

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

Ver. 2.0

The information contained herein is believed to be reliable, but no representations, guarantees or warranties of any kind are made as to its accuracy, suitability for particular applications or results to be obtained.

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This product was developed for the application in this brochure. In case of other applications, please handle under your confirmation of safety for the applications, or please talk to Zeon Corporation beforehand.

# **ZEON CORPORATION**

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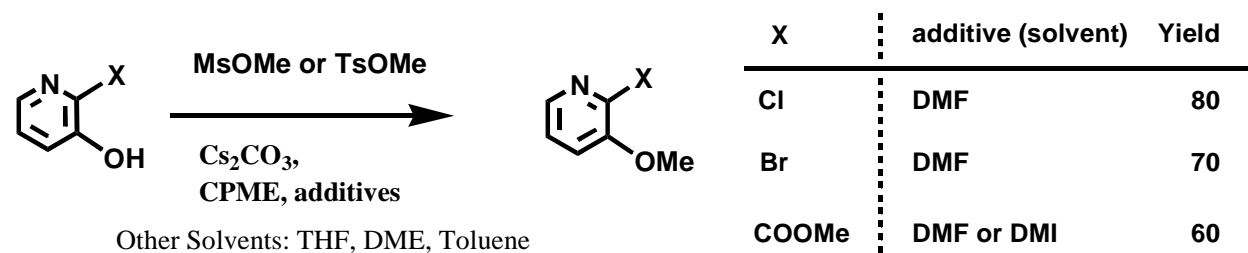
### Papers utilizing CPME

Applications	~2011.1
	Papers
A. Alkylation, Silylation	14
B. Lewis acid	12
C. Bronsted acid	5
D. Basic or Organometals	29
E. Oxidation/Reduction	9
F. Transition metal	13
G. Lipase	2
H. Microreactor	1
I. Polymerisation	2
J. Extraction/Crystallization	3
K. Others	4
<b>Total</b>	<b>94</b>

# A) Alkylation, Silylation

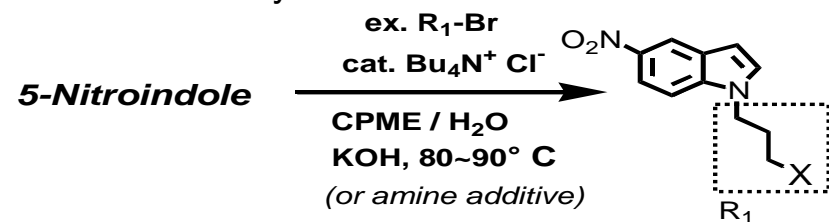
A-1 O-Methylation of Pyridinol

Torisawa, *Fain Kemikaru*. 2006, 35, 53



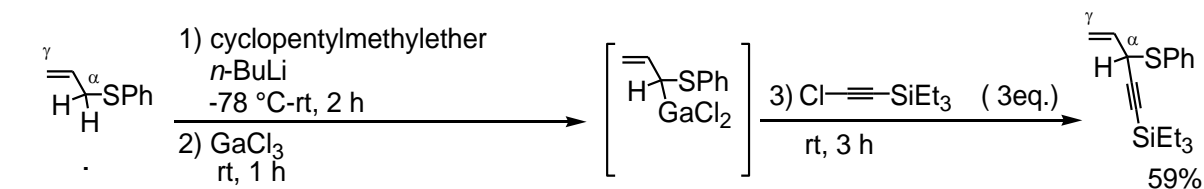
A-2 N-Alkylation under PTC

ibid.



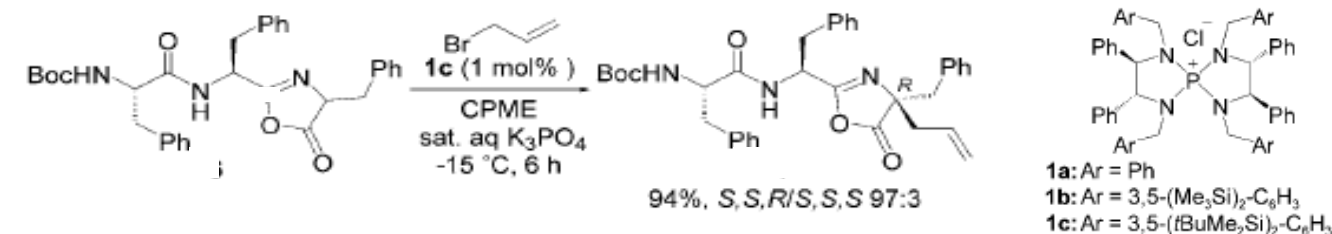
A-3 Regioselective Ethynylation

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

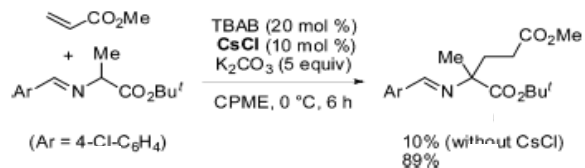


A-4 Asymmetric alkylation

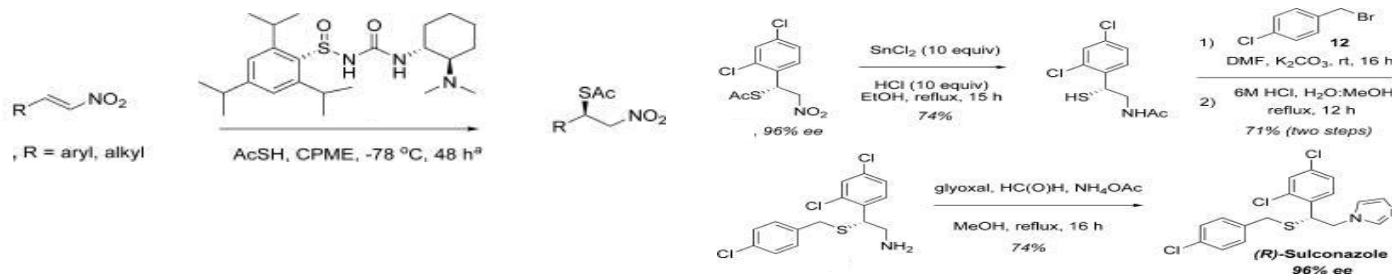
Ooi, *Angew Chem.int.Ed.*, 2008, 47, 1



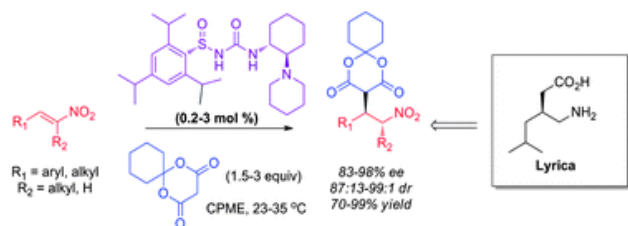
## A-5 Asymmetric conjugate addition

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

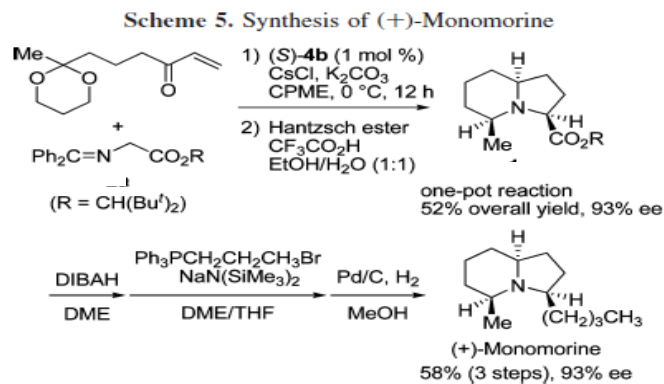
## A-6 Asymmetric conjugate addition

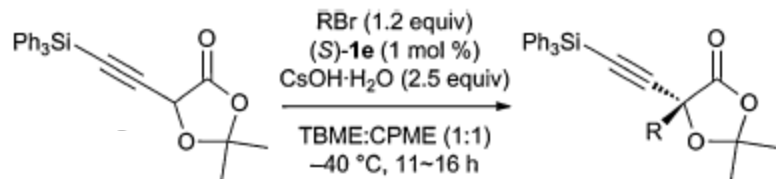
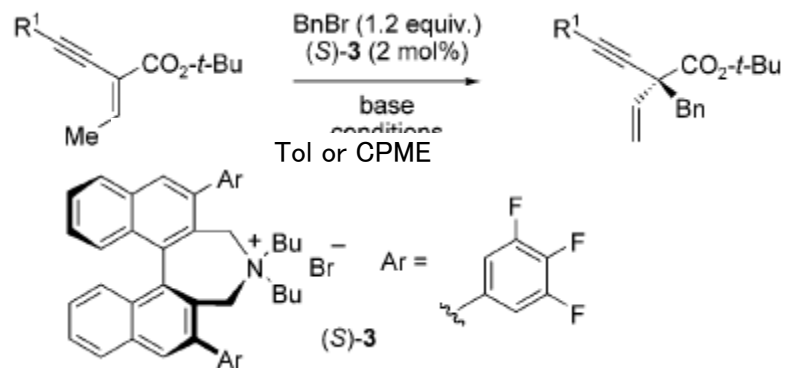
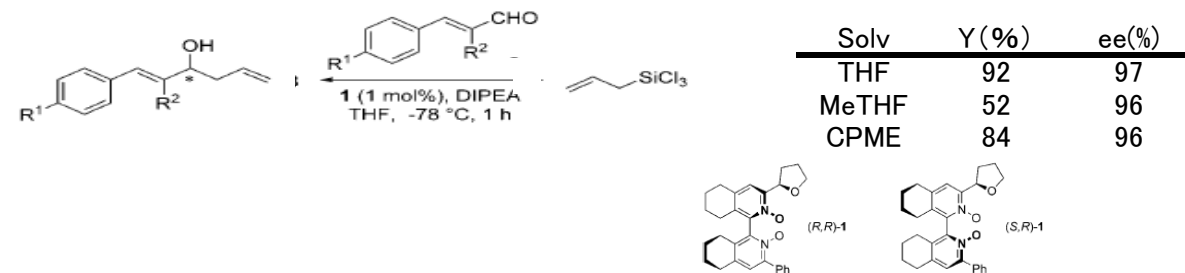
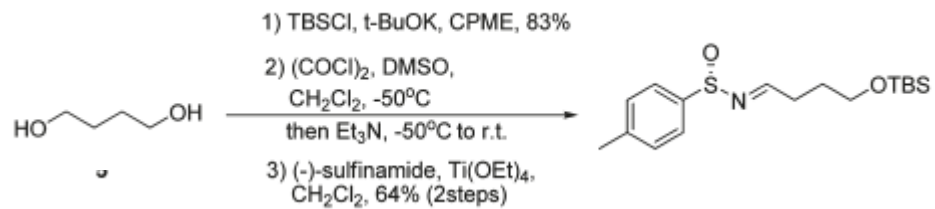
J.A.Ellman, *JACS.* **2009**, *131*, 8754

## A-7 Asymmetric conjugate addition

J.A.Ellman, *Chem. Sci.*, **2012**, *3*, 121

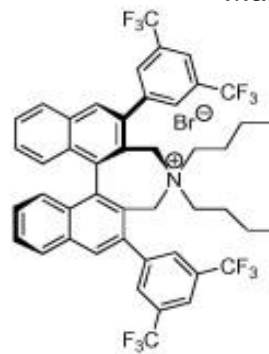
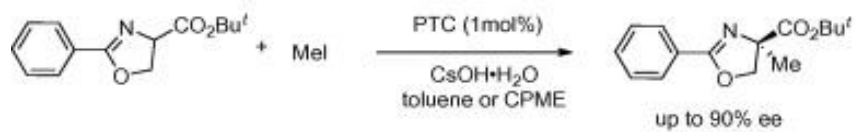
## A-8 Enantioselective one-pot synthesis

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



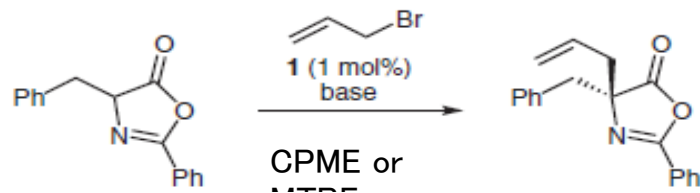
A-13 Methylation

Maruoka, *Tetrahedron Lett.* 2008, 49, 5461



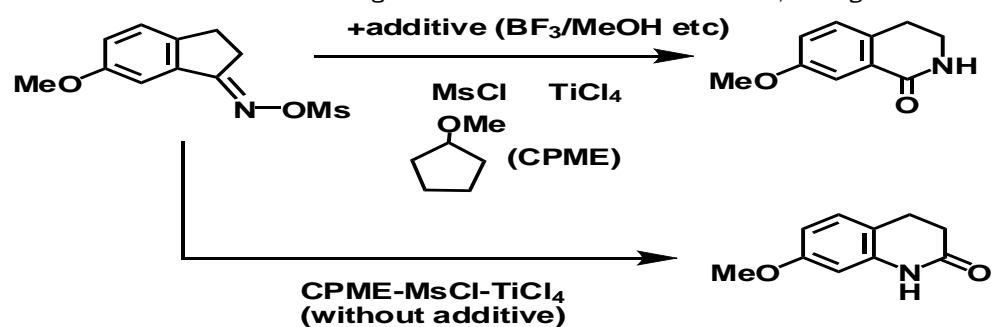
A-14 Allylation

Ooi, *Synlett* 2009, 4, 658

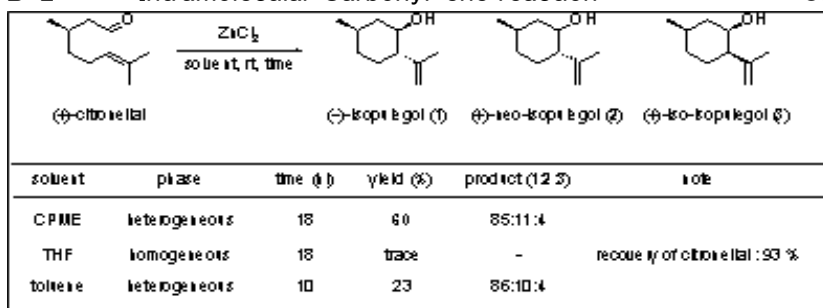


## B) Reactions under Lewis Acid Conditions

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

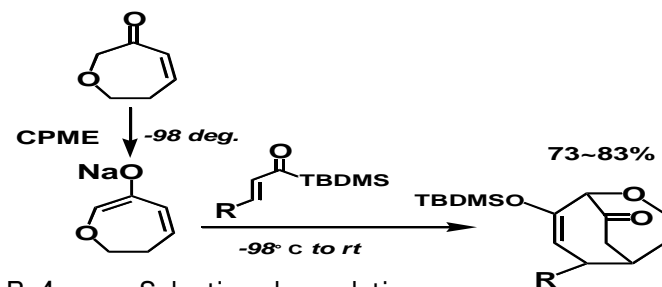


B-2 Intramolecular Carbonyl-ene reaction Onaka, unpublished



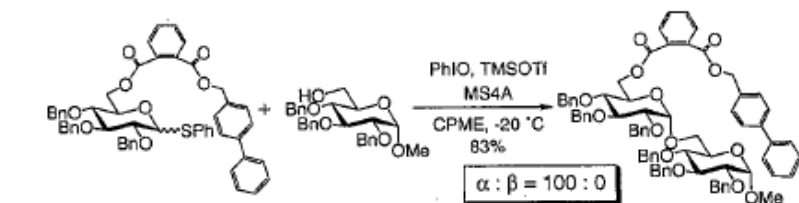
B-3 [3 + 4] Annulation Reaction

Takeda., *Org. Lett.*, **2004**, *6*, 2277.



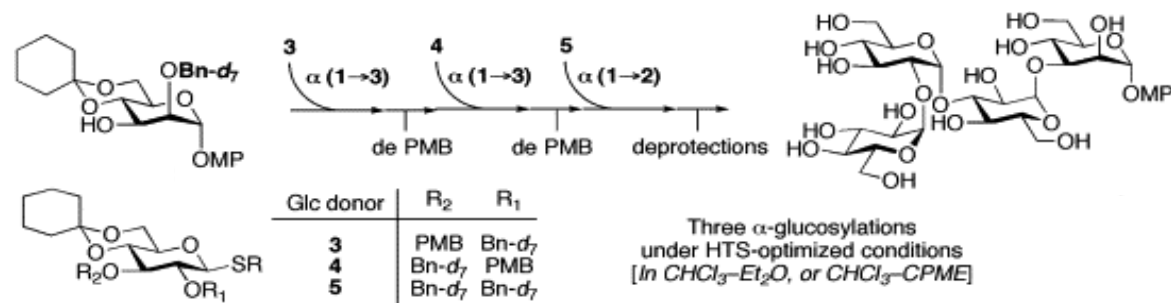
B-4 Selective glycosylation

Fukase, *Tetrahedron: Asymmetry.* **2005**, *16*, 441.



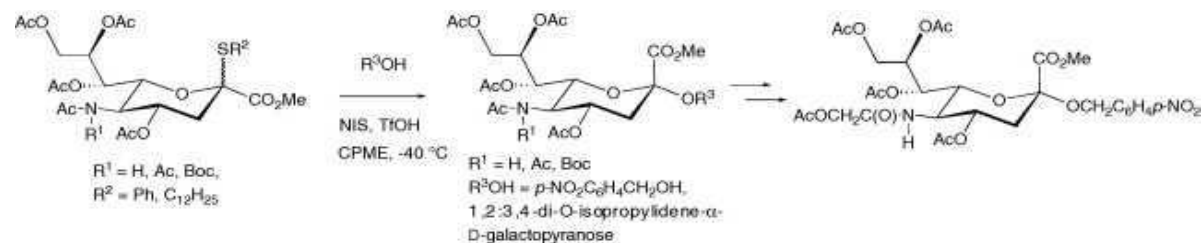
B-5 Selective glycosylation

Itoh, *Tetrahedron*, 2008, 64, 92.



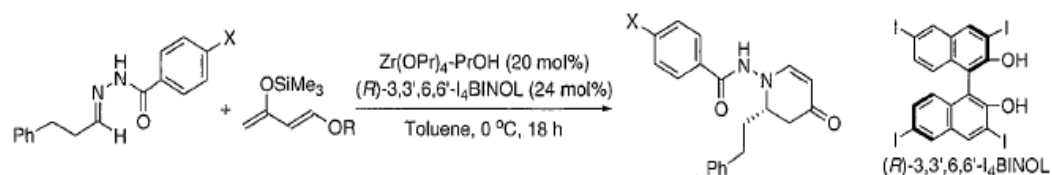
B-6 Selective glycosylation

Ikeda, *Tetrahedron Lett.*, 2007, 48, 7431.



B-7 Hetero Diels-Alder Reaction

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



1a: X=H            2a: R=Me  
1b: X=CF<sub>3</sub>        2b: R=<sup>t</sup>Bu

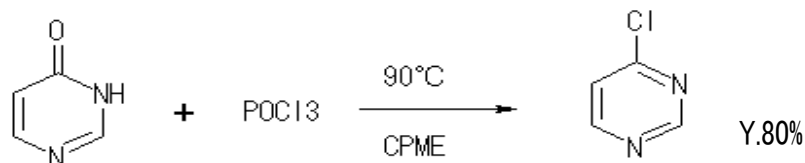
Entry	Solvent	Yield (%)	ee (%)
1	Toluene	35	93
2	Toluene/CH <sub>2</sub> Cl <sub>2</sub> (2/1)	10	85
3	Toluene/ <sup>t</sup> BuOMe (2/1)	39	92
4	<sup>t</sup> BuOMe	57	92
5	CPME <sup>b</sup>	56	93
6	<sup>t</sup> Pr <sub>2</sub> O	16	81
7	Et <sub>2</sub> O	28	88
8	<sup>t</sup> BuOMe/CH <sub>3</sub> CN (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%).

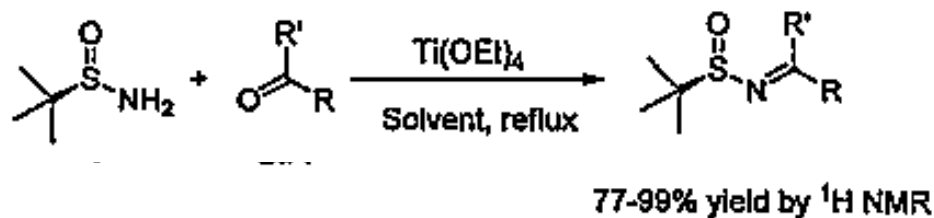
<sup>b</sup> Cyclopentyl methyl ether.

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

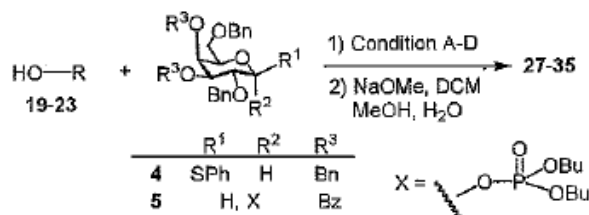
B-8 Chlorination Company-1



B-9 Sulfinyl ketimine J.A.Ellman, *J.Org.Chem*, 2010, 75, 6283

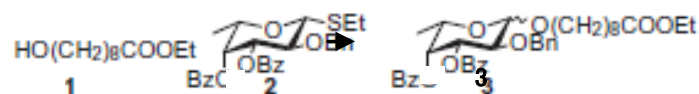


B-10 Selective glycosylation Komba, *J.Appl.Glycosci.*, 2011, 58, 1



Entry	Acceptor	Donor	Condition <sup>1</sup>	Product	mono:di:tri <sup>2</sup>	Yield <sup>3</sup>
1	19	4	A	27 ( $\alpha$ only)	17:14:69	18% (12 steps)
2	20	4	A	28		
3	20	5	B	29 ( $\alpha$ 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 ( $\alpha$ only)	37:46:17	9% (20 steps)
8	22	4	A	32		
9	22	5	B	33 ( $\alpha$ only)	45:11:44	18% (15 steps)
10	23	4	A	34		
11	23	5	B	35 ( $\alpha$ only)	46:40:14	7% (18 steps)

<sup>1</sup>Coupling conditions; A: 6.0 equiv. 4, 18.0 equiv. NIS, 18.0 equiv. TiOH, 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.

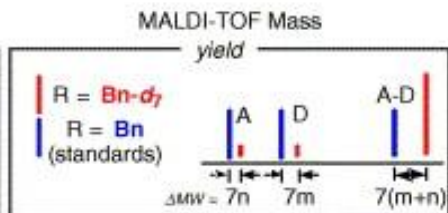
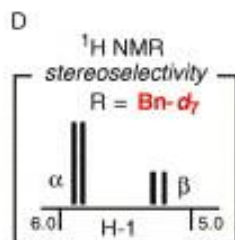
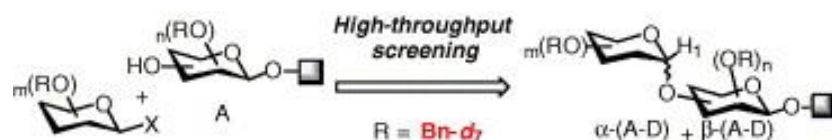


Entry	Solvent	Temp (°C)	Yield <sup>b</sup> (%)		% de <sup>c</sup>
			3 $\alpha$	3 $\beta$	
1	PhCH <sub>3</sub>	-40	41	50	10
2	Et <sub>2</sub> O	-60	50	44	6
3	Et <sub>2</sub> O	-40	66	29	39
4	Et <sub>2</sub> O	-10	78	15	68
5	Et <sub>2</sub> O	0	72	20	57
6	Et <sub>2</sub> O	rt	73	19	59
7	PME	0	80	19	62
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.

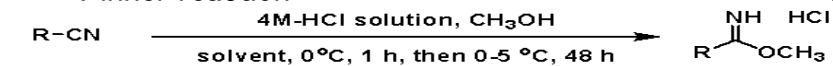
<sup>c</sup> Diastereomeric excess (% de) = [ratio of  $\alpha$  anomer (%)] - [ratio of  $\beta$  anomer (%)].

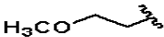
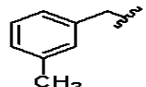



### C) Reactions under Bronsted acid Conditions

#### C-1 Pinner reaction

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



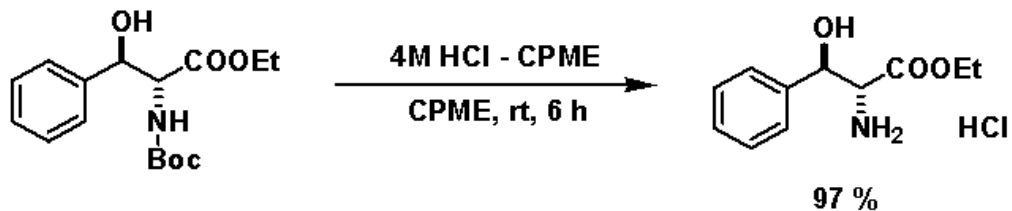
R	solution	solvent	Yield (%)
	1,4-Dioxane	Et <sub>2</sub> O	86 <sup>a)</sup>
	CPME	CPME	90 <sup>b)</sup>
	CPME	CPME	89 <sup>b)</sup>
	CPME	CPME	91 <sup>b)</sup>

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

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

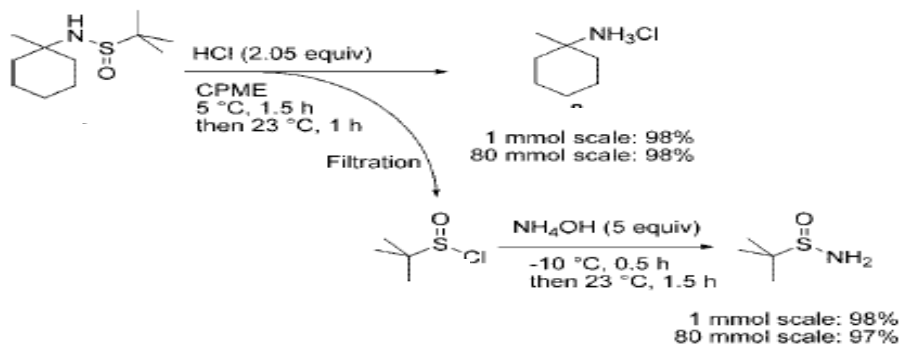
#### C-2 Deprotection of Boc-group

ibid



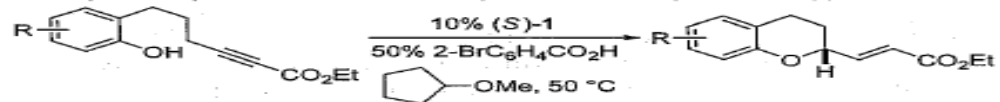
#### C-3 Amination

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



C-4

## Asymmetric Cyclization

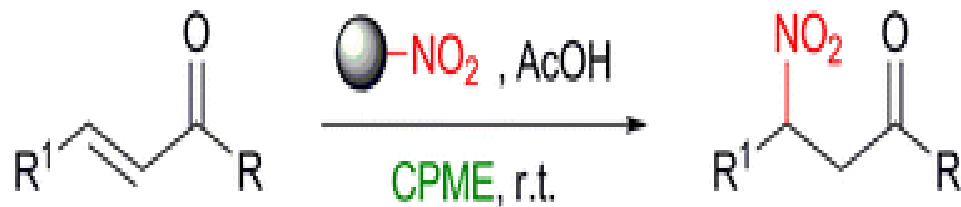
G.C.Fu, *Angew Chem.int.Ed.*, 2009, 48, 2225.**Table 3:** Catalytic enantioselective synthesis of dihydrobenzopyrans.

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.

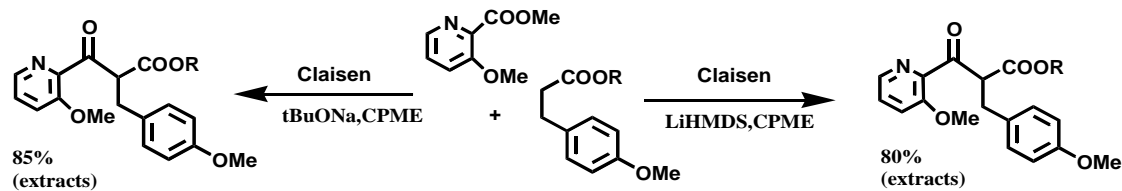
C-5

## Conjugate addition

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

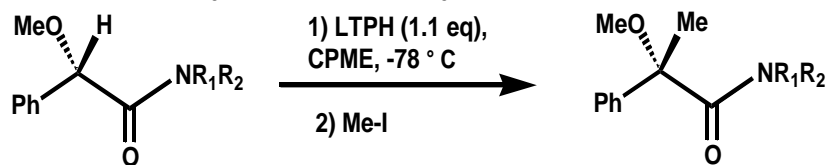
## D) Reaction with Basic or Organometals

D-1 Claisen-Schmidt Condensation Torisawa, Summer Symposium of the Japanese Society for Process Chemistry (2005)



Other Bases: NaH, KHMDS  
Other Solvents: THF, DME, Toluene, EtOH

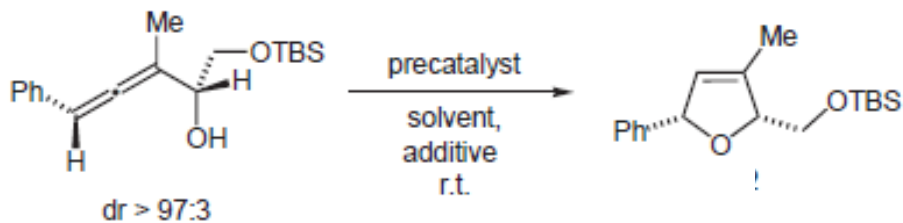
D-2 Chirality Transfer Methylation



Kawabata, *Chem. Commun.* **2003**, 162

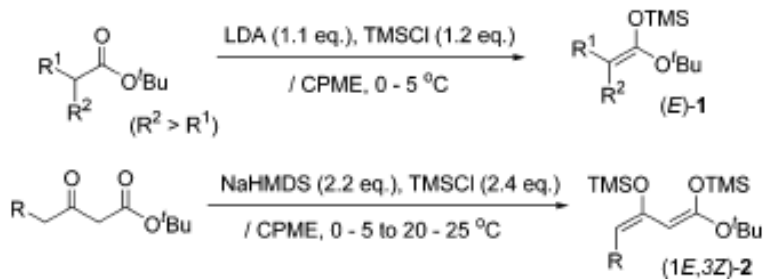
D-3 Chirality Transfer cyclization

Krause, *SYNLETT* **2007**, 1970

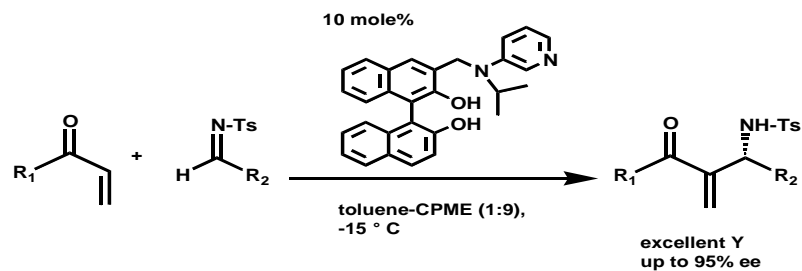


D-4 Selective KSA Formation

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

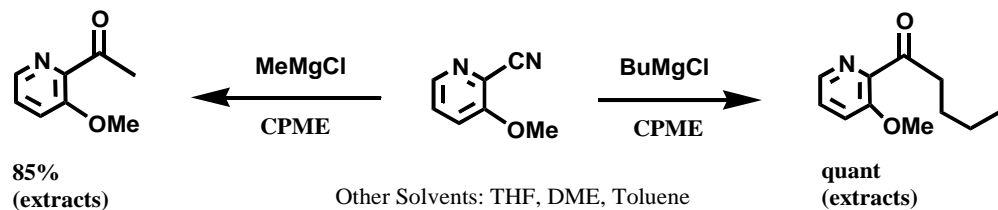


D-5 Symmetric aza-Morita-Baylis-Hillman Reaction



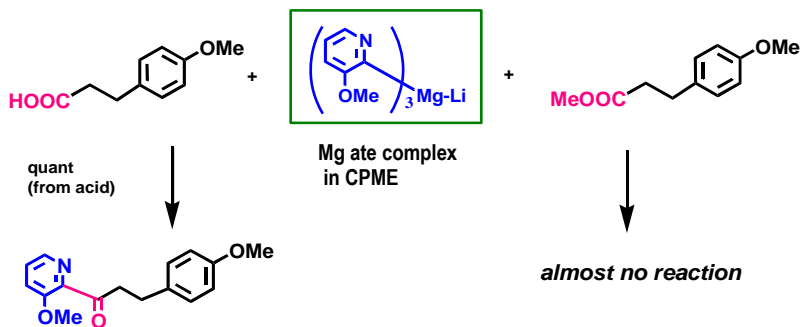
Sasai, *Tetrahedron: Asymmetry*, **2006**, *17*, 578  
idem. *JACS.*, **2005**, *127*, 3680.

D-6 Grignard Addition Reactions



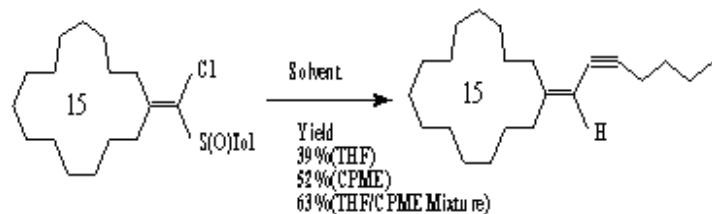
Torisawa, Summer Symposium of the Japanese Society for Process Chemistry (2005)

D-7 New Grignard Addition reactions

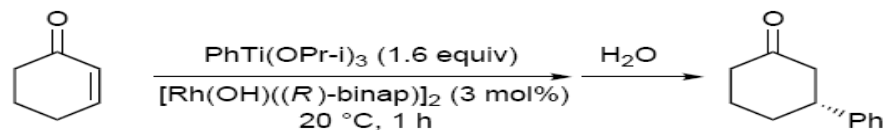


Torisawa, Summer Symposium of the Japanese Society for Process Chemistry (2005)

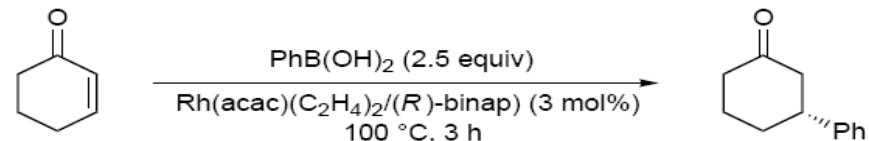
D-8 Vinylic addition via carbenoids



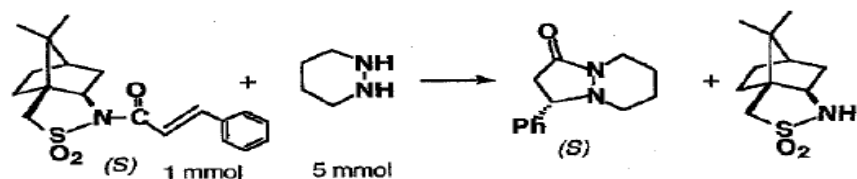
Sato, *Tetrahedron*, **2005**, *61*, 4409.



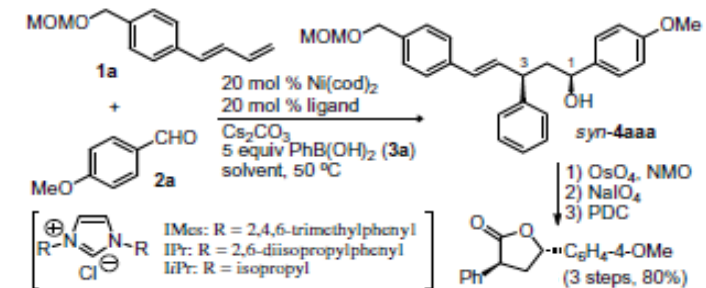
$\text{Et}_2\text{O}$	84% yield	99% ee
THF	85%	98% ee
$\text{CH}_2\text{Cl}_2$	82%	99% ee
<b>CPME</b>	85%	99% ee



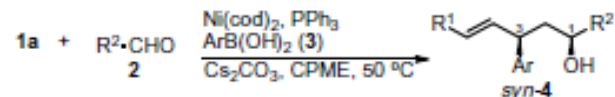
dioxane/ $\text{H}_2\text{O}$ (10/1)	93% yield	97% ee
<b>CPME</b> / $\text{H}_2\text{O}$ (10/1)	80%	98% ee



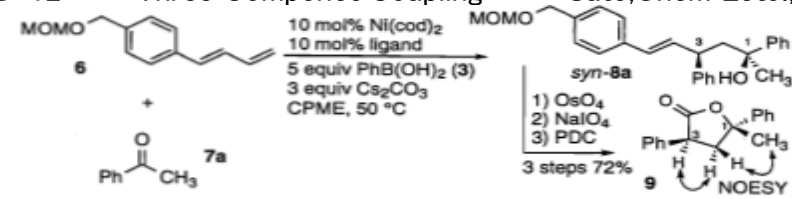
n-BuLi なし	THF, -78°C	収率 80% (44% e.e.)
n-BuLi 3 mmol	THF, 0°C	79% (57% e.e.)
n-BuLi 3 mmol	toluene, 0°C	90% (69% e.e.)
n-BuLi 3 mmol	hexane, 0°C	75% (59% e.e.)
n-BuLi 5 mmol	$\text{C}_6\text{H}_5\text{-O-CH}_3$ , 0°C	85% (74% e.e.)

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

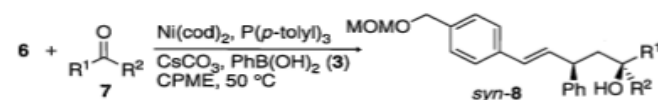
Run	Ligand	Solvent	Cs <sub>2</sub> CO <sub>3</sub> (mol %)	Time (h)	Yield (% <i>syn:anti</i> )
1	IMes HCl	THF	40	60	43 (6:1)
2	IMes HCl	CPME	40	60	40 (>50:1)
3	IMes HCl	CPME	300	36	62 (>50:1)
4	IPr HCl	CPME	300	27	27 (3:1)
5	iPr HCl	CPME	300	17	50 (>50:1)
6	PPh <sub>3</sub>	CPME	300	15	75 (>50:1)
7 <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 %), PPh<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 ( <b>2</b> ) (R <sup>2</sup> =)	Ar-B(OH) <sub>2</sub> ( <b>3</b> ) (Ar=)	yield of <i>syn-4</i> <sup>b</sup> (reaction time)
1	<b>2a</b> : 4-MeOC <sub>6</sub> H <sub>4</sub>	<b>3b</b> : 4-MeOC <sub>6</sub> H <sub>4</sub>	<b>4aab</b> : quant (8 h)
2	<b>2b</b> : Ph	<b>3a</b>	<b>4aba</b> : 80% (10 h)
3 <sup>c</sup>	<b>2c</b> : 4-MeC <sub>6</sub> H <sub>4</sub>	<b>3a</b>	<b>4aca</b> : 72% (12 h)
4	<b>2d</b> : 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	<b>3a</b>	<b>4ada</b> : 33% (12 h)
5	<b>2d</b>	<b>3b</b>	<b>4adb</b> : 57% (17 h)
6	<b>2e</b> : 2-Naphthyl	<b>3a</b>	<b>4aea</b> : 82% (13 h)
7	<b>2f</b> : 2-Furyl	<b>3a</b>	<b>4afa</b> : 65% (16 h)
8 <sup>c</sup>	<b>2g</b> : Me <sub>2</sub> CHCH <sub>2</sub>	<b>3a</b>	<b>4aga</b> : 63% (1 h)
9 <sup>c</sup>	<b>2h</b> : Me <sub>2</sub> CH	<b>3a</b>	<b>4aha</b> : 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> (**3** 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 to 1.<sup>c</sup> Catalyst loading: Ni(cod)<sub>2</sub> (20 mol %), PPh<sub>3</sub> (20 mol %).D-12 Three Component Coupling Sato, *Chem Lett.*, 2009, 38, 594.

Run	Ligand	Time/h	Yield of <i>syn-8a</i> /%
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

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

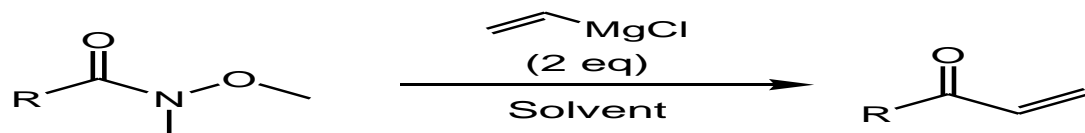
<sup>a</sup>Reaction conditions: diene **6** (1 equiv), ketone **7** (2 equiv), Ni(cod)<sub>2</sub> (10 mol %), P(*p*-tolyl)<sub>3</sub> (10 mol %), PhB(OH)<sub>2</sub> (**3** equiv), Cs<sub>2</sub>CO<sub>3</sub> (3 equiv), CPME, 50 °C. <sup>b</sup>The ratio of *syn* isomer to *anti* isomer was >50 to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

Entry	Ar	1	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>5</sub> H <sub>3</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>5</sub> H <sub>9</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>5</sub> H <sub>9</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>5</sub> H <sub>9</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>5</sub> H <sub>9</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>5</sub> H <sub>9</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>5</sub> H <sub>9</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>5</sub> H <sub>9</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>5</sub> H <sub>9</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>5</sub> H <sub>9</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>5</sub> H <sub>9</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.

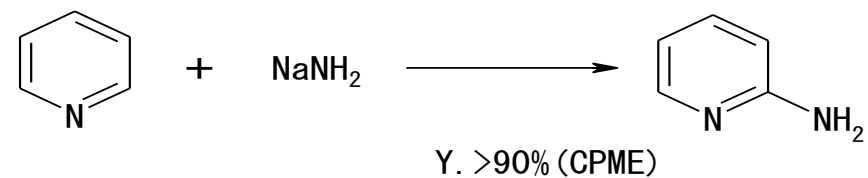
## D-14 Grignard Reaction

Company-2



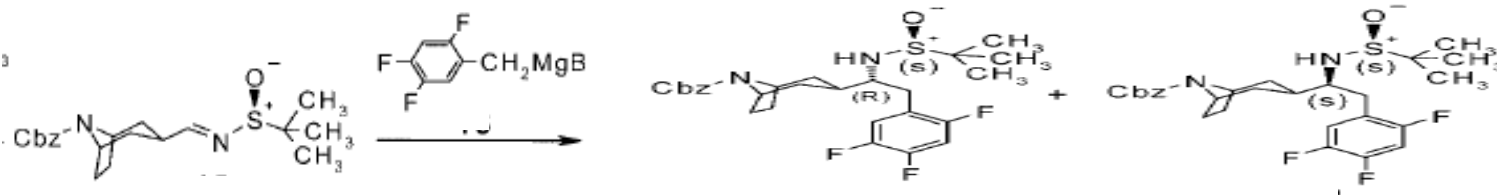
Solvent	Yield (%)
THF	64
CPME	82

D-15 Chichibabian Reaction Company-3

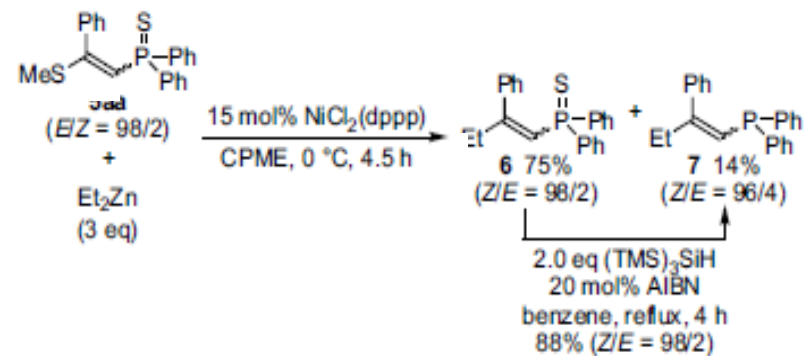


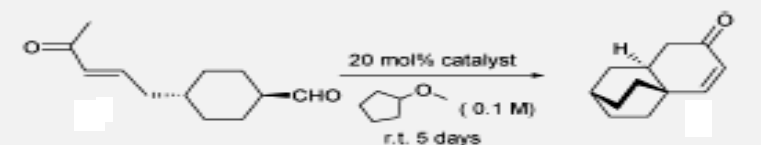
D-16 Grignard Addition

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



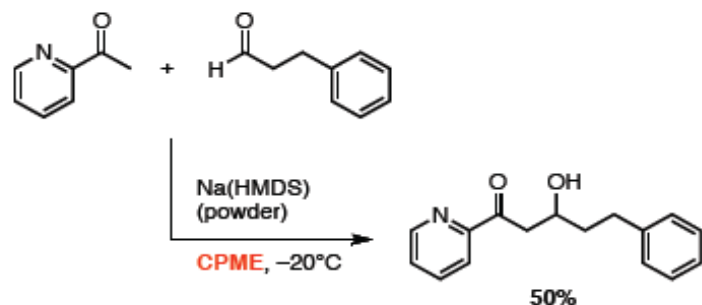
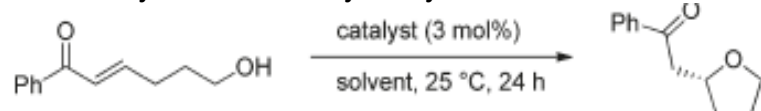
D-17 Cross-coupling with diethylzinc Ohshima, *Tetrahedron*, 2009, 65, 1553.



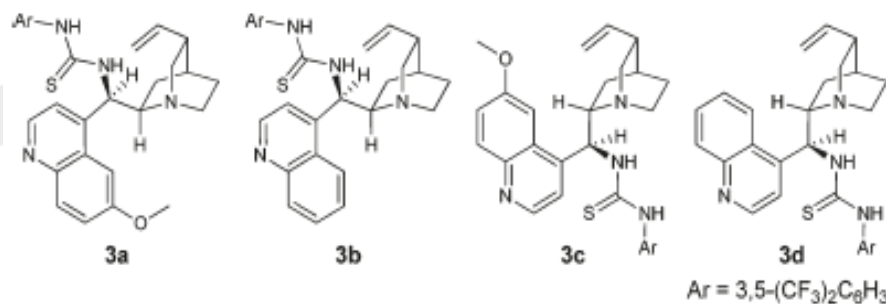
**Table 1** Amino acid salt catalyzed intramolecular Robinson annulation

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

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by HPLC on OJ-H 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.

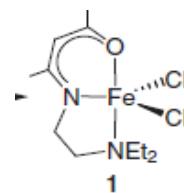
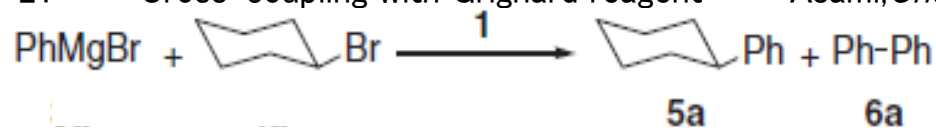
D-20 Asymmetric Catalytic Cycloetherification Matsubara, *JACS*, 2011,

entry	catalyst	solvent	yield (%) <sup>b</sup>	ee (%)
1	3a	$\text{CH}_2\text{Cl}_2$	99	92
2	3a	benzene	97	94
3	3a	THF	73	90
4	3a	$\text{Et}_2\text{O}$	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

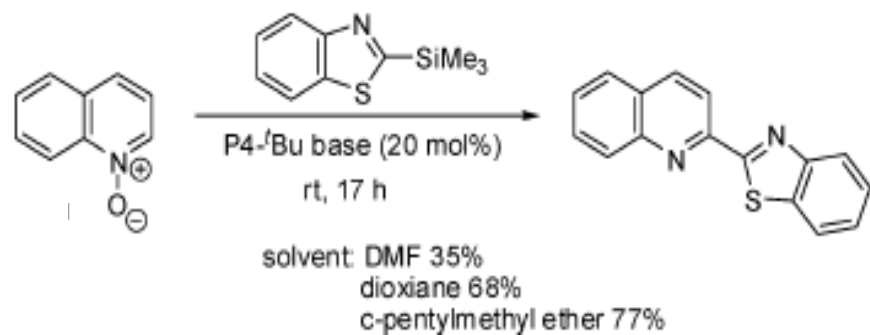
D-21 Cross-coupling with Grignard reagent Asami, *Chem.Lett.* 2011, 40, 983



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

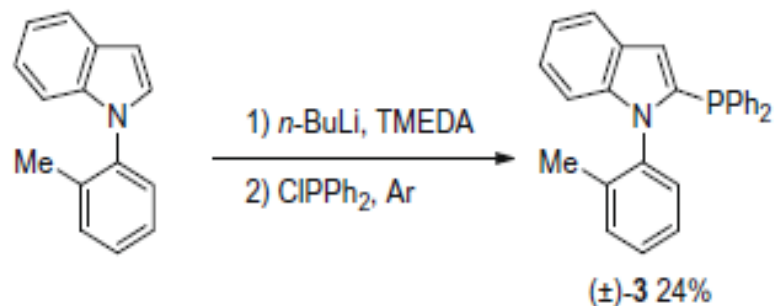
D-22 Functionalisation of heteroaromatic N-oxides

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



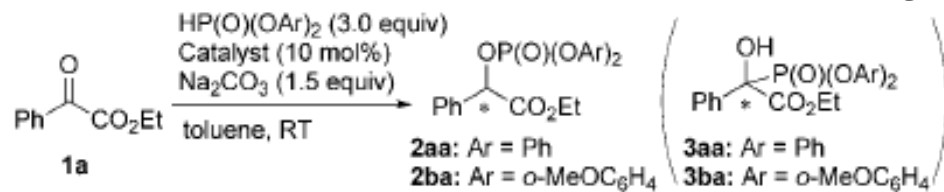
D-23 Phosphinylation

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



D-24

Enantioselective Protonation

Shibata, *Angew.Chem.Int.Ed.*, 2011, 50, 2249

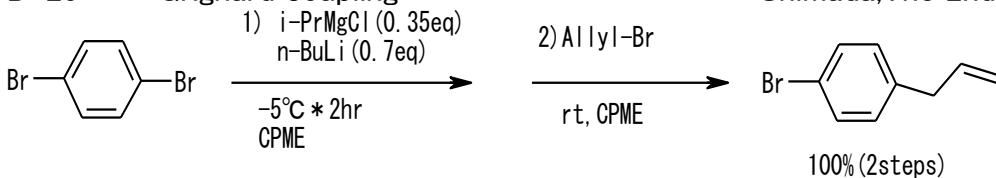
Entry	Catalyst (mol %)	Ar	Yield of <b>2</b> [%]	<i>ee</i> [%] <sup>[a]</sup>
1 <sup>[b]</sup>	quinine (10)	Ph	17 <sup>[c]</sup>	58 ( <i>S</i> )
2	quinine (10)	Ph	99	46 ( <i>S</i> )
3	quinidine (10)	Ph	91	63 ( <i>R</i> )
4	cinchonine (10)	Ph	98	22 ( <i>R</i> )
5	cinchonidine (10)	Ph	88	19 ( <i>S</i> )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

Toluene-CPME

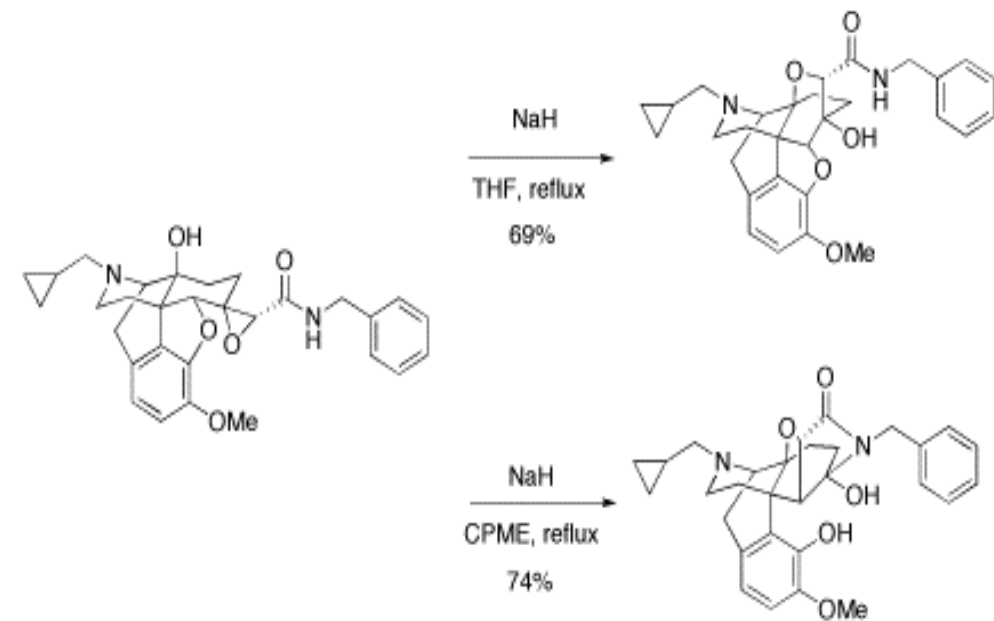
[a] The absolute configuration of **2** is given in parentheses. [b] Reaction carried out without using Na<sub>2</sub>CO<sub>3</sub>. [c] **3aa** (46 %) was obtained. [d] Phosphite (1.3 equiv) and Na<sub>2</sub>CO<sub>3</sub> (0.2 equiv) was used. [e] Cyclo-nentyl methyl ether was used as a solvent.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

D-25

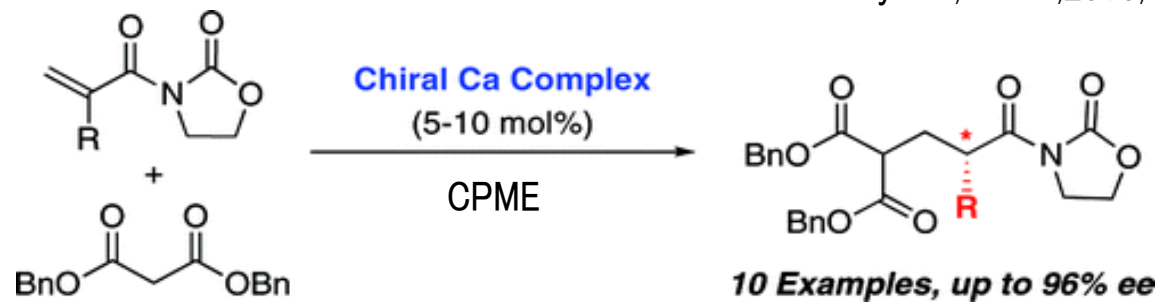
Grignard coupling

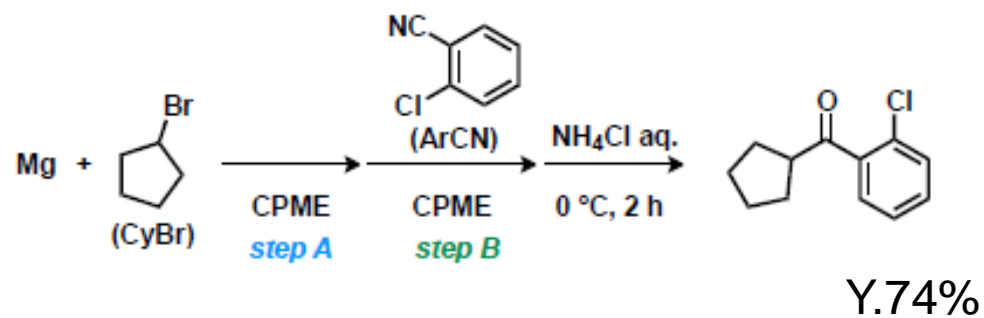
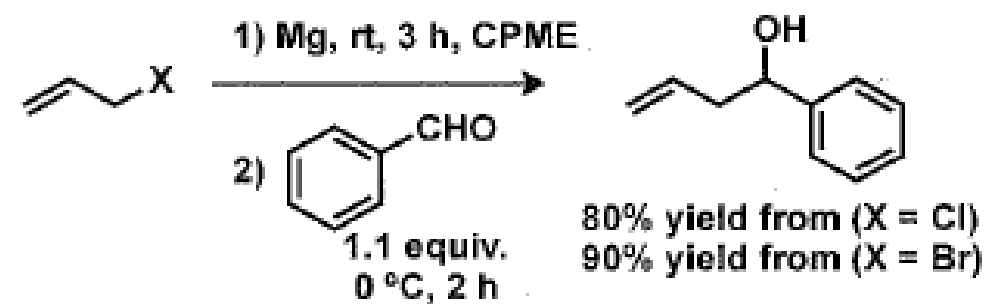
Shimada, *The 2nd International Symposium on Process Chemistry* (2011)

## D-26 Rearrangement

Nagase, *Tetrahedron*, 2011, 67, 6682

## D-27 Protonation

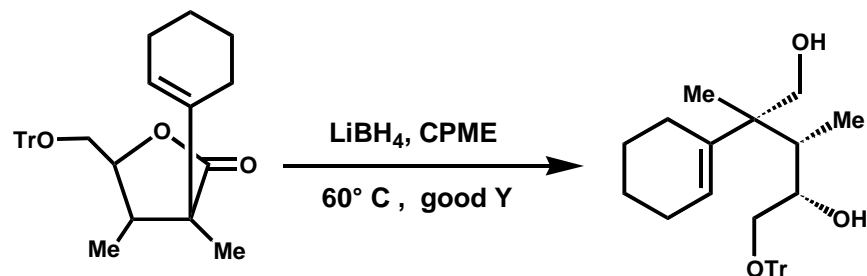
Kobayashi, *JACS*, 2010, 132, 7890



## E) Oxidation and Reduction

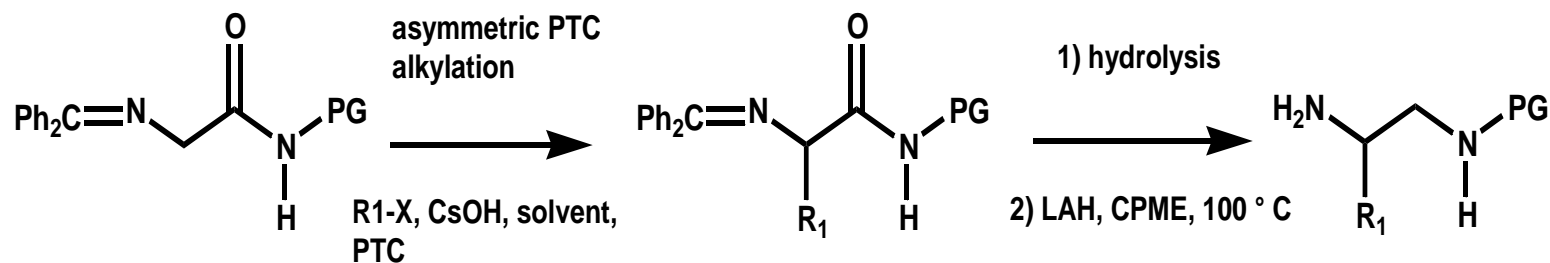
E-1  $\text{LiBH}_4$  Reduction

Zeon Corporation, Cyclopentyl Methyl Ether (CPME) technical data



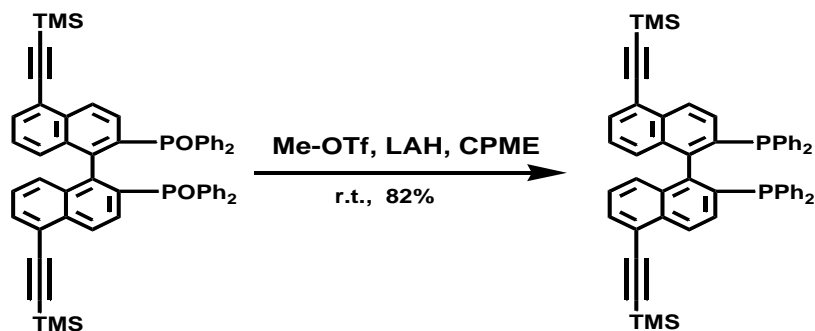
E-2  $\text{LiAlH}_4$  Reduction

Maruoka, *Angew. Chem.int.Ed.*, 2003, 42, 5868

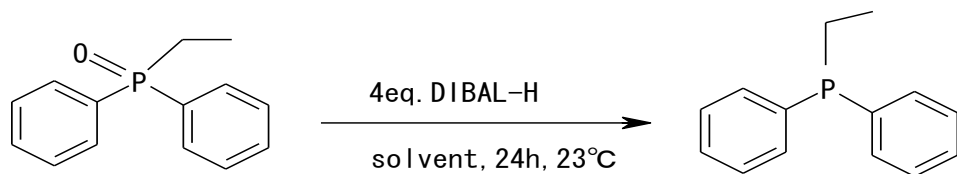


E-3  $\text{LiAlH}_4$  Reduction

Shimada, *J. Org. Chem.*, 2005, 70, 10178.



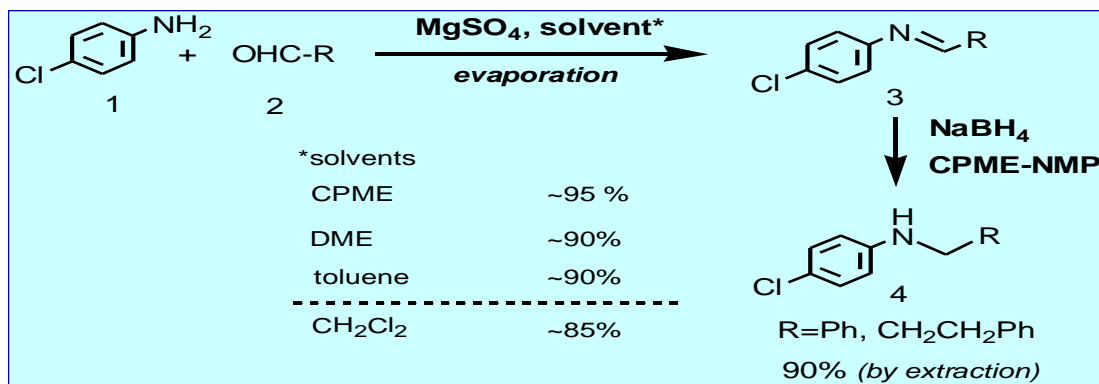
E-4  $i\text{-Bu}_2\text{AlH}$ (DIBAL-H) Reduction Boehringer-Ingelheim Pharma., *J.Org.Chem.* **2008**, *73*,1524



Solvents	%conv
DME	12
ETBE	17
2-MeTHF	35
THP	51
IPE	65
MTBE	72
CPME	72

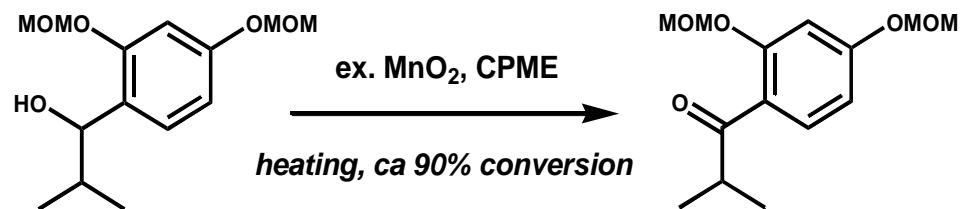
E-5 Reductive Amination

Torisawa, 2006 unpublished

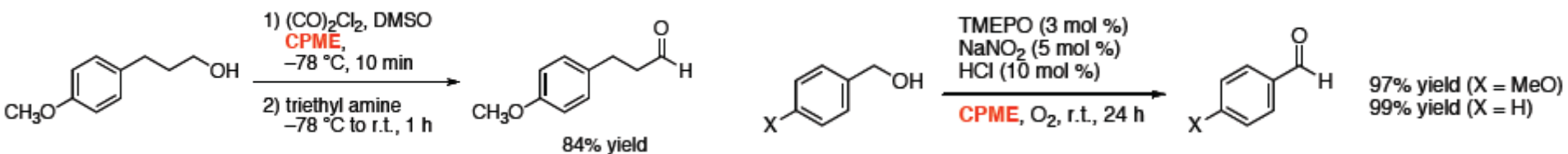


E-6  $\text{MnO}_2$  Oxidation

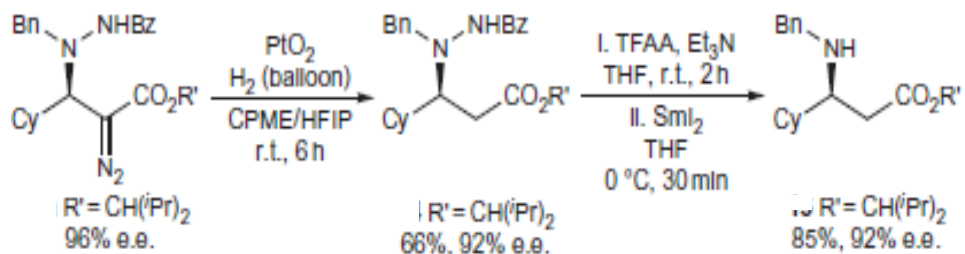
Zeon Corporation, Cyclopentyl Methyl Ether (CPME) technical data



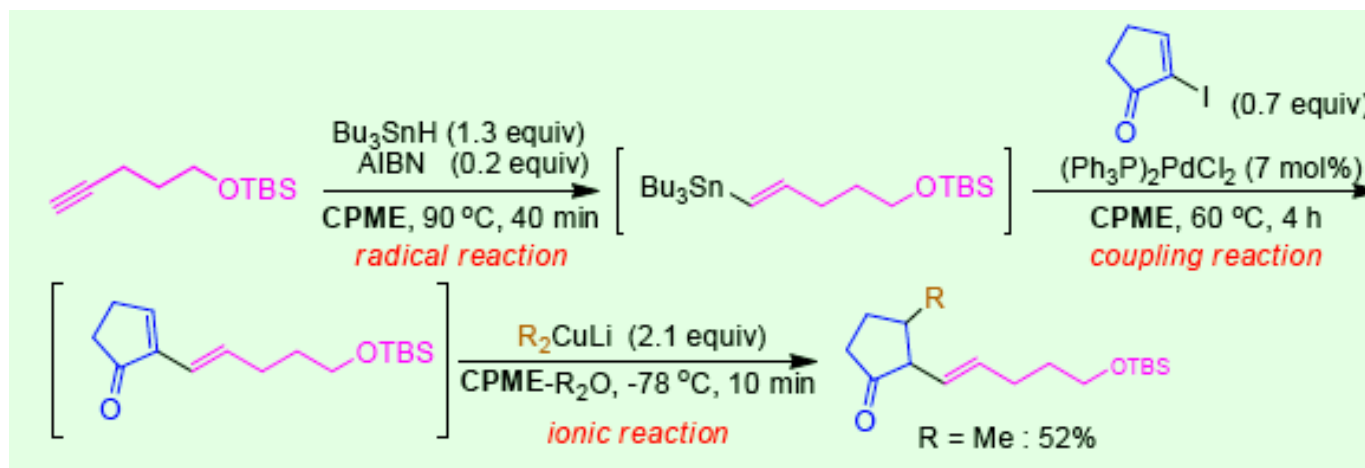
E-7 Swern & TEMPO oxidation Torisawa, unpublished



E-8 Decomposition of azo-group Maruoka, *Nature Chemistry*, 2011, 3, 642



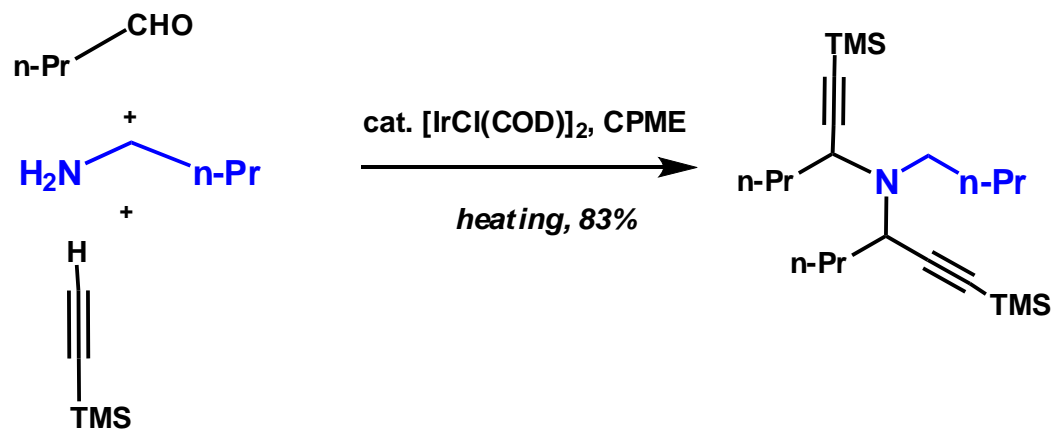
E-9 One pot process via radical reaction Kobayashi, The 2nd International Symposium on Process Chemistry (2011)



## F) Reactions with Transition Metal Catalyst

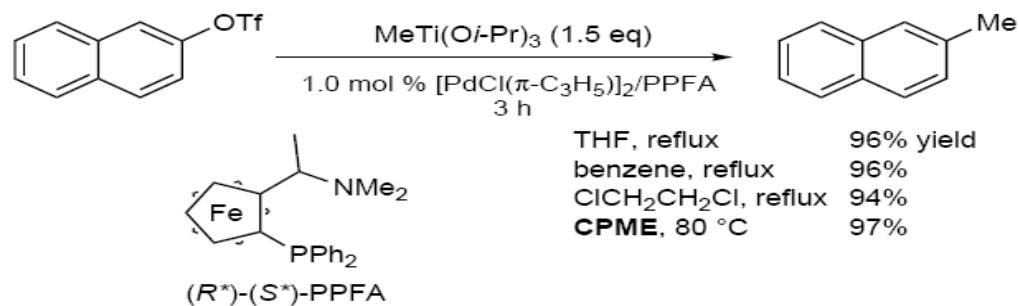
F-1 Ir-catalyzed Multi Component Coupling

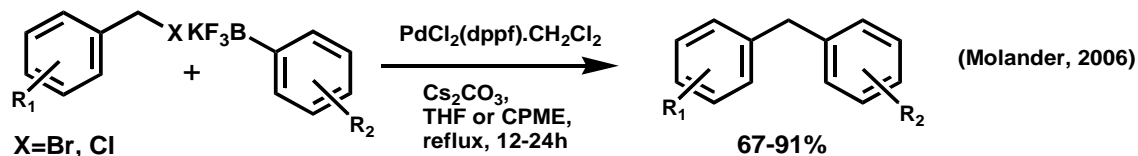
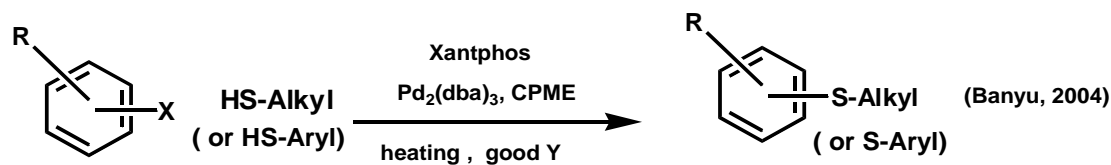
Ishii, *Chem. Commun.*, 2004, 6, 4587.



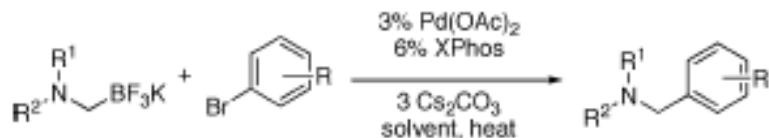
F-2 Pd-catalyzed Coupling of Ti-reagents

Hayashi, unpublished

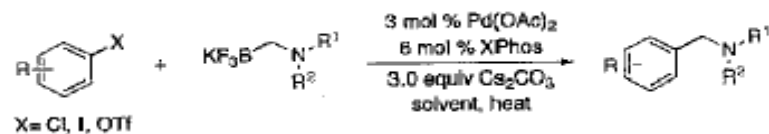




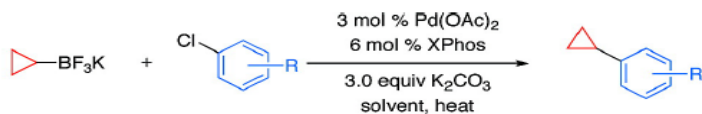
*G.A.Molander. Org. Lett. 2007, 9, 1597.*



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

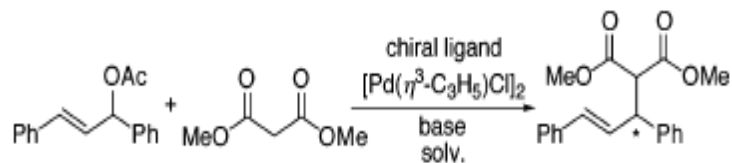


*G.A.Molander. J. Org. Chem., 2008, 73, 7481*



F-4 Asymmetric Allyl coupling

Fujita, *J. Org. Chem.* **2004**, *69*, 6679.

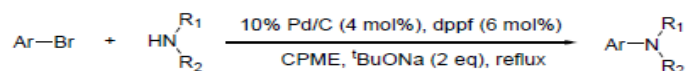


Solvents	Y(%)	ee(%)
THF	98	91
CPME	99	90

F-5 Buchwald-Hartwig Amination

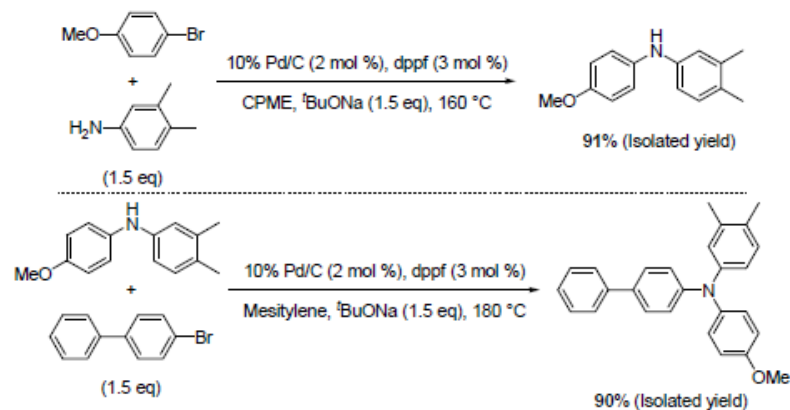
Sajiki, *Gifu Yakkadaigaku Kiyou*, **2006**, *55*, 45.

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



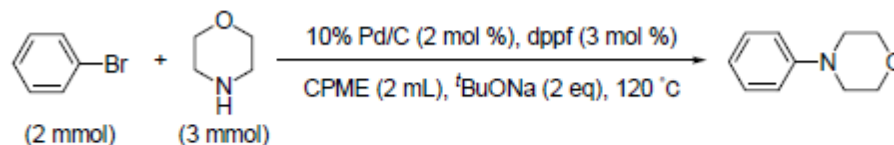
Entry	Product	Yield (%) <sup>a</sup>	Entry	product	Yield (%) <sup>a</sup>
1		70%	4		95%
2 <sup>b</sup>		92%	5		95%
3		76%	6		97%

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



Scheme 9

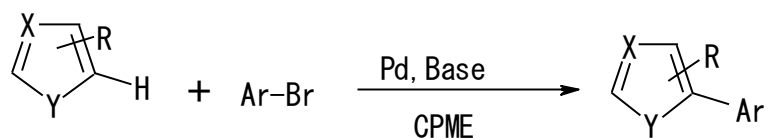
Table 8 Reuse of Pd/C



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

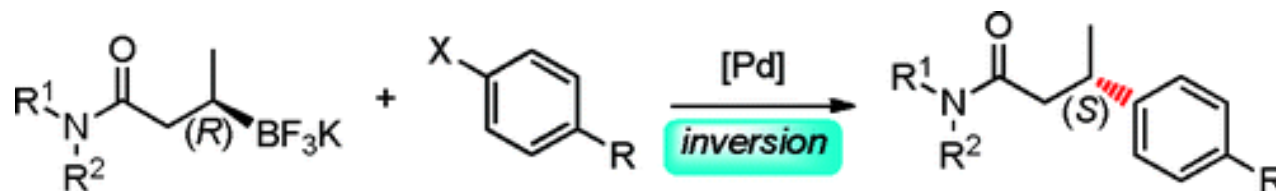
<sup>a</sup> Isolated yield.

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

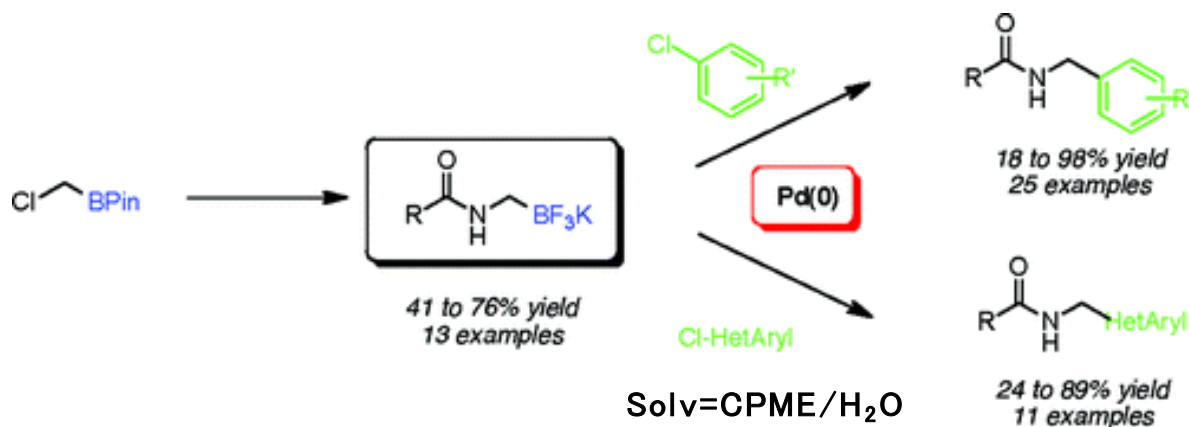
H.Doucet, *ChemSusChem* 2011, 4, 1

Y. 50-quant.

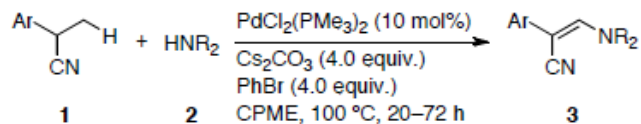
## F-7 Pd-catalyzed Cross-Coupling

G.A.Molander, *J.ACS*, 2010, 132, 17108Solv=CPME/H<sub>2</sub>OR<sup>1</sup>, R<sup>2</sup> = alkyl, aryl, H  
X = Cl, Br

## F-8 Pd-catalyzed Cross-Coupling

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

F-9 Pd-catalyzed oxidative functionalization Kuwano, The 57th Annual Meeting of organometallic chemistry of Japan, 2011

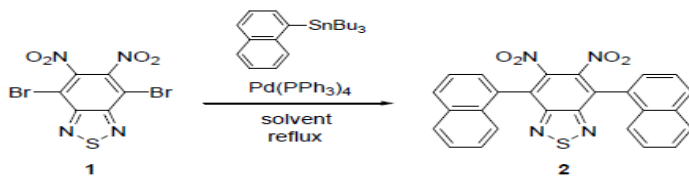


entry	Ar (1)	HNR <sub>2</sub> (2)	3	yield <sup>b</sup>
1	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> (1b)	2a	3b	83%
2	<i>p</i> -MeO <sub>2</sub> CC <sub>6</sub> H <sub>4</sub> (1c)	2a	3c	76%
3	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> (1d)	2a	3d	80%
4	<i>p</i> -MeOC <sub>6</sub> H <sub>4</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.

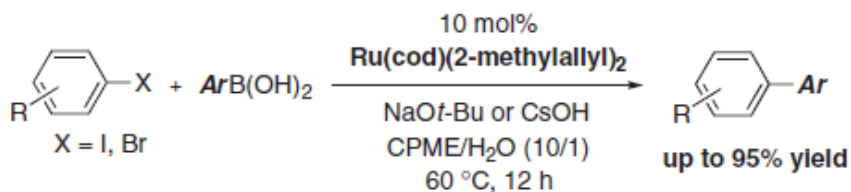
<sup>b</sup> The isolated yield of 3. <sup>c</sup> 2d = *N*-Boc-piperazine.

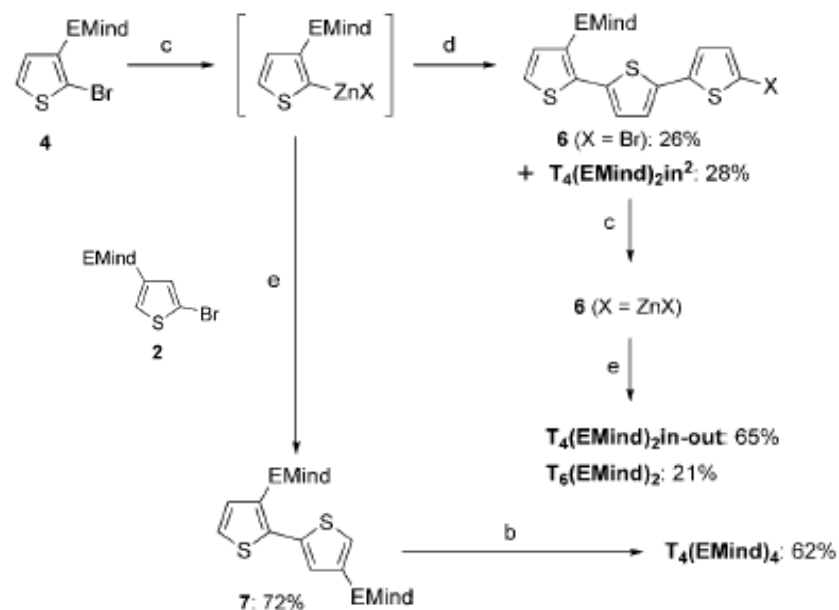
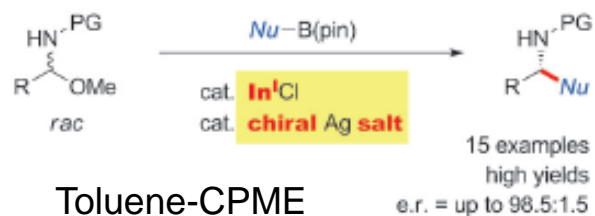
F-10 Pd-catalyzed Stille Coupling Nakamura, unpublished



Entry	Solvent	Temp. [°C]	Time [h]	Yield [%]
1	THF	66 (reflux)	12	6
2	toluene	110 (reflux)	12	26
3	CPME	106 (reflux)	12	72

F-11 Ru-catalyzed Suzuki-Miyaura Coupling Itoh, *Chem. Lett.*, 2010, 39, 1050





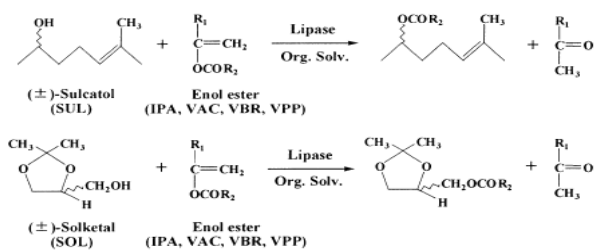
Scheme 3. Synthesis of 5–7 and EMind-oligothiophenes. 1) a)  $[\text{Pd}(\text{PPh}_3)_4]$  (2.5 mol %), toluene, reflux, 12 h; b) 1)  $n\text{BuLi}$ /hexane (1.0–1.1 equiv), THF,  $-80$  to  $-20$  °C, 0.5 h, 2)  $\text{CuCl}_2$  (1.0–1.2 equiv), THF,  $-80$  °C to RT, 0.5–1.0 h; c) 1)  $n\text{BuLi}$ /hexane (1.1 equiv), THF or CPME,  $-80$  °C, 0.5 h, 2)  $\text{ZnCl}_2$ /THF (1.2 equiv), THF or CPME,  $-80$  °C to RT, 0.5 h; d) 5,5'-dibromo-2,2'-bithiophene (0.5 equiv),  $[\text{Pd}(\text{PPh}_3)_4]$  (2.5 mol %), THF, reflux, 48 h; e) 2 (1.1–1.5 equiv),  $[\text{Pd}(\text{PPh}_3)_4]$  (5 mol %), CPME, reflux, 6–12 h.

# G) Reaction with Lipase

G-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

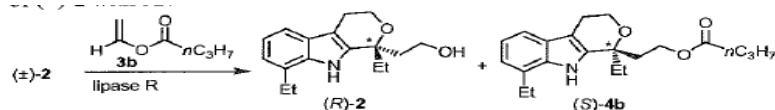
<sup>a</sup>Reaction conditions: racemic alcohol (2 mmol); enol ester (2 mmol); Me<sub>1,78</sub>βCyD (43 mg)-PCL (10 mg) co-lyophilizate; organic solvent (4 ml).

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

G-2

## Selective Acylation

Akai, *Heterocycles*, 2008, 76, 1537



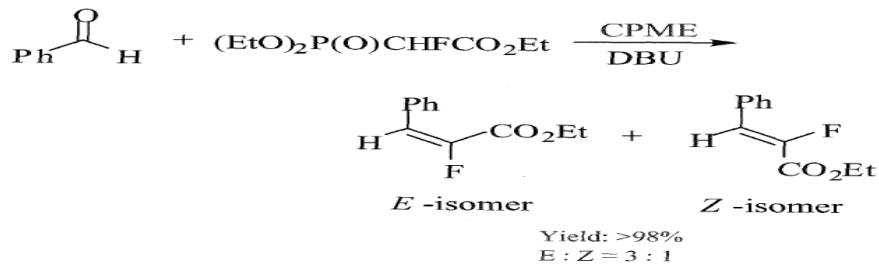
Entry	Solvent <sup>a</sup>	Temp., °C	Time, day	Conv., %	<i>E</i> value	( <i>R</i> )-2, % ee <sup>b</sup>	( <i>S</i> )-4b, % ee <sup>b</sup>
1 <sup>c</sup>	IPE	35	1	52	28	89	81
2	IPE	23	1	26	33	32	92
3	IPE	5	3	9	72	10	97
4	TBME	35	1	44	29	67	87
5	TBME	5	1	23	65	29	96
6	CPME	35	1	31	31	40	91
7	CPME	23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

## H) Microreactor

H-1 Horner-Wadsworth-Emmons reaction

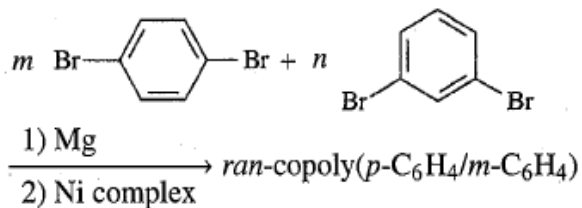
Kitazume, unpublished



## I) Polymerisation

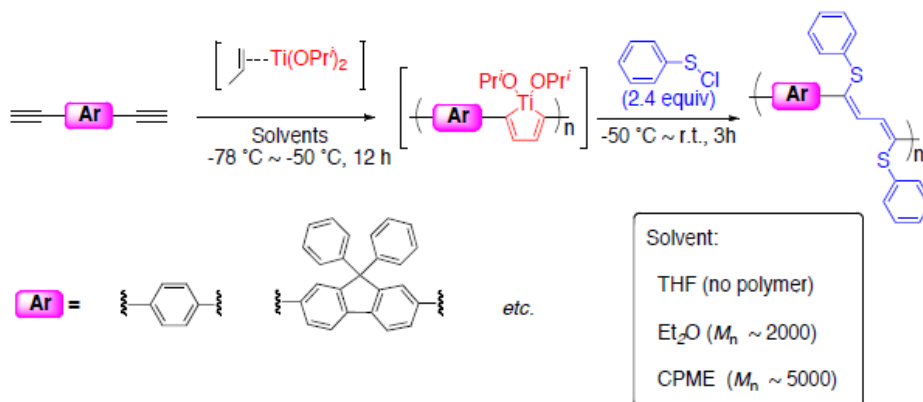
I-1 Cross Coupling

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



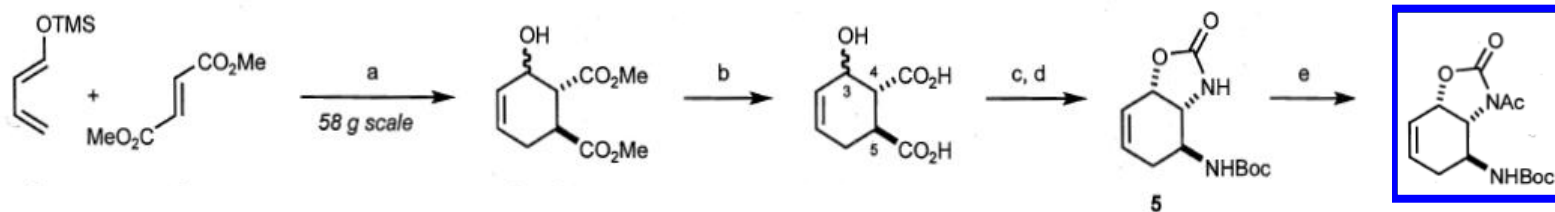
I-2  $\pi$ -Conjugated polymers

Tomita, ACS National Meeting, 2011



## J) Extraction/Crystallization

J-1 Crystallization Shibasaki, *Angew. Chem. Int. Ed.*, 2009, 48, 1070



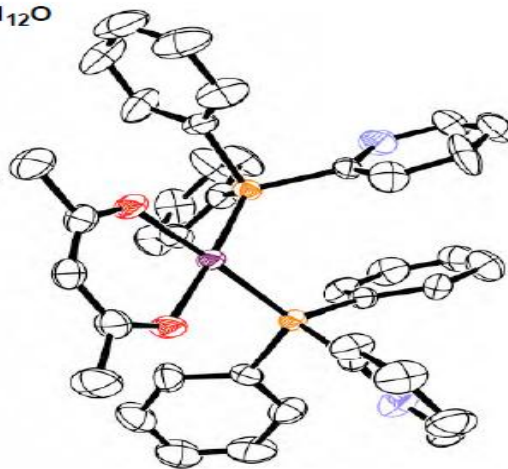
recrystallized from  $\text{CH}_2\text{Cl}_2$ -CPME 95% ee  $\Rightarrow$  99% ee

J-2 Crystallization Oshiki, *Syokubai*, 2008, 50, 133

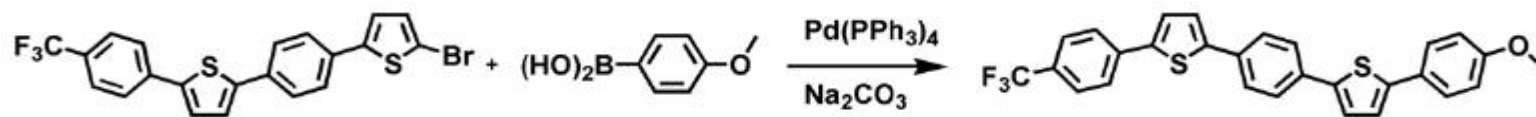


**$\text{Ir}(\text{acac})(\text{PPh}_2\text{py})_2$**

Formula	$\text{C}_{39}\text{H}_{35}\text{IrN}_2\text{O}_2\text{P}_2 \cdot \text{C}_6\text{H}_{12}\text{O}$
Crystal System	monoclinic
Space Group	$\text{Cc}$ (#9)
$a$ , Å	24.269 (2)
$b$ , Å	9.2060 (4)
$c$ , Å	20.344 (2)
$V$ , Å <sup>3</sup>	4067.0 (5)
$d$ , g/cm <sup>3</sup>	1.499
$Z$	4
No. of Reflections	4598
No. Variables	416
R; $R_w$	0.066; 0.084
$R_1$	0.032



J-3 removal of unreacted raw materials Hotta, *Organic Electronics*, 2011, 12, 8

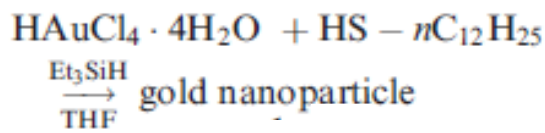


**AC5-1CF<sub>3</sub>-12OMe**

# K) Others

K-1 Gold-nanoparticle

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



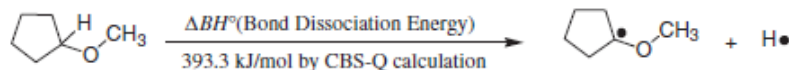
**Table 1** Formation of AuNP with a silane reagent<sup>a</sup>

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 <sub>2</sub> (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>a</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>f</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.

K-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

Solvents	mg/day	ppm
	PDE	Limit Conc
MeCN	4.1	410
DMAc	10.8	1090
DMF	8.8	880
dioxane	3.8	380
1,2-DME	1	100
Ethyleneglycol	6.2	620
Toluene	8.9	890
THF	7.2	720
MeTHF	6.2	
CPME	7.4	

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