



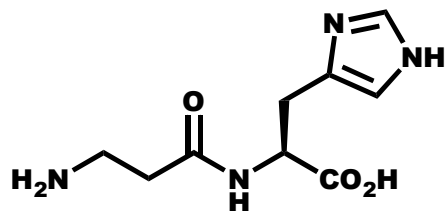
**Hamari Chemicals, Ltd.**

## **Core Reactions**

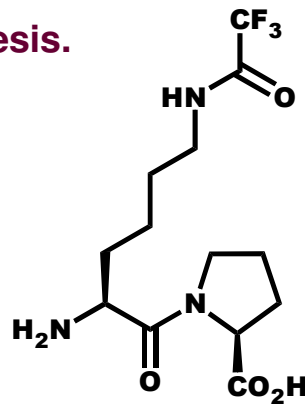
<b>1: Peptide Manufacturing</b>	<b>P2-3</b>
<b>2: Chiral Technology</b>	<b>P4</b>
<b>3: Reduction</b>	<b>P5-6</b>
<b>4: Alkylation &amp; Arylation</b>	<b>P7-8</b>
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<b>6: Heteroaromatics</b>	<b>P10-11</b>
<b>7: Oxidation</b>	<b>P12</b>

# Peptide Manufacturing

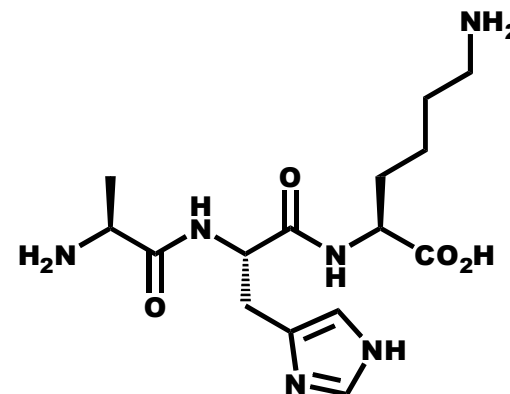
Over 40 years experience in peptide synthesis.



L-Carnosine



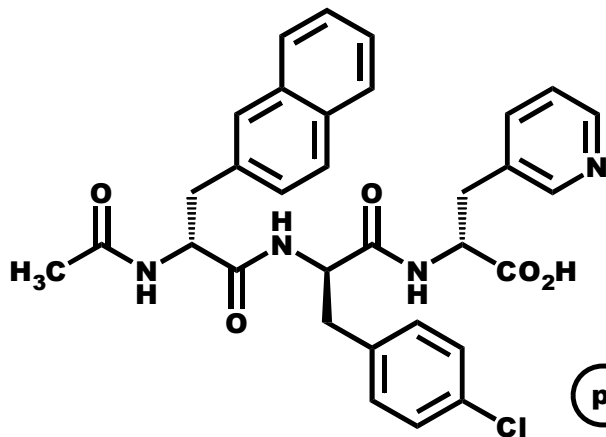
Lys(Tfa)-Pro



Ala-His-Lys

Intermediates and API for LH-RH analogues

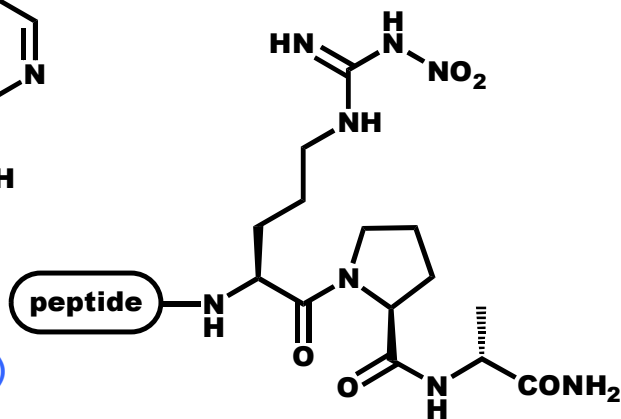
Hamari provides custom process development for intermediates and API of LH-RH analogues such as Degarelix, Abarelix, etc.



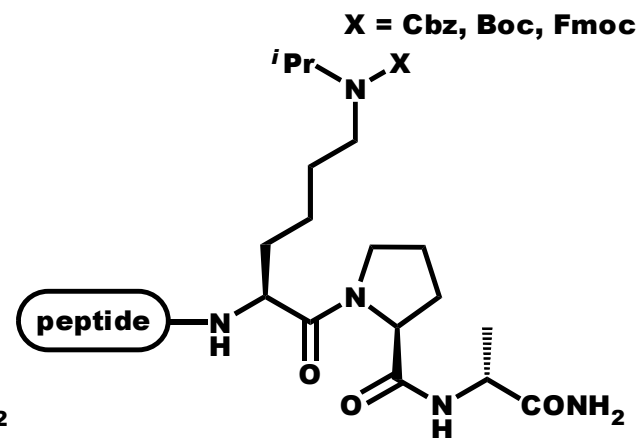
AP0(Ac-D-2-Nal-D-4-CIPhe-D-3-Pal)

Registry Number: 129225-22-5

HPLC purity : > 99%



Peptide-Arg(nitro)-Pro-D-Ala-NH<sub>2</sub>



Peptide-Lys(<sup>i</sup>Pr-X)-Pro-D-Ala-NH<sub>2</sub>



Hamari Chemicals, Ltd.

# Peptide Manufacturing

## Custom Manufacturing

Intermediates for

- ACE inhibitors
- anti-cancer drugs
- HIV protease inhibitors

Cosmetic substances

Dietary supplements

## Capacity

(maximum per year)

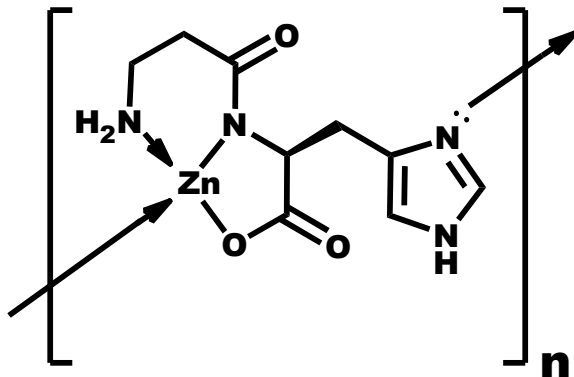
di-peptide	: 50 tons
tri-peptide	: 20 tons
tetra-peptide	: 10 tons
penta-peptide	: 10 tons
hexa-peptide	: 5 tons

## Manufacturing

Experience (2006-2010)

(number of projects)

di-peptide	: 9
tri-peptide	: 10
tetra-peptide	: 7
penta-peptide	: 7
hexa-peptide	: 1
hepta-peptide	: 1
deca-peptide	: 1
peptide mimic	: 1
<b>Total</b>	<b>: 37</b>



**Zinc Carnosine**  
**/ Polaprezinc**

- API in Japan
- Dietary supplement in USA

Expertise in small to medium length peptides.

Extensive technology using Solution Phase Synthesis.

Experience in cGMP synthesis for clinical studies.

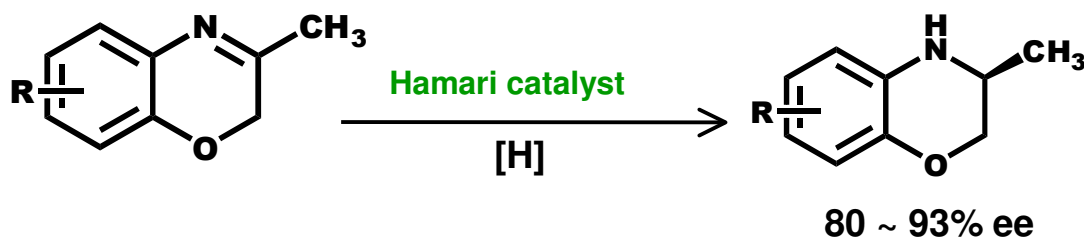
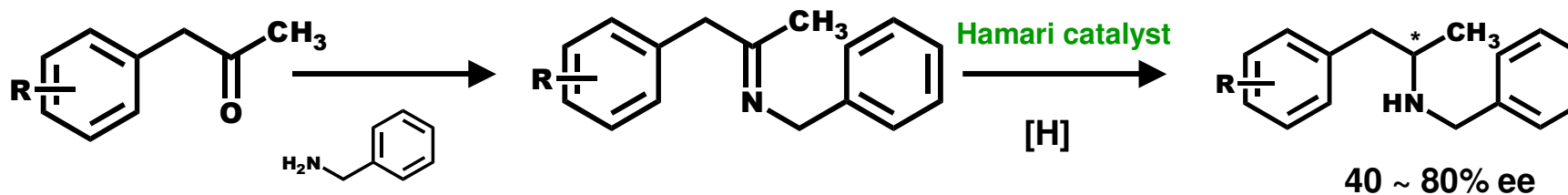
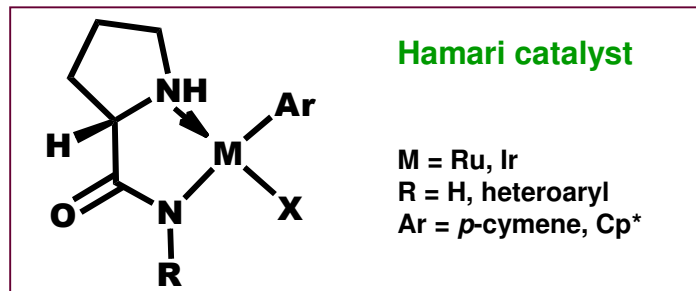
Newly acquired resources and equipment for Solid Phase Synthesis.



Hamari Chemicals, Ltd.

# Chiral Technology

## Asymmetric Transfer Hydrogenation (ATH) using Chiral Ru- and Ir-catalysts



Chiral Catalysts	% ee
arene-Ru(II)-TsDPEN	ca. 20
Hamari catalyst <Ru>	~ 40
Hamari catalyst <Ir>	> 80

**Please note!**

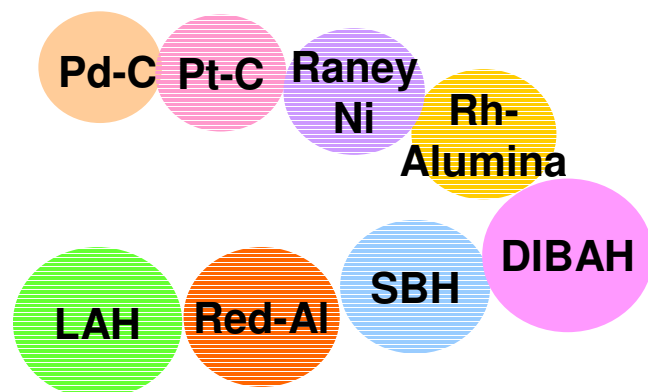
Hamari offers FTE using ATH-technology.



Hamari Chemicals, Ltd.

# Reduction

## Catalysts & Reagents



Extensive experience  
in metal catalysts and hydride-transfer reagents

## Autoclaves

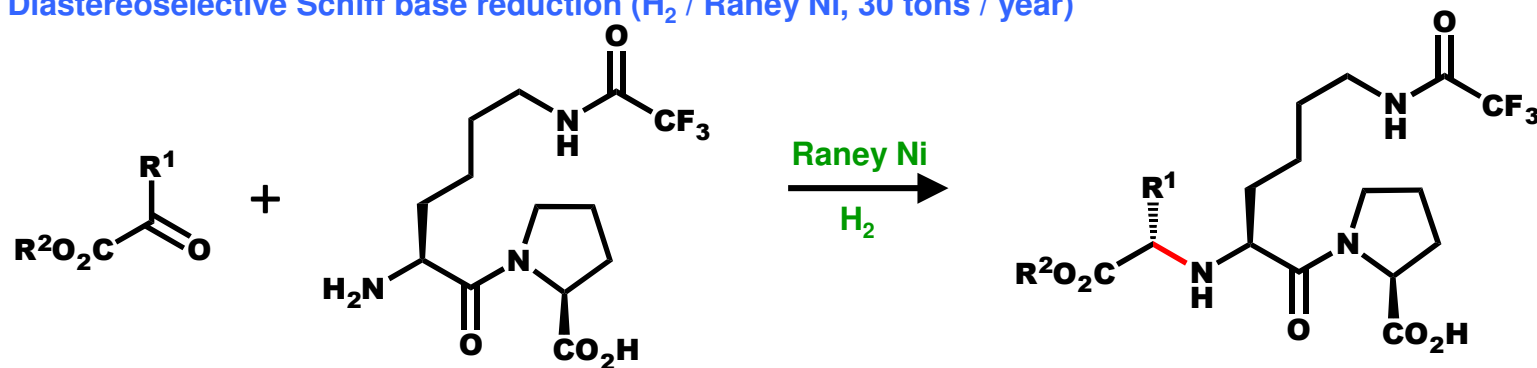
<u>Osaka Hamari</u>		
Hastelloy	500 L	1.0 MPa
SUS	500 L	0.5 MPa
SUS	100 L	0.2 Mpa
SUS	10 L	2.0 Mpa
GL	1000 L	0.1 MPa

<u>Yonezawa Hamari</u>	
SUS 2500 L	1.0 MPa
SUS 1800 L	1.0 MPa
SUS 1700 L	1.0 MPa
SUS 1000 L	0.2 MPa
SUS 500 L	6.8 MPa

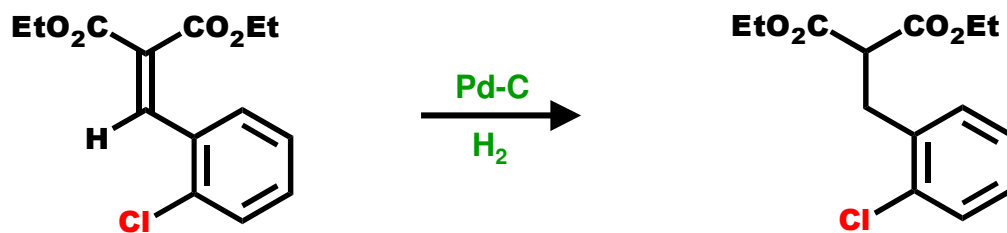


# Reduction

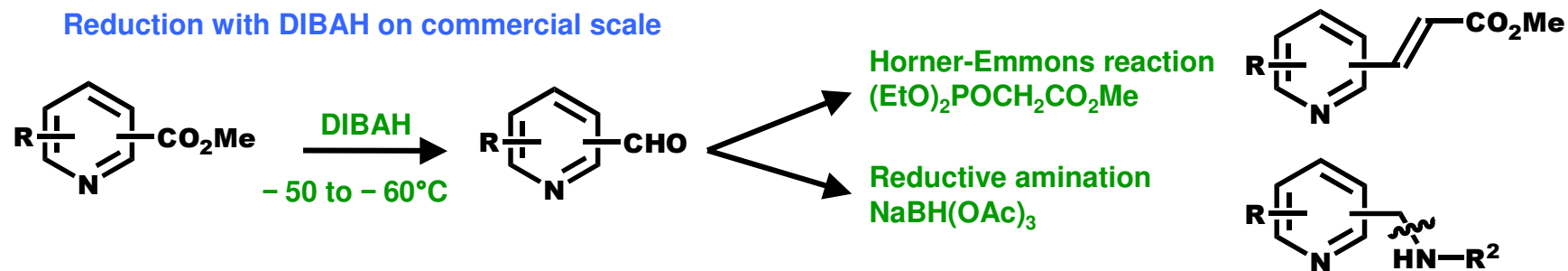
Diastereoselective Schiff base reduction ( $H_2$  / Raney Ni, 30 tons / year)



Chemoselective hydrogenation using Pd-C (without dehalogenation)

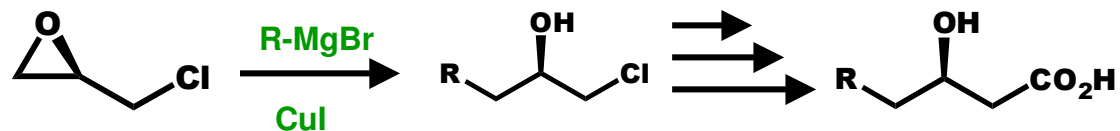


Reduction with DIBAH on commercial scale



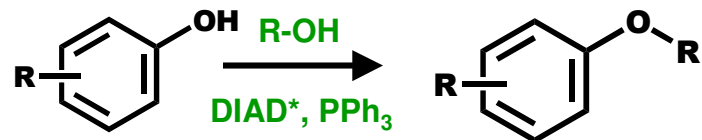
# Alkylation & Arylation

## Grignard Reaction



## Etherification

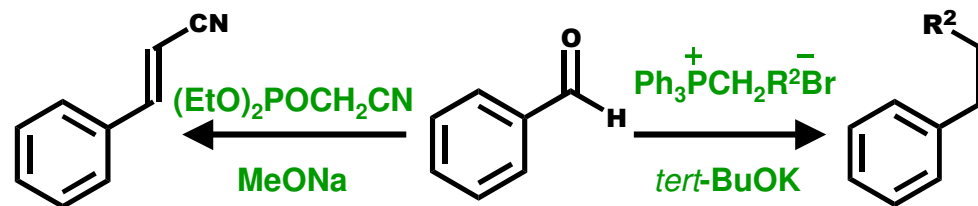
### Mitsunobu reaction



\* DIAD : Diisopropyl azodicarboxylate

## Olefination

### Horner-Emmons and Wittig reactions



PTC-catalyzed (e.g. TBAB)

Mild conditions (< 80°C)

High yield (> 90%)

Cryogenic reactions

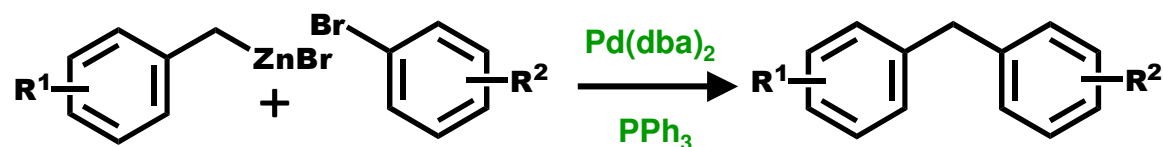
~ -90°C max. 1000 L

~ -50°C max. 3000 L



# Alkylation & Arylation

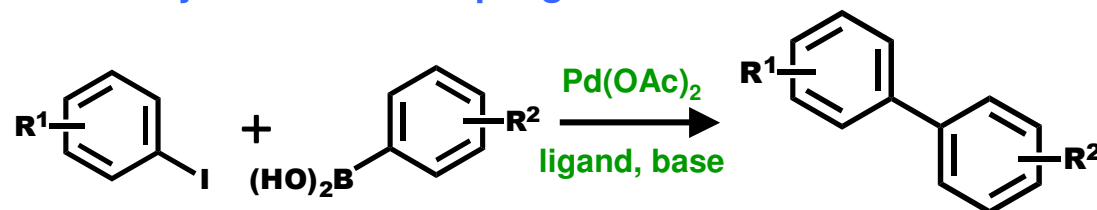
## Negishi Cross Coupling



## Manufacturing Experience

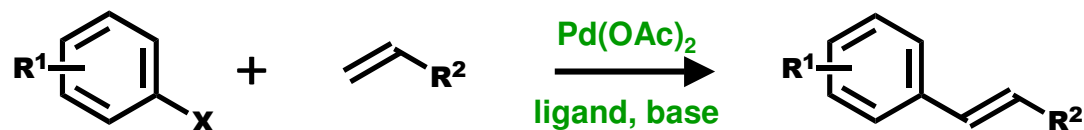
Pilot plant (Osaka)  
cGMP  
Size : 50 kg / Batch  
Residual Pd : ≤ 1 ppm level

## Suzuki-Miyaura Cross Coupling



Commercial (Yonezawa)  
cGMP  
Size : 100 kg / Batch  
Residual Pd : ≤ 1 ppm level

## Mitsunobu-Heck Reaction

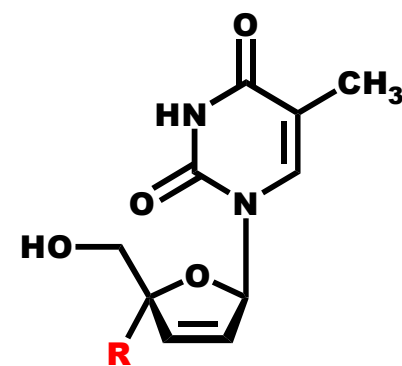
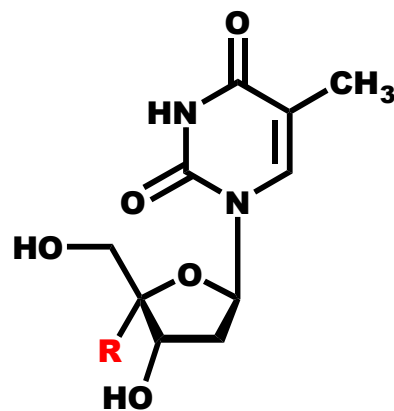
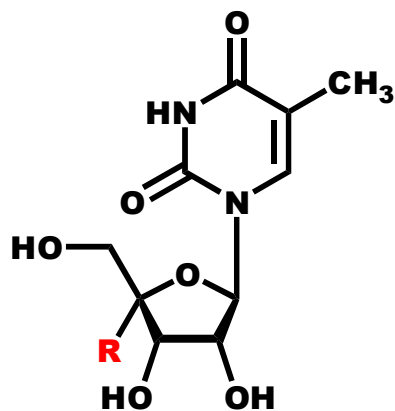
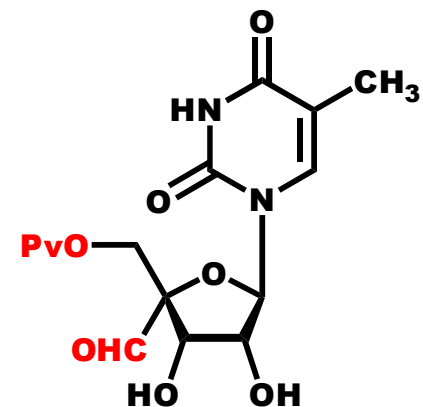
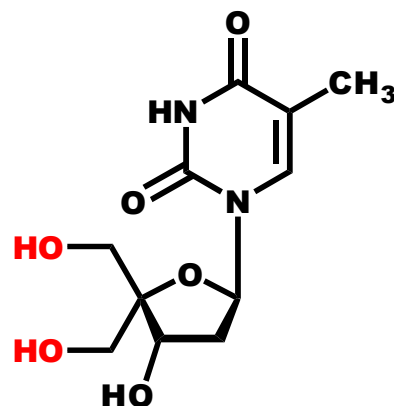
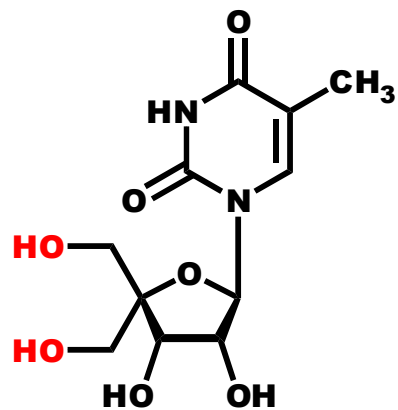


Commercial (Yonezawa)  
cGMP  
Size : 100 kg / Batch  
Residual Pd : ≤ 1 ppm level

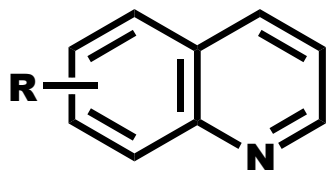


# Nucleosides

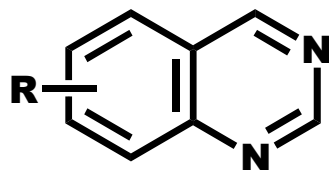
## API and Intermediates for antiviral agents



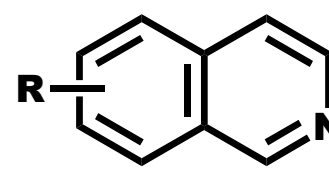
# Heteroaromatics



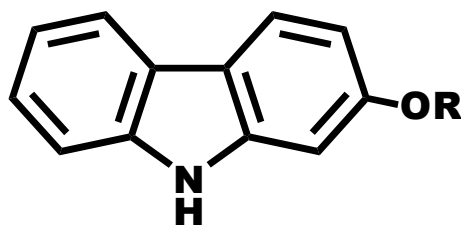
Quinolines



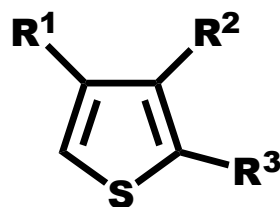
Quinazolines



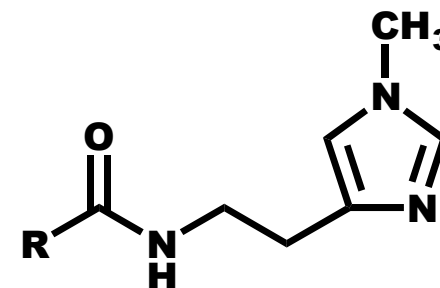
Isoquinolines



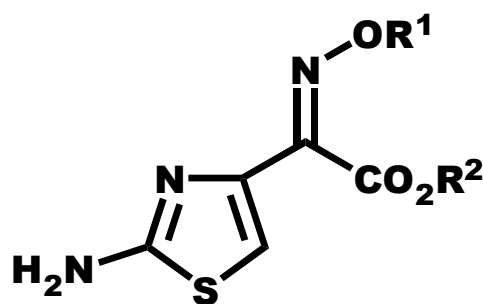
Carbazoles



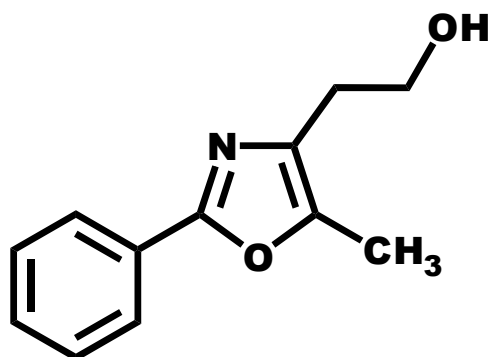
Thiophenes



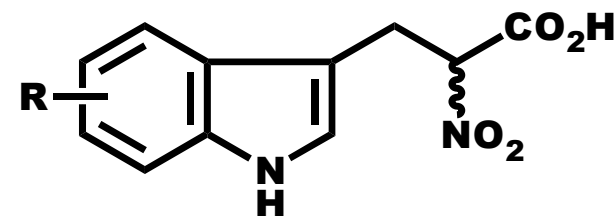
Imidazoles



Aminothiazoles



Oxazoles

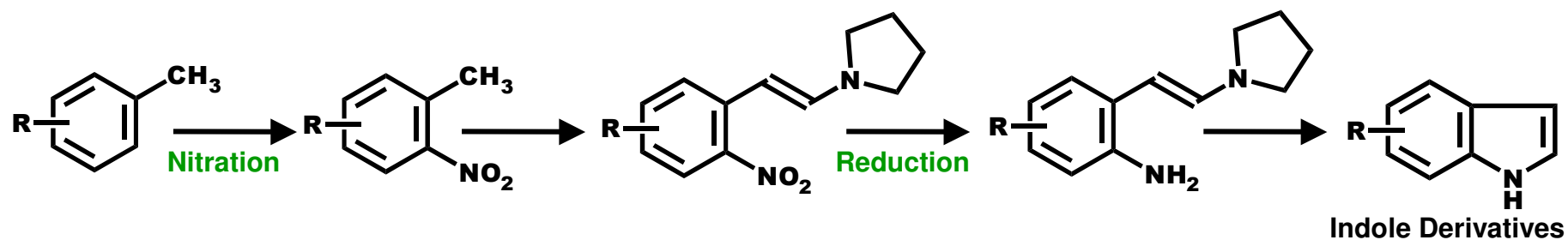


Indoles

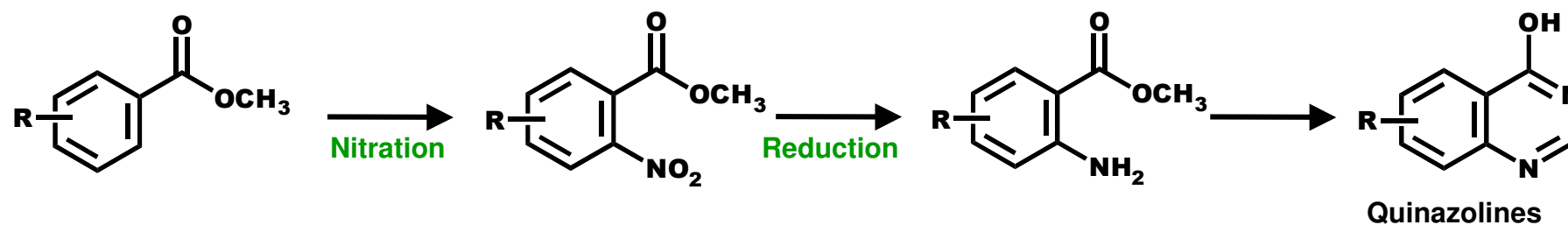


# Heteroaromatics

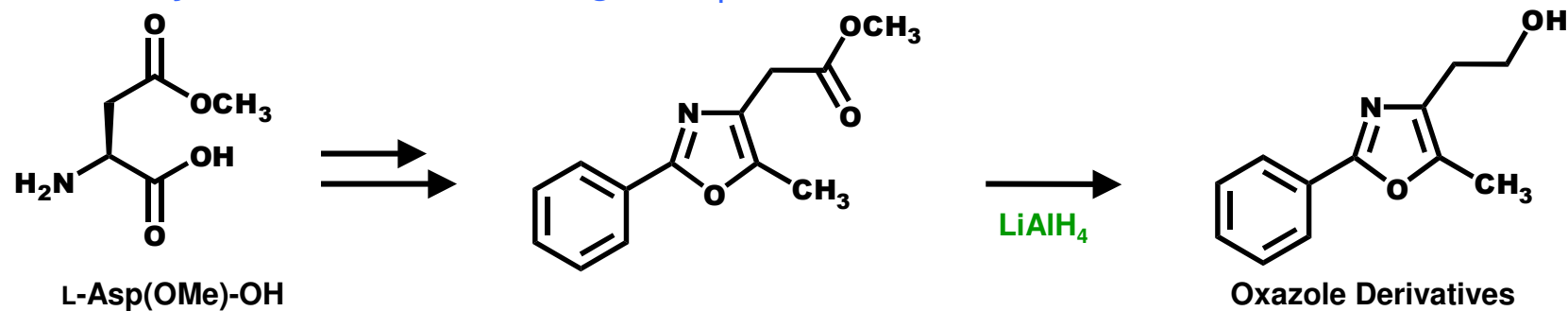
## Leimgruber - Batcho indole synthesis



## Quinazoline synthesis

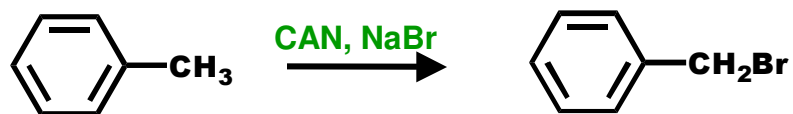


## Oxazole synthesis and the following LiAlH<sub>4</sub> - reduction

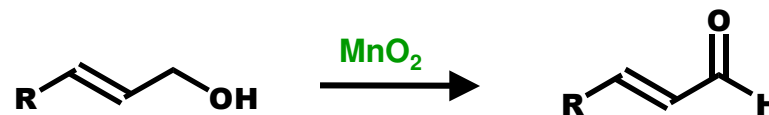


# Oxidation

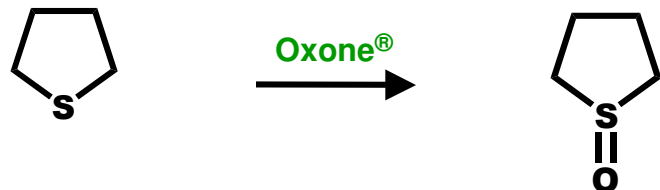
CAN :  $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$



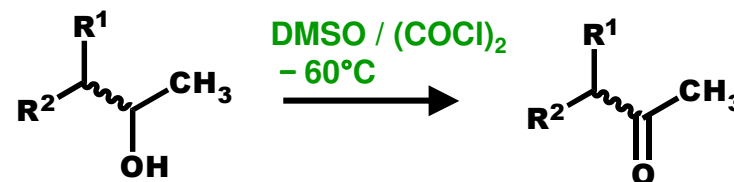
$\text{MnO}_2$  : activated type



Oxone<sup>®</sup> ; Potassium Peroxymonosulfate



Swern and related oxidations



TEMPO (1 mol%)

