Metalloporphyrin

～as efficient Lewis acid catalysts with a unique reaction-field～

and

～Synthetic study toward complex metalloporphyrins～

Literature Seminar
Kenta Saito (D1)

Topics

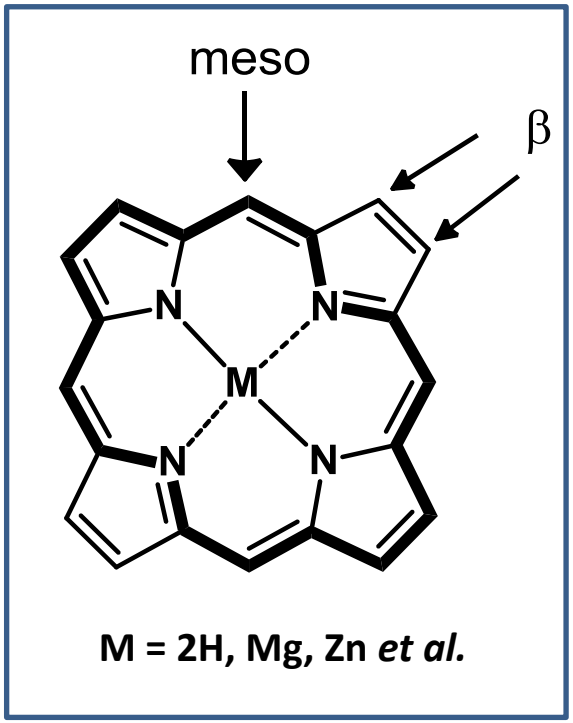
Chapter 1
～as efficient lewis acid catalysts with a unique reaction-field～

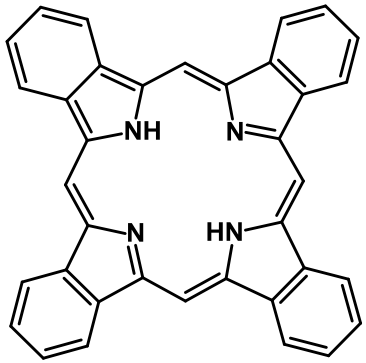
Chapter 2
～Synthetic study toward complex metalloporphyrins～

Introduction : Metalloporphyrins

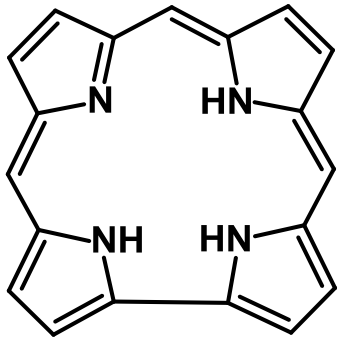
What is Porphyrin?

- Macrocyclic tetrapyrrole in a 18-π aromatic ring system
- Four-fold coordination, bind the vast majority of metals (Mg, Zn, Cu, Fe …)
- Three-dimensional architectures created from planar framework (π-stacking, linker connected at meso position)





Phthalocyanine

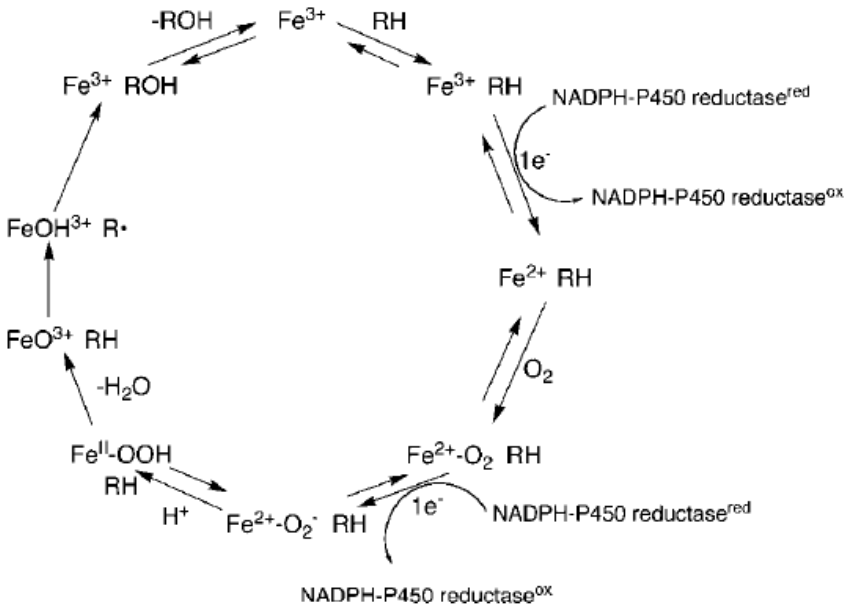


Corrole

Introduction : Cytochromes P450

Mono-oxygenases

Major enzymes involved in drug metabolism



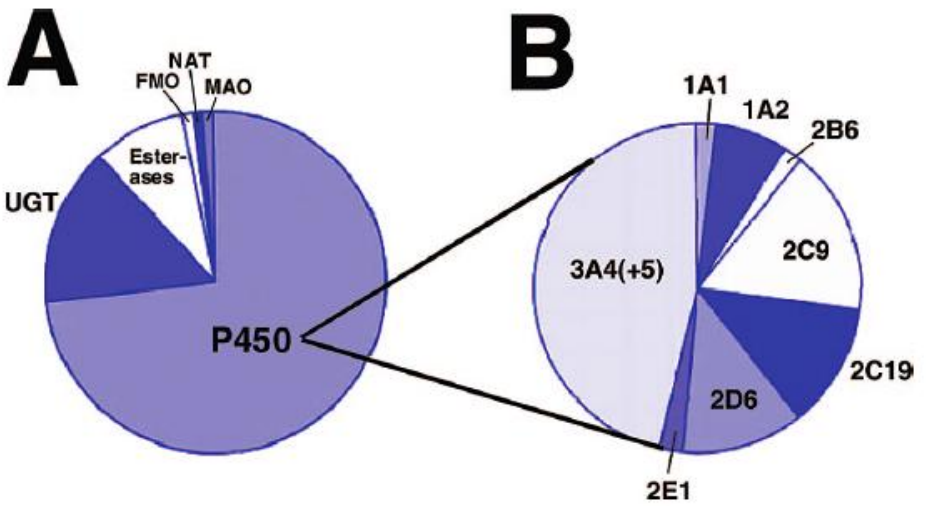
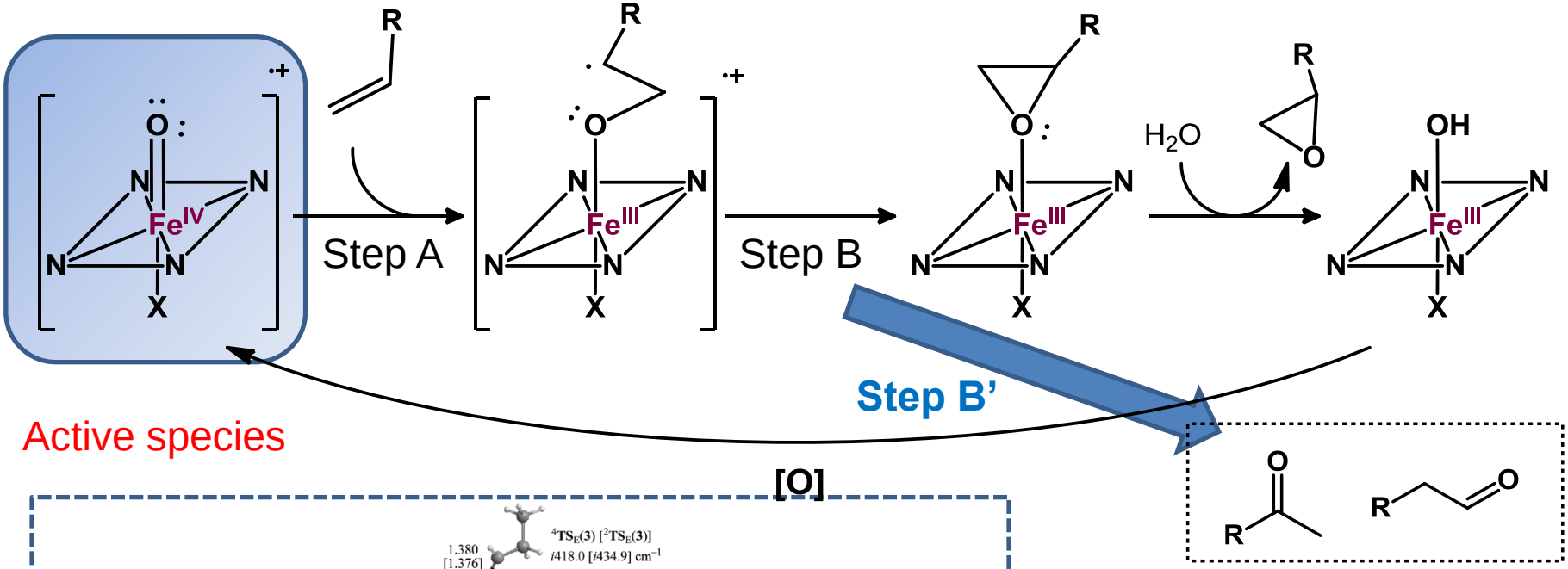


Figure 4. Contributions of enzymes to the metabolism of marketed drugs. The results are from a study of Pfizer drugs (*57*), and similar percentages have been reported by others in other pharmaceutical companies (*58*). (A) Fraction of reactions on drugs catalyzed by various human enzymes. FMO, flavin-containing monoxygenase; NAT, *N*-acetyltransferase; and MAO, monoamine oxidase. (B) Fractions of P450 oxidations on drugs catalyzed by individual P450 enzymes. The segment labeled 3A4 (+3A5) is mainly due to P450 3A4, with some controversy about exactly how much is contributed by other subfamily 3A P450s. Reprinted with permission from ref *57*. Copyright 2004 American Society for Pharmacology and Experimental Therapeutics.

Liver detoxification and hormone biosyntheses

ref) *Chem. Res. Toxicol.* **2008**, *21*, 70
Chem. Res. Toxicol. **2010**, *23*, 1393

Introduction : Oxidative Reaction with P450 / carbonyl byproducts



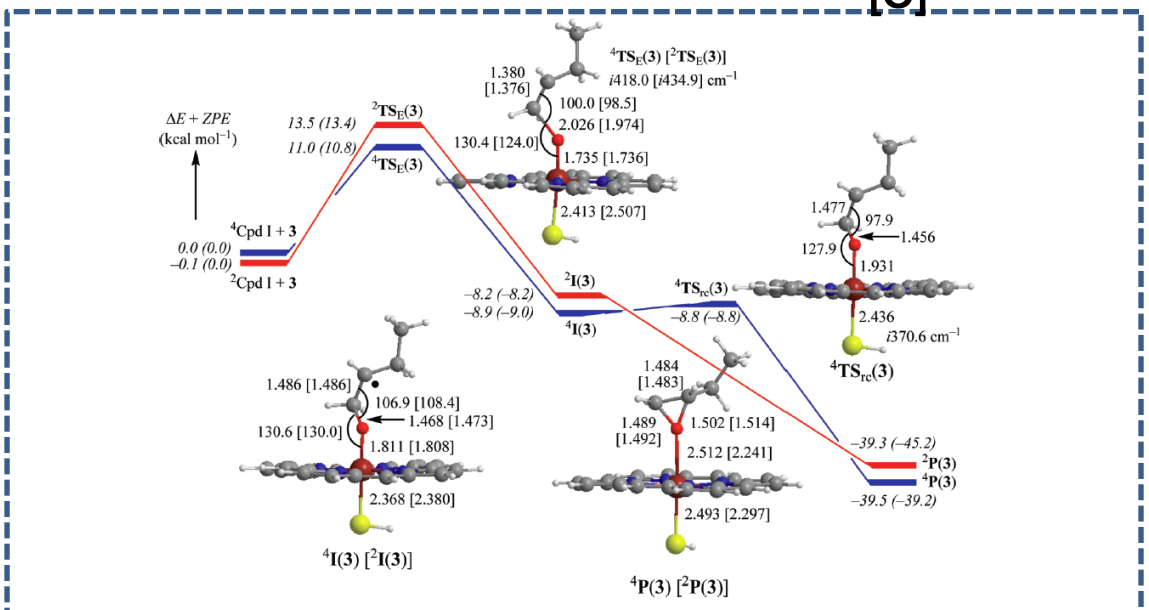


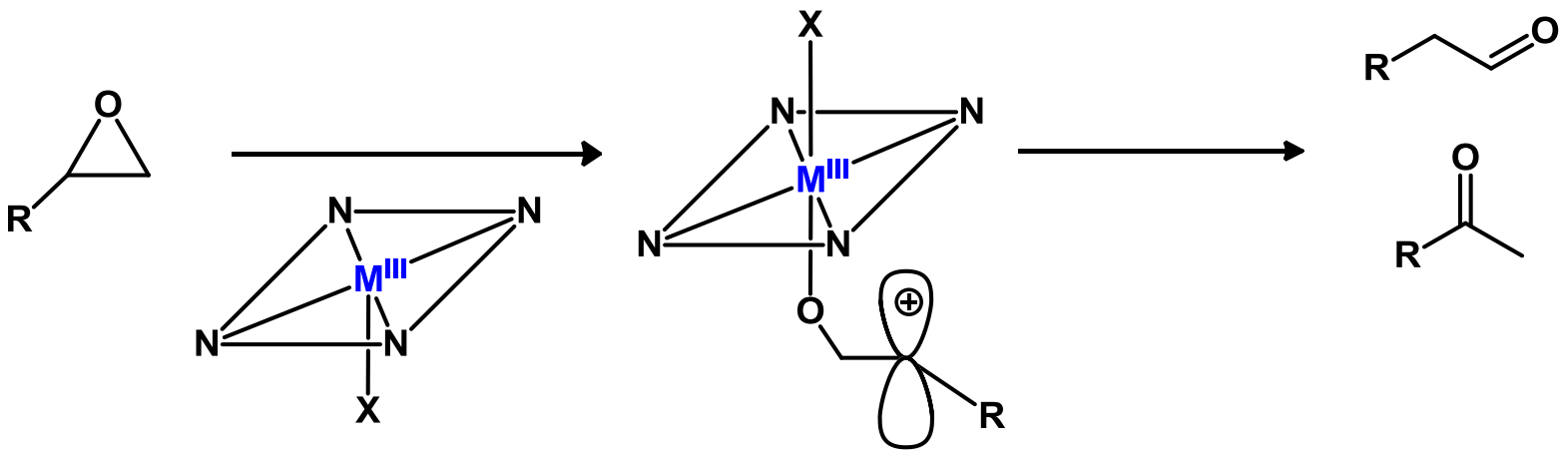
Figure 5. Reaction profile of 1-butene (3) epoxidation by ^{4,2}Cpd I(SH) with energies in kcal mol^{-1}. Also shown are optimized geometries of the critical points along the reaction mechanism obtained at UB3LYP/B1 with distances in angstroms, angles in degrees, and the value of the imaginary frequency in the transition state in wave numbers. Energies reported outside parentheses are obtained with basis set B2 on UB3LYP/B1 optimized geometries and contain ZPE corrections with basis set B1. Inside parentheses are reported energies (including ZPE) calculated at UB3LYP/B2 after a UB3LYP/B2 geometry optimization and frequency.

Step A is the rate-limiting step

Step B is fast, but carbonyl compounds are generated as the byproducts (Step B').

ref) *J. Am. Chem. Soc.* **2010**, *132*, 7656
J. Am. Chem. Soc. **2003**, *125*, 3406

Introduction : Another possible pathway of generating byproducts



Porphyrin's metal center behave as a Lewis acid.

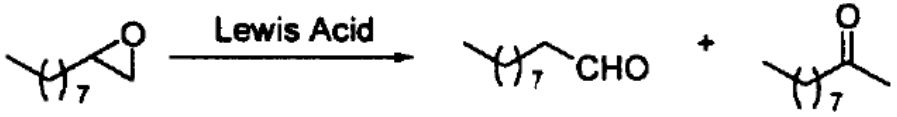
- Large ligand
- Stabilization of the cationic species by the broad π-conjugated plane

⇒ It's possible to contoribute the unique reaction-field.

⇒ Axial ligand, porphyrin : tunable

ref) *Inorg. Chem.* **1994**, *33*, 1731
J. Am. Chem. Soc. **1993**, *115*, 4641

Rearrangement of monoalkyl-substituted epoxides into aldehydes



1a 2a 3a

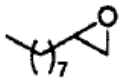
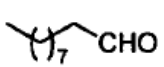
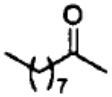
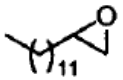
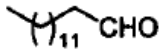
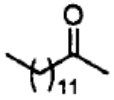
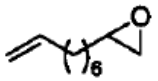
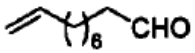
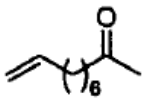
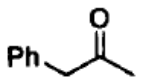
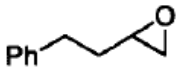
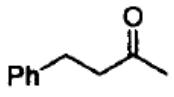
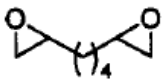
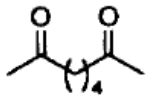
Run	Lewis acid (mol%)	Conditions solvent / time / temp	Yield (%)[a] (2a/3a)[b]
1	$BF_3 \cdot OEt_2$ (100)	CH_2Cl_2 / 0.5h / 0°C	complex mixture
2	$BF_3 \cdot OEt_2$ (5)	CH_2Cl_2 / 24h / 0°C→ r.t.	no reaction
3	$TiCl_4$ (100)	CH_2Cl_2 / 0.5h / 0°C	complex mixture
4	$TiCl_4$ (5)	CH_2Cl_2 / 24h / 0°C→ r.t.	no reaction
5	$MgBr_2 \cdot OEt_2$ (100)	CH_2Cl_2 / 0.5h / 0°C	complex mixture
6	$MgBr_2 \cdot OEt_2$ (5)	CH_2Cl_2 / 24h / 0°C→ r.t.	no reaction
7	Fe(tpp)OTf (2)	$ClCH_2CH_2Cl$ / 4.5h / reflux	93 (93/7)
8	Fe(tpp)OTf (2)	dioxane / 1.5h / reflux	~100 (96/4)
9	Fe(tpp)OTf (2)	toluene / 3h / reflux	~100 (94/6)
10	Fe(tpp)ClO_4 (2)	dioxane / 8h / reflux	79[c] (93/7)

[a] Isolated yield.
[b] Isomer ratios were determined by 270MHz ^{1}H-NMR analysis of the crude reaction mixture.
[c] 15% of 1a was recovered.

stoichiometric amount of LiTMP is the only known method.

ref) *J. Chem. Soc., Chem. Commun.*, **1994**, 2103

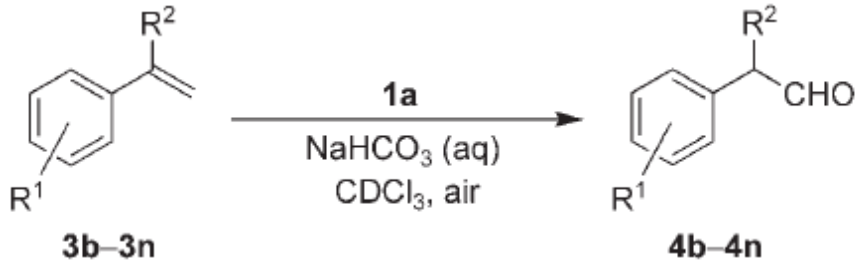
Rearrangement of monoalkyl-substituted epoxides into aldehydes

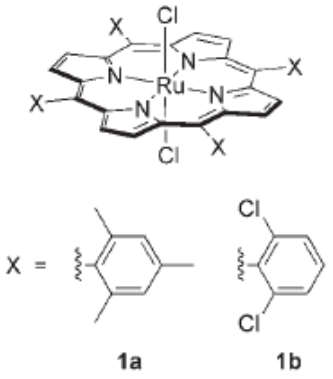
Run	Substrate	Products		Yield (%)[a] (2 / 3)[b]
1	 **1a**	 **2a**	 **3a**	~100 (96/4)
2	 **1b**	 **2b**	 **3b**	~100 (95/5)
3	 **1c**	 **2c**	 **3c**	~100 (94/6)
4	 **1d**	 **2d**	 **3d**	~100 (94/6)
5	 **1e**	 **2e**	 **3e**	~100 (94/6)
6	 **1f**	 **2f**	 **3f**	98 (97/3)

[a] Isolated yield.
[b] Isomer ratios were determined by 270MHz ^{1}H-NMR analysis of the crude reaction mixture.

ref) *Tetrahedron Lett.* **1999**, *40*, 7243

Rearrangement of monoalkyl-substituted epoxides into aldehydes



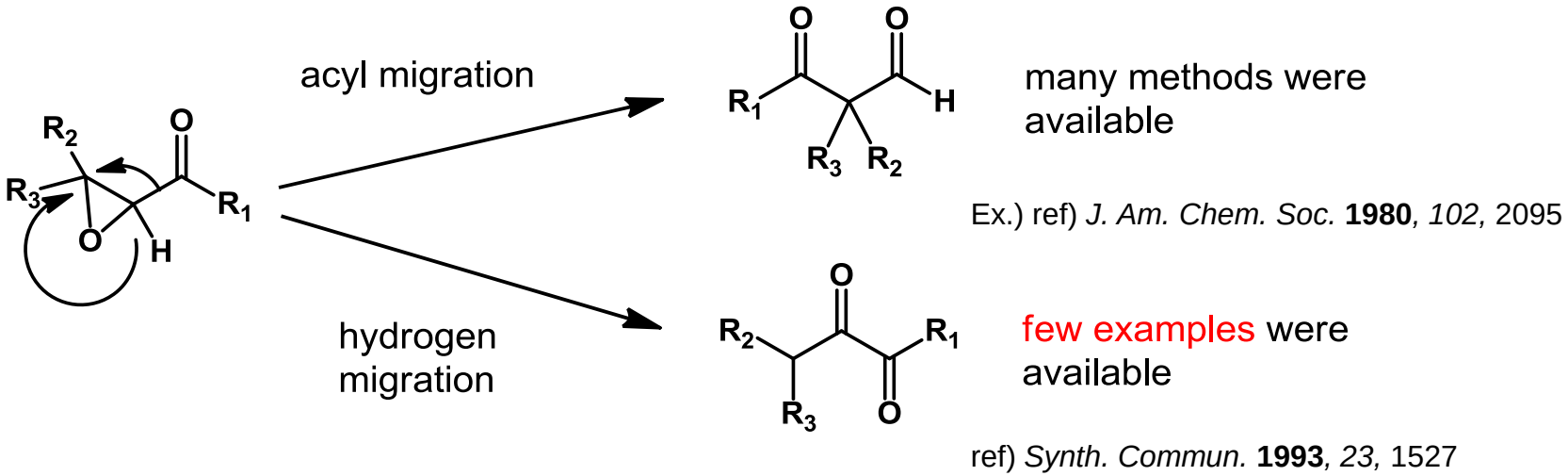


Entry	Substrate	Product	Time [h]	Yield [%][b]
1	**3b** *i*PrO	**4b** *i*PrO, CHO	4.5	92
2	**3c** *t*BuO	**4c** *t*BuO, CHO	7	87
3	**3d** PhO	**4d** PhO, CHO	5	87
4	**3e** BnO	**4e** BnO, CHO	4	89
5	**3f** OMe	**4f** OMe, CHO	7	93
6[c]	**3g** Me	**4g** Me, CHO	5	84
7[c]	**3h** *t*Bu	**4h** *t*Bu, CHO	5	81
8[c]	**3i** F	**4i** F, CHO	7	71
9[c]	**3j** Br	**4j** Br, CHO	7	69
10[c]	**3k** Me	**4k** Me, CHO	7	81
11[c]	**3l** Me, *i*Bu	**4l** Me, *i*Bu, CHO	7	71 (64[d])
12[c]	**3m**	**4m** CHO	5	73
13[c]	**3n** Me, MeO	**4n** Me, MeO, CHO	7	74 (68[d])

[a] Reaction conditions: substrate (0.1 mmol), **1a** (2 mol%), $CDCl_3$ (1 mL), $NaHCO_3$ (4 mol%), H_2O (0.3 mL), open to air, room temperature. [b] Determined by ^1H NMR spectroscopy. [c] **1a** (3 mol%), $NaHCO_3$ (8 mol%), 50°C. [d] Yield of isolated product.

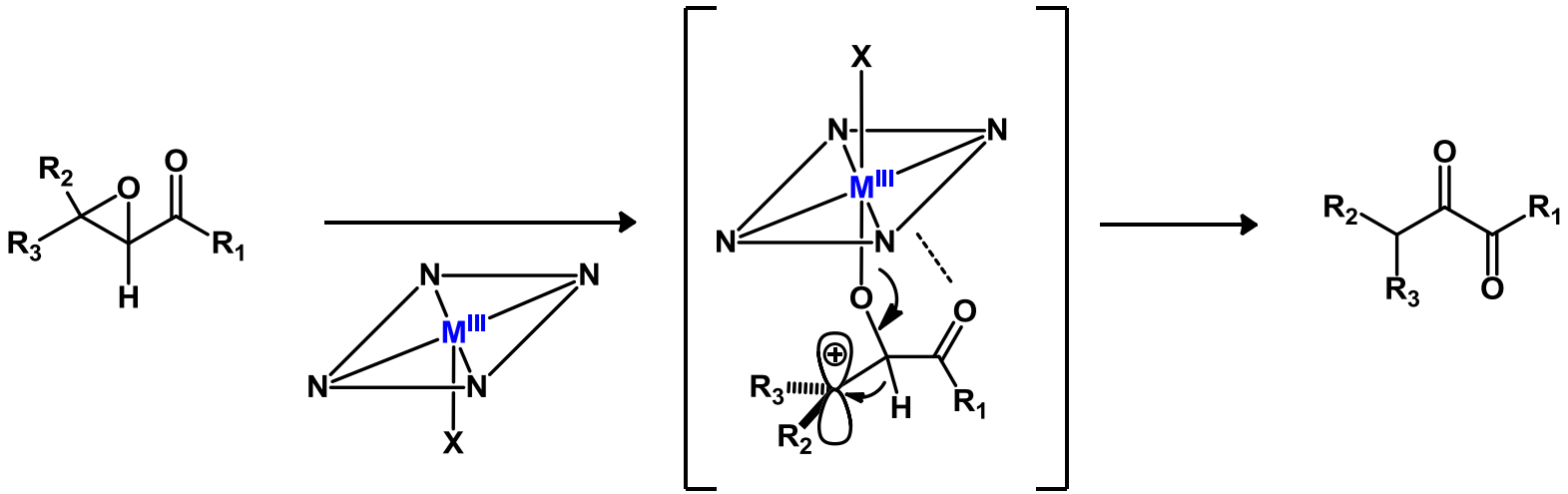
ref) *Angew. Chem. Int. Ed.* **2008**, *47*, 6638

Rearrangement of α,β-epoxyketone into 1,2-diketone

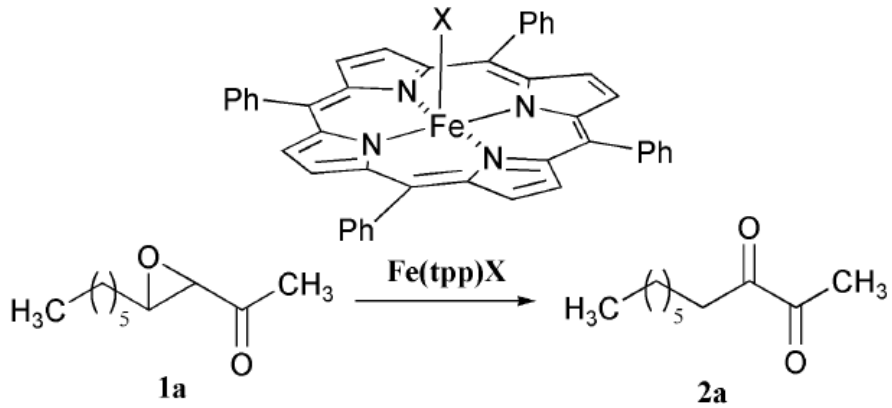


Ex.) ref) *J. Am. Chem. Soc.* **1980**, *102*, 2095

ref) *Synth. Commun.* **1993**, *23*, 1527



Rearrangement of α,β-epoxyketone into 1,2-diketone

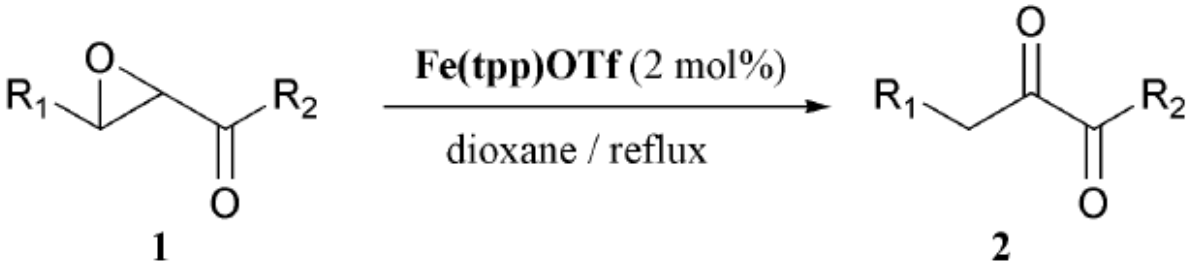


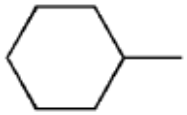
1a **2a**

Entry	Conditions Catalyst/Solvent/Time	Yield of **2a** (%)[a]
1	$Fe(tpp)ClO_4$ (2 mol%)/dioxane/8 h[b]	30[c]
2	Fe(tpp)Cl (2 mol%)/dioxane/48 h[b]	No reaction[d]
3	Fe(tpp)OTf (2 mol%)/dioxane/1.5 h[b]	95
4	Fe(tpp)OTf (2 mol%)/$(CH_2)_2Cl_2$/2 h[b]	50
5	Fe(tpp)OTf (2 mol%)/toluene/2 h[b]	55
6	MABR (2 equiv.)/CH_2Cl_2/48 h[ef]	Complex mixture
7	MABR (2 equiv.)/dioxane/48 h[eg]	Complex mixture
8	BF_3OEt_2 (1 equiv.)/CH_2Cl_2/2 h[h]	Complex mixture
9	BF_3OEt_2 (1 equiv.)/ether/2 h[h]	No reaction[d]
10	$MgBr_2OEt_2$ (1 equiv.)/CH_2Cl_2/1.5 h[h]	0[i]

[a] Isolated yield. [b] Reflux. [c] Recovery of **1a** (45%). [d] Recovery of **1a** (quant). [e] MABR: methylaluminium bis(4-bromo-2,6-di-*tert*-butylphenoxide). [f] −78 °C to rt. [g] −20 °C to rt. [h] 0 °C to rt. [i] 4-Bromo-3-hydroxydecan-2-one **3a** (92%) was obtained.

Rearrangement of α,β-epoxyketone into 1,2-diketone

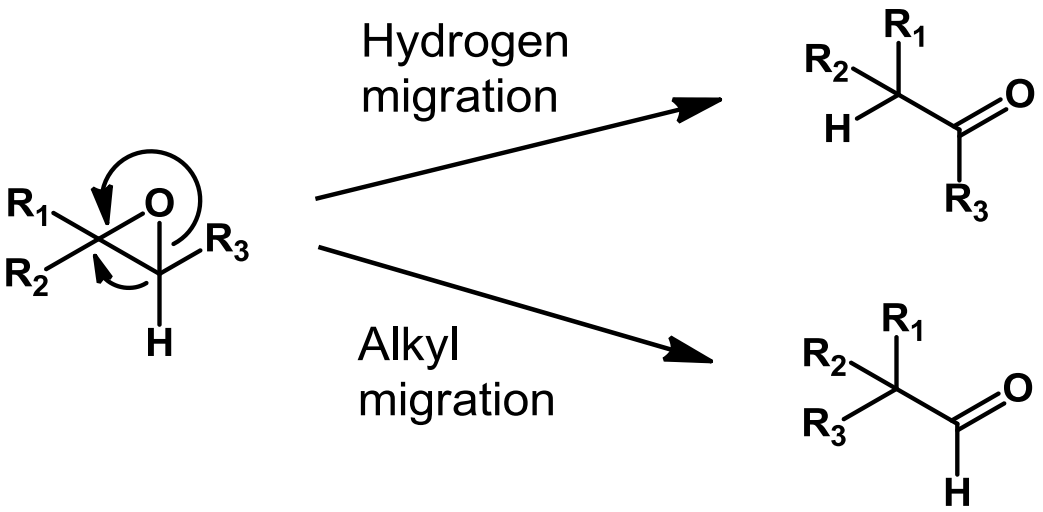


	R_1	R_2	Time	Yield (%)[b]
a	$CH_3(CH_2)_5$-	CH_3-	1.5 h	95
b	$CH_3(CH_2)_8$-	CH_3-	1.5 h	88
c	CH_2=$CH(CH_2)_8$-	CH_3-	2 h	92
d		CH_3-	2.5 h	87
e	$Ph(CH_2)_2$-	CH_3-	1.5 h	87
f	$CH_3(CH_2)_2$-	$CH_3(CH_2)_7$-	1 h	91
g	Ph-	CH_3-	15 m	85
h	Ph-	Ph-	15 m	85

[a] Conditions: **1** (0.5 mmol), Fe(tpp)OTf (2 mol%), dioxane (3 ml), reflux.
[b] Isolated yield.

ref) *Chem. Commun.* **2002**, 2570

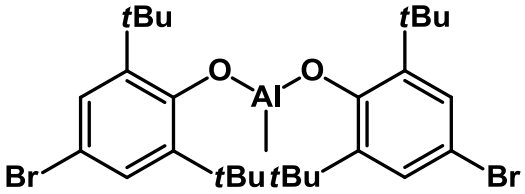
Rearrangement of 2 or 3-substituted epoxide into ketone or aldehyde



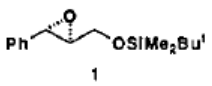
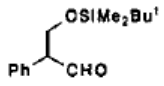
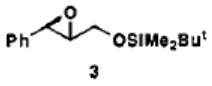
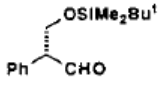
$LiClO_4$-ether
$BiOClO_4$ complex
etc.

Ex.) ref) *J. Org. Chem.* **1996**, *61*, 1877
J. Org. Chem. **1998**, *63*, 8212
Tetrahedron Lett. **2000**, *41*, 1527

equivalent MABR
ONLY

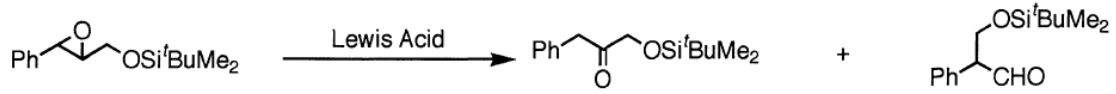


MABR

entry	epoxy silyl ether [b]	β-siloxy aldehyde	yield (%) [c]
1	 1	 2	87
2	 3	 4	85

ref) *J. Am. Chem. Soc.*. **1989**, *111*, 6431

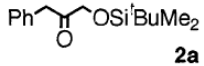
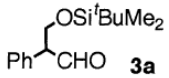
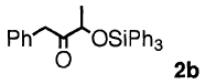
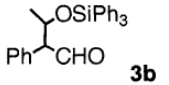
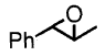
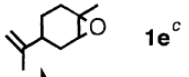
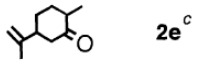
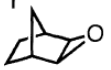
Rearrangement of 2 or 3-substituted epoxide into ketone or aldehyde



trans–**1a** **2a** **3a**

Run	Lewis Acid (mol%)	Conditions: solvent / time / temp	Yield (%)[a]	Ratio (**2a**:**3a**)[b]
1	Mn(tpp)Cl (2)	$(CH_2)_2Cl_2$ / 48 h / 80 °C	no reaction	
2	Fe(tpp)Cl (2)	$(CH_2)_2Cl_2$ / 48 h / 80 °C	no reaction	
3	Mn(tpp)ClO_4 (2)	$(CH_2)_2Cl_2$ / 1 h / 80 °C	98	54:46
4	Fe(tpp)ClO_4 (2)	$(CH_2)_2Cl_2$ / 1 h / 80 °C	100	67:33
5	Fe(tpp)ClO_4 (2)	dioxane / 0.5 h / 80 °C	100	99:1
6	BF_3•OEt_2 (100)	$(CH_2)_2Cl_2$ / 48 h / 80 °C	decompd.	

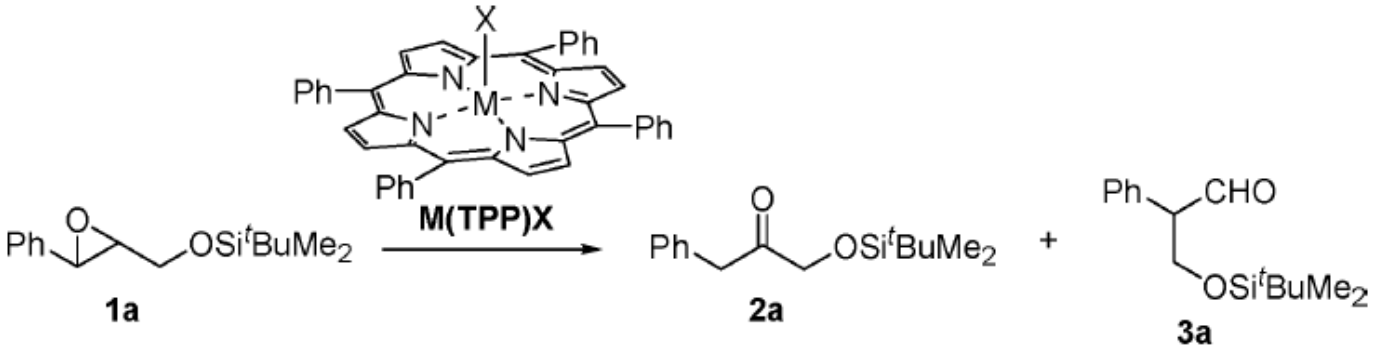
[a] Isolated yield. [b] Determined by 270 MHz ^{1}H-NMR analysis of the crude reaction mixture.

Run	Substrate	Time (h)	Products	Yield (%)[a]
1	 *trans*–**1a**	0.5	 **2a** +  **3a**	100 (**2a**:**3a**=99:1)[b]
2	 *cis*–**1a**	0.5	**2a** + **3a**	100 (**2a**:**3a**=96:4)[b]
3	 **1b**	1.0	 **2b** +  **3b**	91 (**2b**:**3b**=96:4)[b]
4	 **1c**	2.5	 **2c**	90
5	 **1d**	5.5	 **2d**	83
6	 **1e**[c]	8.0	 **2e**[c]	73
7	 **1f**	3.0	 **2f**	77

[a] Isolated yield. [b] The isomer ratios were determined by 270MHz ^{1}H-NMR analysis of the crude reaction mixture.
[c] A 1:1 mixture of *cis* and *trans* isomers.

ref) *Chem. Lett.* **1996**, 1031

Rearrangement of 2 or 3-substituted epoxide into ketone or aldehyde

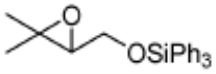
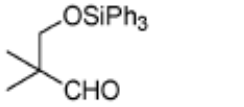
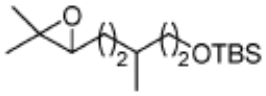
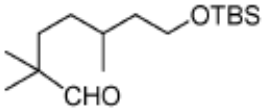
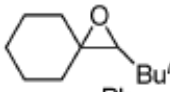
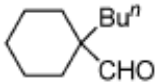
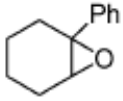
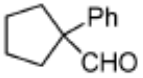
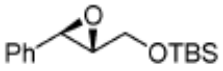
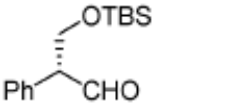
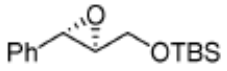
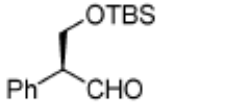
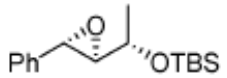
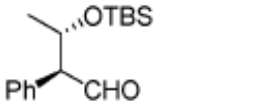
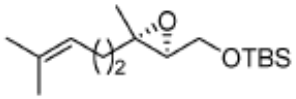
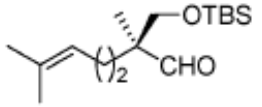
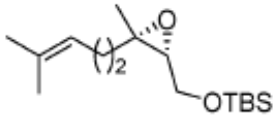
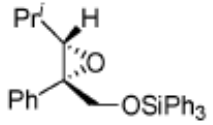
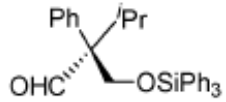


1a **2a** **3a**

entry	catalyst(mol %)/solvents/temp.(°C)/time (h)	yield (%)[a] 2a	3a
1	$Fe(TPP)ClO_4$ (1)/dioxane/100/0.5	>99	0
2	$Fe(TPP)ClO_4$ (1)/$Cl(CH_2)_2Cl$ /83/0.5	65	32
3	$Mn(TPP)ClO_4$ (1)/$Cl(CH_2)_2Cl$/83/1	53	45
4	$Cr(TPP)ClO_4$ (1)/$Cl(CH_2)_2Cl$/83/2	11	87
5	Cr(TPP)OTf (1)/$Cl(CH_2)_2Cl$/83/1	0	97[b]
6	$B(C_6F_5)_3$ (2)/$Cl(CH_2)_2Cl$/83/40	14	15
7	$B(C_6F_5)_3$ (2)/toluene/110/40	no reaction	
8	Cr(salen)OTf (2)/$Cl(CH_2)_2Cl$/83/40[c]	16	40
9	Mn(salen)OTf (2)/$Cl(CH_2)_2Cl$/83/22[d]	33	34

Rearrangement of 2 or 3-substituted epoxide into ketone or aldehyde

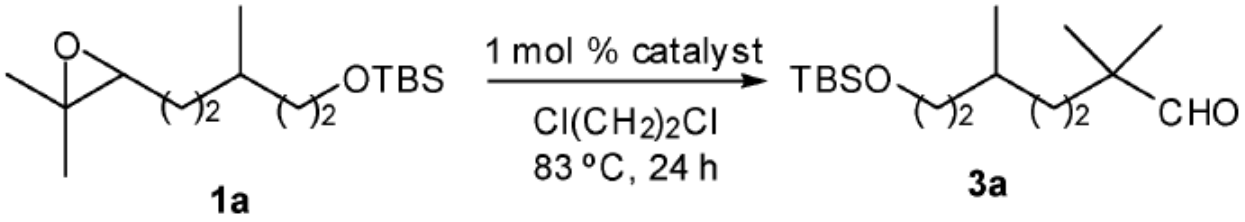
Table 2. Cr(TPP)OTf-Catalyzed Rearrangement of Epoxides to Aldehydes[a]

entry	epoxide	time, h	product	yield, %[b]
1		4		89
2		24		63[c]
3		45		56[d]
4		1		> 99
5	 **1b** (> 99% ee)	1	 **3b** (> 99% ee)	97
6	 **1c** (> 99% ee)	1	 **3c** (> 99% ee)	96
7	 **1d** (96% ee)	1	 **3d** (96% ee)	> 99
8	 **1e** (> 99% ee)	5	 **3e** (> 99% ee)	89
9	 **1f** (93% ee)	6	**3e** (93% ee)	92
10	 **1g** (> 99% ee)	30	 **3g** (97% ee)	85[e]

[a] Reaction conditions: 1 mol % Cr(TPP)OTf, $ClCH_2CH_2Cl$, 83 °C; enantiomeric excess was determined by chiral HPLC analysis or 300 MHz ^1H NMR Mosher's ester analysis; The absolute configuration was determined by comparison of the optical rotations with those of authentic samples.[4b,5c] [b] Isolated yield. [c] Recovery of the starting epoxide, 22%. [d] Recovery of the starting epoxide, 28%. [e] 20 mol % Cr(TPP)OTf was used.

ref) *J. Am. Chem. Soc.* **2004**, *126*, 9554

Rearrangement of 2 or 3-substituted epoxide into ketone or aldehyde

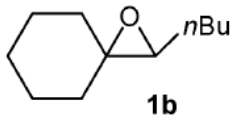
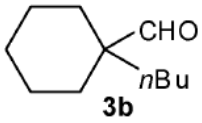
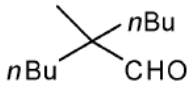
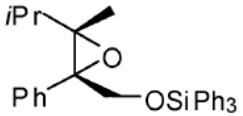
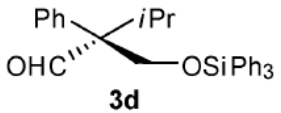
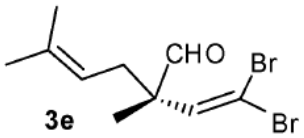
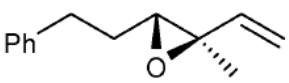
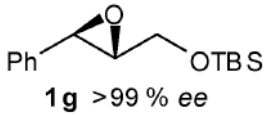
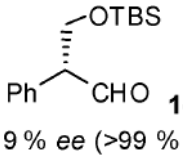
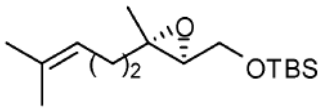
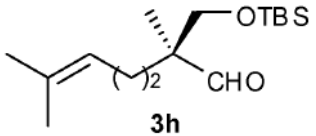


1a **3a**

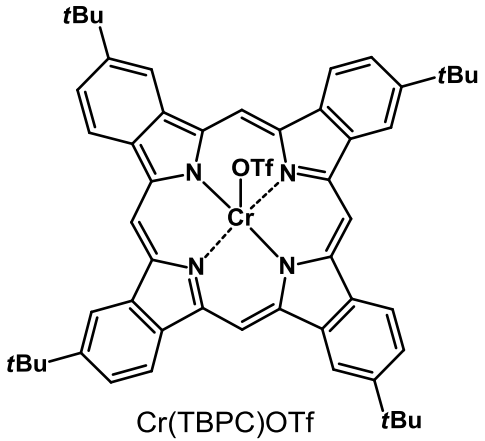
Entry	Catalyst[a]	Yield[b] (%)	Recov.[b] (%) of **1a**
1	Cr(TPP)OTf	63	22
2	Cr(TPFP)OTf	75	6
3	Cr(DPP-Br)OTf	64	23
4	Cr(DPP-2Br)OTf	59	31
5	Cr(DPP-CN)OTf	88	6
6	Cr(DPP-2CN)OTf	87	8
7	Cr(TBPC)OTf[c]	95	0

[a] Molecular structures of Cr(TPFP)OTf, Cr(DPP-Br)OTf, Cr(DPP-2Br)OTf, Cr(DPP-CN)OTf and Cr(DPP-2CN)OTf, see ESI.† [b] Isolated yield. [c] Reaction time: 10 h.

Rearrangement of 2 or 3-substituted epoxide into ketone or aldehyde

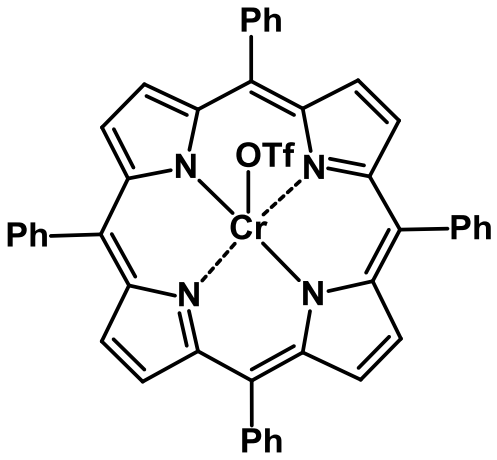
Epoxide **1**	Aldehyde **3**	*t*/h	Yield[c] (%)
 **1b**	 **3b**	15 (45)	>99 (56)
 **1c** *cis*/*trans* = 1:1	 **3c**	20 (95)	>99 (33)
 **1d** >99 % *ee*	 **3d** 98 % *ee* (92 % *ee*)	20 (60)	92 (48)
 **1e** >99 % *ee*	 **3e** >99 % *ee* (92 % *ee*)	2.5 (24)	98 (78)
 **1f** >99 % *ee*	 **3f** >99 % *ee* (>99 % *ee*)	3.0 (24)	98 (83)
 **1g** >99 % *ee*	 **1g** >99 % *ee* (>99 % *ee*)	<0.5 (1.0)	98 (97)
 **1h** >99 % *ee*	 **3h** >99 % *ee* (>99 % *ee*)	2.0 (5.0)	88 (89)

[a] *Conditions*: 1 mol% Cr(TBPC)OTf, $ClCH_2CH_2Cl$, 83 °C; enantiomeric excess was determined by chiral HPLC analysis; the absolute configuration was determined by comparison of the optical rotations with authentic samples (see ESI†). [b] The data in parentheses refer to those in the Cr(TPP)OTf-catalyzed rearrangements; *conditions*: 1 mol% Cr(TPP)OTf, $ClCH_2CH_2Cl$, 83 °C. [c] Isolated yield.

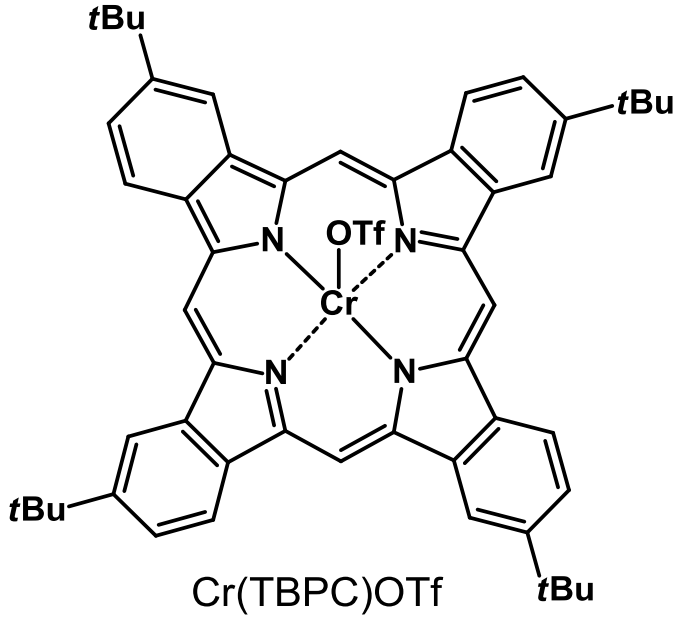


Cr(TBPC)OTf

Rearrangement of 2 or 3-substituted epoxide into ketone or aldehyde



Cr(TPP)OTf



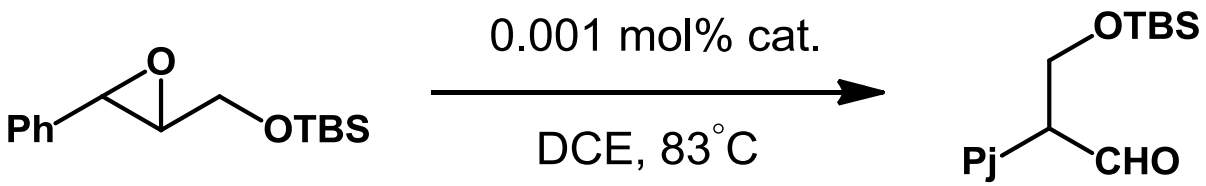
Cr(TBPC)OTf

Lewis acidity

Low → **High**

Stability by
broad π-plane

Rearrangement of 2 or 3-substituted epoxide into ketone or aldehyde



	time	yield
Cr(TPP)OTf	**5 - 6 h (dead end)**	**about 15%**
Cr(TBPC)OTf	**20 h (not deactivated)**	**> 60%**

Cr(TBPC)OTf : TON (over 60,000)

➡ Cr(TBPC)OTf is stable and active catalyst.

Rearrangement of 2 or 3-substituted epoxide into ketone or aldehyde

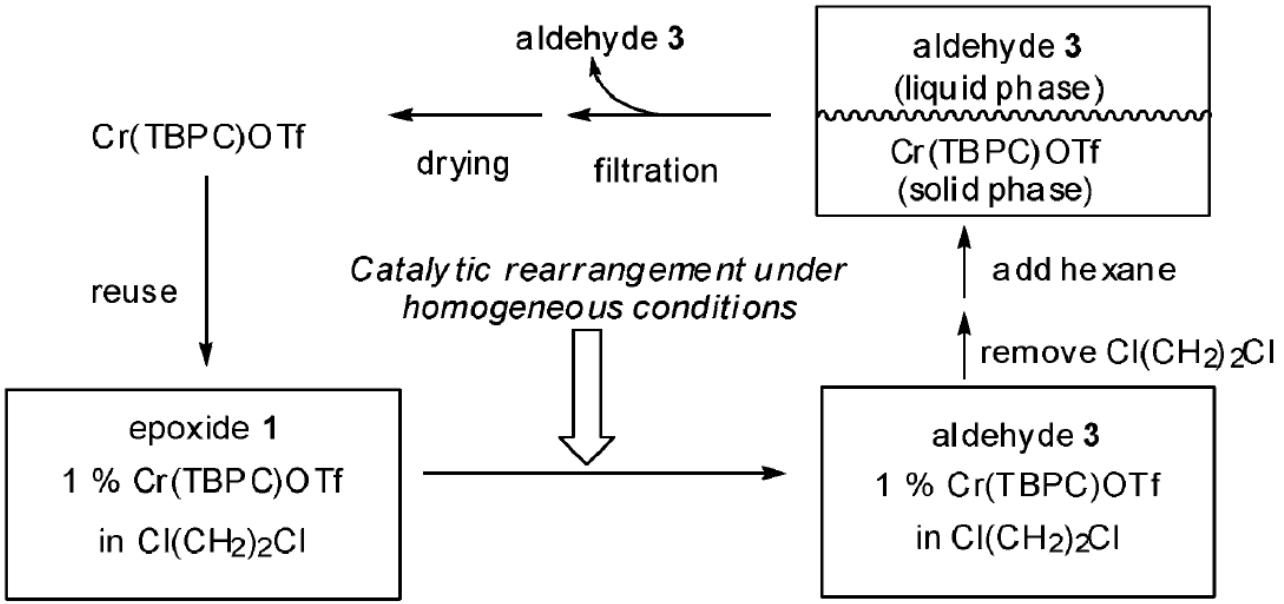


Fig. 2 Simplified representation of recycling of the phthalocyanine-based catalyst, Cr(TBPC)OTf, in the rearrangement of epoxides to aldehydes.

Cr(TBPC)OTf is not soluble in hexane.

➡ Cr(TBPC)OTf and target materials are separetable between each other.

Rearrangement of 2 or 3-substituted epoxide into ketone or aldehyde

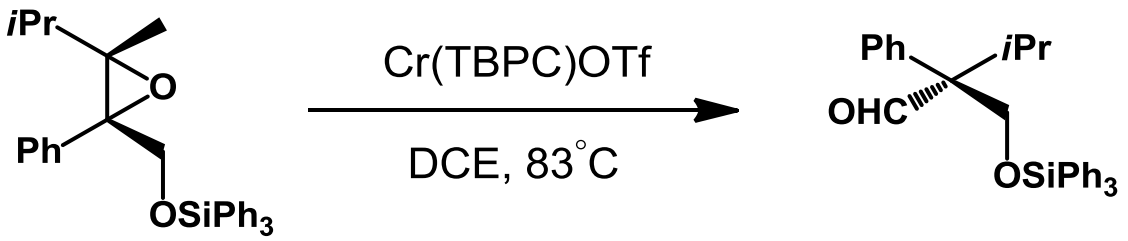


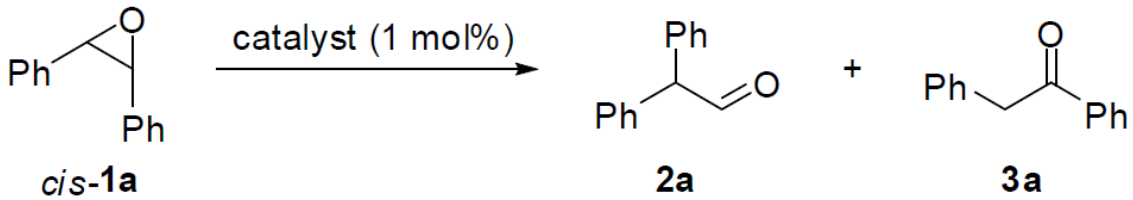
Table 3 Reuse of the phthalocyanine-based catalyst, Cr(TBPC)OTf, in the rearrangement of epoxide **1d** (>99% *ee*) to aldehyde **3d**[a]

Run	Yield[b] (%)	*ee* (%)	Recov.[b] (%) of catalyst
1st	92	98	98
2nd	93	98	98
3rd	90	98	98
4th	92	98	98
5th	90	98	98

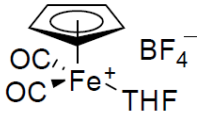
[a] All the reactions were conducted with 1 mol% Cr(TBPC)OTf in dichloroethane at 83 °C. [b] Isolated yield.

ref) *Chem. Commun.* **2009**, 1255

Rearrangement of 2,3-diaryl epoxide into 2,3-diaryl aldehyde



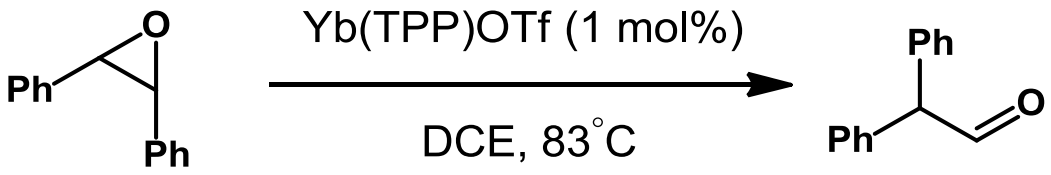
cis-**1a** **2a** **3a**

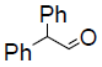
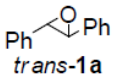
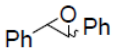
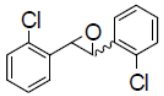
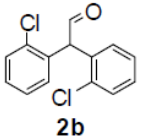
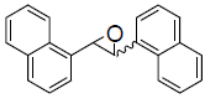
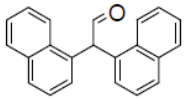
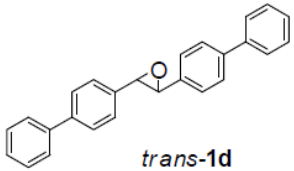
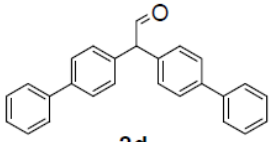
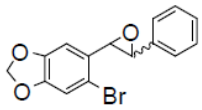
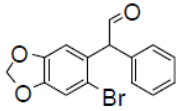
entry	catalyst	conditions solvent/temp/time	yield (%)[a] of **2a**	yield (%)[a] of **3a**
1	Fe(TPP)OTf	DCE/83 °C/1 h	73	23
2	Cr(TPP)OTf	DCE/83 °C/3 h	66	32
3	Yb(TPP)Cl	DCE/83 °C/12 h	no reaction	
4	Yb(TPP)OTf	DCE/83 °C/4 h	89	<5
5	Yb(TPP)OTf	dioxane/100 °C/2 h	55	21
6	Yb(TPP)OTf	toluene/110 °C/6 h	44	21
7	$Er(OTf)_3$	DCM/rt/2 h	73	15
8	$Yb(OTf)_3$	DCM/rt/1 h	62	16
9	$Bi(O)ClO_4$	DCM/rt/10 h	69	13
10	$Bi(OTf)_3$	DCM/rt/1 h	74	13
11		DCM/rt/15 h	75	15
12	$InCl_3$	THF/50 °C/24h	no reaction	
13	$InCl_3$	DCM/40 °C/24h	no reaction	

a) Isolated yield.

Yb is necesarry to maintein selectivity. (Fe and Cr are not suitable)

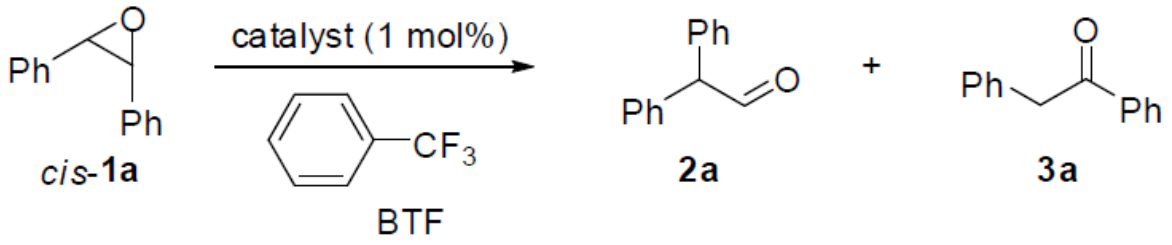
Rearrangement of 2,3-diaryl epoxide into 2,3-diaryl aldehyde

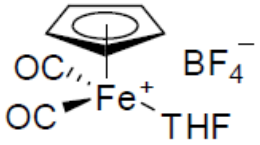


entry	substrate	time (h)	product	yield (%)[b]
1	 *cis*-**1a**	4	 **2a**	89
2	 *trans*-**1a**	4	**2a**	94
3	 **1a** (*cis*/*trans* = 1:1)	4	**2a**	87
4	 **1b** (*cis*/*trans* = 1:1)	12	 **2b**	90
5	 **1c** (*cis*/*trans* = 1:1)	4	 **2c**	87
6	 *trans*-**1d**	5	 **2d**	85
7	 **1e** (*cis*/*trans* = 1:1)	12	 **2e**	92

a) Conditions: Yb(TPP)OTf (1 mol%), DCE, 83 °C. b) Isolated yield.

Rearrangement of 2,3-diaryl epoxide into 2,3-diaryl aldehyde



entry	catalyst	temp (°C)	time (h)	yield (%)[a] of **2a**	yield (%)[a] of **3a**
1	Yb(TPP)OTf	102	3	87	<5
2	$Er(OTf)_3$	rt	10	51	20
3	$Yb(OTf)_3$	rt	9	50	20
4	$Bi(O)ClO_4$	rt	24	40	12
5	$Bi(OTf)_3$	rt	5	51	17
6		rt	24	46	18

a) Isolated yield.

ref) *Heterocycles.* **2009**, *77*, 365

Summery of Chapter 1

Metalloporphyrins are efficient lewis acids for selectivity and activity owing to ligand's effects.

They are tunable by changing axial ligands and porphyrin ligands.

Phthalocyanine ligands produce more lewis acidic and π-electronic reaction fields compared to metalloporphyrin ligands.

They are useful for economical reactions owing to poor solubility to hexane and suitable to BTF as the substitution of harogen-contained solvents like DCM and DCE.

Topics

Chapter 1
～as efficient lewis acid catalysts with a unique reaction-field～

Chapter 2
～Synthetic study toward complex metalloporphyrins～

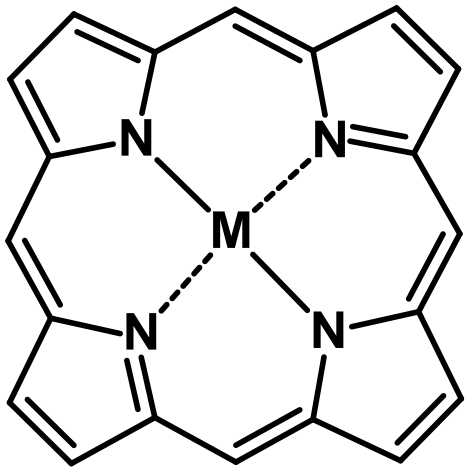
Synthetic difficulty of metalloporphyrin-analog

Zn, Mg and 2H (= por) are well used for study of fluorescence and artificial photosynthesis. But…

Mg(por) is demetalized by very slight amount of acid or very weak acid (ex. HCl from $CHCl_3$, silica gel).

Cu(II) has very strong affinity to porphyrin.

- Insertion to porphyrin very easily at RT.
- Exchange with Zn(por) under heat condition.
- It's difficult to demetalize Cu(por).
  (need strong acidic condition. (ex.) H_2SO_4-TFA)



M(por)

If you use Cu(II) for reactions, you must Zn(por) to mask porphyrin, and Cu(II) used reaction must be conducted under mild condition ,and you have to demetalize Zn(por) if you want to synthesize other-metal-contained metalloporphyrins.

Synthetic difficulty of metalloporphyrin-analog

Transition metals are introduced to porphyrins under heat condition,
but it's impossible to replace Zn(por) with M(por) under neutral condition.

Porphyrins have many active C-H bonds.

→ Many side reactions are occurred in transition-metal-contained reactions.
(many byproducts, difficulty of purification and low yield of target material)

Poor solubility of metalloporphyrins (1.0mM~10mM are favor).

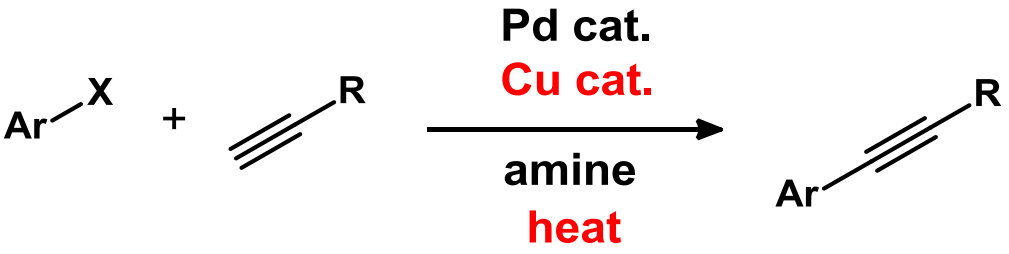
→ In synthesis of derivative of metalloporphyrins, as many reaction's condition are optimized to dense concentration (mainly 100mM~1.0M), the reactions are not suitable to matalloporphyrins as substrates.

→ It's need to use more amount of transition metals to conduct transition metal-catalyzed reaction.

ref) *Synlett.* **2005**, 1306
Chem. Mater. **1999**, *11*, 2974

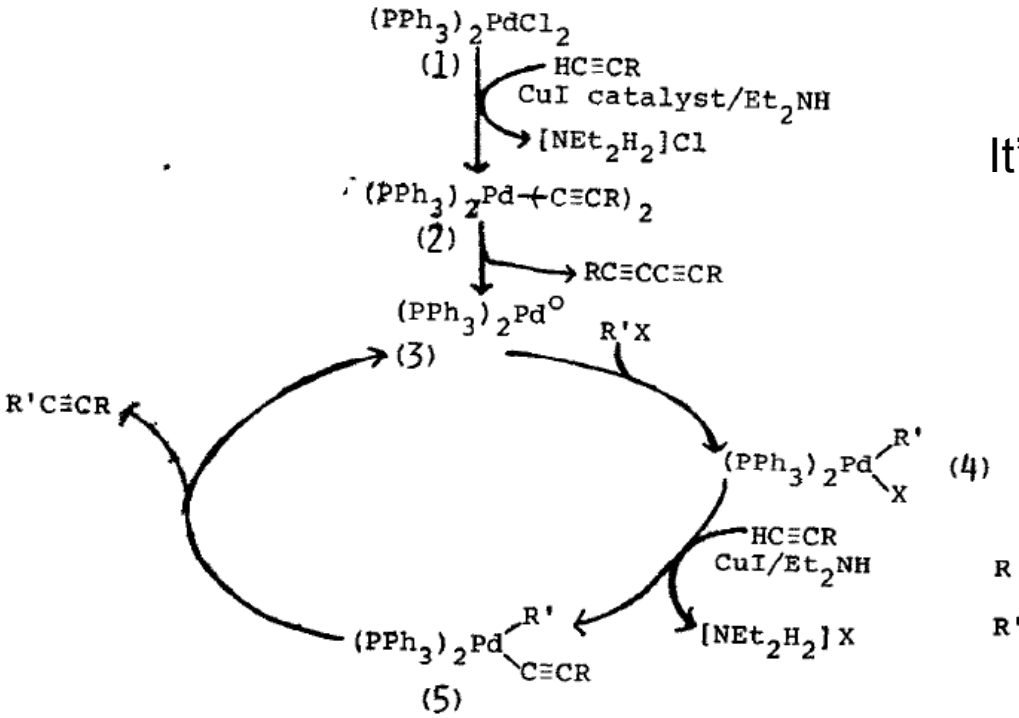
To solve the difficulties of synthesis of metalloporphyrin-analog

Ex.1) Sonogashira coupling



without Cu source

It's difficult to generate Pd-acetylide.



R =H, C_6H_5, CH_2OH

R'=aryl, alkenyl, pyridyl

Synthetic difficulty of metalloporphyrin-analog

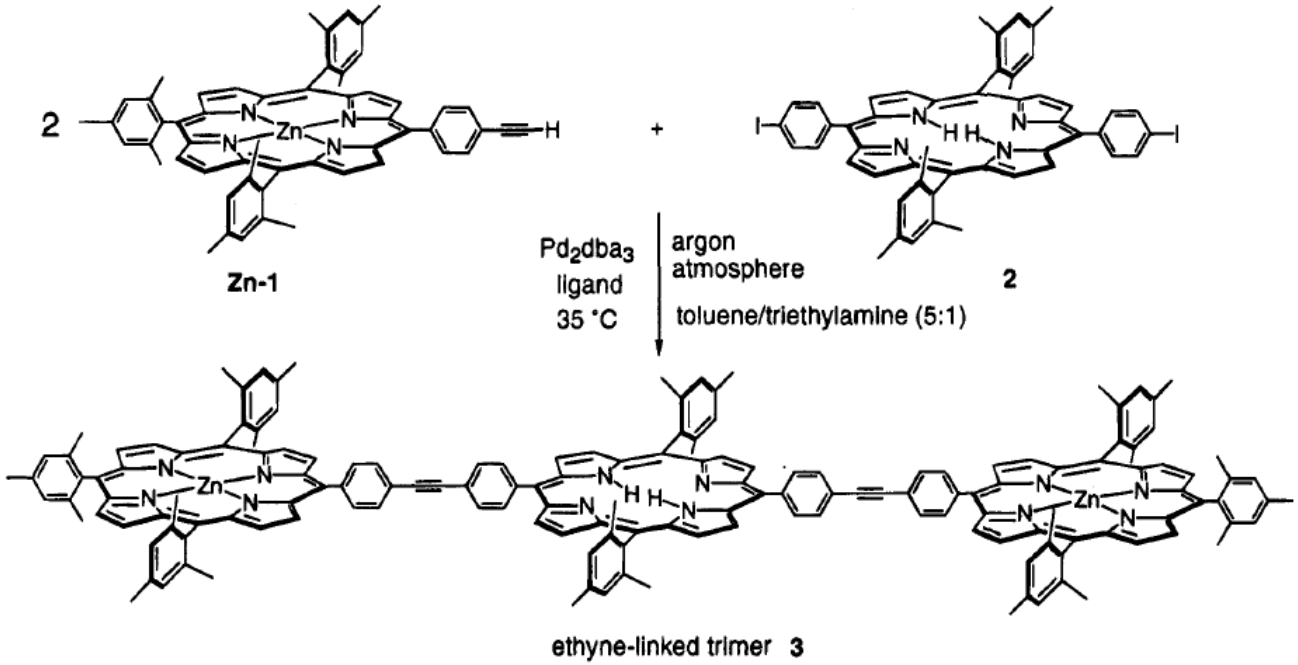


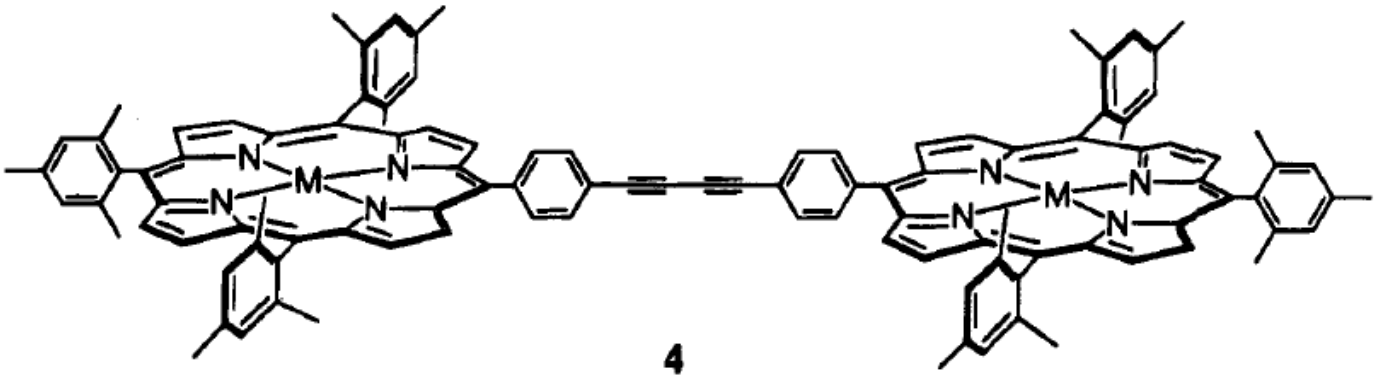
Table 1. Effects of Ligand and Concentration on the Formation of Ethyne-Linked Trimer 3[a]

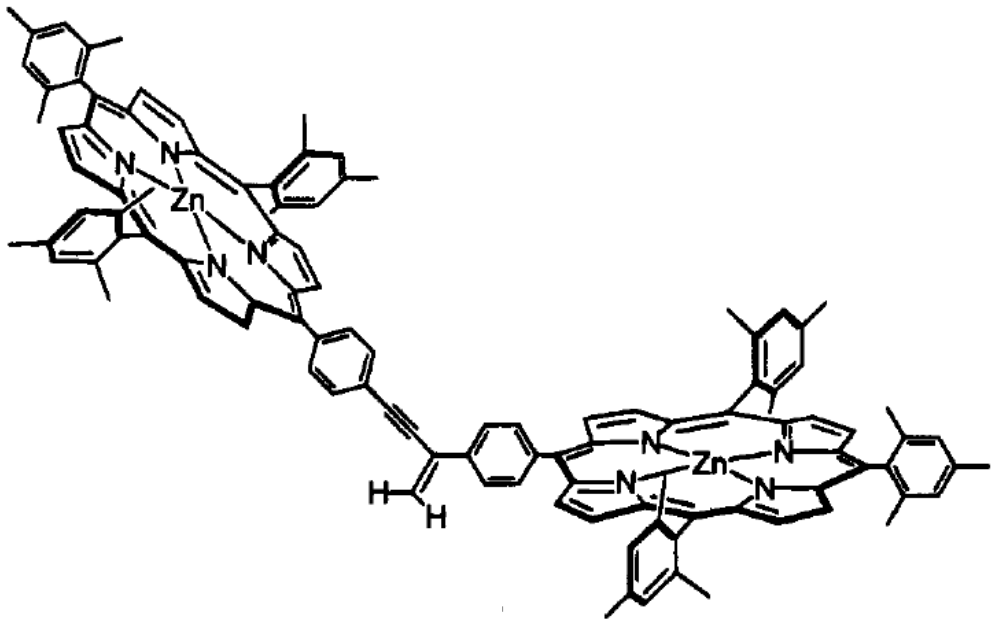
entry	$[Pd_2(dba)_3]$ (mM)	ligand, [ligand] (mM)	[Pd]: [ligand]	time (h)	detection of dimer 4[b]	HMWM: trimer 3[c]	dimer(s): trimer 3[d]	% unreacted porphyrins[e]	% yield of trimer 3
1	0.44	$AsPh_3$, 3.5	1:4	1	−	0.08:1	0.29:1	17	68
2	0.44	$AsPh_3$, 3.5	1:4	2	−	0.1:1	0.34:1	0[f]	61
3	0.44	P(2-furyl)$_3$, 3.5	1:4	2	+	no HMWM	3.2:1	60	7
4	0.44	PPh_3, 3.5	1:4	2	−	no HMWM	0.01:1[g]	96	0
5[h]	0.44	$AsPh_3$, 3.5	1:4	2	+	0.15:1	1.02:1	34	38
				5	+	0.25:1	0.94:1	25	40
				8	+	0.28:1	0.87:1	21	49
6	0.15	$AsPh_3$, 0.6	1:2	1	−	no HMWM	4.2 :1	76	1
7	0.15	$AsPh_3$, 1.2	1:4	1	−	0.14: 1	1.4:1	32	22
8	0.88	$AsPh_3$, 7.0	1:4	1	−	0.09:1	0.65:1	33	24
9[i]	0.44	$AsPh_3$, 3.5	1:4	2	−	0.08:1	0.26:1	0[f]	76

[a] All reactions were performed with 3.5 mM **Zn-1** and 1.46 mM **2** at 35 °C in toluene/triethylamine (5:1) under argon unless noted otherwise. Yields were determined by analytical SEC and calibration with authentic samples of **Zn-1**, **2**, and **3** (see Experimental Section). [b] Reaction samples were analyzed by TLC (silica, toluene/hexanes 3:2) for the presence of butadiyne-linked dimer **4**. [c] Integrated area of all higher molecular weight material (HMWM) relative to trimer peak area. [d] Integrated area of dimer peak (dimer formed by coupling of **Zn-1** and **2**, and butadiyne-linked dimer **4**, if any) relative to trimer peak area. [e] Sum of the integrated areas of peaks from starting materials **Zn-1** and **2**. Up to 14% of the unreacted porphyrins peaks is due to monomeric porphyrin byproducts. [f] Yield of monomeric porphyrin byproducts is 15%. [g] Relative to unreacted starting materials. [h] Reaction in the presence of air. [i] Preparative scale reaction.

ref) *J. Org. Chem.* **1995**, *60*, 5266

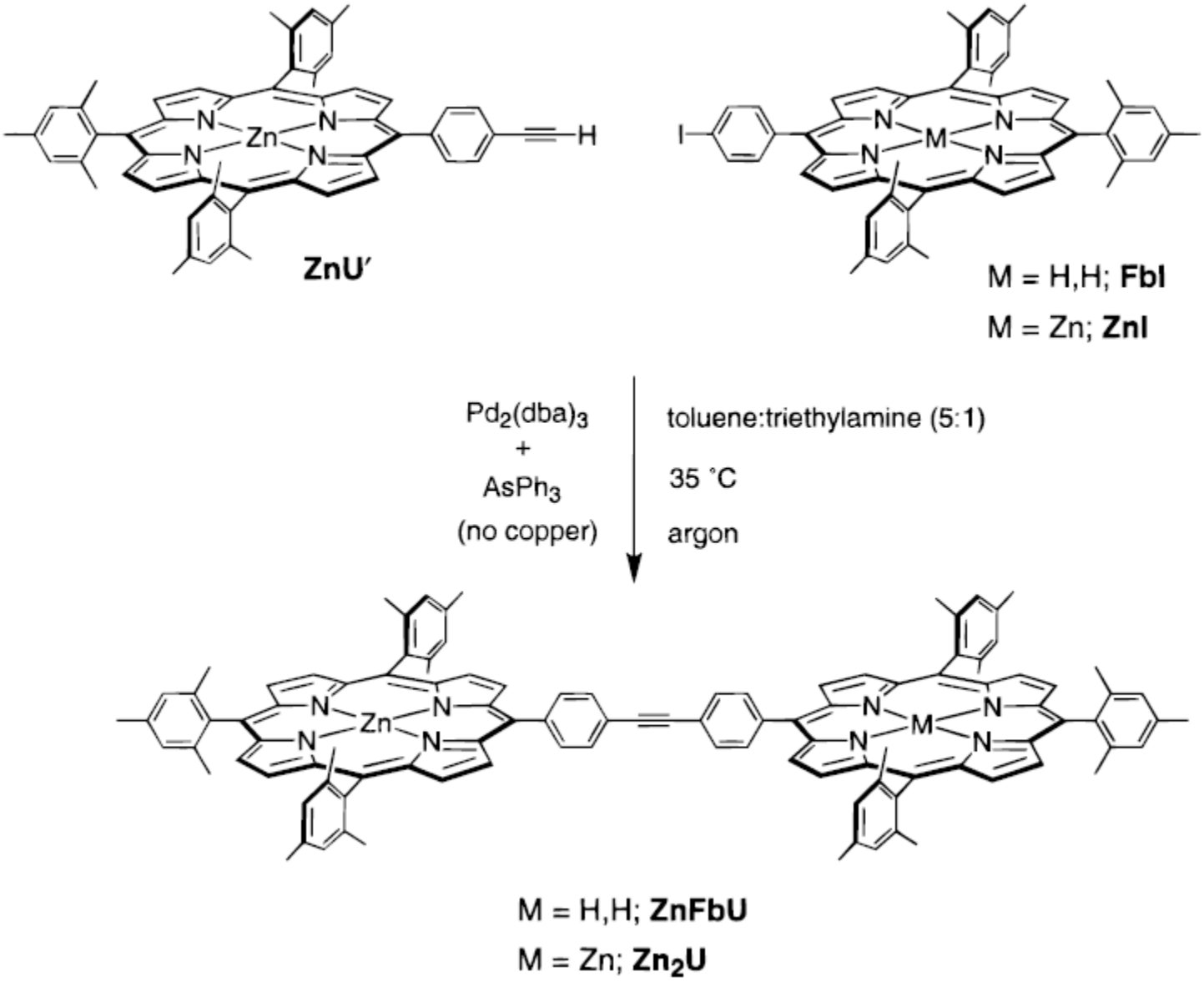
Synthetic difficulty of metalloporphyrin-analog



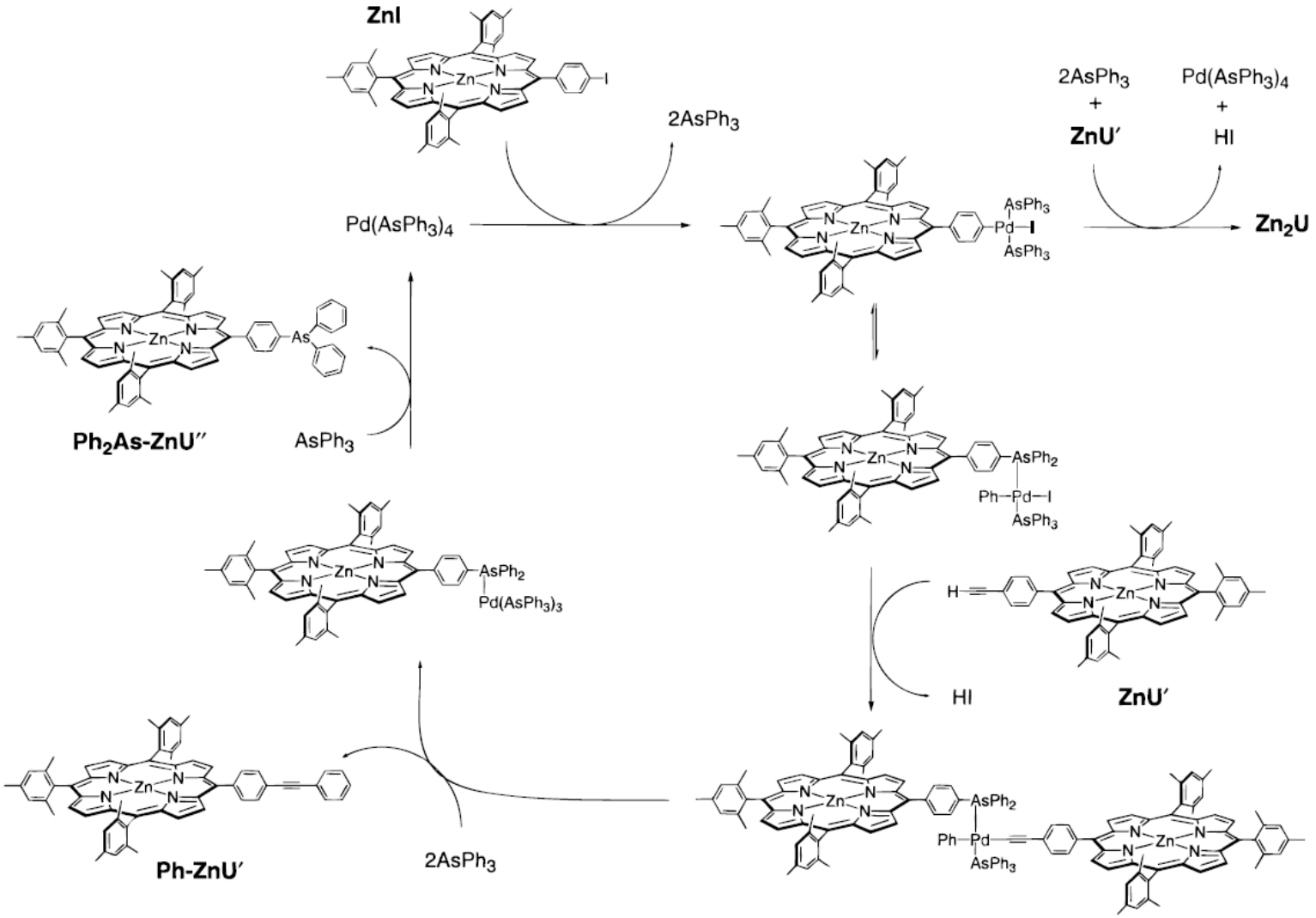


$AsPh_3$ is suitable for the ligand of Sonogashira coupling.
(it is the just ligand for oxidative addition and reductive elimination steps)

Synthetic difficulty of metalloporphyrin-analog



Synthetic difficulty of metalloporphyrin-analog



(Por)-Pd(II) species activate porphyrin's C-H bond and insert $As(PPh_3)_2$ to the starting material (sometimes it makes difficult to purify the products).

Synthetic difficulty of metalloporphyrin-analog

$P(o\text{-tolyl})_3$ is used instead of $As(PPh_3)_3$

entry	[ZnU′], [FbI] (mM)	[catalyst] (mM)	ligand (mM)	t (h)	ratio (LD-MS)[b] of ZnFbU:Ar-ZnFbU	% yield (SEC)[c] of ZnFbU + Ar−ZnFbU
1	2.5	$Pd(OAc)_2$, (0.52)	None	22	NA[d]	30[e]
2[f]	2.5	$Pd(OAc)_2$, (0.52)	$AsPh_3$, (2.0)	22	9:1[g]	66
3	2.5	$Pd(OAc)_2$, (0.53)	P(*o*-tol)$_3$, (2.1)	4	65:1	70
				22	65:1	71
4[h]	2.5	$Pd(OAc)_2$, (0.53)	P(*o*-tol)$_3$, (2.1)	5	20:1	59
				22	25:1	55
5[i]	2.5	$Pd(OAc)_2$, (0.50)	P(*o*-tol)$_3$, (2.0)	5	30:1	62
				22	30:1	67
6[j]	2.5	$Pd(OAc)_2$, (0.25)	P(*o*-tol)$_3$, (1.0)	5	45:1	41
				22	65:1	50
7	2.5	$Pd(O_2CCF_3)_2$, (0.51)	P(*o*-tol)$_3$, (2.1)	6	65:1	60
				23	65:1	64
8	2.5	palladacycle[j]	None	5	0.9:1	35
				23	0.8:1	42

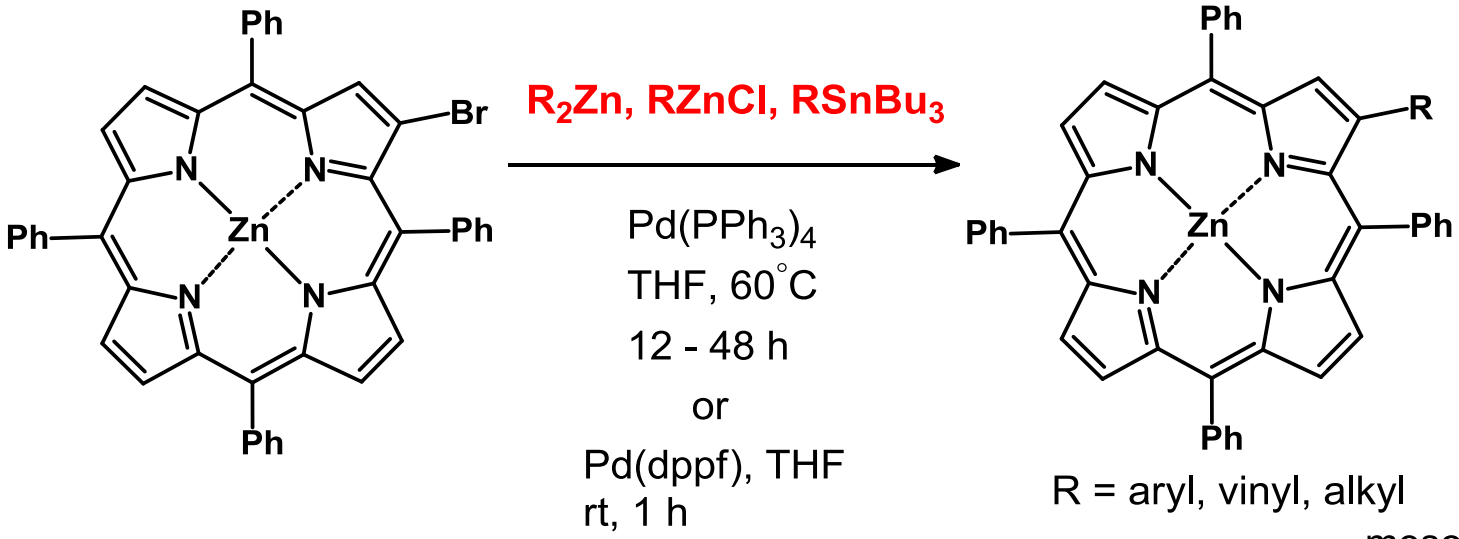
[a] All reactions were performed under argon in a glovebox in toluene/triethylamine 5:1 at 60 °C unless noted otherwise. See Supporting Information for LD-MS data, SEC data, and kinetic plots. [b] Determined by ratioing the LD-MS peak heights for Zn_2U and Ar-Zn_2U. [c] Determined by comparison of the integrated area of the SEC band of the dimers with that of the internal standard ZnTPP (see experimental). [d] Not applicable as no ligands were used. [e] The yield represents only Zn_2U because no ligands were used. [f] Performed at 35 °C for 3.5 h, and then at 60 °C for the remainder. [g] ZnFbU:Ph-ZnFbU ratio. [h] The solvent was toluene/triethylamine 19:1. [i] A toluene stock solution which was 0.06 M in $Pd(OAc)_2$ and 0.26 M in P(*o*-tol)$_3$ was used. [j] *trans*-Di(*μ*-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II).

$P(o\text{-tolyl})_3$ provides lower yield of products, but suppresses the generating of byproduct.

ref) *Chem. Mater.* **1999**, *11*, 2974

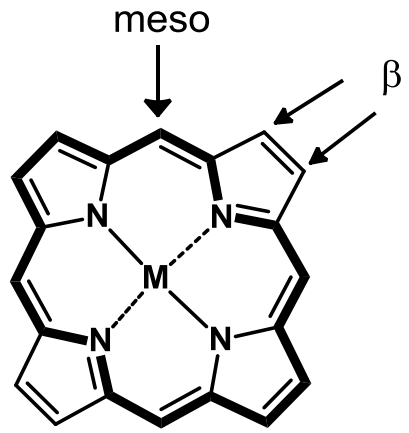
Synthetic difficulty of metalloporphyrin-analog

Ex.2) Metal-mediated cross-coupling reaction



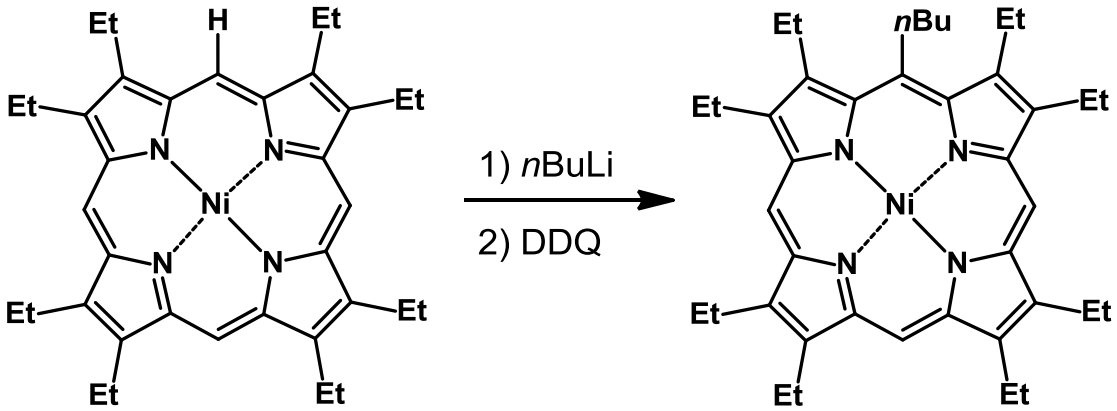
Nucleophylic organometalic reagents (like R-Li, R-MgX) cause reduction of por-Br to generate their respective porphyrin radical anions.

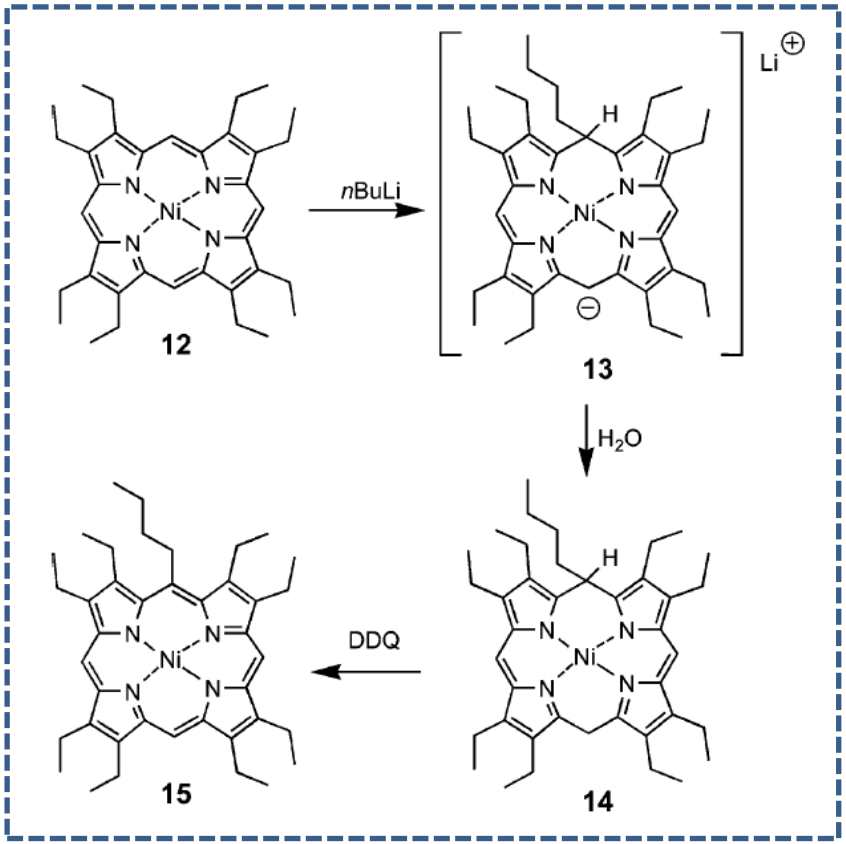
➡ R-Li and R-MgX are not suitable for insertion of R groups to Br-porphyrins.



ref) *J. Am. Chem. Soc.* **1993**, *115*, 2513
J. Org. Chem. **1993**, *58*, 5983

Synthetic difficulty of metalloporphyrin-analog



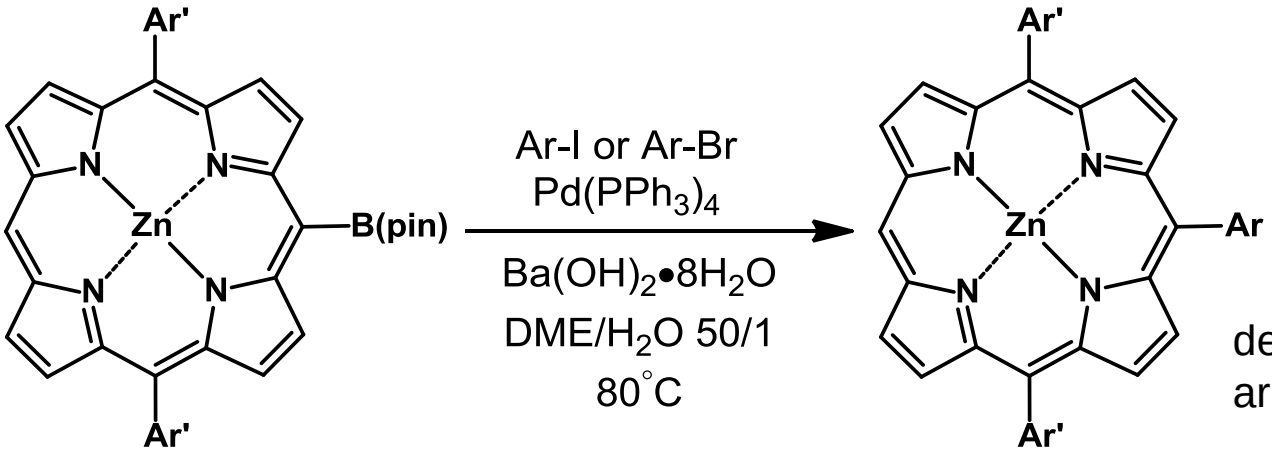


Without Pd source, S_NAr type reaction is occurred.

ref) *Acc. Chem. Res.*. **2005**, *38*, 733

Synthetic difficulty of metalloporphyrin-analog

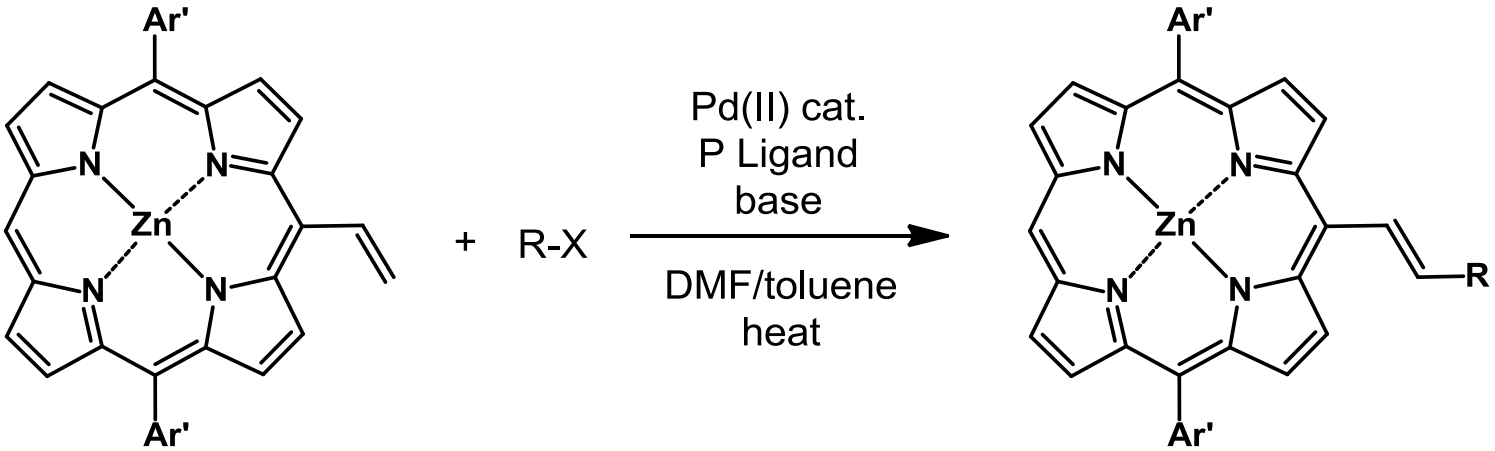
Ex.3) Suzuki-Miyaura coupling



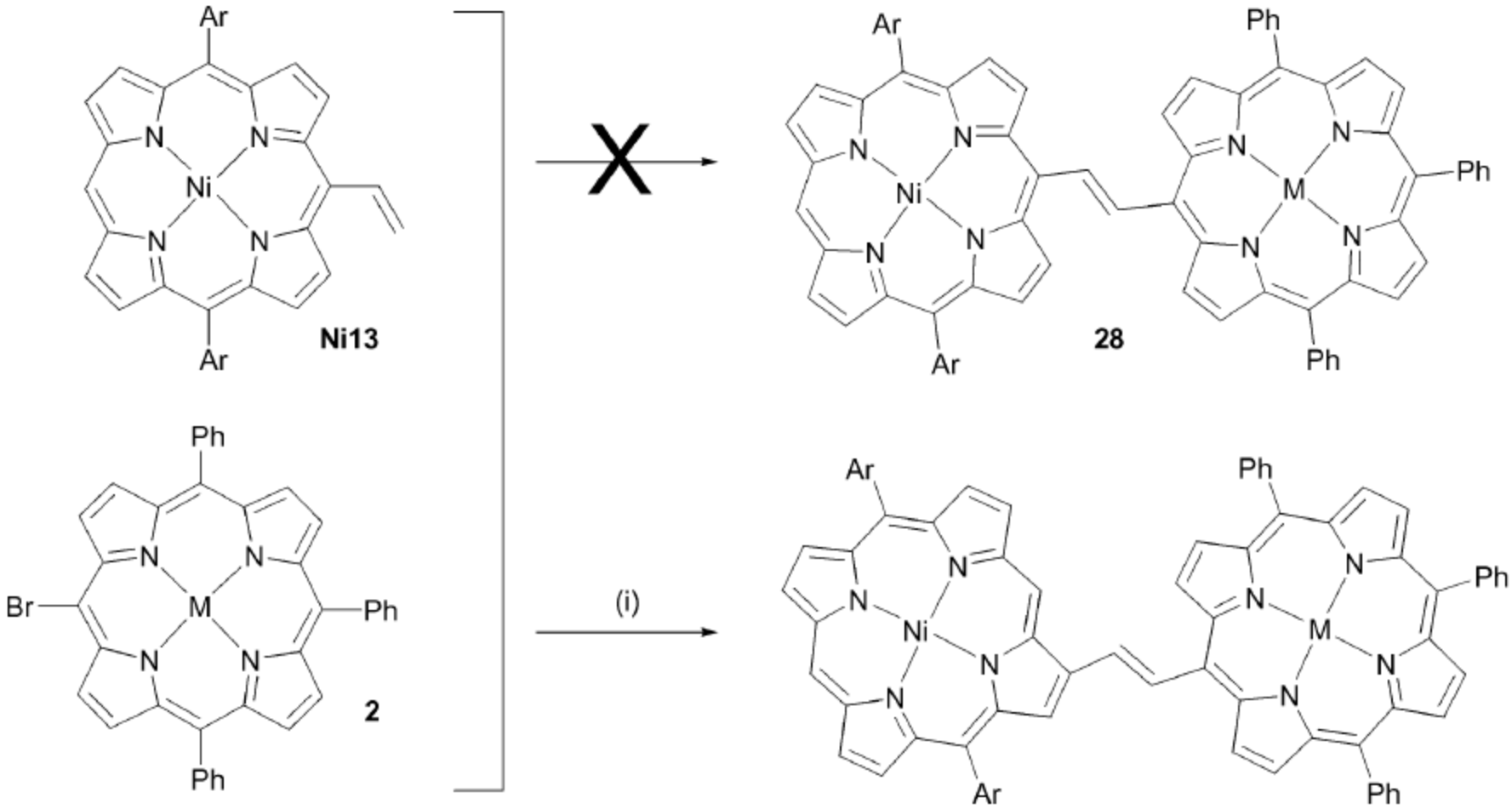
dehalogenized compounds are observed.

ref) *J. Am. Chem. Soc.* **1998**, *120*, 12676
Org. Lett. **2001**, *3*, 4213

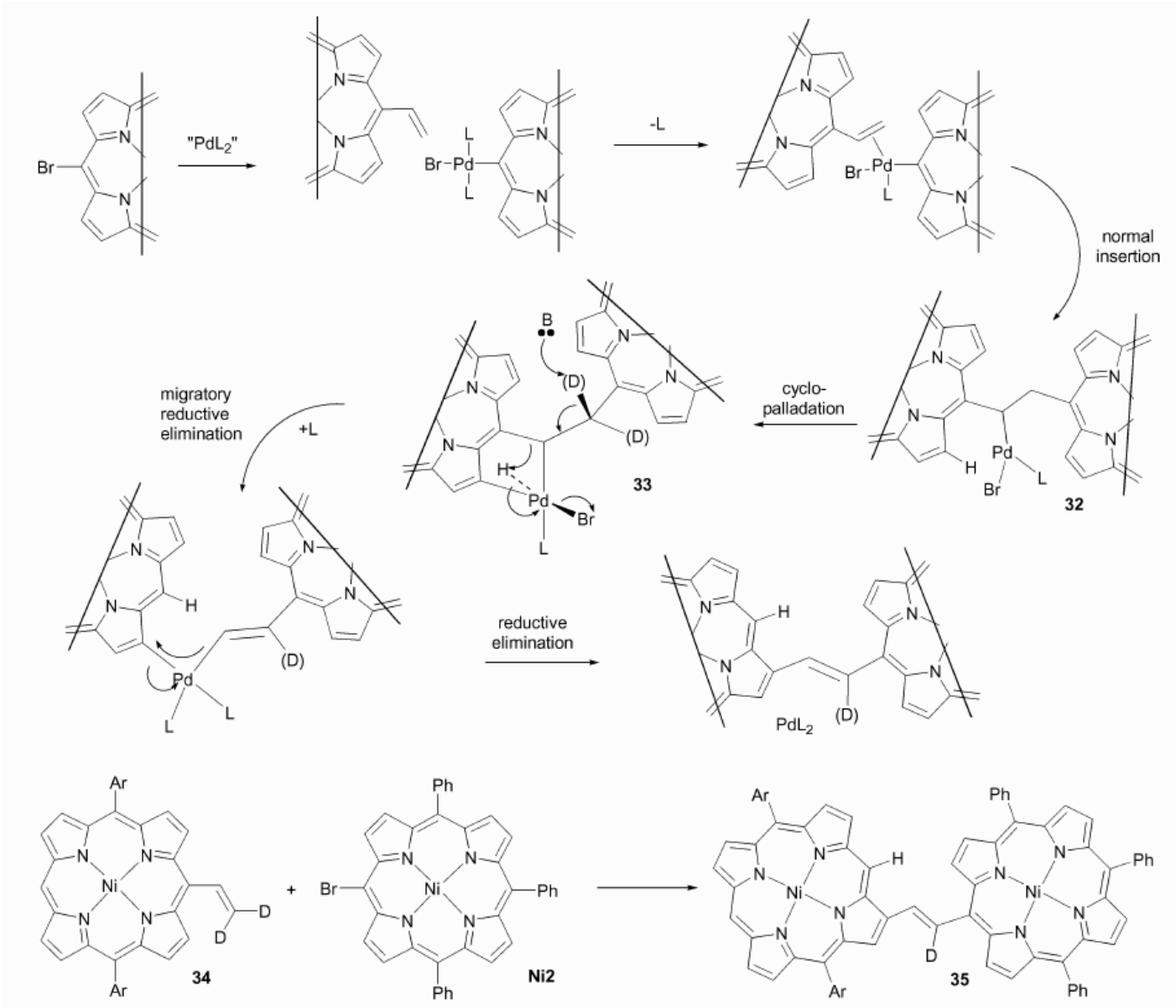
Ex.4) Mizoroki-Heck reaction



Synthetic difficulty of metalloporphyrin-analog

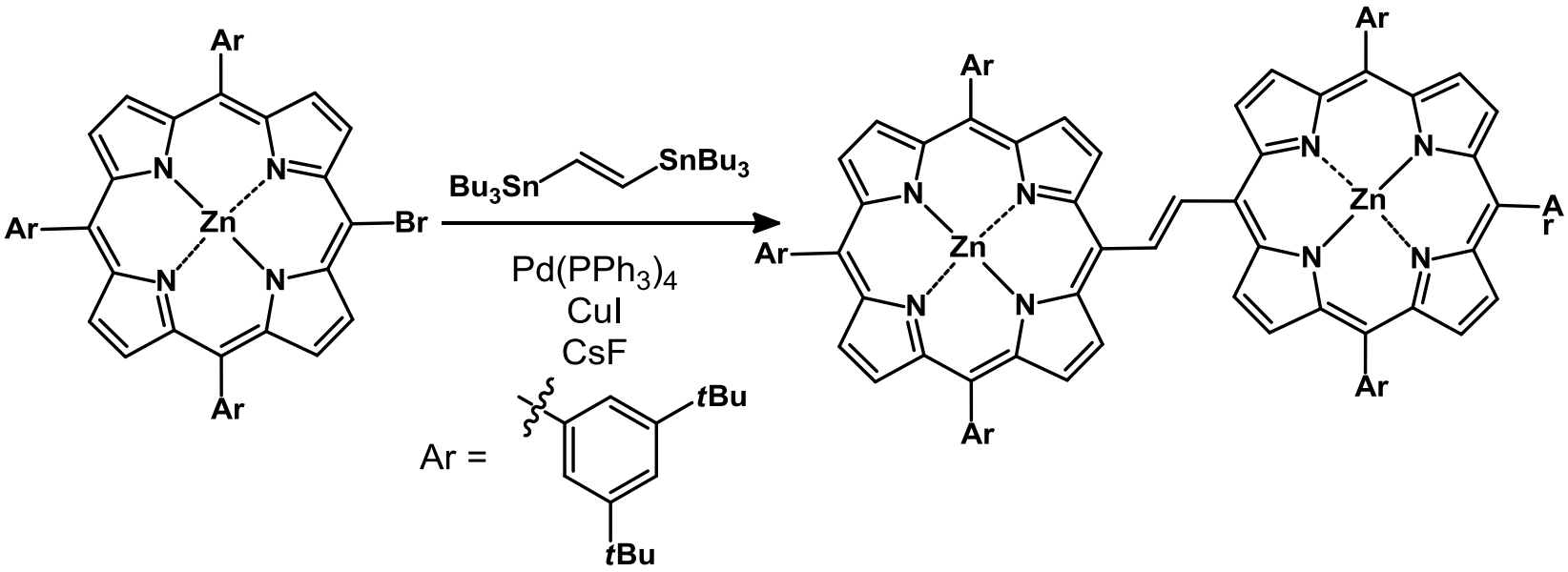


Synthetic difficulty of metalloporphyrin-analog



ref) *Org. Biomol. Chem.* **2006**, *4*, 902

Synthetic difficulty of metalloporphyrin-analog



CuI is must for this Stille coupling.

Porphyrins must be masked by Zn for preventing from insertion of Cu.

ref) *Org. Lett.* **2005**, *7*, 5365

Summery of Chapter 2

It's difficult to synthesize porphyrin-derivatives from porphyrins or metalloporphyrins for active C-H bond and affinity of metals.

- use Zn as masking porphyrin's central site to avoid the connection of Cu. and reaction's condition must be mild.
- use Cu-free-reaction to synthesize porphyrin's derivatives.
- need special reaction's condition for porphyrins.
  (large amount of solvent, avoidance of side-reactions etc.)

References (Reviews)

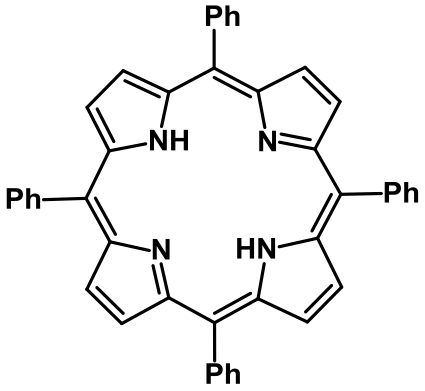
1) *J. Synth. Org. Chem., Jpn.*, **2007**, *65*, 298

2) *J. Synth. Org. Chem., Jpn.*, **2009**, *67*, 595

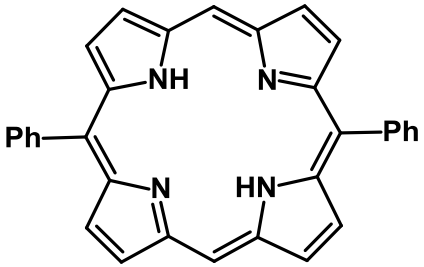
3) *J. Synth. Org. Chem., Jpn.*, **2009**, *67*, 688

Appendix

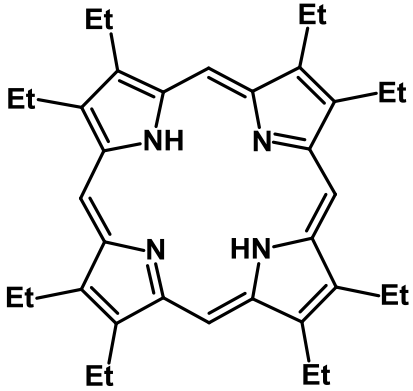
Cost of porphyrins



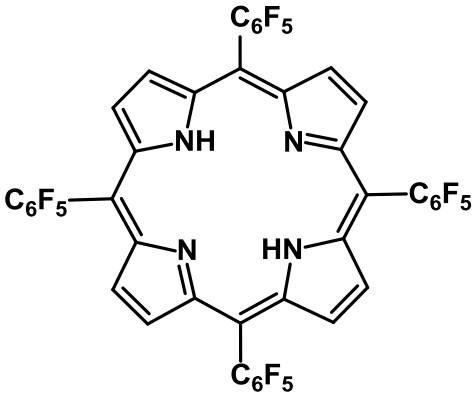
TCI : 16,300yen/1g



TCI : 18,200yen/100mg



TCI : 12,500yen/100mg



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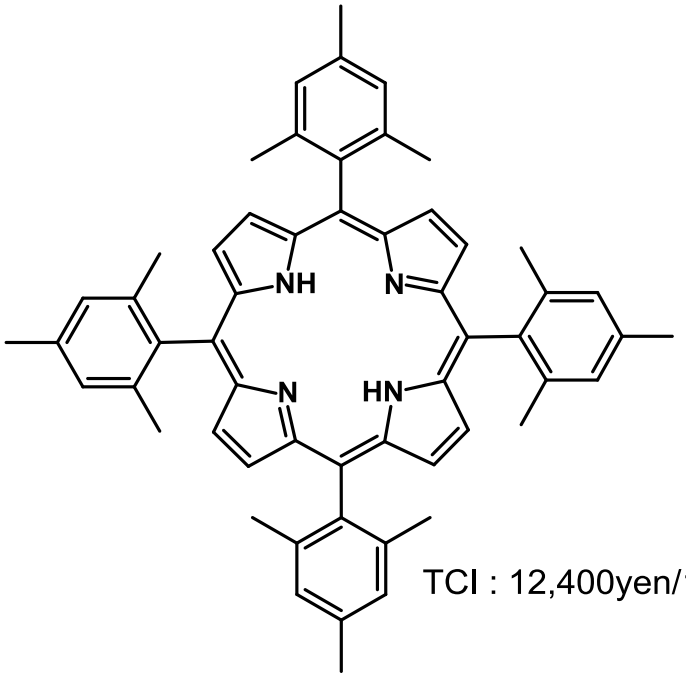

TCI : 12,400yen/100mg