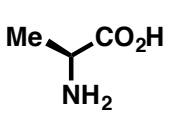

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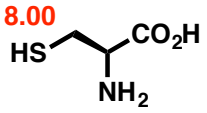

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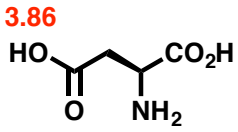

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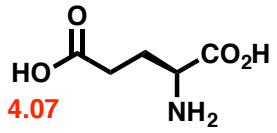

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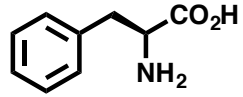

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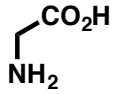

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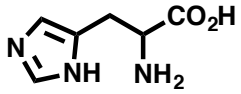

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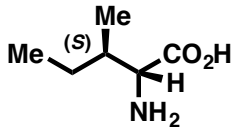

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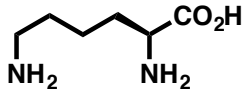

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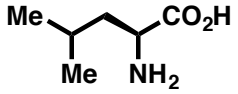

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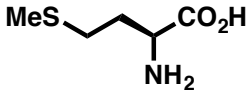

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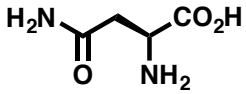

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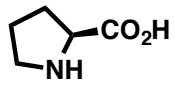

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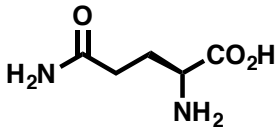

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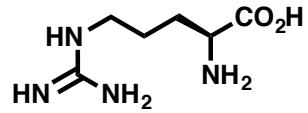

12.48 R

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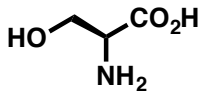

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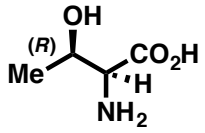

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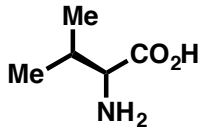

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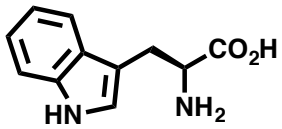

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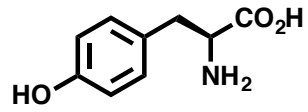


10.07 Y

Tyr

Creativity from the Chiral Pool: Amino Acids

Justine deGruyter

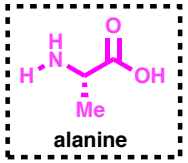
Baran Lab Group Meeting
03.17.2017

Previously on Creativity from the Chiral Pool...
Carvone, Rosen 2012.; *Sugar Edition,* Martinez 2014.

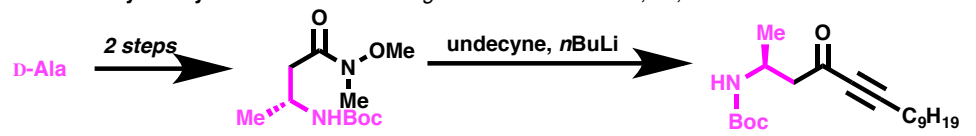
Some recent reviews:
"Recent Advances in Substrate-Controlled Asymmetric Induction Derived from Chiral Pool α-Amino Acids for Natural Product Synthesis"
Molecules. **2016**, *21*, 951.
"α-Amino Acids with Electrically Charged and Polar Uncharged Side Chains as Chiral Synthon: Application to the Synthesis of Bioactive Alkaloids (1996–Dec, 2013)"
Tetrahedron. **2017**, 10.1016/j.tet.2017.02.029

Primary Uses of Chiral Pool Amino Acids:
(a) substrate control: chiral building block; stereocenter present in target molecule and/or lends to generation of new stereocenters
(b) exogenous control: enantioselective agent; chiral catalyst or auxiliary

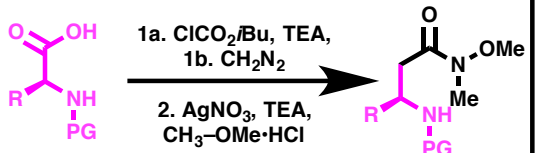
Overview:
- interesting examples that utilize chiral pool AAs in total synthesis
  --> reviewed in alphabetical order by one-letter code
  --> note: not all AAs are covered (lack of material)
- generation of enantiomerically pure heterocycles
- (very!) brief discussion of AAs as chiral catalysts/auxiliaries



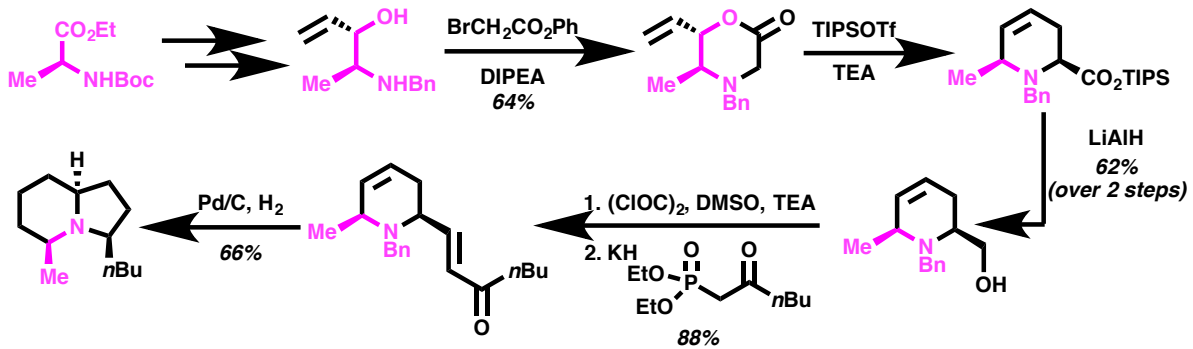
"Total Synthesis of Dendrobate Alkaloid (+)-241D, Isosolenopsin and Isosolenopsin A: Application of a Gold-Catalyzed Cyclization" Gouault. *Org. Biomol. Chem.* **2012**, *10*, 5541.

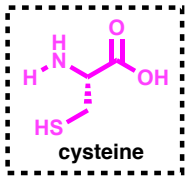


Gouault. *Org. Lett.* **2011**, *13*, 4371.

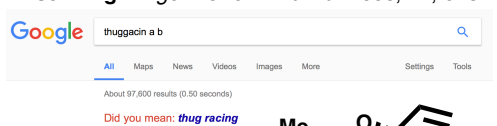


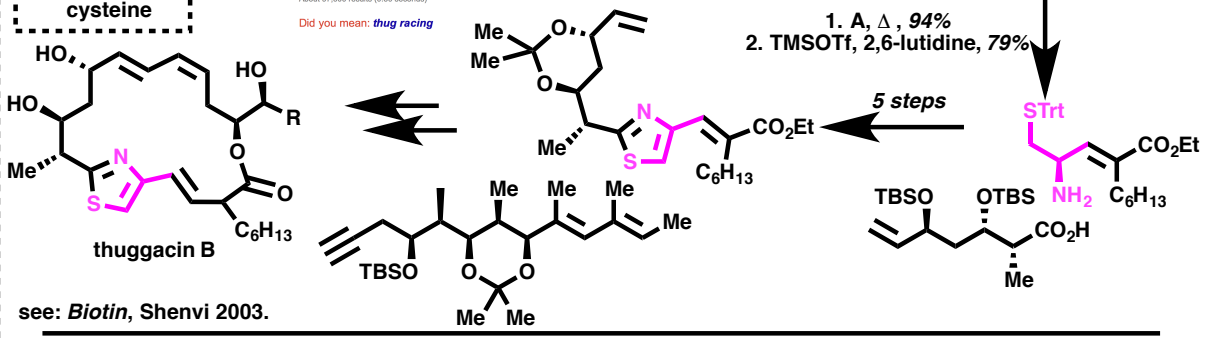
"A General Route for the Synthesis of Enantiopure Indolizidine Alkaloids from α-Amino Acids. Total Synthesis of (+)-Monomorine" Angle. *Tet. Lett.* **1993**, *34*, 3985.



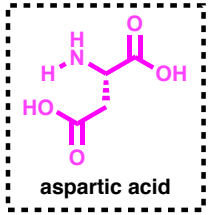


"Total Synthesis of Thuggacin B" Kirschning. *Angew. Chem. Int. Ed.* **2008**, *47*, 9134.

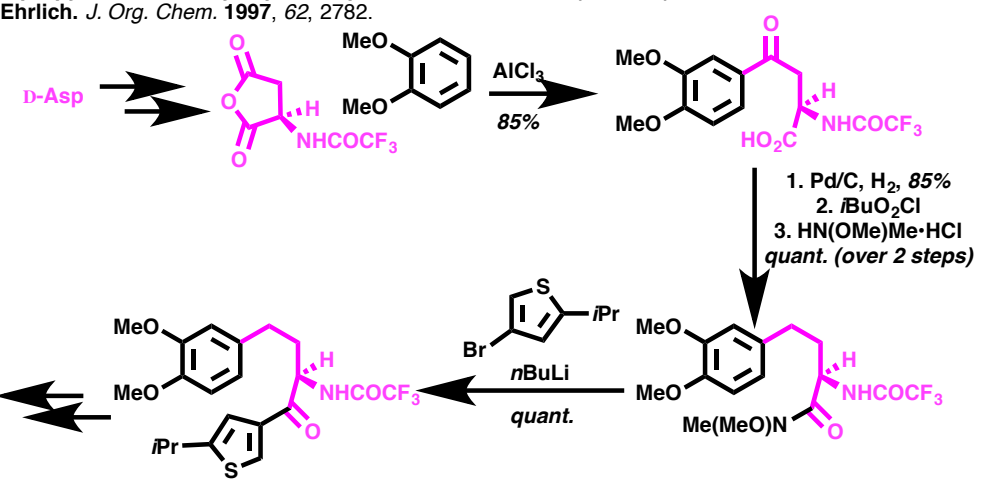




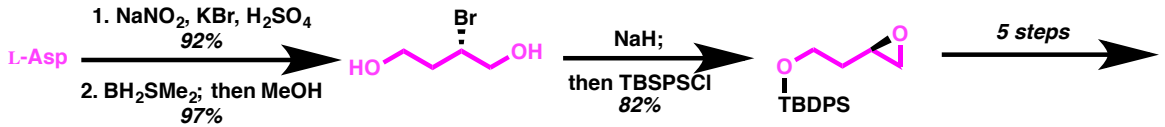
see: ***Biotin***, Shenvi 2003.



"An Efficient Enantoselective Synthesis of the D1 Agonist (5a*R*, 11b*S*)-4,5,5a,6,7,11b,-Hexahydro-2-propyl-3-thia-5-azacyclopenta[c]penanthrene-9,10-diol (A-86929)" Ehrlich. *J. Org. Chem.* **1997**, *62*, 2782.



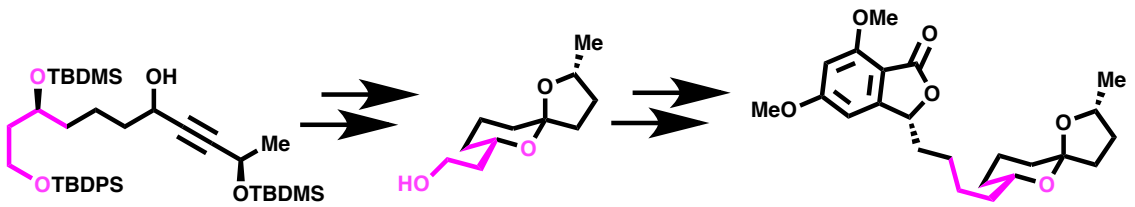
"The First Enantioselective Total Synthesis of the Anti-*Helicobacter pylori* agent (+)-spirolaxine methyl ester" Brimble. *Chem. Commun.* **2005**, 1560.



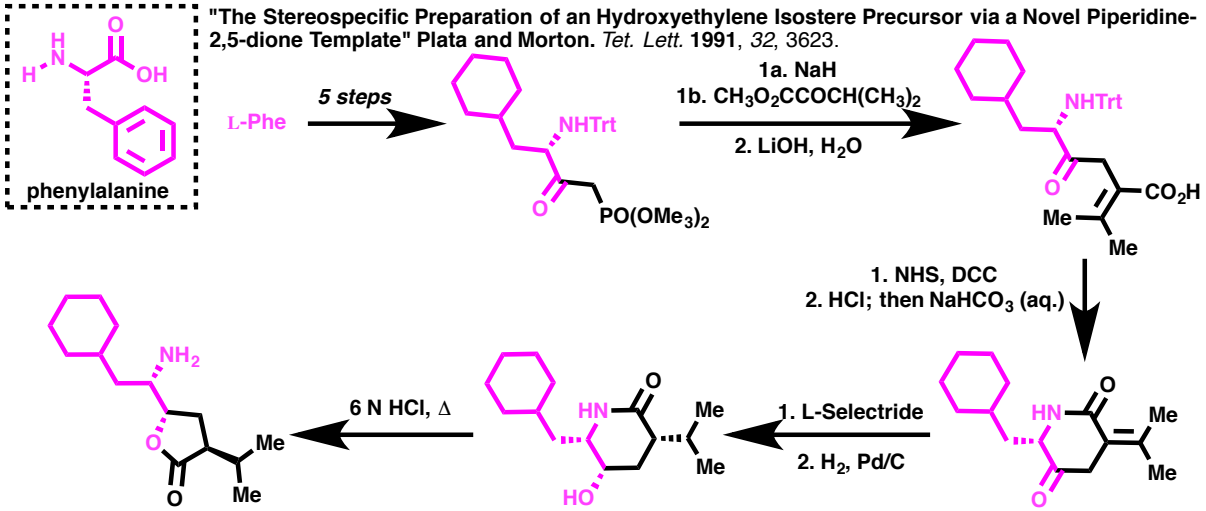
Creativity from the Chiral Pool: Amino Acids

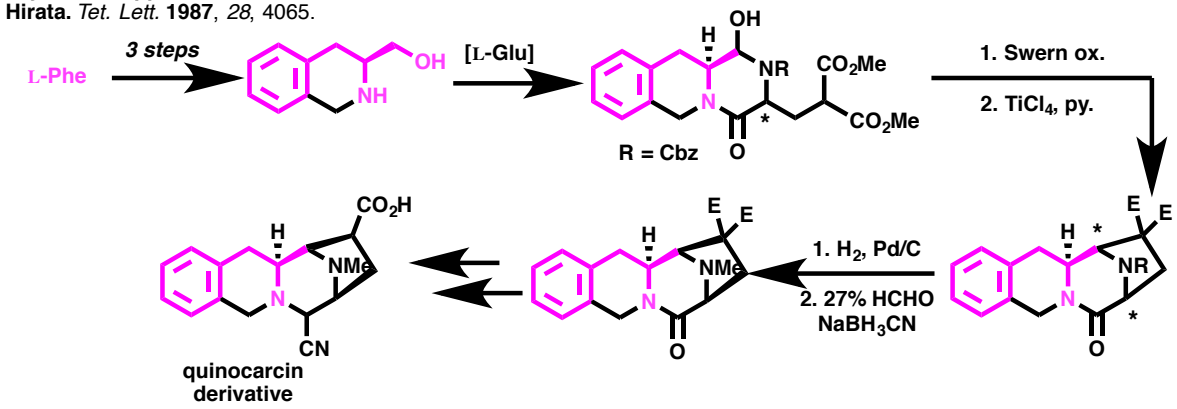
Justine deGruyter

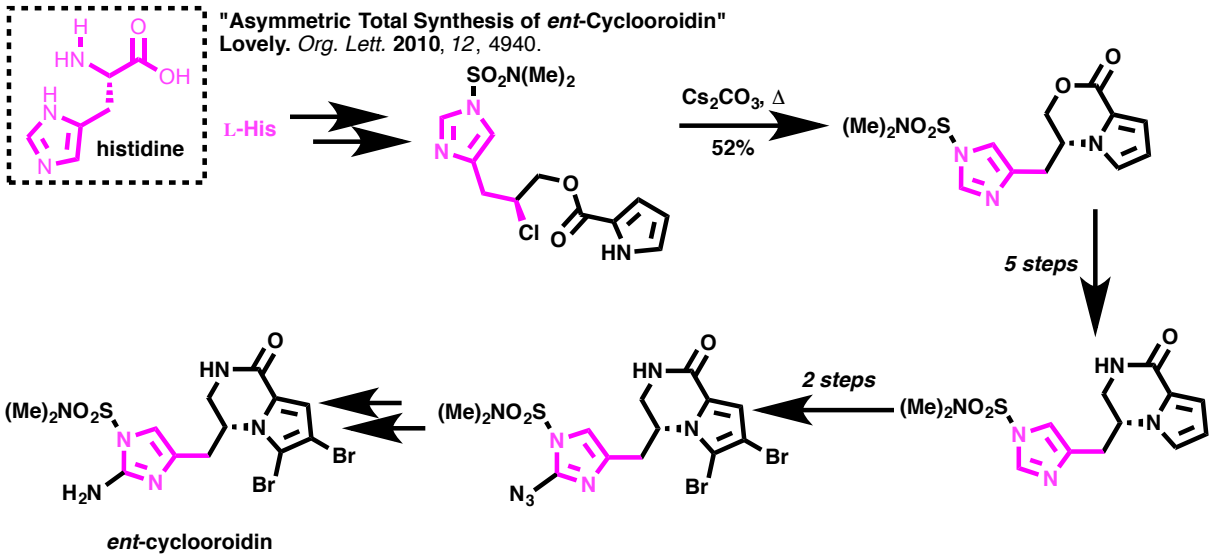
Baran Lab Group Meeting
03.17.2017

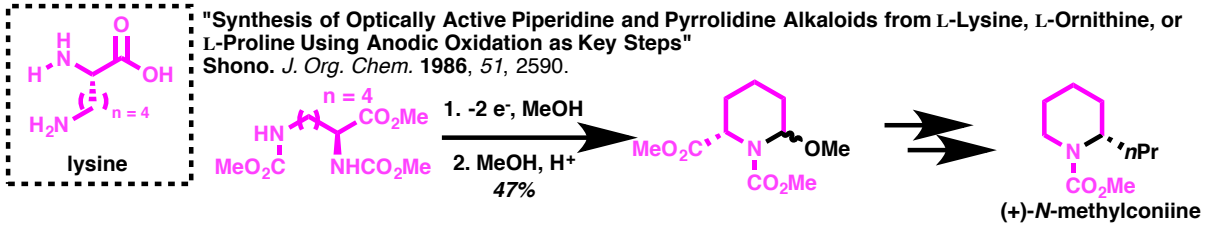


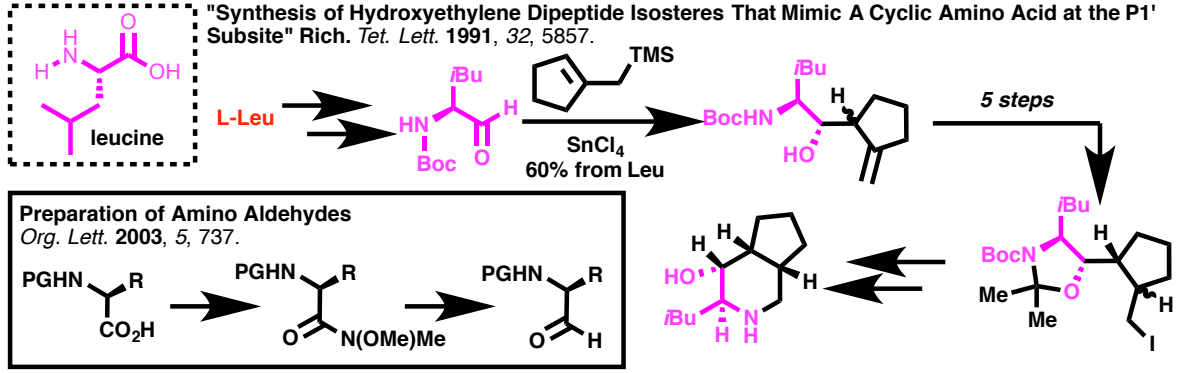
For glutamic acid, see: Rapoport. *J. Org. Chem.* **1998**, *63*, 4069.; ***Henry Rapoport***, Foo 2013.











Creativity from the Chiral Pool: Amino Acids

Justine deGruyter

Baran Lab Group Meeting
03.17.2017

proline

"Total Synthesis and Isolation of Citrinalin and Cyclopiamine Congeners"
Sarpong. *Nature* **2014**, *509*, 318.

D-Pro → *6 steps* → cat. [Ru], L, *98%* → i. A, $SnCl_4$, –78 °C; ii. I_2, DMAP, py., CCl_4, *68% (over 2 steps)*

C: $dppfPdCl_2$ (10 mol%), K_3PO_4, *95% (over 2 steps)*

1. B (20 mol%)
2. PIFA, MeOH, *70% (over 2 steps)*

1. Zn^0, NH_4Cl, HCO_2NH_4, p-TsOH, MeOH
2. $NaCNBH_3$, 1 N HCl, *82% (over 2 steps)*
3. $Pd(OAc)_2$, benzoquinone, H_2SO_4, *71%*
4. Me_2S, methanesulfphonic acid, *96%*

1. Oxone®, Me_2CO, $NaHCO_3$, *56%, 4:1 d.r.*
2. Me_3OBF_4, 4 Å m.s.
3. $NaCNBH_3$, *66% (over 2 steps)*

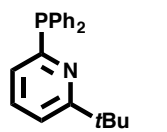
ent-citrinalin B

i. NaH
ii. MeI, K_2CO_3, 60 °C, *78% (over 2 steps)*

cyclopiamine B

[Ru] = $[Ru(Cp)(MeCN)L_2]PF_6$

L =



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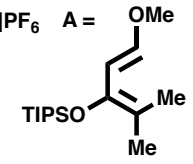

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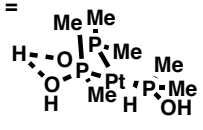

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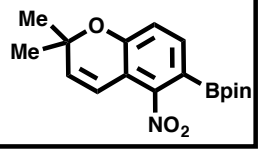
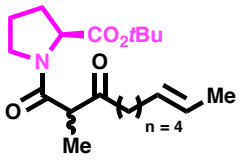
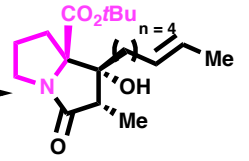


"Biomimetic Total Synthesis of (–)-Penibruguieramine A Using Memory of Chirality and Dynamic Kinetic Resolution"
Kim. *Angew. Chem. Int. Ed.* **2015**, *54*, 10875.

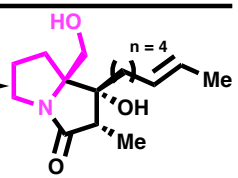
4-hexen-1-ol → Br → i. NaH, *n*BuLi, 0 °C to rt *(76%)*; ii. KOH *(97%)* → L-Pro



NaOEt, EtOH
MoC/DKR



i. TFA
ii. BOP, DIPEA, then $NaBH_4$
86% (over 2 steps)



(–)-penibruguieramine A

see: *Memory of Chirality,* Voica 2008

"Asymmetric Syntheses of 1-Deoxy-6,8a-di-*epi*-castanospermine and 1-Deoxy-6-*epi*-castanospermine"
Suh. *J. Org. Chem.* **2012**, *77*, 5389.

D-Pro-al → TBSCl, DBU, *88%, > 20:1* → 1. TBSOTf, 2,6-lutidine; 2. A, EDCI, HOBt, NMM, *60% (over 2 steps)*

A = HO_2C–OTBS

LHMDS

LDA, mw, *21%*

66%

1-deoxy-6-*epi*-castanospermine

1. Ac_2O, py., *71%*
2. LiAlH, *86%*

63%

Oxone®

1-deoxy-6,8a-di-*epi*-castanospermine

"A Facile Approach to the Synthesis of Securinega Alkaloids: Stereoselective Total Synthesis of (–)-allonorsecurinine"
Srihari. *Tet. Lett.* **2012**, *53*, 5926.

L-Pro → *5 steps* → 1. TFA; 2. K_2CO_3, 65% (over 2 steps)

(–)-allonorsecurinine

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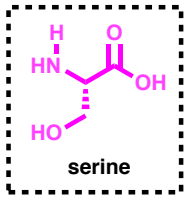
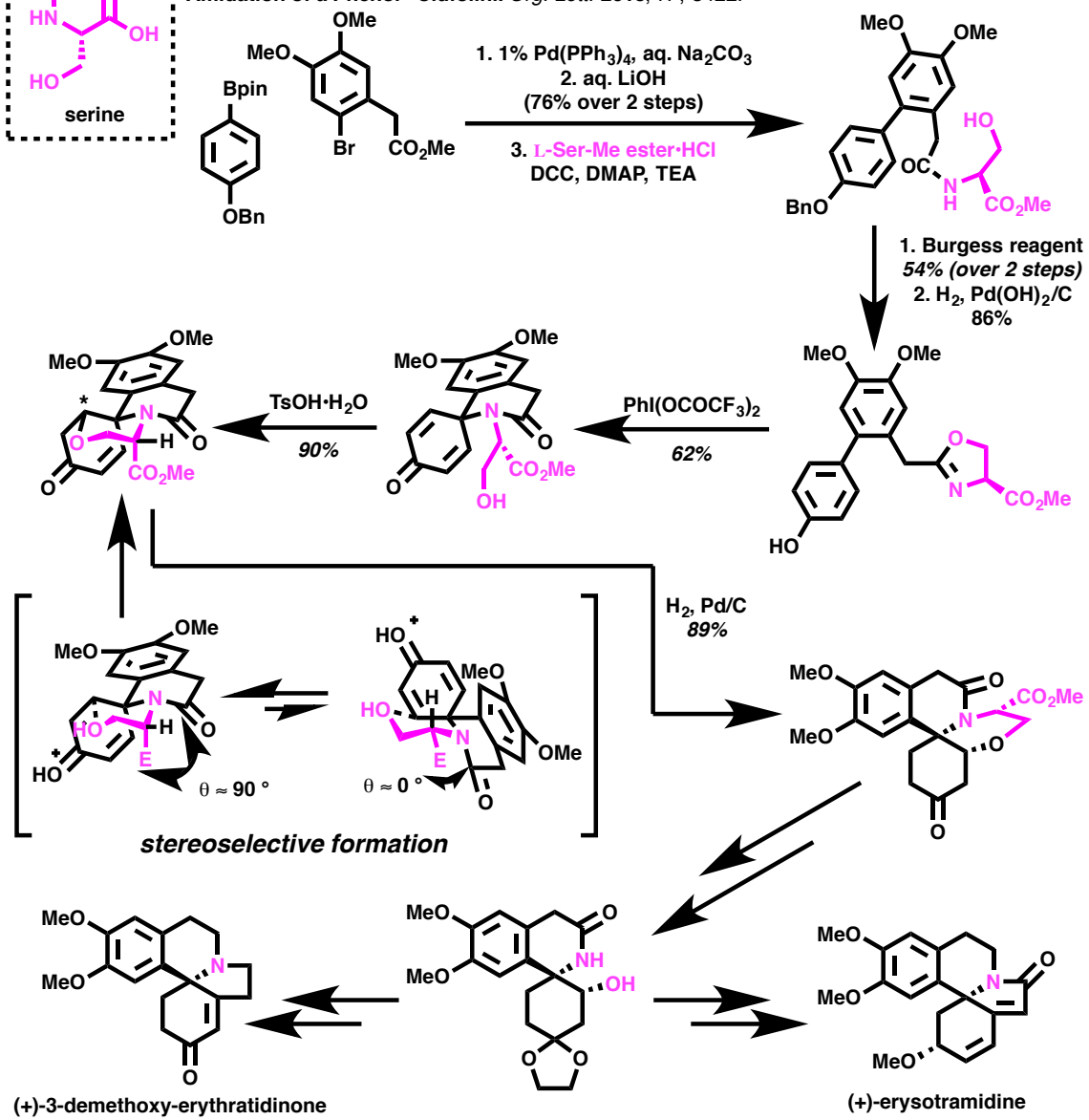
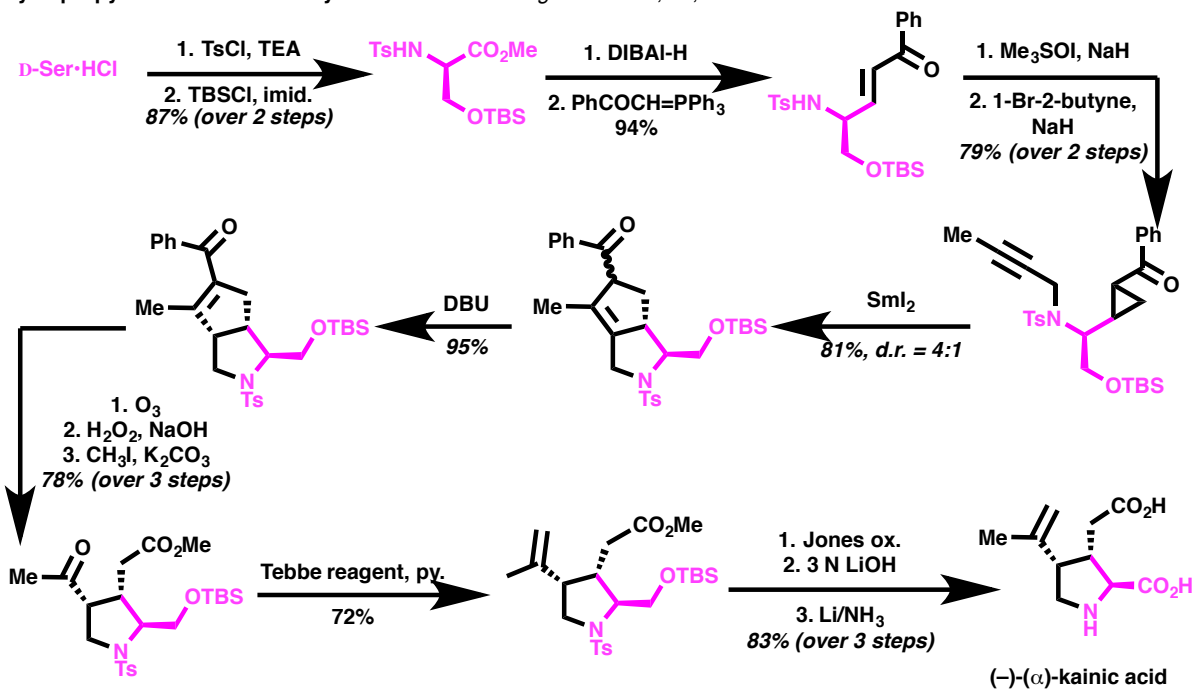


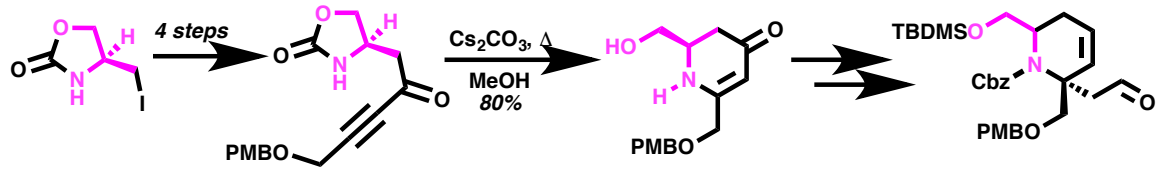
"Total Synthesis of (+)-3-Demethoxyerythratidinone and (+)-Erysotramidine via the Oxidative Amidation of a Phenol" Ciufolini. *Org. Lett.* **2015**, *17*, 3422.



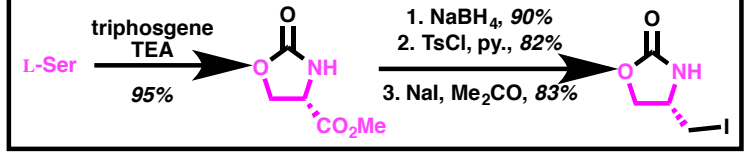
"Total Synthesis of (–)-( )-Kainic Acid via a Diastereoselective Intramolecular [3+2] Cycloaddition Reaction of an Aryl Cyclopropyl Ketone with an Alkyne." Zhou and Li. *Org. Lett.* **2012**, *14*, 2540.

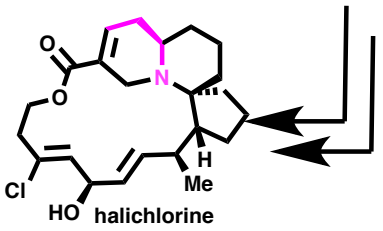


"Total Synthesis of the Marine Alkaloid Halichlorine: Development and Use of a General Route to Chiral Piperidines" Clive. *J. Org. Chem.* **2009**, *74*, 7417.



"Investigations of a Nucleophilic Alaninol Synthon Derived from Serine" Sibi. *J. Am. Chem. Soc.* **1999**, *121*, 7509.





Creativity from the Chiral Pool: Amino Acids

Justine deGruyter

Baran Lab Group Meeting
03.17.2017

threonine

"Total Synthesis of Legionaminic Acid as Basis for Serological Studies"
Seeberger. *J. Am. Chem. Soc.* **2015**, *137*, 2848.

D-Thr → *n*BuLi, furan, $MgBr_2 \cdot OEt_2$ (*80% syn, d.r. = 5:1*) → O_3; then PPh_3, $TMSCHN_2$, *59%*

$LiBH_4$: R' = CHO, R = CO_2Me
NaOCl, cat. TEMPO, KBr: R' = H, R = CH_2OH
NaOCl, cat. TEMPO, KBr: R' = H, R = CHO

1. $LiBH_4$, THF, 0 °C to rt, *92%*
2. NaOCl, cat. TEMPO, KBr
sat. $NaHCO_3$, *quant.*
3. (*E*)-styrylboronic acid, HNR_2
d.r. >19:1 (anti/syn)

legionaminic acid

tryptophan

"The Four-Step Total Synthesis of (–)-Caetominine"
Huang. *Chem. Commun.* **2014**, *50*, 1986.

D-Trp → L-Ala-OMe·HCl, $ClCO_2iBu$, NMM → $HC(OMe)_3$, $Zn/TiCl_4$ → DMDO; then dry DMSO → *epoxidation; ring-opening cyclization; lactamization* → (–)-chaetominine

valine

"Total Synthesis of (–)-L-755,807: Establishment of Relative and Absolute Configurations
Kobayashi and Kogen. *Org. Lett.* **2016**, *18*, 1920.

D-Val → *4 steps* → 1. SO_3·py., DMSO, DIPEA; 2. $BrCH(CO_2tBu)_2$, LHMDS *94% (over 2 steps)* → 1. HCO_2H; 2. NH(OMe)Me·HCl, PyBOP, DIPEA *84% (over 2 steps)* → 1. NH_3; 2. TESOTf, 2,6-lutidine; 3. SiO_2, *86% (over 3 steps)*; 4. $(OMe)_2P(O)Me$, *n*BuLi, *89%* → L-755,807

R = n = 3

"Ir-Catalyzed Reverse Prenylation of 3-Substituted Indoles: Total Synthesis of (+)-Aszonalenin and (–)-Brevicompanine B" Carreira. *J. Am. Chem. Soc.* **2014**, *136*, 16756.

D-Trp / L-Trp → cond. → (+)-*exo* → 1. 2-aminobenzoic acid, TEA, HATU; 2. $AlMe_3$ *85% (over 2 steps)* → (+)-aszonalenin

D-Trp / L-Trp → cond. → (–)-*exo* → 1. Fmoc-Leu, TEA, HATU *82%*; 2. Et_2NH *83%* → (–)-brevicompanine B

cond. = 0.50 mol% $[\{Ir(cod)Cl\}_2]$, KHMDS, 9-BBN-*n*-C_6H_{13} *58%* (1 mol%)

see also: **Baran.** *J. Am. Chem. Soc.* **2015**, *137*, 10160; **Reisman.** *J. Am. Chem. Soc.* **2013**, *135*, 5557.

Creativity from the Chiral Pool: Amino Acids

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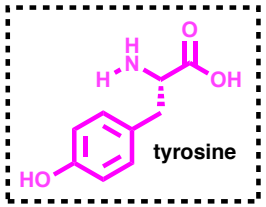
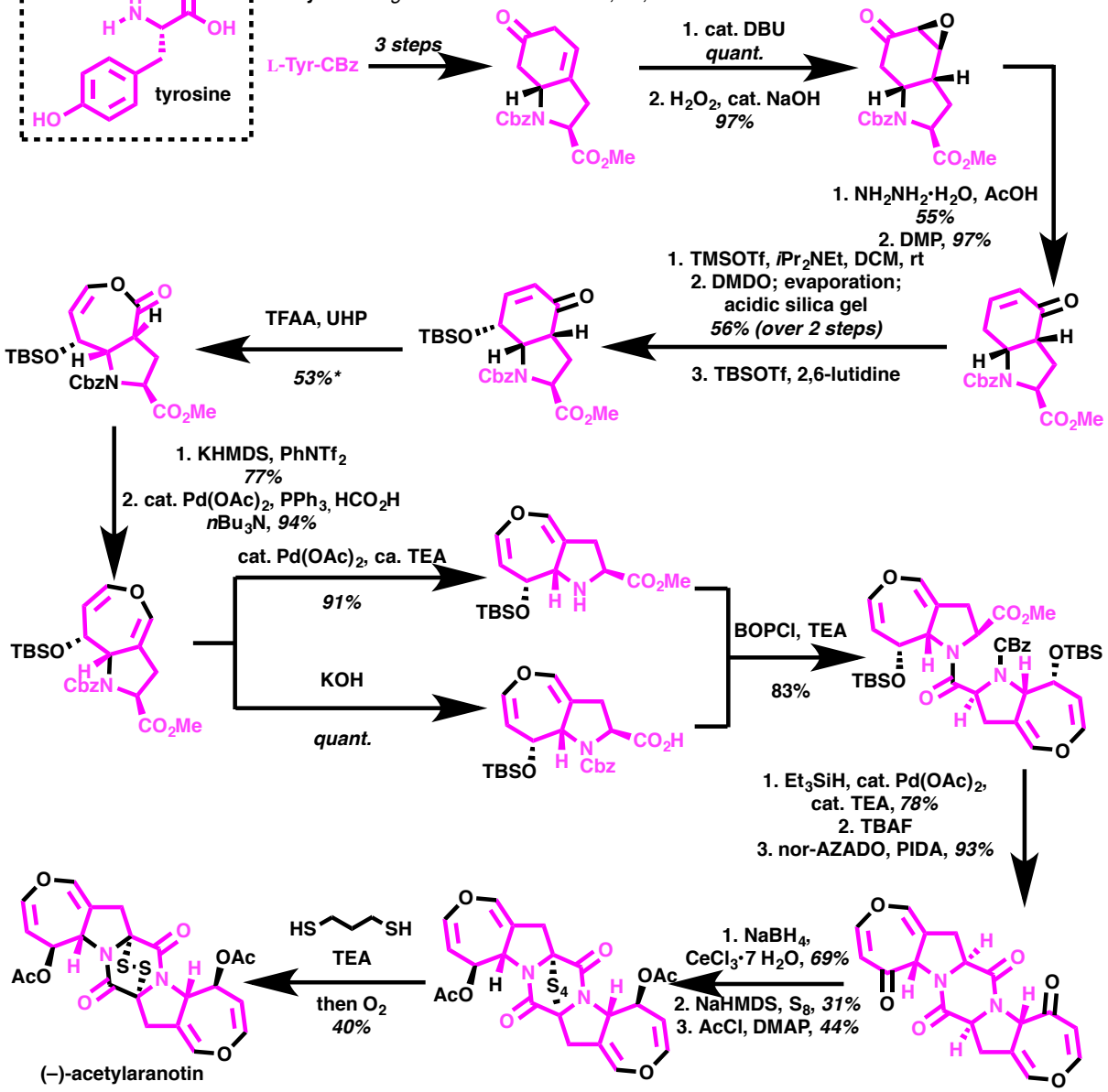
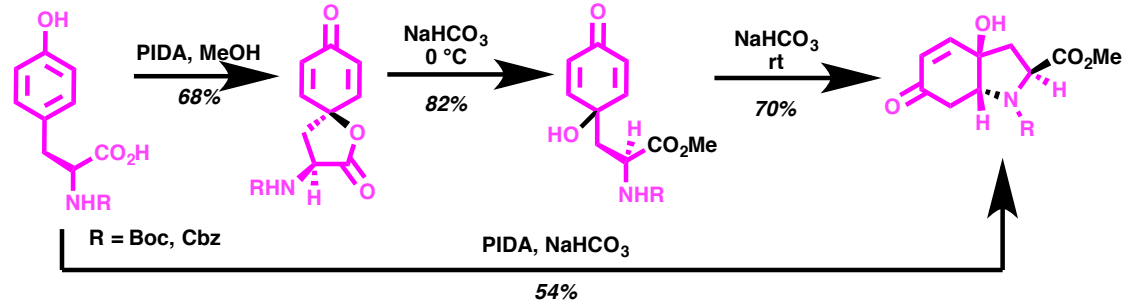


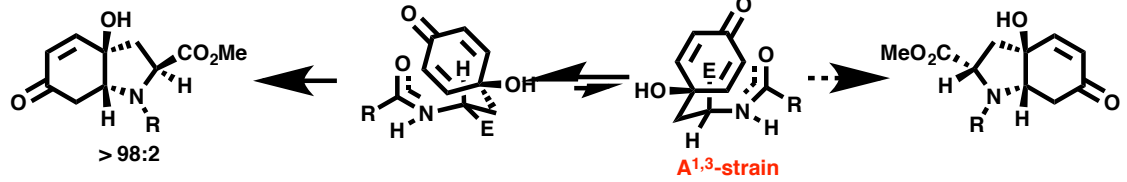
"Total Synthesis of (–)-Acetylaranotin"
Tokuyama. *Angew. Chem. Int. Ed.* **2012**, *51*, 13062.



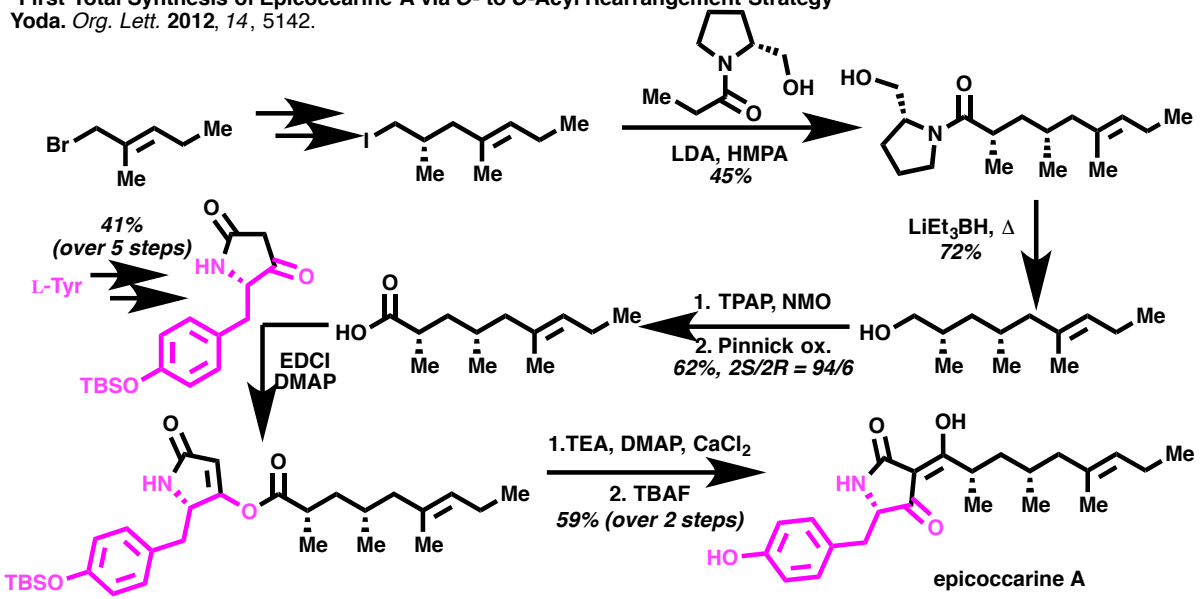
"Studies on the Synthesis of *Stemona* Alkaloids; Stereoselective Preparation of the Hydroindole Ring System by Oxidative Cyclization of Tyrosine" **Wipf.** *Tet. Lett.* **1992**, *33*, 5477.



"Asymmetric Total Synthesis of the *Stemona* Alkaloid (–)-Stenine"
Wipf. *J. Am. Chem. Soc.* **1995**, *117*, 11106.



"First Total Synthesis of Epicoccarine A via *O*- to *C*-Acyl Rearrangement Strategy"
Yoda. *Org. Lett.* **2012**, *14*, 5142.



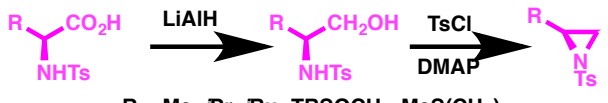
Creativity from the Chiral Pool: Amino Acids

Justine deGruyter

Baran Lab Group Meeting
03.17.2017

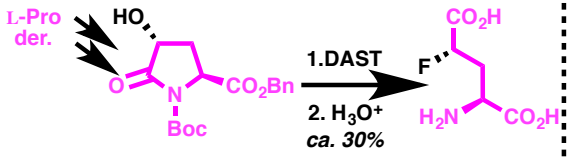
Some interesting/potentially usefully heterocycles

"A Convenient Method for the Preparation of Enantiomerically Pure 2-Substituted *N*-Tosylaziridines" Craig. *Synlett.* **1992**, 41.

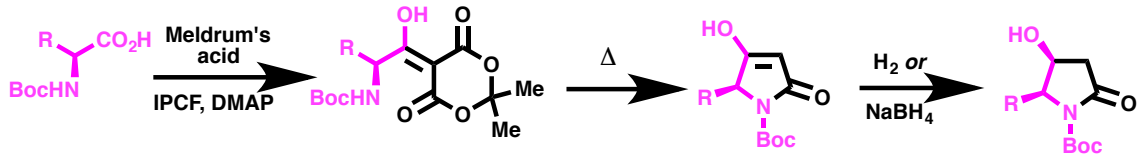


R = Me, *i*Pr, *i*Bu, $TBSOCH_2$, $MeS(CH_2)_2$

"Stereospecific Synthesis of 4-Fluoroglutamic Acids" Young. *Tet. Lett.* **1992**, *33*, 1509.

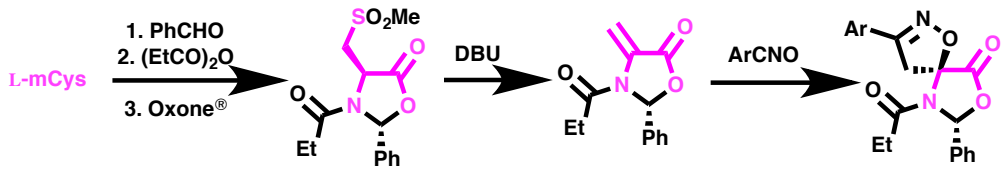


"Stereospecific Synthesis of *N*-Protected Statine and Its Analogues via Chiral Tetramic Acid" Jouin. *J. Chem. Soc. Perkins Trans. 1.* **1987**, 1177.

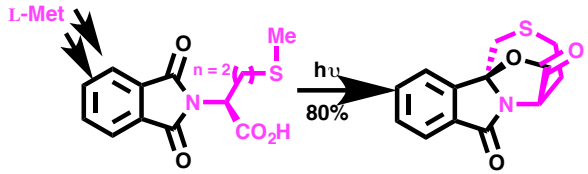


R = *i*Bu, Me, *i*Pr, Bn, $BnOCH_2$, $MeS(CH_2)_2$, $CbzHN(CH_2)_4$, indol-3-yl-CH_2, BOM-imidazole-CH_2

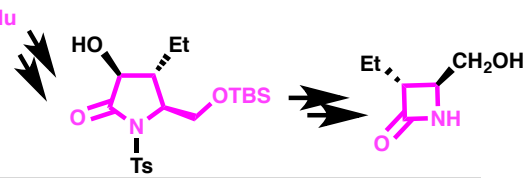
"Asymmetric Synthesis of a Homochiral -Isoxazoline Amino Acid Derivative" Savage. *Heterocycles.* **1994**, *37*, 529.



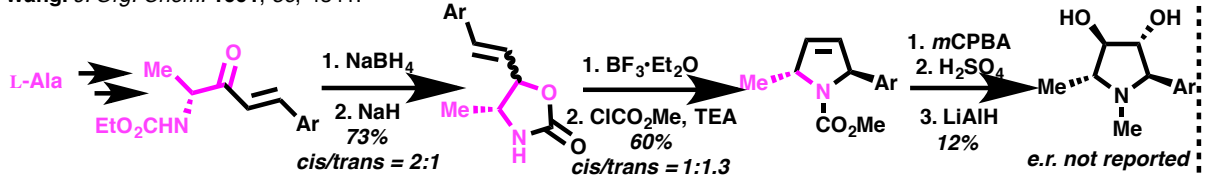
"Photochemistry of *N*-Phthaloyl Derivatives of Methionine" Griesbeck. *Tet. Lett.* **1993**, *34*, 453.



"A Potential Cabapenem Intermediate from L-Glutamic Acid" Somfai. *Tet. Lett.* **1991**, *32*, 283.

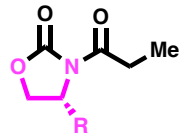


"Decarboxylative Cyclization of Allylic Cyclic Carbamates: Applications to the Total Synthesis of (–)-Codonopsine" Wang. *J. Org. Chem.* **1991**, *56*, 4341.

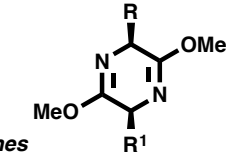


There exists enough literature on the use of amino acids as chiral auxiliaries or catalysts to constitute their own group meeting. Below are examples that I consider to be seminal advances in the field...

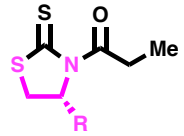
Chiral Auxiliaries



Evans' oxazolidinones



Schollkopf synthesis of chiral amino acids



thiazolidinethiones

Some reviews/communications by reaction type (non-aldol):

"Natural Amino Acids as Chiral Auxiliaries in Asymmetric Diels–Alder Reactions"
Can. J. Chem. **1988**, *66*, 2826.

"Asymmetric control in the Pictet-Spengler Reaction by Means of *N*-Protected Amino Acids as Chiral Auxiliary Groups"
Chem. Eur. J. **1996**, *2*, 1566.

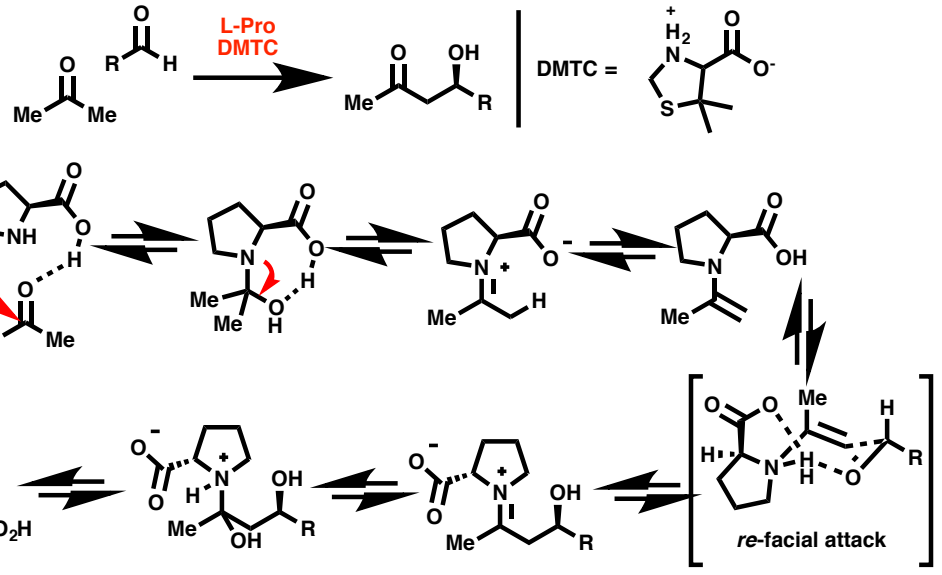
"Amino Acid Esters as Chiral Auxiliaries in Barbier-type Reactions in Aqueous Solution"
Lieb. Anna. Chem. **1991**, 1317.

"Amino Acid Esters as Chiral Auxiliaries in Asymmetric Cycloadditions"
Gazzetta Chimica Italiana. **1991**, *121*, 277.

"Chiral Auxiliaries in Polymer-Supported Organic Synthesis"
Tet. Asymm. **2004**, *15*, 387.

Asymmetric Catalysts

"Amino Acid Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon–Carbon Bond-Formation Reactions" Barbas. *J. Am. Chem. Soc.* **2001**, *123*, 5260.



An oldie but goodie: "The Chiral Pool as a Source of Enantioselective Catalysts and Auxiliaries" *Chem. Rev.* **1992**, *92*, 935.