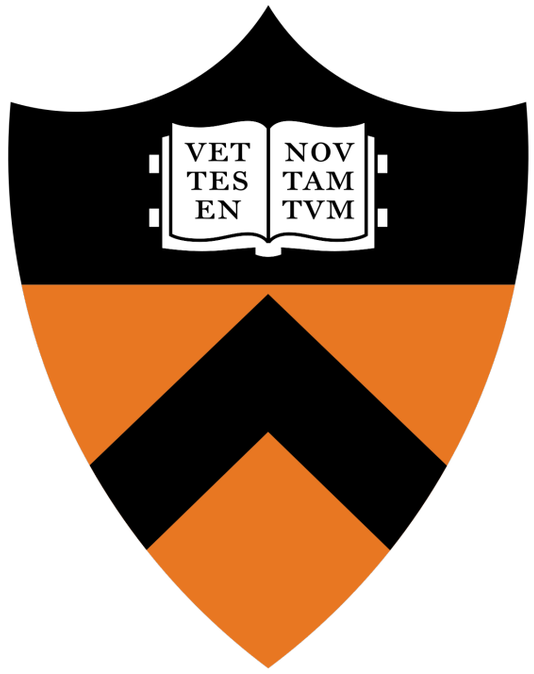
Catalysis by Small Peptides
an Introduction

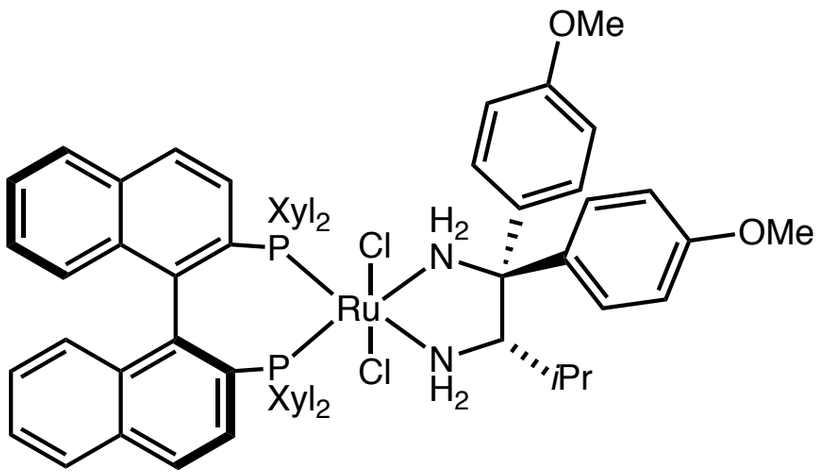


Mario Wiesenfeldt

November 4th, 2020

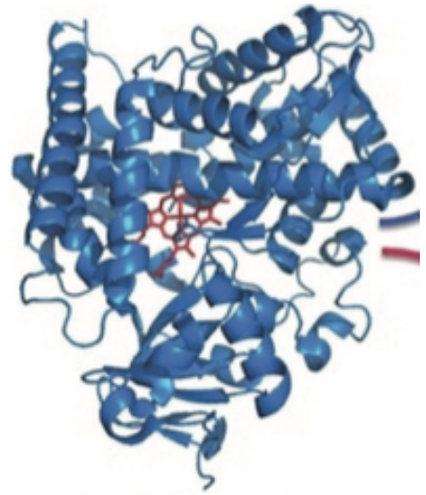
Catalysis by Small Peptides

Catalysis by small molecules



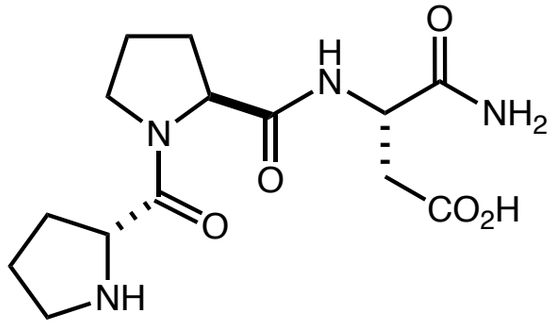
design & understanding → ***diverse reactivity***

Enzyme catalysis



tailor-made non-covalent interactions → ***exceptional selectivity***

Catalysis by small peptides



2–20 amino acids

modular and facile synthesis

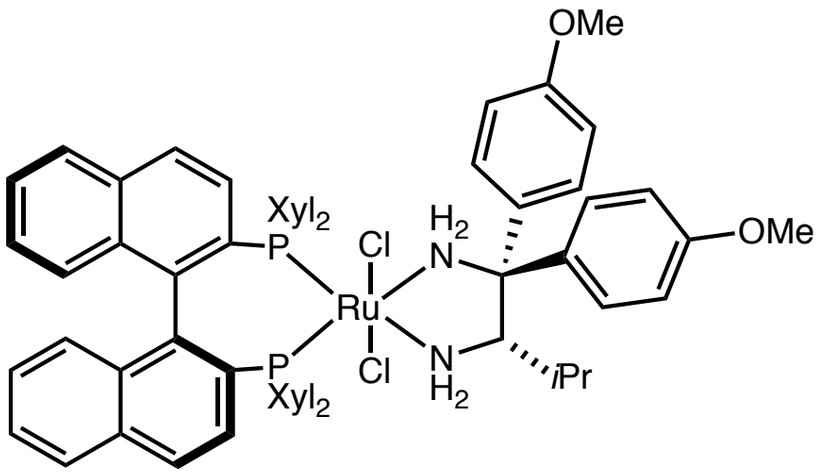
non-covalent interactions with substrates – ***high selectivity***

nonnatural amino acids – ***diverse reactivity***

Comparison between enzymes, transition metals, and small peptides: Lewis, C. J. *ACS Catal.* **2013**, *3*, 2954. (Selected) nobel lectures on asymmetric catalysis and directed evolution: Noyori, R. *Angew. Chem., Int. Ed.* **2019**, *58*, 14420 – Arnold, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

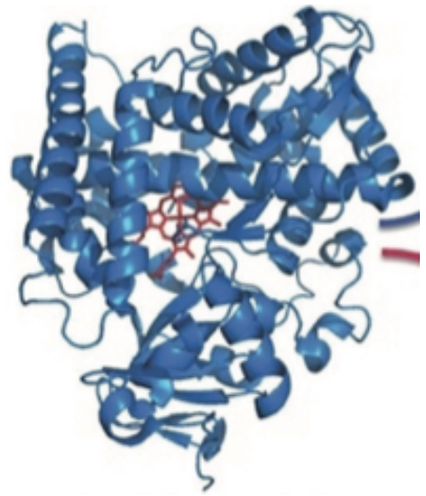
Catalysis by Small Peptides

Catalysis by small molecules



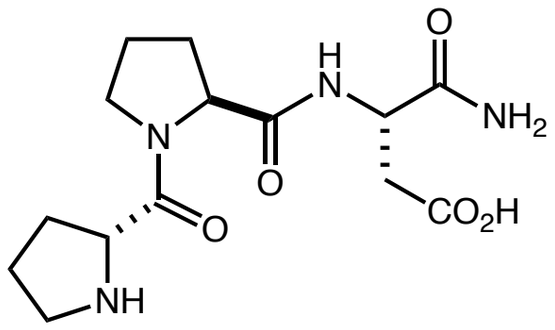
design & understanding → ***enzyme-like selectivity***

Enzyme catalysis



directed evolution or merger with (photo-) catalysis → ***nonnatural reactivity***

Catalysis by small peptides



2–20 amino acids

modular and facile synthesis

*non-covalent interactions with substrates – **high selectivity***

*nonnatural amino acids – **diverse reactivity***

Nonnatural reactivity by photocatalysis: Biegasiewicz, K. F.; Cooper, S. J.; Gao, X.; Oblisnky, D.; Kim, J. H.; Garfinkle, S. E.; Joyce, L. A.; Sandoval, B.; Scholes, G. D.; Hyster, T. *Science* **2019**, *364*, 1166. Comparison between enzymes, transition metals, and small peptides: Lewis, C. J. *ACS Catal.* **2013**, *3*, 2954. (Selected) nobel lectures on asymmetric catalysis and directed evolution: Noyori, R. *Angew. Chem., Int. Ed.* **2019**, *58*, 14420 — Arnold, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

Small Peptides as Organocatalysts

- Introduction
- Catalytically relevant properties of small peptides
- Small peptides as organocatalyst
- Small peptides in Lewis acid and transition metal catalysis
- Small peptides in photoredox catalysis
- Summary

This group meeting does not cover the available literature comprehensively. Instead, selected key studies are discussed in order to explain the underlying concepts.

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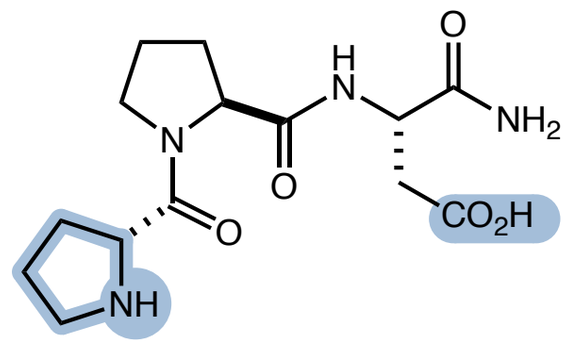
Structure of a Peptide Catalyst

backbone



catalytically active moiety

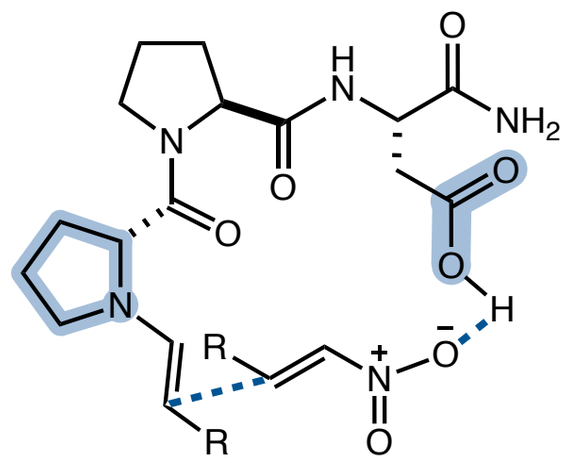
substrate binding moiety

Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1871.

Structure of a Peptide Catalyst

backbone

catalytically active moiety



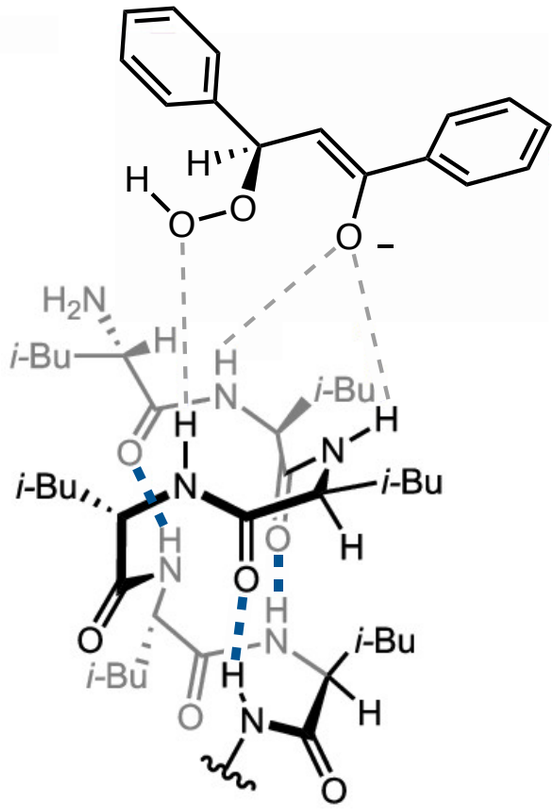
substrate binding moiety

- backbone serves as a tailor-made spacer between the *catalytically active moiety* and the *substrate binding moiety*
- complex three-dimensional geometry determined by primary and secondary protein structure
- conformational flexibility due to high number of rotatable bonds

Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1871.

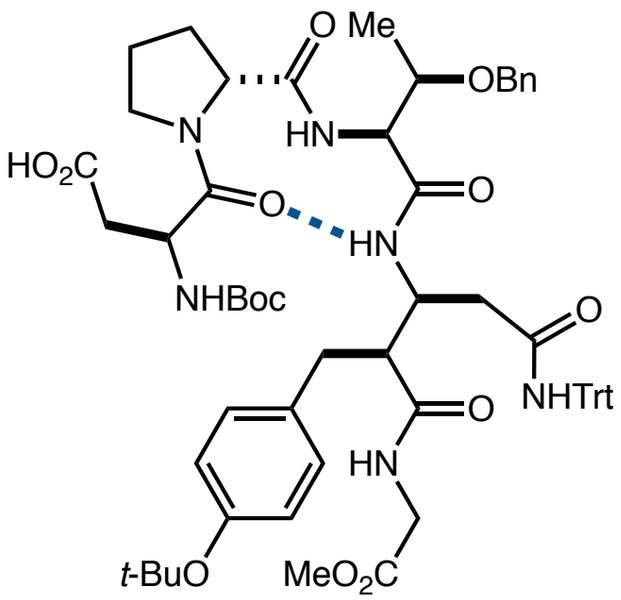
Design of the Secondary Structure

Natural secondary structure motifs



α-helix

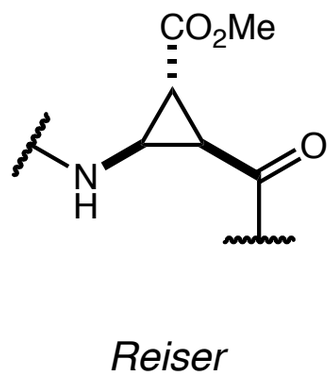
Juliá-Collona epoxidation



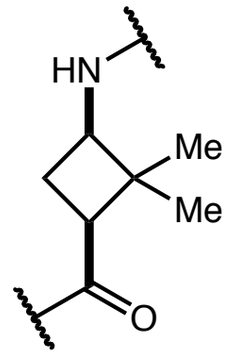
type II β-turn

epoxidation catalyst (Miller)

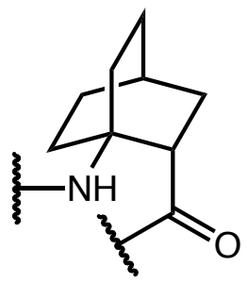
Rigid unnatural amino acids



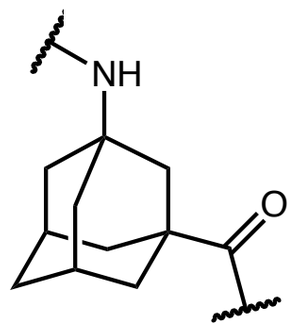
Reiser



Bur



Calmes, Amblard

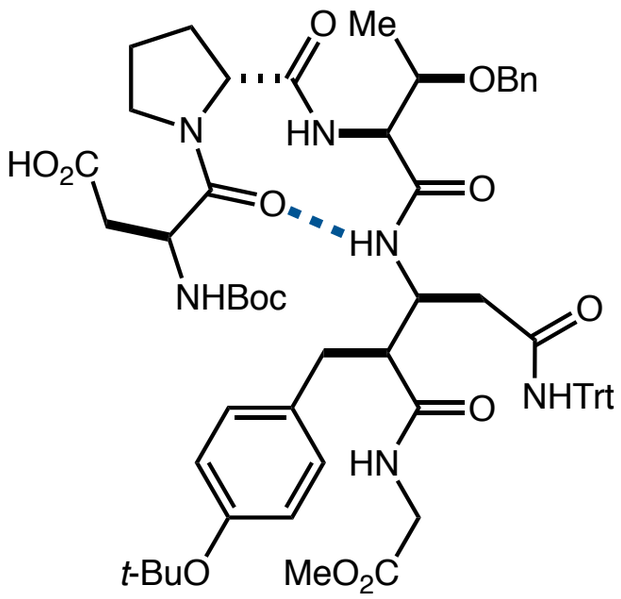


Schreiner

Peptide design is often centered around such structures with reduced conformational flexibility.

Review: Metrano, A. J.; Chinn, A. J.; Shugrue, C. R.; Stone, E. A.; Kim, B.; Miller, S. *Chem. Rev.* **2020**, *asap*.

Design of the Secondary Structure

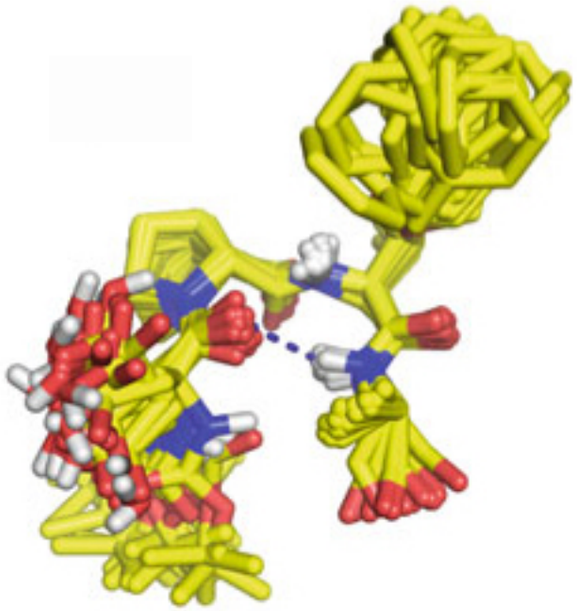


type II β-turn

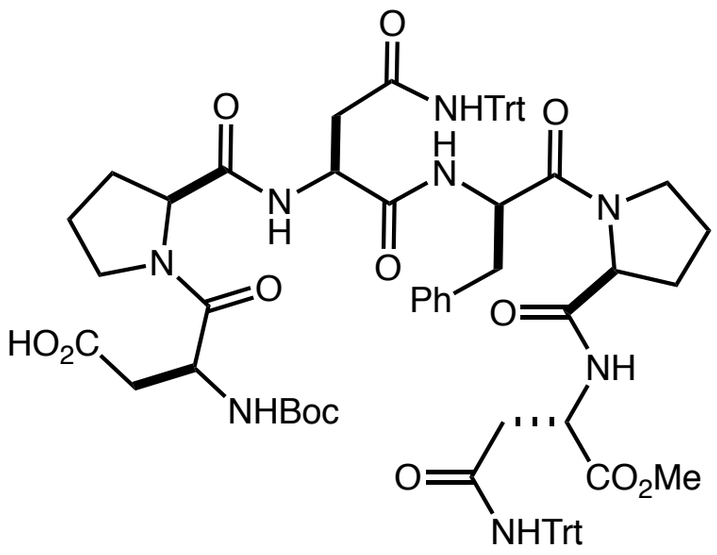
epoxidation catalyst (Miller)

NMR &
calculations

highly regioselective in the epoxidation of farnesol



ensemble of closely related ground-state conformations



epoxidation catalyst (Miller)

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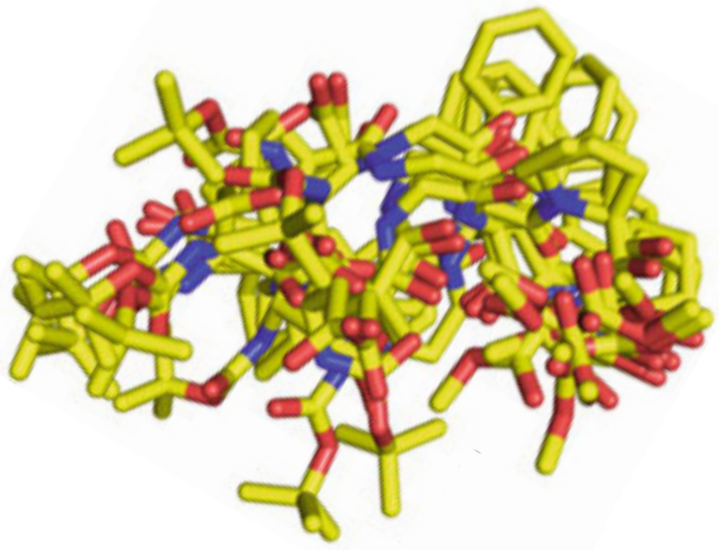
highly regio-and enantioselective in the epoxidation of farnesol



heterogeneous ensemble

Lichtor, P. A.; Miller, S. J. *J. Am. Chem. Soc.* **2014**, *136*, 5301. Abascal, N. C.; Lichtor, P. A.; Giuliano, M. W.; Miller, S. J. *Chem. Sci.* **2014**, *5*, 4504.

Design of the Secondary Structure

NMR &
calculations

Even highly flexible, conformationally heterogeneous peptides may act as highly selective catalysts.

epoxidation catalyst (Miller)

ground-state conformations

NMR &
calculations

highly regio-and enantioselective
in the epoxidation of farnesol

epoxidation catalyst (Miller)

heterogeneous ensemble

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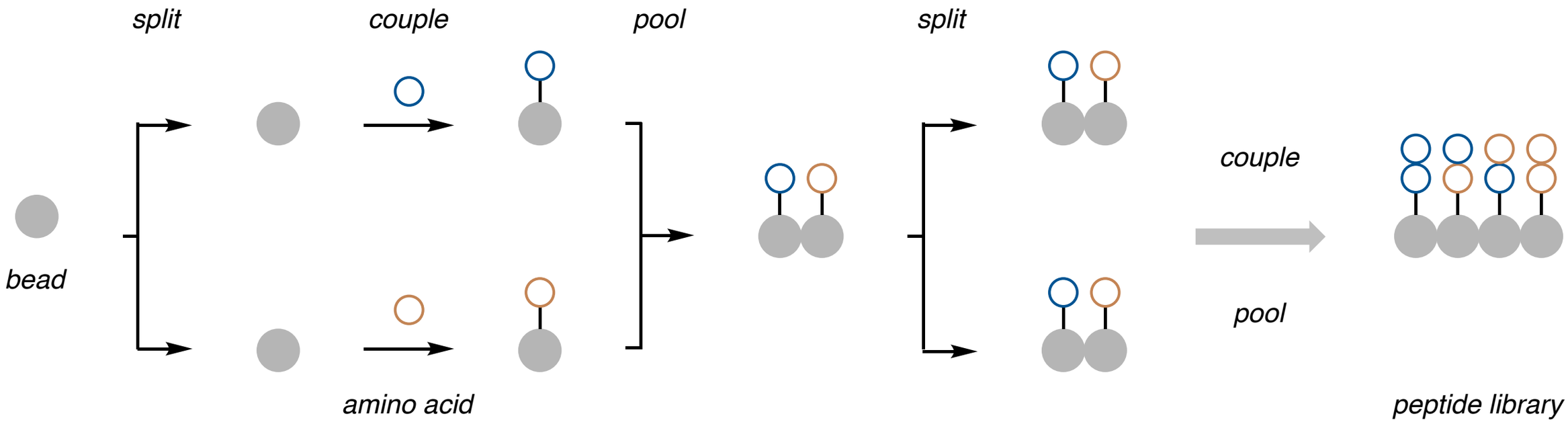
Strategies for Library Screening

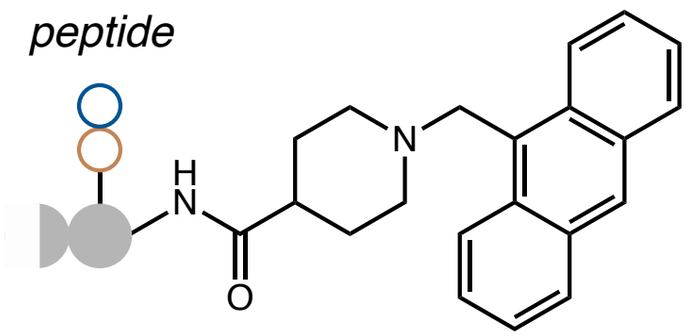
- Facile synthesis of large peptide libraries by split and pool synthesis



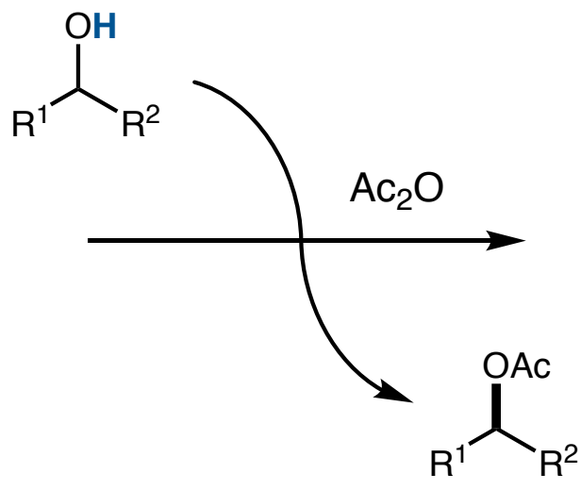
- exponential increase of complexity with the number of cycles
- biased libraries by control the introduction of specific amino acids in each cycle

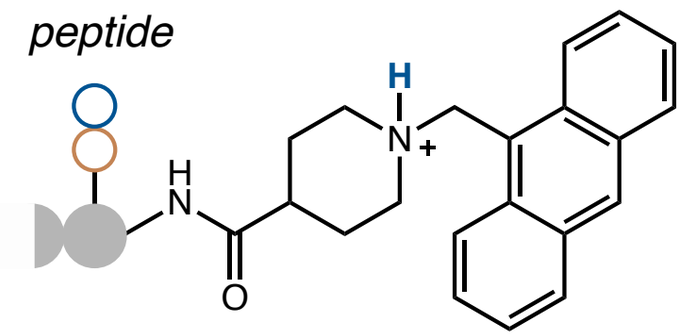
Strategies for Library Screening

- Visualization of hits by co-immobilized fluorescent tags

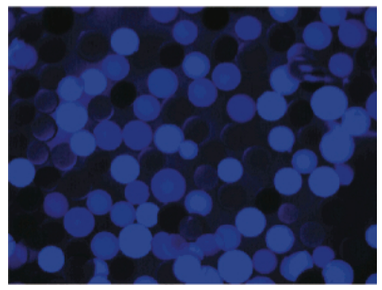


not fluorescent





fluorescent

library synthesis →  → hit validation and sequencing → further optimization

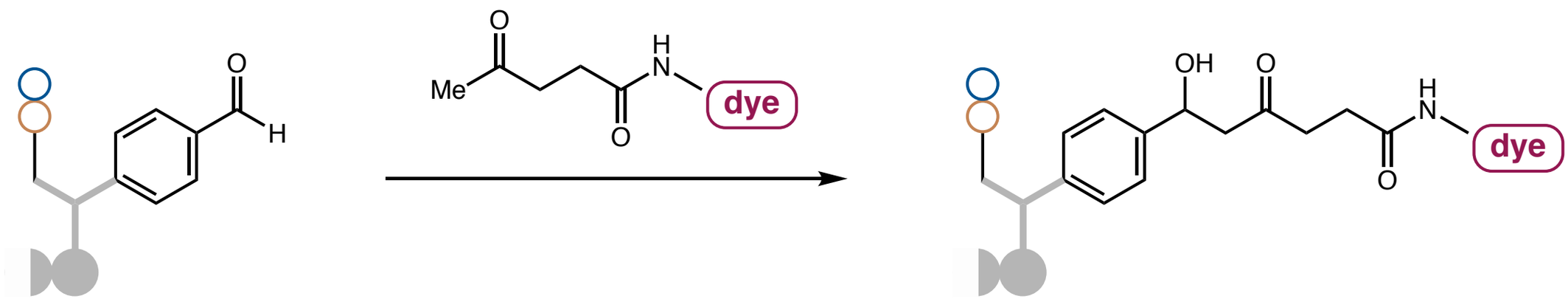
100,000 peptides

screening of ca. 1000 peptides

Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 6496.

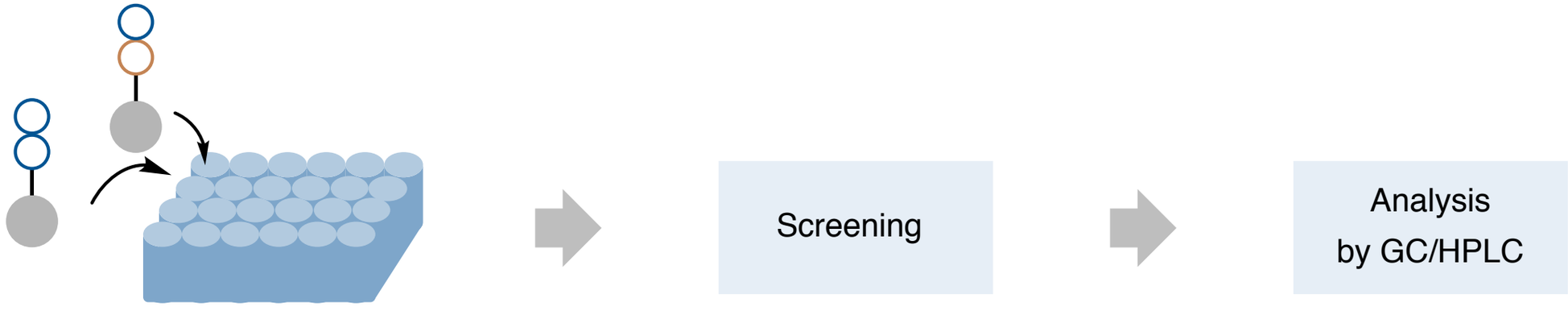
Strategies for Library Screening

- Co-immobilization of substrates



Related work has been reported by Jacobsen, Bradley, Barbas, Davies, Berkessel, Snapper, Hoveyda, and others.

- Sorting of individual beads into individual vials



Lichtor, P.; Miller, S. J. *ACS Comb. Sci.* **2011**, *13*, 321.

Krattiger, P.; McCarthy, C.; Pfaltz, A.; Wennemers, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1722.

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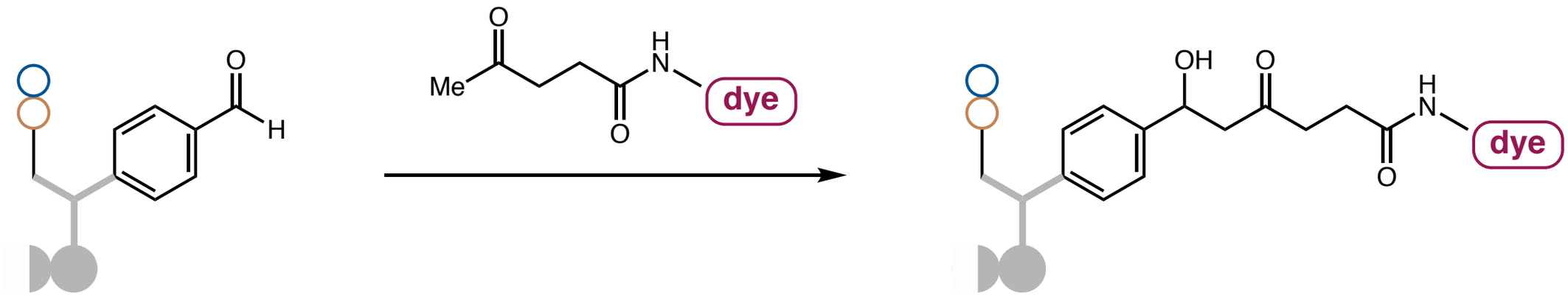
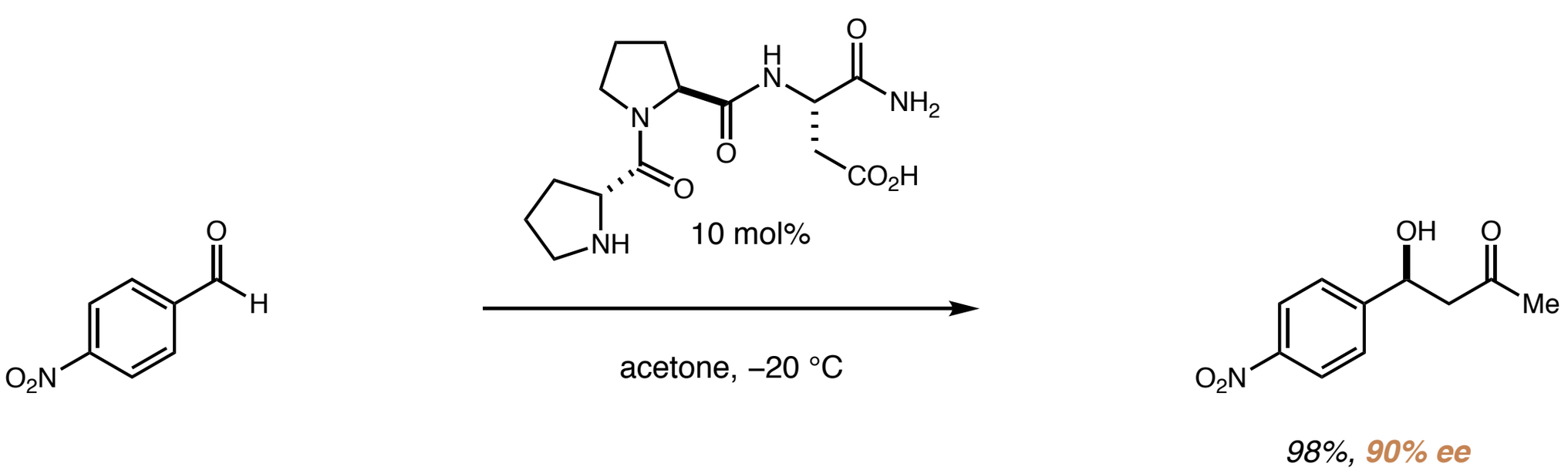
Wennemers' Tripeptide Catalyst

- Hit identification by library screening



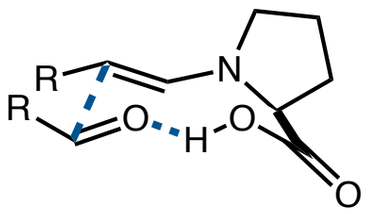
- Optimization in solution



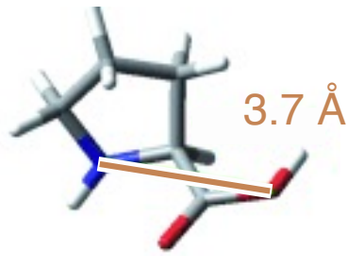
*98%, **90% ee***

Krattinger, P.; Kovasy, R.; Revell, J. D.; Ivan, S.; Wennemers, H. *Org. Lett.* **2005**, *7*, 1101.

Wennemers' Tripeptide Catalyst

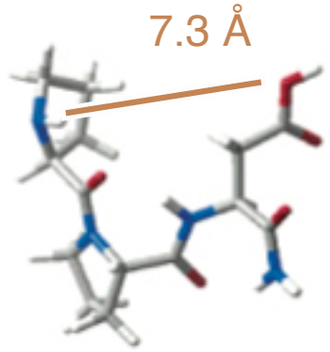


proline-catalyzed aldol reaction

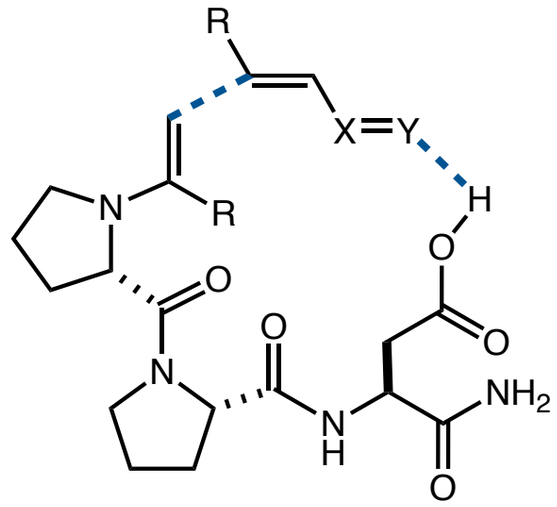


lowest energy configuration of proline

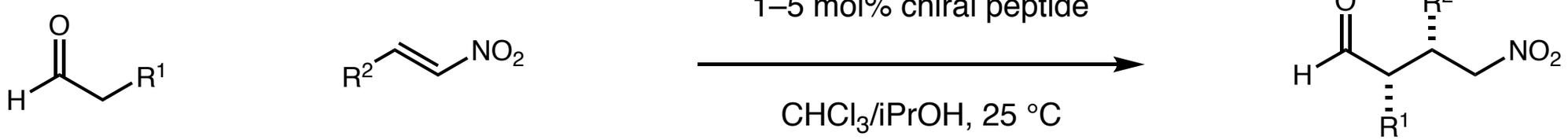
vs



lowest energy configuration of chiral peptide



proposed conjugate addition reaction



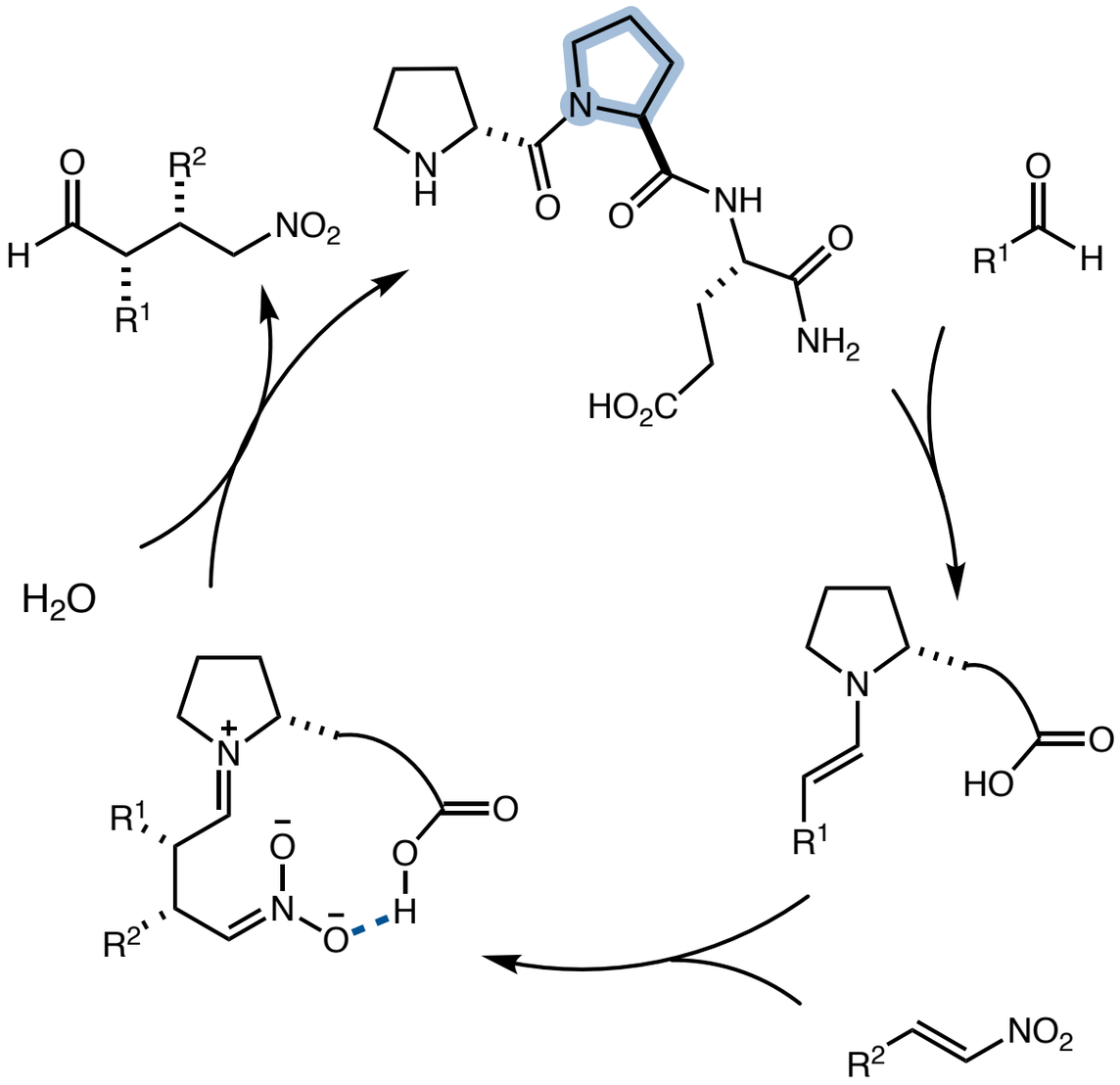
16 examples with >90% ee

reversal of selectivity by switching the enantiomer of a single amino acid

chiral peptide	conversion	syn/anti	ee
H-Pro-Pro-Asp-NH_2	96%	10:1	**–85%**
H-**D**-Pro-Pro-Asp-NH_2	93%	25:1	**95%**

Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1871.

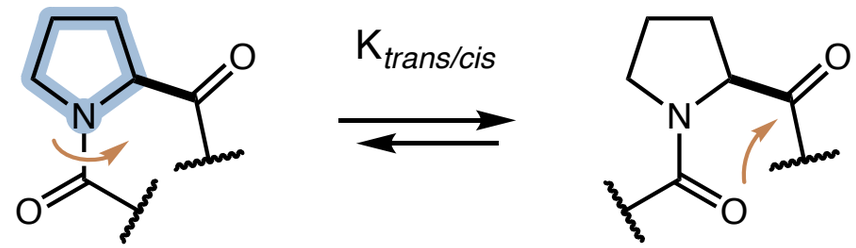
Wennemers' Tripeptide Catalyst



rate- and enantioselectivity determining step

structure activity relationship

- free carboxylic acid required
- D-Pro-Pro moiety is critical
- conformational flexibility in the backbone tolerated
- $K_{trans/cis}$ ratio influences selectivity



cis

lower dipole moment

trans

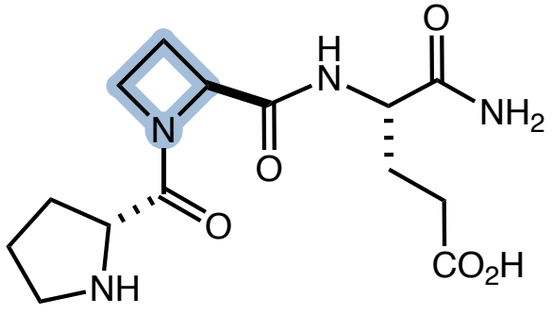
n → π interaction*

Siebler, C.; Maryasin, B.; Kuemin, M.; Erdmann, R. S.; Rigling, C.; Grünenfelder, C.; Ochsenfeld, C.; Wennemers, H. *Chem. Sci.* **2015**, *6*, 6725.

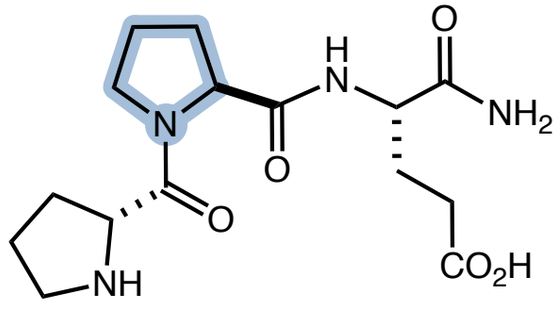
Bächle, F.; Duschmalé, J.; Ebner, C.; Pfaltz, A.; Wennemers, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 12619.

Wiesner, M.; Neuburger, M.; Wennemers, H. *Chem. Eur. J.* **2009**, *15*, 10103.

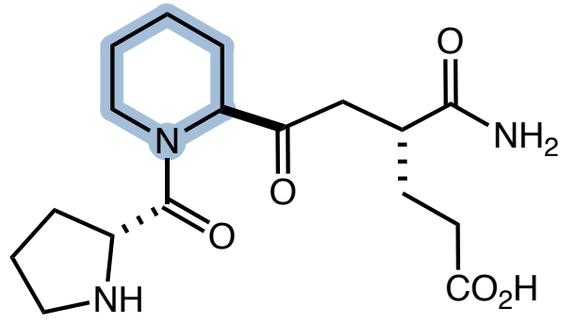
Wennemers' Tripeptide Catalyst



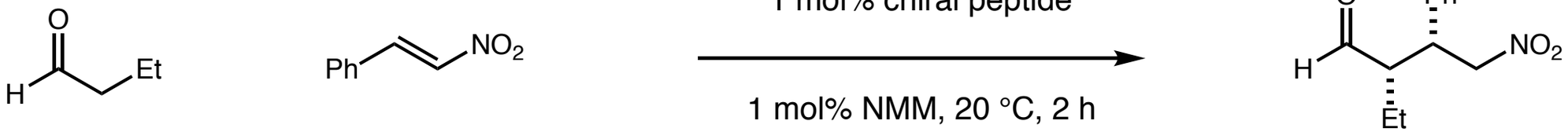
10:1 *trans/cis* ▲

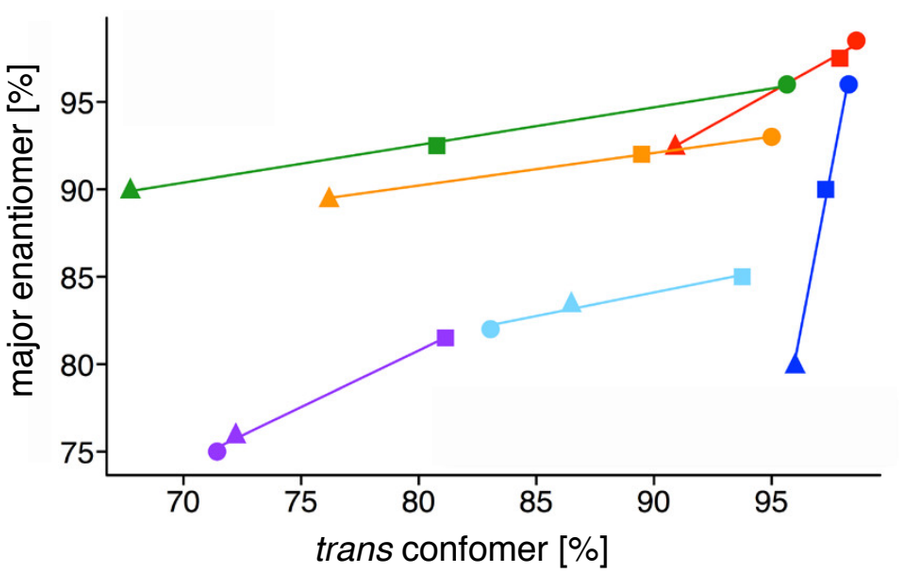


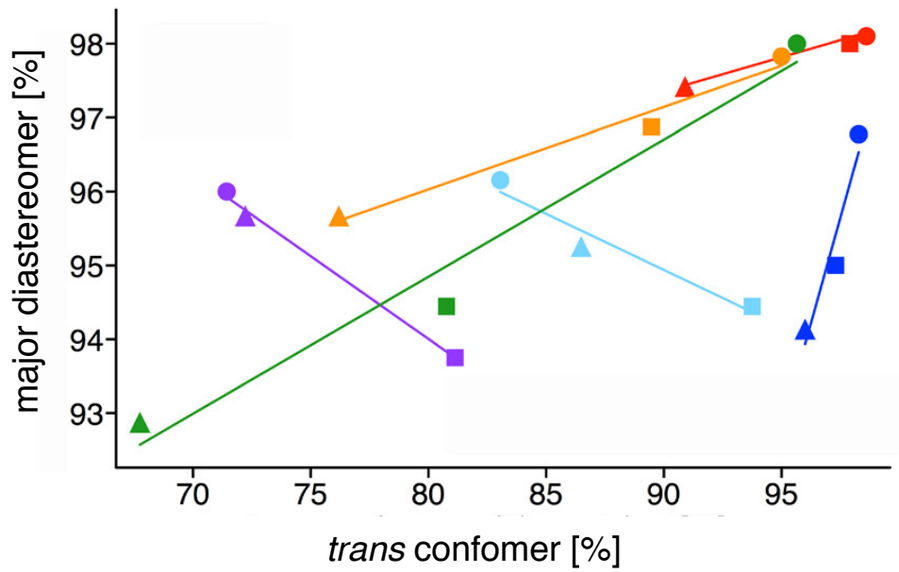
46:1 *trans/cis* ■



71:1 *trans/cis* ●



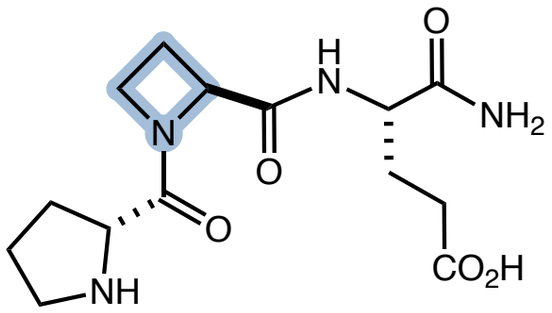




9:1 $CHCl_3$/MeOH
MeOH
Dioxane
THF
MeCN
DMF

Schnitzer, T.; Wennemers, H. *J. Am. Chem. Soc.* **2017**, *139*, 15356.

Wennemers' Tripeptide Catalyst



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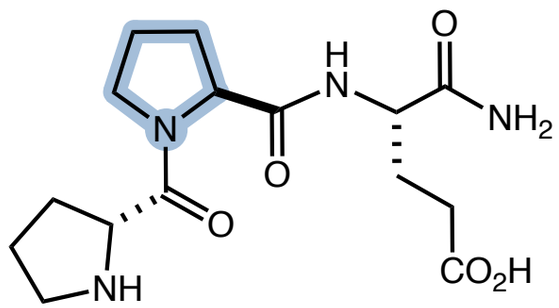

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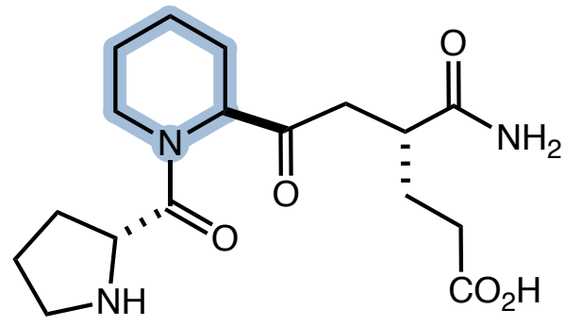
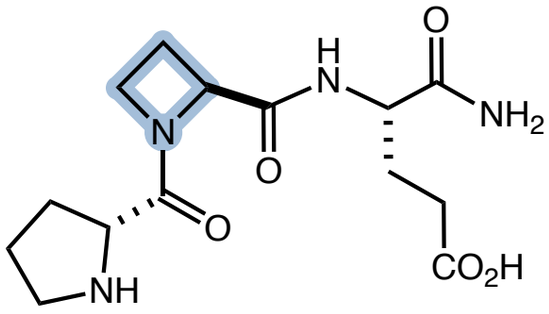


71:1 *trans/cis*

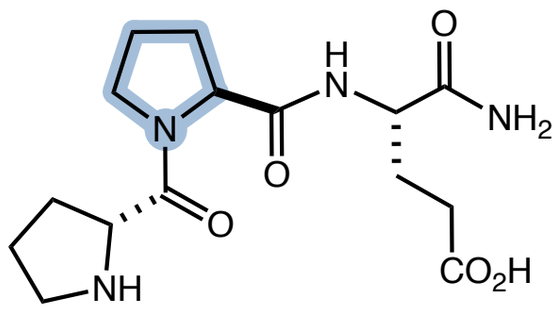
A higher proportion of the *trans* confomer leads to a higher enantio- and diastereoselectivity.

Schnitzer, T.; Wennemers, H. *J. Am. Chem. Soc.* **2017**, *139*, 15356.

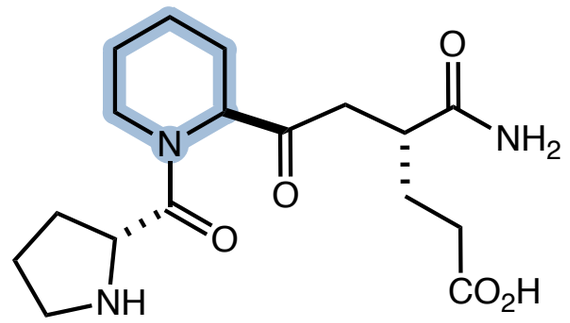
Wennemers' Tripeptide Catalyst



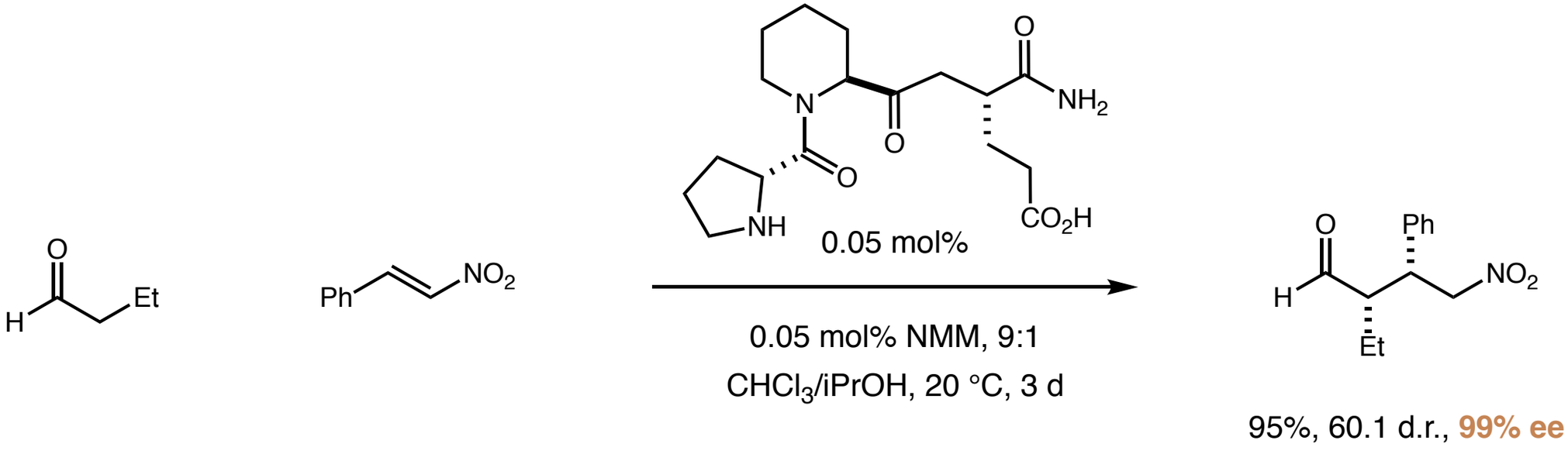
10:1 *trans/cis* ▲



46:1 *trans/cis* ■



71:1 *trans/cis* ●



95%, 60.1 d.r., **99% ee**

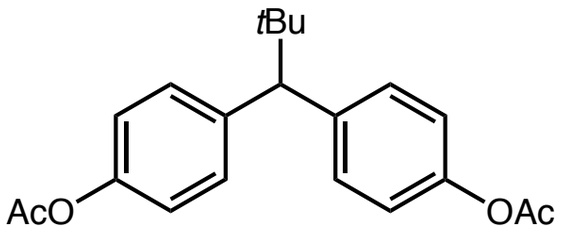
Lowest catalyst loading of a secondary amine organocatalyst reported to date.

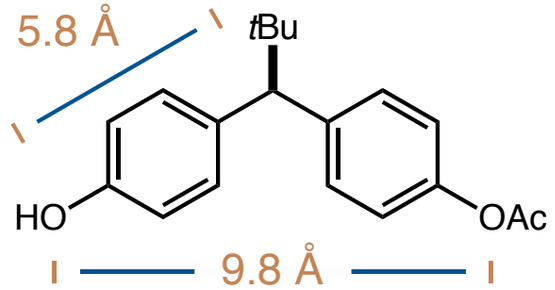
Schnitzer, T.; Wennemers, H. *J. Am. Chem. Soc.* **2017**, *139*, 15356.

Remote Desymmetrization by Chiral Peptides

enzymatic hydrolysis

55% ee at low conversion

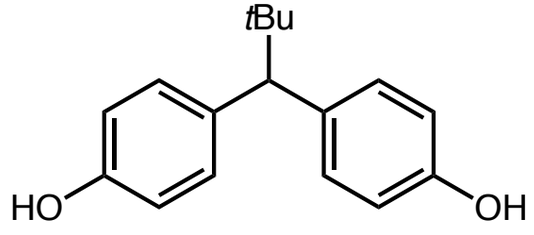




- key intermediate at Merck (Rahway)
- functional groups remote from stereocenter

Can this molecule be accessed by a desymmetrization?

peptide-catalyzed acylation

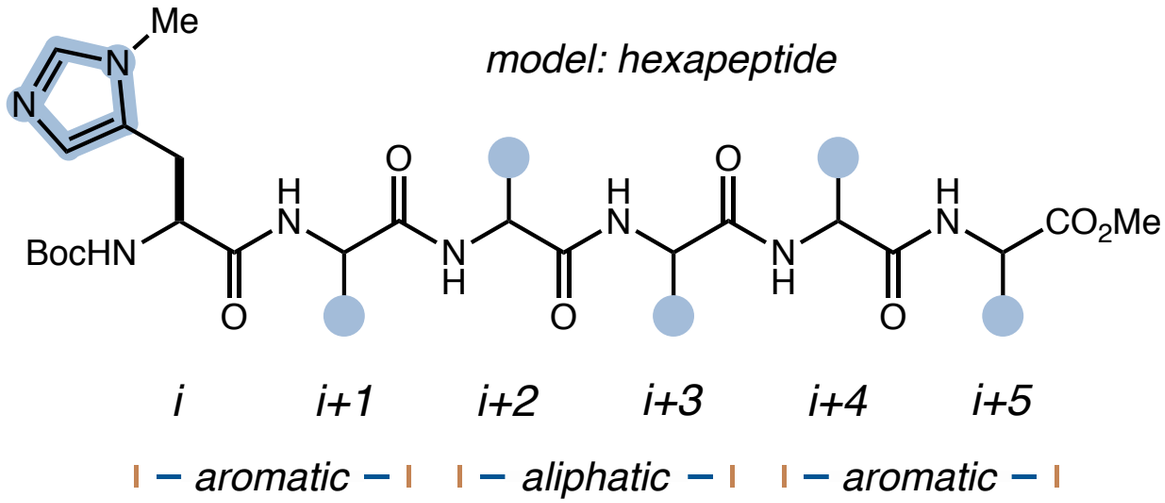


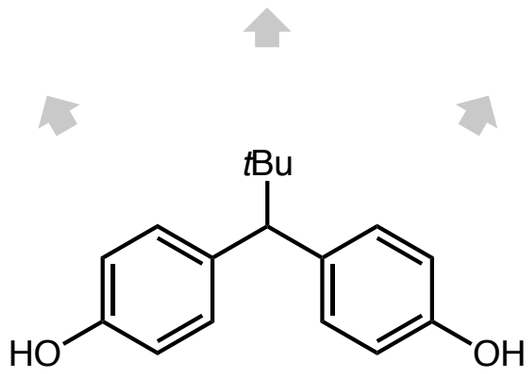
Lewis, C. A.; Gustafson, J. L.; Chiu, A.; Balsells, J.; Pollard, D.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J., T. *J. Am. Chem. Soc.* **2008**, *130*, 16358. Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J., T. *J. Am. Chem. Soc.* **2006**, *128*, 16454.

Remote Desymmetrization by Chiral Peptides

- Design of the initial library

active moiety
previously identified





Lewis, C. A.; Gustafson, J. L.; Chiu, A.; Balsells, J.; Pollard, D.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J., T. *J. Am. Chem. Soc.* **2008**, *130*, 16358. Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J., T. *J. Am. Chem. Soc.* **2006**, *128*, 16454.

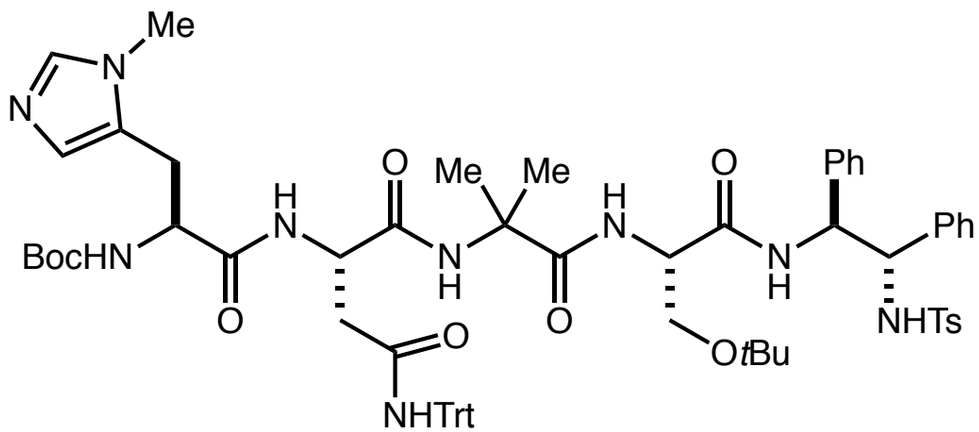
Case Study 2: Remote Desymmetrization by Chiral peptides

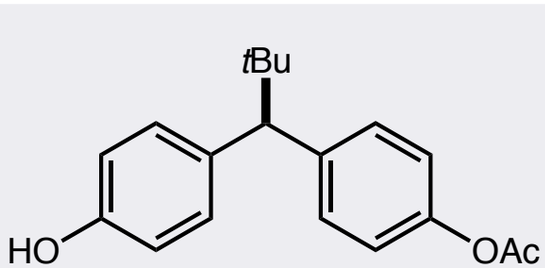
- Optimization workflow

1st generation	*2nd generation*	*3rd generation*	*4th generation*	*5th generation*
42 peptides & reaction conditions	*24 peptides, i+2 & i+3 varied*	*24 peptides, i+1 varied – deleterious*	*i+3–5 & **lower temperature***	*i+4,5 varied – no influence*
*27%, **40% ee***	*25%, **49% ee***	*25%, **49% ee***	*72%, **79% ee***	*78%, **80% ee***

truncation to tetrapeptide

variation of C-terminus

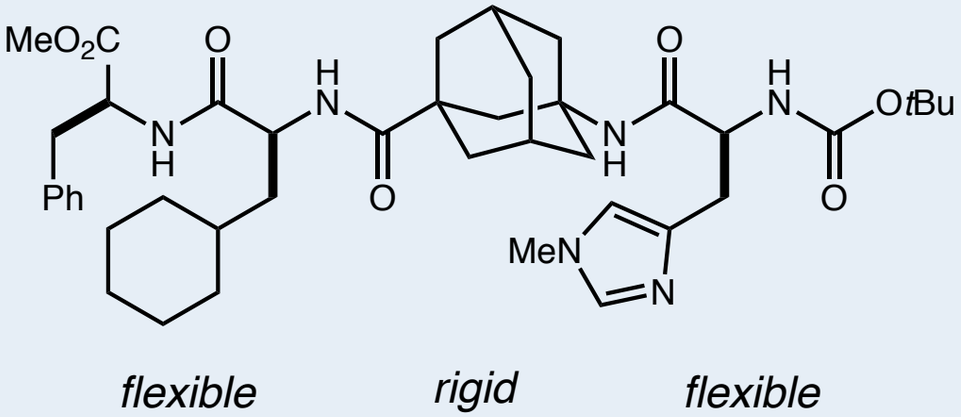


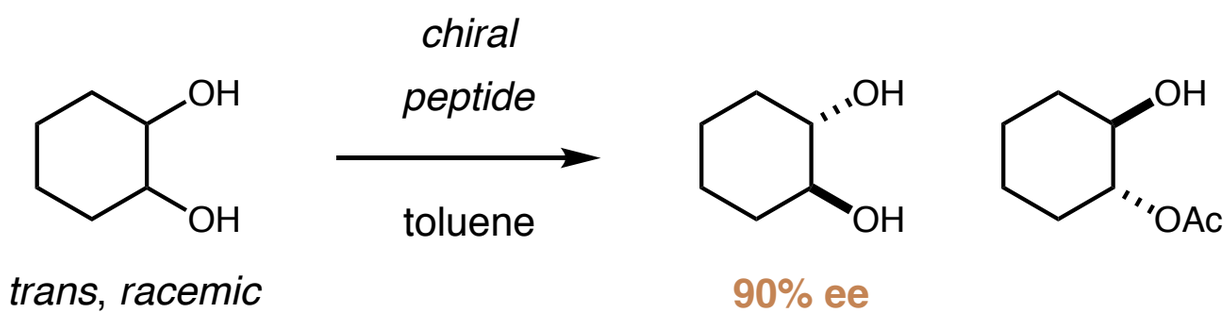


80%, 95% ee

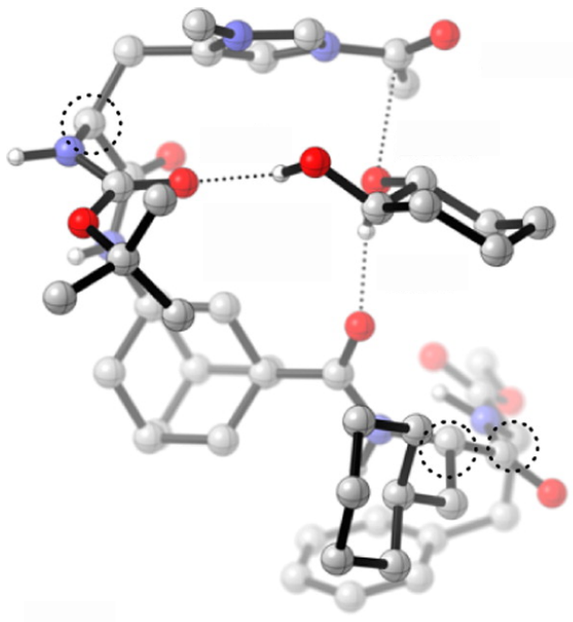
Lewis, C. A.; Gustafson, J. L.; Chiu, A.; Balsells, J.; Pollard, D.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J., T. *J. Am. Chem. Soc.* **2008**, *130*, 16358. Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J., T. *J. Am. Chem. Soc.* **2006**, *128*, 16454.

Schreiner's Lipophilic Oligopeptide Catalyst

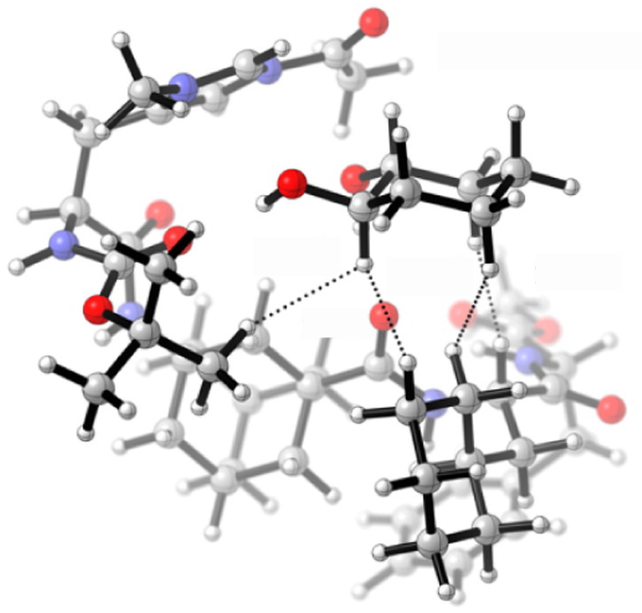




Mechanistic information



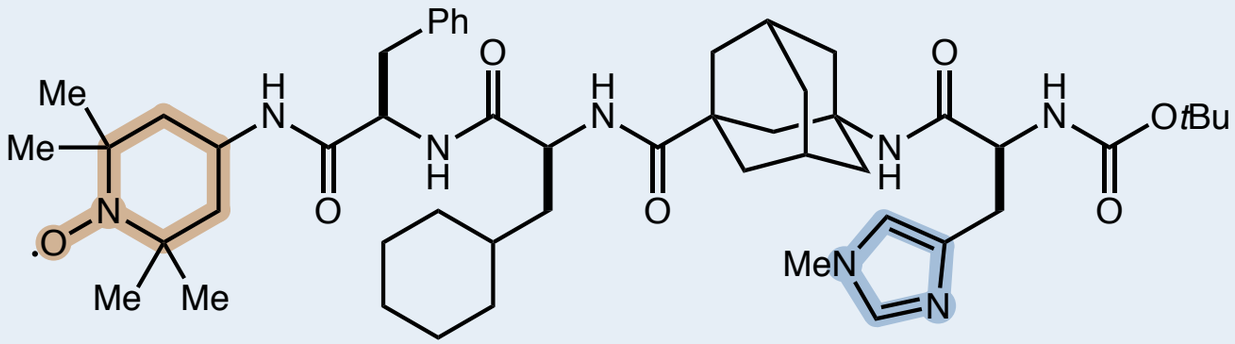
- no secondary structure - central adamantyl group separates both ends
- adamantyl group holds the 3 stereocenters that determine stereochemistry in place
- H-bonding to second hydroxyl group
- Dispersion interaction between hydrophobic substituents and substrate



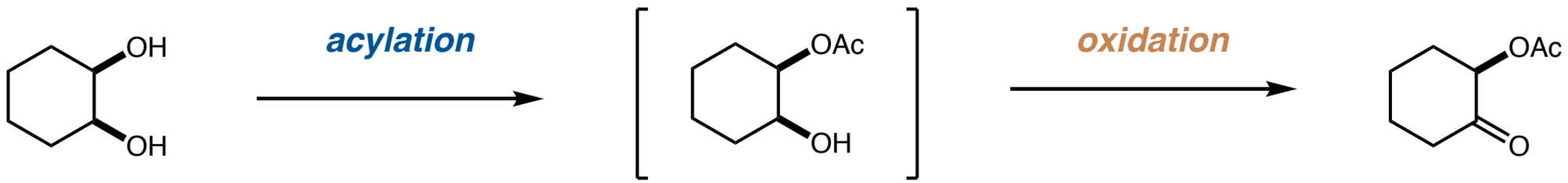
Müller, C. E.; Zell, D.; Hrdina, R.; Wende, R. C.; Wanka, L. Schuler, S. M. M.; Schreiner, P. R. *J. Org. Chem.* **2013**, *78*, 8465.

Müller, C. E.; Wanka, L.; Jewell, K.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6180.

Desymmetrization of cis-Diols



two catalytically active species on a single peptide

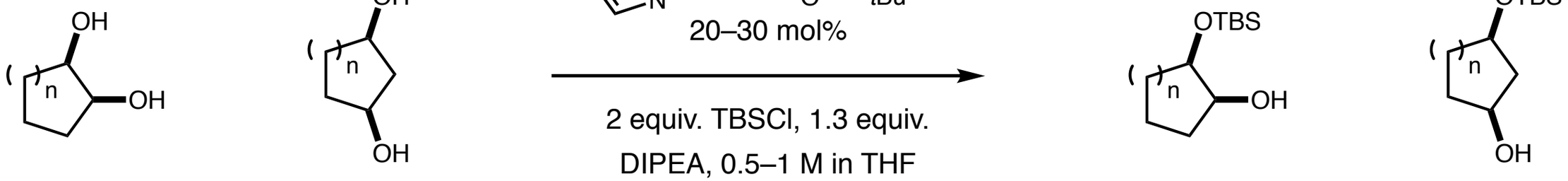


cis, *meso*

acyl group migration

70%, **76% ee**

Silyl protection

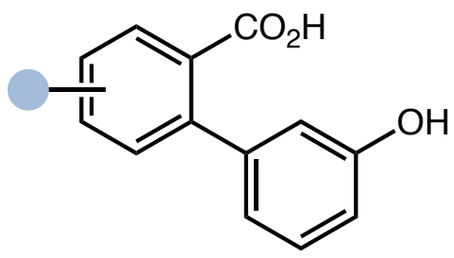


10 examples, **87–96% ee**

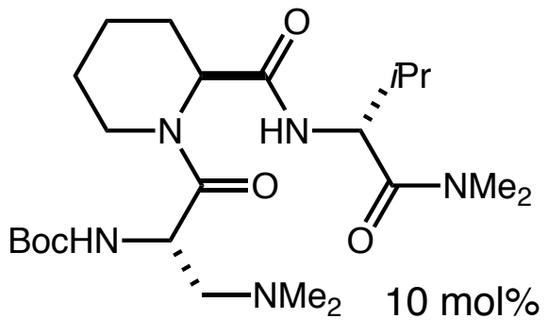
Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67.

Müller, C. E.; Hrdina, R.; Wende, R. C.; Schreiner, P. R. *Chem. Eur. J.* **2011**, *17*, 6309.

Atroposelective Bromination



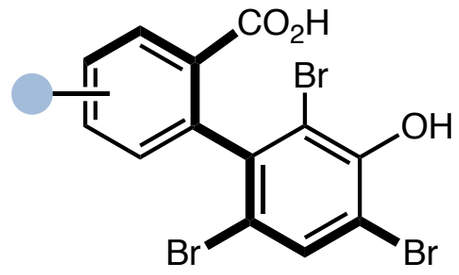
$\Delta G^{\ddagger}$(*rac*) = 7 kcal



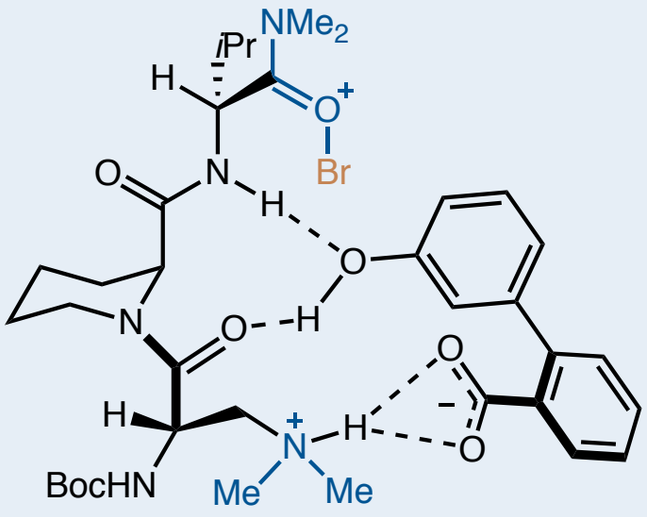
10 mol%

3 equiv. PhthNBr, 0.01 M in 97:3
$CHCl_3$/acetone, 25 °C, 18 h

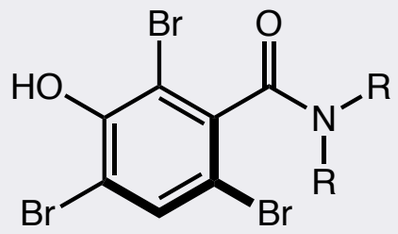
10 examples, ***70–94% ee***



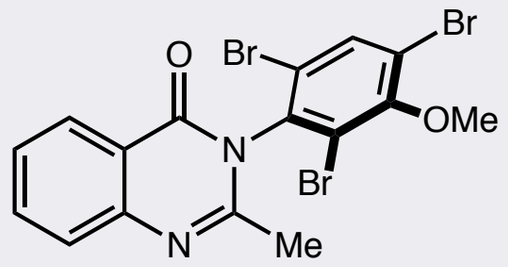
$\Delta G^{\ddagger}$(*rac*) = >30 kcal



Related projects



11 examples, up to ***92% ee***

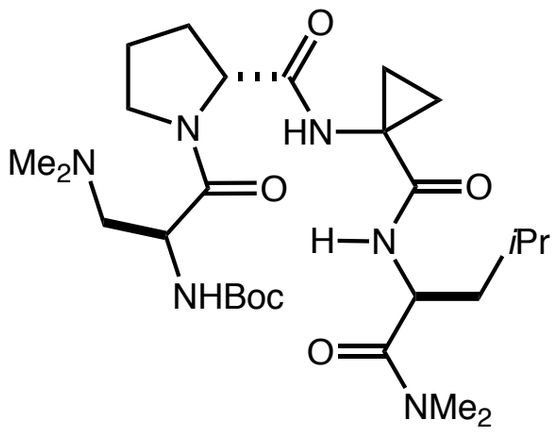


14 examples, up to ***98% ee***

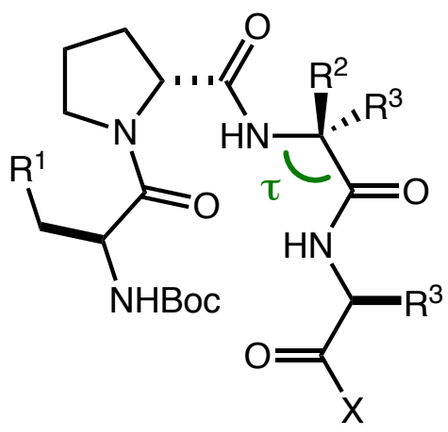
reoptimized peptide backbones used

Diener, M. E.; Metrano, A. J.; Kusano, S.; Miller, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 12369. Barrett, K. T.; Miller, S. J. *J. Am. Chem. Soc.* **2013**, *135*, 2963. Garand, E.; Kamrath, M. Z.; Jordan, P. A.; Wolk, A. B.; Leavitt, C. M.; McCoy, A. B.; Miller, S. J.; Johnson, M. A. *Science* **2012**, *335*, 694. Gustafson, J. L.; Lim, D.; Miller, S. J. *Science* **2010**, *328*, 1251.

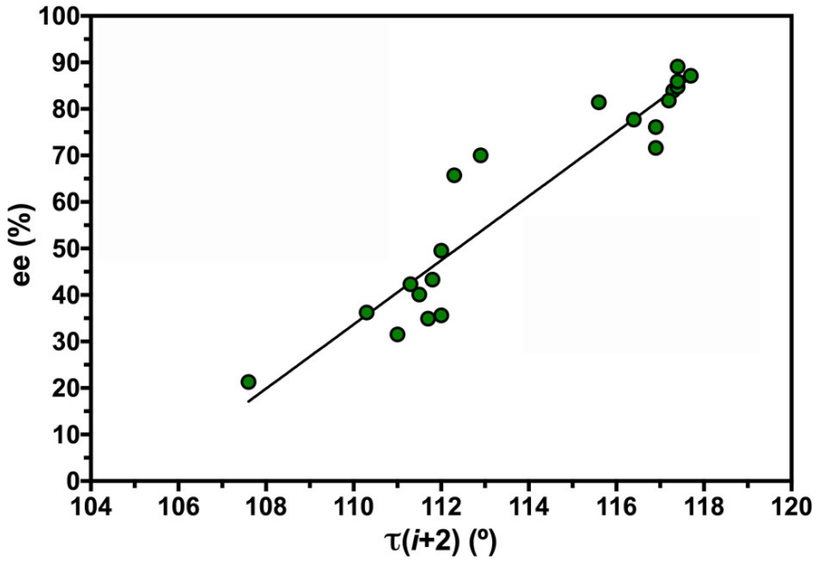
Atroposelective Bromination



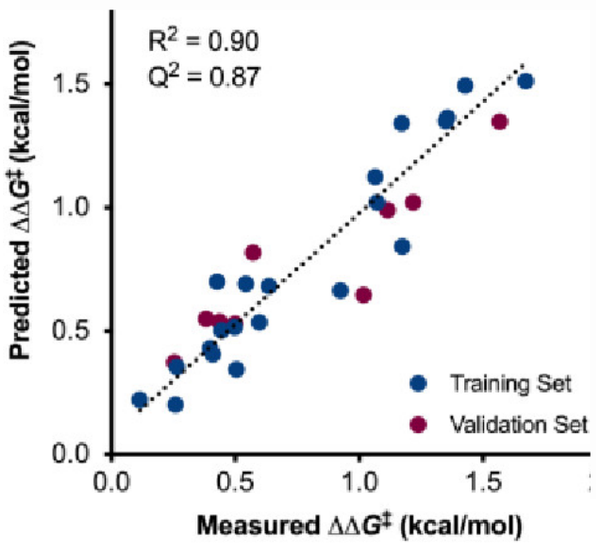
3 different confomers observed by x-ray crystallography



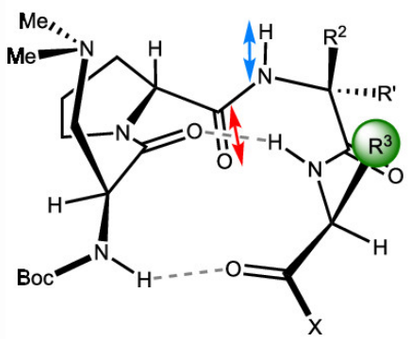
35 distinct peptide – 53 crystal structures

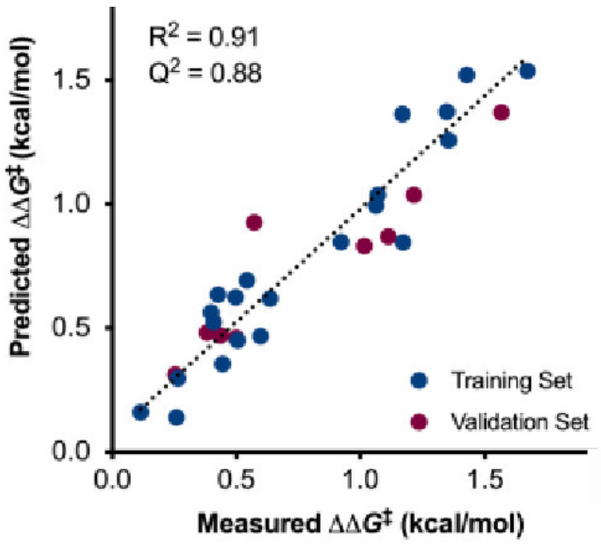


*wider τ-angle ➡ more flexible & **more selective***

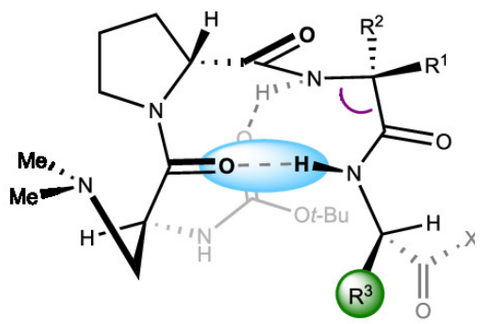


type II' β-turns





type I' β-turns



Crawford, J. M.; Stone, E. A.; Mertrano, A. J.; Miller, S. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2018**, *140*, 868. Mertrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Hurtley, A. E.; Miller, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 491. Mertrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Miller, S. J. *Chem. Commun.* **2016**, *52*, 4816.

Atroposelective Bromination

3 different confomers observed by x-ray crystallograph

35 distinct peptide –

flexible & more selective

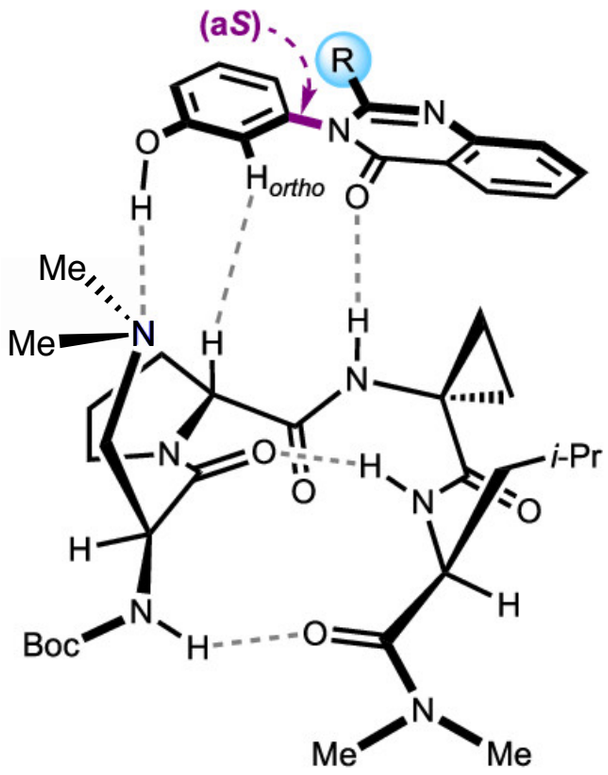
Multiple confomers contribute to a transition state ensemble.

type II' β-turns

type I' β-turns

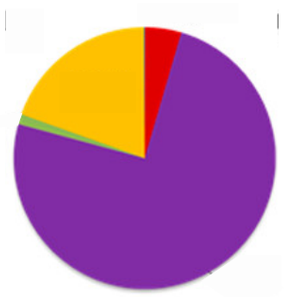
Crawford, J. M.; Stone, E. A.; Mertrano, A. J.; Miller, S. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2018**, *140*, 868. Mertrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Hurtley, A. E.; Miller, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 491. Mertrano, A. J.; Abascal, N. C.; Mercado, B. Q.; Paulson, E. K.; Miller, S. J. *Chem. Commun.* **2016**, *52*, 4816.

Atroposelective Bromination



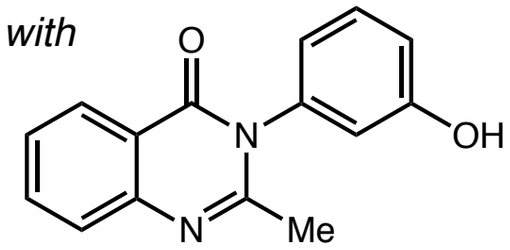
type II' β-turn

only peptide – ground state

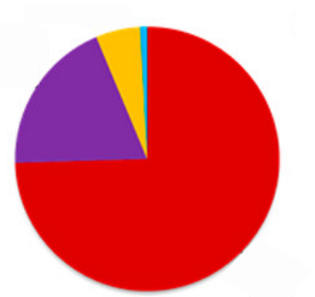


5% vs **75%**

with

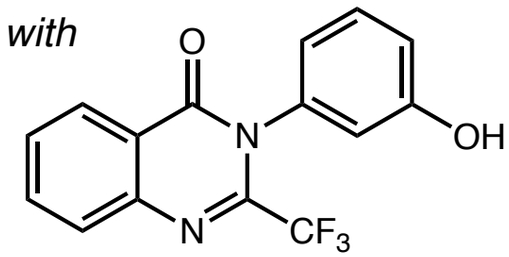


94% ee

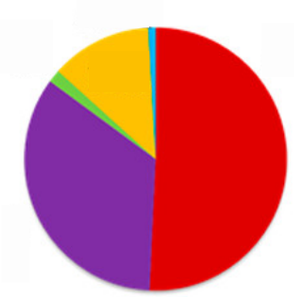


75% vs **19%**

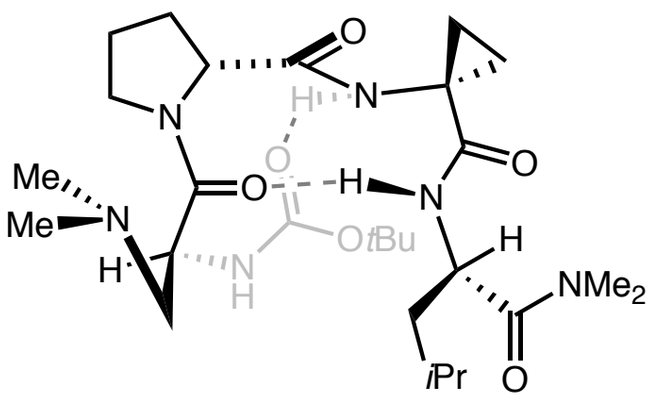
with



26% ee

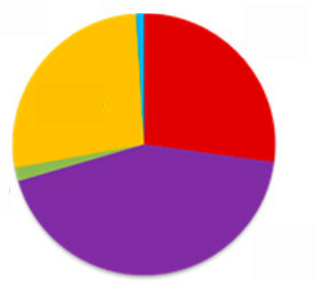


51% vs **34%**



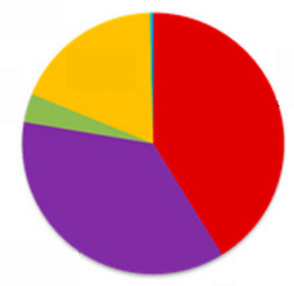
type I' β-turn

opposite enantiomer



27% vs **43%**

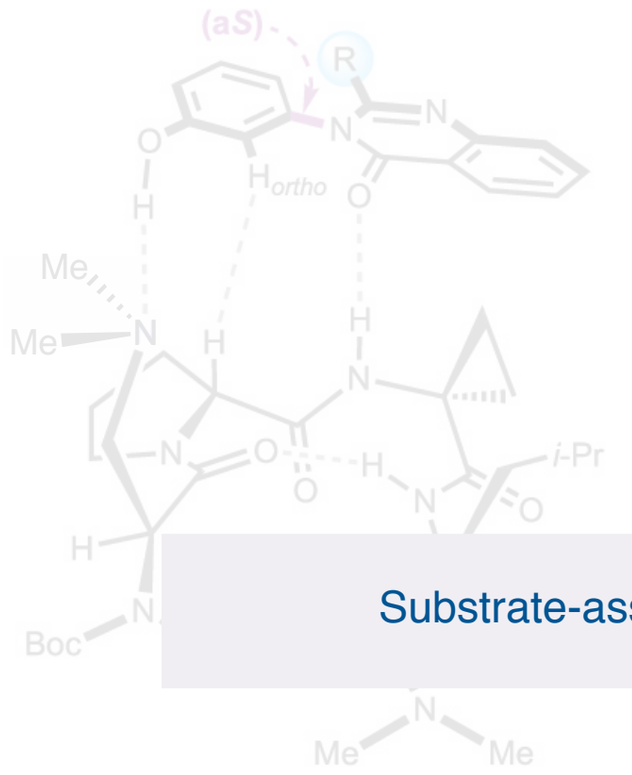
opposite enantiomer



41% vs **36%**

Yan, X. C.; Metrano, A. J.; Robertson, M. J.; Abascal, N. C.; Tirado-Rives, J.; Miller, S. J.; Jorgensen, W. L. *ACS Catal.* **2018**, *8*, 9968.

Atroposelective Bromination



only peptide – ground state

with

94% ee

with

26% ee

Substrate-association enforces a structural change of the peptide – induced fit.

type I' β-turn

opposite enantiomer

27% vs **43%**

opposite enantiomer

41% vs **36%**

type II' β-turn

5% vs **75%**

75% vs **19%**

51% vs **34%**

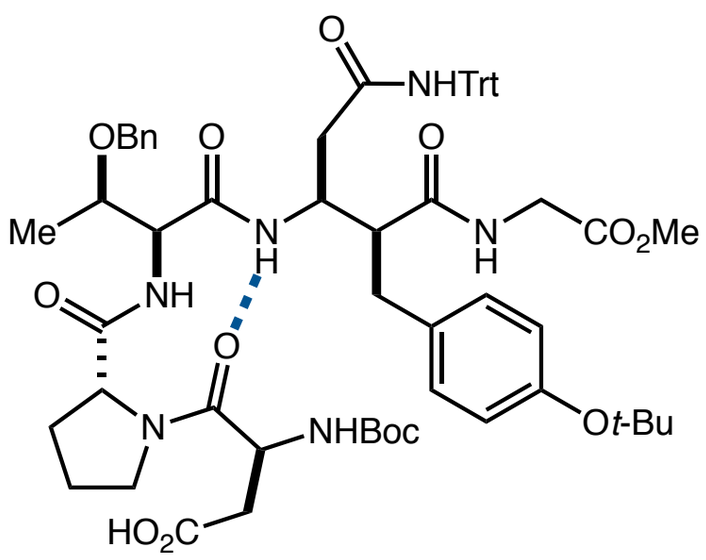
Yan, X. C.; Metrano, A. J.; Robertson, M. J.; Abascal, N. C.; Tirado-Rives, J.; Miller, S. J.; Jorgensen, W. L. *ACS Catal.* **2018**, *8*, 9968.

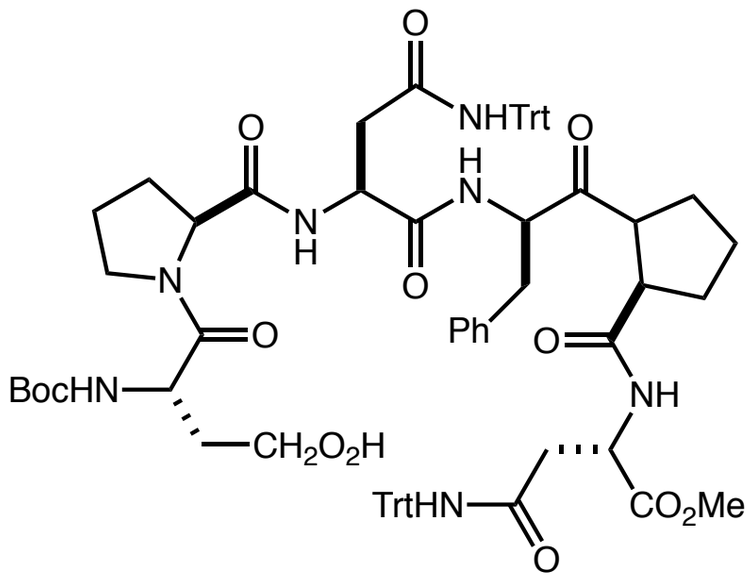
Site-Selective Polyene Oxidation

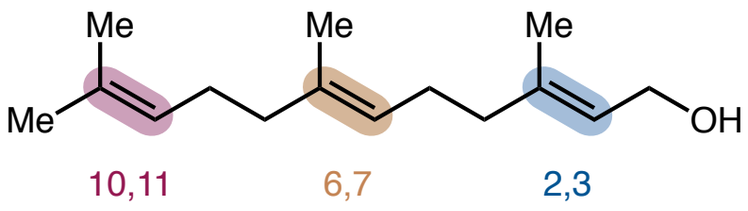
Optimization

Optimization

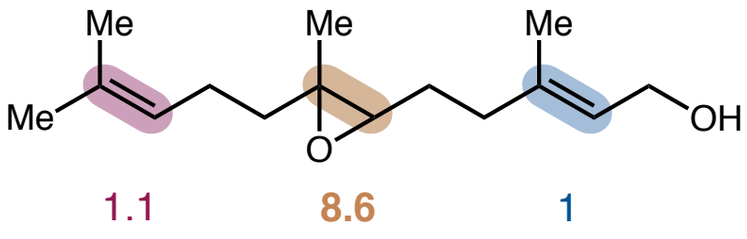
One-bead-one-compound screening

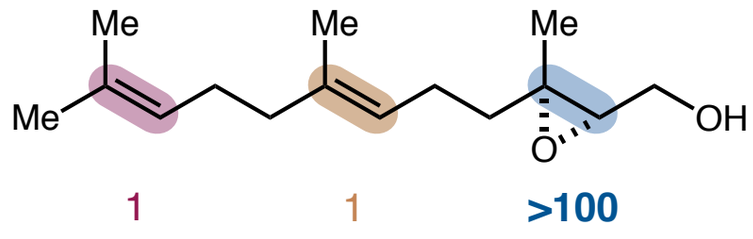






farnesol





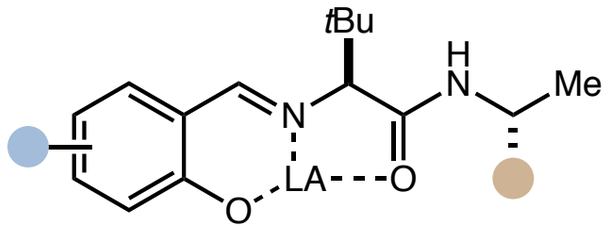
Abascal, N. C.; Lichtor, P. A.; Giuliano, M. W.; Miller, S. J. *Chem. Sci.* **2014**, *5*, 4504. Lichtor, P. A.; Miller, S. J. *J. Am. Chem. Soc.* **2014**, *136*, 5301. Lichtor, P. A.; Miller, S. J. *Nat. Chem.* **2012**, *4*, 990.

Small Peptides as Organocatalysts

- Introduction
- Catalytically relevant properties of small peptides
- Small peptides as organocatalyst
- Small peptides in Lewis acid and transition metal catalysis
- Small peptides in photoredox catalysis
- Summary

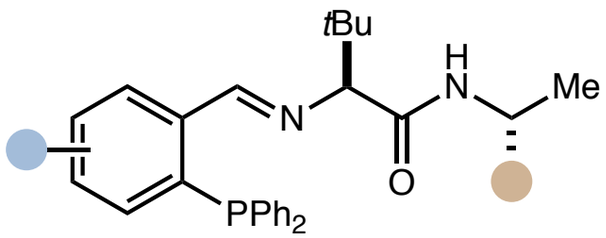
This group meeting does not cover the available literature comprehensively. Instead, selected key studies are discussed in order to explain the underlying concepts.

Pioneering Work on Peptides in Lewis Acid and Transition Metal Catalysis



LA = Ti, Zr, Al

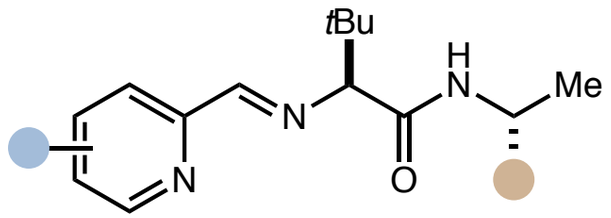
Snapper & Hoveyda: cyanation, alkylation



Hoveyda: copper-catalyzed conjugate additions

Role of the peptide

creation of a chiral environment around the metal catalyst



Hoveyda: copper-catalyzed allylic alkylation

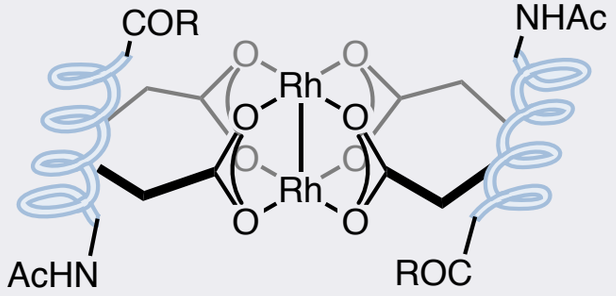
Key references: Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009. Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755. Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984. Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int, Ed.* **2001**, *40*, 1456. Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284.

Helical Peptide-Ligated Rhodium-"Paddlewheel" Complexes

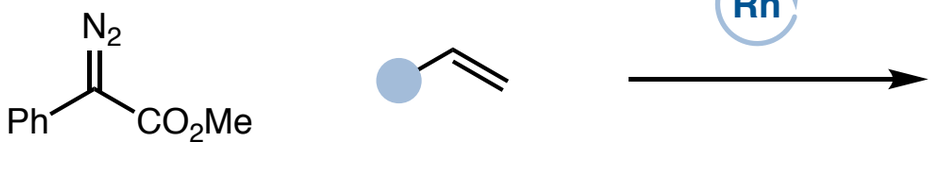
- Enantioselective insertion into Si–H bonds

7 examples with

>90% ee



- Enantioselective cyclopropanation



access to both enantiomers

*in **>90% ee** (7 examples)*

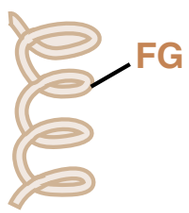
Role of the peptide

creation of a chiral environment around the metal catalyst

Samasivan, R.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 8568.

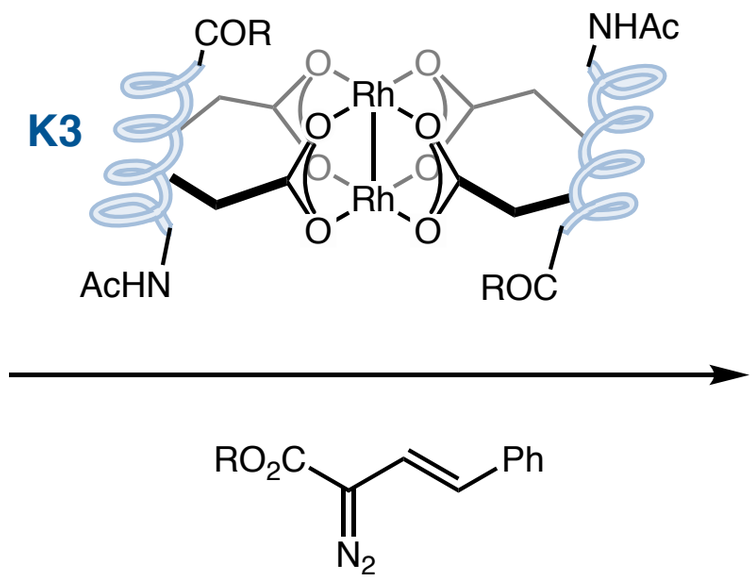
Samasivan, R.; Ball, Z. T. *J. Am. Chem. Soc.* **2010**, *132*, 9289.

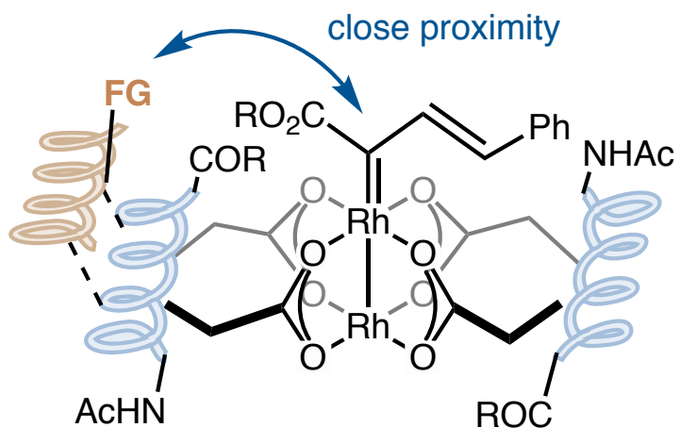
Structure-Selective Protein Functionalization



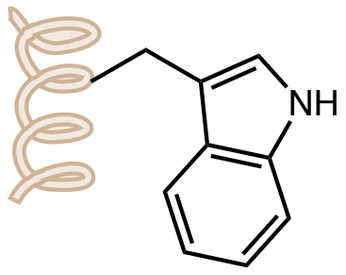
E3

helical peptide





E3/K3 coiled coil assembly places side chain in close proximity of the rhodium carbenoid



> 1000 rate enhancement compared to $Rh_2(OAc)_4$

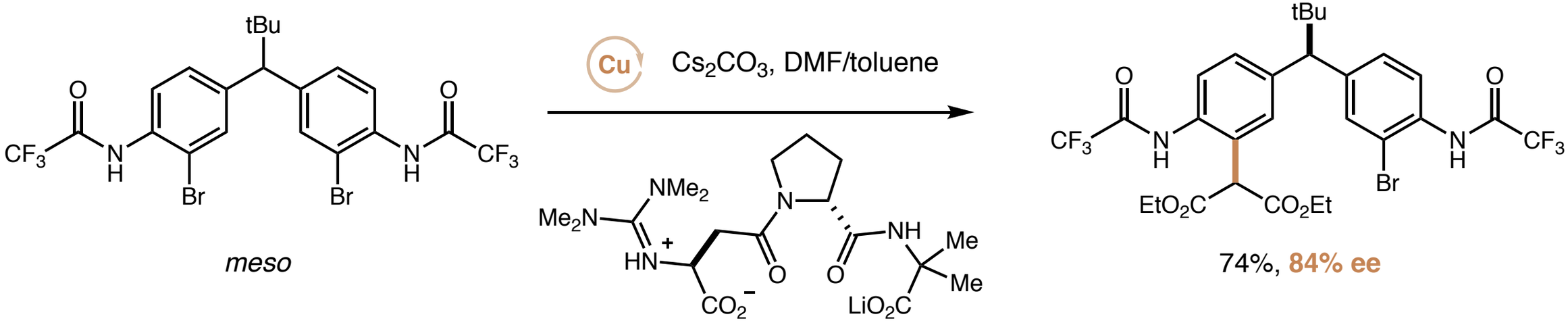
Although tryptophan is most reactive, selective functionalization of E3-tyrosine or phenylalanines occurs even in presence of random tryptophane-containing peptides.

Role of the peptide

substrate recognition by non-covalent interactions

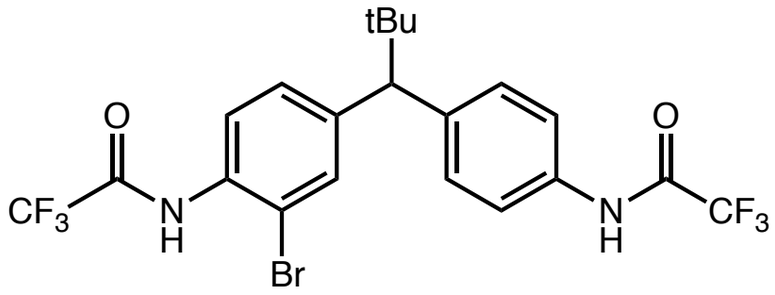
Popp, B. V.; Ball, Z. T. *J. Am. Chem. Soc.* **2010**, *132*, 6660.

Copper-Peptide-Mediated Cross-Coupling of Diarylmethanes

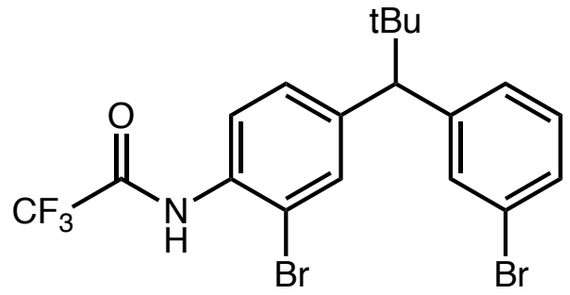


identification of the substrate–peptide interaction

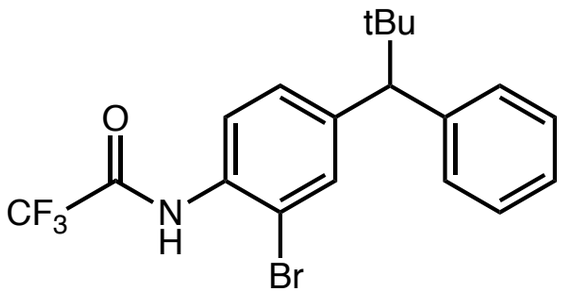
A high k_{rel} in the kinetic resolution of unsymmetrical substrates indicates a substrate–peptide interaction



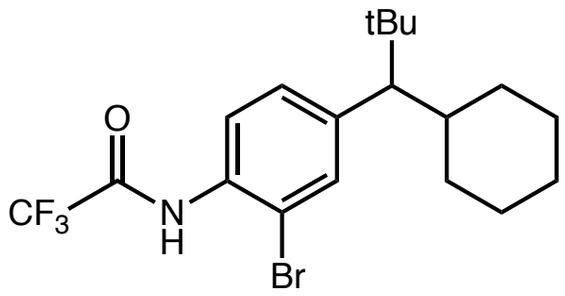
k_{rel} = 5.3



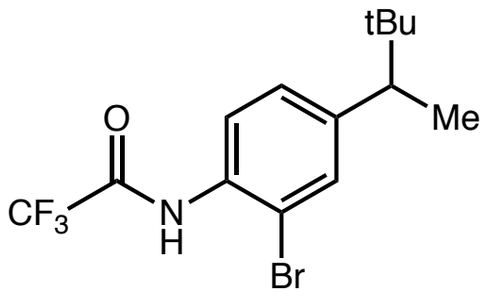
k_{rel} = 11.3



k_{rel} = 10.3



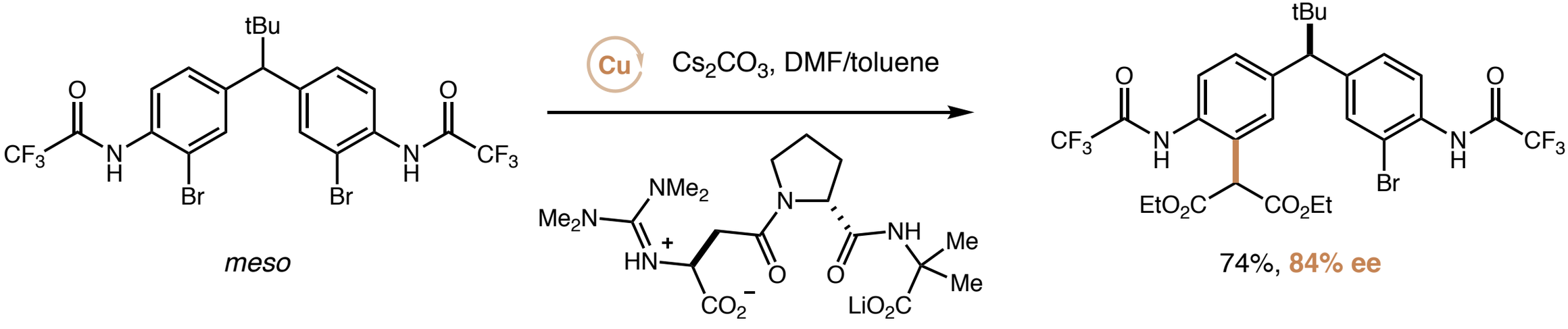
k_{rel} = 1.6



k_{rel} = 1.2

Kim, B.; Chinn, A. J.; Fandrick, D. R.; Senayake, C. H.; Singer, R. A.; Miller, S. J. *J. Am. Chem. Soc.* **2016**, *138*, 7939.

Copper-Peptide-Mediated Cross-Coupling of Diarylmethanes



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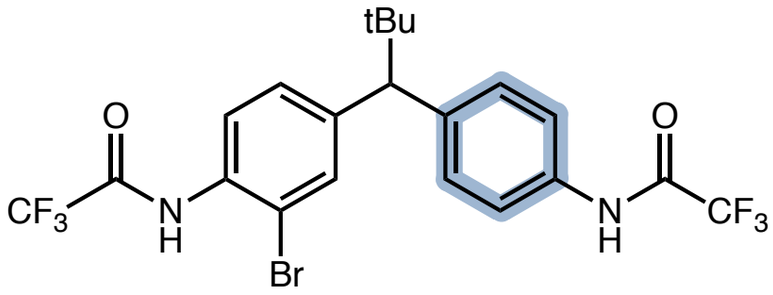
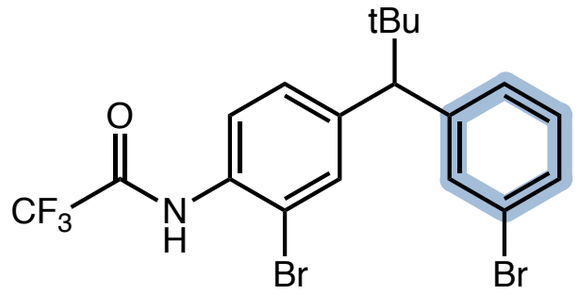
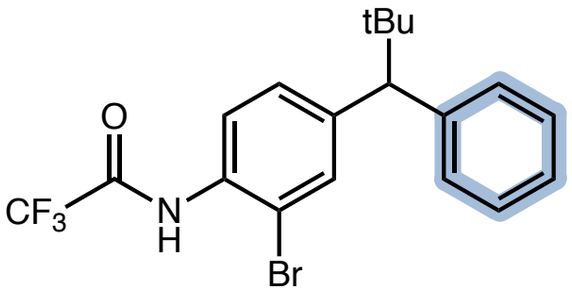


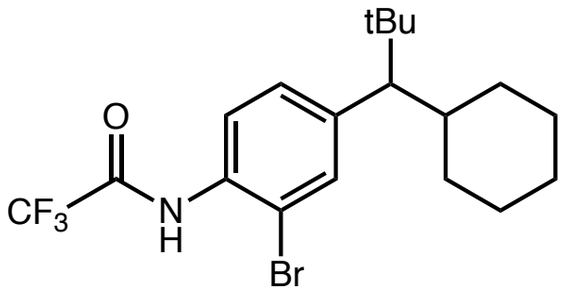
k_{rel} = 5.3



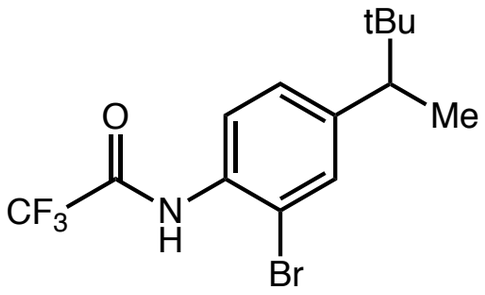
k_{rel} = 11.3



k_{rel} = 10.3



k_{rel} = 1.6



k_{rel} = 1.2

Kim, B.; Chinn, A. J.; Fandrick, D. R.; Senayake, C. H.; Singer, R. A.; Miller, S. J. *J. Am. Chem. Soc.* **2016**, *138*, 7939.

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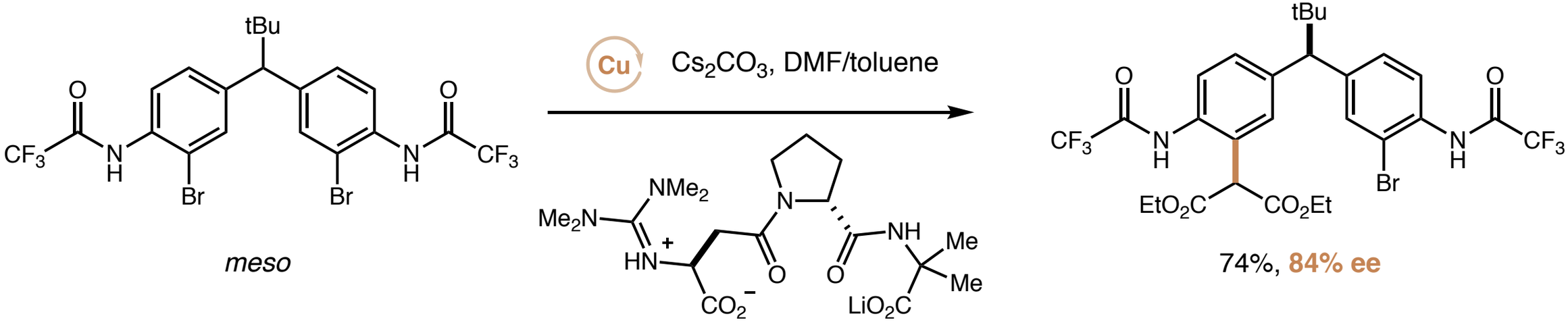
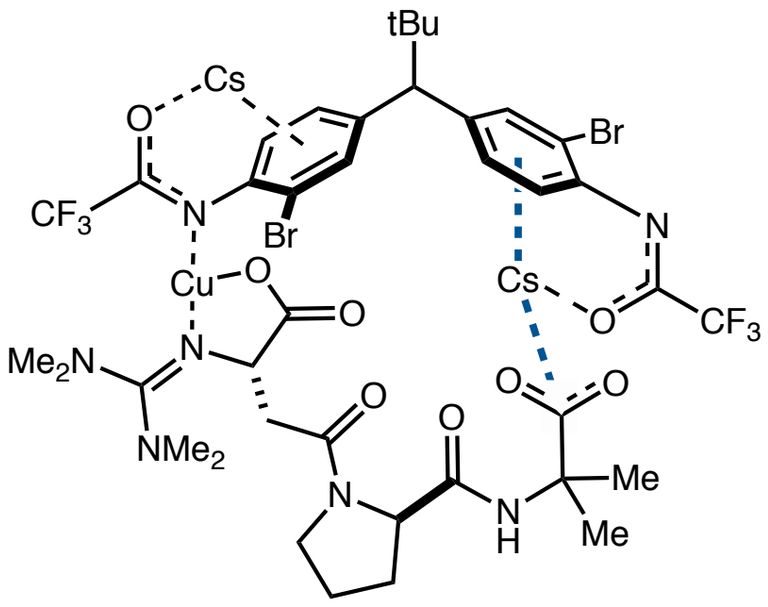


identification of the substrate–peptide interaction



Proposed model

cation-π-interaction between substrate and ligated cesium

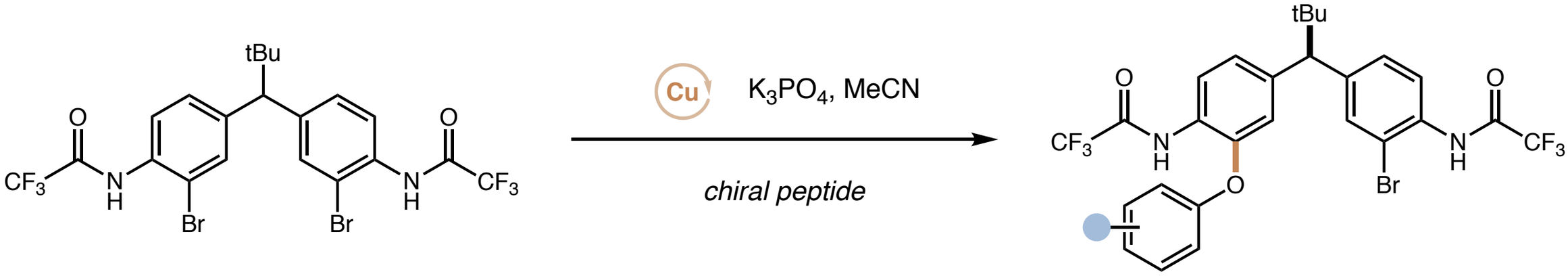
Role of the peptide

substrate recognition by non-covalent interaction

Kim, B.; Chinn, A. J.; Fandrick, D. R.; Senayake, C. H.; Singer, R. A.; Miller, S. J. *J. Am. Chem. Soc.* **2016**, *138*, 7939.

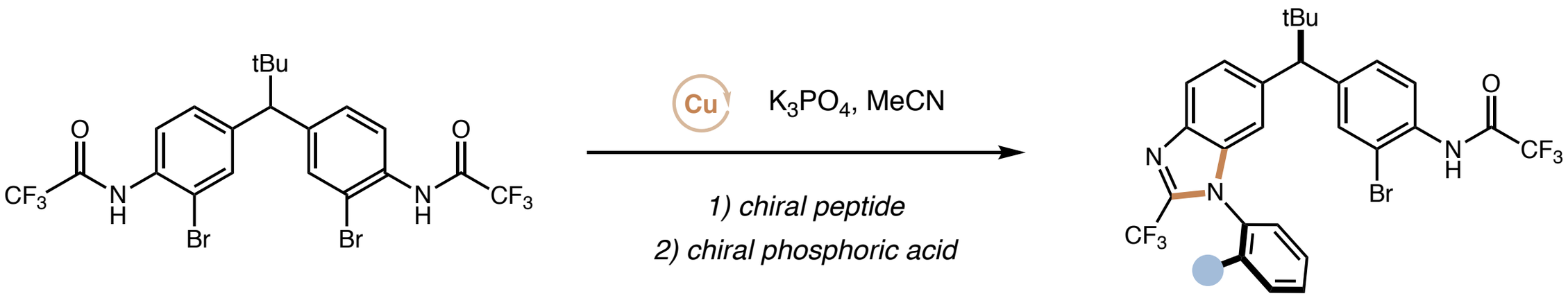
Copper-Peptide-Mediated Cross-Coupling of Diarylmethanes

- C–O coupling



14 alcohols, **84–99% ee**

- C–N coupling and catalyst-controlled cyclodehydration



18 examples, **84–99% ee**

all 4 diastereomers are accessible

Kwon, Y.; Chinn, A. J.; Kim, B.; Miller, S. J. *J. Am. Chem. Soc.* **2018**, *57*, 6251.

Chinn, A. J.; Kim, B.; Kwon, Y.; Miller, S. J. *J. Am. Chem. Soc.* **2017**, *139*, 18107.

Small Peptides as Organocatalysts

- Introduction
- Catalytically relevant properties of small peptides
- Small peptides as organocatalyst
- Small peptides in Lewis acid and transition metal catalysis
- Small peptides in photoredox catalysis
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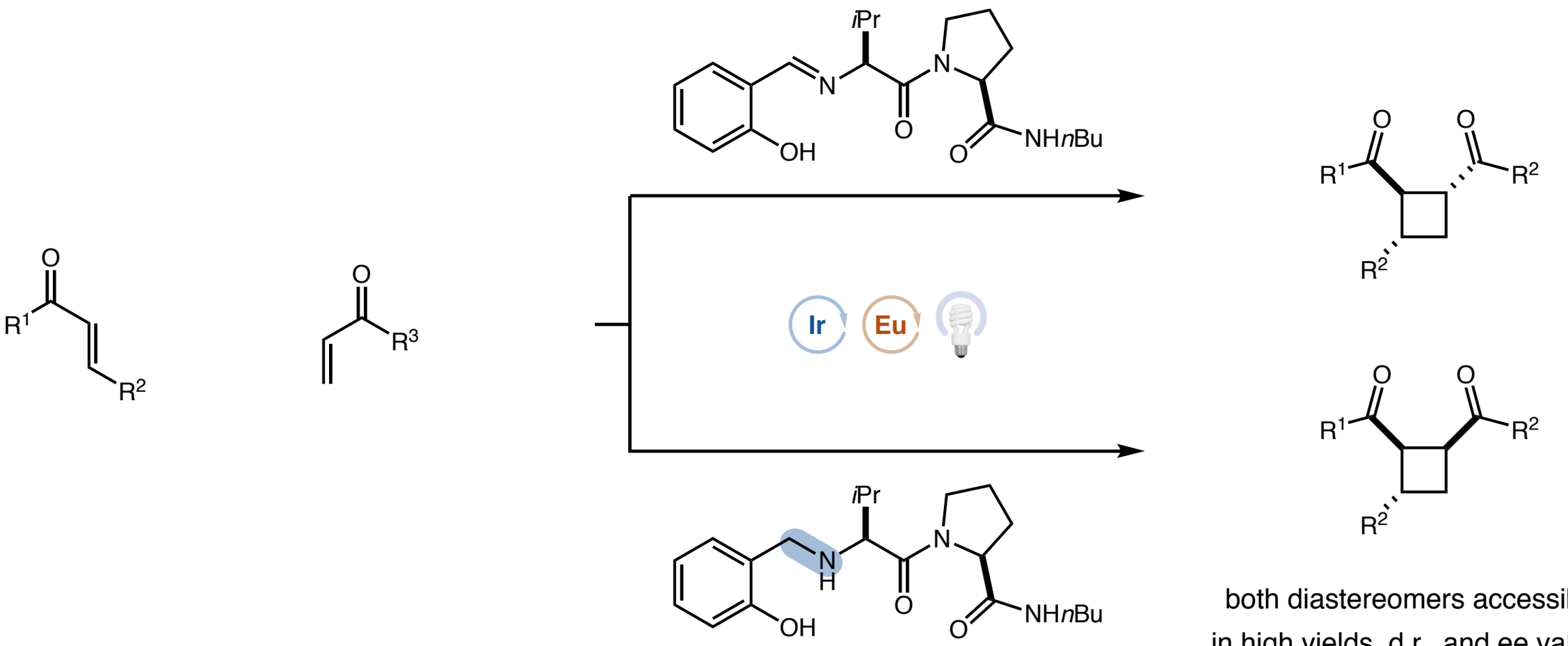
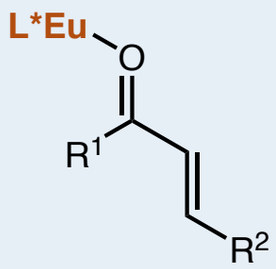
Enantioselective [2+2] Photocycloaddition



both diastereomers accessible
in high yields, d.r., and ee values

via



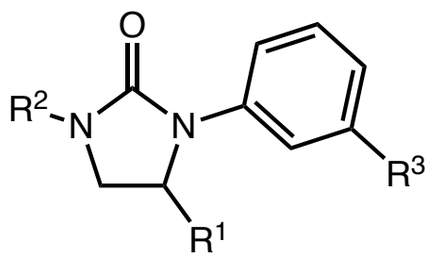
Role of the peptide

creation of a chiral environment
around the metal catalyst

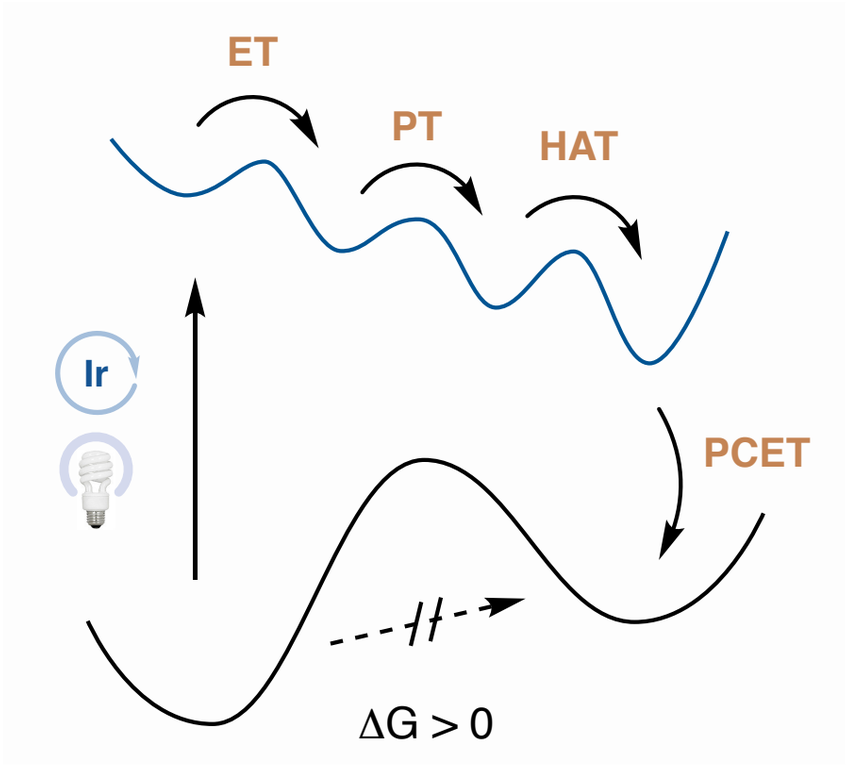
Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392.

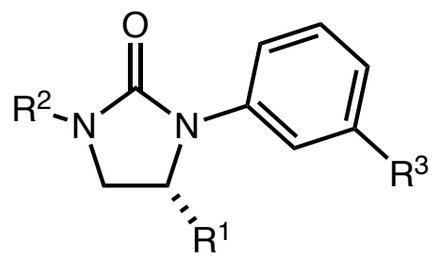
Light-Driven Deracemization

- Photoredox strategy for an out-of-equilibrium deracemization



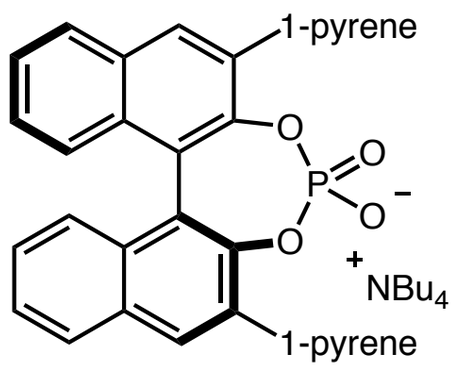
racemic



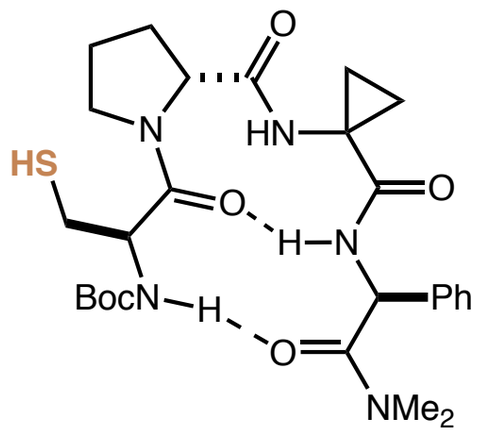


enantioenriched

two chiral co-catalysts



chiral phosphate



chiral peptide

Role of the peptide

chiral hydrogen atom donor

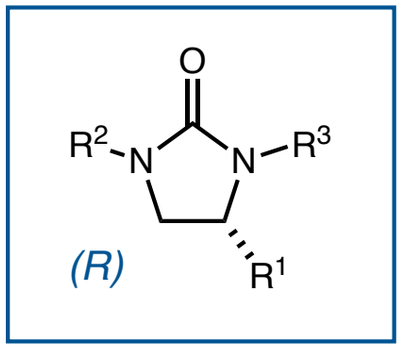
Shin, N. Y.; Ryss, J. M.; Zhang, X.; Miller, S. J.; Knowles, R. R. *Science* **2019**, *366*, 364.

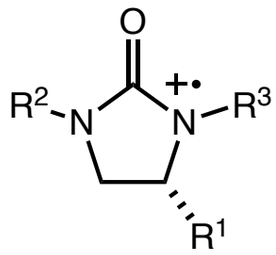
Light-Driven Deracemization

electron transfer

enantioselective proton transfer *(R) is depleted*

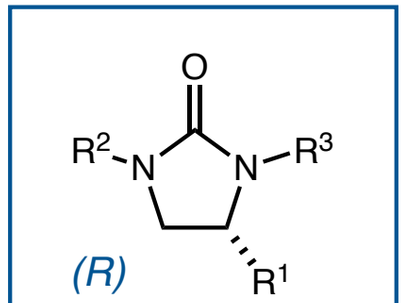
enantioselective hydrogen atom transfer *(S) is enriched*

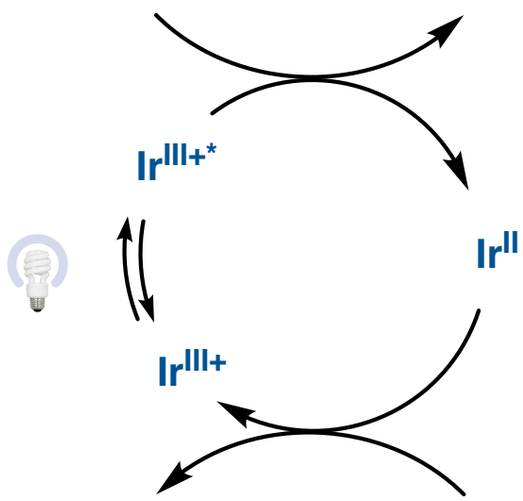


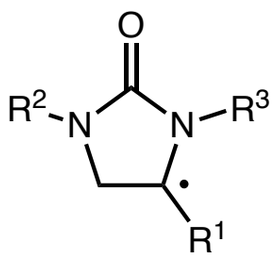


fast

chiral phosphate

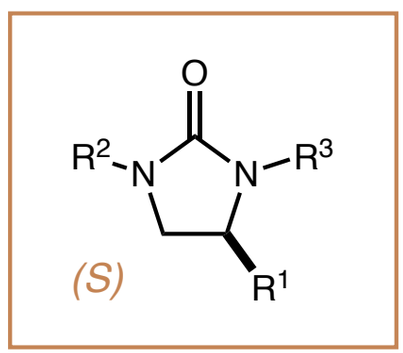


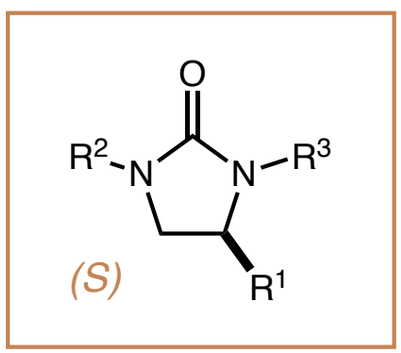


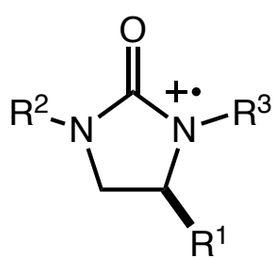


achiral

chiral peptide







slow

chiral phosphate

Summary

- A diverse set of reactivity can be achieved using organocatalytic, organometallic, or merged activation modes.
- Peptides may control selectivity in catalytic transformations using non-covalent interactions.
- Control of the secondary structure is vital in order to place reactive groups in close proximity.
- A variety of screening technologies may assist in the discovery process.

Thank you for your attention.

Questions?