

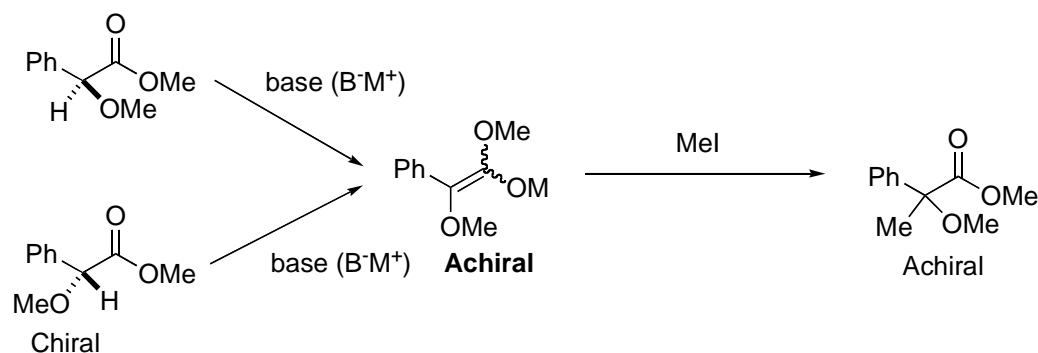
Chiral Memory: Methodology and Applications

Nicholas Perl

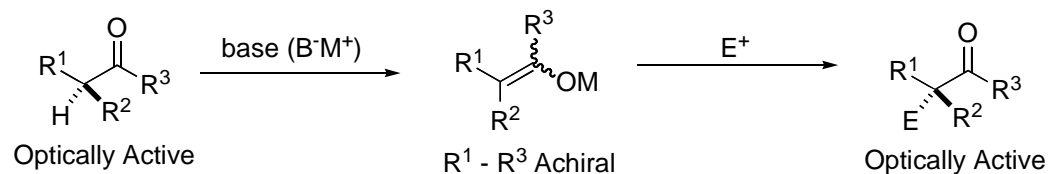
Leighton Group Meeting

October 18, 2005

Traditional Enolate Chemistry

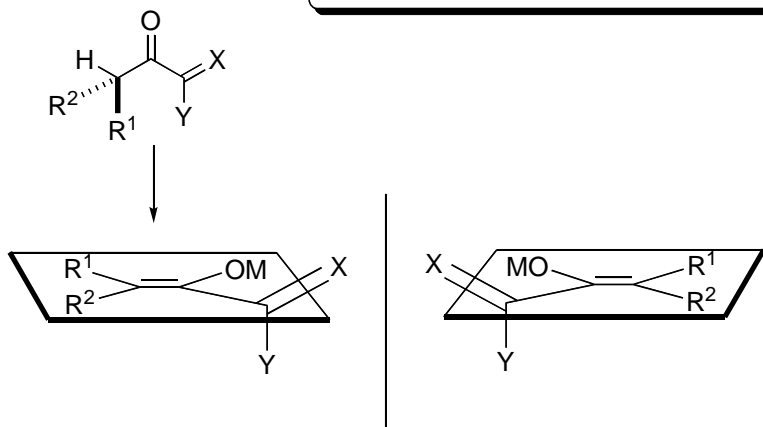
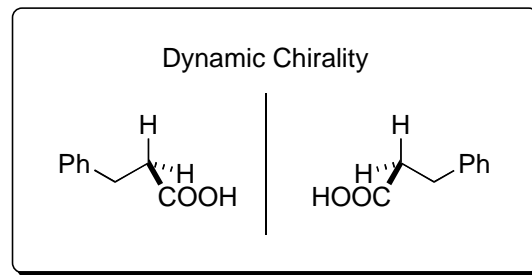
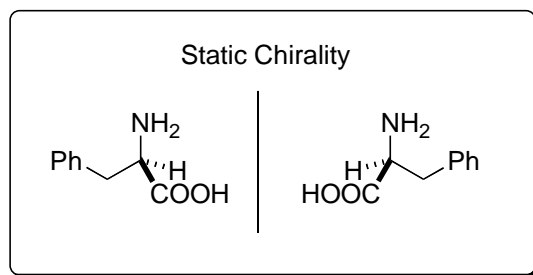


Question: Is there a way to preserve the chirality of the starting material such that addition to an enolate results in a chiral product?



Dynamic Chirality

Answer: Dynamic chirality can preserve the central chirality of the starting material



Racemization Barrier ΔG^\ddagger (kcal/mol)	Racemization $t_{1/2}$ at -78°C	Racemization $t_{1/2}$ at 25°C
12	2.4 s	2.5×10^{-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

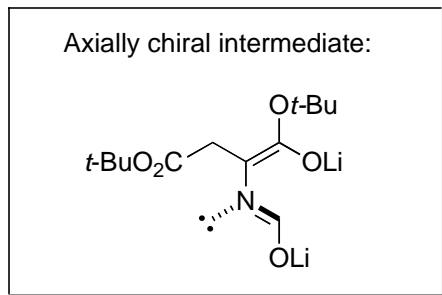
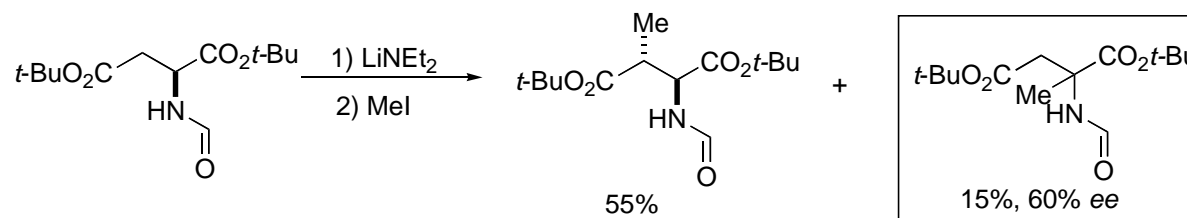
Zhao, H.; Hus, D.C.; Carlier, P.R. *Synthesis*. **2005**, 1.

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

Topics of Discussion

- Enolate chemistry and memory of chirality
 - Using axial chirality to preserve central chirality
 - Using chiral conformations to preserve central chirality
- Radical chemistry
 - Using chiral conformations to preserve central chirality
 - Translating axial chirality to central chirality

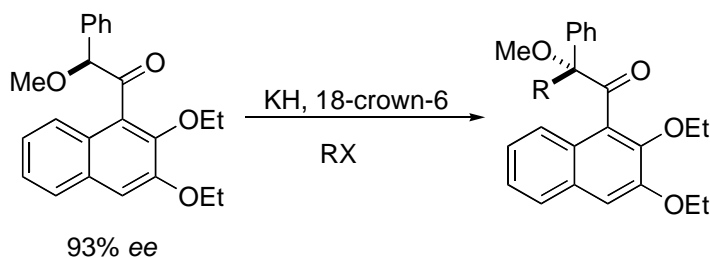
First Example of Chiral Memory?



- Seebach suggests either axially chiral enolate or enolate aggregates to explain optically enriched side product
- Appears that chiral aggregates explain enantioselectivity

First Rationally Designed System

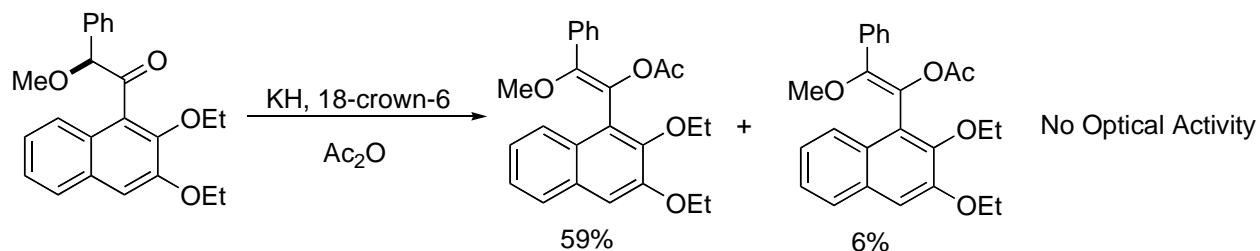
- Requirements:
 - Chiral enolates must form enantioselectively
 - Chiral enolates must not racemize on the reaction time scale
 - Reaction with the electrophile must be selective



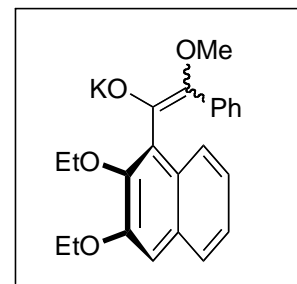
RX	yield, %	ee, %
MeI	48	66
EtI	27	65
PhCH ₂ Br	31	67
H ₂ C=CHCH ₂ Br	36	48

First Rationally Designed System

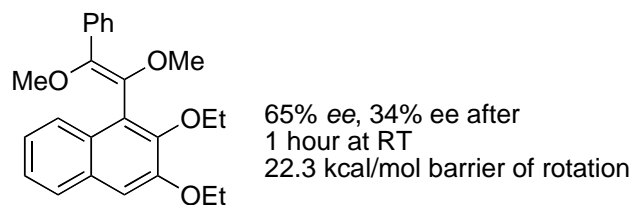
Enolate trapping experiment:



Suspected Enolate Intermediate:

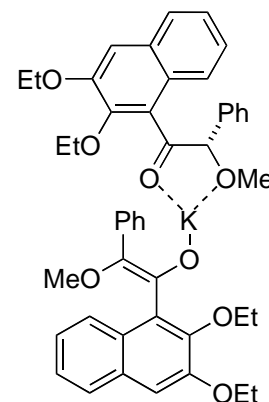


Byproduct of alkylation reaction is optically active:

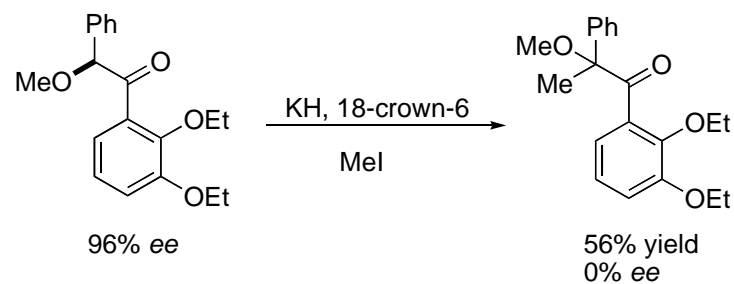


First Rationally Designed System

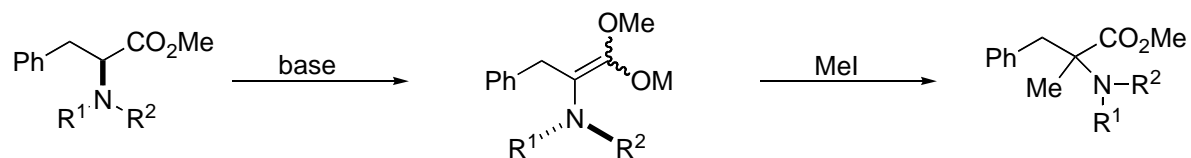
Are chiral aggregates inducing selectivity?



Results with a smaller aromatic group:



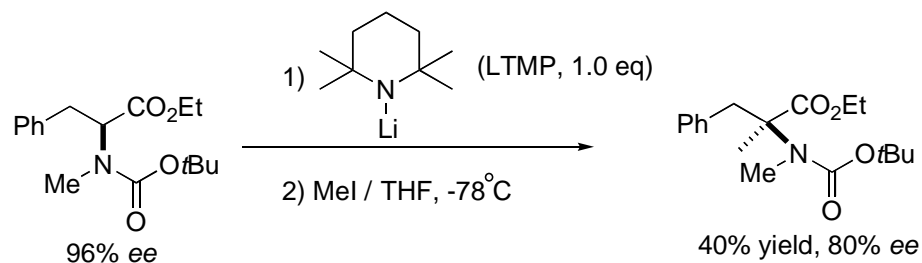
A More Synthetically Useful System



R ¹	R ²	base	yield, %	ee, %
Me	CH ₂ Ph	LDA	45	~0
Me	CHO	LHMDS	66	~0
Me	COPh	LDA	50	12
Me	CO ₂ CH ₂ Ph	LHMDS	40	26
Me	CO ₂ Ad	LHMDS	38	35
Me	CO ₂ <i>t</i> Bu	LHMDS	30	36
H	CO ₂ <i>t</i> Bu	LDA	57	~0

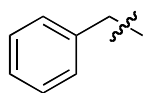
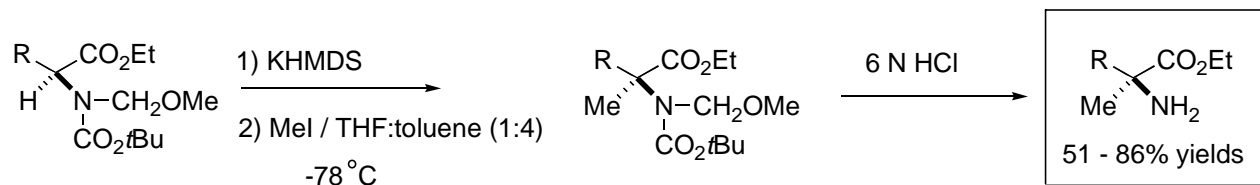
A More Synthetically Useful System

The optimized reaction:

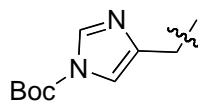


- Unacceptable yield
- Deprotection of N-methyl group is problematic
- Very low yields for electrophiles other than methyl iodide

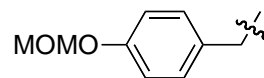
Further Optimization



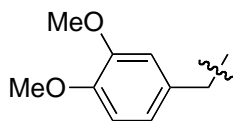
96% y, 81% ee



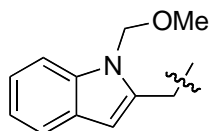
83% y, 93% ee



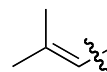
94% y, 79% ee



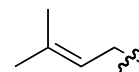
95% y, 80% ee



88% y, 76% ee

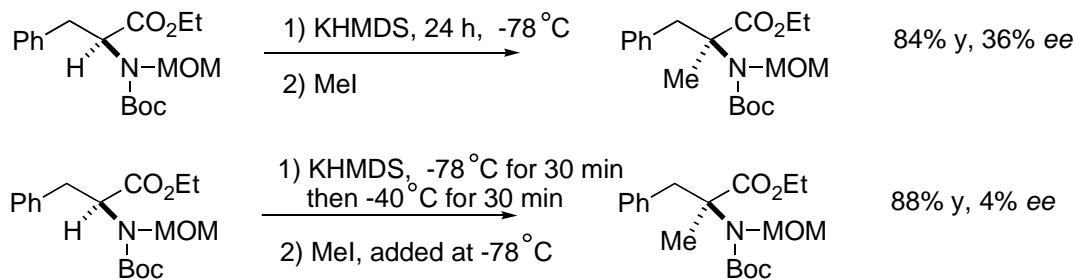
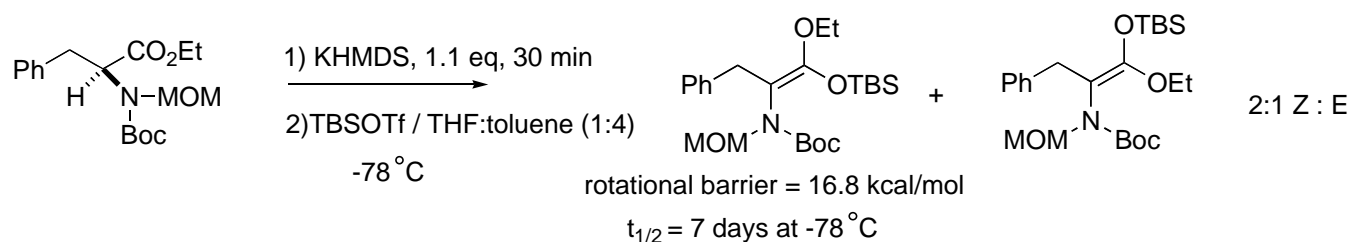


81% y, 87% ee



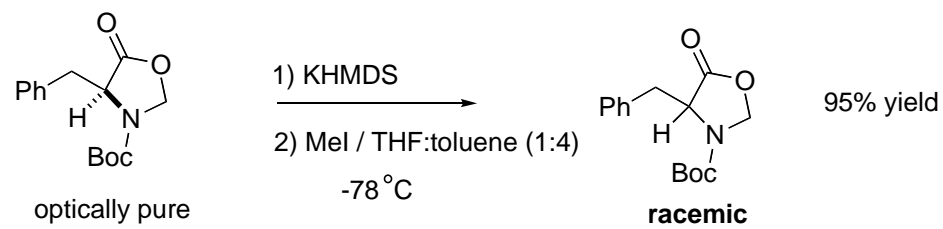
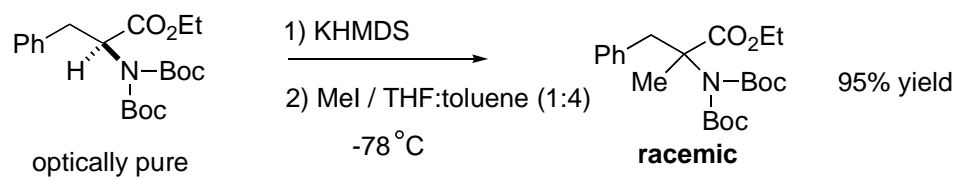
78% y, 78% ee

Mechanistic Insights

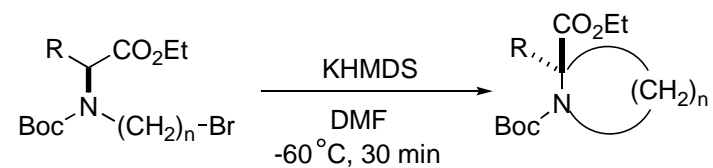


Periodic quenching of reaction mixture demonstrated the half-life of the enolate to be ~22 hours at -78 °C

Mechanistic Insights



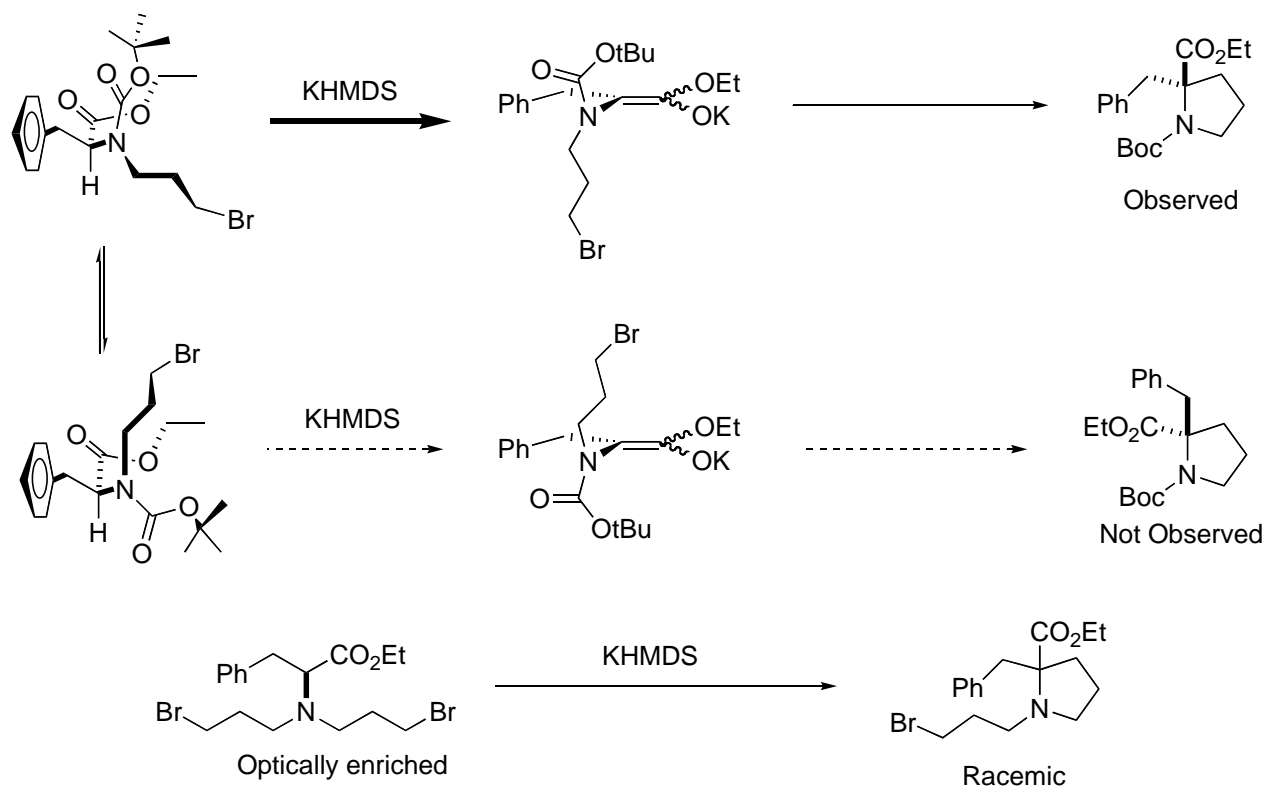
Intramolecular Alkylation



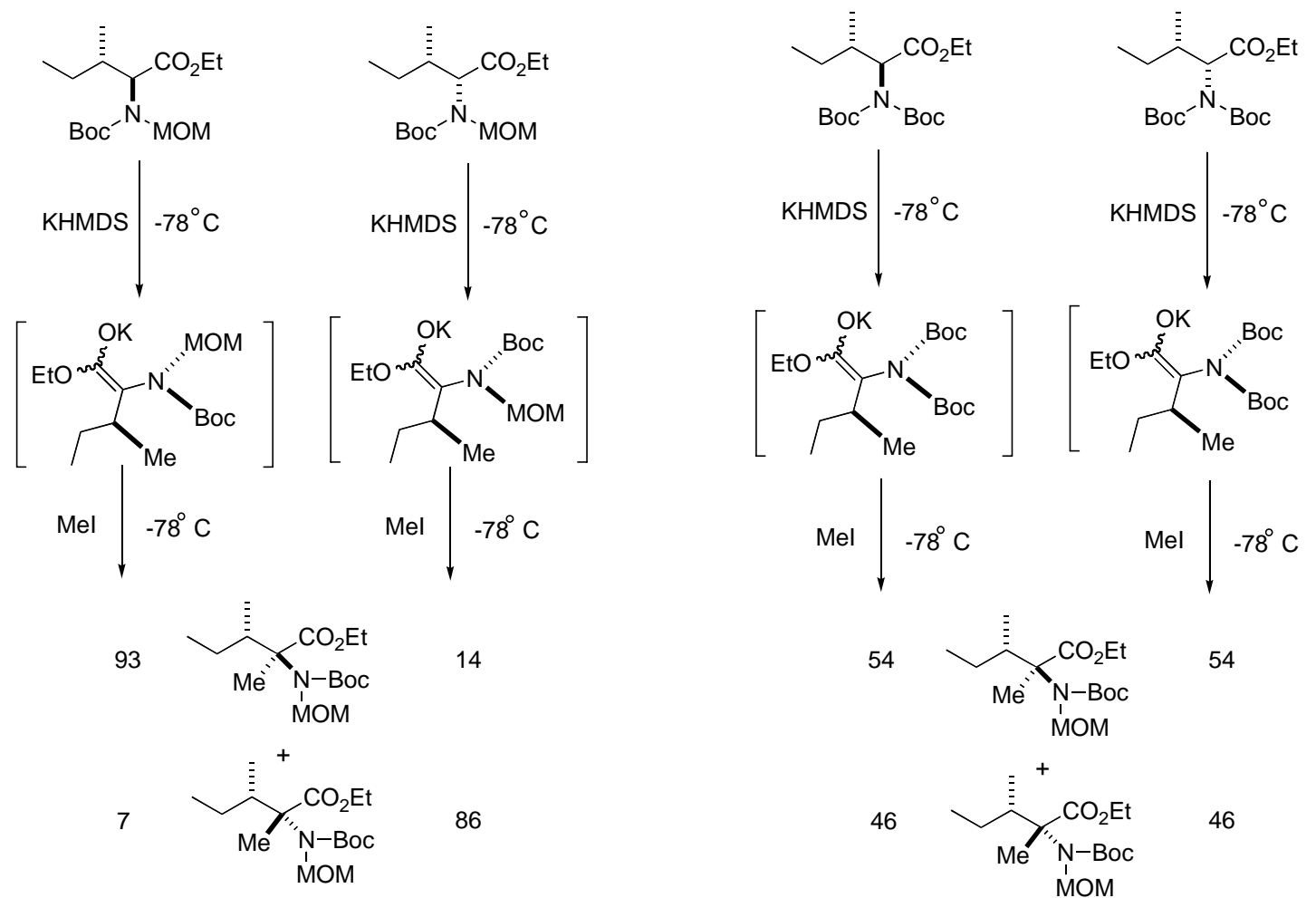
n	R	yield, %	ee, %
3	Bn	94	98
3	4-EtO-C ₆ H ₄ -CH ₂	95	97
3	MeSCH ₂ CH ₂	92	97
3	CH ₃	78	94
3	Bn	91	95
2	Bn	61	95
4	Bn	84	97
5	Bn	31	83
5 [*]	Bn	61	72

* Rxn run for 2 hrs

Stereochemical Rationalization



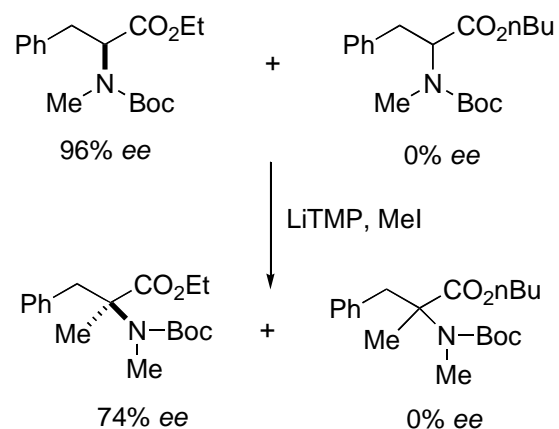
Diastereoselective Alkylation



Kawabata, T.; *et al.* *Org. Lett.* **2000**, 2883.

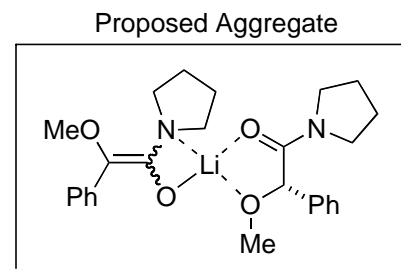
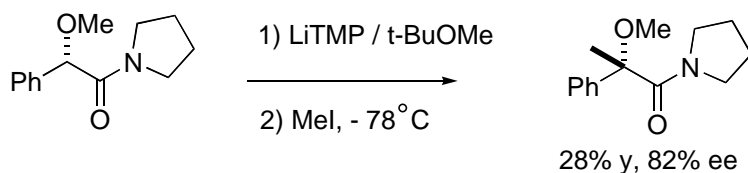
The Aggregate Question

Most of the evidence points towards chiral aggregates playing an insignificant role in chirality transfer



Kawabata, T. *et al.* *J. Am. Chem. Soc.* **1994**, 10809

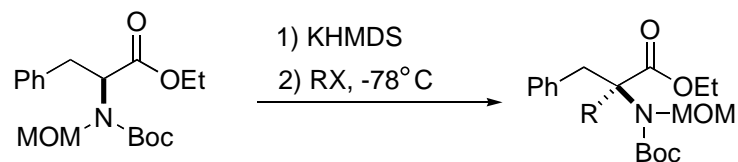
However, aggregates play a role in some systems



Kawabata, T.; Ozturk, O.; Chen, J.; Fujii, K. *Chem. Comm.* **2003**, 162.

The Aggregate Question

In addition, electrophiles other than MeI behave strangely



RX	solvent	yield, %	ee, %
MeI	toluene-THF (4:1)	96	81
MeI	THF	93	35
	toluene-THF (4:1)	90	55
	toluene-THF (4:1)	87	69
	toluene-THF (4:1)	88	48

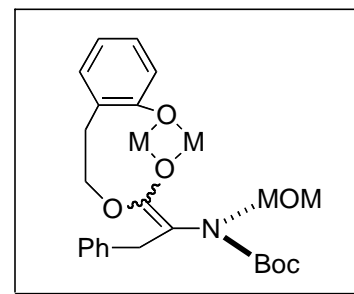
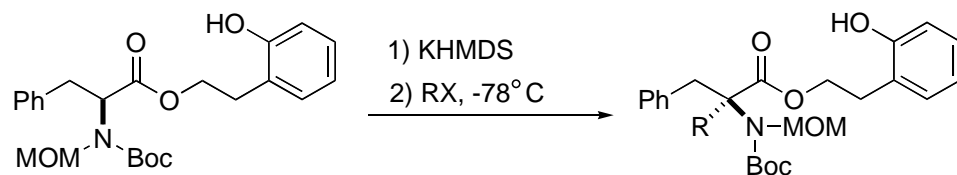
“Higher-order aggregate(s) react mainly with methyl iodide whereas lower-order aggregates react with bulkier electrophiles.”

Kawabata, T.; Kawakami, S.; Fuji, K.; *Tet. Lett.* **2002**, 1465.

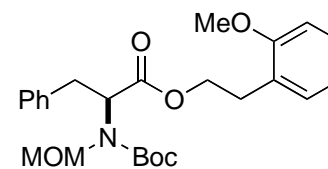
Kawabata, T.; Kawakami, S.; Shimada, S.; Fuji, K. *Tetrahedron.* **2003**, 965.

Control of Aggregation

The following motif was proposed for control of enolate aggregation:



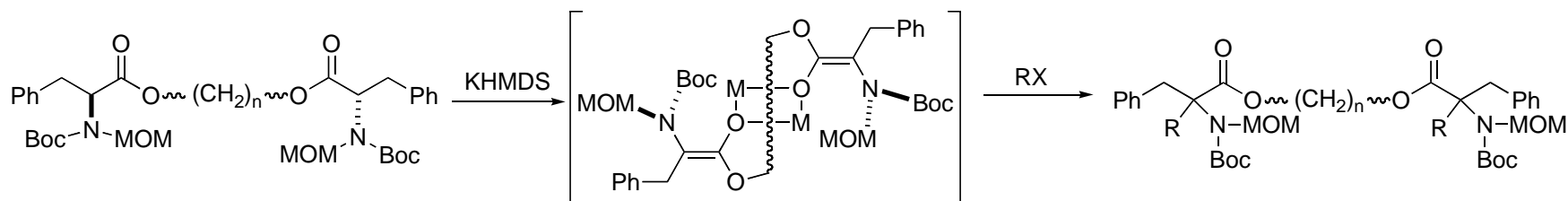
RX	solvent	yield, %	ee, %
MeI	toluene-THF (4:1)	81	88 (81)
MeI	THF	83	75 (35)
	toluene-THF (4:1)	71	82 (55)
	toluene-THF (4:1)	47	87 (69)
	toluene-THF (4:1)	89	83 (48)



Similar results to ethyl ester

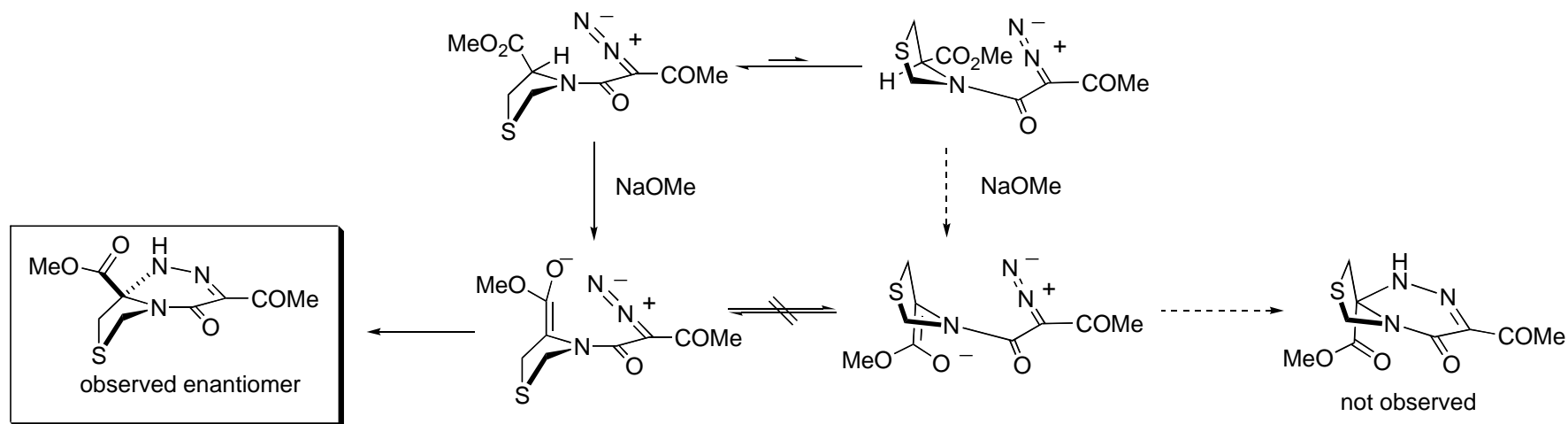
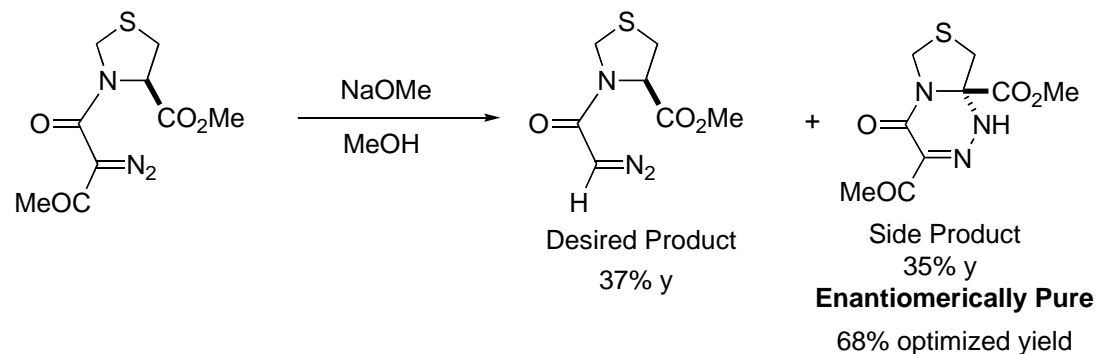
Control of Aggregation

A second motif to control aggregation:



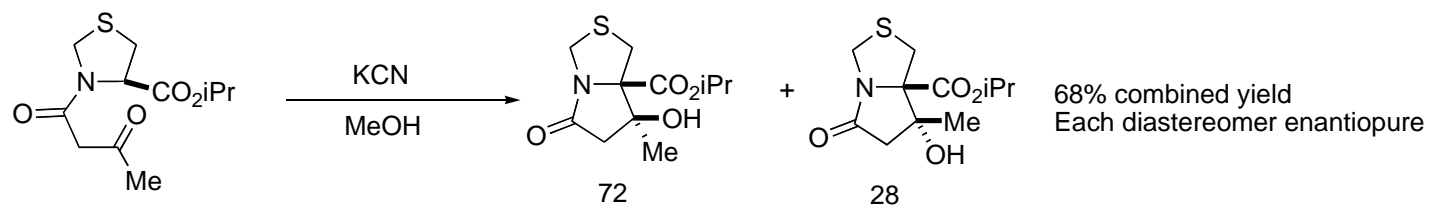
n	RX	solvent	yield, %	<i>dl</i> : <i>meso</i>	<i>ee</i> , %	Total <i>er</i>
2	Mel	Toluene-THF = 4:1	65	2.0 : 1	81	77 : 23
2	Mel	THF	70	2.3 : 1	63	72 : 28
2	Allyl iodide	Toluene-THF = 4:1	37	1.6 : 1	77	74 : 26
2	Allyl iodide	THF	73	1.3 : 1	61	67 : 33
3	Mel	Toluene-THF = 4:1	62	2.4 : 1	78	74 : 26
3	Mel	THF	88	2.0 : 1	71	74 : 26
4	Mel	Toluene-THF = 4:1	78	3.4 : 1	90	85 : 15
4	Mel	THF	89	2.1 : 1	82	78 : 22
4	Allyl iodide	Toluene-THF = 4:1	78	1.9 : 1	81	76 : 24
4	Allyl iodide	THF	91	1.3 : 1	52	65 : 35
5	Mel	Toluene-THF = 4:1	72	2.4 : 1	89	82 : 18
5	Mel	THF	85	1.5 : 1	74	72 : 28

Other Cyclization Reactions

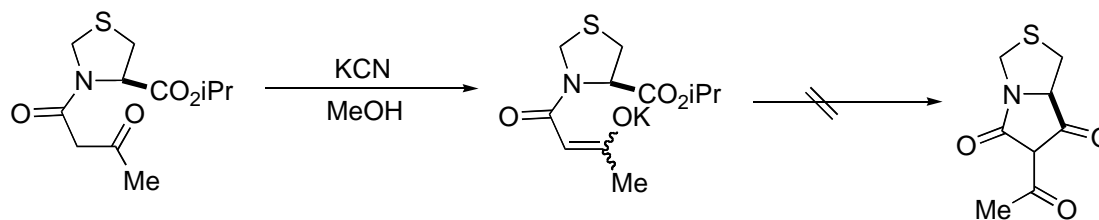


Other Cyclization Reactions

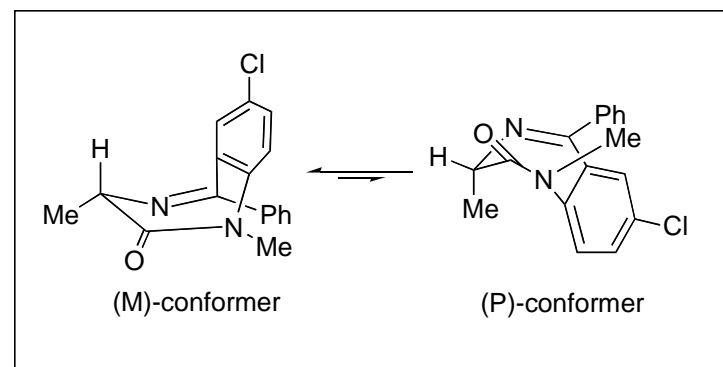
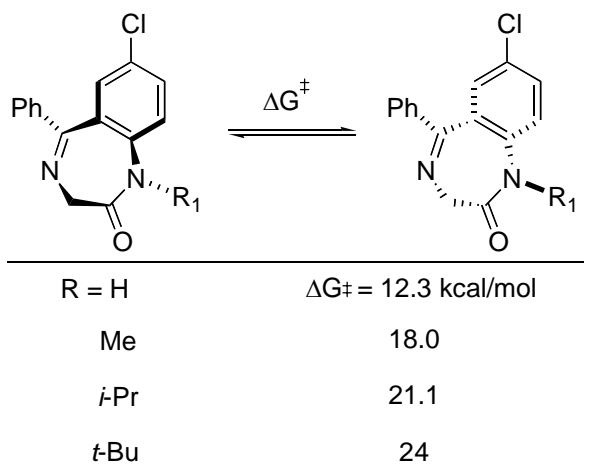
Methodology extended to C-C bond forming reactions



Isopropyl ester dampens the undesired pathway

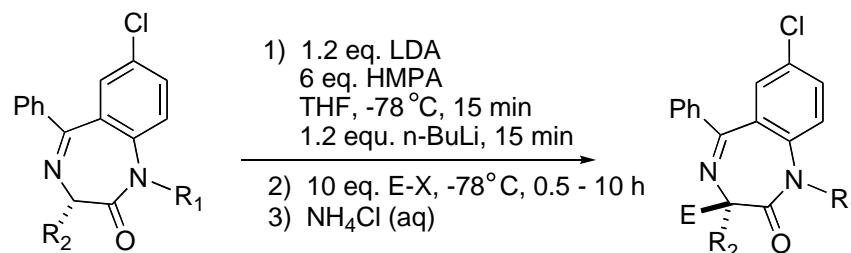


Quaternary 1,4-Benzodiazepine-2-one Scaffolds



Plan: Use the chiral conformation of the heterocycle to transfer the central chirality of the starting material

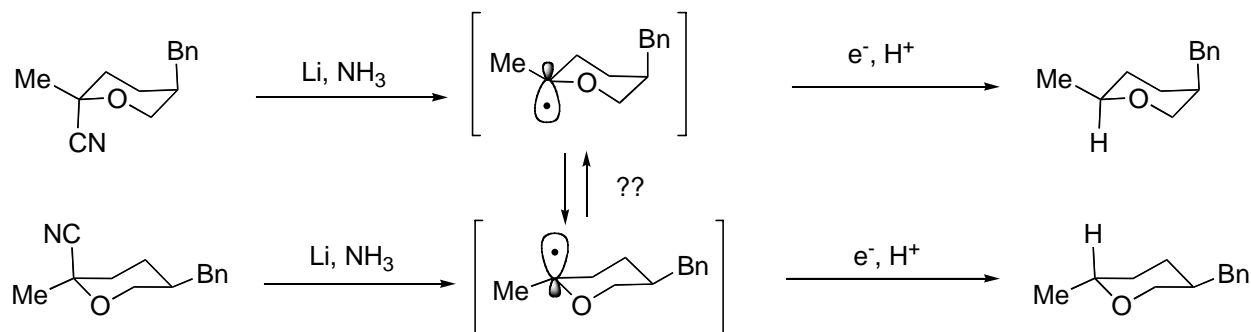
Quaternary 1,4-Benzodiazepine-2-one Scaffolds



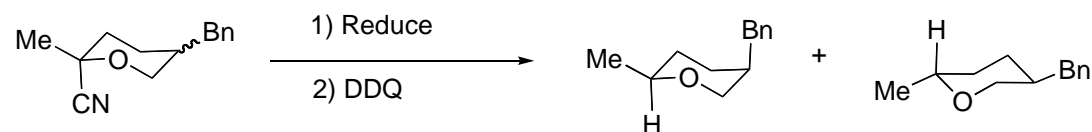
R ₁	R ₂	E-X	yield, %	ee, %
Me	Me	BnBr	72	0
<i>i</i> -Pr	Me	BnBr	74	97
<i>i</i> -Pr	Me	4-MeC ₆ H ₄ CH ₂ Br	68	95
<i>i</i> -Pr	Me	2-PhC ₆ H ₄ CH ₂ Br	70	99
<i>i</i> -Pr	Me	AllylBr	76	94
<i>i</i> -Pr	Me	D-OTFA	85	99
<i>i</i> -Pr	Me	Mel	64	95
<i>i</i> -Pr	Me	AllylBr	57	86

Radical Intermediates and Chiral Memory

- The energy barrier of radical center inversion is negligible. However, can the conformational bias of the tetrahydropyran ring preserve the chirality of a radicalized center?

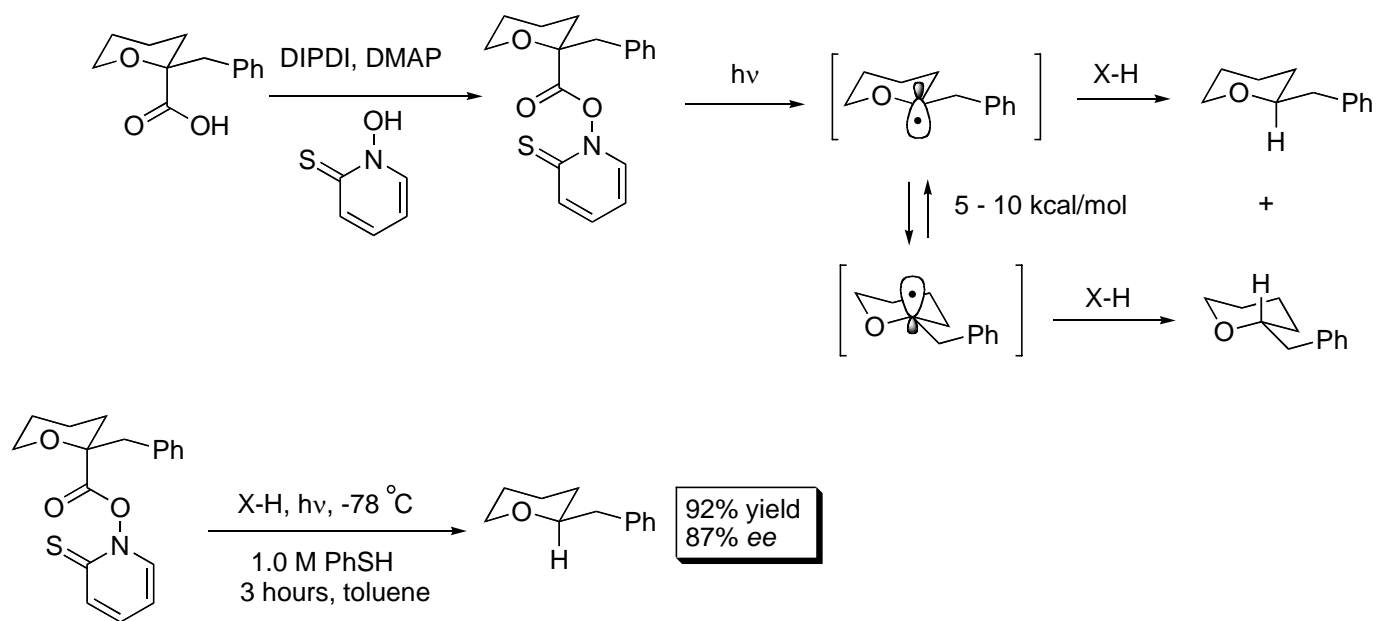


Radicals Intermediates and Chiral Memory

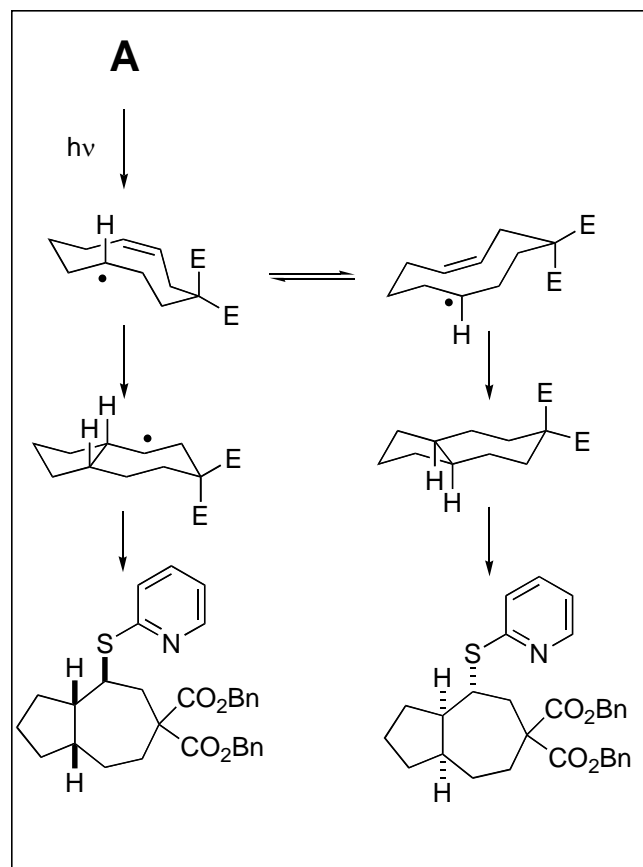
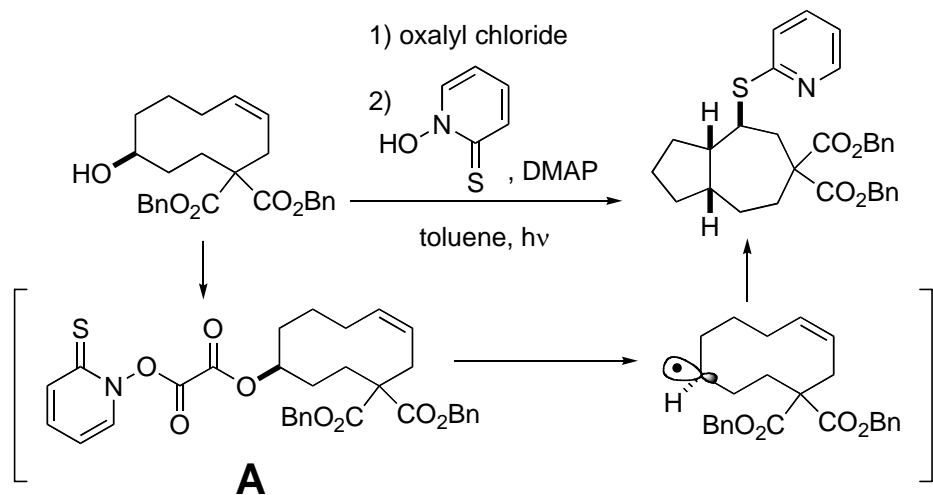


substrate	conditions		
ax	Li/NH ₃ (-78 °C)	66	34
ax	LiDBB (-78 °C)	66	34
ax	Li/NH ₃ (-33 °C)	39	61
ax	LiDBB (-95 °C)	71	29
eq	Li/NH ₃ (-78 °C)	4	96
eq	LiDBB (-78 °C)	5	95
eq	Li/NH ₃ (-33 °C)	5	95

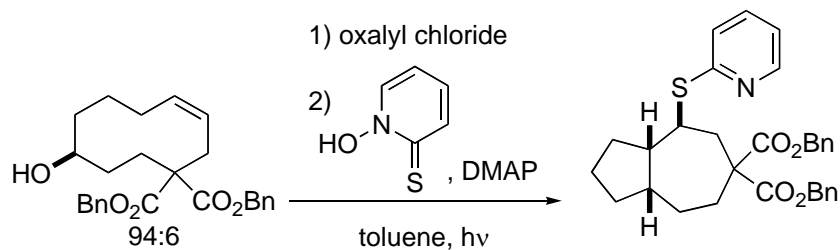
Radical Intermediates and Chiral Memory - Enantioselective Reactions



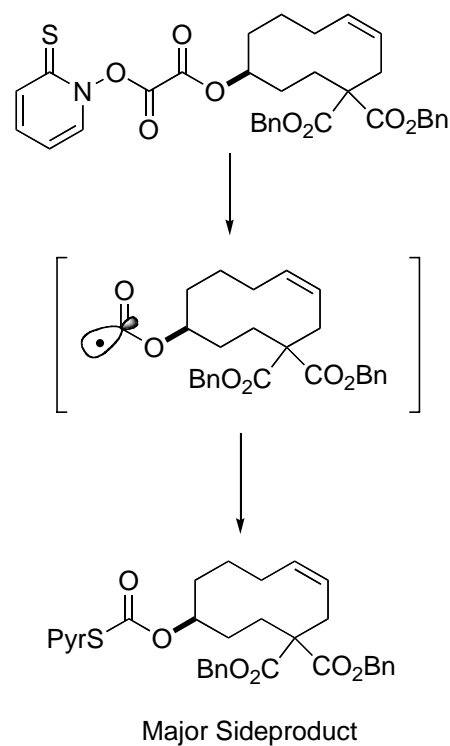
Radical Intermediates and Chiral Memory- Transannular Reactions



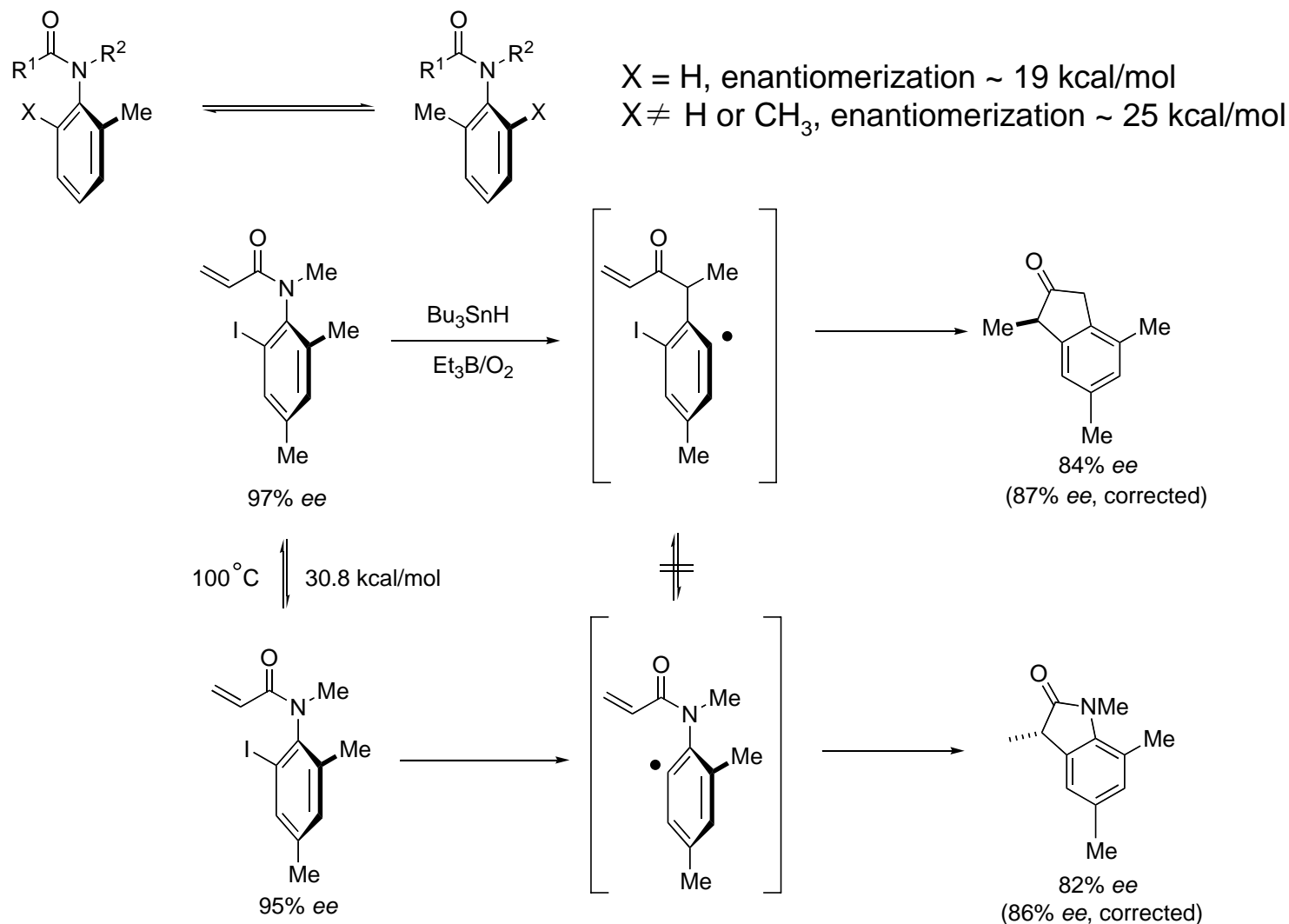
Radical Intermediates and Chiral Memory- Transannular Reactions



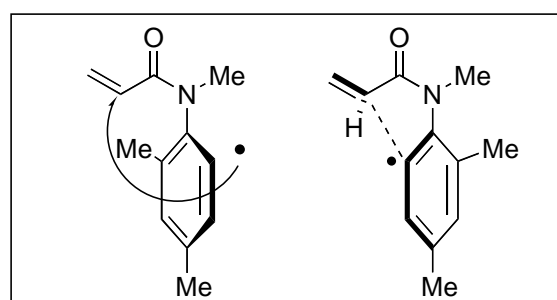
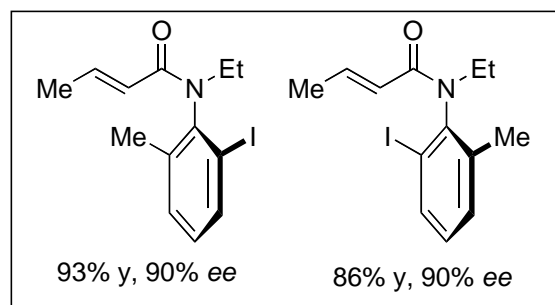
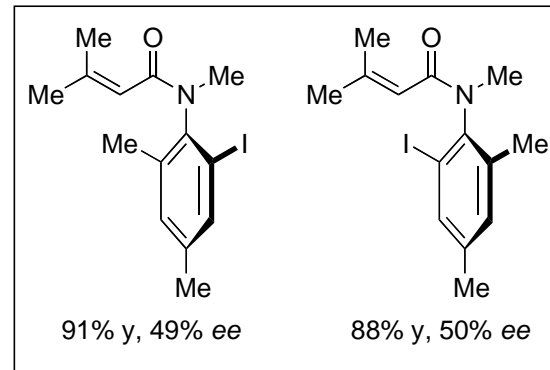
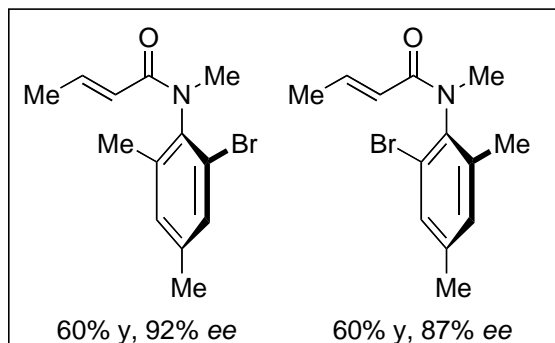
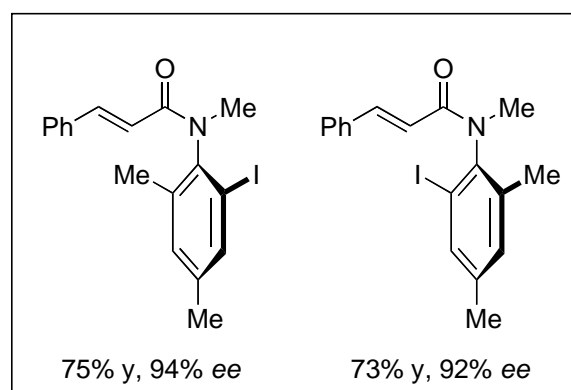
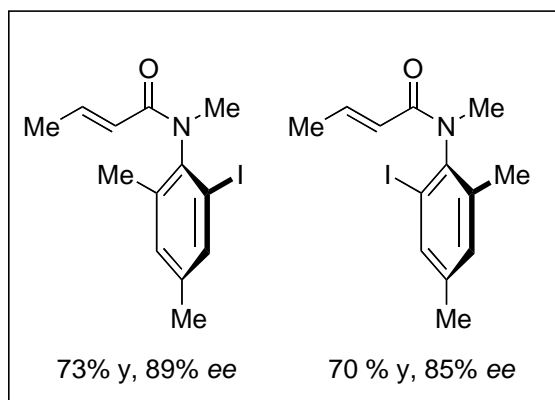
temp° (C)	yield, %	er, %
23	88	63:37
0	67	79:21
-15	51	84:16
-35	43	84:16



Transfer of Chirality Through Radical Intermediates

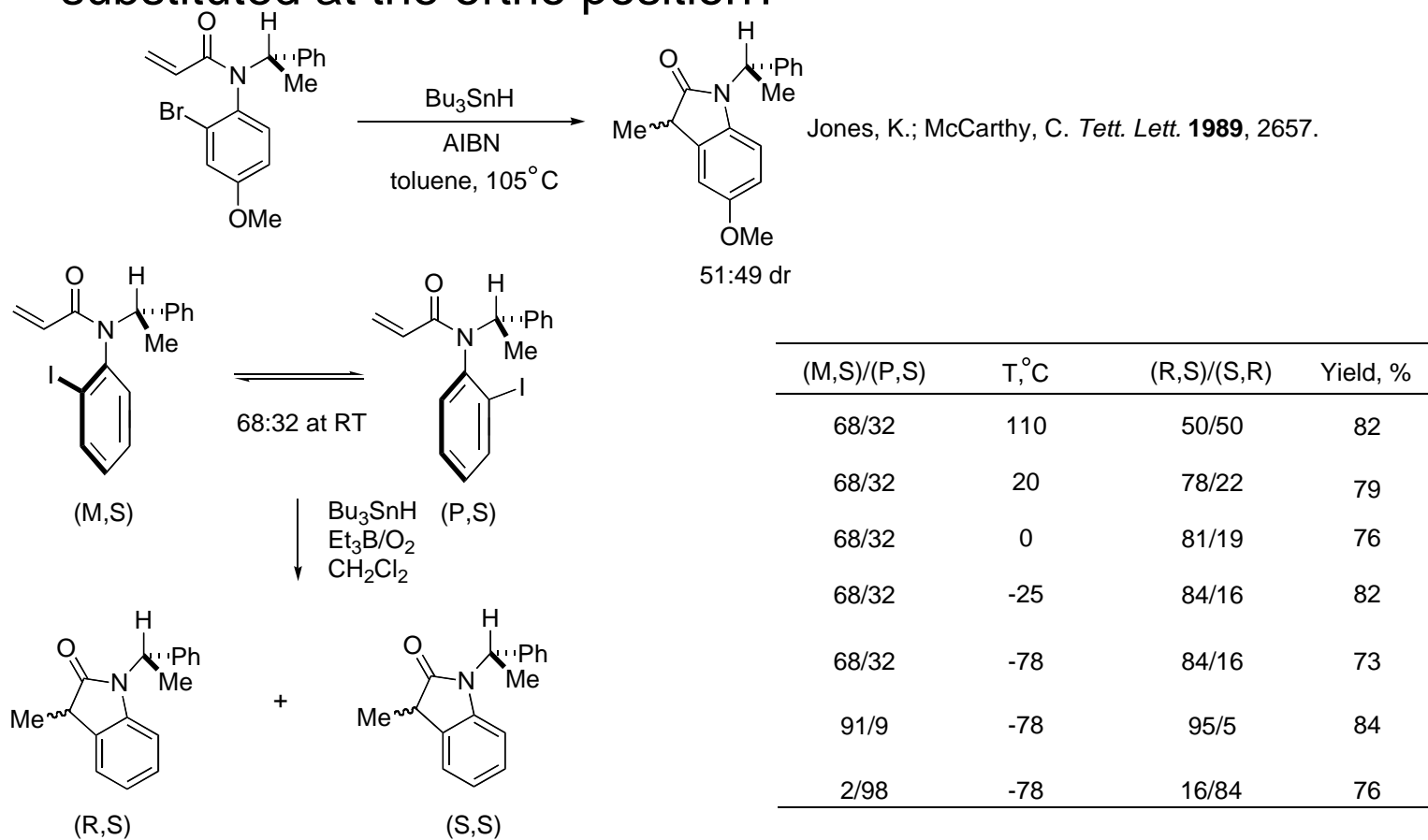


Transfer of Chirality Through Radical Intermediates

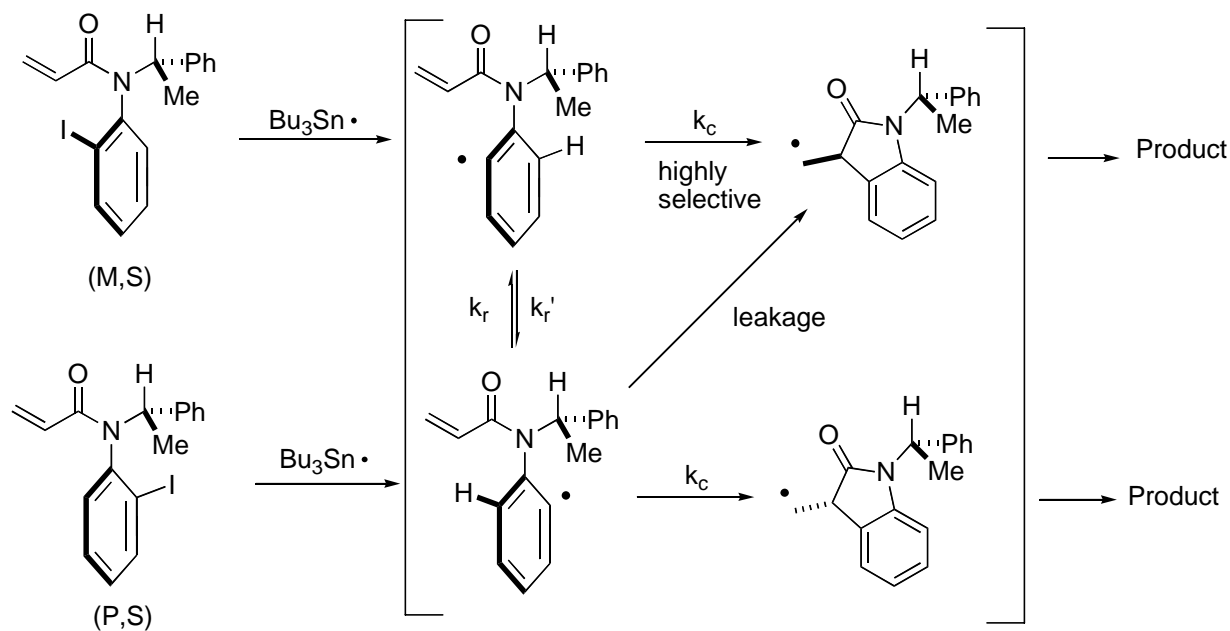


Transfer of Chirality Through Radical Intermediates

The question was now asked: what if the aryl ring is only mono-substituted at the ortho position?

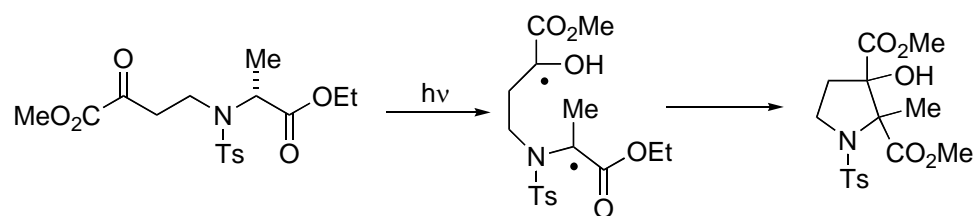


Transfer of Chirality Through Radical Intermediates

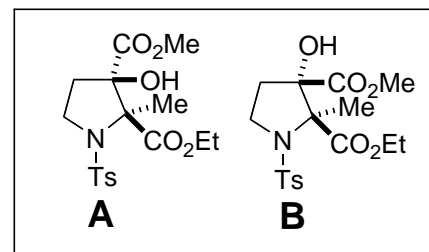


When the methyl group is exchanged for an isopropyl group, the atropisomers can be fully resolved, with radical cyclization taking place in 82 - 88% ee.

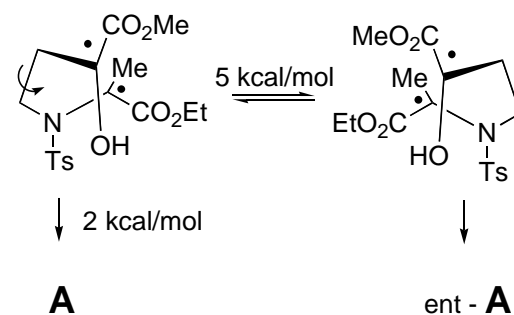
Memory of Chirality in Photochemistry



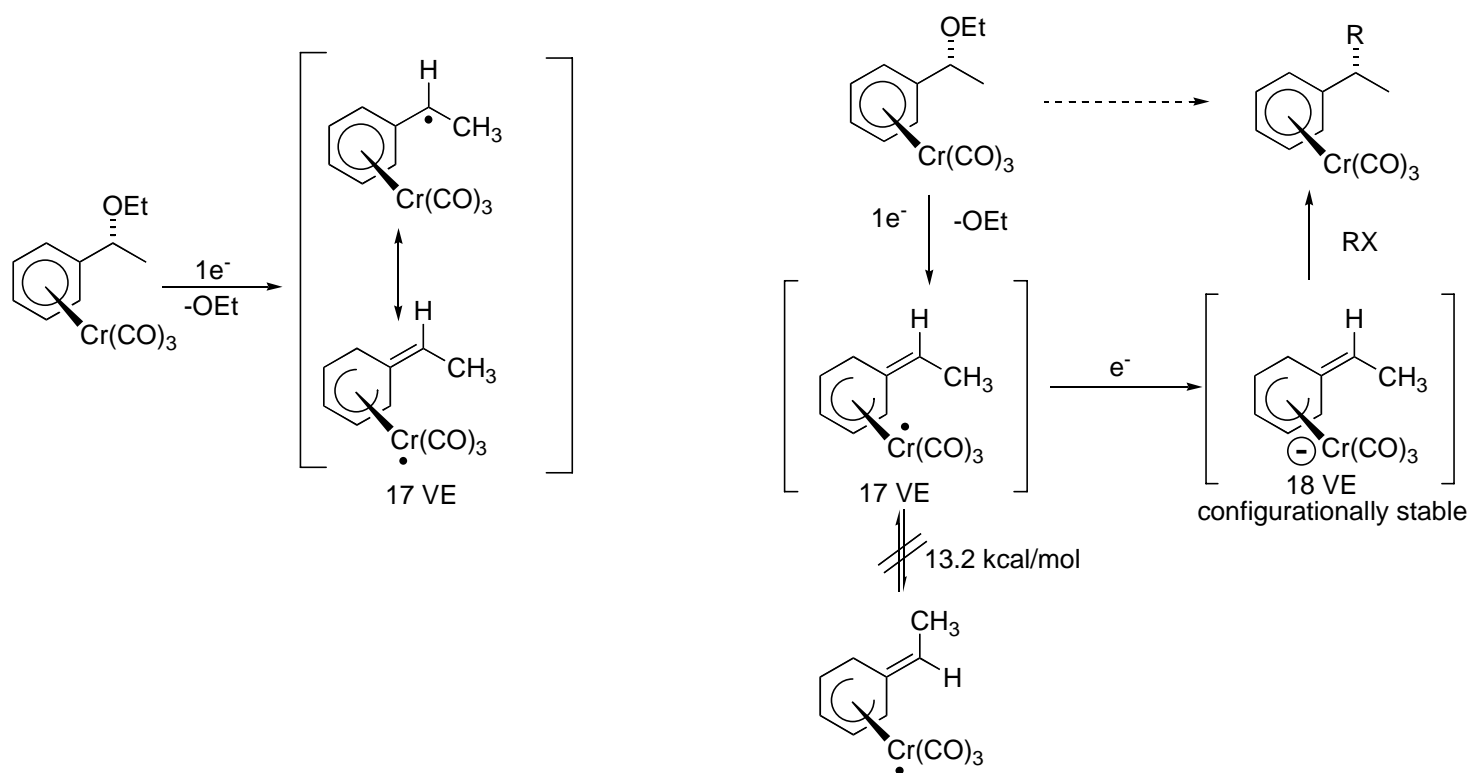
Observed Products:



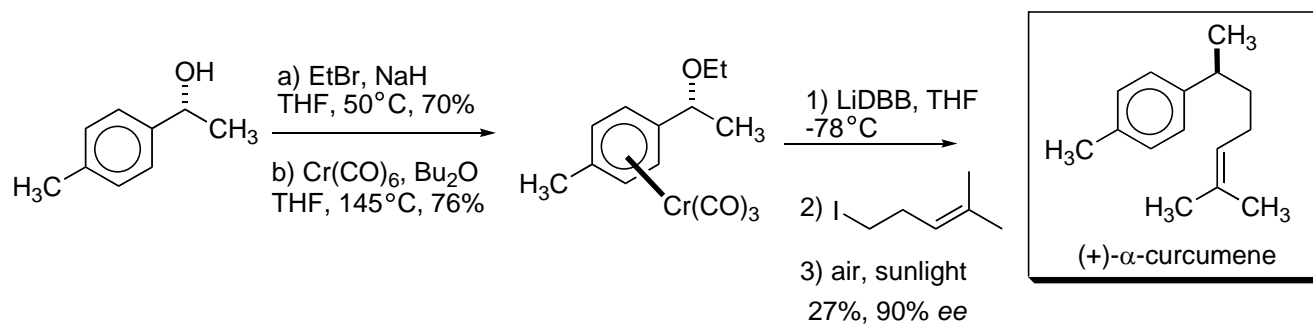
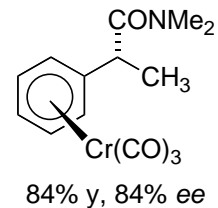
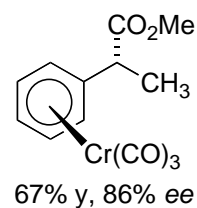
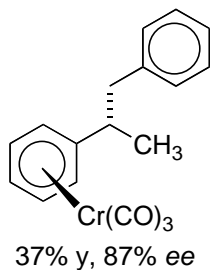
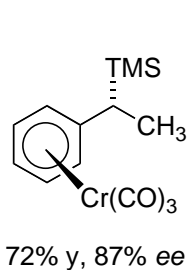
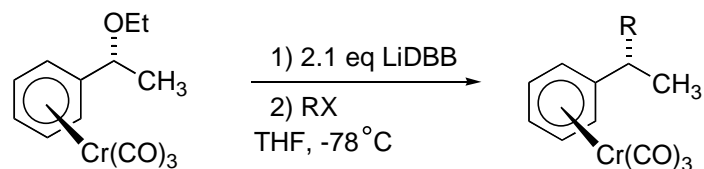
conditions	A:ent-A	B:ent-B	cis:trans	yield, %
h ν / naphalene (1M)	24	16	5.7	47
h ν / naphalene (0.5M)	18	13	5.3	50
h ν / isoprene (0.5)	9.4	3.0	2.9	47
h ν / O ₂	9.6	3.6	2.6	48
h ν / Ar	2.4	1.6	0.9	35
h ν / Benzophenone (1M)	1.4	1.4	0.8	10



Benzylic Substitution Reaction

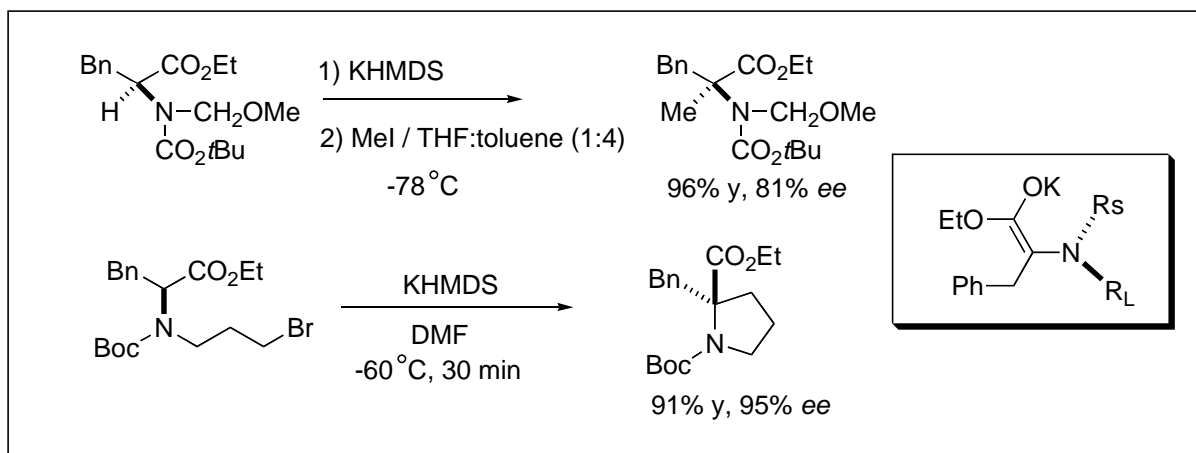


Benzylic Substitution Reaction

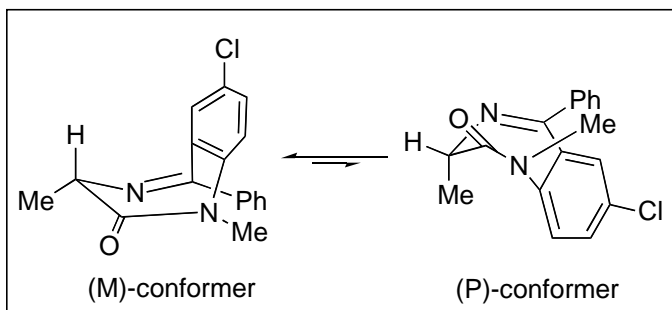


Conclusion

Chiral memory allows for the synthesis of unnatural α,α -disubstituted amino acids in good to high ee.



The energetically favored chiral conformation of benzodiazepine-2-one scaffolds can preserve the chirality of a chiral center.

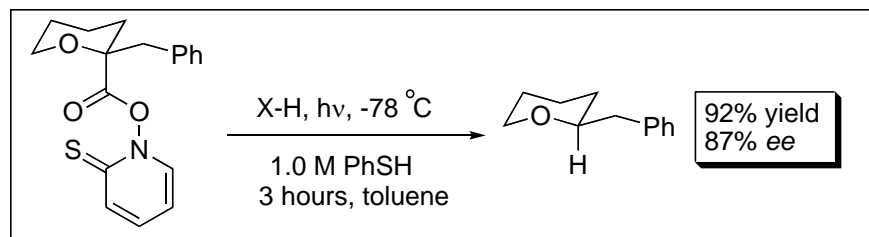


Selected Reviews On Chiral Memory

- Kawabata, T.; Fuji, K. In *Topics in Stereochemistry*, v. 23; Denmark, S. E.; Ed.; John Wiley & Sons Inc.: New York, **2003**, 175-205.
- Fuji, K.; Kawabata, T. *Chem-Eur. J.* **1998**, 4, 373.
- Zhao, H.; Hsu, D.C.; Carlier, P.R. *Synthesis*, **2005**, 1.

Conclusion

The conformation of tetrahydropyran rings can preserve the central chirality lost upon radicalization of a chiral carbon.



Axial chirality can be transferred to central chirality through a short-lived radical intermediate.

