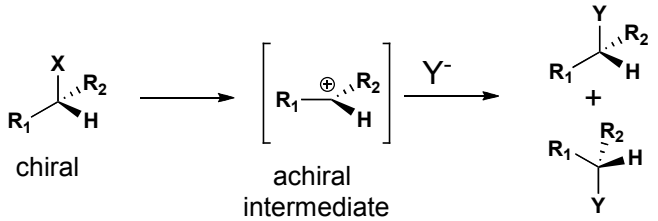
Memory of chirality

Florina Voica

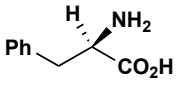
*The concept of **memory of chirality** describes a phenomenon in which the "the chirality of a starting material having a chiral sp^3 carbon is preserved in the reaction product even though the reaction proceeds at the chiral carbon as a reaction center through reactive intermediates such as carbanions, singlet monoradicals, biradicals, or carbenium ions".*

OL, **2002**, *4*, 1875.

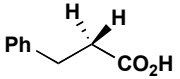
We all know that:



Furthermore:



static chirality



achiral

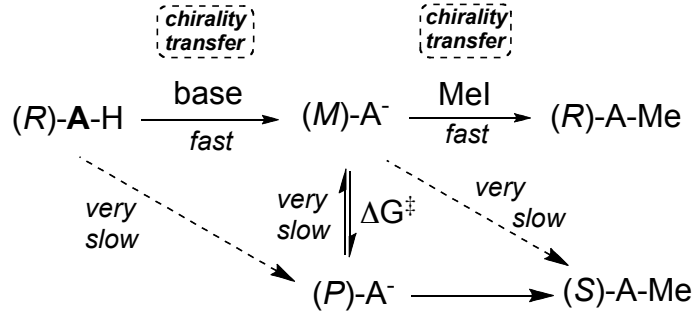
gauche conformers with transient chirality
(dynamic chirality)

Therefore, we can hypothesize that upon erosion of an unique chiral center, a non-racemic product mixture may arise from a "chiral" intermediate.

for a review see: *Synthesis* **2005**, 1.

Requirements for memory of chirality:

- enantioselective formation of a conformationally chiral intermediate from a chiral starting material
- slow rate of racemization of the conformationally chiral intermediate
- enhanced reactivity of the chiral intermediate toward product formation



What would be the ideal characteristics of a conformationally chiral intermediate in order to generate enantioenriched products?

No limitations on the type of the intermediate as long as it resits the forces of racemization:

- assuming the racemization process to be an unimolecular phenomenon, the racemization rate constant can be calculated using the Eyring equation
- best scenario: at -78 °C, for $\Delta G^{\ddagger}$= 16 kcal/mol, $t_{1/2}$ = 20h
- chiral intermediates containing sp^2-sp^2 bonds which commonly have barriers to rotation higher that 16 kcal/mol, could be successfully used to achieve memory of chirality.

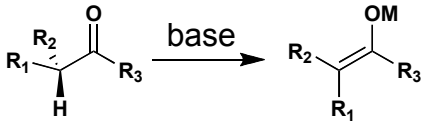
Memory of chirality

Florina Voica

1. Enolate chemistry

1.1 Enantioselective alkylation of ketones

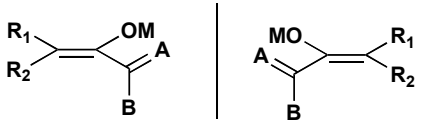
Principle:



achiral-no static chirality

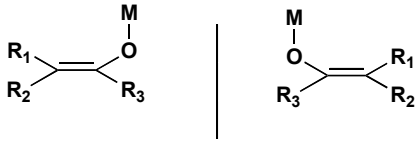
However, under specific conditions:

i.



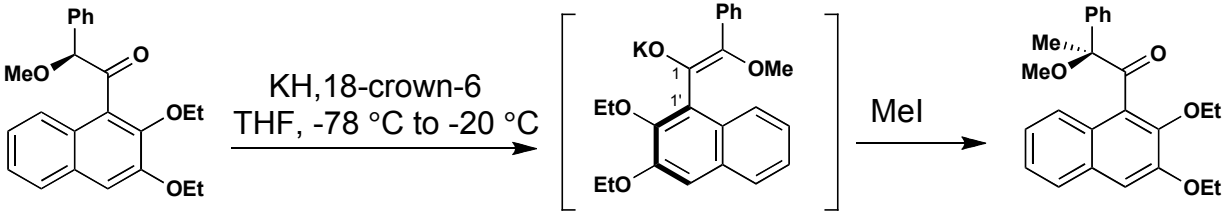
*dynamic chirality - **axial chirality***

ii.



*dynamic chirality - **planar chirality***

Application: *JACS* **1991**, 113, 9694



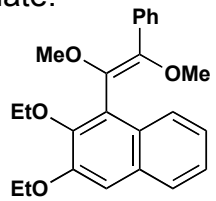
93% ee

chiral enolate with axial chirality

48% (66% ee)

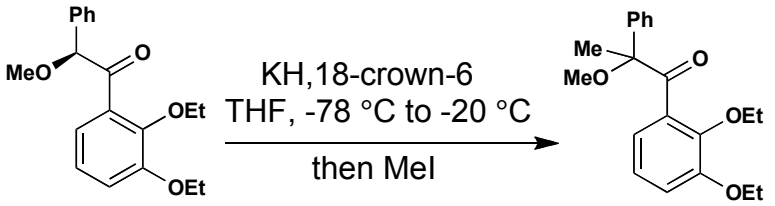
Experimental support for the formation of observed product via the supposed chiral enolate:

1.



isolated byproduct
(optically active)

2.



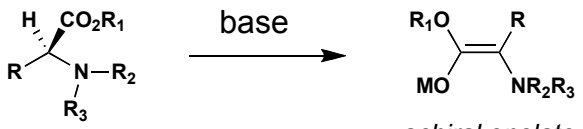
96% ee

51% (0% ee)

3. barrier to rotation across the 1,1' bond calculated to be 22. 6 kcal/mol at 21 °C.

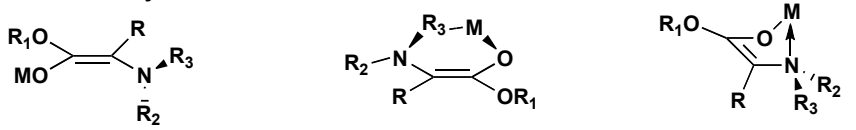
1.2 α-Alkylation of amino-acids

Principle: *Chem-Eur. J.* **1998**, *4*, 373



achiral enolate

Dynamic chirality of the enolate:



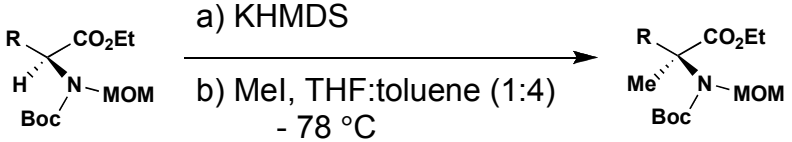
axial chirality *planar chirality* *central chirality*

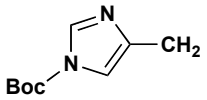
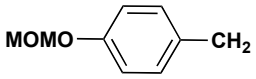
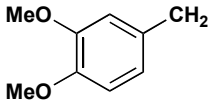
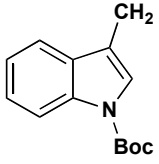
Memory of chirality

Florina Voica

Applications:

A. Intermolecular alkylation

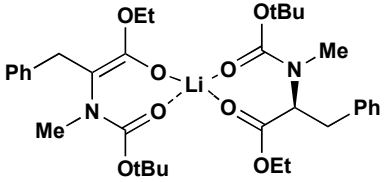


Entry	R	Yield (%)	*ee* (%)
1		83	93
2		94	79
3		80	80
4		88	76

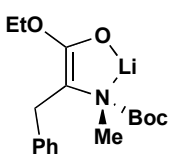
AGIE **2000**, *39*, 2155

Mechanistic studies:

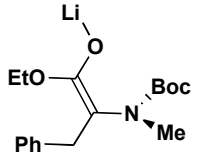
* Possible sources of asymmetric induction:



SM/enolate aggregates

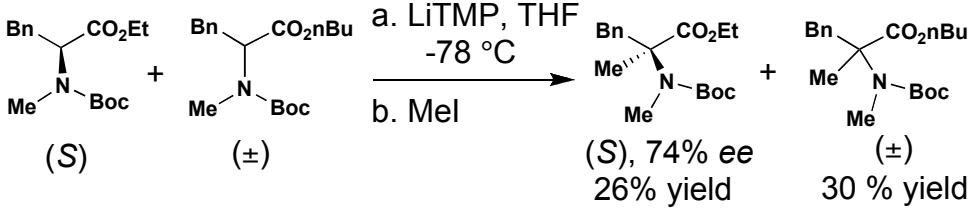


chiral enolate with central chirality



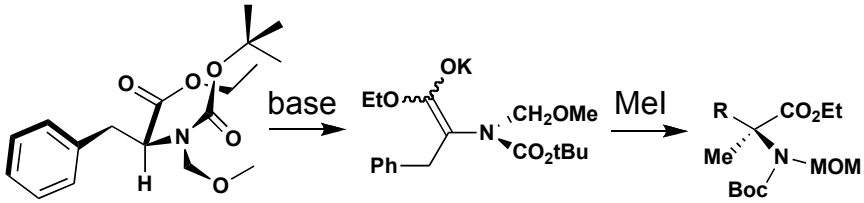
chiral enolate with axial chirality

* To rule out the formation of aggregates:



JACS **1994**, *116*, 10809

* To explain the retained streochemistry of the product:



*most stable conformer (**S**)* (molecular models calculations)

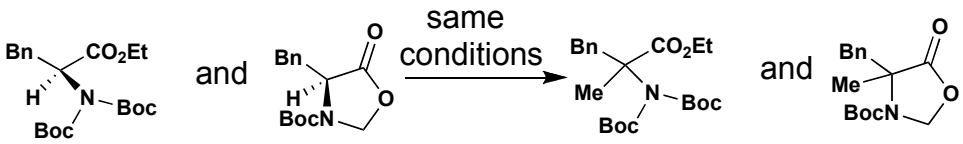
chiral enolate

*product (**S**)*

$\Delta G_{rot(C\text{-}N\ bond)}$ = 16 kcal/mol (at -78 °C)

AGIE **2000**, *39*, 2155

* To certify the implication of an axially chiral enolate:



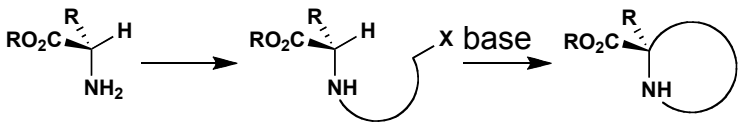
Synthesis, **2005**, 1368

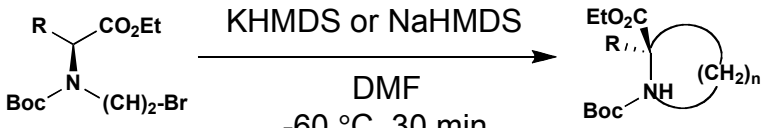
racemic mixtures

Memory of chirality

Florina Voica

B. Intramolecular α-alkylation



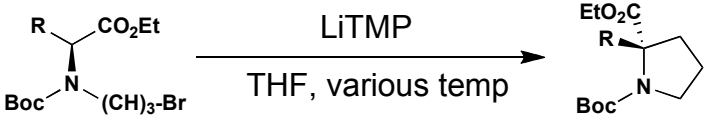


retention

Entry	R	n	Yield (%)	*ee* (%)
1	$PhCH_2$	3	94	98 (*S*)
2	$MeSCH_2CH_2$	3	92	97
3	Me_2CH	3	78	94
4	Me	3	91	95 (*R*)
5	$PhCH_2$	2	61	95
6	$PhCH_2$	4	84	97
7	$PhCH_2$	5	31	83 (*S*)

JACS **2003**, *125*, 13012

Alternatively,

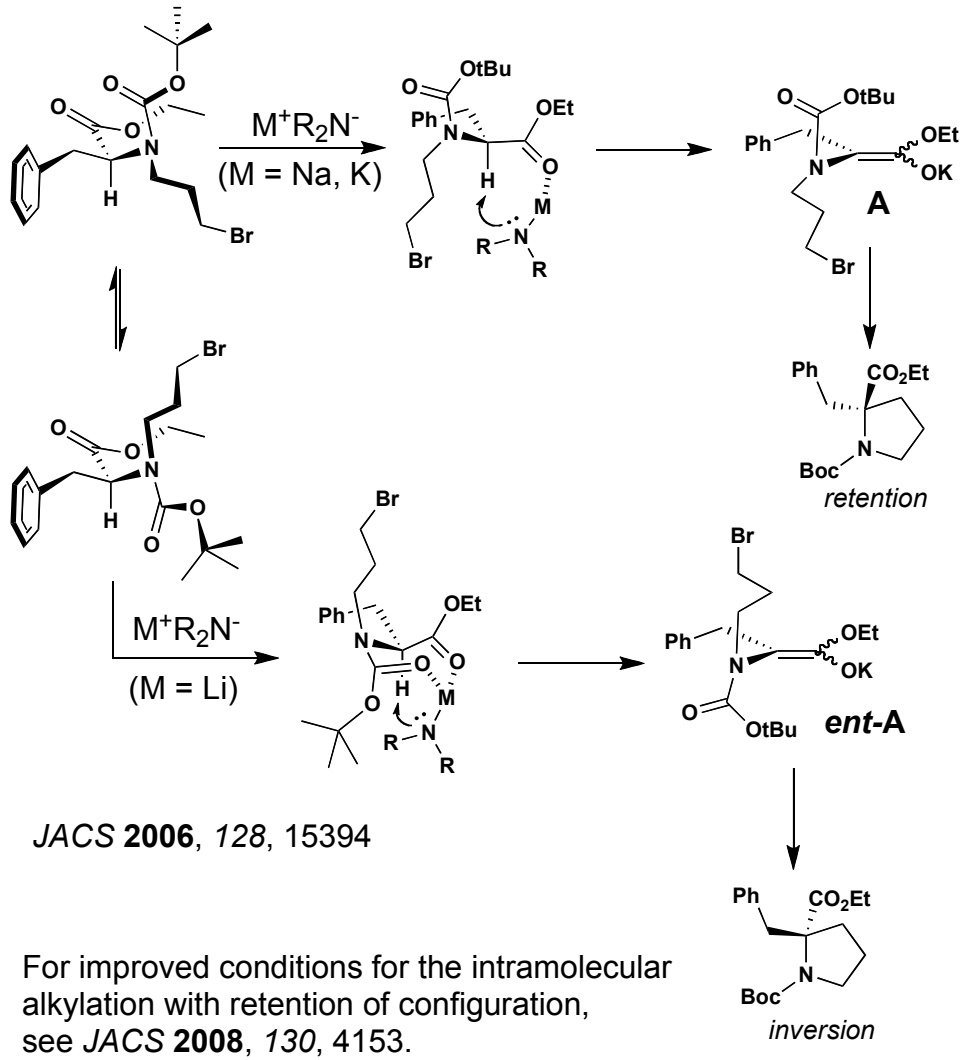


inversion

For the same R substituents, the yields are comparable with the ones observed in the previous study. The *ee*s for are the inverted product in the 81--91% range.

JACS **2006**, *128*, 15394

Mechanistic considerations:



JACS **2006**, *128*, 15394

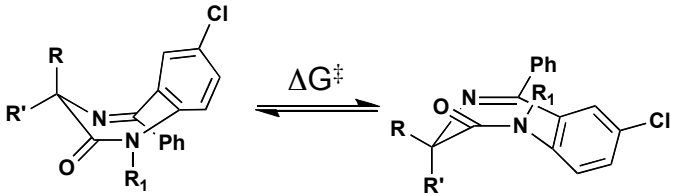
For improved conditions for the intramolecular alkylation with retention of configuration, see *JACS* **2008**, *130*, 4153.

Memory of chirality

Florina Voica

1.3 Alkylation of benzodiazepines

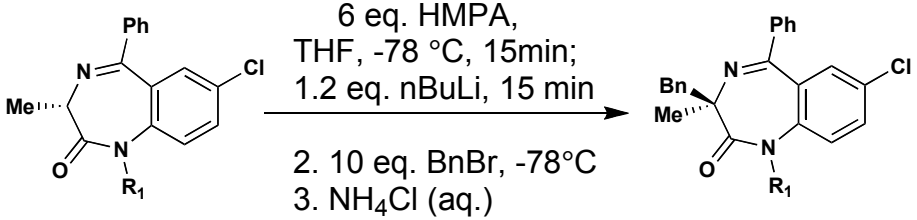
1,4-Benzodiazepin-2-ones are chiral, existing as (*M*)- or (*P*)-conformational isomers,



For R=R'=H, the equilibrium is influenced by the nature of R:

R_1	$\Delta G^{\ddagger}$ (kcal/mol)
H	12.3
Me	18
iPr	21.1
tBu	> 24

For R or R'≠ H, the pseudoequatorial conformer is favored!



R_1=Me
R_1=iPr

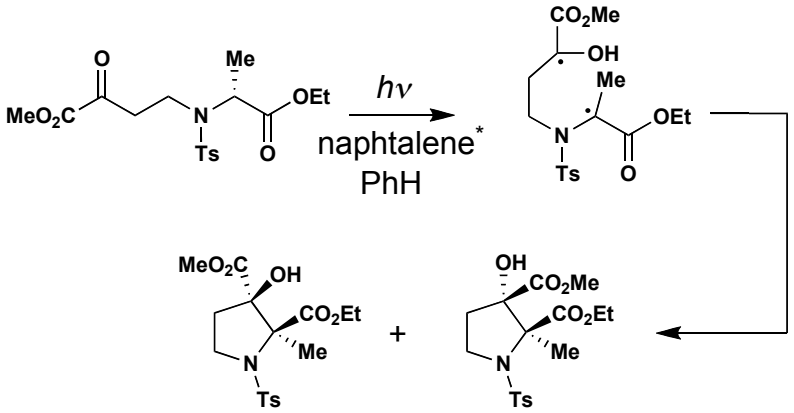
72% (0% *ee*)
74% (97% *ee*)

High enantioselectivities observed when other electrophiles (MeI, allylBr, 4-$MeC_6H_4CH_2Br$) are used

JACS **2003**, *125*, 11482
OL **2005**, *7*, 5305

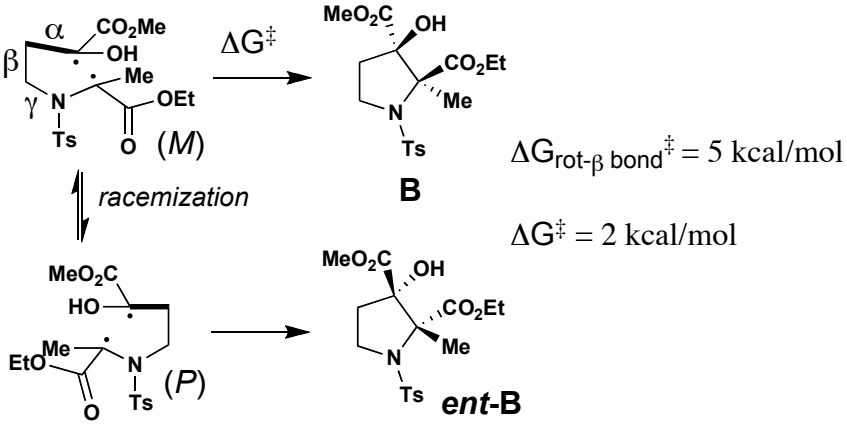
2. Radical chemistry

2.1 Memory of chirality due to spinisomers



* naphtalene is a triplet quencher

Proposed mechanism:



The observed *ee*s are due to a slow racemization compared to the cyclization of the singlet diradical.

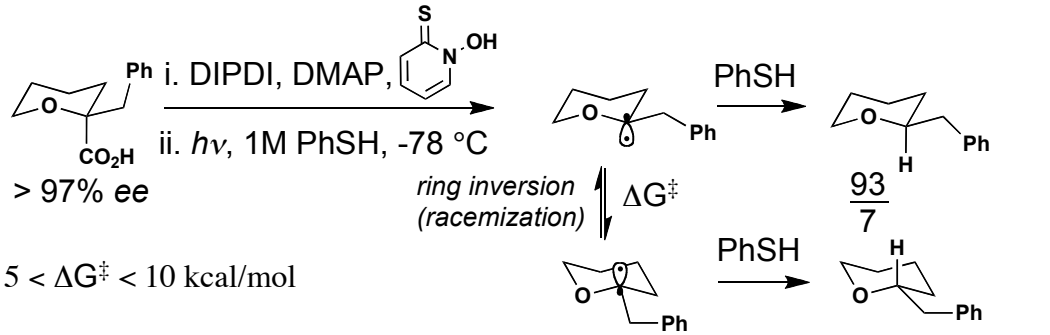
AGIE **1999**, *38*, 2586

Memory of chirality

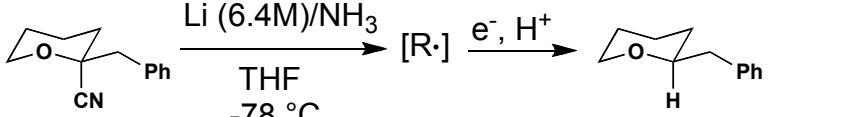
Florina Voica

2.2 Memory of chirality due to radical conformers

A. Enantioselective radical quenching

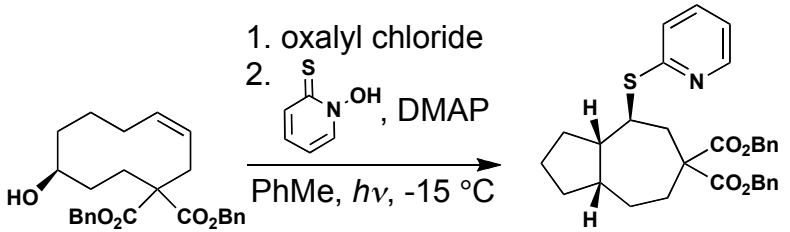


- Bu_2SnH reacts slowly as a proton donor, leading to racemic mixtures
- dilute concentrations of tBuSH or PhSH determine a decrease in *ee*s
- an increase in the temperature leads to low enantiomeric excess

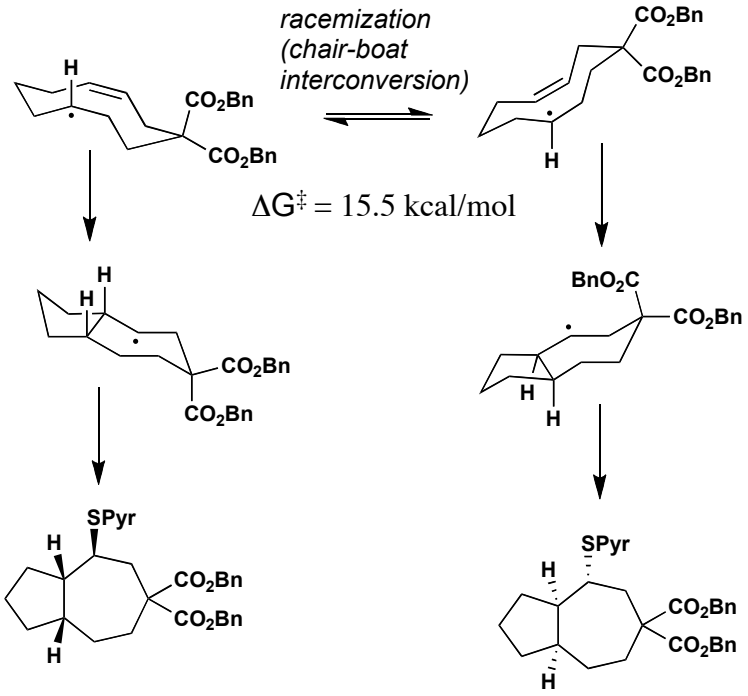


JACS **1998**, *120*, 5589
JACS **2000**, *122*, 9386

B. Intramolecular radical cyclization



Proposed mechanism:

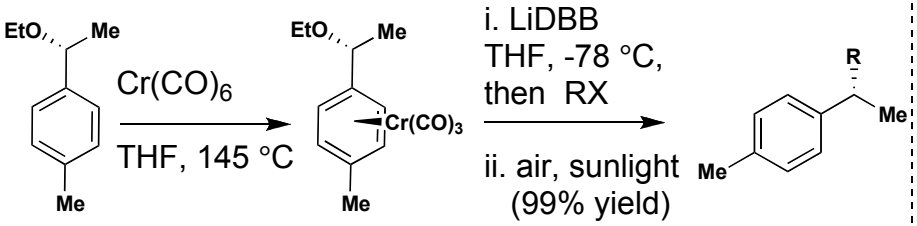


OL **2004**, *6*, 2713

Memory of chirality

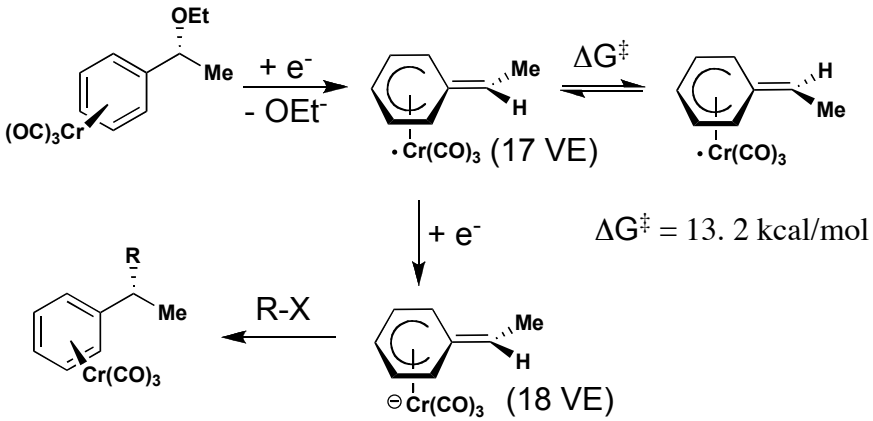
Florina Voica

C. Umpolung benzylic substitution via chiral organometallic intermediates



RX: TMSCl	72% yield (87% *ee*)
BnBr	37% yield (87% *ee*)
$Me_2NC(O)Cl$	67% yield (86% *ee*)

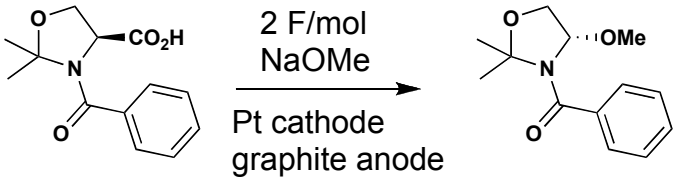
Mechanism:



AGIE **1999**, *38*, 1620

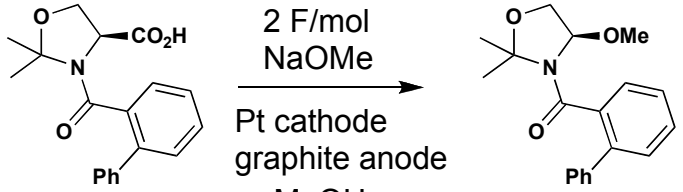
3. Memory of chirality via carbocation intermediates

Initial result:

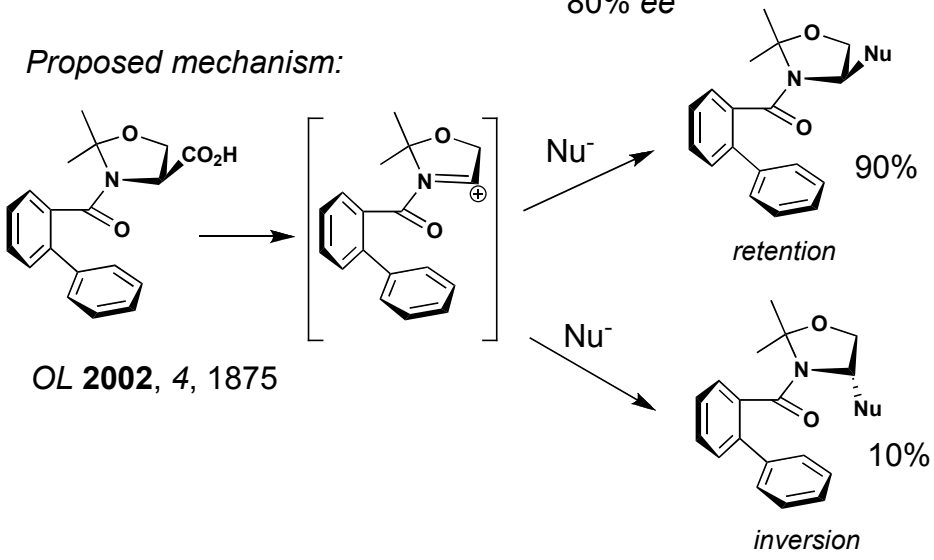


OL **2000**, *2*, 1689

Improvement:



Proposed mechanism:



OL **2002**, *4*, 1875