iSm2
Institut des Sciences Moléculaires de Marseille
UMR 6263

Synthèse Totale et StéRéO Réactivité Organique

Memory of chirality

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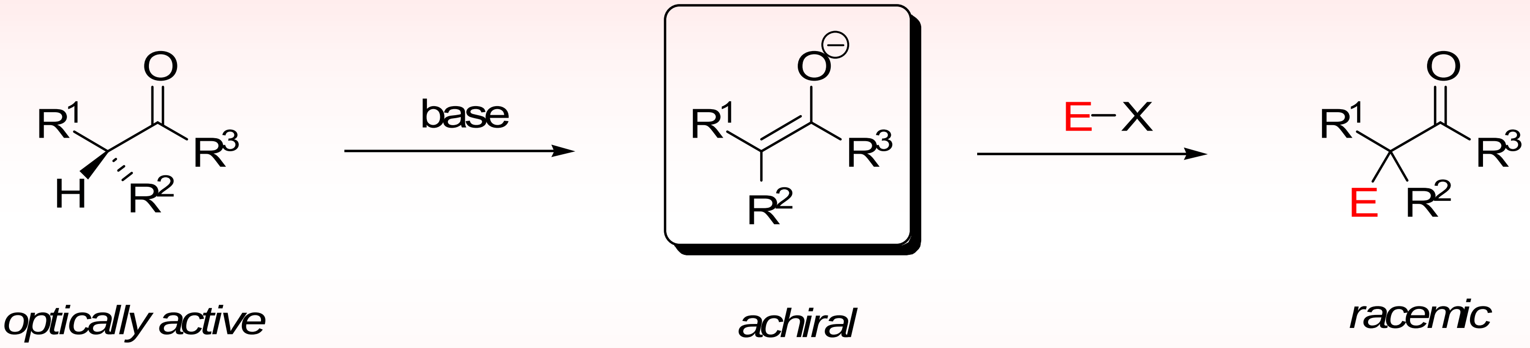
Bibliographical seminar, 19 / 06 / 08

Introduction

➡ Ideas widely accepted and teached:

- 

- To obtain optically active products, chiral source must be use

➡ **Use of Memory Of Chirality (MOC)**

Contents

1-Generalities

2-MOC in carbanion chemistry

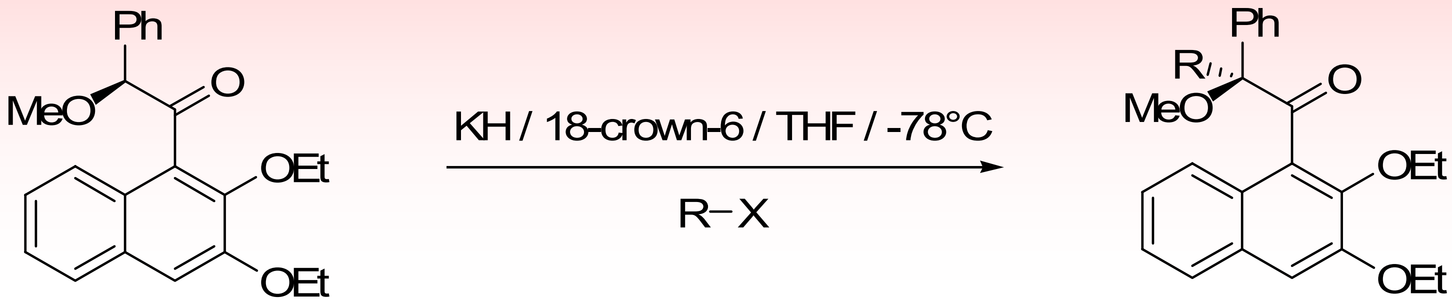
3-MOC in carboradical chemistry

4-MOC in carbocation chemistry

1-Generalities

1.1-First example

➡ Enantioselective alkylation reaction at an asymmetric carbon adjacent to a carbonyl group[1]



93% ee

R-X	Yield (%)	ee (%)
MeI	48	66
EtI	27	65
$PhCH_2Br$	31	67
$CH_2{=}CHCH_2Br$	36	48

Kaoru FUJI

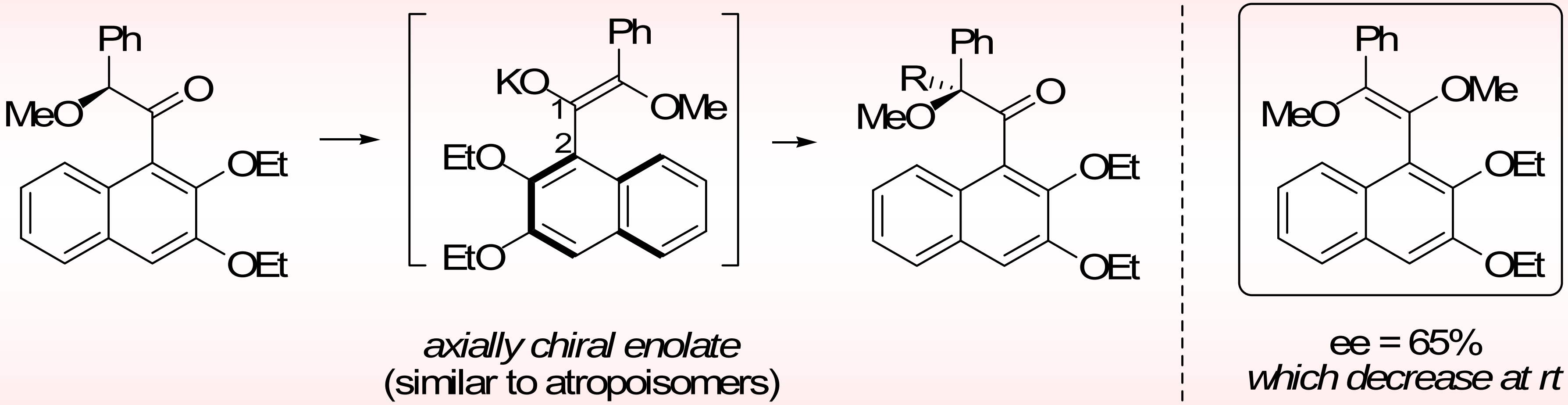
Takeo KAWABATA

(1) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694

1-Generalities

1.1-First example

Idea : Enolate is not always achiral



Two step transfert of chirality :
Central → Axial (C_1-C_2 bond) → Central

(1) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694

1-Generalities

1.2-Definitions

➡ No unique definition :

- *“Central chirality at a carbon alpha to a carbonyl group is preserved as a transient axial chirality of the intermediate enolate and is then regenerated as central chirality in the reaction product”*[1]

- *“The chirality of the strating material is preserved in a reactive intermediate for a limited time”*[2]

- *“The chirality of a starting material having a chiral sp^3-carbon is preserved in the reaction product even thought the reaction proceeds at the chiral carbon as a reaction center through reactive intermediates such as carbanion, singlet monoradicals, biradicals or carbenium ions”*[3]

- *“Formal substitution at an sp^3 stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system”*[4]

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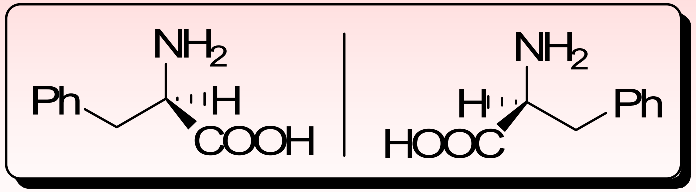
(1) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694
(2) Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373
(3) Wanyoike, G. N.; Onomura, O.; Maki, T.; Matsumura, Y. *Org. Lett.* **2002**, *4*, 1875
(4) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1

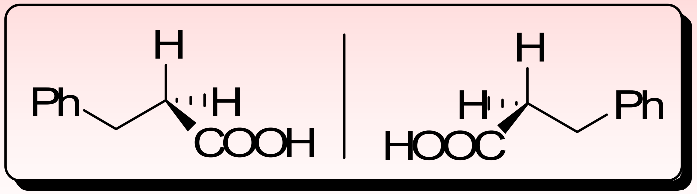
1-Generalities

1.3-Concepts

Dynamic (or conformational) **chirality**[2] =
Enantiomeric form (specific conformation) on a specific timescale

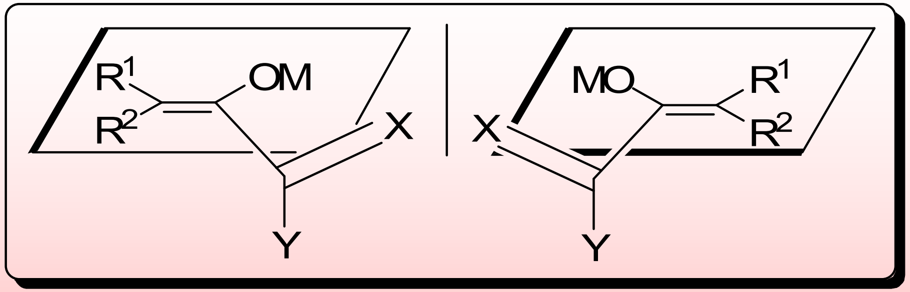


Static chirality

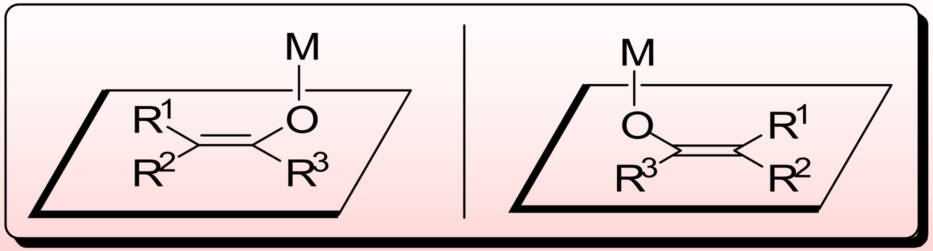


Dynamic chirality

Case of enolate : on a specific timescale, an enolate is not always achiral



Axial chirality



Planar chirality

Formation of chiral intermediate is not sufficient

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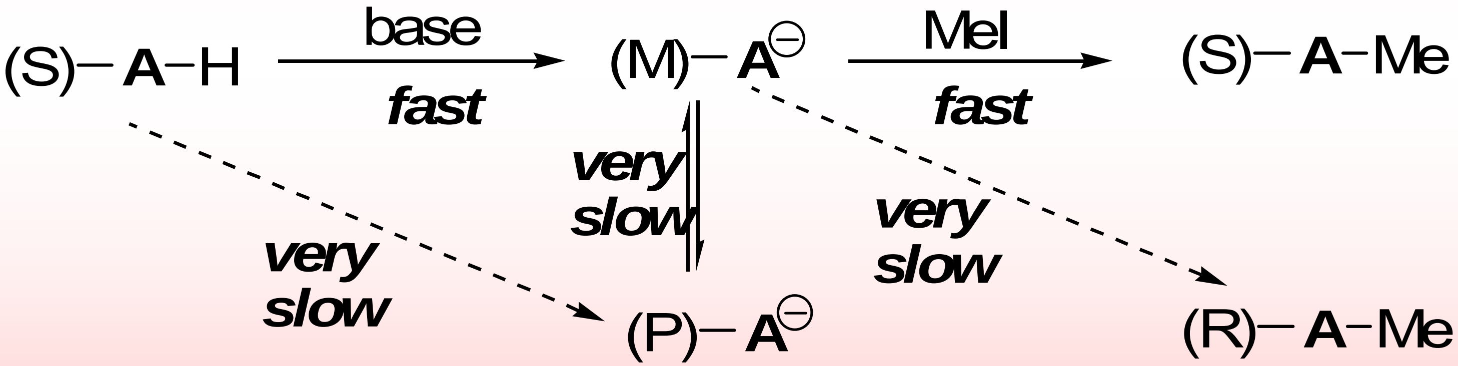
(2) Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373

1-Generalities

1.3-Concepts

Requirements for MOC :[4]

-Chiral intermediate must be formed enantioselectively
-Chiral intermediate must not readily racemize
-Chiral intermediate must react with high stereospecificity



What kind of timescale is needed ?

(4) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1

1-Generalities

1.3-Concepts

Eyring equation provides chemical foundation to design MOC methods[4]

Racemization barrier $\Delta G^{\neq}$ (kcal/mol)	Racemization $t_{1/2}$ at -78°C	Racemization $t_{1/2}$ at 25°C
12	2.4s	3.5 10^{-5} s
14	7 min	1.0 10^{-3} s
16	20 h	3.0 10^{-2} s
18	148 d	0.9 s
20	70 years	26 s

- A barrier of 16 kcal/mol give sufficient time to the intermediate to react without significant racemization
- Design points for MOC :
  -rarely sp3-sp3 bond ($\Delta G^{\neq}$ <7 kcal/mol)
  -often sp2-sp2 bond ($\Delta G^{\neq}$ >16 kcal/mol)

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(4) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis* **2005**, 1

Contents

1-Generalities

1.1-First example

1.2-Definitions

1.3-Concepts

2-MOC in carbanion chemistry

2.1-α-alkylation of amino-acids derivatives

2.2-Enantioselective synthesis of azacyclic amino acids

2.3-Enantioselective synthesis of quaternary benzodiazepinones

2.4- Access to enantioenriched α-subsituted valine

3-MOC in carboradical chemistry

3.1-MOC in benzylic substitution induced by electron transfer

3.2-MOC controlled by slow ring inversion

3.3-MOC in photochemistry

3.4-MOC in radical cyclizations

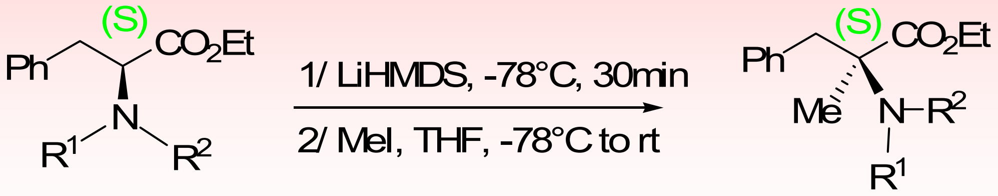
4-MOC in carbocation chemistry

4.1-Non-Kolbe Reaction

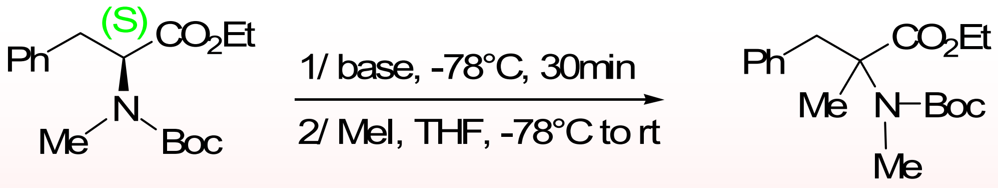
2- MOC in carbanion chemistry

2.1-α-alkylation of amino-acids derivatives

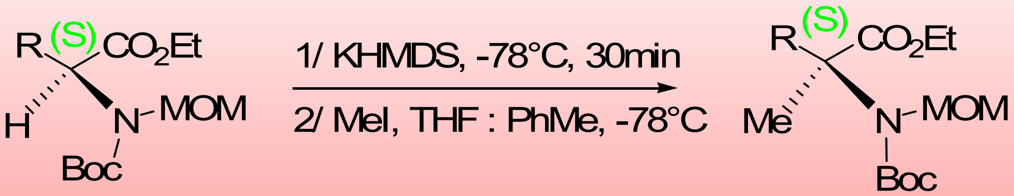
Enantioselective α-alkylation of AA esters without external chiral sources[5,6]



R^1 = Me, R^2 = Boc
Yield = 30%, ee = 36%



LiTMP (*1eq*) : Yield = 40%, ee = 82% (S)
KHMDS (*1.2eq*) : Yield = 79%, ee = 20% (R)



7 examples
Yield = 78-96%, ee = 76-93% (S)

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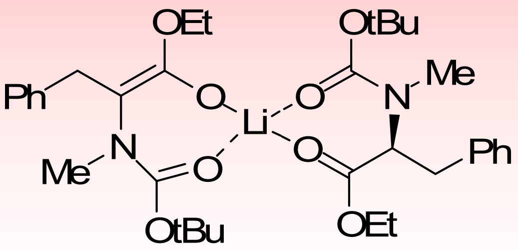
(5) Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809
(6) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2155

2- MOC in carbanion chemistry

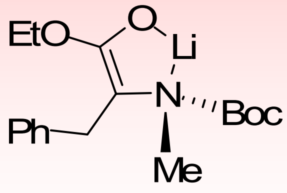
2.1-α-alkylation of amino-acids derivatives

Mecanism investigations[5,6]

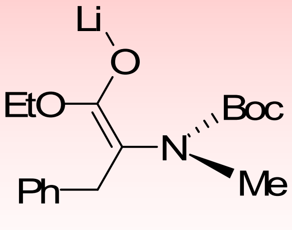
Plausible intermediates :



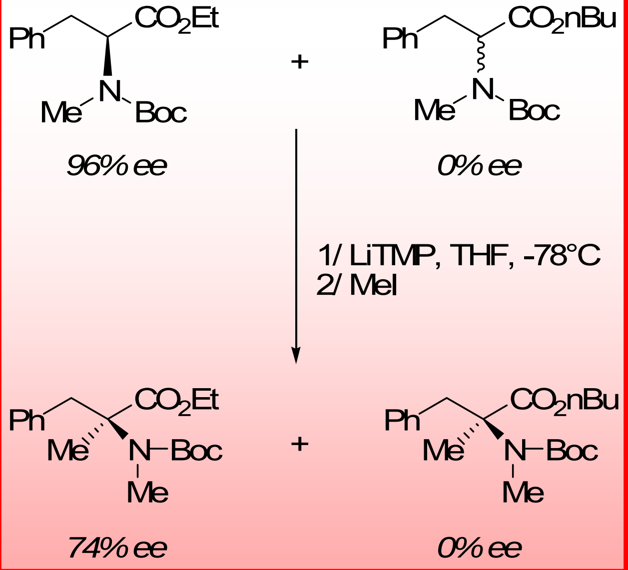
chiral enolate/SM aggregate



chiral N atom species



C-N axially chiral enolate



$t\ rac_{1/2}$ = 22h at -78°C
Formation of a slowly racemizing axially chiral enolate

Gives racemic methyl product

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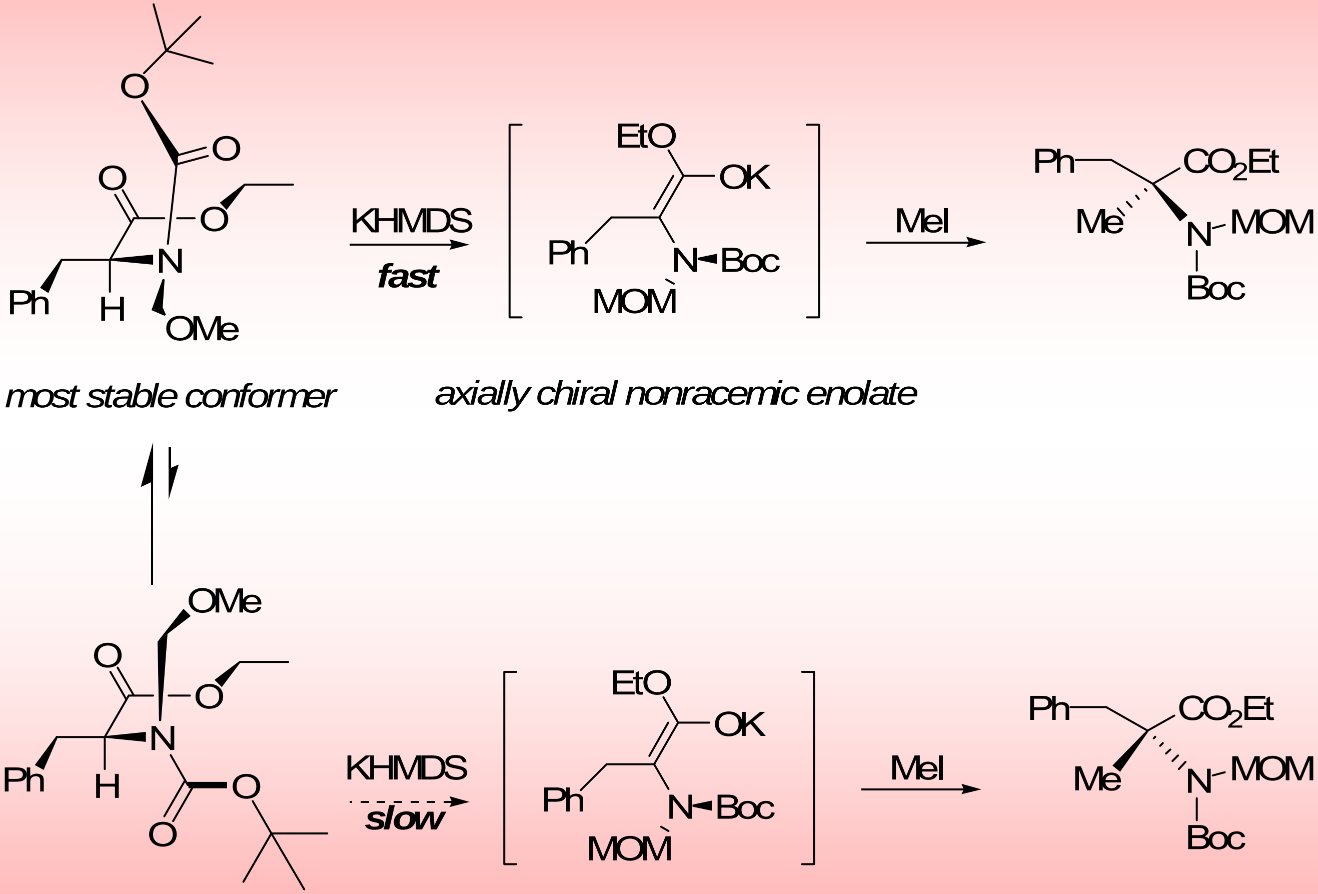
(5) Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc.* **1994**, *116*, 10809

(6) Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2155

2- MOC in carbanion chemistry

2.1-α-alkylation of amino-acids derivatives

MM3 calculations :



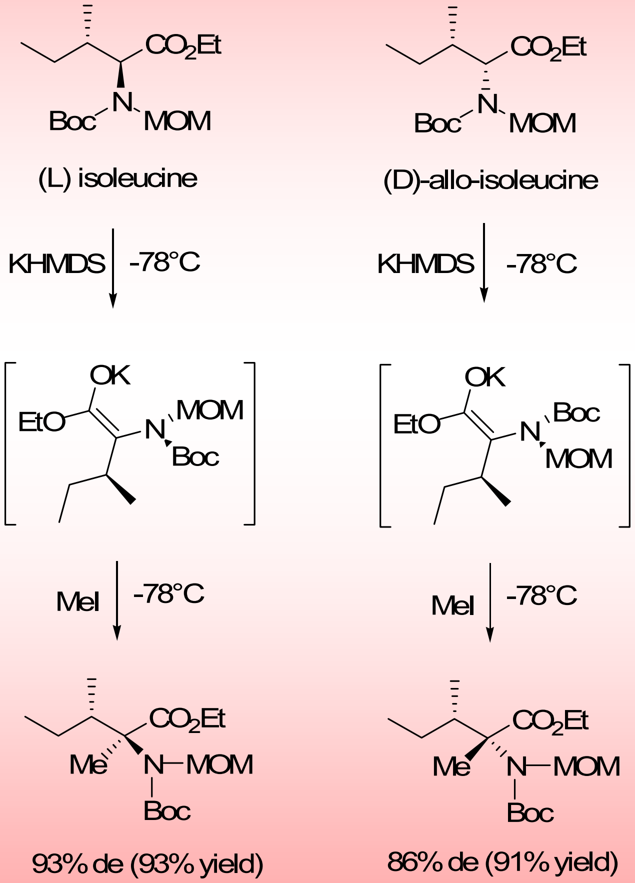
Axially chiral enolate is generated in enantiopure form

2- MOC in carbanion chemistry

2.1-α-alkylation of amino-acids derivatives

Case of diastereomers :

Structural influence of nearby chiral center ?[7]



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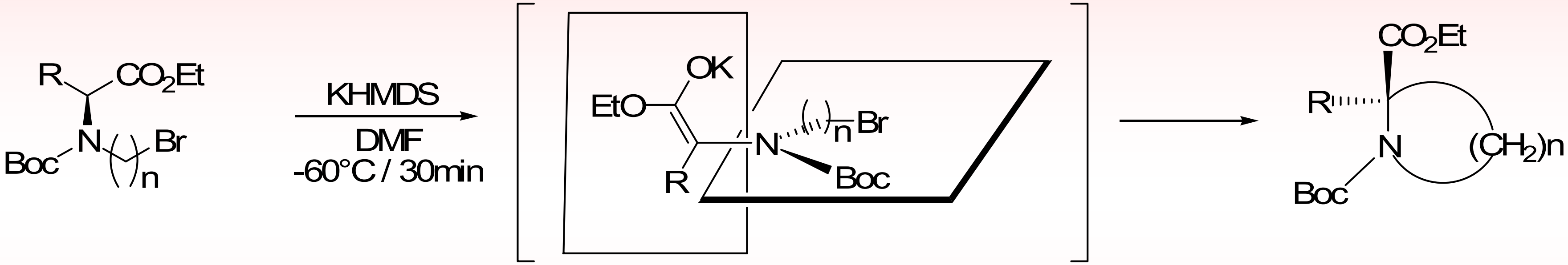
(7) Kawabata, T; Chen, J.; Suzuki, H.; Fuji, K. *Synthesis* **2005**, 1368

2- MOC in carbanion chemistry

2.2-Enantioselective synthesis of azacyclic amino acids

First[8,9] and recent[10] studies



R = Bn, n = 2, 3, 4, 5

KHMDS / DMF / -60°C / 30min
61-94% yield, 72-98% ee

KOH / DMSO / 20°C
73-97% yield, 88-99% ee

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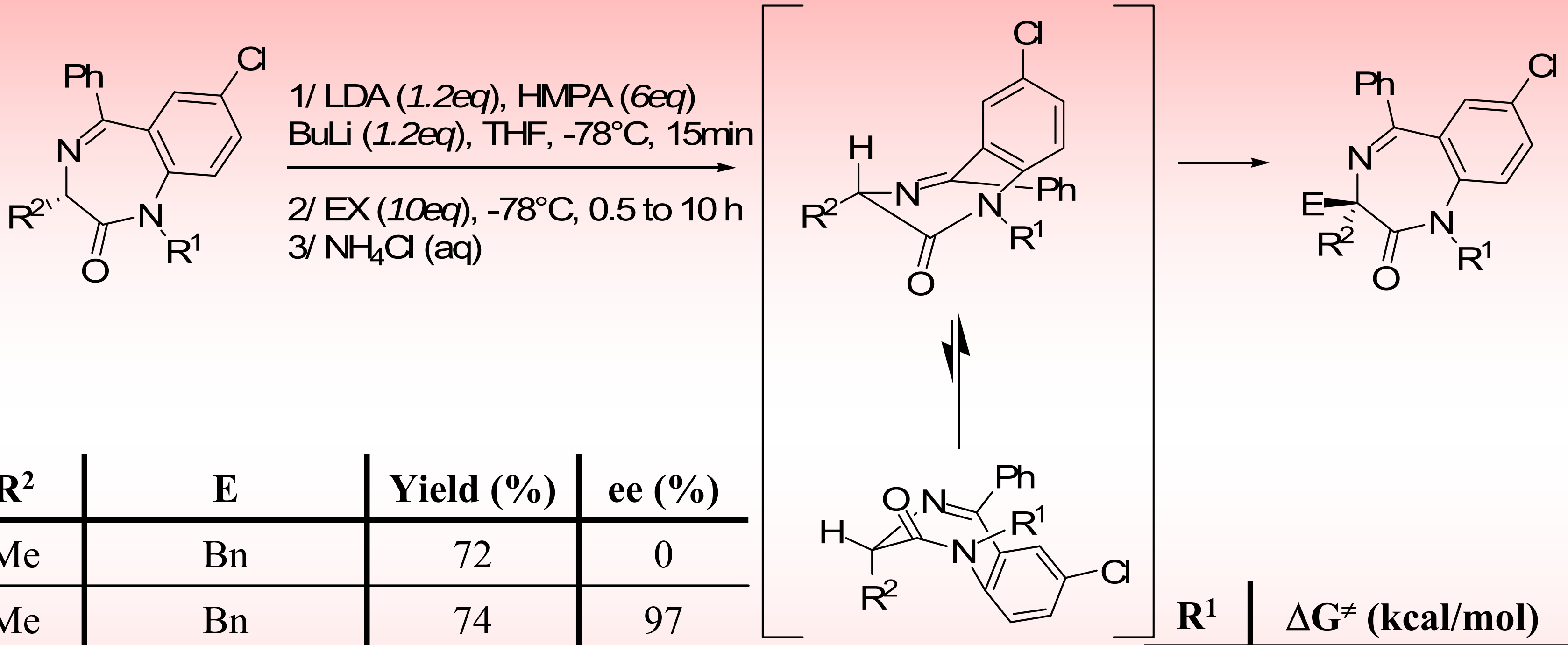
(8) Kawabata, T.; Kawakami, S.; Majumbar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012

(9) Kawabata, T.; Matsuda, S.; Kawakami, S.; Monguchi, D.; Moriyama, K. *J. Am. Chem. Soc.* **2006**, *128*, 15394

(10) Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 4153

2- MOC in carbanion chemistry

2.3-Enantioselective synthesis of quaternary benzodiazepinones[11]



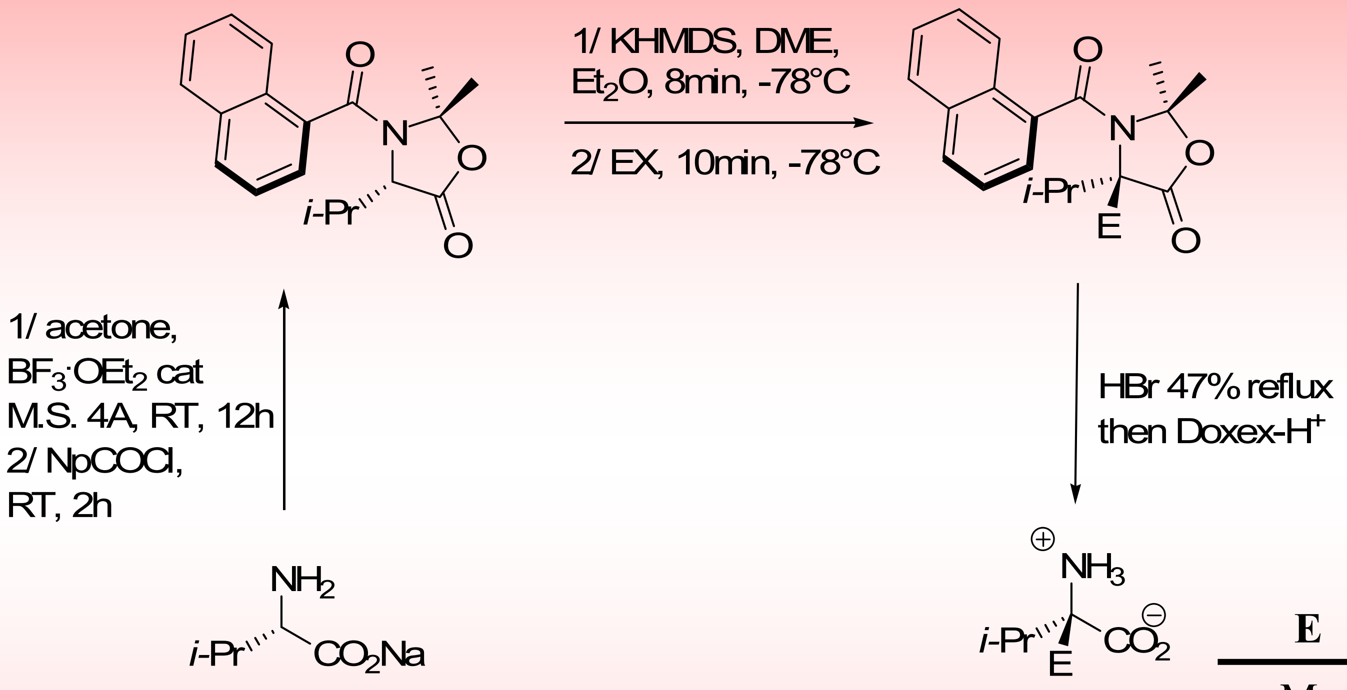
R^1	R^2	E	Yield (%)	ee (%)
Me	Me	Bn	72	0
iPr	Me	Bn	74	97
iPr	Me	4-$MeC_6H_4CH_2$	68	95
iPr	Me	2-$PhC_6H_4CH_2$	70	99
iPr	Bn	Me	64	95
iPr	Bn	allyl	57	86

R^1	$\Delta G^{\neq}$ (kcal/mol)
H	12.3
Me	18.0
iPr	21.1
tBu	>24

(11) Carlier, P. R.; Zhao, H.; DeGuzman, J.; Lam, P. C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 11482

2- MOC in carbanion chemistry

2.4- Access to enantioenriched α-subsituted valine[12]



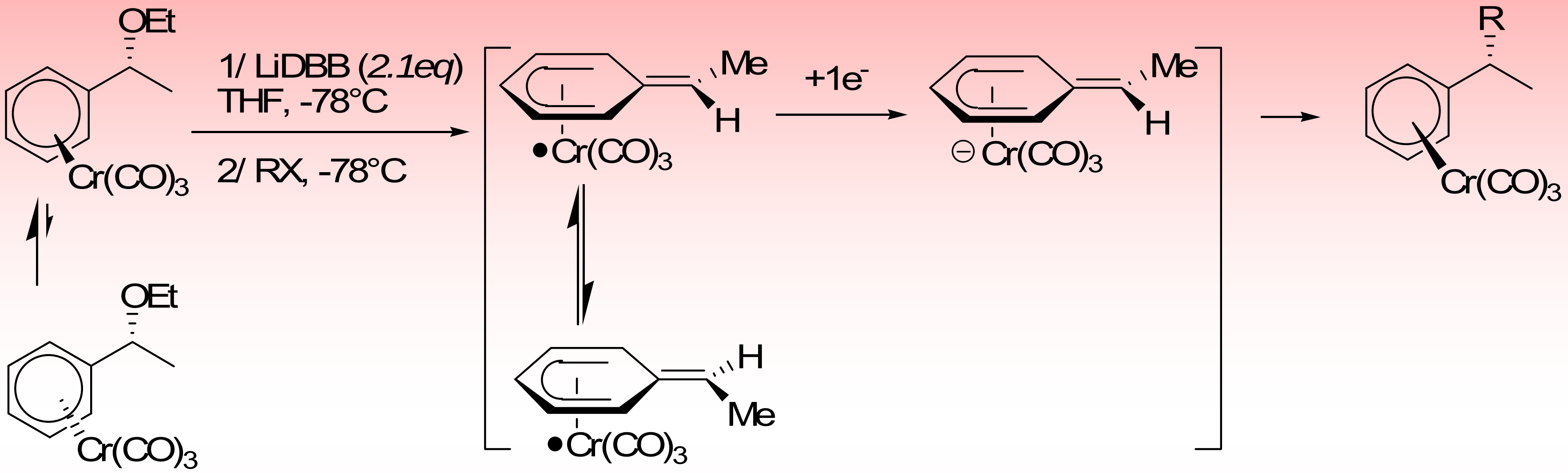
E	Yield (%)	ee (%)
Me	74	78
Et	59	91
Allyl	88	88
Bn	72-98	73-91

(12) Branca, M.; Gori, D.; Guillot, R.; Alezra, V.; Kouklovsky, C. *J. Am. Chem. Soc.* **2008**, *130*, 5864

Contents

3- MOC in carboradical chemistry

3.1-MOC in benzylic substitution induced by electron transfer[14]

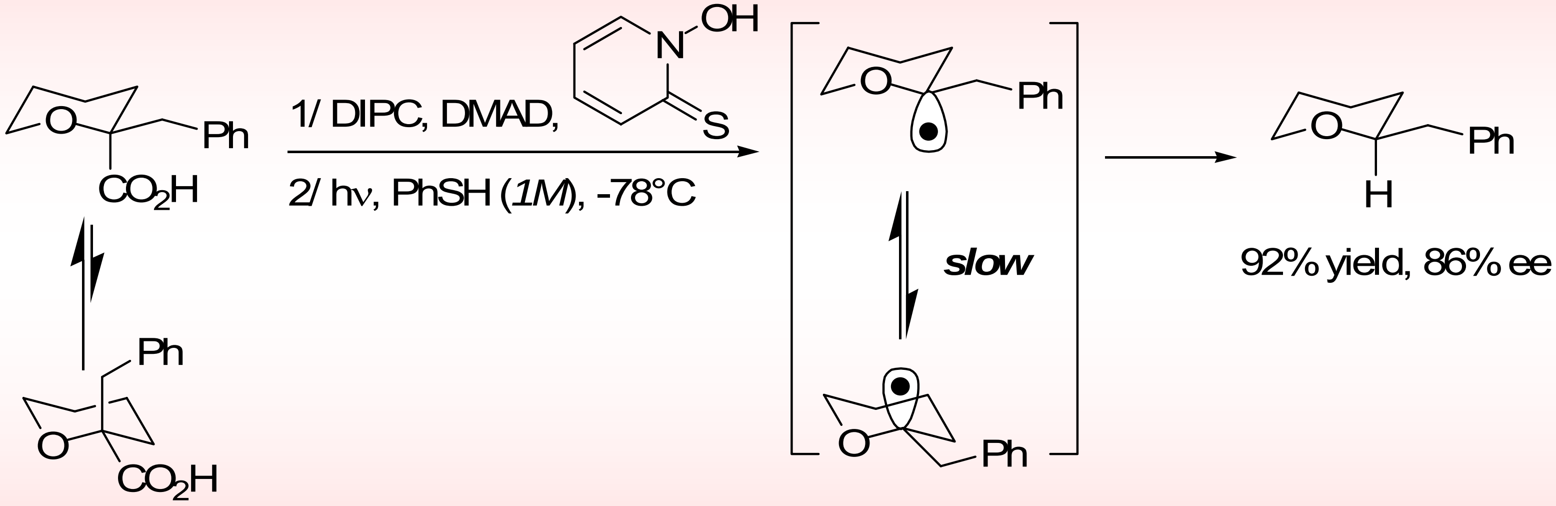


RX	Yield (%)	ee (%)
TMSCl	72	87
$PhCH_2Br$	37	87
MeOC(O)Cl	67	86
$Me_2NC(O)Cl$	57	84

(14) Schmalz, H.-G.; de Konig, C. B.; Bernicke, D.; Siegel, S.; Pfletschinger, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 1620

3- MOC in carboradical chemistry

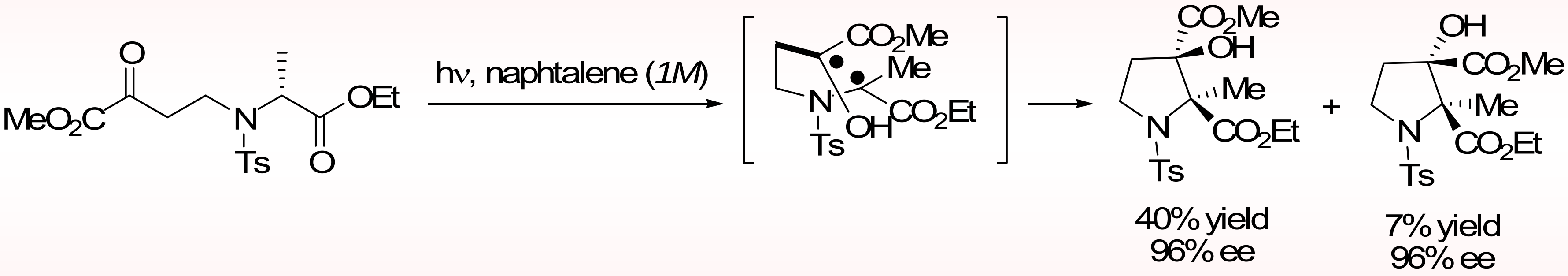
3.2-MOC controlled by slow ring inversion[15]



(15) Buckmelter, A. J.; Kim, A. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2000**, *122*, 9386

3- MOC in carboradical chemistry

3.3-MOC in photochemistry[16]



Racemization barrier : 5 kcal/mol

Cyclisation barrier : 2 kcal/mol

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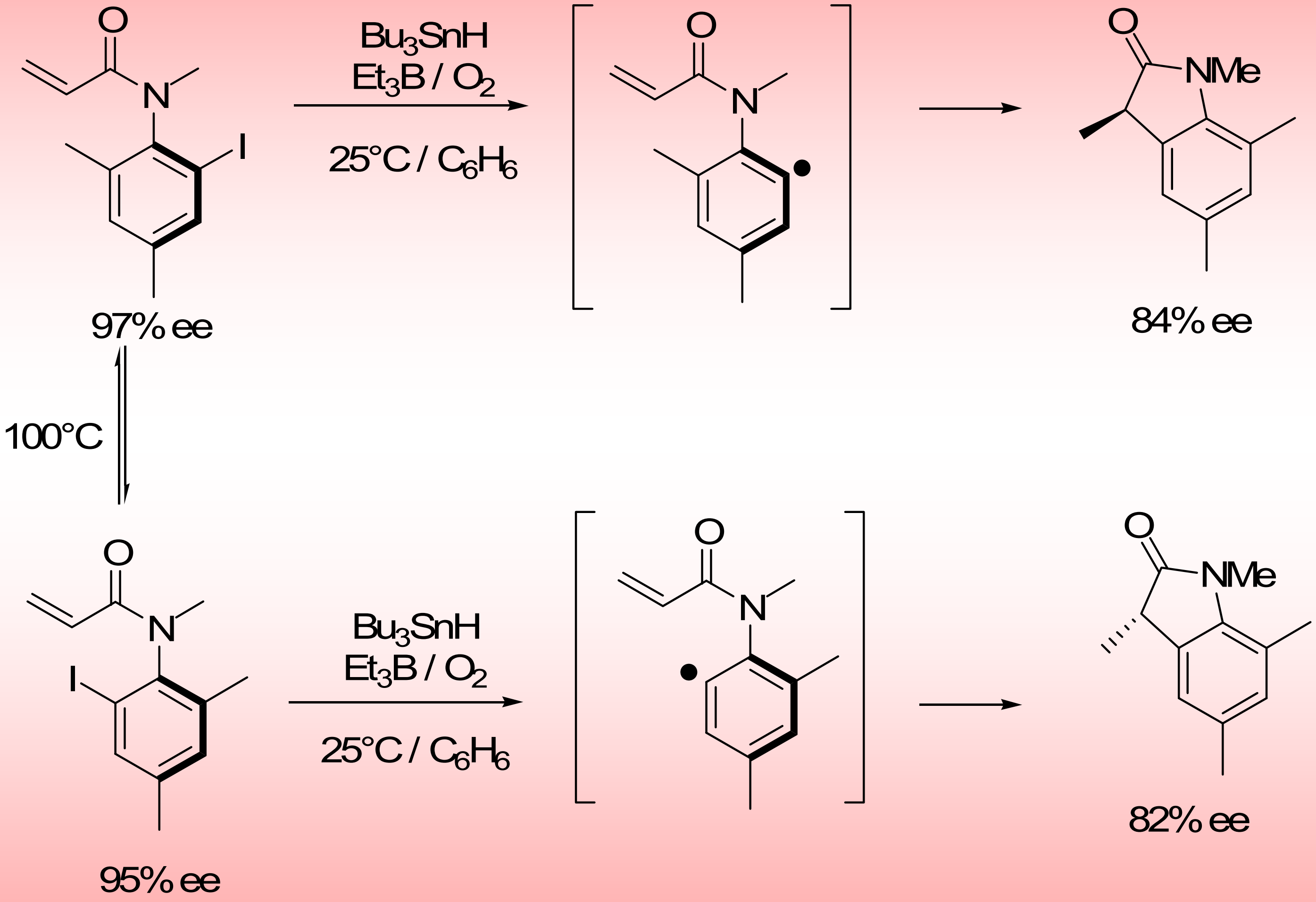
(16) Giese, B.; Wettsein, P.; Stähelin, C.; Barbosa, F.; Neuburger, M.; Zenher, M.; Wessig, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 2586

3- MOC in carboradical chemistry

3.4-MOC in radical cyclizations[17]



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(17) Curran, D. P.; Liu, W.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012

Contents

1-Generalities

1.1-First example

1.2-Definitions

1.3-Concepts

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2.2-Enantioselective synthesis of azacyclic amino acids

2.3-Enantioselective synthesis of quaternary benzodiazepinones

2.4- Access to enantioenriched α-subsituted valine

3-MOC in carboradical chemistry

3.1-MOC in benzylic substitution induced by electron transfer

3.2-MOC controlled by slow ring inversion

3.3-MOC in photochemistry

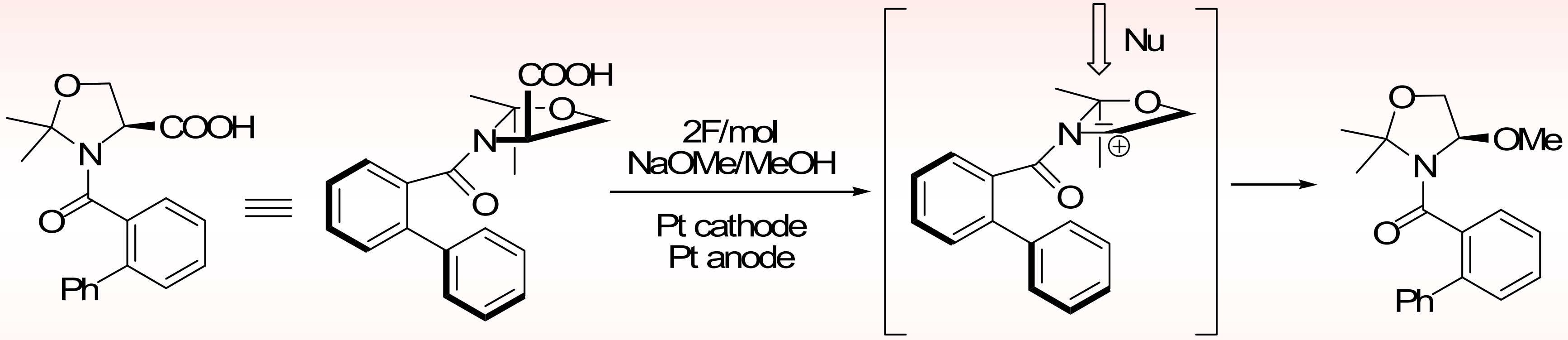
3.4-MOC in radical cyclizations

4-MOC in carbocation chemistry

4.1-Non-Kolbe Reaction

4- MOC in carbocation chemistry

4.1-Non-Kolbe Reaction[18,19]



most chiral conformation

98% yield
80%ee

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(18) Matsumura, Y.; Shirakawa, Y.; Satoh, Y.; Umino, M.; Tanaka, T.; Maki, T.; Onomura, O. *Org. Lett.* **2000**, *2*, 1689

(19) Wanyoike, G. N.; Onomura, O.; Maki, T.; Matsumura, Y. *Org. Lett.* **2002**, *4*, 1875

Conclusion

➡

- New way of enantioselective synthesis
- No need of external chiral sources

➡

- Limited substrates