Covering Uncharted Chemical Space Based on 1,2-strained Azacycloallene Cycloaddition on DNA-Encoded Library

2020. 7. 18. Literature Session
M1 Takeuchi Aoi

Contents

- **Introduction**

- **Reaction Development**

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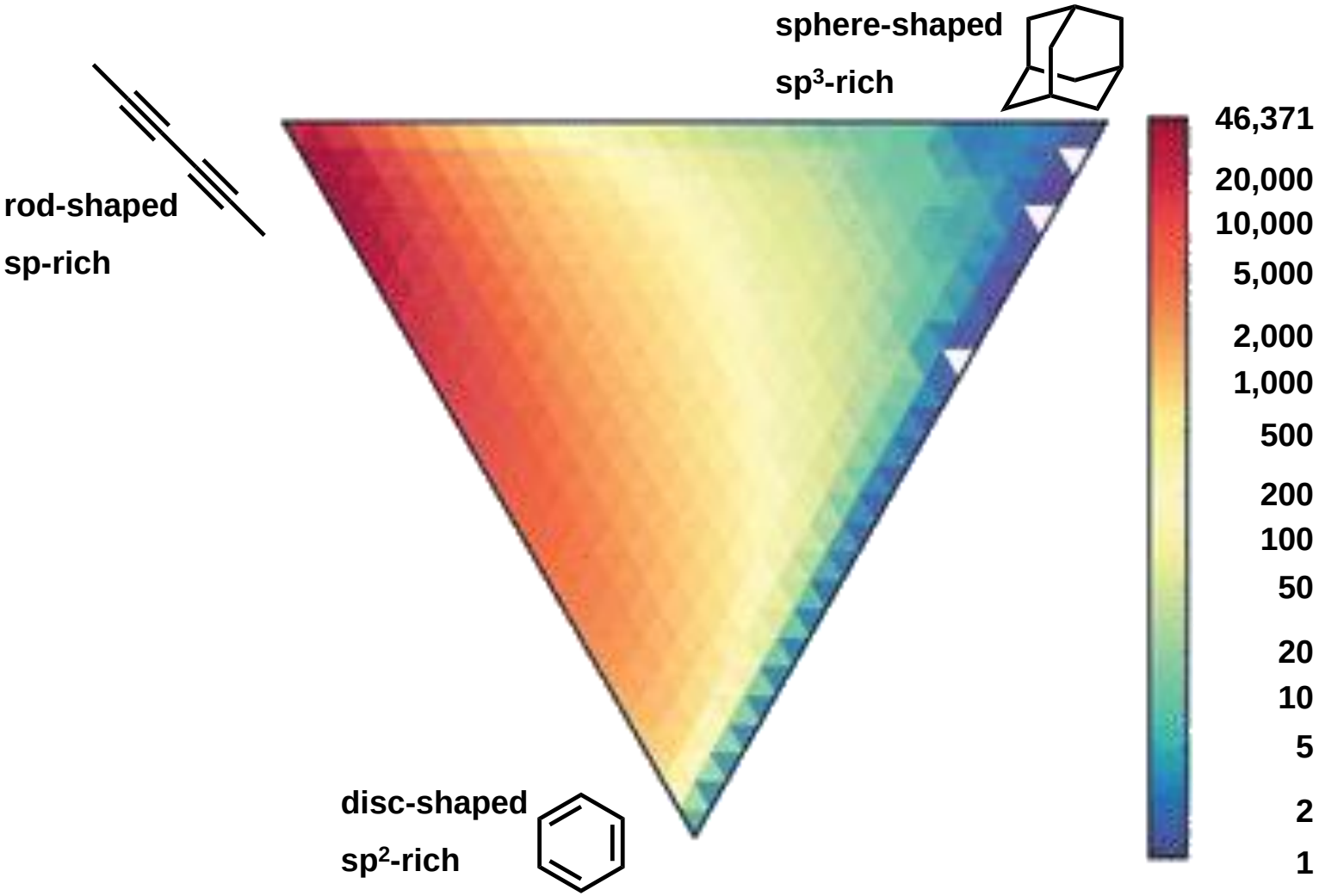
Underexplored 3D Chemical Space



principal moments of inertia (PMI) density plot of drug-like small molecules in ChEMBL[1)]

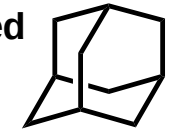
chemical space with increased three-dimensionality is less populated in medicinal chemistry

1) Meyers, J.; Carter, M.; Mok, N.; Brown, N. *Future Med. Chem.*, **2016**, *8*, 1753.

Expectations and Approaches toward 3D Chemical Space

sphere-shaped

sp^3-rich



enhanced three-dimensionality leads to

- **greater aqueous solubility**
- **poorer crystal lattice packing**
- **improved ADMET properties**

natural products[1)]

- **biologically active**
- **rich in stereogenic centers**
- **various physicochemical properties**

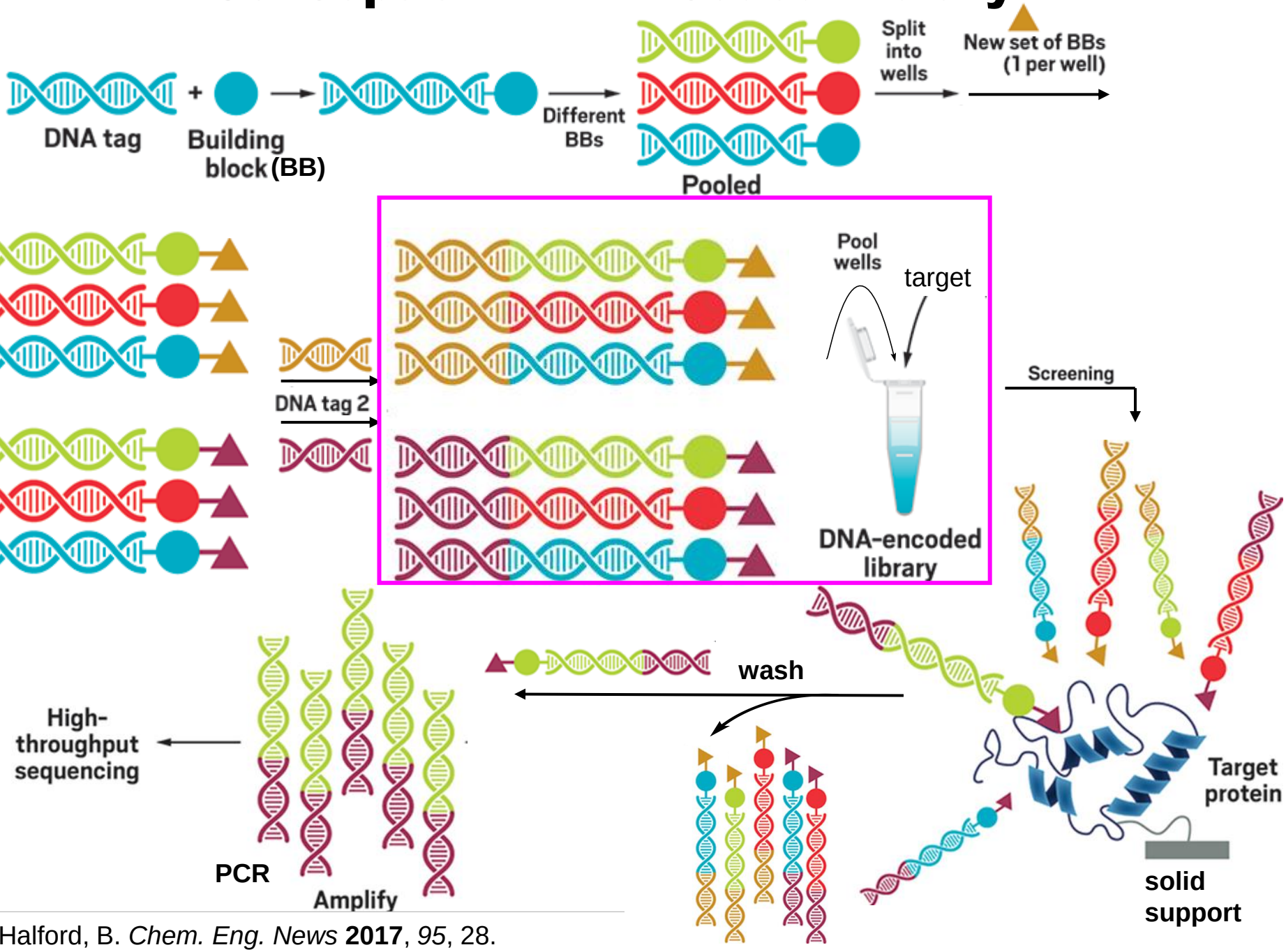
reaction development

construct sp^3-rich structures on library

e.g.
compound library
fragment library
DNA-Encoded Library (DEL)

1) Over, B., Wetzel, S., Grütter, C., Nakai, Y., Renner, S., Rauh, D., Waldmann, H. *Nat. Chem.*, **2013**, *5*, 21.

Concept of DNA-Encoded Library[1)]



1) Halford, B. *Chem. Eng. News* **2017**, *95*, 28.

Limitations of on-DNA Reactions

limitations in DEL synthesis [1)]

- **work in aqueous media**

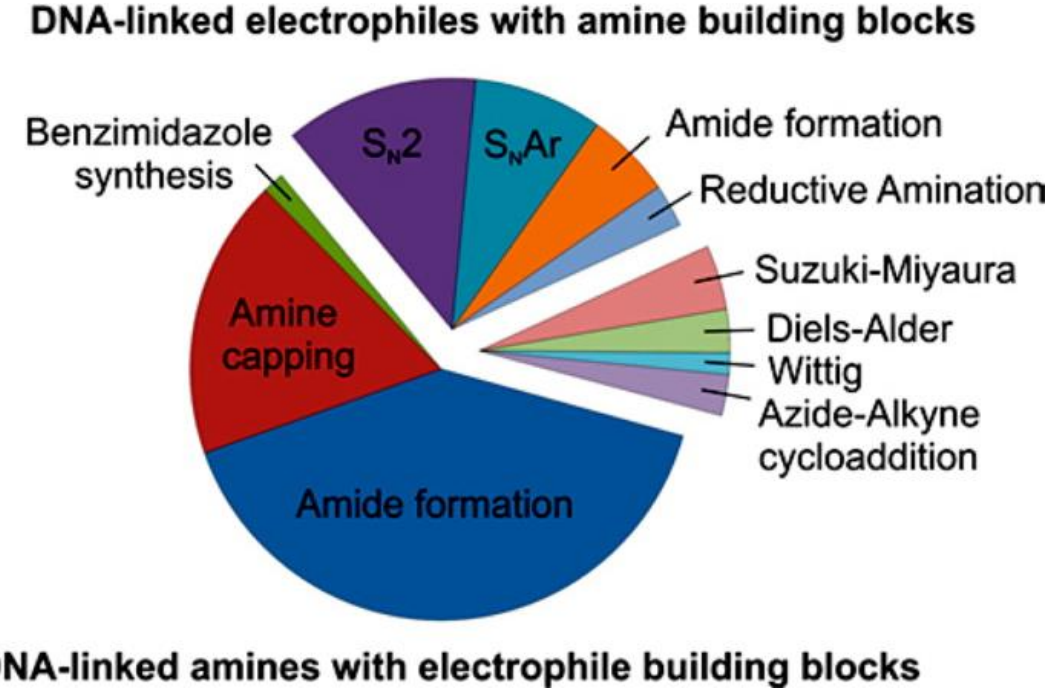
  - poor solubility of DNA in organic solvent

- **keep DNA and nucleobases intact from reagents and reaction conditions**

  - negative affect the final decoding of a library

- **low concentration of the DNA substrate (<1 mM)**
- **wide substrate scope**

reactions used for DEL[2)]



synthetic limitations make it challenging to construct sp^3-rich scaffolds on DEL

1) Kölmel, K.; Loach, R.; Knauber, T.; Flanagan, M. *ChemMedChem*, **2018**,*13*, 2159.
2) Franzini, R. M.; Randolph, C. *J. Med. Chem.* **2016**, *59*, 6629.

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Author's Profile

Neil. K. Garg

- **B.S.: Chemistry, New York University (2000)**
  advised by Prof. Marc Walters
- **Ph.D.: Organic Chemistry, California Institute of Technology (2005)**
  advised by Prof. Brian M. Stoltz
- **Postdoctoral fellow, University of California, Irvine (2005-2007)**
  advised by Prof. Larry Overman
- **Assistant Professor, University of California, Los Angeles (2007-2012)**
- **Associate Professor, University of California, Los Angeles (2012-2013)**
- **Professor, University of California, Los Angeles (2013-)**

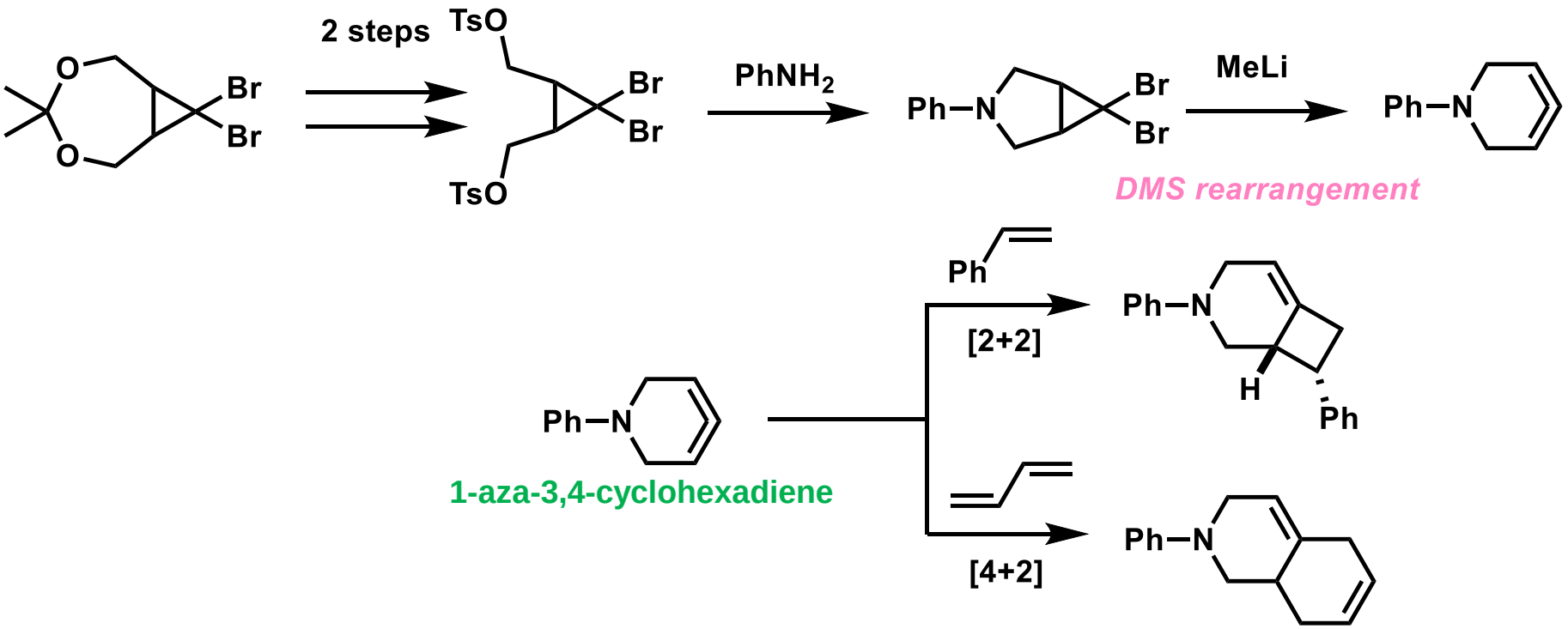
Focus Areas

- ☐ **natural product synthesis**
- ☐ **reaction discovery**

1,2-Strained Azacyclic Allenes

1-aza-3,4-cyclohexadiene

- underwent Diels–Alder cycloadditions, and [2+2] cycloadditions[1)]



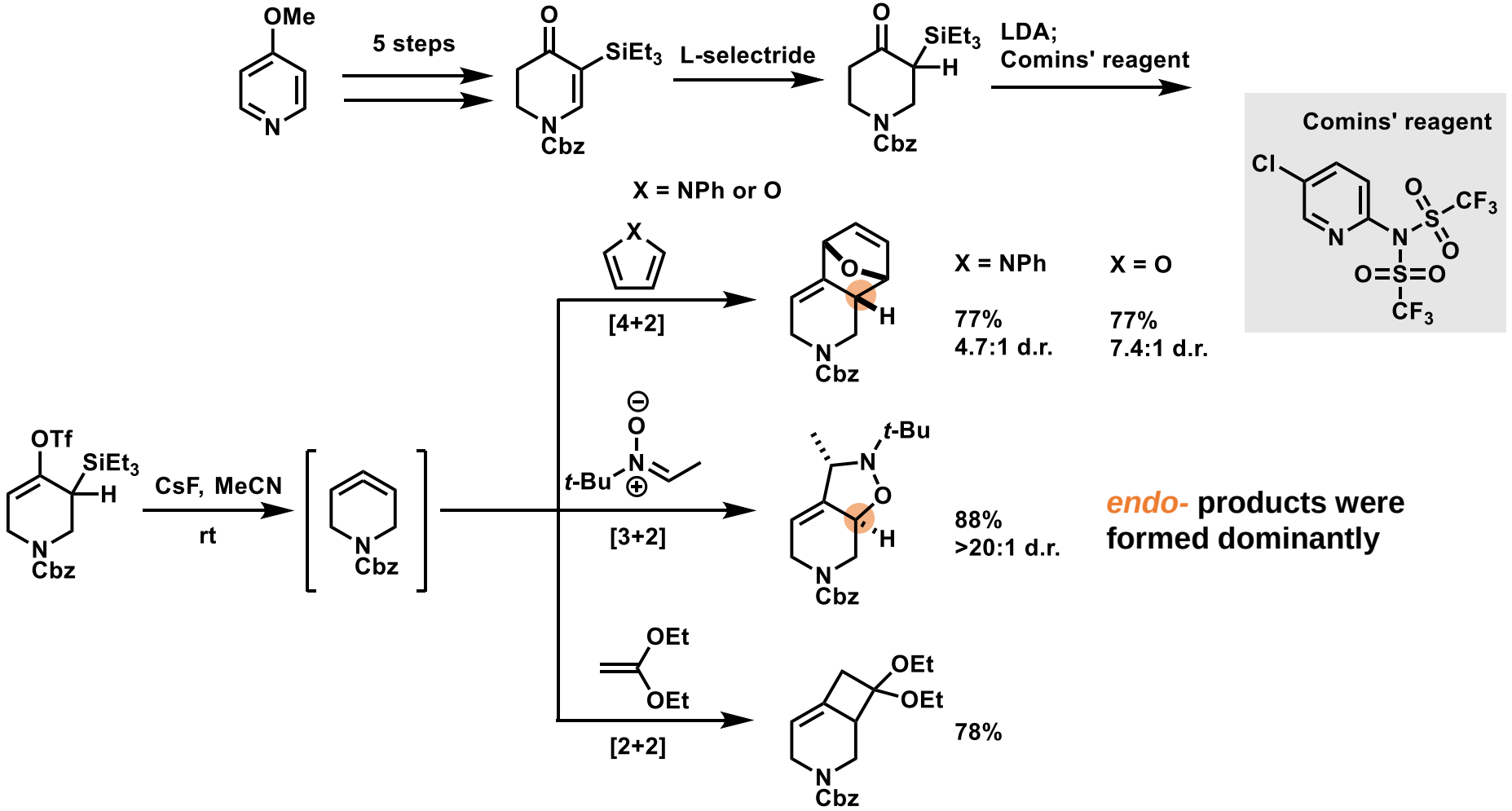
synthesized through Doering–Moore–Skattebøl (DMS) rearrangement

- **require harsh, strongly basic reaction conditions for generation (i.e. alkyllithium)**
- **low yield**

mild generation of azacyclic allenes would utilize themselves into DEL applications

1) Christl, M.: Braun, M.: Wolz, E.: Wagner, W. *Chem. Ber.* **1994**, *127*, 1137.

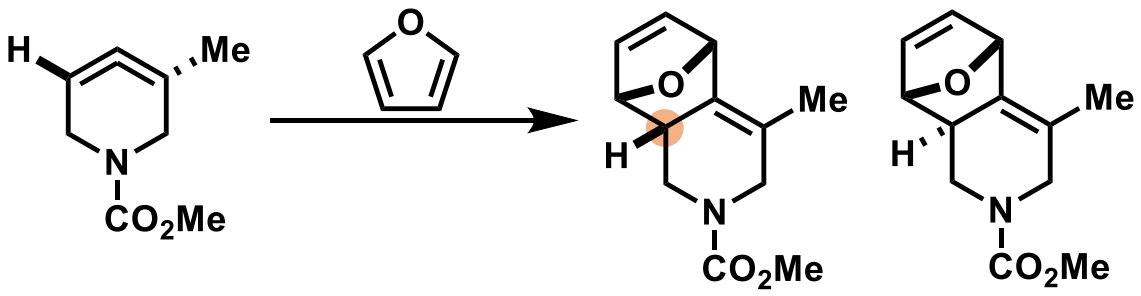
Mild Generation and Cycloaddition of 1,2-strained Azacyclic Allenes



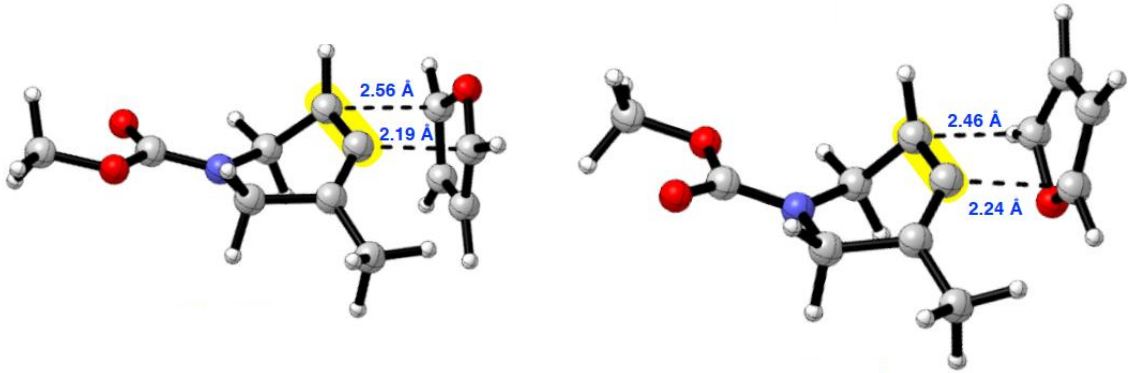
***endo-* products were formed dominantly**

Computational Support of Diastereoselectivity

computational insight (level of theory: ωB97XD/6-311+G(d,p)/SMD(MeCN)//ωB97XD/6-31G(d))



endo **product** ***exo*** **product**

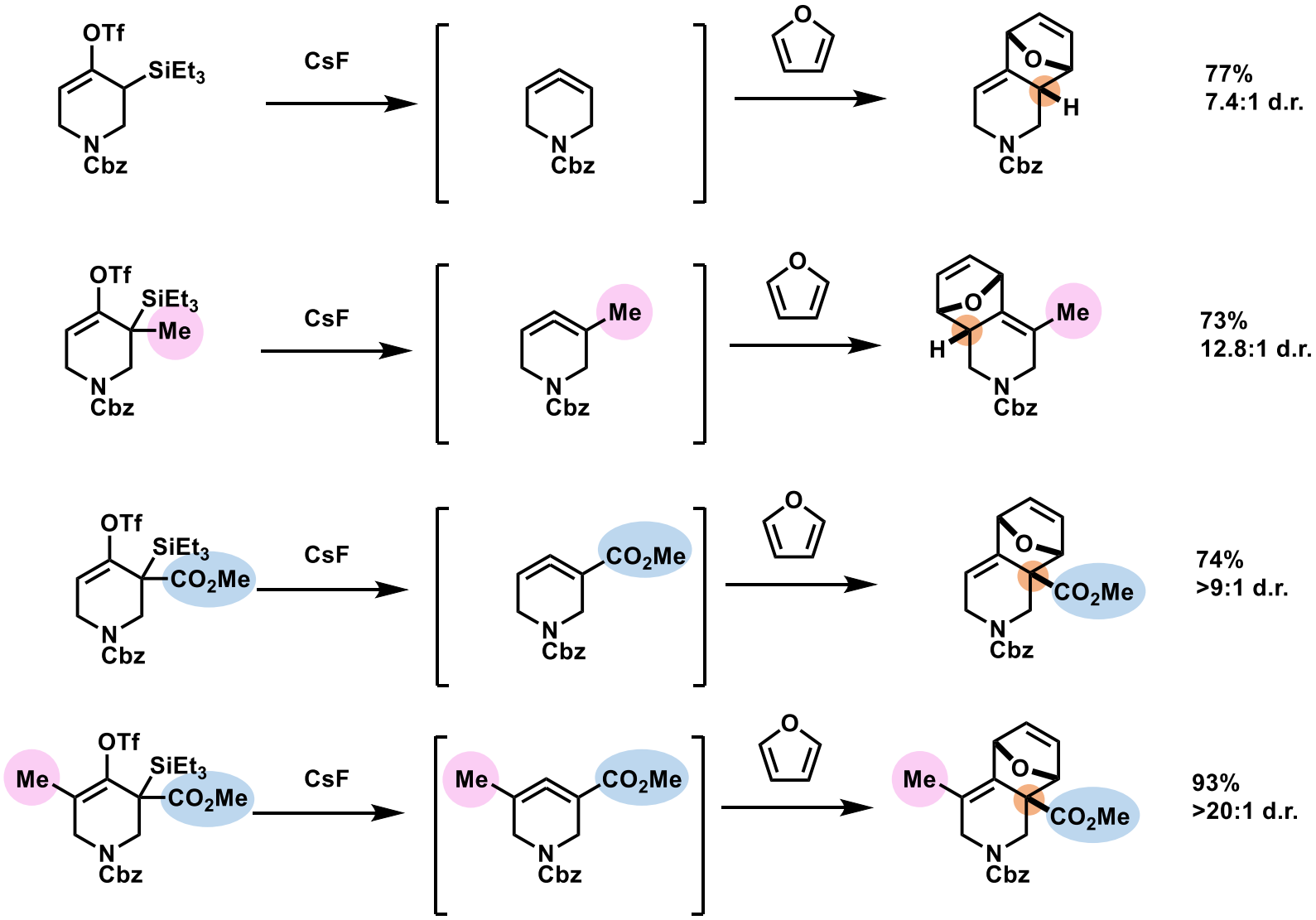


endo **product**
ΔG‡ = 19.1 kcal/mol

exo **product**
ΔG‡ = 21.5 kcal/mol

diastereoselectivity is kinetically controlled

Regioselectivity Controlled by Substituents



cycloaddition occurred on the olefin which is
- distal to electron-donating methyl group
- proximal to electron-withdrawing ester group

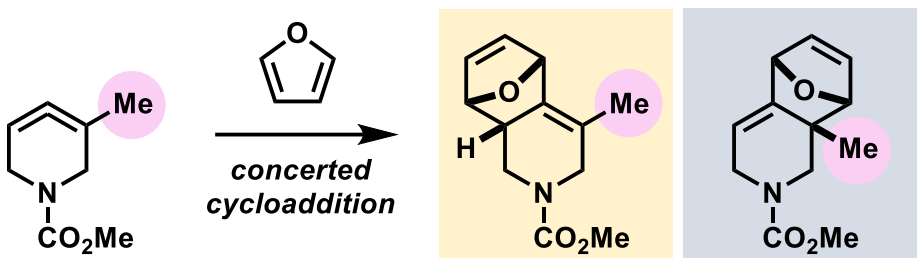
Computational Understanding of Regioselectivity

distortion/interaction activation strain analysis[1]

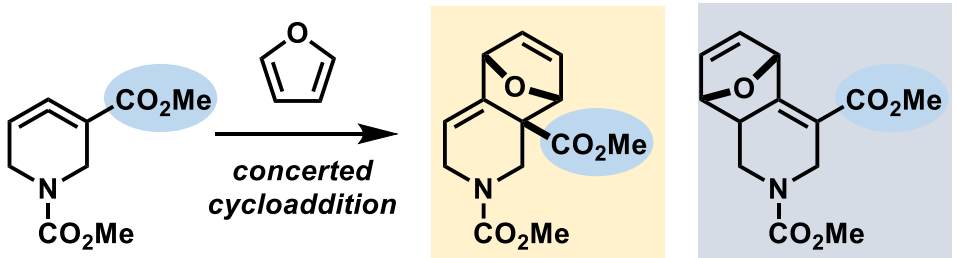
For bimolecular reactions,

$$\Delta E = \Delta E_{dist} + \Delta E_{int}$$

ΔE : activation energy
ΔE_{dist} : energetic cost to distort the reactants into geometries they have in transition states
ΔE_{int} : energetic benefit from orbital interaction between the two molecules



(kcal mol^{-1})	difference	*observed*	*not observed*
ΔE_{dist}	-0.3	10.9	11.2
ΔE_{int}	-1.3	-6.3	-5.0
ΔE	-1.6	4.6	6.2



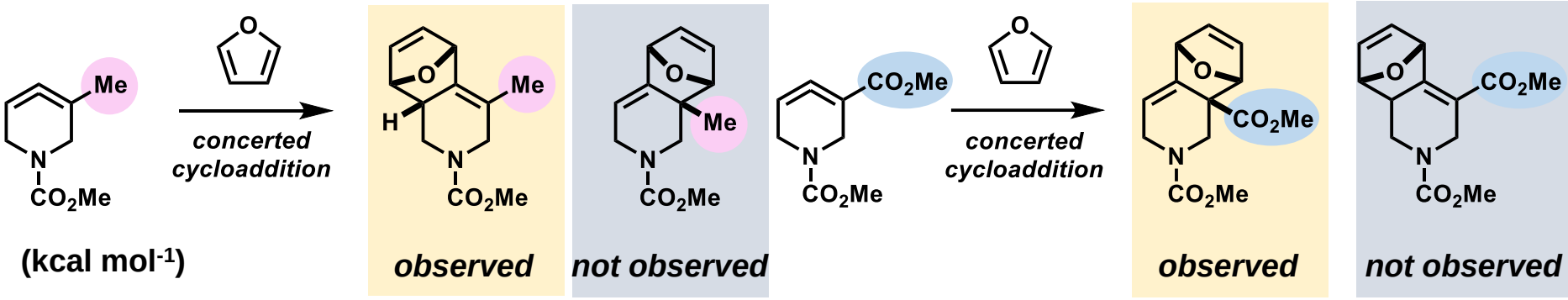
	difference	*observed*	*not observed*
ΔE_{dist}	0.7	8.2	7.5
ΔE_{int}	-5.4	-9.8	-4.4
ΔE	-4.7	-1.6	3.1

level of theory: ωB97XD/6-311+G(d,p)/SMD(MeCN)

ΔE_{int} is the major contributor to the regioselectivity

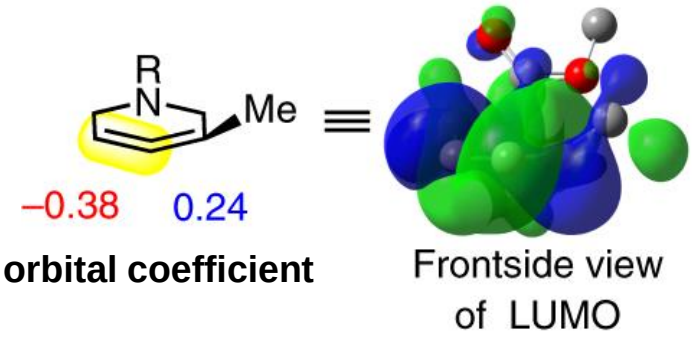
1) Bickelhaupt, F. M.;Houk, K. N. *Angew. Chem. Int. Ed.* **2017**, *56*, 10070.

Computational Understanding of Regioselectivity

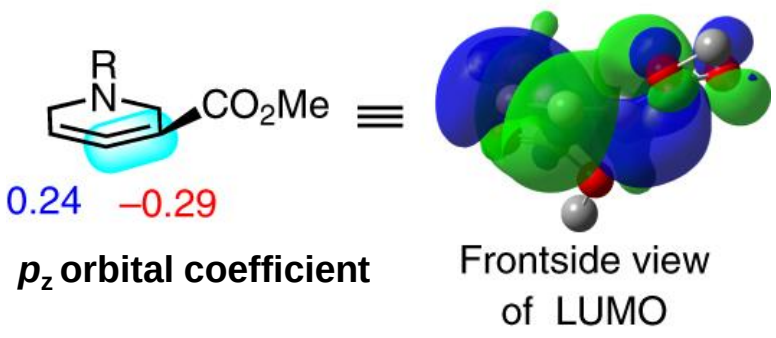


(kcal mol^{-1})

Hartree-Fock molecular orbital calculation



p_z orbital coefficient



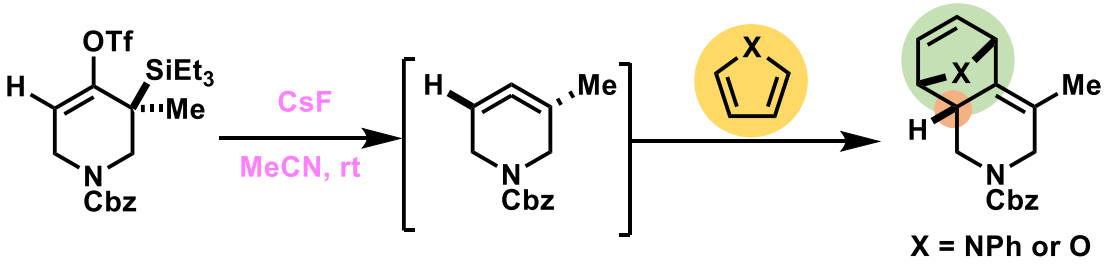
p_z orbital coefficient

R =CO_2Me, level of theory: HF/6-31G(d)

cycloaddition occurred on the olefin with a larger orbital coefficient

the change in LUMO coefficient by olefin substituents switched the regioselectivity of cycloaddition

Summary of the Chapter



1,2-strained azacyclic allene

mild condition
(alkyllithium-free, room temperature)

[4+2], [3+2], [2+2] cycloaddition

diastereoselective
regioselective

DNA-compatible reaction

construction of various sp³-rich structure

This reaction would be applied to the structure diversification on DNA-encoded library

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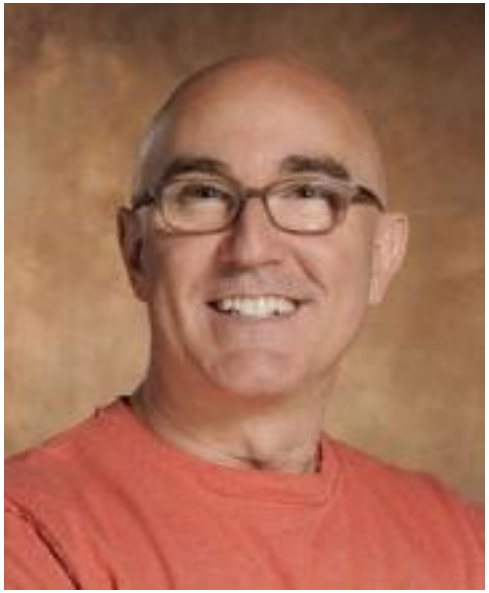


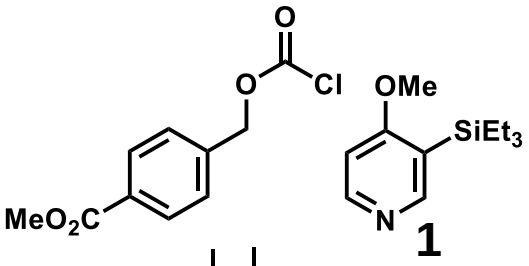
Stuart L. Schreiber

- **B.A.: Chemistry, the University of Virginia (1977)**
  advised by Prof. R. J. Sundberg
- **Ph.D.: Chemistry, Harvard University**
  advised by Prof. Robert B. Woodward (-1979)
  Prof. Yoshito Kishi (-1981)
- **Assistant Professor, Yale University (1981)**
- **Associate Professor, Yale University (1984)**
- **Professor, Yale University (1986)**
- **Professor, Harvard University (1988)**

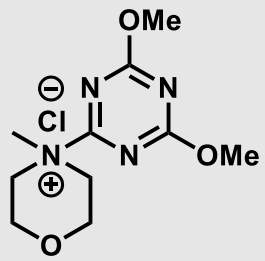
Focus Areas – Science of therapeutics

- ☐ **diversity-oriented synthesis (DOS)**
- ☐ **cancer therapeutics**
- ☐ **microbial therapeutics**
- ☐ **treatment of genetic prion disease and Alzheimer's disease**

DNA-Conjugation with Allene Precursor

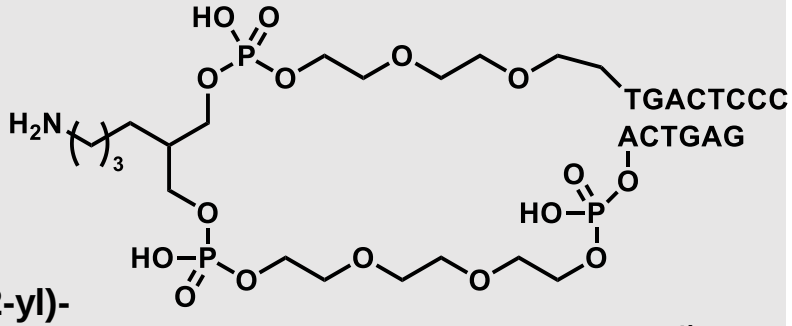


3 steps

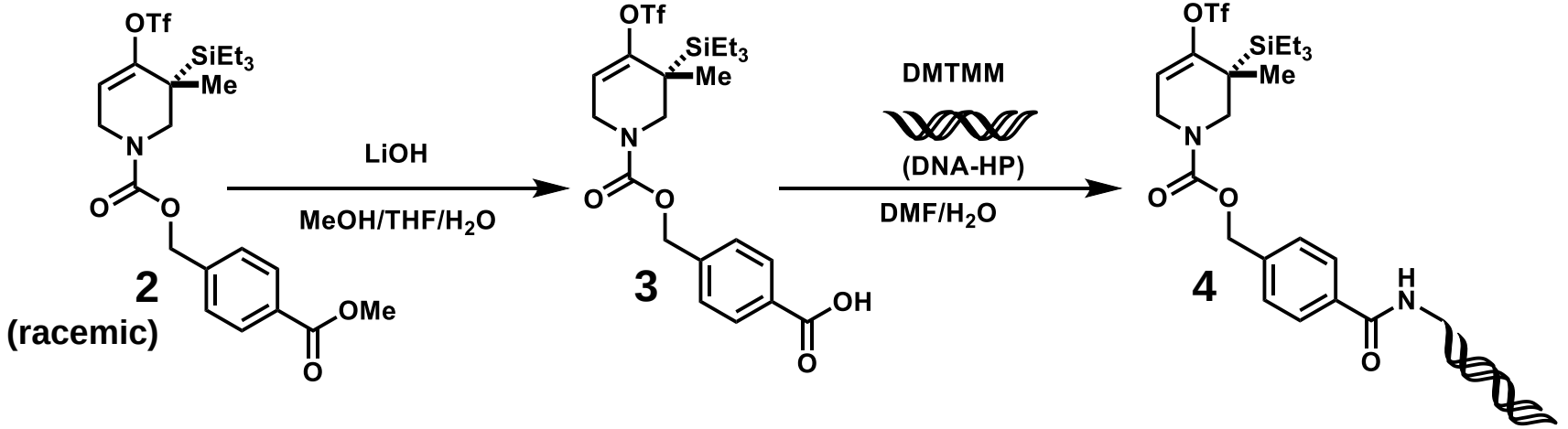


4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride (DMTMM)

water-soluble condensing agent

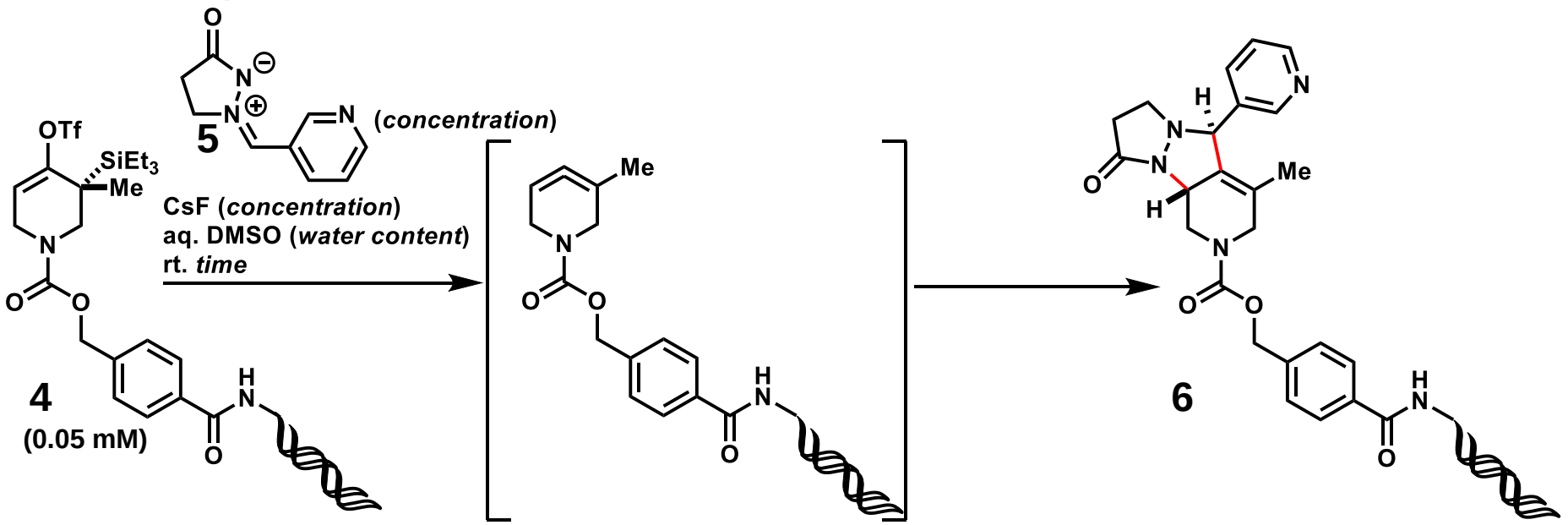


DNA headpiece (DNA-HP) [1)]



1) Clark, M. A; Acharya, R. A; Arico-Muendel, C. C; Belyanskaya, S. L; Benjamin, D. R; Carlson, N. R; Centrella, P. A; Chiu, C. H; Creaser, S. P; Cuozzo, J. W; Davie, C. P; Ding, Y.; Franklin, G J.; Franzen, K. D; Gefter, M. L; Hale, S. P; Hansen, N. J V; Israel, D. I; Jiang, J.; Kavarana, M. J; Kelley, M. S; Kollmann, C. S; Li, F.; Lind, K.; Mataruse, S.; Medeiros, P. F; Messer, J. A; Myers, P.; O'Keefe, H.; Oliff, M. C; Rise, C. E; Satz, A. L; Skinner, S. R; Svendsen, J. L; Tang, L.; van Vloten, K.; Wagner, R. W; Yao, G.; Zhao, B.; Morgan, B. *Nat. Chem. Biol.* **2009**, *5*, 647.

Investigation of on-DNA Strained Allene Generation



#	5 [mM]	CsF [mM]	%DMSO	t [h]	4 [%]	6 [%]
1	15	50	25	24	100	0
2	15	50	50	24	97	3
3	15	50	75	24	0	100
4	100	375	75	1	28	72
5	100	750	75	1	1	99
6	15	~6	90	1	0	100
7	15	~3	90	1	27	73

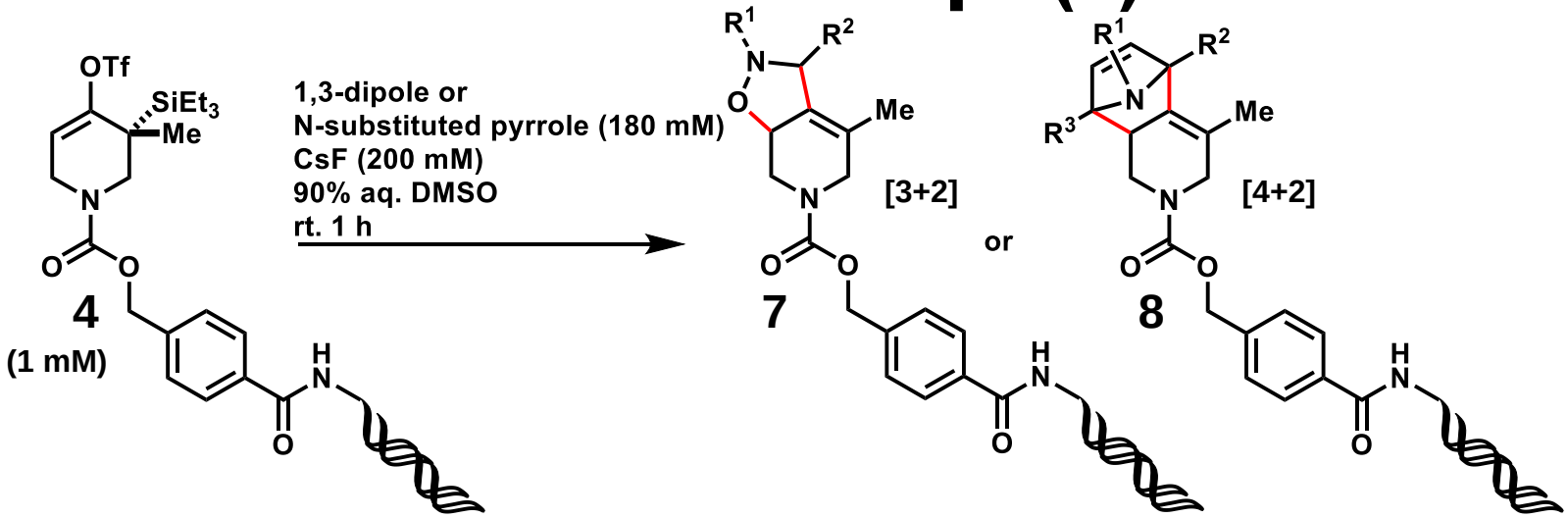
the conversion rate was calculated from AUC of UV_{260} absorption by UPLC-MS

The rate of conversion were

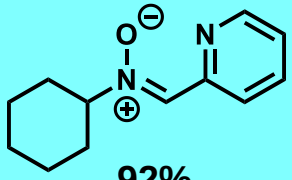
- decreased by the water content critically
- increased by higher fluoride concentrations

(higher water content slowed down the reaction due to fluoride ion hydration)

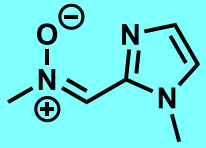
Substrate Scope (1)



1,3-dipole


92%


>95%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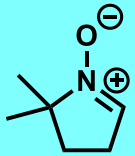
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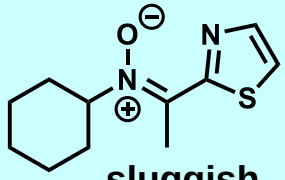
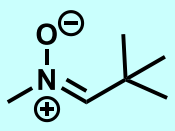

sluggish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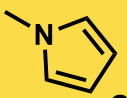
N-substituted pyrrole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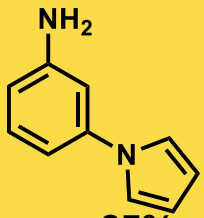
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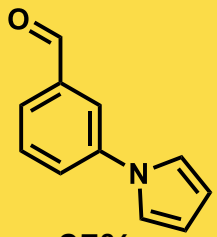
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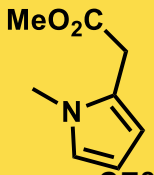
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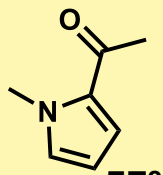
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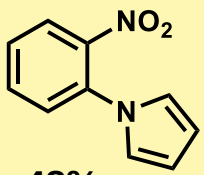
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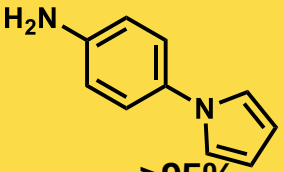
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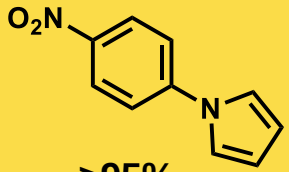
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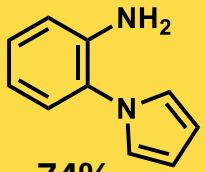
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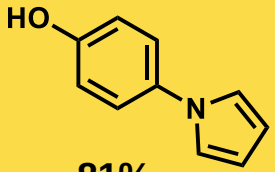
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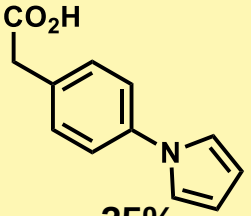
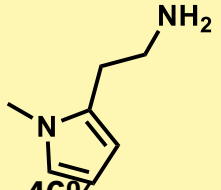
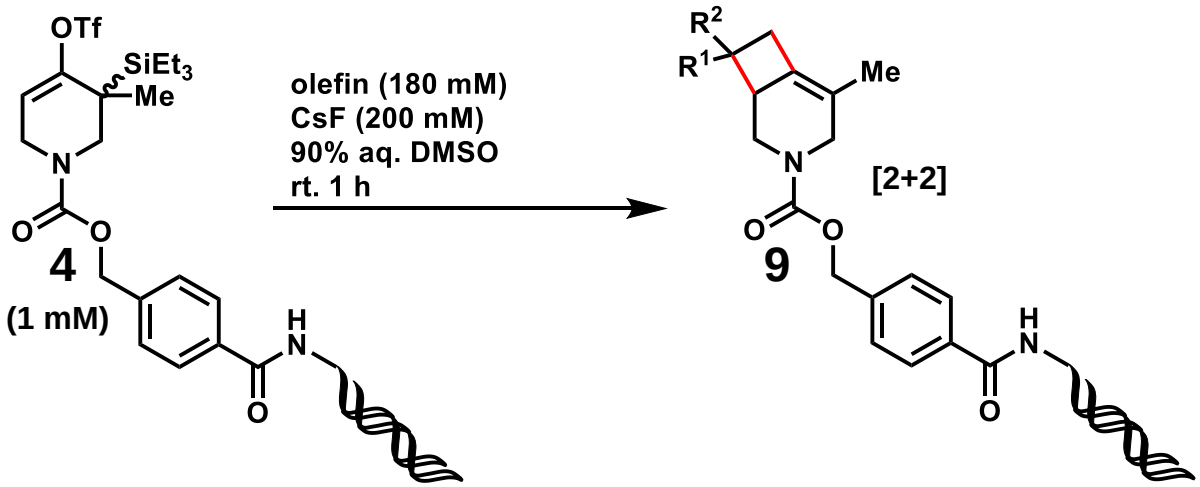

25%

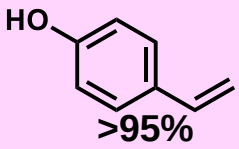

46%

the conversion rate (%AUC) was calculated from UV_{260} peak area by UPLC-MS

Substrate Scope (2)



olefin



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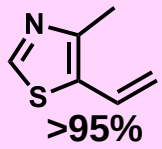

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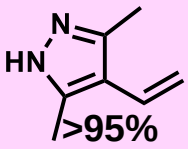

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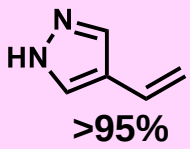

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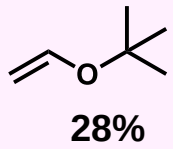

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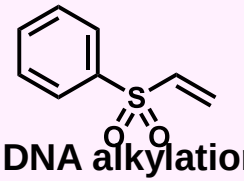
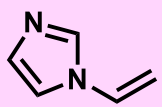


DNA alkylation



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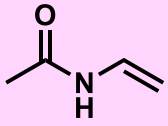

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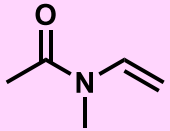

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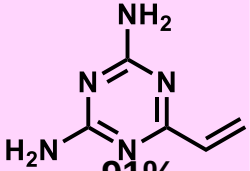

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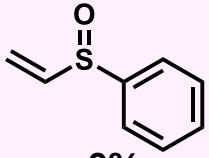

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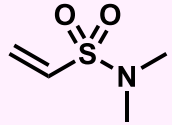
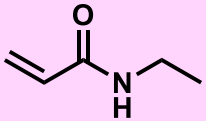


DNA alkylation



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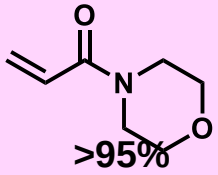

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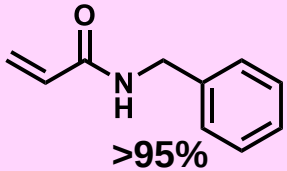

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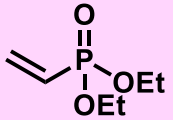

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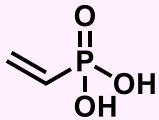

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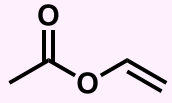

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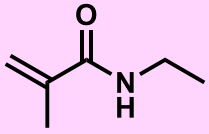

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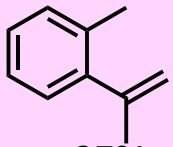
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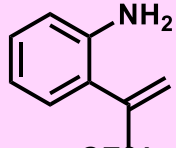

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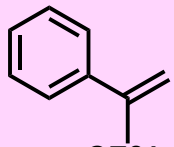
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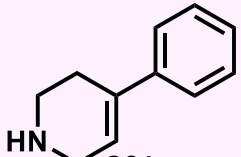

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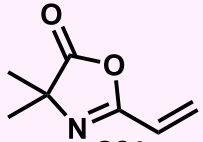
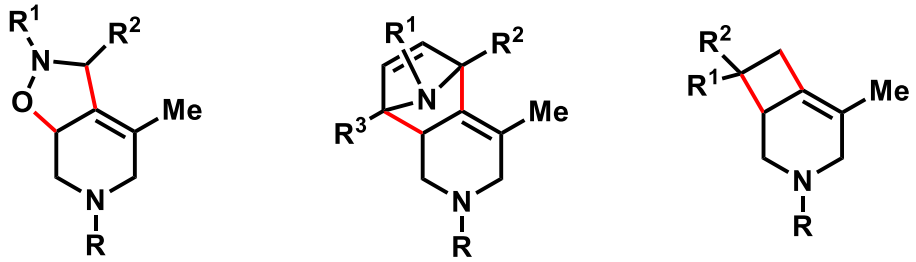


0%

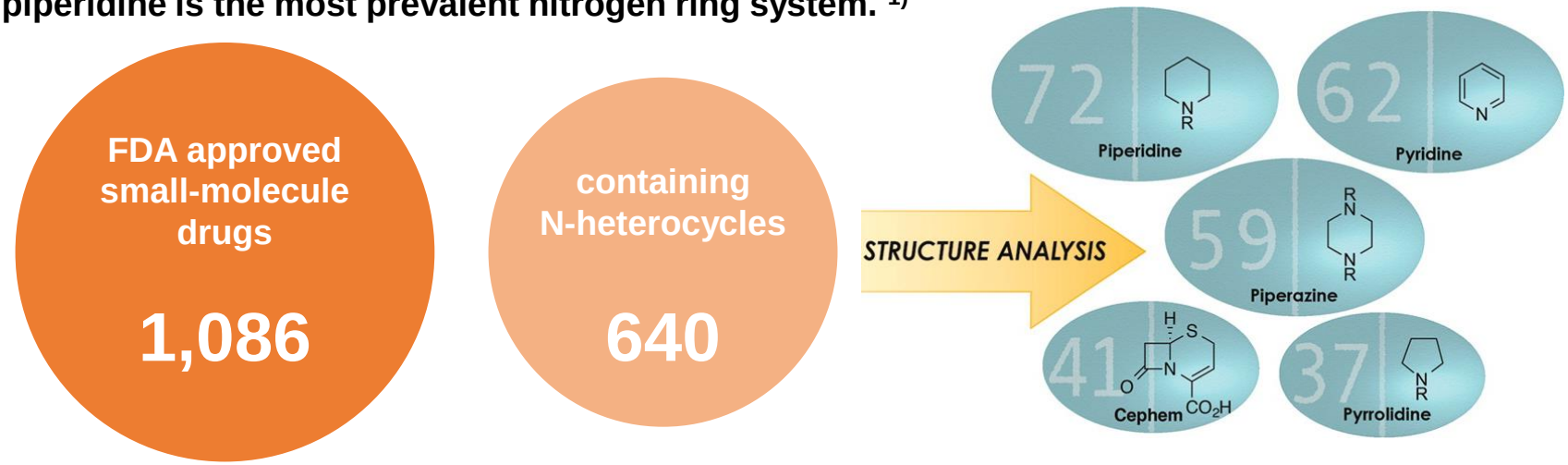
the conversion rate (%AUC) was calculated from UV_{260} peak area by UPLC-MS

Utility of Constructed Structures



substructure search of cores 7-9 in the ChEMBL database returned zero hits
→ uncharted chemical space

59% of small-molecule drugs contain a nitrogen heterocycle
piperidine is the most prevalent nitrogen ring system. [1)]

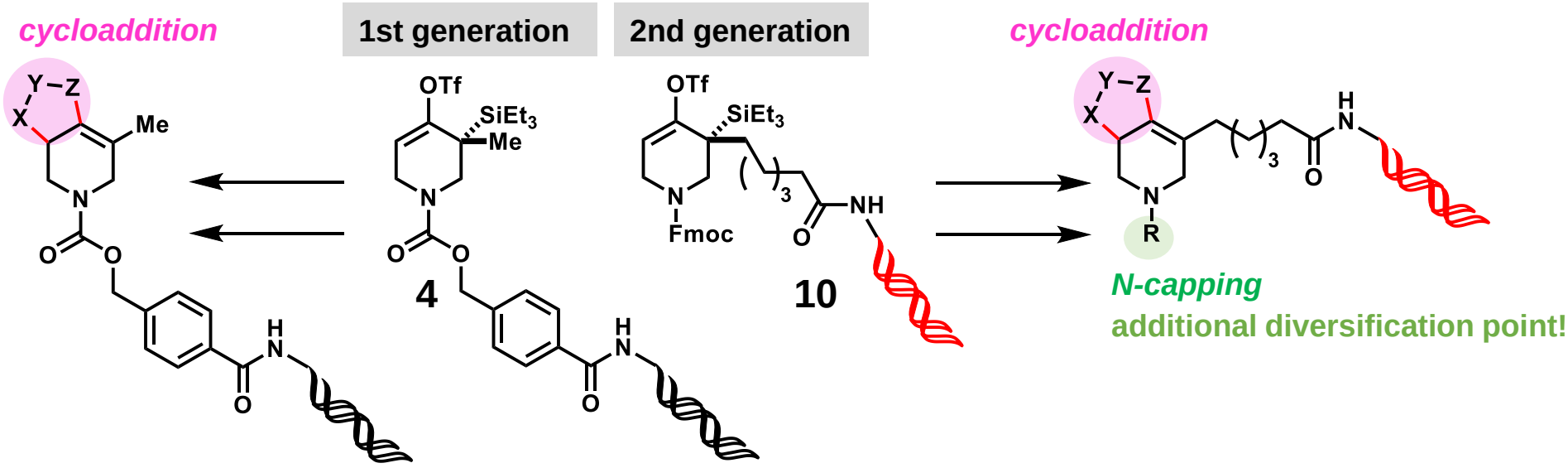


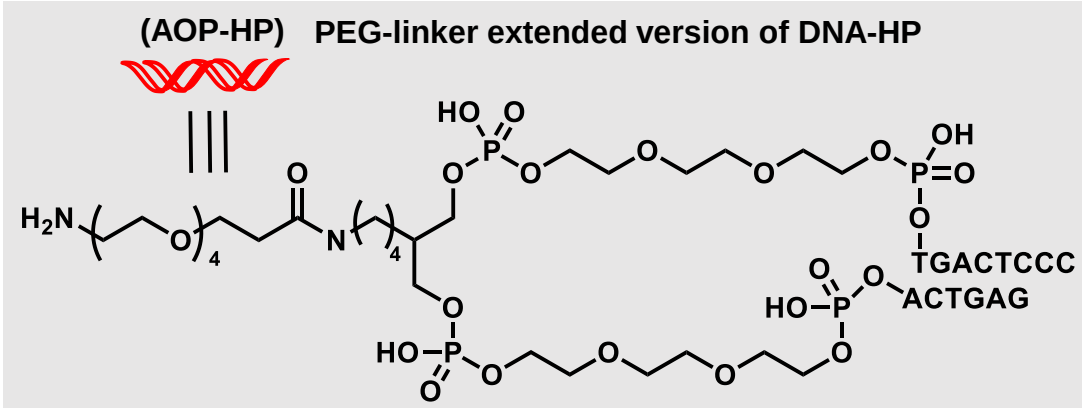
constructed, uncharted chemical space is expected to have medicinal importance

1) Vitaku, E.; Smith, D.; Njardarson, J. *J. Med. Chem.* **2014**, *57*, 10257.

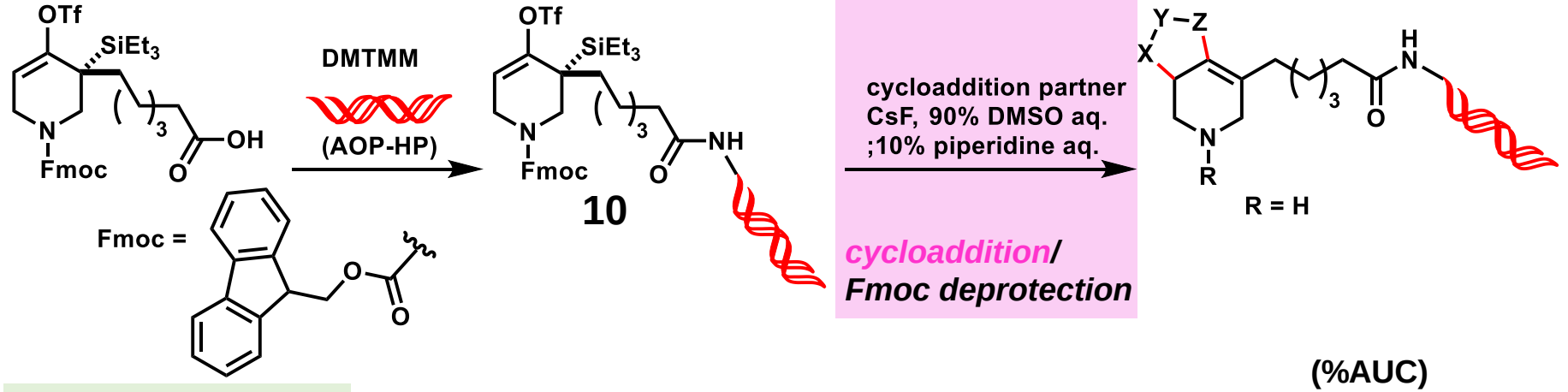
Substrate Modification toward Further Diversification

- for extension of DNA-encoded library space, it is important to make another diversification point than strained allene cycloaddition
- the allene precursor was modified to exploit the piperidine nitrogen for diversification





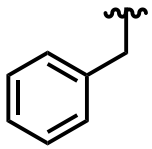
Substrate Modification toward Further Diversification



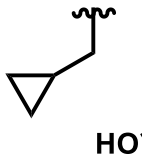
(%AUC)

aldehyde
reductive amination

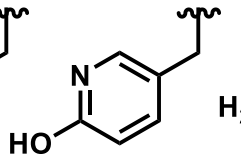
R =



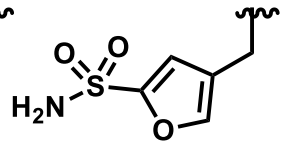
20-98%



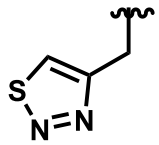
48-90%



27-99%



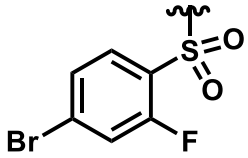
25-98%



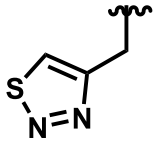
79-100%

sulfonyl chloride
sulfonylation

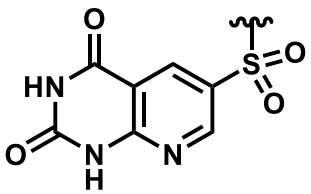
R =



50-94%



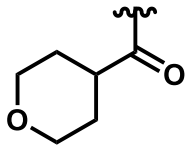
32-94%



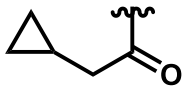
84-100%

NHS-ester
acylation

R =



43-92%

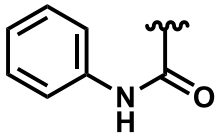


52-100%

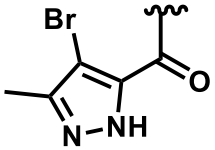
- lower conversion rate
- generation of unknown by-products

isocyanate
carbamoylation

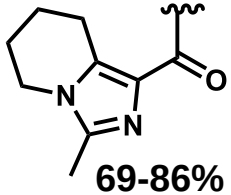
R =



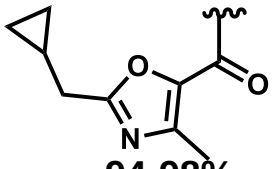
61-92%



93-94%



69-86%

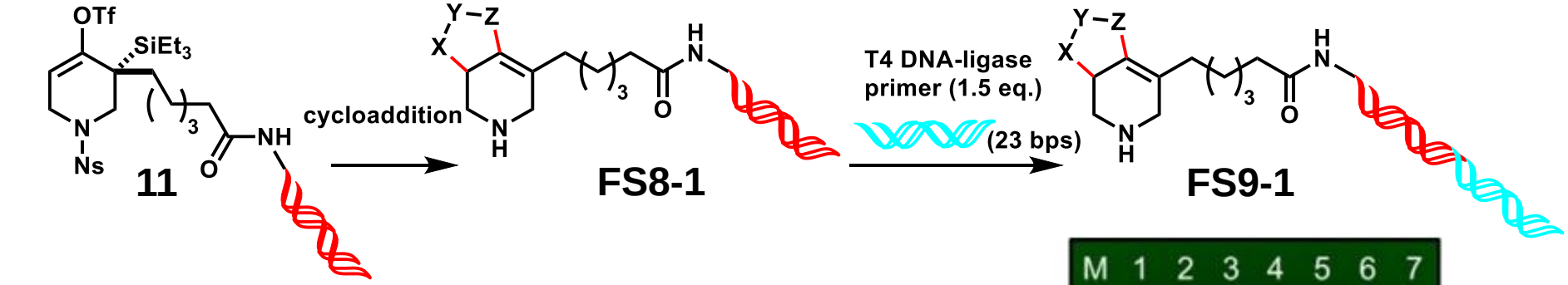


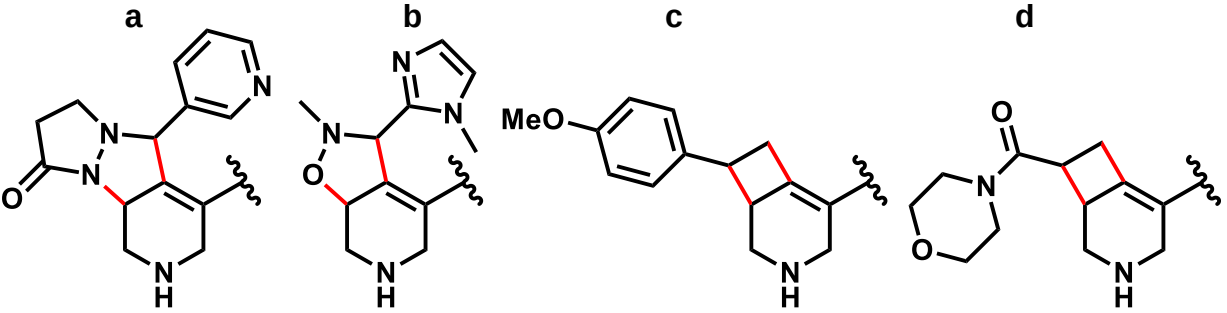
94-98%

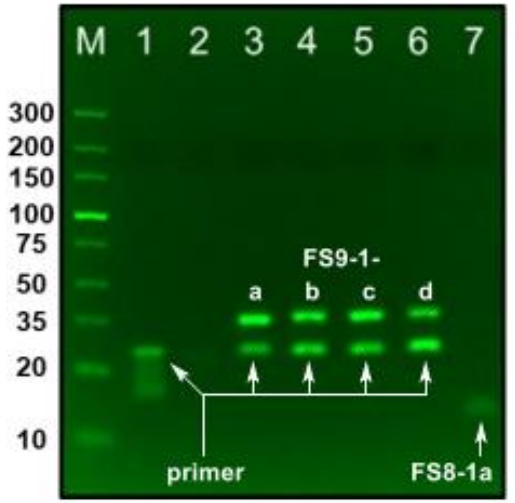
N-capping

Proof of DNA-Compatibility of Cycloaddition

- DNA ligation reactions of four piperidine-DNA conjugates

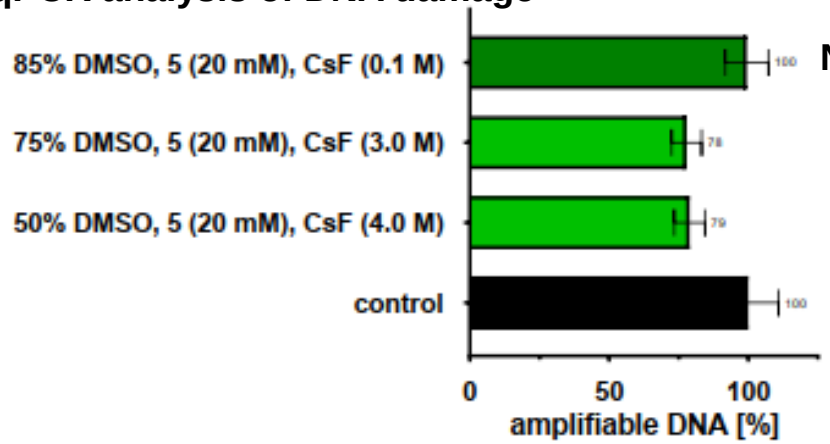






ligation was confirmed by gel electrophoretic analysis

- qPCR analysis of DNA damage

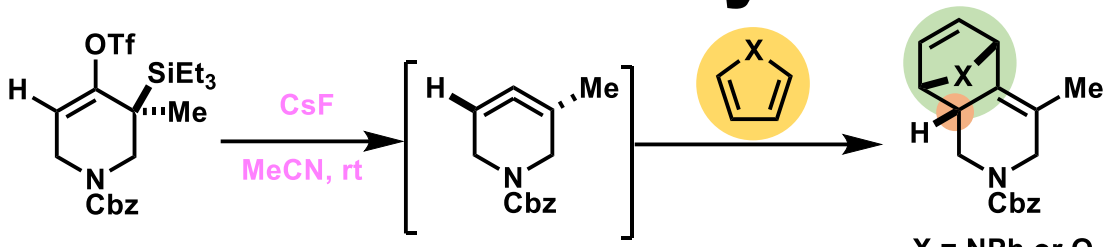


No DNA degradation

DNA-compatibility was confirmed by DNA ligation and qPCR analysis

Summary

off-DNA



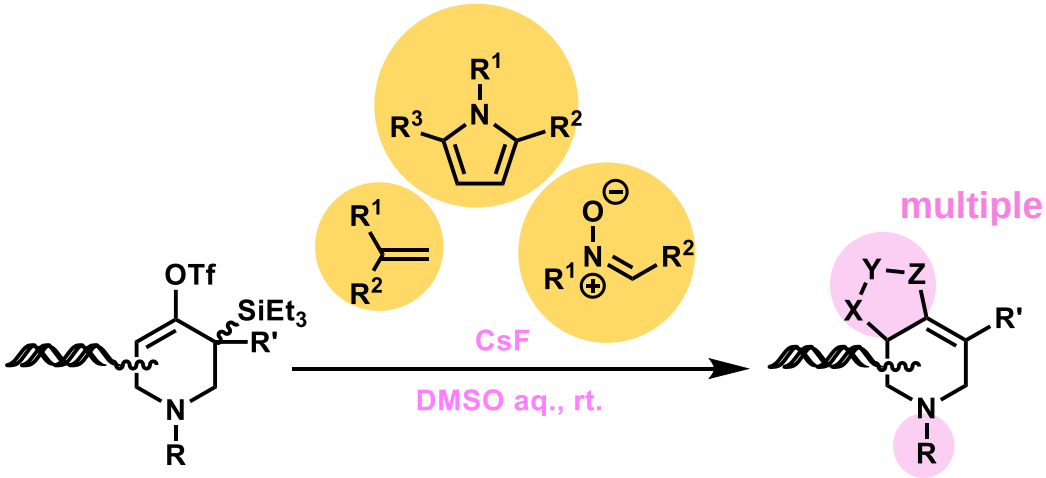
1,2-strained azacyclic allene

mild condition
(alkyllithium-free, room temperature)

[4+2], [3+2], [2+2] cycloaddition

diastereoselective
regioselective

on-DNA



multiple diversification point

single precursor → *diverse molecular architecture*
uncharted chemical space