KING'S College LONDON
University of London

June 29, 2004

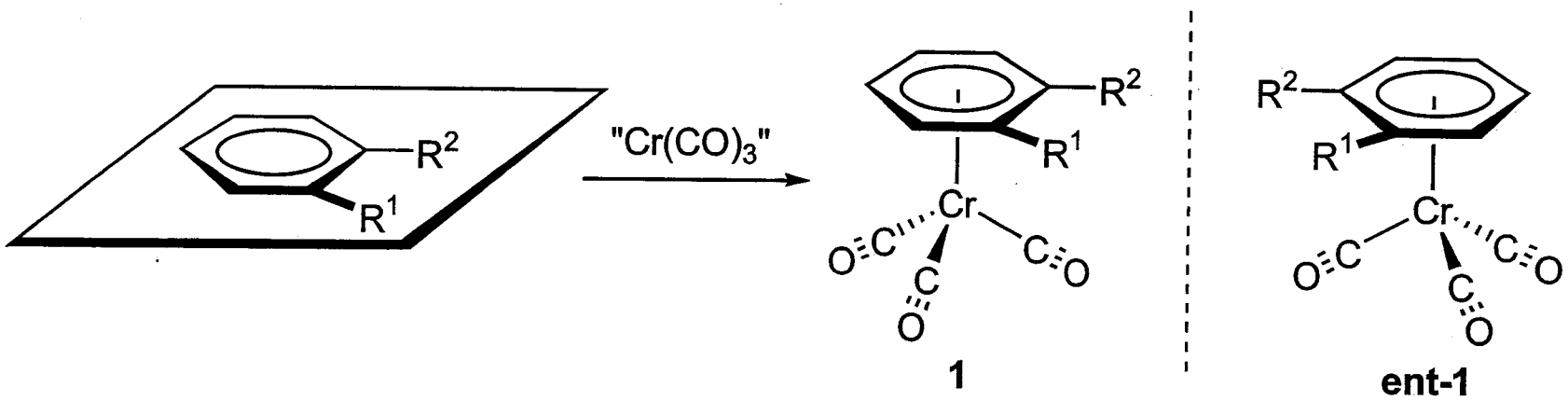
Synthesis, Structural Aspects and Applications of Planar Chiral (Arene)tricarbonylchromium(0) Complexes

by

Hasim Ibrahim

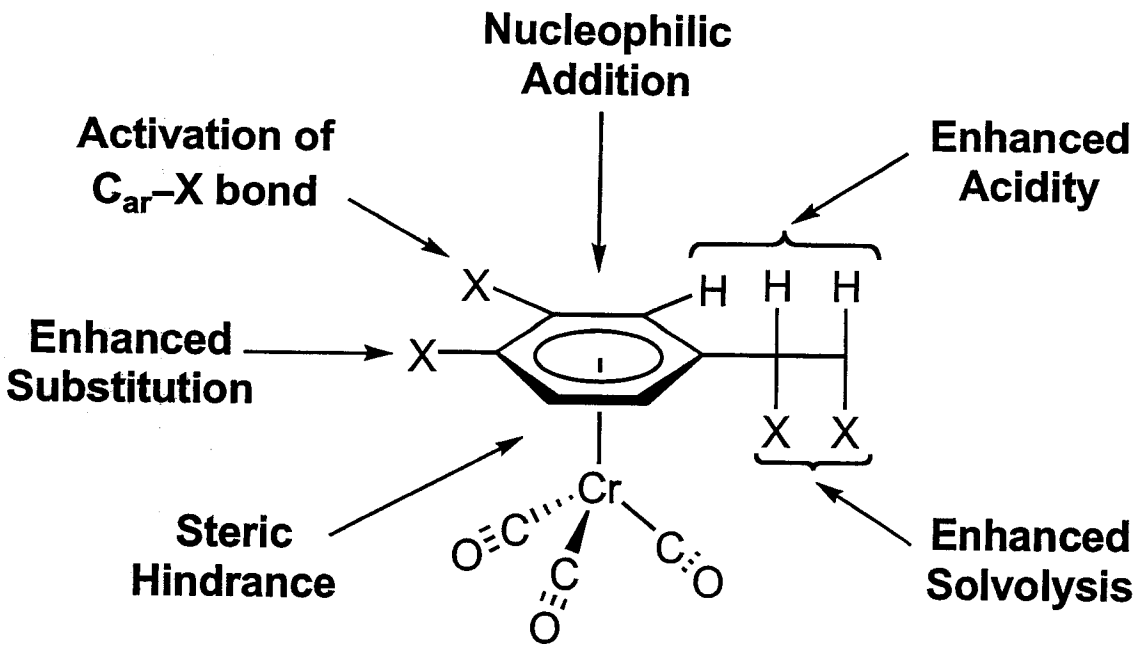
Thesis advisor: Professor Sue Gibson

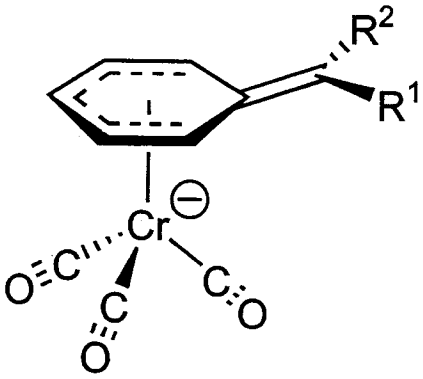
Planar Chirality



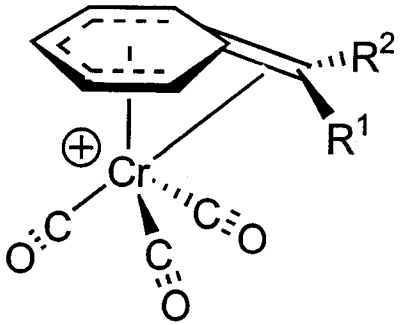
The same applies for Cp-rings, rigid paracyclophanes and other aromatic systems.

Reactivity changes upon complexation

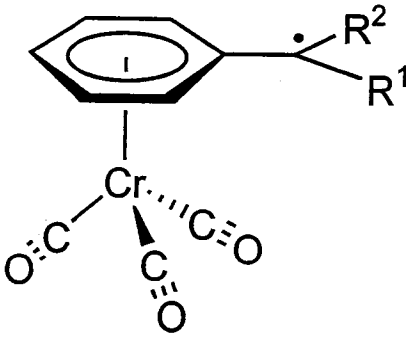




anion



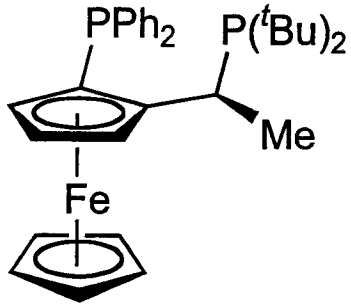
cation

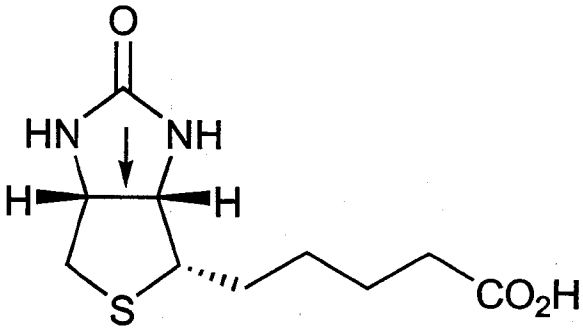


radical

Planar chiral ligands in industrial production processes

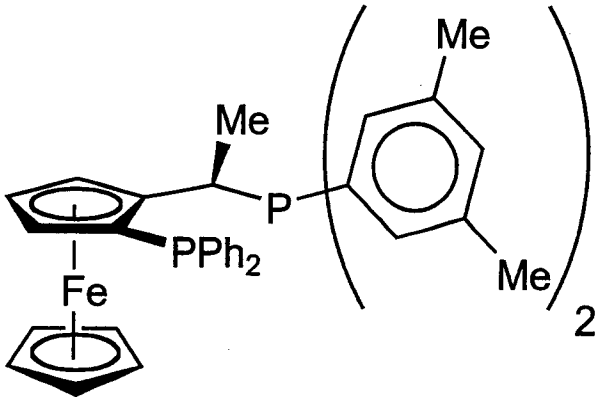
Ligand used by Lonza AG for the rhodium catalysed asymmetric hydrogenation of a tetrasubstituted alkene

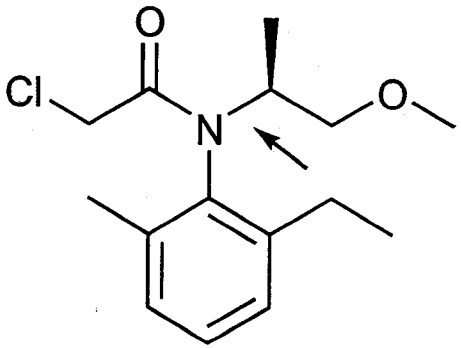




(+)-Biotin

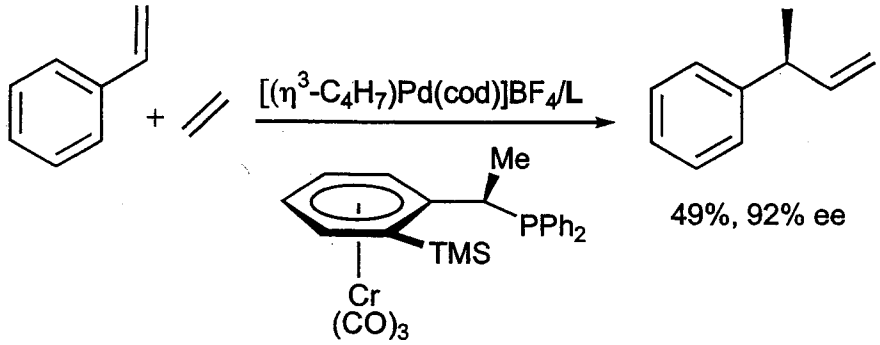
Ligand used by Norvatix for the iridium catalysed asymmetric hydrogenation of an imine



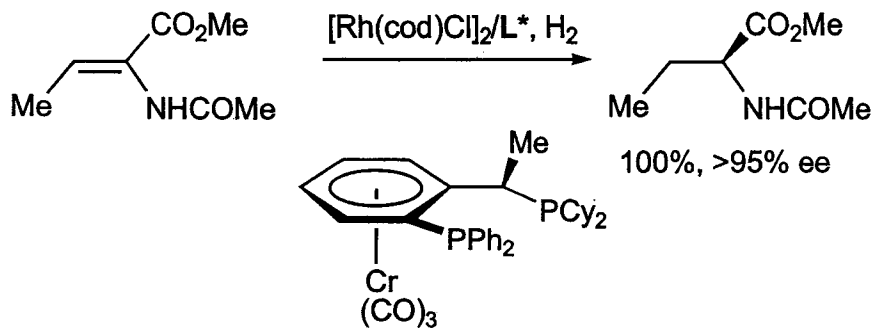


***(S)*-Metachlor**

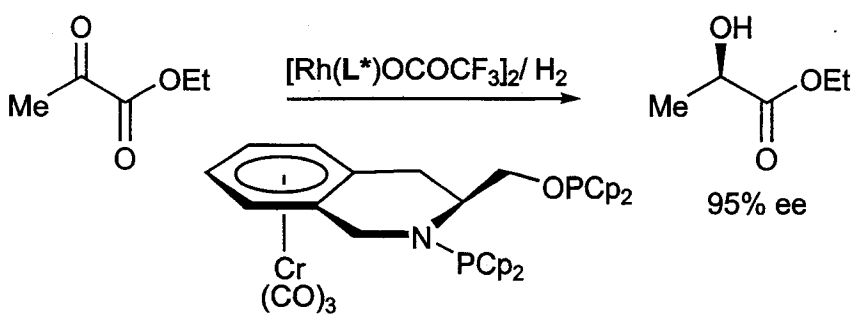
A. Togni, *Angew. Chem. Int. Ed. Engl.*, 1996, **35**, 1475.



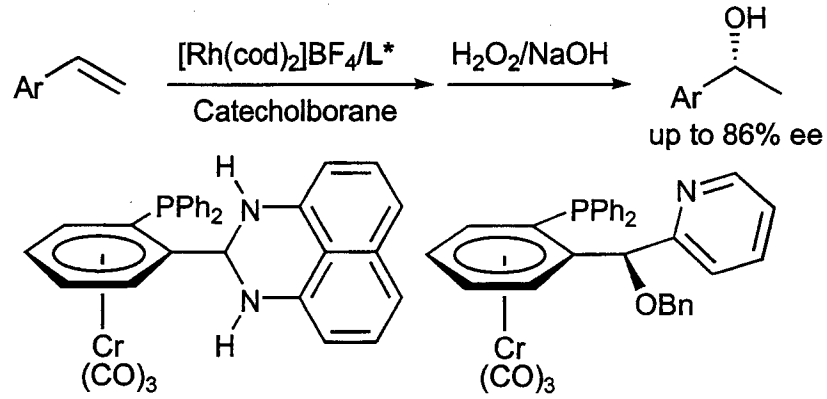
Salzer and Vogt, *OM*, 1999, **18**, 4390.



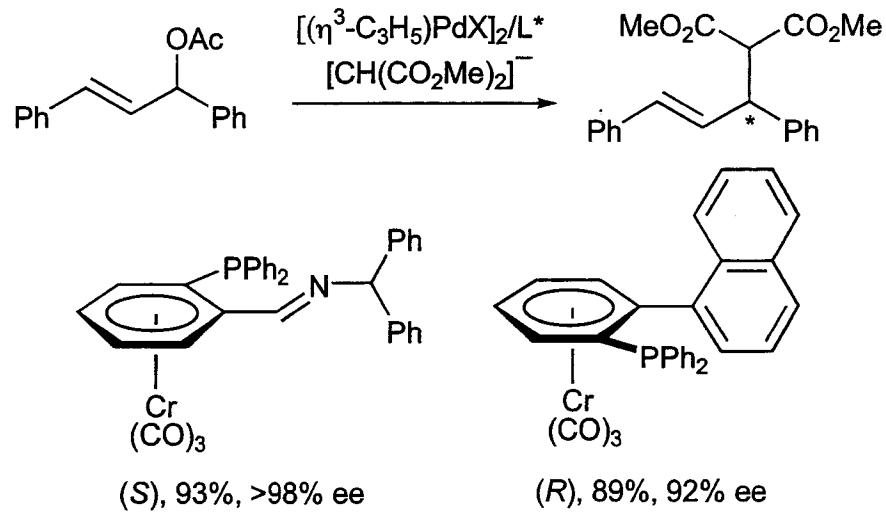
Salzer and Togni, *OM*, 2000, **19**, 539.



Agbossou-Niedercorn, *THL*, 2001, **42**, 2809.

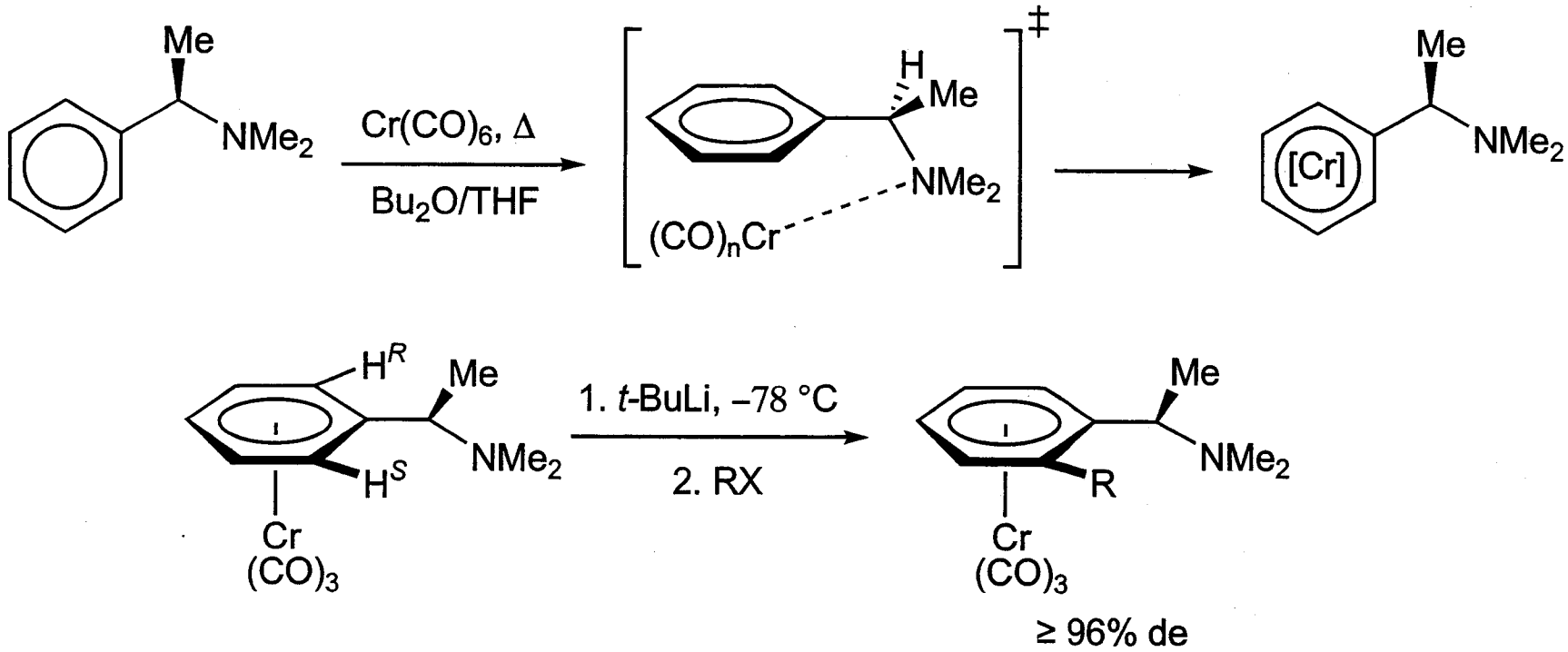


Chung, *OM*, 1998, **17**, 3236;
THA, 1999, **10**, 347.



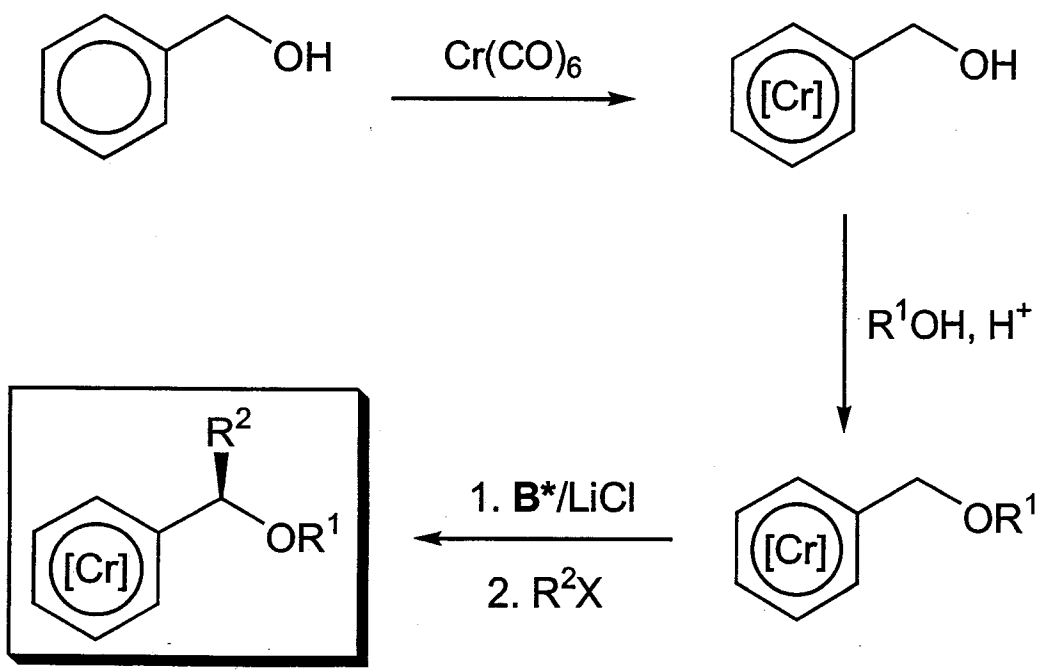
Chung, *THL*, 2000, **41**, 5083.
Nelson, *OL*, 1999, **1**, 1379.

For a review of this area, see: Gibson and Ibrahim, *CC*, 2002, 2465.



benzylic substitution
unselective ortho-substitution
nucleophilic arene addition

Pioneering work was done by Ugi: Ugi, *JACS,* 1970, **92**, 5389; Ugi, *JCE*, 1972, **49**, 294.
Davies, *JCS, Perkin 1*, 1987, 1805.
Heppert and Aubé, O*M*, 1988, **7**, 2581; Heppert and Aubé, *OM*, 1990, **9**, 727.

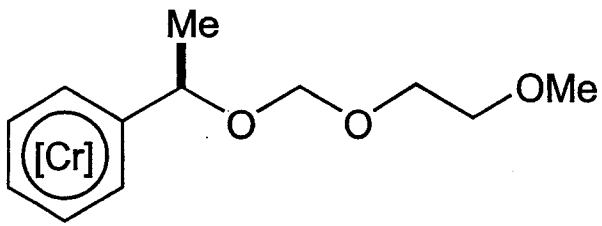


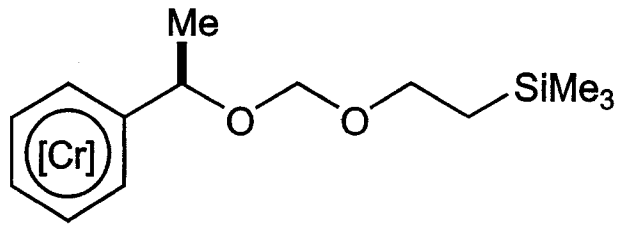
high yield
up to 99% ee

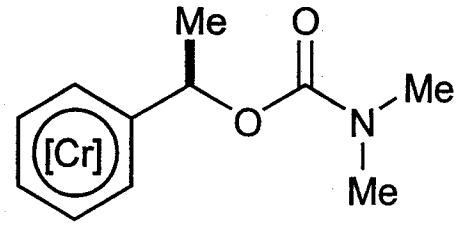
R^1 = Me, Bn
R^2 = alkyl, Bn, SR, SiR_3

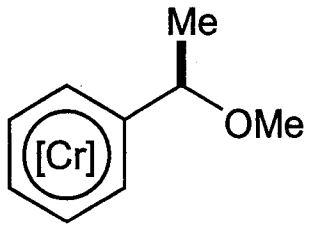
Cowton, Gibson, Schneider, Smith, *CC*, 1996, 839.

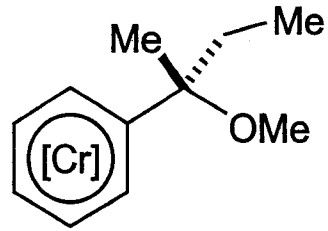
Strategy: enhancing ligating ability of the ether side-chain

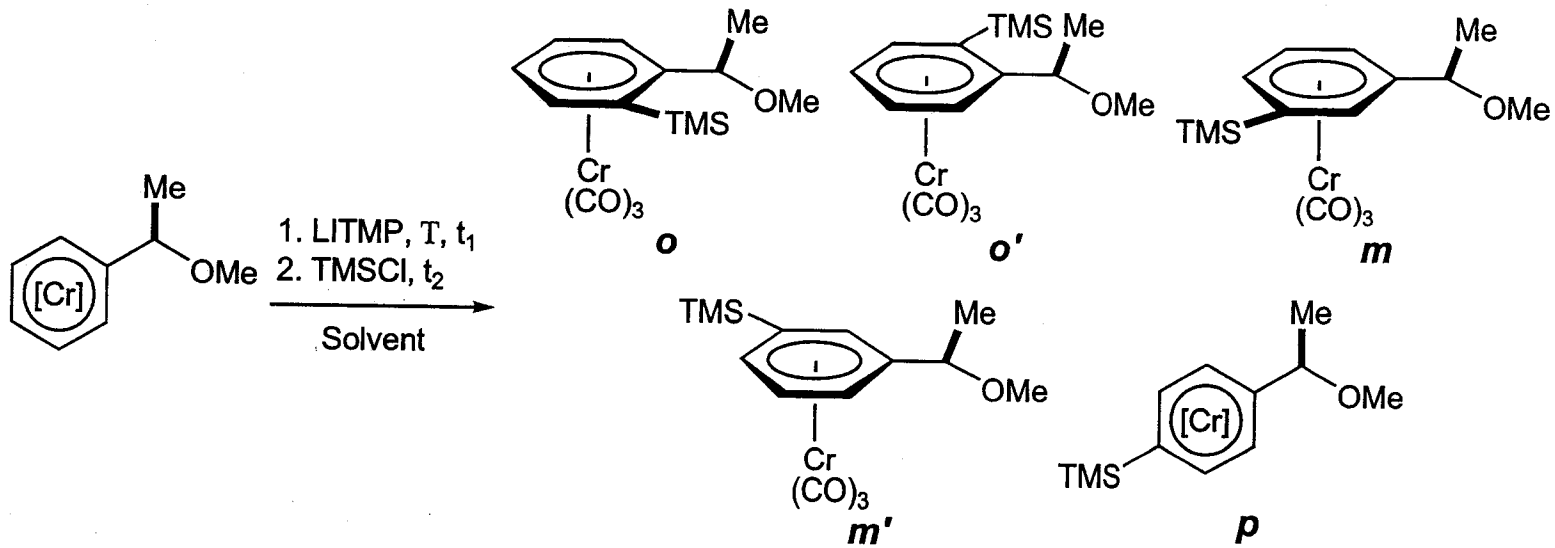






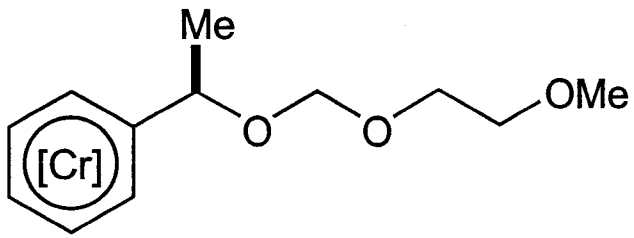




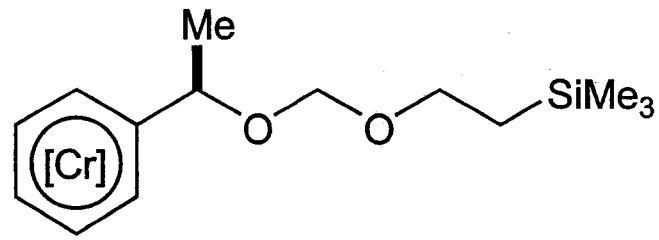


Entry	Method	T/°C	Solvent	Additive	t_1 [h]	t_2 [h]	**84** [%][a]	**111** [%][a]	o [%][b]	o' [%][b]	m,m'/p [%][b]
1	EQ	−78	THF	-	2	3	27	63	42	6	52
2	EQ	−78	THF	-	0.5	3	23	56	52	-	48
3	EQ	−100	THF	-	0.5	3	59	31	45	-	55
4	EQ	−78	THF	LiCl	0.5	3	37	48	52	2	46
5	ISQ	−78	THF	-	-	1	93	-	-	-	-
6	ISQ	−78	THF	-	-	5	14	63	60	trace	40
7	ISQ	−78	Hexane	-	-	5	88	-	-	-	-

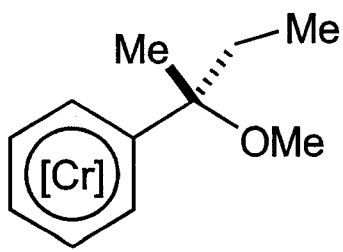
[a] Isolated yields. [b] Ratios from the ^{1}H NMR spectrum of **111**.



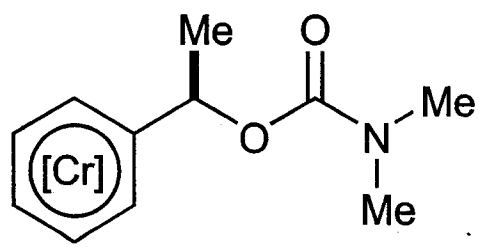
mixture of silylated products
(asymmetric methylation gave 98% ee)



mixture of silylated products
major product: *meta*!

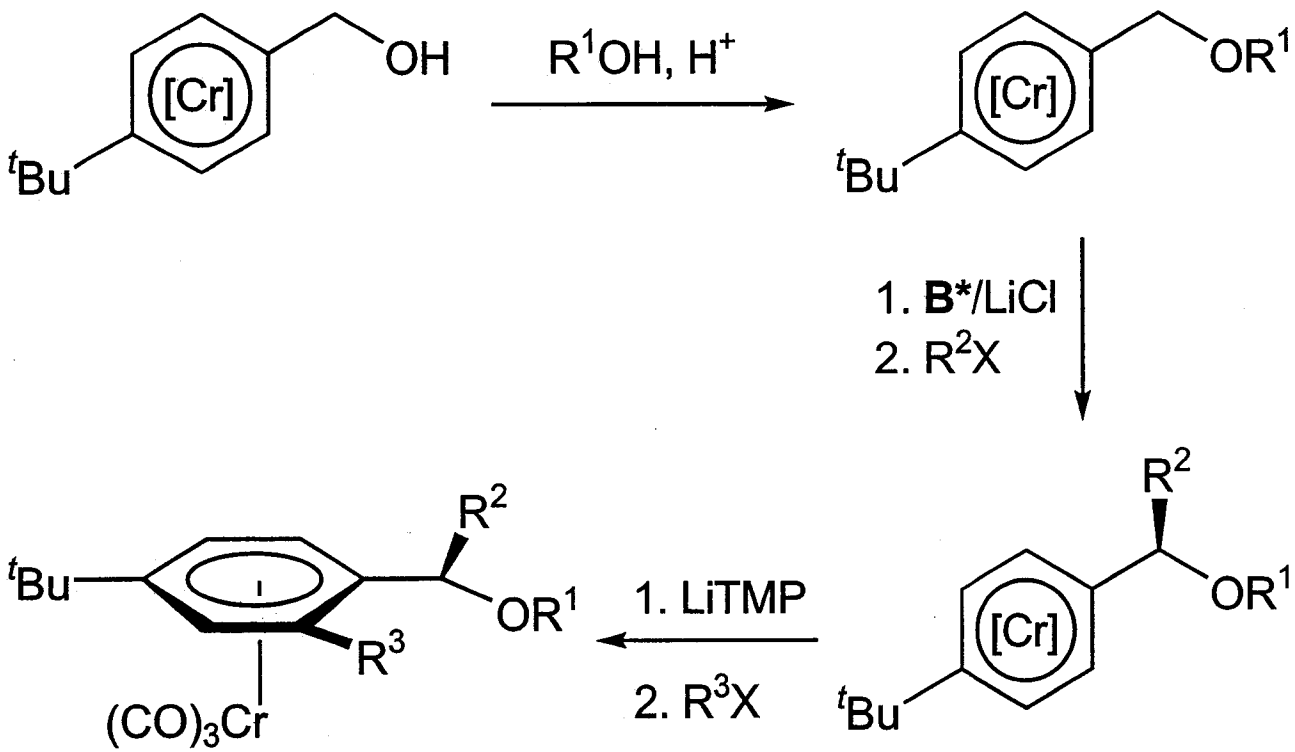


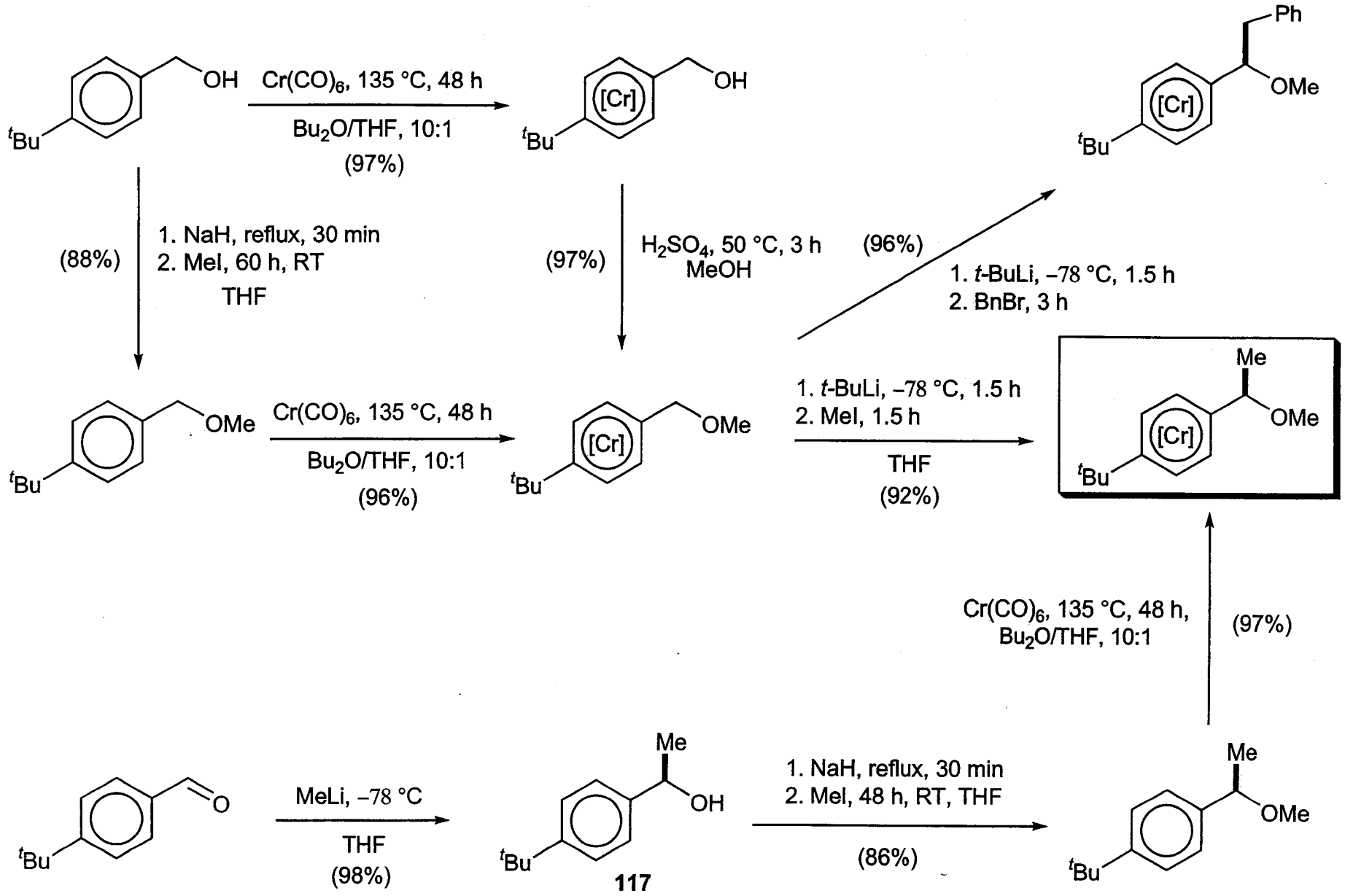
mixture of silylated products
major product: *para*

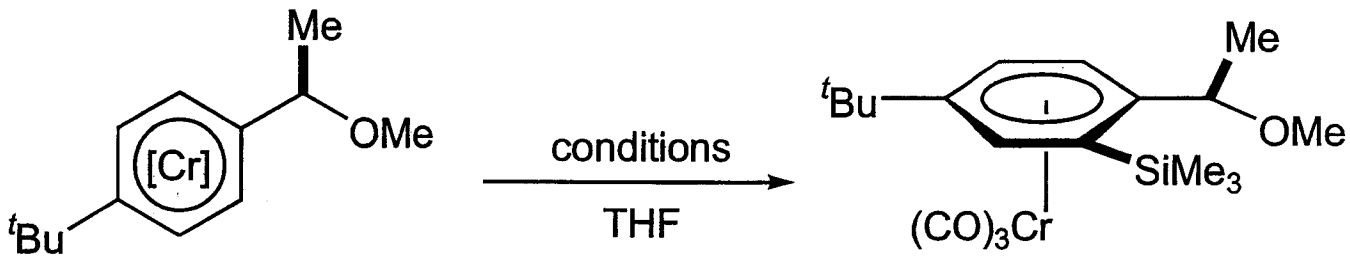


((asymmetric methylation gave 92% ee))

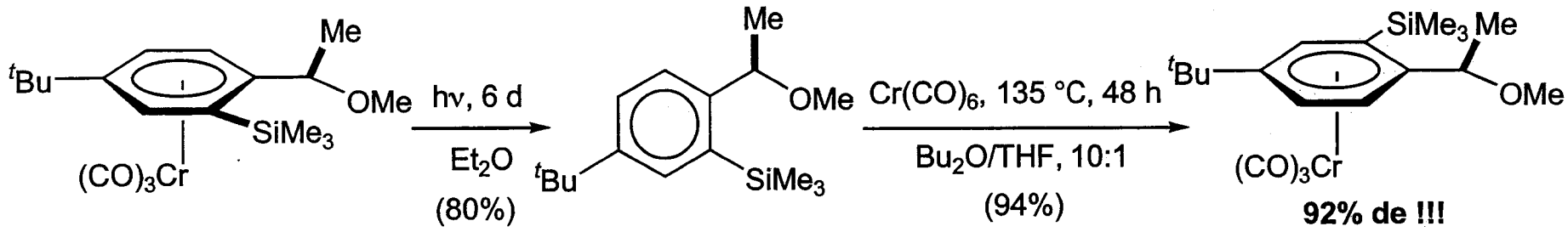
A possible solution…??

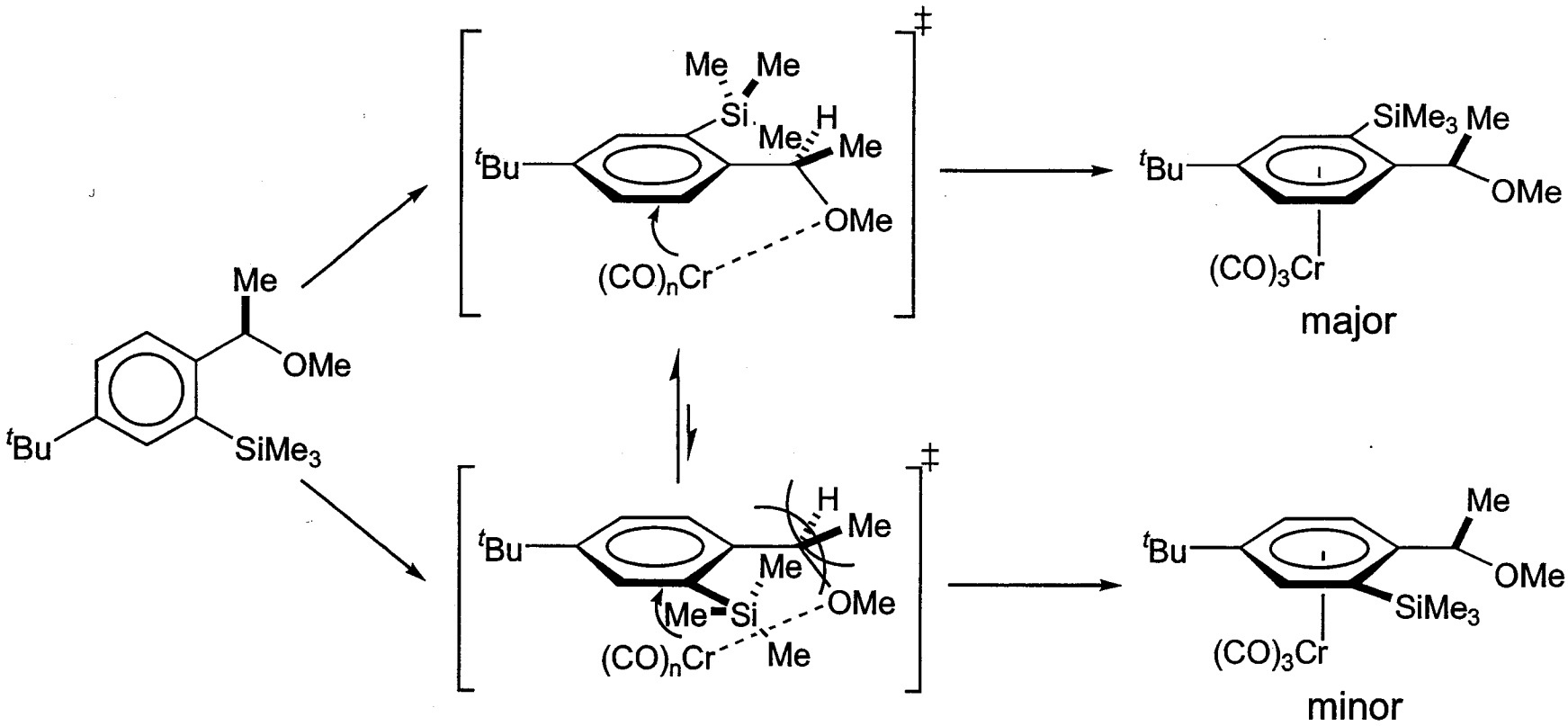


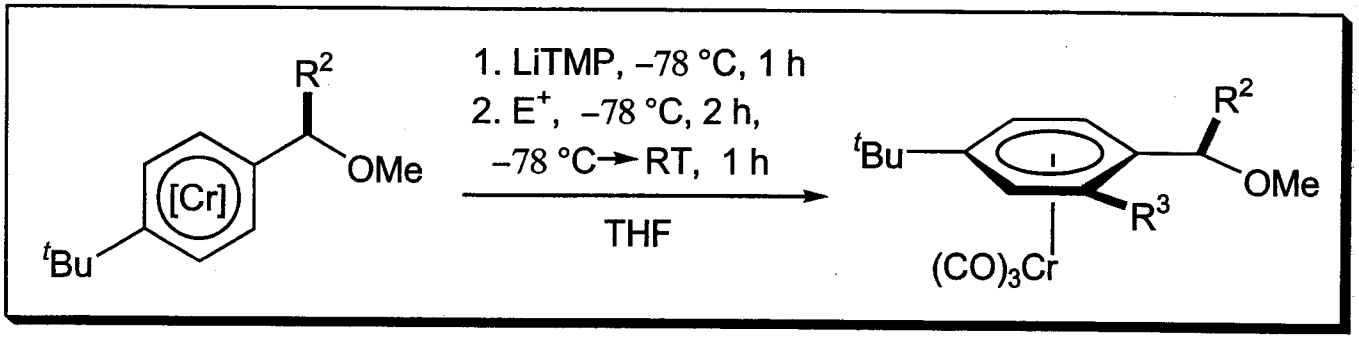

OH
Cr(CO)6, 135 °C, 48 h
Bu2O/THF, 10:1
(97%)
[Cr]
OH
tBu
(88%)
1. NaH, reflux, 30 min
2. MeI, 60 h, RT
THF
(97%)
H2SO4, 50 °C, 3 h
MeOH
(96%)
1. t-BuLi, −78 °C, 1.5 h
2. BnBr, 3 h
Ph
OMe
OMe
Cr(CO)6, 135 °C, 48 h
Bu2O/THF, 10:1
(96%)
1. t-BuLi, −78 °C, 1.5 h
2. MeI, 1.5 h
THF
(92%)
Me
Cr(CO)6, 135 °C, 48 h,
Bu2O/THF, 10:1
(97%)
O
MeLi, −78 °C
THF
(98%)
117
1. NaH, reflux, 30 min
2. MeI, 48 h, RT, THF
(86%)

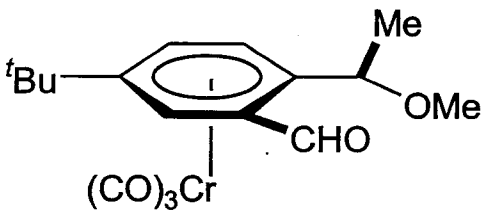


Me_3SiCl, LiTMP, –78 °C, 5.5 h	(60%)
1. LiTMP, –78 °C, 1 h 2. Me_3SiCl, –78 °C → –45 °C, 12 h	(89%)
1. LiTMP, –78 °C, 1 h 2. Me_3SiCl, –78 °C, 2 h, –78 °C → RT, 1 h	(98%)

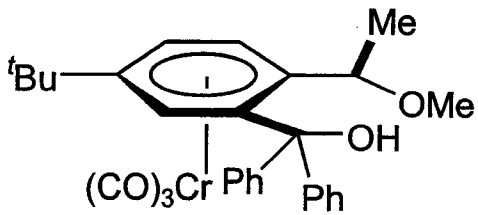

Me
tBu
OMe
SiMe3
(CO)3Cr
hν, 6 d
Et2O
(80%)
Me
OMe
tBu
SiMe3
Cr(CO)6, 135 °C, 48 h
Bu2O/THF, 10:1
(94%)
SiMe3
Me
tBu
OMe
(CO)3Cr
92% de !!!


Me
OMe
tBu
SiMe3
Me Me
Si
Me H
Me
OMe
(CO)nCr
‡
SiMe3 Me
OMe
(CO)3Cr
major
H
Me
Me
Me Si
OMe
(CO)nCr
Me
minor

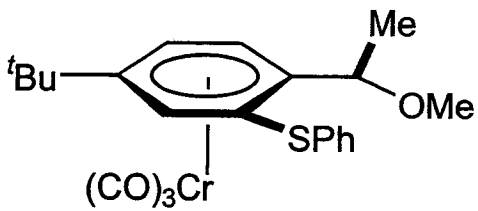




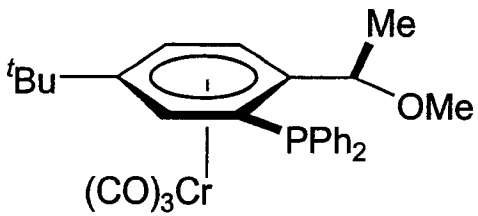
36% (unoptimised)



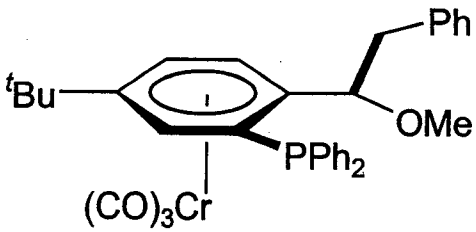
93%



98%

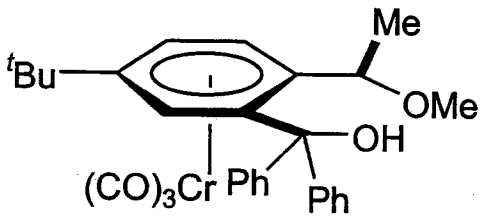


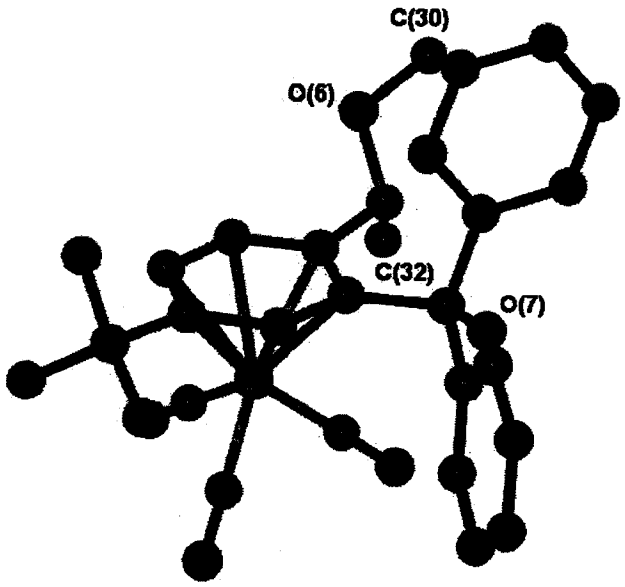
93%

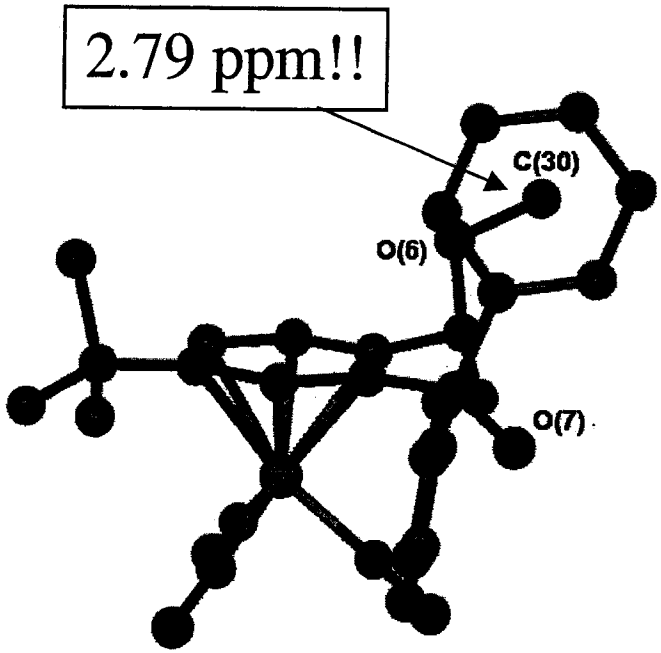


87%

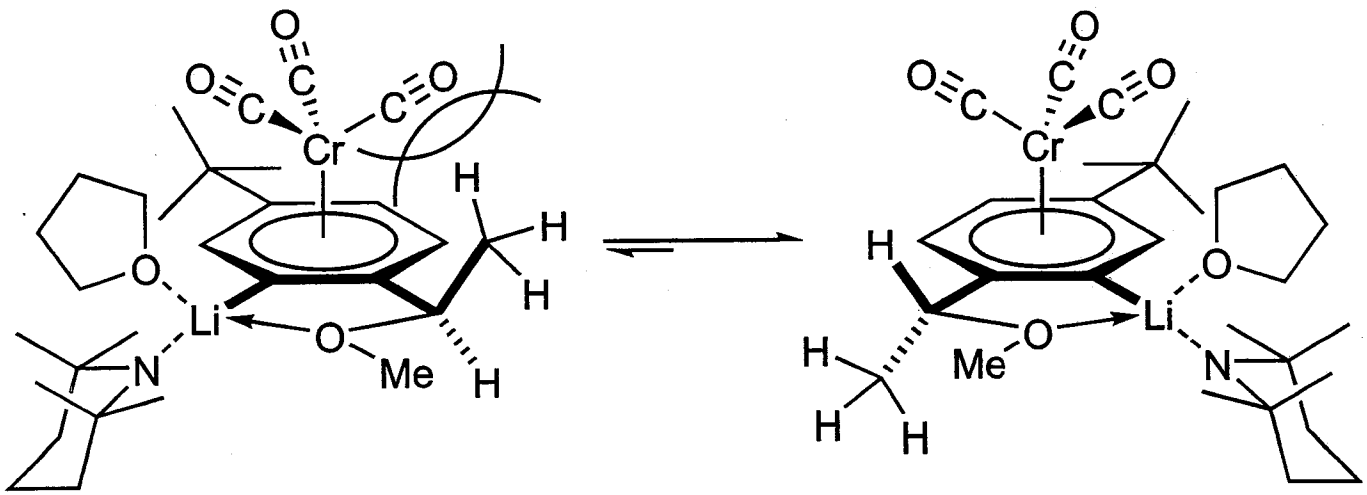
Gibson and Ibrahim, *CC*, 2001, 1070.

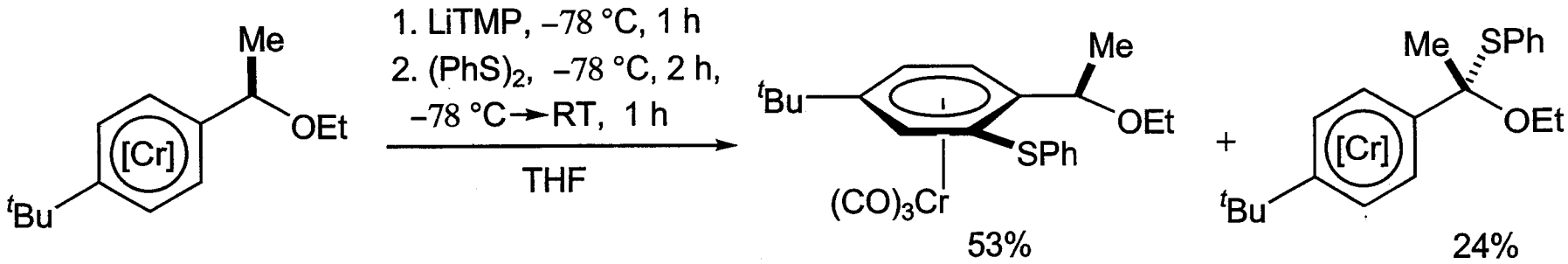

Me
tBu
OMe
OH
(CO)3Cr
Ph
Ph


C(30)
O(6)
C(32)
O(7)

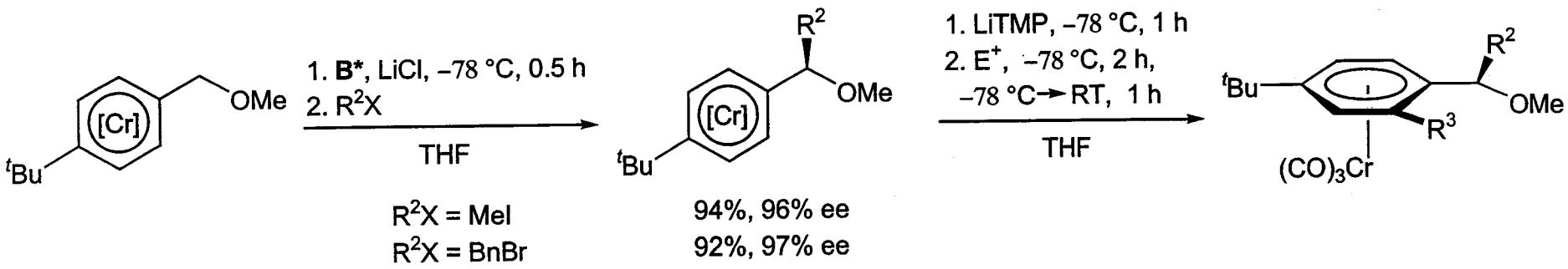

2.79 ppm!!
C(30)
O(6)
O(7)

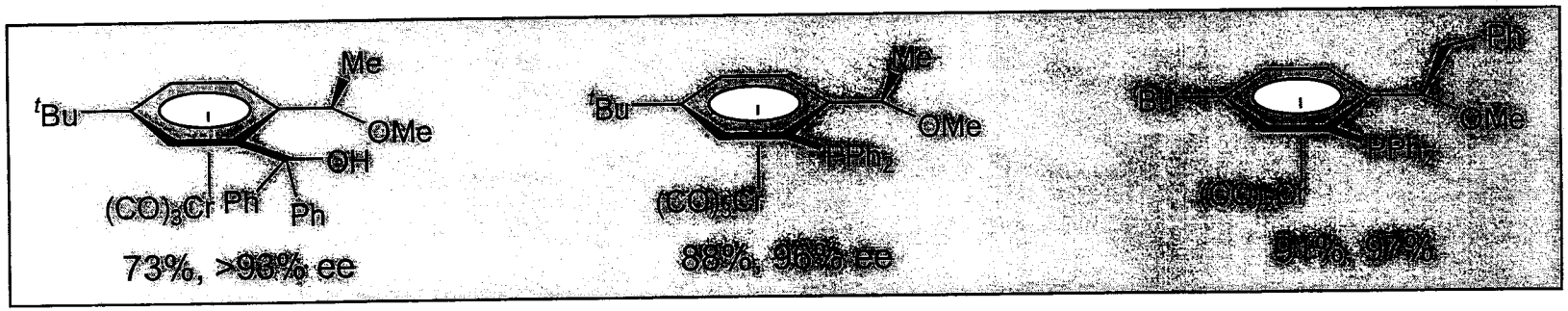
Model for the observed diastereoselectivity

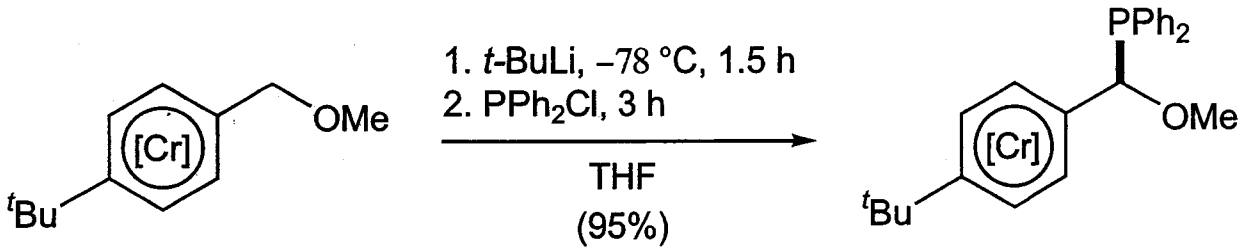


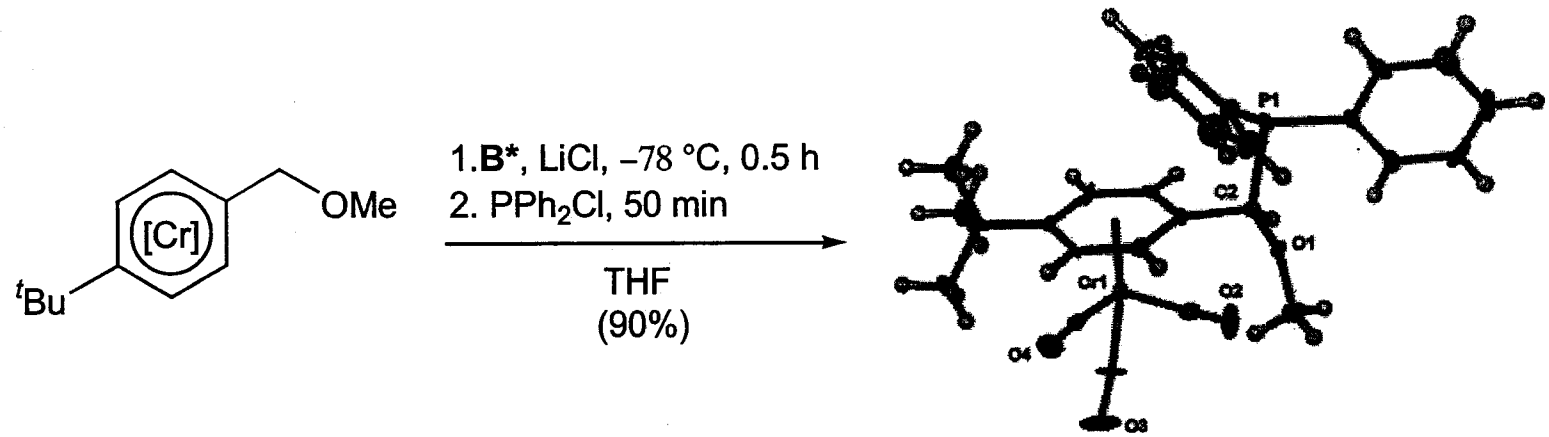

Me
OEt
[Cr]
tBu
1. LiTMP, −78 °C, 1 h
2. (PhS)2, −78 °C, 2 h,
−78 °C → RT, 1 h
THF
Me
tBu
OEt
SPh
(CO)3Cr
53%
+
Me
SPh
OEt
[Cr]
tBu
24%

Synthesis of optically active complexes



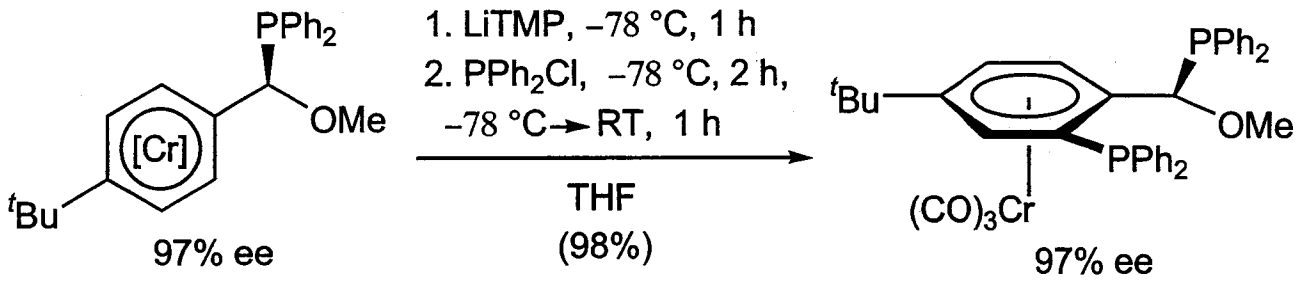


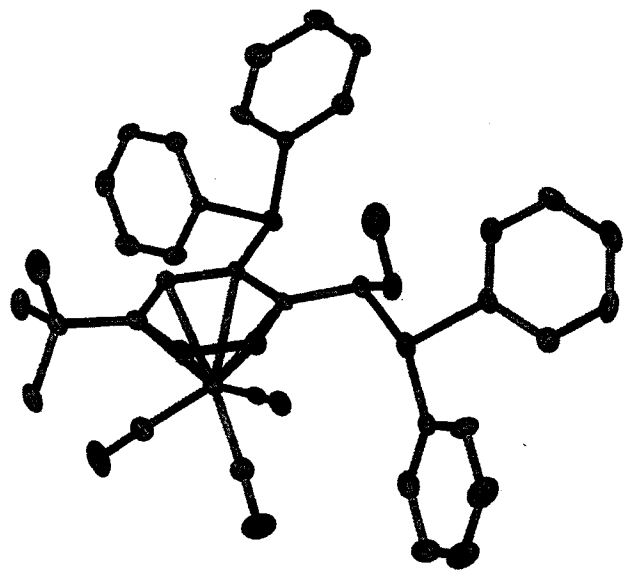




97% ee

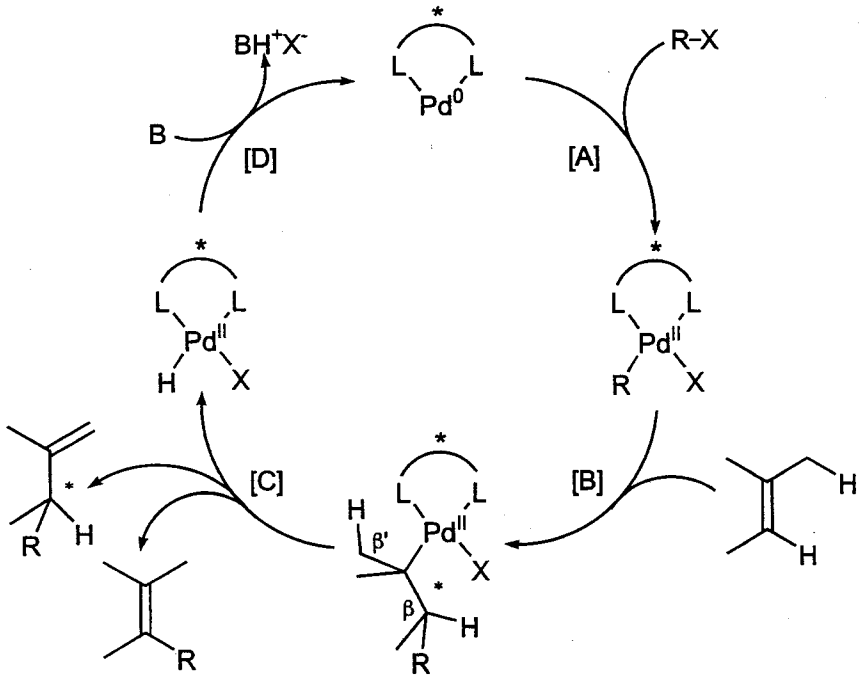
Gibson, Ibrahim, Pasquier and Steed, *TH*, 2002, **58**, 4617.



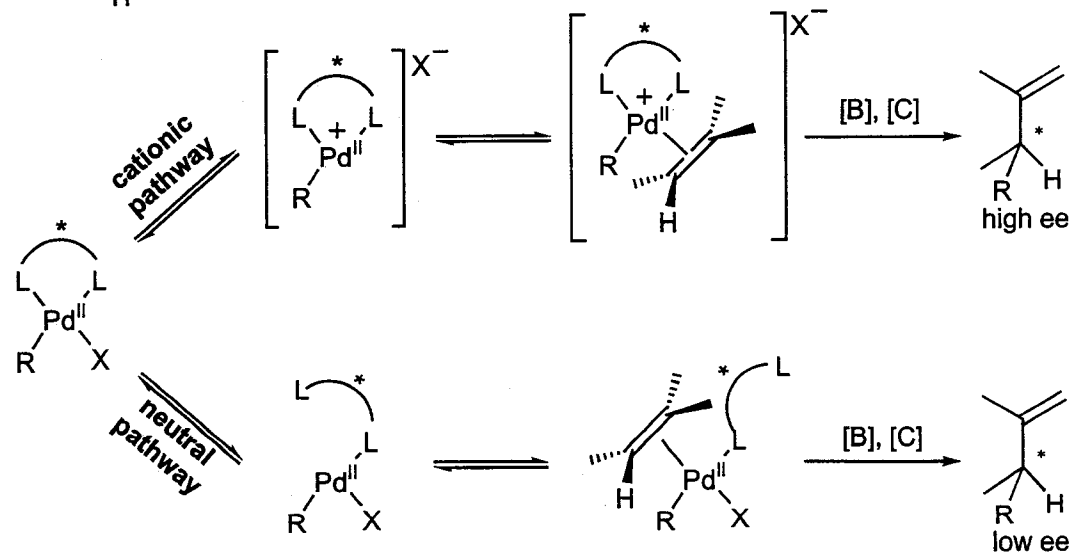


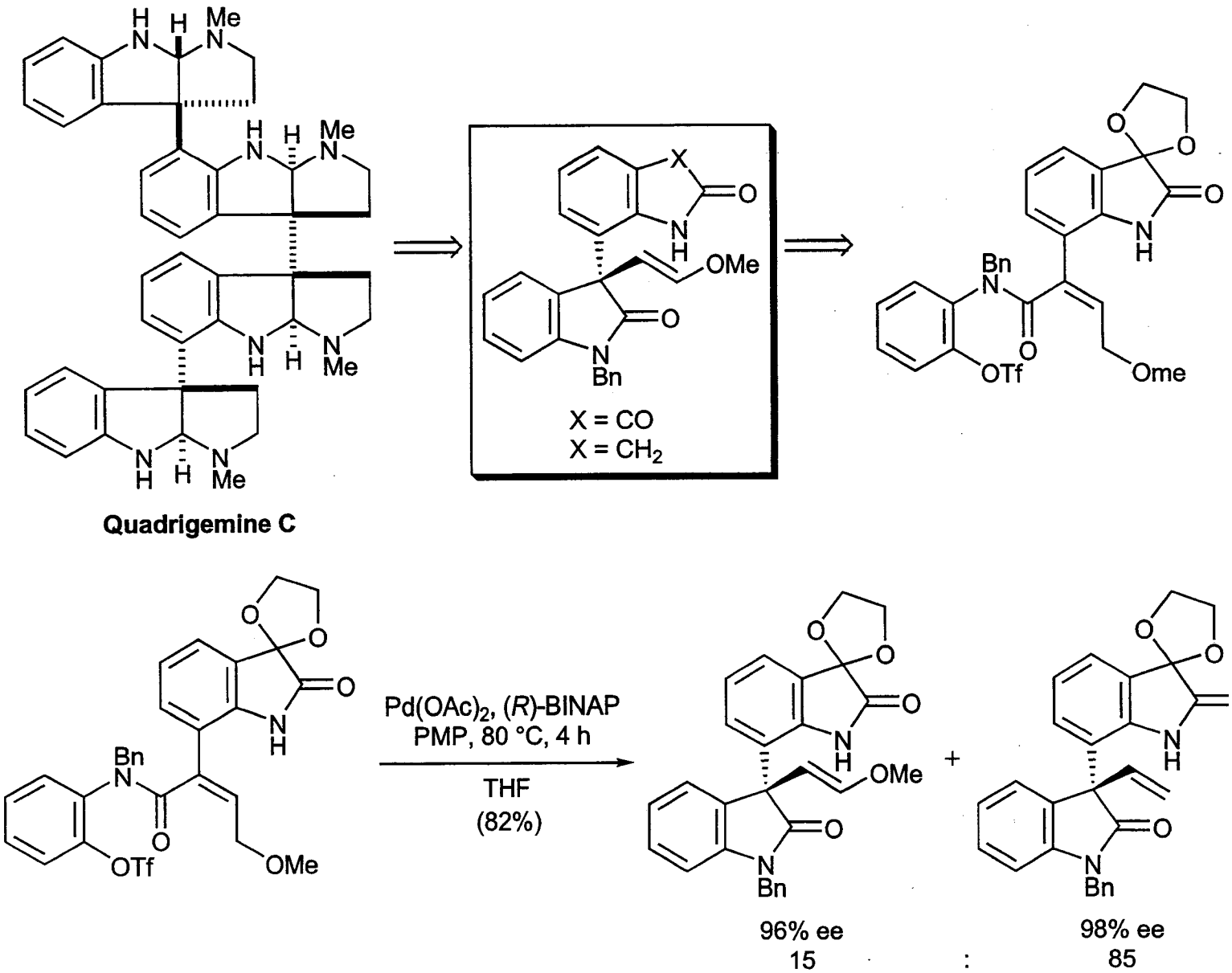
rac-Hasiphos

Application of (–)-*Hasiphos* in the intermolecular asymmetric Heck reaction

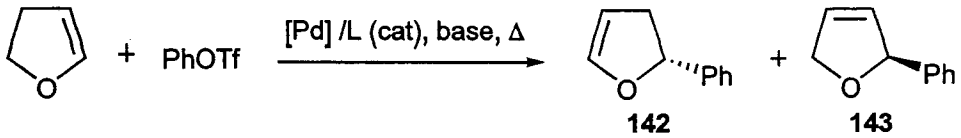


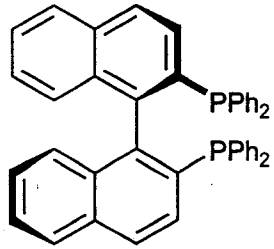
For an excellent review, see:
Shibasaki and Vogl, *JOMC*, 1999, **576**, 1.



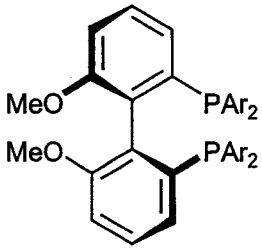


Overman, *ACIE*, 2001, **40**, 1439.

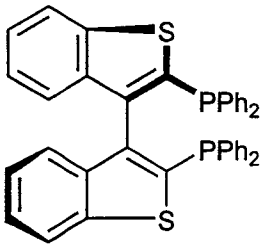




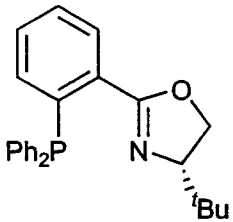
(*R*)-**142** 46%, >96% ee
(*S*)-**143** 24%, 17% ee
(Ozawa and Hayashi)



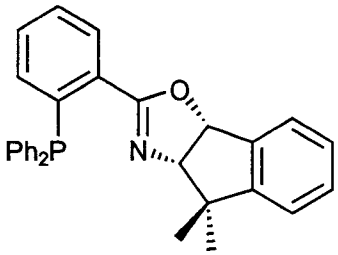
Ar = 3,5-(*t*-Bu)$_2$-C$_6$H$_3$
(*S*)-**142** ca 65%, >98% ee
(*S*)-**143** ca 3%, >98% ee
(Pregosin)



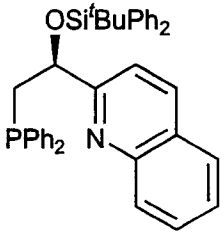
(*R*)-**142** 84%, 91% ee
(Tietze)



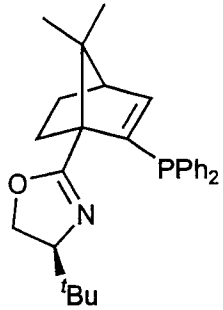
(*R*)-**143** 87%, 97% ee
(Pfaltz)



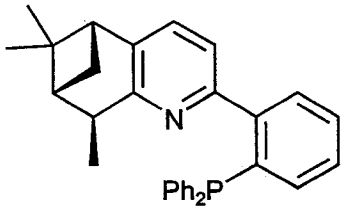
(*R*)-**143** 81%, 96% ee
(Hashimoto)



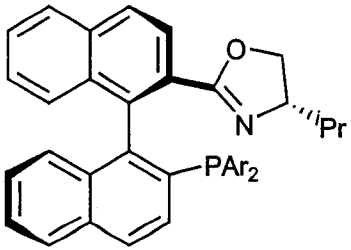
(*S*)-**143** 99% ee
(Pfaltz)



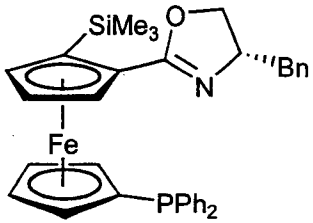
(*R*)-**143** 100% convn, 96% ee
(Gilbertson)



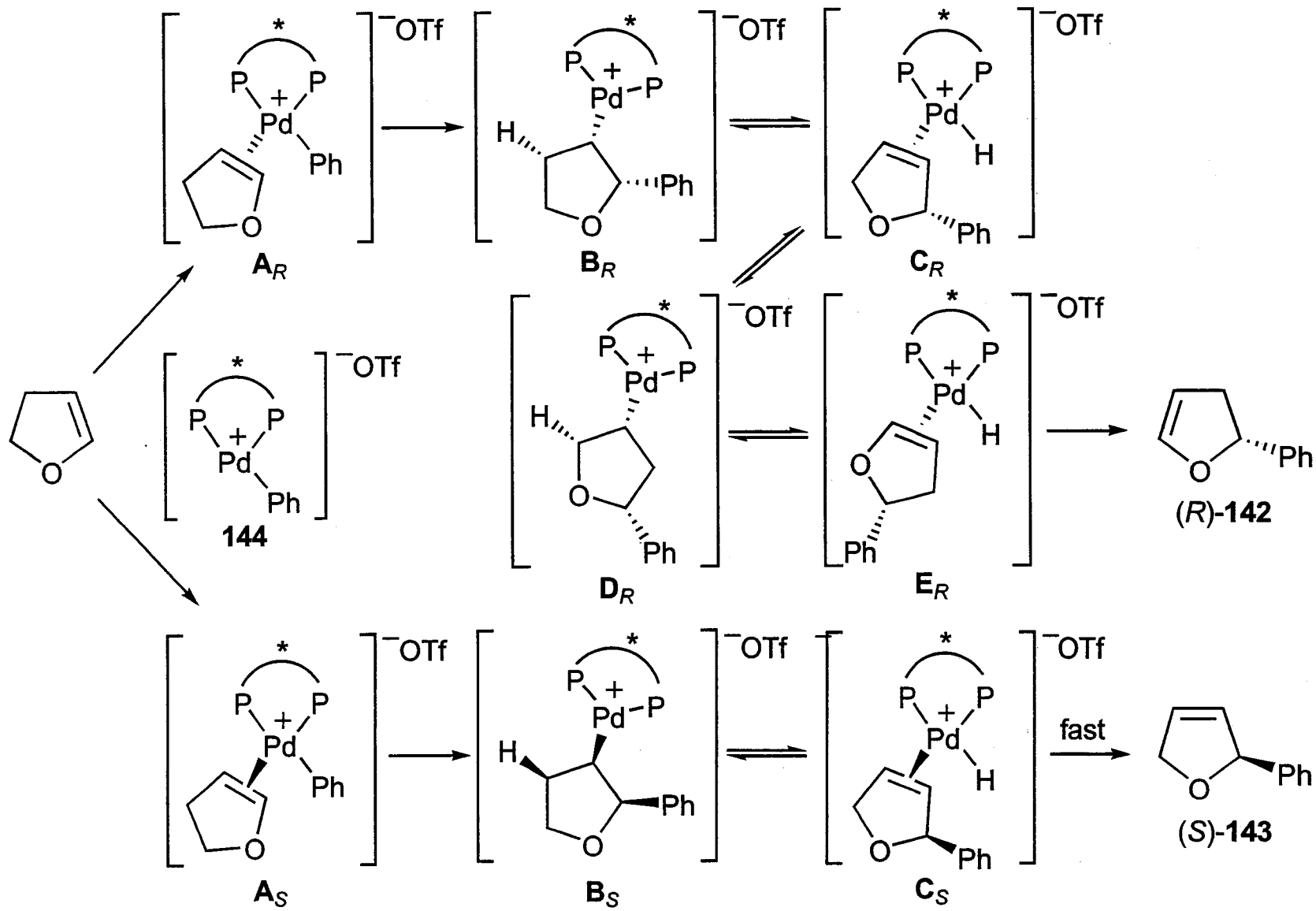
(*R*)-**143** 68%, 88% ee
(Malkov and Kocovsky)

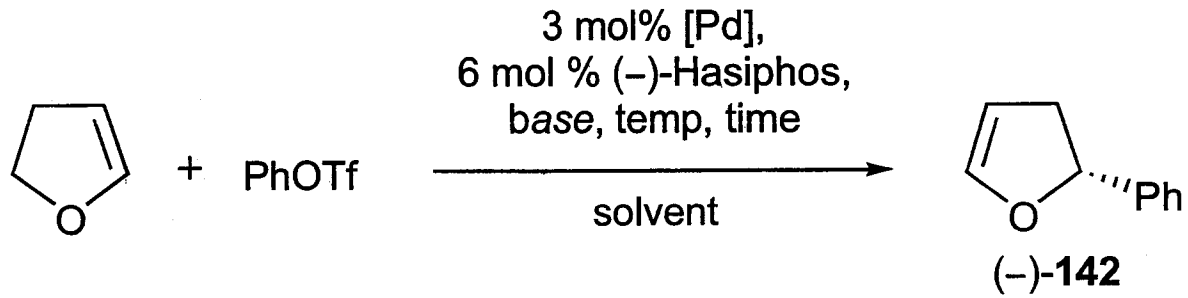


(*S*)-**143**: Ar = Ph, 85%, 74% ee
Ar = 3,5-Me$_2$-C$_6$H$_3$, 85%, 86% ee
Ar = 3,5-(*t*-Bu)$_2$-C$_6$H$_3$, 26%, 98% ee
(Pregosin)

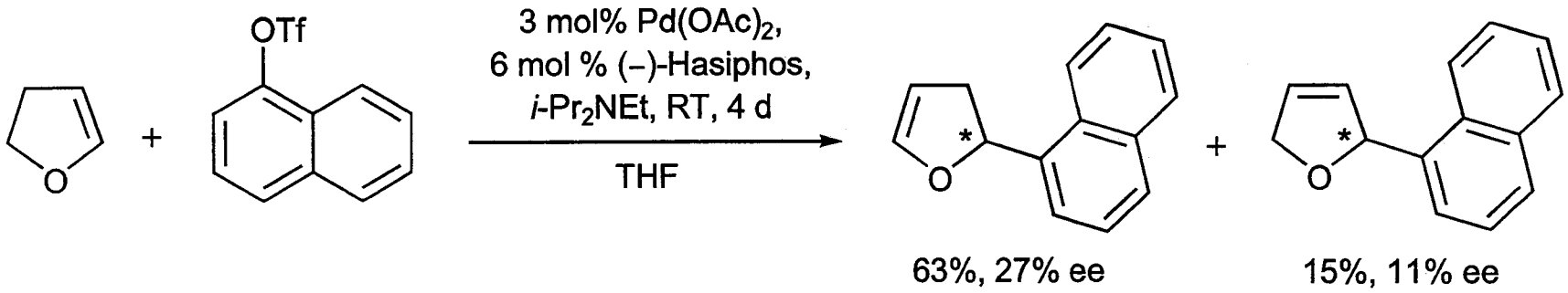


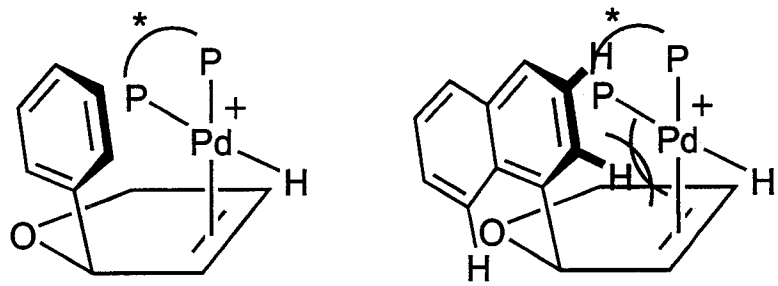
(*R*)-**143** 75%, 92% ee
(Hou)


OTf
A$_R$
B$_R$
C$_R$
144
D$_R$
E$_R$
(R)-142
A$_S$
B$_S$
C$_S$
fast
(S)-143

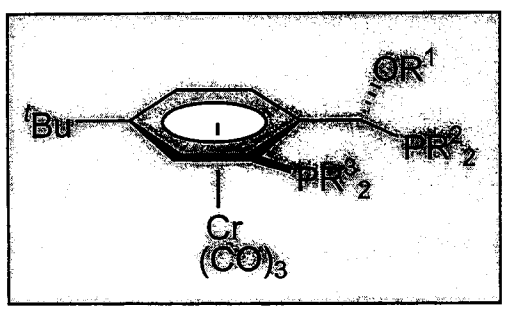


Entry	[Pd]	base	Solvent	Temp (°C)	time (h)	yield (%)	ee (%)
1	$Pd(OAc)_2$	i-Pr_2NEt	THF	40	34 and 14	78	56
2	$Pd(OAc)_2$	i-Pr_2NEt	THF	RT	72	60	60
3	$Pd(OAc)_2$	TMP	THF	RT	72	75	60
4	$Pd(OAc)_2$	PS	THF	RT and 40	72 and 96	-	-
5	$Pd(OAc)_2$	i-Pr_2NEt	Benzene	40	42	73	53
6	$Pd_2(dba)_3$	i-Pr_2NEt	THF	RT and 40	72 and 96	28	58



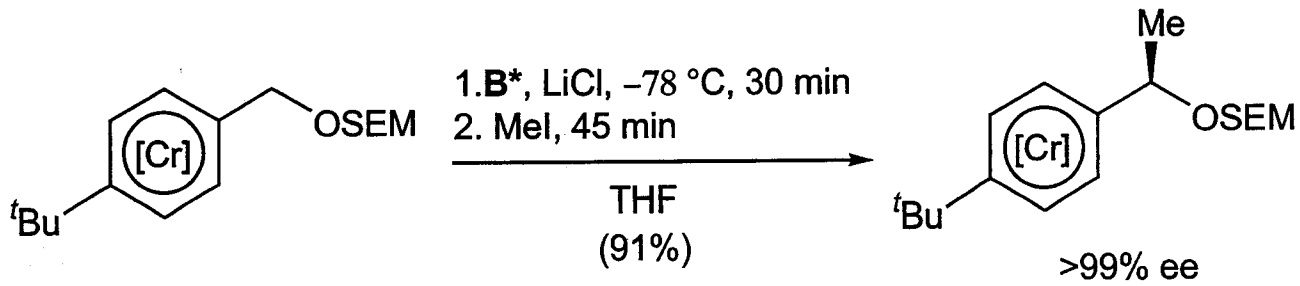


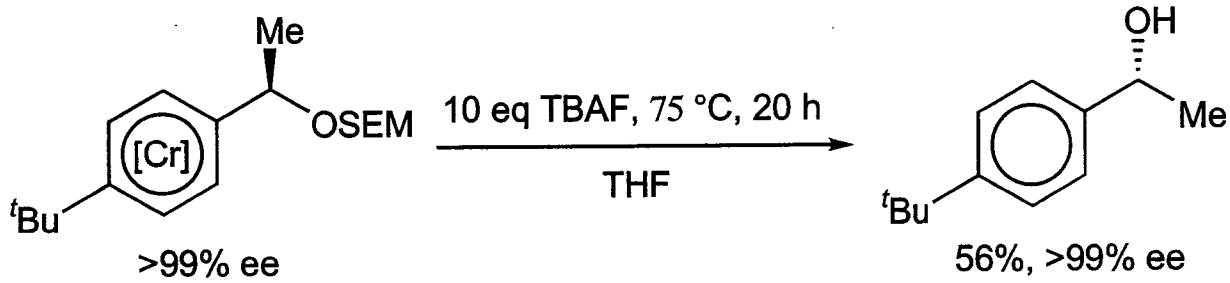
C_1 C_2

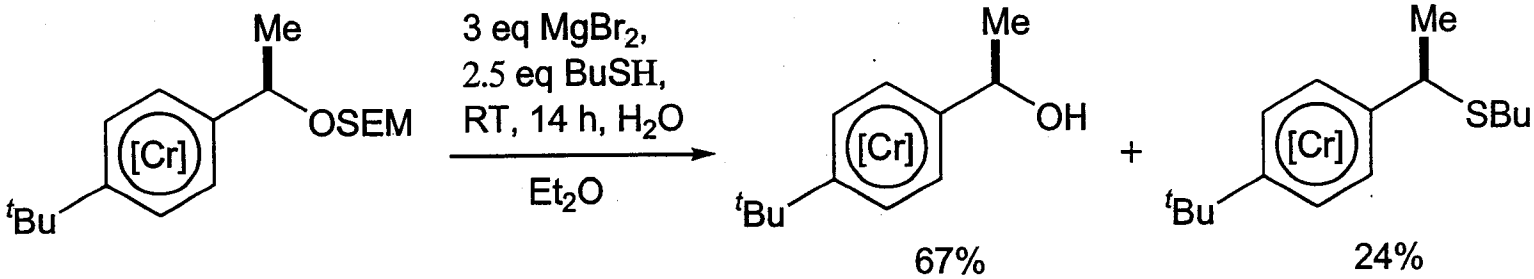


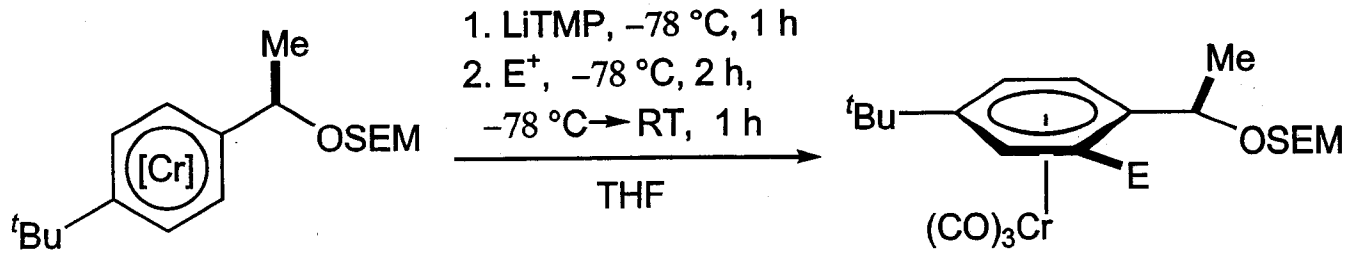
Gibson, Ibrahim, Pasquier and Swamy, *THA*, 2003, **14**, 1455;
Gibson, Ibrahim, Pasquier and Swamy, *THA*, 2004, **15**, 465.

Elaboration of secondary benzylic SEM ether chromium complexes in the synthesis of secondary benzylic alcohols



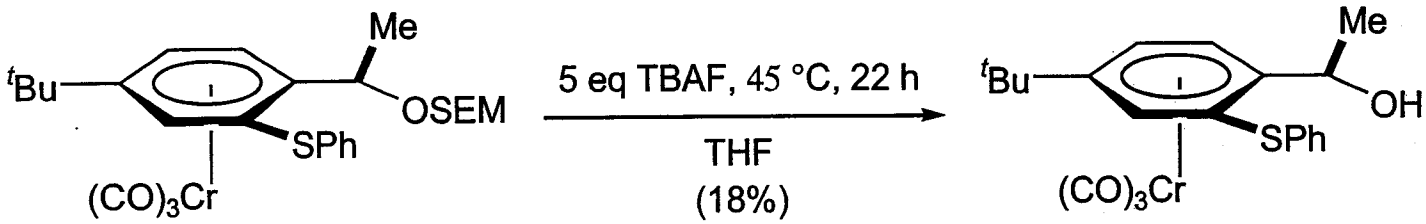


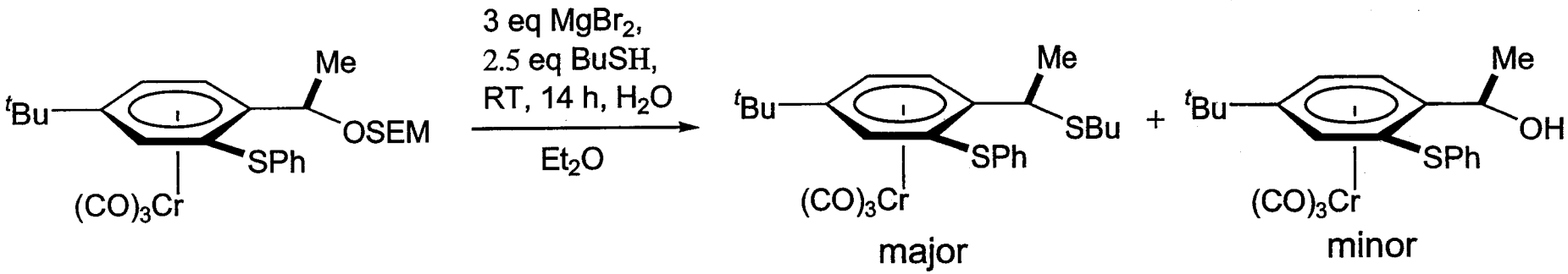




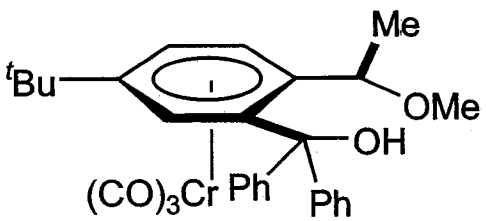
E^+ = PhSSPh — E = PhS, 94%

E^+ = Ph_2CO — E = CPh_2OH, 49%

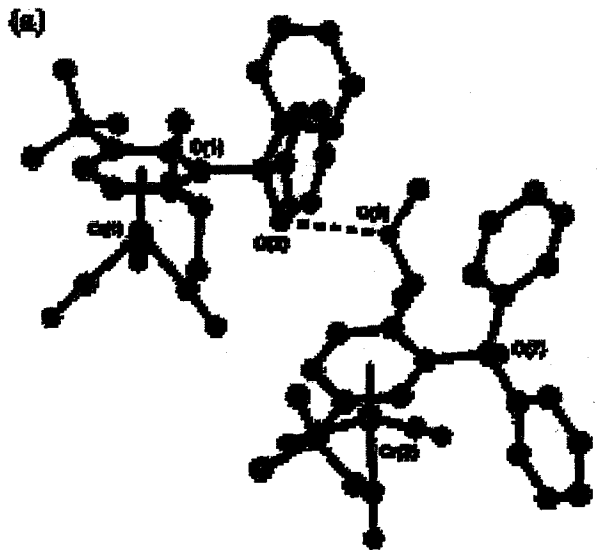




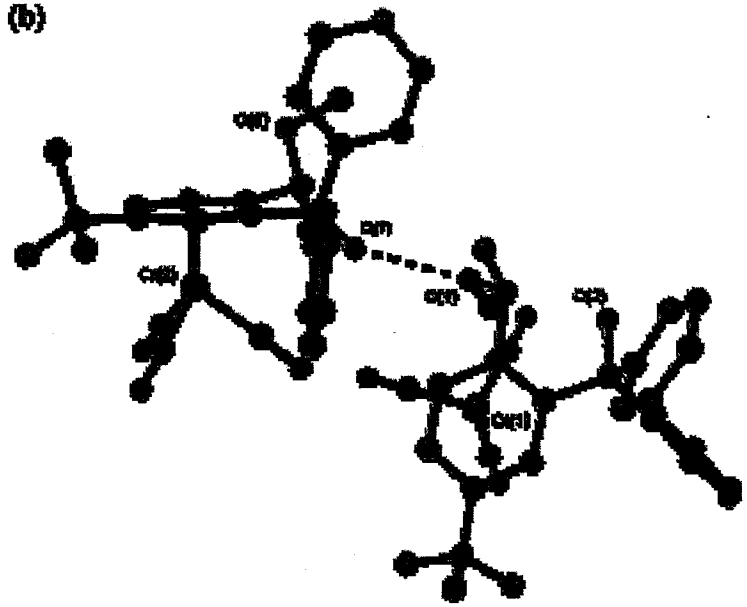
Intermolecular interactions in triphenylmethanol derived mono- and dichromium tricarbonyl complexes



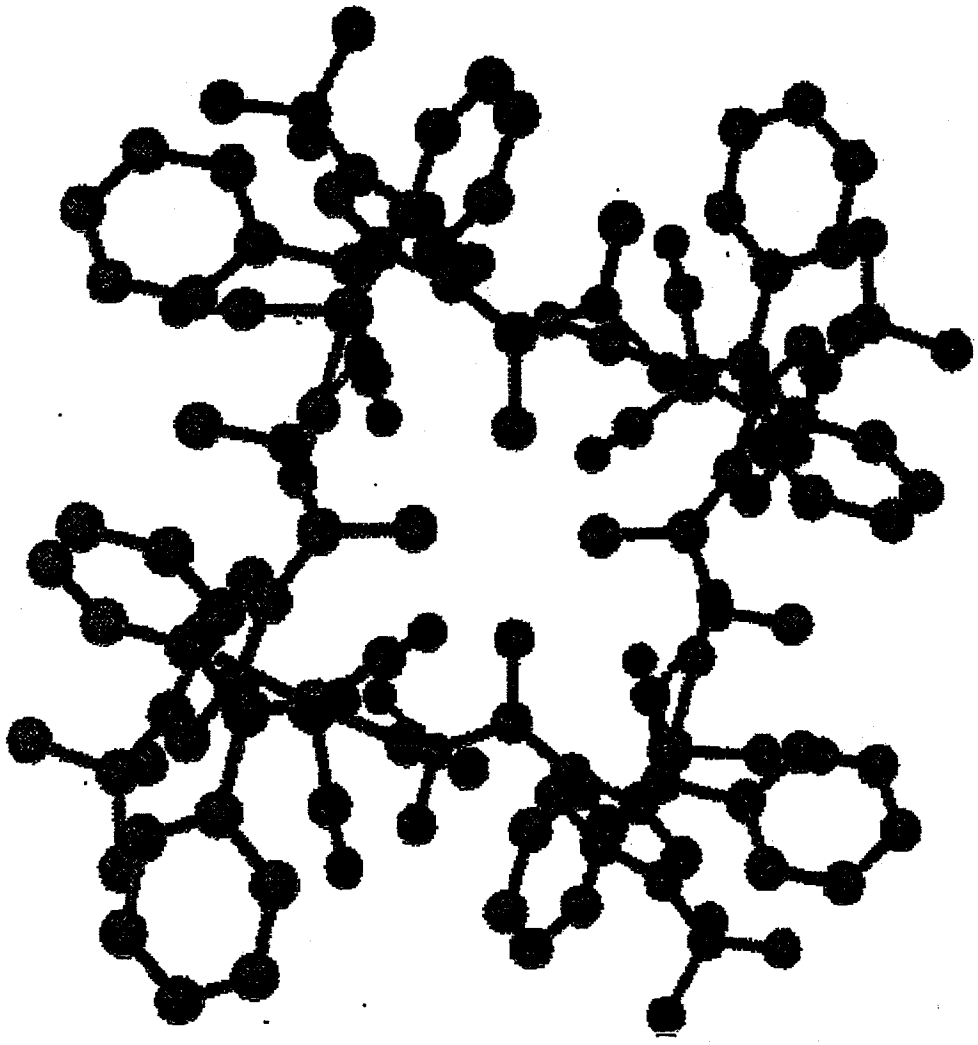
Racemic x-ray structure displays isolated homochiral *RR*···*RR* hydrogen bonds and heterochiral *SS*···*RR* hydrogen bonds between the OH functionality and the OMe group in an infinite hydrogen-bonded chain comprising the sequence: *SS*···*RR*···*RR*···*SS*···*SS*···*RR*···



Heterochiral *SS*···*RR* hydrogen bond induces a twist of ca. 30°.

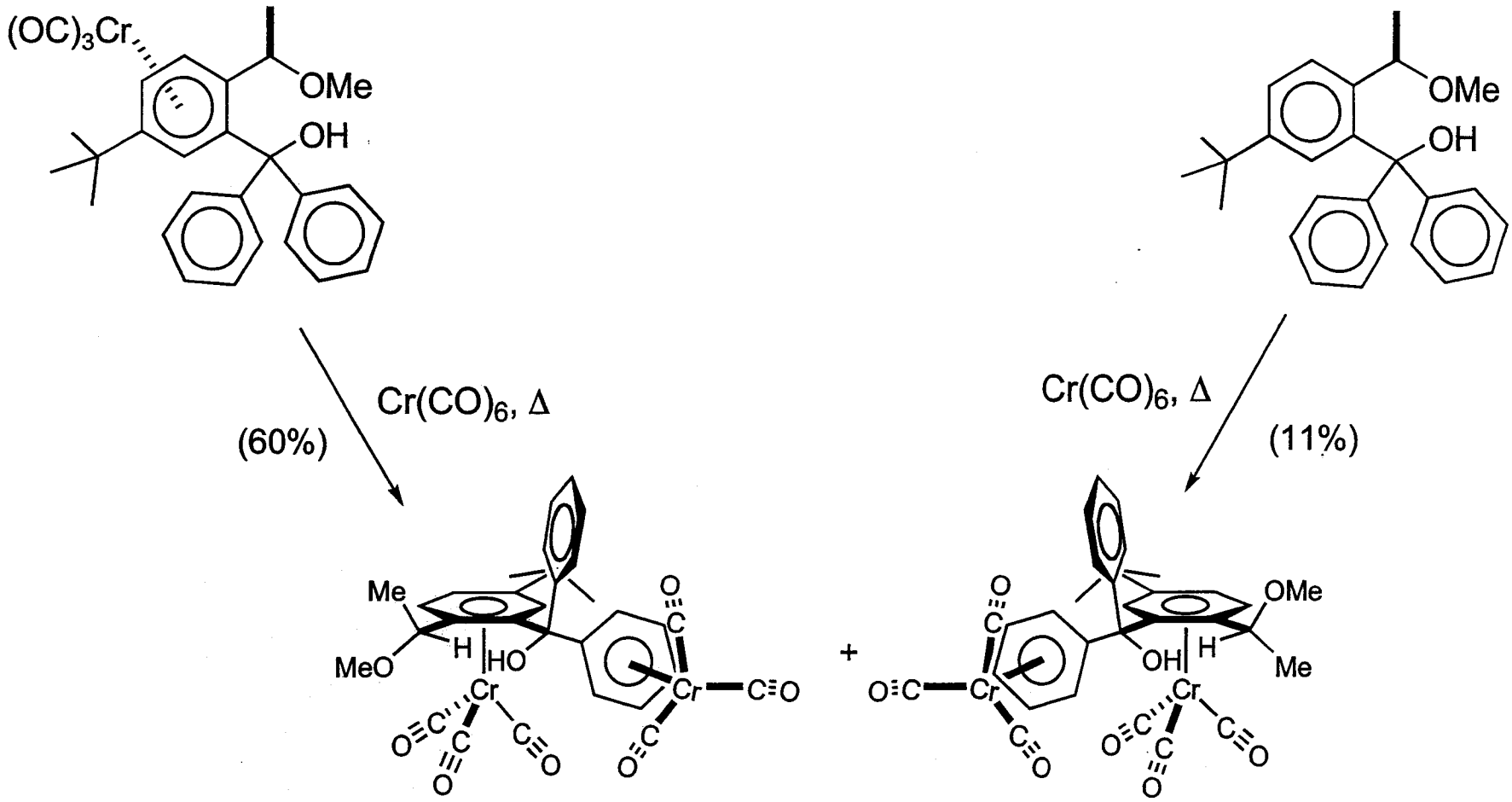


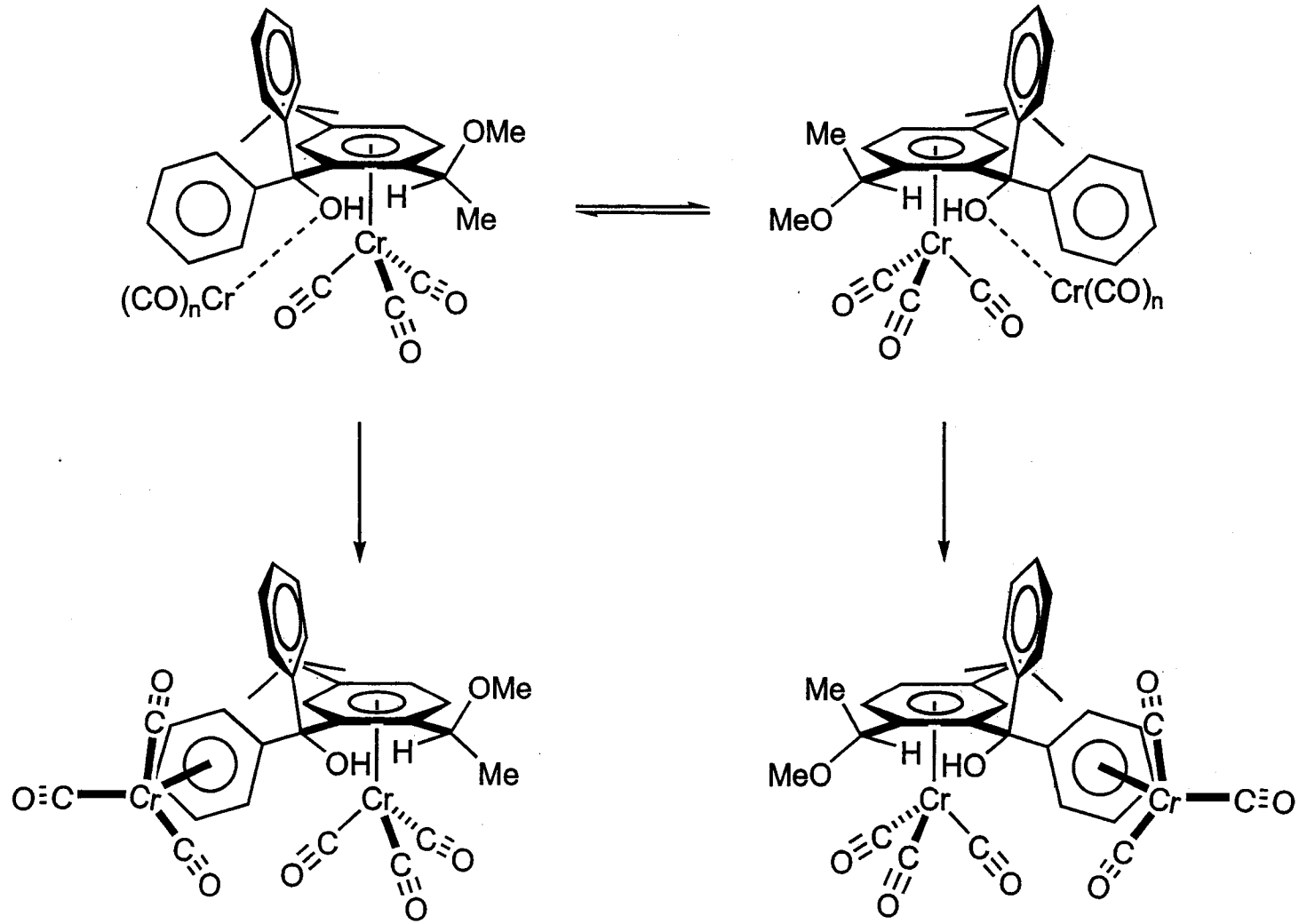
Homochiral *RR*···*RR* hydrogen bond induces a twist of ca. 90°.

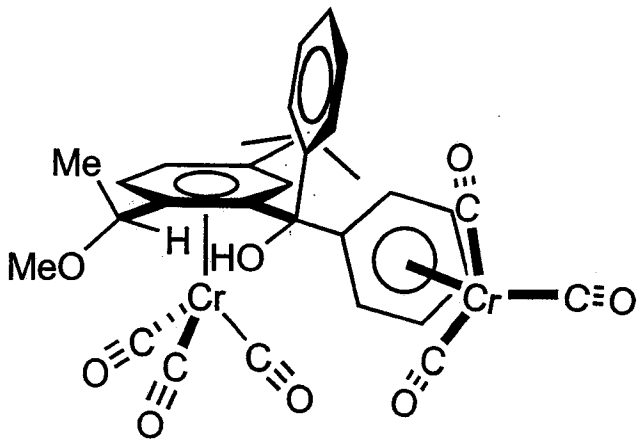


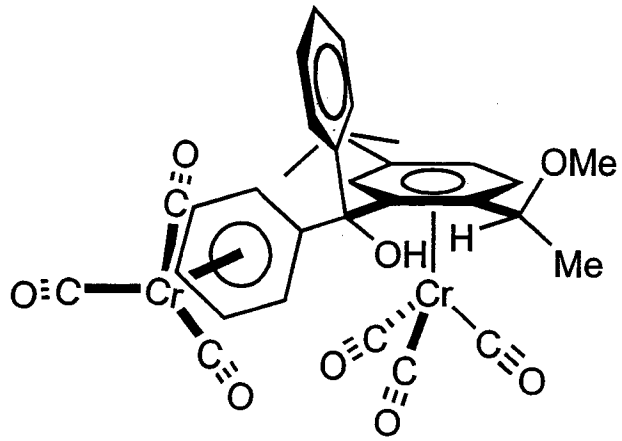
The noncrystallographic 4-fold helix of the optically active hydroxy ether complex

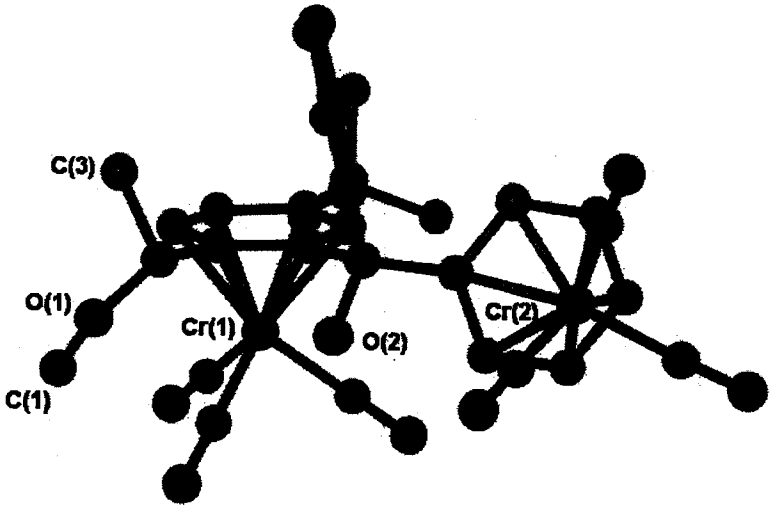
Gibson, Ibrahim and Steed, *JACS*, 2002, **124**, 5109.

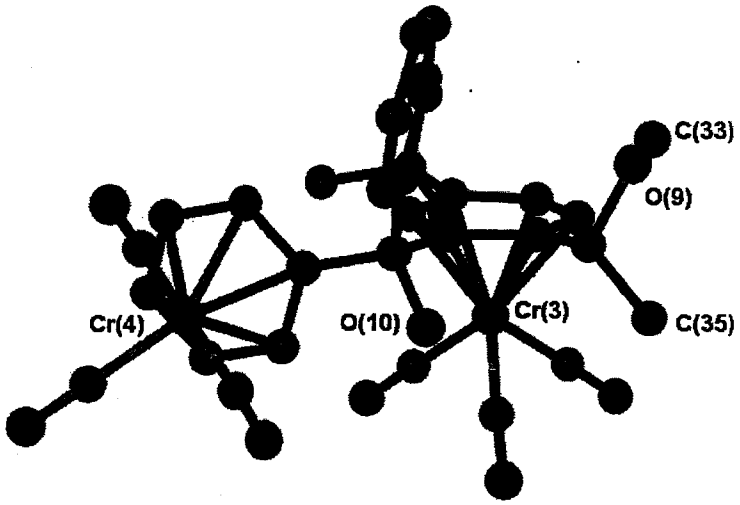

(OC)3Cr
OMe
OH
Cr(CO)6, Δ
(60%)
Me
MeO
H
HO
Cr
C≡O
+
OMe
OH
H
Me
Cr(CO)6, Δ
(11%)

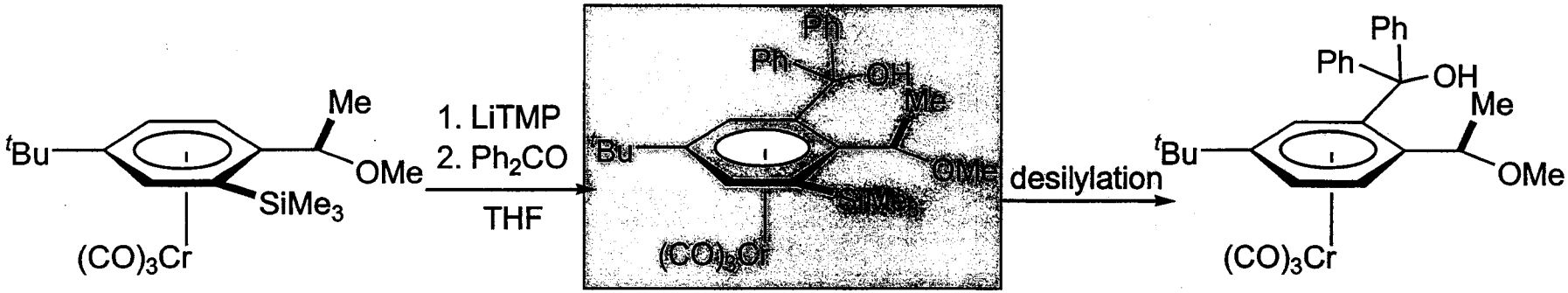

OMe
OH
H
Me
(CO)nCr
Cr
Me
MeO
H
HO
Cr(CO)n
OMe
OH
H
Me
Me
MeO
H
HO

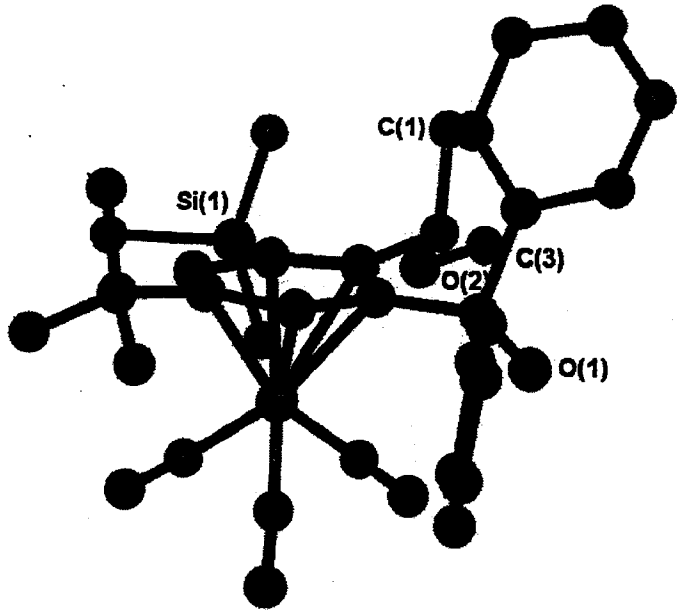

Me
MeO
H
HO
Cr
Cr
O
C
C≡O
O≡C
C
C≡O
O≡C
C
O


O
C
OMe
OH
H
Me
O≡C
Cr
C≡O
Cr
O≡C
C
C≡O
O


C(3)
O(1)
C(1)
Cr(1)
O(2)
Cr(2)


C(33)
O(9)
Cr(4)
O(10)
Cr(3)
C(35)


tBu
Me
OMe
SiMe3
(CO)3Cr
1. LiTMP
2. Ph2CO
THF
Ph
Ph
OH
Me
tBu
OMe
SiMe3
(CO)3Cr
desilylation
Ph
Ph
OH
Me
tBu
OMe
(CO)3Cr


C(1)
Si(1)
C(3)
O(2)
O(1)

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

June 29, 2004

Catalytic Asymmetric Heteroatom Functionalisation of β-Ketoesters

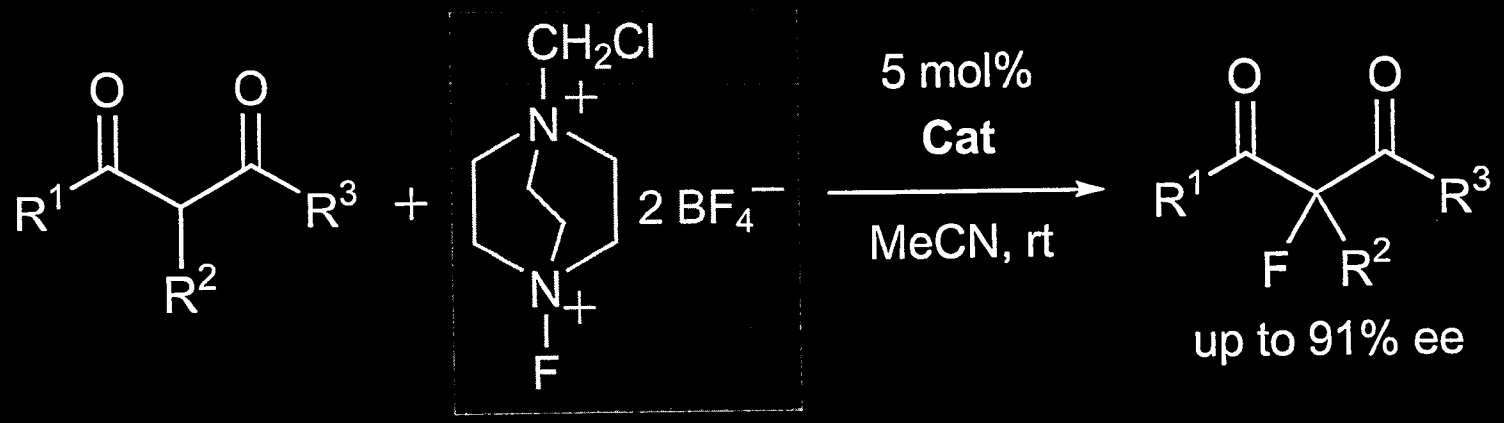
By

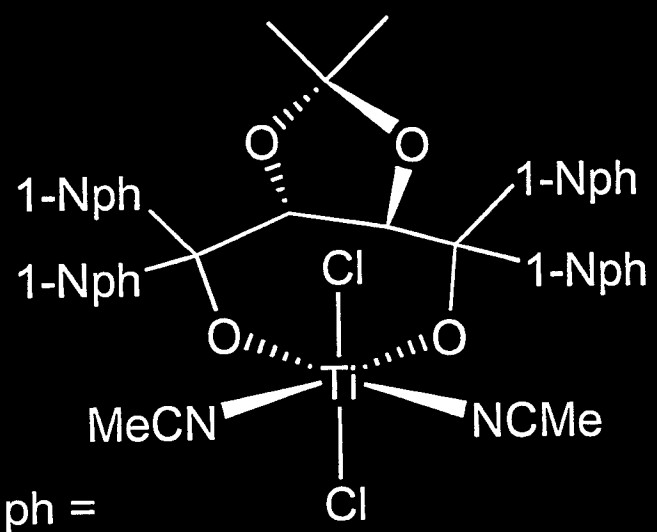
Hasim Ibrahim

Group of Professor Antonio Togni

- Introduction
- Alkoxylation
- Mercaptanation
- Cyanation/Bromination
- Chlorination/Fluorination

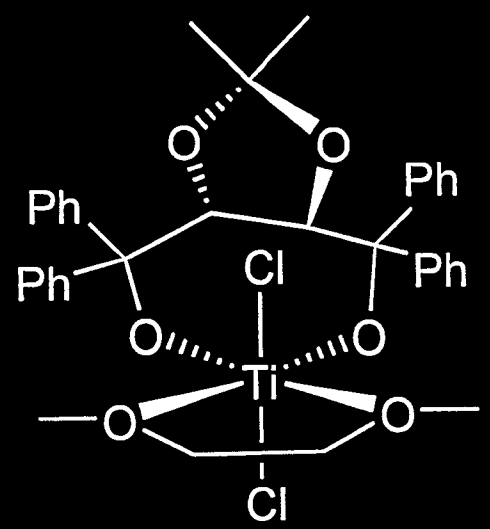
Catalytic enantioselective electrophilic fluorination





1-Nph = 1-naphthyl

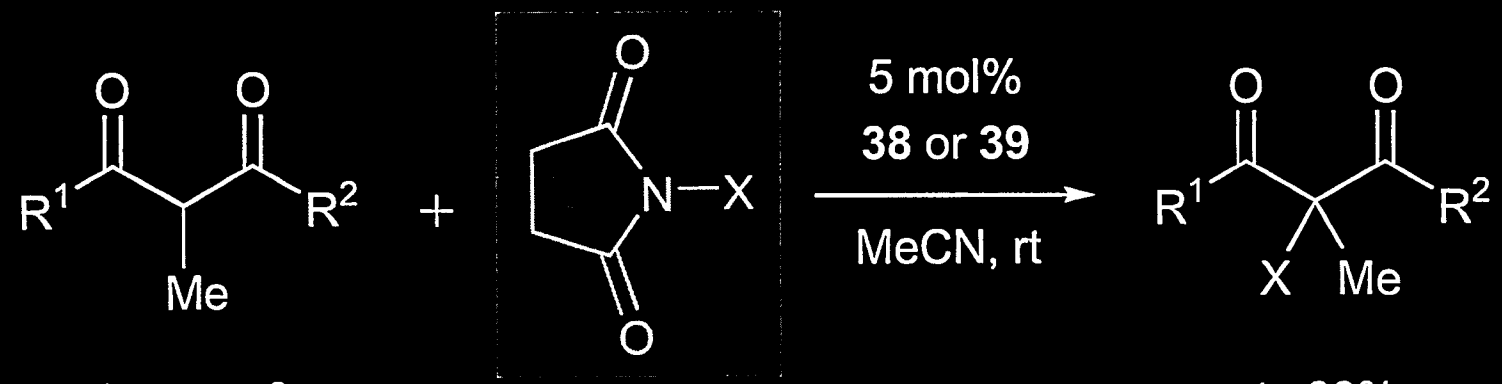
Cat 1



Cat 2

Hintermann and Togni, *ACIE*, 2000, **39**, 4359-4362.

Catalytic enantioselective electrophilic halogenation reactions



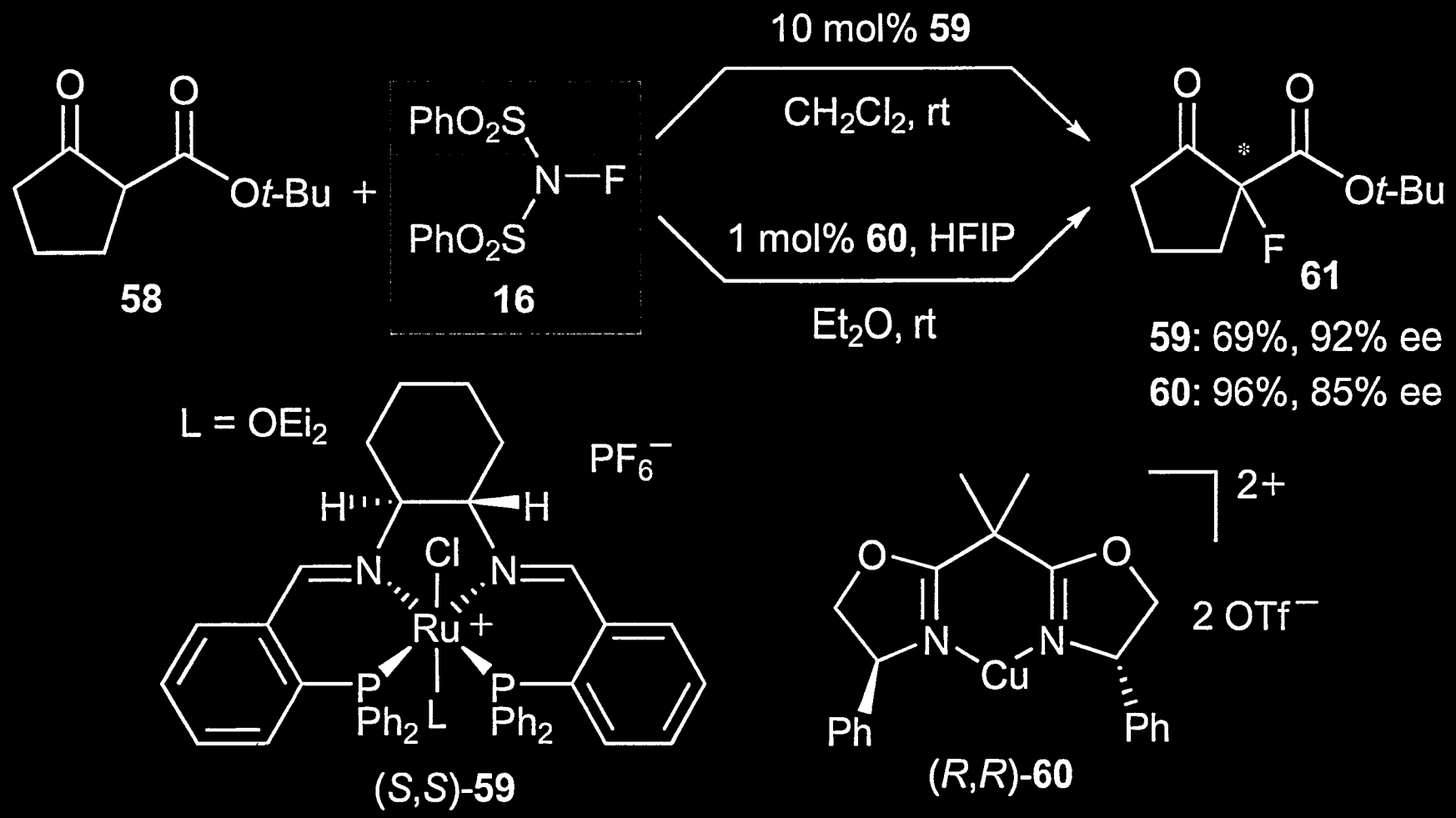
70 R^1 = Et, R^2 = Ph_2CH

X = Cl

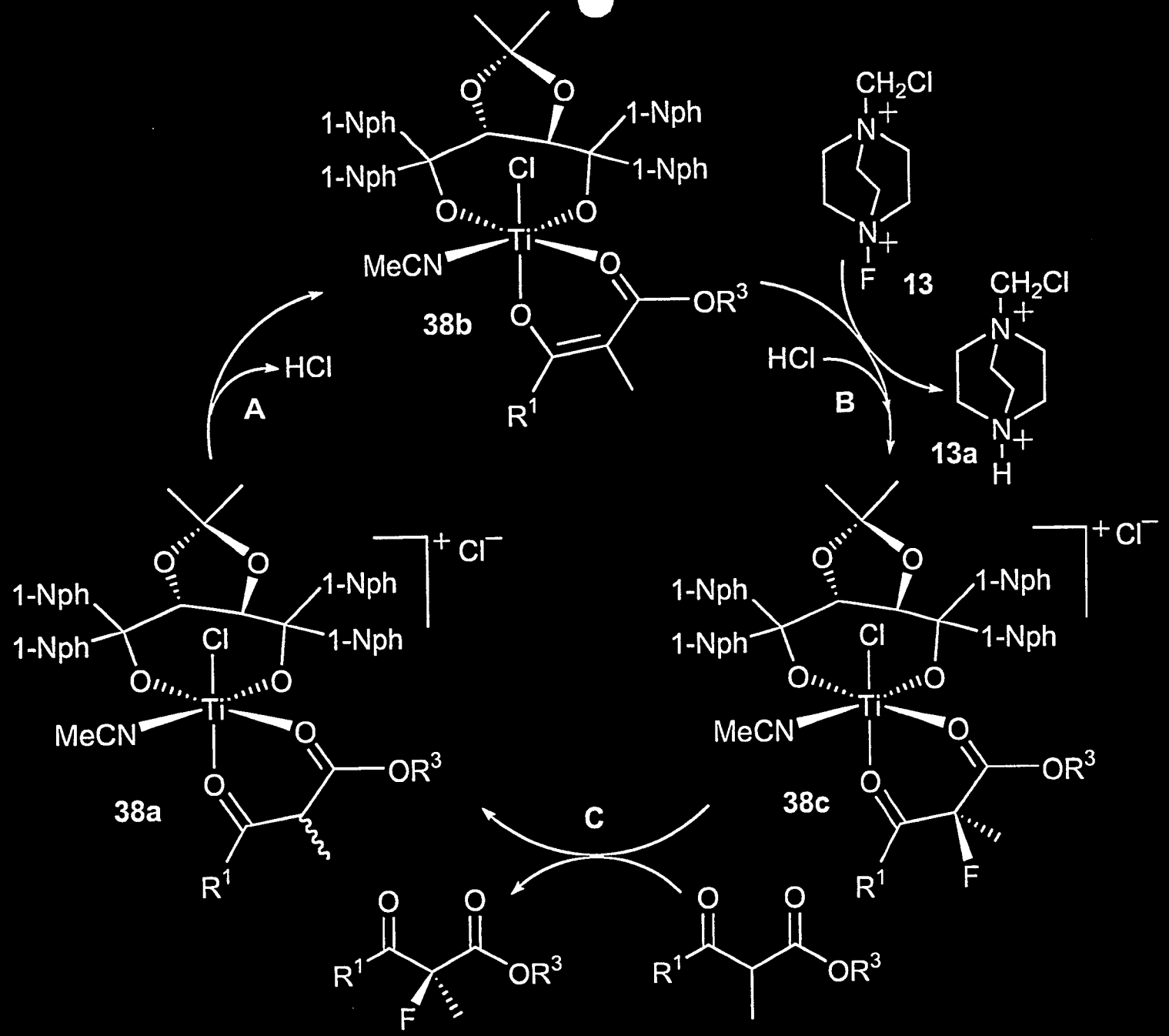
X = Br

up to 88% ee

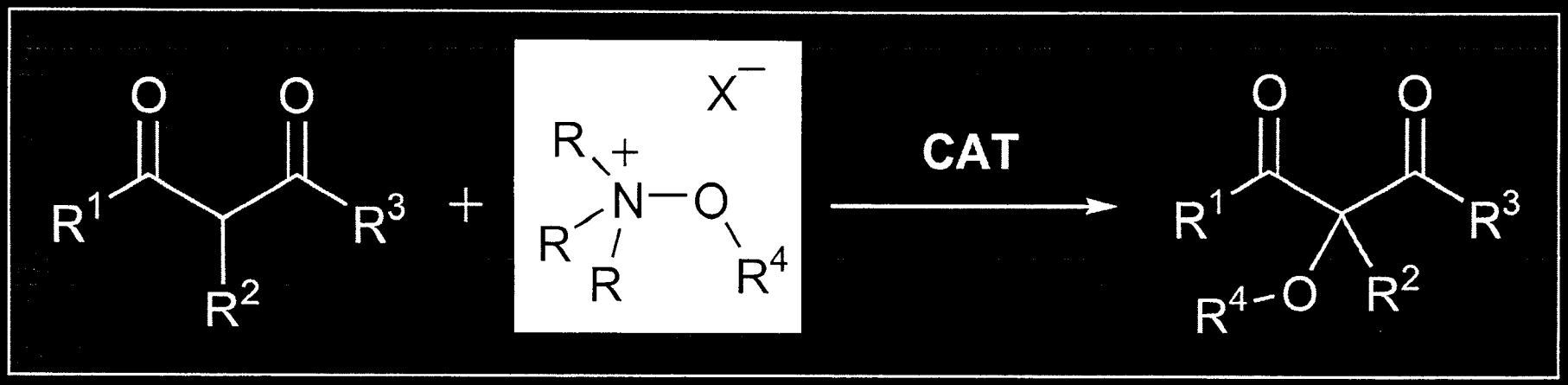
up to 23% ee



For a review on asymmetric halogenation reactions, see:
Ibrahim and Togni, *CC*, 2004, 1107.

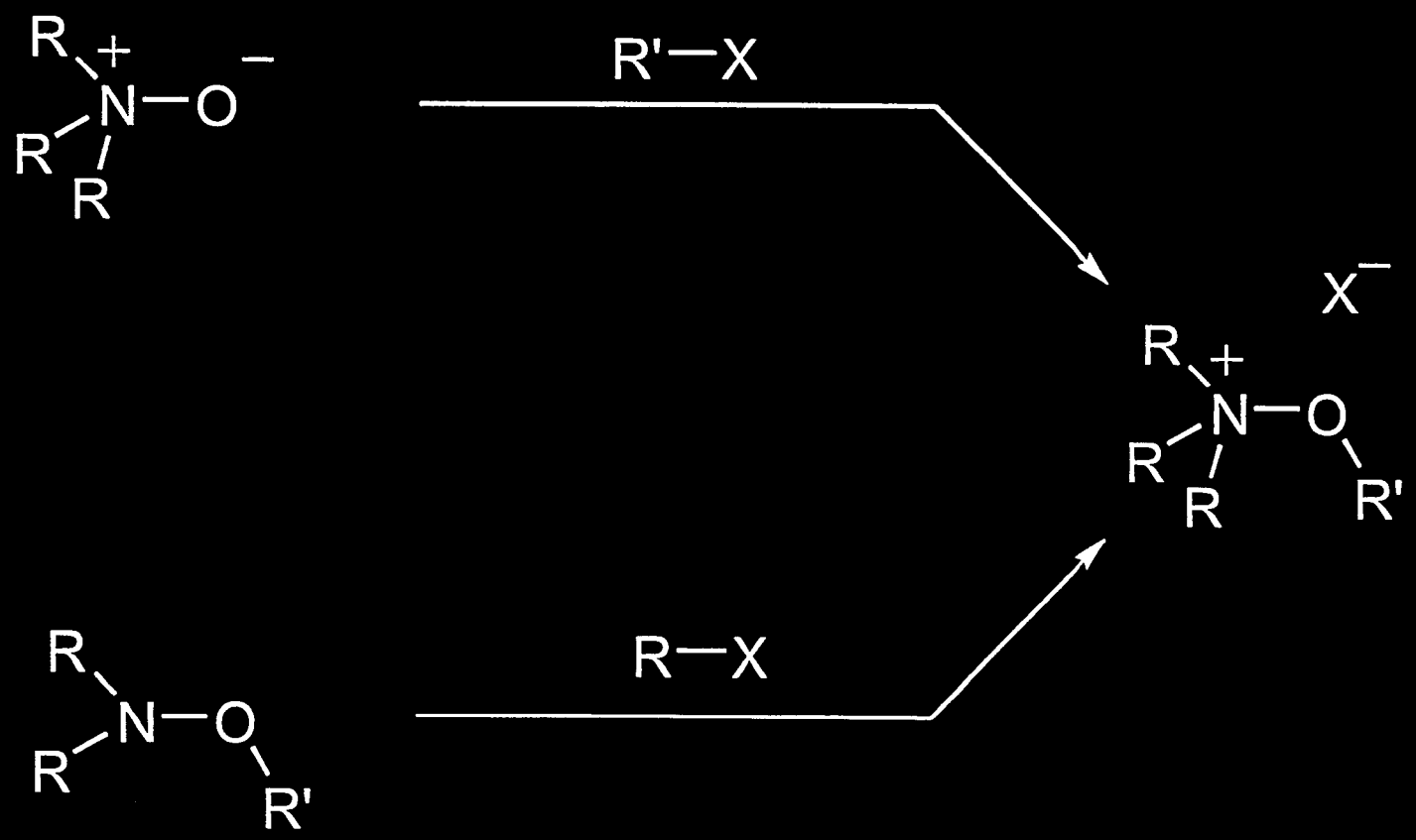

1-Nph
1-Nph
1-Nph
1-Nph
Cl
Ti
MeCN
OR3
R1
38b
HCl
A
CH2Cl
N+
F
13
HCl
B
13a
H
+ Cl−
38a
38c
C
F

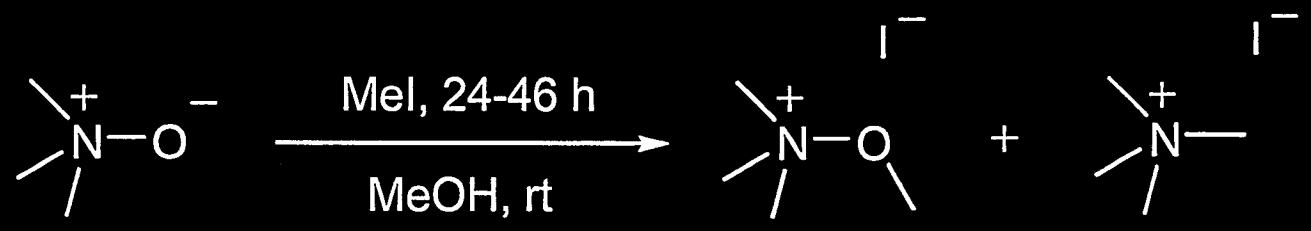
Alkoxylation

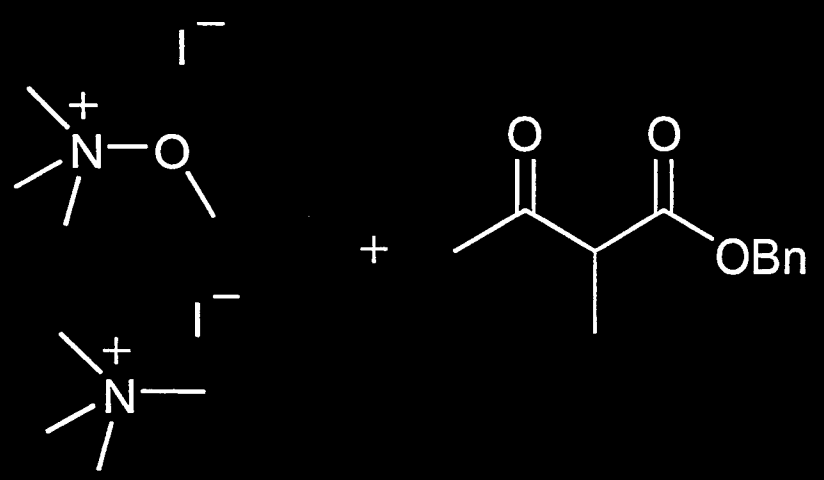


- Is there a mechanistic resemblance to fluorinations with F-TEDA?

- Would be a useful synthetic transformation!

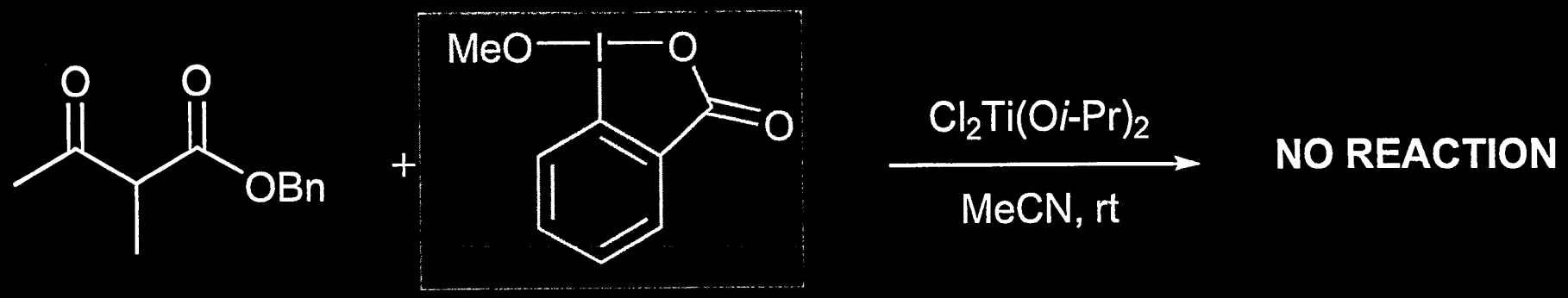

R'—X
R—X
X⁻
R'

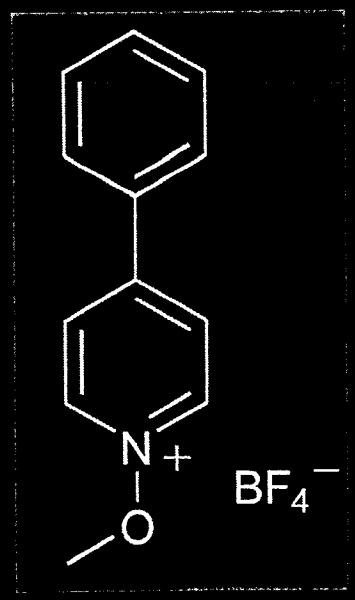


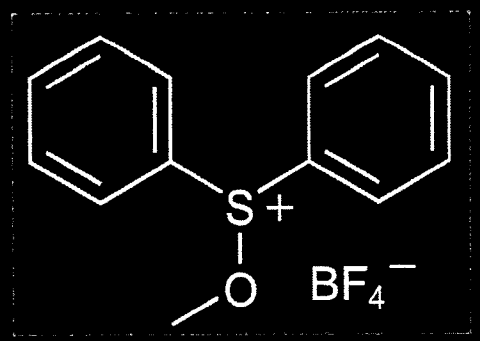


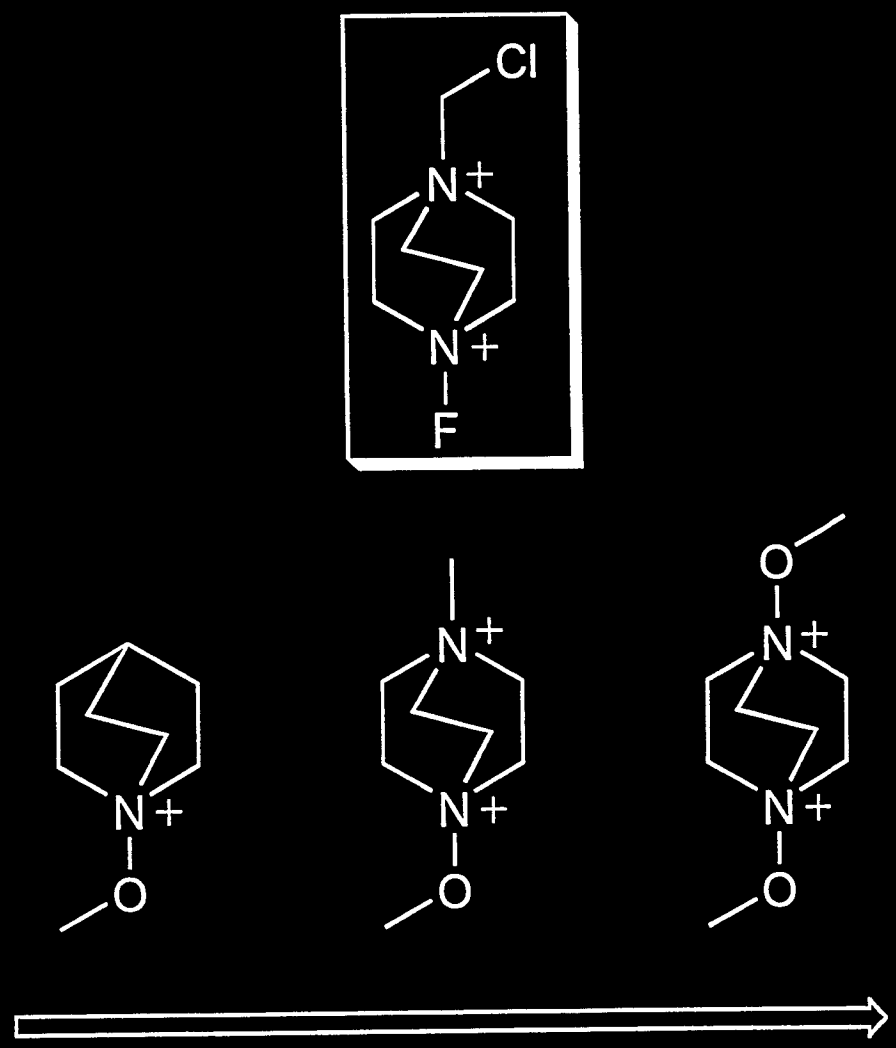
NO REACTION

Dunstan and Goulding, *JCS*, 1899, **75**, 797.

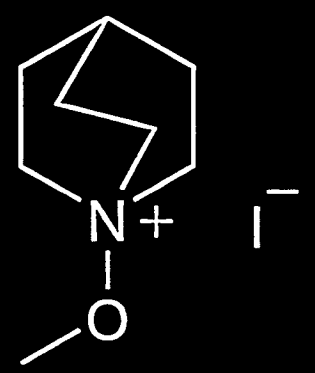

O
O
OBn
+
MeO
I
O
O
$Cl_2Ti(Oi\text{-}Pr)_2$
MeCN, rt
NO REACTION
Cl_3TiCp
CH_2Cl_2, rt
NO REACTION

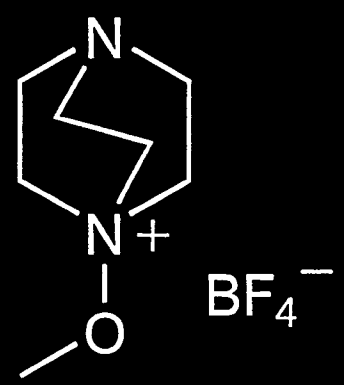

N+
O
BF_4^-

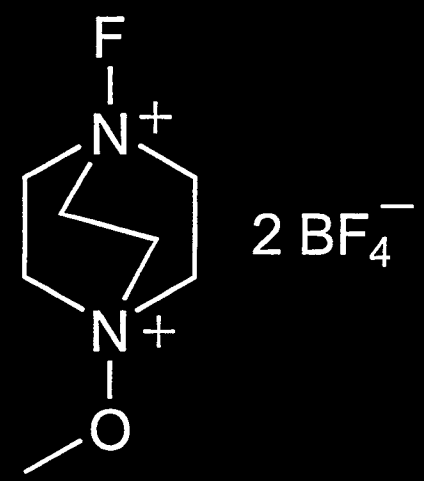

S+
O
BF_4^-


Cl
N+
N+
F
N+
O
N+
N+
O
O
N+
N+
O
increased electrophilicity

Literature:

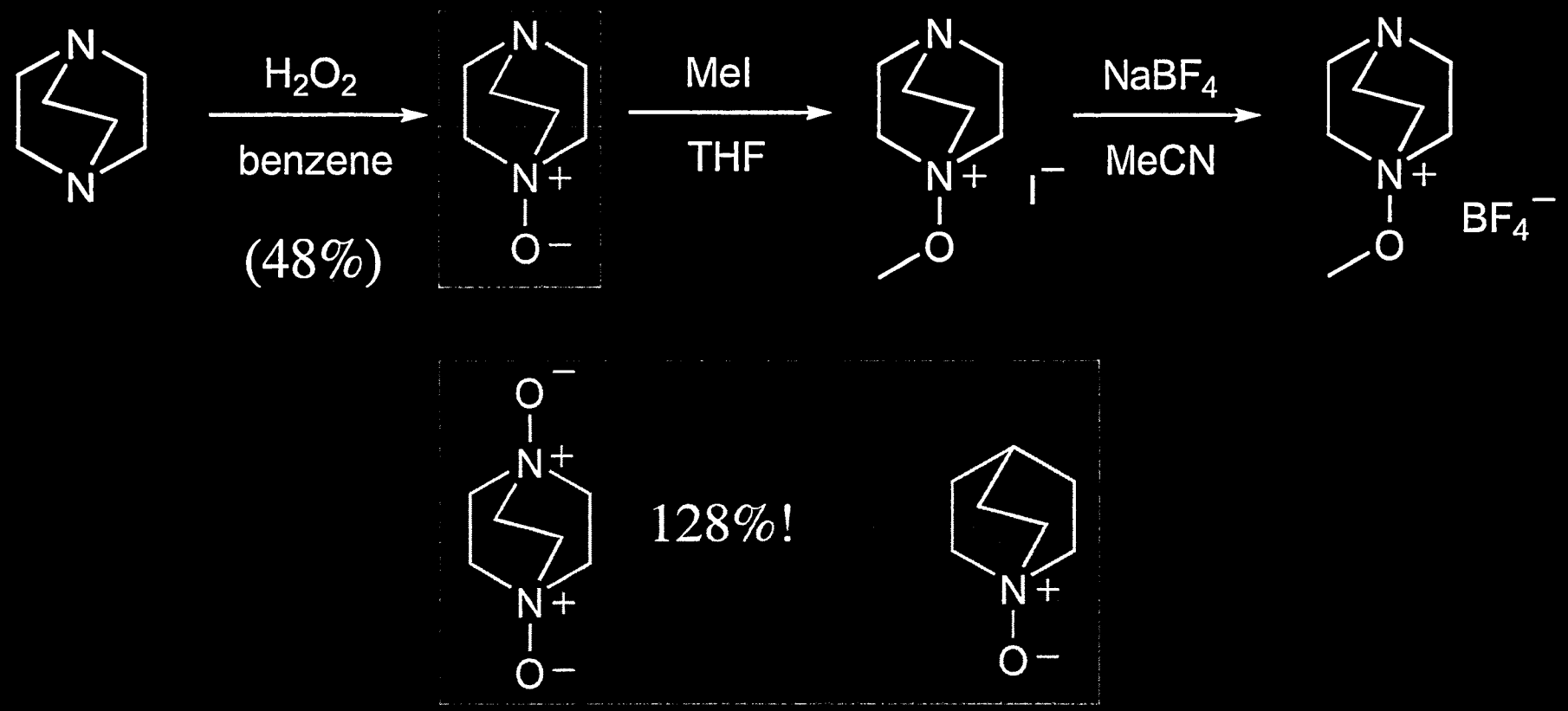




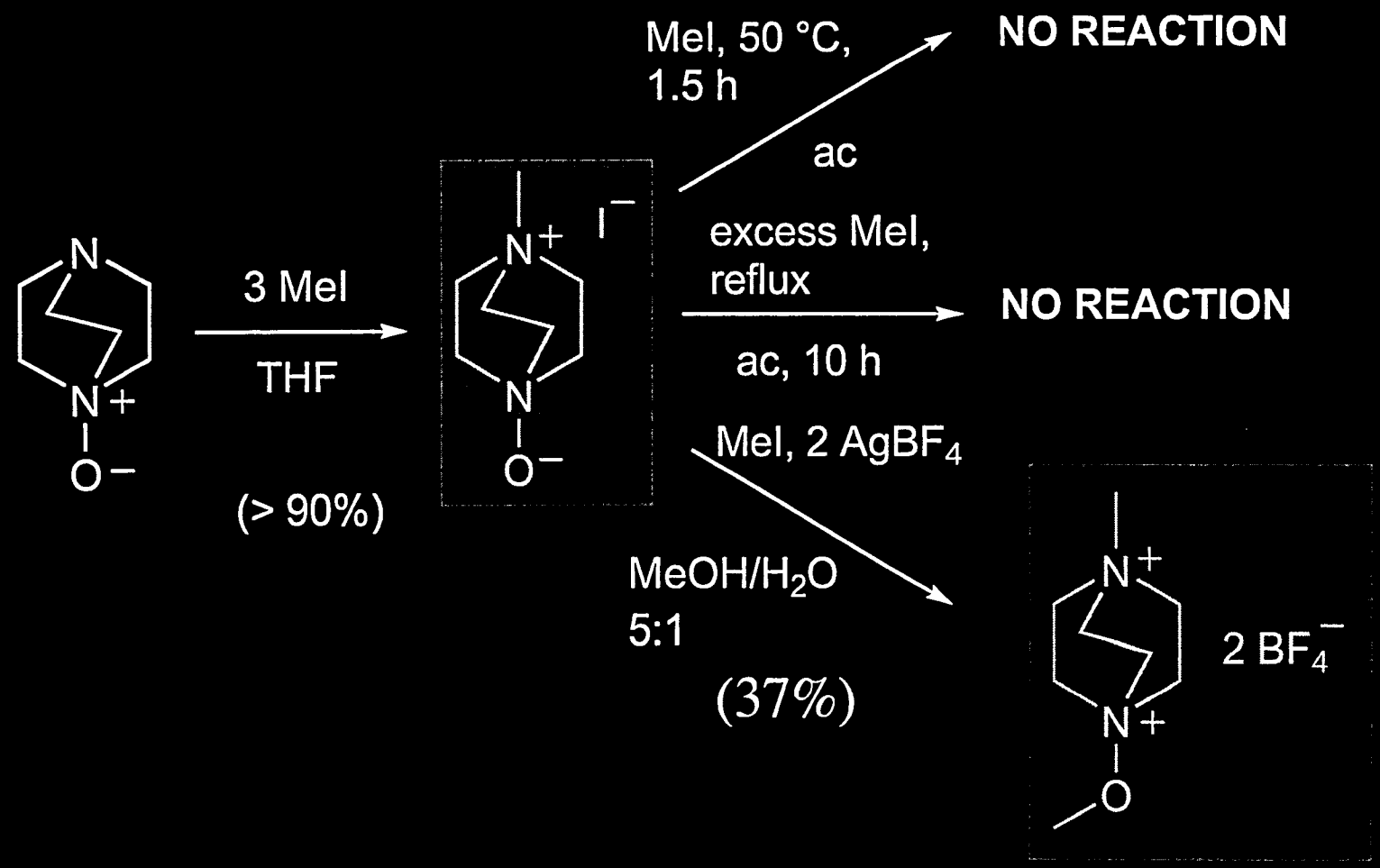


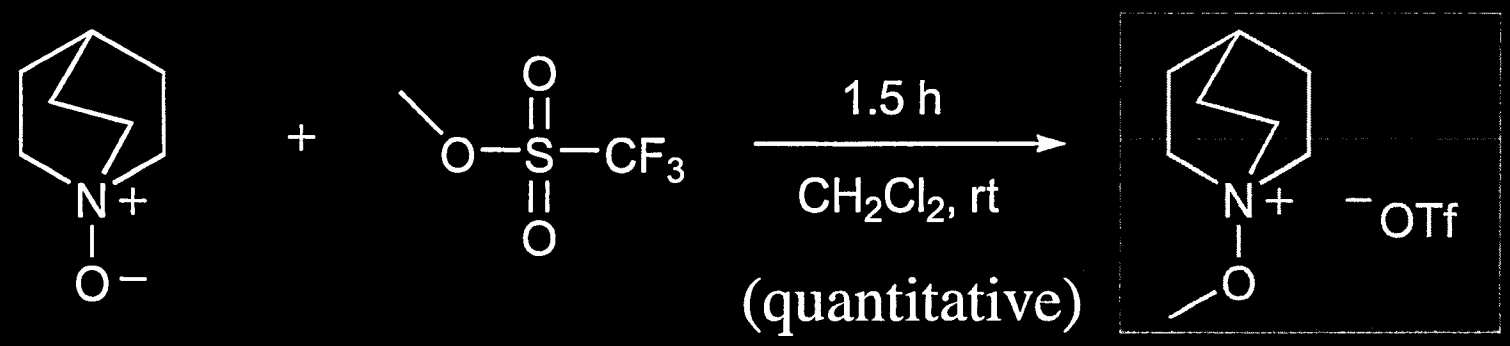
Khimiko-Farmatsevticheskii Zhurnal (1969), 3(3), 15-19.
Analysis: Mp and Microanalysis

US Patent 5,631,372; Poss et al.



Farkas et al., *J. Chem. Eng. Data*, 1968, **13**, 278.


3 MeI
THF
(> 90%)
MeI, 50 °C,
1.5 h
ac
NO REACTION
excess MeI,
reflux
ac, 10 h
NO REACTION
MeI, 2 AgBF4
MeOH/H2O
5:1
(37%)
2 BF4−

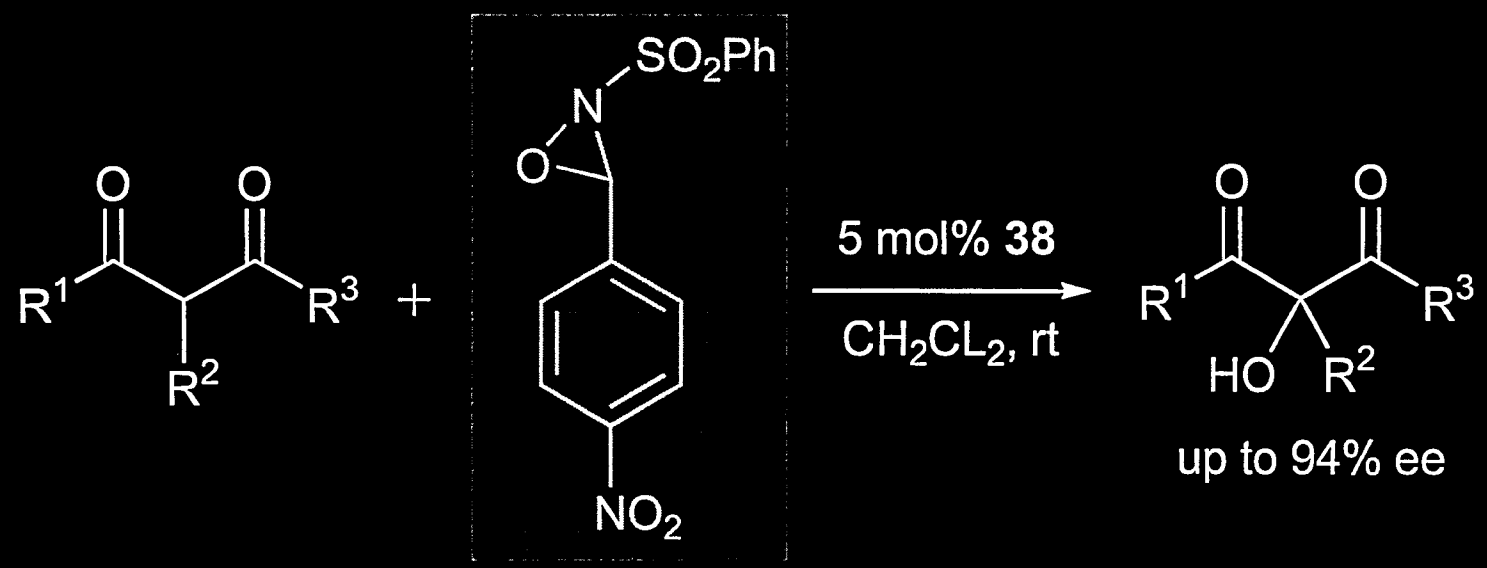


- No reaction was detected by ^{1}H-NMR in a standard catalytic run with TADDOL-complex at rt and at 60 ° C over prolonged reaction periods!!

- No reaction was observed in a standard catalytic run with benzyl acetoacetate!

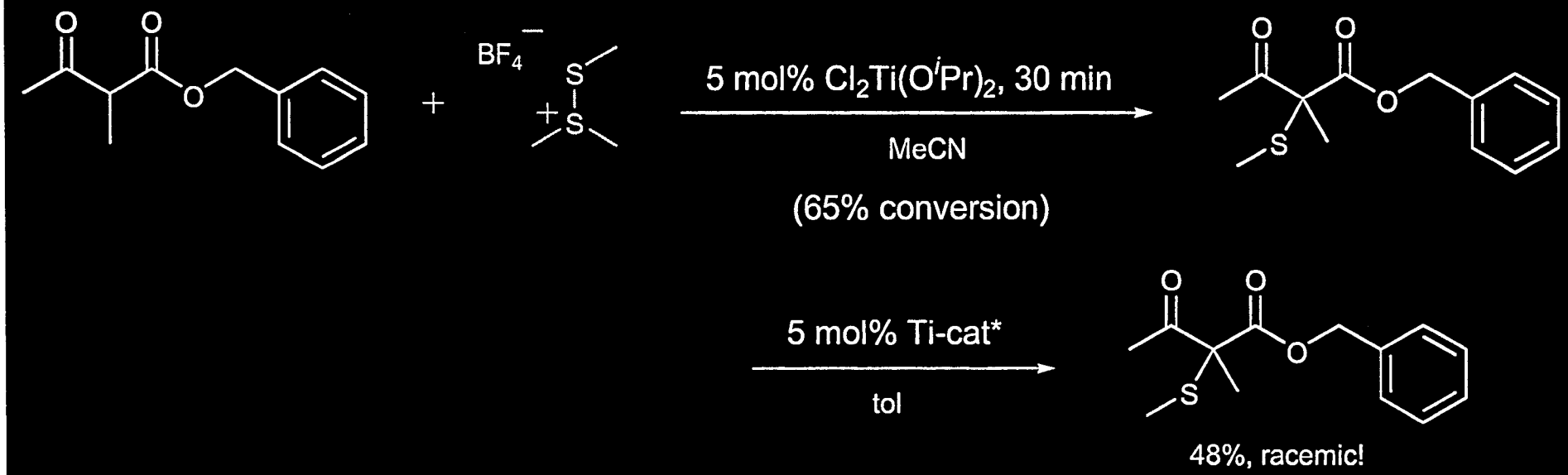
- Diammonium salt gave no reaction at 60 ° C.

Catalytic enantioselective electrophilic hydroxylation



Toullec, Bonaccorsi, Mezzetti and Togni, *Proc. Natl. Acad. Sci*, 2004, **101**, in press.

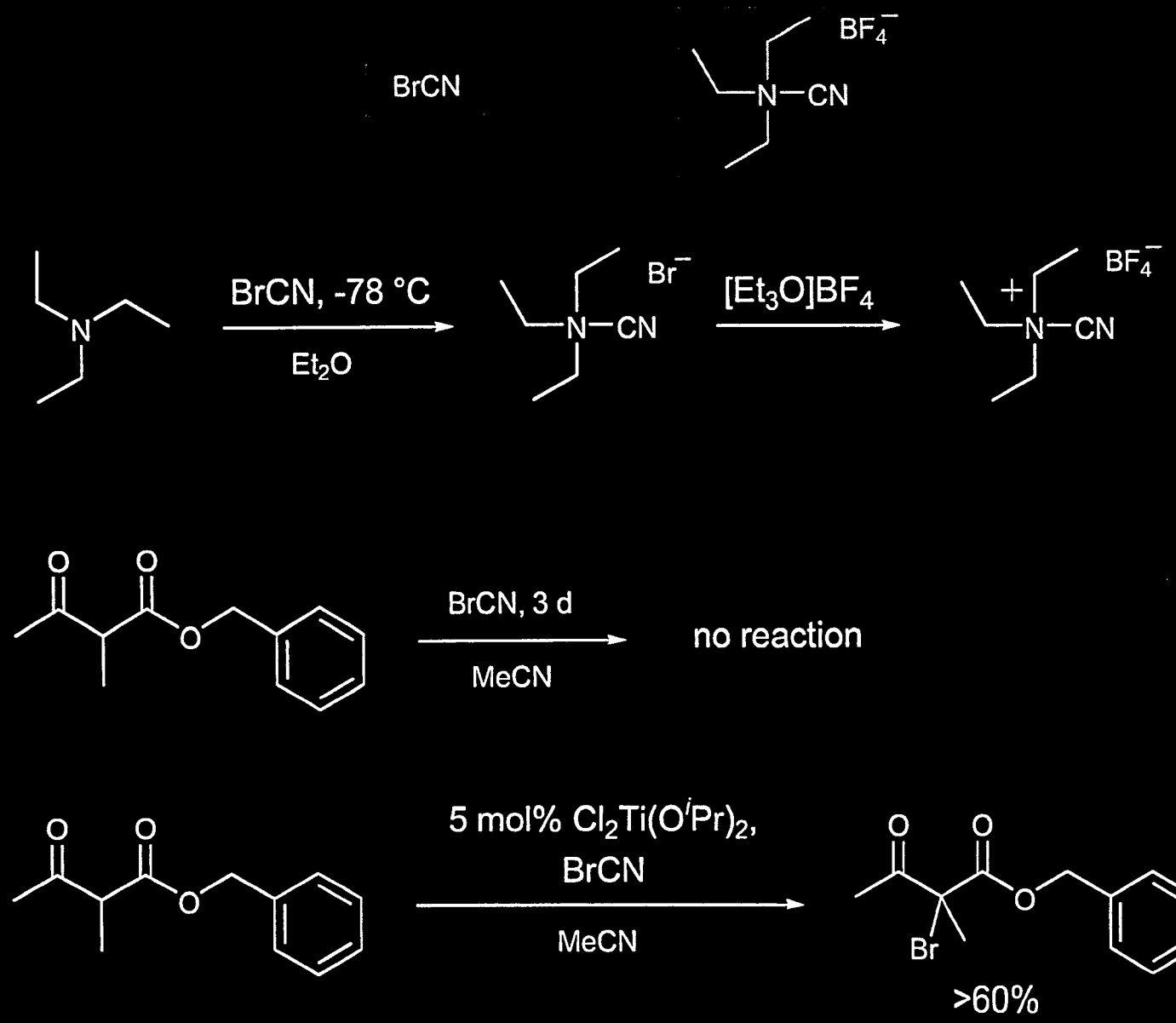
Mercaptanation

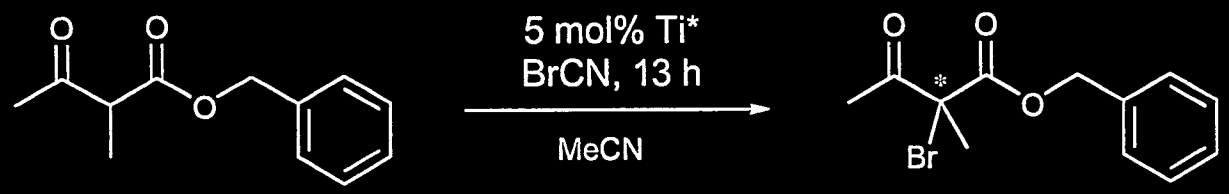


✓Reagent reacts on its own, but slower.

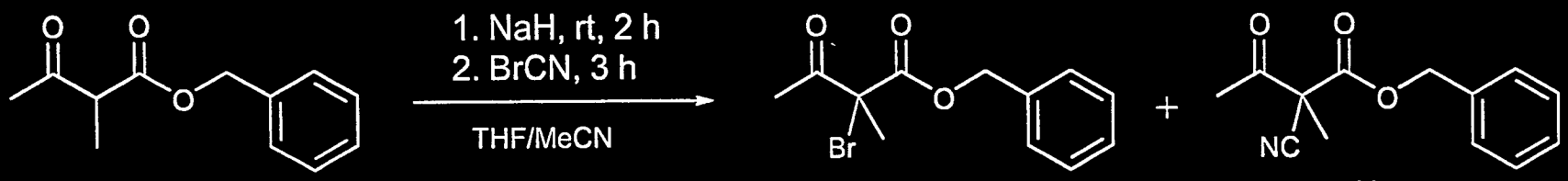
✓No reaction took place with $(MeS)_2$.

Cyanation (Bromination)



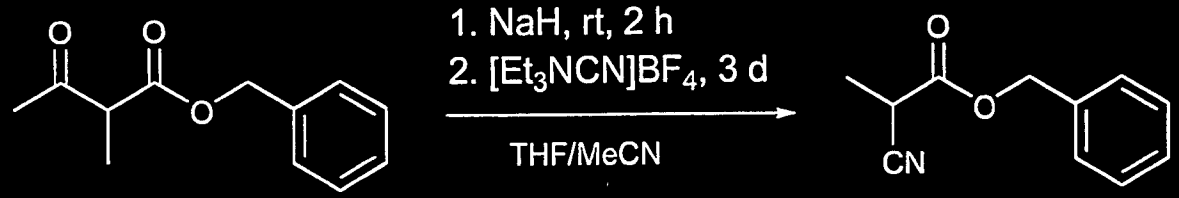


racemic!!



12%

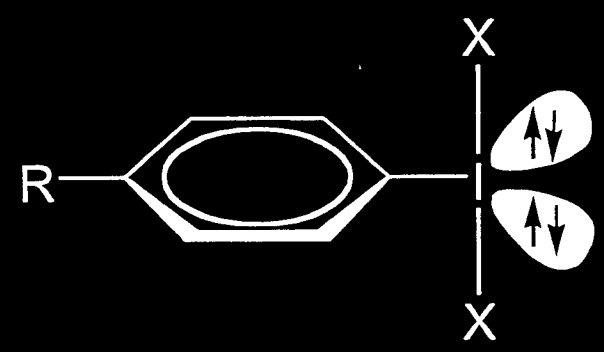
58%
(most likely)



15%
unoptimized yield

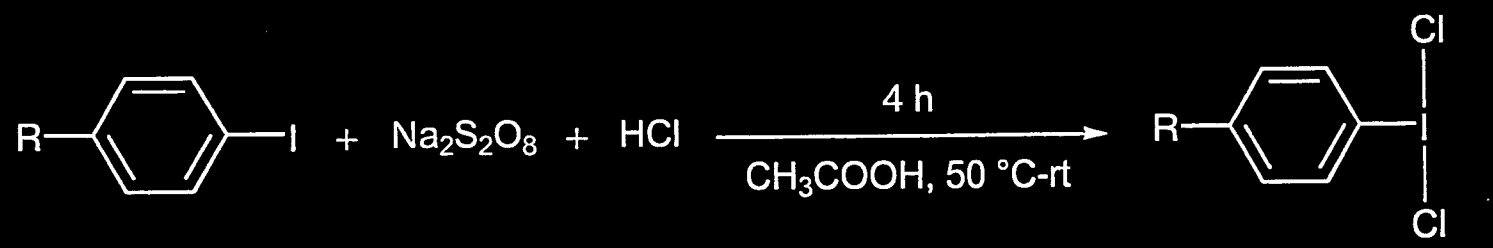
No reaction took place when a Ti-catalyst was used!!!

Chlorination/Fluorination



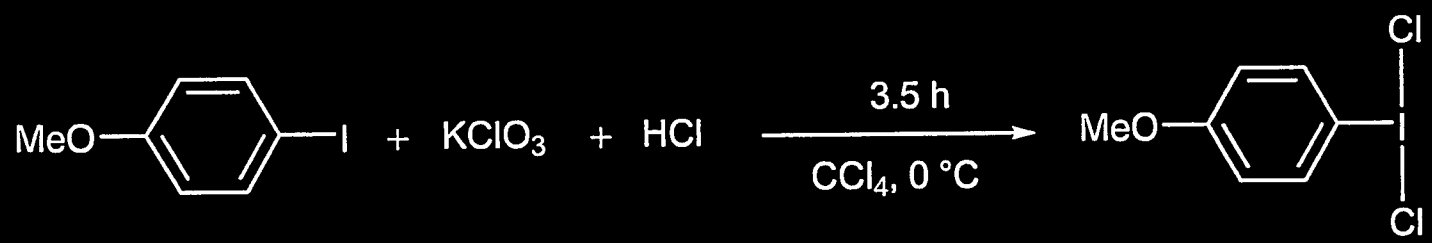
X = Cl, F

- T-shaped, trigonal bipramidal structure
- 3c-4e bonding
- I-X bond referred to as hypervalent bond: longer and weaker than a covalent bond
- this results in high reactivity of such molecules



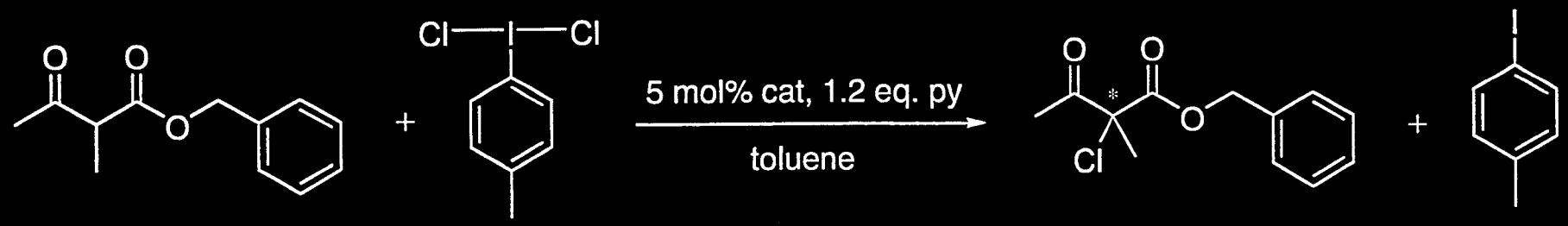
R = Me: 92% (traces of iodotoluene)

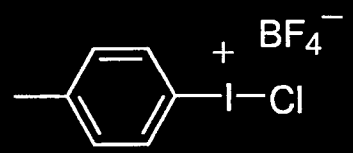
R = NO_2: 83% (81% $ArICl_2$ contents)

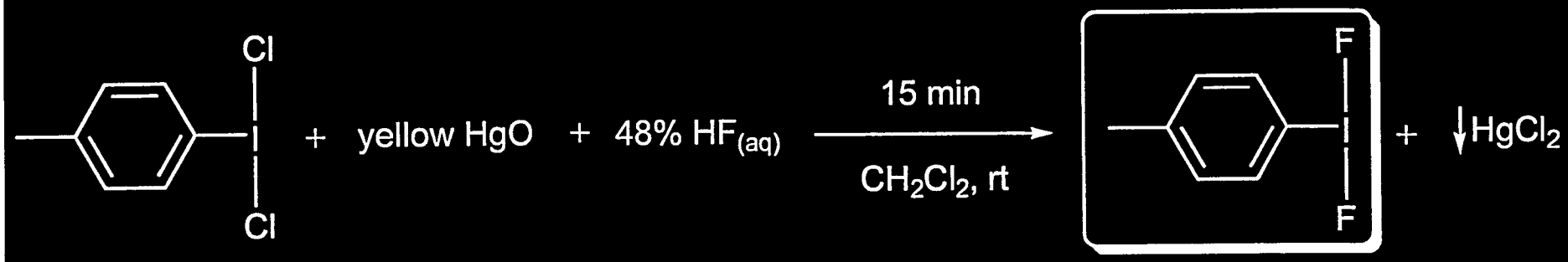


47% (ca. 66% $ArICl_2$ contents)

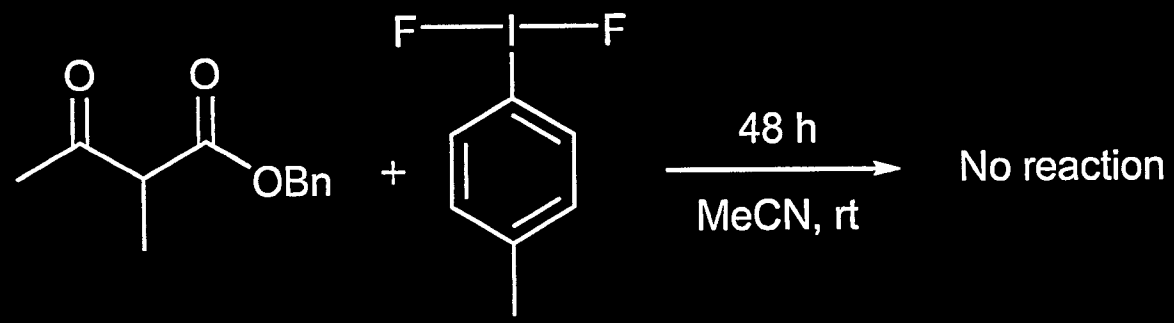
$ArICl_2$ are used as starting point for the synthesis of derivatives bearing other heteroatoms.



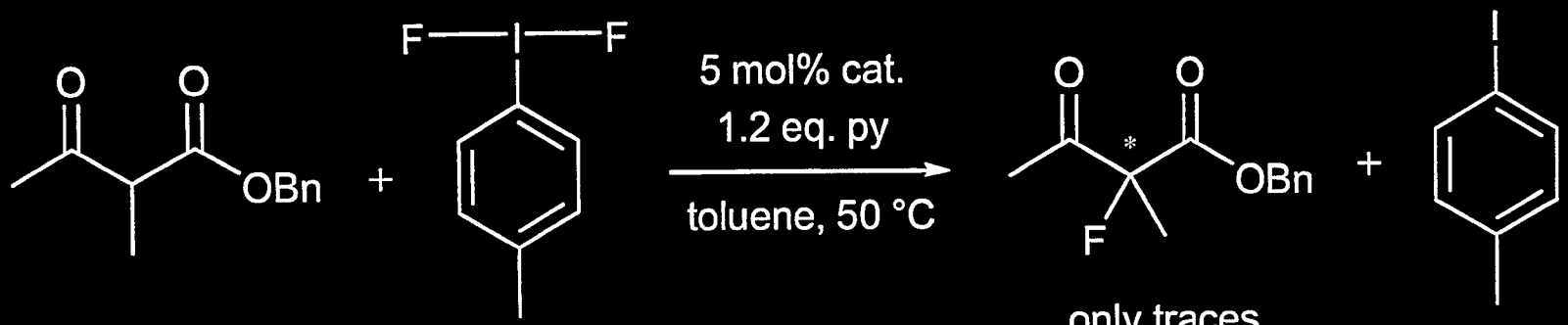
conditions	% ee
slow addition, rt, 60 min	45
slow addition, 50 °C, 20 min	**70-72**
slow addition, 70 °C, 15 min	68
fast addition, 50 °C, 30 min	38
syringe pump, 50 °C, 105 min	32
slow addition of  50 °C, 20 min	33



99%, ca. 90% $ArIF_2$ contents



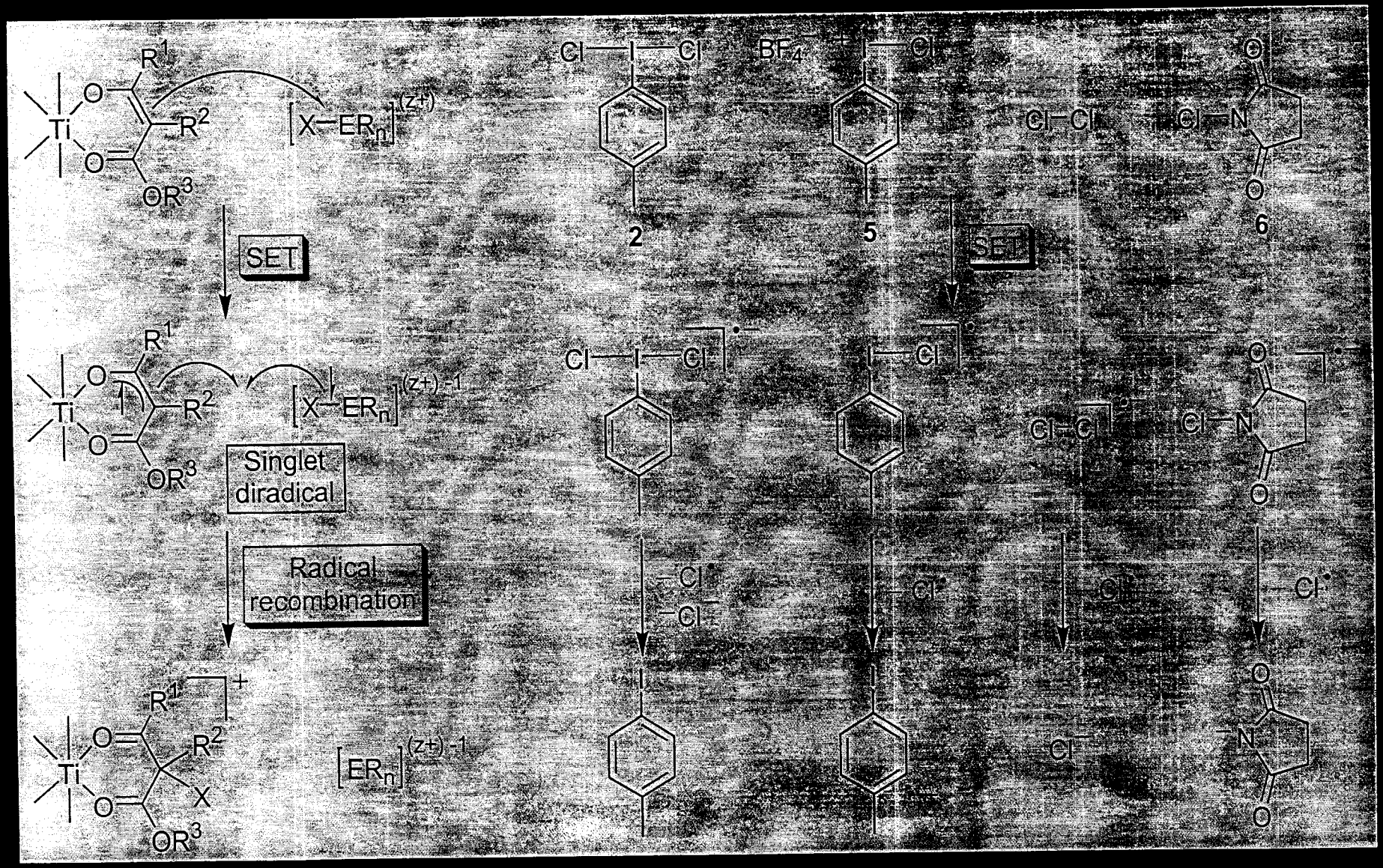
No reaction



only traces

Also tried BF_3 activation below -20 °C, no reaction took place!

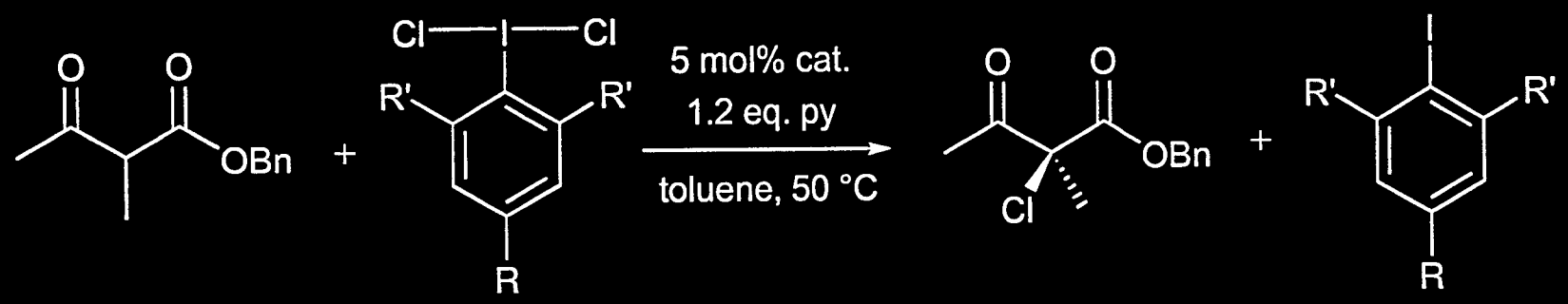
??? SET ???



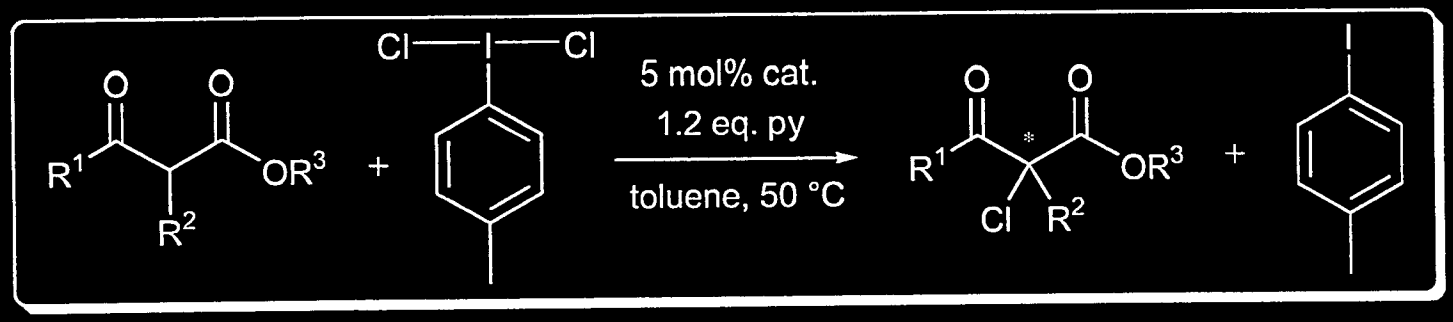
Enantioselective chlorination using chlorine!?

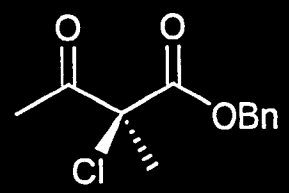
(slow injection *via* a syringe)

t = rt	complete conv., 19% ee
t = 50 °C	61%, 30 % ee

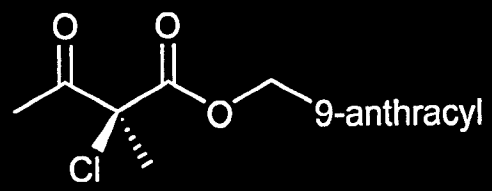


R' = H, R = Me	67%, 71% ee
R' = H, R = OMe	28%, 69 % ee
R' = H, R = NO_2	37%, 67% ee
R' = R = Me	ca 30%, 70±1 ee

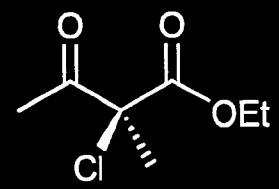




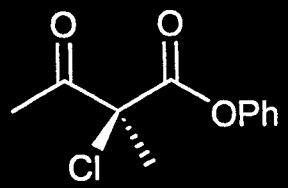
67%, 71% ee (60% ee)



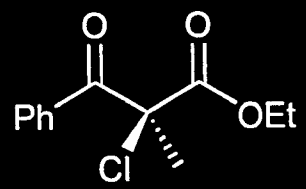
82%, 70% ee



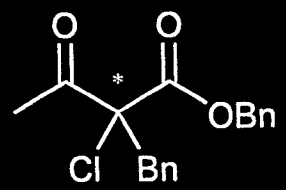
68%, 66% ee (42% ee)



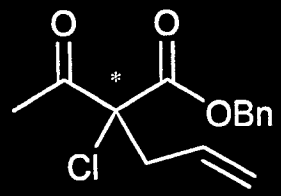
37%, 60% ee



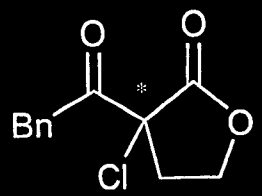
83%, 15% ee (59% ee)

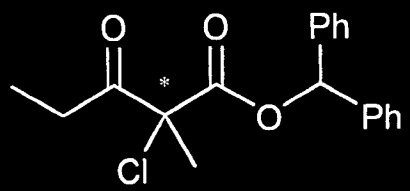


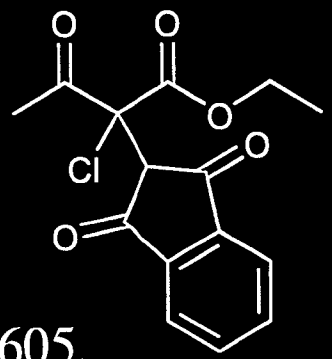
82%, 26% ee



83%, <10% ee







Ibrahim, Kleinbeck and Togni, *HCA*, 2004, **87**, 605.