Powdered KOH in DMSO: An Efficient Base for Asymmetric Cyclization via Memory of Chirality at Ambient Temperature

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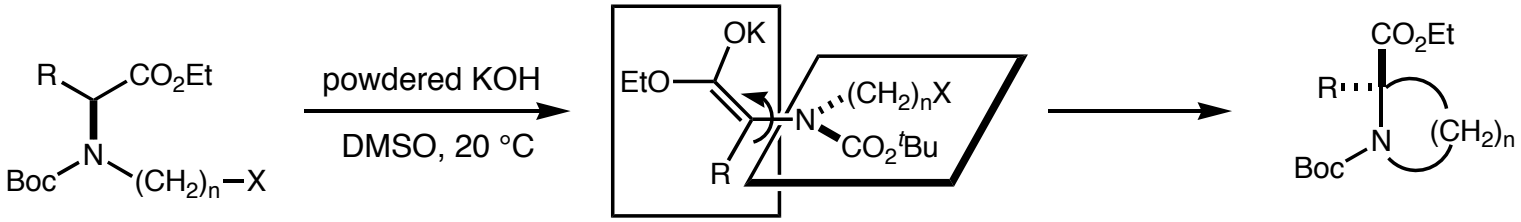
Institute for Chemical Research, Kyoto University Uji, Kyoto, Japan

Journal of the American Chemical Society, **2008**, *130*, 4153-4157.



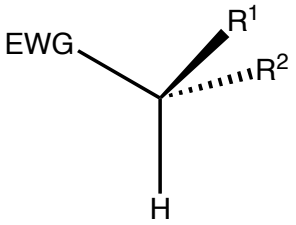
Wipf Group Saturday Morning Meeting
Current Literature Abstracts & Reports
Rob Lettan March 29th, 2008

Memory of Chirality

Defined As:

"A 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." -T. Kawabata

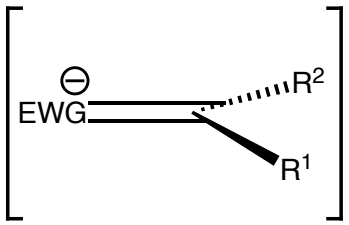
Chiral Starting Material



sp^3
tetrahedral

Deprotonation

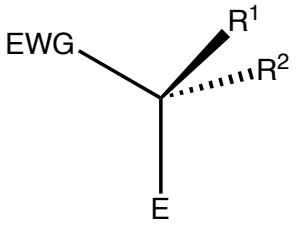
Dynamically Chiral Intermediate



sp^2
trigonal planar

Electrophile Addition

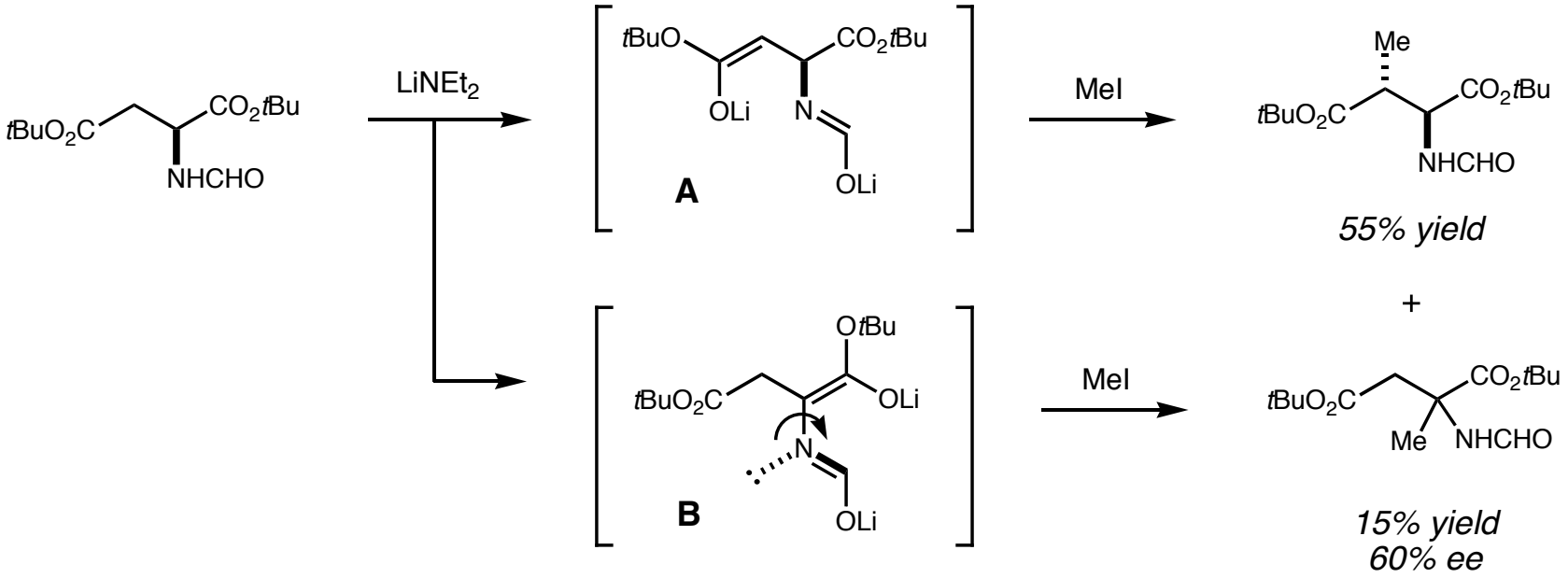
Retention of Chirality



sp^3
tetrahedral

Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373-376.

First Reported Observation of Chiral Memory



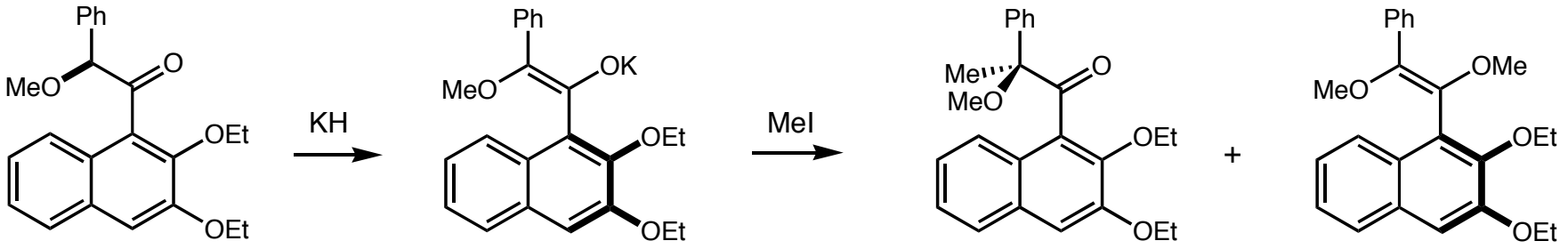
Postulated Origins of selectivity:

1) "The achiral enolate intermediate **B** forms mixed aggregates with the chiral dilithio derivative **A**."

2) "The 6-atom-8-electron π-system is axially chiral... If this interpretation should turn out to be valid, simple amino acids may also be alkylate via derivatives of type **B** (R instead of CH_2CO_2tBu) without racemization.

Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971.

The First Rationally Designed MOC Process



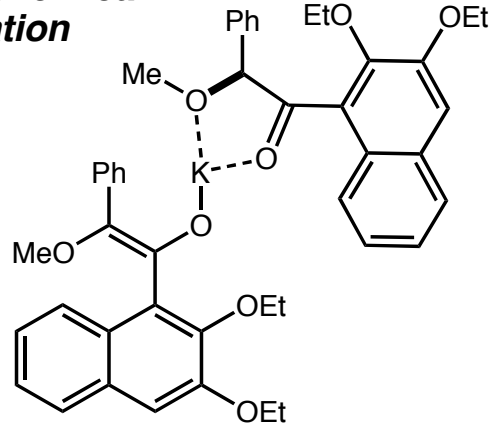
93% ee

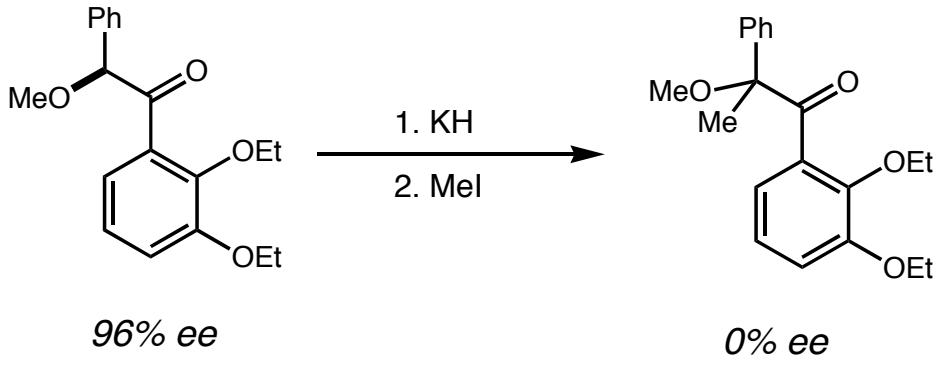
"chiral" intermediate

66% ee

≥ 65% ee

Possible Alternative Stereochemical Origination



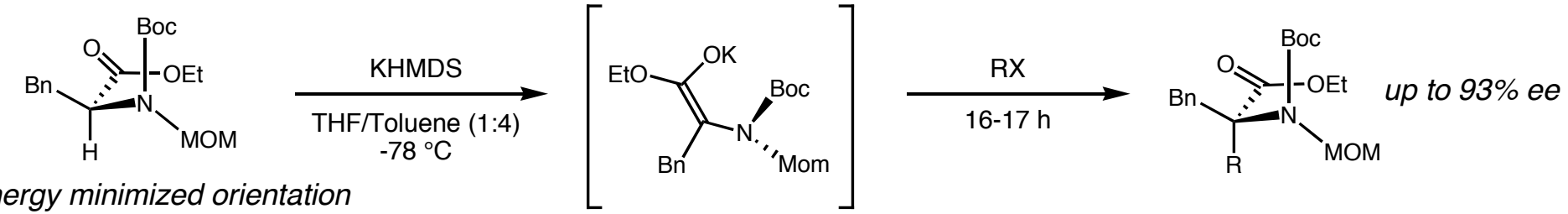


96% ee

0% ee

Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694-9696.

The First Rationally Designed MOC Process



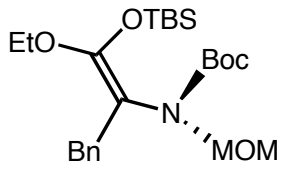
energy minimized orientation for deprotonation

Experimental Support for *MOC*

Variation in reaction time enolate intermediate of prior to MeI quench:

Barrier of Rotation = 16.0 kcal·mol^{-1}

VT NMR experimentation:

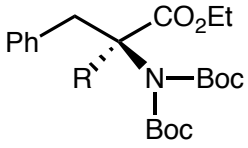


Z:E = 2:1

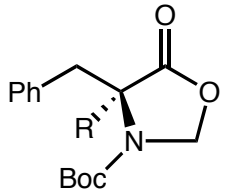
Barrier of Rotation = 16.8 kcal·mol^{-1}
(AB quartets from CH_2 of MOM)

Half-Life = 5 x 10^{-4} at 365 K
7 days @ -78 °C

Comparable substrates:



1: R = H
3: R = Me



2: R = H
4: R = Me

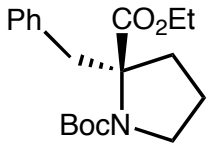
Alkylation of **1** or **2** led to racemic **3** or **4**.

Kawabata, T.; Suzuki, T.; Nagae, Y.; Fuji, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2155-2157.

Intramolecular MOC Approaches

Alkylations:

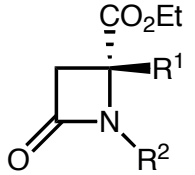
cyclic amino acids



98% ee

Kawabata et al.
J. Am. Chem. Soc. **2003**, *125*, 13012-13013.

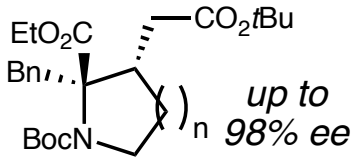
2-azetidinones



82% ee

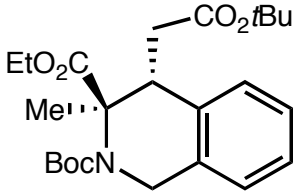
González-Muñiz, R. et al.
Tetrahedron **2006**, *62*, 130-138.

Michael Additions:



up to 98% ee

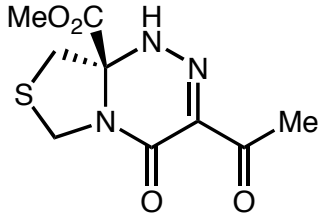
n = 1, 2, 3



95% ee

Kawabata et al.
Org. Biomol. Chem. **2005**, *125*, 1609-1611.

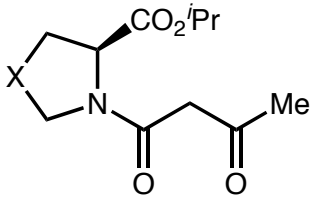
Enolate Additions to Diazoacetals:



> 99% ee

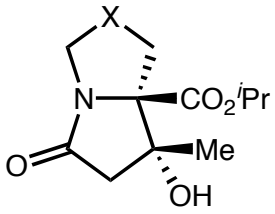
Stoodley et al.
J. Chem. Soc., Perkin Trans. 1, **1993**, 1761-1770.

Aldol Cyclizations:



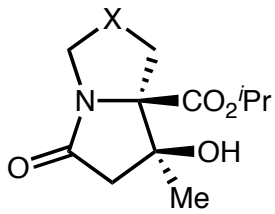
Base

X = O, CH_2
> 99% ee



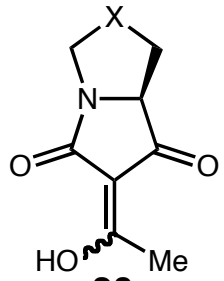
18

+



19

+



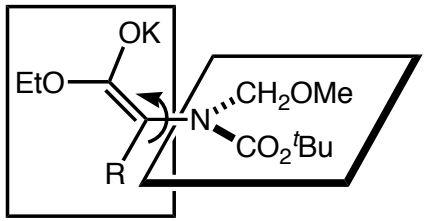
20
minor

3 : 1

Stoodley et al. *Tetrahedron Lett.* **2002**, *43*, 3919-3922.

Asymmetric MOC Cyclization at Ambient Temperature

Overcoming Racemization



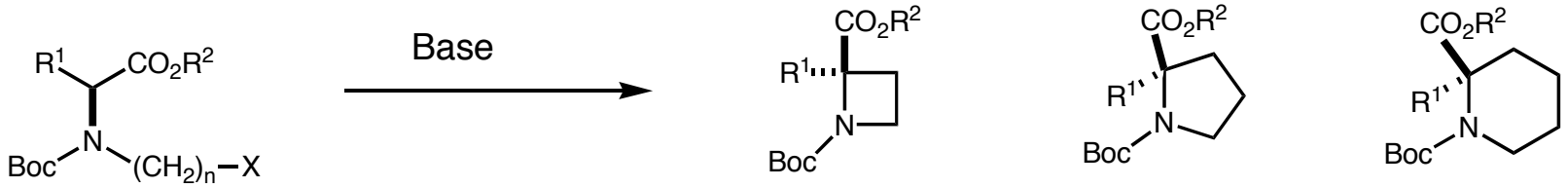
ΔG = 16 kcal/mol

$t_{1/2}$ (-78 °C) = 22 h

$t_{1/2}$ (20 °C) = < 0.1 sec

Possibility of an *intramolecular* MOC reaction in which "the chiral enolate intermediate reacts very rapidly within the time-scale of their racemization."

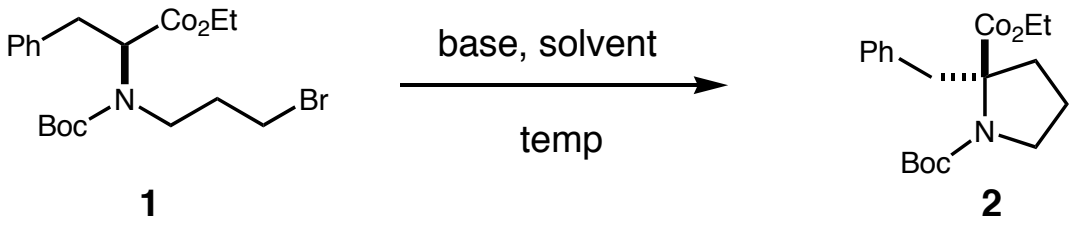
Reactivity vs Racemization?



Enantioselective approaches to rigified cyclic amino acids have played an important role in drug design and development, and in the design of novel peptides.

Revied on cyclic amino acids: Park, K.-H.; Kurth, M. J. *Tetrahedron*, **2002**, *58*, 8629-8659.

Base/Solvent Screening



1 **2**

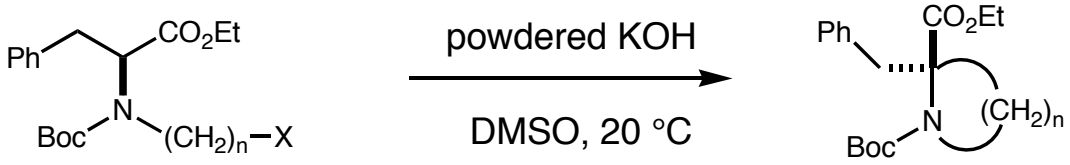
entry	base (mol equiv)	solvent	temp, time (h)	yield	ee
1	KHMDS (1.2)	DMF	-60°C, 0.5	94	98
2	KHMDS (1.2)	DMF	0°C, 0.2	97	93
5	KOH (3.0)	DMF	20°C, 0.2	89	98
6	KOH (3.0)	DMSO	20°C, 0.2	91	99
11	KOH (3.0)	1% H_2O DMSO	20°C, 0.2	98	99

LiOH was uneffective, NaOH and CsOH had inferior results

Increased amounts of H2O led to decreased reactivity

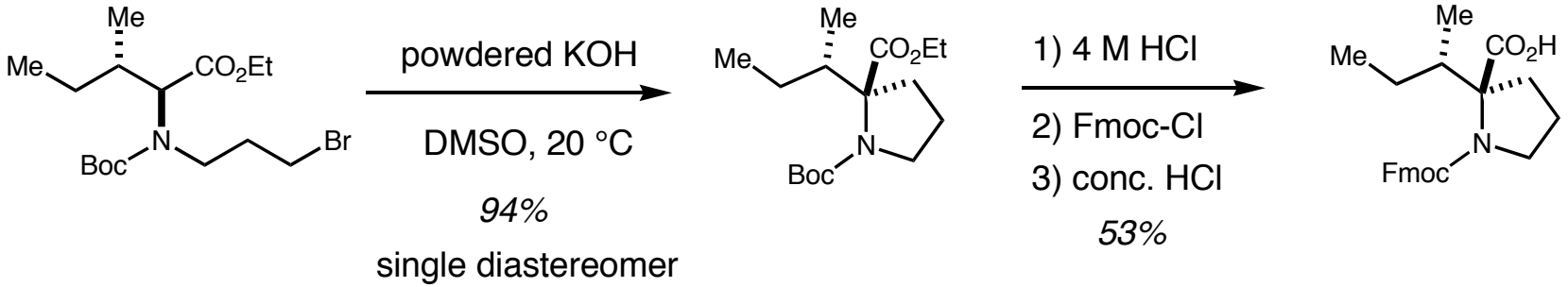
Solvents: CH_2Cl_2 proved uneffective, THF was inferior, and EtOH gives saponification.

Substrate Scope

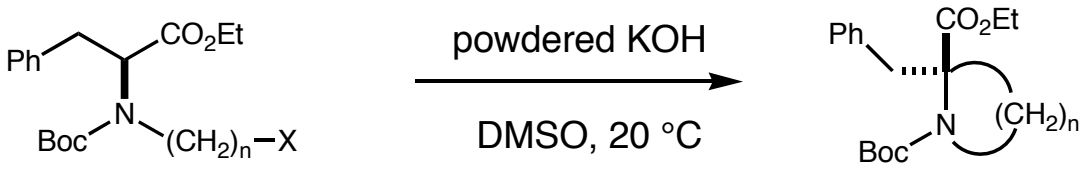


entry	n	X	time (h)	yield	ee
1	2	Br	2	82	99
4	3	Br	2	91	99
7	4	Br	12	73	90
10	4	I	2	97	97
footnote 17	5	X	?	25	49

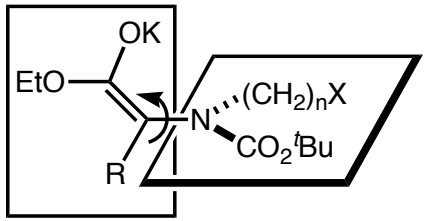
Similar trend also observed with valine and methionine derived substrates.



Mechanistic Investigation

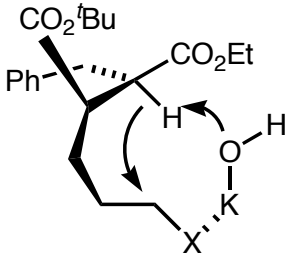


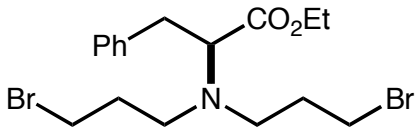
Dynamic Chirality



vs

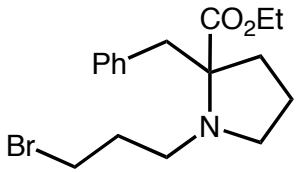
Concerted S_Ei Process





powdered KOH

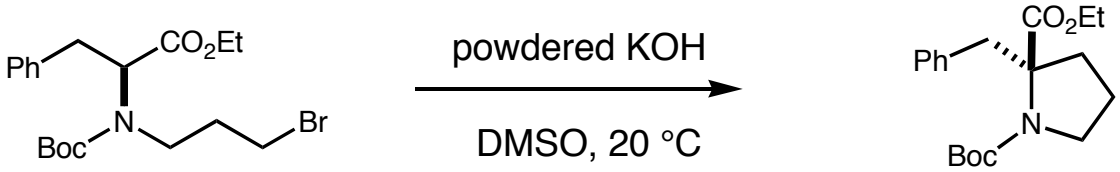
DMSO, 20 °C



racemic

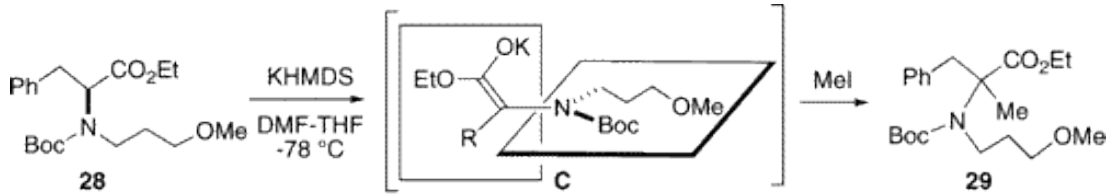
***Concerted S_Ei Process* is not plausible reaction pathway**

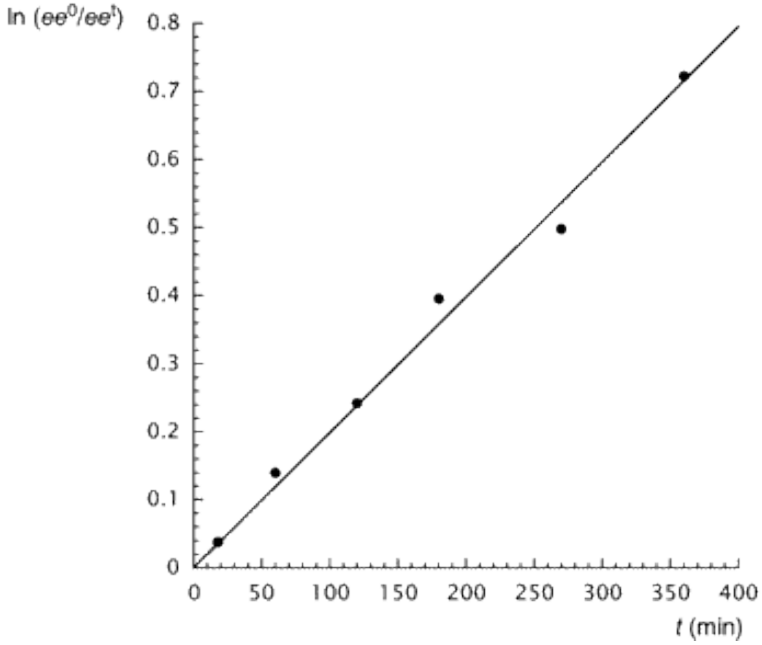
Barrier of Racemization



Difficult to determine barrier of rotation b/c of relative rate of intramolecular cyclization.

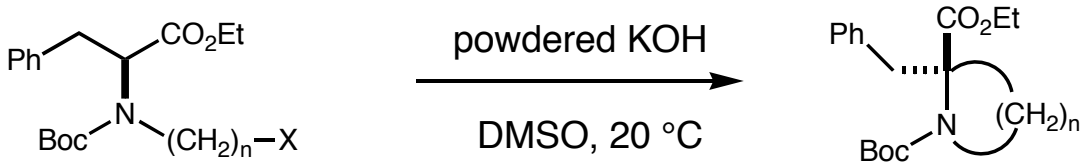
Analogous Substrate:



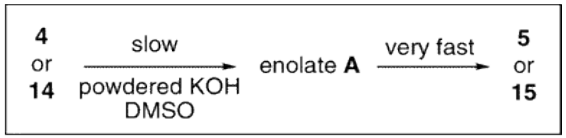


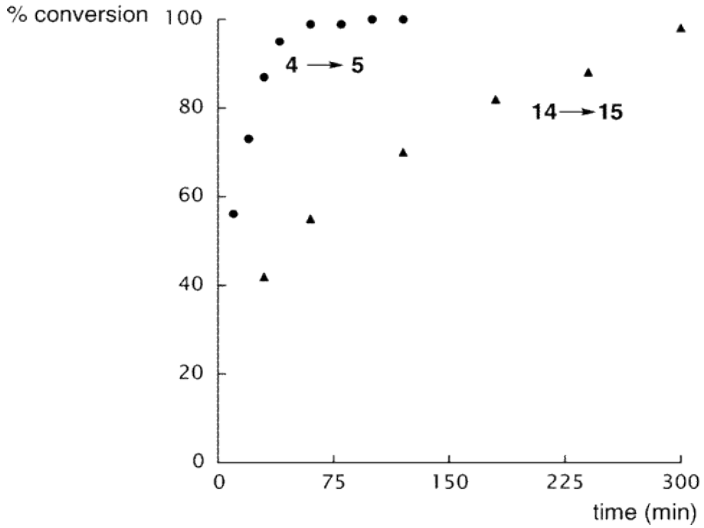
Barrier of Racemization = 15.5 kcal/mol at -78 °C ffrom the slope, 2k = 1.99 x 10-3 min-1

Relative Rate of Cyclization



entry	n	X	time (h)	yield	ee
1 (**4**→**5**)	2	Br	2	82	99
7 (**14**→**15**)	4	Br	12	73	90





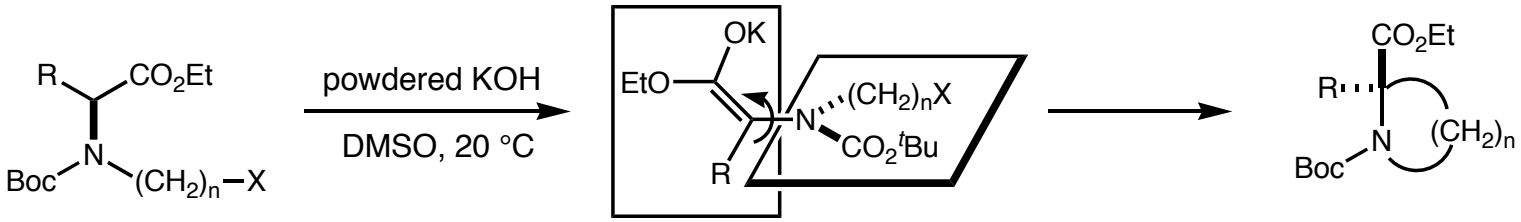
Suggested Reasoning:

Inductive effects of bromide could slightly increase the acidity of α proton

or

chelation assisted deprotonation

Summary



Kawabata and coworkers demonstrated a highly enantioselective memory of chirality cyclization at ambient temperature.

The obtained cyclic amino acids are important role motifs in drug design and development, and in the design of novel peptides.

Interestingly, the cyclization of 4-membered ring systems occurs 2 to 3 times faster than the corresponding 6-membered variants.

The use of KOH in DMSO in the generation of highly reactive enolates under relatively mild conditions for enantioselective reactions has had little to no previous precedence, and could prove useful in the future for C-C bond forming processes.