Hamari Chemicals can offer your company…

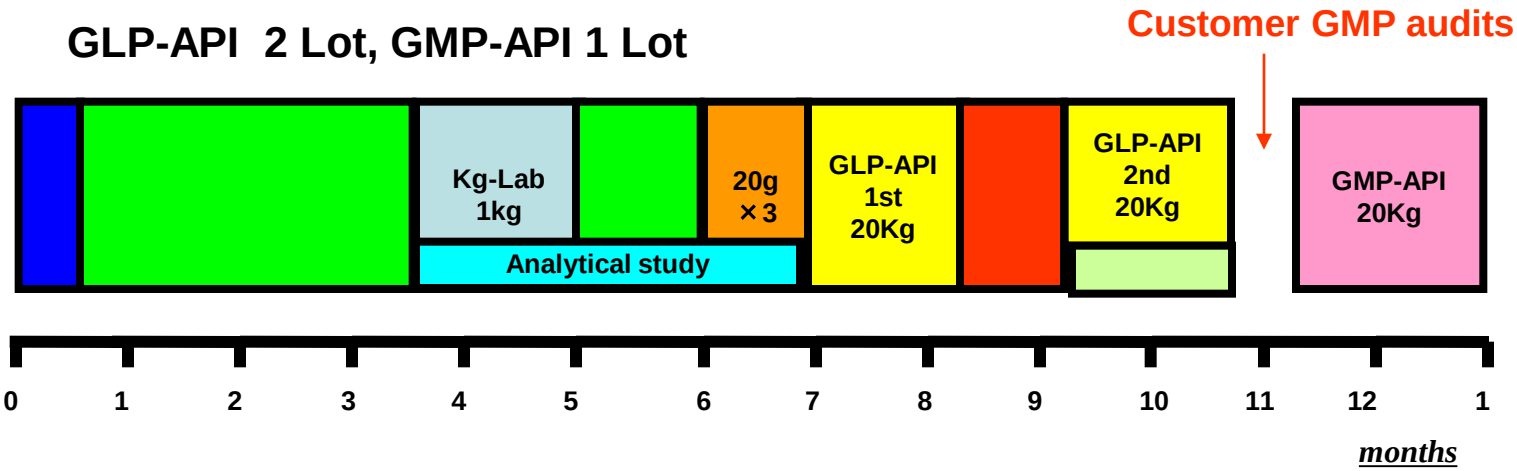
- Cost performance, high quality, and environmentally friendly services.
- More than 55 years of experience in custom manufacturing.
- More than 60 reactions on commercial scale (500 – 5000 L).
- cGMP Manufacturing facilities.
- Process development, Method validation and Stability testing.
- FTE-Full Time Equivalent study.
- API Development Service for IND and NDA.

Timeline of IND Project

Actual Example

- **IND Project** (total steps 5)

GLP-API 2 Lot, GMP-API 1 Lot



- Technical feasibility study, Raw material availability and Price idea
- Process development and Firm quotation for pilot quantities
- Kg-Lab production
- Small samples for determining specification
- GLP Production and Reports
- Process optimization and Establishing specification
- Analytical development
- Analytical method Validation
- GMP Production and Reports

Upon Request Hamari Can Provide:

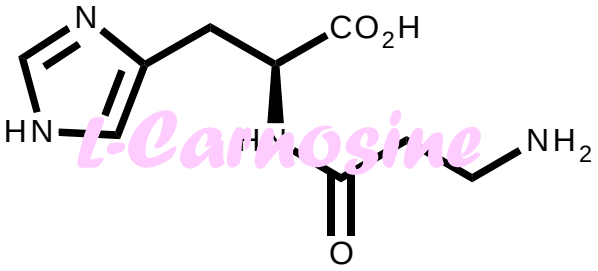
- Master Plan and Protocol
- Weekly Report
- Monthly Report
- End of Synthesis Process Development Report
- End of Campaign Manufacturing Report
- Telephone Conferences

Hamari's Technology

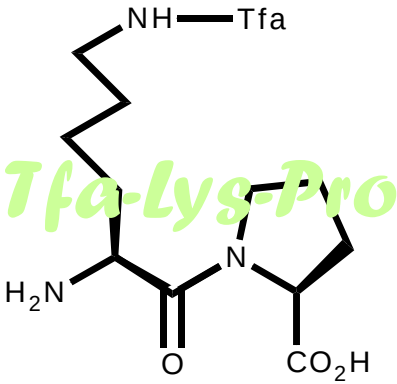
■ Peptides	→ Using SPPS and Solution phase synthesis.
■ Reduction	→ Reductive amination using metal catalysts.
■ Chiral Technology	→ Asymmetric transfer Hydrogenation
■ Alkylation	→ Negishi and Suzuki reaction
■ Heterocyclics	→ Indoles and Quinolines using Nitration
■ Oxidation	→ Swern, OXONE,TEMPO, $RuCl_3$ and Sharpless
■ Halogenation	→ Chlorination ($POCl_3$), Bromination (NBS, Br_2)
■ Etherification	→ Phase transfer catalyst such as TBAB
■ Glycosylation	→ Using trichloroacetimidate as the glycosyl donor
■ Nucleic Acid	→ API for antiviral agents

Peptide Manufacturing

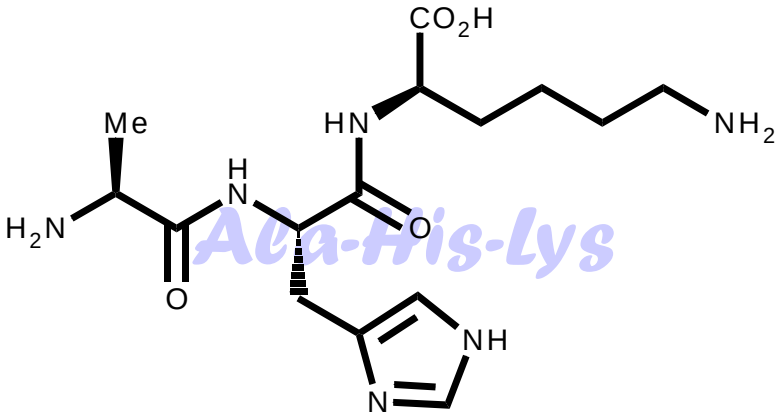
◆***More than 30 years of experience in peptide synthesis.***



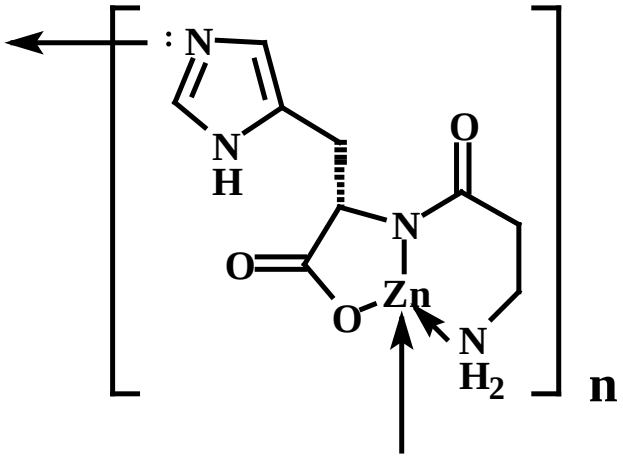
l-Carnosine



Tfa-Lys-Pro



Ala-His-Lys



Zinc Carnosine / Polaprezinc

- **API in Japan**
- **Dietary supplement in USA**

Capacity / kg to ton scale

Capacity	*(maximum per year)*
di-peptide	*: 50 tons*
tri-peptide	*: 20 tons*
tetra-peptide	*: 10 tons*
penta-peptide	*: 10 tons*
hexa-peptide	*: 5 tons*

Peptide Manufacturing

- ***Expertise in small to medium length molecular peptides.***
- ***Extensive technology using Solution Phase Synthesis.***
- ***Experience in cGMP synthesis for clinical studies.***
- ***NEW-Acquired resources and equipment for Solid Phase Synthesis.***

Manufacturing Experience

Peptide projects

di	*-peptide*	*:*	*9*
tri	*-peptide*	*:*	*10*
tetra	*-peptide*	*:*	*7*
penta	*-peptide*	*:*	*6*
hexa	*-peptide*	*:*	*1*
hepta	*-peptide*	*:*	*1*
Nona	*-peptide*	*:*	*1*
deca	*-peptide*	*:*	*1*
Peptide mimic		*:*	*1*
Total projects (2006-2011)			*37*

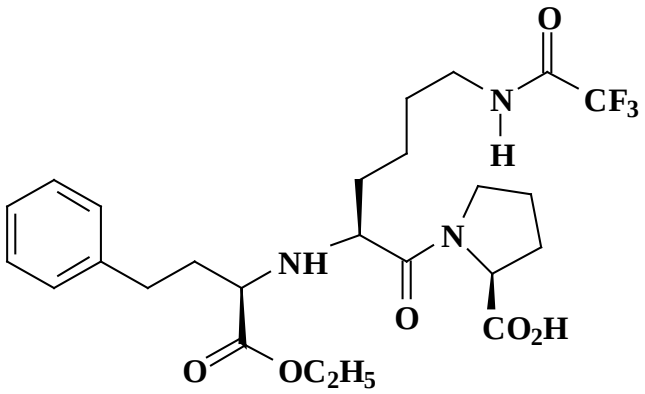
Custom Manufacturing

- **Intermediates for**
  - **ACE inhibitors**
  - **Anti-cancer drugs**
  - **HIV protease inhibitors**
- **Cosmetic substances**
- **Dietary supplements**

Peptides - Custom Manufacturing

ACE Inhibitors

Lisinopril Ester/FARGA-3 *(Europe)*



Manufacturing

- ◆Commercial (Yonezawa)
- ◆Capacity : 30 tons / year
- ◆Purity: >99%, RSS: <0.5%
- ◆In accordance with cGMP

Di-peptide Derivative *(Japan)*

Manufacturing

- ◆Commercial (Yonezawa)
- ◆Capacity : 1.5 tons / year
- ◆In accordance with cGMP

Di-peptide Derivative *(Japan)*

Manufacturing

- ◆Commercial (Yonezawa)
- ◆Capacity : 500kg / year
- ◆In accordance with cGMP

Peptides - Custom Manufacturing

Anti-Cancer Drugs

***Commercial* : Currently ongoing**

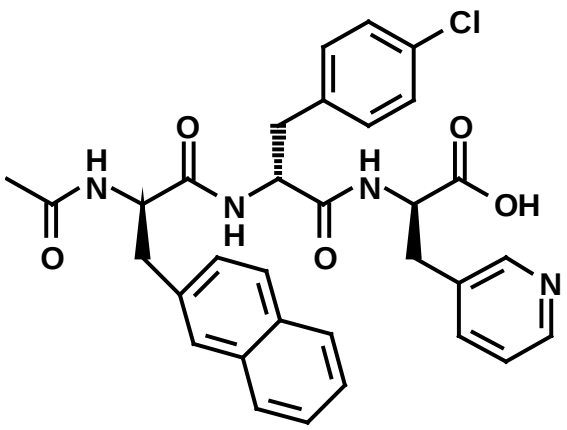
- ***Hexa-peptide* 150 kg / year (25 kg / Lot) *His, Trp, Ser, etc…***
- ***Tri-peptide* 30 kg / year (15 kg / Lot) *Arg, etc…***

***IND Products* : 2006-2011**

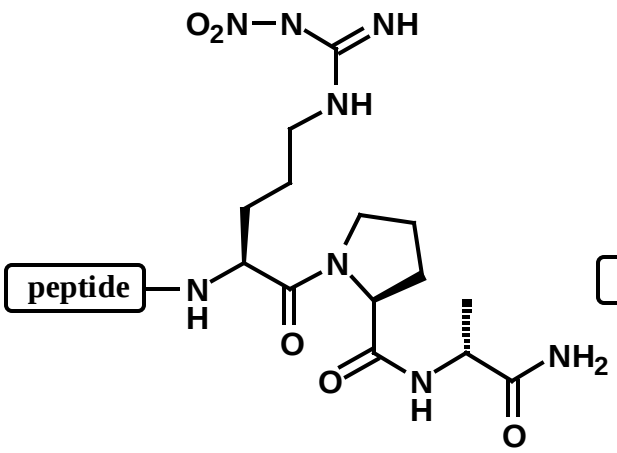
Tri-peptide	***1 Projects***	***30 kg***	***(2008)***
Tetra-peptide	***2 Projects***	***1kg, 1kg***	***(2010)***
Penta-peptide	***4 Projects***	***10 kg, 15 kg, 10 kg***	***(2008)***
Deca-peptide	***1 Project***	***50 g***	***(2008)***
Hepta-peptide	***1 Project***	***1 kg***	***(2009)***
Peptide mimic	***2 Projects***	***10 kg***	***(2006)***
		2 kg, 8 kg	***(2007)***

Peptides - Custom Manufacturing

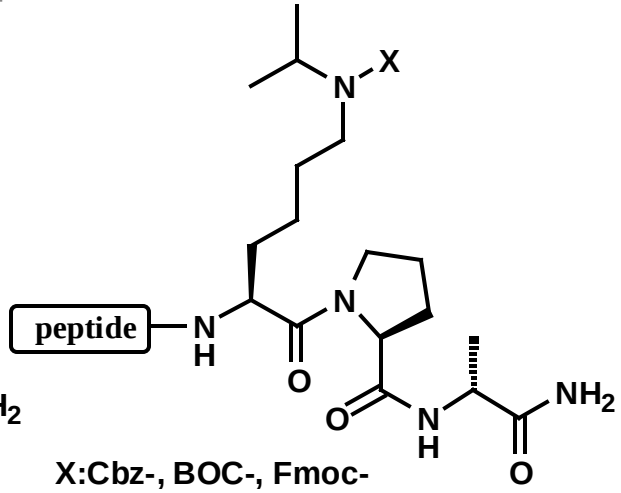
Intermediates and API for LH-RH analogues



APO(Ac-D-2-Nal-D-4-ClPhe-D-3-Pal)
Registry Number:129225-22-5



Peptide-L-Arg(nitro)-Pro-D-Ala-NH2



X:Cbz-, BOC-, Fmoc-

Peptide-Lys(Ipropyl.X)-Pro-D-Ala-NH2

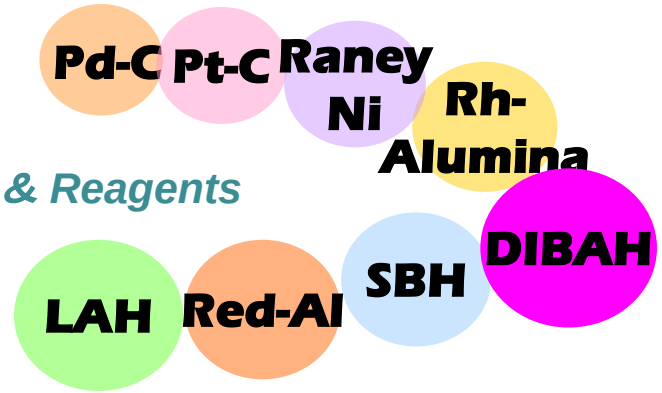
HPLC purity : NLT 99%

◆**We are able to provide our process development for intermediates and API of LH-RH analogs such as Degarelix and Abarelix etc…**

Reduction Reactions

■*Extensive experience in safely handling Metal catalysts.*

■*Our capability to use chemical reagents*

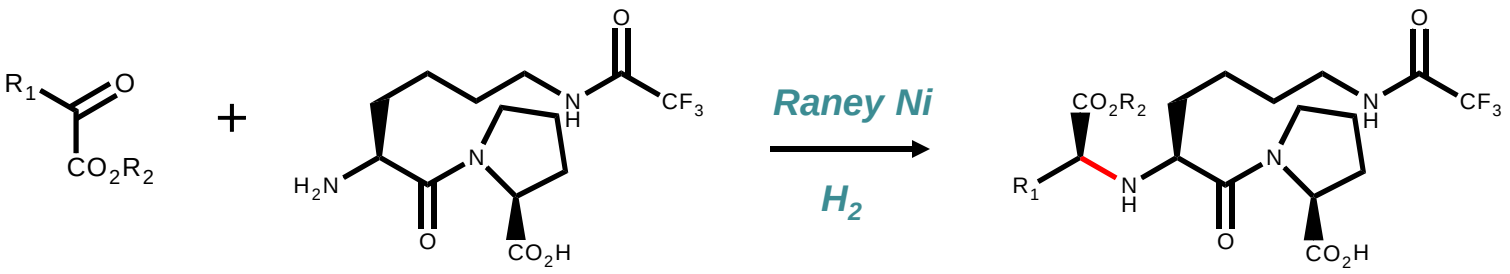


Autoclaves

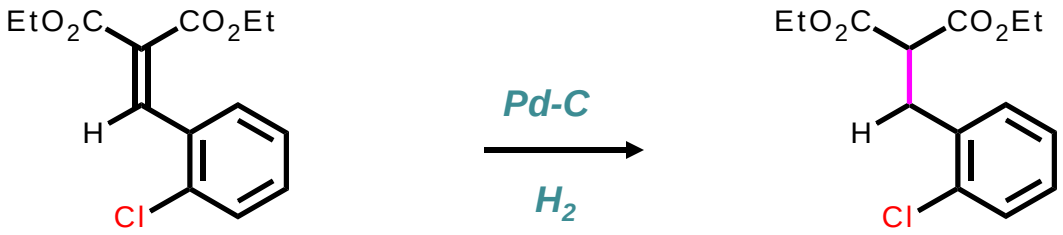
Osaka		Yonezawa	
500L Hastelloy	1.0 MPa	2500L SUS	1.0 MPa
500L SUS	0.5 MPa	1800L SUS	1.0 MPa
100L SUS	0.2 Mpa	1700L SUS	1.0 MPa
10L SUS	2.0 Mpa	1000L SUS	0.2 MPa
1000L GL	0.1 Mpa	500L SUS	6.8 MPa

Reduction Experience

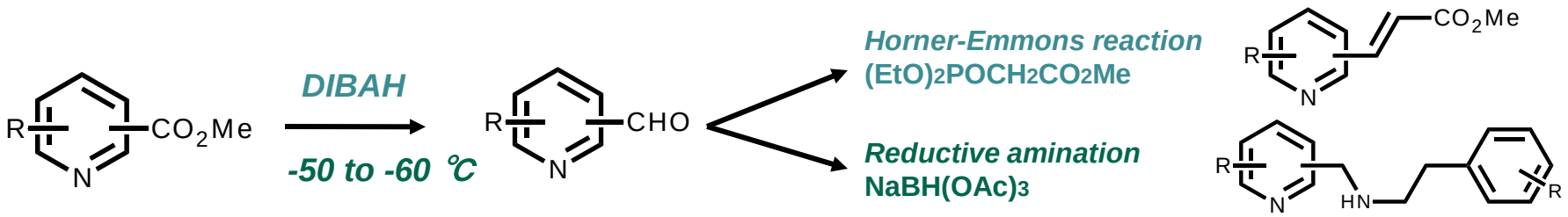
Asymmetric Schiff base reduction (H_2 / Raney Ni , 30 tons / year)



Selective hydrogenation by using Pd-C（without dehalogenation）

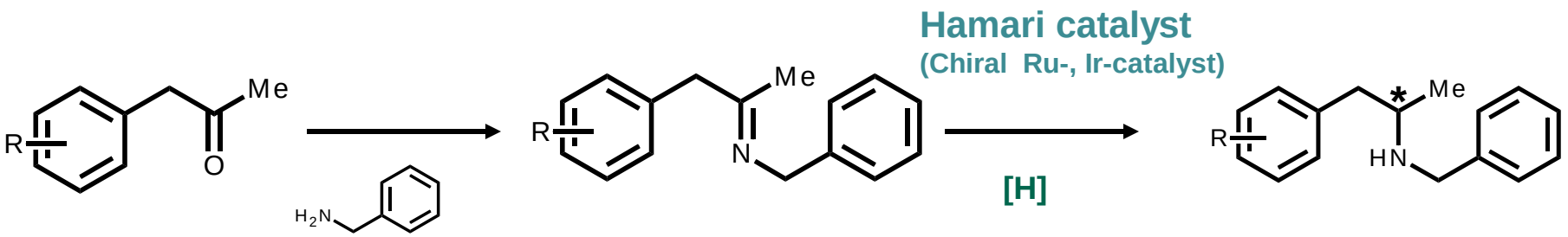


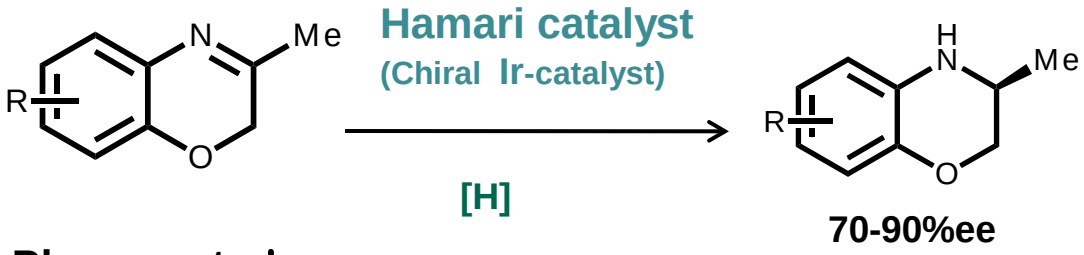
Reduction with DIBAH on commercial scale



Hamari Chiral Technology

Asymmetric Transfer Hydrogenation *using Chiral Ru- and Ir -catalysts*



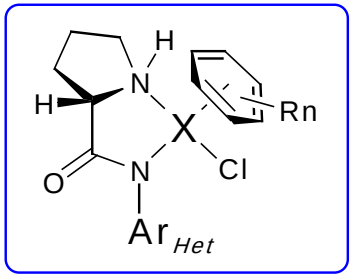


Chiral Ru-complex	ee(%) .
arene-Ru(Ⅱ)-TsDPEN	ca.20%ee
Hamari catalyst Ru	40%ee
Hamari catalyst Ir	80%ee

Please note !

- **Asymmetric synthesis Instead of optical resolution.**
- **When it is not appropriate to use other catalysts.**

Hamari is able to provide
Full Time Equivalent study needed for your custom synthesis
Using our Asymmetric Transfer Hydrogenation technology.



X=Ru , Ir

Hamari Chemicals, Ltd.

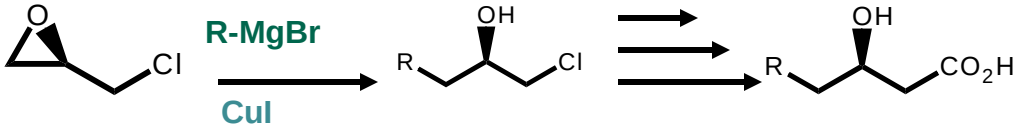
Alkylation

Cryogenic reactions

- ～ - 90℃ max. 1000L
- ～ - 50℃ max. 3000L

Base um (*n*-BuLi), LDA, NaH, *tert*-BuOK, *tert*-BuONa, MeONa, Li, *etc.*

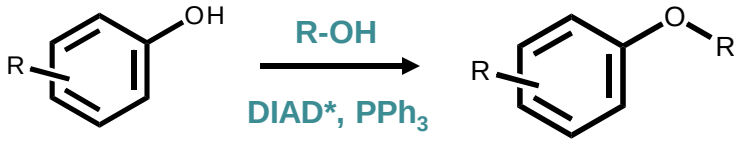
Grignard Reaction



Etherification

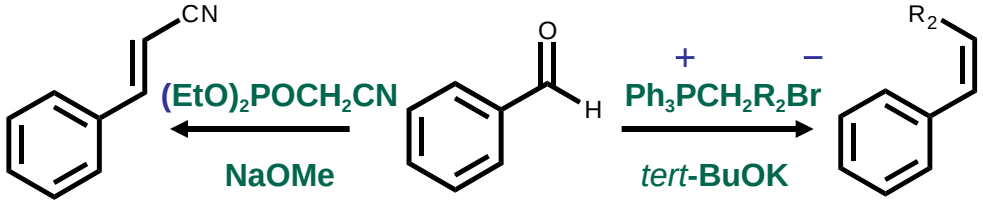
PTC-catalyzed (e.g. TBAB)
Mild condition (<80℃)
High yield (>90%)

Mitsunobu reaction using DIAD

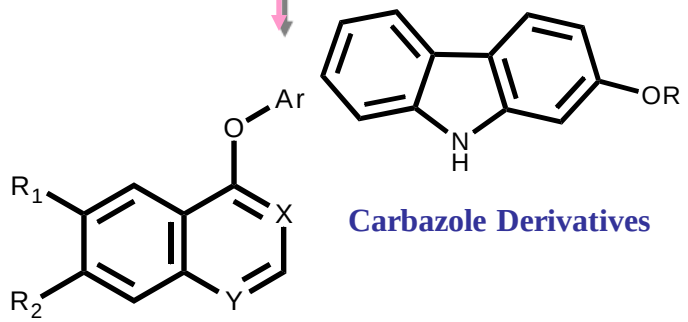


* DIAD : Diisopropyl azodicarboxylate

Olefination -Horner-Emmons and Wittig reactions



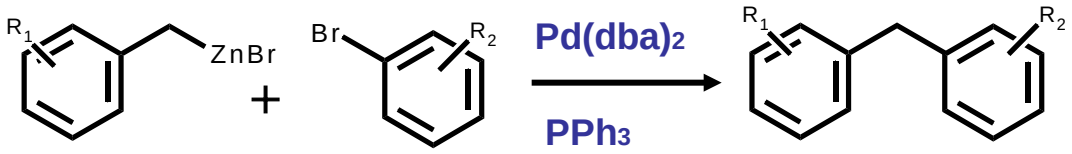
Horner-Emmons　　Wittig



Carbazole Derivatives

Quinoline & Quinazoline Derivatives

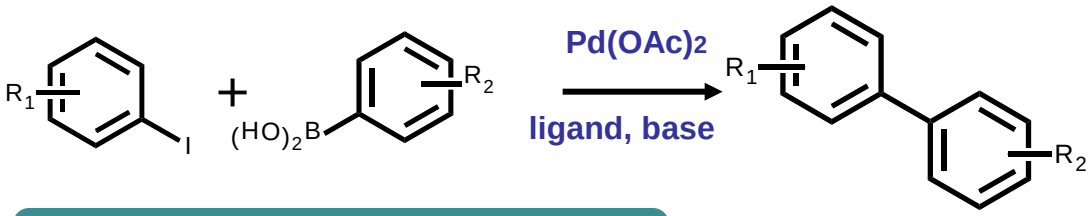
Negishi Cross Coupling



Manufacturing

- Pilot plant : Osaka
- Manufacturing : 50kg / Batch
- Residual Pd : NMT 1 ppm level
- In accordance with cGMP

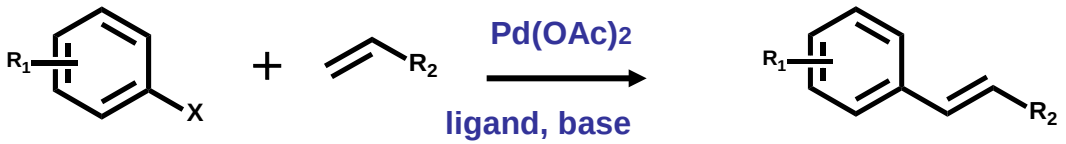
Suzuki-Miyaura Cross Coupling



Manufacturing

- Commercial : Yonezawa
- Manufacturing : 100kg / Batch
- Residual Pd : NMT 1 ppm level
- In accordance with cGMP

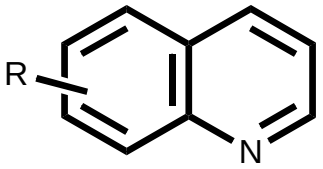
Mizoroki-Heck Reaction



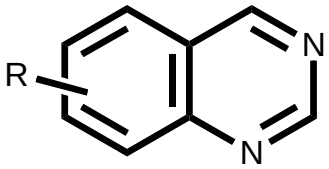
Manufacturing

- Commercial : Yonezawa
- Manufacturing : 100kg / Batch
- Residual Pd : NMT 1 ppm level
- In accordance with cGMP

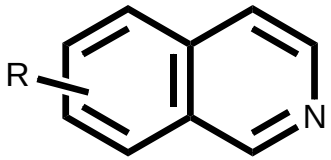
Heterocyclic Derivatives



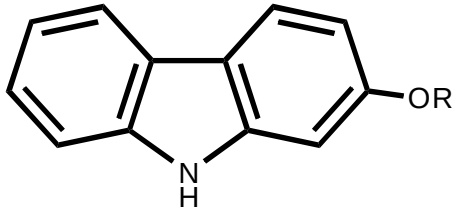
Quinolines



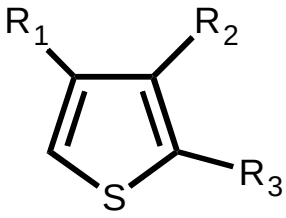
Quinazolines



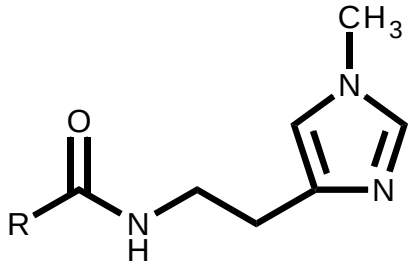
Isoquinolines



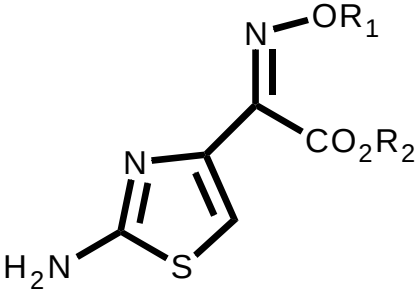
Carbazoles



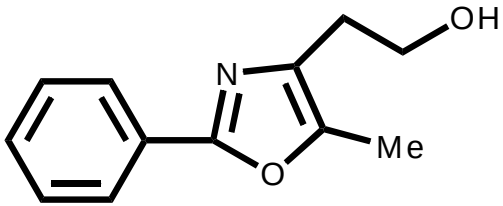
Thiophenes



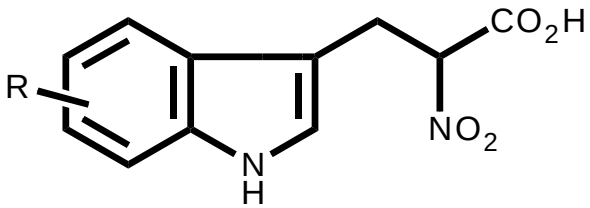
Imidazoles



Aminothiazoles



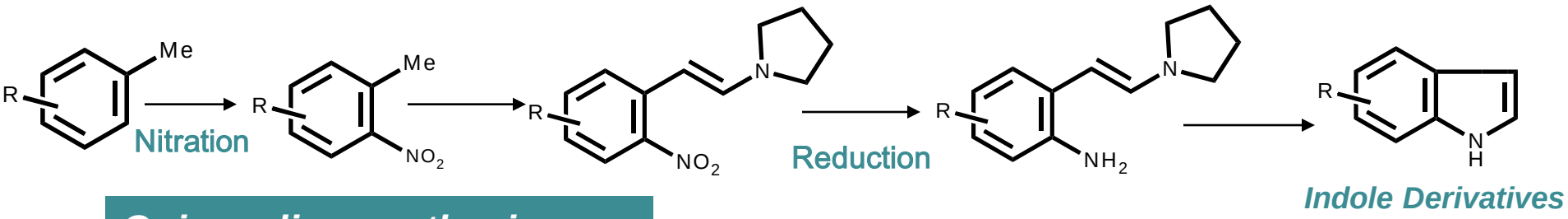
Oxazoles



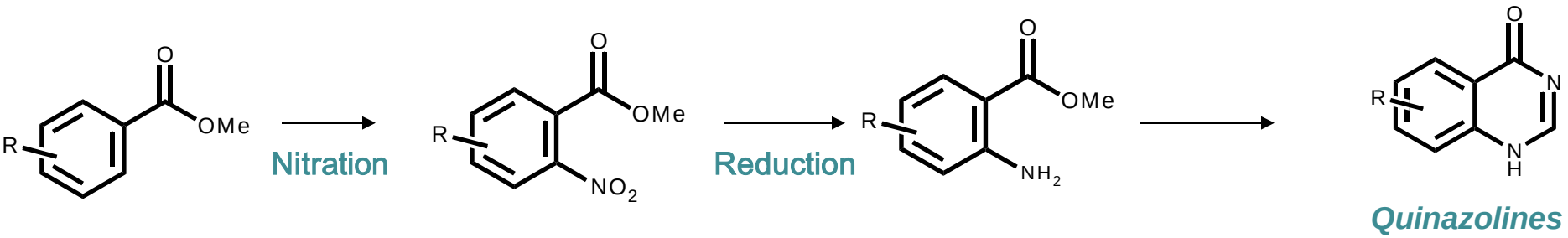
Indoles

Heterocyclic Derivatives

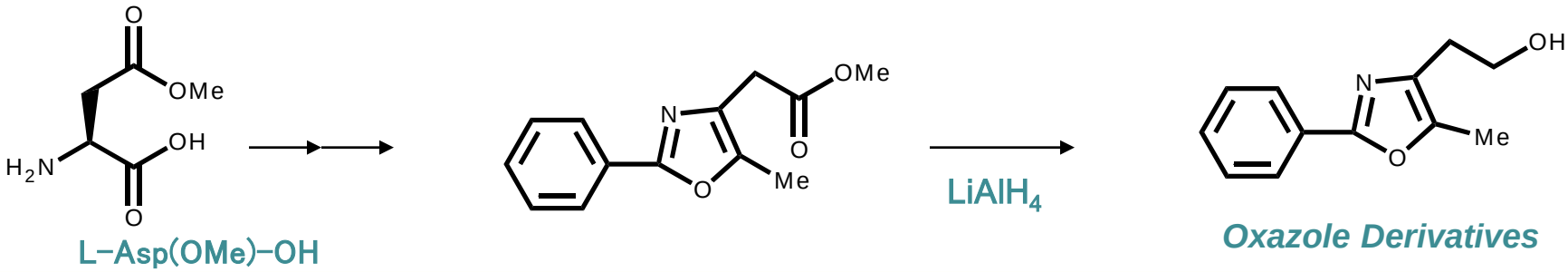
Leimgruber - Batcho indole synthesis



Quinazolins synthesis



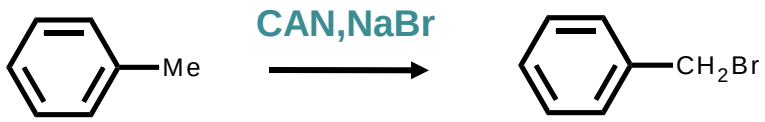
Oxazole synthesis and the following $LiAlH_4$ - reduction



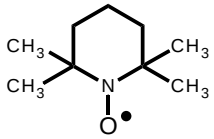
Oxidation

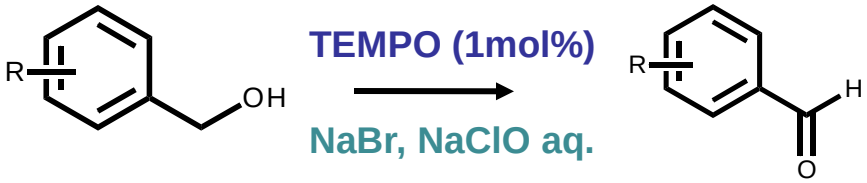
Safely handling reagents such as CAN, TEMPO,Oxone® MnO2 and Sulfonium salts (Swern oxid.)

CAN : $(NH_4)_2Ce(NO_3)_6$



TEMPO

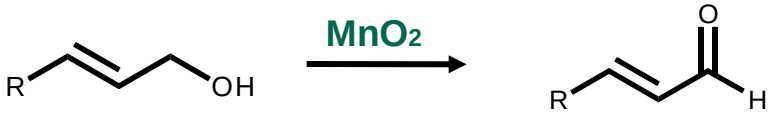


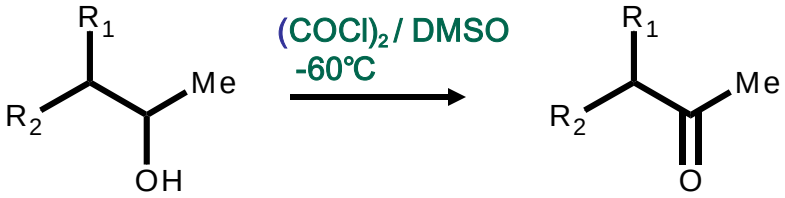


Oxone® ; Potassium Peroxymonosulfate

Swern and related oxidations

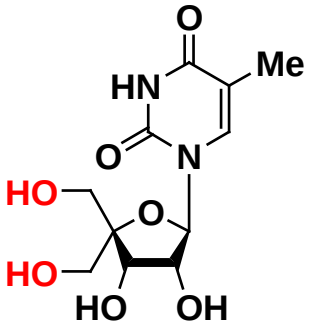
MnO_2 : activated type

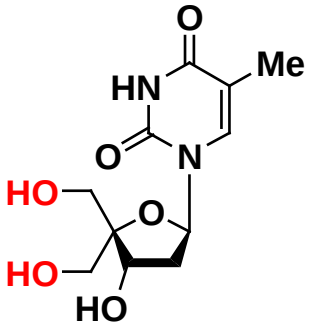


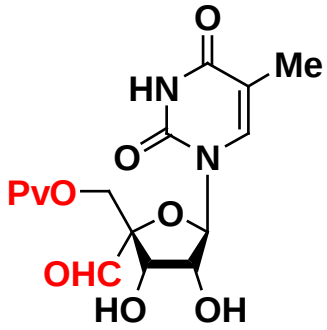


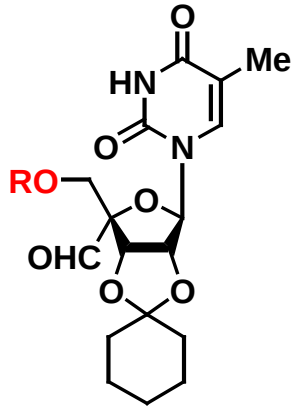
Nucleic Acid Derivatives

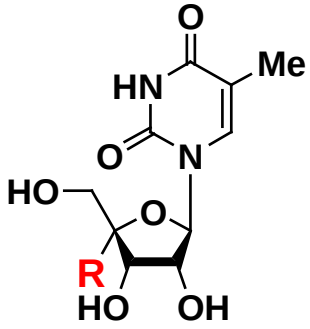
API and Intermediates for antiviral agents

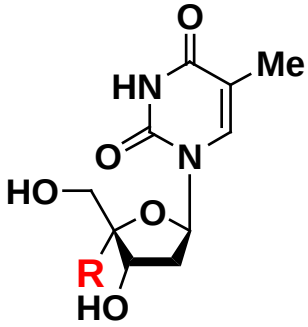


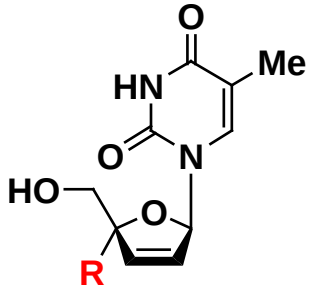












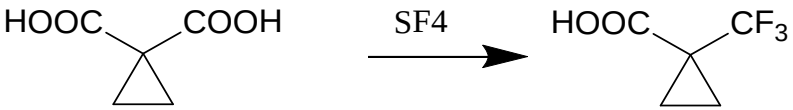
IND Products : **2007-2010**

Anti HIV project ; non-GMP 2Lot(1kg, 15kg), GMP 1Lot 1(3kg)

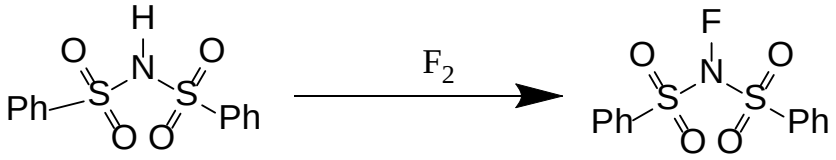
Types of reactions that Hamari is able to perform through our affiliates

- **Fluorination Reactions**

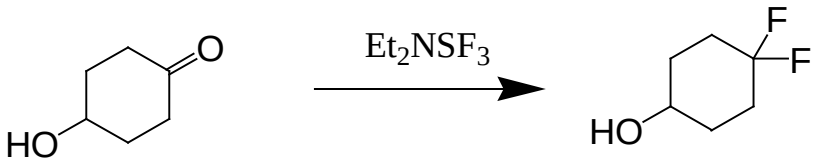
Sulfur Tetrafluoride



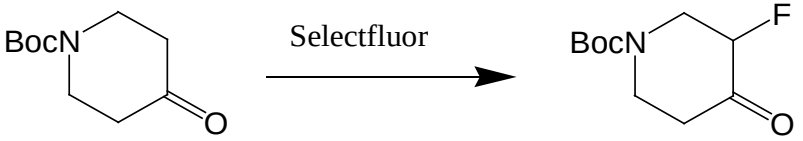
Fluorine



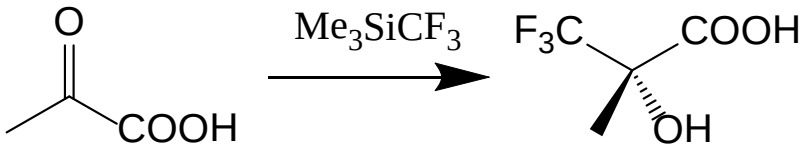
Nucleophilic Fluorinations



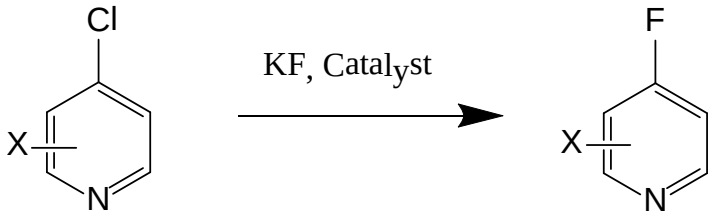
Electrophilic Fluorinations



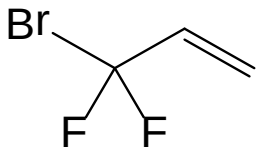
(Perfluoroalkyl) Trimethylsilanes

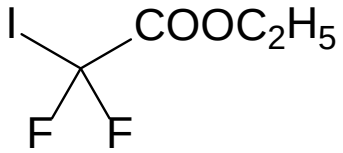


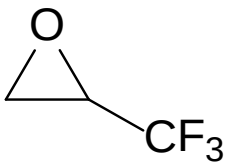
Halogen Exchange

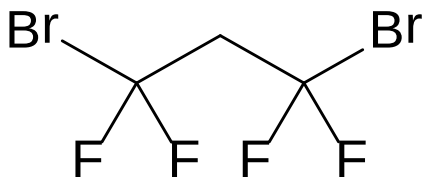


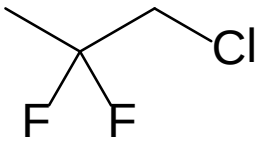
Fluorinating Building Blocks Available

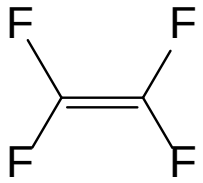




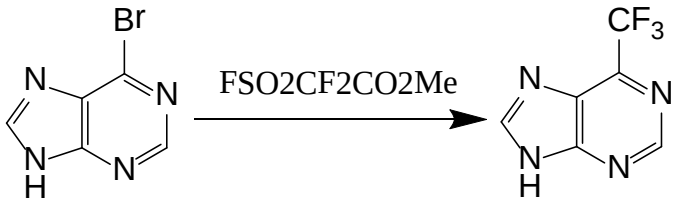








Methods for Introduction of CF_n Groups



CF_n-transfer reagents= CF_2I_2, $FSO_2CF_2CO_3Me$, $PhSO_2CF_2H$, $PhSO_2CFH_2$

Types of reactions that Hamari is unable to perform

- High temperature reactions (200-300℃)
- Precise Distillations for Purification
- Phosgene Chemistry
- Reductions using Diborane
- Oxidations using Ozone
- Photo-reactive Chemistry

Thank you very much for your time and attention
“Your Partner for the Future”

CPhI Worldwide 2011

In Frankfurt , Booth #30H02

Hamari Chemicals, Ltd.

http://www.hamarichemicals.com