins); Dr. Shibuguchi Lit. Seminar 2006.02.01 (C–H borylation).

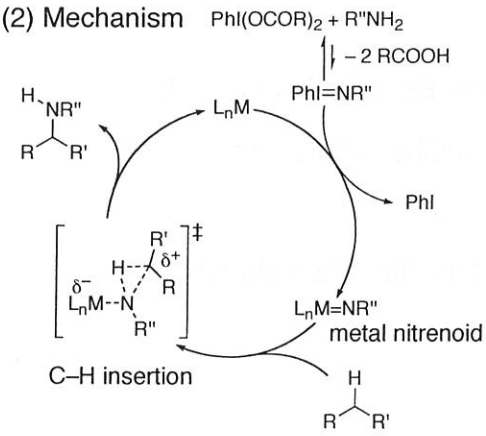
2.1 Nitrene-Based Catalysis Methods

2.1.1 Background

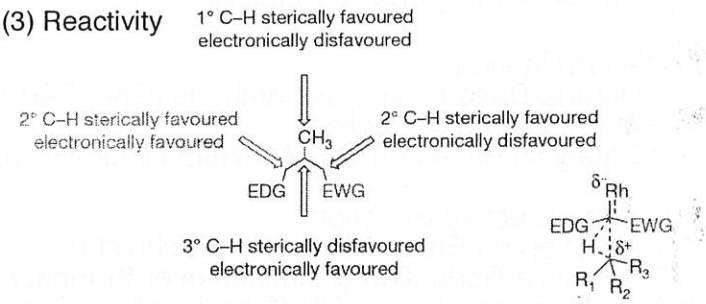
(1) General Scheme



(2) Mechanism



(3) Reactivity

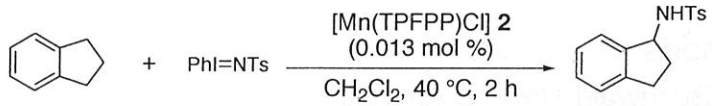


Facile C–H insertion at activated sites
positive charge buildup at insertion site
stabilized when R = N, O, aryl, vinyl

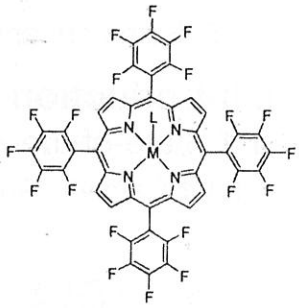
2.1.2 Selected Examples of Racemic Intermolecular C–H Amination

(1) Che's Work

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



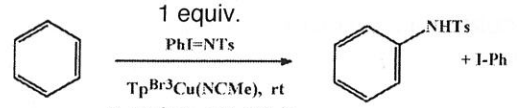
1 equiv. 2 equiv. y. 34%
TON 2600



1: M = Ru(II), L = CO
2: M = Mn(III), L = Cl

(2) Pérez's Work

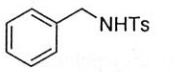
Pérez, P. J.; et al. *J. Am. Chem. Soc.* **2003**, *125*, 12078.
See also: Che, C.-M.; et al. *Org. Lett.* **2004**, *6*, 2405.



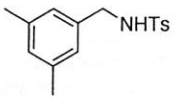
excess (solvent)

y. 40%
C–H amination of sp^2 bond is rare.

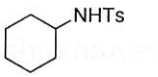
Other substrates



1 h, y. >99%
(excess alkane)

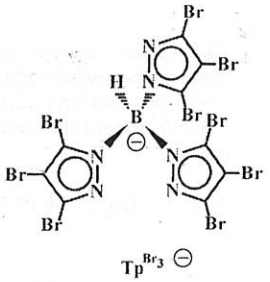


1 h, y. >99%
(excess alkane)



12–18 h, y. 65%
(excess alkane)

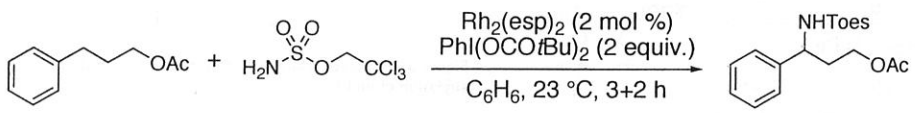
benzylic sp^3 C–H
> sp^2 C–H
~ aliphatic sp^3 C–H



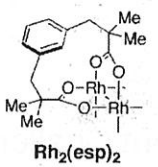
Tp^{Br3} ⊖

(3) Du Bois' Work

Du Bois, J.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 562; and references therein.



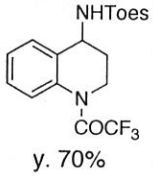
1.0 equiv. $TcesNH_2$ 1.0 equiv. y. 74%



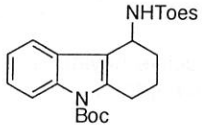
$Rh_2(esp)_2$

Other Rh dimer catalysts gave less satisfactory results (≤35% yields).

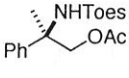
Other substrates



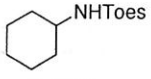
y. 70%



y. 50%



y. 27%
99.9% ee (stereospecific)
(5 equiv. alkane)



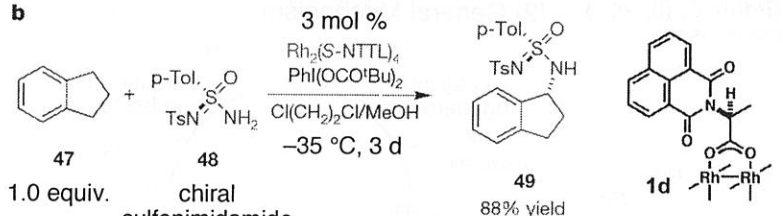
y. 95%
(5 equiv. alkane)

2.1.3 Selected Examples of Diastereo- and Enantioselective C–H Amination

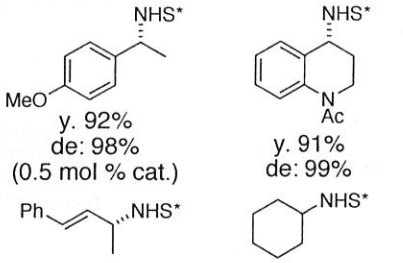
(1) Diastereoselective/Intermolecular (Müller/Dodd/Dauban)

Müller, P.; Dodd, R. H.; Dauban, P.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 343; and references therein.

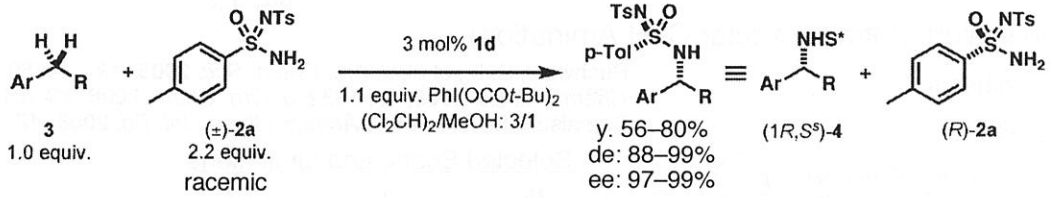
Reaction Using Chiral Sulfonimidamide



Other substrates

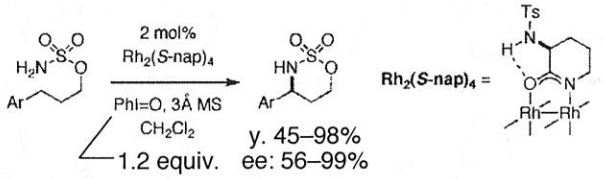


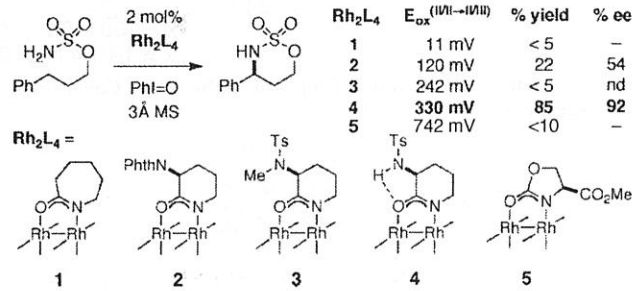
Kinetic Resolution of (±)-**2a**



(2) Enantioselective/Intramolecular (Du Bois)

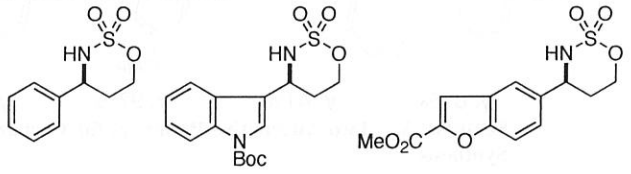
Du Bois, J.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 9220; and references therein.





Rh_2L_4	$E_{ox}^{(II/II\rightarrow III/II)}$	% yield	% ee
1	11 mV	< 5	–
2	120 mV	22	54
3	242 mV	< 5	nd
4	**330 mV**	**85**	**92**
5	742 mV	<10	–

Selected Examples

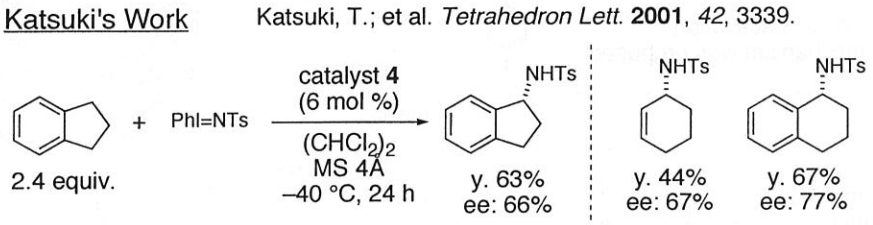


- Selection of a suitable ligand (**4**) is important for both reactivity and selectivity.

(3) Enantioselective/Intermolecular (Katsuki, Hashimoto, Davies)

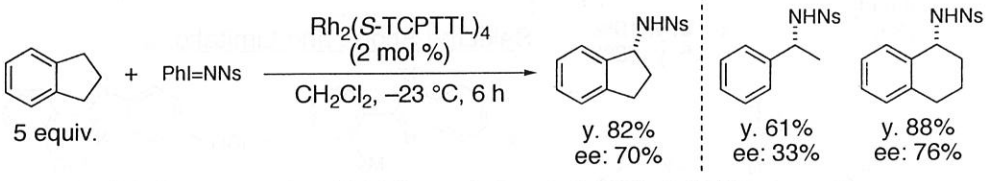
Katsuki's Work

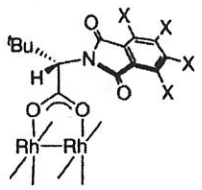
Katsuki, T.; et al. *Tetrahedron Lett.* **2001**, *42*, 3339.



Hashimoto's Work

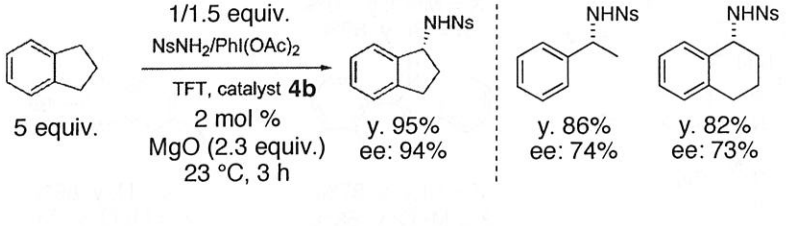
Hashimoto, S.; et al. *Tetrahedron Lett.* **2002**, *43*, 9561.

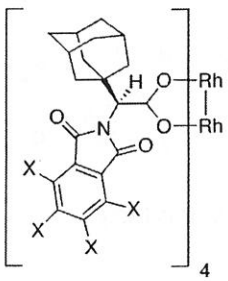




Davies's Work

Davies, H. M. L.; et al. *Org. Lett.* **2006**, *8*, 5013.





X = F: Rh_2(*S*-TFPTTL)$_4$
X = Cl: Rh_2(*S*-TCPTTL)$_4$

X = H
Rh_2(*S*-PTAD)$_4$ **(4a)**

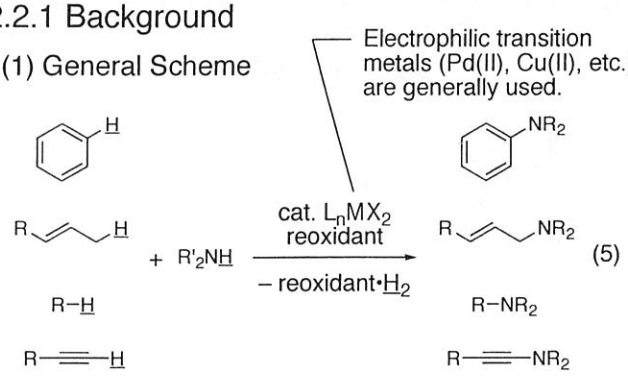
X = Cl
Rh_2(*S*-TCPTAD)$_4$ **(4b)**

2.2 Catalysis Based on C–H Activation

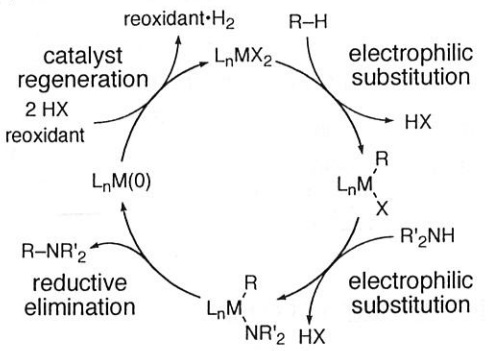
For details of formal C–H amination of alkenes, see: Handa Lit. Seminar 2006.07.15 (oxidative amination of olefins).

2.2.1 Background

(1) General Scheme



(2) General Mechanism

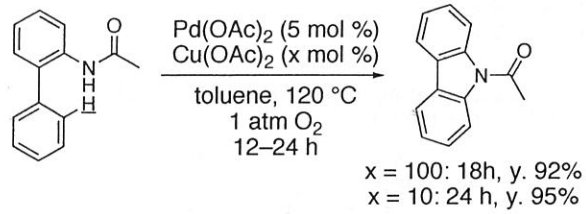


2.2.2 Buchwald's Work (Intramolecular C–H Amination)

(1) Carbazole Synthesis

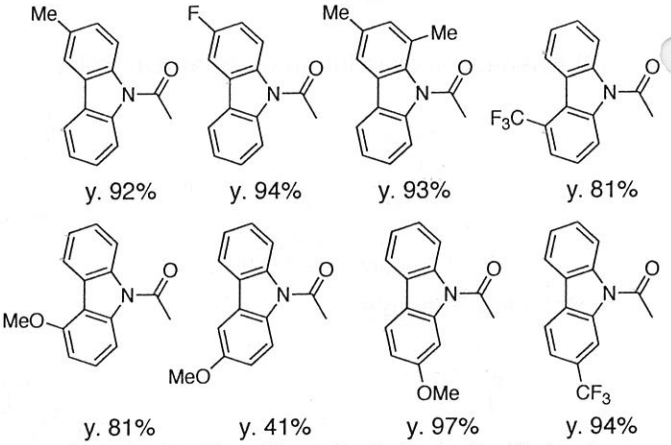
Buchwald, S. L.; et al. *J. Am. Chem. Soc.* **2005**, *127*, 14560; *Angew. Chem., Int. Ed.* **2008**, *47*, 1932; *J. Org. Chem.* **2008**, *73*, *ASAP*. See also: Shi, Z.-J.; et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115.

Optimized Results

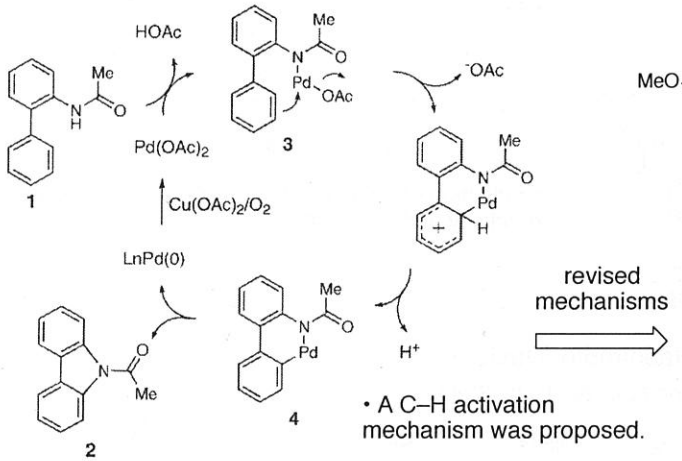


x = 100: 18h, y. 92%
x = 10: 24 h, y. 95%

Selected Scope and Limitations



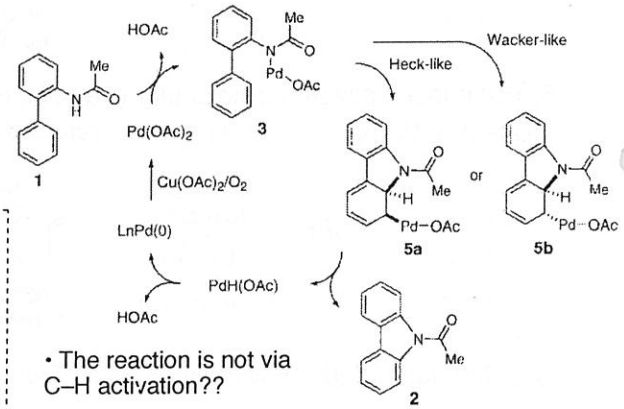
SCHEME 2. Our Initial Proposed Pathway for Carbazole Synthesis



• A C–H activation mechanism was proposed.

revised mechanisms

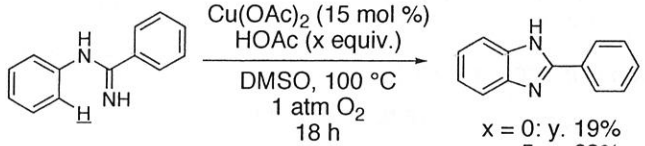
SCHEME 3. Two Alternative Pathways for Carbazole Synthesis



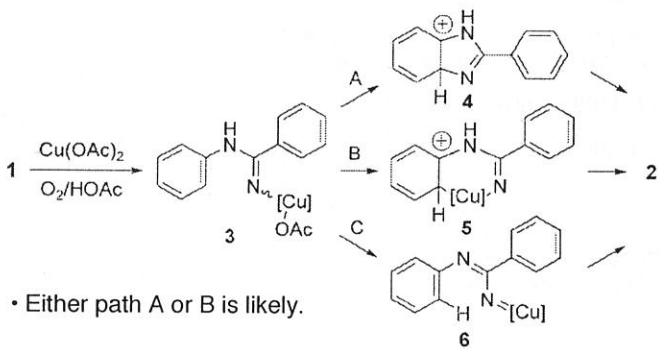
• The reaction is not via C–H activation??

(2) Benzimidazole Synthesis

Optimized Results



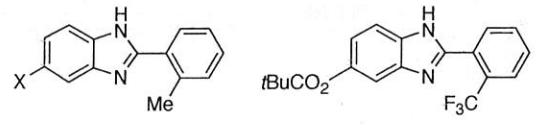
x = 0: y. 19%
x = 5: y. 63%



• Either path A or B is likely.

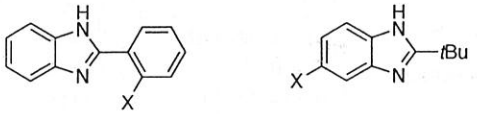
Scheme 2. Possible reaction pathways for the conversion of **1** into **2**.

Selected Scope and Limitations



X = H: y. 89%
X = MeO: y. 70%
X = Br: y. 89%

y. 88%



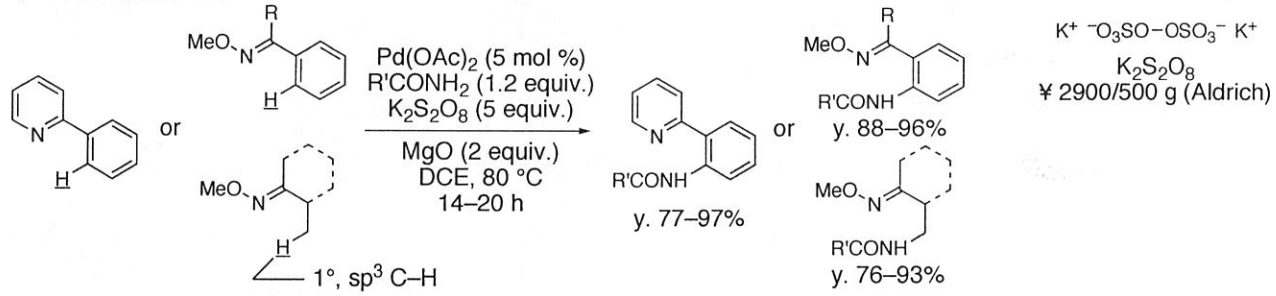
X = CF_3: y. 87%
X = MeO: y. 68%
X = TBS: y. 80%

X = H: y. 86%
X = MeO: y. 83%
X = Br: y. 89%

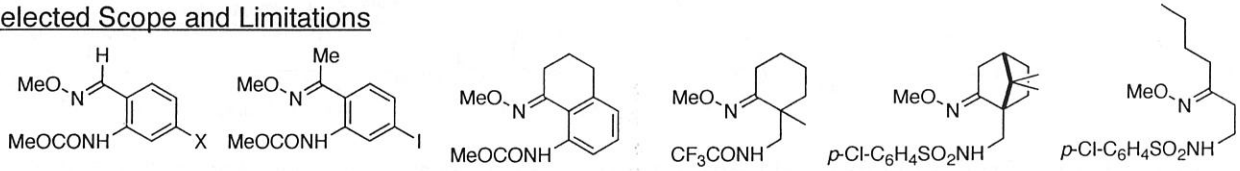
2.2.3 Yu/Che's Work (Directed Intermolecular C–H Amination)

Yu, W.-Y.; Che, C.-M.; et al. *J. Am. Chem. Soc.* **2006**, *128*, 9048.
See also: Itano Lit. Seminar 2007.05.23 (Sanford's C–H oxidation)

Optimized Results

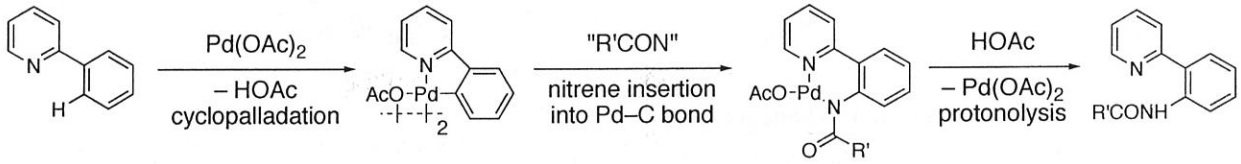


Selected Scope and Limitations

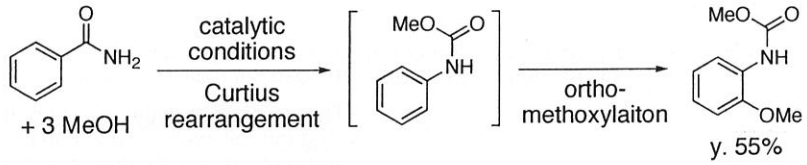


X = H: y. 92%
X = Me: y. 95%
y. 87%
y. 94%
y. 89%
y. 93%
y. 76%

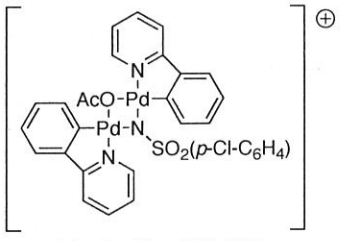
Proposed Mechanism



Preliminary Mechanistic Studies



• A Curtius rearrangement product obtained under the reaciton conditions support the formation of nitrene intermediate.

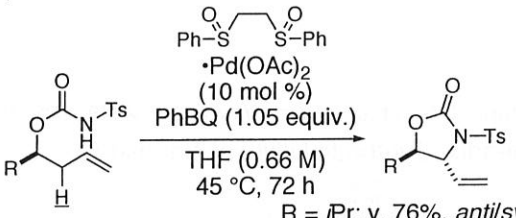


detected by ESI-MS

2.2.4 White's Work (Allylic Amination)

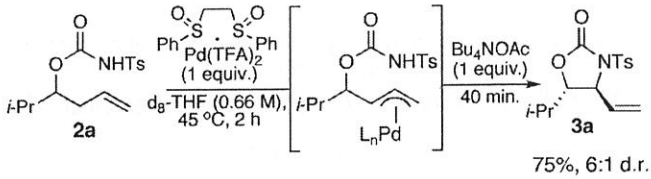
White, M. C.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 7274; *J. Am. Chem. Soc.* **2008**, *130*, 3316. See also: White, M. C.; et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 6448 and references therein.

(1) Intramolecular Process



R = *i*Pr: y. 76%, *anti*/*syn* = 6/1
R = *t*Bu: y. 8%, *anti*/*syn* = 18/1
R = *n*Pr: y. 86%, *anti*/*syn* = 1.6/1

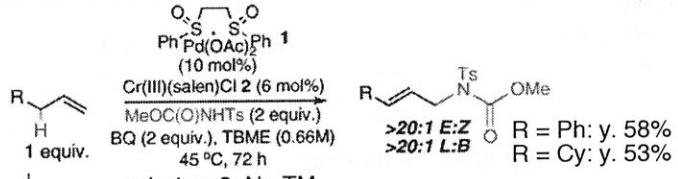
Scheme 4



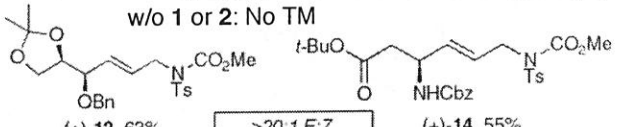
75%, 6:1 d.r.

• Bis(sulfoxide) ligand enhances the formation of allylpalladium intermediate.
• Initial alkene isomerization followed by hydroamination is less likely.

(2) Intermolecular Process

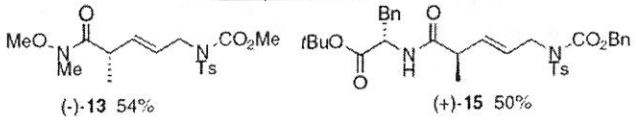


w/o **1** or **2**: No TM



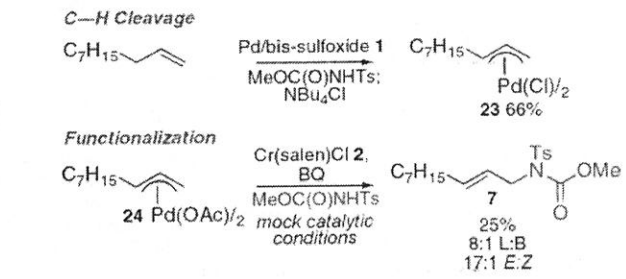
(+)-**12** 63%
(+)-**14** 55%

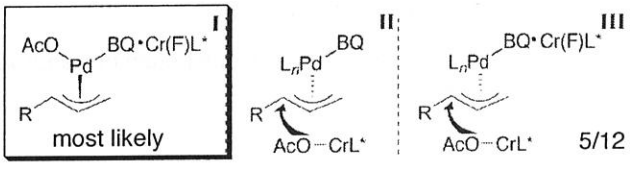
>20:1 E:Z
>20:1 L:B
no erosion in ee



(-)-**13** 54%
(+)-**15** 50%

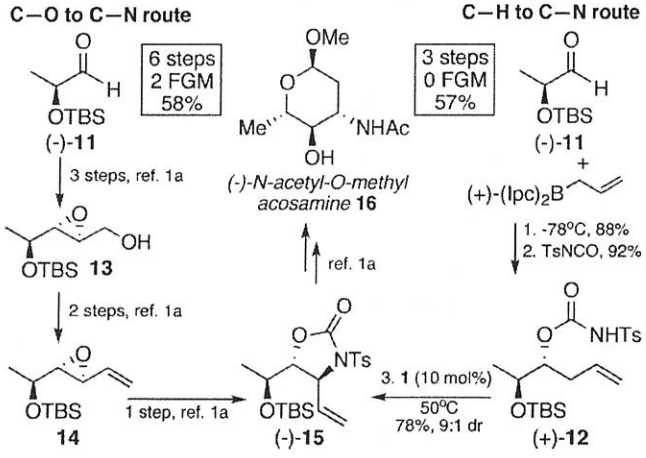
Scheme 3. Stoichiometric Studies To Evaluate the Role of (salen)CrCl **2**



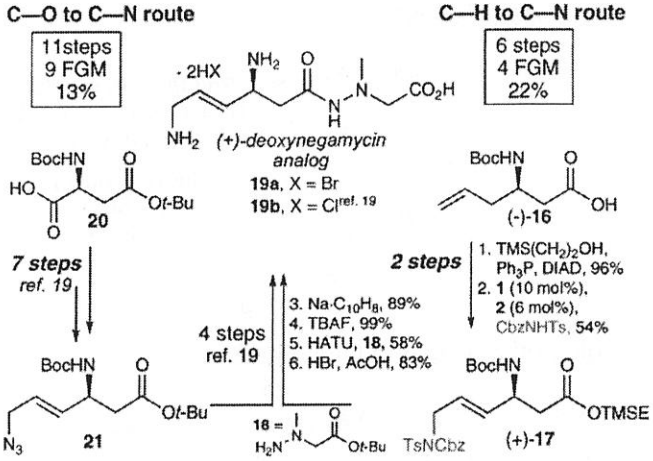


(3) Synthetic Application

Scheme 3 Application of Intramolecular Process



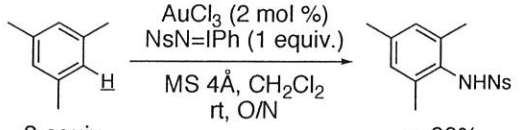
Scheme 1 Application of Intermolecular Process



2.2.5 He's Work (Au-Catalyzed C–H Amination)

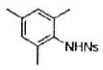
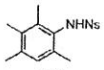
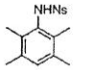
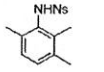
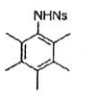
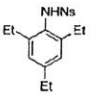
He, C.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 12058.

(1) Optimized Reaction Conditions



sp² C–H > benzylic C–H

Table 2. $AuCl_3$–Catalyzed Nitrene Insertion into Aromatic C–H Groups[a]

Entry[a]	Substrate	Product	Yield(%)[b]	Entry[a]	Substrate	Product	Yield(%)[b]
1			90	4			75
2			67	5			73[c]
3			61	6			70[d]

[a] All reactions were carried out by using 50 mg PhI=NNs in 4 mL solvent at a ratio of hydrocarbons/PhI=NNs = 8:1. [b] Isolated yield. [c] All three products with a ratio of 1:1:1 based by ^1H NMR. [d] With <5% of benzylic nitrene insertion based on ^1H NMR.

• Note: Benzene and toluene yielded <5% of C–H amination product (because of electronic effect??).

(2) Mechanistic Study

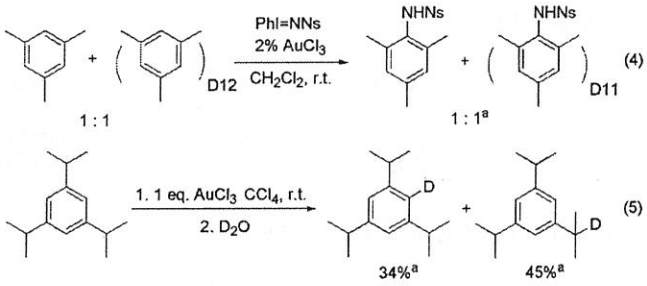
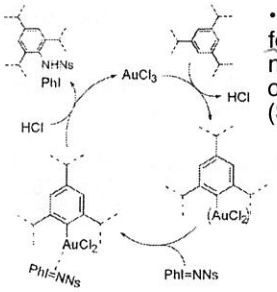


Figure 1. Amination of benzylic C–H groups catalyzed by $AuCl_3$ and isotope labeling experiments. [a] ^1H NMR ratio and conversion.



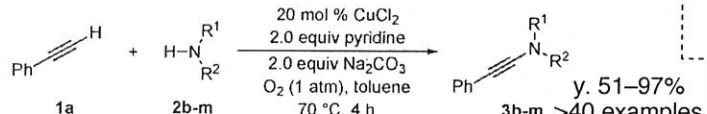
• They proposed initial Au–C bond formation followed by insertion of nitrene to explain the different reactivity obtained in the Au-catalyzed system. (See 2.1.2 (2) (p. 2) for comparison.)

2.2.6 Stahl's Work (Amination of Termial Alkynes)

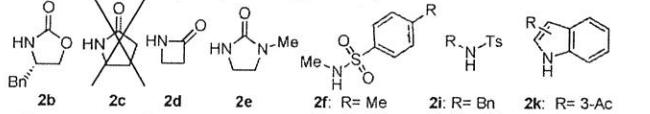
Stahl, S. S.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 833.

(1) Optimized Reaction Conditions

Table 2. Cu-Catalyzed Oxidative Coupling of Phenylacetylene with Nitrogen Nucleophiles[a]



Nitrogen Nucleophiles: (5 equiv. in general)



2b 2c 2d 2e 2f: R= Me 2g: R= NO_2 2h: R= OMe 2i: R= Bn 2j: R= *n*-Bu 2k: R= 3-Ac 2l: R= 3-CO_2Me 2m: R= 2-CO_2Et

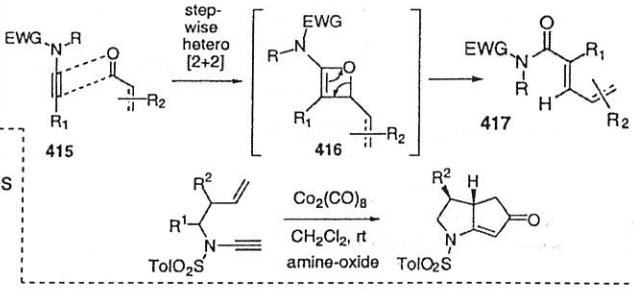
2c: not applicable

Alkynes: R' = TIPS [TIPS = (*i*-Pr)$_3$Si] (**1b**)
n-C_6H_{13} (**1c**)
TBSO$(CH_2)_3$ (TBS = *t*-BuMe$_2$Si) (**1d**)
TBSOCH_2 (**1e**), 4-MeOC_6H_4 (**1f**)

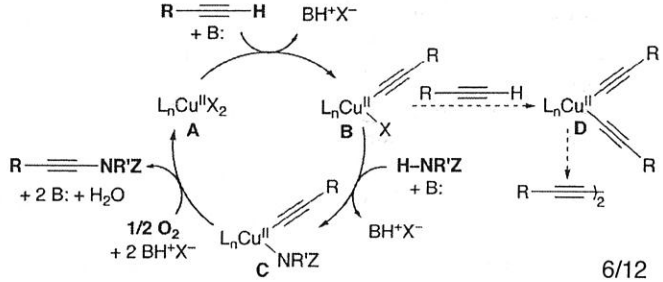
Nitrogen Nucleophiles: **2a - 2m** (see Table 2)

• The addition of an excess amount of nitrogen nucleophiles suppressed alkyne dimerization.

Appendix. Synthetic Utility of Ynamides



(2) Proposed Mechanism



3. Chemoselective Reaction

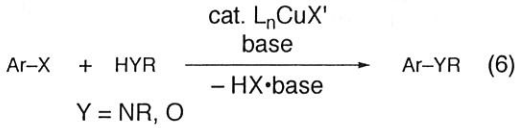
3.1 Arylation on Either NH or OH (Buchwald)

Buchwald, S. L.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 3490.
See also: Buchwald, S. L.; et al. *Org. Lett.* **2002**, *4*, 3703.

3.1.1 Background of Cu-Catalyzed C–N/C–O Bond Formation (Ullmann Reaction)

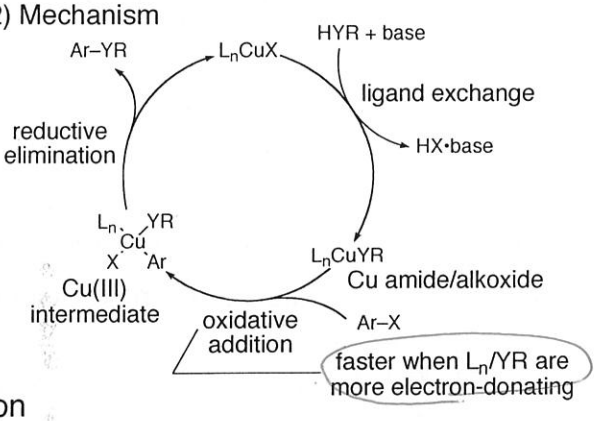
Review: Thomas, A. W.; et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400; Kunz, K.; et al. *Synlett* **2003**, 2428; Beletskaya, I, P.; et al. *Coord. Chem. Rev.* **2004**, *248*, 2337.
For mechanism, see: Hartwig, J. F.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 9971.

(1) General Scheme



- Aryl halide: I, Br, Cl (reactivity: I > Br > Cl)
- Amine/alcohols: 1°/2°-alkyl/arylamines and alcohols
- Cu source: CuI, etc. (generally 5–20 mol %)
- Effective ligand: diamine, 1,3-diketone, etc.
- Base: K_2CO_3, K_3PO_4, Cs_2CO_3, etc.
- Solvent: toluene, DMF, alcohol, etc.

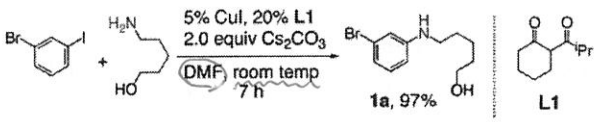
(2) Mechanism



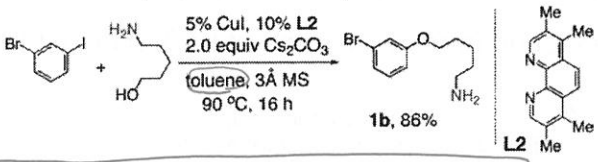
配位性の高いligandがよい.

3.1.2 Selective C–N and C–O Bond Formation

Scheme 1. N-Arylation of 5-Amino-1-pentanol

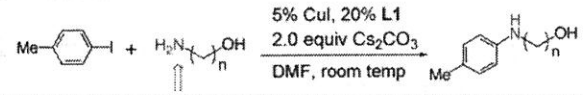


Scheme 2. O-Arylation of 5-Amino-1-pentanol

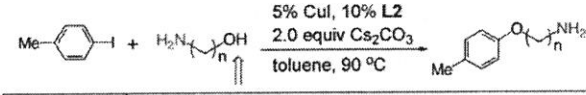


- highly coordinative ligand and solvent: C–N > C–O
- less coordinative ligand and solvent: C–O > C–N
- 1,2- and 1,3-aminoalcohols: ligandless conditions favorable
- highly coordinative conditions: Oxidative addition might be rds and more electron-donating amide would react faster –> preferential C–N bond formation??
- less coordinative conditions: Ligand exchange might be rds and deprotonated OH on Cs_2CO_3 would react faster than neutral NH –> preferential C–O bond formation??

Table 1. Effect of Spacer Length of N- and O-Arylation Reactions[a,b]



a, n =	2	3	4	5	6
CN Yield, %	45[c] (92)[d]	96	99	97	99
CN : CO	3:1 (40:1)	45:1	>50:1	>50:1	>50:1

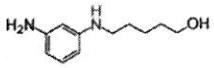
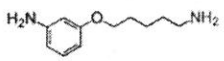
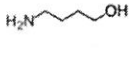
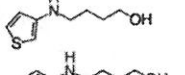
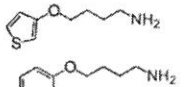
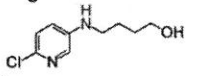
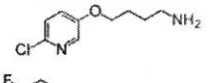
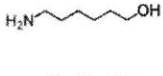
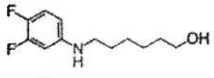
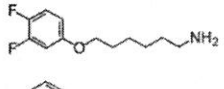
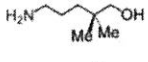
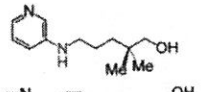
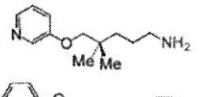
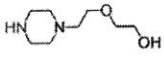
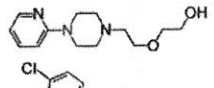
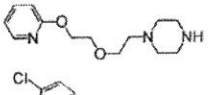
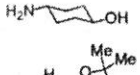
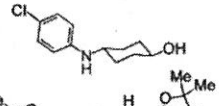
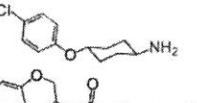
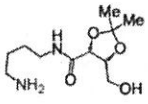
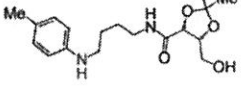
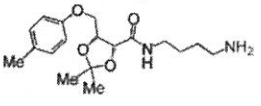


b, n =	2	3	4	5	6
CO Yield, %	16[c]	28[c] (64)[e]	91	90	89
CO:(CN+double)	1:6	1:4 (2:1)	18:1	20:1	24:1

まだまだ.

[a] Using 1.5–2.0 equiv of aminoalcohol. [b] Isolated yields, average of two runs. [c] GC yield. [d,e] Ligand-free conditions; see Supporting Information.

Table 2. Copper-Catalyzed N- and O-Arylation of Aminoalcohols[a]

entry	aminoalcohol	ArI	C-N product	C-N, %[b,c] (N:O)	C-O product	C-O, %[d,e,f] (N:O)
1				**9a**, 84 (>50:1)		**9b**, 79 (16:1)
2				**10a**, 85 (>50:1)		**10b**, 80 (20:1)
3				**11a**, 84 (25:1)		**11b**, 78 (16:1)
4				**12a**, 93 (>50:1)		**12b**, 79 (18:1)
5				**13a**, 83 (20:1)		**13b**, 80 (15:1)
6				**14a**, 83 (18:1)		**14b**, 81 (15:1)
7				**15a**, 80 (20:1)		**15b**, 80 (18:1)
8				**16a**, 85 (20:1)		**16b**, 81 (16:1)

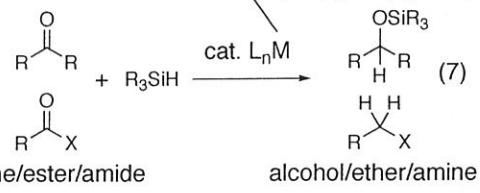
[a] Isolated yields, average of two runs. [b] With **L1**. [c] Selectivity: %CN:%CO. [d] With **L2**. [e] Selectivity: %CO:(%CN + % double). [f] Balance: ArH (from ArI) and Ar_2O.

3.2 Selective Reduction of Amides over Ketones/Esters (Ito, Nagashima)

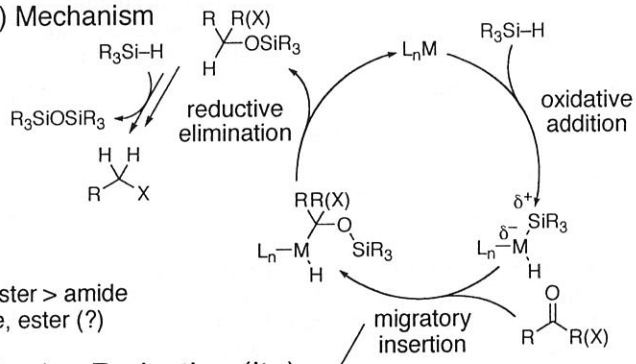
Ito, Y.; et al. *Tetrahedron Lett.* **1998**, *39*, 1017; Nagashima, H.; et al. *Chem. Commun.* **2007**, 4916, and references therein.

3.2.1 Background of Transition Metal-Catalyzed Hydrosilylation of Carbonyl Compounds

(1) General Scheme — low-valent, coordinatively unsaturated M are used (Rh(I), Ru(0), etc.)

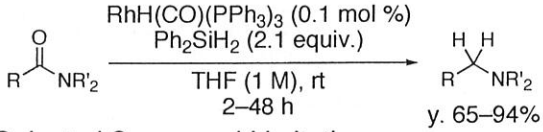


(2) Mechanism



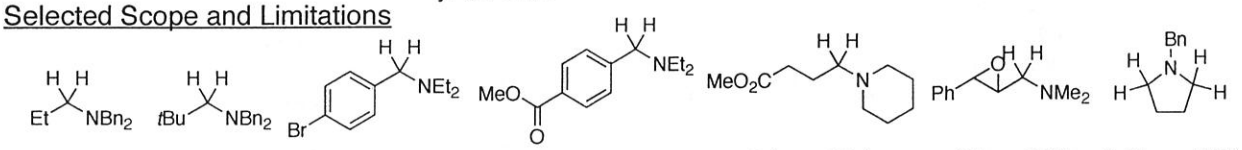
- general reactivity toward hydride reduction: ketone > ester > amide
- general reactivity in the hydrosilylation: amide > ketone, ester (?)

3.2.2 $RhH(CO)(PPh_3)_3$-Catalyzed Amide-Selective Reduction (Ito)



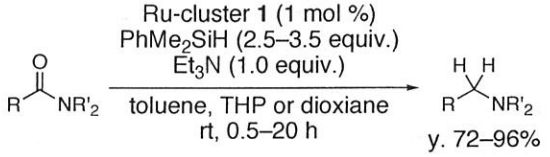
- tertiary amide only
- ester, Br, epoxide, Bn tolerant

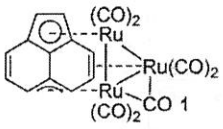
Selected Scope and Limitations



1 h, y. 96% | 48 h, y. 86% | 20 h, y. 85% | 4.5 h, y. 70% | 3 h, y. 98% | 3 h, y. 65% | 3.5 h, y. 70%

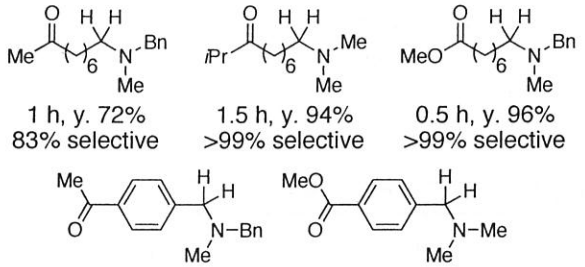
3.2.3 Ru-Cluster-Catalyzed Amide-Selective Reduction in the Presence of Et_3N (Nagashima)





- tertiary amide only
- esters and ketones tolerant
- Et_3N completely retarded reduction of ketones and esters (Fig. 1).

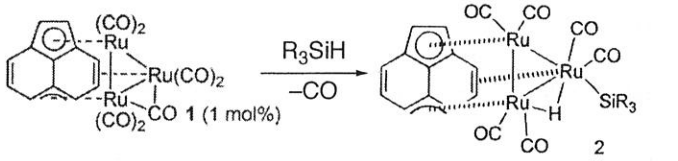
Selected Scope and Limitations

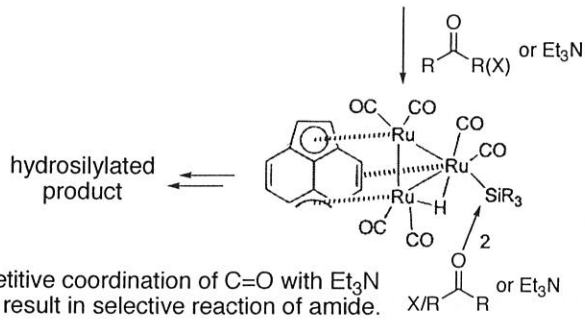


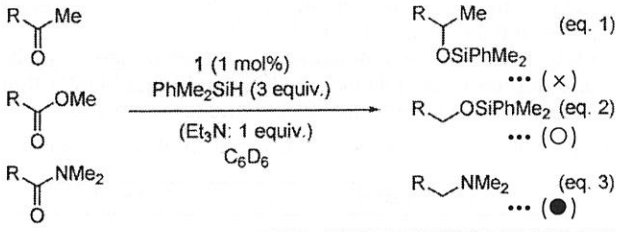
1 h, y. 72%, 83% selective | 1.5 h, y. 94%, >99% selective | 0.5 h, y. 96%, >99% selective

18 h, y. 88%, >99% selective | 3.5 h, y. 81%, >99% selective

Mechanism (my speculation)







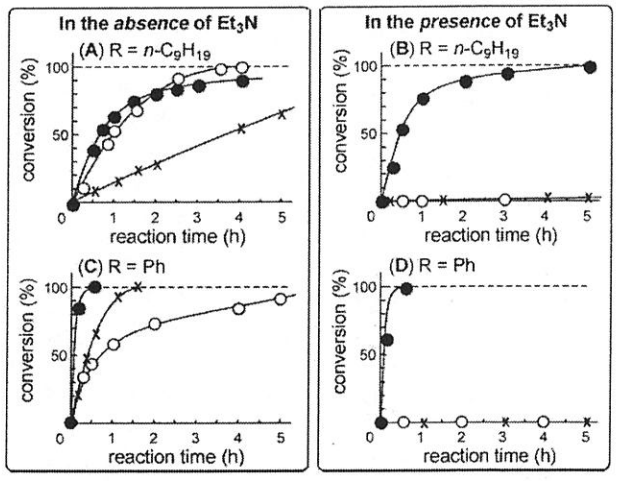


Fig. 1 The reaction profiles of eqns 1–3. Reactions were carried out using carbonyl compounds (0.2 mmol), $PhMe_2SiH$ (0.6 mmol) and **1** (0.002 mmol) in the absence (**A** and **C**) or presence (**B** and **D**) of Et_3N (0.2 mmol; 1 equiv. with respect to the carbonyl compound) at room temperature. The reaction of methyl benzoate was performed at 50 °C; eqn 1 (×), eqn 2 (○), eqn 3 (●).

3.3 Acylation of OH over NH (Ohshima/Mashima)

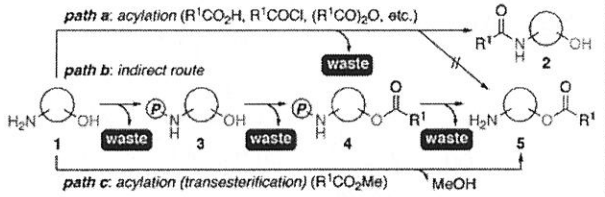
Ohshima, T; Mashima, K.; et al. *J. Am. Chem. Soc.* **2008**, *130*, 2944.

3.3.1 Background of Selective Acylation of Alcohols in the Presence of Amines

Review: Melman, A.; et al. *Org. Biomol. Chem.* **2004**, *2*, 1563.

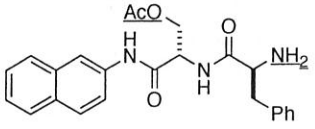
(1) General Consideration

Scheme 1. Acylation of Aminoalcohol **1**



- Selective acylation of alcohols in the presence of amines (path c) is generally difficult; multistep protection-deprotection sequence (path b) is more reliable but it consumes many reagents and generates much wastes.

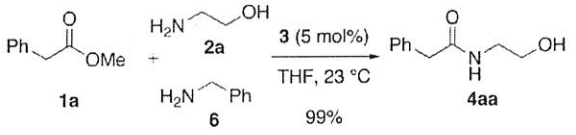
(2) Precedents



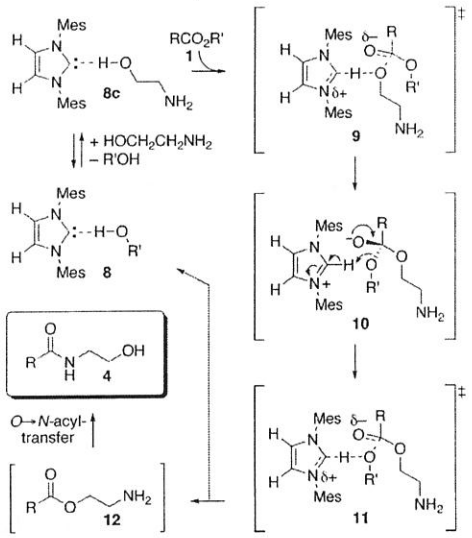
- lipase-catalyzed selective acylation of Ser-OH in the presence of primary amine (*N*-terminus of peptide)

Klibanov, A. M.; et al. *J. Am. Chem. Soc.* **1991**, *113*, 6328.

- Movassaghi reported NHC-catalyzed selective transamidation of aminoalcohols in the presence of benzylamine, and they proposed selective deprotonation of alcohols by NHC would accelerate transesterification step (**9**–**11**).



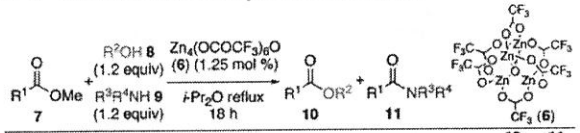
Scheme 1. Proposed Reaction Mechanism

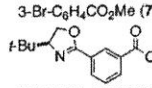


Movassaghi, M.; et al. *Org. Lett.* **2005**, *7*, 2453.

3.3.2 Zn-Cluster-Catalyzed Selective Acylation of Alcohols in the Presence of Amines

Table 1. Chemoselective Acylation of Alcohols

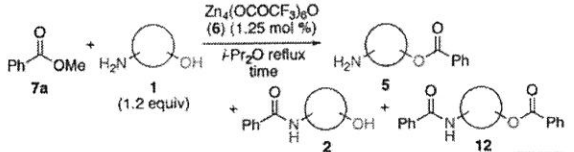


entry	R^1CO_2Me **7**	R^2OH **8**	R^3R^4NH **9**	**10** (%)[a]	**11** (%)[a]
1	$PhCO_2Me$ (**7a**)	*cyclo*-Hex-OH (**8a**)	*cyclo*-Hex-NH_2 (**9a**)	96[b]	1[b]
2	**7a**	$CH_3(CH_2)_5$-OH (**8b**)	$CH_3(CH_2)_5$-NH_2 (**9b**)	92[b]	8[b]
3	**7a**	*cyclo*-Hex-OH (**8a**)	$CH_3(CH_2)_5$-NH_2 (**9b**)	92[b]	5[b]
4	**7a**	$CH_3(CH_2)_5$-OH (**8b**)	*cyclo*-Hex-NH_2 (**9a**)	99[b]	1[b]
5	**7a**	*t*-Bu-CH_2-OH (**8c**)	*t*-Bu-CH_2-NH_2 (**9c**)	94[b]	1[b]
6	**7a**	*n*-Pr_2CH-OH (**8d**)	*n*-Pr_2CH-NH_2 (**9d**)	90[b]	1[b]
7	**7a**	PhCH(Me)OH (**8e**)	PhCH(Me)NH_2 (**9e**)	76[b]	<1[b]
8	**7a**	 n = 1 (**8f**)	 n = 1 (**9f**)	95	n.d.[c]
9	**7a**	n = 2 (**8g**)	n = 2 (**9g**)	78	n.d.[c]
10	**7a**	*cyclo*-Hex-OH (**8a**)	pyrrolidine (**9h**)	82[b]	9[b]
11	**7a**	*cyclo*-Hex-OH (**8a**)	piperidine (**9i**)	83[b]	6[b]
12	**7a**	*cyclo*-Hex-OH (**8a**)	morpholine (**9j**)	86[b]	11[b]
13[d]	4-CH_3-$C_6H_4CO_2Me$ (**7b**)	**8a**	**9a**	>99	n.d.[c]
14[d]	4-Cl-$C_6H_4CO_2Me$ (**7c**)	**8a**	**9a**	>99	<1
15[d]	4-Br-$C_6H_4CO_2Me$ (**7d**)	**8a**	**9a**	94	1
16	4-NO_2-$C_6H_4CO_2Me$ (**7e**)	**8a**	**9a**	>99	<1
17	4-NC-$C_6H_4CO_2Me$ (**7f**)	**8a**	**9a**	91	1
18[d]	4-THPO-$C_6H_4CO_2Me$ (**7g**)	**8a**	**9a**	>99	<1
19	3-Br-$C_6H_4CO_2Me$ (**7h**)	**8a**	**9a**	>99	n.d.[c]
20	 (**7i**)	**8a**	**9a**	>99	<1
21	(*E*)-PhCH=$CHCO_2Me$ (**7j**)	**8a**	**9a**	>99	<1
22	$PhCH_2CH_2CO_2Me$ (**7k**)	**8a**	**9a**	94[b]	<1[b]
23	$CH_3(CH_2)_{16}CO_2Me$ (**7l**)	**8a**	**9a**	98	n.d.[c]
24[d]	TBSO$(CH_2)_9CO_2Me$ (**7m**)	**8a**	**9a**	87	n.d.[c]

[a] Isolated yield. [b] GC yield. [c] Not detected. [d] Reaction time was 24 h.

- Zn-cluster **6** would selectively activate alcohols in the presence of amine nucleophiles, making alcohols more nucleophilic than the amines.
- Bimetallic activation of both alcohols and esters would be plausible.

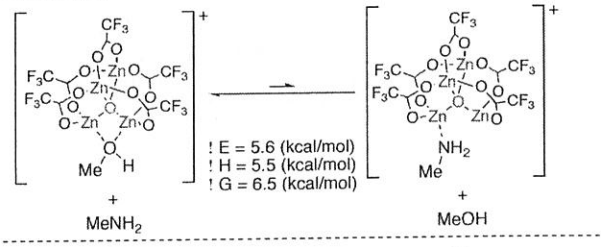
Table 2. Chemoselective Acylation of Aminoalcohols **1**

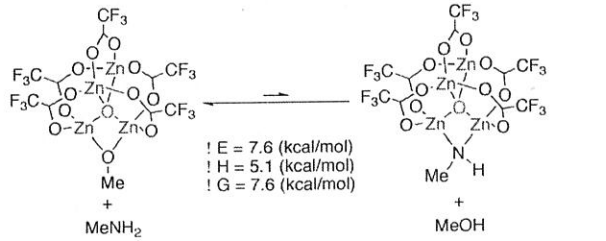


entry	aminoalcohol **1**	time (h)	ester **5** (%)[a]	amide **2** (%)[b]	**12** (%)[b]
1	 (**1a**)	24	n.d.[c]	77	23
2	H_2N-$(CH_2)_6$-OH (**1b**)	18	82	n.d.[c]	18
3	H_2N-$(CH_2)_8$-OH (**1c**)	20	90	n.d.[c]	7
4	H_2N-$(CH_2)_{10}$-OH (**1d**)	20	90	n.d.[c]	7
5[d]	 (**1e**)	24	99	n.d.[c]	n.d.[c]
6[d]	 n = 1 (**1f**)	18	88	n.d.[c]	17
7[d]	n = 2 (**1g**)	18	92	n.d.[c]	7

[a] Isolated yield after Boc protection. [b] Isolated yield. [c] Not detected. [d] Solvent was toluene.

B3LYP/6-31G(d,p)





4. Regioselective Reaction

4.1 Acylation of Natural Products (Miller)

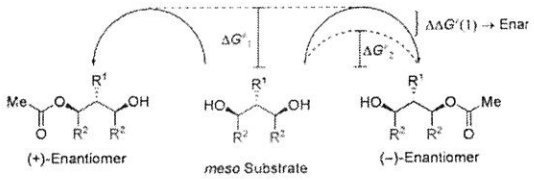
Miller, S. J.; et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 5616.

4.1.1 Background of Selective Acylation of Polyols

Review: Melman, A.; et al. *Org. Biomol. Chem.* **2004**, *2*, 1563.

(1) General Consideration

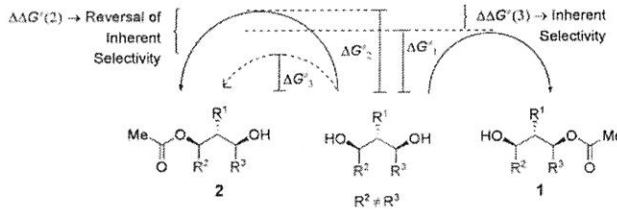
(a) Enantioselective Catalysis



Achiral Catalyst → $(\Delta G'_1 - \Delta G'_1) = 0$ → Racemic

Chiral Catalyst → $(\Delta G'_1 - \Delta G'_2) \neq 0$ → Enantioenriched

(b) Site-Selective Catalysis



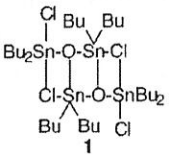
Achiral Catalyst → $(\Delta G'_2 - \Delta G'_1) \neq 0$ → Inherent Selectivity

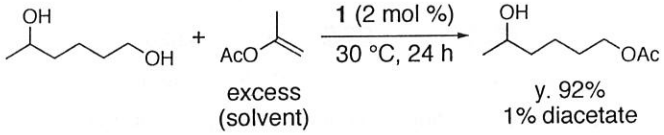
Chiral Catalyst → $(\Delta G'_2 - \Delta G'_3) \neq 0$ → Regioenriched

• Site-selective activation of alcohols is thought to be much more difficult than desymmetrization of meso-diols because catalysts have to overcome inherent reactivity difference.

(2) Precedents

1°-Selective

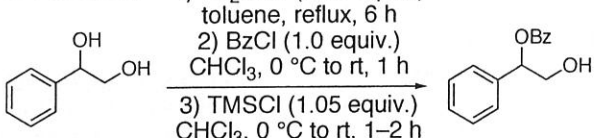




y. 92%
1% diacetate

Otera, J.; et al. *J. Org. Chem.* **1998**, *63*, 2420.

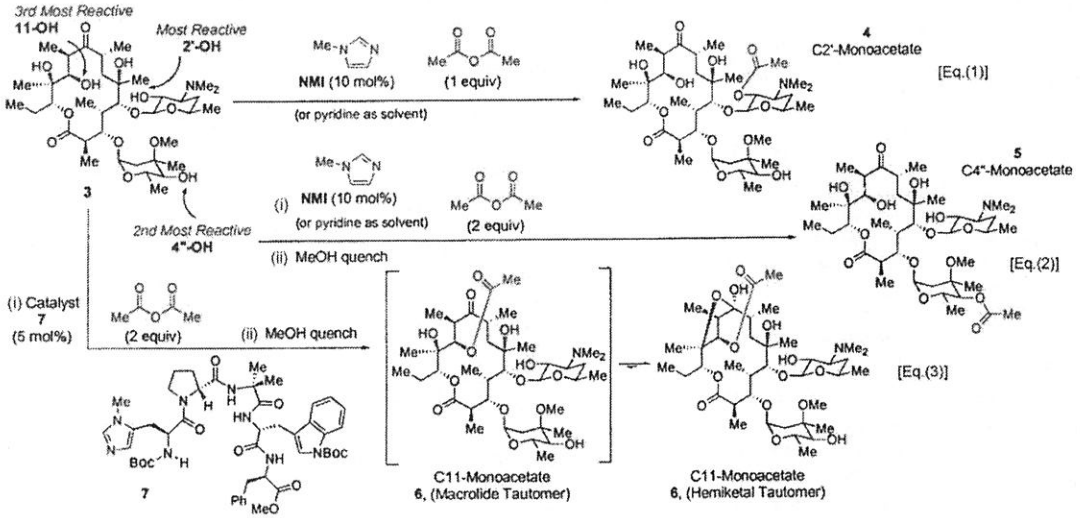
2°-Selective



y. 83%
2°/1° = 98/2

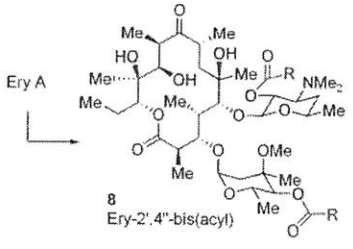
Roelens, S.; et al. *J. Org. Chem.* **1990**, *55*, 5132.

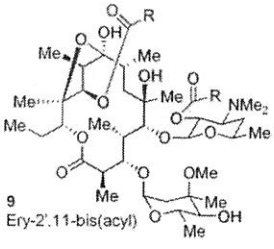
4.1.2 Miller's Approach to Overcome Inherent Selectivity Difference by Peptide Catalysts

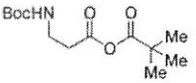
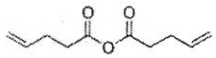
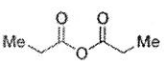


• Miller's peptide catalyst **7** could overcome inherent selectivity difference of erythromycin A **3** obtained by NMI as a catalyst, although the actual mechanism of activation is still not clear (hydrogen-bonding interactions?)

Table 1: Site-selective reactions of erythromycin A with achiral catalyst versus **7**.



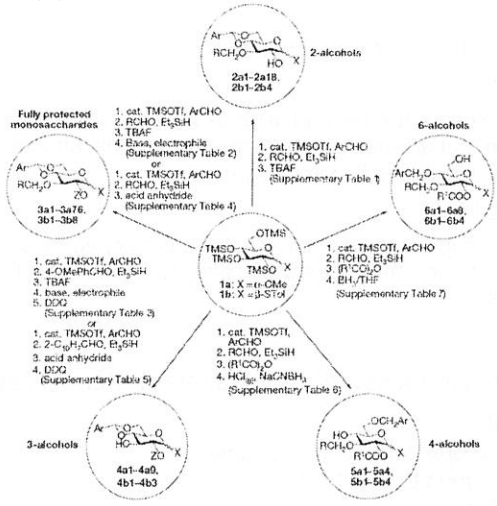


entry	acylating agent	with NMI 8:9	with 7 8:9
1 **8a, 9a:** R = $(CH_2)_6CH_3$		>10:1[b]	1:9 (58%)
2 **8b, 9b:** R = $(CH_2)_2NHBoc$		5:1[b]	1:>10 (53%)
3 **8c, 9c:** R = $(CH_2)_2CH=CH_2$		2:1[b]	1:5 (56%)
4 **8d, 9d:** R = Et		2:1[b]	1:3.5 (28%)

4.2 Acylation of Carbohydrates (Kawabata) Kawabata, T.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 12890.

4.2.1 Background of Selective Acylation(Protection) of Carbohydrates

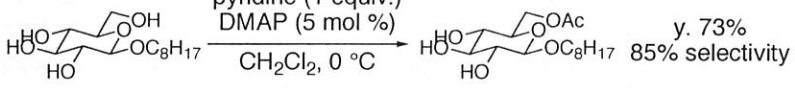
(1) General Consideration



• Selective protection of carbohydrates generally requires multistep protection-deprotection sequence.
Hung, S.-C.; et al. *Nature* **2007**, *446*, 896.

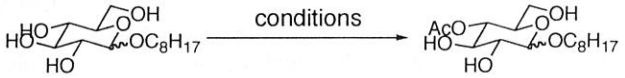
(2) Precedents

1°-Selective



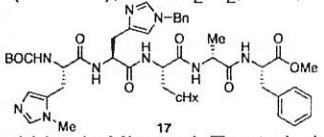
Albert, M.; et al. *Org. Lett.* **2004**, *6*, 945.

2°-Selective



Ac_2O (0.7 equiv.), K_2CO_3 (10 equiv.)
DMAP (5 mol %), $CHCl_3$, 23 °C, 1 h — y. 98%, 61% selectivity (for α-anomer)

Ac_2O (0.7 equiv.)
17 (2 mol %), tol/CH_2Cl_2, 0 °C, 15 h — y. 100%, 58% selectivity (for β-anomer)

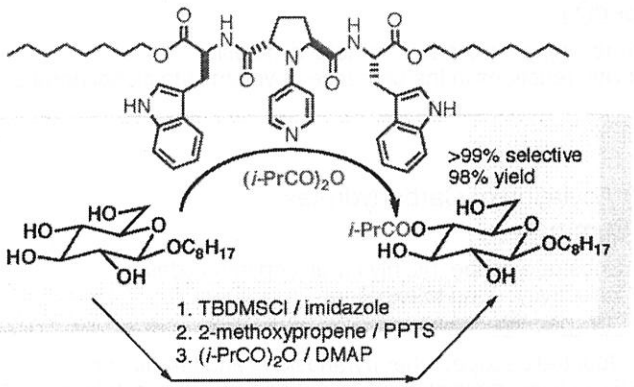


17

Yoshida, J.; Mizutani, T.; et al. *J. Chem. Soc., Perkin Trans. 1* **1999**, 465;
Miller, S. J.; et al. *Tetrahedron* **2003**, *59*, 8869.

4.2.2 Kawabata's Catalytic Approach to One Step Regioselective Protection of Carbohydrates

(a) catalytic one-step process



(b) conventional protection/deprotection procedure

Substrate Generality

(a) octyl β-D-glucopyranoside — R=*i*-Pr : >99% regioselective, 98% yield (-50 °C, 38 h); R=CH_3 : 96% regioselective, 96% yield (-20 °C, 24 h)

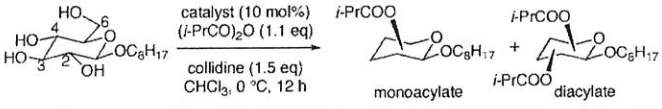
(b) octyl β-D-thioglucopyranoside — R=*i*-Pr : 97% regioselective, 92% yield (-60 °C, 72 h); R=CH_3 : 95% regioselective, 99% yield (-60 °C, 41 h)

(c) octyl α-D-glucopyranoside — R=*i*-Pr : 54% regioselective, 75% yield (20 °C, 12 h)

(d) octyl β-D-mannopyranoside — R=*i*-Pr : 85% regioselective, 61% yield (-50 °C, 120 h)

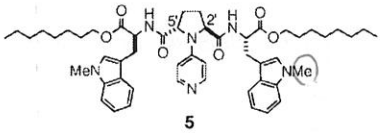
(e) octyl β-D-galactopyranoside — R=*i*-Pr : 91% regioselective, 46% yield (20 °C, 12 h)

Table 4. Effects of Catalysts on Regioselectivity of Acylation of Octyl β-D-Glucopyranoside[a]



entry	catalyst	monoacylate (%)	regioselectivity[b] 6-*O*:4-*O*:3-*O*:2-*O*	diacylate (%)	recovery (%)
1	**1**	97	0:98:2:0	2	0
2	**5**[c]	69	14:60:26:0	20	8
3	**6**[c]	74	7:65:28:0	15	4
4	**7**[c]	62	13:66:20:1	13	22
5	DMAP	61	33:24:43:0	21	14

[a] The reactions were carried out with a substrate concentration of 0.1 M. [b] Regioselectivity (%) among four monoacylates. [c] Catalyst structures:



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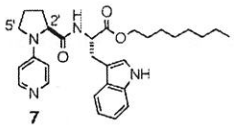

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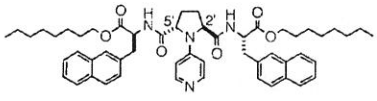

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• completely 4-OH selective for octyl β-D-glucopyranoside
• Regioselectivity is rather sensitive to structure of carbohydrates.
• Multiple hydrogen-bonding interactions between carbohydrates and the catalyst would make possible the selective acylation of more hindered alcohols (Table 4 and Figure 5).

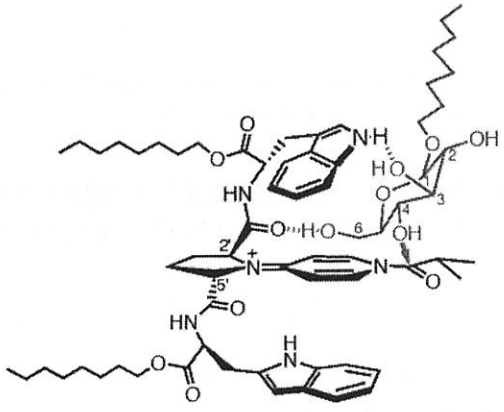


Figure 5. Proposed transition state model for the chemo- and regioselective acylation of octyl β-D-glycopyranoside catalyzed by **1**.

5. Summary and Perspective

5.1 Summary and Perspective

5.1.1 C–H Amination

(1) Nitrene-Based Catalysis

Summary

- Substrate scope: mainly electron-rich, benzylic C–H
- Selectivity: Both intra- and intermolecular enantioselective reactions are possible.

Perspective

- Substrate scope: simple alkanes, electron-deficient C–H
- Selectivity: improvement of enantioselectivity for intermolecular reacitons

(2) Catalysis Based on C–H Activation

Summary

- Substrate scope: arenes and alkanes having coordinating groups, terminal alkenes, terminal alkynes, mainly amides
- Selectivity: regioselective in many cases

Perspective

- Substrate scope: simple alkanes, alkyl- and arylamines
- Selectivity: regio- and enantioselectivity for unfunctionalized hydrocarbons

5.1.2 Chemoselective Reaciton

(1) Arylation on Either NH or OH

Summary

- Substrate scope: aliphatic primary amines and alcohols
- Selectivity: good except for 1,2- and 1,3-aminoalcohols

Perspective

- Substrate scope: anilines and phenols
- Selectivity: NH- and OH-selective reaction for 1,2- and 1,3-aminoalcohols

(2) Selective Reduction of Amides over Ketones/Esters

Summary

- Substrate scope: tertiary amides only
- Selectivity: good to excellent

Perspective

- Substrate scope: primary/secondary amides, more functionalized substrates
- Selectivity: reduction in the presence of aldehydes and alkenes

(3) Acylation of OH over NH

Summary

- Substrate scope: 1°- and 2°-aliphatic alcohols and aminoalcohols, aliphatic and aromatic esters
- Selectivity: excellent except for 1,2-aminoalcohols

Perspective

- Substrate scope: application for total synthesis
- Selectivity: reactions in the presence of various functional gorups

5.1.3 Regioselective Reaciton

(1) Acylation of Natural Products

Summary

- Substrate scope: applicable only for erythromycin
- Selectivity: good

Perspective

- Substrate scope: other natural products
- Selectivity: General strategy of selective activation is required for the catalyst development.

(2) Acylation of Carbohydrates

Summary

- Substrate scope: mainly for glucopyranosides
- Selectivity: good to excellent

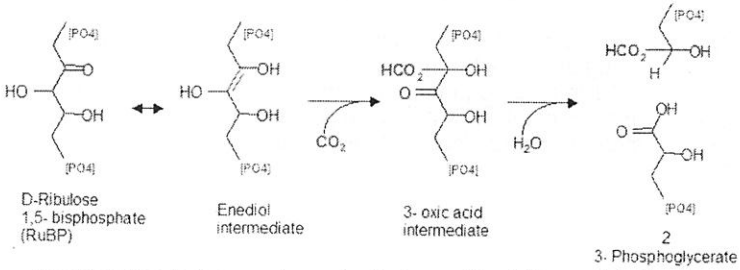
Perspective

- Substrate scope: other pyranosides and furanosides
- Selectivity: development of 2, 3-OH-selective catalysts

5.2 Future Challenges in Catalysis

5.2.1 CO_2 Fixation

Reaction Mechanism of CO_2 Fixation Catalyzed by Rubisco



- The reaction is thermodynamically favorable (ΔG = –41 kJ/mol).
- Mg ion is required for this reaction.

For Rubisco, see: http://ja.wikipedia.org/wiki/RubisCO.
See also: Lorimer, G. H.; et al. *Nature* **1989**, *337*, 229.
For CO_2 co-polymerization, see: Chen Lit. Seminar 2008.03.12.

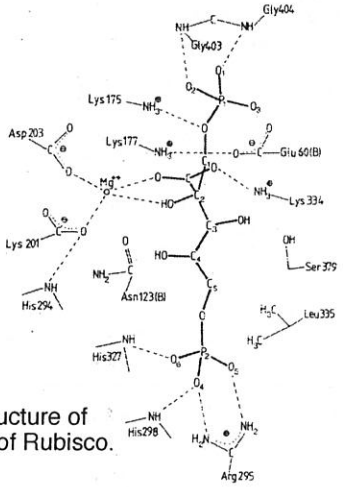
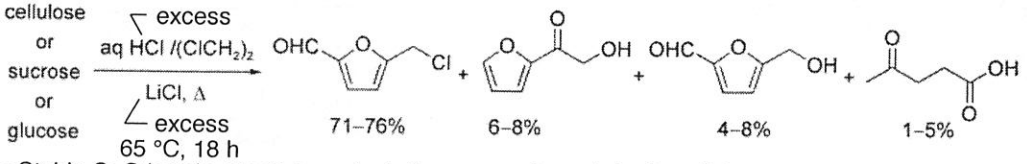


Figure. Structure of active site of Rubisco.

5.2.2 Reformation of Renuable Carbon Sources

Reformation of Cellulose under Acidic Conditions

Mascal, M.; et al. *Angew. Chem., Int. Ed.* **2008**, *47*, *Early View.*



- Stable C–O bonds of cellulose, including anomeric carbohydrate linkages, were cleaved under highly acidic conditions.