Peptide Catalyst in Synthetic Organic Chemistry

2011.11.08
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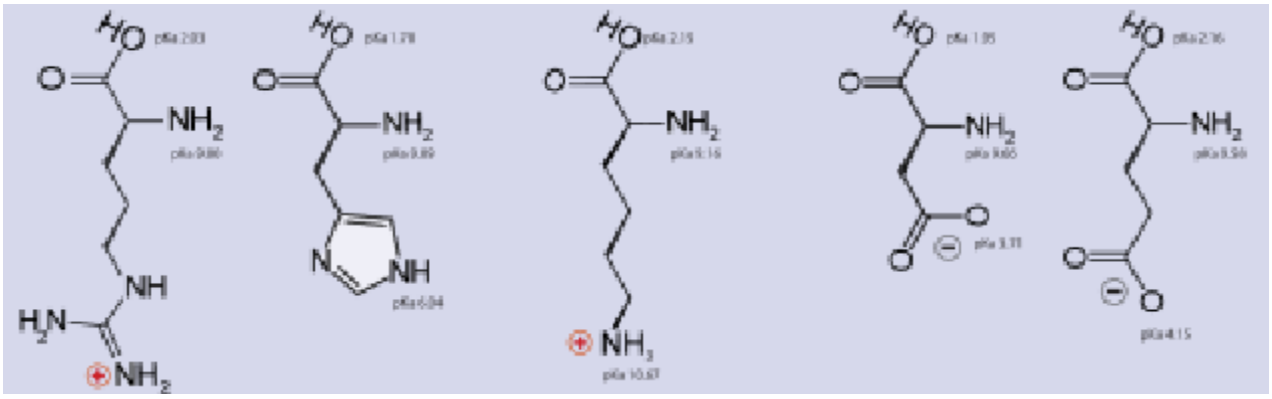
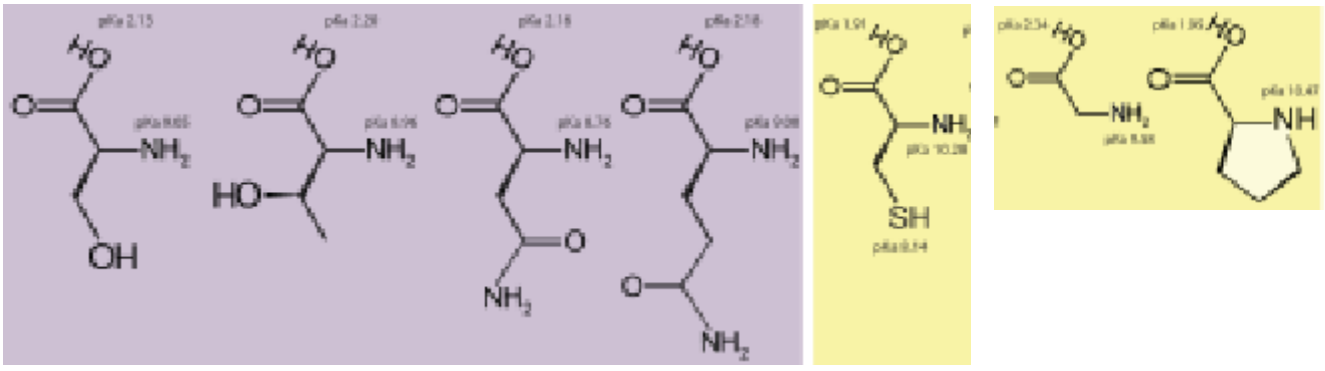
Contents

Wikipedia: Amino acid: http://en.wikipedia.org/wiki/Amino_acid

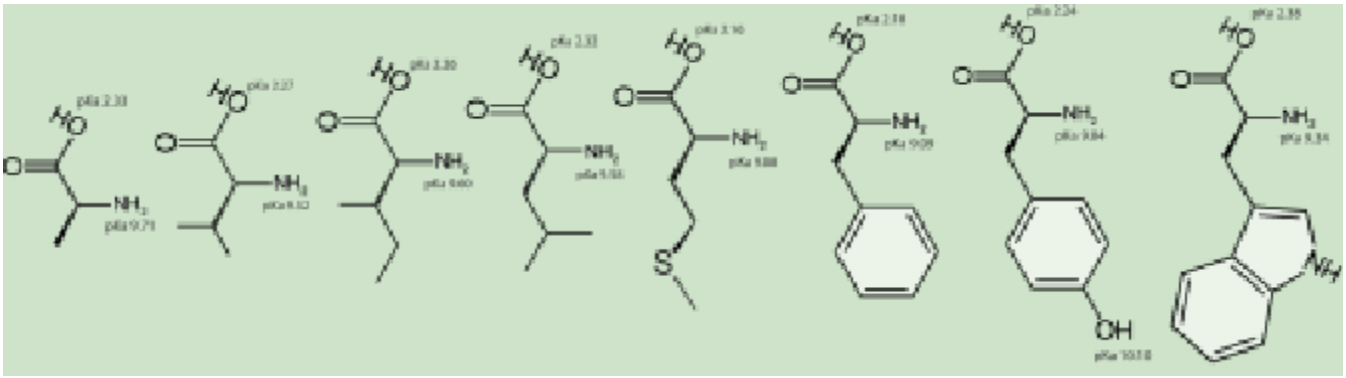
Arginine (Arg, R) **Histidine (His, H)** **Lydine (Lys, K)** **Aspartic acid (Asp, D)** **Glutamic acid (Glu, E)**



Serine (Ser, S) **Threonine (Thr, T)** **Asparagine (Asn, G)** **Glutamine (Gln, Q)** **Cysteine (Cys, C)** **Glycine (Gly, G)** **Proline (Pro, P)**



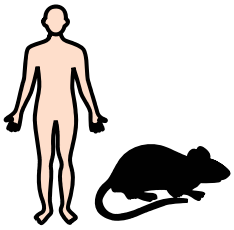
Alanine (Ala, A) **Valine (Val, V)** **Isoleucine (Ile, I)** **Leucine (Leu, L)** **Methionine (Met, M)** **Phenylakanine (Phe, F)** **Tyrosine (Tyr, Y)** **Tryptophan (Trp,W)**



1. Introduction

1-1. Outline of Idea

review: Itsuno, S. *et al.* Polymeric Chiral Catalyst Design and Chiral Polymer Synthesis, 2011, Wiley. ISBN-10: 0470568208

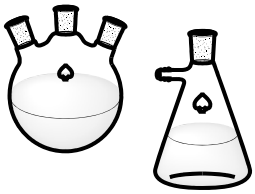


Life

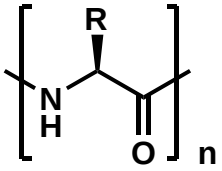
Catalyze

Enzymes

- High
  - efficientry
  - selectivity
  - substrate specificity
- Mild condition
- In water.



Many chemical reactions

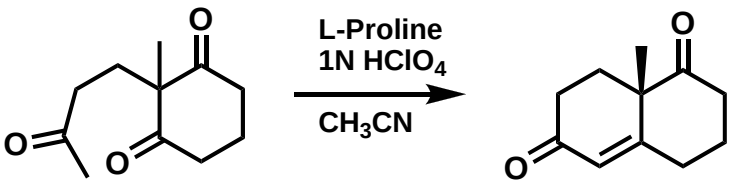


Amino acids

By using artificial peptide, high performance reaction can be achieved?

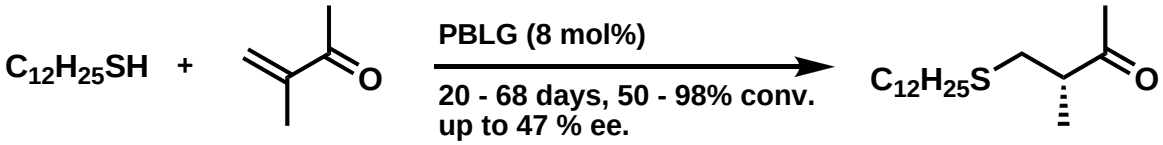
1-2. Typical Works in the Peptide Catalyst Field in 20th Century

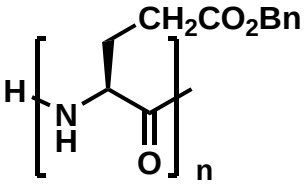
Wiechert, R. *et al. ACIE*, 1971, *10*, 496.
" Amino acid catalyzed asymmetric Robinson annulation"



87%, 84 % ee.

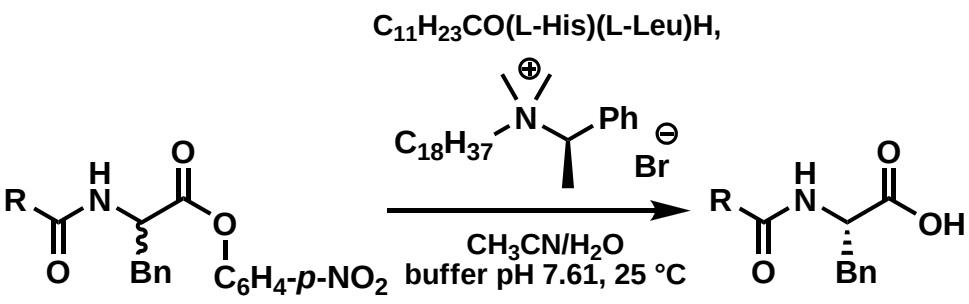
Inoue, S. *et al. Die Mukromolekulure Chemie,* 1975, *176*, 2751.
" Poly(amino acid)-catalyzed asymmetric protonation"



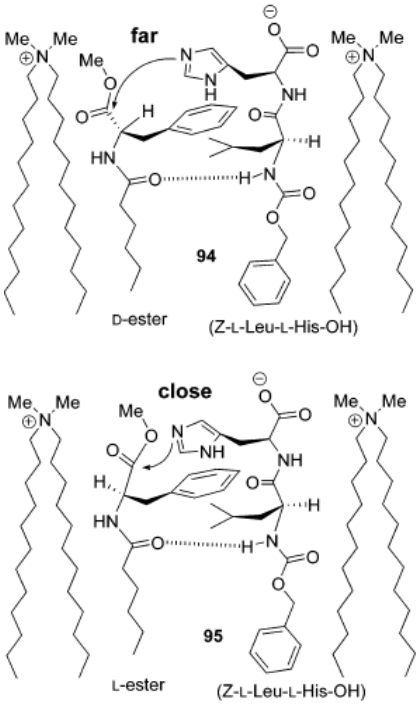


PBLG: poly (5-benzyl L-glutamate), n = 1 - 20

Ohkubo, K. *et al. J. Chem. SOC. Chem. Commun*. 1980, 637.
" Enantioselective hydroysis of ester by amino acid dimer"

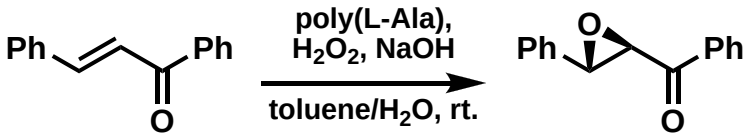


k^L/k^D = up to 5.7
(*ca.* 70% ee.)



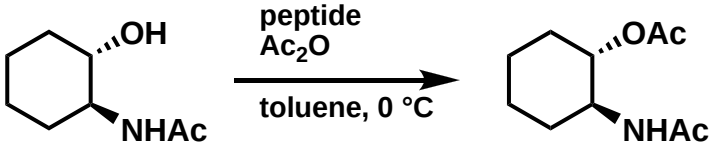
Miller, S. J. *et al. Chem. Rev.* 2007, *107*, 5759.

Julia, S. *et al. ACIE*, 1980, *19*, 929.
" Asymmetric epoxidation (Julia-Colonna reaction)"

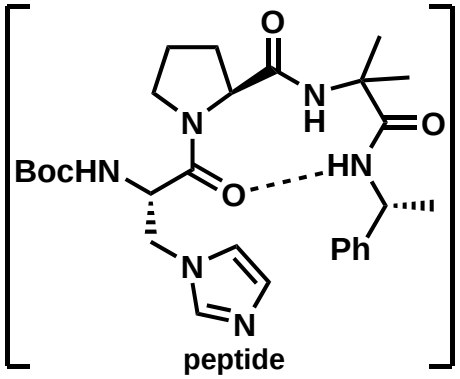


85%, 93% ee.

Miller, S. J. *et al. JACS.* 1998, *120*, 1629.
" Kinetic resolution in the acetylation of alcohols"



> 90%, 84% ee.



List, B. *et al. JACS.* 2000, 122, 2395.
" Asymmetric aldol reaction"

97%, 96% ee.

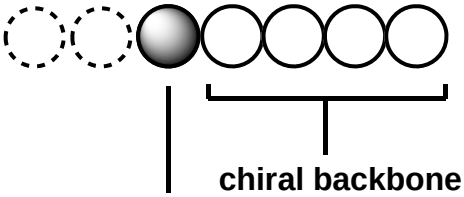
1-3. Features of Peptide Catalyst

Advantages
- **Tolerances of oxygen ansd water: easy handling.**
- **Easy synthesis and valious amino acid monomers are available: high diversity.**

Disadvantages
- **Reaction forms are limited to organocatalytic reactions.**
- **Tremendous screenning is requiered to optimize catalyst.**

2. Design of Peptide

2-1. Basic Structure of Peptide Catalyst



chiral backbone (steric, hydrogen bond, π-π stacking)

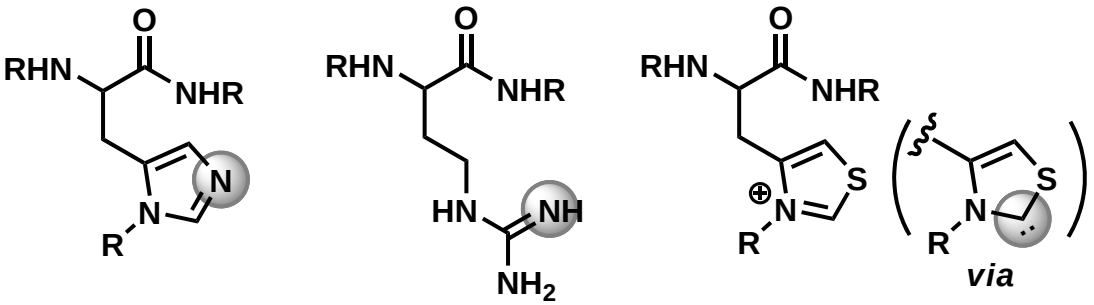
active site

2-2. Active Site

review: Miller, S. J. *et al. Chem. Rev.* 2007, *107*, 5759.

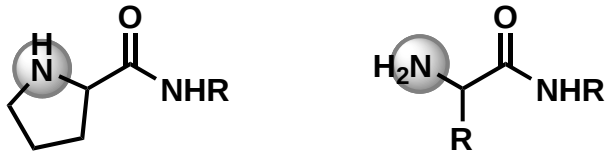
Peptide catalized reactions are organocatalyst.

Base or nucleophile:



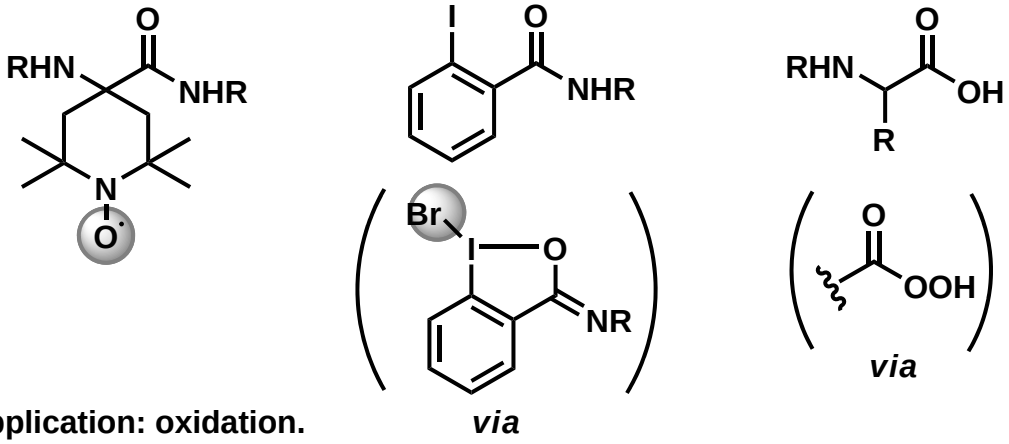
application: conjugate addition (-> protonation), MBH reaction, protonation of silyl enorl ether, hydrolysis of ester, Strecker reaction, Stetter reaction, acylation, phosphorylation

Enamine / iminium formation:



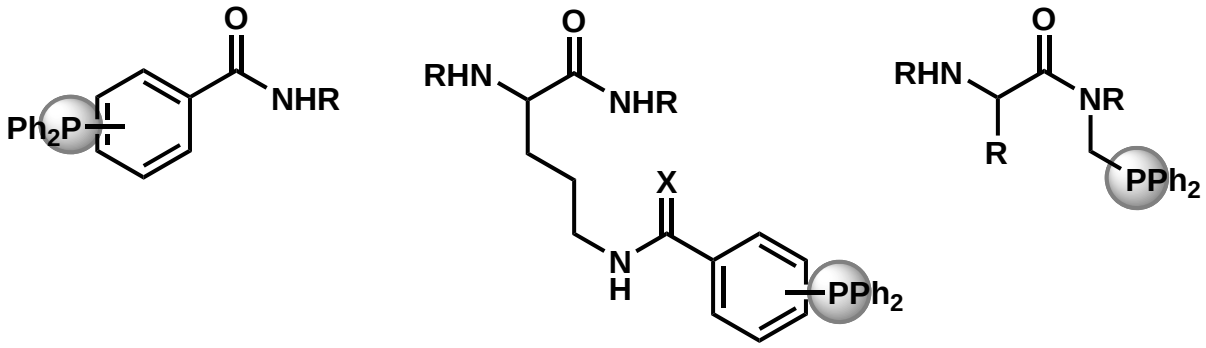
application: aldol reaction, conjugate addition (epoxidation).

Oxidant



application: oxidation. ***via***

Ligand



application: metal catalyzed reaction.

2-3. Chiral Backbone

2-3-1. Structure of Peptide

review: Balaram, P. *et al. Chem. Rev.* 2001. *101*. 3131.

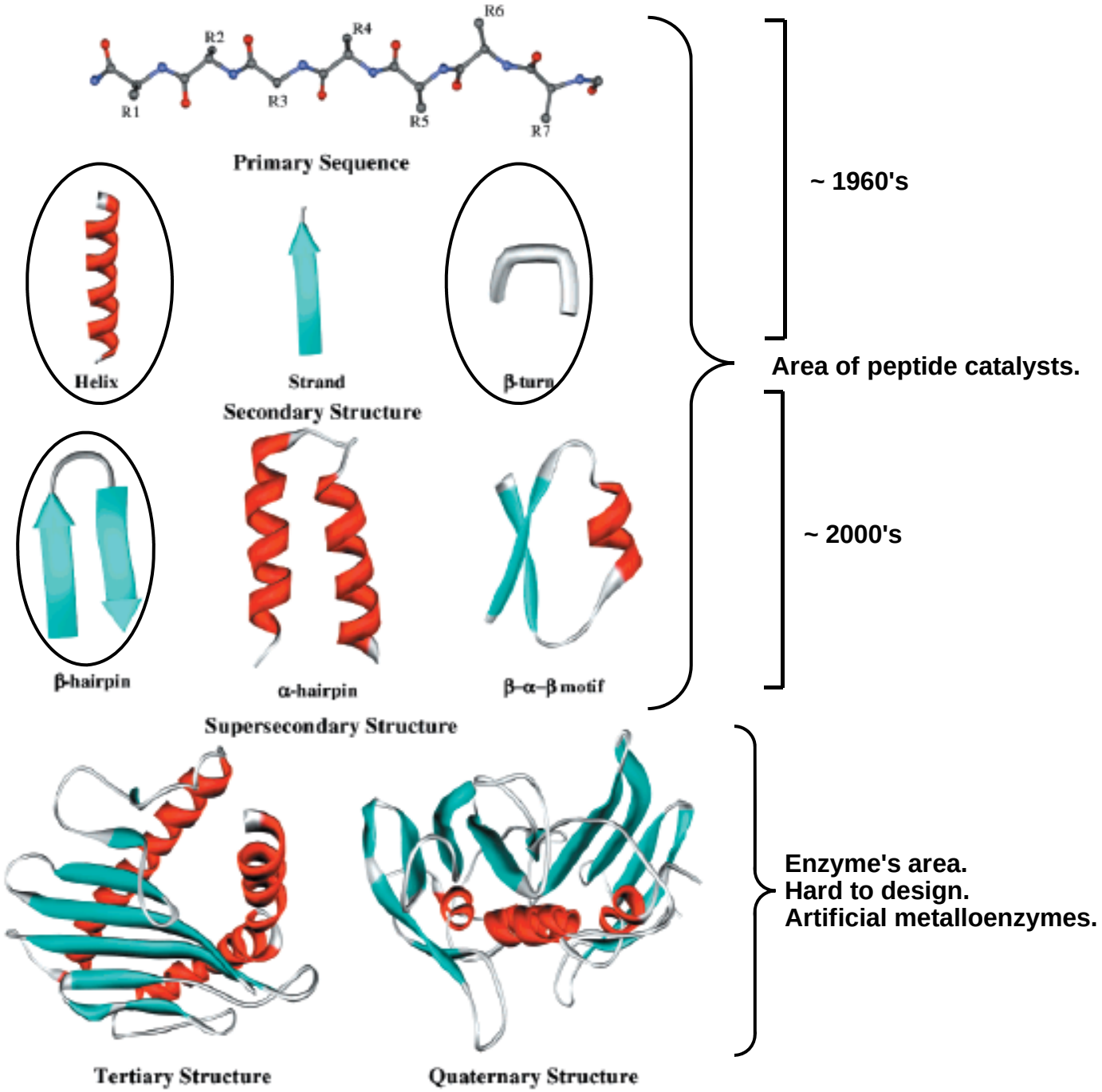
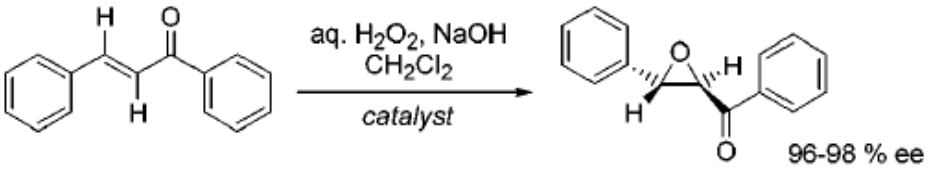


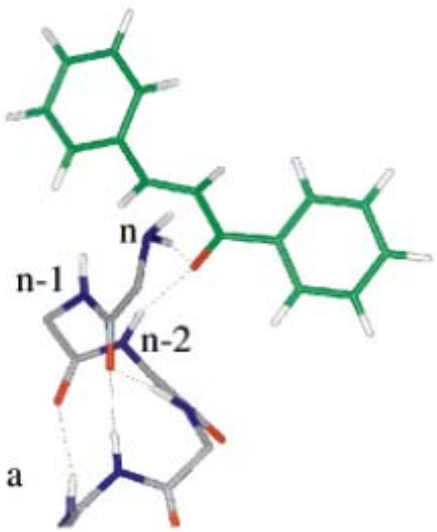
Fig. 2-1: Various levels of structural organization observed in protein structures. Main structures of paptide catayst are showed in the circles.

2-3-2. Helices

Berkessel, A. *et al. Org. Lett.* 2001, *3*, 3839. Also see above Julia-Colonna reaction.



catalyst: **(*L*-Leu)$_5$** on TentaGel S NH_2



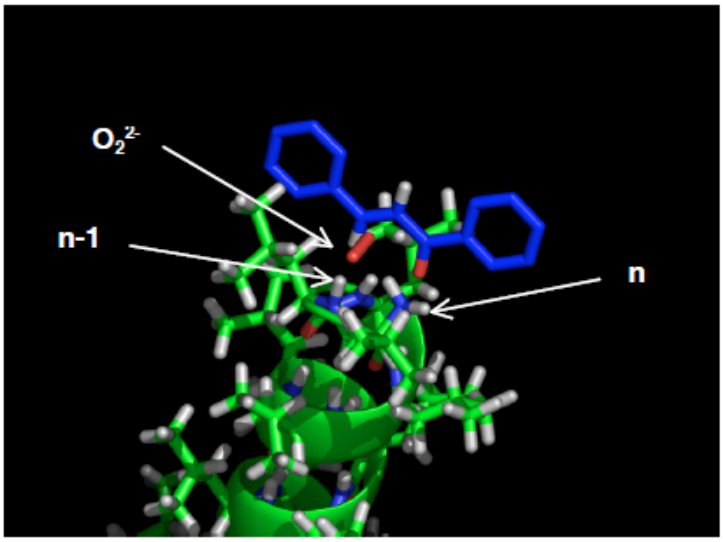


Fig. 2-2: A interactoin of peptide and substrate. left: *Org. Lett*.
right: Hughes, R, M. *Design Strategies for Peptide-Based Asymmetric Catalysis,* http://images.dcheetahimages.com/www.organicdivision.org/ama/orig/Fellowship/2005_2006_Awardees/Essays/Hughes.pdf

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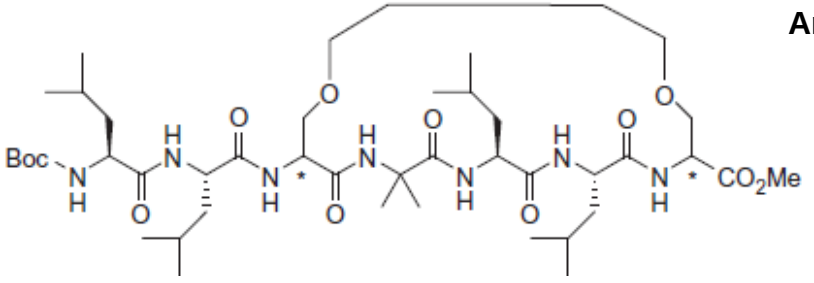
Construction of helices **(see also Mr. Sakaoka's literature seminar in 2010/7/14.)**

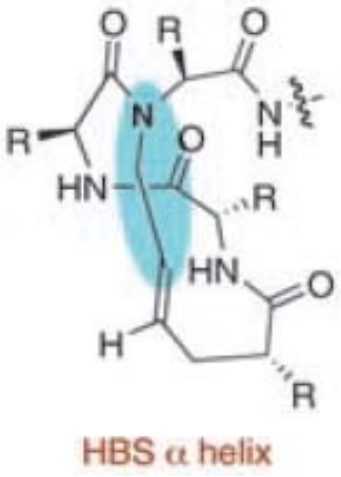
1. Residues with large helix-forming propensities.
-> Leu, Val, Phe, Met, etc... (hydrophobic side chains.)
It seems that the electrostatic (i, i + 4) interactions eg) Gln•Asp, Glu•Asn) are rare in peptide catalyst field. Maybe ionic functional groups give wrong effect to reaction.

2. Covalent helix-stabilization.
-> Linking (i, i + 3 or 4) residues.

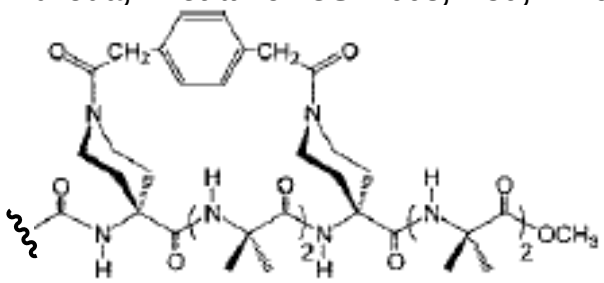
Kurihara, M. *et al*. *Tetrahedon Lett.* 2011, *52*, 798.



Arora, P. S. *et al. ACIE.* 2005, *44*, 6525.



Kuroda, R. *et al. JACS.* 2008, *130*, 12266.



3. Aib type peptide.
-> Aib: α-aminoisobutyric acid; one of the (α,α)-dialkylglycines.

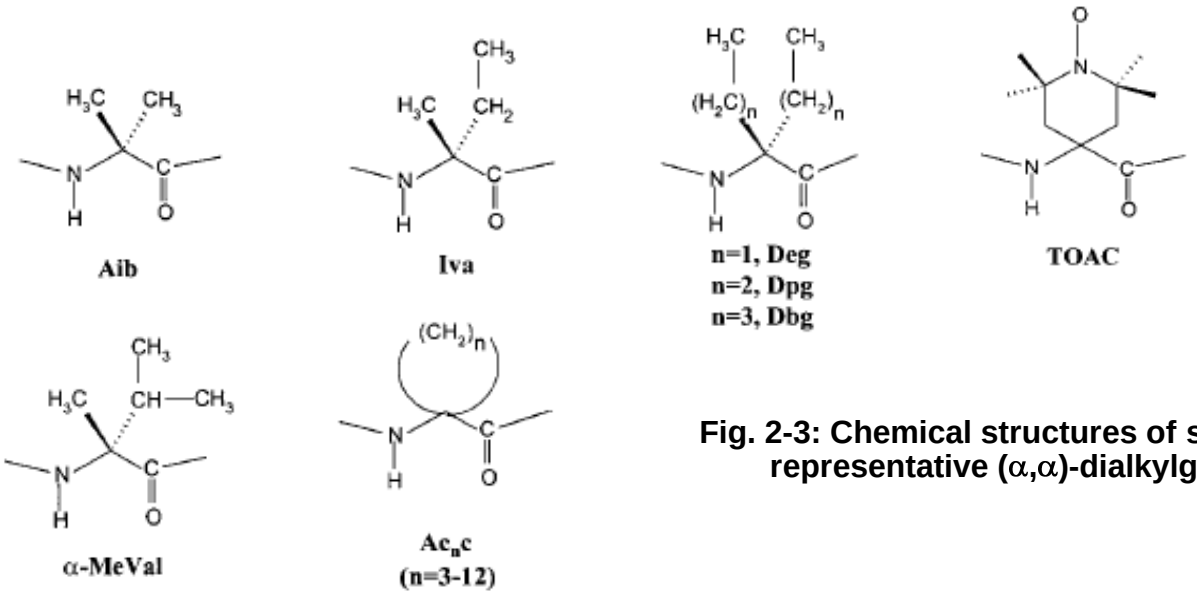


Fig. 2-3: Chemical structures of some representative (α,α)-dialkylglycines.

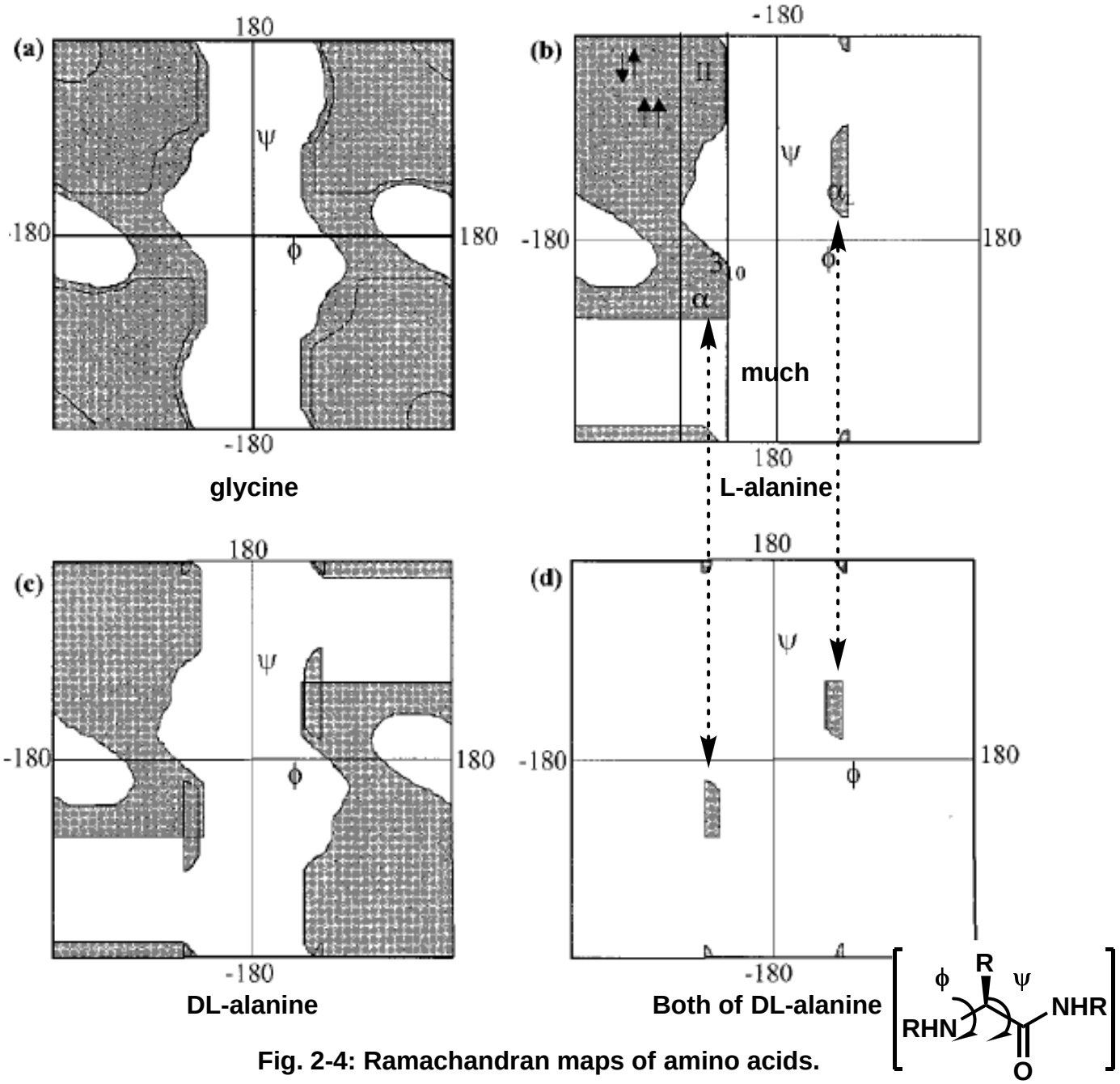
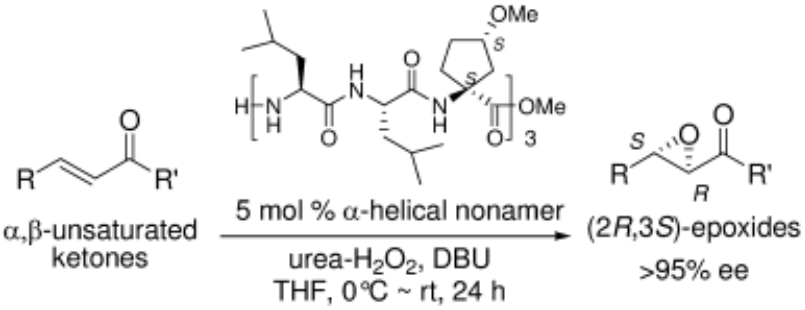
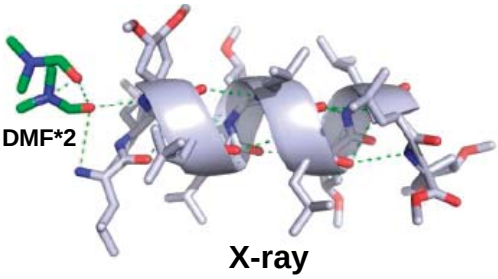


Fig. 2-4: Ramachandran maps of amino acids.

Tanaka, M. *et al. Org. Lett.* 2010, *12*, 3564.





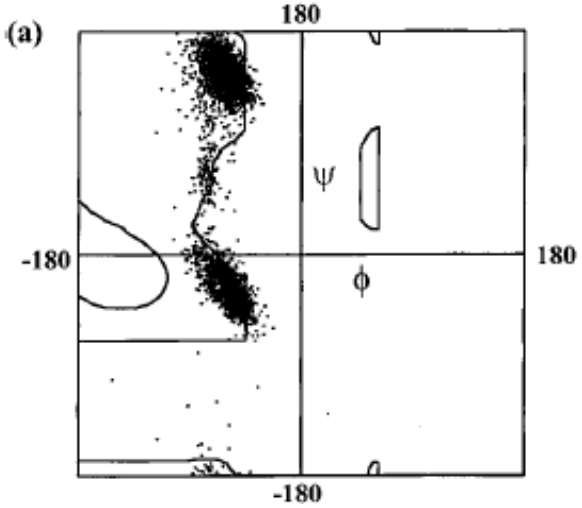
X-ray

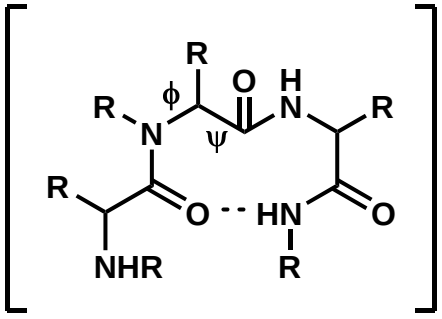
higher selectivity and substrate scope than original reaction.

2-3-3. β-turns

Hydrogen bond between (i, i + 3) (< 7 Å). Desighned from three amino acid.

1. Proline.



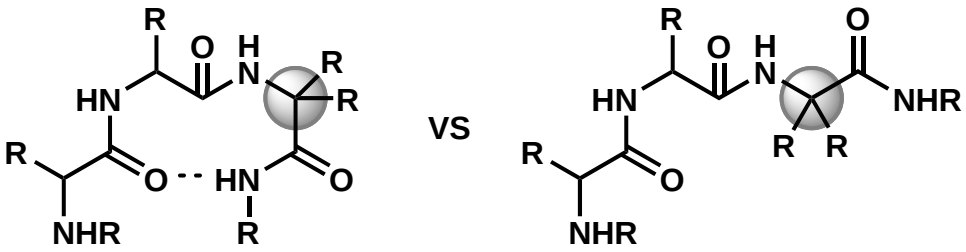


compatible with the i + 1 position of type I/III and type II turns.

Fig. 2-5: Crystallographically observed ϕ, ψ values of L-Pro residues from 538 independent protein crystal structures.

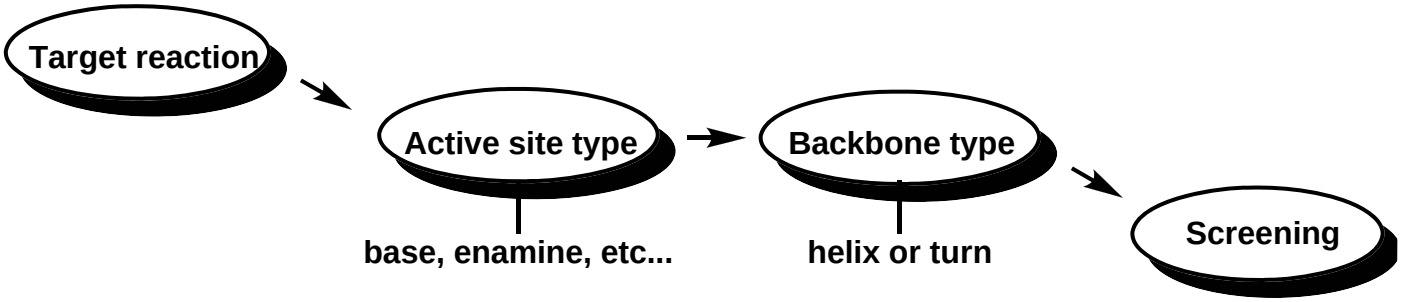
These two are very important elements for peptide catalysts!

2. Aib type peptide.



-> When dialkyl amino acid is i + 3 position, β-turn is stabilized.

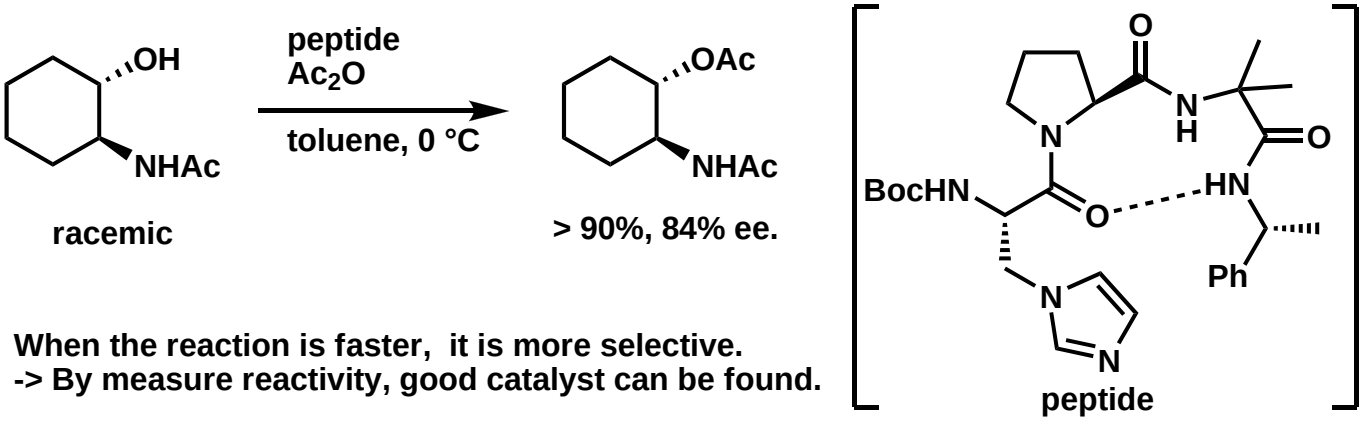
2-4. How to Screening?



The sequences of amino acides are infinite, so huge screenings are required for development of peptide catalyst.screening methods.

Fluoresence Assey in Enantioselective Acyl Transfer Reaction.
Miller, S. J. *et. al. JACS.* 1999, *121*, 4306.
***ivid.* 2000, *122*, 11270.**
***ivid.* 2001, *123*, 6496.**

Miller, S. J. *et al. JACS.* 1998, *120*, 1629.
see also Miller, S. J. *et. al. J. Org. Chem*. 1998, *63,* 6784. (*N*-Me His as a active site.)



When the reaction is faster, it is more selective.
-> By measure reactivity, good catalyst can be found.

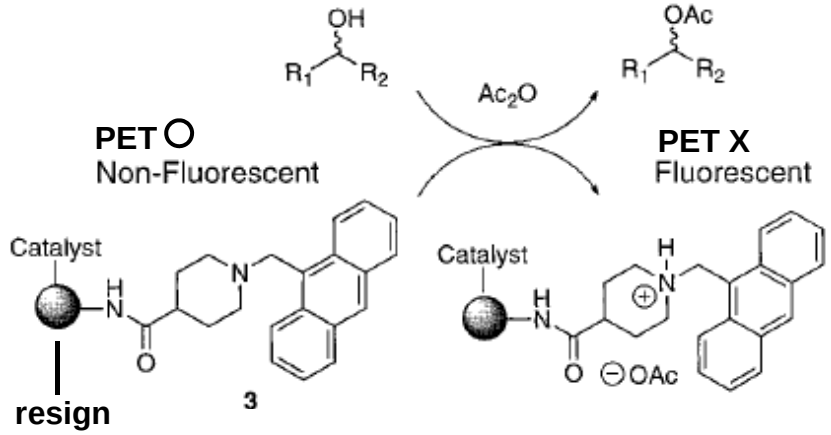
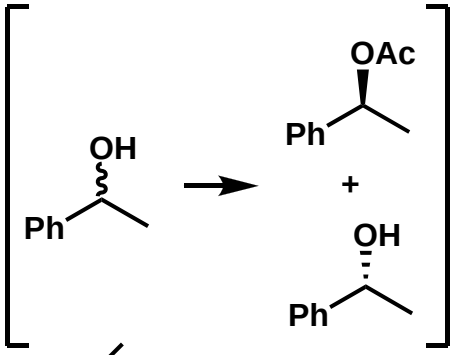


Fig. 2-6: Mechanisum of fluorescence.



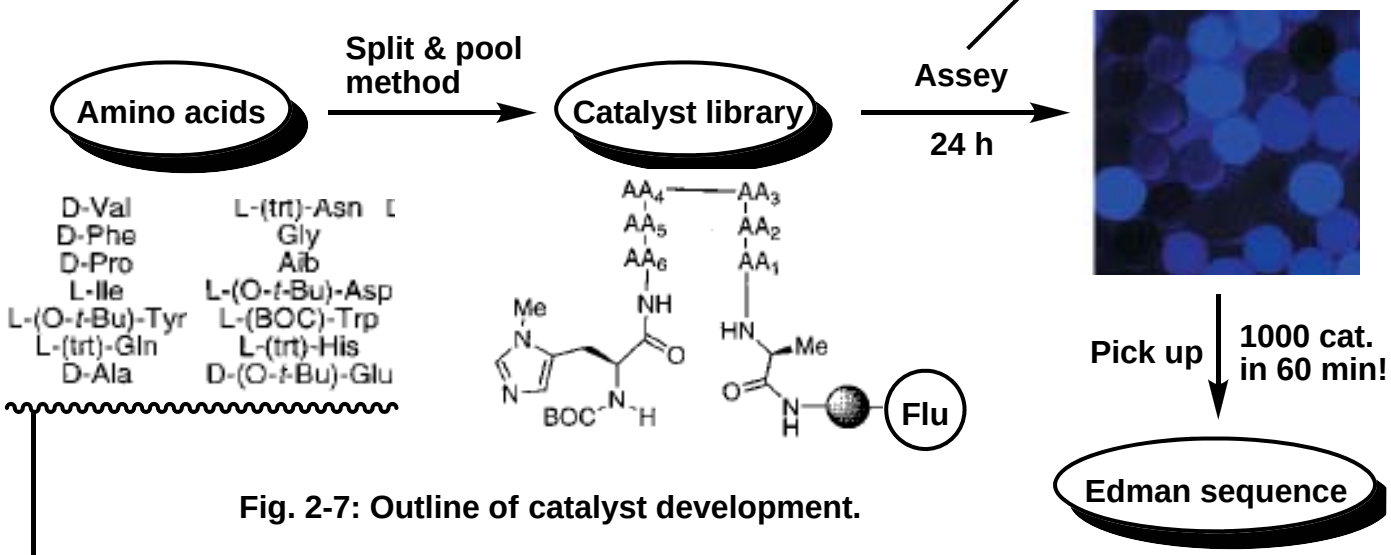
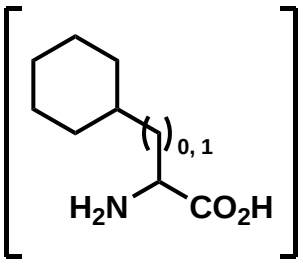


Fig. 2-7: Outline of catalyst development.

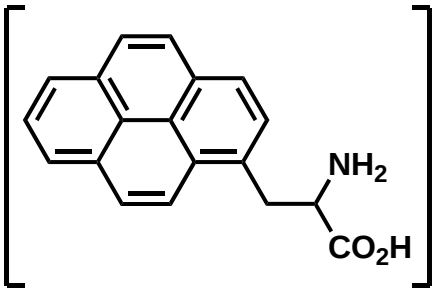
Reason of this choice is not written in the paper.
D-Pro(L-His + D-Pro is better than L-Pro, *JOC*.) and Aib are turn elements.
Gly is less hinder, Val, Ile, Phe, Ala is middle hinder, trt or tBu protected amino acid and Trp is higher hinder amino acid.

How do we choose amino acid monomer in library synthesis?

1. Choose β-turn element.
   -> It seems β-turn (β-hairpin) type peptide catalysts more effective than helix type one.
   ex) Pro, Aib, Ach, etc.
2. Choose aliphatic amino acids.
   ex) Val, Leu, Ile, Chg, Cha, etc.
3. Choose aromatic amino acids.
   ex) Phe, His, Trp, Bn-Asn, Bn-Ser, Bn-His, trt-Asn, trt-His, Pya, etc.
4. Choose bulky side-cained amino acids.
   ex) ^{t}Bu-Asn, ^{t}Bu-Ser, trt-Asn, trt-Gln, trt-His, Pya, etc.



Chg = cyclohexyl glycine
Cha = cyclohexyl alanin

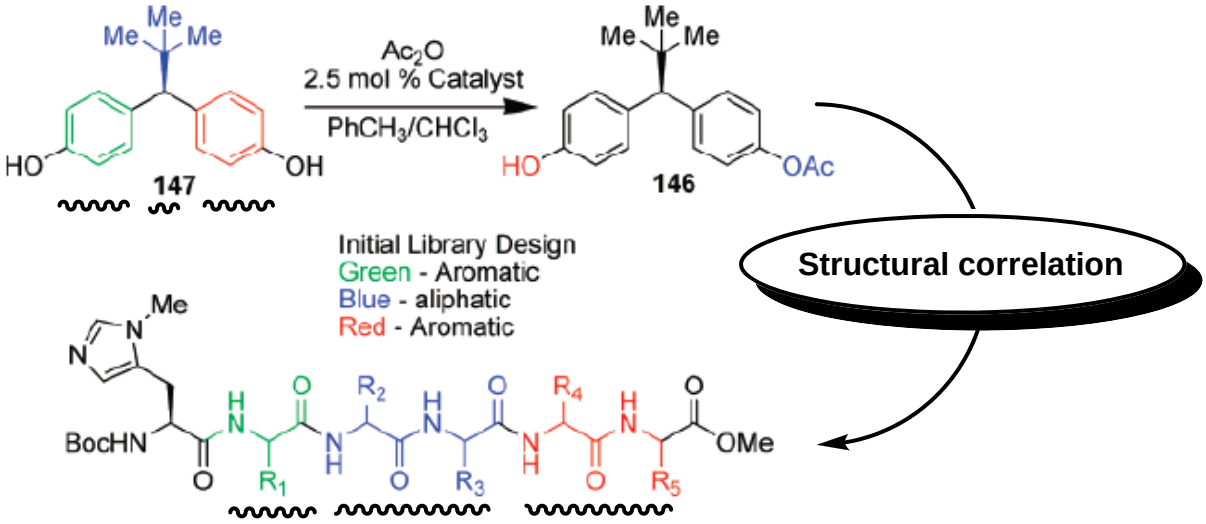


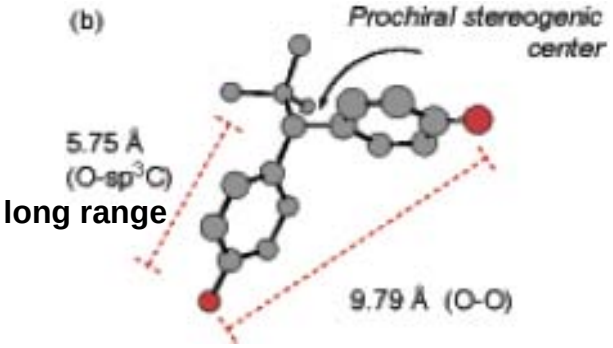
Pya = 1-pyrenyl alanine

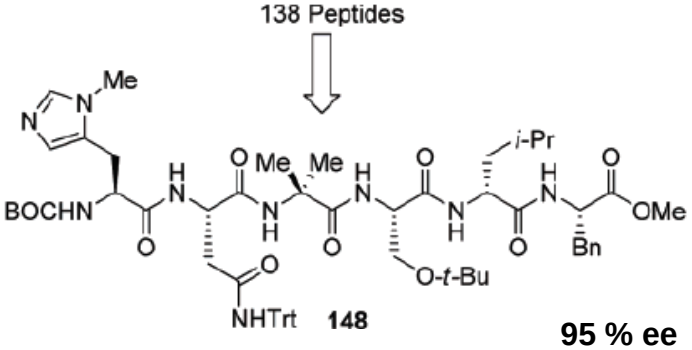
How do we set amino acid monomer in library synthesis?

-> Absolute randam screening gives us too large library (see after the next page.)
The reasonable sequence methodology is desirable.

Miller, S. J. *et al. JACS.* 2006, *128*, 16454.







95 % ee

Fig. 2-8: Substrate form (MM calc.)

Split & pool method

Knapp, R. J. *et al*, *Nature* 1991, 354, 82.

Stuart L. Schreiber Reserch Labolatry
http://www.broadinstitute.org/chembio/lab_schreiber/anims/animations/smdbSplitPool.php

1) Synthesis beads are split and placed into separate reaction tubes

Resin - typically 10^6 synthesis beads are used containing a core structure

The number of identical compounds on each bead can range from 10^{13} to 10^{16} depending on the bead's size and material.

steps: ① ② ③ ④ ⑤ ⑥ ⑦ Ⓒ Ⓢ Ⓟ

2) Couple building blocks
(typically 10 different building blocks in 10 separate tubes; only 2 are shown)

steps: ① ② ③ ④ ⑤ ⑥ ⑦ Ⓒ Ⓢ Ⓟ

3) Pool beads

steps: ① ② ③ ④ ⑤ ⑥ ⑦ Ⓒ Ⓢ Ⓟ

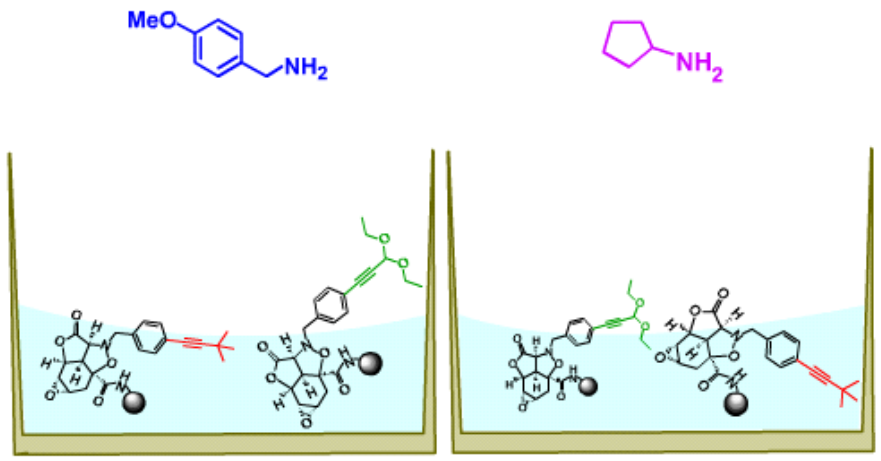
4) Repeat the process
split the beads...

steps: ① ② ③ ④ ⑤ ⑥ ⑦ Ⓒ Ⓢ Ⓟ

This method gives us wide library.
ex) When we synthesize hexamer with 10 kinds of amino acid monomers, max 10^6 (= 1000000, 100–œ!) unique catalyst are avalable.

5) Repeat the process

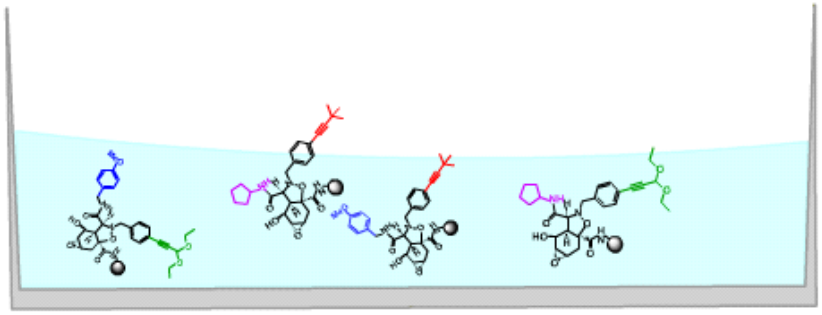
... add different building blocks...
(typically 10; only 2 are shown)



steps: ① ② ③ ④ ⑤ ⑥ ⑦ Ⓒ Ⓢ Ⓟ

6) Repeat the process

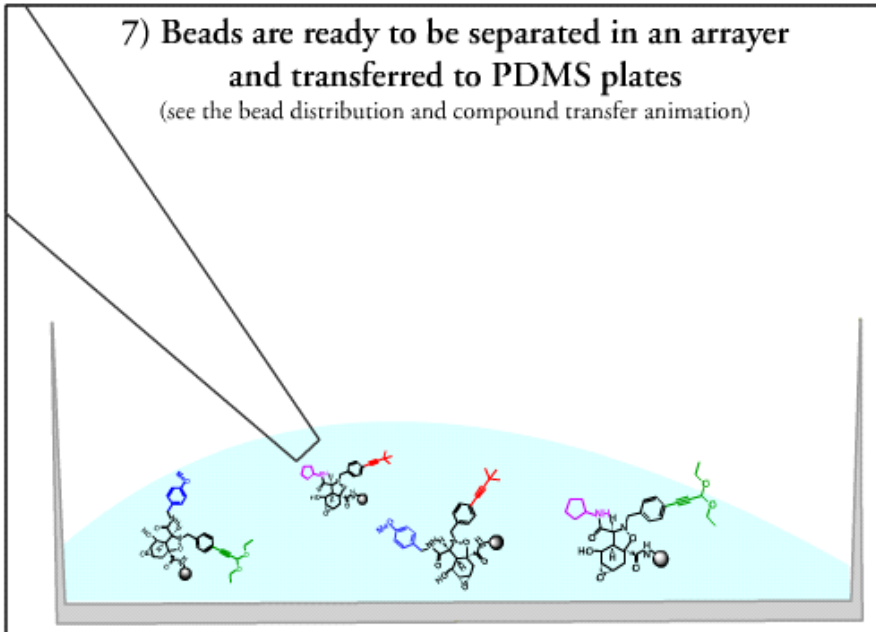
...pool again



steps: ① ② ③ ④ ⑤ ⑥ ⑦ Ⓒ Ⓢ Ⓟ

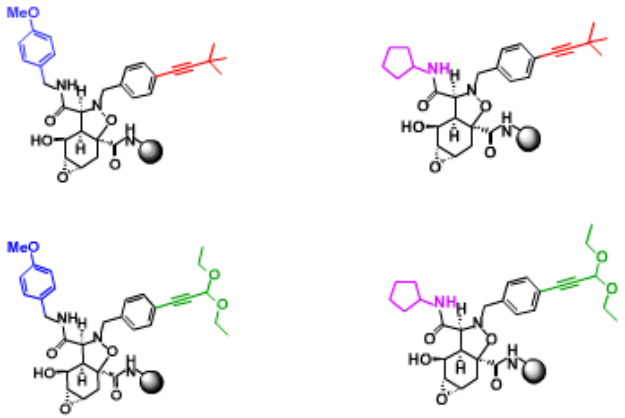
7) Beads are ready to be separated in an arrayer and transferred to PDMS plates

(see the bead distribution and compound transfer animation)



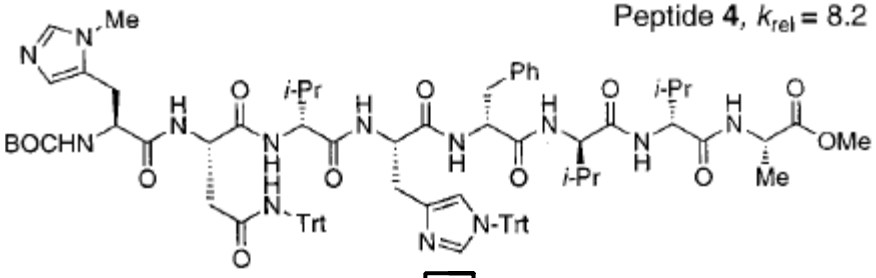
steps: ① ② ③ ④ ⑤ ⑥ ⑦ Ⓝ Ⓒ Ⓢ Ⓟ

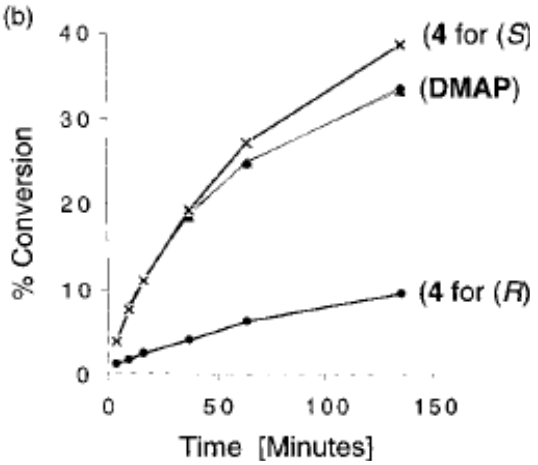
Ideally, all possible combinations of building blocks have been coupled.



steps: ① ② ③ ④ ⑤ ⑥ ⑦ Ⓝ Ⓒ Ⓢ Ⓟ

Hit peptide for acylation.



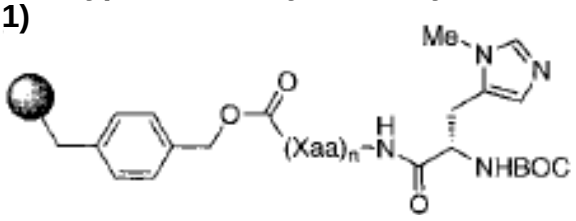


Make second genelation liblary based on 4.

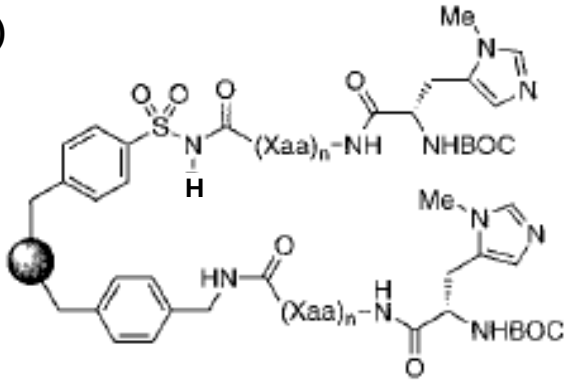
homogeneous condition: not on regin

Average 35% mutation using 14 unique amino acid by split & pool method.
Two types of librarys were synthesized.

1)



2)



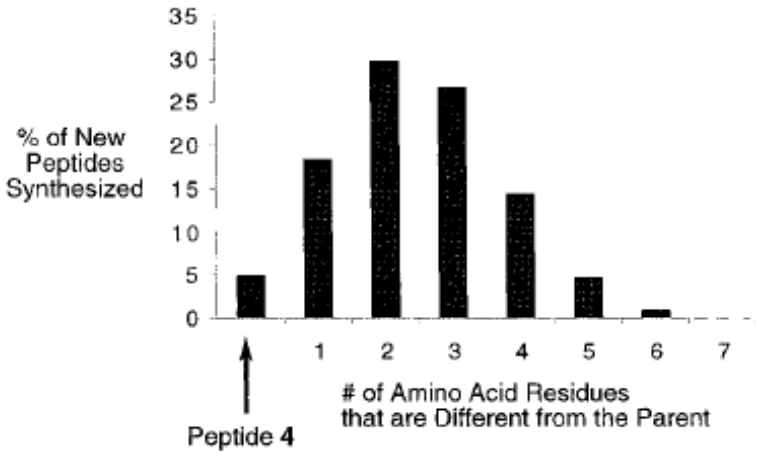
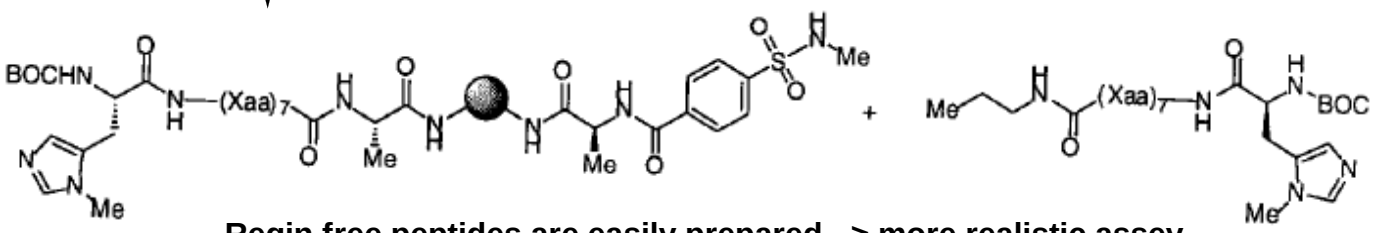


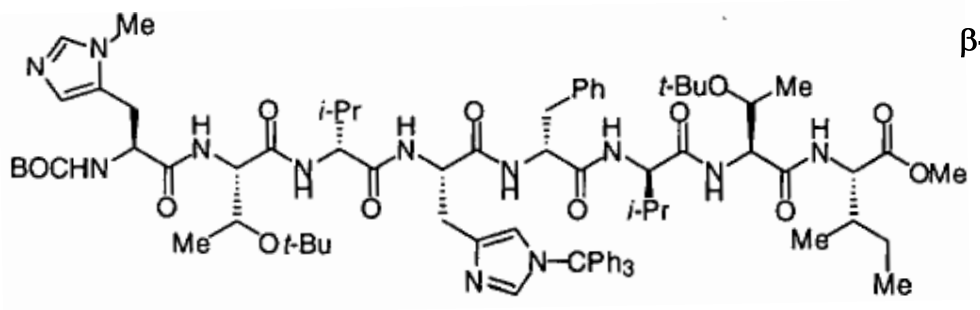
Fig. 2-8: Mutation ratio of peptide.

1) $TMSCHN_2$
2) ^{n}propylamine



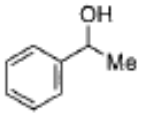
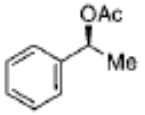
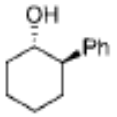
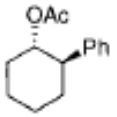
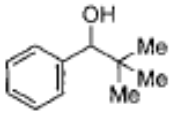
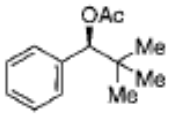
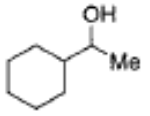
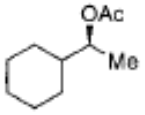
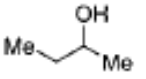
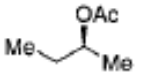
Regin free peptides are easily prepared. -> more realistic assey.

Screening 80 peptide by multi-well-plate.



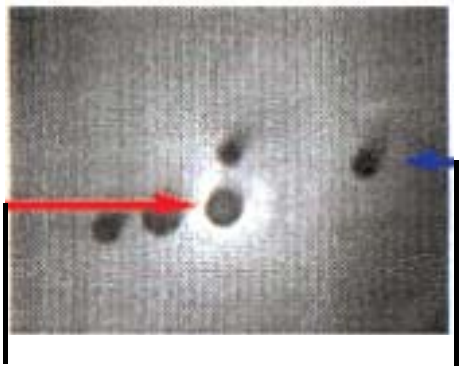
β-hairpin?

Table 2. Kinetic Resolution Results Employing Peptide **13** (2.5 mol %) as a Catalyst[a]

Entry		Racemic Substrate	Preferred Product Enantiomer	k_{rel}[b]
1	**2**:			20
5	**17**:			>50
7	**19**:			30
8	**20**:			9.0
9	**21**:			4.0

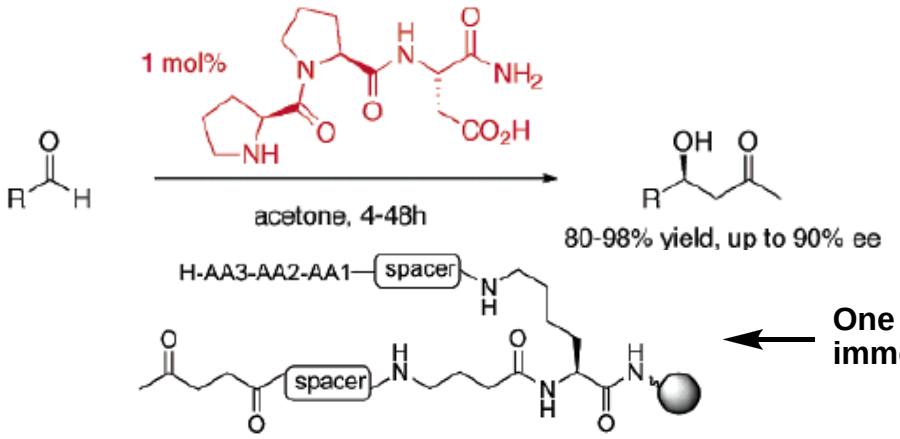
[a] Reactions were carried out at −65 °C in PhMe (2.5 mol % **13**). Reactions were run to 40−50% conversion. [b] k_{rel} values were determined according to the method of Kagan (ref 13) employing chiral GC or HPLC analyses. See Supporting Information for details.

As another method, fluorecent gel and bead condition is repoeted. *JACS.* 2000, *122*, 11270.



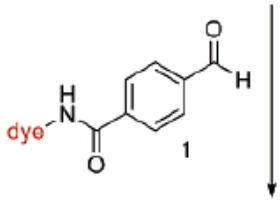
Hit **Miss**

In the case of asymmetric aldol reaction.
Wennemers, H. *et. al. Org. Lett.* 2005, *7*, 1101.



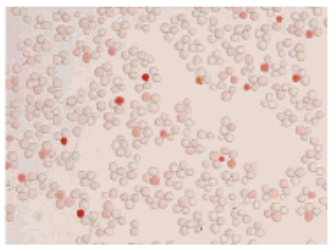
split & pool

One substrate and peptide cat. are immobilized on a same bead.

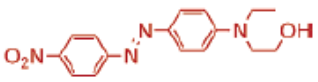


1. DMF or CH_3OH, 1-2h, rt
2. washing

Another substrate has coloring moiety.



Pick up colored beads (*ca.* 1 out of 100). Then analysis.

spacer = $[NH(CH_2)_5CO]_3$ dye-OH = 

Disperse Red 1

Fig. 2-9:

Limitation of these method: in the case of asymmetric electrophilic epoxydation.
Miller, S. J. *et al. ACS Comb. Sci*. 2011, *13*, 321.

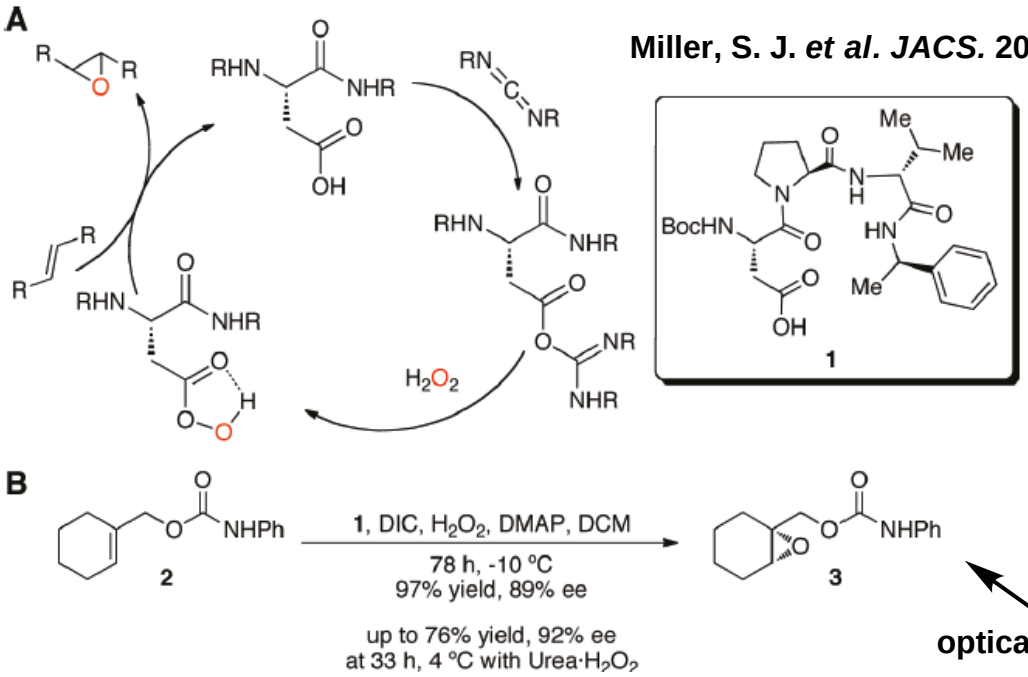


Fig. 2-10: Reaction mechanism.

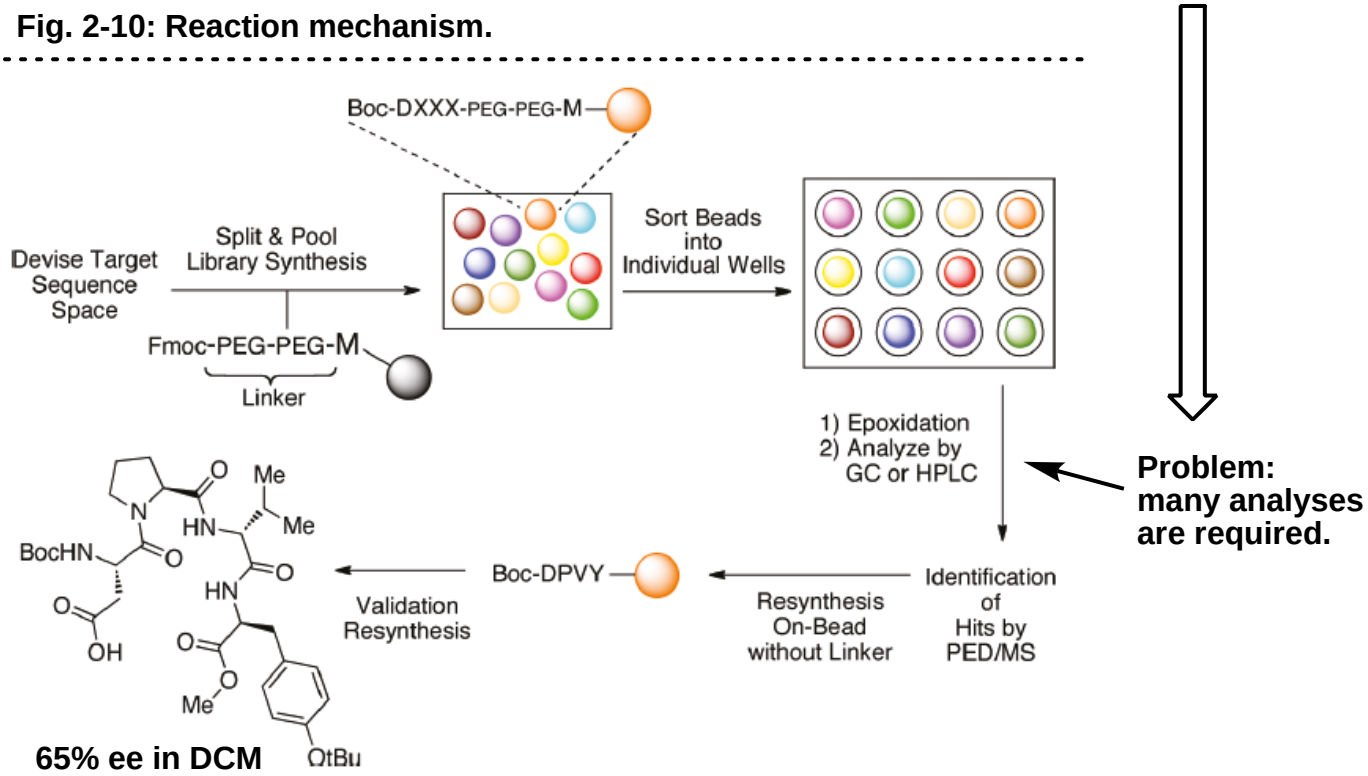
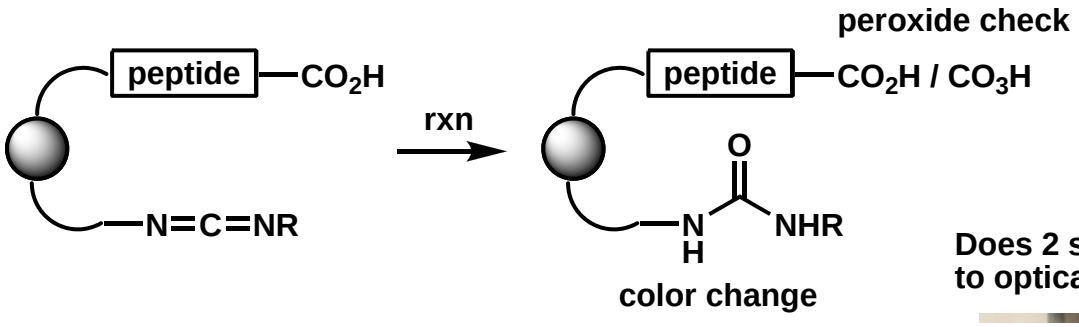


Fig. 2-11: Outline.

My opinion...



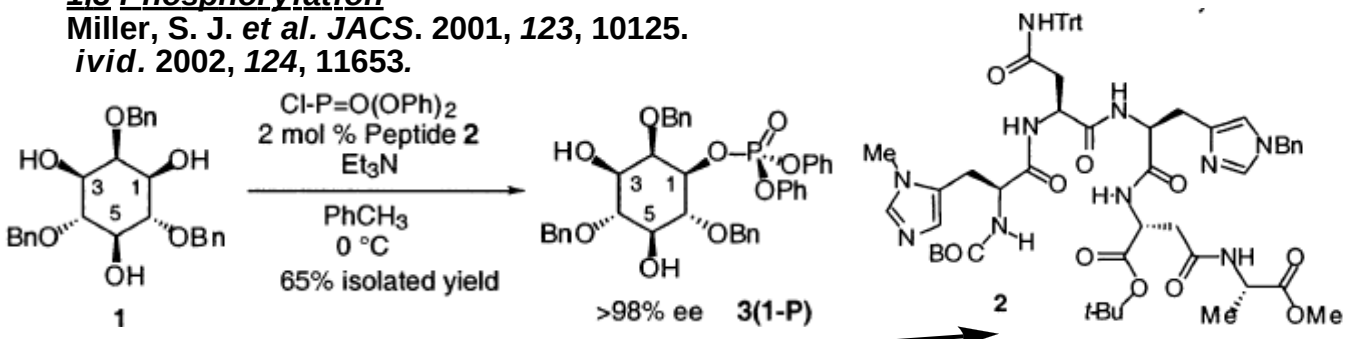
3. Miller's Works

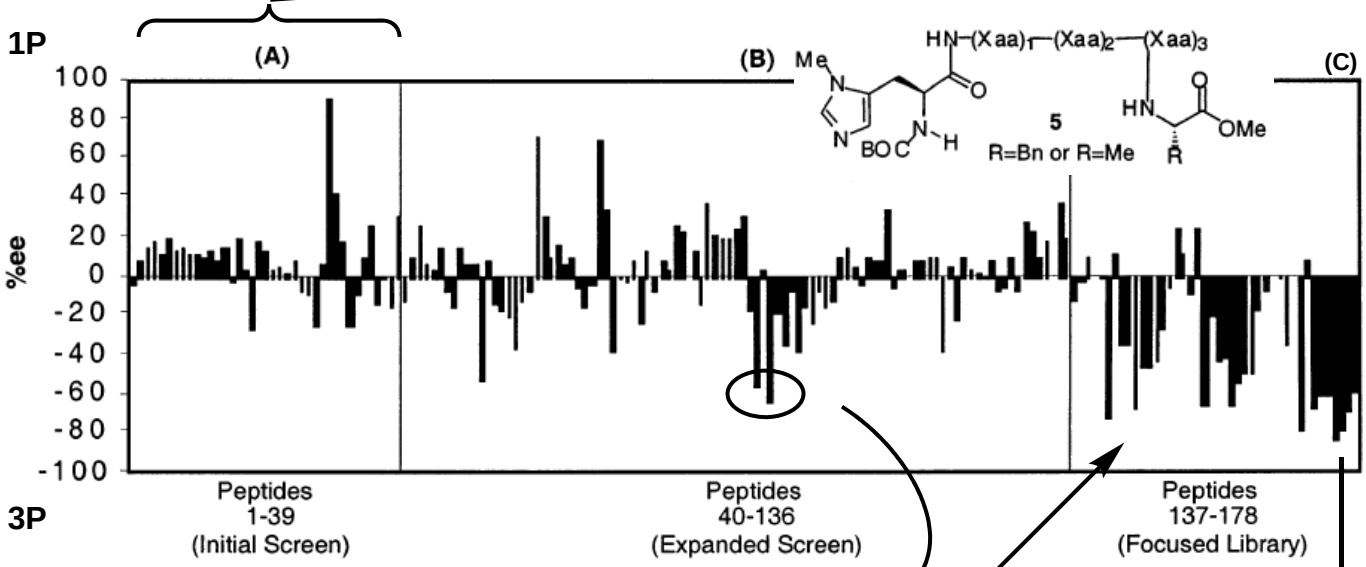
Famous people in peptide catalyst chemistry.
- **Scott J. Miller, Yale Univ.**
- **Helma Wennemers, Basel Univ.**
- **Carlos F. Barbas, The Scripps Research Institute.**

3-1. Enantio and Regioselective Phosphorylation myo-Inositol.

1,3 Phosphorylation

Miller, S. J. *et al. JACS*. 2001, *123*, 10125.
***ivid.* 2002, *124*, 11653.**





acylation cat. (previously) **randomization algorithm**

Fig. 3-1: Screening of β-hairpin peptides.

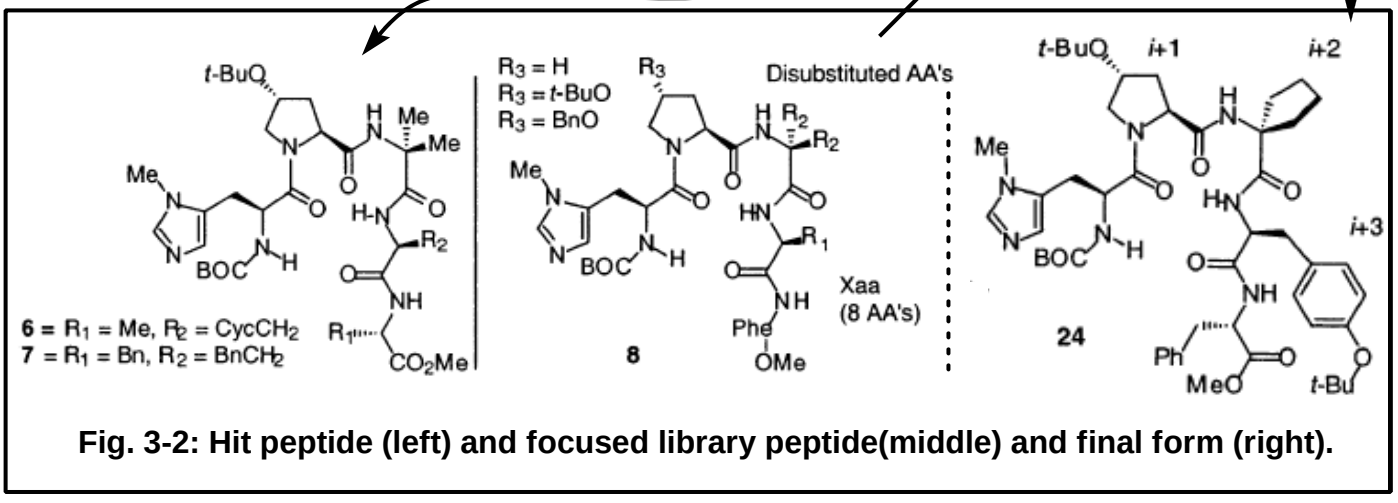
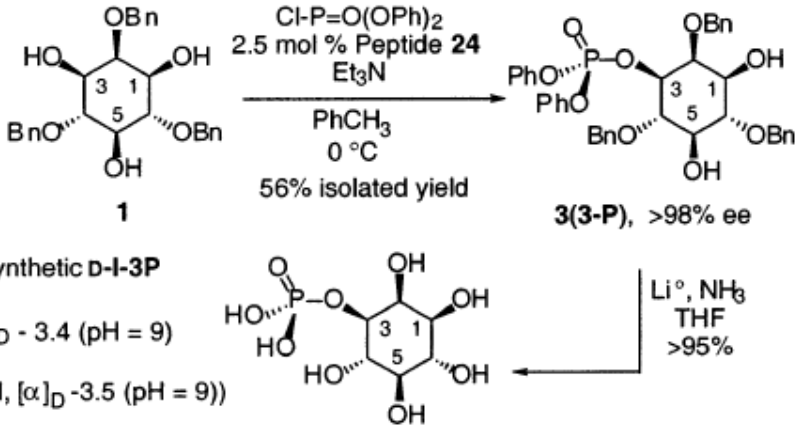
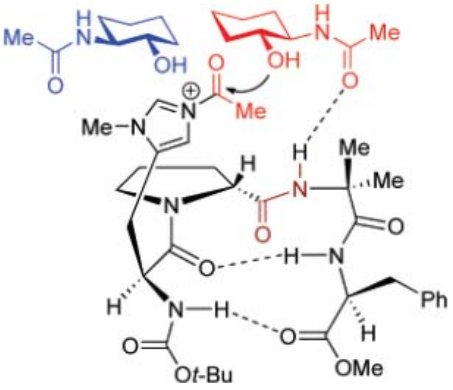


Fig. 3-2: Hit peptide (left) and focused library peptide(middle) and final form (right).

cf) randomizer: Research Randomizer, version 2.1 [Internetbased computer program]; http://www.randomizer.org
They used the 16 amino acids monmer.

Scheme 2

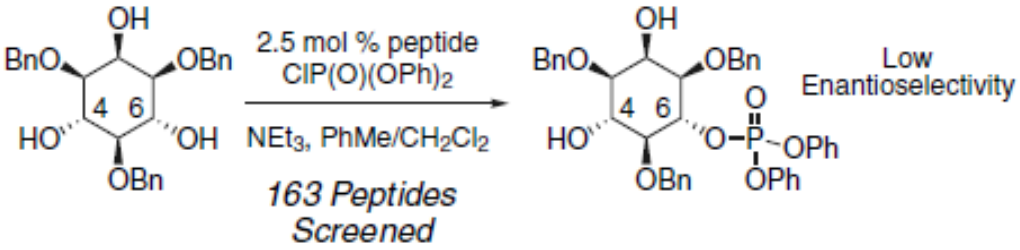


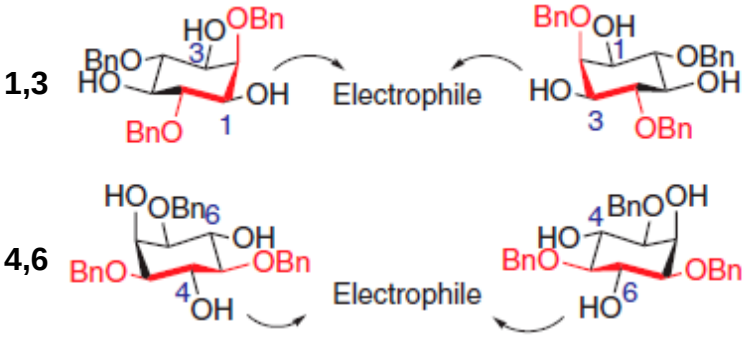


cf) model of acylation.

6-Phosphorylation

Miller, S. J. *et al. PNAS*. 2010, *107*, 20620.



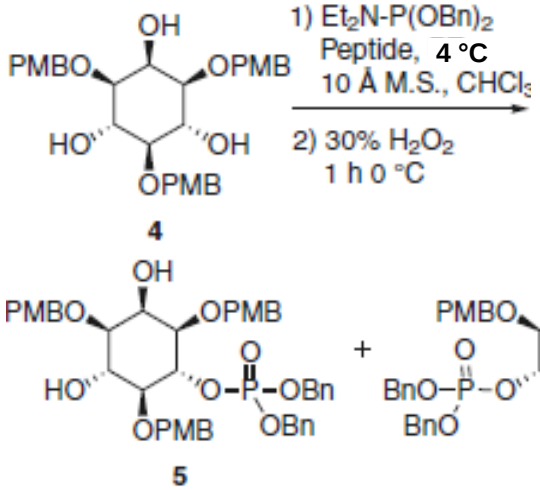


In 4,6 case, the difference of stelic environment is less than 1,3.

Fig. 3-3: Difficulty of 4,6 desymmetrization.

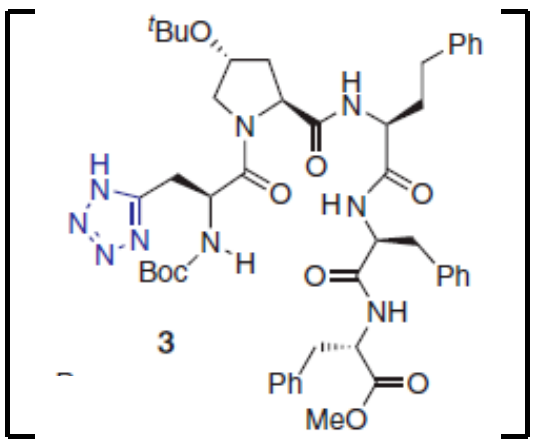
Pmh-P(V) reagent system had been faild. So Miller's group tred Atz-P(III) reagent system. (Pmh: π-methyl histidine, Atz: tetrazolyl alanine)

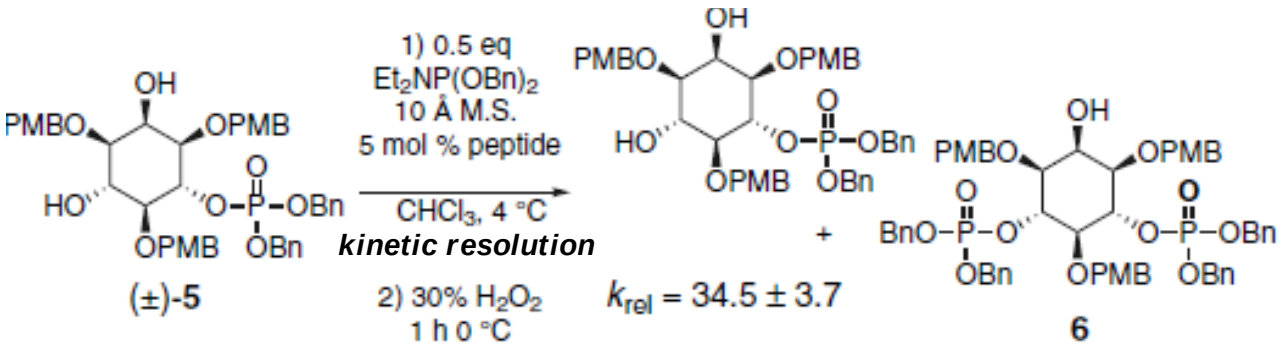
After screening...



71%, 70 % ee unsatisfactory

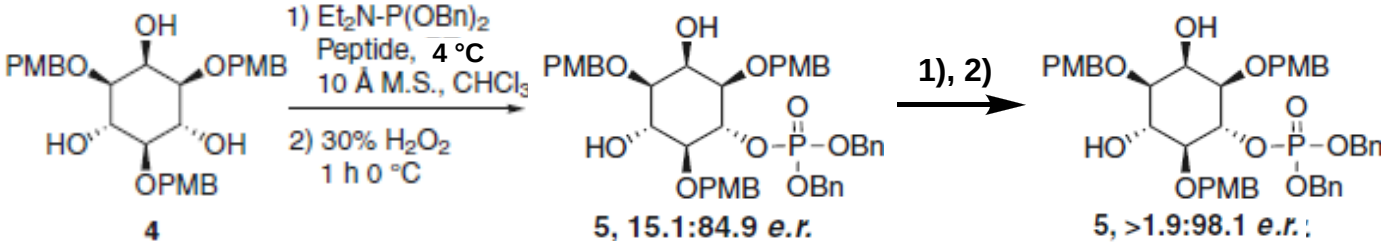
16%





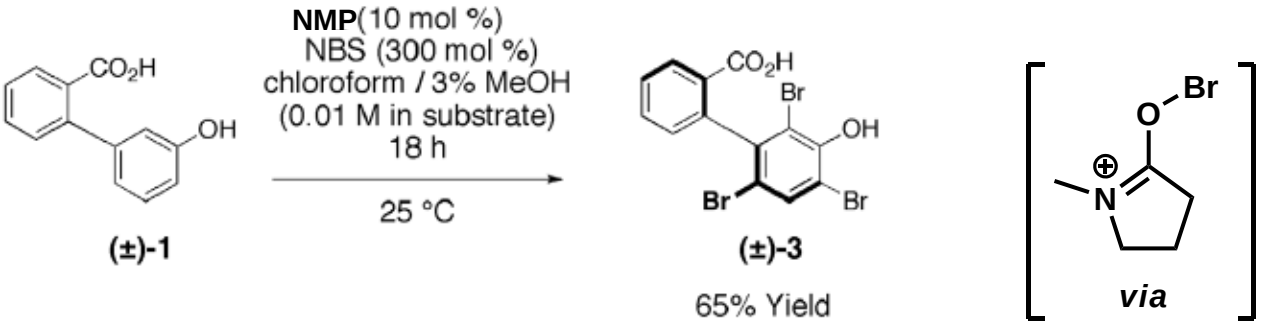
Hydrogen bond between P=O and peptide is necessary for high ee.
When P=O is change to P=S, k_{rel} = 8.4 ± 2.8.

This kinetic resolution applies 5 (70 % ee) -> ee is increase.

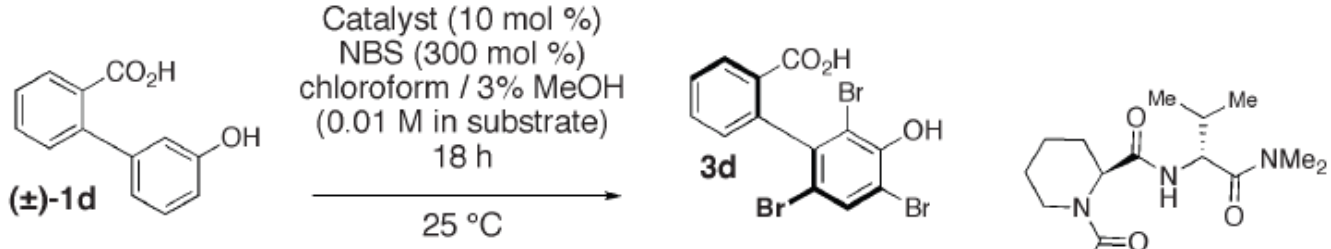


3-2. Dynamic Kinetic Resolution of Biaryl Atropisomers

Miller, S. J. *et al. Scince,* 2010, *328*, 1251.
Miller, S. J. *et al. ACIE,* 2011, *50*, 5125.



Lewis base catalyzed electrophilic bromination



Entry	Catalyst	Yield (%)	E.r.
1	Boc-β-Dmaa-Pro-(D)Val-(*R*)-αMba (**4**)	90	75.0:25.0
2	Boc-β-Dmaa-Pip-(D)Val-(*R*)-αMba (**5**)	87	90.0:10.0
8	Boc-β-Dmaa-Pip-(D)Val-NMe_2 (**11a**)	90	**92.0:8.0**
9	Boc-β-Dmaa-Pip-(D)Val-OMe (**11b**)	90	65.0:35.0

Fig. 3-4: Screening of peptide.

Entry	Racemic Starting Material	Product	Yield (%)	E.r.
1	(±)-1d	3d	80	97.0:3.0
2	(±)-12	13	85	97.0:3.0
3	(±)-14	15	75	96.5:3.5
4	(±)-16	17	70	96.0:4.0
5	(±)-18	19	80	94.0:6.0
6	(±)-20	21	70	97.0:3.0
7	(±)-22	23	65	96.5:3.5
8	(±)-24	25	85	87.0:13.0
9	(±)-26	27	77*	85.0:15.0
10	(±)-28	29	70	95.0:5.0

* 400 mol % of NBP.

Scope: 11a (10 mol%), NBP (300 mol%), $CHCl_3$ / 3% acetone (0.01 M), 25 °C

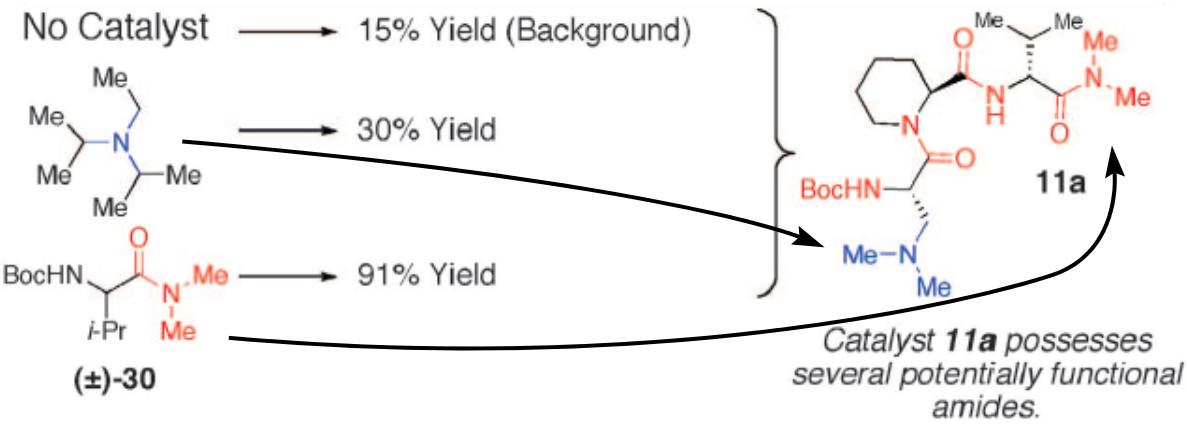
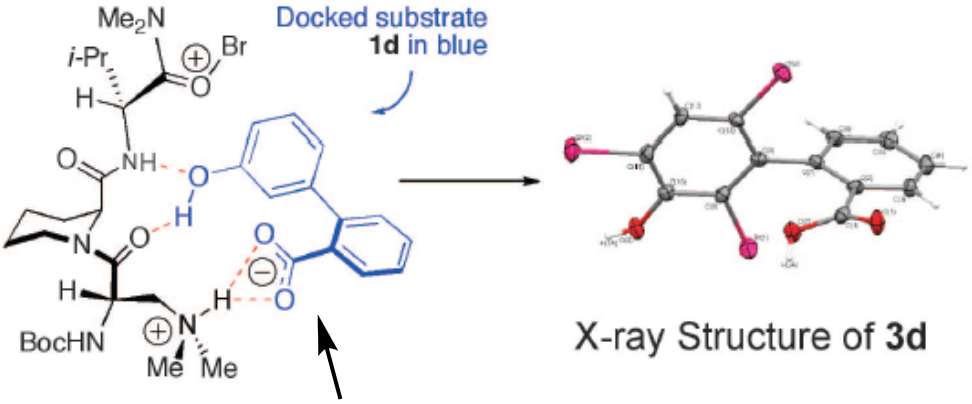


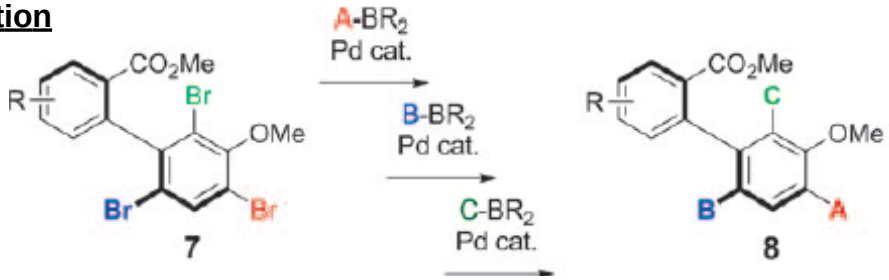
Fig. 5. Assessment of the catalytic efficiency of simple functional groups. *i*-Pr, *iso*-propyl group.

Fig. 6. X-ray structure of the major enantiometer of **3d** (right) and a possible docking model explaining selectivity (left). Structure shown is an Oak Ridge thermal ellipsoid plot.



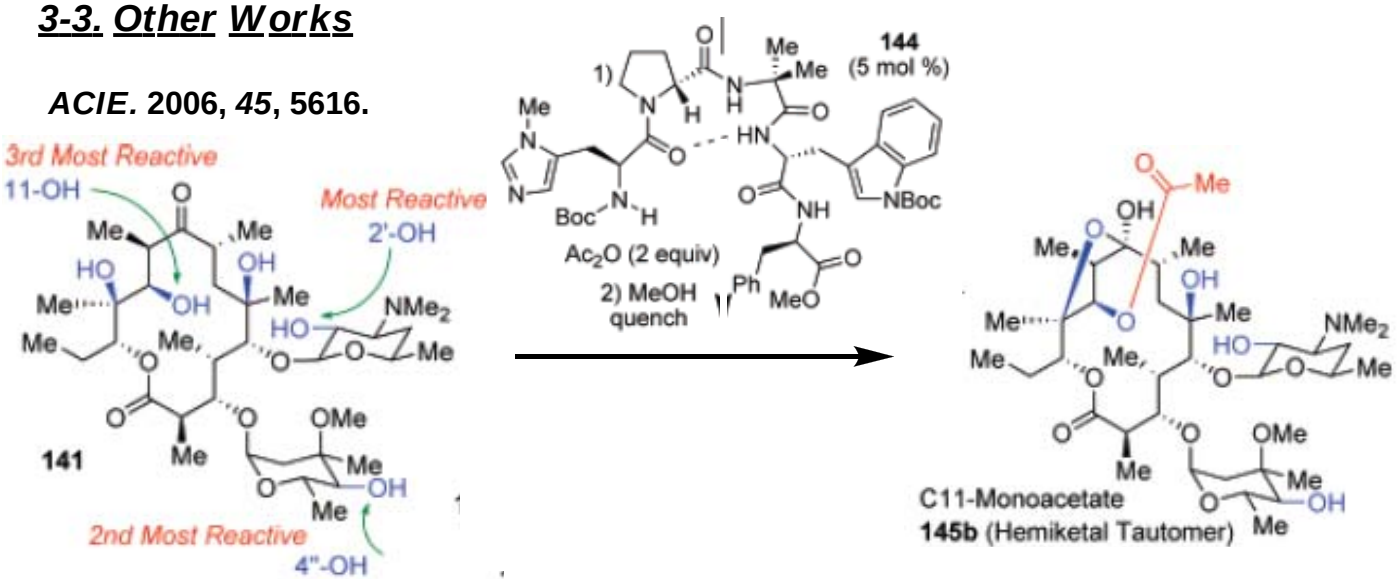
When CO_2H change to CO_2Me, CONBn, NO_2, ee decreases.

Aplication

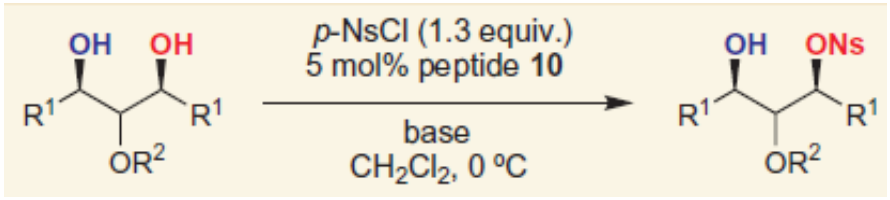


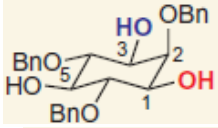
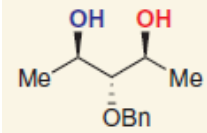
3-3. Other Works

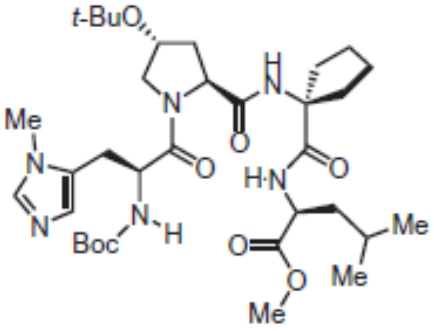
***ACIE.* 2006, *45*, 5616.**



***Nature Chem.* 2009, *1*, 630.**

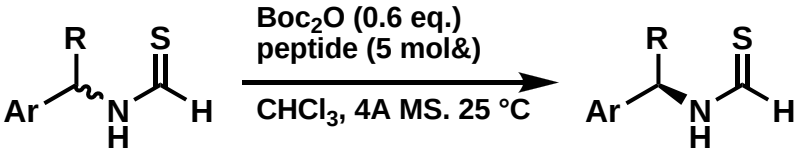


	A	76%	97.0:3.0
	B	66%	95.0:5.0
	A	74%	89.0:11.0
	B	65%	86.0:14.0



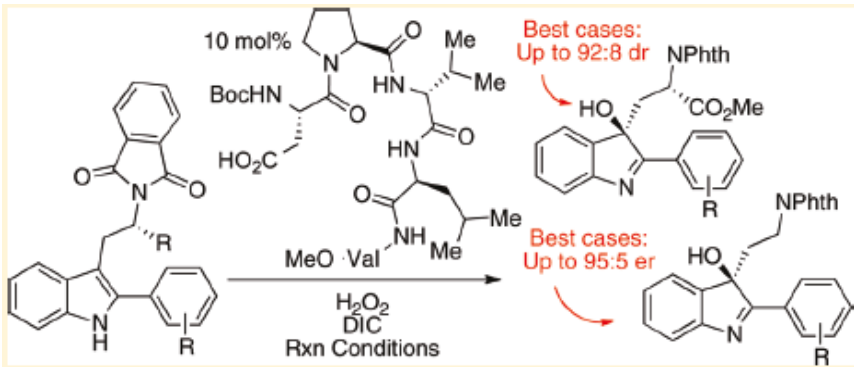
A: $NaHCO_3$, B: 2,6-lutidine

***JACS*, 2010, *132*, 2870.**



up to 95 % ee
-NCHO: very slow

***JACS*, 2011, *133*, 9104.**



No *N* oxidation.

4. Artificial Metalloenzymes

4-1. Peptide as a Ligand of the Transition Metal

Limitation of peptide catalyst: reaction types are confinded to organocatalitic reactions.
-> redox reactions, eg. C-H activation, are difficult.

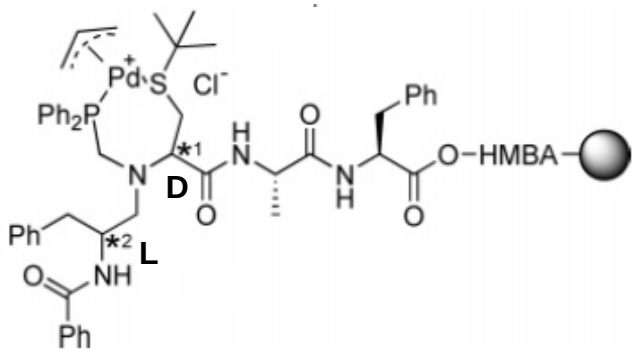
⇩ **to solve this problem...**

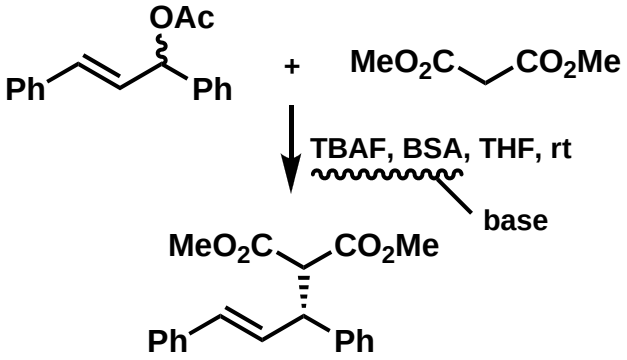
Is the transition metal - peptide system desireble?

Examples

review: Kamer, P. C. J. *et al. Chem. Eur. J*. 2011, *17,* 4680.

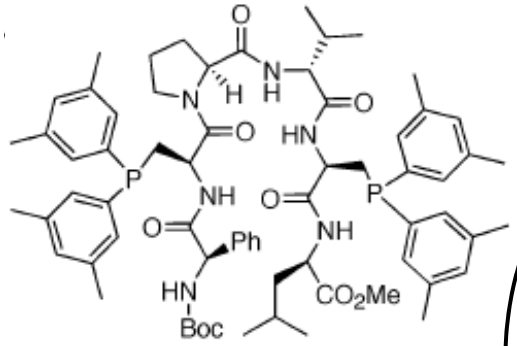
Meldal, M. *et al. J. Comb. Chem*. 2007, *9*, 79.
"Tsuji-Trost reaction"



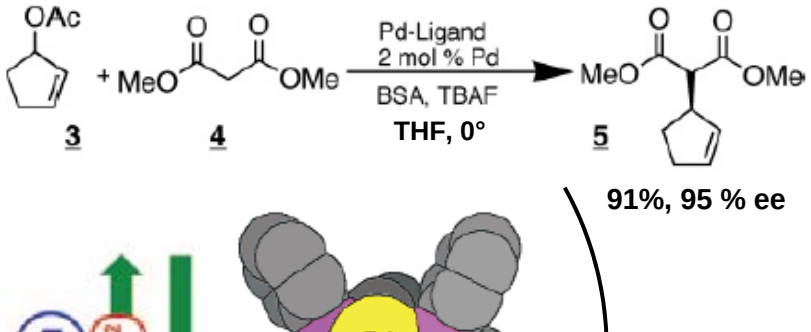


94%, 60 % ee

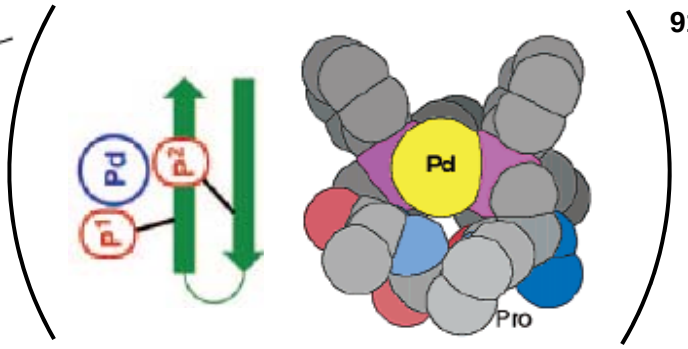
Gilbertson, S. R. *et al. JACS.* 2000, *122*, 6522., *JOC,* 2004, *69*, 8077.



β-hairpin



91%, 95 % ee



In abobe cases, moderate to good selectivities are observed.
But are there any needs of pepride backbone?
I'm interesting in these reaction if there is some interaction (hydrogen bond) between ligand and substrate. But if not, I think that the role of peptide is only a divergence.
(Of course, the divergence is important to asymmetric synthesis.)

4-2. Artificial Metalloenzymes

reviews:
Ward, T. R. *et al. Chem. Commun.* 2011, *47*, 8470.
Ward, T. R. *Acc. Chem. Res.* 2011, *44,* 47.
Kamer, P. C. J. *et al. Chem. Eur. J*. 2011, *17,* 4680.
Roelfes, G. *et al. Chem. Cat. Chem. 2010, 2,* 916.

What is artificial metalloenzymes?

-> Combination of transition metal catalyst and protein.
Kaiser and Whitesides proposed in 1970's.
Artificial metalloenzymes harnes the chiral space of enzyme for stereo and substrate selectivities.

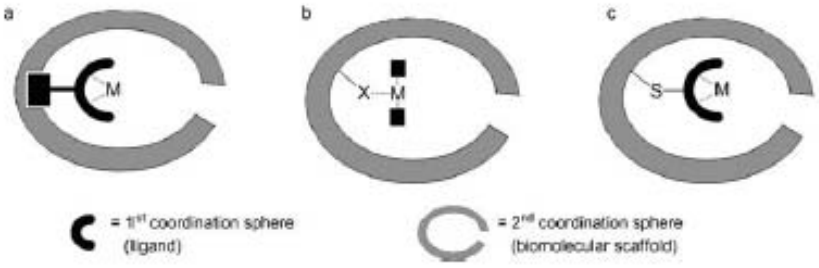


Figure 1. Representation of the concept of artificial metalloenzymes and the various anchoring strategies: a) supramolecular, b) dative, and c) covalent. M denotes the catalytically active transition metal.

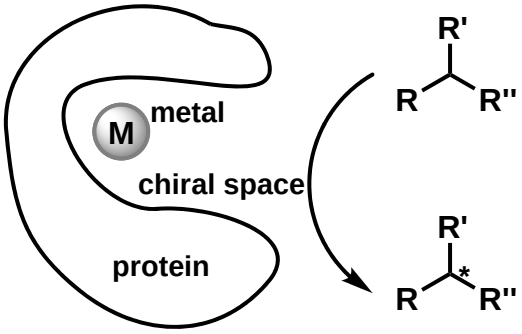


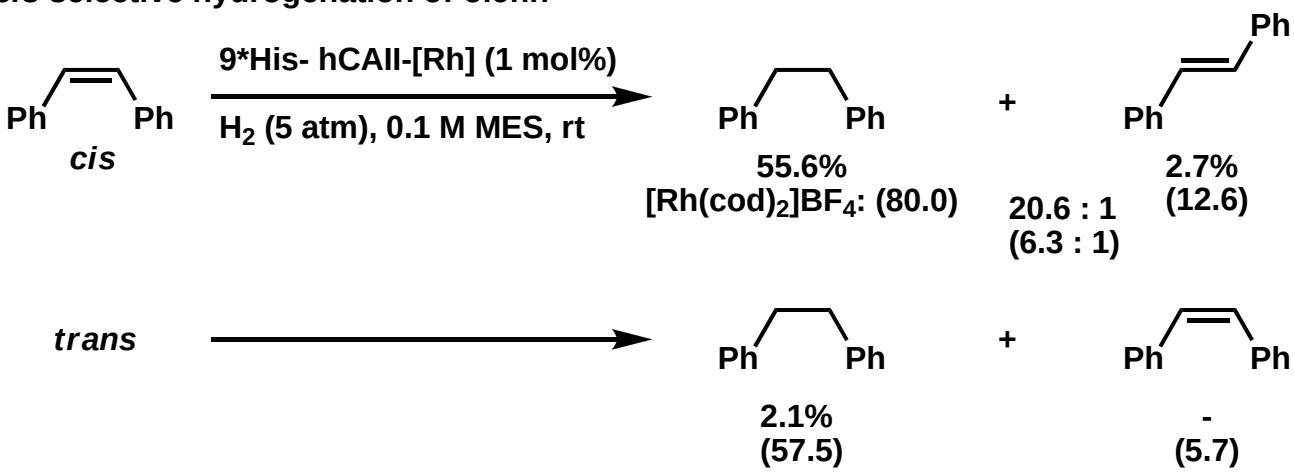
Fig. 4-1: Model of metalloenzyme

4-2-1. Dative Anchoring

-> Direct coordination of transition metals to protein.

Example

Kazlauskas, R. J. *et al. Chem. Eur. J*. 2009, 15, 1370.
"*cis* selective hydrogenation of olefin"



hCAII = human carbonic anhydrase isoenzyme II
9*His means nine His residues at surface of enzyme are replaced by Arg, Ala, Phe.

Why they chose hCAII?

1. hCAII has zinc. Zinc and rhodium have similar ionic radius.
2. hCAII's coordinate site has His. Imidazoyl group is good ligand for Rh.
3. CAs has cysteine and it interfere with binding of Rh. But hCAII's cysteine is not surface.
4. They previously reported metal exchange of hCAII.

After choosing protein, they screened hCAII and mutated hCAIIs.

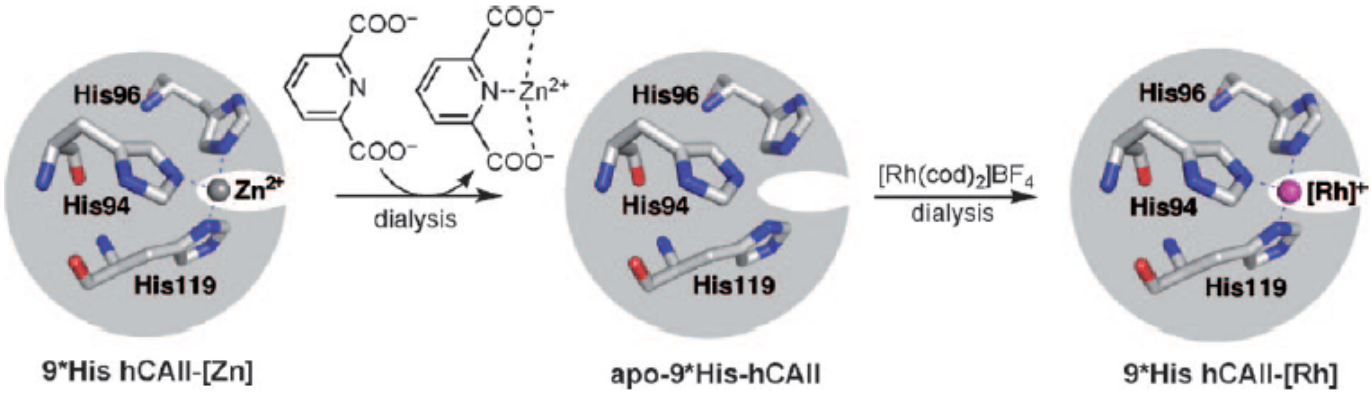


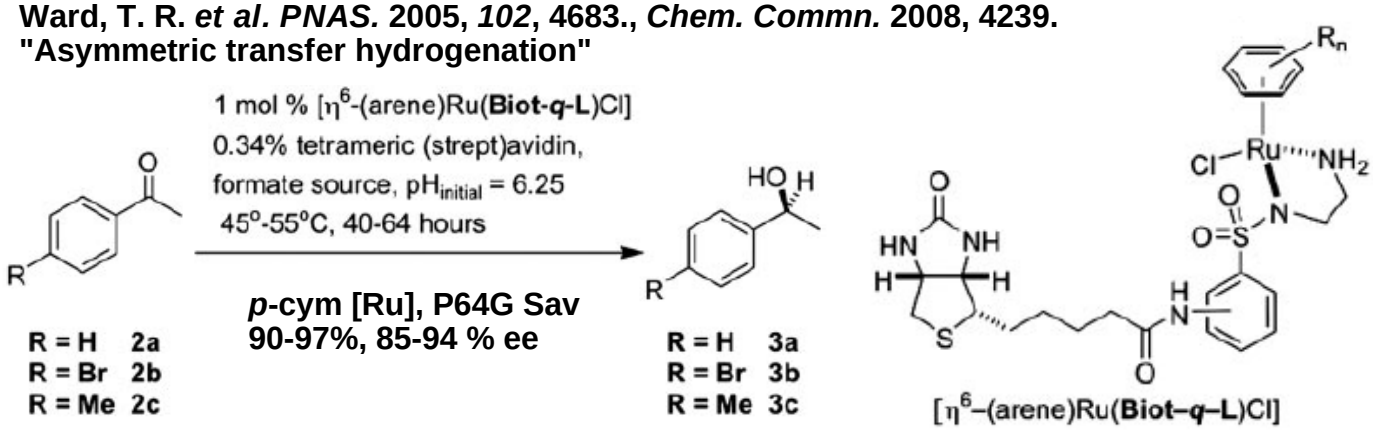
Fig.4-2: Exchange of metal in the enzyme.

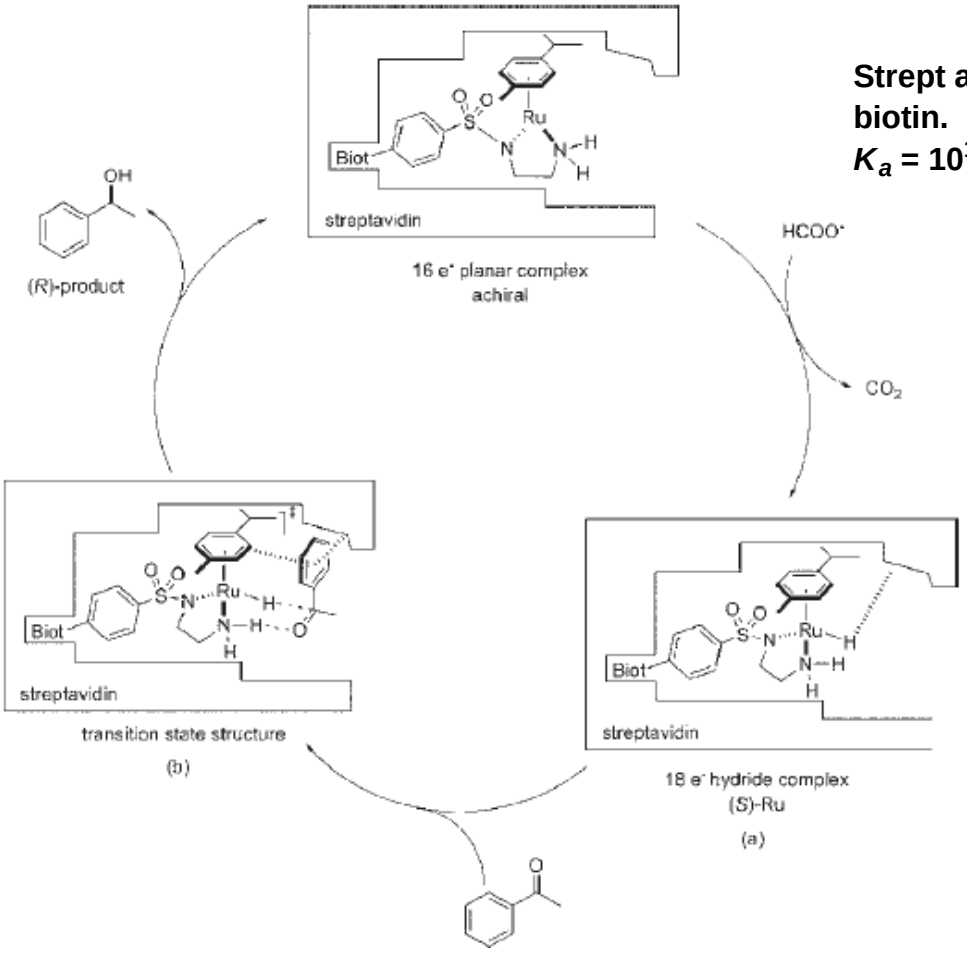
4-2-2. Supramolecular Anchoring

-> Ligand of metal is coordinate (not covalent) with protein.

Example

Ward, T. R. *et al. PNAS.* 2005, *102*, 4683., *Chem. Commn.* 2008, 4239.
"Asymmetric transfer hydrogenation"

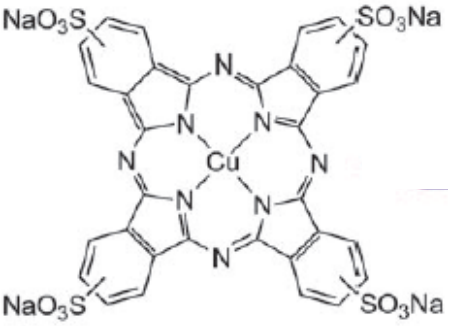




Strept avidin: tightly bind to biotin.
$K_a = 10^{15}$ M^{-1}

cf) Reduction of imine, *ACIE*, 2011, 50, 3026.

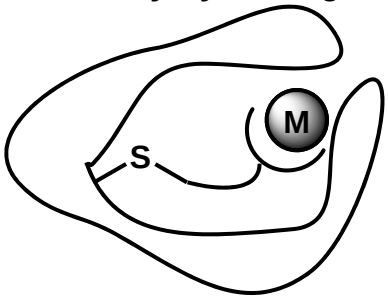
Other combination:
- **HSA (human serum albumin) + polphyrin-SO_3Na.**
- **Antibody + α**



Binding:
Tyr161- Cu
Arg114, His146, Lys190-SO_3-
etc.

4-2-3. Covalent Anchoring

-> Ligand of metal is connected protein covalently.
Usually Cys is targeted as a linking amino acid.



Othes reactions:
Oxidation (SA + Mn or V)
a) *Chem. Commun*. 2008, 1665.
b) *JACS*. 2008, *130* (25), 8085.

Tsuji-Trost reacgtion
***ACIE.* 2008, *47*, 701.**

5. Summary & Future Direction

Peptide catalyst:
(+)
- **Highy divergence and high selectivity.**
- **Especially desymmetlization is powerful.**

(-)
- **Reaction types are limited in organocatalyst field.**
- **It needs tremendous screening.**

Efficient screening method is require!

Metalloenzyme:
(+)
- **Potentially highy divergence and high selectivity.**

(-)
- **Available metals are limited.**
- **Sensitive purity of protein.**
- **Narrow substrate scope.**

Under development.
Towards *in vivo* reaction!