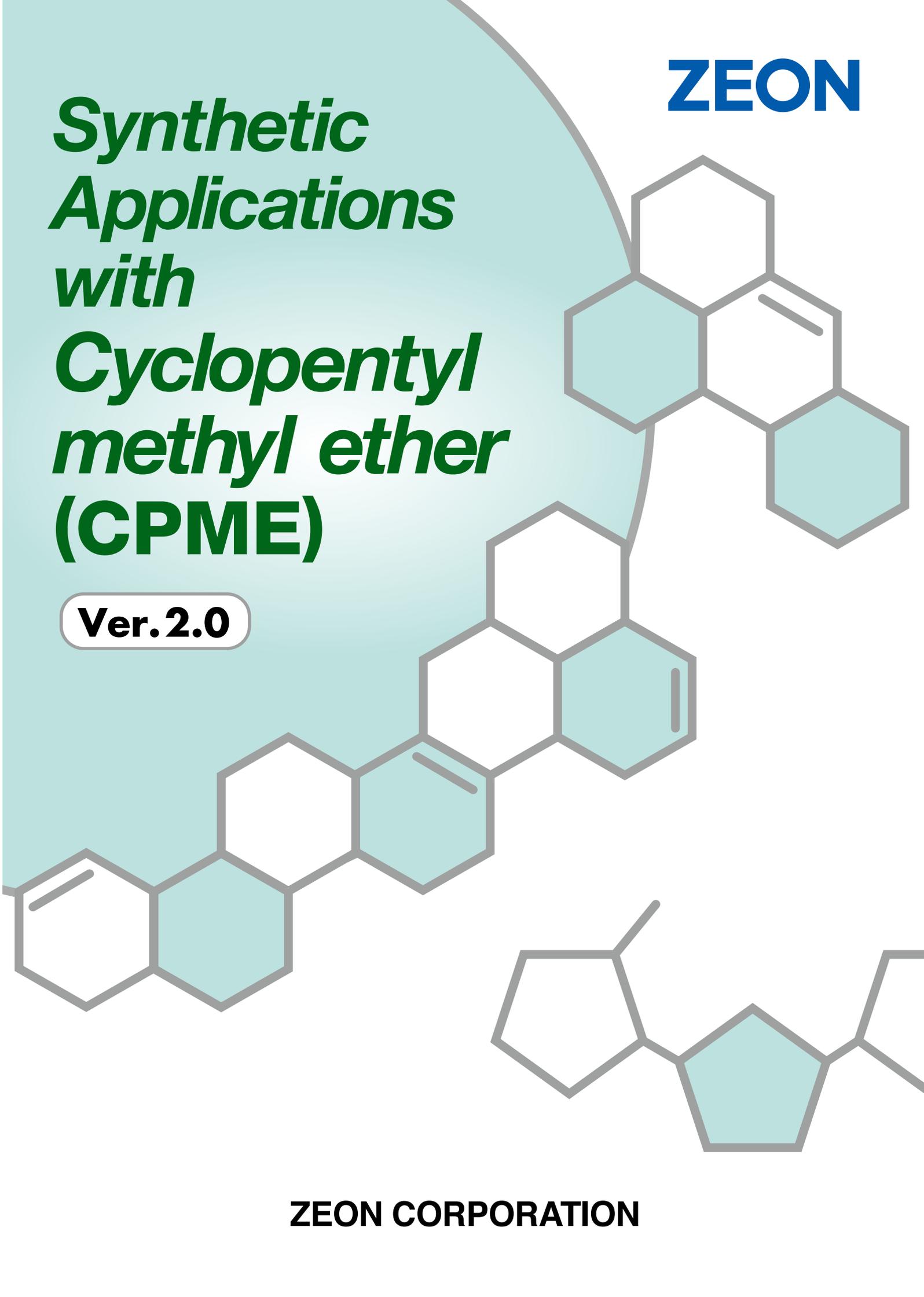


**ZEON**

***Synthetic  
Applications  
with  
Cyclopentyl  
methyl ether  
(CPME)***

**Ver. 2.0**



**ZEON CORPORATION**

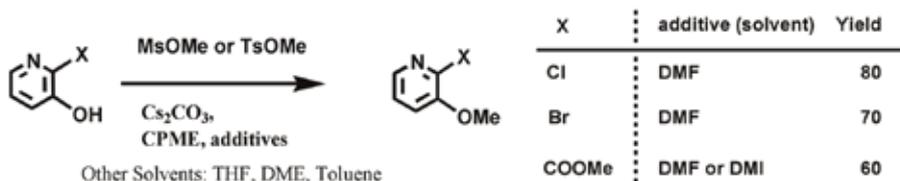
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# 1. Alkylation, Silylation

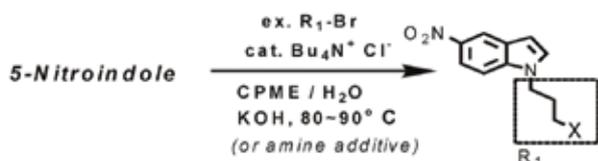
## 1-1 O-Methylation of Pyridinol

Torisawa, *Fine Chemical* 2006, 35, 53



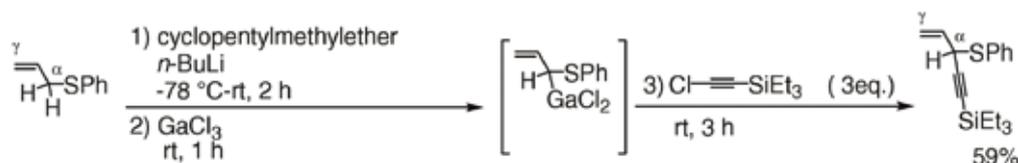
## 1-2 N-Alkylation under PTC

ibid



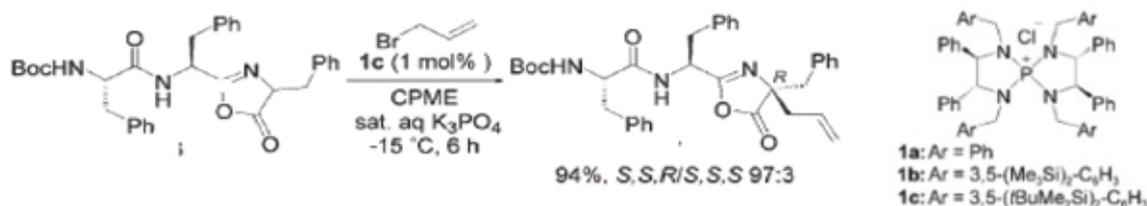
## 1-3 Regioselective Ethynylation

Yamaguchi, The 126th Annual Meeting of the Pharmaceutical Society of Japan (2005)



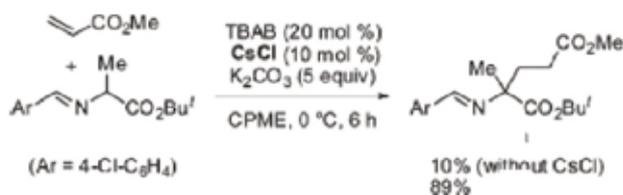
## 1-4 Asymmetric alkylation

Ooi, *Angew. Chem. int. Ed.*, 2008, 47, 1



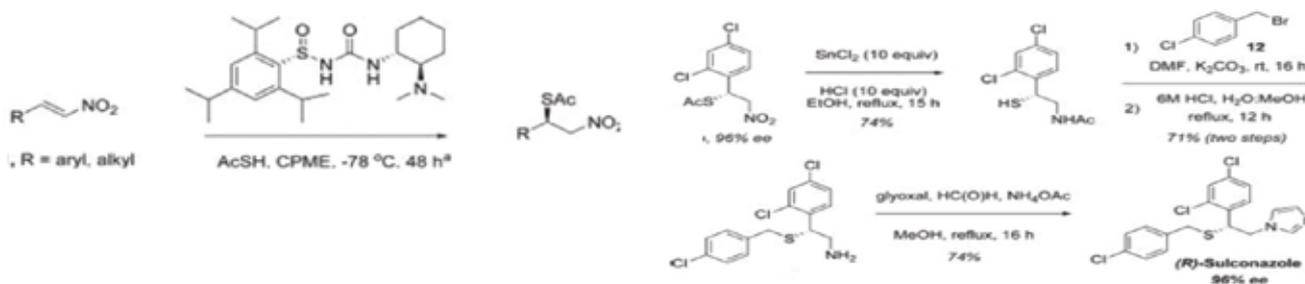
## 1-5 Asymmetric conjugate addition

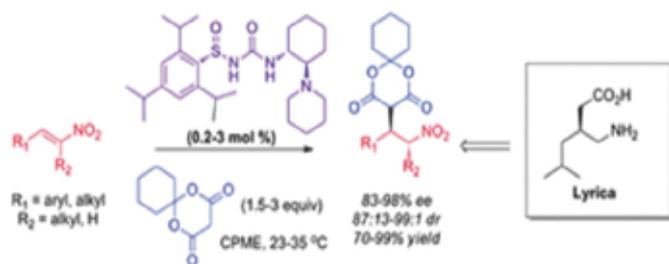
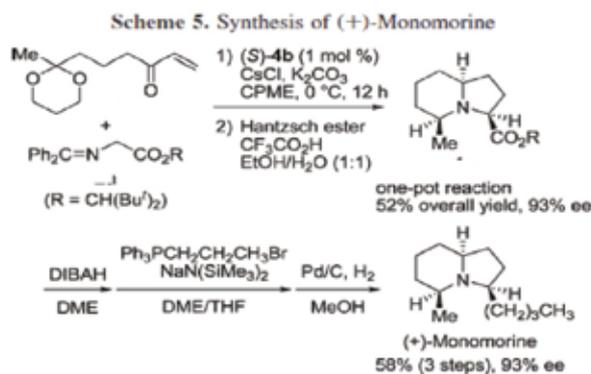
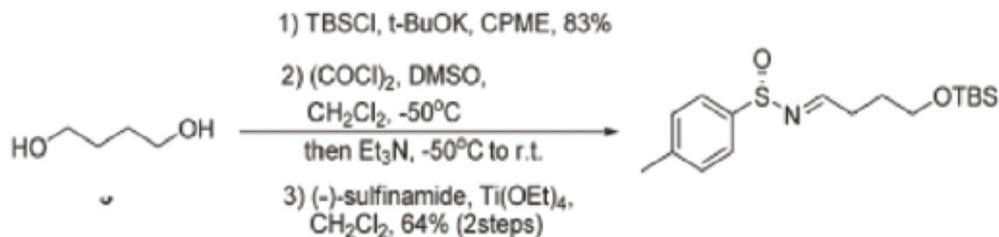
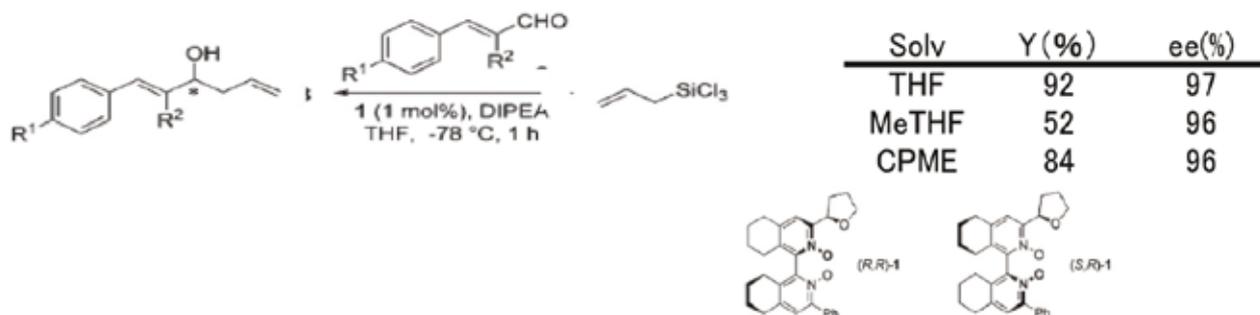
Maruoka, *Org. Lett.* 2009, 11, 2023

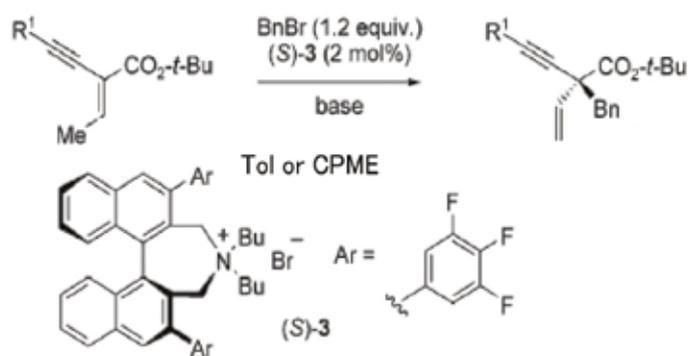
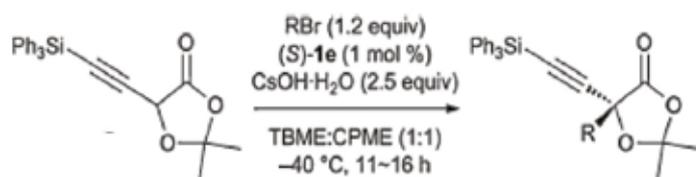
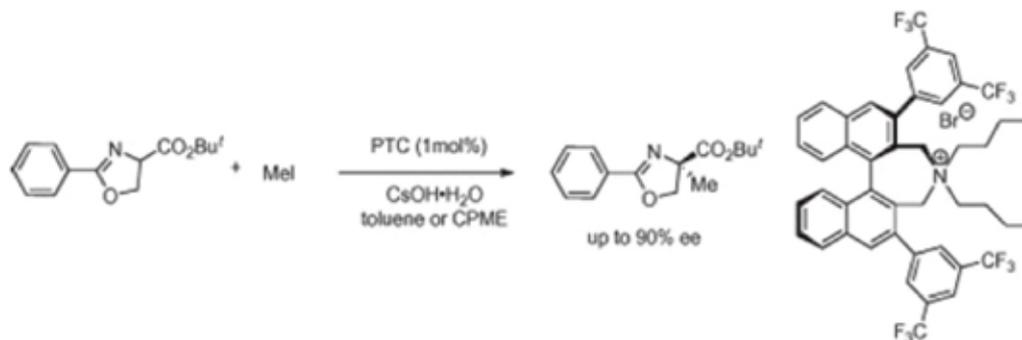
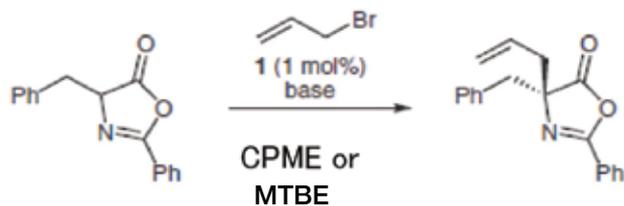


## 1-6 Asymmetric conjugate addition

J.A.Ellman, *JACS* 2009, 131, 8754

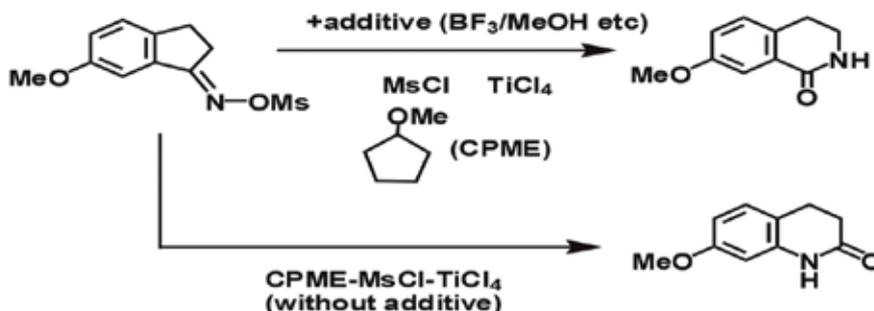


**1-7** Asymmetric conjugate additionJ.A.Ellman, *Chem.Sci.*, 2012, 3, 121**1-8** Enantioselective one-pot synthesisMaruoka, *Org. Lett.* 2009, 11, 2023**1-9** Selective O-SilylationKamimura, *J. Org. Chem.* 2010, 75, 3579**1-10** Enantioselective allylationM.Kotora, *Chem. J.* 2010, 16, 9442

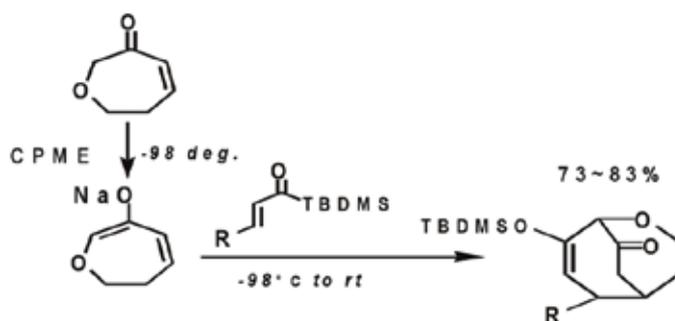
**1-11** Phase-Transfer-Catalyzed Olefin Isomerization/-Alkylation Maruoka, *Adv. Synth Catal.* 2010, 352, 165**1-12** 5-silylethynyl-1,3-dioxolan-4-one as a new prochiral template Maruoka, *Chem. Commun.*, 2010, 46, 7593**1-13** MethylationMaruoka, *Tetrahedron, Lett*, 2008, 49, 5461**1-14** AllylationOoi, *Synlett* 2009, 4, 658

## 2. Reactions under Lewis acid Conditions

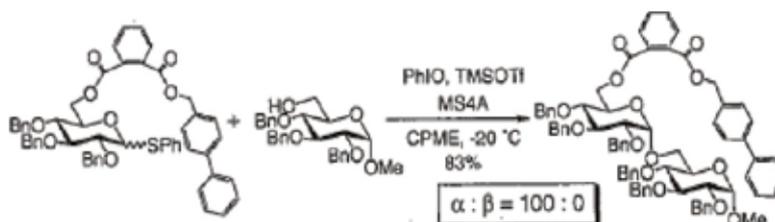
### 2-1 Beckmann Rearrangement of Indanones Torisawa, *Bioorganic & Medical Chem. Lett.* 2007, 17, 453



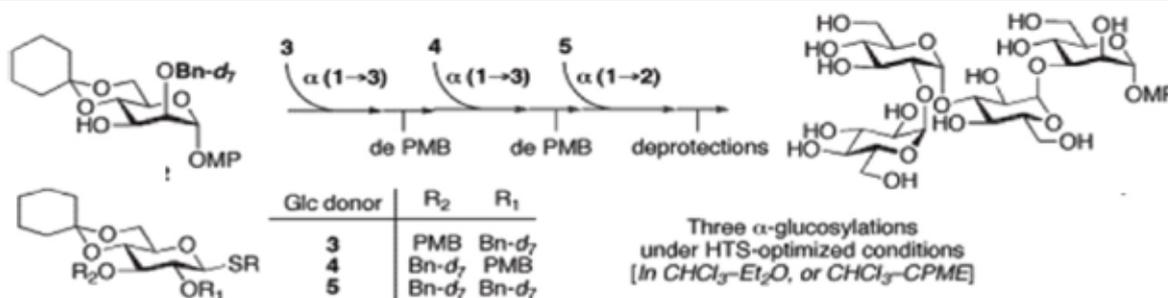
### 2-2 [3+4] Annulation Reaction Takeda., *Org.Lett.*, 2004, 6, 2277



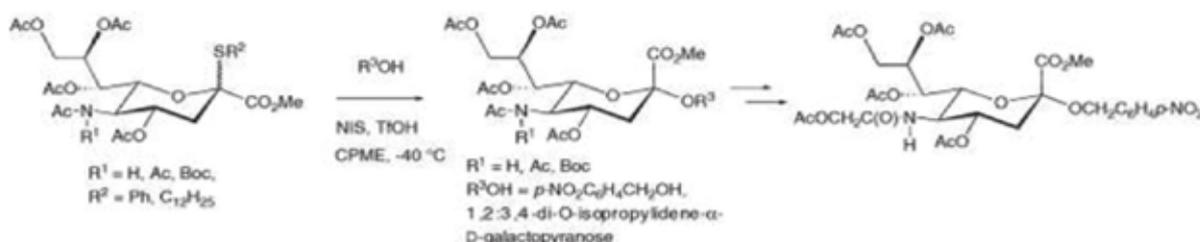
### 2-3 Selective glycosylation Fukase, *Tetrahedron: Asymmetry.* 2005, 16, 441



### 2-4 Selective glycosylation Itoh, *Tetrahedron*, 2008, 64, 92

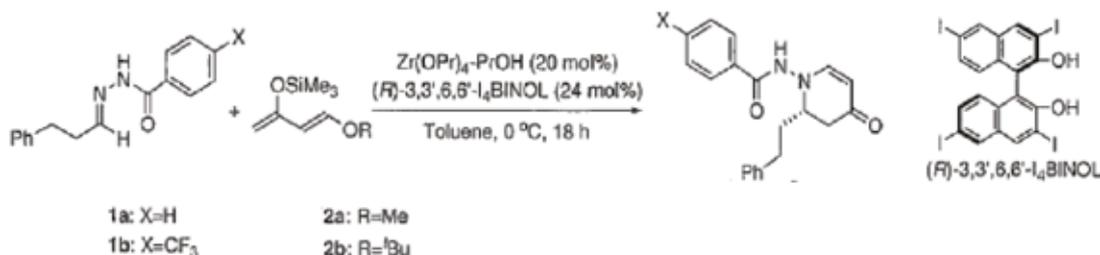


### 2-5 Selective glycosylation Ikedo, *TetrahedronLett.*, 2007, 48, 7431



## 2-6 Hetero Diels-Alder Reaction

Kobayashi, *Tetrahedron Lett.*, 2005, 46, 1803.



Entry	Solvent	Yield (%)	ee (%)
1	Toluene	35	93
2	Toluene/CH <sub>2</sub> Cl <sub>2</sub> (2/1)	10	85
3	Toluene/ <sup>t</sup> BuOMe (2/1)	39	92
4	<sup>t</sup> BuOMe	57	92
5	CPME <sup>b</sup>	56	93
6	<sup>t</sup> Pr <sub>2</sub> O	16	81
7	Et <sub>2</sub> O	28	88
8	<sup>t</sup> BuOMe/CH <sub>3</sub> CN (2/1)	76	88
9	<sup>t</sup> BuOMe/THF (2/1)	81	88
10	<sup>t</sup> BuOMe/DME (2/1)	73	92
11	<sup>t</sup> BuOMe/DME (4/1)	78	91
12 <sup>c</sup>	<sup>t</sup> BuOMe/DME (4/1)	70	91

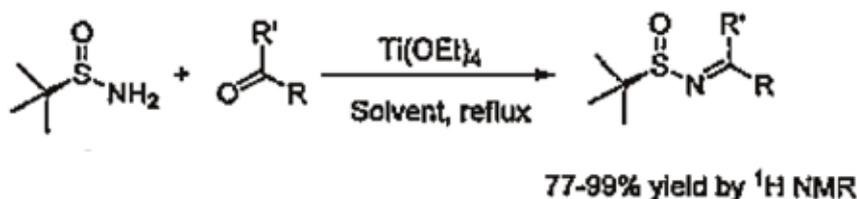
<sup>a</sup> The reactions were performed at 0 °C for 18 h in the presence of the zirconium catalyst (20 mol%).

<sup>b</sup> Cyclopentyl methyl ether.

<sup>c</sup> Using Zr catalyst (10 mol%) at -10 °C for 48 h.

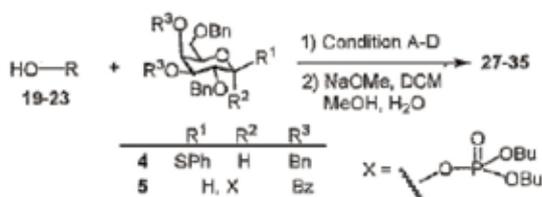
## 2-7 Sulfinyl ketimine

J.A.Ellman, *J.Org.Chem*, 2010, 75, 6283



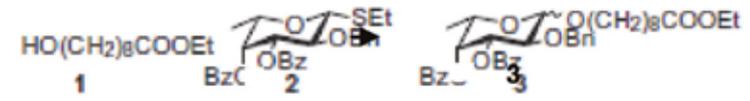
## 2-8 Selective glycosylation

Komba, *J.Appl. Glycosci*, 2011, 58, 1



Entry	Acceptor	Donor	Condition <sup>1</sup>	Product	mono:di:tri <sup>2</sup>	Yield <sup>3</sup>
1	19	4	A	27 (α only)	17:14:69	18% (12 steps)
2	20	4	A	28		
3	20	5	B	29 (α only)	24:33:43	23% (17 steps)
4	20	5	C	29	29:46:25	
5	20	5	D	29	33:55:12	
6	21	4	A	30		
7	21	5	B	31 (α only)	37:46:17	9% (20 steps)
8	22	4	A	32		
9	22	5	B	33 (α only)	45:11:44	18% (15 steps)
10	23	4	A	34		
11	23	5	B	35 (α only)	46:40:14	7% (18 steps)

<sup>1</sup>Coupling conditions; A: 6.0 equiv. 4, 18.0 equiv. NIS, 18.0 equiv. TfOH, DCM, -30 °C, 1 day; B: 6.0 equiv. 5, 18.0 equiv. TMSOTf, CPME, -15 °C, 1 day; C: 6.0 equiv. 5, 42.0 equiv. TMSOTf, CPME, -15 °C, 1 day; D: 6.0 equiv. 5, 42.0 equiv. TMSOTf, CPME, -30 °C, 1 day. <sup>2</sup>The ratio of monosaccharide:disaccharide:trisaccharide was calculated from the area under the peaks in the HPLC detected at 254 nm. <sup>3</sup>Isolated overall yield of trisaccharides.



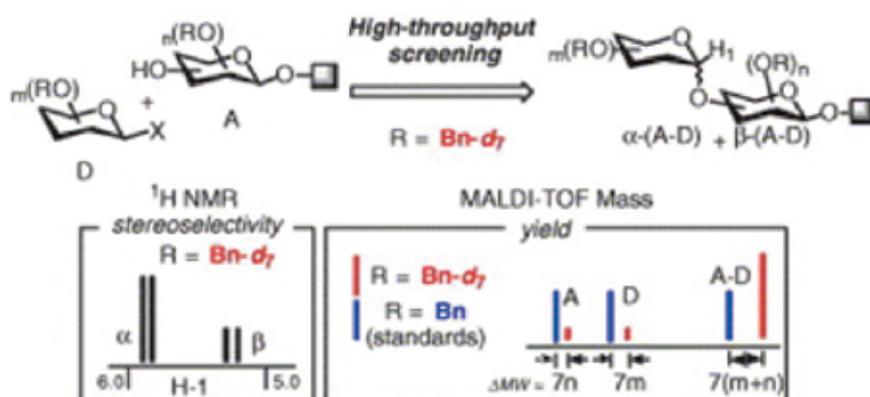
Entry	Solvent	Temp (°C)	Yield <sup>b</sup> (%)		% de <sup>c</sup>
			3 $\alpha$	3 $\beta$	
1	PhCH <sub>3</sub>	-40	41	50	10
2	Et <sub>2</sub> O	-60	50	44	6
3	Et <sub>2</sub> O	-40	66	29	39
4	Et <sub>2</sub> O	-10	78	15	68
5	Et <sub>2</sub> O	0	72	20	57
6	Et <sub>2</sub> O	rt	73	19	59
7	PME	0	80	19	62
8	PME	-10	82	13	73
9	THF	0	53	44	9
10	CH <sub>2</sub> Cl <sub>2</sub>	-60	18	63	-56
11	CH <sub>2</sub> Cl <sub>2</sub>	-40	23	66	-48
12	CH <sub>2</sub> Cl <sub>2</sub>	0	50	50	0
13	CH <sub>3</sub> CN	-40	34	61	-28

<sup>a</sup> All reactions were continued for 1–2 h.

<sup>b</sup> Isolated yield based on the donor.

<sup>c</sup> Diastereomeric excess (% de) = [ratio of  $\alpha$  anomer (%)] – [ratio of  $\beta$  anomer (%)].

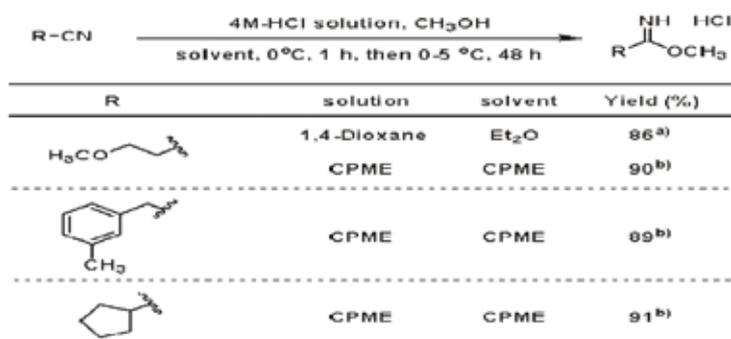
## 2-10 Glycosylation

Itoh, *Tetrahedron Lett*, 2005, 46, 3521

## 3. Reactions under Bronsted acid Conditions

### 3-1 Pinner reaction

Torisawa, *Synth. Commun.*, 2009, 39, 2008

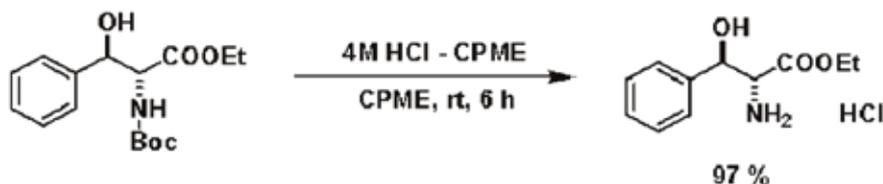


a) U.S.Pat.No.: US 6806380 B2

b) Work-up of CPME process is only filtration and washing.

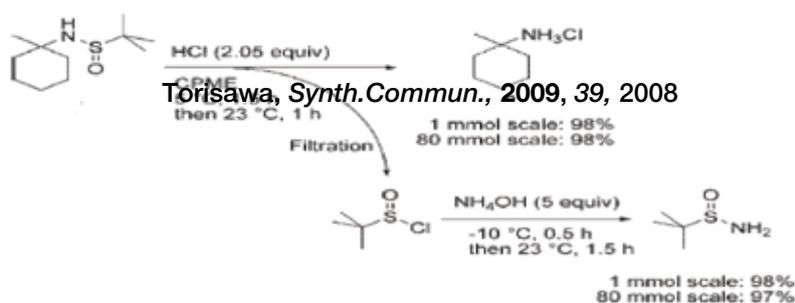
### 3-2 Deprotection of Boc-group

ibid



### 3-3 Amination

J.A.Ellman, *J.Org.Chem.*, 2009, 74, 2646



Torisawa, *Synth. Commun.*, 2009, 39, 2008

### 3-4 Asymmetric Cyclization

G.C.Fu, *Angew Chem. int. Ed.*, 2009, 48, 2225.

Table 3: Catalytic enantioselective synthesis of dihydrobenzopyrans.

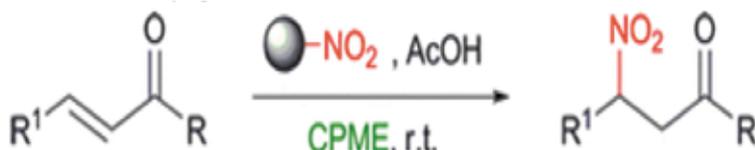
$$\text{R-Substrate} \xrightarrow[\text{50\% 2-BrC}_9\text{H}_4\text{CO}_2\text{H, 50}^\circ\text{C}]{\text{10\% (S)-1, OMe}} \text{R-Product}$$

Entry	Substrate	ee [%]	Yield [%] <sup>[a]</sup>
1		88	86
2		63	82
3		84	89
4		84	79

All data are the average of two experiments. [a] Yield of purified product.

### 3-5 Conjugate addition

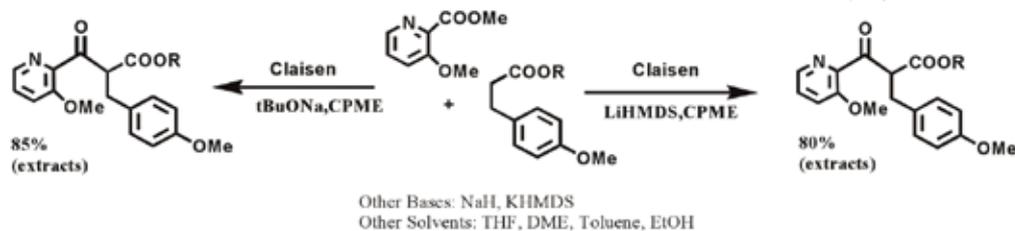
Roberto Balliani, *Green Chem.*, 2011, 13, 2026



## 4. Reaction with Base or Organometals

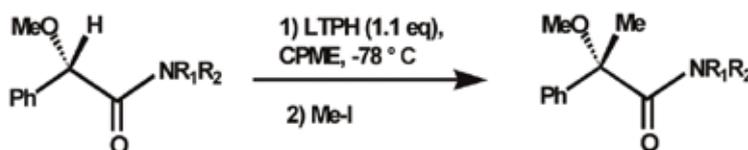
### 4-1 Claisen-Schmidt Condensation

Torisawa, Summer Symposium of the Japanese Society for Process Chemistry (2005)



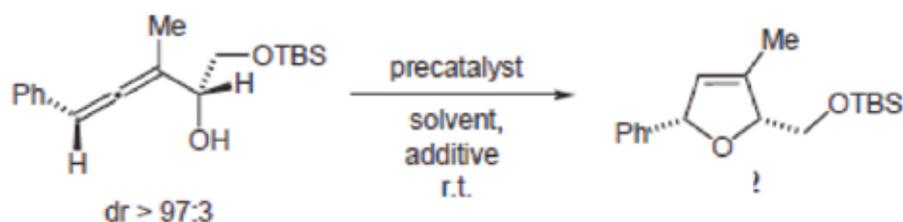
### 4-2 Chirality Transfer Methylation

Kawabata, *Chem. Commun.* 2003, 162



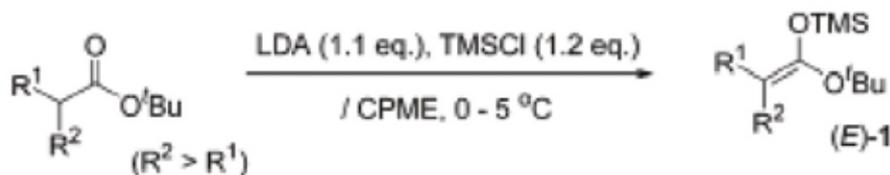
### 4-3 Chirality Transfer cyclization

Krause, *SYNLETT.* 2007, 1970



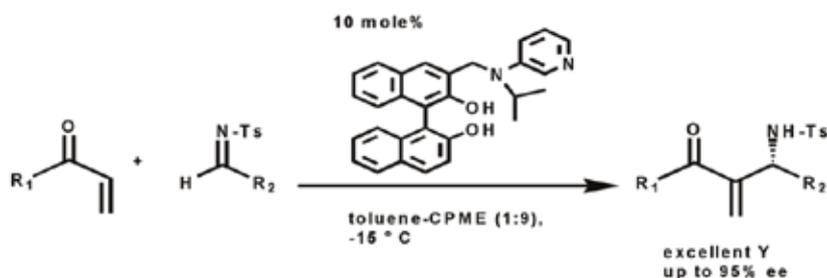
### 4-4 Selective KSA Formation

Tanabe, *J.Org.Chem.*, 2007, 72, 8142



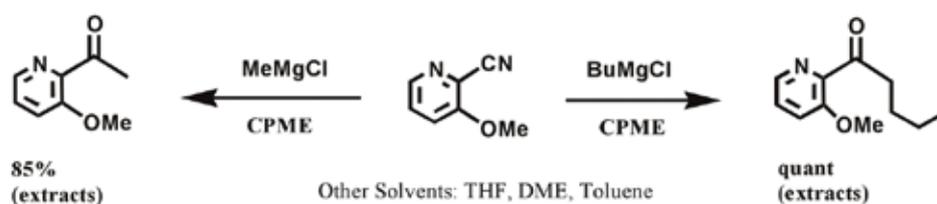
### 4-5 Symmetric aza-Morita-Baylis-Hillman Reaction

Sasai, *Tetrahedron: Asymmetry* 2006, 17, 578  
idem. *JACS.*, 2005, 127, 3680



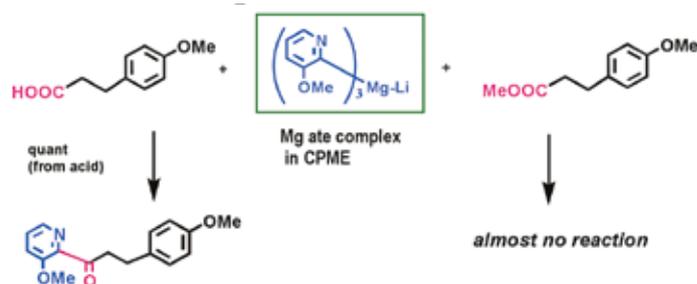
### 4-6 Grignard Addition Reactions

Torisawa, Summer Symposium of the Japanese Society for Process Chemistry (2005)



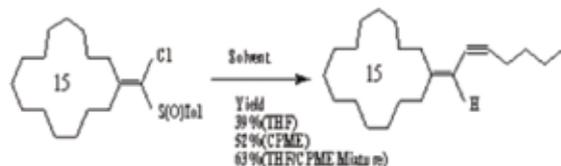
## 4-7 New Grignard Addition reactions

Torisawa, Summer Symposium of the Japanese Society for Process Chemistry (2005)



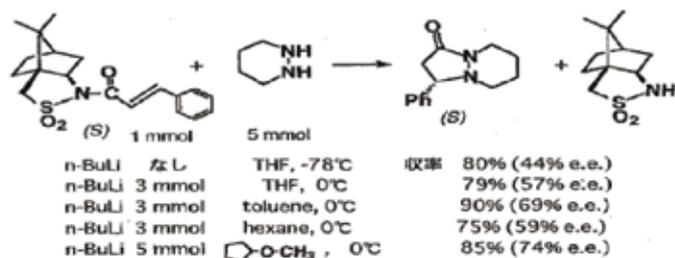
## 4-8 Vinylic addition via carbenoids

Sato, *Tetrahedron*, 2005, 61, 4409



## 4-9 Asymmetric Michael Addition

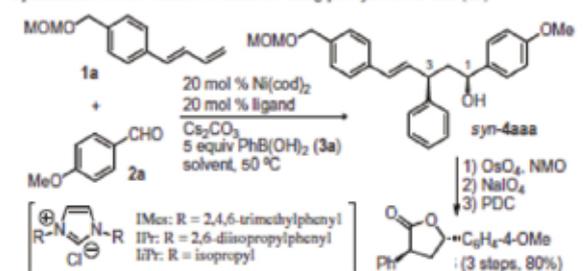
Matsuyama, The 87th Spring Meeting of Chemical Society of Japan (2007)



## 4-10 Three Component Coupling

Sato, *Tetrahedron Lett.*, 2008, 49, 5073.

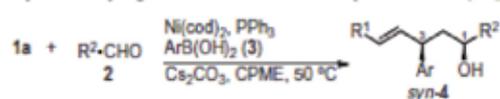
Table 1  
Optimization of the reaction conditions using phenylboronic acid (3a)



Run	Ligand	Solvent	Cs <sub>2</sub> CO <sub>3</sub> (mol %)	Time (h)	Yield (% syn:anti)
1	IMes-HCl	THF	40	60	43 (6:1)
2	IMes-HCl	CPME	40	60	40 (>50:1)
3	IMes-HCl	CPME	300	36	62 (>50:1)
4	IPr-HCl	CPME	300	27	27 (3:1)
5	IIPr-HCl	CPME	300	17	50 (>50:1)
6	PPh <sub>3</sub>	CPME	300	15	75 (>50:1)
7 <sup>a</sup>	PPh <sub>3</sub>	CPME	300	15	80 (>50:1)

<sup>a</sup> Catalyst loading: Ni(cod)<sub>2</sub> (10 mol %), IPrPh<sub>3</sub> (10 mol %).

Table 2  
Three-component coupling of various substrates in the presence of ArB(OH)<sub>2</sub> (3)<sup>a</sup>



Run	Aldehyde (2) (R <sup>2</sup> =)	Ar-B(OH) <sub>2</sub> (3) (Ar=)	yield of syn-4 <sup>b</sup> (reaction time)
1	2a: 4-MeOC <sub>6</sub> H <sub>4</sub>	3b: 4-MeOC <sub>6</sub> H <sub>4</sub>	4aab: quant (8 h)
2	2b: Ph	3a	4aba: 80% (10 h)
3 <sup>c</sup>	2c: 4-MeC <sub>6</sub> H <sub>4</sub>	3a	4aca: 72% (12 h)
4	2d: 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	3a	4ada: 33% (12 h)
5	2d	3b	4adb: 57% (17 h)
6	2e: 2-Naphthyl	3a	4aea: 82% (13 h)
7	2f: 2-Furyl	3a	4afa: 65% (16 h)
8 <sup>c</sup>	2g: Me <sub>2</sub> CHCH <sub>2</sub>	3a	4aga: 63% (1 h)
9 <sup>c</sup>	2h: Me <sub>2</sub> CH	3a	4aha: 86% (2 h)

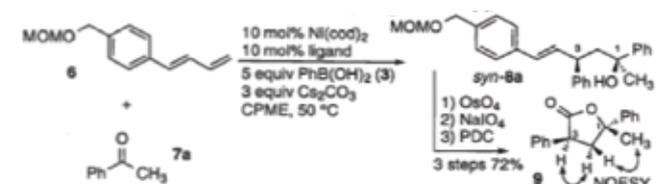
<sup>a</sup> Reaction conditions: diene (1 equiv), aldehyde (2 equiv), Ni(cod)<sub>2</sub> (10 mol %), PPh<sub>3</sub> (10 mol %), ArB(OH)<sub>2</sub> (5 equiv), Cs<sub>2</sub>CO<sub>3</sub> (3 equiv), CPME, 50 °C.

<sup>b</sup> In all cases, the ratio of syn-isomer to anti-isomer was >50:1.

<sup>c</sup> Catalyst loading: Ni(cod)<sub>2</sub> (20 mol %), PPh<sub>3</sub> (20 mol %).

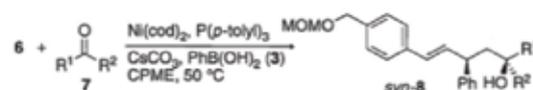
## 4-11 Three Component Coupling

Sato, *Chem. Lett.*, 2009, 38, 594.



Run	Ligand	Time/h	Yield of <i>syn</i> -8a/%
1	PPh <sub>3</sub>	75	73
2	PPh <sub>2</sub> Me	17	29
3	PCy <sub>3</sub>	10	40
4	P( <i>p</i> -tolyl) <sub>3</sub>	20	79
5	P( <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	9	71

\*Reaction conditions: **6** (1 equiv), **7a** (2 equiv), Ni(cod)<sub>2</sub> (10 mol %), ligand (10 mol %), PhB(OH)<sub>2</sub> (5 equiv), Cs<sub>2</sub>CO<sub>3</sub> (3 equiv), CPME, 50 °C. <sup>b</sup>The ratio of *syn* isomer to *anti* isomer was >50 to 1.

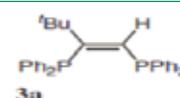


Run	Ketone 7		Time/h	Yield of <i>syn</i> -8/%	
	R <sup>1</sup> =	R <sup>2</sup> =			
1	7b	4-MeOC <sub>6</sub> H <sub>4</sub>	Me	15	8b: 25
2	7c	4-MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub>	Me	13	8c: 92
3	7d	F	Me	14	8d: 85
4	7e	CF <sub>3</sub>	Me	13	8e: 89
5	7f	CF <sub>3</sub>	Et	11	8f: 77
6	7g	<i>i</i> -Pr	Me	13	8g: 29
7	7h	<i>t</i> -Bu	Me	15	8h: 24
8	7i	n = 1		12	8i: 32
9	7j	n = 2		13	8j: 66
10	7k	n = 3		12	8k: 29

\*Reaction conditions: diene **6** (1 equiv), ketone **7** (2 equiv), Ni(cod)<sub>2</sub> (10 mol %), P(*p*-tolyl)<sub>3</sub> (10 mol %), PhB(OH)<sub>2</sub> (5 equiv), Cs<sub>2</sub>CO<sub>3</sub> (3 equiv), CPME, 50 °C. <sup>b</sup>The ratio of *syn* isomer to *anti* isomer was >50 to 1.

## 4-12 Grignard Coupling

Ohshima, *Synthesis*, 2008, 2659.



Entry	Ar	I	R	Solvent	Time (h)	2	Yield (%)
1	2-MeC <sub>6</sub> H <sub>4</sub>	1b	<i>n</i> -Bu	Et <sub>2</sub> O	5	2b	95
2	3-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1c	<i>n</i> -Bu	Et <sub>2</sub> O	5	2c	70
3	2-pyridyl	1d	<i>n</i> -Bu	Et <sub>2</sub> O	5	2d	70
4	4-MeOC <sub>6</sub> H <sub>4</sub>	1e	<i>n</i> -Bu	<i>i</i> -Pr <sub>2</sub> O	5	2e	93
5	2-MeOC <sub>6</sub> H <sub>4</sub>	1f	<i>n</i> -Bu	<i>i</i> -Pr <sub>2</sub> O	5	2f	90
6	4-(Me <sub>2</sub> N)C <sub>6</sub> H <sub>4</sub>	1g	<i>n</i> -Bu	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	12	2g	82
7	Ph	1a	Ph(CH <sub>2</sub> ) <sub>3</sub>	Et <sub>2</sub> O	5	2h	95
8	Ph	1a	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	5	2i	97
9	2-MeC <sub>6</sub> H <sub>4</sub>	1b	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	5	2j	65
10	3-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1c	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	5	2k	86
11	2-pyridyl	1d	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	5	2l	95
12	4-MeOC <sub>6</sub> H <sub>4</sub>	1e	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	12	2m	87 (93 <sup>a</sup> )
13	2-MeOC <sub>6</sub> H <sub>4</sub>	1f	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	12	2n	29
14	4-(Me <sub>2</sub> N)C <sub>6</sub> H <sub>4</sub>	1g	<i>c</i> -C <sub>6</sub> H <sub>11</sub>	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	5	2o	60
15	4-( <i>i</i> -Pr)C <sub>6</sub> H <sub>4</sub>	1h	<i>i</i> -Pr	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	13	2p	89 <sup>b</sup>
16	4-MeOC <sub>6</sub> H <sub>4</sub>	1e	<i>i</i> -Pr	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	12	2q	80 <sup>c</sup>
17	4-(Me <sub>2</sub> N)C <sub>6</sub> H <sub>4</sub>	1g	<i>i</i> -Pr	<i>c</i> -C <sub>3</sub> H <sub>7</sub> OMe	13	2r	90 <sup>d</sup>
18	Ph	1a	<i>t</i> -Bu	Et <sub>2</sub> O	5	2s	0

<sup>a</sup> Performed on a 5 mmol scale.

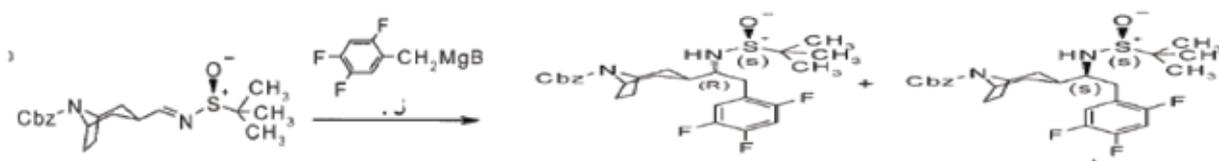
<sup>b</sup> An 88:12 mixture of isopropylated **2p** and 1-propyl-4-isopropylbenzene (**2p'**) was obtained.

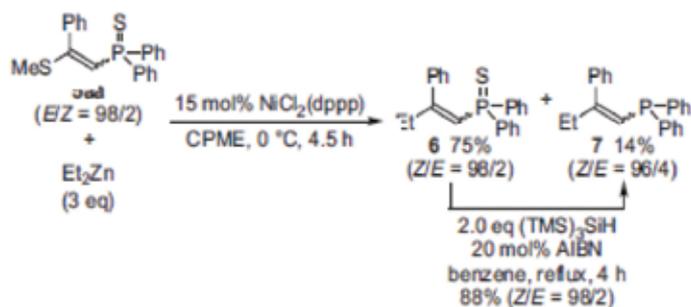
<sup>c</sup> A 77:23 mixture of isopropylated **2q** and 4-propylanisole (**2q'**) was obtained.

<sup>d</sup> A 77:23 mixture of isopropylated **2r** and *N,N*-dimethyl-4-propylaniline (**2r'**) was obtained.

## 4-13 Grignard Addition

Novartis Pharmaceuticals Corp., *J. Org. Chem.*, 2008, 73, 9016





**Table 1** Amino acid salt catalyzed intramolecular Robinson annulation

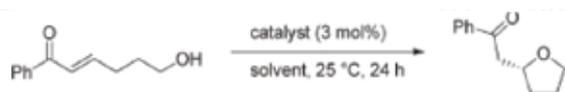
Reaction scheme showing the intramolecular Robinson annulation of a cyclic aldehyde and an alkene using a chiral amino acid salt catalyst (20 mol%) and a chiral auxiliary (0.1 M) at room temperature for 5 days.

Entry	Catalyst	Yield <sup>a</sup> (%)	ee <sup>b</sup> (%)
1 <sup>c</sup>	M - H	NR <sup>d</sup>	—
2	- Li	23	91
3	- Li	54 <sup>e</sup>	96 <sup>f</sup>
4	- Na	38	91
5	- K	14	70
6	- Rb	17	92
7	- Cs	50	94
	- Cs	29 <sup>g</sup>	96 <sup>f</sup>
	- N <sup>+</sup> Bu <sub>4</sub>	31	97
	- N <sup>+</sup> Bu <sub>4</sub>	84 <sup>g</sup>	97 <sup>f</sup>
	- N <sup>+</sup> Bu <sub>4</sub>	71 <sup>e</sup>	96 <sup>f</sup>
	- N <sup>+</sup> Bu <sub>4</sub>	80 <sup>h</sup>	96 <sup>h</sup>
8 <sup>c</sup>	Ph-CH(NH <sub>2</sub> )-COOLi	25	90
9 <sup>c</sup>	MeO-C <sub>6</sub> H <sub>4</sub> -CH(NH <sub>2</sub> )-COOLi	36	94
10 <sup>c</sup>	Ph-CH(NH <sub>2</sub> )-COOLi	56	88
11 <sup>c</sup>	Me-CH(NH <sub>2</sub> )-COOLi	36	64
12 <sup>c</sup>	Me-CH(NH <sub>2</sub> )-COOLi	NR <sup>d</sup>	—
13 <sup>c</sup>	Indole-CH(NH <sub>2</sub> )-COOLi	NR <sup>d</sup>	—

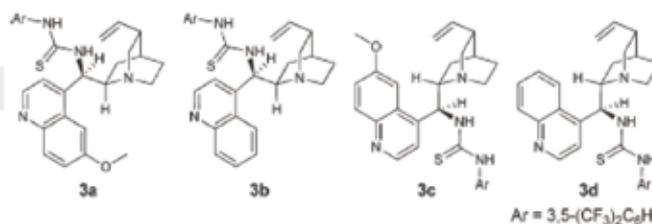
<sup>a</sup> Isolated yield. <sup>b</sup> Determined by HPLC on OJ-HI column. <sup>c</sup> CH<sub>2</sub>Cl<sub>2</sub> is used as solvent. <sup>d</sup> NR = no reaction. <sup>e</sup> Et<sub>2</sub>O is used as solvent. <sup>f</sup> 1st run, 50 mol% silica gel absorbed catalyst is used. <sup>g</sup> 2nd run, using 50 mol% recovered silica gel absorbed catalyst from 1st run. <sup>h</sup> 3rd run, using 50 mol% recovered silica gel absorbed catalyst from 2nd run.

## 4-16 Asymmetric Catalytic Cycloetherification

Matsubara, *JACS*, 2011,



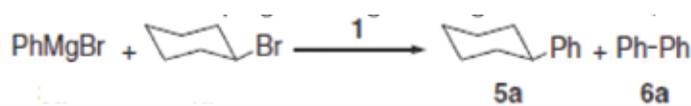
entry	catalyst	solvent	yield (%) <sup>b</sup>	ee (%)
1	3a	CH <sub>2</sub> Cl <sub>2</sub>	99	92
2	3a	benzene	97	94
3	3a	THF	73	90
4	3a	Et <sub>2</sub> O	99	94
5	3a	CPME <sup>c</sup>	99	95
6 <sup>d</sup>	3a	CPME <sup>c</sup>	95	96
7	3b	CPME <sup>c</sup>	99	89
8	3c	CPME <sup>c</sup>	99	-96
9	3d	CPME <sup>c</sup>	99	-94



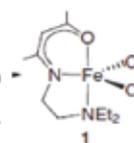
<sup>a</sup> Reactions were run using 1a (0.25 mmol) and the catalyst (0.0075 mmol) in the solvent (0.5 mL). <sup>b</sup> Isolated yields. <sup>c</sup> CPME = cyclopentyl

## 4-17 Cross-coupling with Grignard reagent

Asami, *Chem. Lett.* 2011, 40, 983

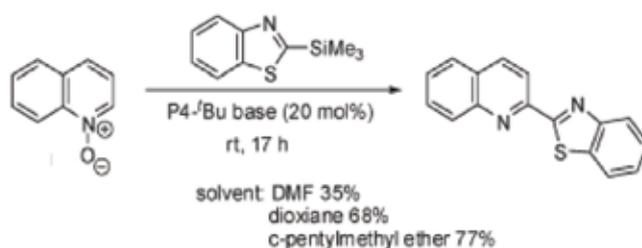


Entry	Solvent	Catalyst /mol%	PhMgBr /equiv	Addition rate/min	Time /min	Temp /°C	Yield/% <sup>b</sup>	
							5a	6a
1	Et <sub>2</sub> O	1.0	1.2	fast	60	4	88	11
2	CPME	1.0	1.2	fast	60	4	81	12
3	THF	1.0	1.2	fast	60	4	34	5
4	DME	1.0	1.2	fast	60	4	20	26



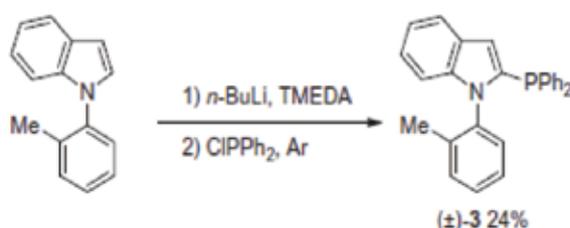
## 4-18 Functionalisation of heteroarmatic N-oxides

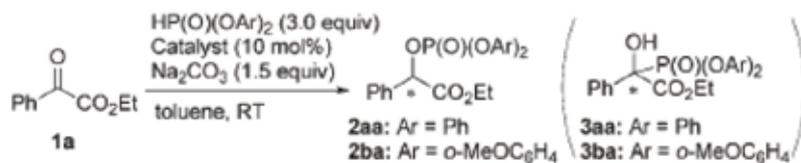
Kondo, *Org. Biomol. Chem.*, 2011, 9, 78



## 4-19 Phosphinylation

Fujita, *Tetrahedron: Asymmetry*, 2010, 21, 711

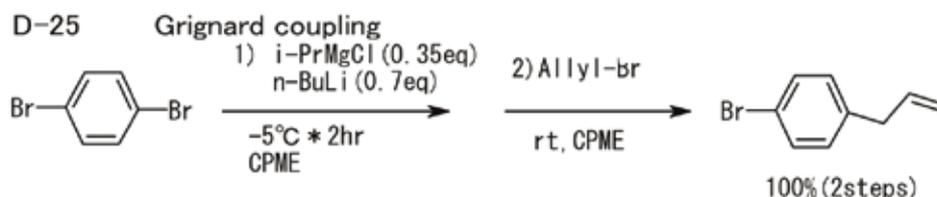




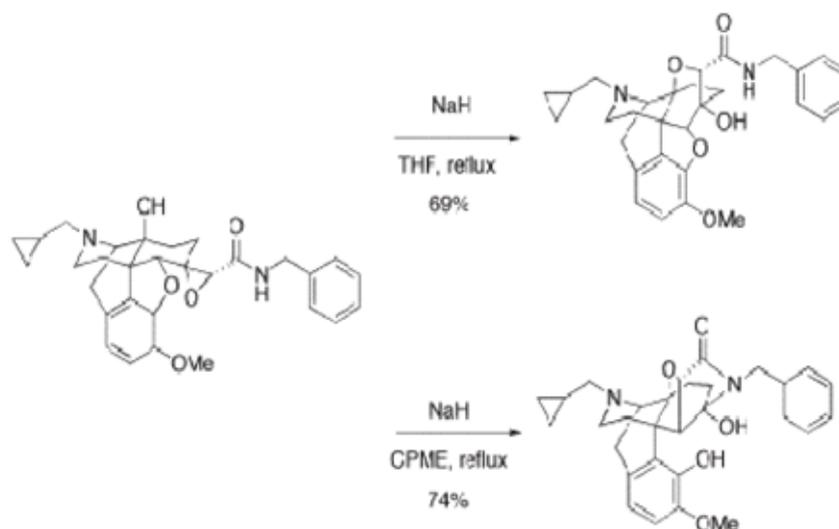
Entry	Catalyst (mol%)	Ar	Yield of 2 [%]	ee [%] <sup>[a]</sup>
1 <sup>[b]</sup>	quinine (10)	Ph	17 <sup>[c]</sup>	58 (S)
2	quinine (10)	Ph	99	46 (S)
3	quinidine (10)	Ph	91	63 (R)
4	cinchonine (10)	Ph	98	22 (R)
5	cinchonidine (10)	Ph	88	19 (S)
6	Ac-quinidine (10)	Ph	97	39 (S)
7 <sup>[d]</sup>	quinidine (10)	Ph	93	64 (R)
8 <sup>[d,e]</sup>	quinidine (10)	Ph	94	70 (R)
9 <sup>[d,e]</sup>	quinidine (10)	o-MeOC <sub>6</sub> H <sub>4</sub>	79	74 (R)
10 <sup>[d,e,f]</sup>	quinidine (10)	o-MeOC <sub>6</sub> H <sub>4</sub>	98	92 (R)
11 <sup>[d,e,f]</sup>	quinidine (2)	o-MeOC <sub>6</sub> H <sub>4</sub>	94	92 (R)
12 <sup>[d,e,f]</sup>	quinine (10)	o-MeOC <sub>6</sub> H <sub>4</sub>	97	91 (S)
13 <sup>[d,e,f,g]</sup>	quinidine (10)	o-MeOC <sub>6</sub> H <sub>4</sub>	98	90 (R)

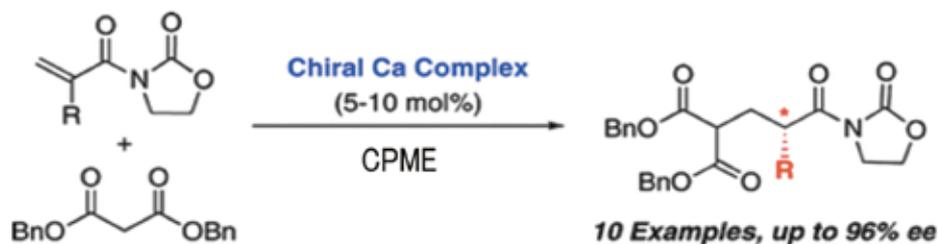
Toluene-CPME

[a] The absolute configuration of 2 is given in parentheses. [b] Reaction carried out without using Na<sub>2</sub>CO<sub>3</sub>. [c] 3aa (46%) was obtained. [d] Phosphite (1.3 equiv) and Na<sub>2</sub>CO<sub>3</sub> (0.2 equiv) was used. [e] Cyclohexyl methyl ether was used as a solvent. [f] The reaction was carried

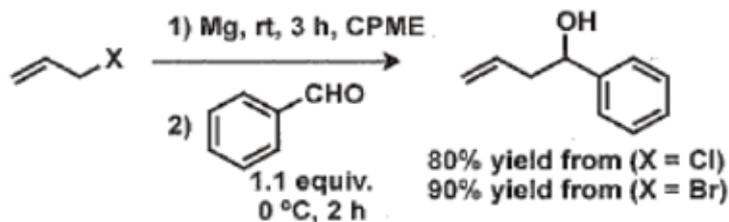
4-21 Grignard coupling Shimada, *The 2nd International Symposium on Process Chemistry*(2011)

## 4-22 Rearrangement

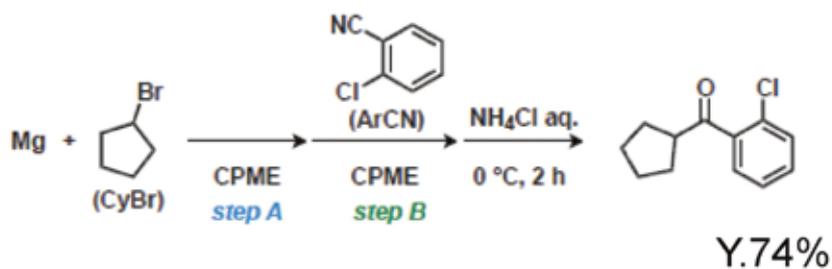


**4-23 Protonation**Kobayashi, *JACS*, 2010, 132, 7890**4-24 Grignard**

Zeon Corporation, Internal data

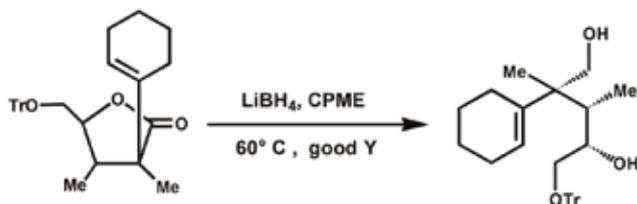
**4-25 Addition of Grignard reagent to CN-group**

Zeon Corporation, Internal data

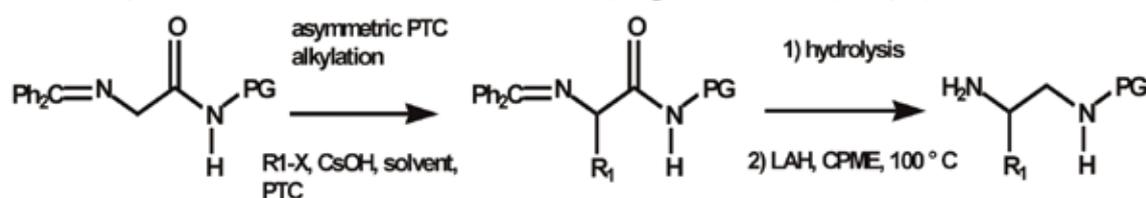


## 5. Oxidation/Reduction

### 5-1 LiBH<sub>4</sub> Reduction Zeon Corporation, Cyclopentyl Methyl Ether (CPME) technical data



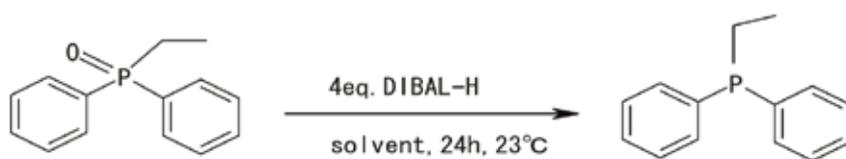
### 5-2 LiAlH<sub>4</sub> Reduction Maruoka, *Angew Chem. int. Ed.*, 2003, 42, 5868



### 5-3 LiAlH<sub>4</sub> Reduction Shimada, *J. Org Chem.*, 2005, 70, 10178.

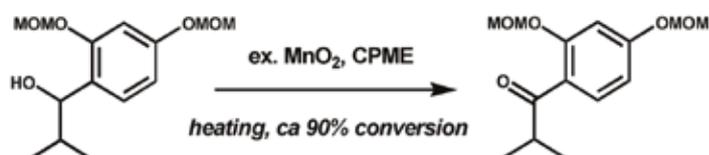


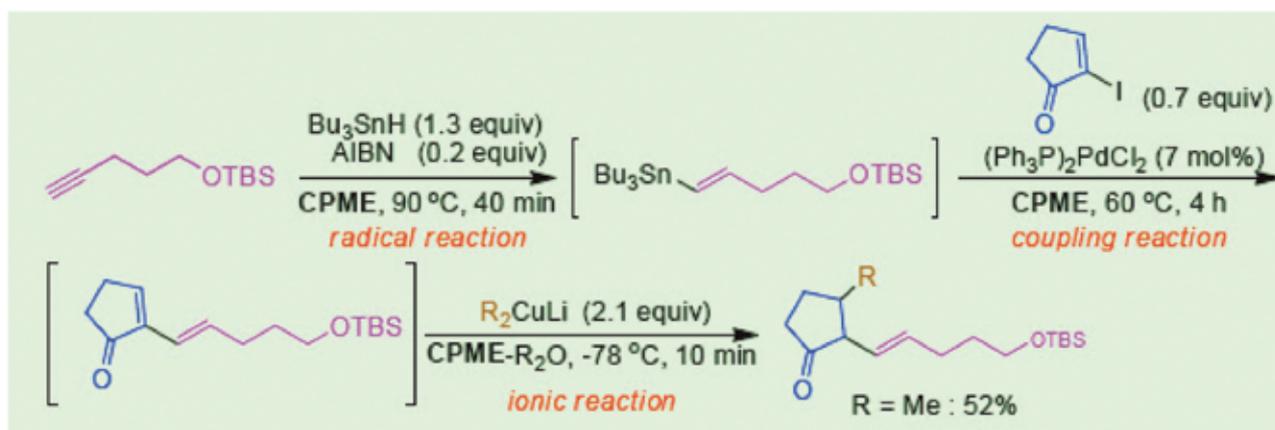
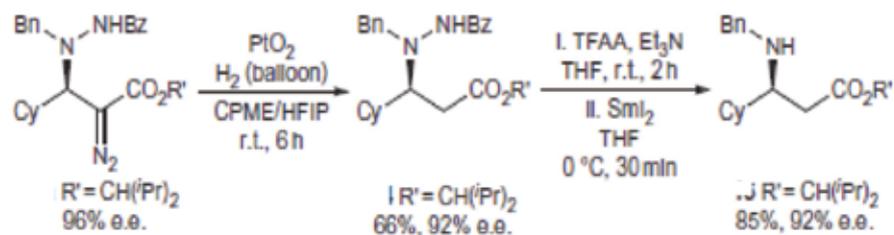
### 5-4 i-Bu<sub>2</sub>AlH(DIBAL-H) Reduction Boehringer-Ingelheim Pharma., *J. Org Chem.* 2008, 73, 1524



Solvents	%conv
DME	12
ETBE	17
2-MeTHF	25
THP	25
IPE	65
MTBE	72
CPME	72

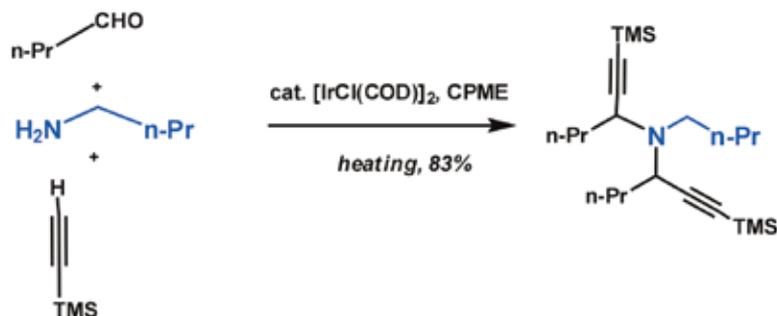
### 5-5 MnO<sub>2</sub> Oxidation Zeon Corporation, Cyclopentyl Methyl Ether (CPME) technical data



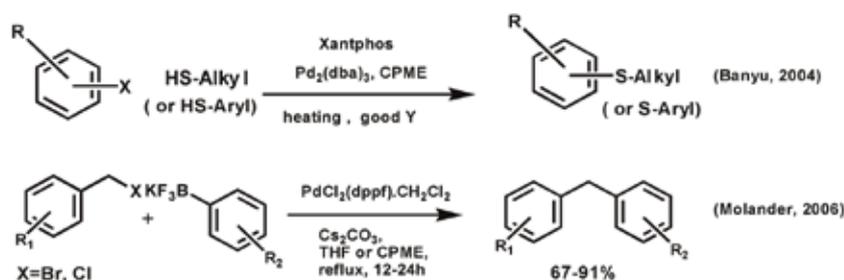


## 6. Reactions with Transition Metal Catalyst

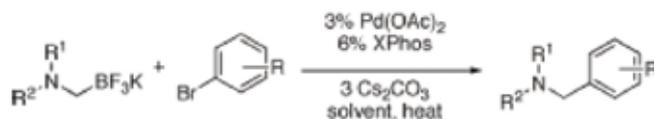
### 6-1 Ir-catalyzed Multi Component Coupling Ishii, *Chem. Commun.*, 2004, 6, 4587



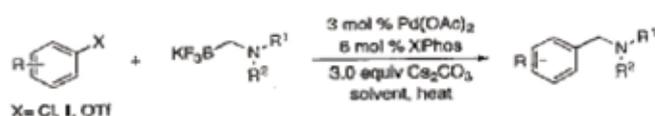
### 6-2 Pd-catalyzed Transformation Mase, *Org. Lett.*, 2004, 6, 458 G.A.Molander, *J. Org. Chem.*, 2006, 71, 9198



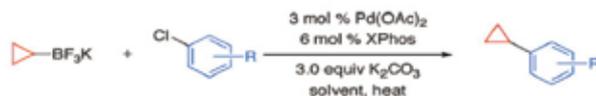
G.A.Molander. *Org. Lett.* 2007, 9, 1597



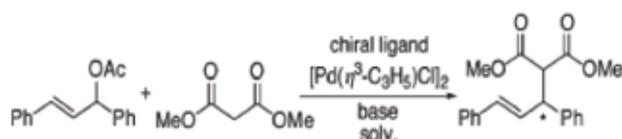
G.A.Molander. *J. Org. Chem.*, 2008, 73, 2052.



G.A.Molander. *J. Org. Chem.*, 2008, 73, 7481



### 6-3 Asymmetric Allyl Coupling Fujita, *J. Org. Chem.* 2004, 69, 6679



Solvents	Y(%)	ee(%)
THF	98	91
CPME	99	90

## 6-4 Buchwald-Hartwig Amination

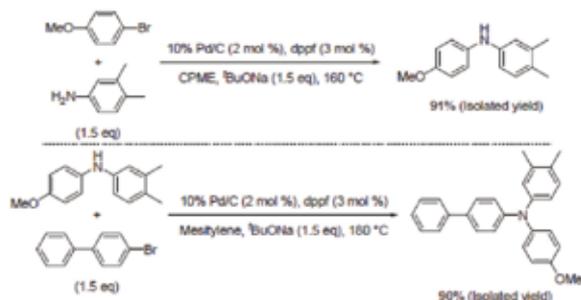
Sajiki, *Gifu Yakkadaigaku Kiyou*, 2006, 55, 45.

Table 7 Pd/C-Catalyzed Aromatic Amination in the Presence of dppe and <sup>t</sup>BuONa

$$\text{Ar-Br} + \text{HN} \begin{matrix} \text{R}_1 \\ \text{R}_2 \end{matrix} \xrightarrow[\text{CPME, } ^t\text{BuONa (2 eq), reflux}]{10\% \text{ Pd/C (4 mol\%), dppe (6 mol\%)}} \text{Ar-N} \begin{matrix} \text{R}_1 \\ \text{R}_2 \end{matrix}$$

Entry	Product	Yield (%) <sup>a</sup>	Entry	product	Yield (%) <sup>a</sup>
1		70%	4		95%
2 <sup>b</sup>		92%	5		95%
3		76%	6		97%

<sup>a</sup> Isolated yield. <sup>b</sup> Ca<sub>2</sub>CO<sub>3</sub> was used as a base.



Scheme 9

Table 8 Reuse of Pd/C

$$\text{C}_6\text{H}_5\text{-Br} + \text{N} \begin{matrix} \text{O} \\ \text{---} \\ \text{O} \end{matrix} \xrightarrow[\text{CPME (2 mL), } ^t\text{BuONa (2 eq), 120 }^\circ\text{C}]{10\% \text{ Pd/C (2 mol\%), dppe (3 mol\%)}} \text{C}_6\text{H}_5\text{-N} \begin{matrix} \text{O} \\ \text{---} \\ \text{O} \end{matrix}$$

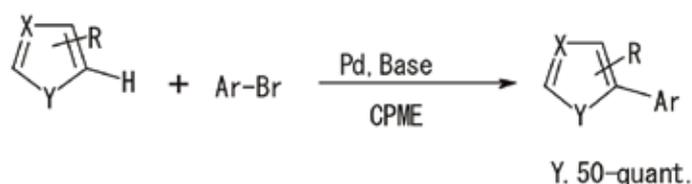
(2 mmol) (3 mmol)

Recycle	10% Pd/C (mg)	Yield (%) <sup>a</sup>
1st	42.6	82
2nd	48.6	89
3rd	48.0	86
4th	43.5	95

<sup>a</sup> Isolated yield.

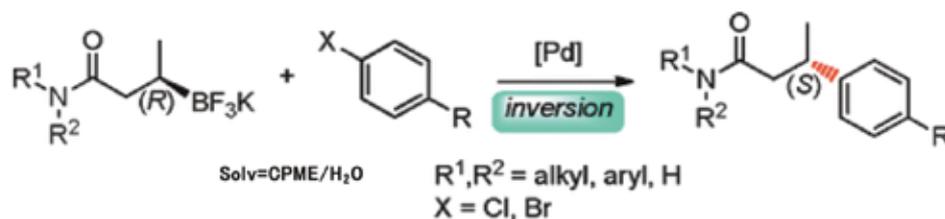
## 6-5 Pd-catalyzed direct C-H arylation

H.Doucet, *Chem Sus Chem*, 2011, 4, 1



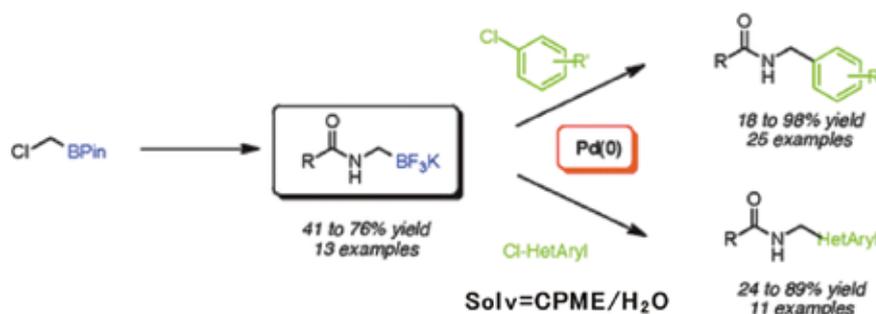
## 6-6 Pd-catalyzed Cross-Coupling

G.A.Molander, *J.ACS*, 2010, 132, 17108



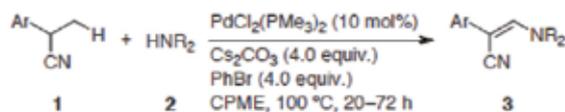
## 6-7 Pd-catalyzed Cross-Coupling

G.A.Molander, *Org. Lett.*, 2010, 12, 4876



## 6-8 Pd-catalyzed oxidative functionalization

Kuwano, The 57th Annual Meeting of organometallic chemistry of Japan, 2010



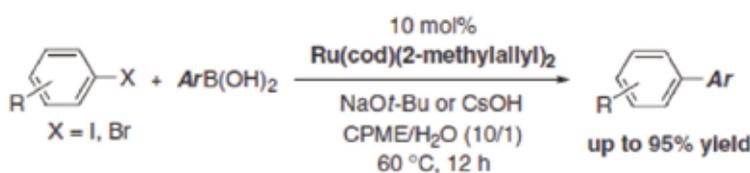
entry	Ar (1)	HNR <sub>2</sub> (2)	3	yield <sup>b</sup>
1	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> (1b)	2a	3b	83%
2	<i>p</i> -MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> (1c)	2a	3c	76%
3	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> (1d)	2a	3d	80%
4	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> (1e)	2a	3e	41%
5	1a	piperidine (2b)	3f	92%
6	1a	pyrrolidine (2c)	3g	50%
7	1a	2d <sup>c</sup>	3h	60%

<sup>a</sup> All reactions were conducted in CPME (2.0 mL). The ratio of **1** (0.4 mmol):2:[PdCl<sub>2</sub>(PMe<sub>3</sub>)<sub>2</sub>]:Cs<sub>2</sub>CO<sub>3</sub>:PhBr was 10:20:1:40:40.

<sup>b</sup> The isolated yield of **3**. <sup>c</sup> 2d = *N*-Boc-piperazine.

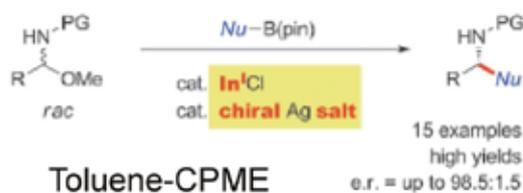
## 6-9 Ru-catalyzed Suzuki-Miyaura Coupling

Itoh, *Chem. Lett.*, 2010, 39, 1050



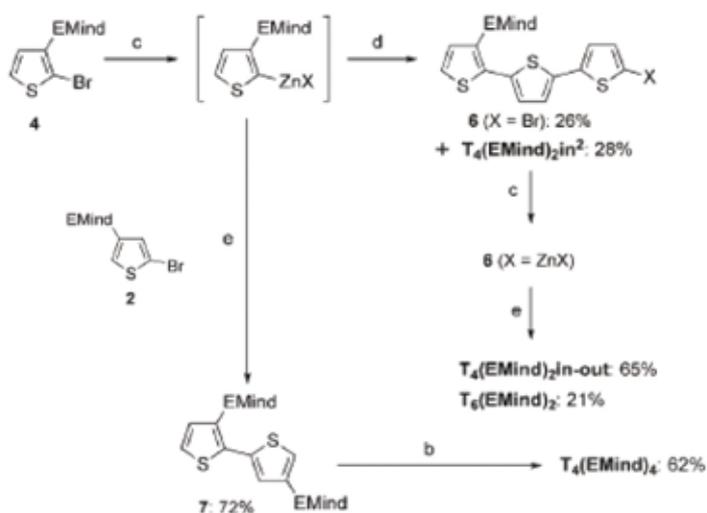
## 6-10 Asymmetric Hosomi-Sakurai Reactions

Kobayashi, *Angew. Chem. Int. Ed.*, 2011, 50, 11121



## 6-11 Pd-catalyzed Negishi Coupling

Tamao, *Chem. Asian J.*, 2011, 6, 350

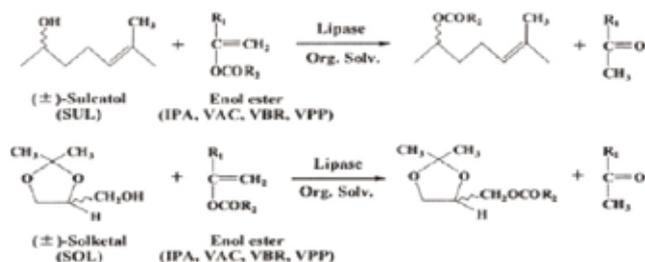


Scheme 3. Synthesis of **5-7** and EMind-oligothiophenes. 1) a) [Pd(PPh<sub>3</sub>)<sub>4</sub>] (2.5 mol%), toluene, reflux, 12 h; b) 1) *n*BuLi/hexane (1.0–1.1 equiv), THF, –80 to –20 °C, 0.5 h, 2) CuCl<sub>2</sub> (1.0–1.2 equiv), THF, –80 °C to RT, 0.5–1.0 h; c) 1) *n*BuLi/hexane (1.1 equiv), THF or CPME, –80 °C, 0.5 h, 2) ZnCl<sub>2</sub>/THF (1.2 equiv), THF or CPME, –80 °C to RT, 0.5 h; d) 5,5'-dibromo-2,2'-bithiophene (0.5 equiv), [Pd(PPh<sub>3</sub>)<sub>4</sub>] (2.5 mol%), THF, reflux, 48 h; e) 2 (1.1–1.5 equiv), [Pd(PPh<sub>3</sub>)<sub>4</sub>] (5 mol%), CPME, reflux, 6–12 h.

# 7. Reaction With Lipase

## 7-1 Selective Acylation

Fukunaga, *Biotechnology Letters*, 2005, 27, 383



Isopropenyl acetate (IPA) R <sub>1</sub> =CH <sub>3</sub> , R <sub>2</sub> =CH <sub>3</sub>	Vinyl butyrate (VBR) R <sub>1</sub> =H, R <sub>2</sub> =(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>
Vinyl acetate (VAC) R <sub>1</sub> =H, R <sub>2</sub> =CH <sub>3</sub>	Vinyl propionate (VPP) R <sub>1</sub> =H, R <sub>2</sub> =CH <sub>2</sub> CH <sub>3</sub>

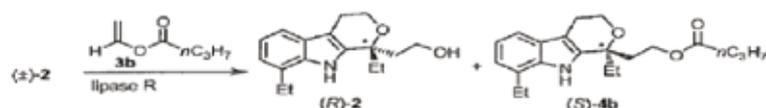
Racemic alcohol	Enol ester	Solvent	Enzyme activity [mmol (h · g lipase) <sup>-1</sup> ]	<i>E</i> value <sup>b</sup>
SUL	VAC	IPE	28	27
SUL	VAC	CPME	19	31
SUL	VPP	IPE	29	26
SUL	VPP	CPME	26	45
SUL	VBR	IPE	39	101
SUL	VBR	CPME	15	∞
SOL	IPA	IPE	5	4
SOL	IPA	CPME	8	3
SOL	VAC	IPE	40	3
SOL	VAC	CPME	197	3
SOL	VPP	IPE	68	6
SOL	VPP	CPME	667	8
SOL	VBR	IPE	173	11
SOL	VBR	CPME	456	13

<sup>a</sup>Reaction conditions: racemic alcohol (2 mmol); enol ester (2 mmol); Me<sub>1,7</sub>βCyD (43 mg)-PCL (10 mg) co-lyophilizate; organic solvent (4 ml).

<sup>b</sup>The enantio-preferred products were (*R*)-acyloxy sulcatol and (*S*)-acyloxy solketal for SUL and SOL, respectively.

## 7-2 Selective Acylation

Akai, *Heterocycles*, 2008, 76, 1537



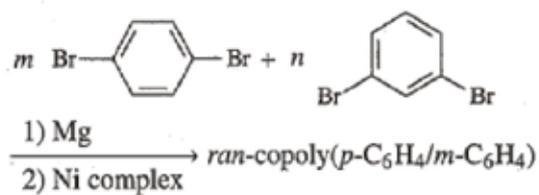
Entry	Solvent <sup>a</sup>	Temp., °C	Time, day	Conv., %	<i>E</i> value	( <i>R</i> )-2, % ee <sup>b</sup>	( <i>S</i> )-4b, % ee <sup>b</sup>
1 <sup>c</sup>	IPE	35	1	52	28	89	81
2	IPE	23	1	26	33	32	92
3	IPE	5	3	9	72	10	97
4	TBME	35	1	44	29	67	87
5	TBME	5	1	23	65	29	96
6	CPME	35	1	31	31	40	91
7	CPME	23	1	12	31	13	93
8	CPME	5	3	23	131	29	98
9	THF	35	7	<5	—	—	—
10	toluene	35	1	26	54	34	95

a) IPE: *i*-Pr<sub>2</sub>O, TBME: *t*-BuOMe, CPME: Cyclopentyl methyl ether. b) The optical purity was determined by HPLC analysis using Daicel CHIRALCEL OD-H. c) Cited from Entry 2 in Table 1.

## 8. Polymerisation

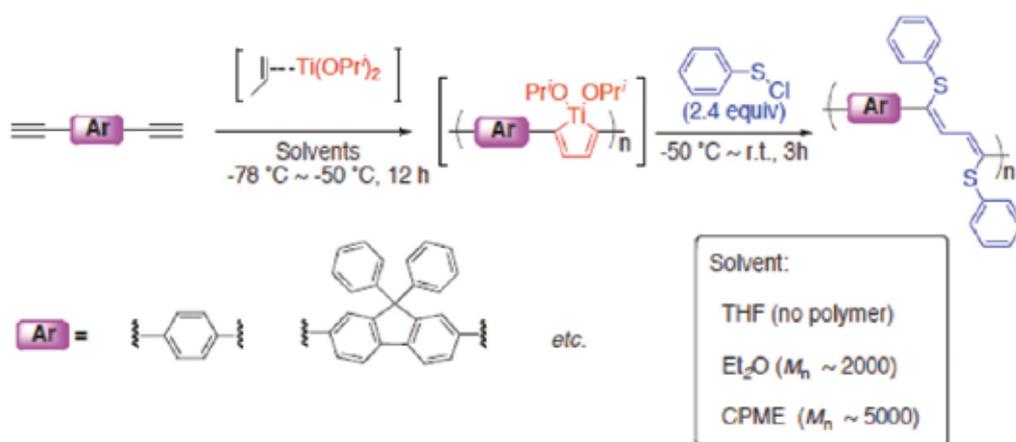
### 8-1 Cross Coupling

Yamamoto, *Polymer Journal*, 2003, 35, 7, 603



### 8-2 $\pi$ -Conjugated polymers

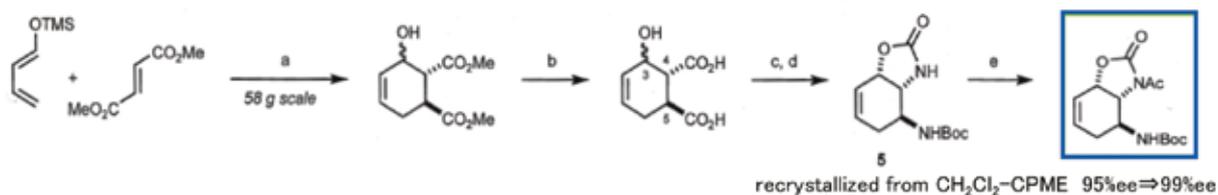
Tomita, ACS National Meeting, 2011



## 9. Extraction/Crystallization

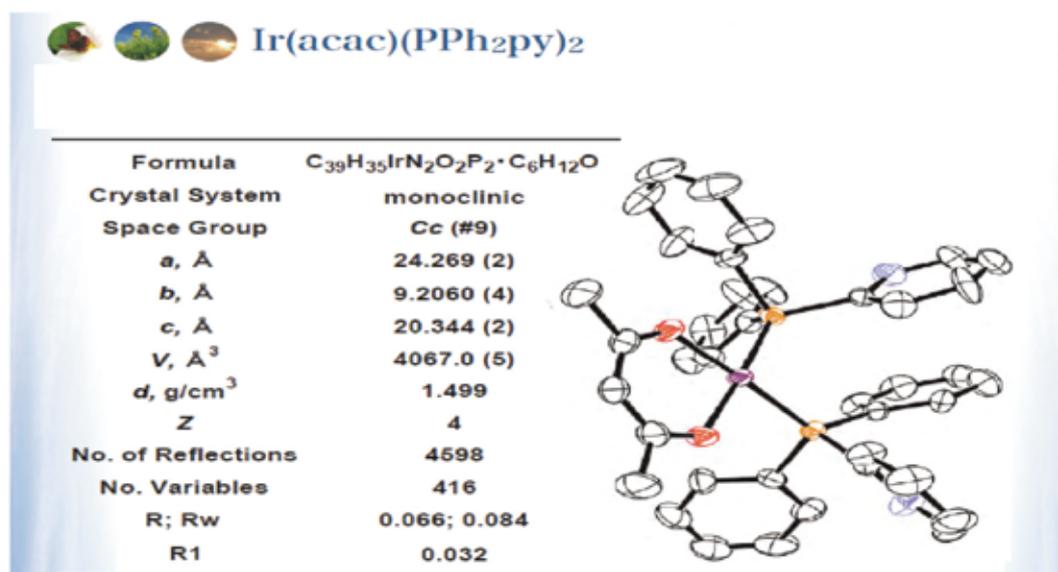
### 9-1 Crystallization

Shibasaki, *Angew. Chem. Int. Ed.*, 2009, 48, 1070



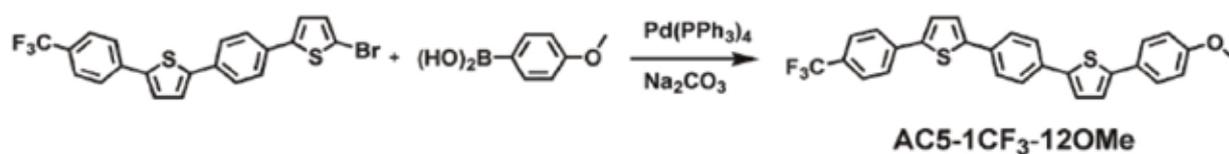
### 9-2 Crystallization

Oshiki, *Syokubai*, 2008, 50, 133



### 9-3 Removal of unreacted raw materials

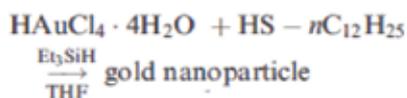
Hotta, *Organic Electronics*, 2011, 12, 8



# 10. Others

## 10-1 Gold-nanoparticle

Mori, *Chem. Commun.*, 2008, 3882



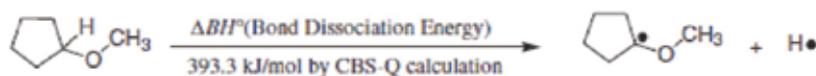
**Table 1** Formation of AuNP with a silane reagent<sup>a</sup>

Entry	Silane	Solvent	Yield/mg	Size/nm
1	Et <sub>3</sub> SiH	THF	15.1	8.6 ± 0.65
2	Et <sub>3</sub> SiH <sup>b</sup>		15.7	8.4 ± 0.64
3	HSiMe(OEt) <sub>2</sub>	THF	8.9	— <sup>c</sup>
4	HMe <sub>2</sub> SiOSiMe <sub>3</sub>		18.0	— <sup>c</sup>
5	(HMe <sub>2</sub> Si) <sub>2</sub> O		— <sup>d</sup>	—
6	(HMeSiO) <sub>n</sub>		— <sup>d</sup>	—
7	Et <sub>3</sub> SiH	<sup>t</sup> Bu <sub>2</sub> O	13.2	9.3 ± 0.91
8		CPME <sup>e</sup>	14.6	8.8 ± 0.58
9		<sup>t</sup> BuOCH <sub>3</sub>	8.9	9.5 ± 0.84
10		Et <sub>2</sub> O	— <sup>f</sup>	—
11		1,4-Dioxane	— <sup>f</sup>	—
12		DME	— <sup>f</sup>	—
13		PhOCH <sub>3</sub>	— <sup>f</sup>	—

<sup>a</sup> Unless noted, the reaction was performed with dodecanethiol (0.1 mmol), HAuCl<sub>4</sub>·4H<sub>2</sub>O (0.1 mmol) and Et<sub>3</sub>SiH (0.1 mmol) with 10 mL of the solvent at 25 °C. <sup>b</sup> 10.0 mmol of Et<sub>3</sub>SiH was employed. <sup>c</sup> Non-spherical nanoparticles ranging in size from 6–60 nm formed. <sup>d</sup> Insoluble precipitate formed. <sup>e</sup> Cyclopentyl methyl ether. <sup>f</sup> Precipitation occurred during the reaction of HAuCl<sub>4</sub> with thiol.

## 10-2 Hard formation of Peroxide

Sakakibara, *Chem. Lett.*, 37,774 (2008)



$$\Delta BH^\circ_{298}(\text{C-H:ether}) = \Delta H^\circ_{298}(\text{ether radical}) - \Delta H^\circ_{298}(\text{parent ether}) + \Delta H^\circ_{298}(\text{H}^\bullet)$$

$\Delta H_f^\circ$ (Heat of Formation), Structure

← MM3 Force Field Evaluation

### 10-3 Toxicological Data

Merck, & Co., INC, *Org. Process Res. Dev.*, 2011, 15, 939

Solvents	m g / d a y	
	P D E	L i m i t C o n c
M e C N	4 . 1	4 1 0
D M A c	1 0 . 8	1 0 9 0
D M F	8 . 8	8 8 0
d i o x a n e	3 . 8	3 8 0
1 , 2 - D M E	1	1 0 0
E t h y l e n e g l y c o l	6 . 2	6 2 0
T o l u e n e	8 . 9	8 9 0
T H F	7 . 2	7 2 0
M e T H F	6 . 2	
C P M E	7 . 4	

### 10-4 Solvent selection guide

Glaxo Smith Kline plc., *Green. Chem.* 2011, 13, 854

Solvent	Cas number	Melting point °C	Boiling Point °C	Waste recycling, incineration, VOC, and biotreatment issues	Environmental Impact fate and effects on the environment	Health acute and chronic effects on human health and exposure potential	Flammability & Explosion storage and handling	Reactivity/ Stability factors affecting the stability of the solvent	Life Cycle Score Environmental Impacts to produce the solvent
t-Amyl methyl ether	994-05-8	-80	86	5	5	5	5	9	8
t-Butylmethyl ether	1634-04-4	-109	55	4	5	5	3	9	8
<b>CPME</b>	<b>5614-37-9</b>	<b>-140</b>	<b>106</b>	<b>6</b>	<b>4</b>	<b>4</b>	<b>5</b>	<b>8</b>	<b>4</b>
t-Butyl ethyl ether	637-92-3	-74	70	5	5	4	4	9	8
<b>2-MeTHF</b>	<b>96-47-9</b>	<b>-137</b>	<b>78</b>	<b>4</b>	<b>5</b>	<b>4</b>	<b>3</b>	<b>6</b>	<b>4</b>
Diethyl ether	60-29-7	-116	35	4	4	5	2	4	6
Bis(2-methoxyethyl)	111-96-6	-68	162	4	5	2	8	4	6
Dimethyl ether	115-10-6	-141	-25	3	5	7	1	4	7
1,4-Dioxane	123-91-1	12	102	3	4	4	4	5	6
Tetrahydrofuran	109-99-9	-108	65	3	5	6	3	4	4
1,2-Dimethoxyethane	110-71-4	-58	85	4	5	2	4	4	7
Diisopropyl ether	108-20-3	-86	68	4	3	8	1	1	9

Major issues
Few issues

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