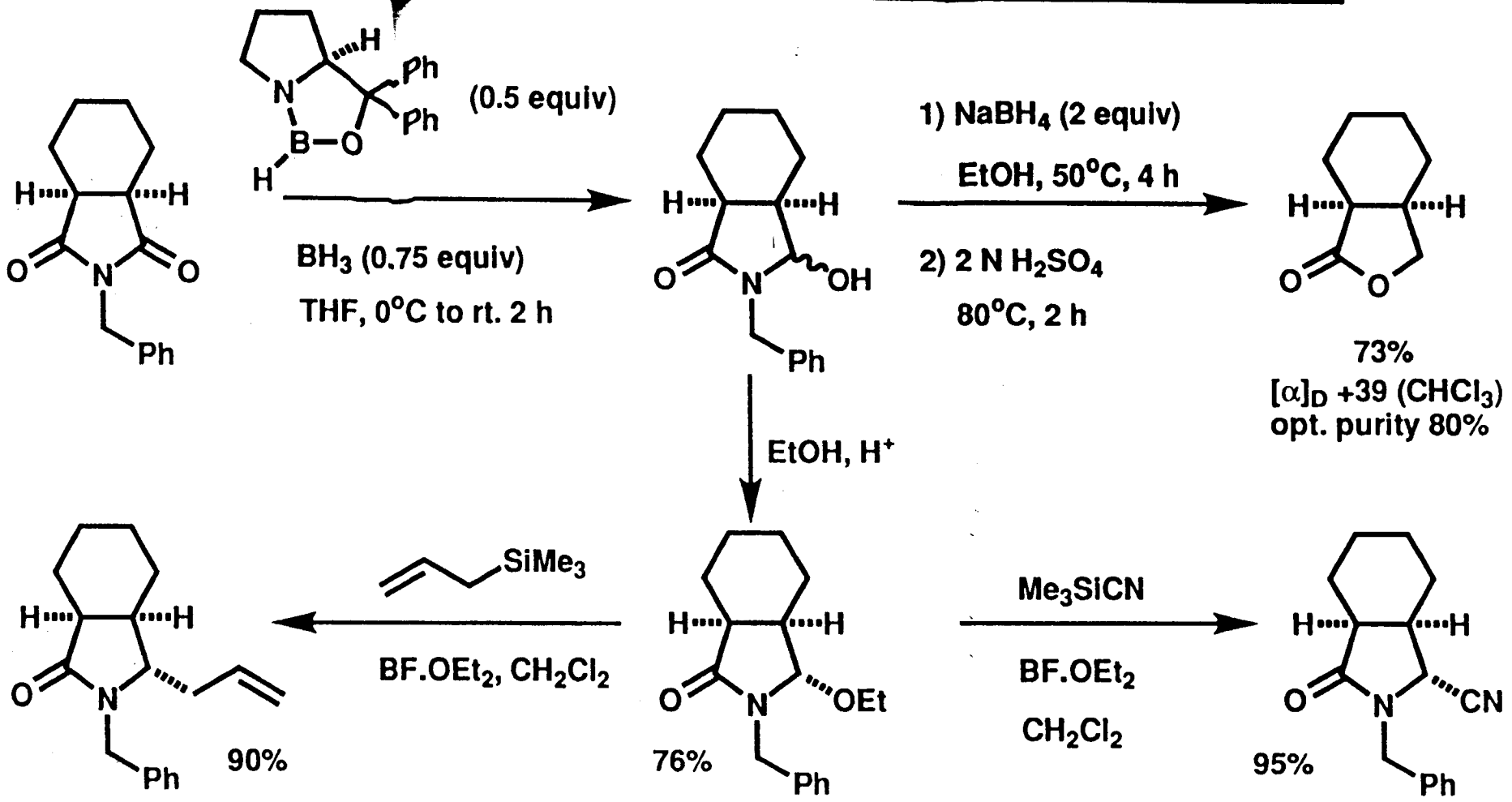
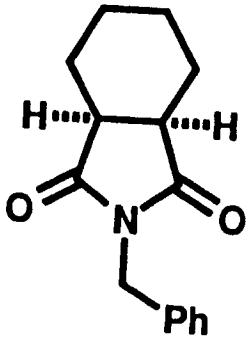
ENANTIOSELECTIVE REDUCTION OF *MESO*-IMIDES

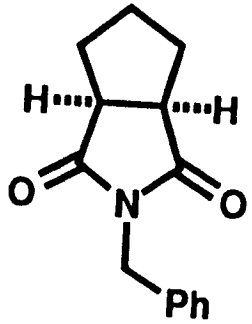


R. Romagnoli

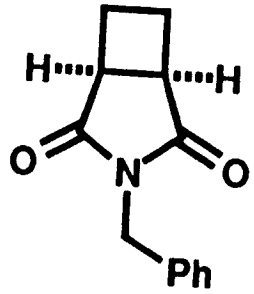
ENANTIOSELECTIVE REDUCTION: EXAMPLES



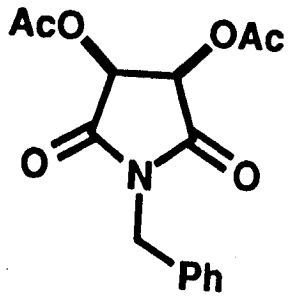
ee 75%



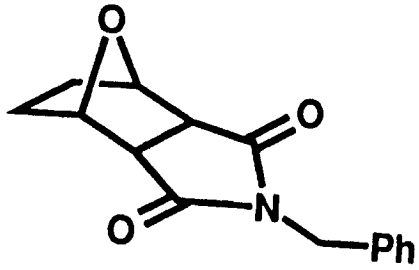
opt. purity 77%



opt. purity 89%

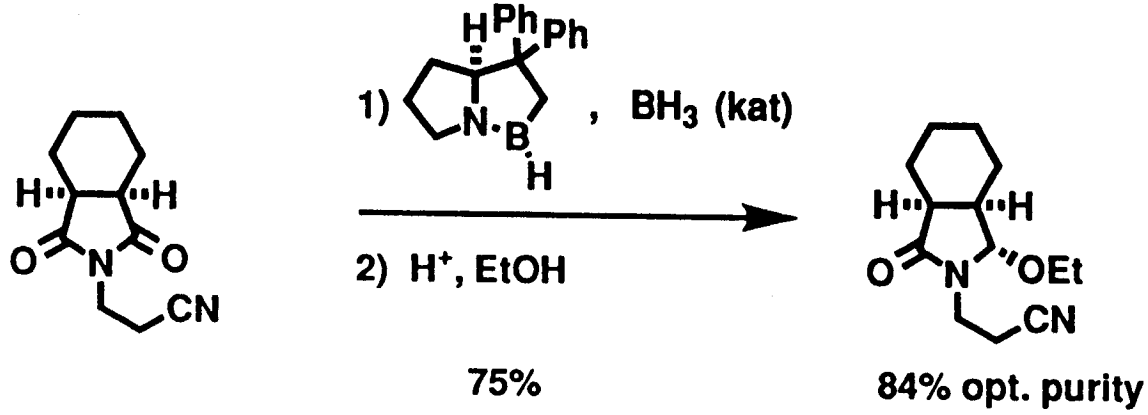


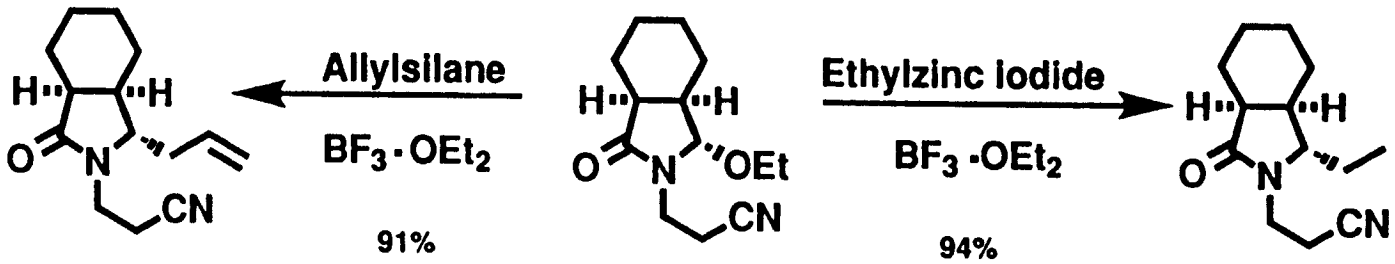
ee 87%

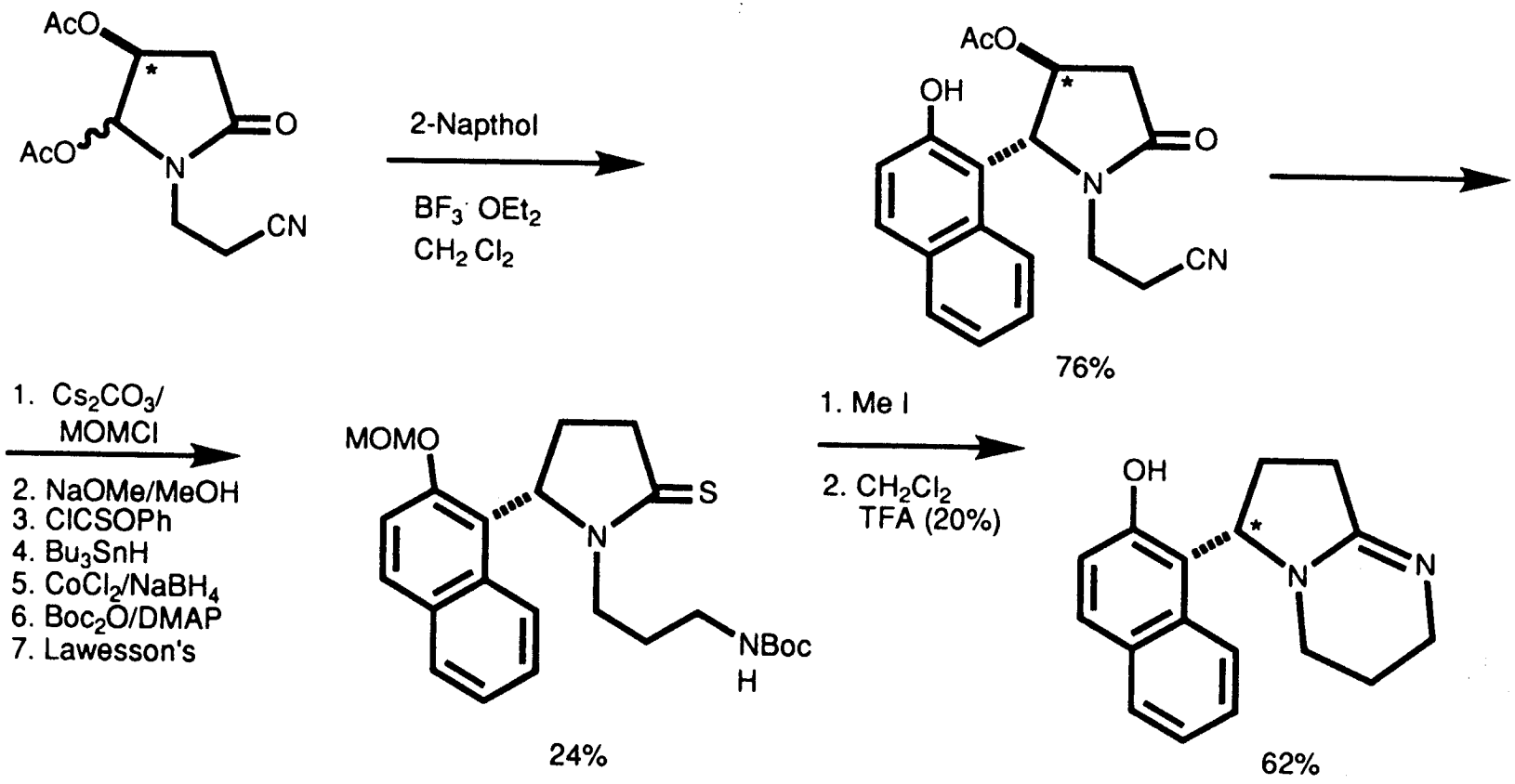


ee 76%

ENANTIOSELECTIVE REDUCTIONS OF CYCLIC *MESO*-IMIDES

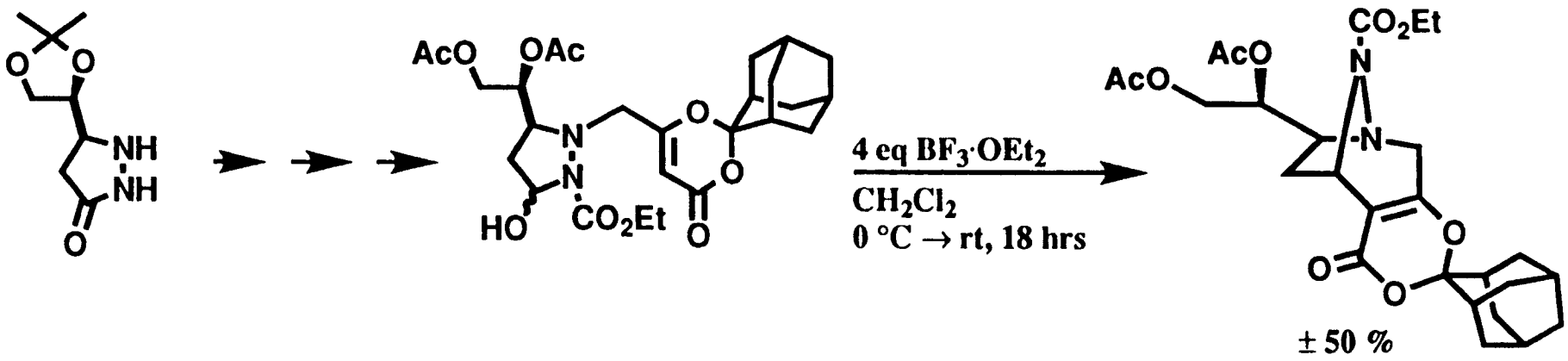




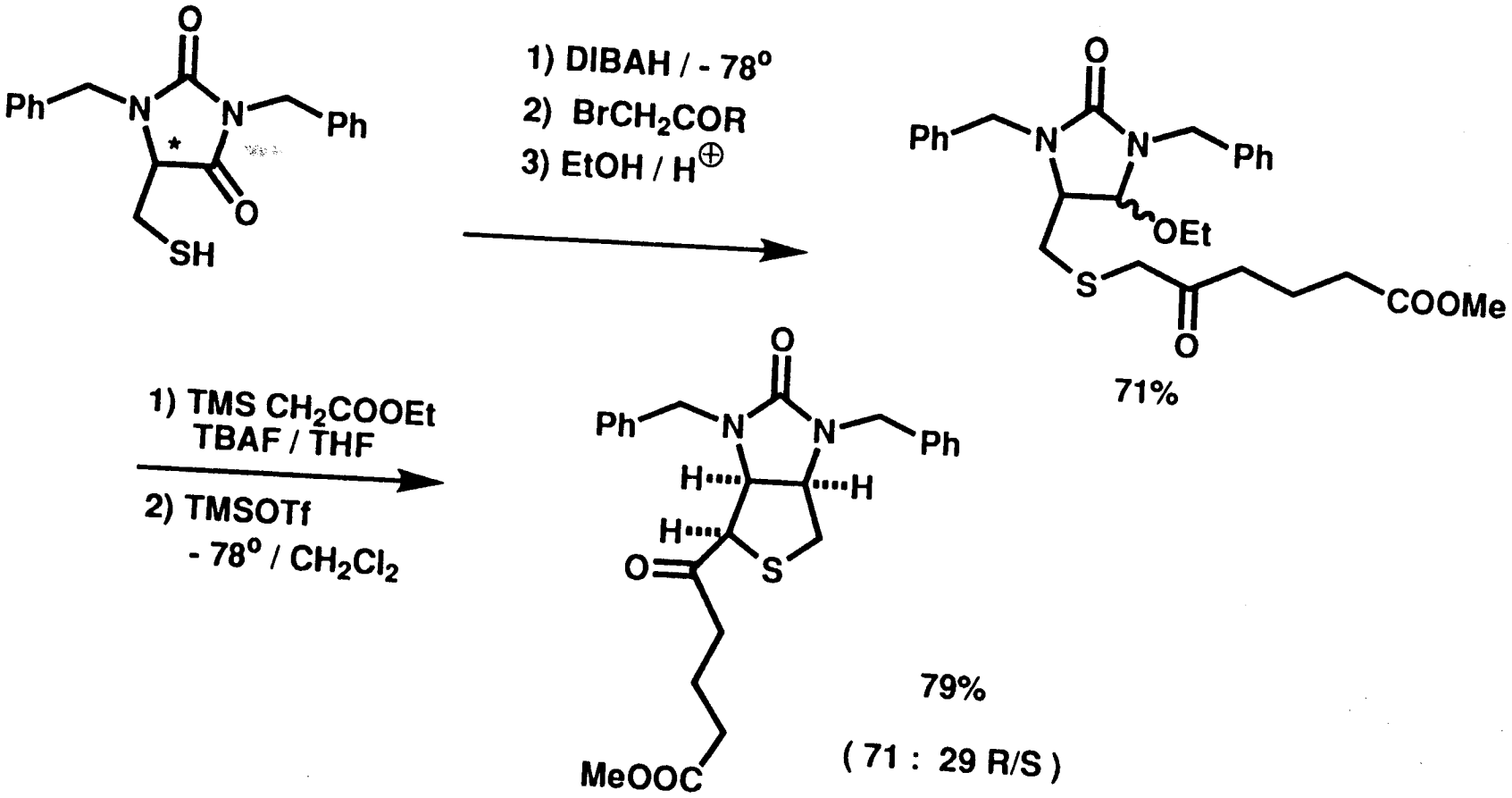

AcO
AcO
O
N
CN
2-Napthol
$BF_3 \cdot OEt_2$
CH_2Cl_2
AcO
OH
O
N
CN
76%
1. Cs_2CO_3/ MOMCl
2. NaOMe/MeOH
3. ClCSOPh
4. Bu_3SnH
5. $CoCl_2/NaBH_4$
6. Boc_2O/DMAP
7. Lawesson's
MOMO
S
N
NBoc
H
24%
1. Me I
2. CH_2Cl_2
TFA (20%)
OH
N
N
62%

J. Dijkink

SYNTHESIS OF AZACOCAINE

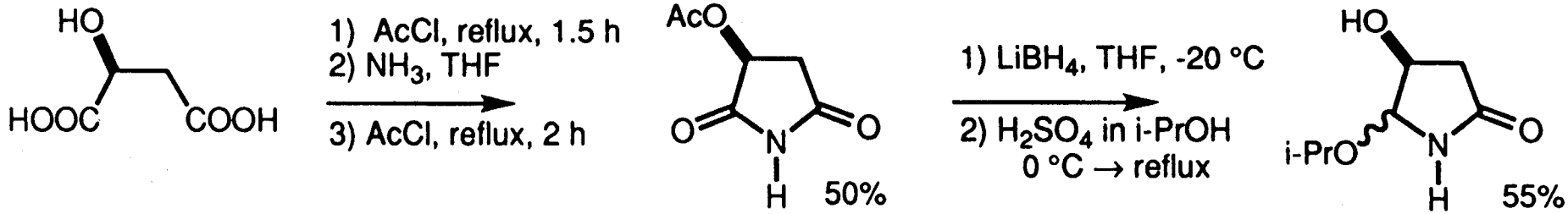


BIOTIN ULTIMATE SYNTHESIS



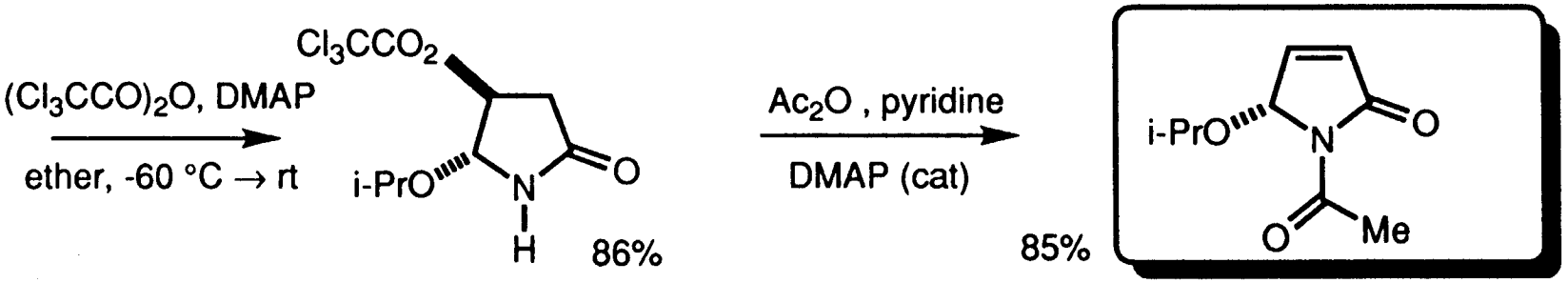
Overall yield 56.5 % (40% R isomer)

M. J. Moolenaar



for first step, see
Chamberlin and Chung, *J. Am. Chem. Soc.* **1983**, *105*, 3653.

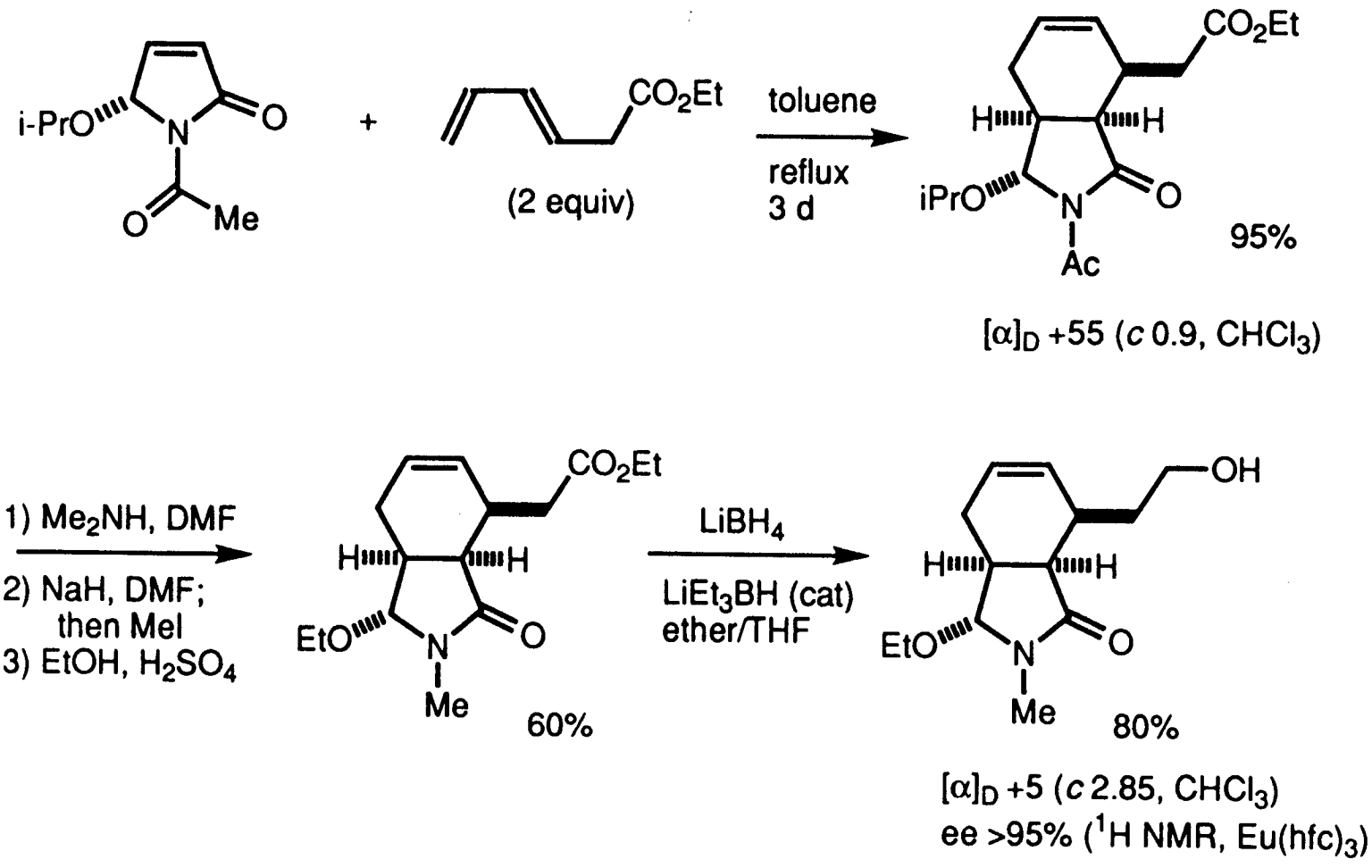
trans/cis = 4:1



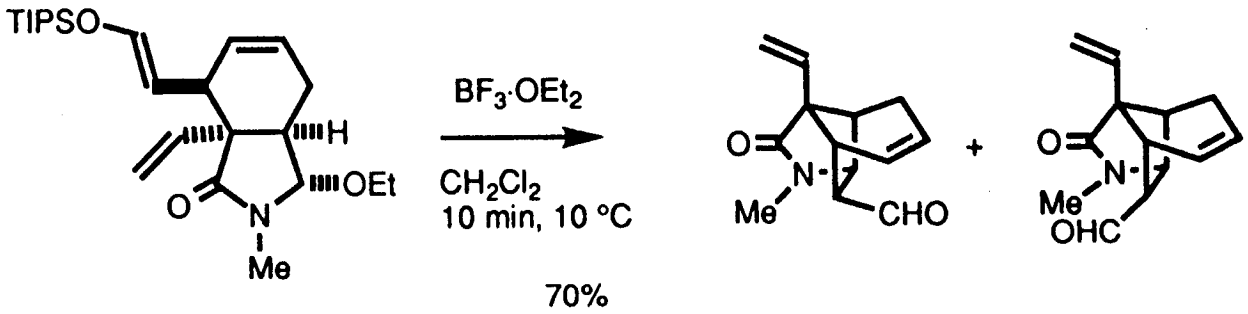
pure stereoisomer, mp 100-102 °C
$[\alpha]_D$ = 16 (c = 0.60, $CHCl_3$)

mp 49-49.5 °C
$[\alpha]_D$ = -149 (c = 0.50, $CHCl_3$)

stable in refluxing toluene for at least 20 h!!

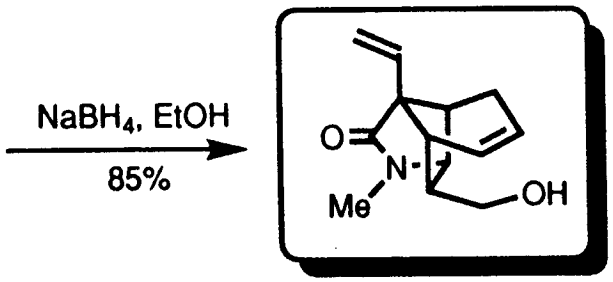

i-PrO
N
O
O
Me
+
CO2Et
(2 equiv)
toluene
reflux
3 d
CO2Et
H
H
iPrO
N
O
Ac
95%
[α]D +55 (c 0.9, CHCl3)
1) Me2NH, DMF
2) NaH, DMF;
then MeI
3) EtOH, H2SO4
CO2Et
H
H
EtO
N
O
Me
60%
LiBH4
LiEt3BH (cat)
ether/THF
OH
H
H
EtO
N
O
Me
80%
[α]D +5 (c 2.85, CHCl3)
ee >95% (1H NMR, Eu(hfc)3)

N-ACYLIMINIUM ION CYCLISATION



E : *Z* = 3 : 1

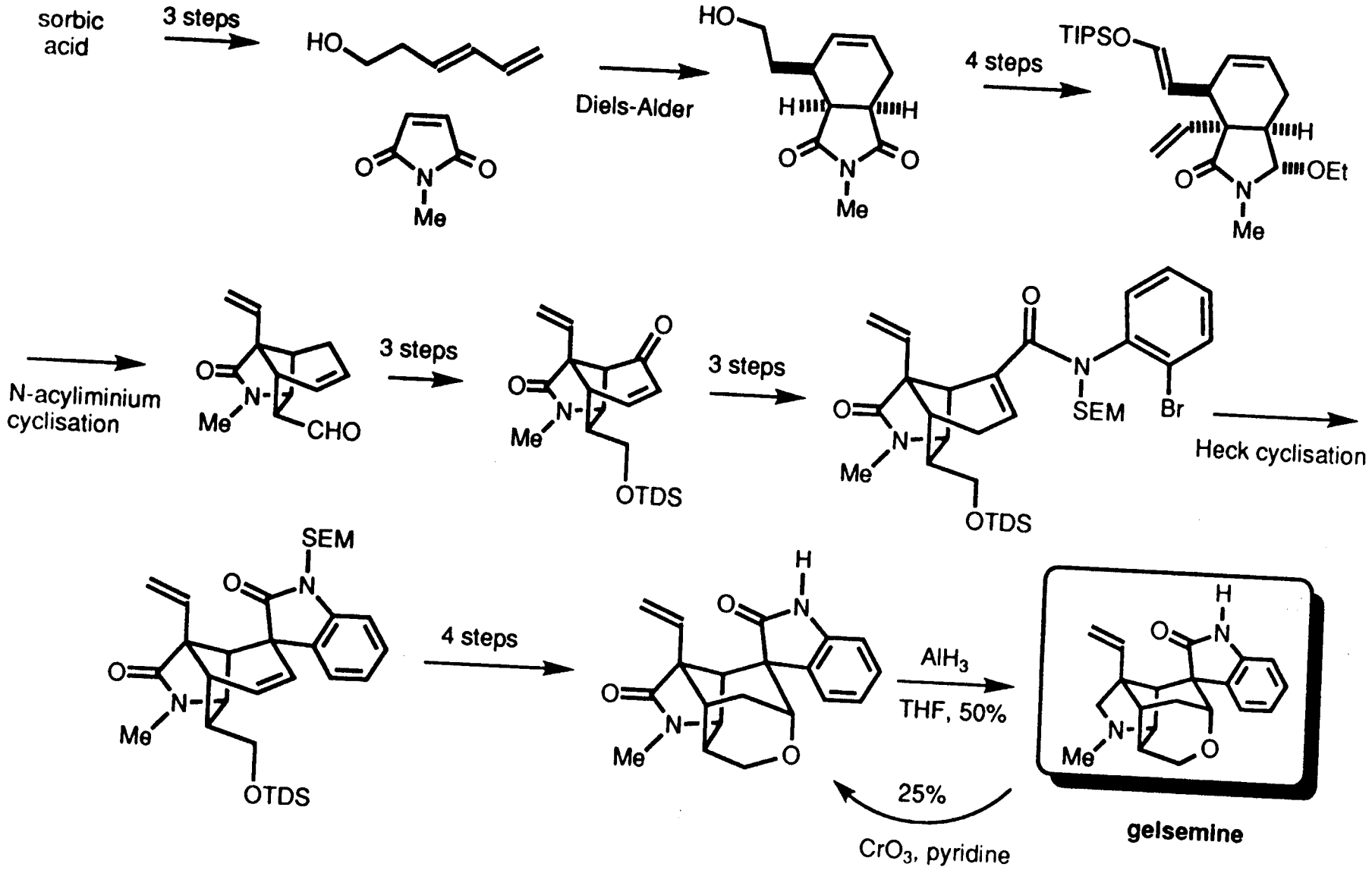
3 : 1 separated by chromatography

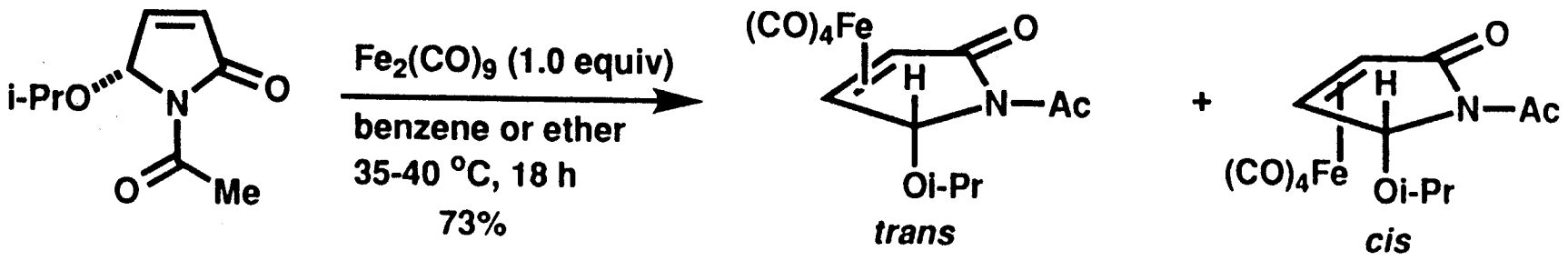


tricyclic alcohol

key intermediate

mp 97-98 °C

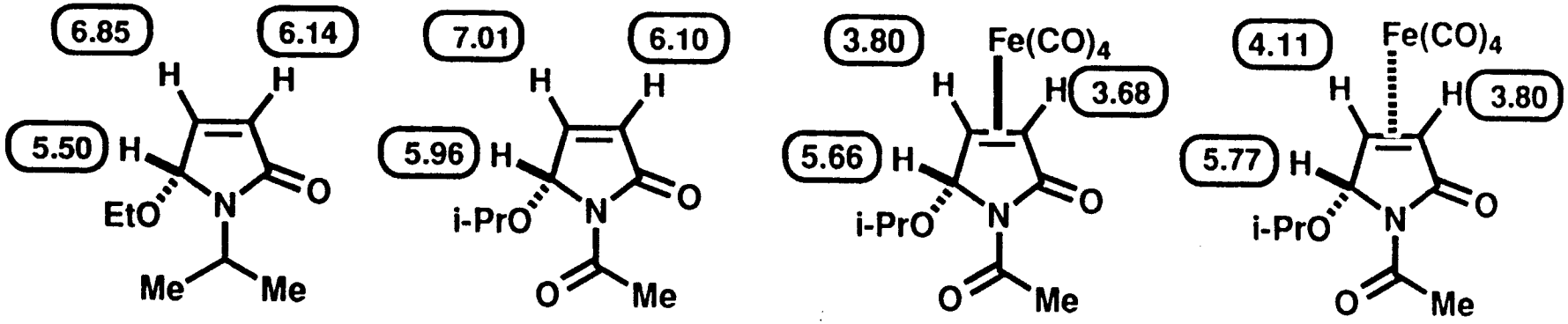

sorbic acid
3 steps
HO
O
N
O
Me
Diels-Alder
HO
H
H
O
N
O
Me
4 steps
TIPSO
H
OEt
O
N
Me
N-acyliminium cyclisation
O
N
Me
CHO
3 steps
O
O
N
Me
OTDS
3 steps
O
N
SEM
Br
O
N
Me
OTDS
Heck cyclisation
SEM
O
N
O
N
Me
OTDS
4 steps
H
O
N
O
N
Me
O
AlH3
THF, 50%
25%
CrO3, pyridine
H
O
N
N
Me
O
gelsemine



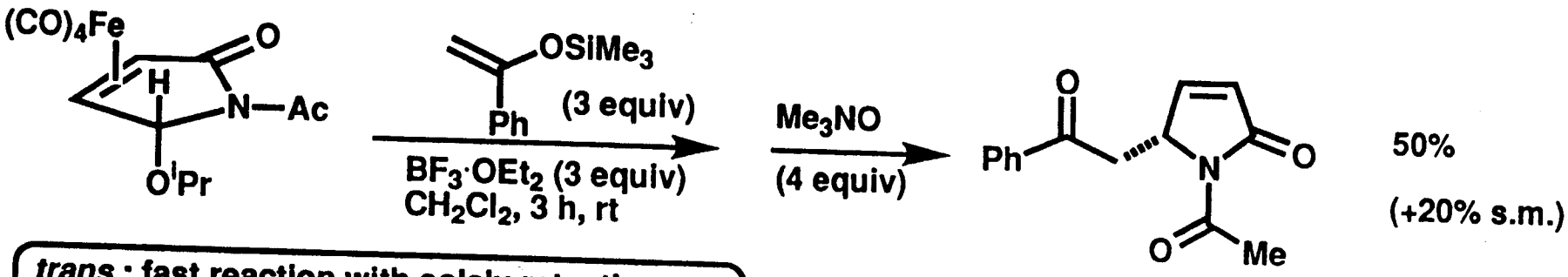
$[\alpha]_{578}^{20}$ = +368 (c = 0.10, pentane) $[\alpha]_{578}^{20}$ = -328 (c = 0.52, pentane)

after 3 h < 5 : > 95 kinetic ratio
after 18 h 33 : 67 thermodynamic ratio
(separable by flash chromatography)

^{1}H NMR chemical shift data (ppm):



REACTION OF IRON COMPLEX WITH SILYL ENOL ETHER

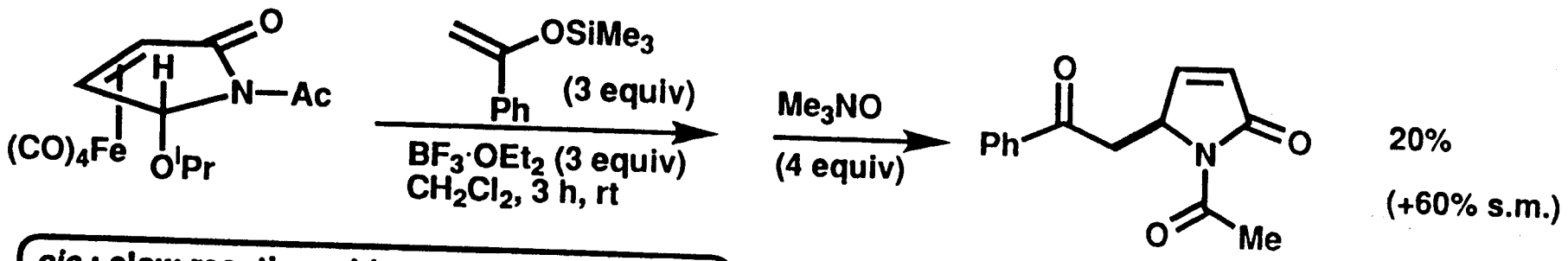


trans **: fast reaction with solely retention**

mp 130.5-132.5°C (dec)

$[\alpha]_D$ = -345 (c = 0.35, $CHCl_3$)

ee > 95% (NMR)



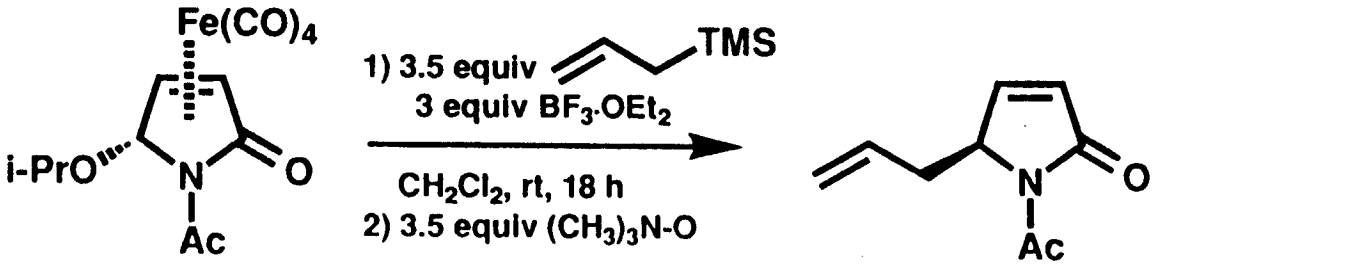
cis **: slow reaction with mainly inversion**

mp 116-123.5°C

$[\alpha]_D$ = +130 (c = 0.34, $CHCl_3$)

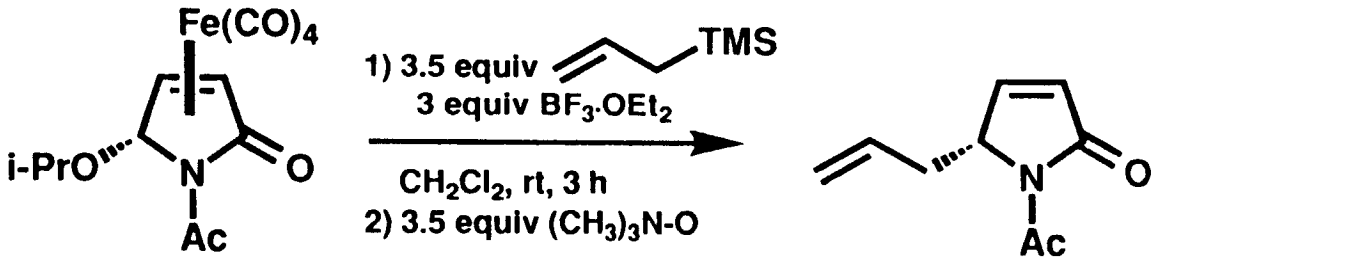
ee 33% (NMR)

ALLYL SILANE ADDITION IRON CARBONYL COMPLEX



cis

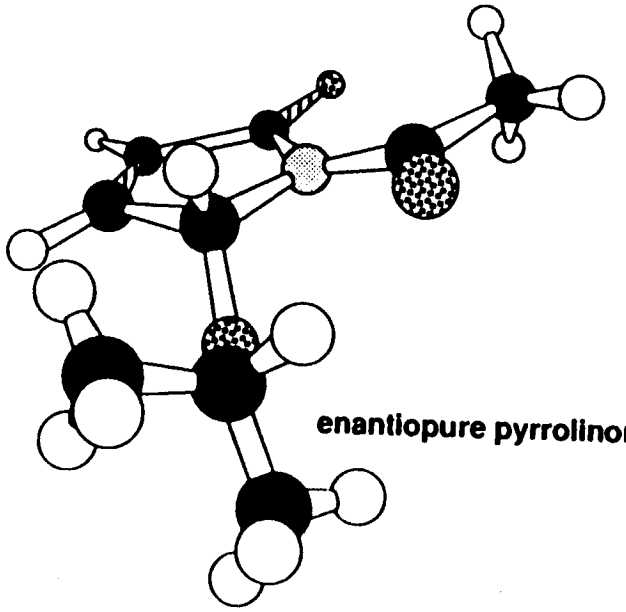
53% [55% e.e.]



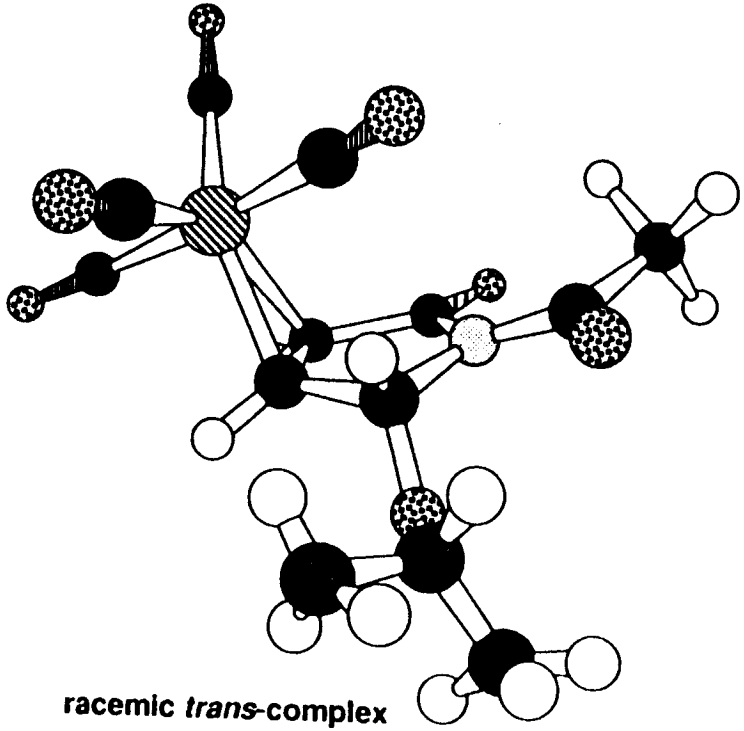
trans

51% [>95% e.e.]

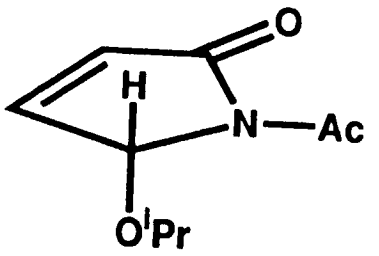
X-RAY CRYSTAL STRUCTURES

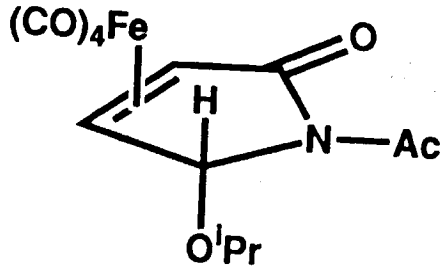


enantiopure pyrrolinone



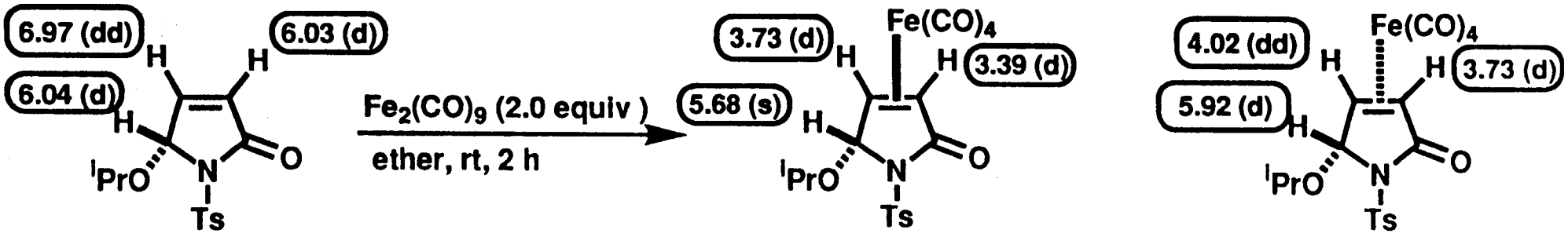
racemic *trans*-complex





K. Goubitz and J. Fraanje of the Department of Crystallography are kindly ackowledged for the determination of these X-ray crystal structures

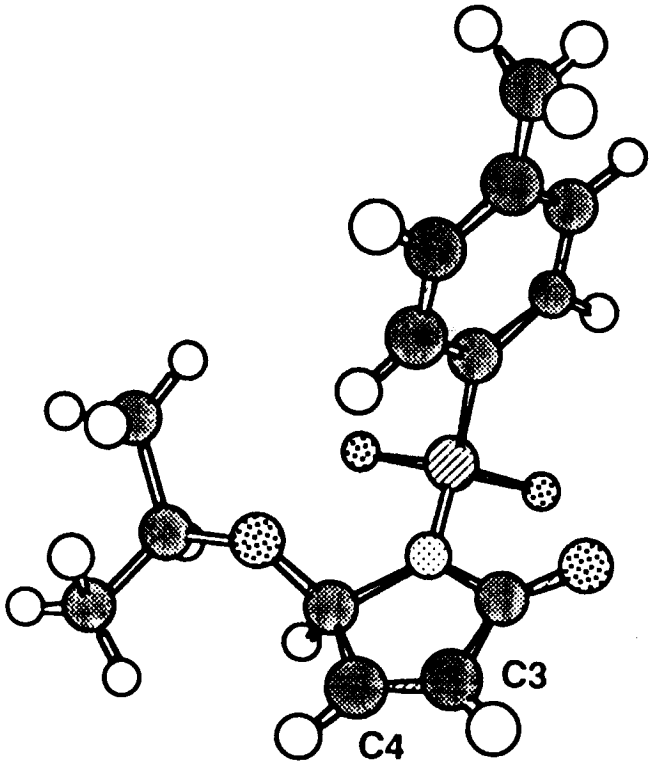
PREPARATION OF THE IRON CARBONYL COMPLEX



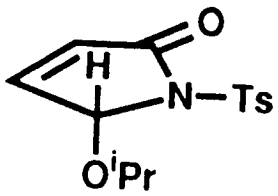
5-10% *trans*
(not isolated)

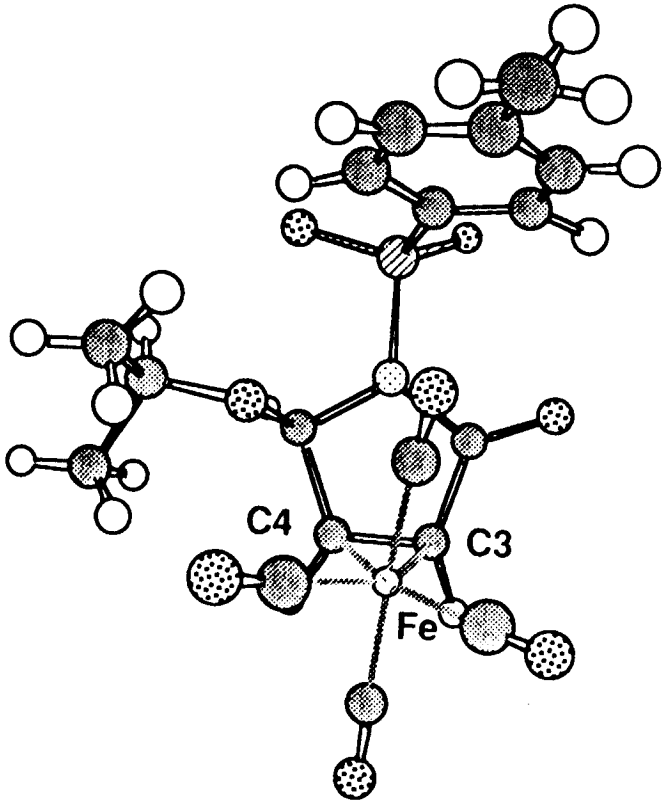
yellow crystals
air stable
70%

Values in boxes are chemical shifts in ppm, multiplicity in parentheses (250 MHz, $CDCl_3$).

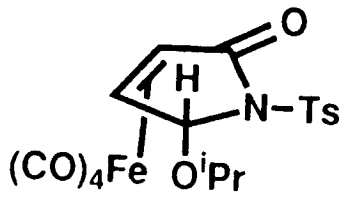


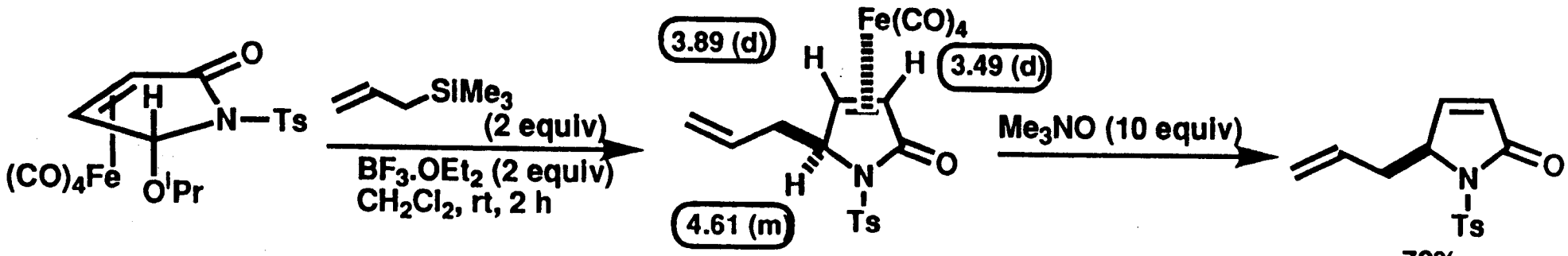
C(3) - C(4): 1.320(8) Å





C(3) - C(4): 1.40(1) Å

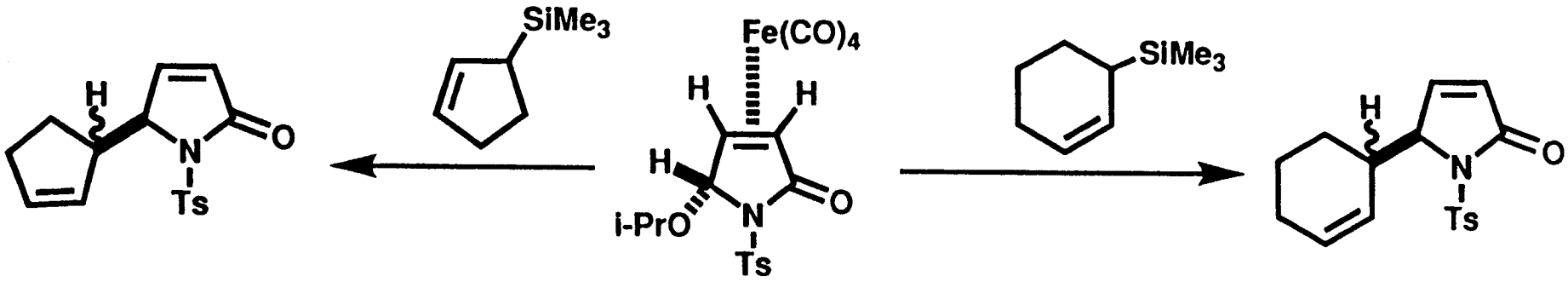




72%
mp 147-148 °C
$[\alpha]_D$ = 227 (c = 0.225, $CHCl_3$)
crude >95% ee

quantitative

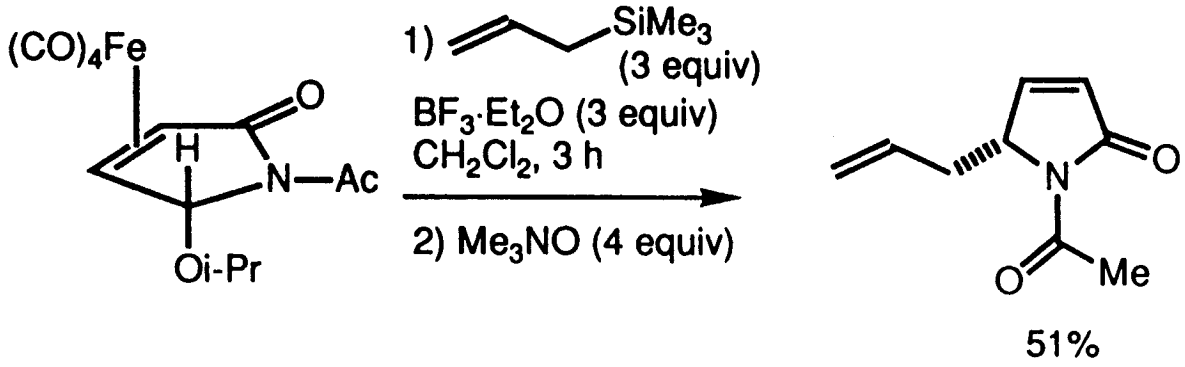
cis **but surprisingly: <u>fast</u> reaction with <u>inversion</u>**



34% (83:17)

60% (95:5)

REACTION OF THE IRON COMPLEXES WITH ALLYLTRIMETHYLSILANE



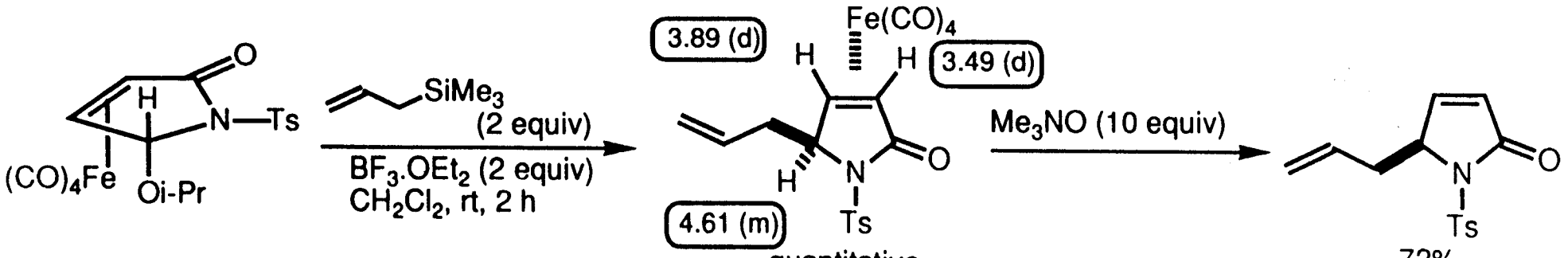
51%

$[\alpha]_D$ = -282 (c = 0.76, $CHCl_3$)

>95% ee

trans: fast reaction with solely retention

The corresponding *cis* -complex reacts slowly under the same conditions to give the allylated product in 53% yield, 55% ee in favour of the inverted product.



quantitative

72%

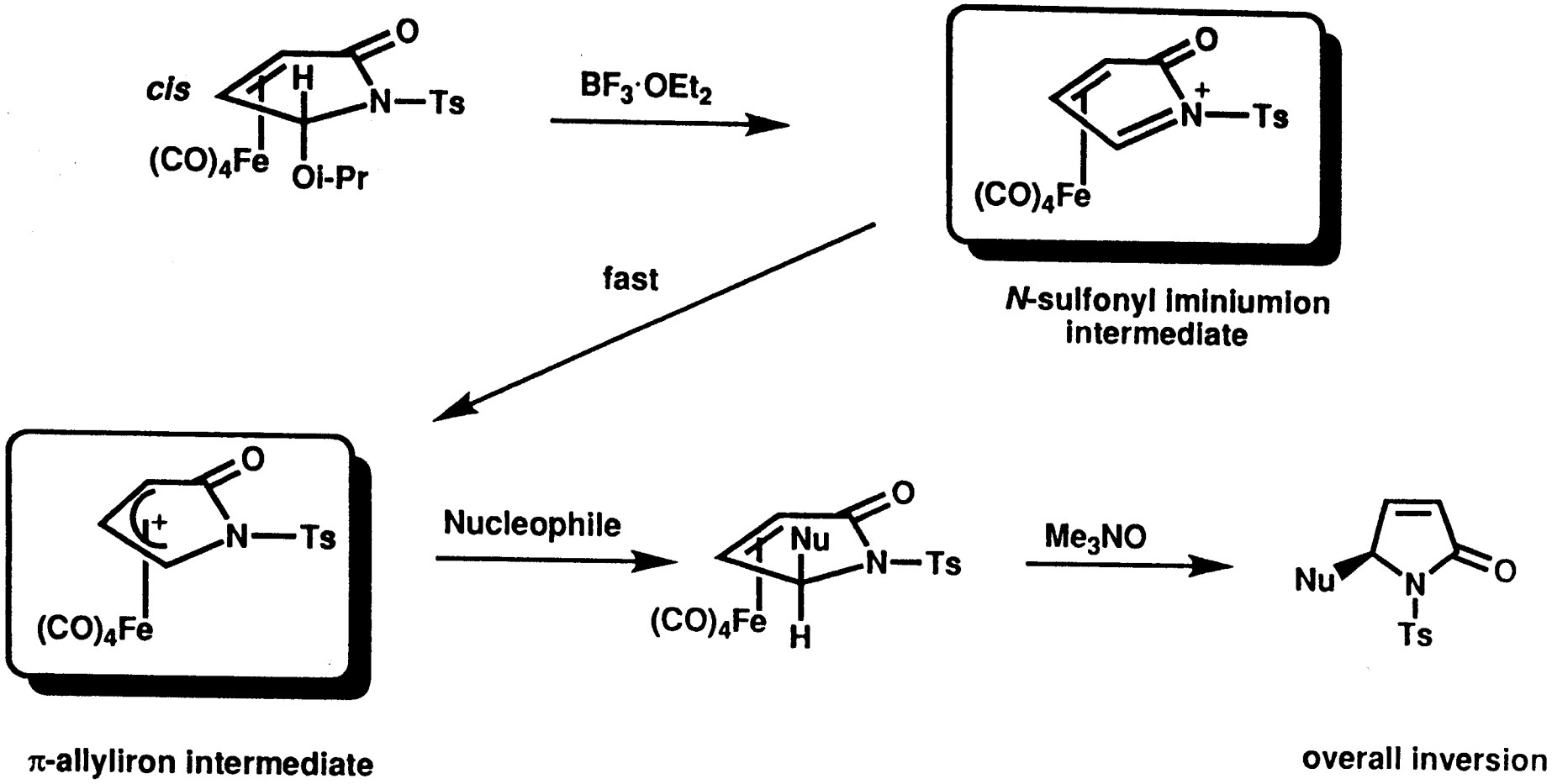
mp 147-148 °C

$[\alpha]_D$ = 227 (c = 0.225, $CHCl_3$)

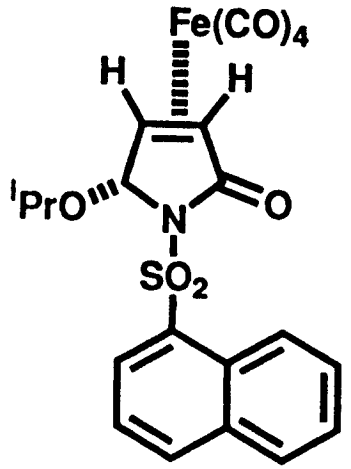
crude >80% ee

cis but surprisingly: fast reaction with mainly inversion

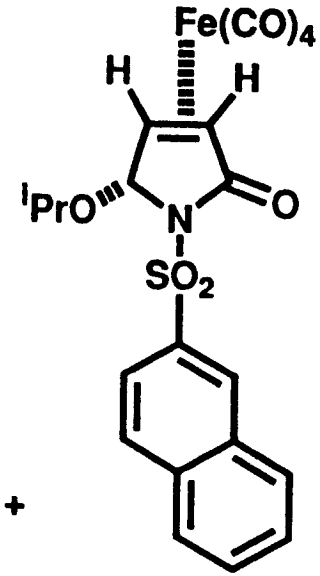
RATIONALE - THE INTERMEDIATE CATION



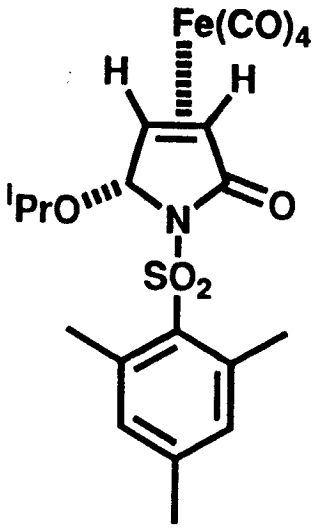
IRON COMPLEXES OF OTHER *N*-SULFONYL PYRROLINONES



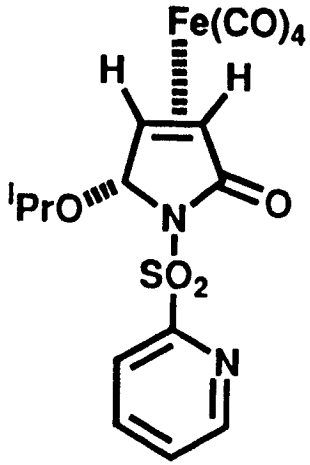
38% (c:t = 100:28) + 46% s.m.



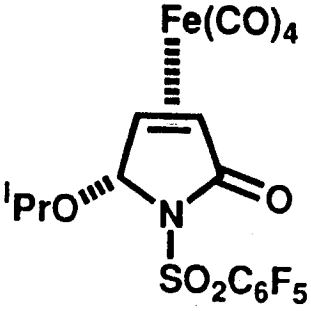
64% (c:t ≈ 5:1) + 32% s.m.



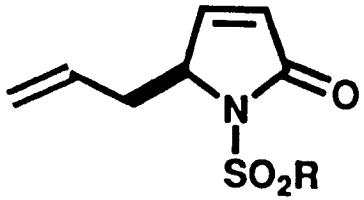
30% (cis only) + 40% s.m.



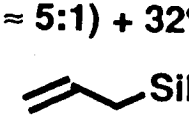
20% (c:t = 3:1) + 5% s.m.



14% (cis only)



R = 1-naphthyl: 51% + 11% s.m.

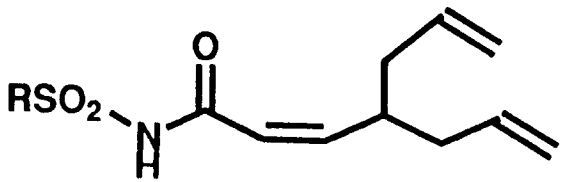


(3 equiv)

$BF_3.OEt_2$ (2 equiv)
CH_2Cl_2, rt, night

R = 2-naphthyl: 67% + 9% s.m.

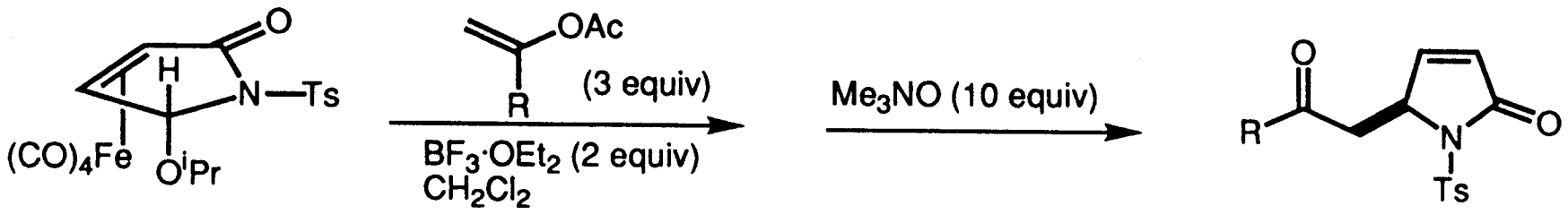
R = mesitylene: 48% + 13% of



R = 2-pyridyl: 42% + trace of red. prod. + 19% s.m.

R = pentafluorphenyl: complex mixture

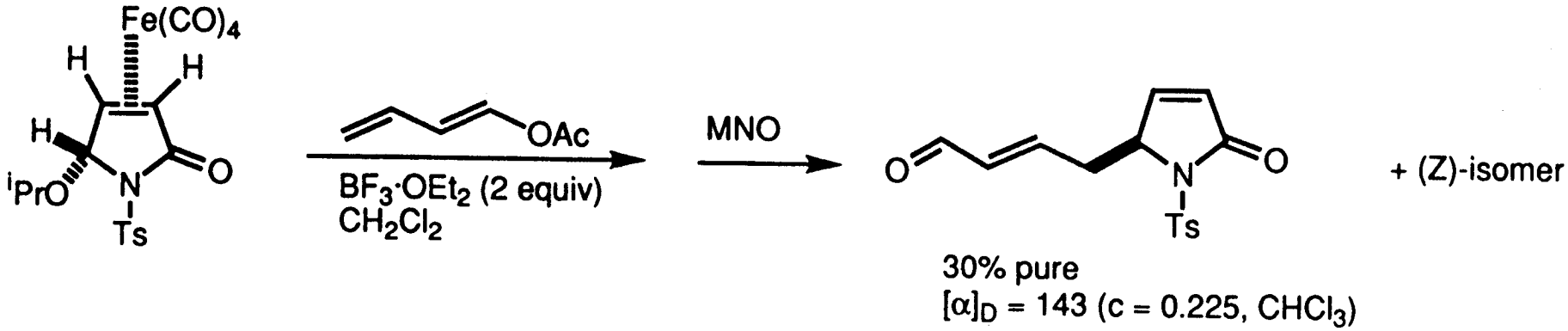
REACTION OF THE COMPLEX WITH ENOLACETATES



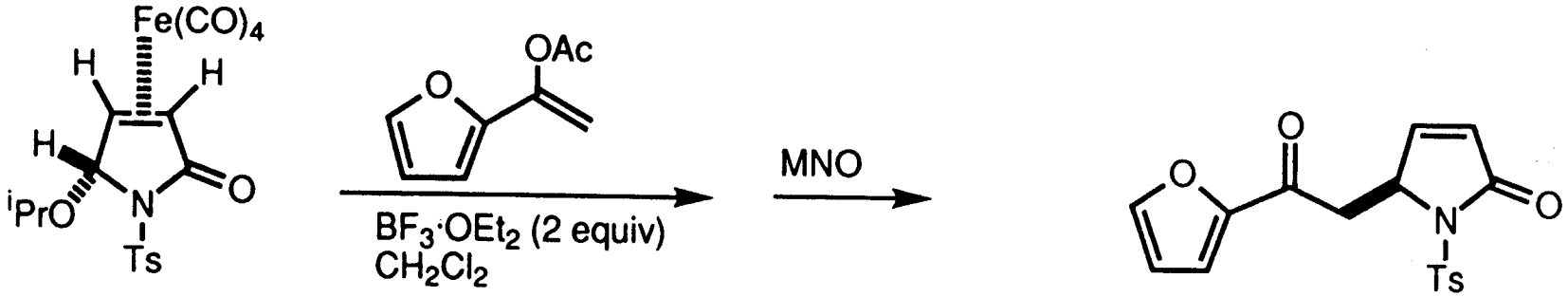
R = Me: 49%
R = Ph: 58%
$[\alpha]_D$ = 102 (c = 0.78, $CHCl_3$)
R = H: 5%

No coupled products are observed with silylenolethers, alkylenolethers, enoltriflates and enoltrifluoroacetates.

REACTION OF THE COMPLEX WITH MODIFIED ENOLACETATES

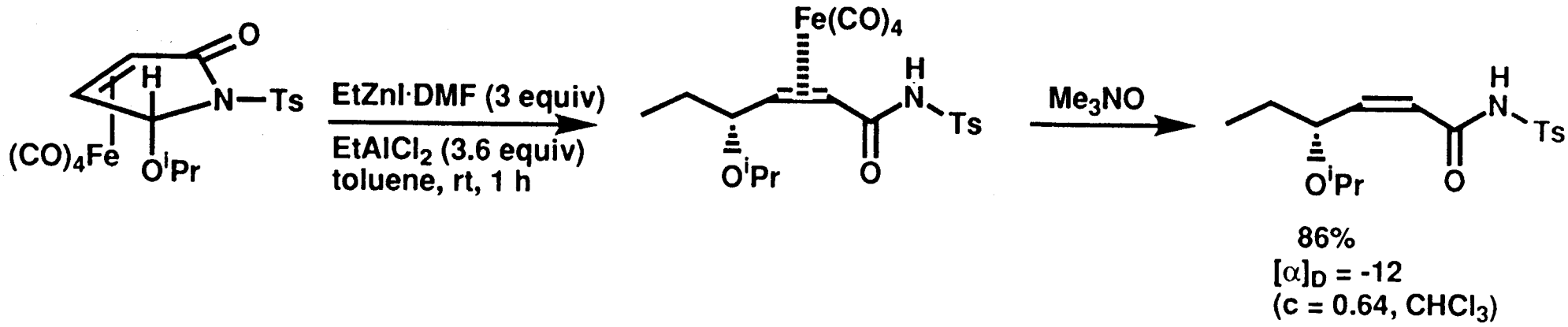


30% pure
$[\alpha]_D$ = 143 (c = 0.225, $CHCl_3$)

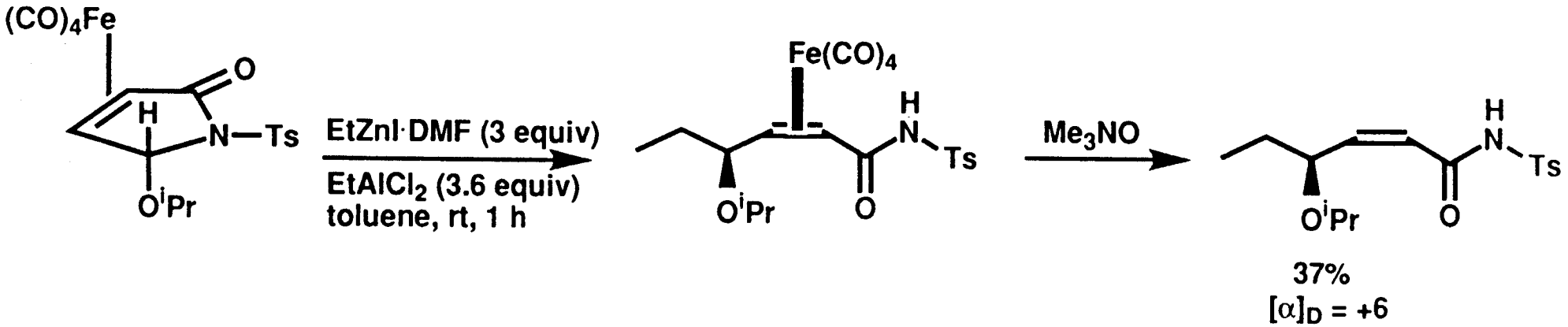


60%
$[\alpha]_D$ = 174 (c = 0.36, $CHCl_3$)

REACTION OF THE IRON COMPLEX WITH ETHYLZINC IODIDE

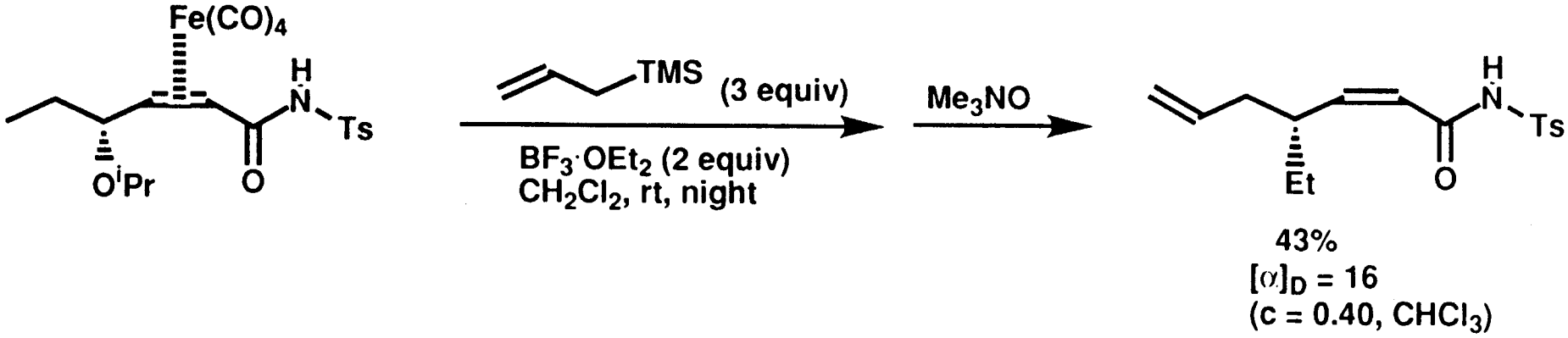


86%
$[\alpha]_D$ = -12
(c = 0.64, $CHCl_3$)



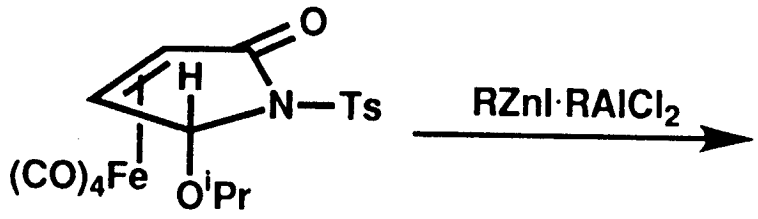
37%
$[\alpha]_D$ = +6
(c = 0.18, $CHCl_3$)

STRUCTURE PROOF OF THE RING OPENING PRODUCT

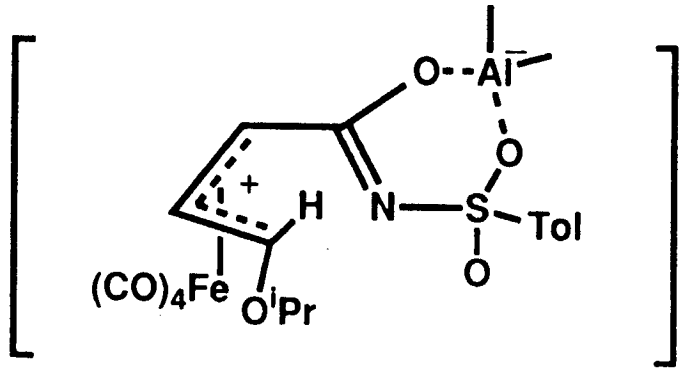


43%
$[\alpha]_D = 16$
(c = 0.40, $CHCl_3$)

PROPOSED REACTION PATHWAY OF THE RING OPENING



RZnI·RAlCl2



EtZnI·DMF (3 equiv)
MeAlCl2 (3.6 equiv)
toluene, rt, 1 h
or
MeZnI·DMF (3 equiv)
EtAlCl2 (3.6 equiv)
toluene, rt, 1 h

mixture of products R=Me and R=Et

"R⁻"
attack *trans* to iron