

# **Asymmetric Intermolecular Transformations with Amino Acid derived Enolates *via* Memory of Chirality**

Literature Presentation

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# Memory of chirality

“A ‘memory of chirality reaction’ can be defined as a formal substitution at an  $sp^3$  stereogenic centre that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that centre and despite the fact that no other permanently chiral elements are present in the system.”

H. Zhao, D. Hsu, P. R. Carlier, *Synthesis* **2005**, 1-17

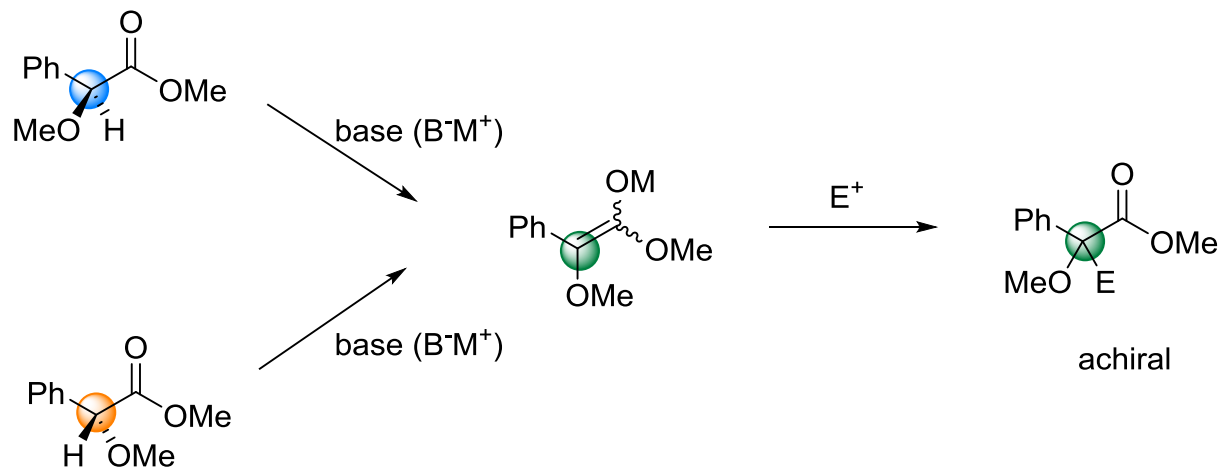
Reviews on asymmetric synthesis *via* memory of chirality:

T. Kawabata, K. Fuji, *Top. Stereochem.* **2003**, p. 175-205

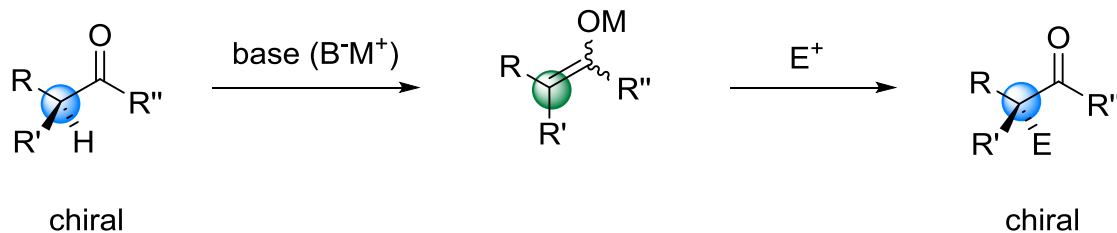
H. Zhao, D. C. Hsu, P. R. Carlier, *Synthesis* **2005**, p. 1-16

N. T. Patil, *Chem. – Asian J.* **2012**, p.2189-2194

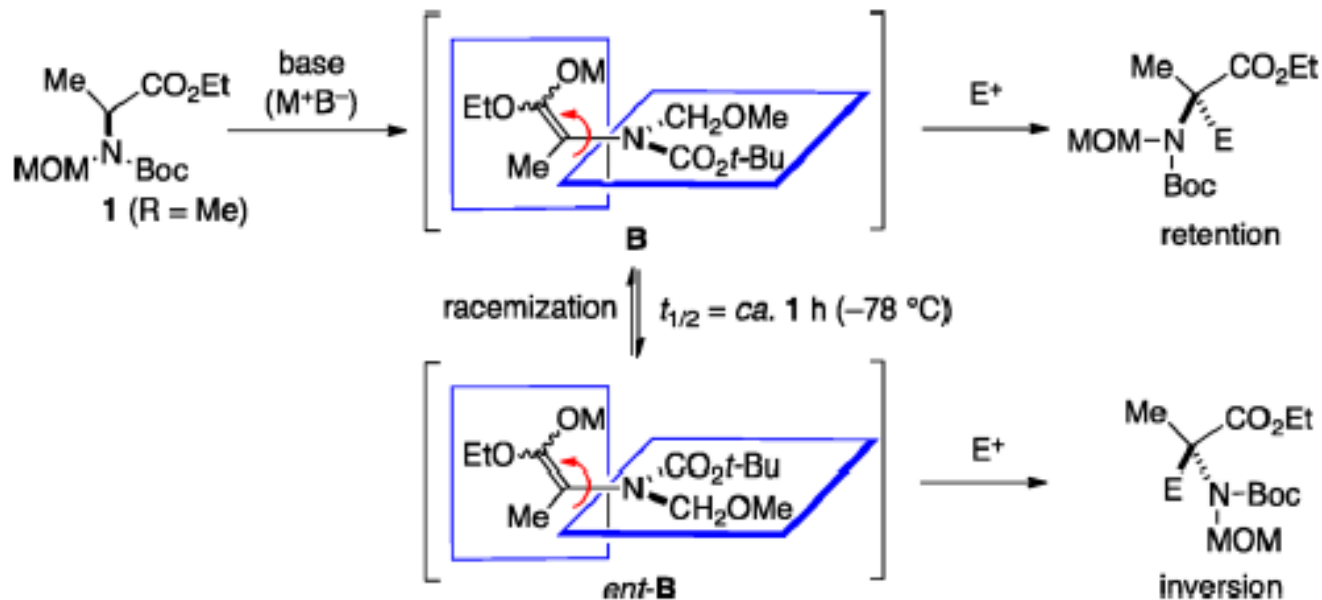
# Enolate chemistry and memory of chirality



Is there a way to preserve the chirality of the starting material in the enolate?

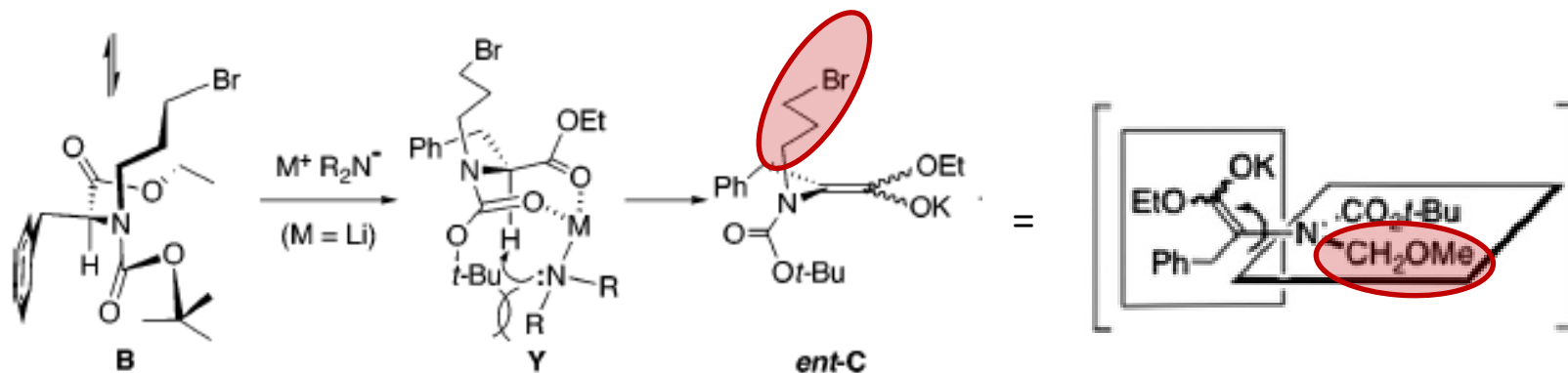
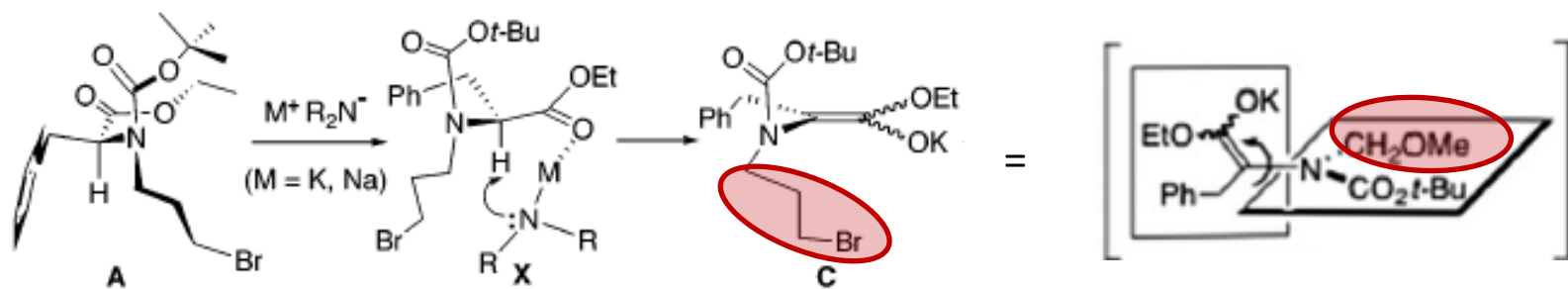


# Axially chiral enolates



- Reaction with electrophile competes with racemization
- High enantioselectivity is only expected when the reaction of **B** with  $E^+$  is faster than its racemization

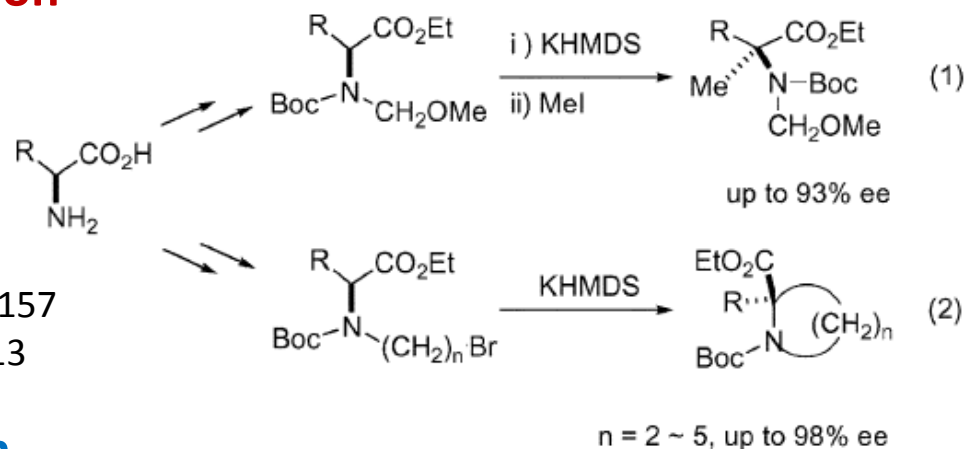
# Enantioselective formation of enolate



T. Kawabata, *J. Am. Chem. Soc.* **2006**, p. 15394-15395

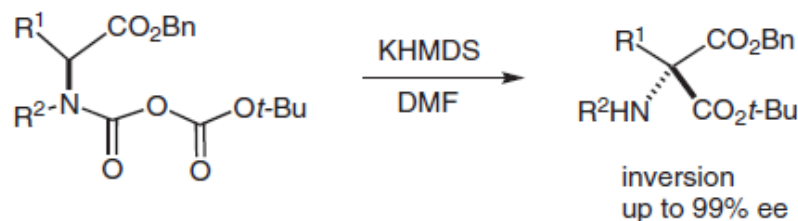
# Kawabata's work

- Intra-/intermolecular **alkylation**



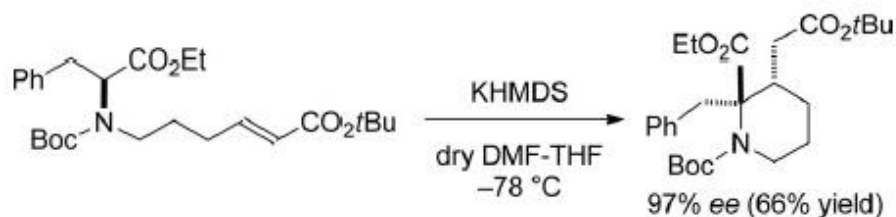
*Angew. Chem. Int. Ed.* **2000**, p. 2155-2157  
*J. Am. Chem. Soc.* **2003**, p. 13012-13013

- Intramolecular **acyl migration**



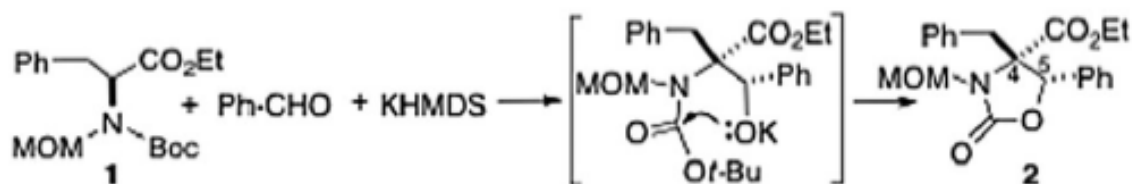
*Synlett* **2011**, p. 543-546

- Intramolecular **conjugate addition**



*Org. Biomol. Chem.* **2005**, p. 1609-1611  
*Chem. Eur. J.* **2012**, p. 15330-15336

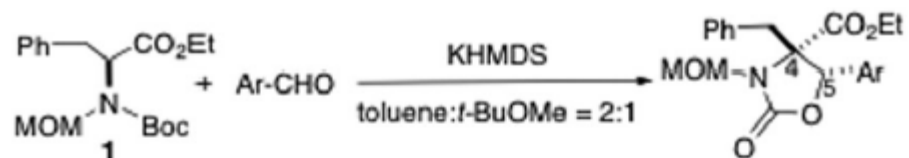
# Asymmetric aldol reaction *via* memory of chirality



Entry	Procedure <sup>a</sup>	Solvent	Temp/ °C	Time	Yield <sup>b,c</sup> (%)	ee <sup>d</sup> (%)
1	I	Tol: THF = 4:1	-78	2.5 h	85	32
2	II	Tol: THF = 4:1	-78	10 min	2	99
3	II	Tol: THF = 4:1	-30	10 min	7	96
4	II	Tol: THF = 4:1	-30	4 h	96	71
5	II	Tol	-30	6 h	57	80
6	III	Tol	-30	6 h	86	83
7	III	Tol	-50	10 h	65	87
8	III	Tol: THF = 2:1	-50	12 h	86	78
9	III	Tol: <i>t</i> -Pr <sub>2</sub> O = 2:1	-50	12 h	95	84
10	III	Tol: <i>t</i> -BuOMe = 2:1	-50	12 h	Quant.	81
11	III	Tol: <i>i</i> -Pr <sub>2</sub> O = 2:1	-60	12 h	70	86
12	III	Tol: <i>t</i> -BuOMe = 2:1	-60	12 h	69	92
13 <sup>e</sup>	III	Tol: <i>t</i> -BuOMe = 2:1	-50	12 h	31 <sup>f</sup>	89
14 <sup>g</sup>	III	Tol: <i>t</i> -BuOMe = 2:1	-50	12 h	Quant. <sup>h</sup>	82

- First example of asymmetric intermolecular aldol between an auxiliary and aromatic aldehyde *via* MOC
- Chiral oxazolidone **2** with contiguous tetra- and trisubstituted chiral centers is formed
- The solvent system is key to high ee and good yield
- Only one diastereoisomer of **2** is isolated
- Inversion of configuration

# Variation of aromatic aldehyde

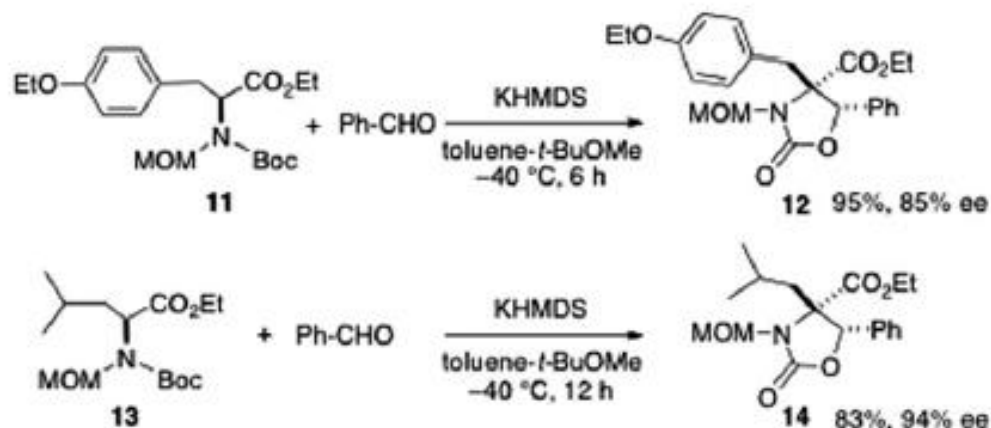


Entry	Ar	Temp/°C	Time/h	Product <sup>b,c</sup>	Yield (%)	ee (%)
1		-60	6	2 <sup>d</sup>	69	92
2		-60	12	3 <sup>e</sup>	67	88
3		-60	6	4 <sup>e</sup>	66	88
4		-50	6	5 <sup>e</sup>	64	78
5		-50	12	6 <sup>e</sup>	95	80
6		-50	12	7 <sup>e</sup>	67	89
7		-60	6	8 <sup>e</sup>	44	89

- Only aromatic aldehydes gave good results
- Various substitution on the aromatic ring is tolerated



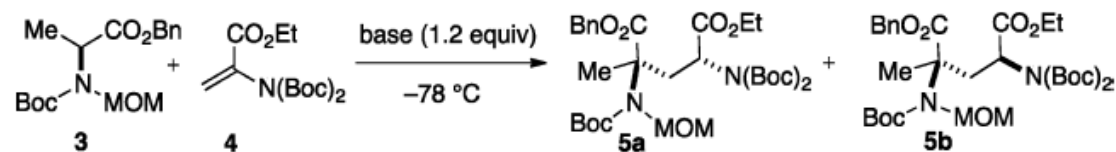
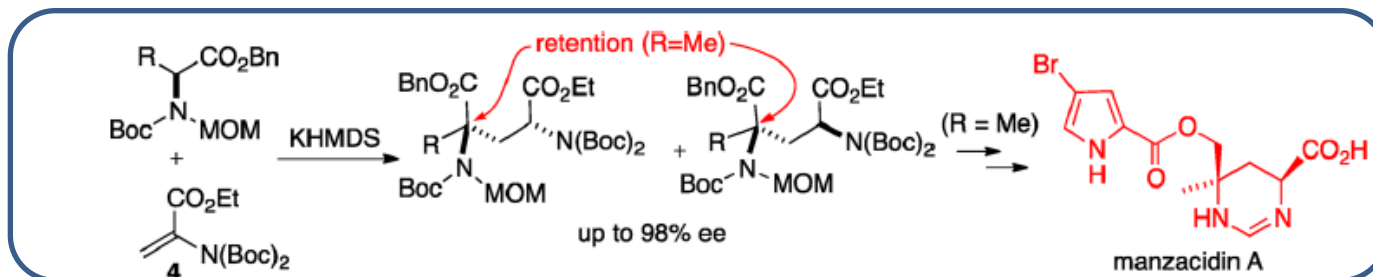
# Variation of enolate



- These aldol reactions seem to proceed with **inversion of configuration** (unlike methylation)

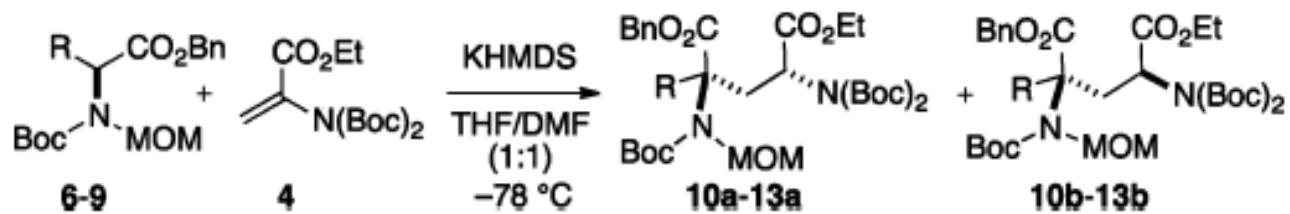
→ The reacting enantioface of the axially chiral enolates is reverse to each other depending on the electrophile.

# Intermolecular conjugate addition



entry	base (1.2 equiv)	solvent	procedure <sup>b</sup>	yield	5a:5b <sup>c,d</sup>	ee of 5a (%) <sup>e,f</sup>	ee of 5b (%) <sup>e,g</sup>
1	KHMDS <sup>h</sup>	toluene/THF (4:1)	I	68%	1:1	— <sup>i</sup>	82
2	NaHMDS <sup>i</sup>	toluene/THF (4:1)	I	quant	1:1	63	— <sup>i</sup>
3	LDA	toluene/THF (4:1)	I	25%	1:1	— <sup>i</sup>	— <sup>i</sup>
4	KHMDS <sup>k</sup>	toluene	I	75%	1:1	92	92
5	KHMDS <sup>h</sup>	THF	I	quant	1:1	74	— <sup>i</sup>
6	KHMDS <sup>k</sup>	toluene/DMF (1:1)	I	31%	1:2	91	94
7	KHMDS <sup>h</sup>	THF/DMF (1:1)	I	83%	1:2	93	93
8	KHMDS <sup>n</sup>	THF/DMF (1:1)	II	quant	1:2	97	97
9 <sup>l</sup>	KHMDS <sup>n</sup>	THF/DMF (1:1)	II	98%	1:2	97	98
10	KHMDS <sup>h</sup>	THF/DMF (1:1)	II <sup>m</sup>	90%	1:2	— <sup>i</sup>	97
11	KHMDS <sup>h</sup>	THF/DMF (1:1)	III	70%	1:2	22	22

# Different amino acid derivatives



entry	R	time (h)	product (yield)	<b>a:b</b> <sup>b-d</sup>	ee (%) <sup>e,f</sup> <b>a, b</b>
1	PhCH <sub>2</sub> ( <b>6</b> )	0.3	<b>10</b> (quant)	3:2	97, 97
2 <sup>g</sup>	<i>i</i> -Pr ( <b>7</b> )	24	<b>11</b> (50%)	1:0	87
3	<i>i</i> -Bu ( <b>8</b> )	2	<b>12</b> (62%)	1:2	97, 97
4	MeS(CH <sub>2</sub> ) <sub>2</sub> ( <b>9</b> )	0.2	<b>13</b> (quant)	1:2	91, 92

Two diastereoisomers were observed in most cases and the conjugate addition occurs with retention of configuration, as anticipated.