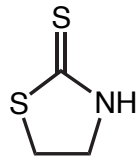
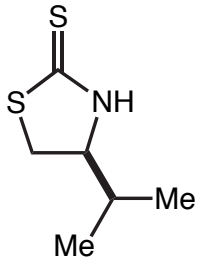
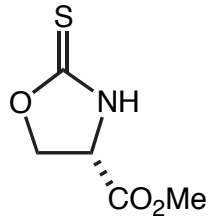
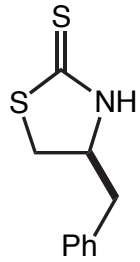
Thione-Based Auxiliaries in Organic Synthesis







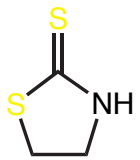


An Evans Group Evening Seminar

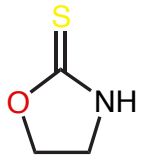
Wade Downey

Friday, March 1, 2002

Thione-Based Auxiliaries in Organic Synthesis



Thiazolidinethione



Oxazolidinethione

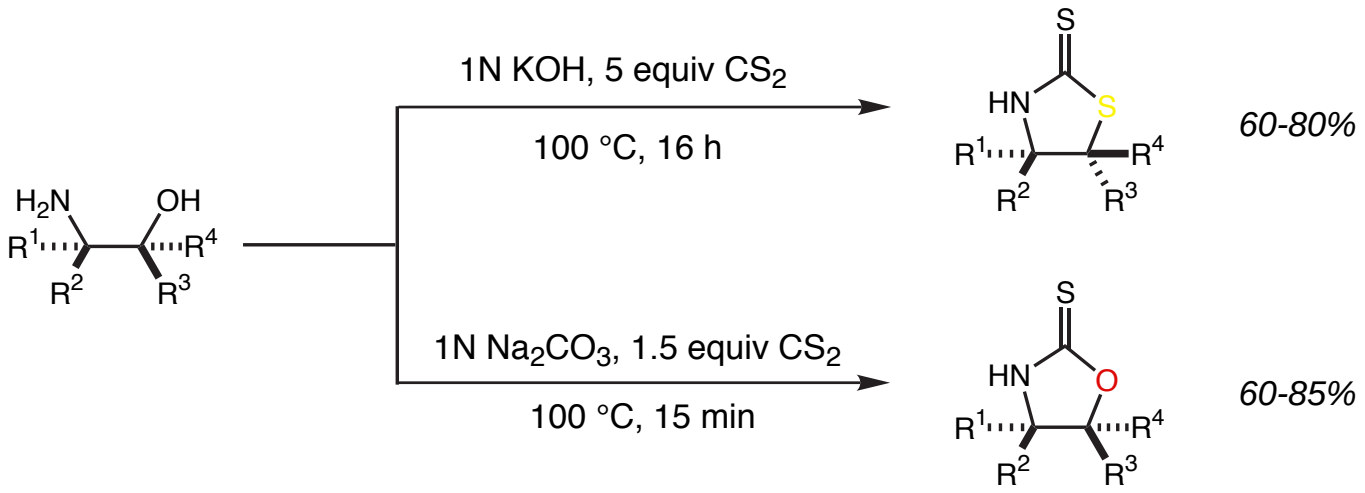
Seminar Scope

1. Auxiliary synthesis
2. Half-reduction
3. Amine acylation
4. Aldol-type reactions
5. Iminium additions
6. Other reactions
   a. Claisen condensation
   b. Diels-Alder
   c. Rearrangements
   d. Selenylation
   e. Reductive coupling
   f. Photochemistry

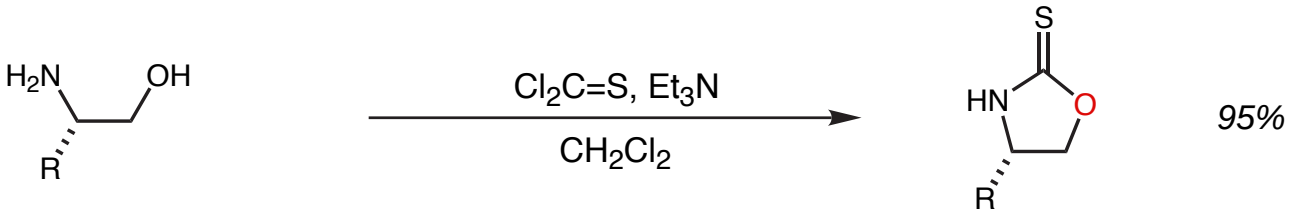
Relevant Reviews:

Fujita, E.; Nagao, Y. *Adv. Heterocycl. Chem.* **1989**, *45*,1-36.
Mukaiyama, T.; Kobayashi, S. *Org. React.* **1994**, *46*, 1-103.

Auxiliary Synthesis



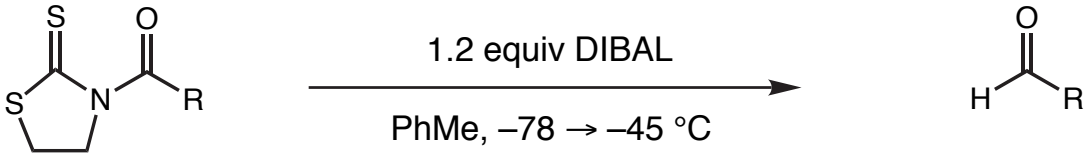
Le Corre, M. *J. Org. Chem.* **1995**, *60*, 6604-6607.



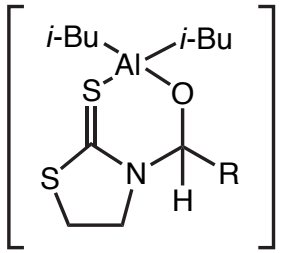
- Thiones were acylated easily with Et_3N and the appropriate acid chloride.

Crimmins, M. *J. Org. Chem.* **2001**, *66*, 894-902.

Half-Reduction: Mukaiyama



R	Yield (%)
$PhCH_2CH_2$	93
$PhCH_2$	64
$CH_3CH_2C(Ph)H$	75
$PhCH_2CH_2CH_2$	90
$Br(CH_2)_9CH_2$	88
Ph	49
$PhCH{=}CH_2$	74

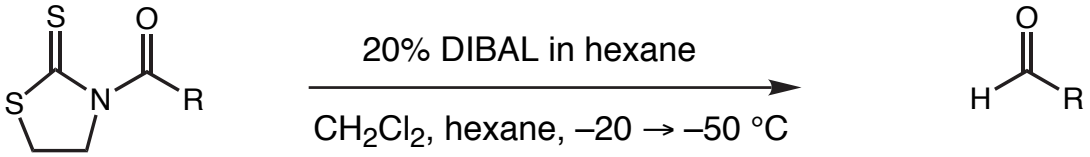


Proposed intermediate

• Comparable yields with tri-*t*-butoxyaluminum hydride

Mukaiyama, T. *Chem. Lett.* **1977**, 1443-1446.
Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979,** *52*, 555-558.

Half-Reduction: Nagao and Fujita

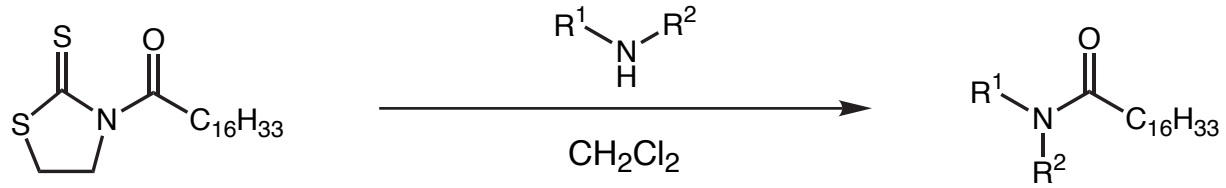


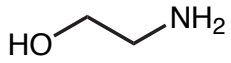
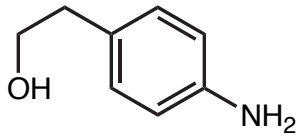
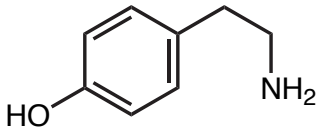
R	Yield (%)
$Me(CH_2)_3CH_2$	54
$Me(CH_2)_7CH_2$	72
$Me(CH_2)_{13}CH_2$	79
Ph	93
$PhCH{=}CH_2$	64

- Yields are comparable to Mukaiyama's.
- DIBAL was "injected dropwise onto a yellow solution . . . until the original yellow colour of the reaction medium vanished."
- Full reduction with $NaBH_4$ proceeded with >90% yields.

Nagao, Y.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1978**, 1443-1446.
Nagao, Y.; Fujita, E. *J. Chem. Soc., Perkin Trans 1* **1980**, 2470-2473.

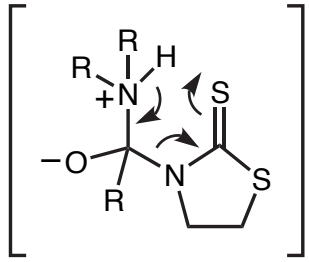
Aminolysis: Nagao and Fujita



R^1	R^2	*t*	Yield (%)
Butyl	H	1 min	96
Cy	H	5 min	92
4-MeC_6H_4	H	6 d	93
Bn	CH_3	8 min	95
–$(CH_2)_4$–		1 min	98
		20 min	91
		7 d	61[a]
		3 min	95[b]

a) solvent = THF
b) solvent = EtOH-THF

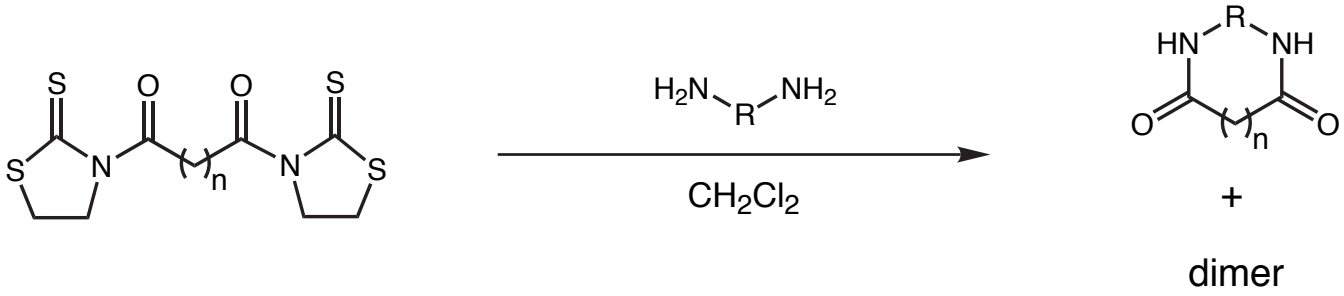
- Similar aminolyses were successful for other *N*-acylated thiones (aryl, alkyl, unsaturated).
- "Stirring was continued until the original yellow color of the solution disappeared."



Proposed Transition State

Nagao, Y.; Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 841-844.

Macrolactamization: Nagao and Fujita

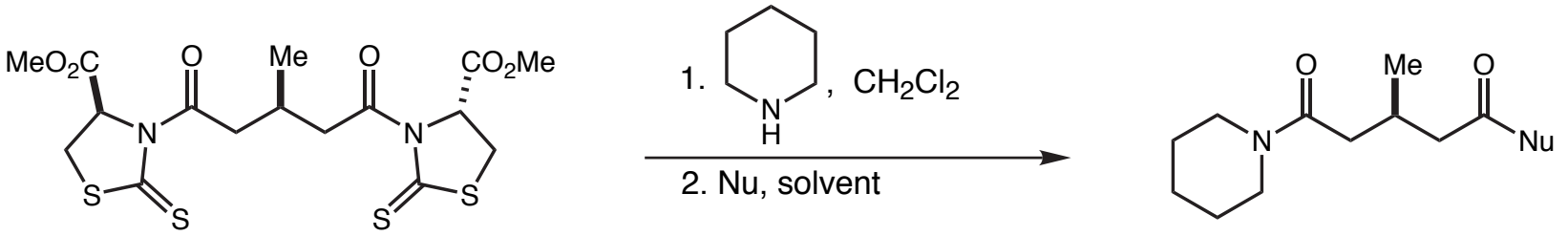


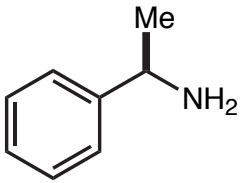
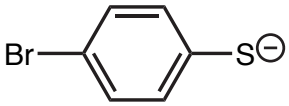
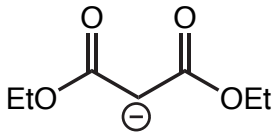
n	R	Monomer Yield (%)	Dimer Yield (%)
2	$-(CH_2)_2-$	0	84
4	$-(CH_2)_4-$	0	80
8	$-(CH_2)_6-$	66	12
12	$-(CH_2)_6-$	83	8
8	$-(CH_2)_3NH(CH_2)_4-$	89	0
12	$-(CH_2)_3NH(CH_2)_4-$	85	5

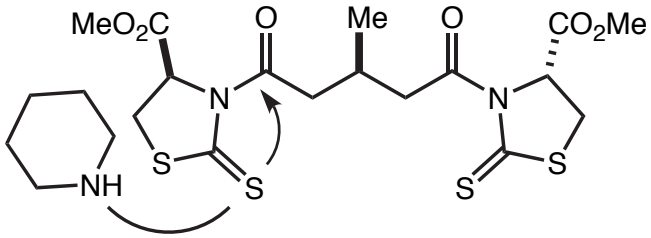
- This process has been to applied to the total synthesis of codonocarpine, lunarine, and lunaridine.

Nagao, Y.; Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 4931-4934.
Nagao, Y.; Fujita, E. *Chem. Lett.* **1980**, 159-162.
Fujita, E. *Pure Appl. Chem.* **1981**, *53*, 1141-1154.
Nagao, Y.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1981**, 286-287.
Nagao, Y.; Fujita, E. *Heterocycles* **1981**, *15*, 1037-1040.

Desymmetrization: Nagao and Fujita



Nu	Solvent	Yield (%)
	CH_2Cl_2	69
	THF	72
	THF	63
	THF	73



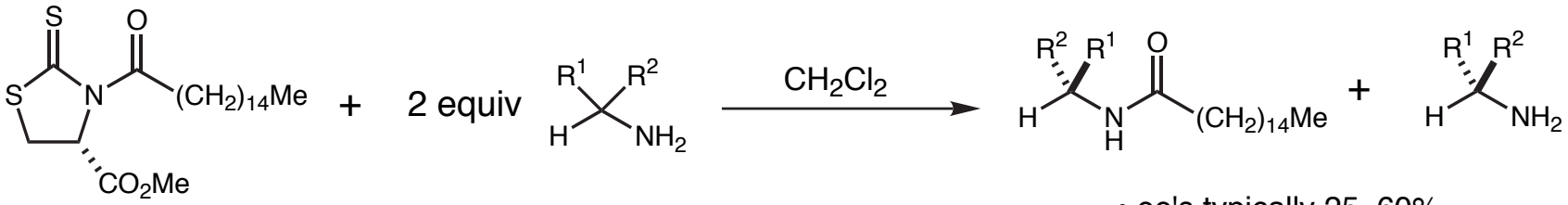
Proposed Model: First nucleophile attacks least favored hindered of four carbonyl faces.

- Dipole-minimized structure supported by crystal structure
- Initial amide product isolable (*74% yield, 10:1 dr)*

Nagao, Y.; Fujita, E. *J. Am. Chem. Soc.* **1982**, *104*, 2079-2081.
Nagao, Y.; Fujita, E. *J. Org. Chem.* **1983**, *48*, 132-133.
Nagao, Y.; Fujita, E. *Tetrahedron* **1984**, *40*, 1215-1223.

Aminolysis: Nagao and Fujita

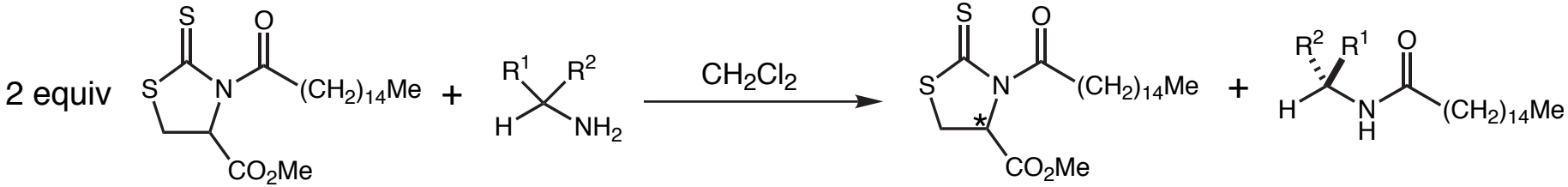
Kinetic Resolution of Racemic Amines



- ee's typically 25–60%
- yield of amides >90%

Nagao, Y.; Fujita, E. *Tetrahedron Lett.* **1982**, *23*, 201-204.

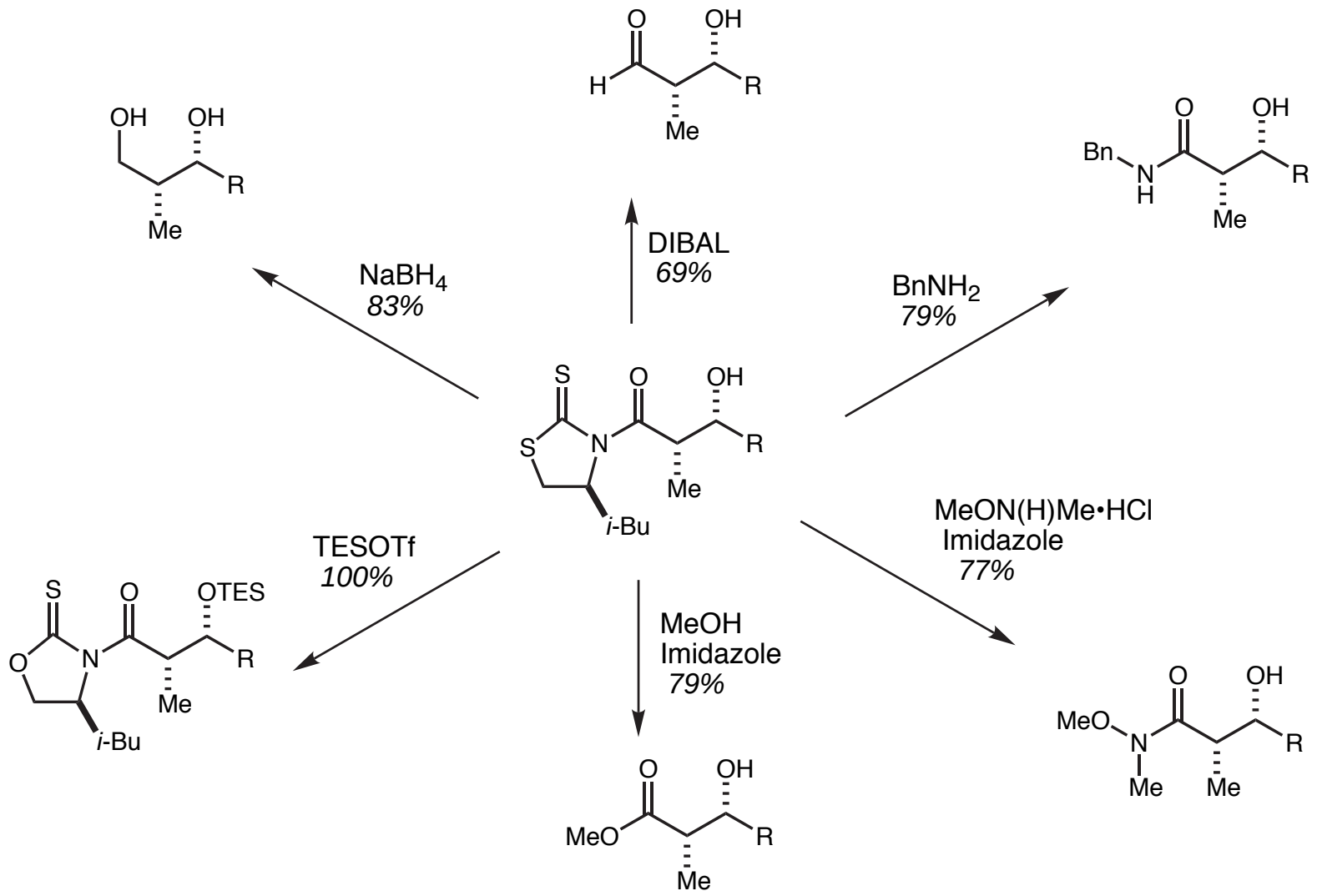
Absolute Structure Determination of Amines



- Rotation of recovered thione starting material indicates absolute structure of starting amine.

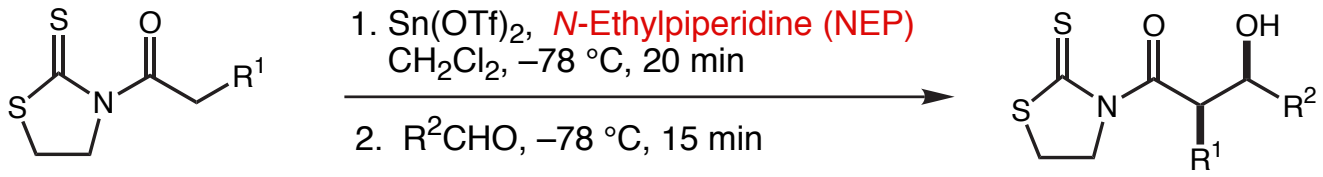
Nagao, Y.; Fujita, E. *Tetrahedron Lett.* **1982**, *23*, 205-208.

Thiazolidinethione Adduct Derivatization



Crimmins, M. *Org. Lett.* **2000**, *2*, 775-777.

Aldol: Mukaiyama

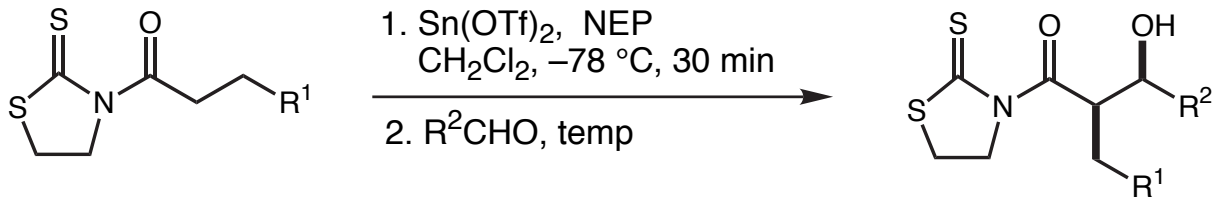


R^1	R^2	Yield (%)	syn:anti
H	Ph	90	–
	$BnCH_2$	88	–
	i-Pr	94	–
Me	Ph	94	32:1
	$BnCH_2$	91	32:1
	i-Pr	95	32:1
$BnCH_2$	Ph	88	32:1
	$BnCH_2$	95	32:1

- Prior to this report, Mukaiyama had used these enolization conditions extensively for crossed aldols of ketones.
- dr's were determined by ^{13}C NMR.

Mukaiyama, T. *Chem. Lett.* **1982**, 1903-1906.

Other Enolates: Mukaiyama

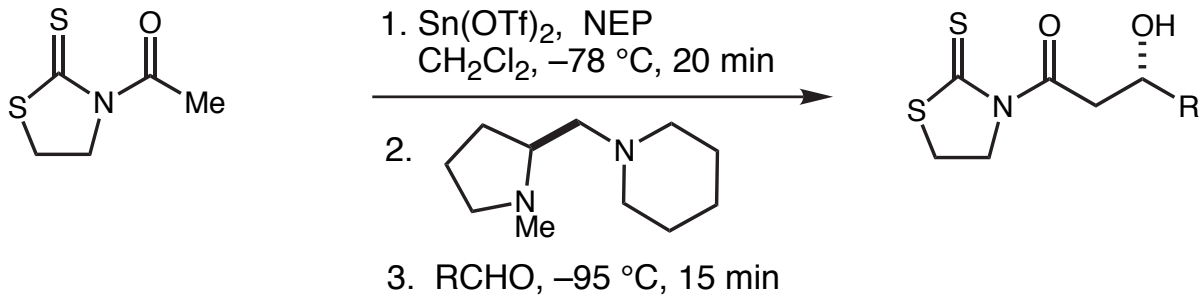


R^1	R^2	Yield (%)	syn:anti
MeO (–78 °C)	Ph	95	1:3
	$BnCH_2$	82	5:1
	$PhCH{=}CH_2$	73	1:1
	i-Pr	68	2:1
	Pentyl	77	6:1
Cbz(Bn)N (–40 °C)	Ph	83	9:1
	$BnCH_2$	99	19:1
	Me	97	19:1
	Pentyl	99	19:1
Boc(Bn)N (–40 °C)	Ph	94	9:1
	$BnCH_2$	96	19:1
	Me	99	19:1
	i-Pr	82	19:1
	Pentyl	98	19:1

- No elimination products were observed.
- No mention of results with chiral ligand
- This methodology was employed in the total synthesis of (±)-thienamycin.

Mukaiyama, T. *Chem. Lett.* **1985**, 1045-1048.

Aldol: Mukaiyama

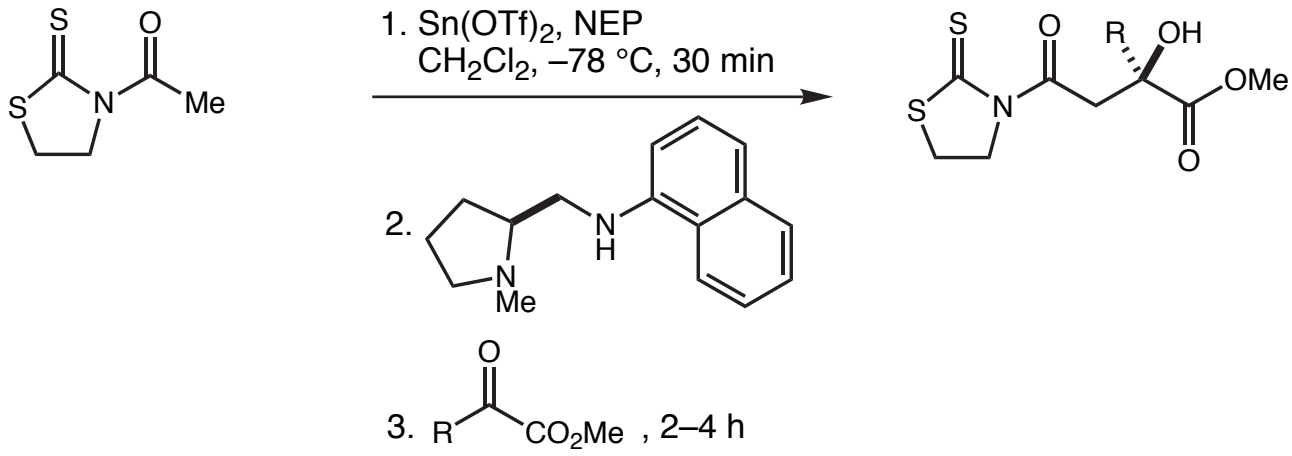


R	Yield (%)	ee (%)
Ph	79	65
$BnCH_2$	76	90
Et	70	90
i-Pr	63	90
Pentyl	65	90
Cy	81	88

- Absolute stereochemistry proven only for benzaldehyde adduct
- Prior to this report, the "Mukaiyama Ligand" had been used for enantioselective crossed aldols and ketone homoaldols.

Mukaiyama, T. *Chem. Lett.* **1983**, 297-298.

Pyruvate Aldol: Mukaiyama

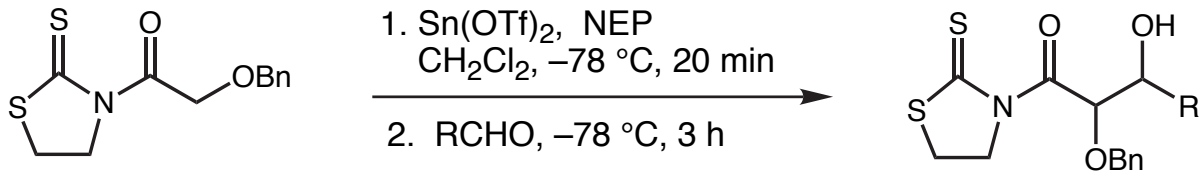


R	Yield (%)	ee (%)
Ph	78	95
Me	74	85
i-Pr	75	95
i-Bu	65	95
$MeO_2C(CH_2)_2$	80	95

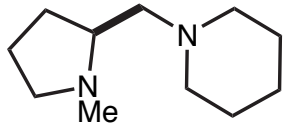
- Previous aldol ligand afforded only 18% ee.
- A scan of ligands showed the 1-naphthyl moiety to be superior to cyclohexyl, phenyl, 2,6-xylyl, and 2-naphthyl.
- ee's determined by use of chiral shift reagent

Mukaiyama, T. *Chem. Lett.* **1983**, 1799-1802.

Aldol: Mukaiyama



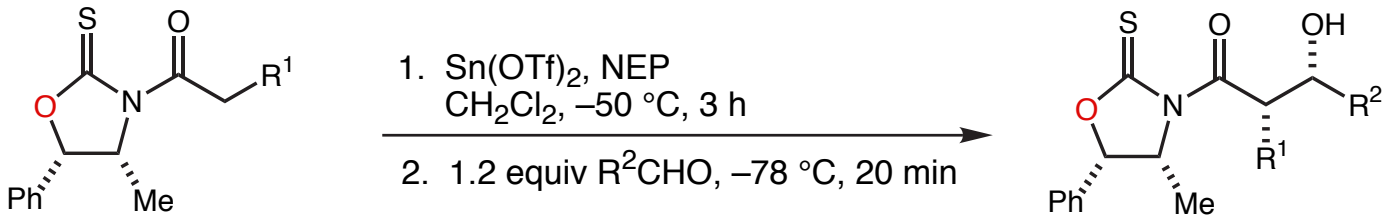
R	L*	Yield (%)	syn:anti	ee (%)
Ph	none	95	1:3	–
$BnCH_2$		62	3:1	–
i-Pr		60	1.6:1	–
Pentyl		62	3:1	–
Cy		74	1.3:1	–
Ph	**1**	93	1:4	90
$BnCH_2$		81	1:7	94
i-Pr		70	1:10	87
Pentyl		75	1:4.9	90
Cy		68	1:13	87

1 = 

- TMEDA as ligand resulted in diastereoselectivity similar to that induced by the chiral ligand.
- Note that even in the absence of ligand, PhCHO is anti selective.

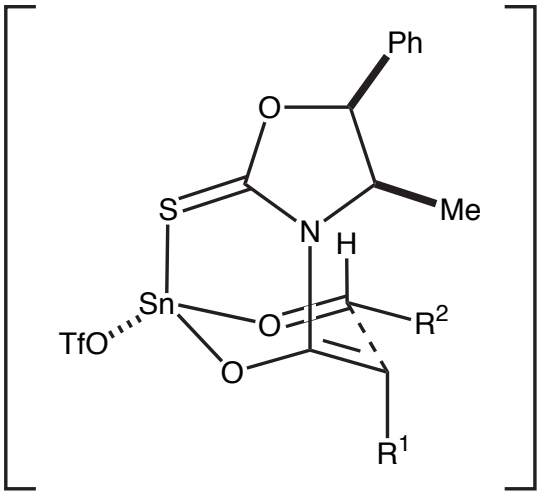
Mukaiyama, T. *Chem. Lett.* **1984**, 753-756.

Aldol: Nagao and Fujita



Non-Evans syn!

R^1	R^2	dr	Isolated Yield (%)
H	Me	3.2:1	62
H	Pr	4.5:1	64
H	*i*-Pr	8:1	68
Me	*i*-Pr	10:1	71
Me	Ph	5:1	65

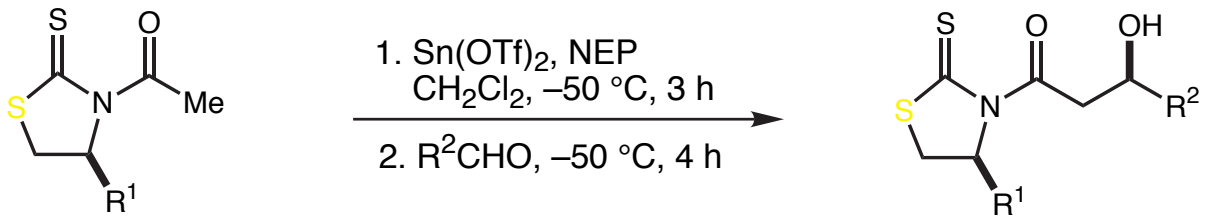


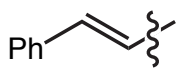
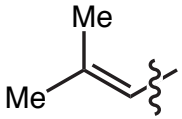
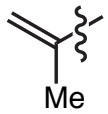
Proposed Transition State

- Chelated transition-state structure predicts "Non-Evans" selectivity.
- Enolization conditions from Mukaiyama
- Mukaiyama also postulates a chelated transition state for his racemic tin-mediated aldol.

Nagao, Y.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418-1419.

Acetate Aldol: Nagao and Fujita

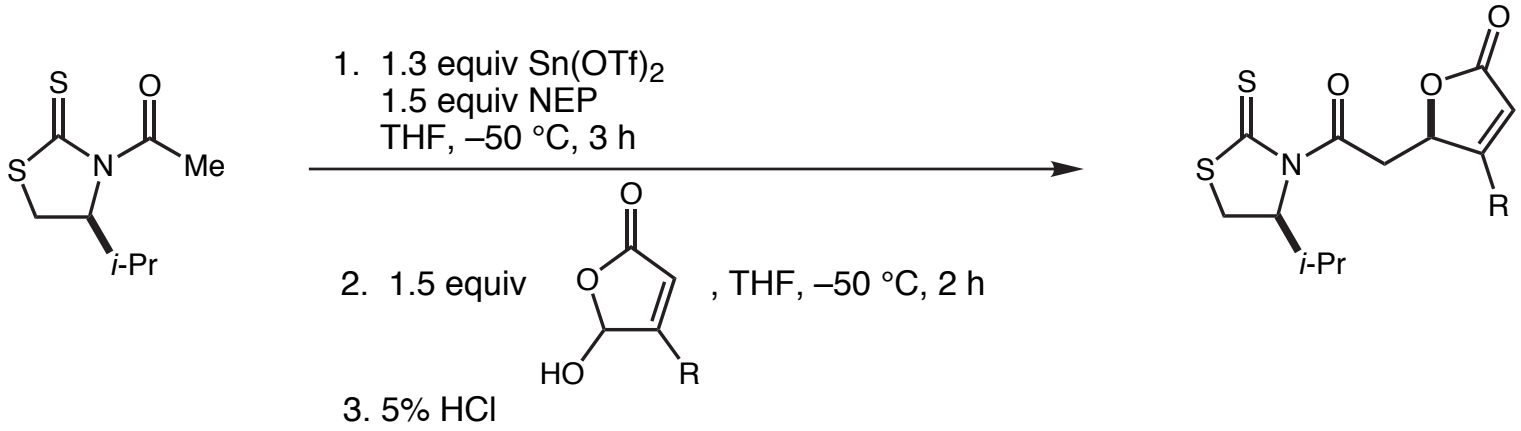


R^1	R^2	dr	Total Yield (%)
Et		13:1	77
***i*-Pr**		**33:1**	81
Et		8:1	72
***i*-Pr**		**36:1**	70
Et		13:1	74

- Note the change to thiazolidinethione auxiliary.
- A footnote suggests that saturated aldehydes are just as selective.
- 1.2 equiv $Sn(OTf)_2$ and 1.2 equiv NEP were optimal. **Excess base led to dehydration products**. Excess $Sn(OTf)_2$ led to lower yields, presumably due to aldehyde polymerization.
- No mention of propionates

Nagao, Y.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391-2393.

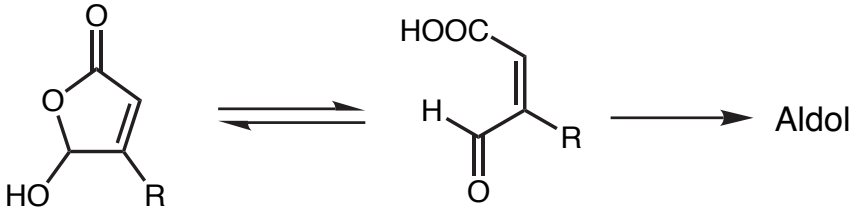
Aldol: Nagao



R	dr	Yield (%)
H	99:1	86
Me	99:1	85
Et	66:1	90
Pr	99:1	85
i-Pr	99:1	93
Ph	99:1	81

- 4-acetoxy lactone is unreactive under the reaction conditions.

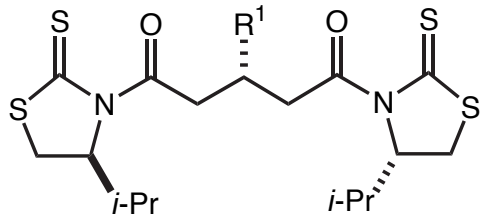
Starting lactone is an aldehyde precursor:



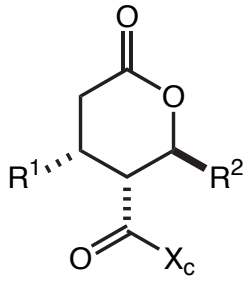
- Lactonization occurs during the acid workup.

Nagao, Y. *J. Org. Chem.* **1989**, *54*, 5211-5217.

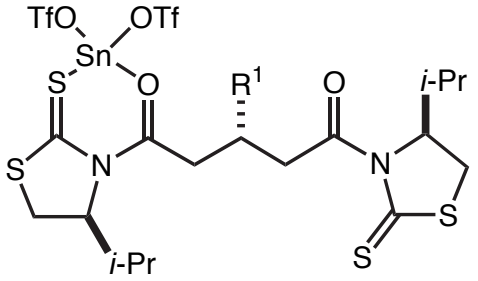
δ-Lactone: Nagao



1. 3.3 equiv $Sn(OTf)_2$
   3.7 equiv NEP
   CH_2Cl_2, –40 °C, 2 h
2. 1.1 equiv R^2CHO, –40 °C, 1 h
3. K_2CO_3, DMF, rt, 1 h



R^1	R^2	Yield (%)
Me	Ph	52
Me	Me	23
Me	*i*-Pr	30
Me	*s*-Bu	22
Me	Hexyl	30
N(Bn)Cbz	Me	25



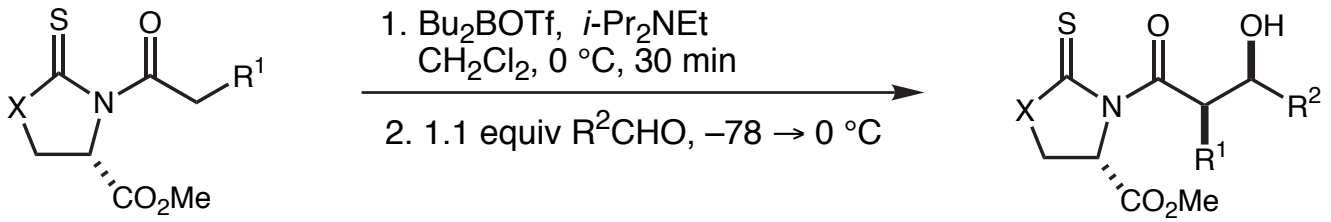
Rationale:

- Initial aldol adduct cyclizes under K_2CO_3/DMF conditions.
- All product lactones were "optically pure" by HPLC and ^1H NMR.
- Starting material recovered in 5-32% yield

- In order to avoid steric repulsion between R^1 and the isopropyl group, Sn may coordinate as shown.
- Dipole-minimized conformation based upon crystal structure

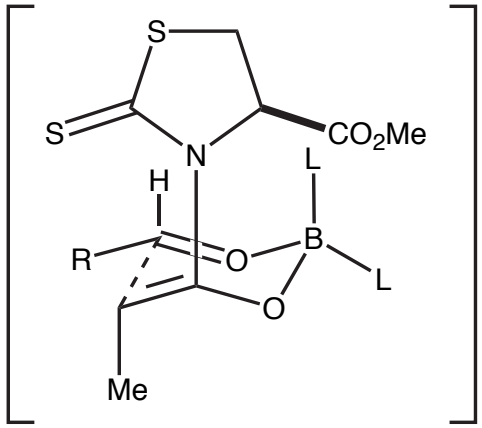
Nagao, Y. *Chem. Lett* **1992**, 335-338.

Aldol: Miller



X	R^1	R^2	Yield (%)	dr
S	Me	Ph	76	66:1
S	Me	*i*-Pr	87	66:1
S	Et	Ph	90	24:1
S	Et	*i*-Pr	85	99:1
S	SPh	Pr	87	99:1
O	Me	Ph	89	99:1
O	Me	*i*-Pr	81	99:1

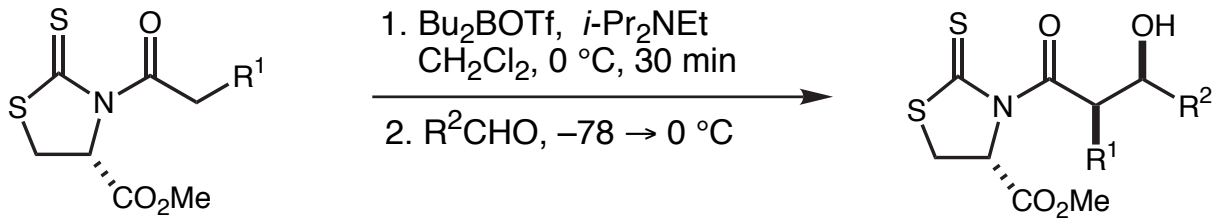
- $Sn(OTf)_2$ afforded "Evans-syn" aldol adducts, unlike the Nagao/Fujita results!
- Absolute stereochemistry was proven by optical rotation of methanolysis products.
- dr is calculated from the ee reported by Miller for the methanolysis products.
- No oxidative workup is required.

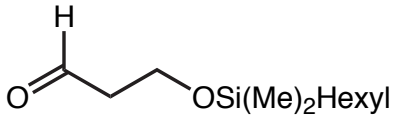
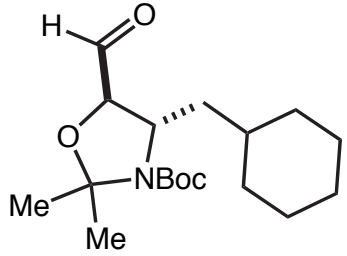


Proposed Transition State

Hsiao, C.; Miller, M. *Tetrahedron Lett.* **1985**, *26*, 4855-4858.
Hsiao, C.; Miller, M. *J. Org. Chem.* **1987**, *52*, 2201-2206.

Aldol: Miller

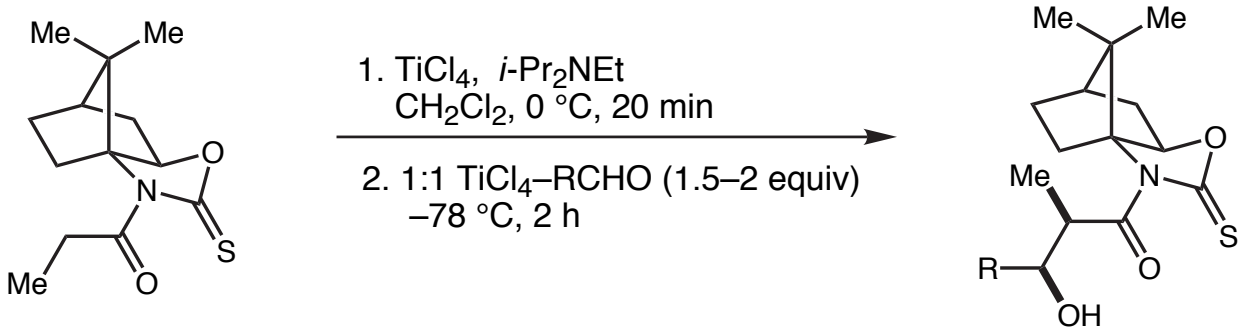


R^1	R^2CHO	Yield (%)	dr
Et		58	99:1
i-Pr		73	ND
$CH_2CH{=}CH_2$	MeCHO	28	ND

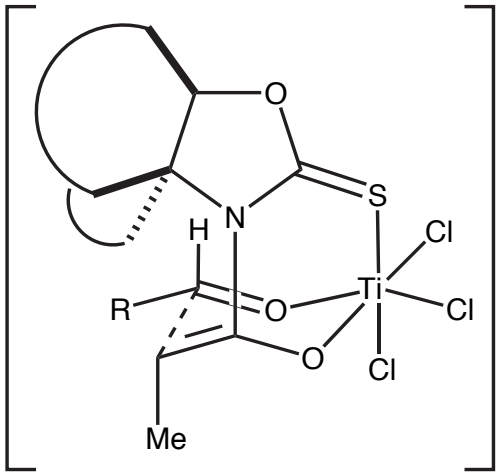
- The Miller system appears to be compatible with functionalized aldehydes and enolates.

Miller, M., *Tetrahedron* **1990**, *46*, 8067-8074.
Boyd, S.; Hsiao, C. *J. Org. Chem.* **1991**, *56*, 438-442.
Miller, M., *Tetrahedron Lett.* **1991**, *32*, 2577-2580.

Aldol: Yan



R	Yield (%)	dr
Ph	84	32:1
Pr	82	99:1
MeCH=CH	83	99:1
i-Pr	88	50:1

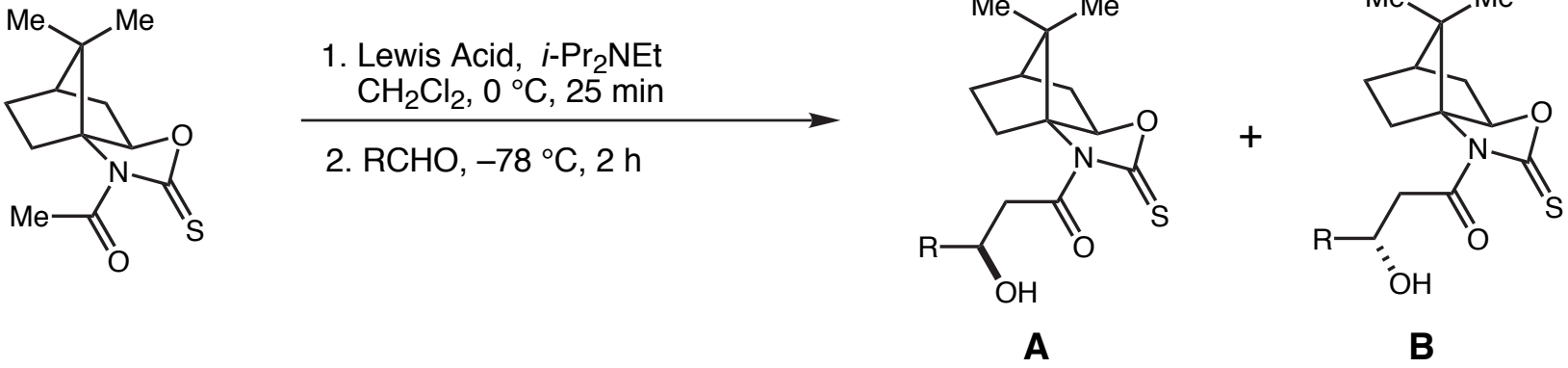


Proposed Transition State

- Corresponding oxazolidinones, under the same conditions, afforded ~1:1 mixture of epimers at the α-carbon.
- Boron enolates yield Evans syn products in high dr. Lithium enolates yield Non-Evans syn products (dr = 2-9:1).
- A subsequent paper showed that aldehyde-$TiCl_4$ complex was unnecessary for Non-Evans syn selectivity.

Yan, T. *Tetrahedron Lett.* **1991**, *32*, 5563-5566.
Yan, T. *Tetrahedron Lett.* **1993**, *34*, 3559-3562.
Yan, T. *J. Am. Chem. Soc.* **1993**, *115*, 2613-2621.

Acetate Aldol: Yan

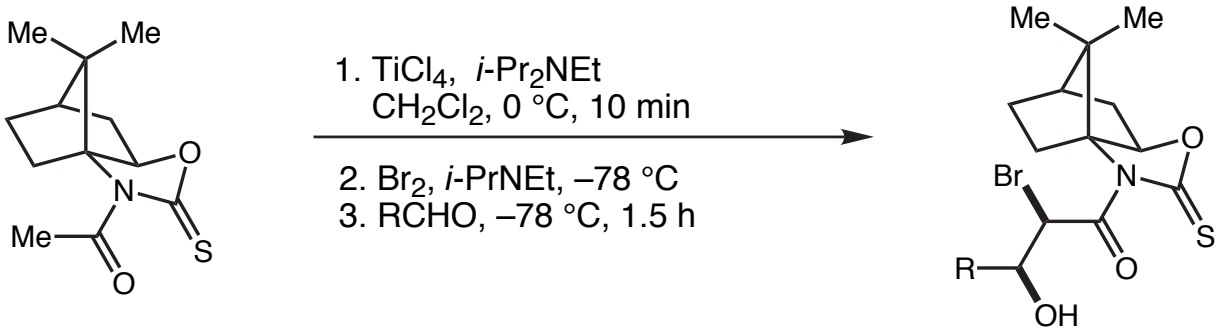


Lewis Acid	R	Yield (%)	A:B
Bu_2BOTf	Ph	74	1:3
	Pr	83	1:3
	MeCH=CH	69	1:12
	i-Pr	69	1:3
9-BBN(OTf)	Ph	86	24:1
	Pr	88	7:1
	MeCH=CH	84	99:1
	i-Pr	84	6:1
$TiCl_4$	Ph	91	10:1
	Pr	85	19:1
	MeCH=CH	86	13:1
	i-Pr	86	16:1

- The authors propose that the 9-BBN-mediated aldol proceeds through a boat-like transition state, whereas the Bu_2BOTf reaction occurs via the usual chair.
- The titanium-mediated reaction is believed to proceed *via* a chelated transition state.
- Boron enolates of the corresponding oxazolidinone auxiliary show the same trend: Bu_2BOTf affords Evans syn, and 9-BBN(OTf) affords non-Evans syn, although diastereoselectivity is modest (2-3:1).

Yan, T. *J. Org. Chem.* **1994**, *59*, 8187-8191.
Yan, T. *J. Org. Chem.* **1995**, *60*, 3301-3306.

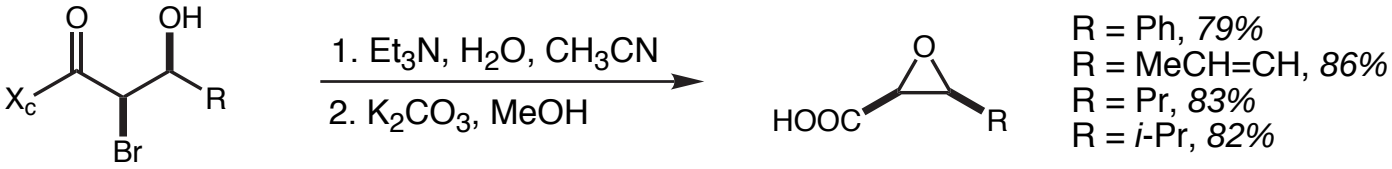
Bromoacetate Aldol: Yan



R	Yield (%)	dr
Ph	94	99:1
MeCH=CH	90	99:1
Pr	91	99:1
i-Pr	91	99:1

• dr determined by 400 MHz ^{1}H NMR

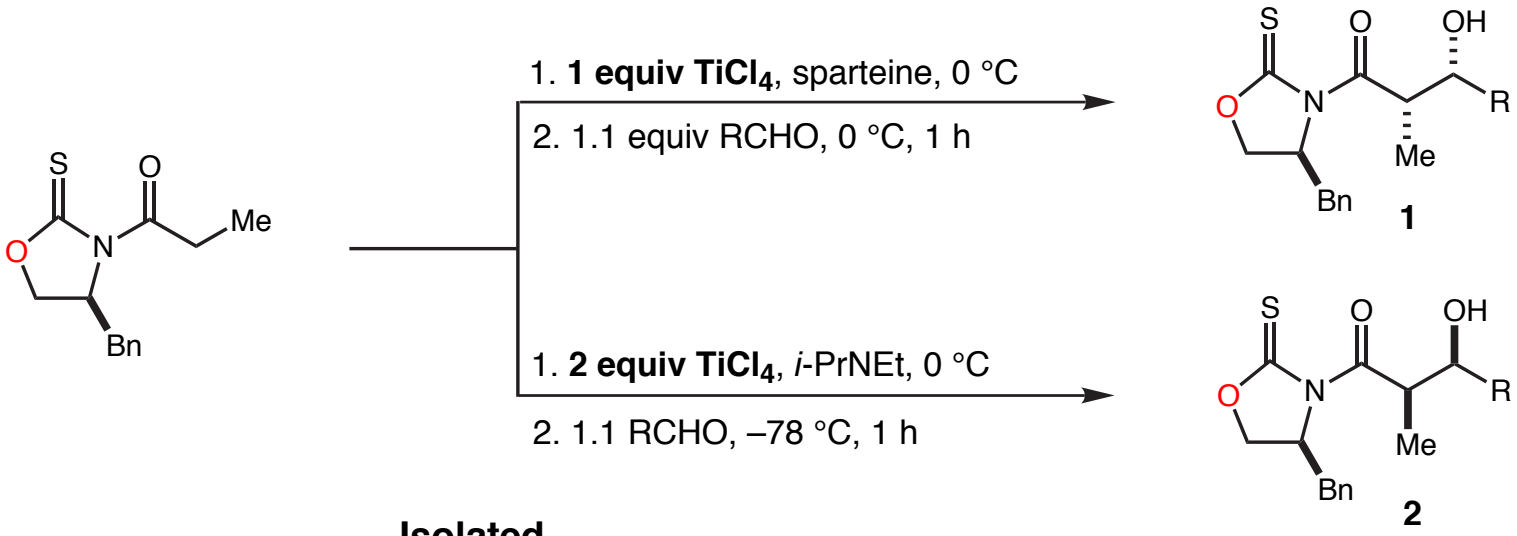
Epoxide Formation:



R = Ph, *79%*
R = MeCH=CH, *86%*
R = Pr, *83%*
R = *i*-Pr, *82%*

Yan, T. *Tetrahedron Lett.* **1999**, *40*, 3577-3580.
Yan, T. *Tetrahedron: Asymmetry* **1999**, *10*, 3249-3251.

Aldol: Crimmins



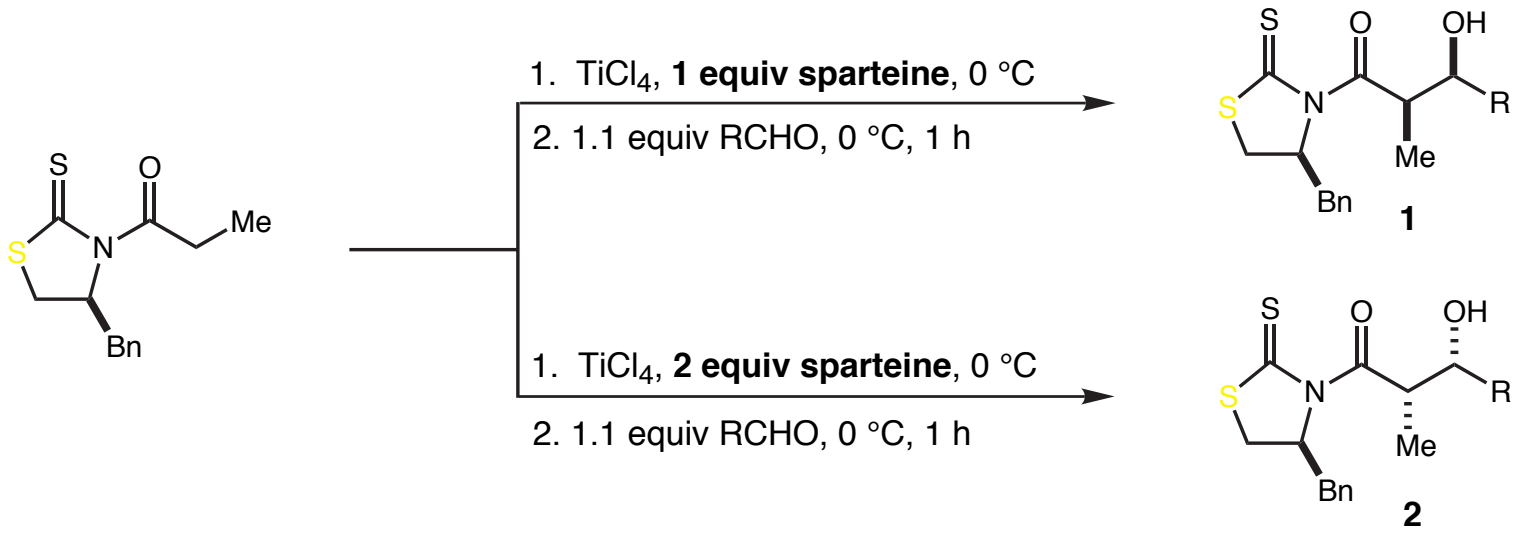
R	$TiCl_4$	Isolated Yield (%)	1:2
Et	1 equiv	80	44:1
i-Pr		90	32:1
Ph		89	36:1
MeCH=CH		65	37:1
CH_2=CH		80	90:1
Et	2 equiv	80	1:22
i-Pr		87	1:19
Ph		88	1:41
MeCH=CH		81	1:18
CH_2=CH		44	1:99

a) Reaction at –78 °C

- NMR experiments suggest that a different enolate species forms upon addition of second equivalent of $TiCl_4$.
- Hunig's base or TMEDA in the place of sparteine resulted in lower yields (50-60%) but similar selectivity.
- The chirality of sparteine was shown to have no impact on diastereoselectivity.

Crimmins, M.; King, B.; Tabet, E. *J. Am. Chem. Soc.* **1997**, *119*, 7883-7884.

Aldol: Crimmins

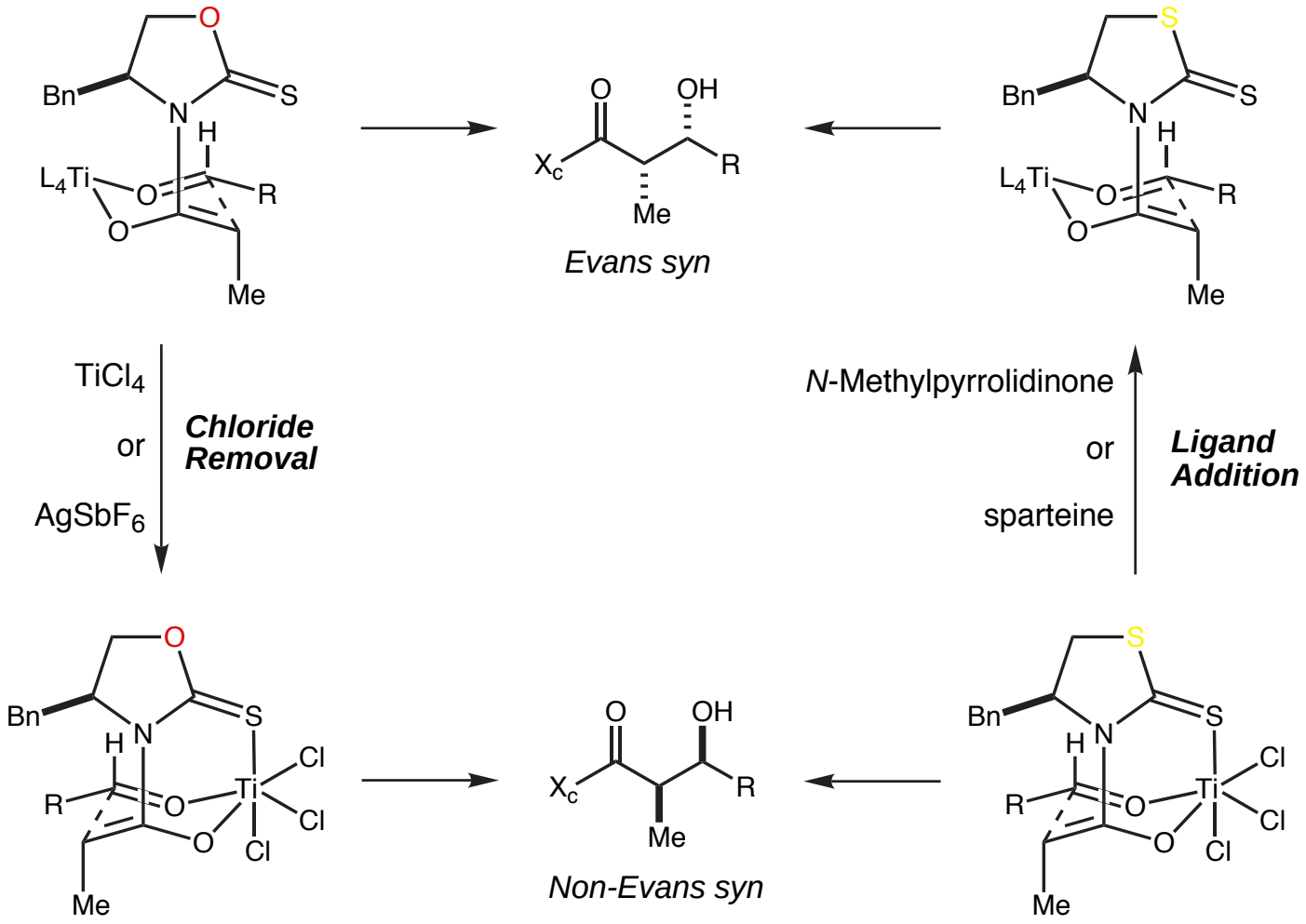


base	R	Yield (%)	1:2
1 equiv	*i*-Bu	57	22:1
	i-Pr	60	19:1
	Ph	52	41:1
	MeCH=CH	45	18:1
	CH_2=CH	49	142:1
2 equiv	*i*-Bu	71	1:44
	i-Pr	75	1:32
	Ph	62	1:36
	MeCH=CH	64	1:37
	CH_2=CH	77	1:90

- Use of *i*-Pr_2NEt as base resulted in lower selectivity (typically 10:1).
- Use of TMEDA in the place of sparteine caused no significant change in selectivity, but lowered yields ~10%.
- Changes in Lewis acid stoichiometry had no effect on diastereoselectivity.

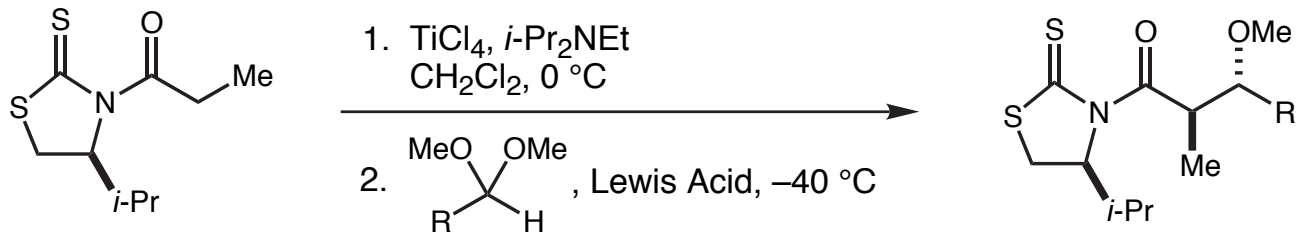
Crimmins, M. *Org. Lett.* **2000**, *2*, 775-777.

Aldol: Crimmins

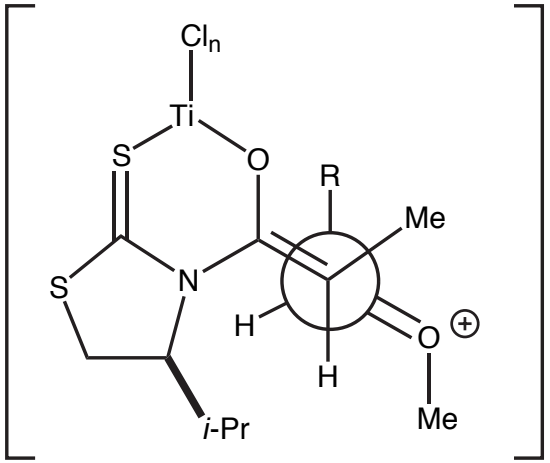


Crimmins, M. *J. Am. Chem. Soc.* **1997**, *119*, 7883-7884.
Crimmins, M. *Org. Lett.* **2000**, *2*, 775-777.
Crimmins, M. *J. Org. Chem.* **2001**, *66*, 894-895.

Acetal Addition: Urpi and Romea



Lewis Acid	T (°C)	R	Isolated Yield (%)	dr
BF_3•OEt_2	–78	Ph	75	6:1
	–78	4-$MeOC_6H_4$	77	4.3:1
	–78	4-ClC_6H_4	81	10:1
$SnCl_4$	–78	4-$NO_2C_6H_4$	70	6:1
	–50	Pr	64	13:1
	–50	*i*-Bu	76	12:1
	–20	*i*-Pr	50	7:1

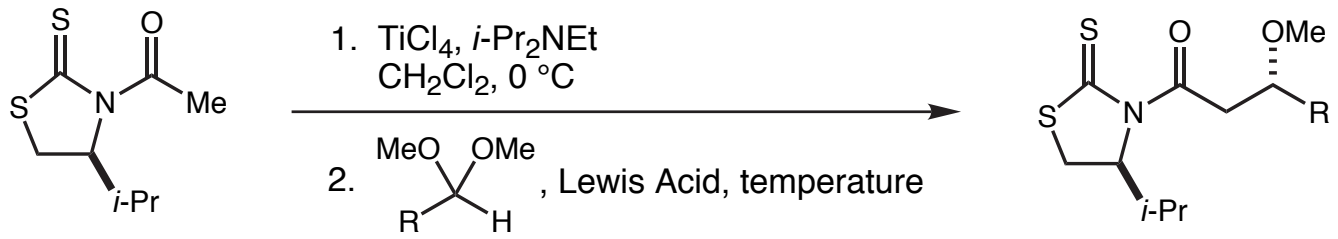


Proposed Transition State

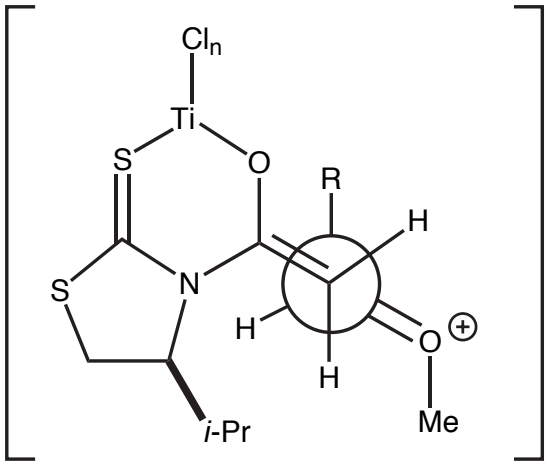
- Second Lewis acid necessary to activate acetal
- Less reactive aldehydes require higher temperatures and the stronger $SnCl_4$.

Urpi, F.; Romea, P. *Org. Lett.* **2001**, *3*, 615-617.

Acetal Addition: Urpi and Romea



L.A.	T (°C)	R	Isolated Yield (%)	dr
BF_3•OEt_2	–78	Ph	77	7:1
	–78	4-$MeOC_6H_4$	87	13:1
	–78	4-ClC_6H_4	81	7:1
$SnCl_4$	–20	Me	57	3:1
	–20	Pr	62	3:1
	–20	*i*-Bu	70	4:1
	–20	*i*-Pr	60	2.4:1

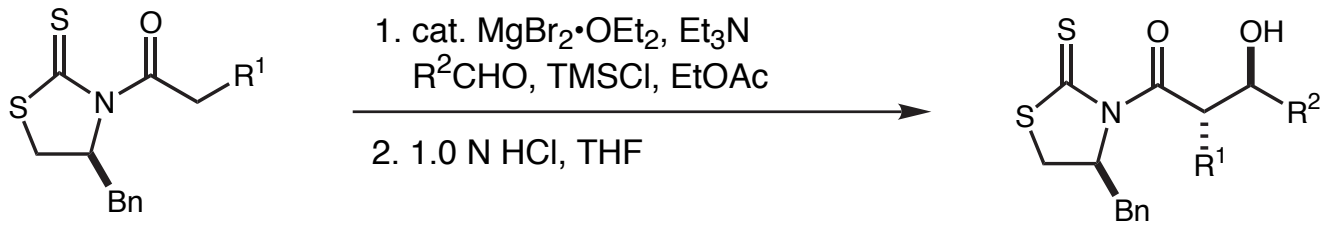


Proposed Transition State

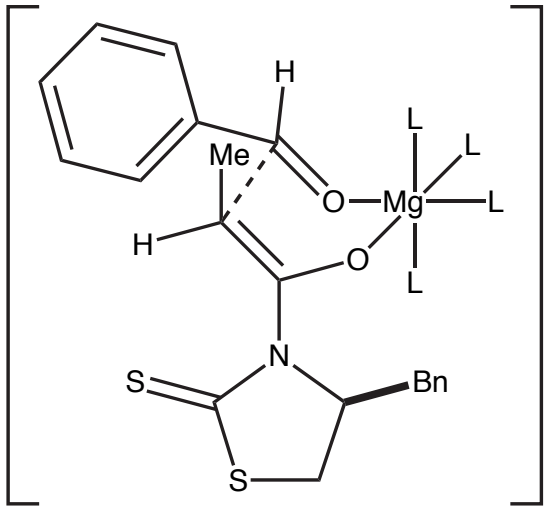
- Yields are very similar to propionate case.
- Compared to the propionate cases, selectivity is similar for BF_3, worse for $SnCl_4$.

Urpi, F.; Romea, P. *Tetrahedron Lett.* **2001**, *42*, 4629-4631.

Aldol: Evans



R^1	R^2	Mol % Catalyst	Isolated Yield (%)	dr
Me	Ph	10	85	19:1
Me	4-MeC_6H_4	10	92	19:1
Me	4-$MeOC_6H_4$	10	91	19:1
Me	PhCH=CH	10	87	10:1
Me	PhCH=C(Me)	10	90	19:1
Me	2-naphthyl	10	84	7:1
Me	CH_2=C(Me)	10	56	7:1
Et	Ph	20	88	10:1
Allyl	Ph	10	91	13:1
Bn	Ph	10	84	8:1
i-Bu	Ph	15	93	19:1



Proposed Transition State

- TMSCl is necessary to turn over the catalytic cycle.
- Aliphatic aldehydes are unreactive or self-condense.

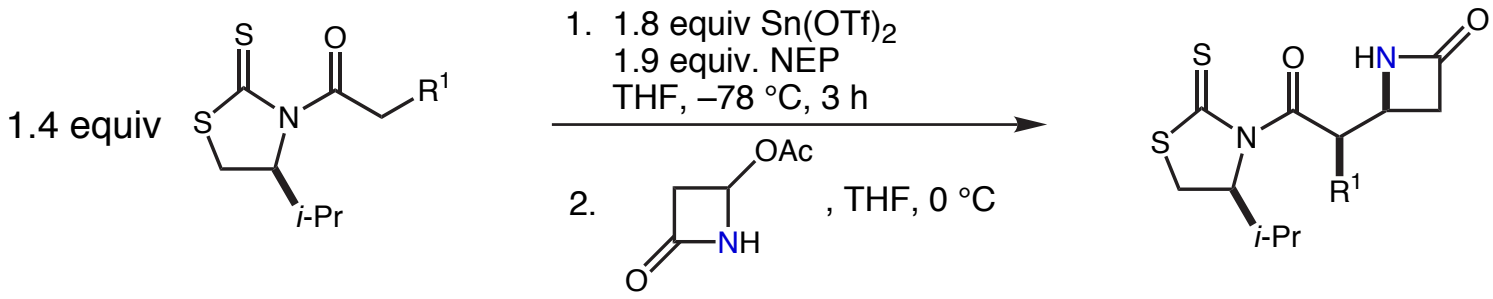
Evans, D.; Downey, C.; Shaw, J.; Tedrow, J. *Org. Lett.*, accepted.

The Aldol Comparison

	Lewis Acid	Base	O/S	Ac?	Yield (%)	dr	Major Diastereomer
Mukaiyama	$Sn(OTf)_2$	NEP	S	Only	63-81	~20:1	
Nagao/Fujita	$Sn(OTf)_2$	NEP	O	No	65-71	~8:1	Non-Evans syn
			S	Yes	70-81	~25:1	Non-Evans syn
Miller	Bu_2BOTf	*i*-Pr_2NEt	both	No	76-90	~20:1	Evans syn
Yan	$TiCl_4$	*i*-Pr_2NEt	O	Yes	82-88	~50:1	Non-Evans syn
	Bu_2BOTf		O	No	78-86	~20:1	Evans syn
	9-BBN(OTf)		O	Only	84-91	~20:1	
Crimmins	$TiCl_4$	sparteine	O	No	65-90	~25:1	Either syn
			S	No	52-77	~25:1	Either syn
Urpi	$TiCl_4$	*i*-Pr_2NEt	S	Yes	50-81	~8:1	Non-Evans anti
Evans	$MgBr_2 \cdot OEt_2$	Et_3N	S	No	56-93	~15:1	Evans anti

- Mukaiyama: stoichiometric chiral ligand
- Nagao/Fujita: applied to many syntheses
- Miller: ester substituent on auxiliary
- Yan: camphor-based auxiliary
- Crimmins: either syn diastereomer
- Urpi: anti addition to dimethyl acetals
- Evans: anti selective, mild Lewis acid

Iminium Addition: Nagao and Fujita

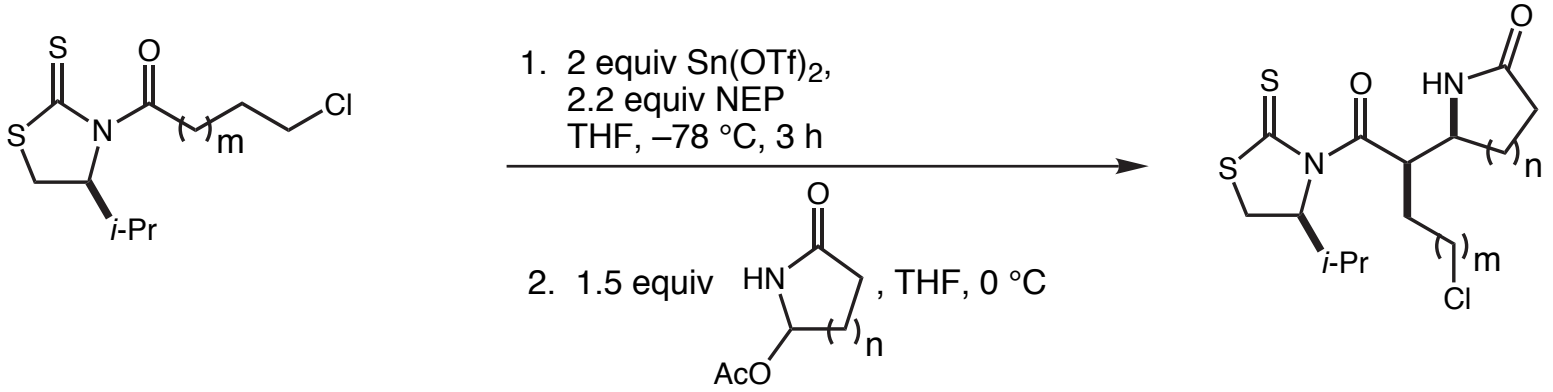


R^1	dr	Total Yield (%)
H	19:1	82
Me	"10–50:1"	"75-85"
OBn	32:1	79
OMe	32:1	55
SBn	32:1	84
SMe	24:1	72
N(H)Cbz	99:1	52

- Reactions complete within 30 min
- Acetate and propionate nucleophiles were enolized at –50 °C.
- Yield of propionate adducts not specified

Nagao, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**,*108*, 4673-4675.
Nagao, Y.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1986**, 602-603.

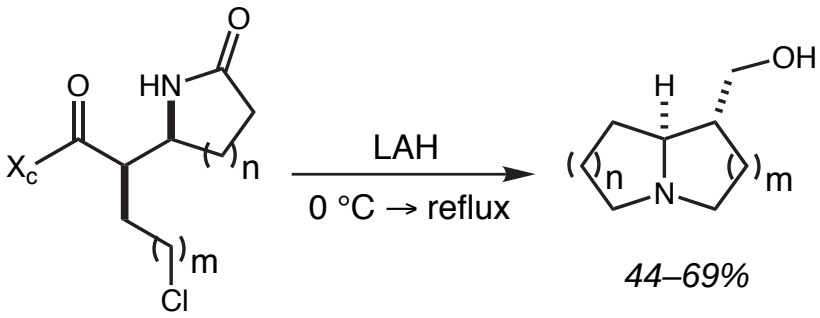
Iminium Addition: Nagao and Fujita



m	n	dr	Total Yield (%)
1	1	66:1	64
2	1	28:1	72
1	2	39:1	57
2	2	28:1	73

• Reactions complete within 2 h

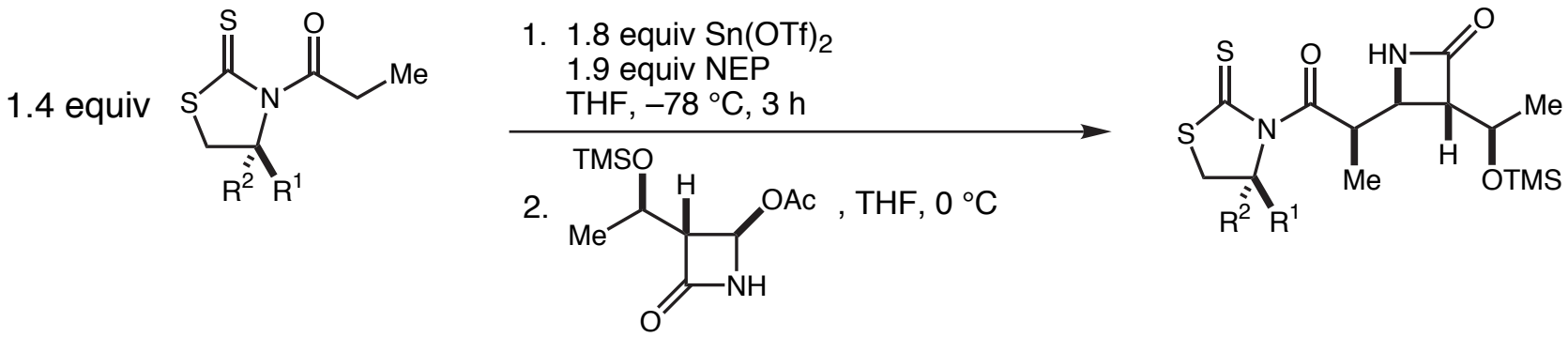
Further Elaboration: Alkaloids



44–69%

Nagao, Y.; Fujita, E. *J. Am. Chem. Soc.* **1988**,*110*, 289-291.

Iminium Addition: Nagao

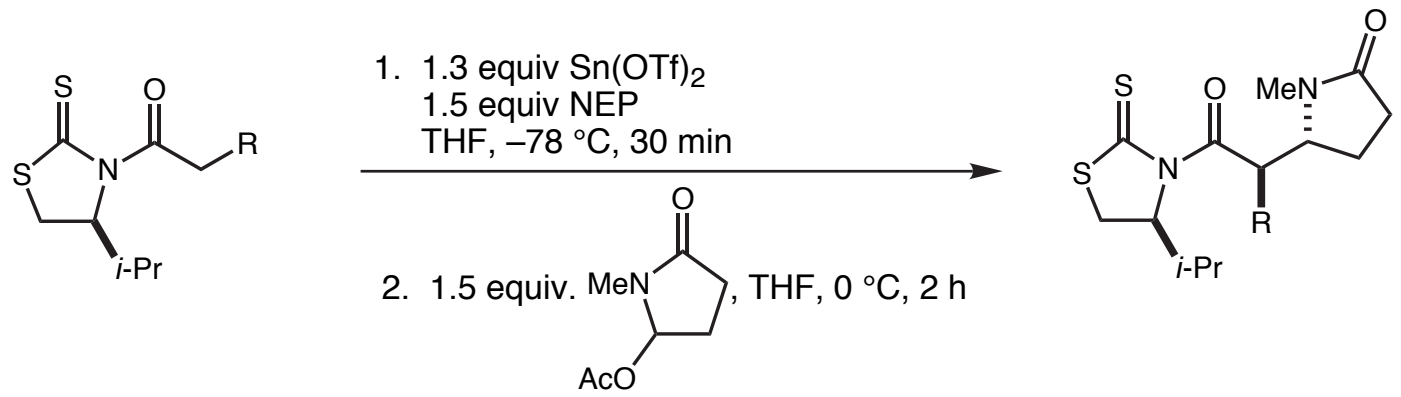


R^1	R^2	dr	Yield (%)
Et	H	9:1	80
i-Pr	H	10:1	74
H	H	4:1	73
Me	Me	6:1	80

- Matched case required for synthetically useful selectivity
- Selectivity much lower than for unsubstituted azetidinones.

Nagao, Y. *J. Org. Chem.* **1992**, *57*, 4243-4249.

Iminium Addition: Nagao



R	dr[a]	Isolated Yield (%)	purified dr[b]
H	1:1	NR	NR
SPh	3.6:1	57	10:1
SC_6H_{11}	1.6:1	46	4.9:1
SBn	1.6:1	57	6:1

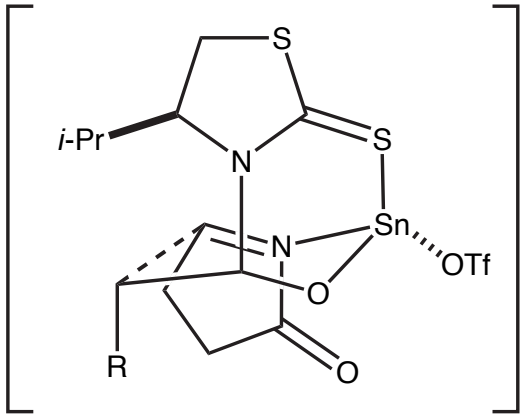
a) dr = major : Σ minor b) dr of chromatographically purified product

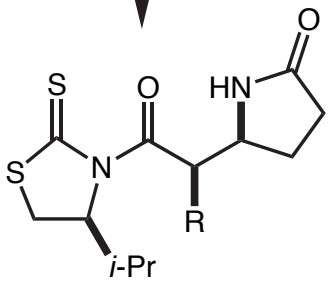
Why this turnover to anti selectivity?

Nagao, Y. *Tetrahedron Lett.* **1988**,*47*, 6133-6136.

Iminium Addition: Nagao

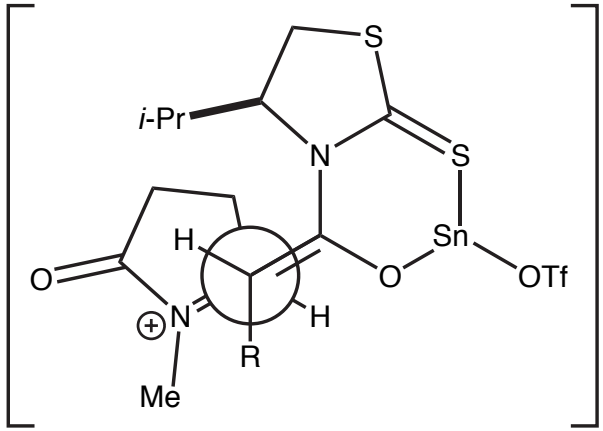
Cyclic

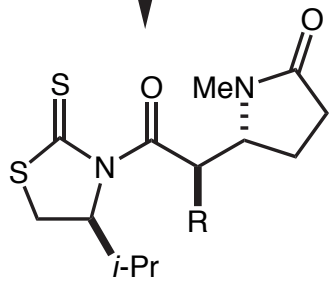




Syn

Acyclic

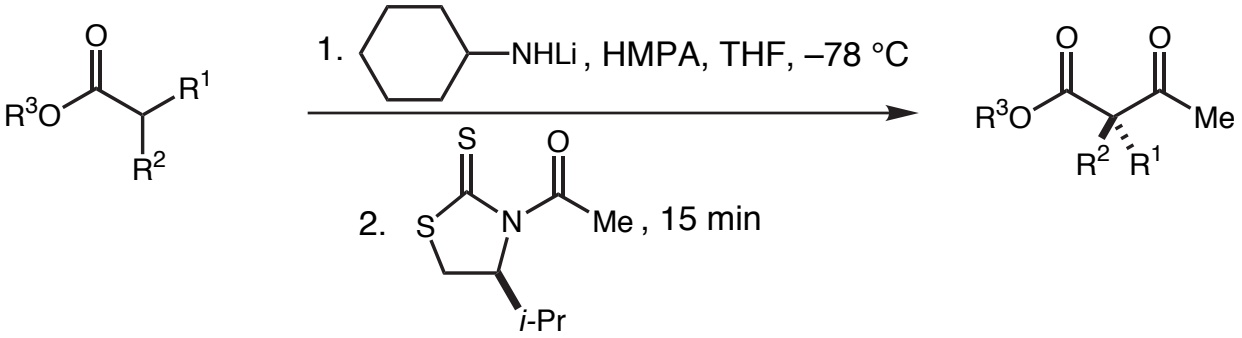




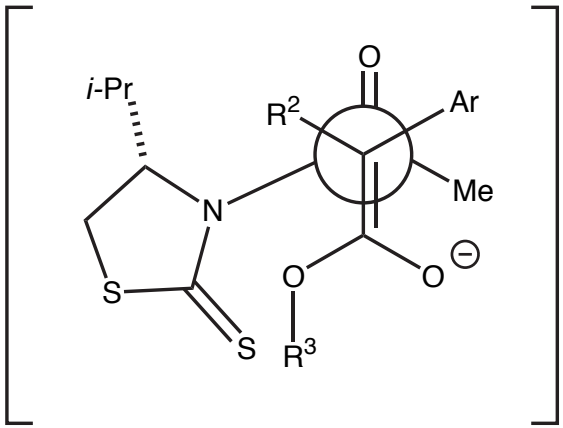
Anti

Nagao, Y. *Tetrahedron Lett.* **1988**,*47*, 6133-6136.

Crossed Claisen: Nagao



R^1	R^2	R^3	Yield (%)	ee (%)
Ph	Me	*t*-Bu	77	96
Ph	Me	Me	57	94
Ph	Bu	*t*-Bu	29	87
4-$MeOC_6H_4$	Me	*t*-Bu	72	95
Bu	Me	*i*-Pr	62	22



Proposed Transition State

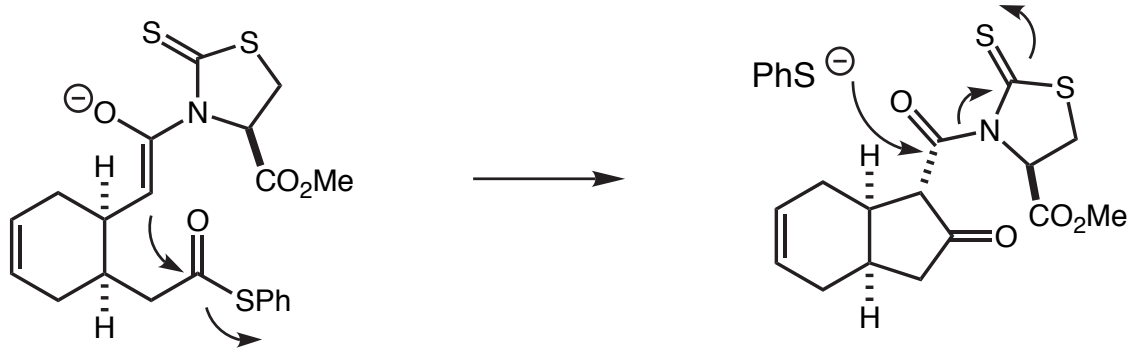
- Isobutyrylthione behaved analogously in both yield and selectivity.
- HMPA, aromatic R^1 appear to be essential for high selectivity.
- Large R^2 led to decreased yields.

Nagao, Y. *J. Org. Chem.*, **1988**, *53*, 5983-5986.

Dieckmann Annulation: Nagao and Fujita

Initial Observation:

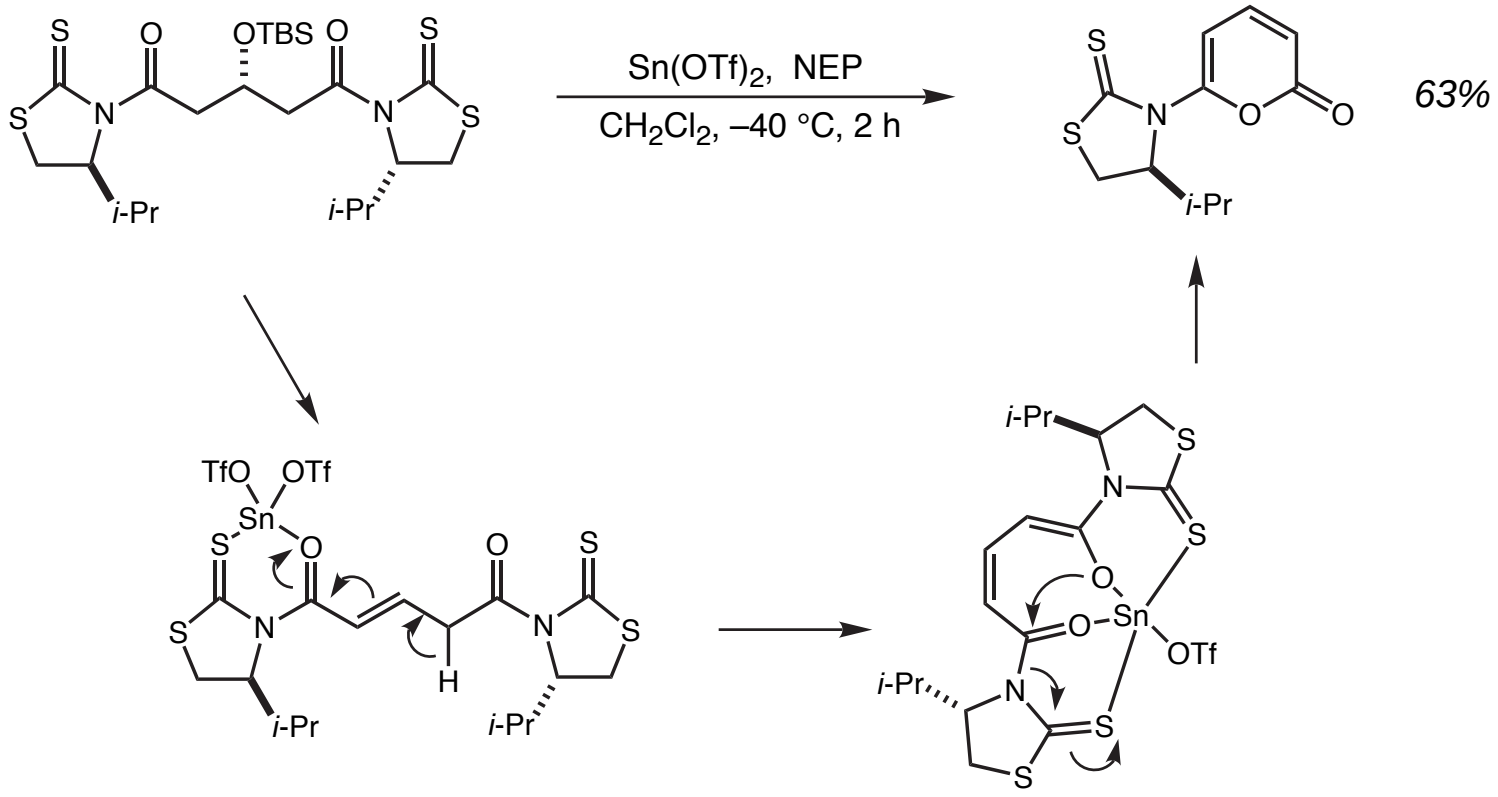
Rationale:



- Reaction was later repeated with a methyl ester in the place of the thioester.

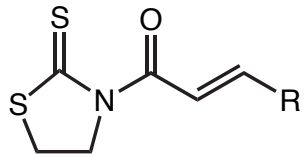
Nagao, Y., Fujita, E. *Chem. Lett.* **1987**, 1861-1864.
Nagao, Y. *J. Org. Chem.*, **1988**, *53*, 5983-5986.

Pyrone Synthesis: Nagao



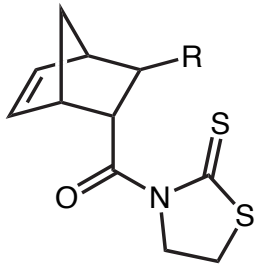
Nagao, Y. *Chem. Lett* **1992**, 2035-2038.

Diels-Alder: Evans



10 mol% $Cu(OTf)_2$, 11 mol% **L***

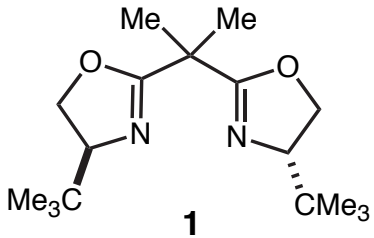
CH_2Cl_2



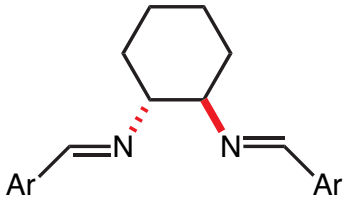
R	L*	Isolated Yield (%)	endo:exo	endo ee (%)
Me	1	82	96:4	94
Ph	1	86	92:8	97
COOEt	1	88	84:16	96
Me	2	86	93:7	–91
Ph	2	84	92:8	–92
COOEt	2	99	90:10	–88

- Thiones react at lower temperatures than oxazolidinones (typically –40 °C instead of –20 °C).
- Thiones and oxazolidinones react comparably with Cu(II)box. With the bisimine ligand, however, thiones exhibit much better endo:exo selectivity (done typically 2–4:1).

L* =



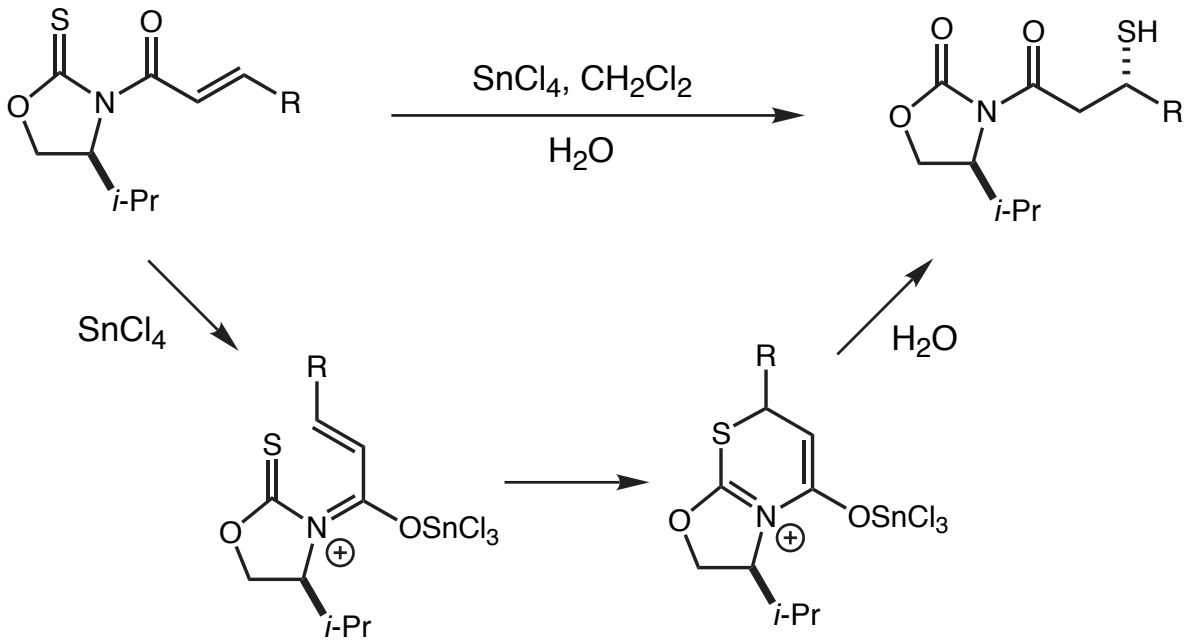
1



2 (Ar = 2,6-Cl_2Ph)

Evans, D.; Miller, S.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460-6461.
Evans, D.; Lectka, T.; Miller, S. *Tetrahedron Lett.* **1993**, *34*, 7027-7030.

Thione-Based Rearrangements



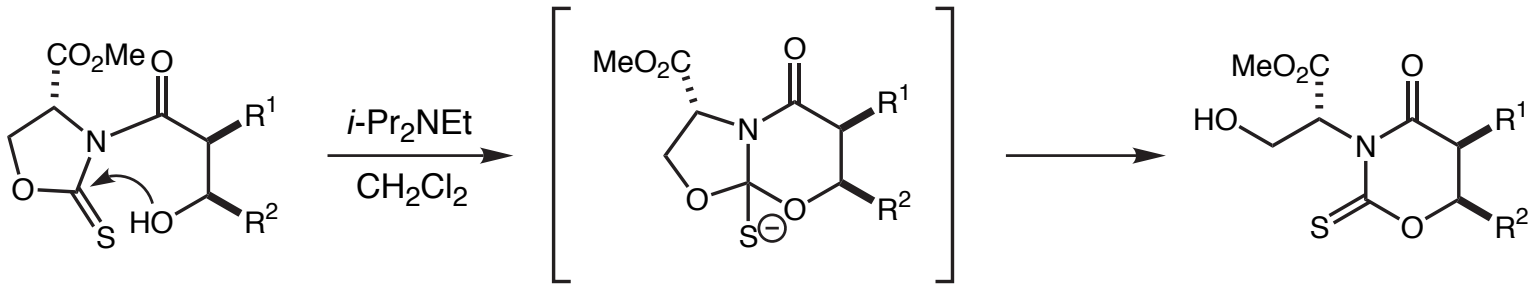
R	Total Yield (%)	dr
Me	72	50:1
Et	67	50:1
i-Pr	70	50:1
Ph	80	7:1
4-ClPh	70	3:1

- Reactions were conducted at –78 °C except for aromatic substrates, which were warmed to room temperature.
- The camphor-based auxiliary was superior in both yield (typically 85%) and selectivity (by ~5%) but is more difficult to draw.
- Reactions were 0.01 to 0.05 M in substrate.

Palomo, C. *J. Am. Chem. Soc.* **2001**, *123*, 5602-5603.

Thione-Based Rearrangements

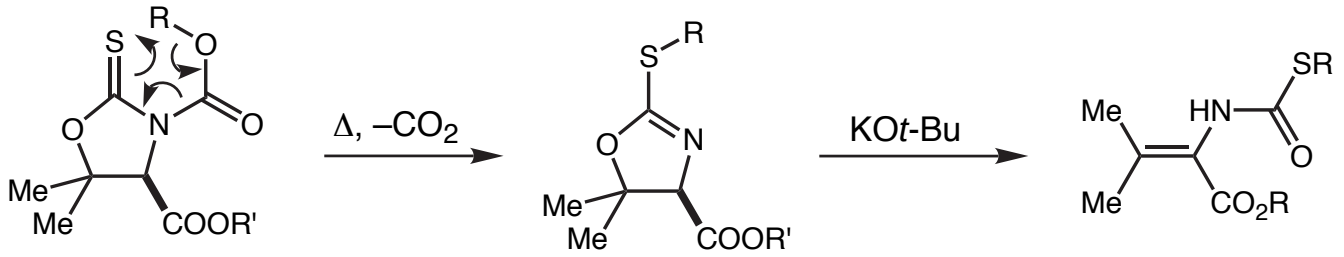
Aldol Product Rearrangement



- Propionates are unreactive.
- Competitive with methanolysis for hindered substrates

Adamczyk, A. *Tetrahedron Lett.* **1995**, *36*, 5303-5306.

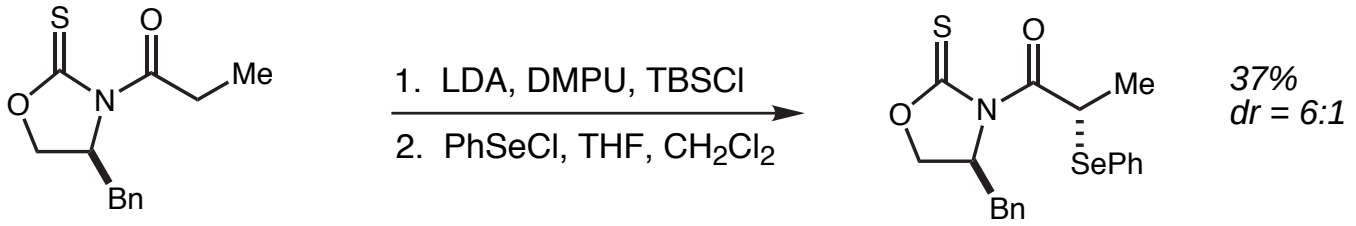
Thermal Carbamate Rearrangement



Hoppe, D. *Chem. Ber.* **1976**, *109*, 3062-3078.

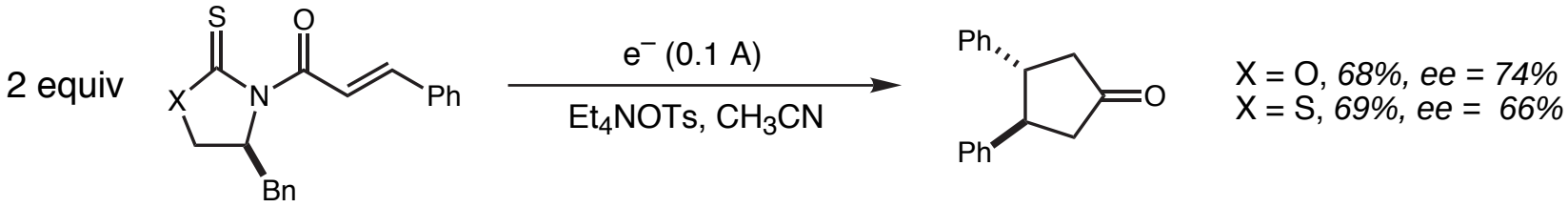
Other Reactions

Selenylation



Holmes, A. *Tetrahedron: Asymmetry* **1992**, *3*, 1289-1302.

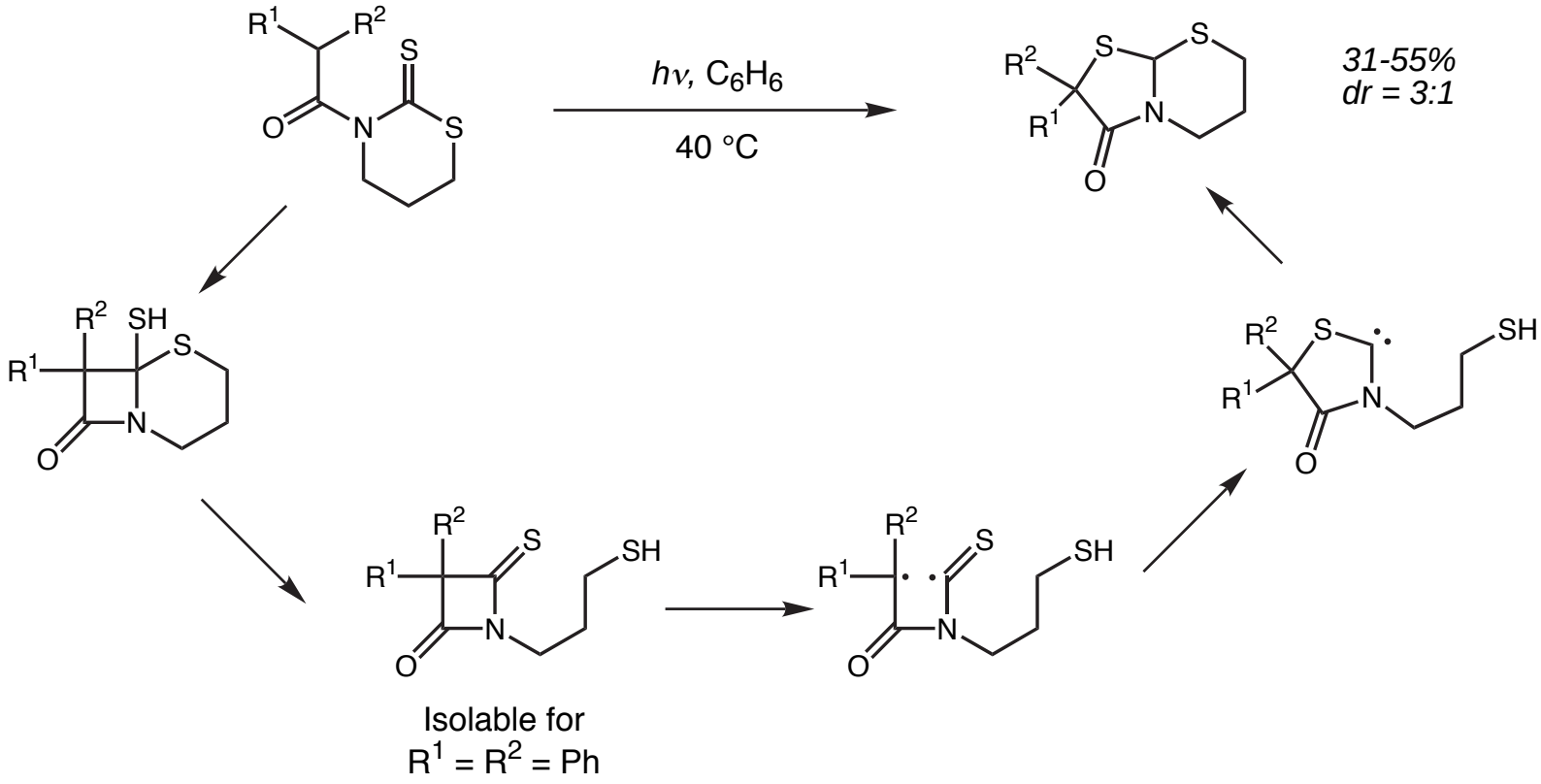
Electroreductive Coupling



- Decarboxylation occurs under the reaction conditions.

Kise, N. *J. Org. Chem.* **1998**, *63*, 7931-7938.

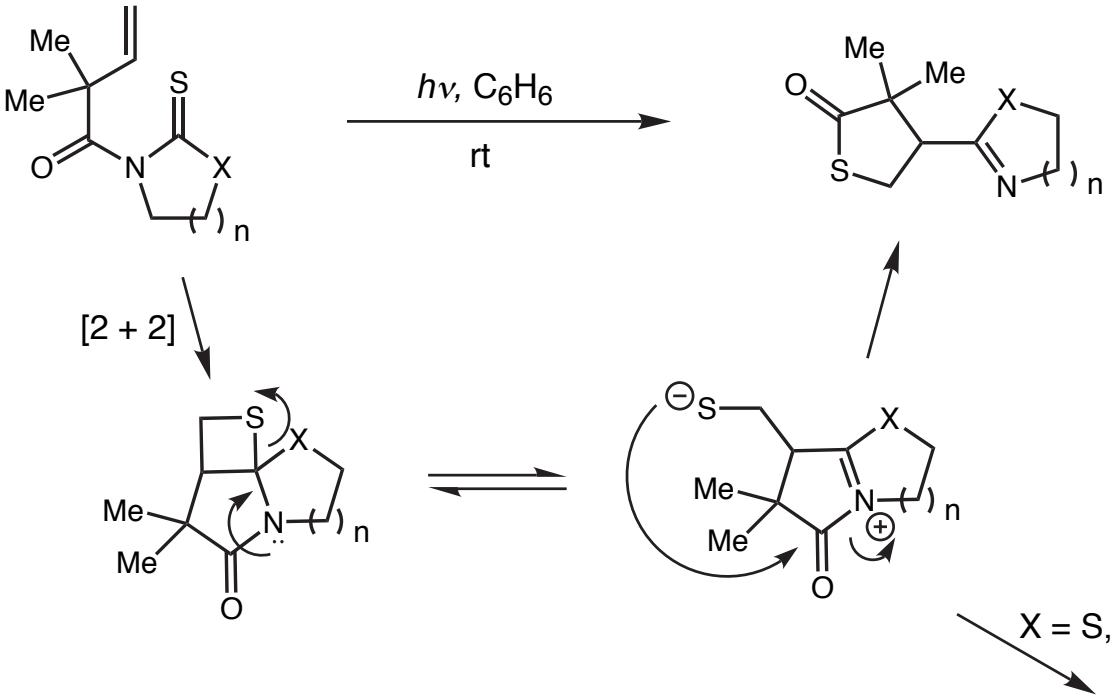
Photochemical Rearrangement: Sakamoto



- "Impossible to determine stereochemistry"
- Major byproduct is deacylated thione.
- Endocyclic-oxygen analog gives similar results.
- Thiazolidinethiones and oxazolidinethiones yield solely deacylation products.

Sakamoto, M. *J. Chem. Soc., Perkin Trans 1* **1991**, 2541-2545.

Photochemical Rearrangement: Sakamoto



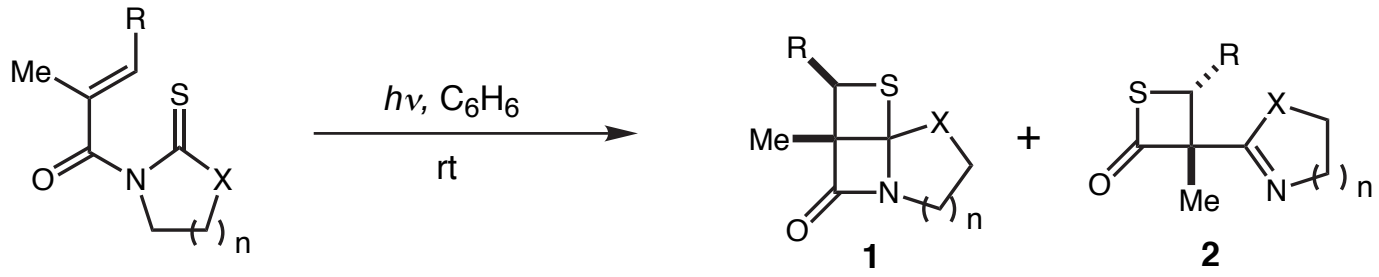
A

X	n	Yield (%)
S	1	74
S	2	0
O	1	56
O	2	77

- Product structure confirmed by X-ray crystallography
- For X = S, n = 2, product **A** was formed in 64% yield:

Sakamoto, M., Nishio, T. *J. Org. Chem.* **1992**, *57*, 3735-3738.

Photochemical Rearrangement: Sakamoto

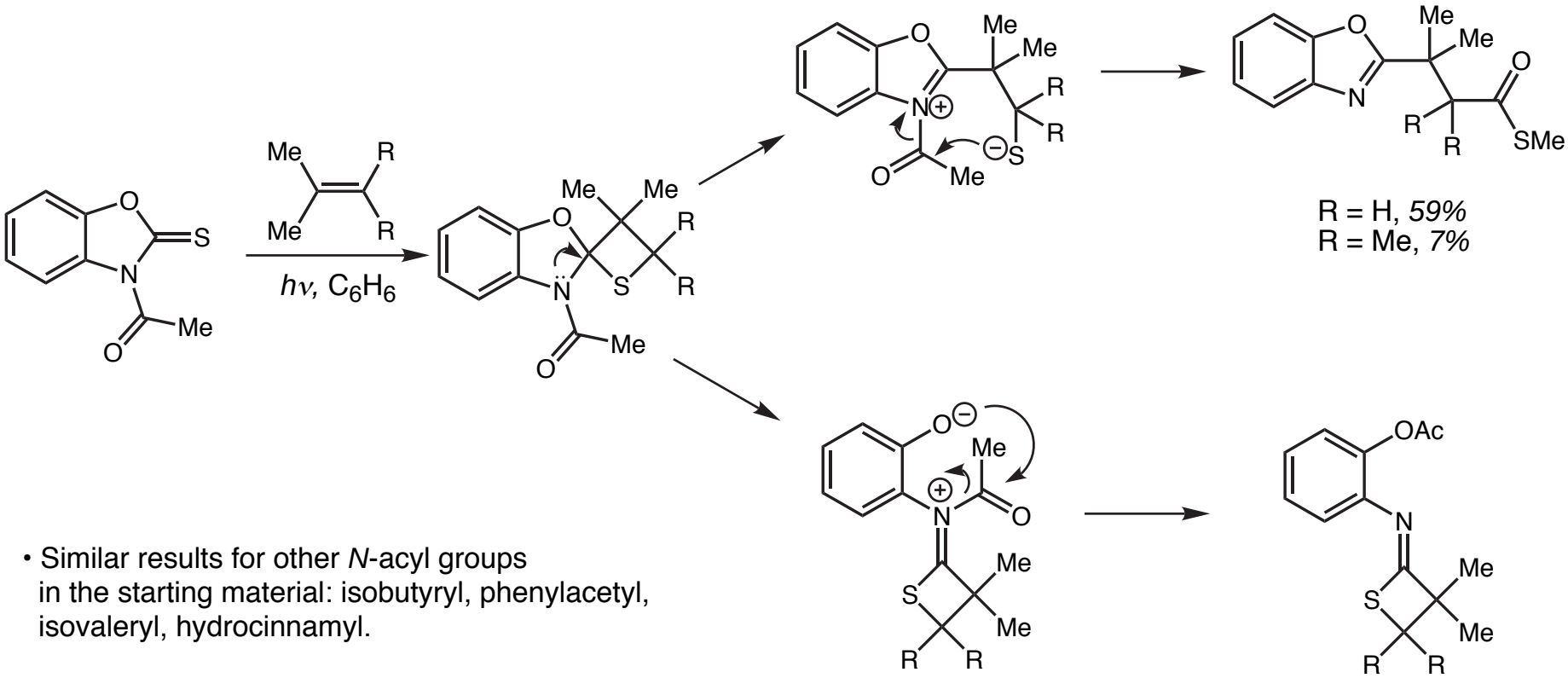


X	n	R	Yield (%) 1	2
S	1	H	30	30
S	1	Me	67	0
O	1	H	44	0
O	1	Me	33	0
O	2	H	0	33
O	2	Me	0	66

- Stereochemistry supported by NOE studies
- Proposed mechanism is analogous to previous case.

Sakamoto, M. *J. Chem Soc., Perkin Trans 1* **1994**, 2983-2986.

Photochemical [2 + 2]: Nishio



- Similar results for other *N*-acyl groups in the starting material: isobutyryl, phenylacetyl, isovaleryl, hydrocinnamyl.
- MO calculations suggest that substitution α to sulfur stabilizes the iminothietane.
- *E*/*Z* selectivity of the iminothietane products was not mentioned; in fact, the product in the paper is drawn as *E*, despite the *Z*-configured crystal structure featured in the text.

Nishio, T. *J. Chem. Soc., Perkin Trans 1* **2000**, 3039-3046.

Summary

- Thioimides have been used extensively as acylating agents, especially for amide synthesis.
- Half-reduction of thioimides directly to aldehydes is possible.
- By far, the aldol is the most common reaction with thioimide auxiliaries. Yield and selectivity vary, but the best systems are viable options to the venerable oxazolidinones.
- Facile cleavage may be the thioimide's greatest asset.
- Other enolate reactions include Claisen, Dieckmann, iminium addition, and selenylation.
- With few exceptions, soft enolization is essential.
- Thiocarbonyl photochemistry may lead to multiple products. No asymmetric reactions have been reported.
- Rearrangement of aldol products and starting acylthiones is a potential danger.
- More complex enolates and aldehydes have been used in the context of natural product synthesis by the following groups: Crimmins, Horikawa, Huber, Kibayashi, Kocienski, Nagao/Fujita, Paquette, Rizzacasa, Romo, Shiori, Sulikowski, Thomas, and Urpi/Vilarrasa.