Asymmetric Synthesis Using Chiral Sulfinyl Groups

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OUTLINE

I. Introduction

II. Some Examples of Chiral Sulfoxides in Asymmetric Reactions

III. Asymmetric Heck Reaction Using Chiral Sulfoxides

IV. Asymmetric Synthesis Using Chiral Sulfinimines

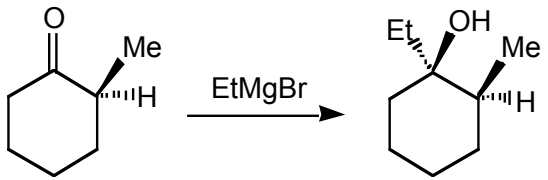
- a) α-Branched and α,α-Dibranched Amines
- b) α- and β-Amino Acids
- c) Aziridines
- d) α- and β-Aminophosphonic Acids

V. Application in Solid-Phase Synthesis

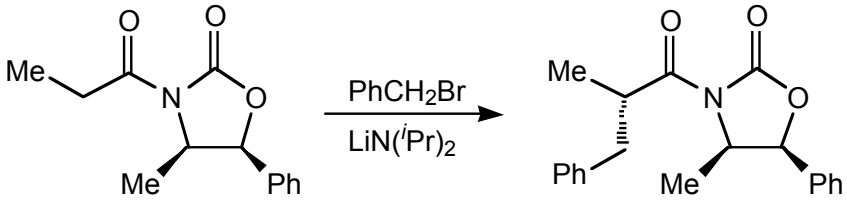
VI. Conclusions

Methods of Asymmetric Synthesis

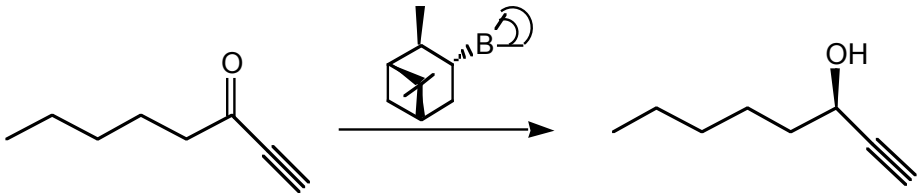
1. Substrate-Controlled



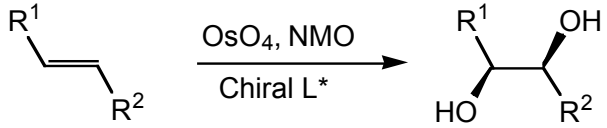
2. Auxiliary-Controlled



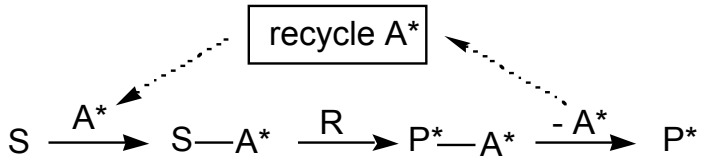
3. Reagent-Controlled



4. Catalyst-Controlled

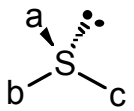


General Scheme for Auxiliary-Controlled Methods



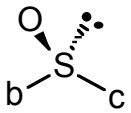
A chiral auxiliary can be on either nucleophiles or electrophiles.

Sulfur-containing compounds

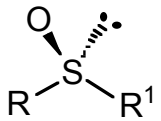


Distorted tetrahedron
- Chiral
- Configurationally stable

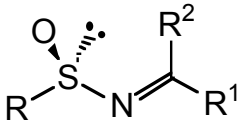
Sulfinyl compounds



Sulfoxides

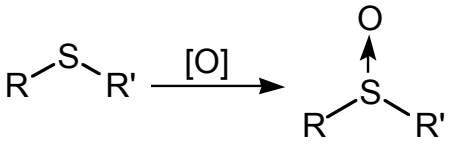


Sulfinimines



Preparation of Chiral Sulfoxides

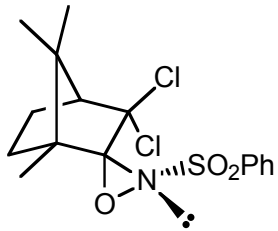
1. Asymmetric Oxidation



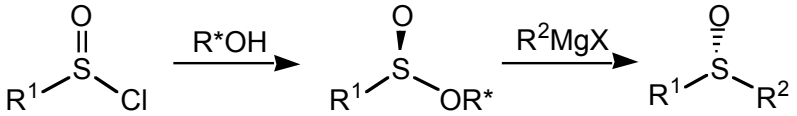
$Ti(O^iPr)_4$ / (+)-DET / ^tBuOOH

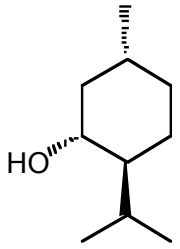
$Ti(O^iPr)_4$ / (+)-DET / $PhC(CH_3)_2OOH$

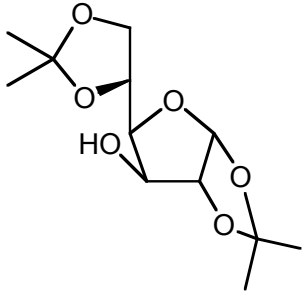
$Ti(O^iPr)_4$ / (+)-BINOL / ^tBuOOH



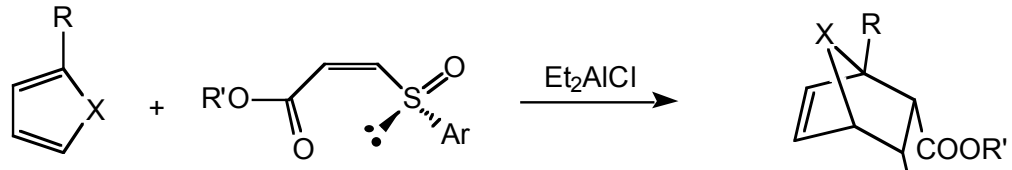
2. Asymmetric Synthesis (Nucleophilic Substitution on Chiral Sulfur)



R*OH = 

or 

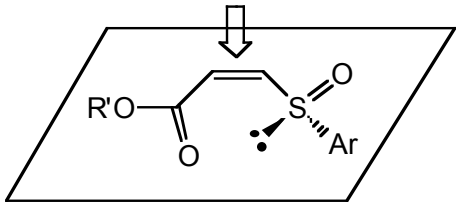
Asymmetric Diels-Alder Reaction Using Chiral Sulfoxides



X = CH_2, R = H;
X = $(CH_2)_2$, R = H;
X = O, R = MeO.

R' = Me, Menthyl
Ar = 4-MeC_6H_4, 2-Py

86-99% de
70-98% yield

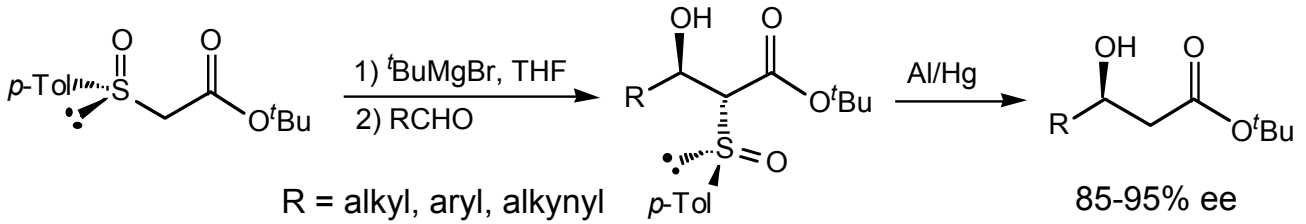


Takahashi, T.; Kotsubo, H.; oizumi, T. *Tetrahedron Asymmetry* **1991**, *2*, 1035-1039.

Arai, Y.; Hayashi, Y.; Yamanoto, M.; Takayema, H.; Koizumi, T. *J. Chem. Soc. Perkin Trans. 1* **1988**, 3133-3141.

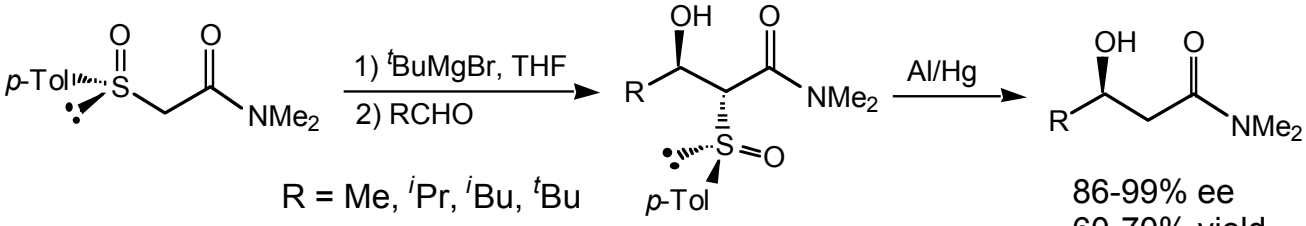
Alonso, Ines.; Carrentero, J. C.; Ruano, J. L. G. *J. Org. Chem*. **1994**, *59*, 1499-1508

Asymmetric Aldol Reaction Using Chiral Sulfoxides



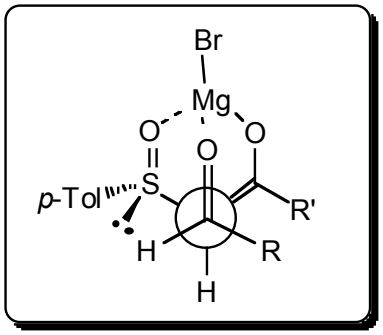
R = alkyl, aryl, alkynyl

85-95% ee
73-85% yield



R = Me, ^{i}Pr, ^{i}Bu, ^{t}Bu

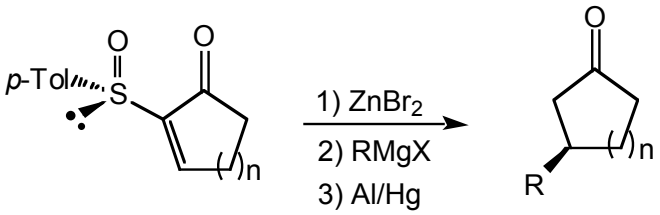
86-99% ee
60-70% yield



Solladie, G.; Bauder, C.; Arce-Dubois, E.; Pasturel-Jacope, Y. *Tetrahedron Lett.* **2001**, *42*, 2923-2925.

Solladie, G.; Hamdouchi, C. *Synthesis* **1991**, 979-982.

Asymmetric Michael Additions Using Chiral Sulfoxides

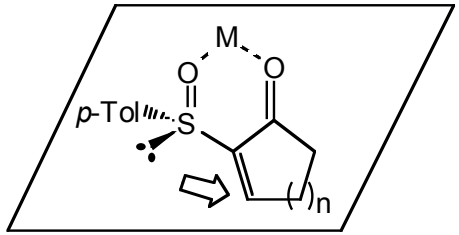


80-98% ee

67-90% yield

n = 1 or 2

R = Me, Et, ^{t}Bu, CH_2=CH, Ph, Ar

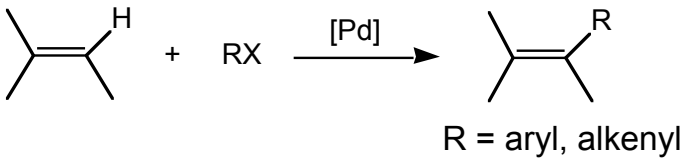


Posner, G. H. *Acc. Chem Res.* **1987**, *20*, 72-78.

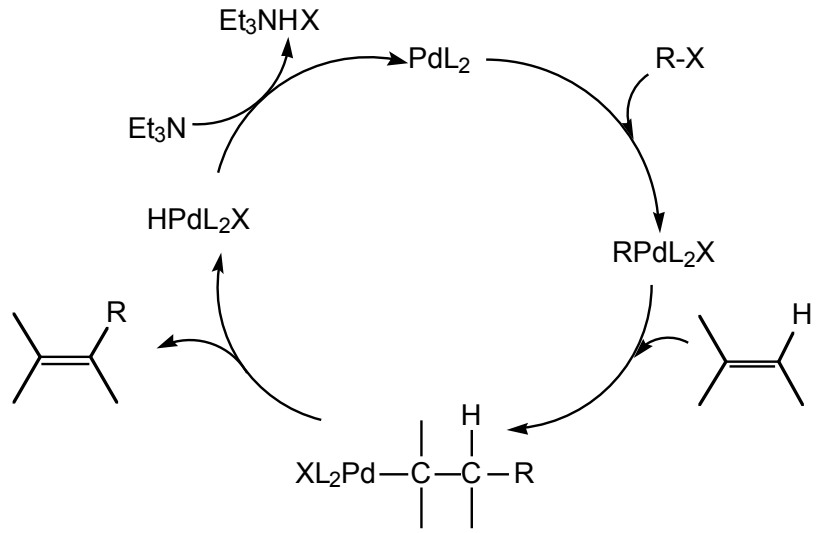
Iwata, C.; Fujita, M.; Hattori, K.; Uchide, S.; Imanishi, T. *Tetrahedron Lett.* **1985**, 26, 2221-2224.

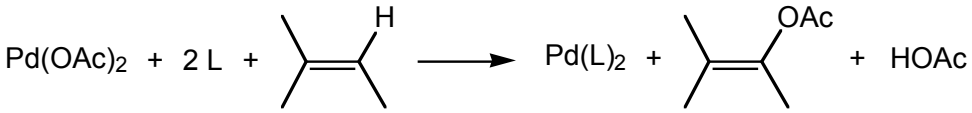
** Carreno, M. C. *Chem. Rev*. **1995**, *95*, 1717-1760.

Catalytic Cycle of the Heck Reaction

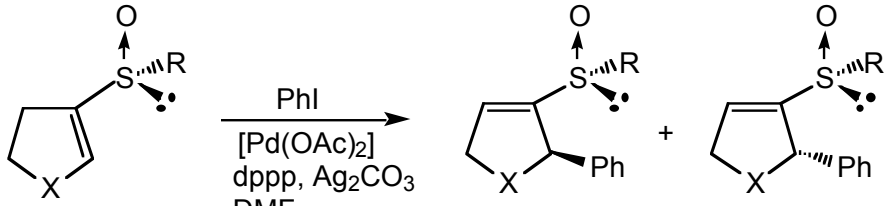


R = aryl, alkenyl





Heck Reaction of α,β-Unsaturated Sulfoxides with Iodobenzene



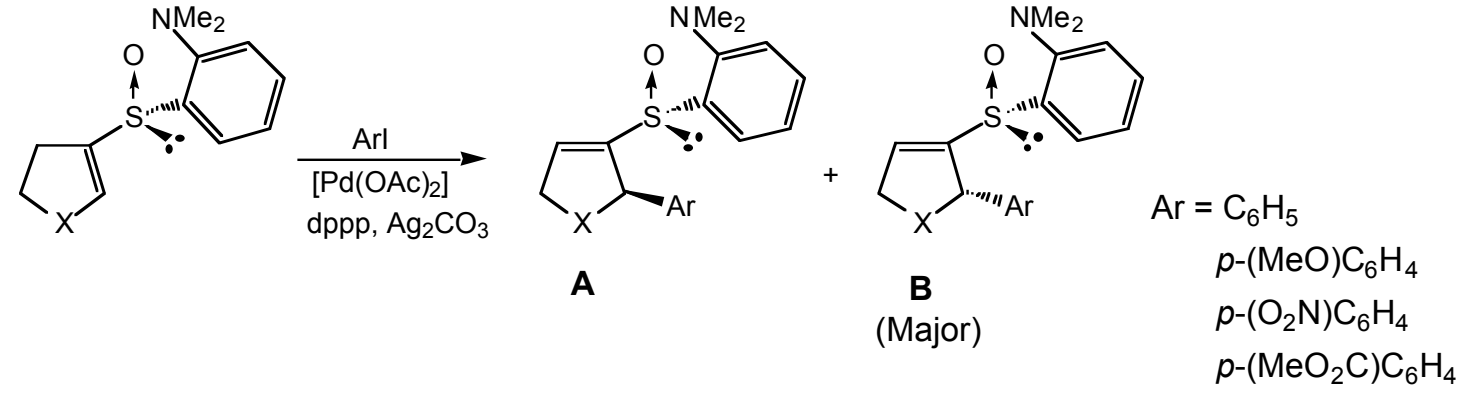
Entry	X	R	**A:B** ratio	Yield, %
1	O	Ph	77:23	68
2	O	2,4-$Me_2C_6H_3$	78:22	80
3	O	*o*-(MeO)C_6H_4	75:25	47
4	O	*o*-(Me_2N)C_6H_4	6:94	80
5	O	*t*-Bu	-[a]	-
6	CH_2	*p*-Tol	60:40	62
7	CH_2	*t*-Bu	-[a]	-
8	CH_2	*o*-(Me_2N)C_6H_4	8:92	76

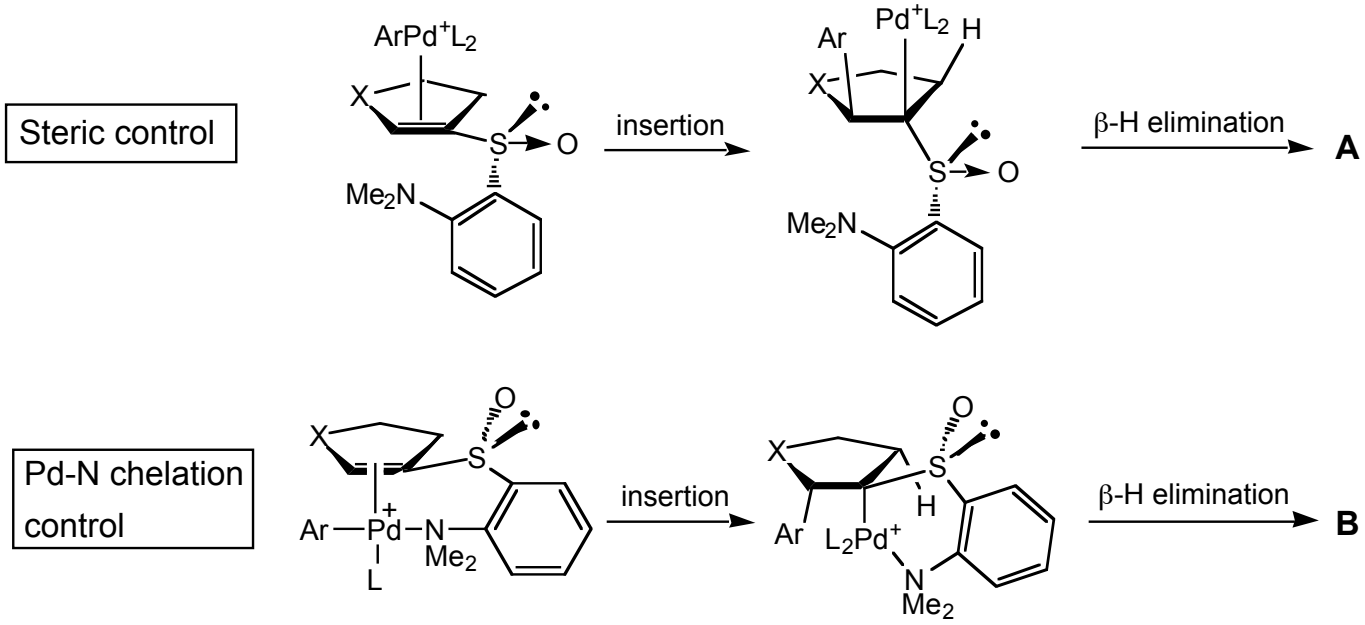
a. Complex mixture of products.

Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129-7130.

Buezo, N. D.; Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890-3900.

Mechanistic Hypothesis for the stereoselectivity of the Heck Reaction

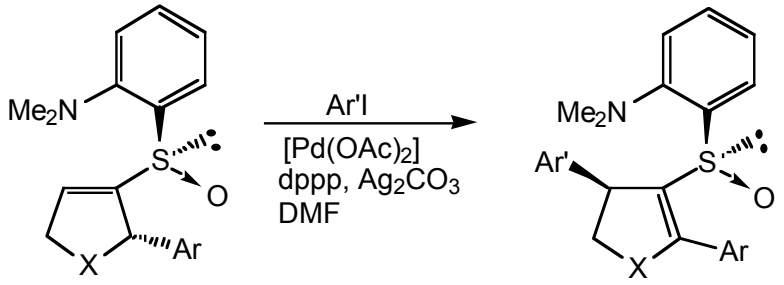




Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129-7130.

Buezo, N. D.; Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890-3900.

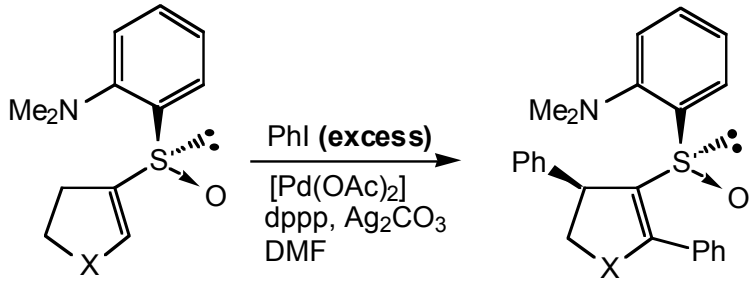
Second Heck Reaction of α,β-Unsaturated Sulfoxides with Iodoarenes



One isomer
Yield: 70-84%

Ar' = C_6H_5
p-$(MeO)C_6H_4$
p-$(NO_2)C_6H_4$

Double Heck Reaction of α,β-Unsaturated Sulfoxides with Iodobenzene

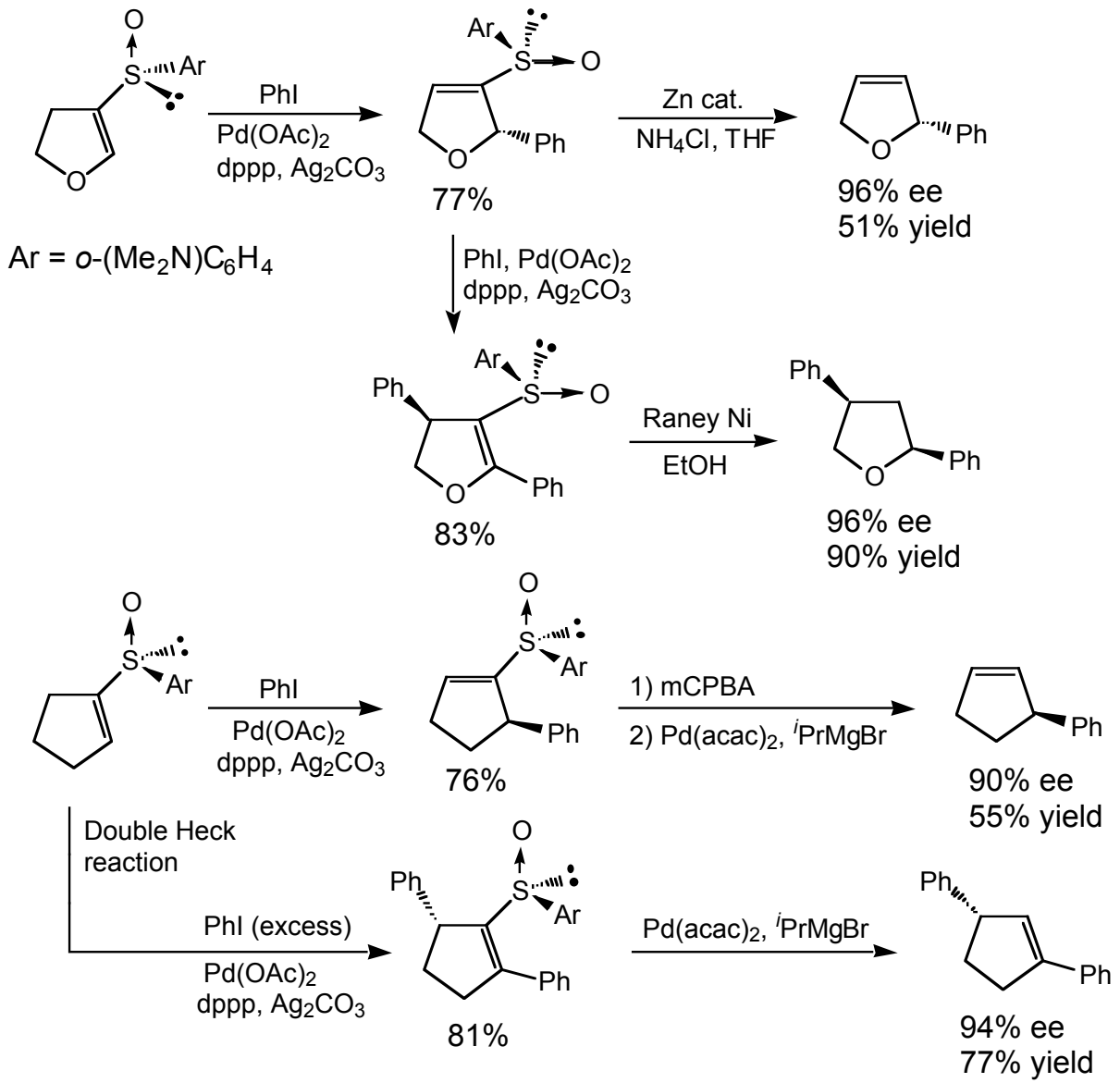


X = O, 55%
= CH_2, 81%

Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129-7130.

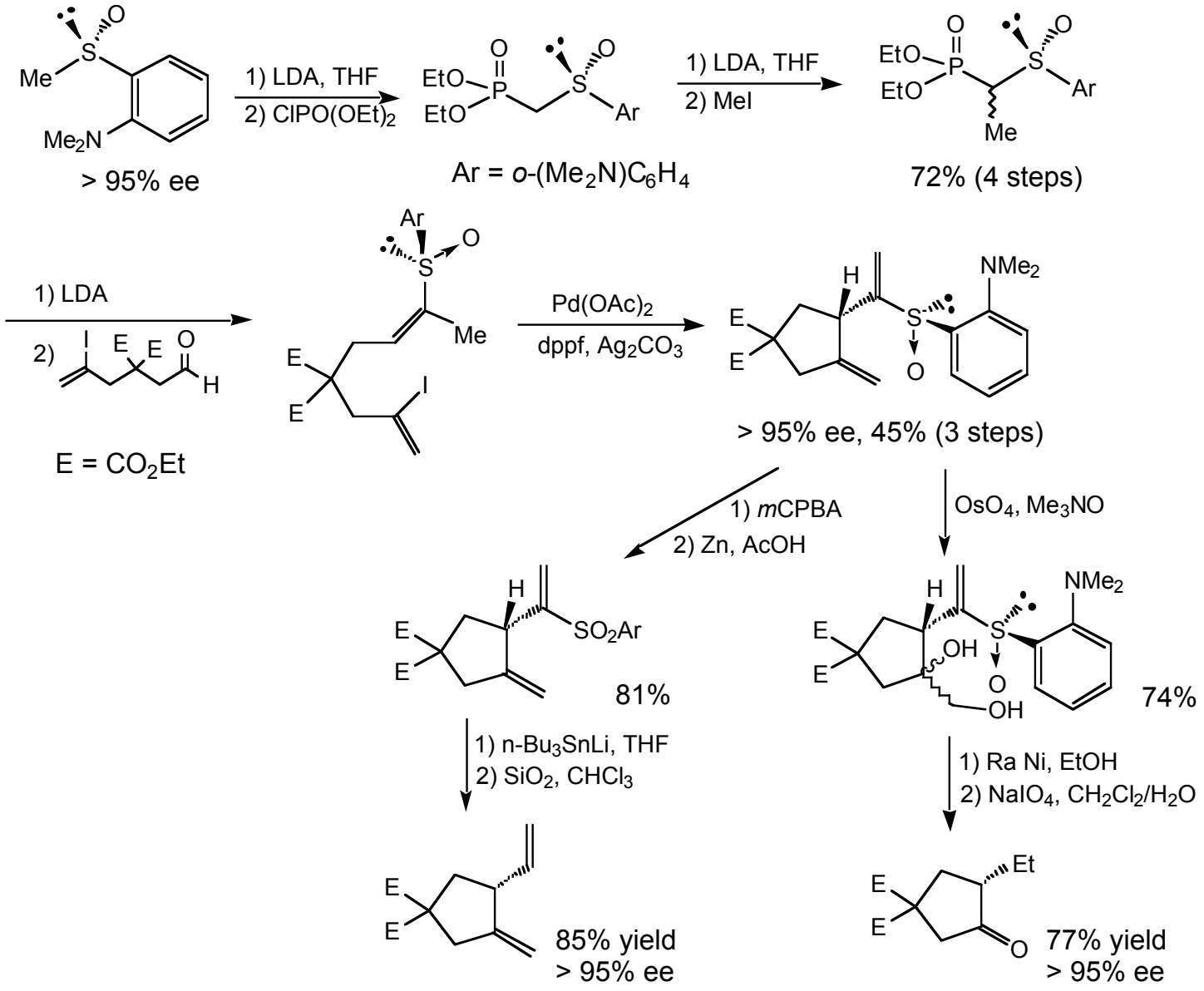
Buezo, N. D.; Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890-3900.

Enantioselective Synthesis of Aryl-Substituted Five-Membered Ring



Buezo, N. D.; Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890-3900.

Asymmetric Intramolecular Heck Reaction Using α,β-Unsaturated Sulfoxides

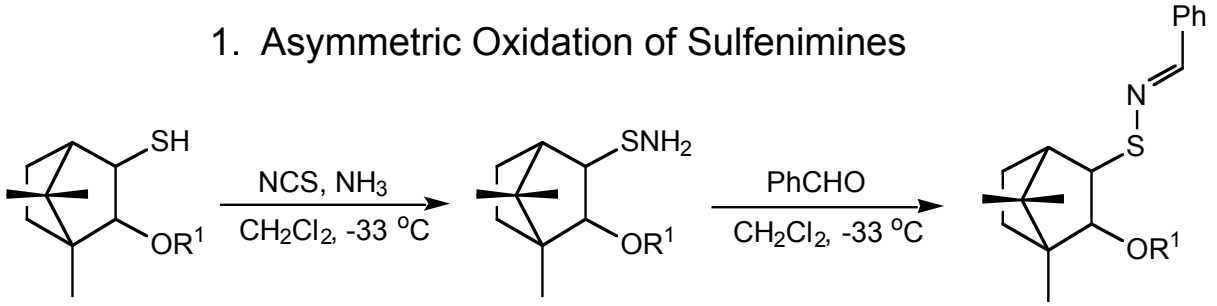


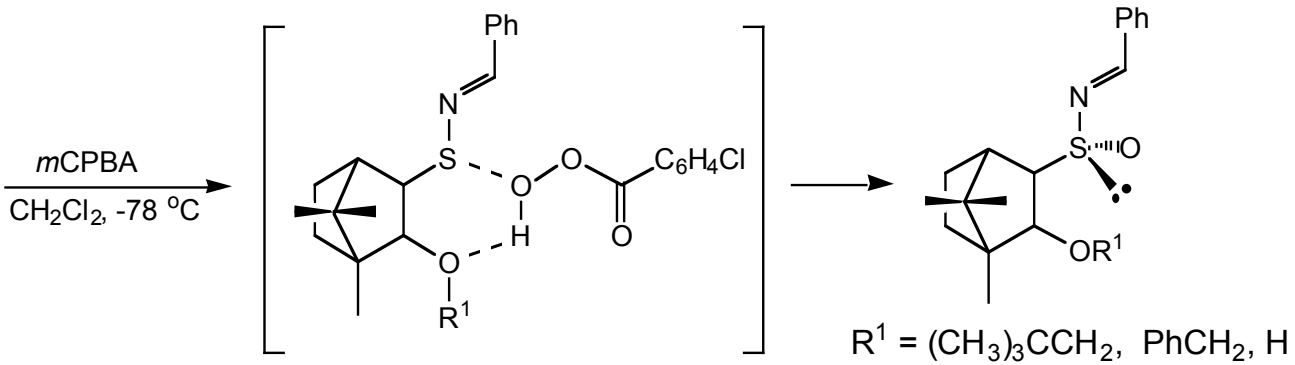
Buezo, N. D.; Mancheno, O. G.; Carretero, J. C. *Org. Lett.* **2000**, *2*, 1451-1454

Preparation of Enantiomerically Pure Sulfinimines

1. Asymmetric Oxidation of Sulfenimines

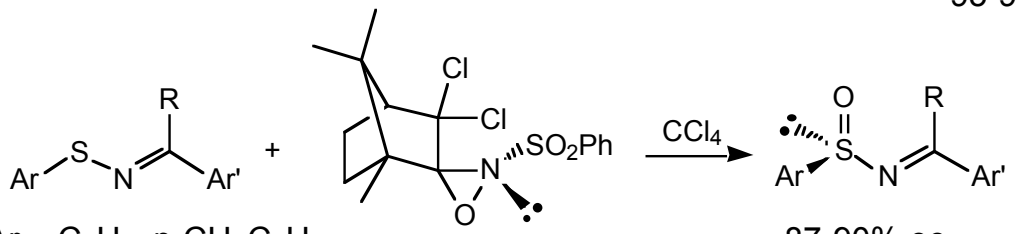
A)





R^1 = $(CH_3)_3CCH_2$, $PhCH_2$, H
up to 98% de
95-97% yield

B)

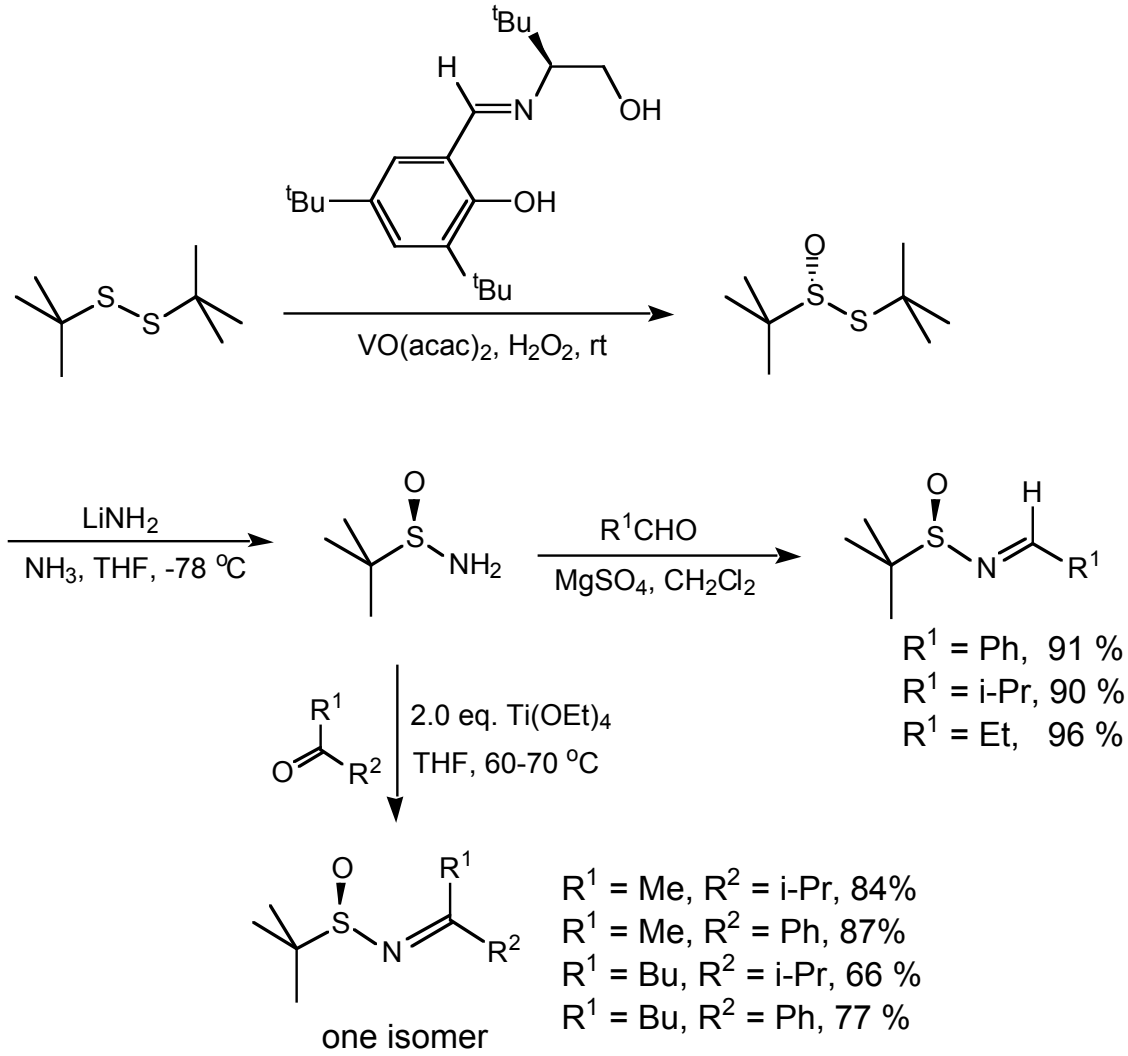


Ar = C_6H_5, p-$CH_3C_6H_4$
Ar' = C_6H_5, o-$CH_3C_6H_4$
R = H, CH_3

87-90% ee
89-96% yield (cryst. pure)

Yang, T.-K.; Chen, R.-Y.; Lee, D.-S.; Peng, W.-S.; Jiang, Y.-Z.; Mi, A.-Q.; Jong, T.-T. *J. Org. Chem.* **1994**, *59*, 914-921.
Davis, F. A,; Reddy, R. T.; Han, W.; Reddy, R. E. *Pure Appl. Chem.* **1993**, *65*, 633-640.
Davis, F. A,; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387-6387.

C)



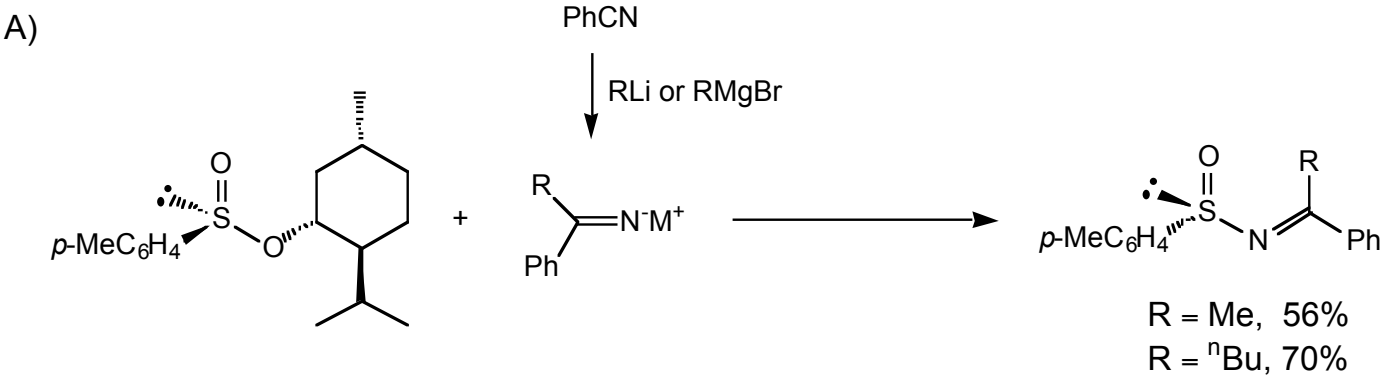
Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913-9914.

Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268-269.

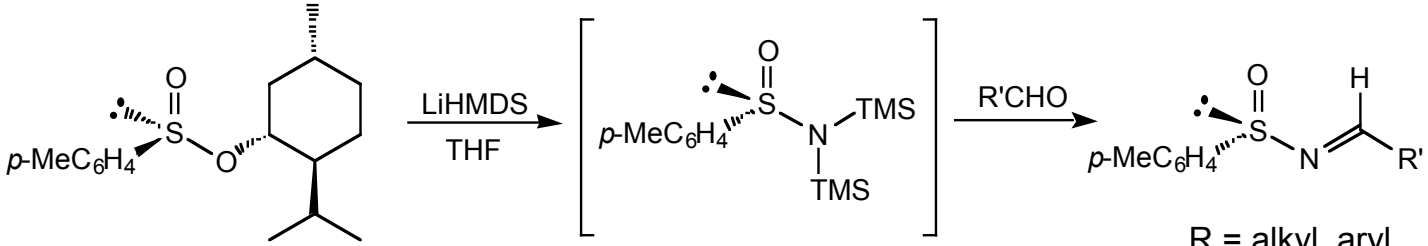
Preparation of Enantiomerically Pure Sulfinimines

2. Asymmetric Iminolysis of Sulfinates

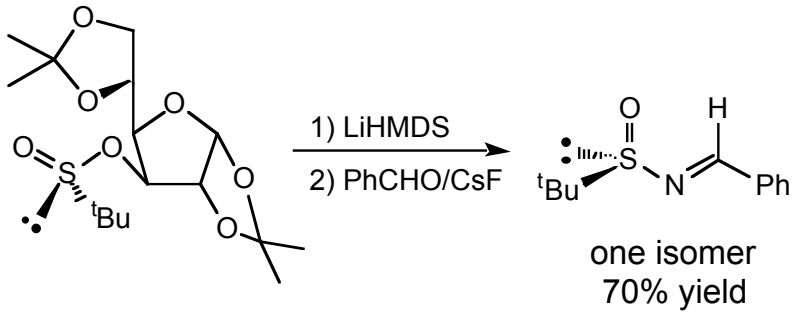
A)



B)



C)

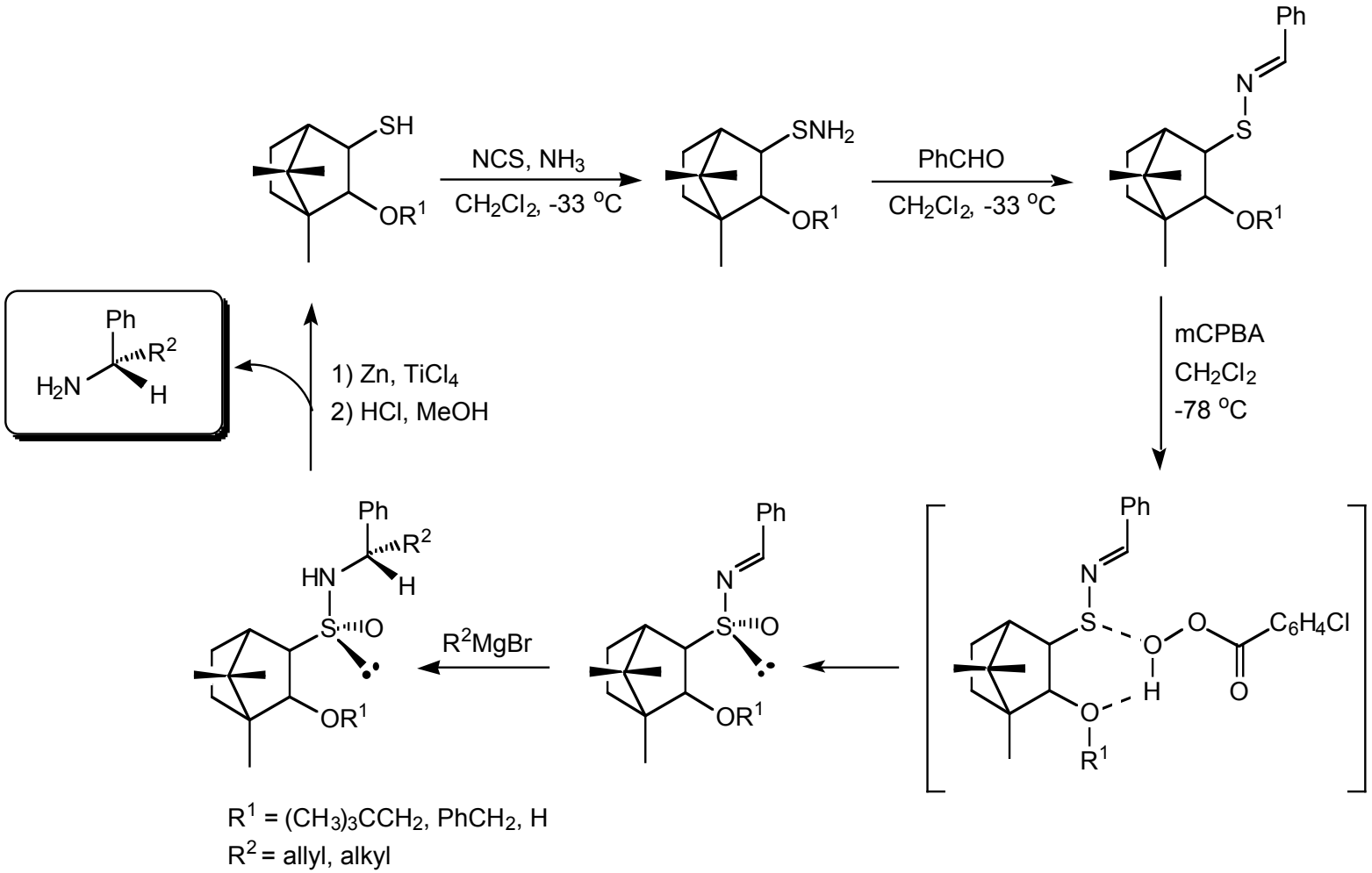


Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4-6.

Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett.* **1993**, *34*, 6229-6232.

Garcia Ruano, J. L.; Fernandez, I.; Prado Catalina, M. D.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407-3414.

Asymmetric Synthesis of α-Branched Amines - Method I

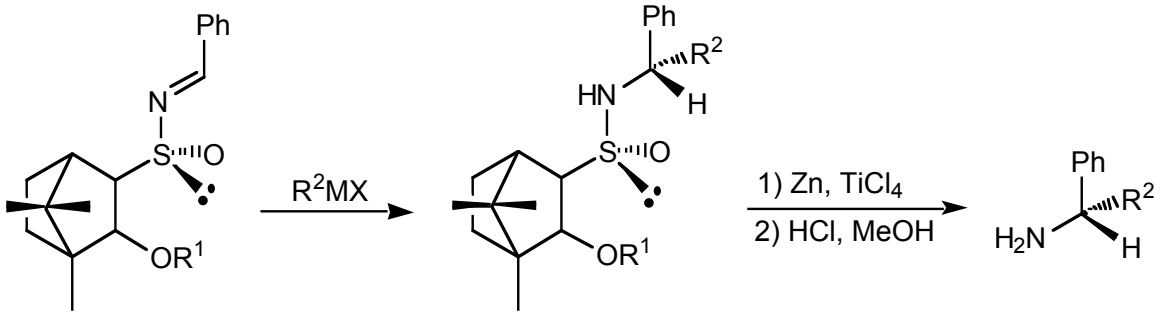


R^1 = $(CH_3)_3CCH_2$, $PhCH_2$, H

R^2 = allyl, alkyl

Yang, T.-K.; Chen, R.-Y.; Lee, D.-S.; Peng, W.-S.; Jiang, Y.-Z.; Mi, A.-Q.; Jong, T.-T. *J. Org. Chem.* **1994**, *59*, 914-921.

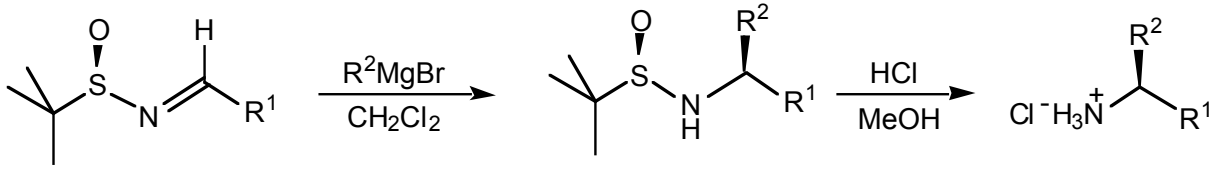
Reactions of Sulfinimines and Grignard Reagents



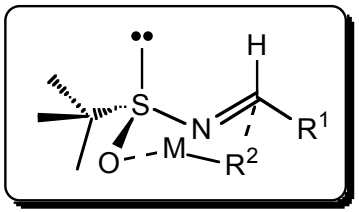
Entry	R^1	R^2MX	Sulfinamide		Amine	
			Yield, %	% de	Yield, %	% ee
1	$(CH_3)_3CCH_2$	CH_2=$CHCH_2MgBr$	96	> 98	80	99
2	$(CH_3)_3CCH_2$	CH_3MgI	96	> 97	56	> 99
3	$(CH_3)_3CCH_2$	t-C_4H_9MgBr	60	> 98	80	> 98
4	$PhCH_2$	CH_2=$CHCH_2MgBr$	84	> 98	80	> 98
5	$PhCH_2$	CH_3MgI	84	> 98	-	-
6	$PhCH_2$	t-C_4H_9MgBr	50	> 98	-	-

Yang, T.-K.; Chen, R.-Y.; Lee, D.-S.; Peng, W.-S.; Jiang, Y.-Z.; Mi, A.-Q.; Jong, T.-T. *J. Org. Chem.* **1994**, *59*, 914-921.

Asymmetric Synthesis of α-Branched Amines -- Method II

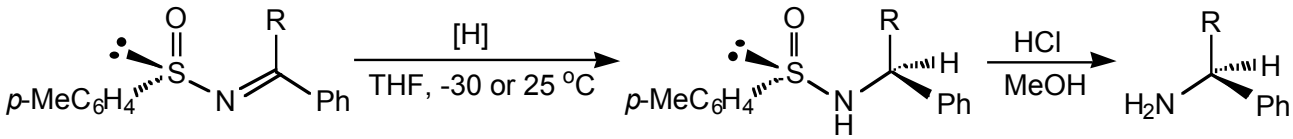


Entry	R^1	R^2	Sulfinamide		Amine	
			Yield, %	dr	Yield, %	Config.
1	Et	Me	96	93:7	97	S
2	Et	i-Pr	97	92:8	92	R
3	Et	Ph	100	96:4	90	R
4	i-Pr	Me	99	98:2	97	S
5	i-Pr	Et	100	97:3	93	S
6	i-Pr	Ph	98	89:11	91	R
7	Ph	Me	96	97:3	88	S
8	Ph	Et	98	92:8	94	S

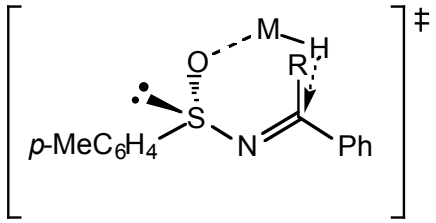


Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913-9914.

Asymmetric Synthesis of α-Branched Amines - Method III

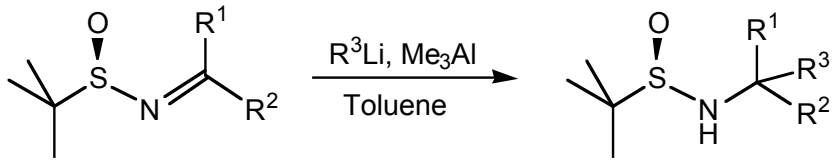


- R = Me, Et, *n*-Bu
- DIBAL or $LiAlH_2(OMe)_2$: 88-92% de, 90-96% yield.
- Optically pure amine then easily obtained from column chromatography with high yield.
- $LiAlH_4$ and $NaBH_4$ gave lower optical yield.



Annuniziata, R.; Cinqini, M.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 339-343.
Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4-6.

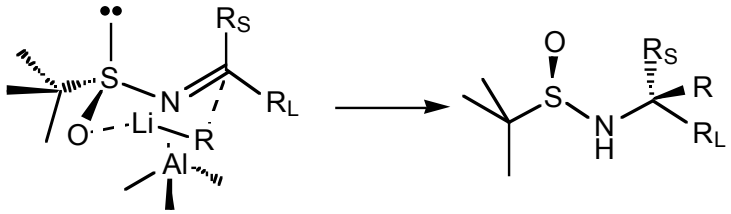
Asymmetric Synthesis of α,α-Dibranched Amines

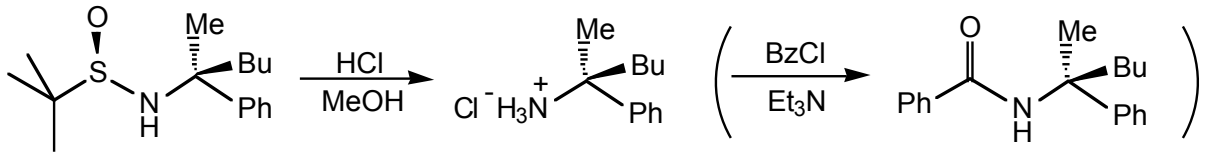


Entry	R^1	R^2	R^3	Me_3Al (eq.)	Config.	Yield, %	dr
1	Me	i-Pr	Ph	0	R	65	94:6
2	Me	i-Pr	Ph	1.1	R	93	97:3
3	Me	Ph	Bu	0	S	26	99:1
4	Me	Ph	Bu	1.1	S	86	98:2
5	Me	Bu	Ph	0	R	67	63:37
6	Me	Bu	Ph	1.1	R	93	89:11
7	Bu	Ph	Me	1.1	R	Quant.	99:1
8	Me	i-Pr	Bu	1.1	S	61	99:1
9	Bu	i-Pr	Me	0	R	54	82:18
10	Bu	i-Pr	Me	1.1	R	82	91:9

Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268-269.

Proposed Model Consistent with Observed Stereoselection





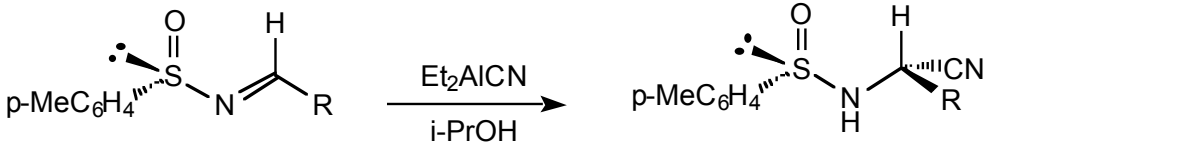
Quant. yield

Quant. yield

** First general method for the asymmetric synthesis of chiral acyclic α,α-dibranched amines.

Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268-269.

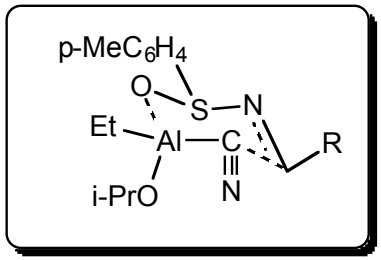
Asymmetric Synthesis of α-Amino Acids - Method I

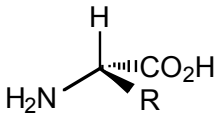


R = Ph, tBu

84-90% yield
82-86% de (cryst. > 96% de)

6M HCl



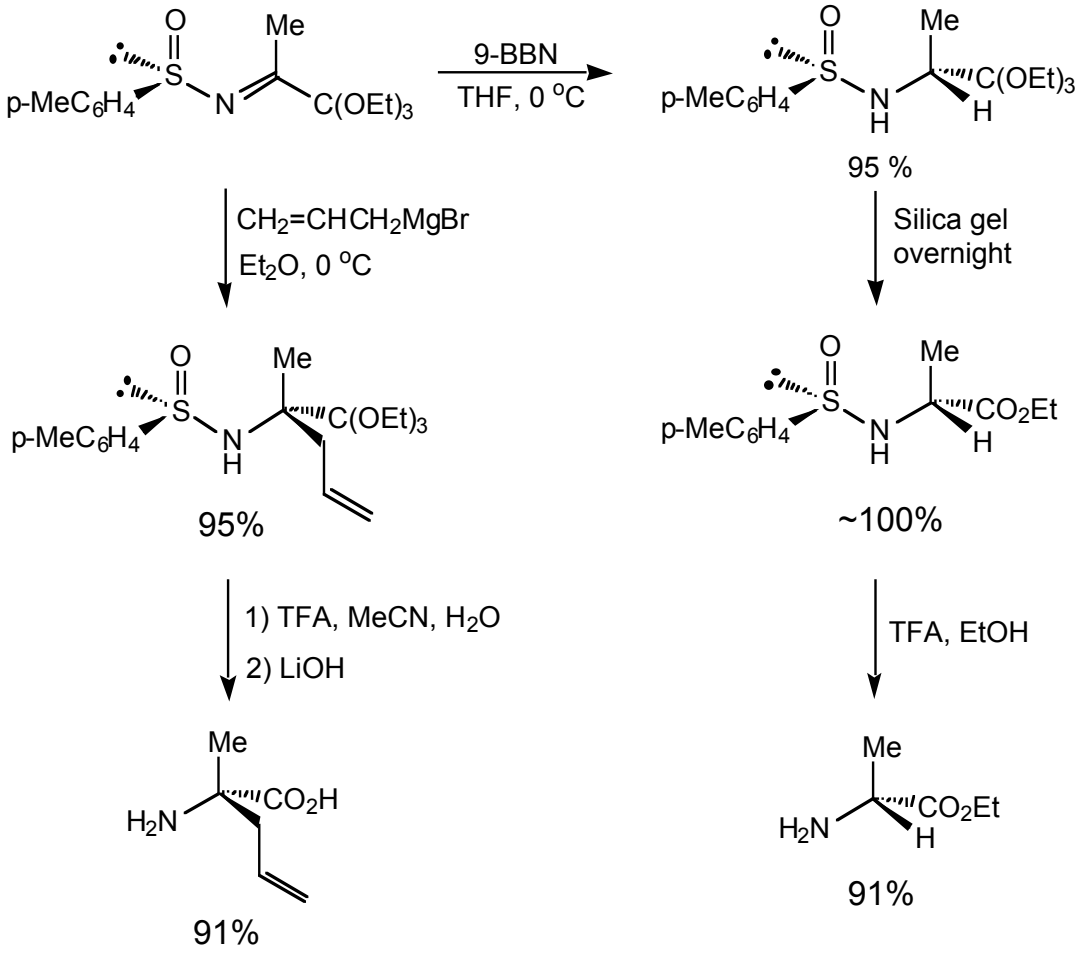


70-86% yield
> 95% ee

Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y. *J. Org. Chem.* **1996**, *61*, 440-441.

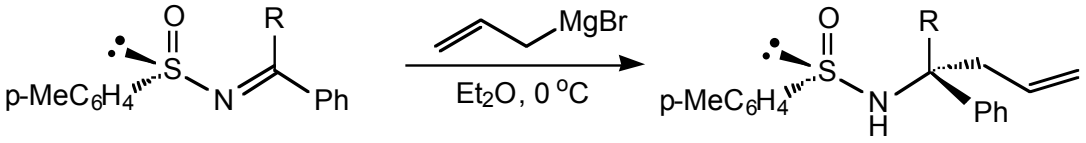
Davis, F. A.; Lee, S.; Zhang, H.; Fanelle, D. L. *J. Org. Chem.* **2000**, *65*, 8704-8708.

Asymmetric Synthesis of α-Amino Acids - Method II

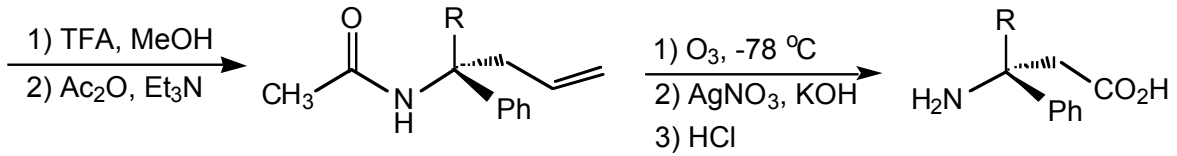


Hua, D. H.; Lagneau, N.; Wang, H.; Chen, J. *Tetrahedron: Asymmetry* **1995**, *6*, 349-352.

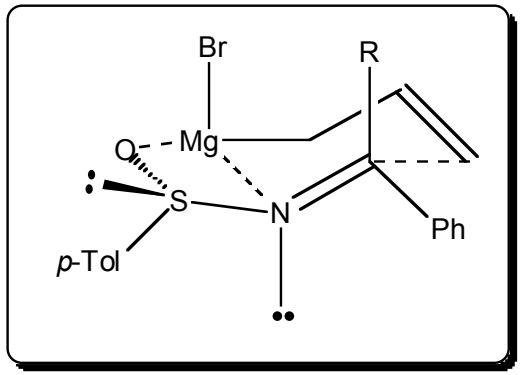
Asymmetric Synthesis of β-Amino Acids - Method I



R = Me, 98%, one diastereomer
R = n-Bu, 84%, de = 82%

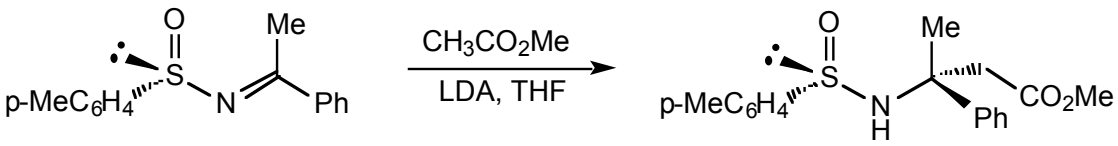


50-52% (5 steps)

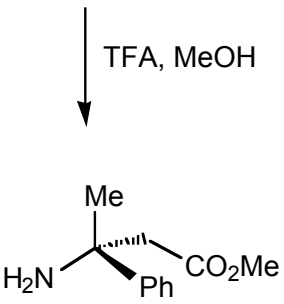


Hua, D. H.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4-6.

Asymmetric Synthesis of β-Amino Acids - Method II



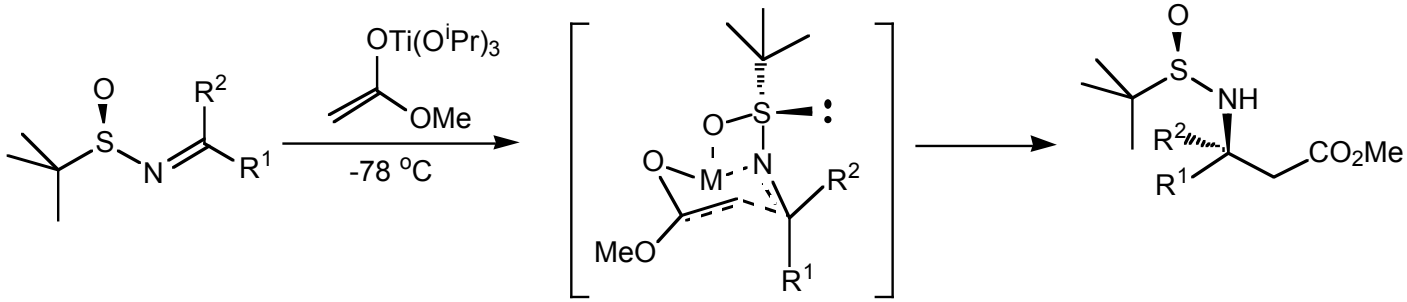
>97% de
84% yield



85%

Davis, F. A,; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387-6389.

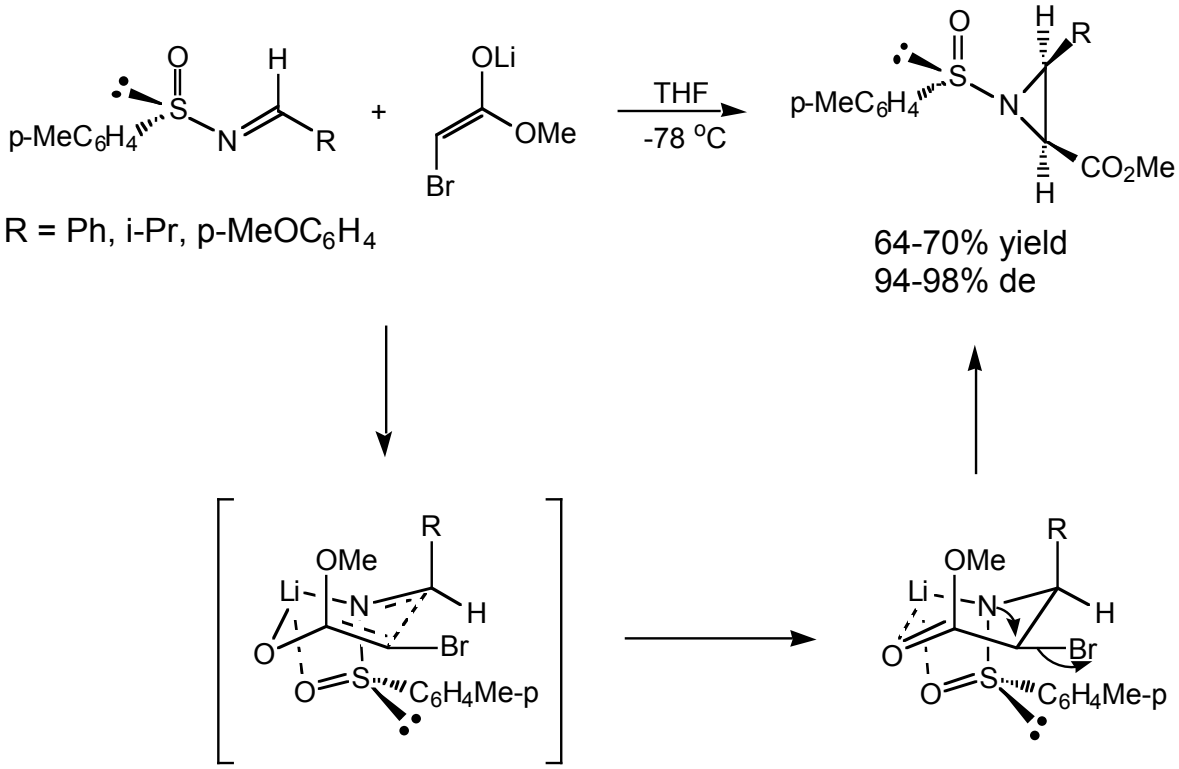
Asymmetric Synthesis of β-Amino Acids - Method III



Entry	R^1	R^2	Yield, %	dr
1	Me	H	94	99:1
2	i-Pr	H	85	98:2
3	i-Bu	H	80	98:2
4	Ph	H	90	98:2
5	3-Pyr.	H	70	95:5
6	i-Pr	Me	85	99:1
7	Ph	Me	89	98:2

Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12-13.

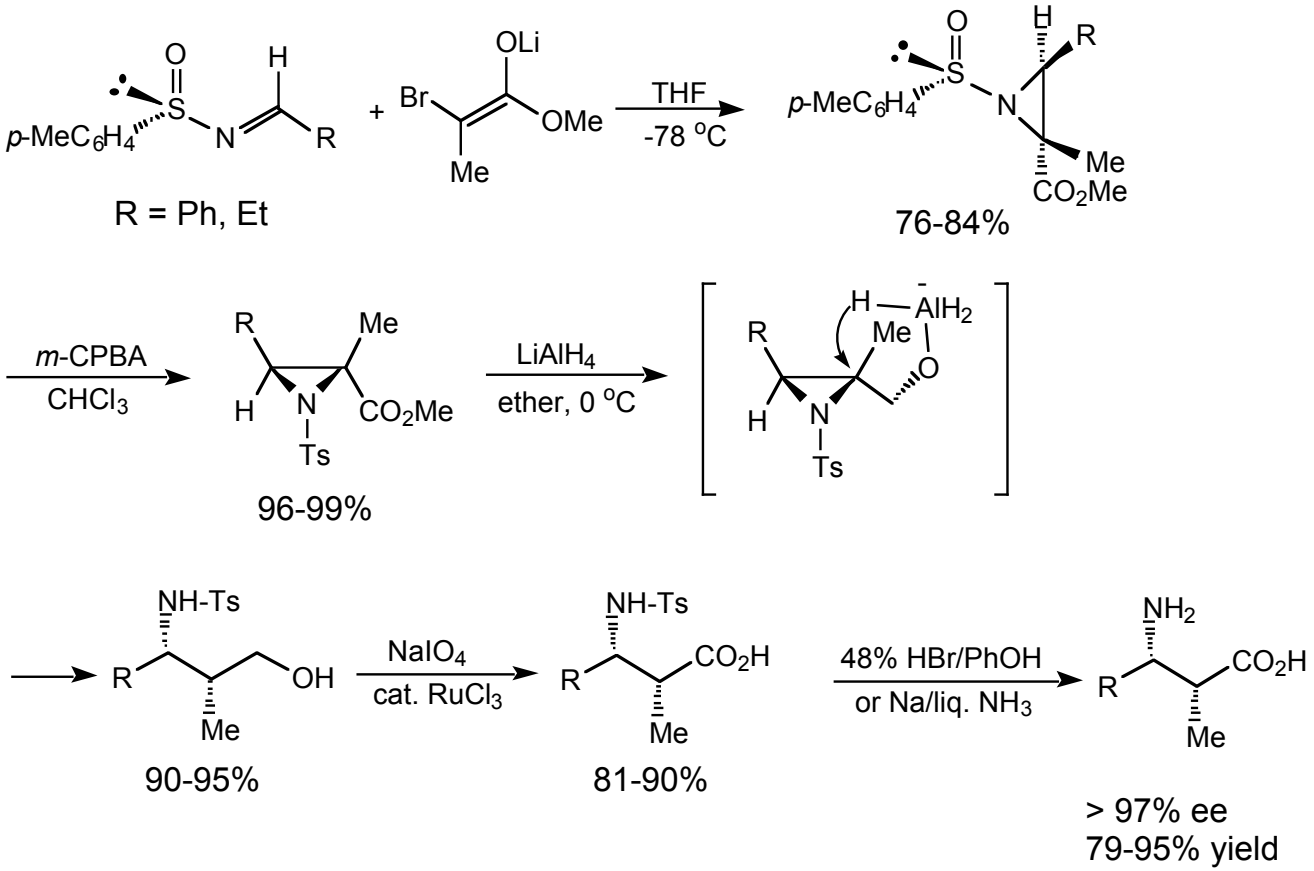
Asymmetric Synthesis of Aziridine-2-Carboxylate Esters



Davis, F. A,; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243-3245.

Davis, F. A.; Zhou, P. *Tetrahedron Lett.* **1994**, *35*, 7525-7528.

Asymmetric Synthesis of α-Alkyl-β-Amino Acids Using Aziridines

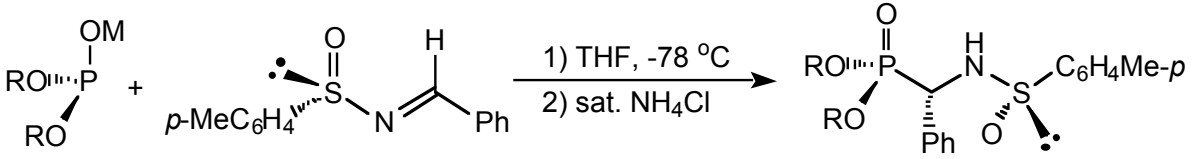


Davis, F. A.; Zhou, P. *Tetrahedron Lett.* **1994**, *35*, 7525-7528.

Davis, F. A.; Reddy, G. V.; Liang, C.-H. *Tetrahedron Lett.* **1997**, *35*, 5139-5142.

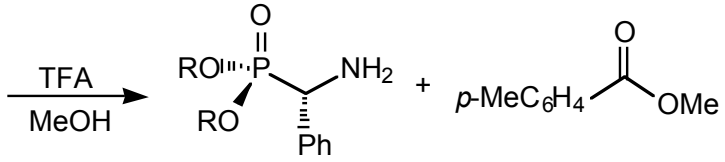
Tanner, D.; Gautn, O. R. *Tetrahedron* **1995**, *51*, 8279-8288.

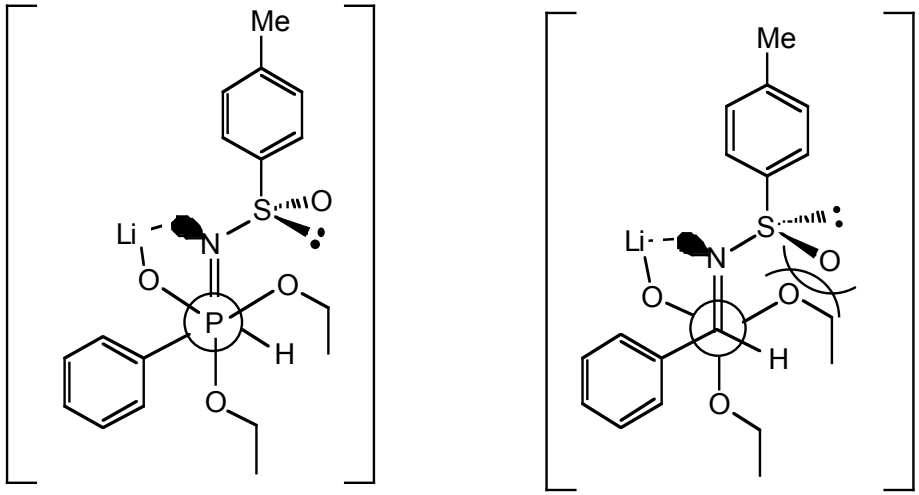
Asymmetric Synthesis of α-Aminophosphonic Acids



R = Et, *i*-Pr
M = Li, Na

93-97% de
80-82% yield





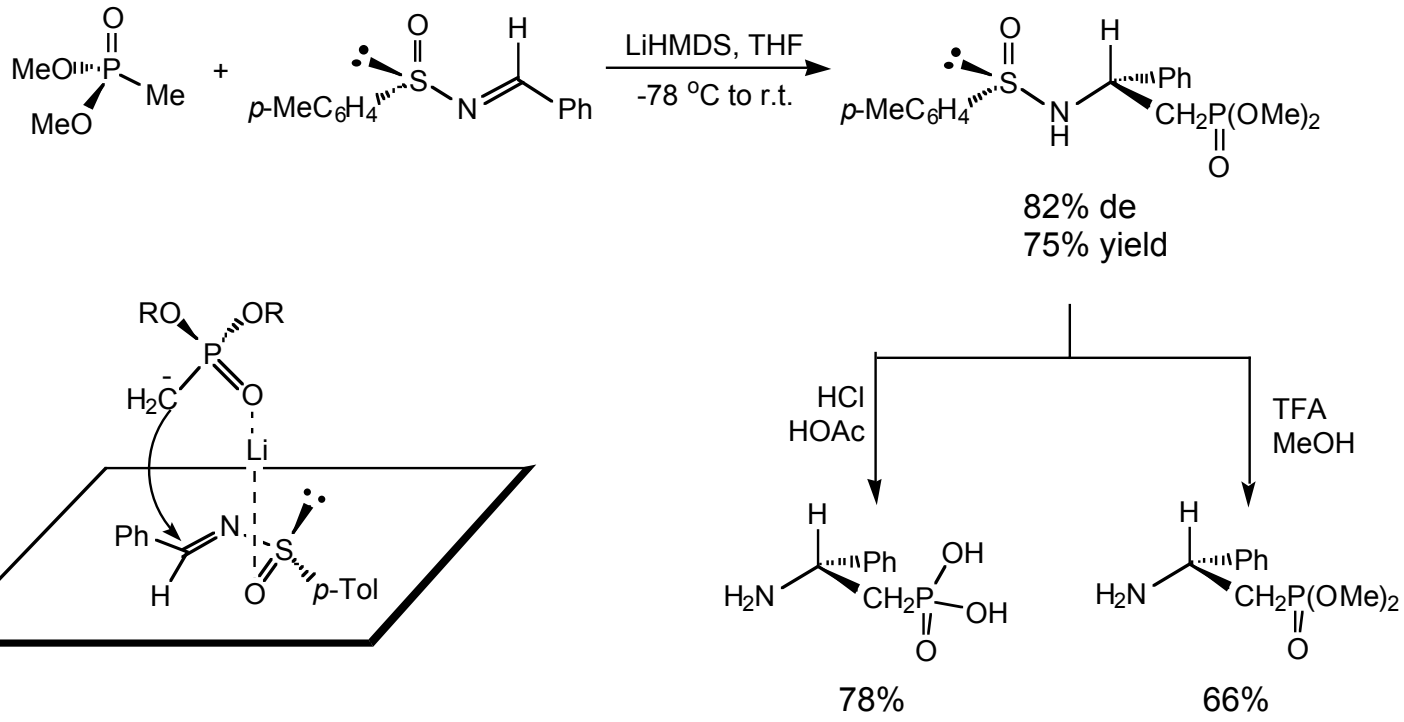
favored

disfavored

Lefebvre, I M.; Evans, S. A. *J. Org. Chem.* **1997**, *62*, 7532-7533.

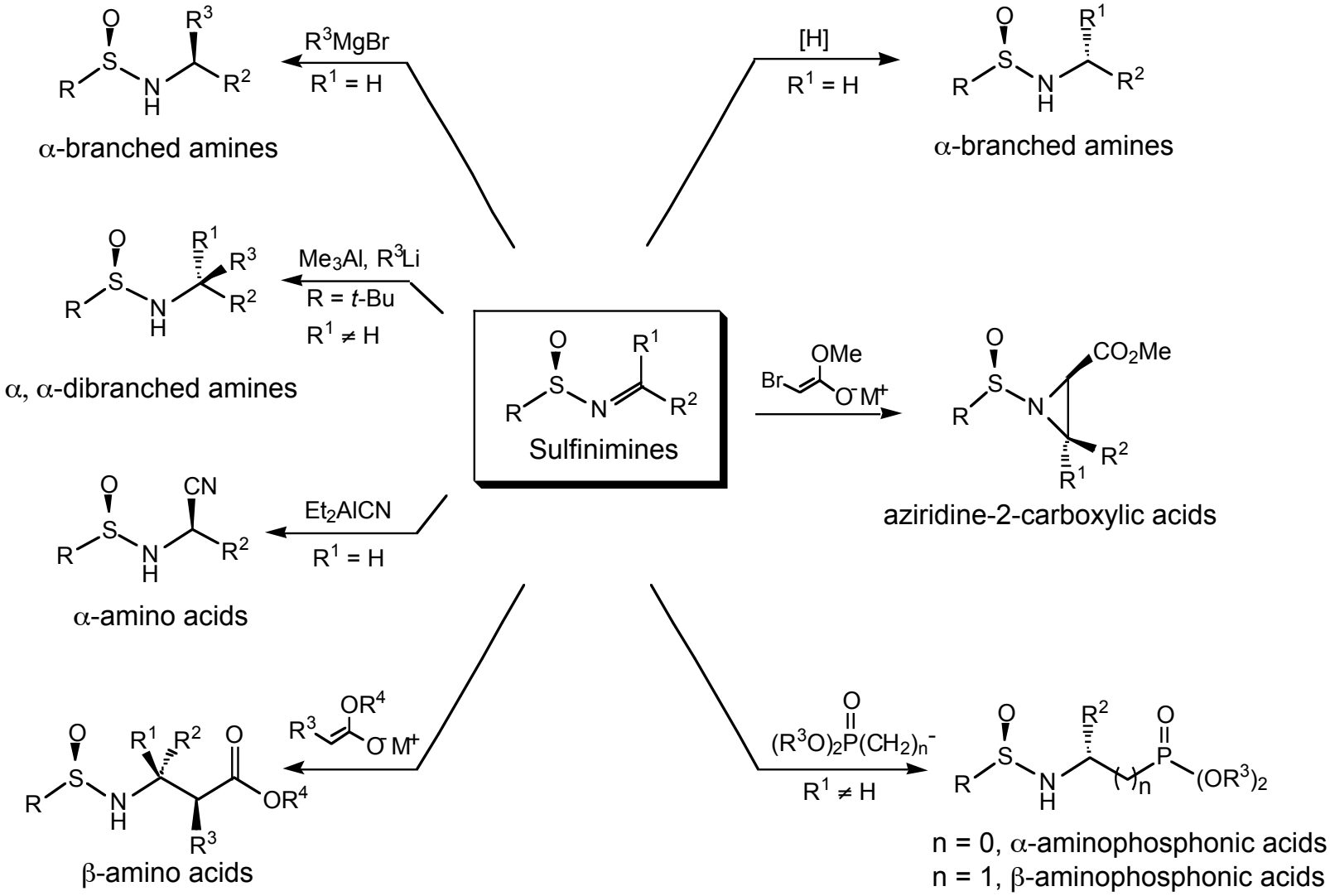
Smith, A. B., III Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10879-10880.

Asymmetric Synthesis of β-Aminophosphonic Acids

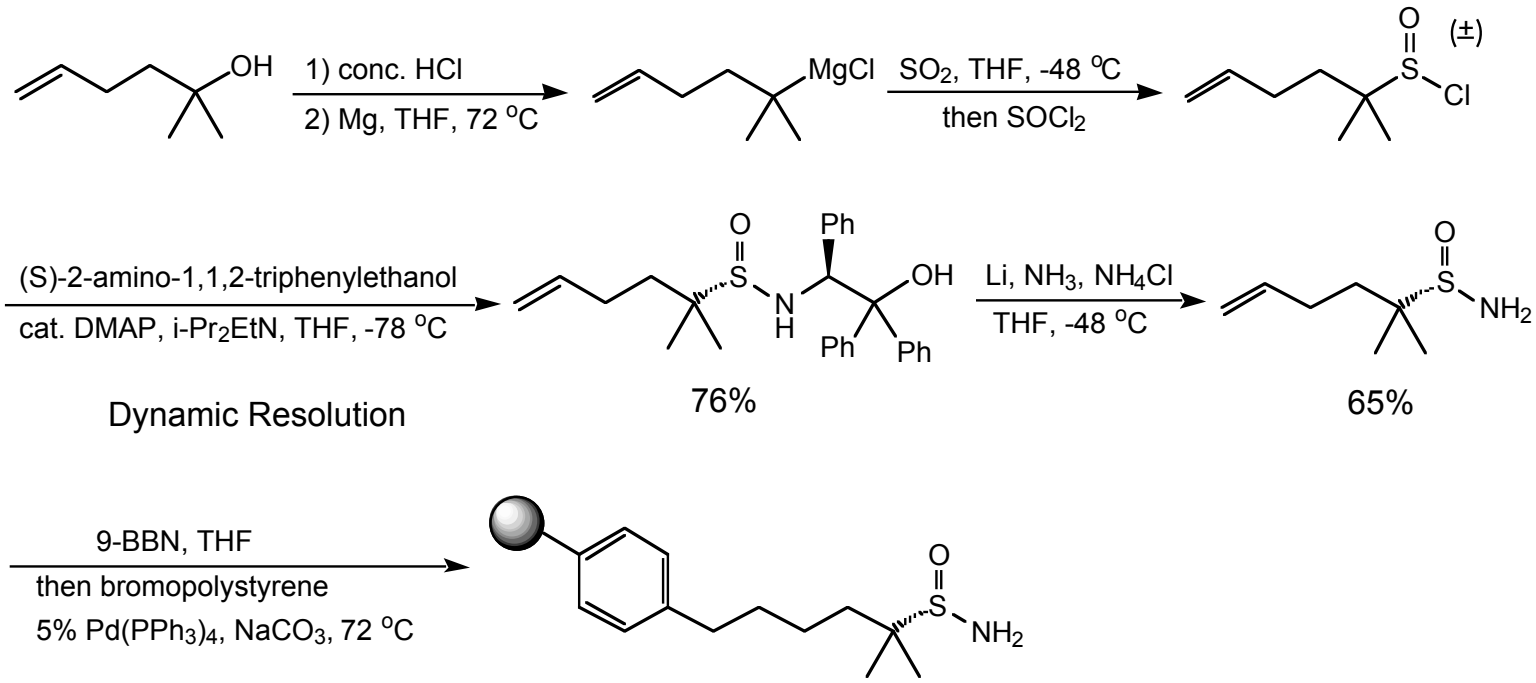


Mikolajczyk, M.; Lyzwa, P.; Drabowicz, J.; Wieczorek, M. W.; Blaszczyk, J. *Chem. Commun.* **1996**, 1503-1504.

Chiral Intermediates for Synthesis of Important Amine Derivatives

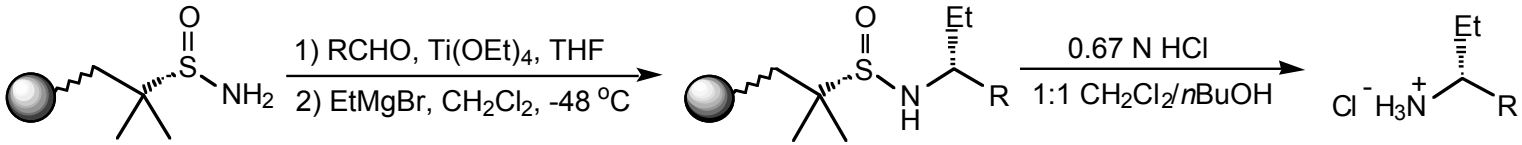


Synthesis of a Support-Bound *tert*-Butanesulfinamide



Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127-10128.

Solid-Phase Synthesis of α-Branched Amines

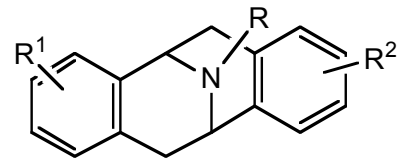


Entry	R	Yield, %	dr
1	*i*-Pr	95	97:3 (97:3)
2	Ph	95	88:12 (92:8)
3	Bn	90	89:11 (92:8)
4	*p*MeOPh	95	96:4 (99:1)

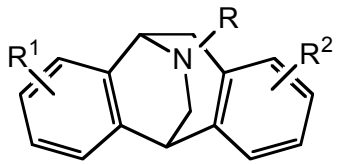
Note: Numbers in parentheses represent solution-phase results.

Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127-10128.

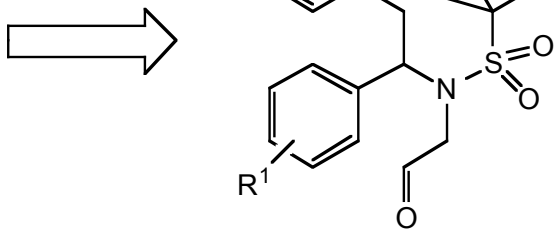
Pomeranz-Fritsch Synthesis of Pavine and Isopavine Alkaloids



Pavine classes of alkaloids

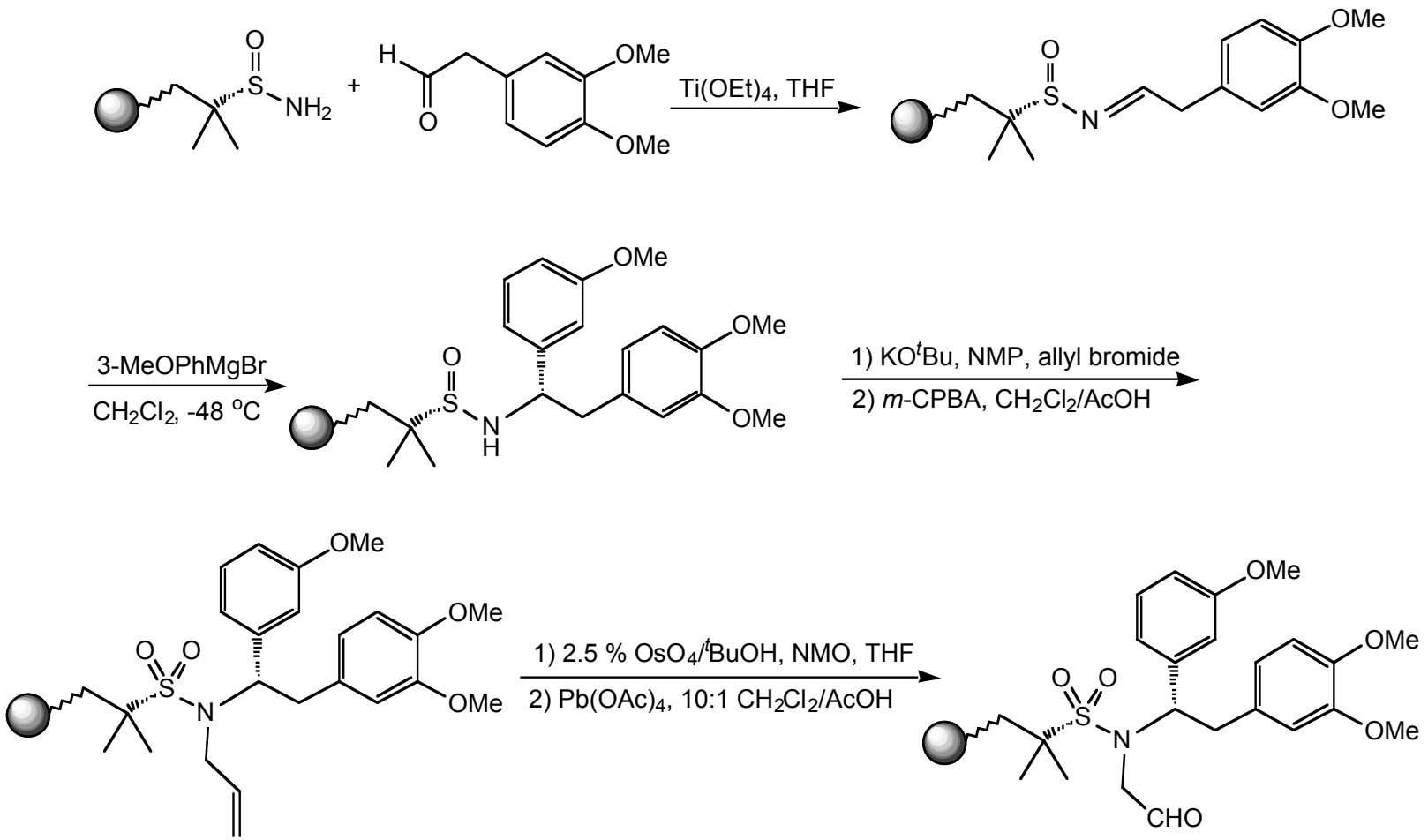


Isopavine classes of alkaloids



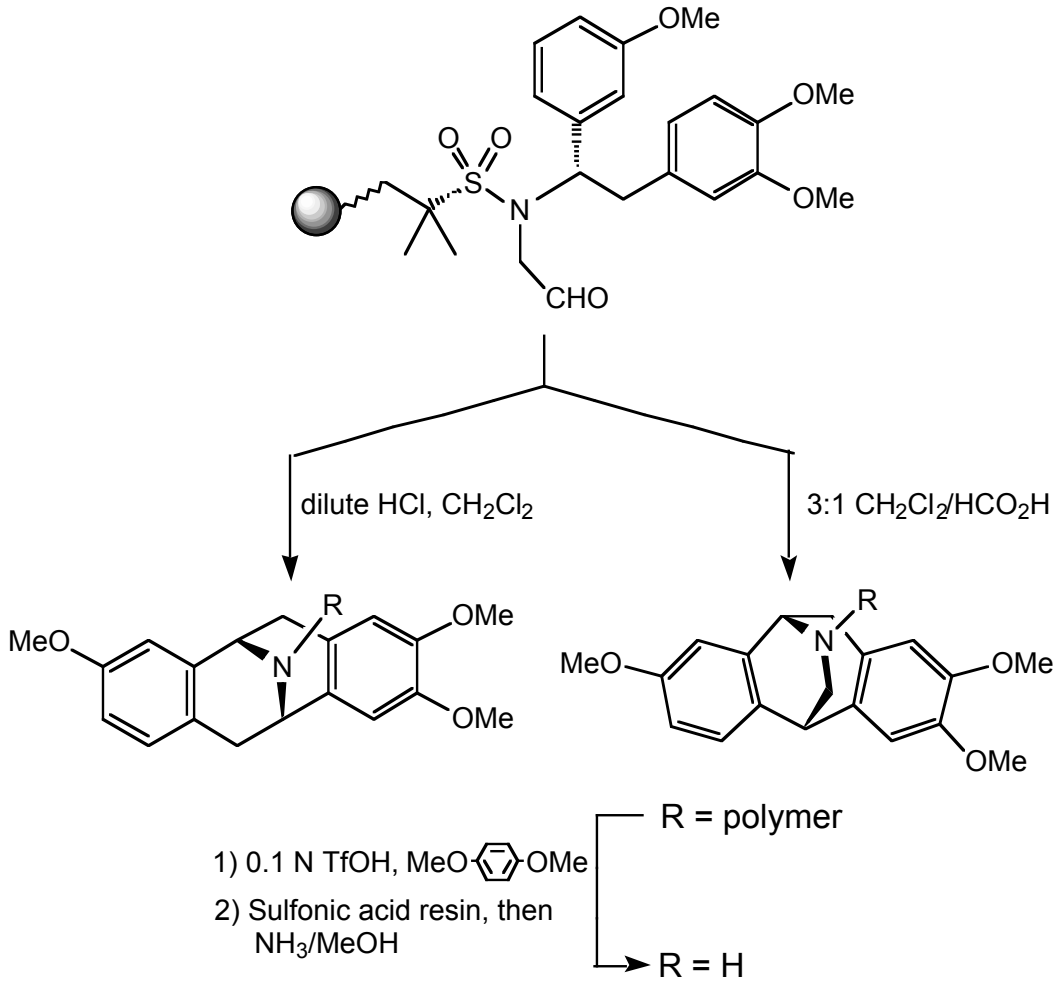
Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127-10128.

Solid-Phase Pomeranz-Fritsch Synthesis of Pavine and Isopavine Alkaloids



Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127-10128.

Solid-Phase Pomeranz-Fritsch Synthesis of Pavine and Isopavine Alkaloids

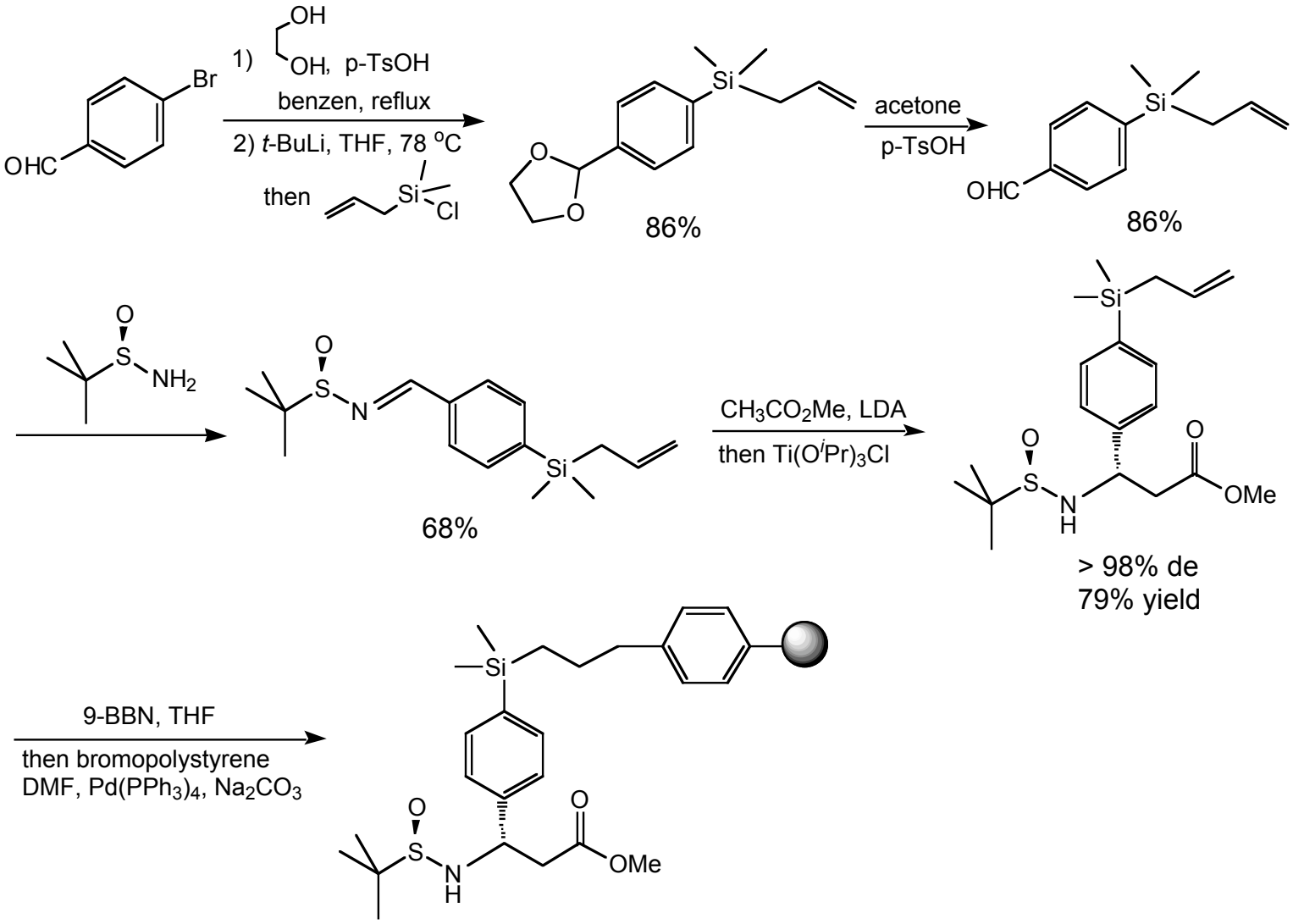


45% overall yield
86:14 enantiomeric ratio

47% overall yield
86:14 enantiomeric ratio

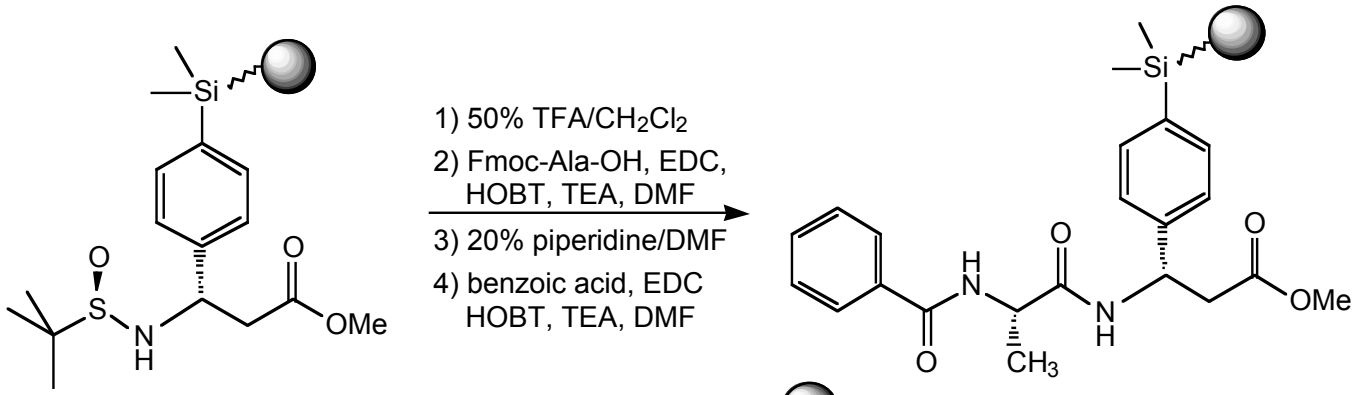
Dragoli, D. R.; Burdett, M. T.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 10127-10128.

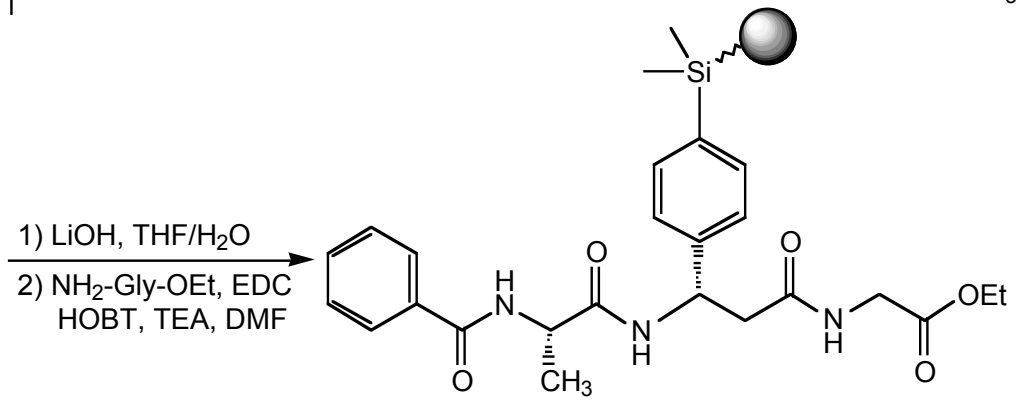
Synthesis of Polymer-Bound Chiral 3-Phenyl β-Alanine Building Block

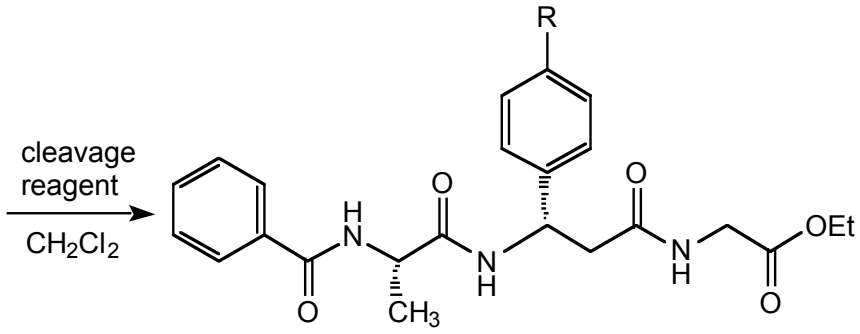


Lee, Y.; Silverman, R. B. *Org. Letter* **2000**, *3*, 303-306.

Solid-Phase Synthesis of Chiral 3-Aryl β-Amino Acid Containing Peptides







Reagent	R	Yield (%)	Purity (%)
50% TFA	H	88	> 95
Br_2	Br	95	> 95
ICl	I	95	> 95

Lee, Y.; Silverman, R. B. *Org. Letter* **2000**, *3*, 303-306.

Conclusions

- Chiral sulfoxides have been used in a variety of stereoselective carbon-carbon bond-forming reactions, such as Aldol reaction, Diels-Alder reaction and Michael additions.

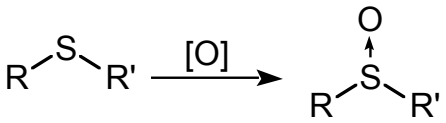
- Chiral sulfoxides can be used in asymmetric Heck reaction as stereochemical controllers, by the coordination of Pd to an amino group tethered to the sulfoxides, rather than by direct steric control. This chiral auxiliary-based procedure constitutes an alternative to the use of chiral bidentate ligands in asymmetric Heck reaction.

- Sulfinimines are being utilized as versatile chiral nitrogen intermediates for the preparation of a range of chiral amines, including α-branched and α,α-dibranched amines, α- and β-amino acids, aziridines and α- and β-amino phosphonic acids.

- Solid-phase asymmetric synthesis of amine and amino acid containing molecules has also been studied. These studies should provide for the generation of combinatorial libraries.

Preparation of Chiral Sulfoxides

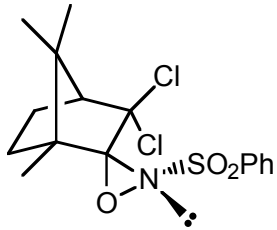
1. Asymmetric Oxidation



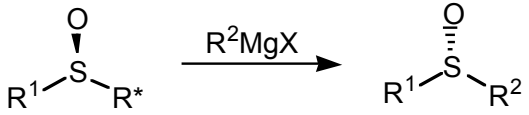
$Ti(O^iPr)_4$ / (+)-DET / ^tBuOOH

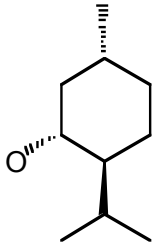
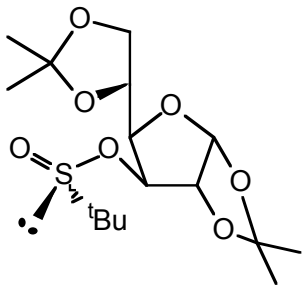
$Ti(O^iPr)_4$ / (+)-DET / $Ph(CH_3)_2OOH$

$Ti(O^iPr)_4$ / (+)-BINOL / ^tBuOOH

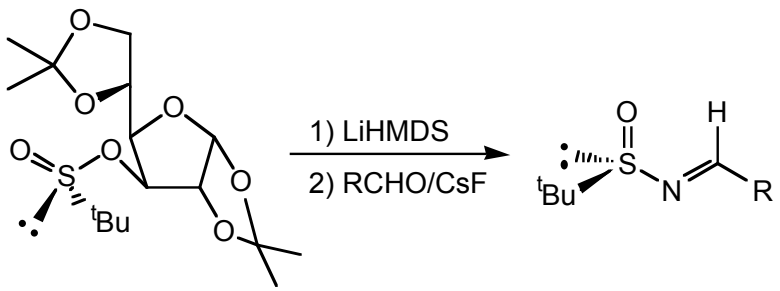


2. Asymmetric Synthesis (Nucleophilic Substitution on Chiral Sulfur)



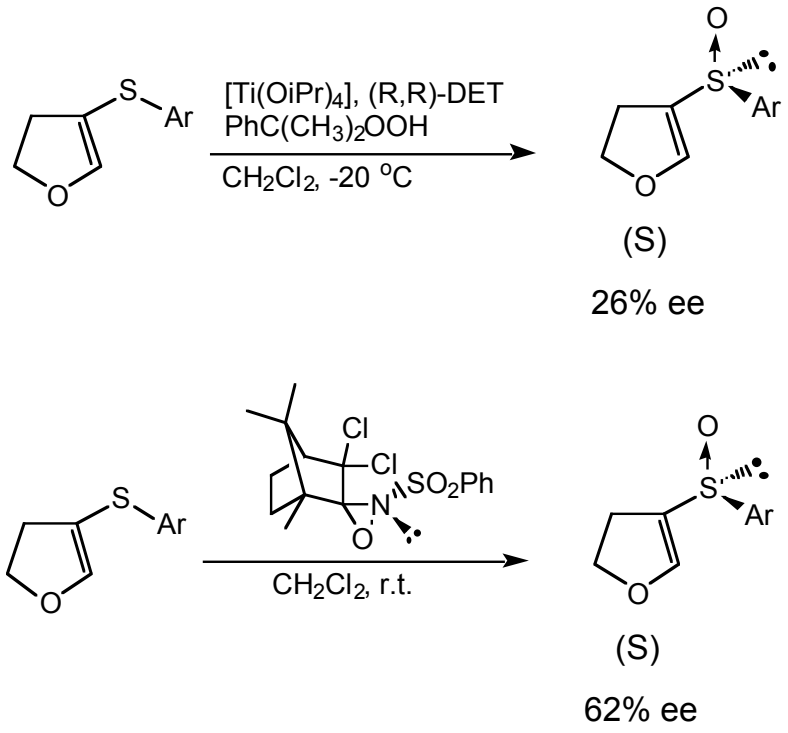
R* =  or 

Asymmetric Iminolysis of Sulfinates



Garcia Ruano, J. L.; Fernandez, I.; Prado Catalina, M. D.; Cruz, A. A. *Tetrahedron: Asymmetry* **1996**, *7*, 3407-3414.

Attempted Enantioselective Synthesis of α,β-Unsaturated Sulfoxides by Asymmetric Oxidation

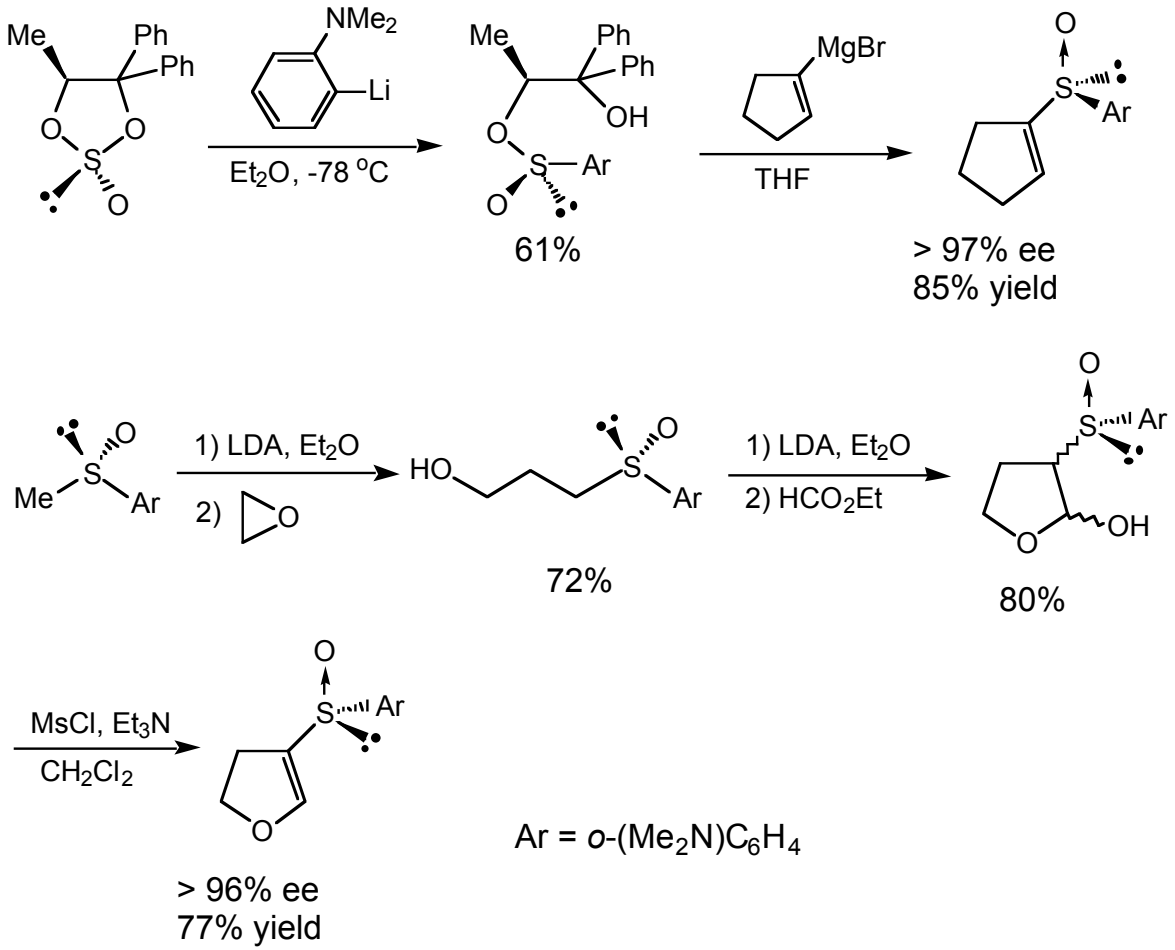


Ar = *o*-$(Me_2N)C_6H_4$

Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129-7130.

Buezo, N. D.; Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890-3900.

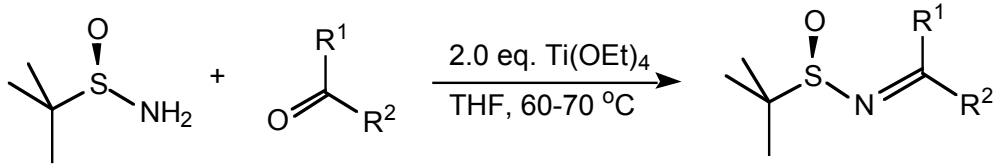
Asymmetric Synthesis of α,β-Unsaturated Sulfoxides Using Enantiomerically Pure Sulfoxides



Buezo, N. D.; Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem. Eur. J.* **2001**, *7*, 3890-3900.

Asymmetric Synthesis of α,α-Dibranched Amines

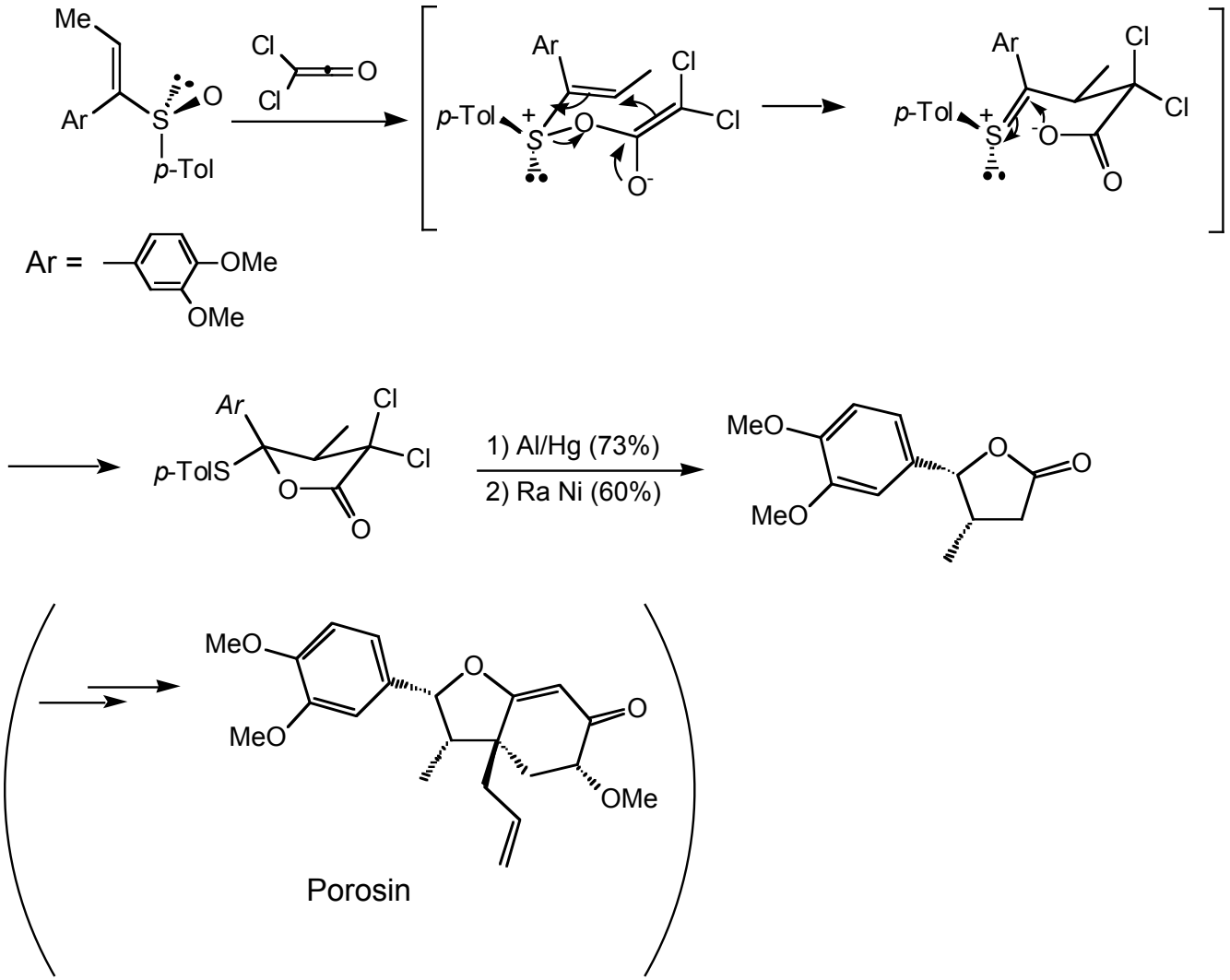
Condensations of Ketones with Sulfinamide



Entry	R^1	R^2	Yield, %	(*E*:*Z*)
1	Me	i-Pr	84	One isomer
2	Me	Ph	87	One isomer
3	Bu	i-Pr	66	One isomer
4	Bu	Ph	77	One isomer
5	Me	Bu	77	5:1

Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268-269.

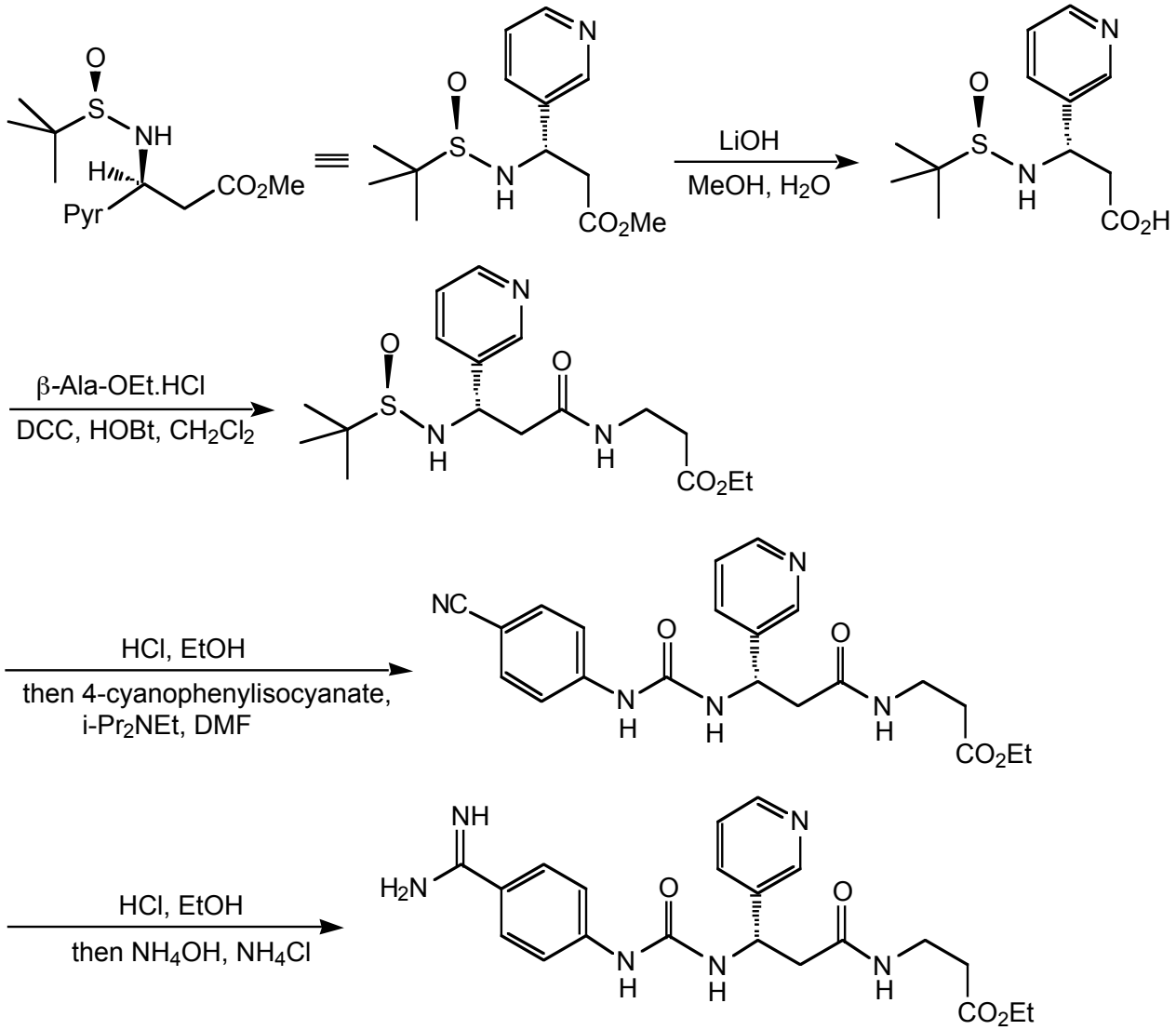
Pummerer Rearrangement



Marino, J. P.; Pradilla, R. F.; Laborde, E. *Synthesis* **1987**, 1088-1092.

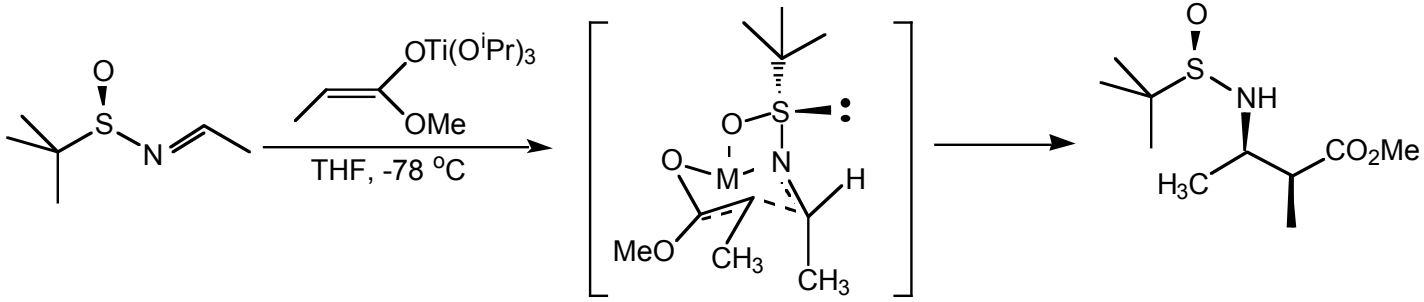
** Carreno, M. C. *Chem. Rev*. **1995**, *95*, 1717-1760.

Asymmetric Synthesis of β-Amino Acids - Method IV



Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12-13.

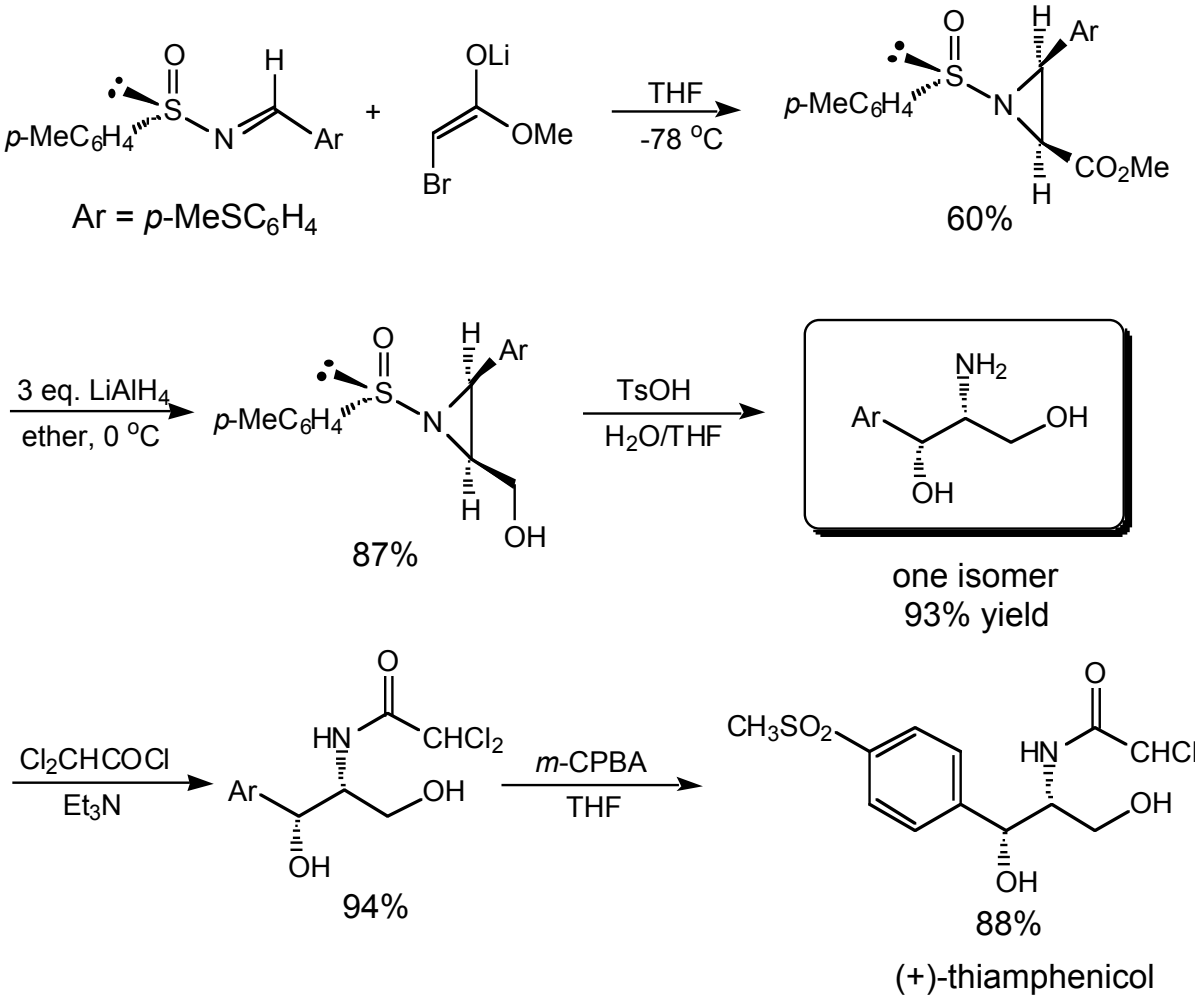
Asymmetric Synthesis of β-Amino Acids - Method IV



Zimmerman-Traxler Transition State

Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12-13.

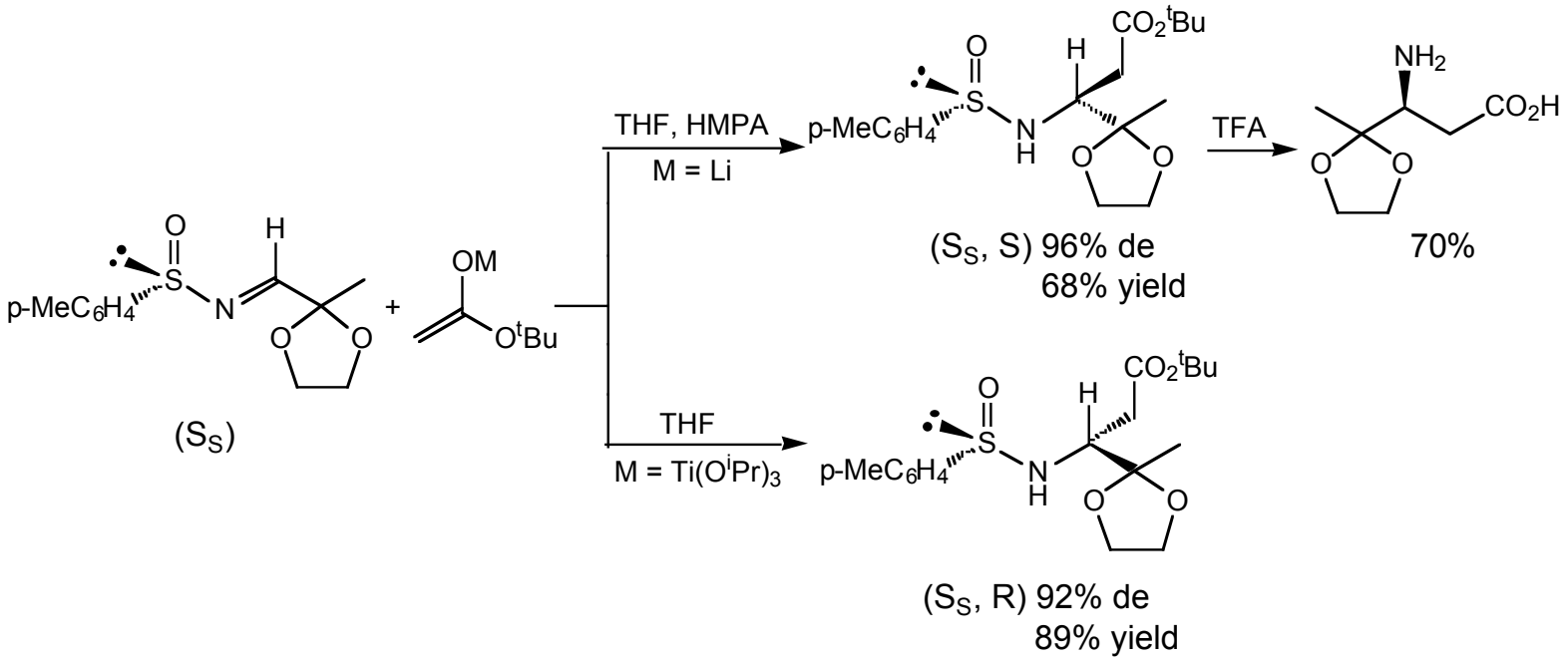
Asymmetric Synthesis of Aziridines and Its Application

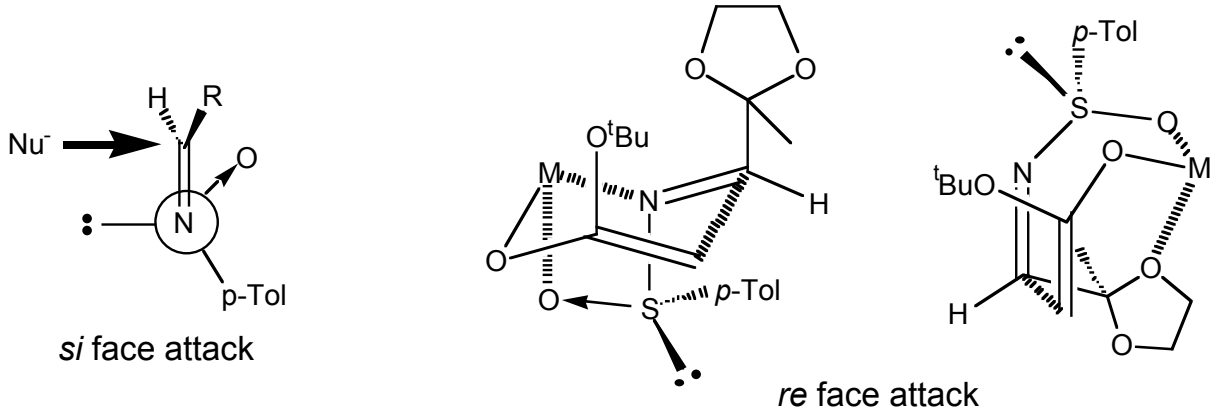


Davis, F. A.; Zhou, P. *Tetrahedron Lett.* **1994**, *35*, 7525-7528.

Davis, F. A,; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243-3245.

Asymmetric Synthesis of β-Amino Acids - Method III





Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881-3884.

Asymmetric Synthesis Using Sulfinimines

1) α-Branched Amines
   α,α-Dibranched Amines

2) α-Amino Acids
   β-Amino Acids

3) Aziridine Derivatives

4) α-Amino Phosphonic acids
   β-Amino Phosphonic acids