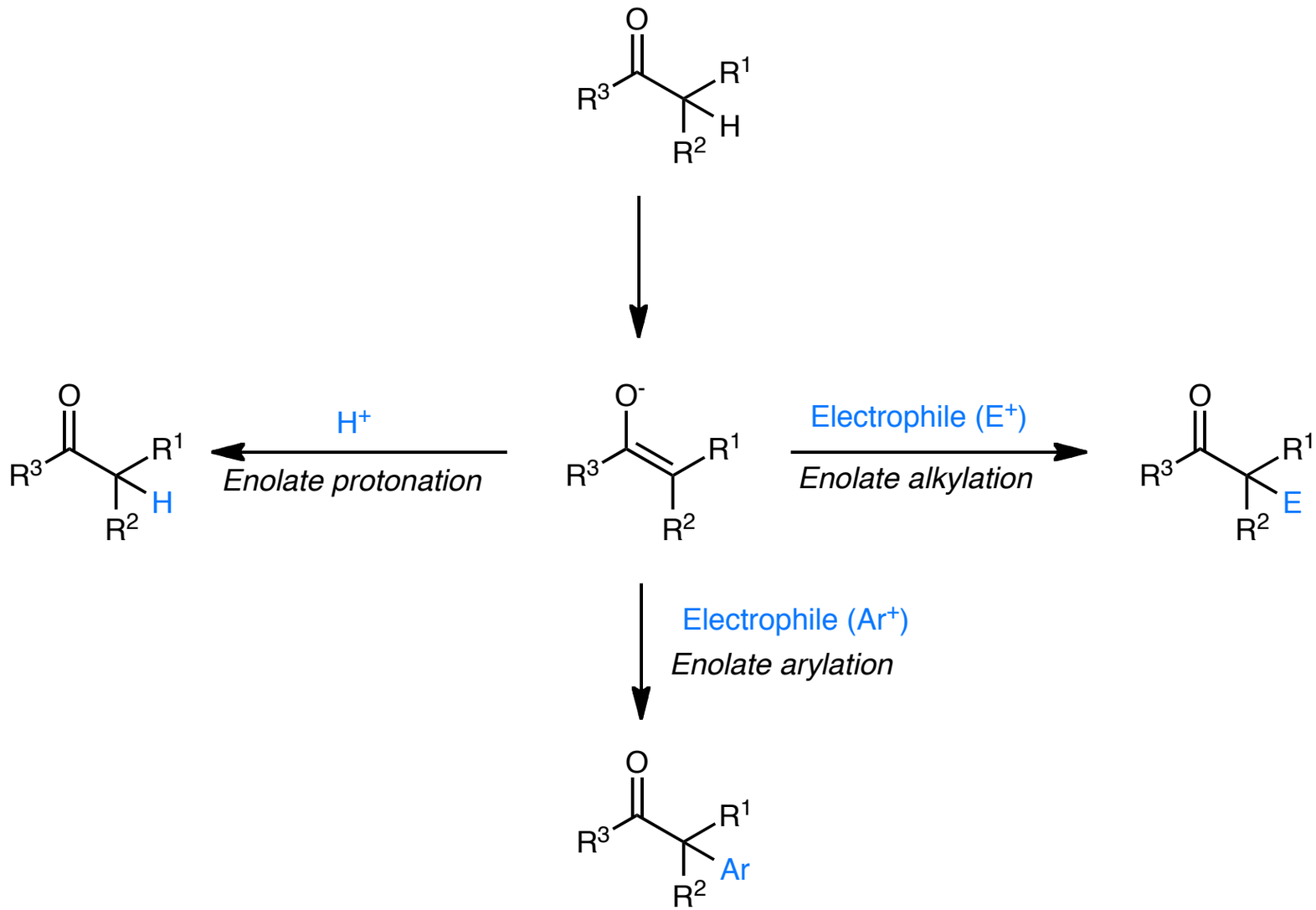
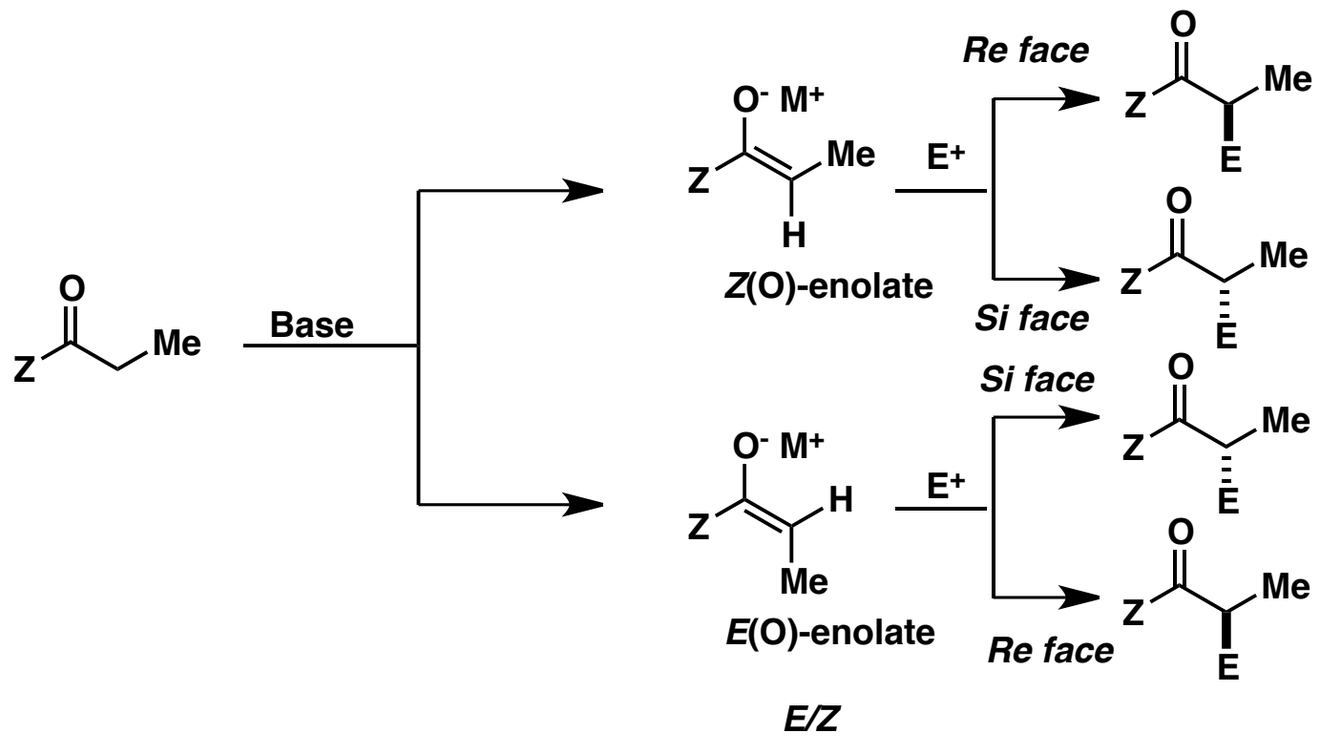
Enolate Chemistry



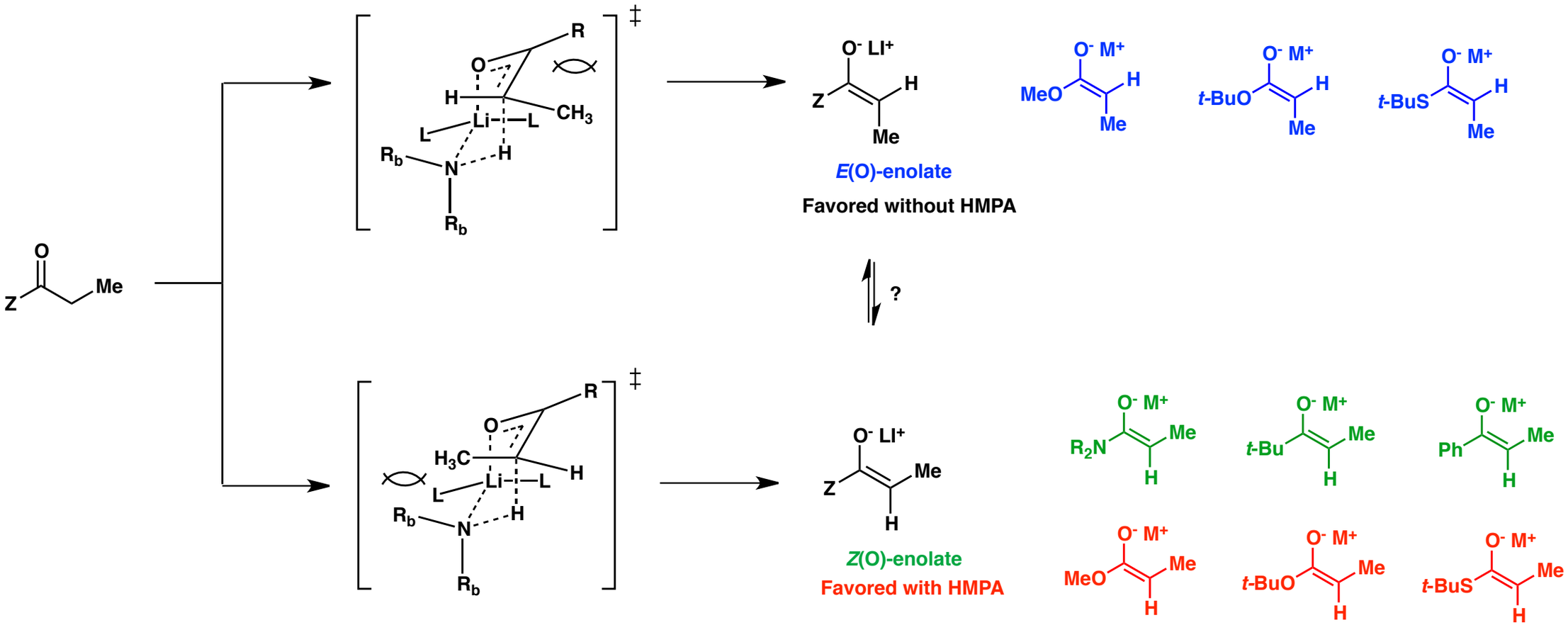
The Chemistry of Enolates: Introduction



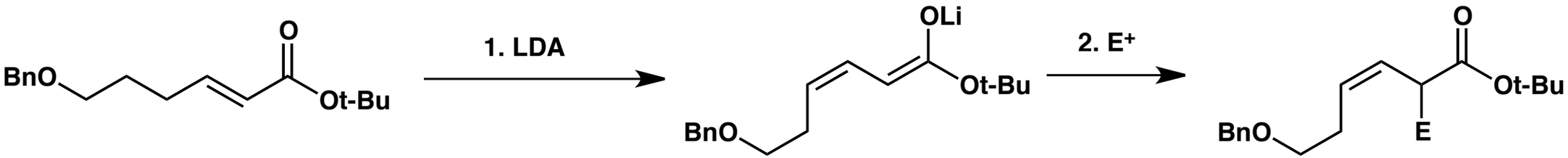
Base \ Z =	OMe	O*t*-Bu	S*t*-Bu	NR_2	Et	*i*-Pr	*t*-Bu	Ph
LDA	95:5	95:5	90:10	0:100	70:30	40:60	0:100	0:100
LDA-HMPA	16:84	9:91			5:95			
LHMDS	n.r.	n.r.		n.r.	34:66	0:100	0:100	0:100
LTMP				0:100	84:16		0:100	0:100
$(Me_2PhSi)_2NLi$					0:100			

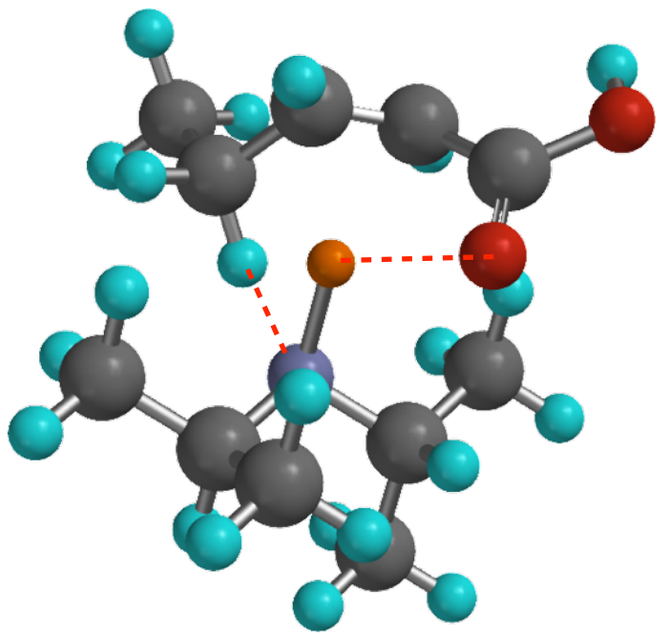
Ireland's Model for Kinetic Enolization

Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* 1975, 3975.
Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* 1976, *98*, 2868.

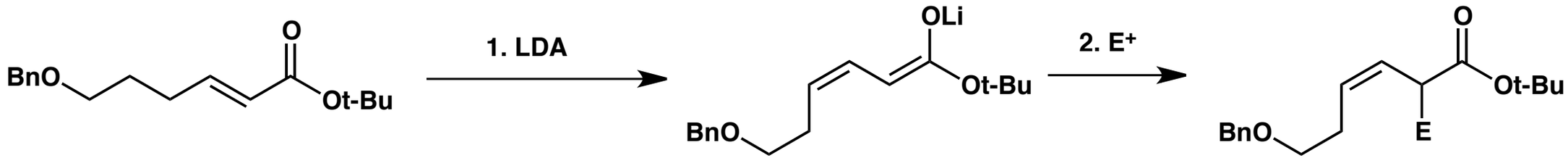


Diastereoselective Enolization



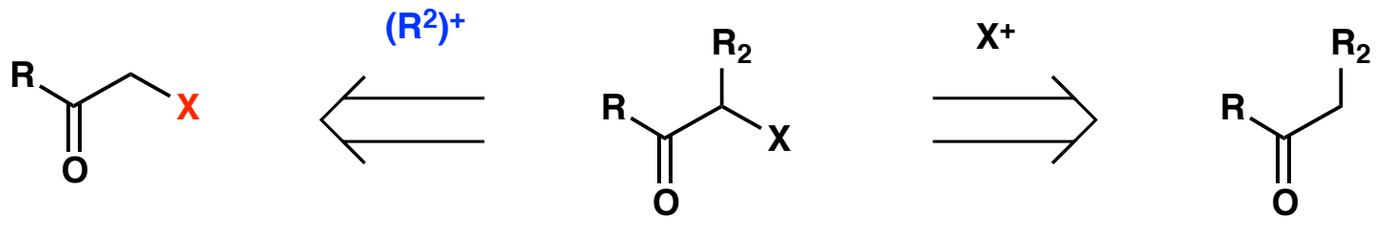


Diastereoselective Enolization



Reactions of Enolates

R^2 = 1° alkyls, allyl, benzyl



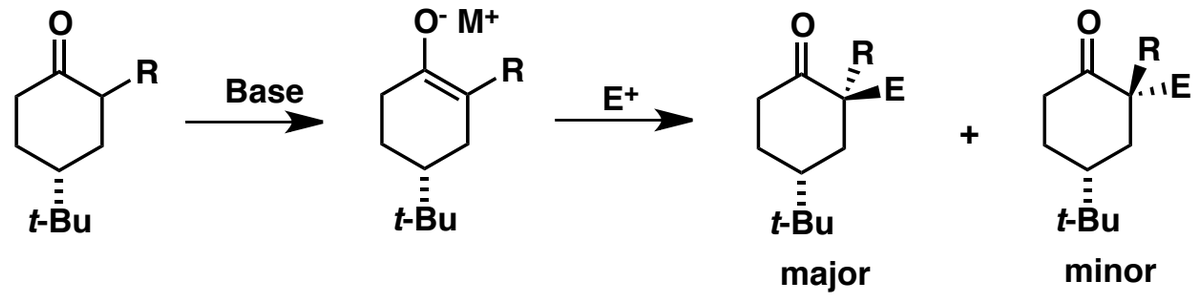
X = OPG, NR_2, halogen, etc.

X = OH, N_3, $=N_2$, NR_2, halogen, etc.

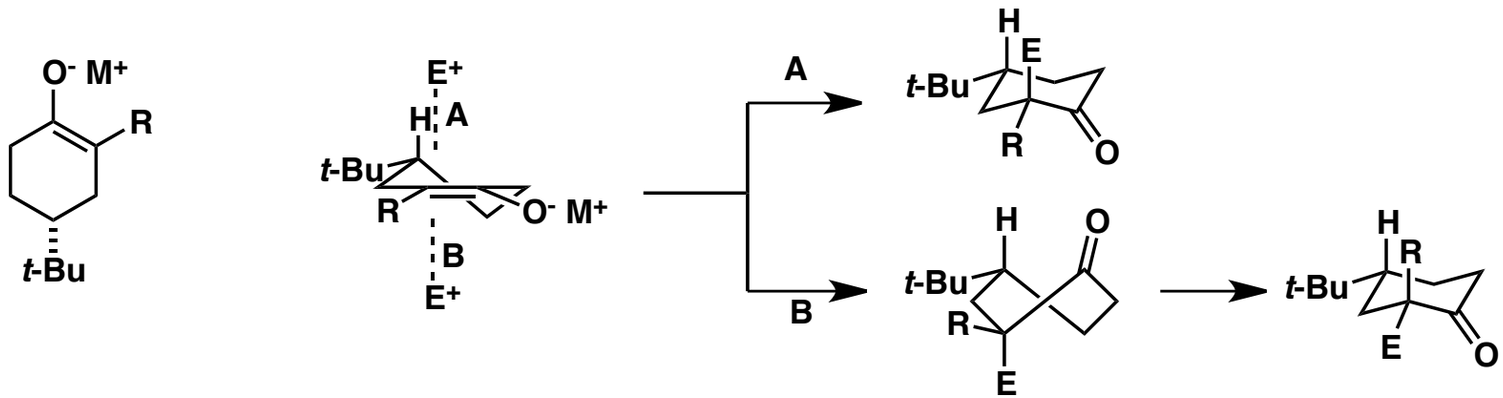
Diastereoselective Alkylation of Cyclic Enolates

Reaction of enolates: Cyclic systems

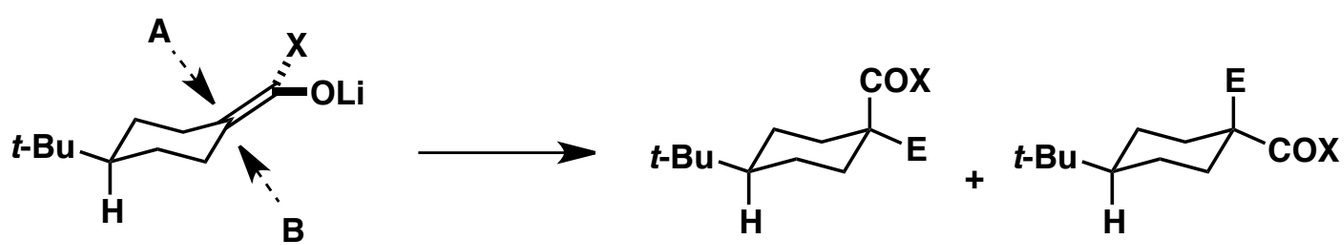
1. Stereoelectronic effects



1:9 to 1:1

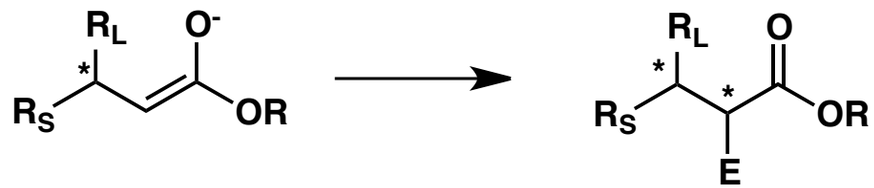


2. Steric Effects

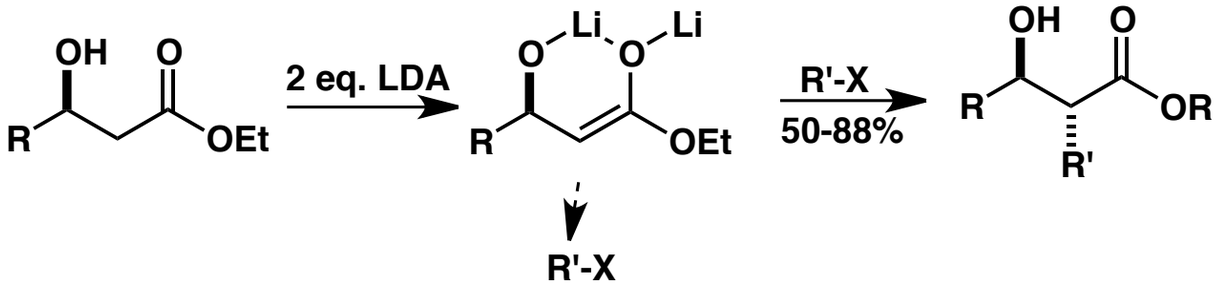


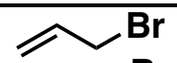
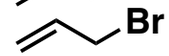
ca. 6:1

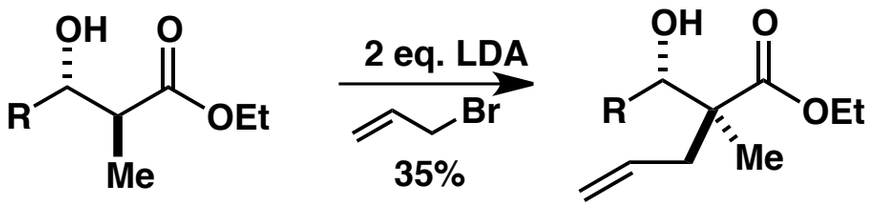
Diastereoselective Alkylation of Acyclic Enolates



1. Frater alkylation of β-hydroxycarbonyl compounds

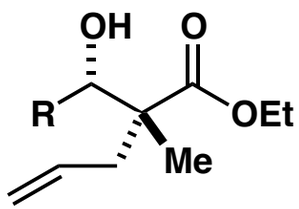


R	R'-X	Diastereosel.
Me		96:4
COOEt		>95:5
COOEt	BnBr	>91:9
COOEt	MeI	>91:9



91:9

How can we access the other diastereomer?



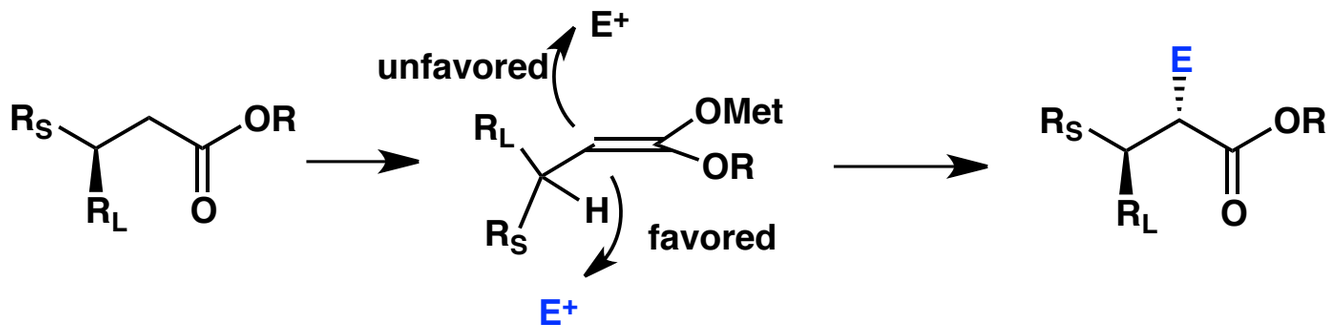
(96:4, 42%)

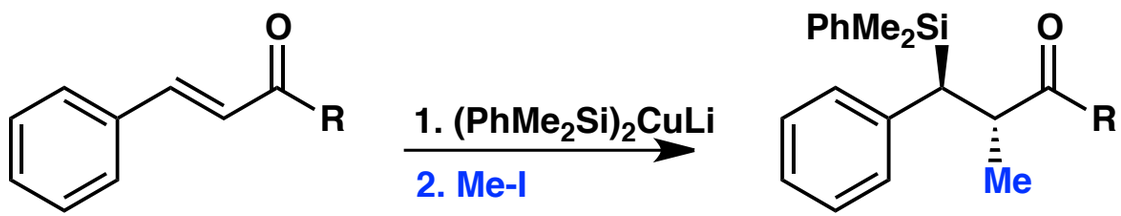
References:

Frater *Helv. Chim. Acta* 1979, *62*, 2825, 2829. *Ibid*. 1980, *63*, 1383. *Tetrahedron Lett.* 1981, *22*, 425.
Seebach *Helv. Chim. Acta* 1980, *63*, 2005. *Ibid.* 1980, *63*, 197. *Angew. Chem. Int. Ed. Engl.* 1981, *20*, 971.

Diastereoselective Alkylation of Acyclic Enolates

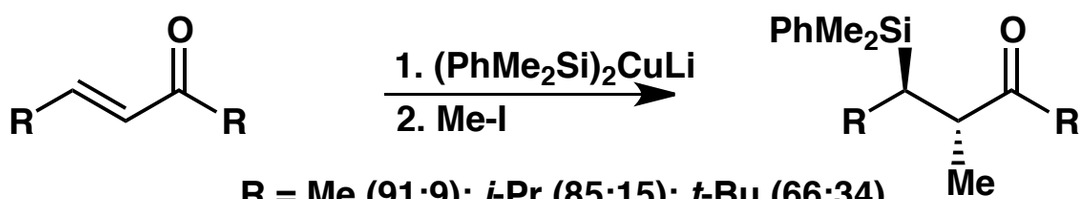
2. controled by the allylic strain





R	Diastereosel.
OMe	97:3
Me	98:2
H	92:8
Ph	98:2
NMe_2	97:3

Other alkylating agents: Et-I, Bu-I, $PhCH_2Br$, allyl-Br, ECH_2Br. Selectivity: ≥94%

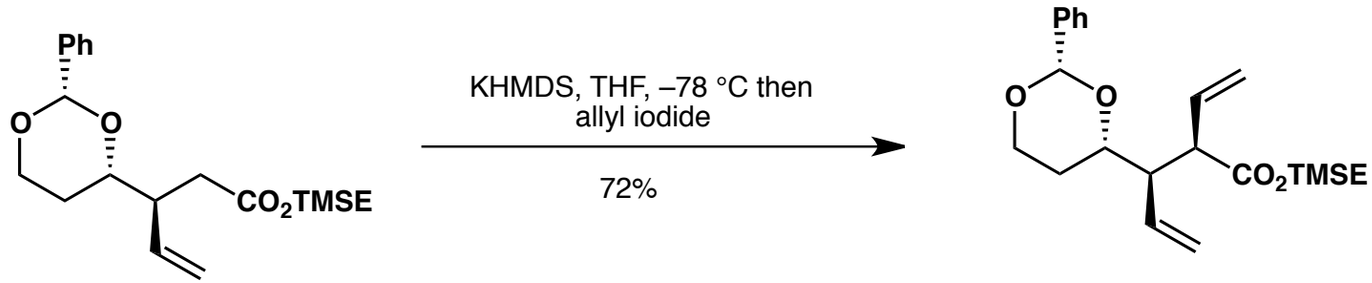


R = Me (91:9); *i*-Pr (85:15); *t*-Bu (66:34)

References: Fleming *J. Chem. Soc. Chem. Comm.* 1984, 28, 29. *Ibid.* 1985, 318. *Ibid.* 1984, 904. *J. Organomet. Chem.* 1984, *271*, 281.

Diastereoselective Enolate Alkylation

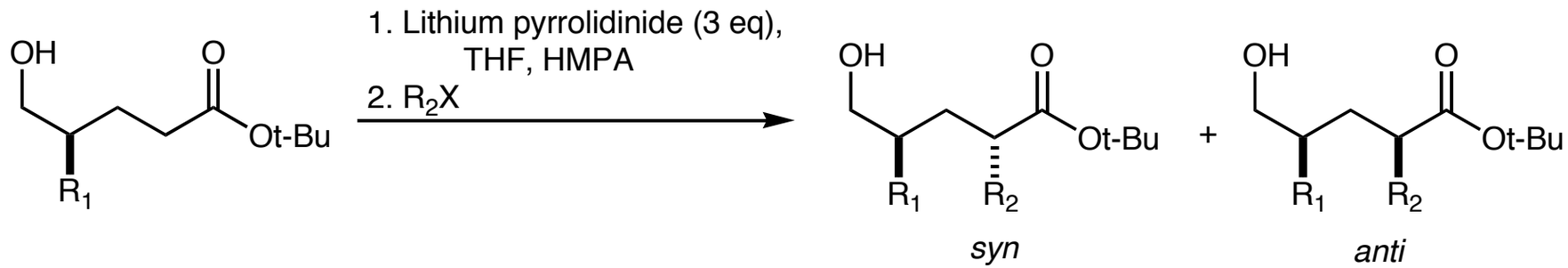
Hanessian, S.; Yang, Y.; Giroux, S.; Mascitti, V.; Ma, J. U.; Raeppel, F. *J. Am. Chem. Soc.* **2003**, *125*, 13784.



Diastereoselective Alkylation of Acyclic Enolates

Remote Chelation:

K. Narasaka *Bull. Chem. Soc. Jpn.* **1988**, *61*, 571.

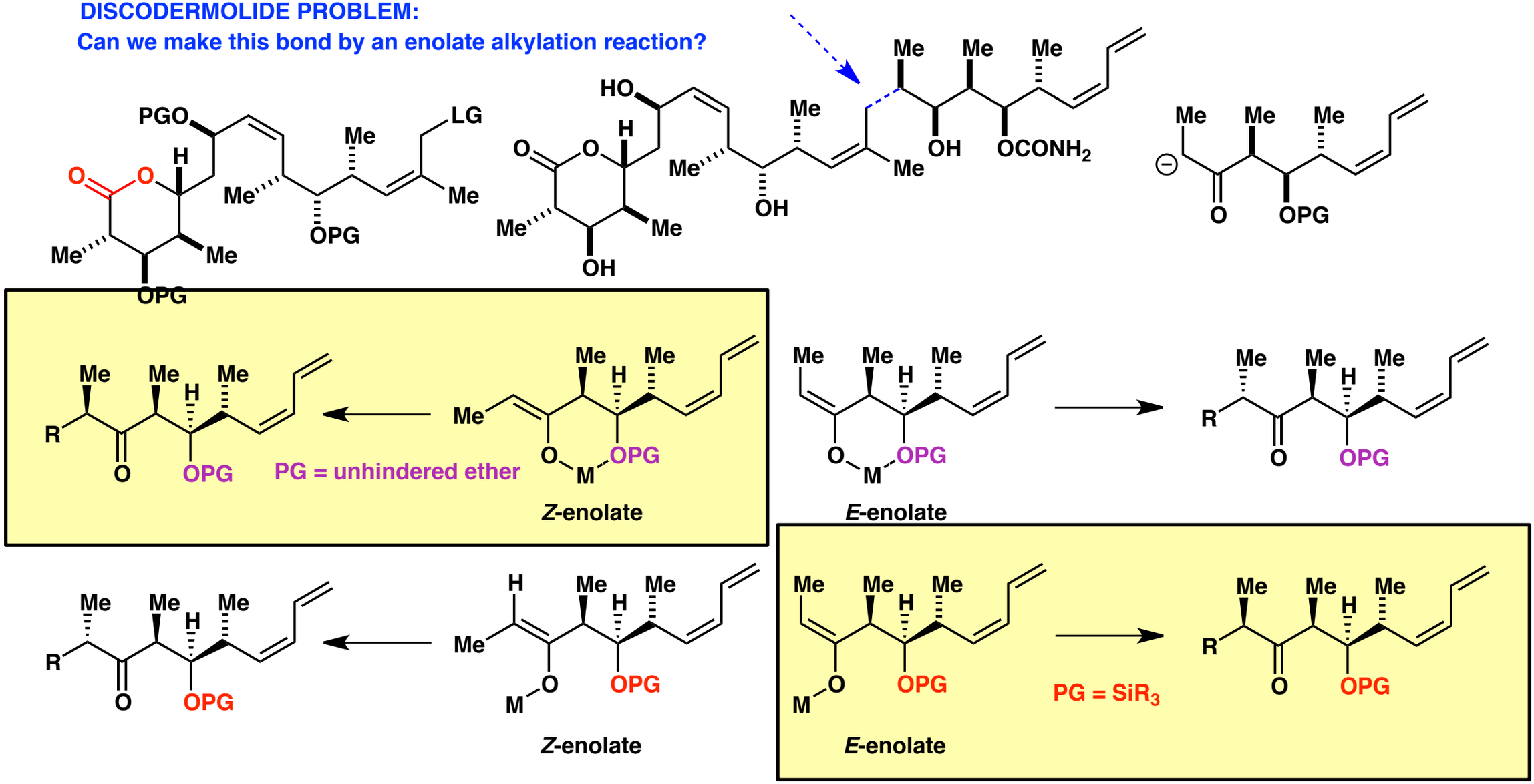


R_1	R_2-X	*syn:anti* (yield)
Me	Me_2SO_4	4 : 1 (78%)
Allyl	Me_2SO_4	85 : 15 (81%)
Allyl	BnBr	90 : 10 (96%)
Bn	Me_2SO_4	90 : 10 (80%)
Bn	BuI	91 : 9 (76%)

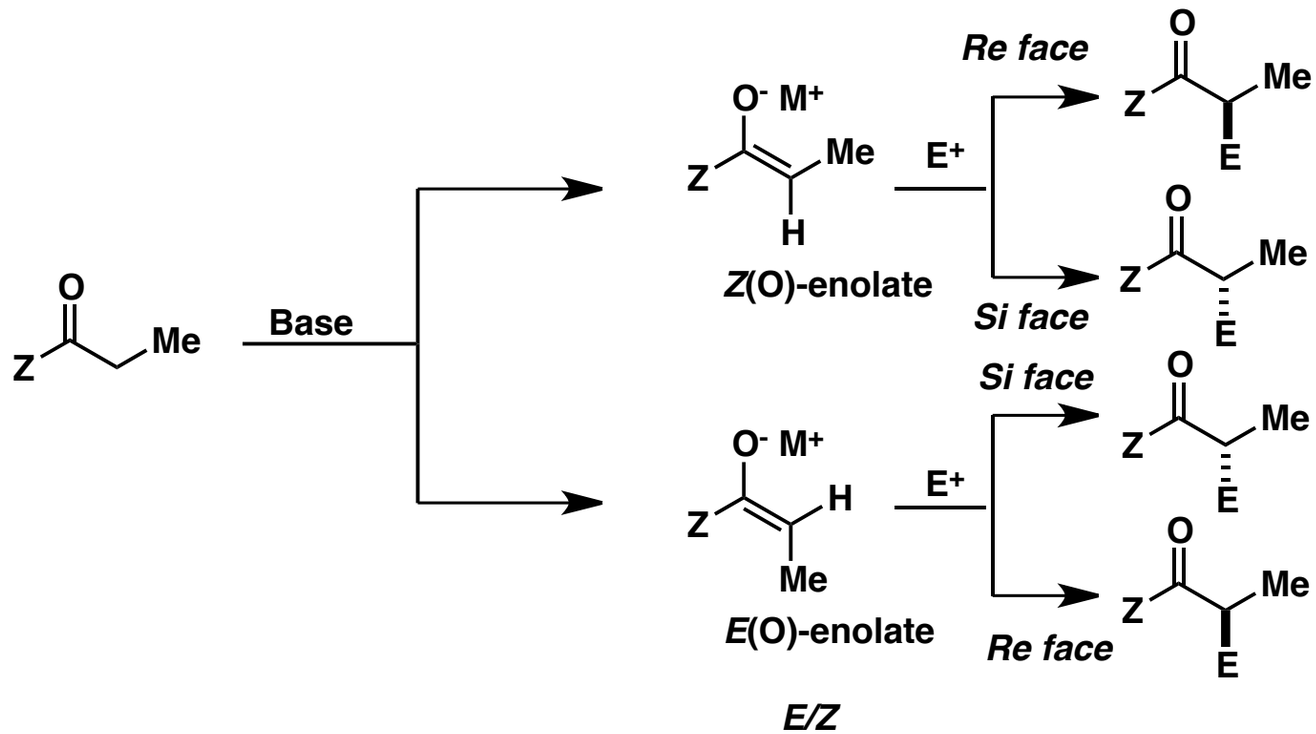
Discodermolide Retrosynthetic Analysis

DISCODERMOLIDE PROBLEM:

Can we make this bond by an enolate alkylation reaction?



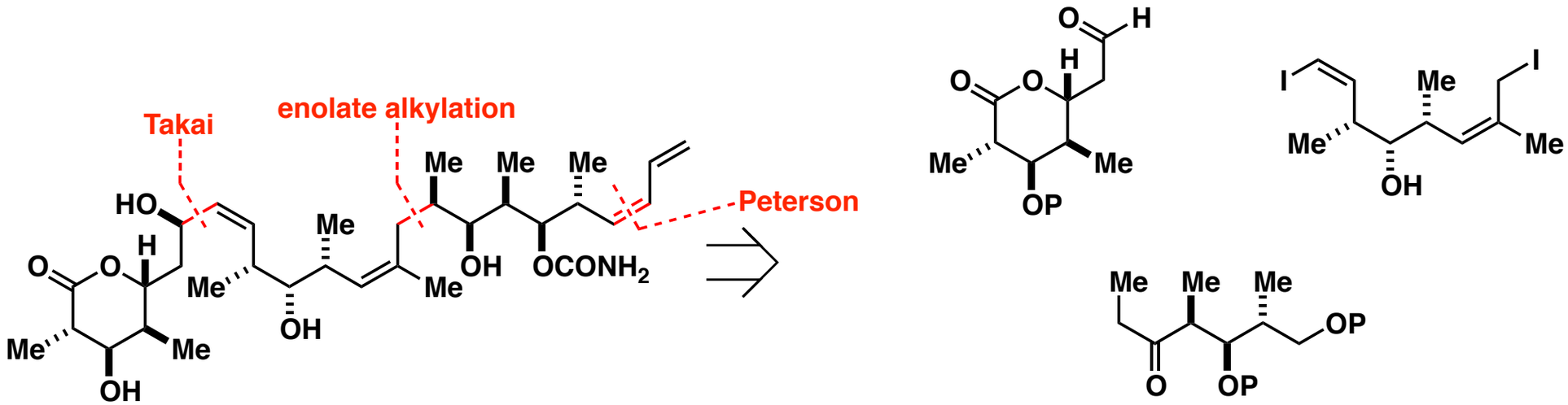
The Chemistry of Enolates: Introduction

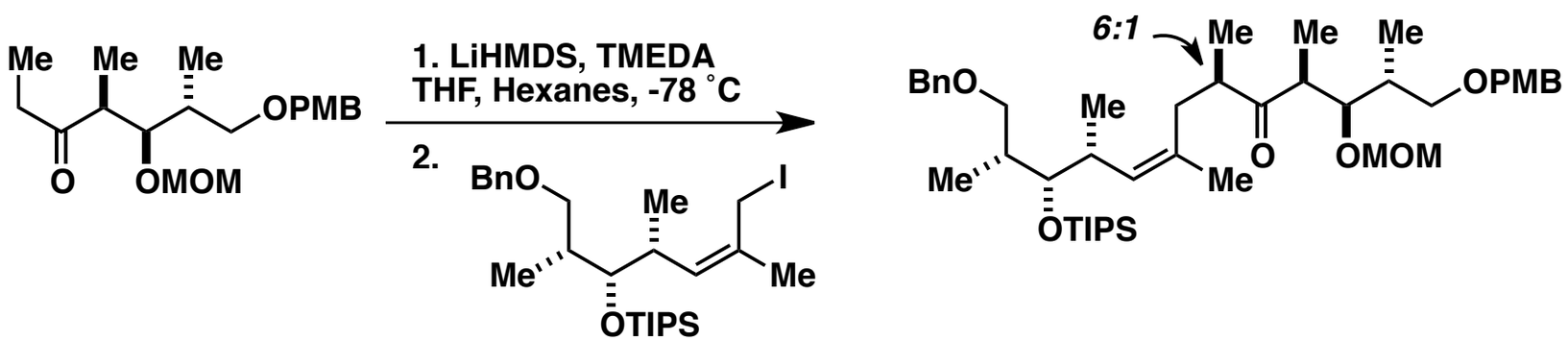


Base \ Z =	OMe	O*t*-Bu	S*t*-Bu	NR_2	Et	*i*-Pr	*t*-Bu	Ph
LDA	95:5	95:5	90:10	0:100	70:30	40:60	0:100	0:100
LDA-HMPA	16:84	9:91			5:95			
LHMDS	n.r.	n.r.		n.r.	34:66	0:100	0:100	0:100
LTMP				0:100	84:16		0:100	0:100
$(Me_2PhSi)_2NLi$					0:100			

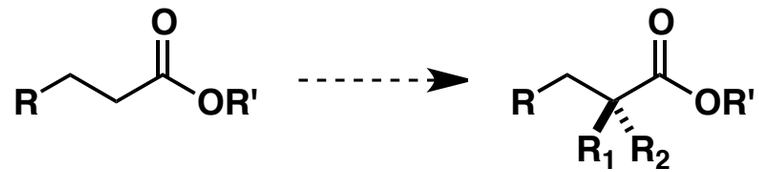
Total Synthesis of Discodermolide: Chelation-controlled Alkylation of Enolate

Myles *J. Org. Chem.* **1997**, *62*, 6098-6099



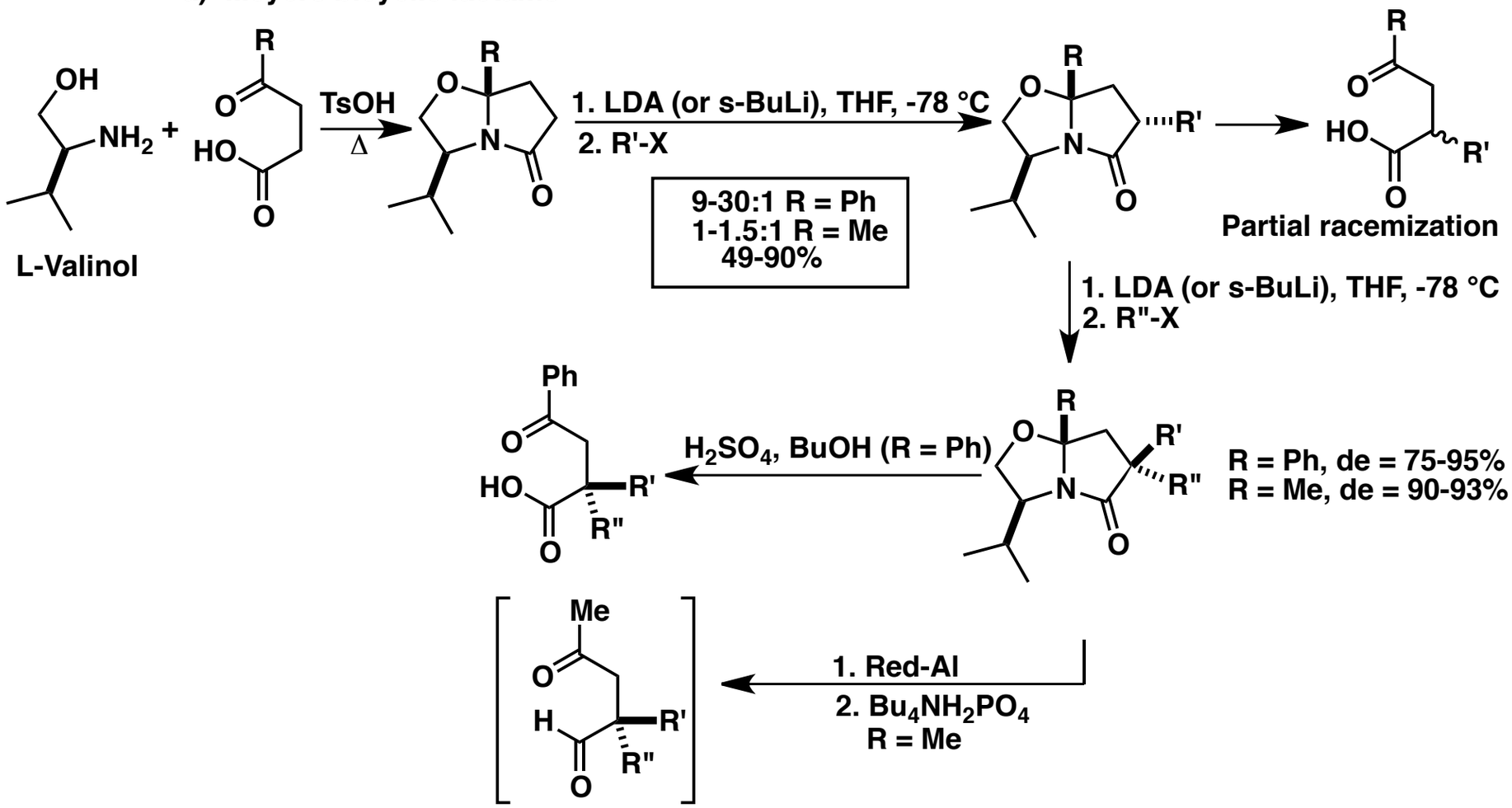


Enolate Alkylation: Chiral Auxiliaries



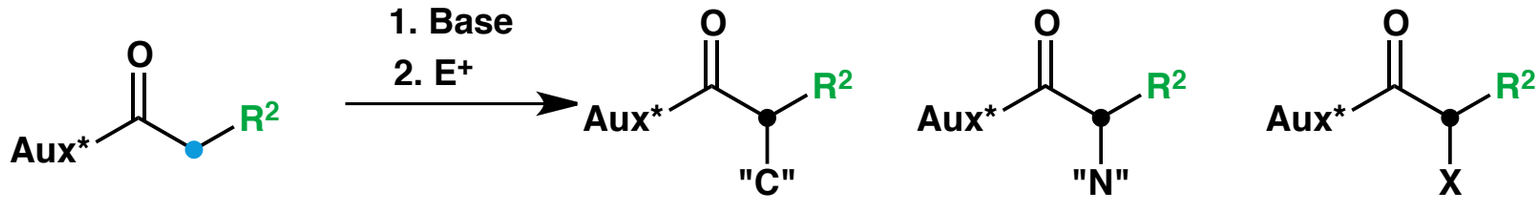
1. Alkylation of cyclic enolates

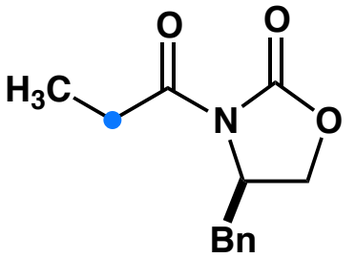
a) Meyers bicyclic lactams



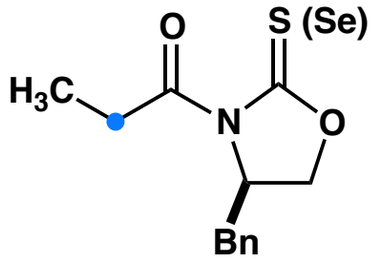
Initial communication: Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1146.

Stereoselective Enolate Alkylation: Chiral Auxiliaries

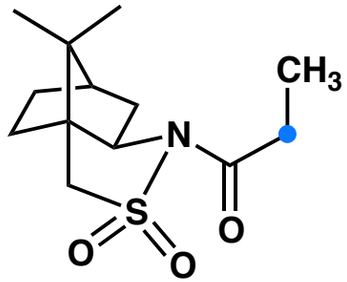




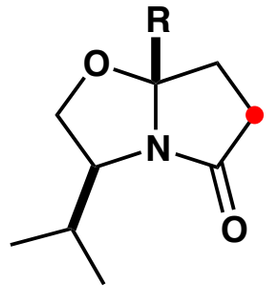
Evans



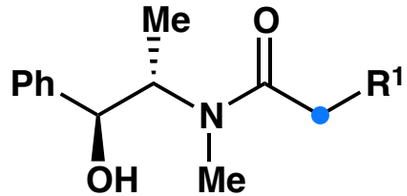
Crimmins



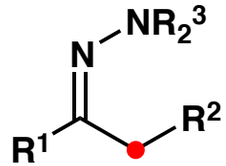
Oppolzer



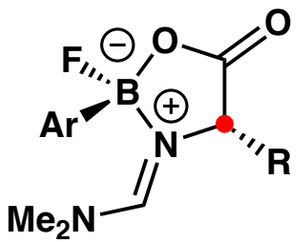
Meyers



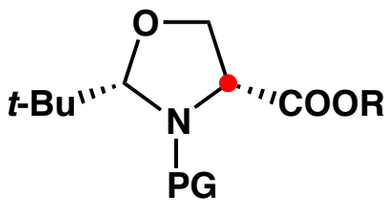
Myers

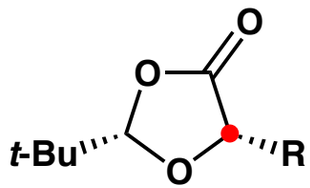


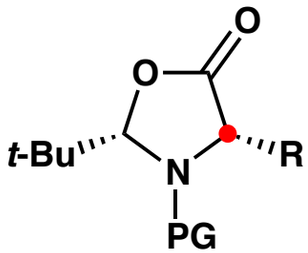
Enders



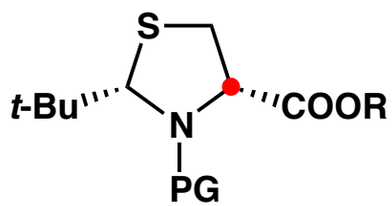
Vedejs

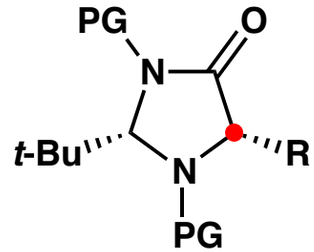


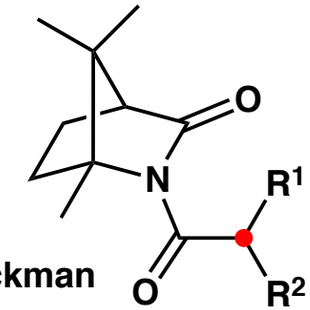




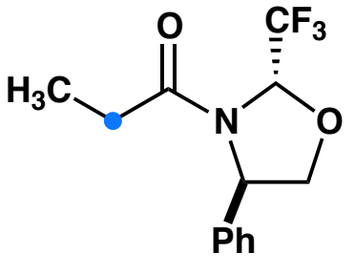
Seebach



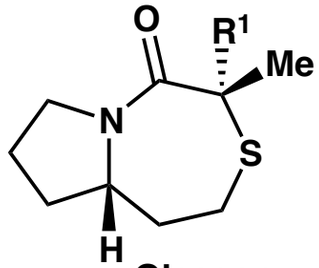




Boeckman

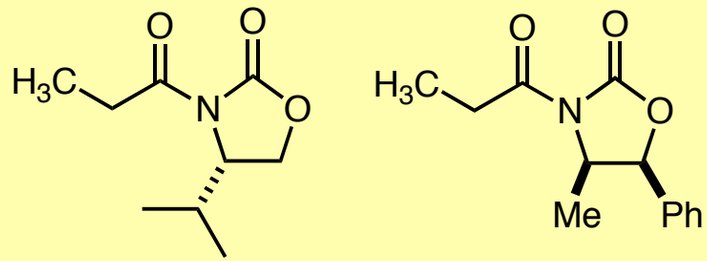


Brigaud

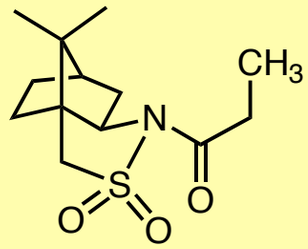


Gleason

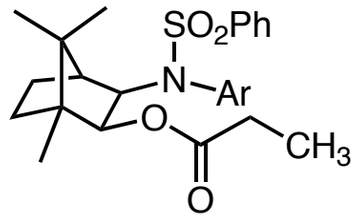
Enolate Alkylation: Chiral Auxiliaries



EVANS' IMIDES



OPPOLZER

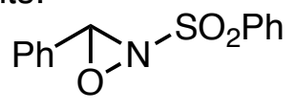


HELMCHEN

Other similar reactions:

1. Oxidations
2. Halogenations
3. Electrophilic aminations

Reagents:

O^+: 

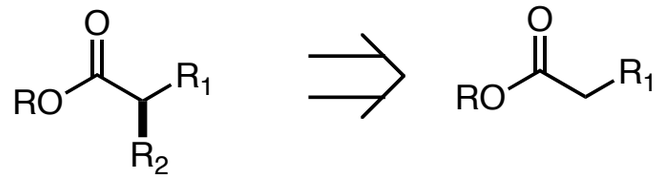
MoOOPh (Oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide): MoO_5-pyridine-HMPA

Br^+, Cl^+: NBS, NCS

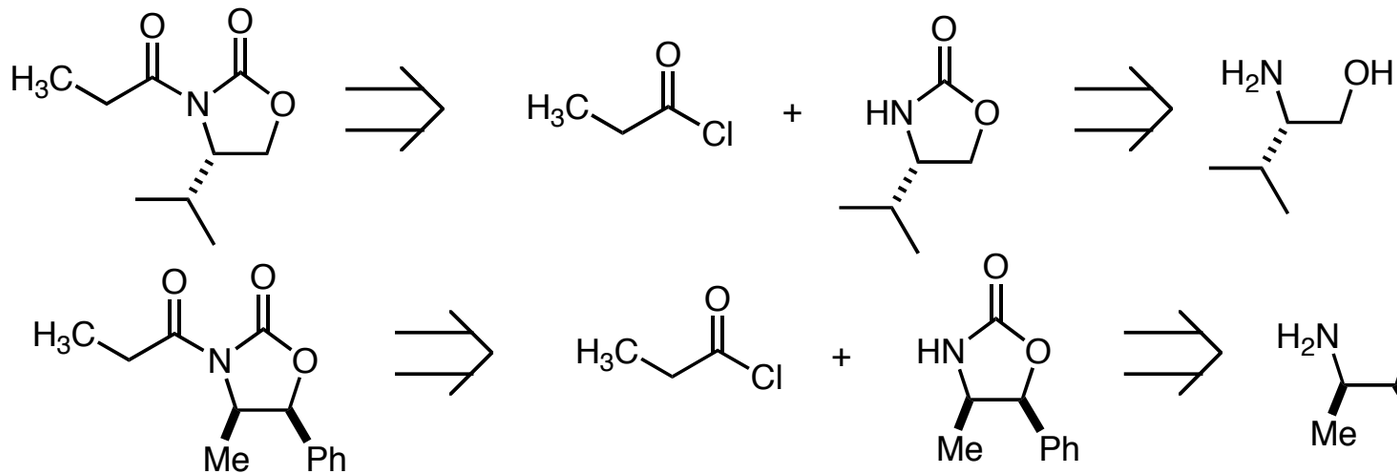
NH_2^+: $ArSO_2N_3$; BocN=NBoc

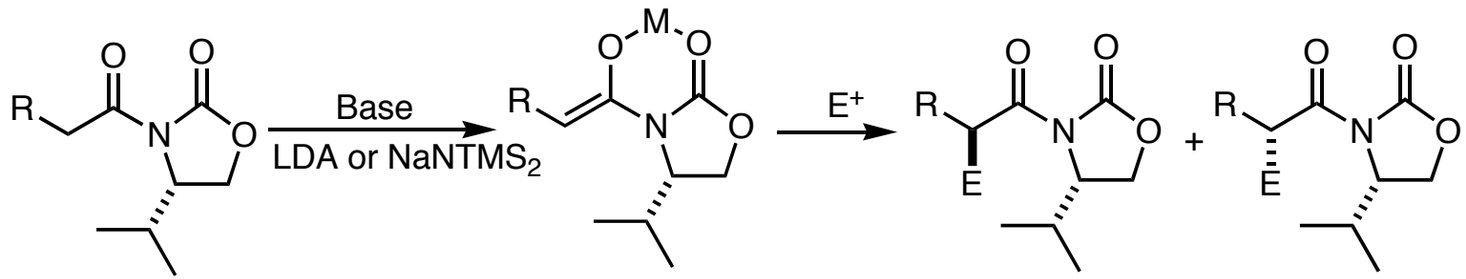
Enolate Alkylation: Chiral Auxiliaries

a) Evans' Oxazolidinone



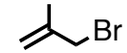
R_2 = C, N, O, X





R = Me, Et, *n*-C_8H_{17}

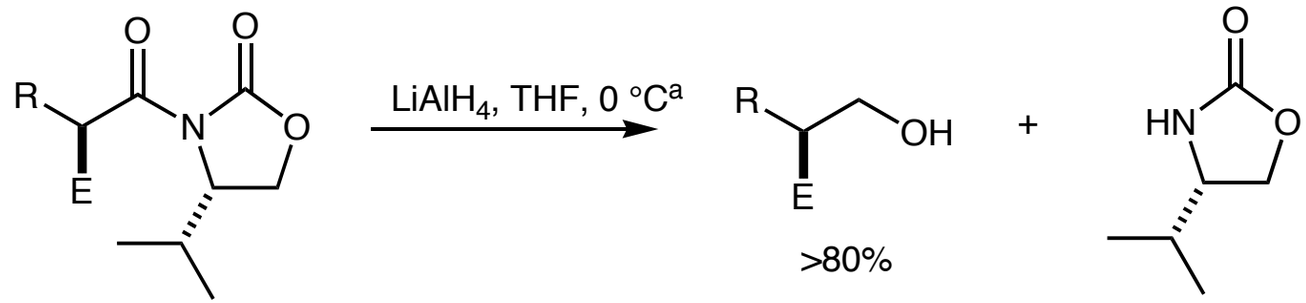
M = Li, THF <0 °C
M = Na, THF -78 ° to 0 °C

E^+	Ratio
BnBr	>99:1
	98:2
	98:2
$BnOCH_2Br$	98:2
EtO_2CCH_2Br	95:5
MeI	91:9
EtI	94:6

References:
D. A. Evans *J. Am. Chem. Soc.* **1982**, *104*, 1737. See also: *J. Am. Chem. Soc.* **1990**, *112*, 5290.
Synthesis of the chiral auxiliary: *J. Org. Chem.* **1985**, *50*, 1830. *Org. Synth.* **1989**, *68*, 77.

Enolate Alkylation: Chiral Auxiliaries

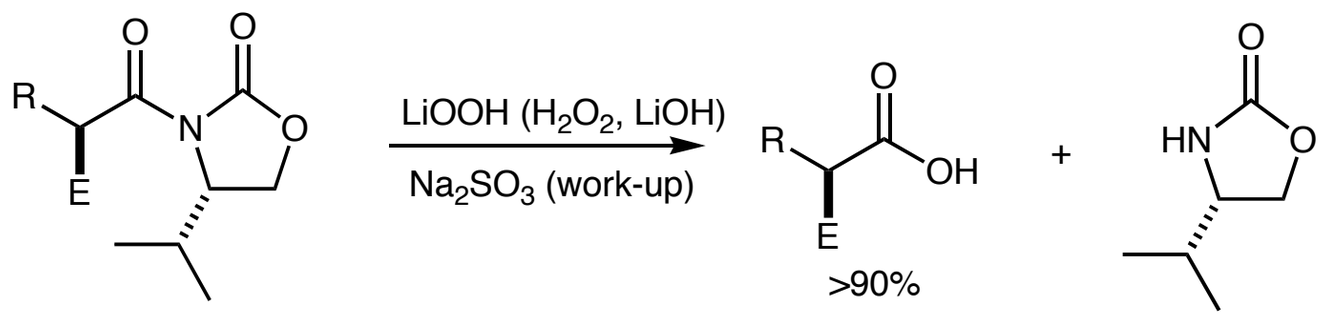
Cleavage of the chiral auxiliary:



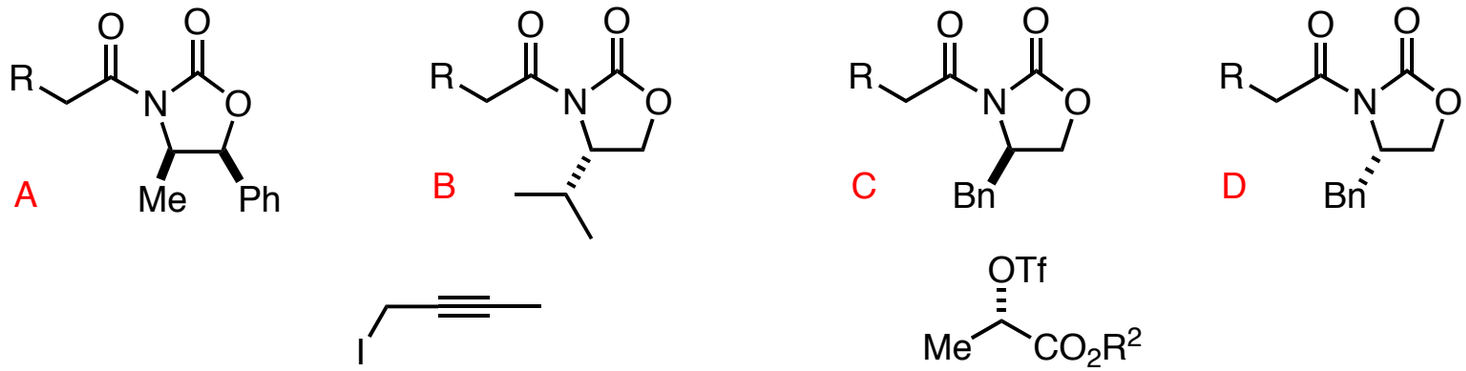
Other reagents: LiOBn,[b] $Ti(OBn)_4$,[c] BrMgOMe,[d] $Me_2AlN(OR)R$,[e] LiOH,[f] $LiBH_4$[g]

References

a,b: *J. Am. Chem. Soc.* **1982**, *104*, 1737.
c,f: *Tetrahedron Lett.* **1987**, *28*, 1123.
d: *J. Am. Chem. Soc.* **1985**, *107*, 4346.
e: *Tetrahedron Lett.* **1986**, *27*, 799.
g: *Tetrahedron Lett.* **1986**, *27*, 4957.



Evan's Auxiliary: Other Alkylating Reagents - Cleavage Conditions



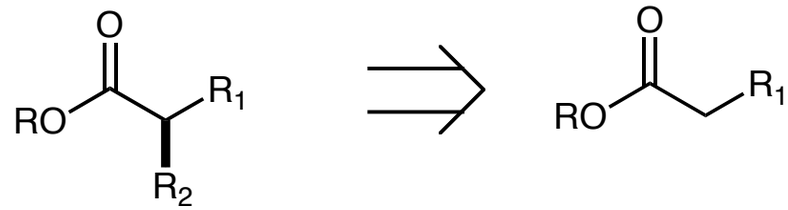
NaHMDS, A
Liebigs Ann. Chem. **1989**, 1081

LDA, C
J. Org. Chem. **1995**, *60*, 4782.

Reagents	Products	Reference
KOH, LiOH, $LiOH/H_2O$	R'COOH	JACS 88, 1238; TL 1987, 6141.
$LiBH_4$, $LiAlH_4$	$R'CH_2OH$	JACS 92, 9434. 1982, 1737. TL 1986, 5683. 1986, 4957. Syn. Comm. 1990, 307 JOC 1991, 2476.
LiOR, NaOR, BrMgOR, $Ti(OR)_4$	R'COOR	TL 1986, 1007. JACS 1987, 7151. 1981, 2127. 1982, 1737 Liebigs Ann. Chem. 1989, 1081 JACS 1990, 4011, 5290.
LiSR, $BnSAlMe_3Li$	R'COSR	TL 1990, 31, 2849. JACS 1993, 4497 1992, 2260. Synlett 1994, 637.
N_2H_4, n-amylONO, NH_4Cl, $Cp_2Ti(Zr)Cl_2$	$R'CONR_2$	JACS 92, 9434. TL 91, 3519. JOC JOC 1994, 3506.
MeONHMe•HCl, $AlMe_3$	Weinreb amide	TL 1986, 799

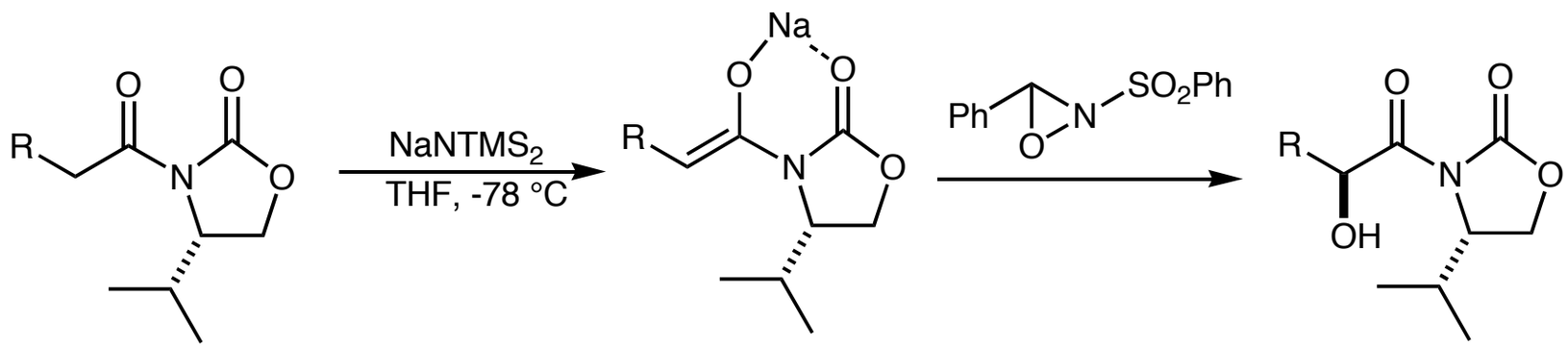
Enolate Alkylation: Chiral Auxiliaries

a) Evans' Oxazolidinone



$R_2 = NH_2$, OH

Synthesis of α-hydroxy acids



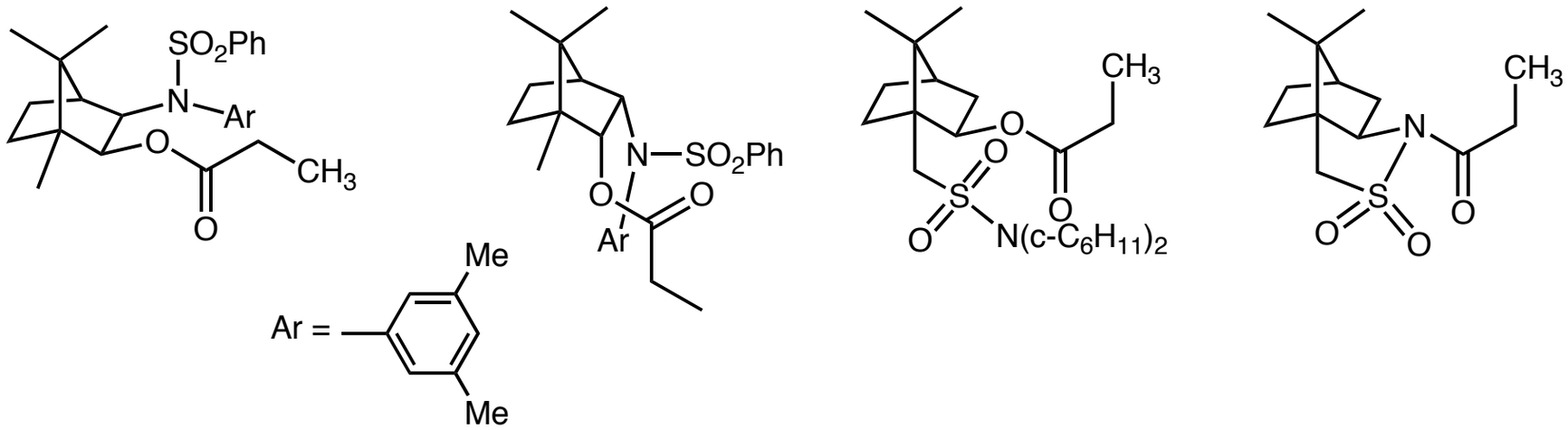
R = Me, Et, *n*-C_8H_{17}

88-98% de

References: D. A. Evans *J. Am. Chem. Soc.* **1985**, *107*, 4346.

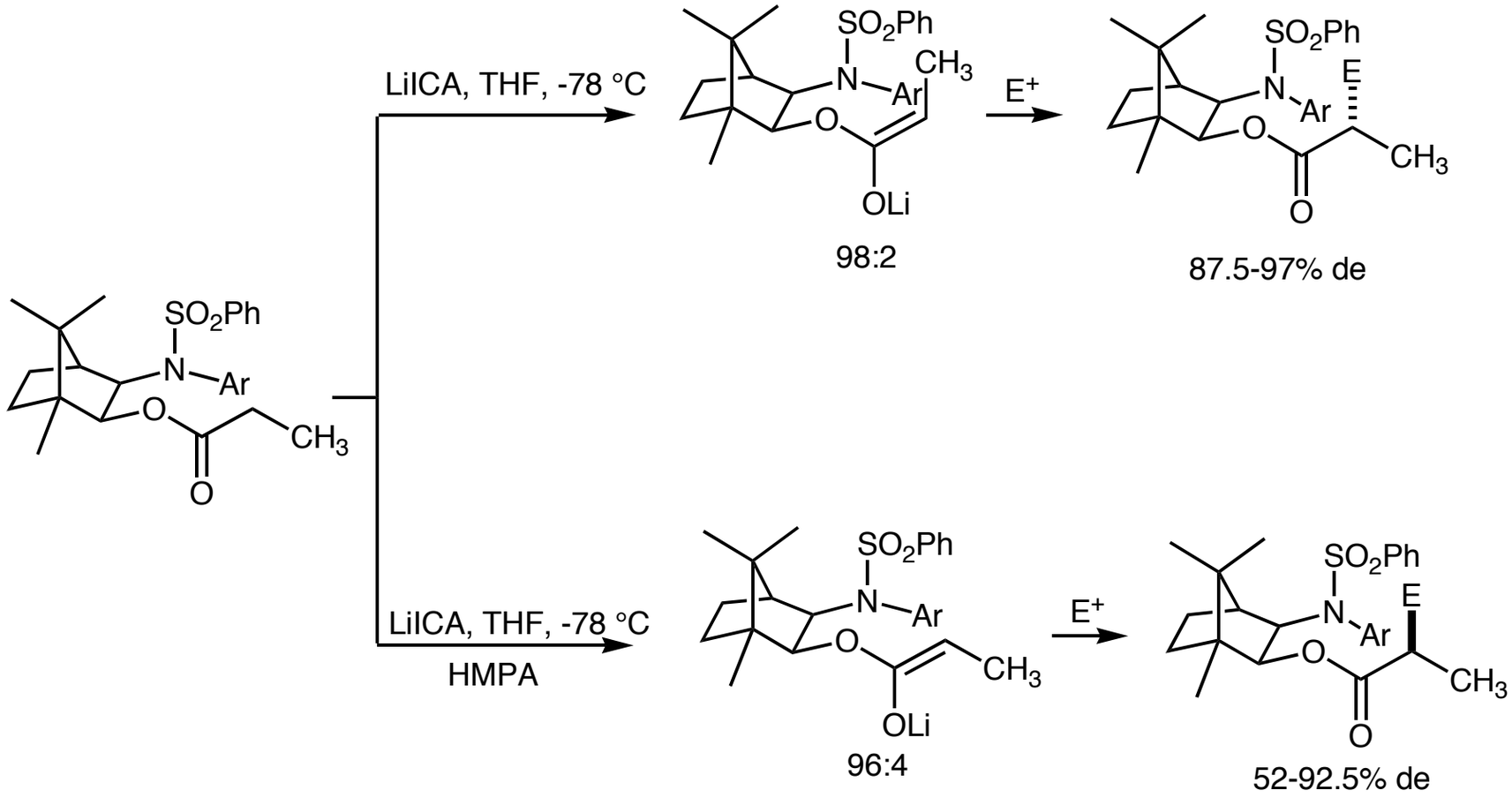
Enolate Alkylation: Chiral Auxiliaries

b) Camphor-derived Chiral Auxiliaries (Oppolzer / Helmchen)



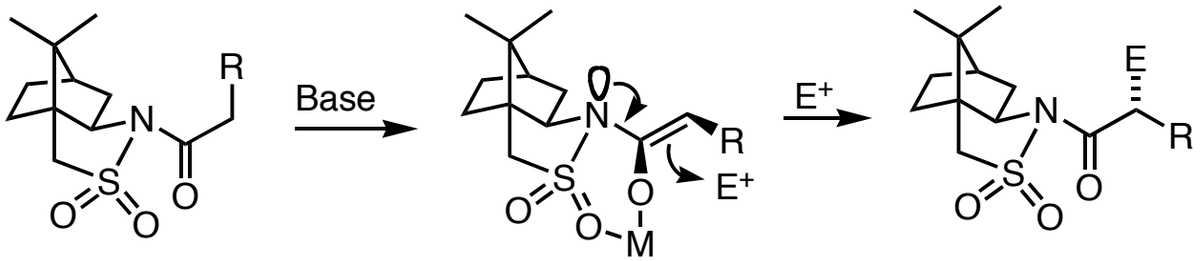
b) Oppolzer's and Helmchen's auxiliaries

Helmchen, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 207. *Tetrahedron Lett.* **1983**, *24*, 3213.



Enolate Alkylation: Chiral Auxiliaries

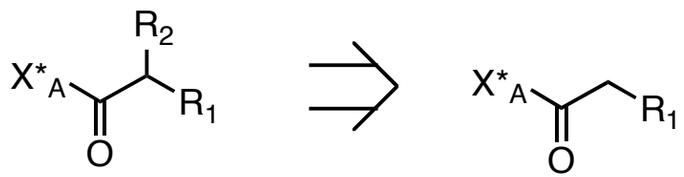
Oppolzer, W. *Tetrahedron Lett.* **1989**, *30*, 5603. *Tetrahedron Lett.* **1989**, *30*, 6009.

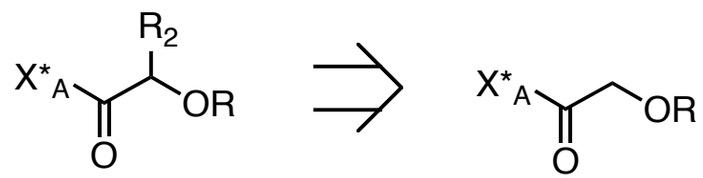


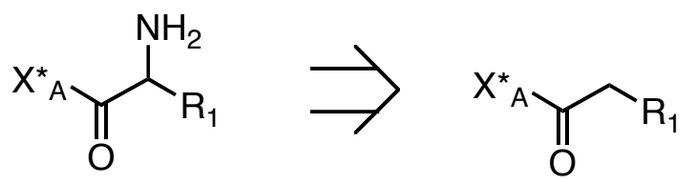
90.1-99% de
(>99% after purification)

Base: KHMDS, NaHMDS, or BuLi

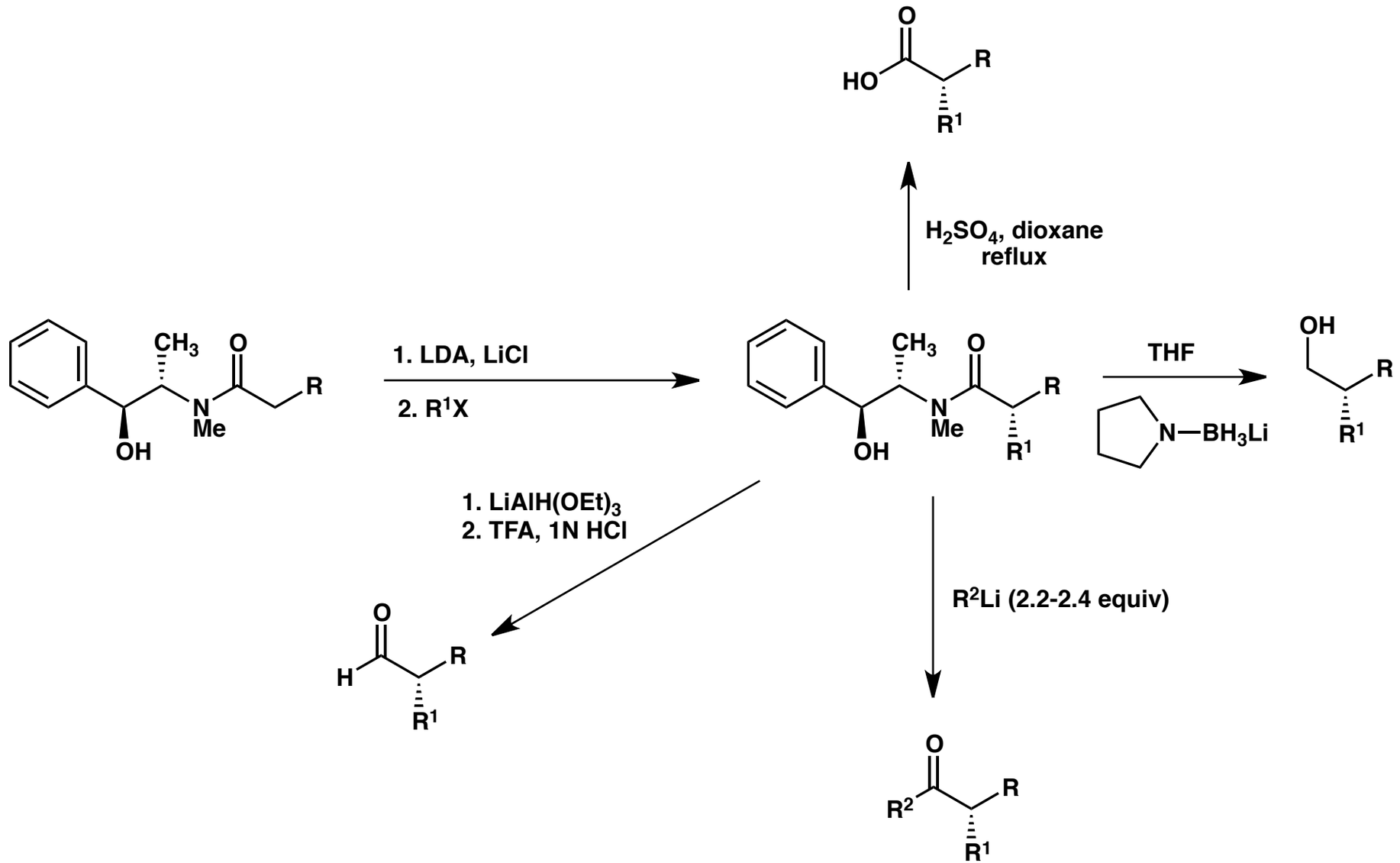
Cleavage: LiOOH ou $LiAlH_4$





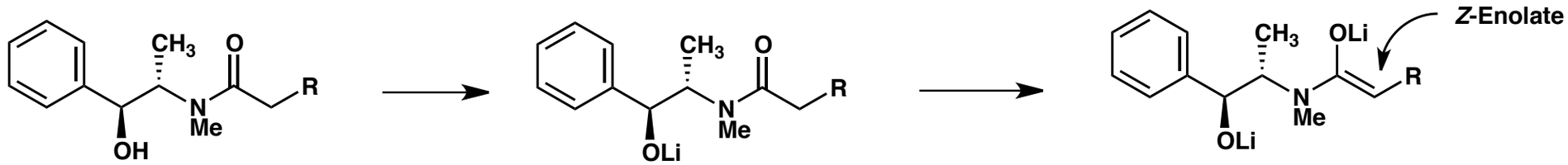


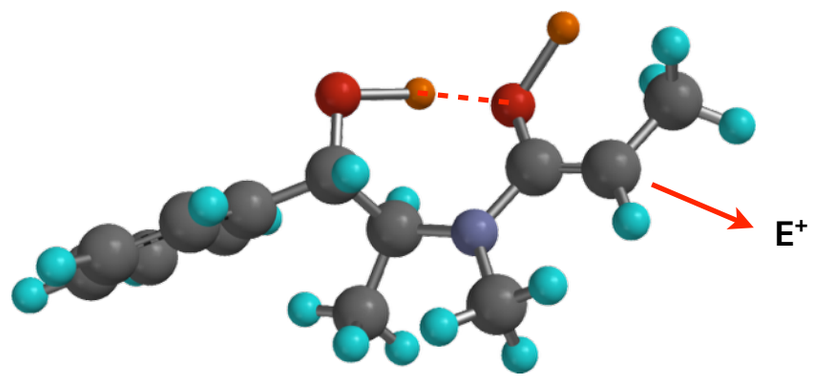
Myer's Pseudoephedrine Chiral Auxiliary



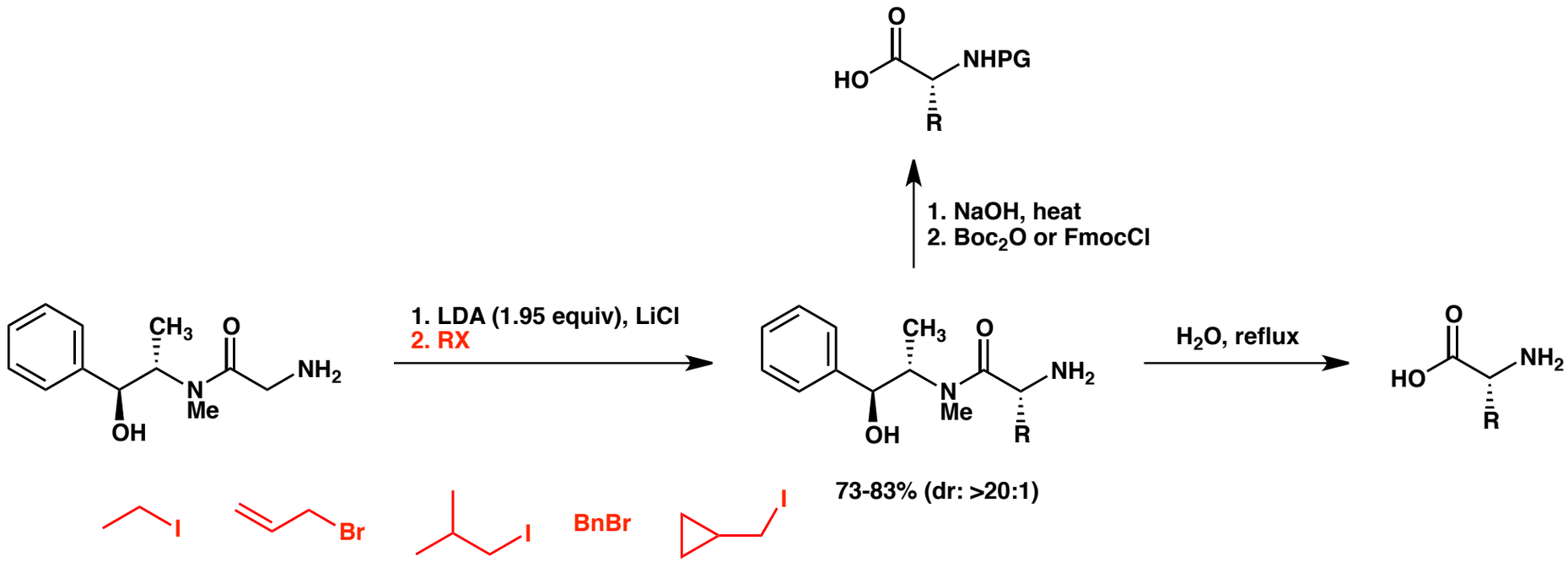
Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361.
Full paper: Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

Myer's Pseudoephedrine Chiral Auxiliary: Chiral Induction



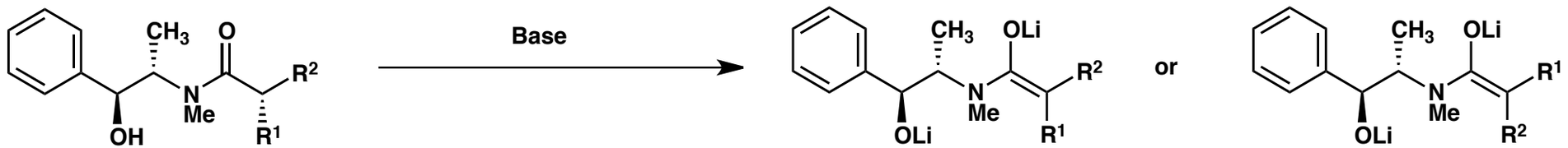


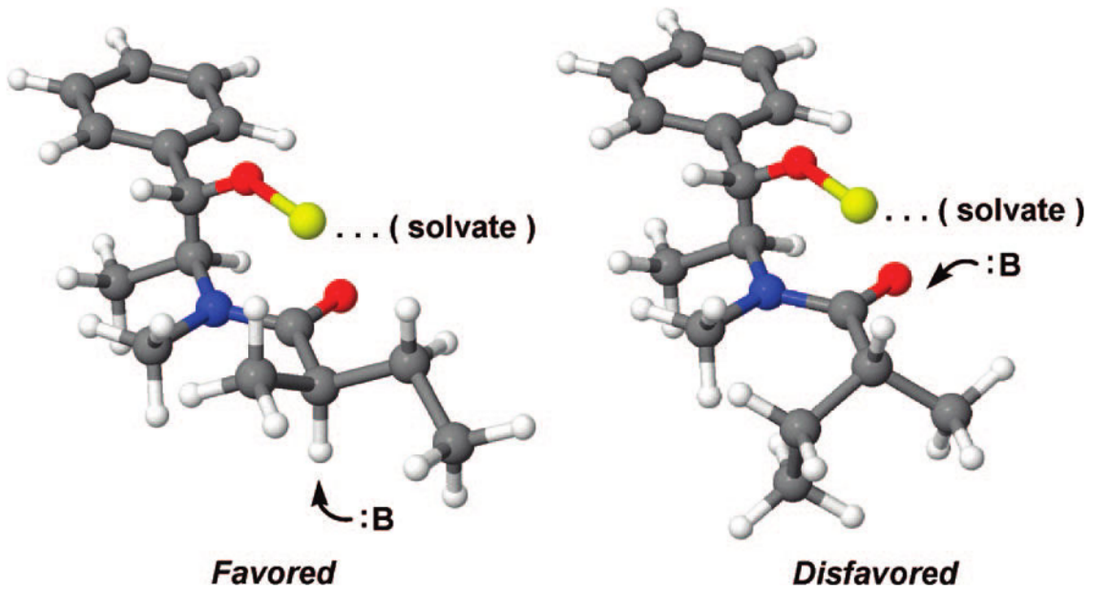
Myer's Pseudoephedrine Chiral Auxiliary



Myers, A. G.; Gleason, J. L.; Yoon, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 8488.
Full paper: Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656.

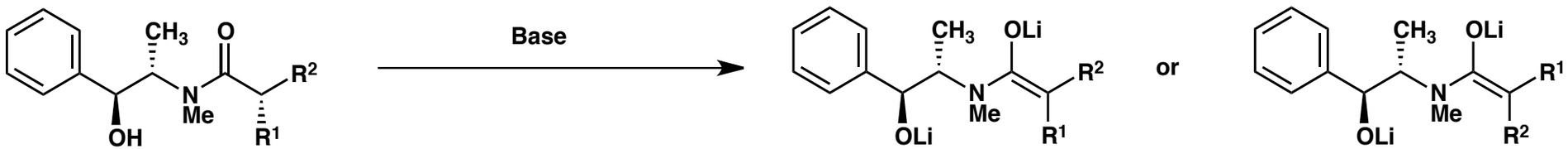
Myer's Pseudoephedrine Chiral Auxiliary: Quaternary Centers

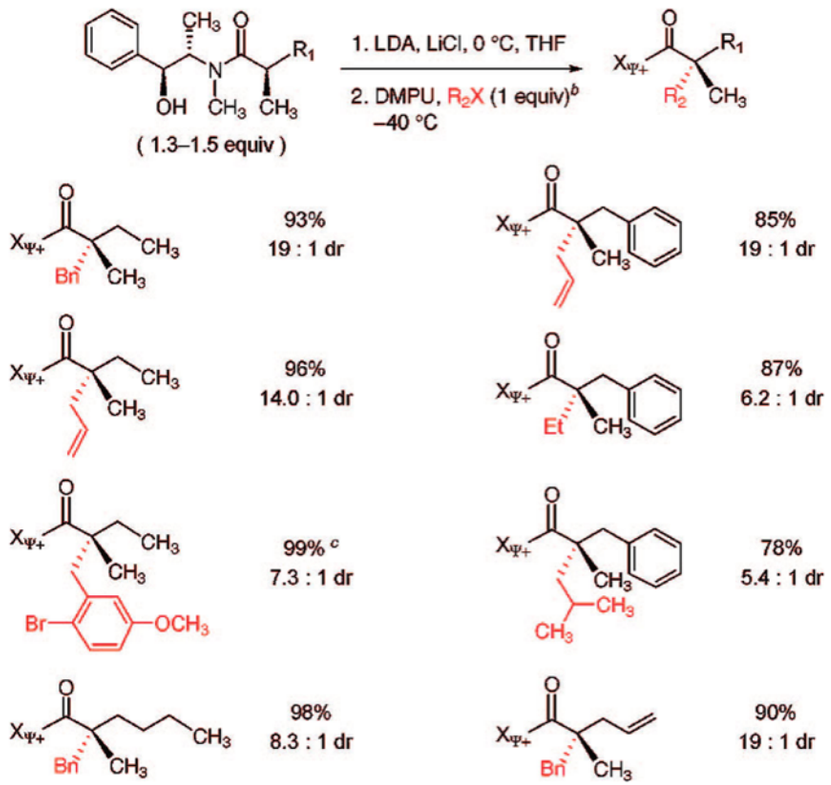




Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231.

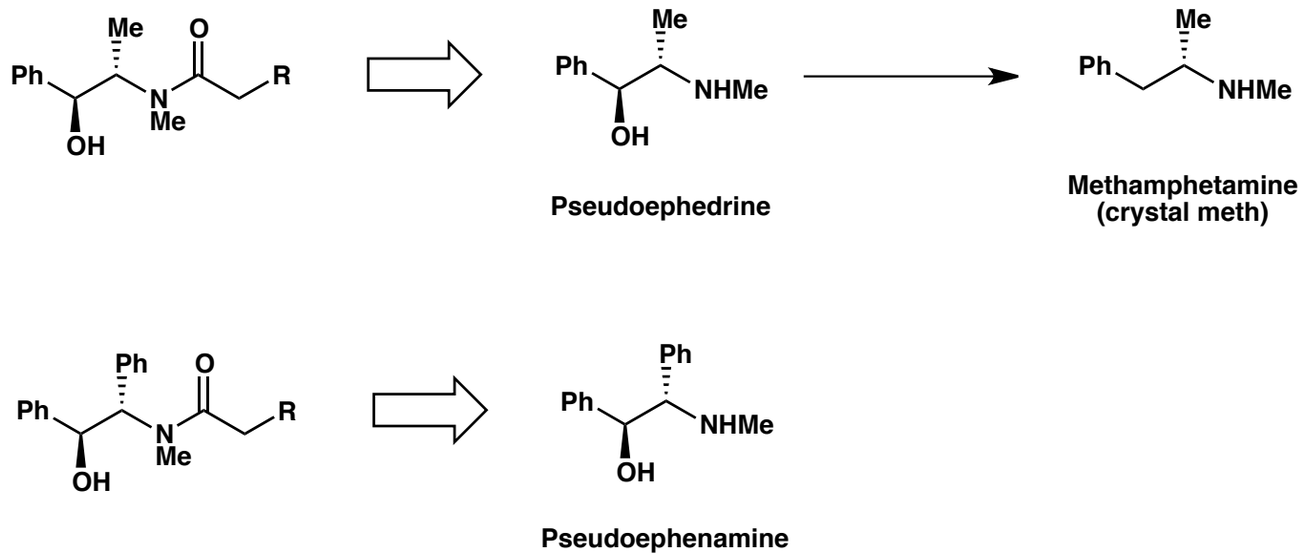
Myer's Pseudoephedrine Chiral Auxiliary: Quaternary Centers





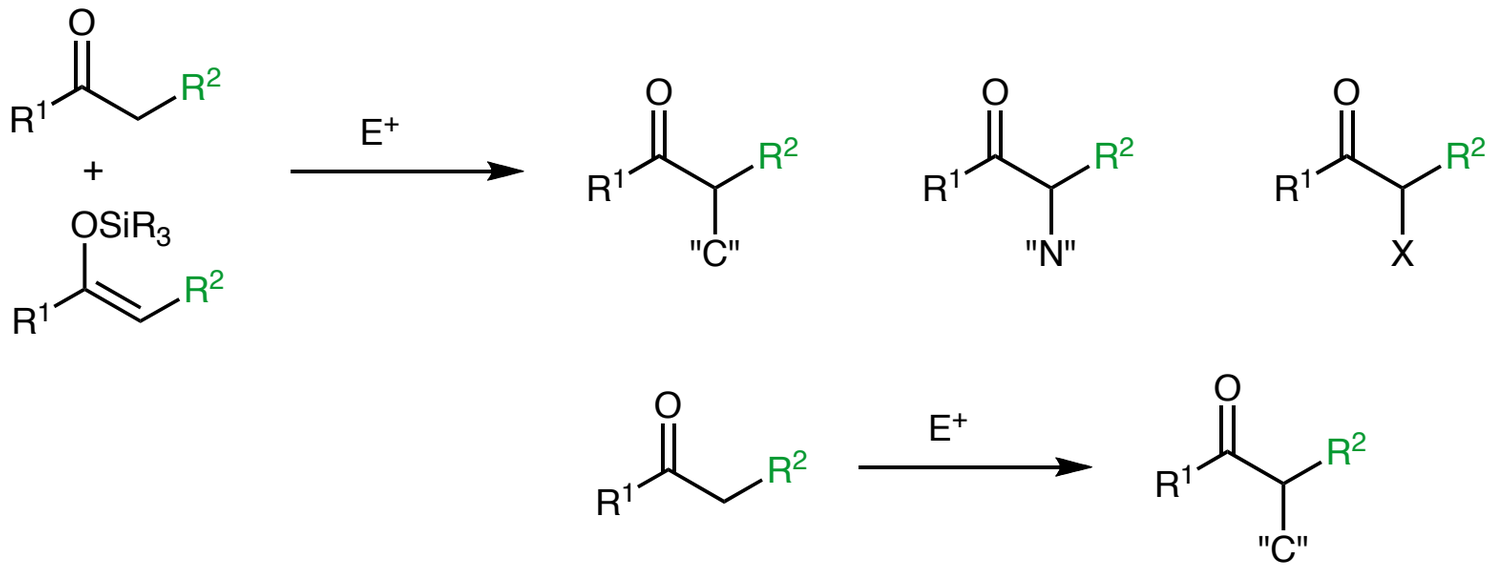
Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231.

Myer's Pseudoephedrine Chiral Auxiliary: Quaternary Centers



Second generation: Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 4568. (pseudoephenamine)
Hugelshofer, C. L.; Mellem, K. T.; Myers, A. G. *Org. Lett.* **2013**, *15*, 3134. (amino acid synthesis)

Alkylation of Enolates: External Chirality



R^2 = EWG group

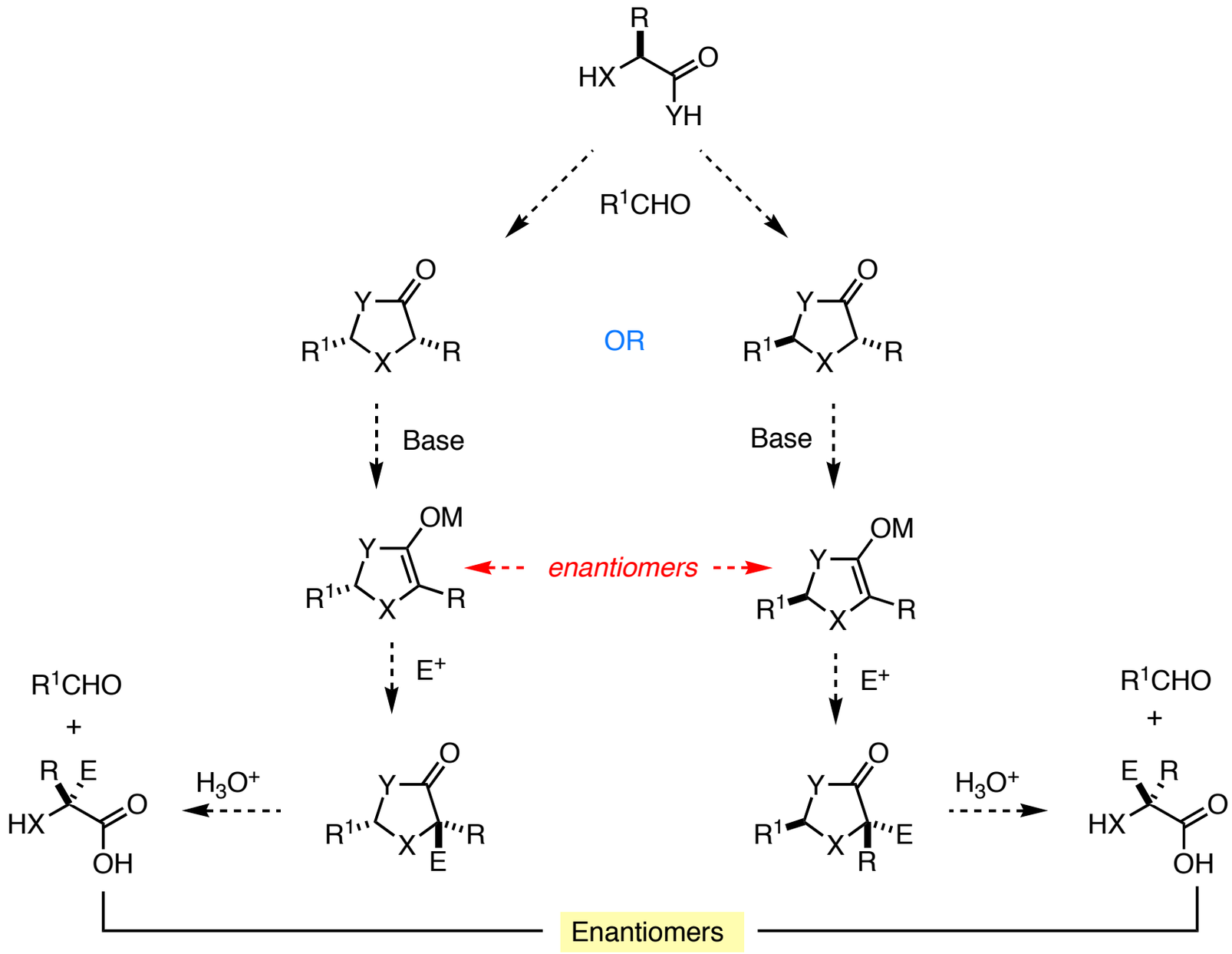
Phase transfer catalyst

Electrophile activation

Memory of chirality

E^+	E^+	E^+	E^+
alkyl halide (activated)	arylation	allylation	acylation
CH_3I BnBr Allyl bromide $ROCH_2X$	ArX needs Pd (catalyst)	π-allyl complex (Pd, Mo, Ir, etc.)	intramolecular

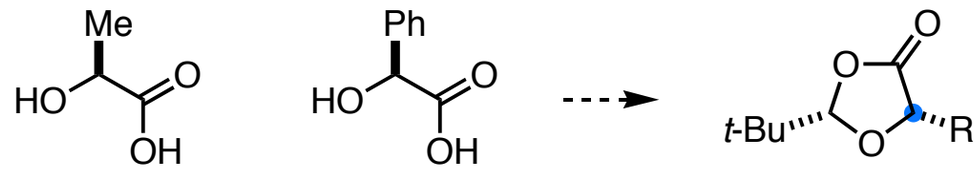
Self-Regeneration of Stereocenters



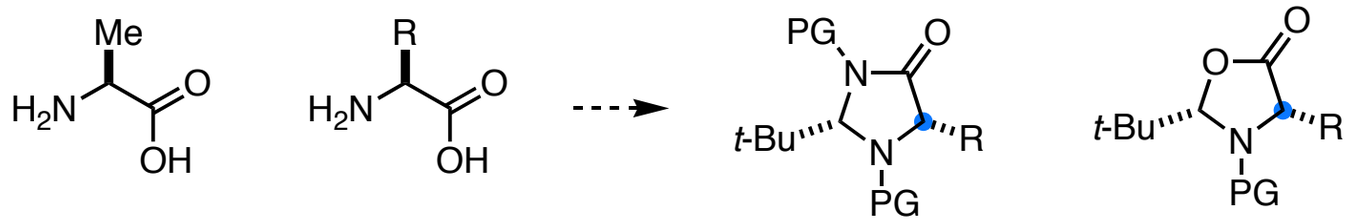
Self-Regeneration of Stereocenters: Structural Variations

⇨ *cis*-isomer is usually formed under thermodynamic conditions in usually >90% dr

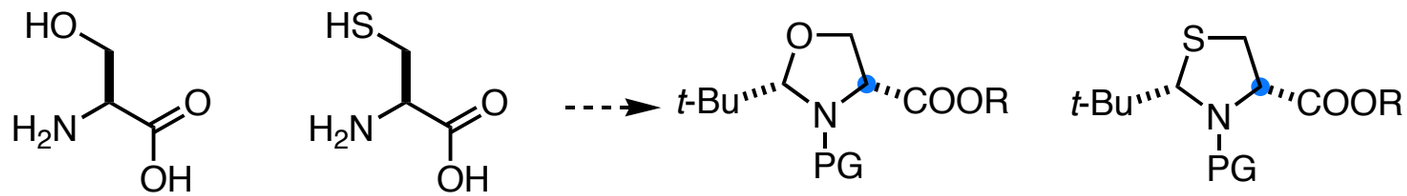
α-hydroxyacids



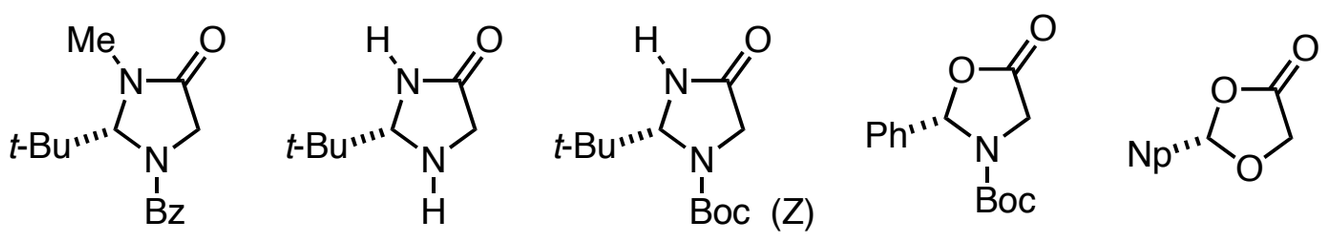
α-aminoacids



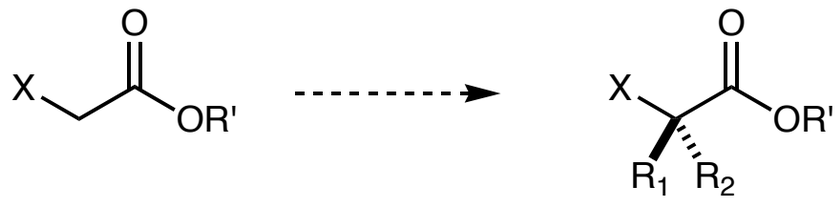
serine, cysteine
threonine, etc.



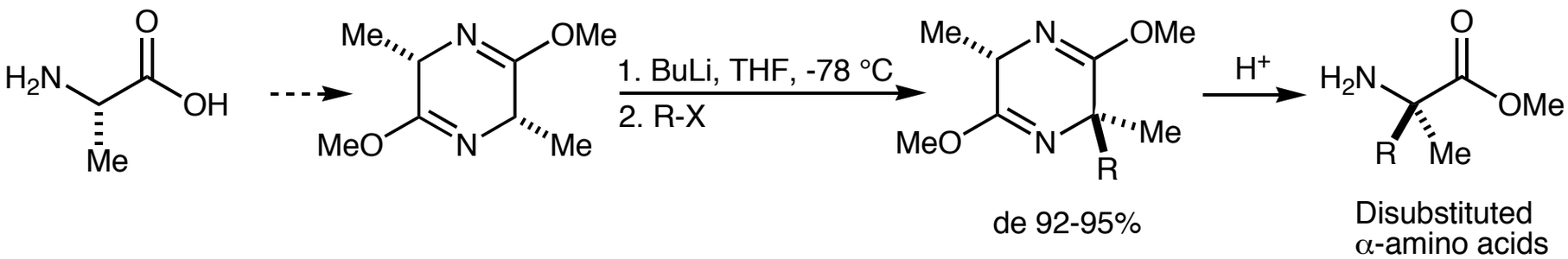
The following have also been prepared by multistep synthesis or by separation of the enantiomers (chromatography or chemical resolution)



Enolate Alkylation: Chiral Auxiliaries (Part I)



c) Bislactim Ether Protocol (Schollkopf, Williams)



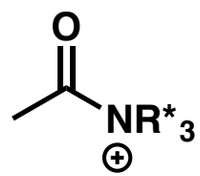
References:

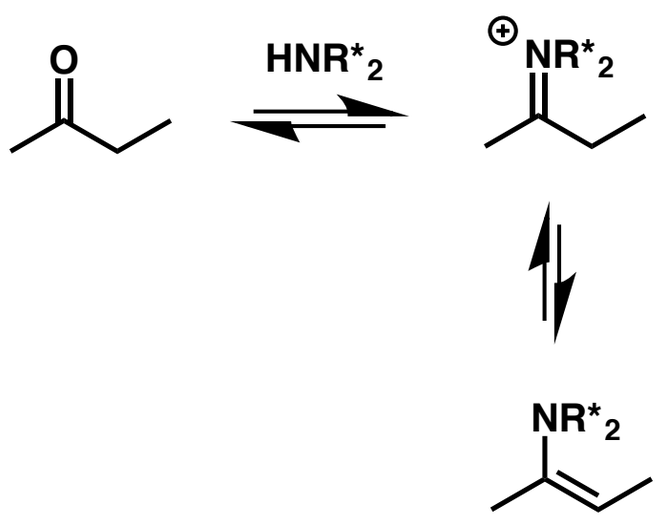
Schollkopf, U. *Pure & Appl. Chem.* **1983**, *55*, 1799. *Chem. Scripta* **1985**, *25*, 105. *Liebigs Ann. Chem.* **1986**, 2150. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 693.
Seebach, *Ang. Chem. Int. Ed. Engl.* **1986**, *25*, 345. *J. Org. Chem.* **1991**, *56*, 2553.
Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 1547. *Tetrahedron Lett.* **1988**, *29*, 6075. *J. Org. Chem.* **1990**, *55*, 3723.
Dellaria, J. F. *Tetrahedron Lett.* **1988**, *29*, 6079. *J. Org. Chem.* **1989**, *54*, 3916.

(Part II) Organocatalysis: Introduction

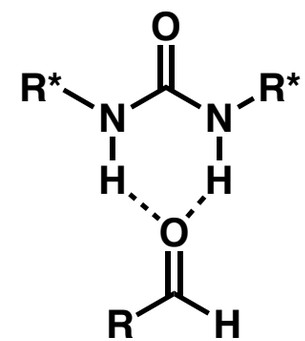
- Organocatalysis: catalyst that is constituted of a low molecule weight organic molecule.
- Asymmetric organocatalysis: organic molecule is chiral, non-racemic

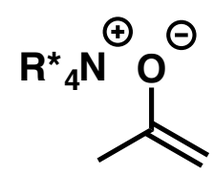
Covalent Catalysis



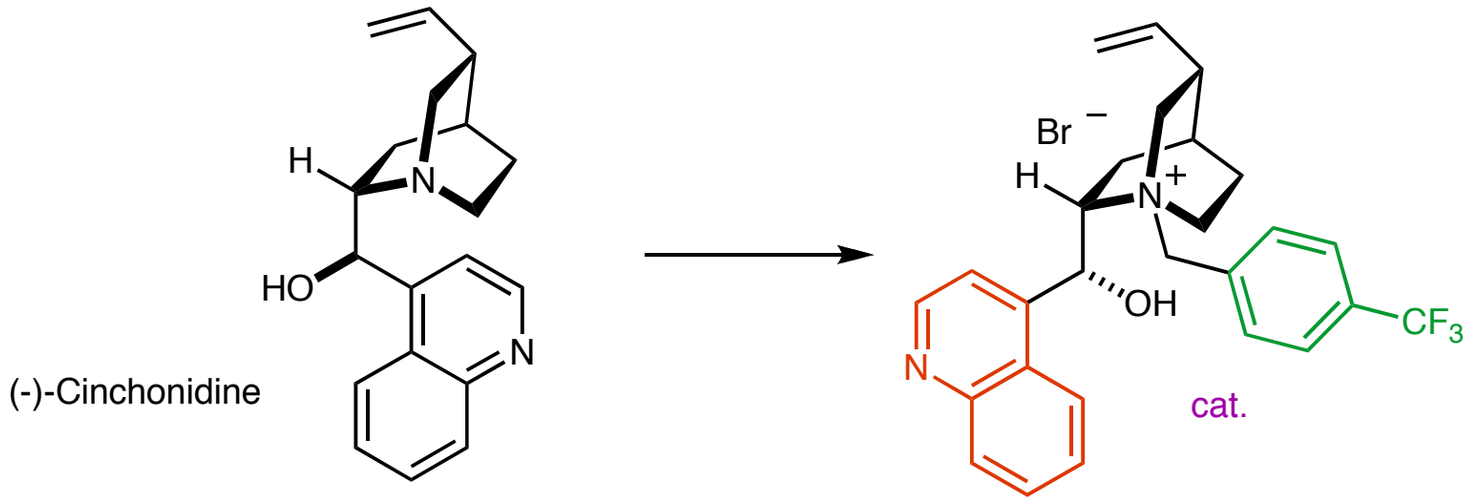


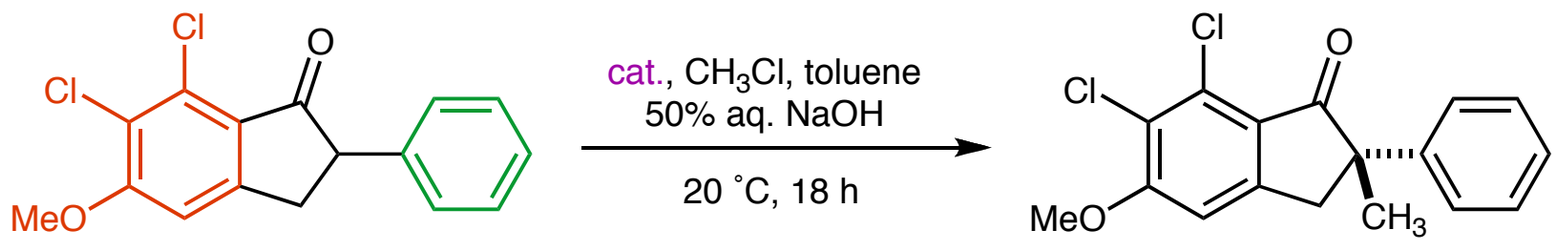
Non-Covalent Catalysis





Enolate Alkylation by Phase Transfer Catalysis





92% ee, 95% yield

↓

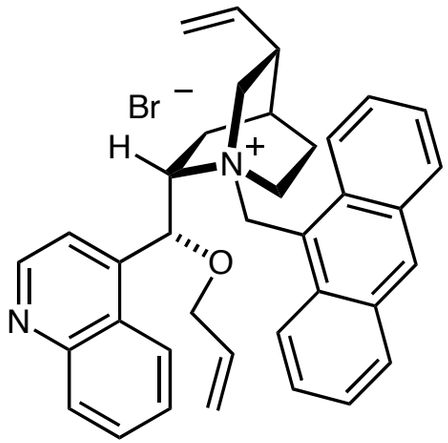
↓

MK-0197

U.-H. Dolling, Davis, Grabowski *J. Am. Chem. Soc.* **1984**, *106*, 446.

- Generate a compact ion pair
- Enolate geometry is fixed
- Aromatic component on both sides (acidity of H)

Enantioselective Alkylation of Stabilized Enolate Under PTC



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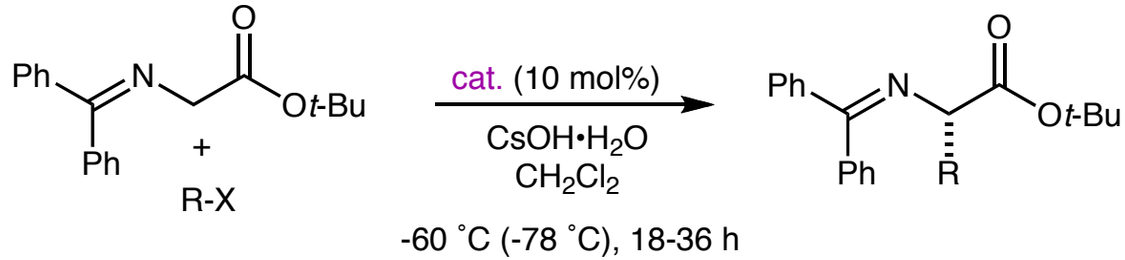
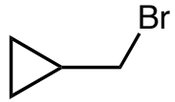
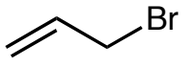
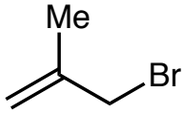
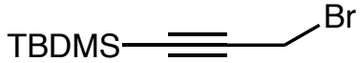
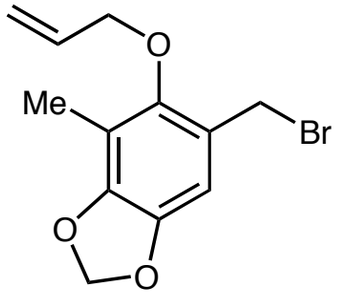
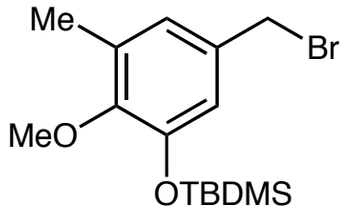


R-X	yield (%)	ee (%)
CH_3I	71	97
EtI	82	98
BuI	79	99.5
	75	99
	89	97
	91	92
	68	95
BnBr	87	94



81%, 96% ee



67%, 97% ee

Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415.
Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347-5350.
Corey, E. J.; Bo, Y. X.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000-13001.

Alkylation of Glycine Schiff Base Under PTC

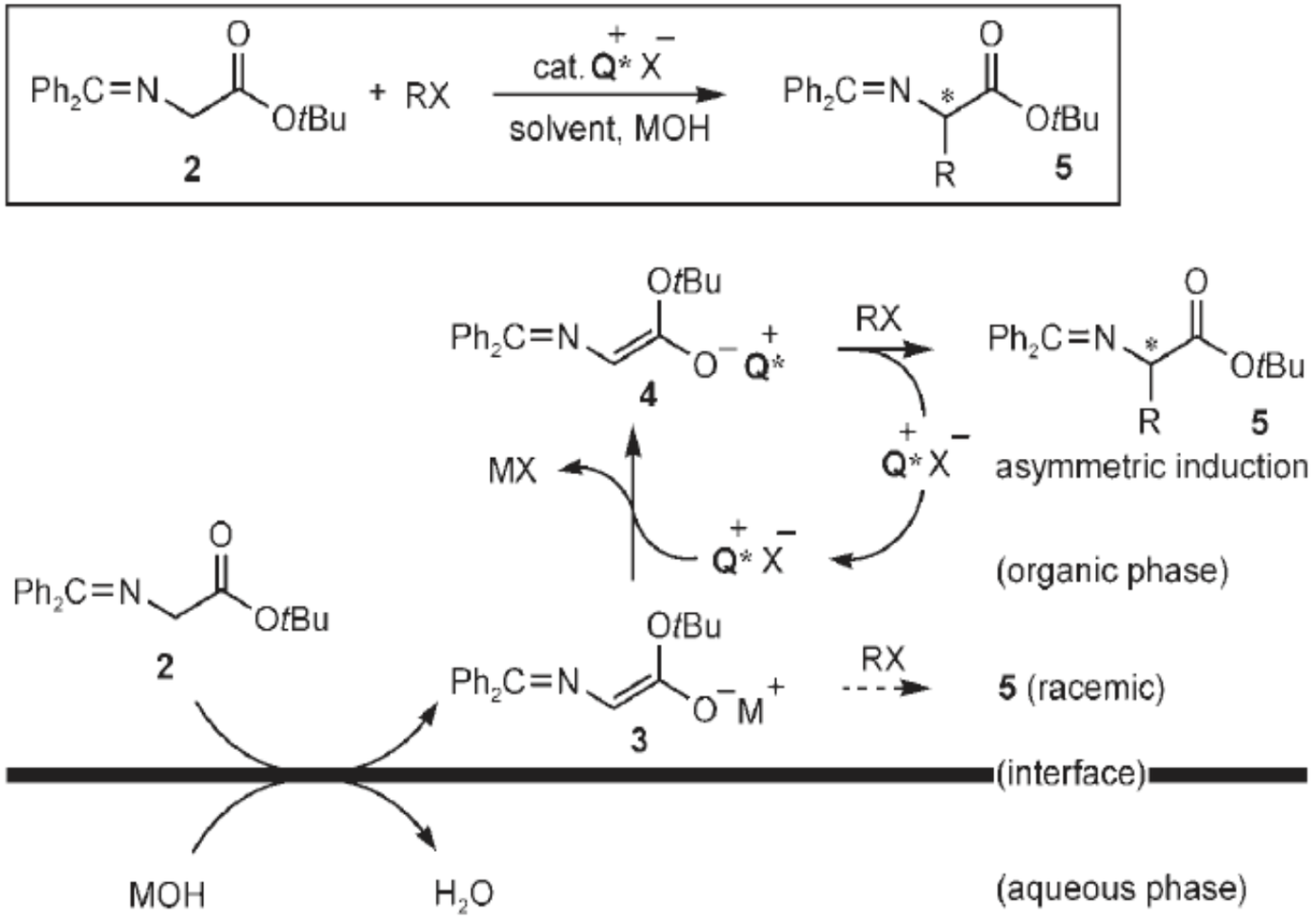
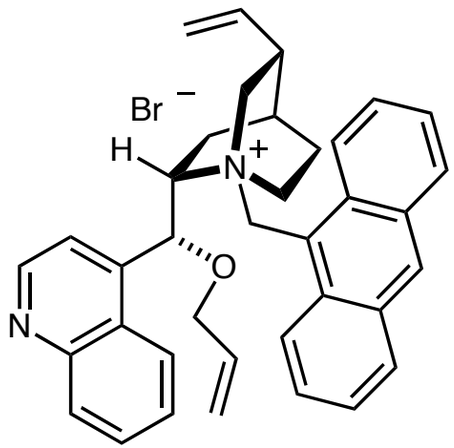


Figure 1. General mechanism for the asymmeric alkylation of active methylene compounds, with a glycine Schiff base used as an example.

Enantioselective Alkylation of Stabilized Enolates Under PTC



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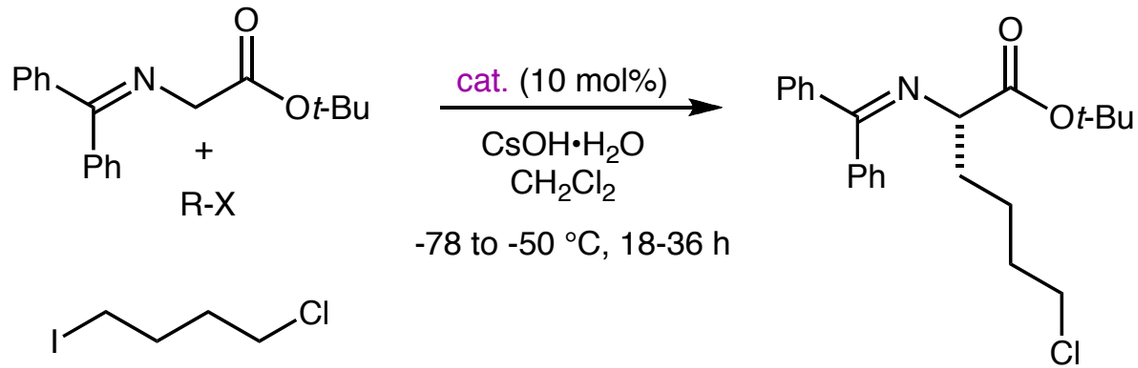
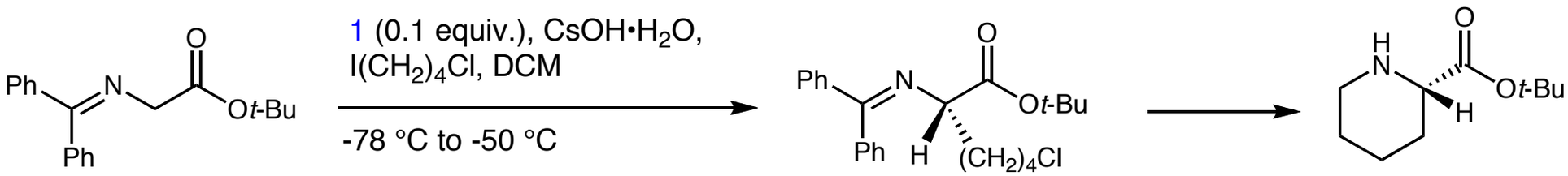
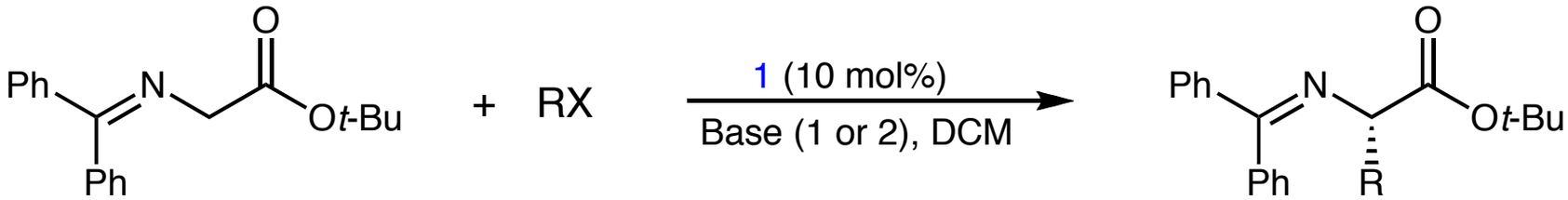
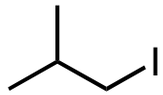
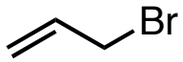
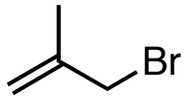
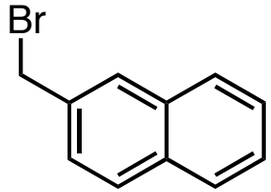
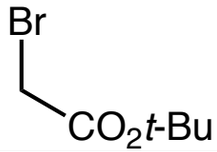




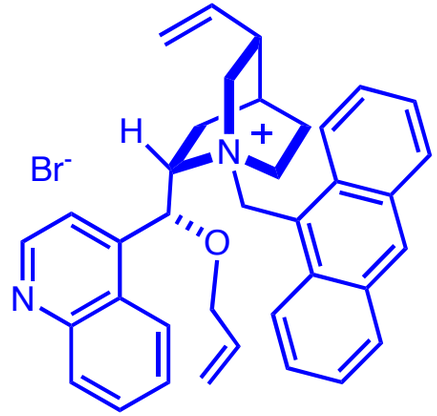
99% ee, 88% yield

Enantioselective Alkylation of Stabilized Enolates Under PTC

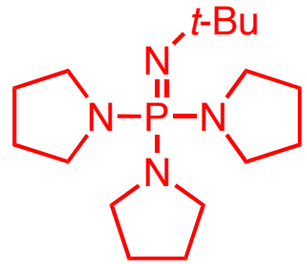


Entry	R-X	Base	Temp, Time	yield (%)	ee (%)
1	CH_3I	2	-78 °C, 4 h	92	94
2	EtI	1	-50 °C, 6 h	89	89
3	*n*-BuI	1	-50 °C, 3.5 h	88	91
4		1	-50 °C, 24 h	93	97
5		2	-78 °C, 6 h	96	90
7		2	-78 °C, 4 h	91	94
8	BnBr	2	-78 °C, 2 h	88	91
9		2	-78 °C, 6 h	91	85
		2	-78 °C, 4 h	89	56

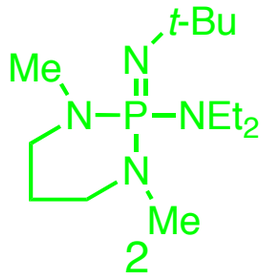
O' Donnell, M. & al. *Tetrahedron Lett.* **1998**, *39*, 8775-8778.



1

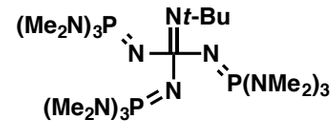


1



2

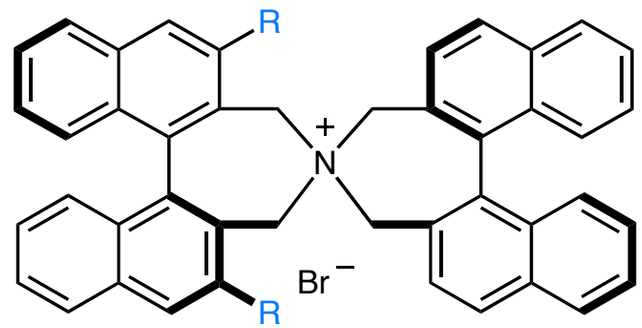
PHOSPHAZENE BASES



t-BuP4
(Schwesinger base)
pKa = 42.7 (CH_3CN)

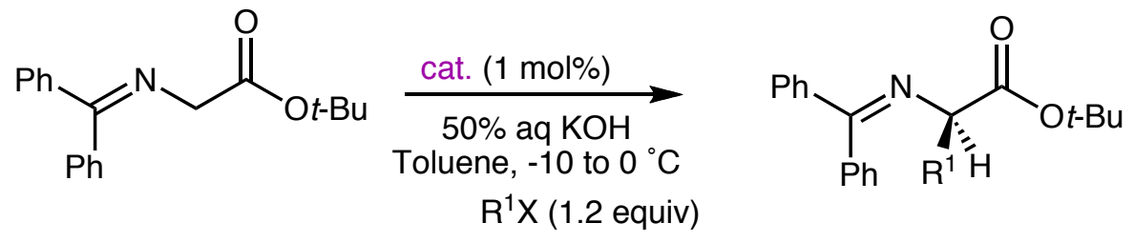
BEMP: pKa 27.6 (CH_3CN)

Enantioselective Alkylation of Stabilized Enolates Under PTC

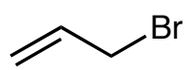
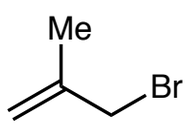


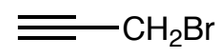
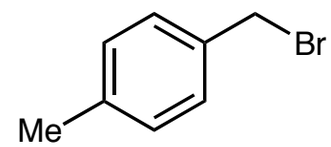
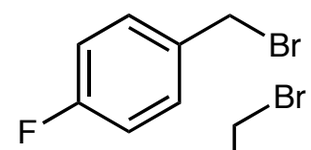
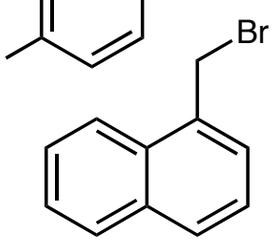
R = β-Naph

cat.



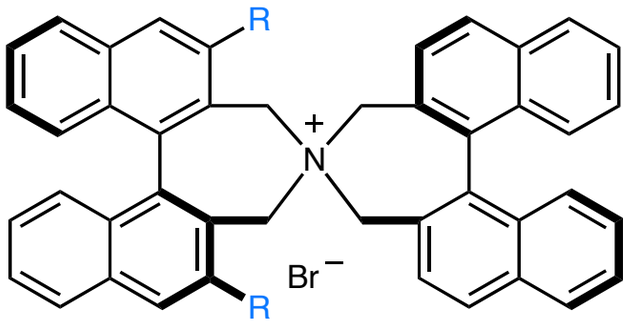
KOH is a major advantage

R^1X	yield (%)	ee (%)
BnBr	95	96
CH_3I	64	90
EtI	41	95
	74	92
	82	93

R^1	R^2X	yield (%)	ee (%)
		90	95
		80	96
		81	96
		60	96

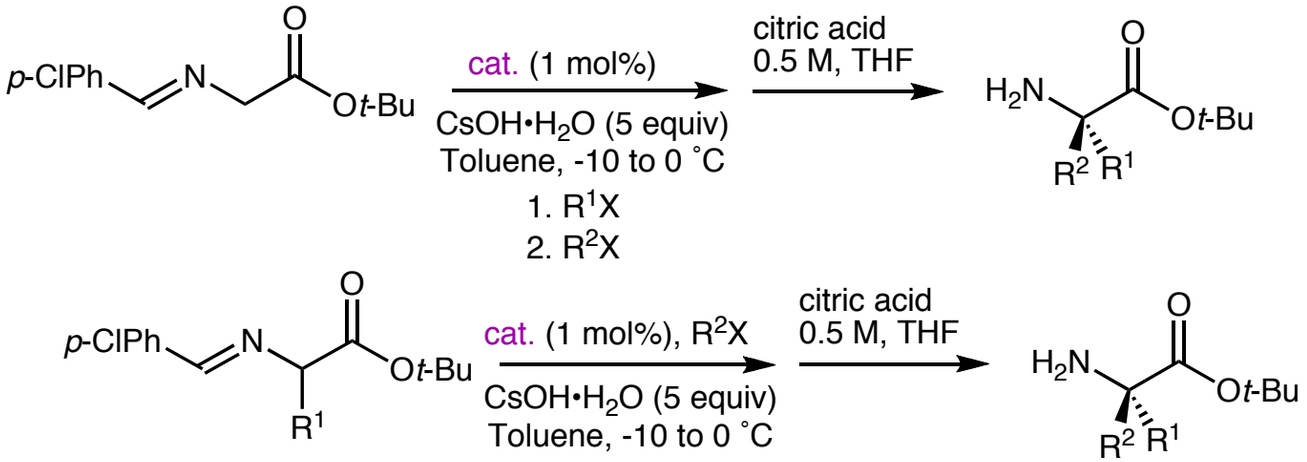
Maruoka *J. Am. Chem. Soc.* **1999**, *121*, 6519-6520

Synthesis of α,α-Disubstituted-α-amino Acids by PTC



R = β-Naph or 3,4,5-$F_3C_6H_2$

cat.



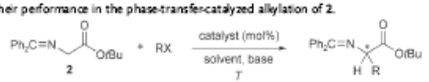
R^1X	R^2X	yield (%)	ee (%)
Allyl bromide	BnBr	80	98
Allyl bromide	$\equiv$—CH_2Br	58	96
Allyl bromide	Me, Br	60	97
BnBr	Allyl bromide	74	92

R^1	R^2X	yield (%)	ee (%)
Me	BnBr	85	98
	Br	73	98
	EtI	71	99
	$BrCH_2COOt$-Bu	60	93
	N-Boc(indole)CH_2Br	78	91
Bn	allylbromide	71	97
i-Bu	BnBr	64	92
i-Bu	allylbromide	70	93

Maruoka *J. Am. Chem. Soc.* **2000**, *122*, 5228-5229

Tabulation of PTC for the Alkylation of Glycine Schiff Base

Table 3: Comparison of representative catalysts in their performance in the phase-transfer-catalyzed alkylation of 2.



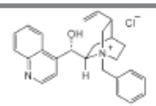
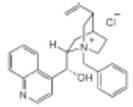
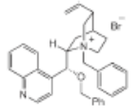
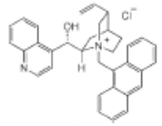
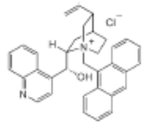
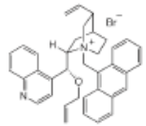
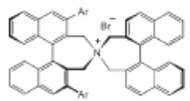
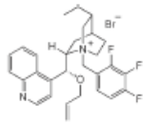
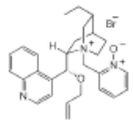
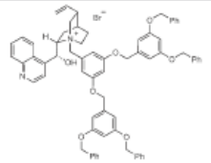
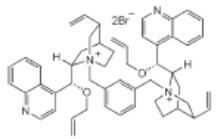
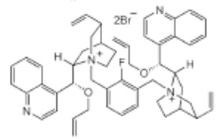
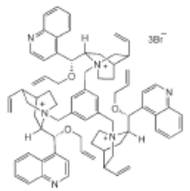
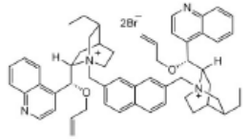
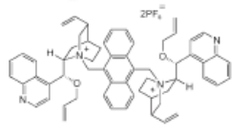
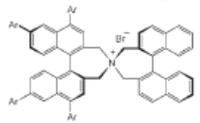
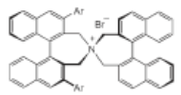
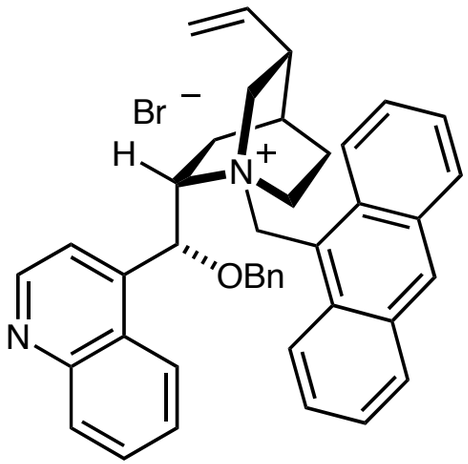
Entry	Catalyst (mol%)	Solvent Base	T [°C]	Yield, ee [%] with $PhCH_2Br$ with $CH_2{=}CHCH_2Br$	Number of RX (or E⁺)	Yield [%]	ee [%]	Ref.
1	8c (10) 	CH_2Cl_2 50% NaOH	25	75, 66 (R) 75, 66 (R)	6	60–82	42–66	[10a]
2	17a (10) 	CH_2Cl_2 50% NaOH	25	85, 64 (S) 78, 62 (S)	4	78–85	48–64	[10a]
3	17c (10) 	toluene/CH_2Cl_2 (7:3) 50% NaOH	5	87, 81 (S) –	–	–	–	[10c]
4	8d (10) 	toluene 50% KOH	25	63, 89 (R) 62, 88 (R)	7	40–86	67–89	[13a,c]
5	17d (10) 	toluene 50% KOH	25	68, 91 (S) 76, 88 (S)	8	41–84	68–91	[13a,c]
6	17e (10) 	CH_2Cl_2 CsOH·H_2O	−78 or −60	87, 94 (S) 89, 97 (S)	11	67–91	92–99.5	[14]
7	(S,S)-20e Ar = 3,4,5-$F_3C_6H_2$ (1) 	toluene 50% KOH	0	90, 99 (R) 80, 99 (R)	14[H]	80–98	96–99	[16e]
8	26e (10) 	toluene/$CHCl_3$ (7:3) 50% KOH	−20	96, 98 (S) 95, 96 (S)	12	60–96	94–>99	[18]
9	26h (5) 	toluene/$CHCl_3$ (7:3) 50% KOH	−20	93, 98 (S) 94, 97 (S)	9	80–97	97–>99	[19]

Table 3: (Continued)

Entry	Catalyst (mol%)	Solvent Base	T [°C]	Yield, ee [%] with $PhCH_2Br$ with $CH_2{=}CHCH_2Br$	Number of RX (or E⁺)	Yield [%]	ee [%]	Ref.
10[H]	17g (10) 	toluene/$CHCl_3$ (7:3) 50% KOH	−20	94, 72 (S) –	3	87–94	68–72	[20a]
11	29a (5) 	toluene/$CHCl_3$ (7:3) 50% KOH	−20	94, 95 (S) 86, 94 (S)	12	50–98	90–99	[21a]
12	29b (5) 	toluene/$CHCl_3$ (7:3) 50% KOH	−20	94, 98 (S) 92, 97 (S)	6	81–94	97–>99	[21b]
13	30 (3) 	toluene/$CHCl_3$ (7:3) 50% KOH	−20	94, 94 (S) 90, 95 (S)	10	65–95	90–97	[22]
14	31 (1) 	toluene/$CHCl_3$ (7:3) 50% KOH	0	95, 97 (S) 95, 97 (S)	13	70–95	94–>99	[23]
15	32d (5) 	toluene/$CHCl_3$ (7:3) 50% KOH	0	62, 84 (S) 70, 90 (S)	4	62–72	84–90	[25]
16	(S,S)-33c Ar = 3,5-$Ph_3C_6H_2$ (1) 	toluene 50% KOH	0	88, 96 (R) 92, 88 (R)	4	88–93	88–96	[26]
17	(S,S)-20d Ar = 3,5-$Ph_3C_6H_2$ + [18]crown-6 (34) (0.1) 	toluene 50% KOH	0	98, 98 (S) 87, 85 (S)	4[H]	70–98	85–98	[28]

Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.

Enantioselective Alkylation of Stabilized Enolates Under PTC



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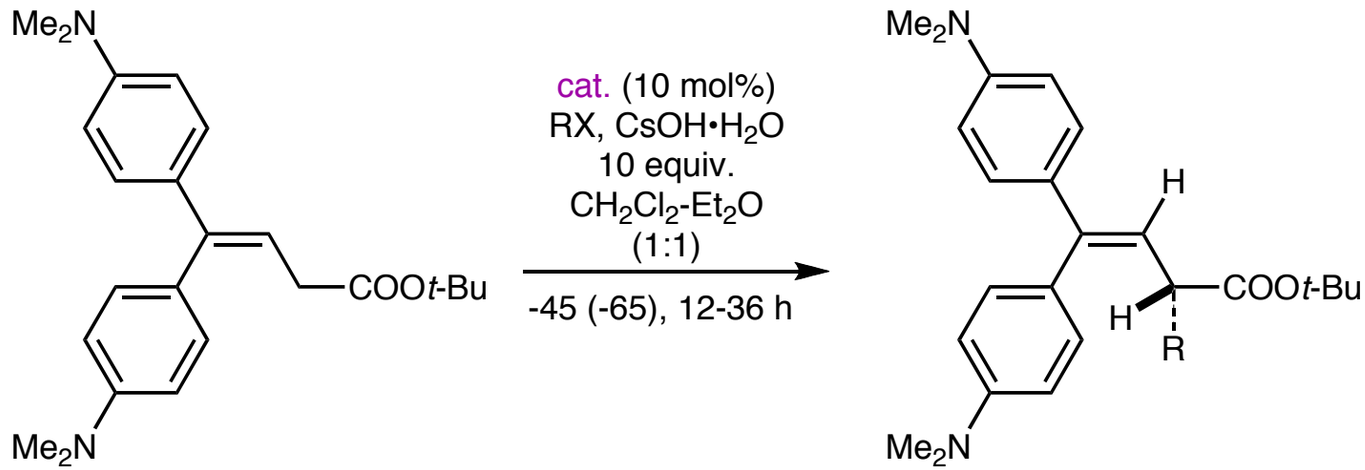
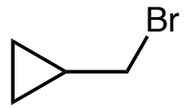
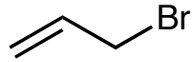
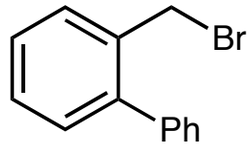
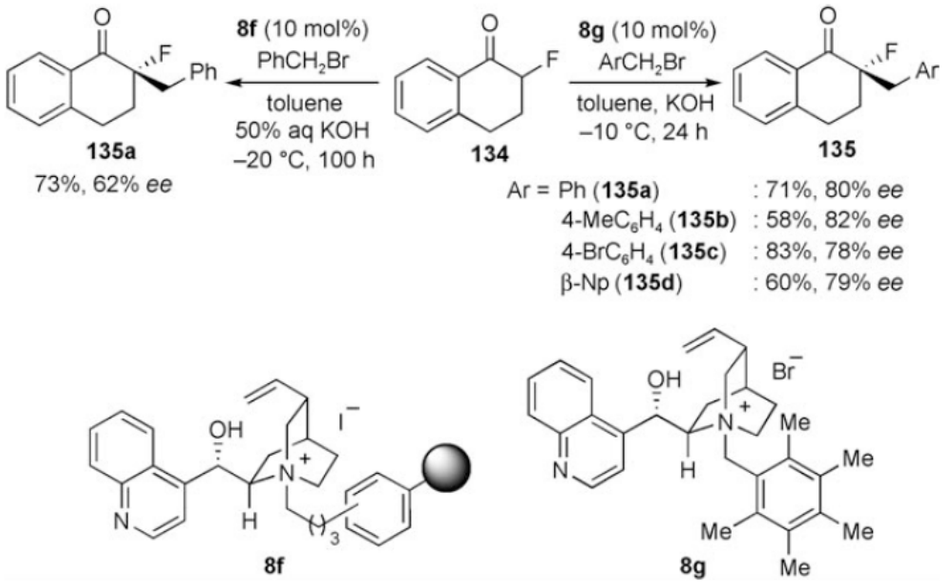
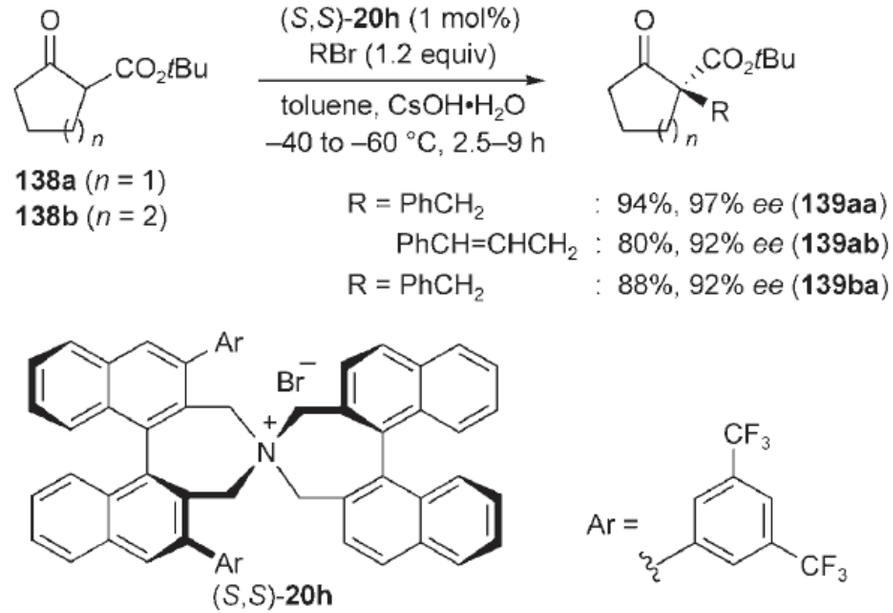


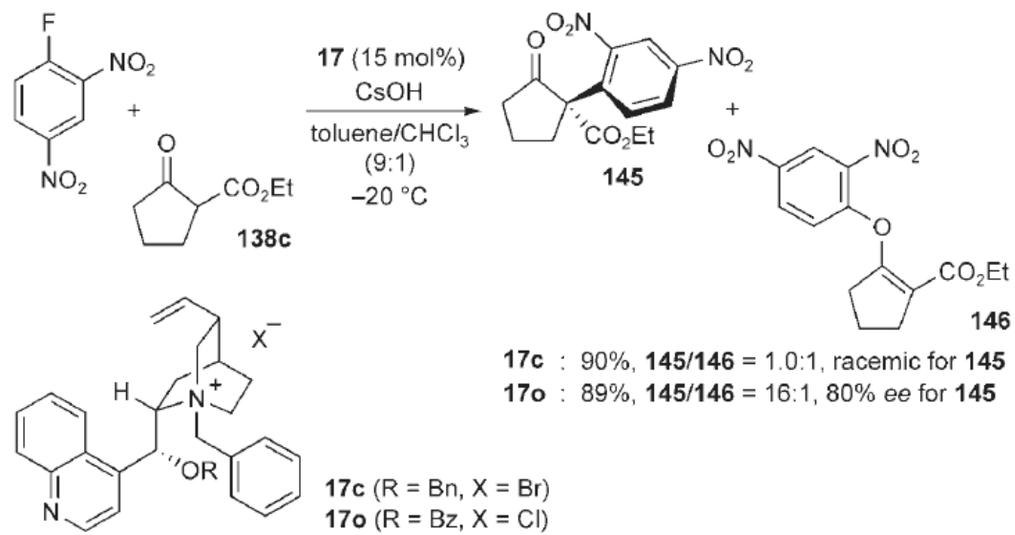
R-X	yield (%)	ee (%)
CH_3I	68	98
BuI	73	95
$Cl(CH_2)_3I$	71	95
	75	99
	76	96
BnBr	83	94
	81	98

PTC Alkylations: Other Applications

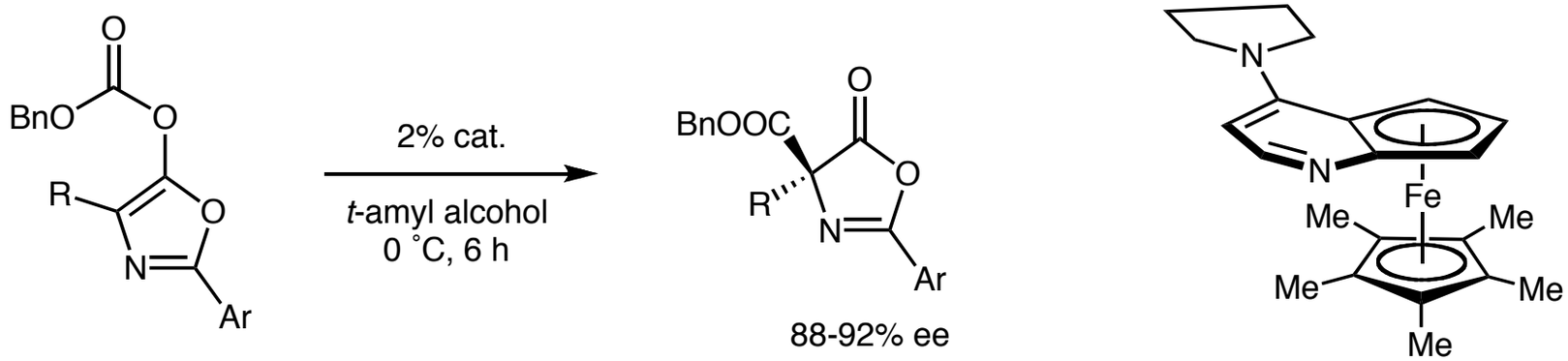


Scheme 78. Asymmetric alkylation of α-fluorotetralone **134**.

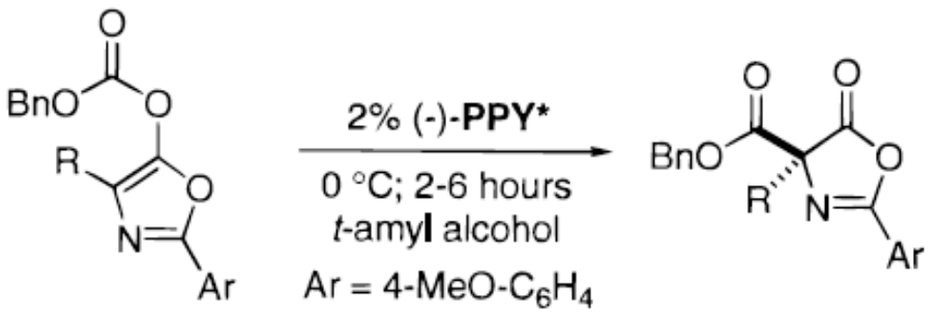




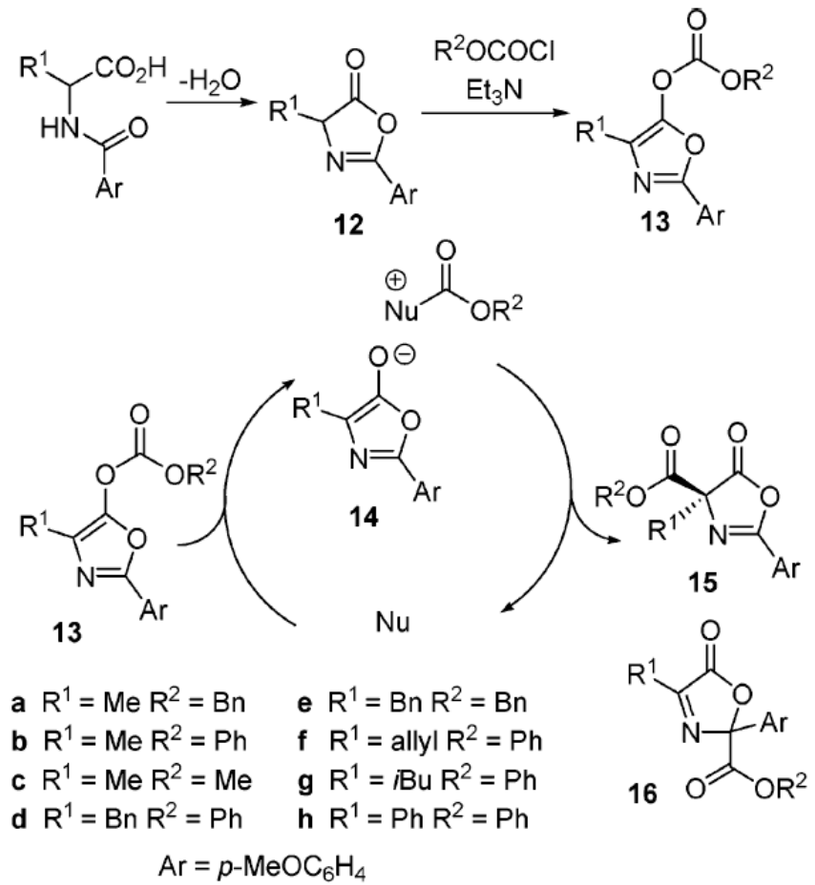
Carboxylation of Enolates



Scheme 2. Steglich Rearrangement

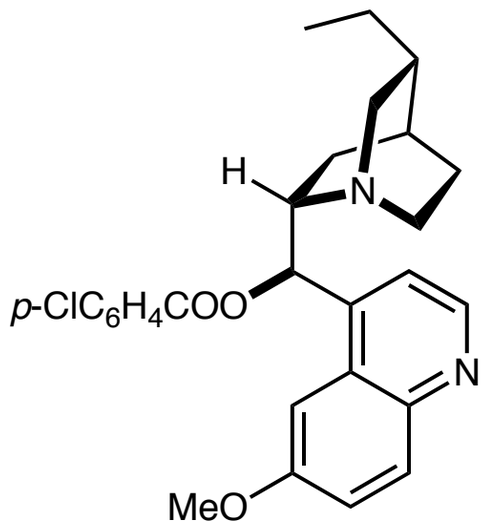


R	% ee	% yield
Me	91	94
Et	90	93
CH_2Ph	90	93
allyl	91	93
CH_2CHMe_2	92	95
CH_2CH_2SMe	88	94

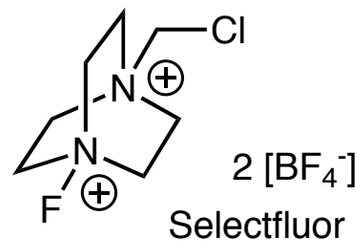


Fu, G. C., *J. Am. Chem. Soc.* **1998,** 120, (44), 11532

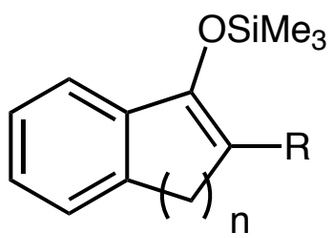
A.2.4 Enolate Chemistry: Halogenation



DHQB

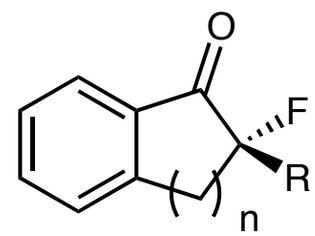


Chiral Flurorinating Reagent



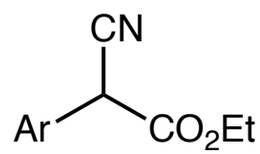
DHQB/Selectfluoro

MeCN
-20 ˚C, overnight



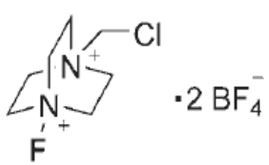
42-91% ee
71-99% yield

R = Bn, Me, Et, COOEt
n = 1, 2

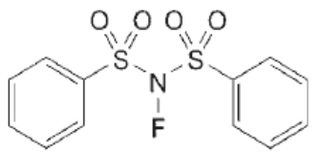


76-83% ee

Organocatalytic Fluorination Reactions

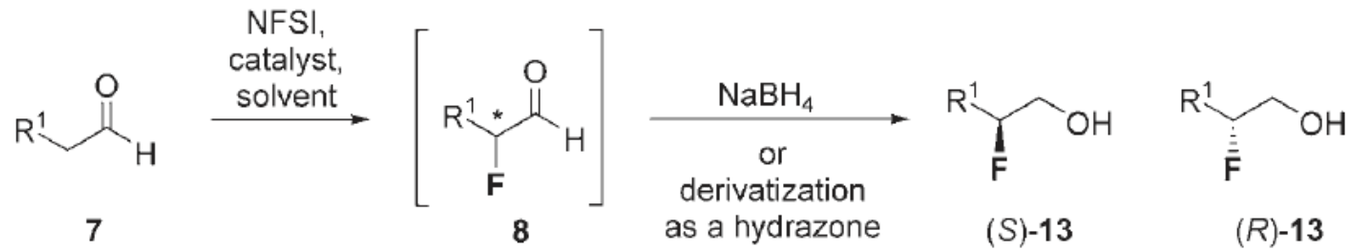


1: Selectfluor

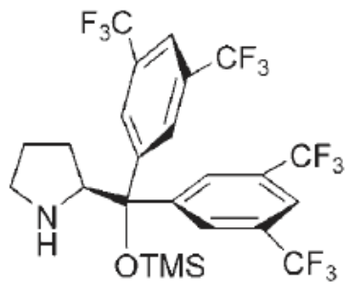


2: *N*-fluorobenzene-sulfonimide (NFSI)

Scheme 1. Sources of electrophilic fluorine.



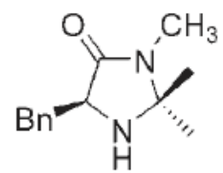
Jørgensen:



14

Conditions:
Catalyst **14** (1 mol%)
MTBE, RT
eight linear aldehydes
55-95% yield, 91-97% *ee* (*S*)

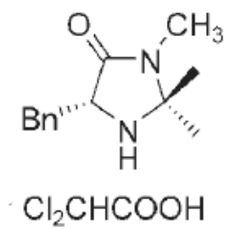
Barbas:



15

Conditions:
Catalyst **15** (30-100 mol%)
DMF, 4 °C
six linear aldehydes
40-90% yield, 86-96% *ee* (*S*)

MacMillan:



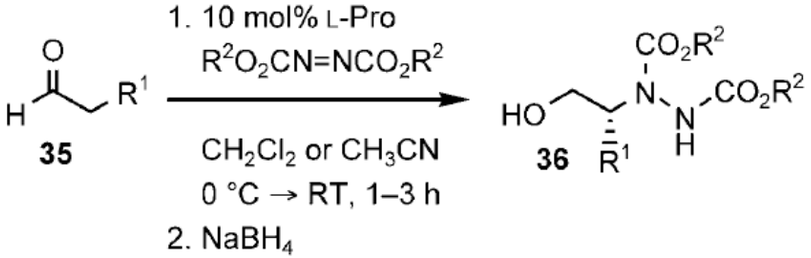
16

Conditions:
Catalyst **16** (20 mol%)
THF/*i*PrOH (9:1), -10 °C
nine linear aldehydes,
54-96% yield, 91-99% *ee* (*R*)

Scheme 5. Highly enantioselective organocatalytic α-fluorination of aldehydes from the groups of Jørgensen,[13] Barbas,[14] and MacMillan.[15] Bn = benzyl; TMS = trimethylsilyl.

Barbas, C. F., *Angew. Chem. Int. Ed.* **2005,** 44, 3706. MacMillan, D. W. C., *J. Am. Chem. Soc.* **2005,** 127, 8826.
Jorgensen, K. A., *Angew. Chem. Int. Ed.* **2005,** 44, 3703.

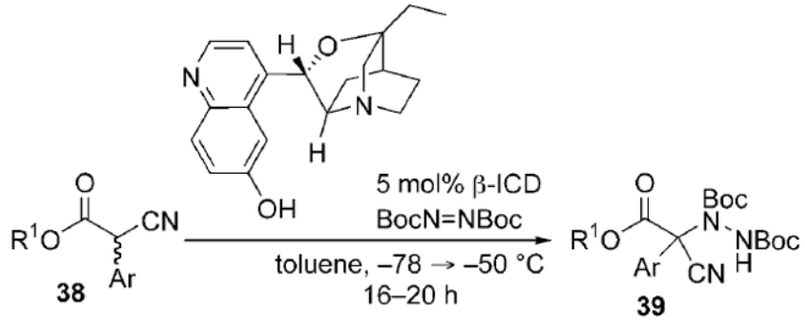
Table 7: α Amination of enolizable aldehydes catalyzed by L-proline.



(14)

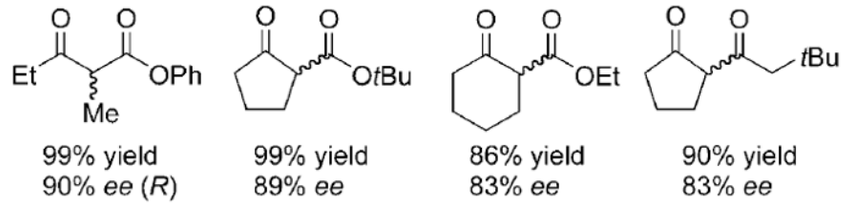
Entry	R^1	R^2	Yield [%]	*ee* [%]
1	Me	Et	67	93
2	Et	Et	77	95
3	*i*Pr	Et	83	93
4	*t*Bu	Et	57	91
5	allyl	Et	92	93
6	Bn	Et	68	89
7	*i*Pr	Bn	99	96
8	*n*Pr	Bn	93	95
9	*n*Bu	Bn	94	97
10	Me	Bn	97	95
11	Bn	Bn	95	95

Table 8: α Amination of α-cyanoacetates catalyzed by β-isocupreidine.



(15)

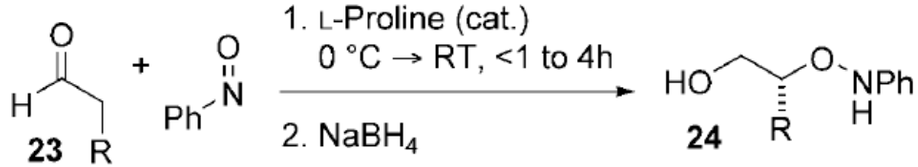
Entry	Ar	Yield [%]	*ee* [%]
1	Ph	99	>98
2	2-F-C_6H_4	99	98
3	3-Me-C_6H_4	99	97
4	4-Cl-C_6H_4	99	98
5	4-NO_2-C_6H_4	99	91
6	4-MeO-C_6H_4	95	89
7	2-naphthyl	99	98
8	2-thienyl	99	97



Scheme 7. α Amination of β-dicarbonyl compounds.

Catalytic Asymmetric Hydroxylation of Enolates: Organocatalysis

Table 5: α Oxygenation of enolizable aldehydes catalyzed by L-proline.

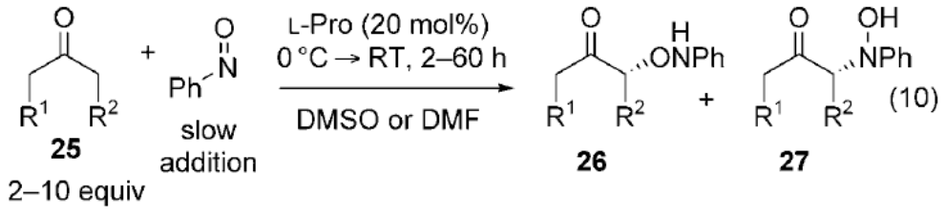


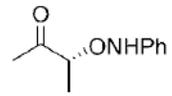
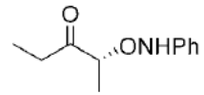
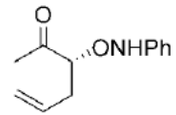
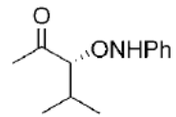
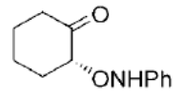
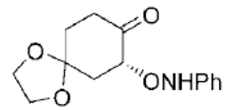
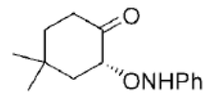
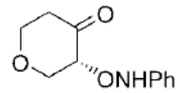
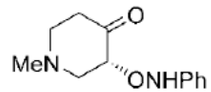
Entry	R	Solv.	L-Proline [mol %]	Yield [%]	*ee* [%]
1	Me	$CHCl_3$	5	88	97
2	*n*Bu	$CHCl_3$	5	79	98
3	*i*Pr	$CHCl_3$	5	85	99
4	$CH_2CH{=}CH_2$	$CHCl_3$	5	80	99
5	Bn	$CHCl_3$	5	95	97
6	Ph	$CHCl_3$	5	60	99
7	$(CH_2)_2OTIPS$[a]	$CHCl_3$	5	76	98
8	(*N*-methylindol-3-yl)methyl	$CHCl_3$	5	83	98
9	*n*Pr	DMSO	20	71	99
10	$CH_2{=}CHCH_2CH_2$	DMSO	20	73	99
11	$BnOCH_2$	DMSO	20	54	99
12	$BocNH(CH_2)_4$	DMSO	20	61	94
13	Et	CH_3CN	30	87	99

TIPS = triisopropylsilyl.

Catalytic Asymmetric Hydroxylation of Enolates: Organocatalysis

Table 6: α Oxygenation of ketones catalyzed by L-proline.



Entry	Product **26**	**26**/**27**	Yield [%]	*ee* [%]
1		81:19	93	> 99
2		98:2	66	99
3		88:22	87	> 99
4		90:10	64	> 99
5		> 99:1	91	> 99
6		> 99:1	96	> 99
7		> 99:1	84	> 99
8		> 99:1	53	96
9		> 99:1	44	99

Proline Catalyzed Amination

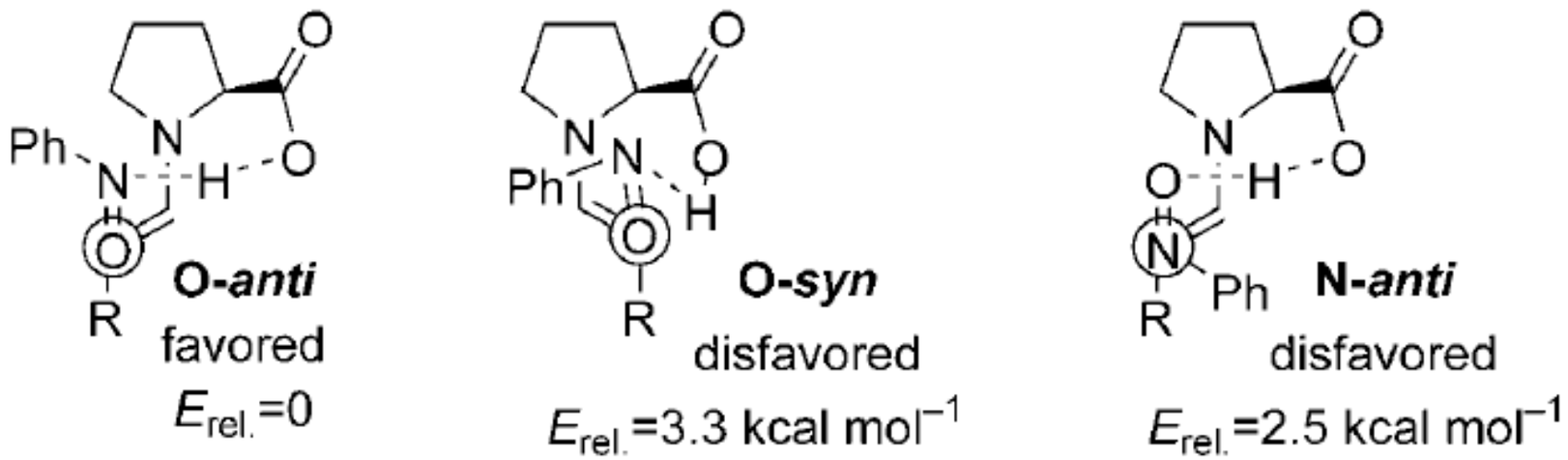
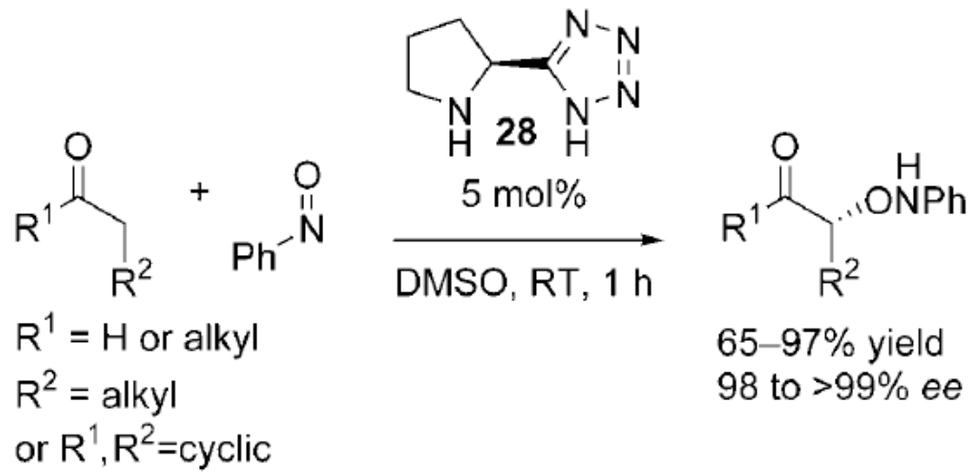
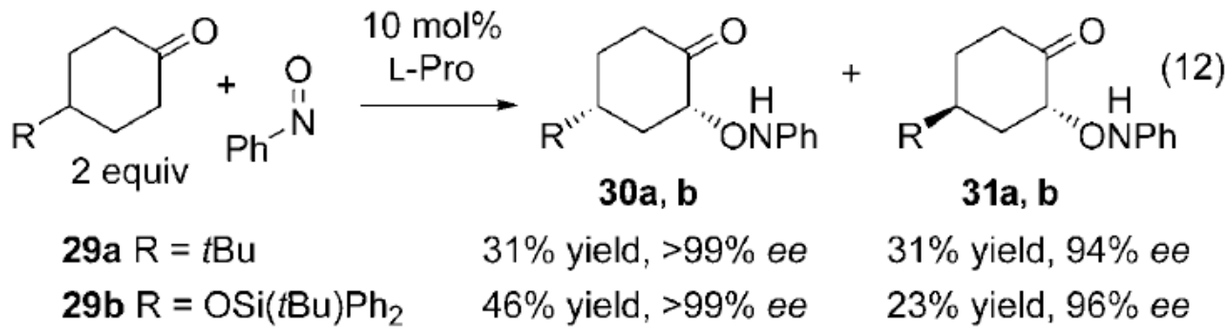


Figure 5. Possible transition state in the reaction of a proline enamine with nitrosobenzene.

Catalytic Asymmetric Hydroxylation of Enolates: Organocatalysis





Proc. Natl. Acad. Sci. U. S. A. **2004,** 101, (15),