Trans-cyclooctene and Its Application

Reporter: Peng Yan

Supervisor: Ping Lu

Fudan University

2019-11-1

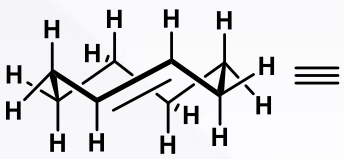
CONTENTS

Part 1

Background

02 The Reaction of TCO

crown confomation



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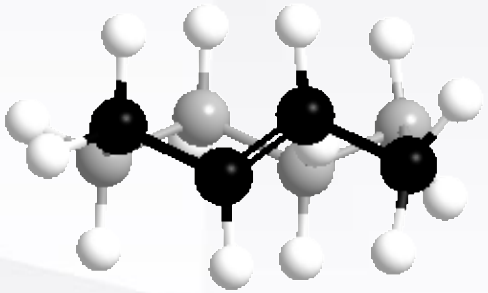
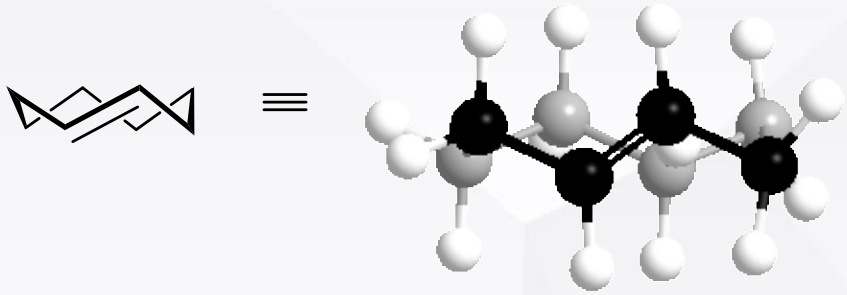


M. T. Taylor, M. L. Blackman, O. Dmitrenko, J. M. Fox, *J. Am. Chem. Soc*., **2011**, *133*, 9646.

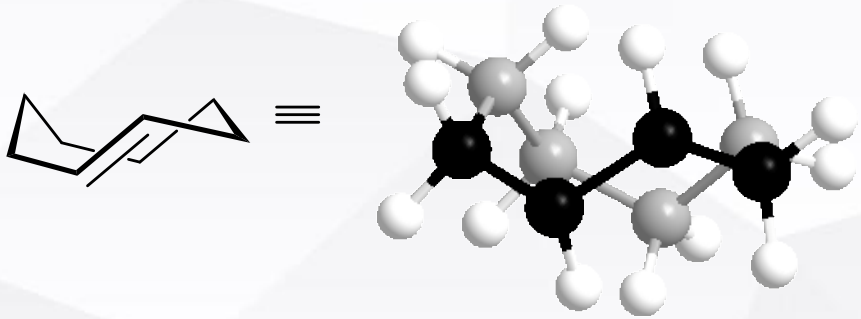
02 The Reaction of TCO

crown confomation



0.0 kcal/mol

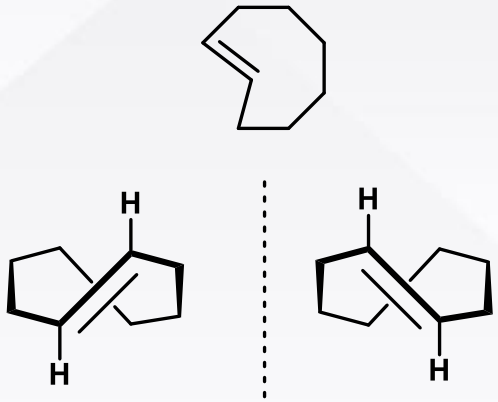
half chair conformation



5.6 kcal/mol

M. T. Taylor, M. L. Blackman, O. Dmitrenko, J. M. Fox, *J. Am. Chem. Soc.*, **2011**, *133*, 9646.

01 Optically Active TCO



pR *pS*

Barrier to racemization
= 35.6 kcal/mol

$K_2PtCl_4 + C_2H_4 \rightarrow K[PtCl_3(C_2H_4)] + KCl$

$K[PtCl_3(C_2H_4)] + Am^* \rightarrow [PtCl_2(C_2H_4)Am^*] + KCl$

($Am^* = (+)\text{-}C_6H_5CH(CH_3)NH_2$)

$[PtCl_2(C_2H_4)Am^*] + trans\text{-}C_8H_{14} \rightarrow [PtCl_2(C_8H_{14})Am^*] + C_2H_4$

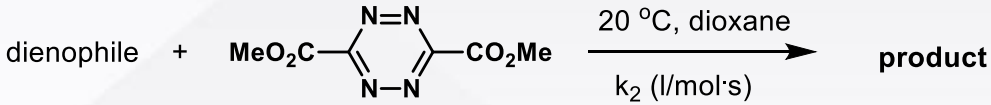
trans-dichloro-[(-)-*trans*-cyclooctene]-[(+)-α-methylbenzylamine]-platinum(II)

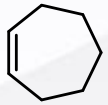
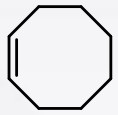
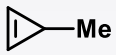
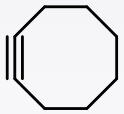
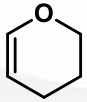
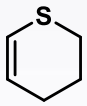
trans-dichloro-[(+)-*trans*-cyclooctene]-[(+)-α-methylbenzylamine]-platinum(II)

$[PtCl_2(C_8H_{14})Am^*] + 4KCN \rightarrow K_2Pt(CN)_4 + 2KCl + Am^* + trans\text{-}C_8H_{14}$

W. G. R. Funke, F. N. Jones, A. C. Cope, *J. Am. Chem. Soc.*, **1966**, *88*, 4693

02 The Reaction of TCO



site: $10^5 \cdot k_2$ (l/mol·s)					
					
44800000	329000	23500	86.6	8370	cis: 3380 trans: 1270000000
					
54900000	4.86	104000			2970000
					
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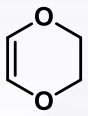
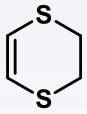
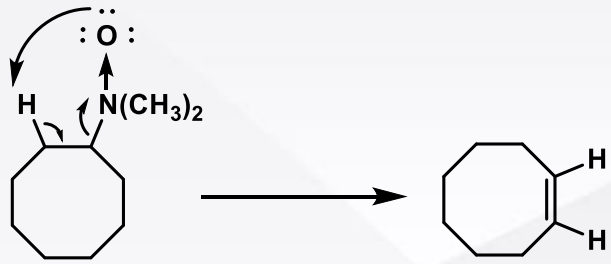
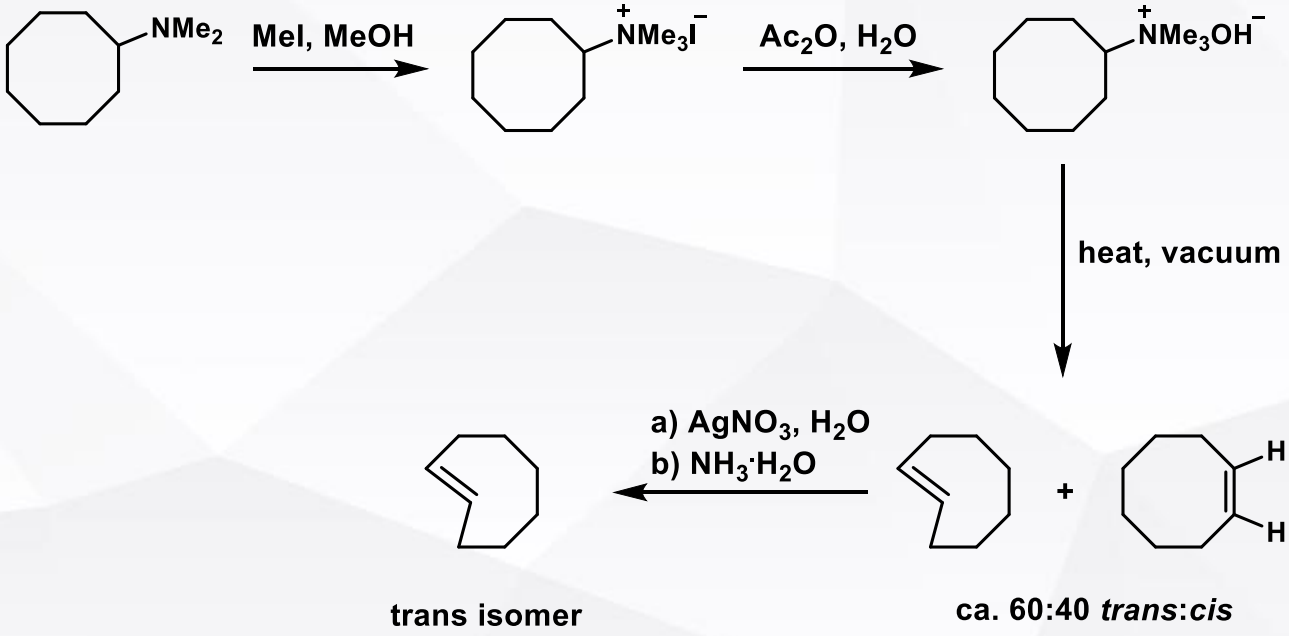
					
35.5	13200	67.7	3.35 (40 °C)		192000

F. Thalhammer, U. Wallfahrer, J. Sauer, *Tetrahedron Lett.*, **1990**, *31*, 6851.

Cope Elimination:



cis



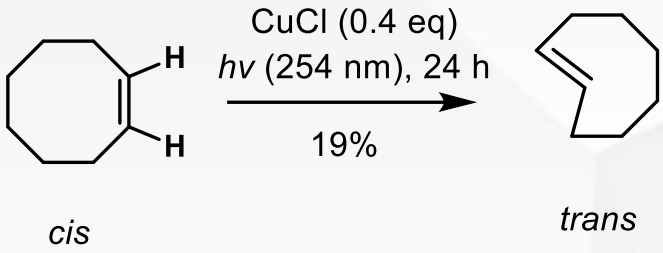
trans isomer

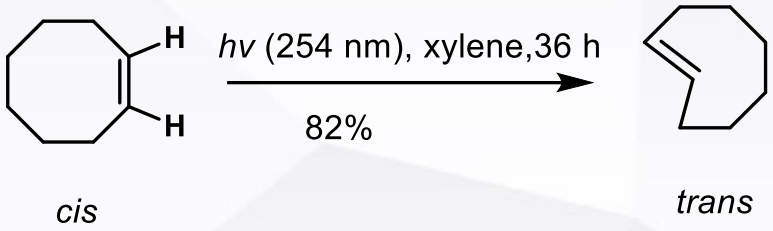
ca. 60:40 *trans*:*cis*

K. Ziegler, H.Wilms, *Ann*., **1950**, *1*, 567.*; S. W. Fenton, C. F. Spencer,* A. C. Cope, *J. Am. Chem. Soc.*, **1952**, *74,* 5884.

R. A. Pike, C. F. Spencer, A. C. Cope, *J. Am. Chem. Soc.*, **1953**, *75*, 3212.

01 New Synthesis Method

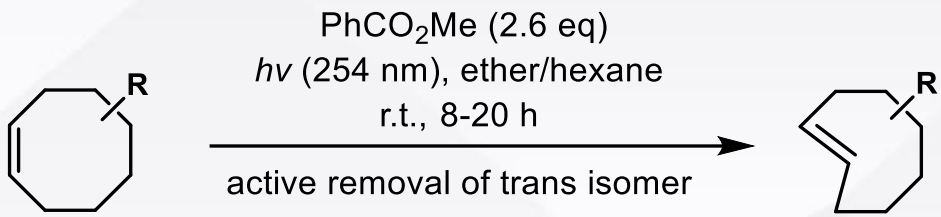


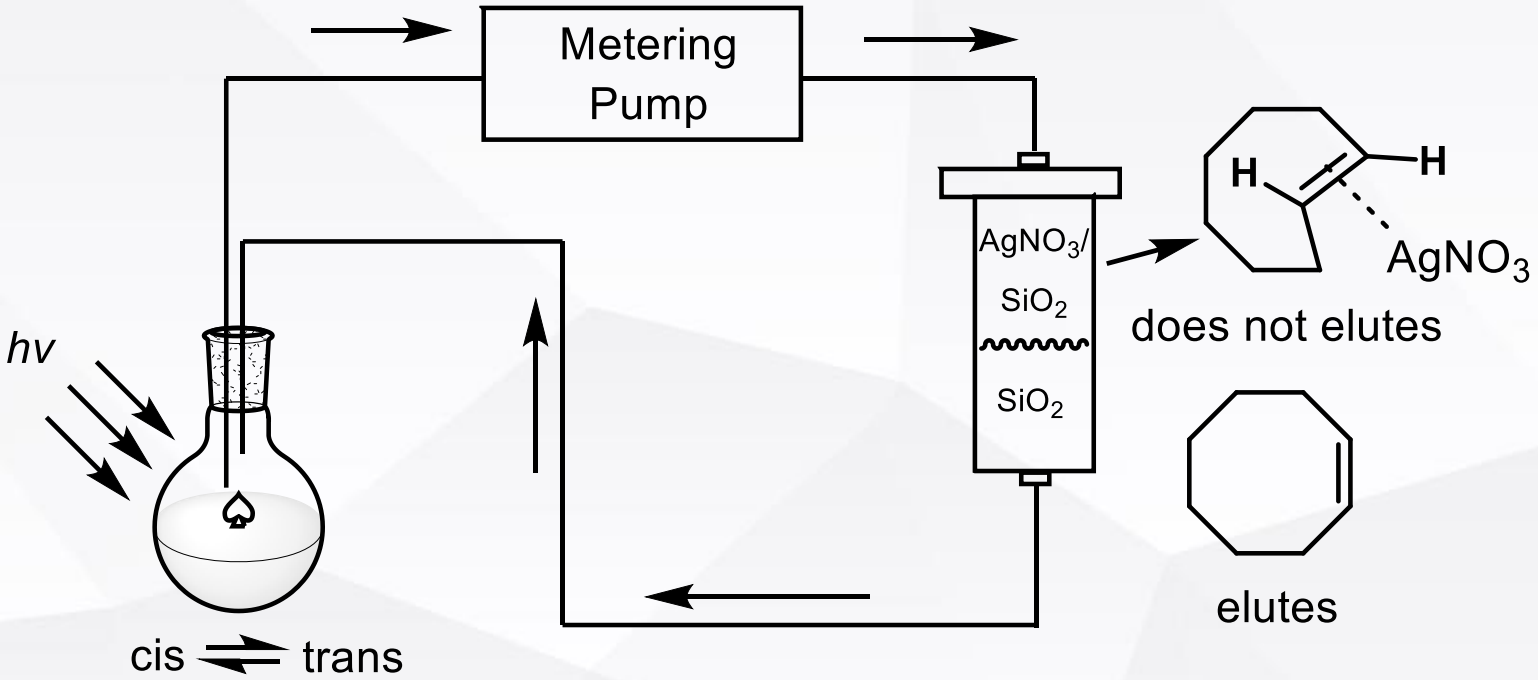


J. Deyrup, M. Betkouski, *J. Org. Chem.*, **1972**, *37*, 3561.

J. S. Swenton, *J. Org. Chem.*, **1969**, *34*, 3217.

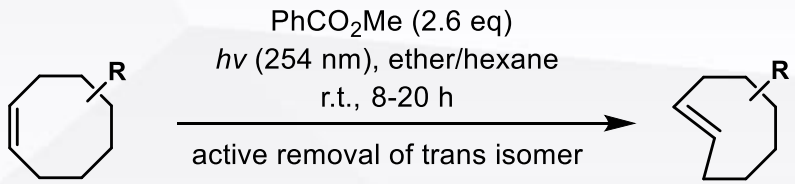
01 New Synthesis Method



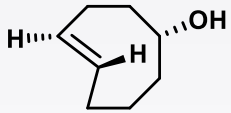


M. Royzen, G. P. A. Yap, J. M. Fox, *J. Am. Chem. Soc.*, **2008**, *130*, 3760

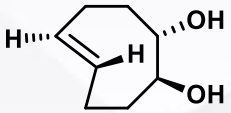
01 New Synthesis Method



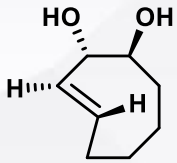
68%



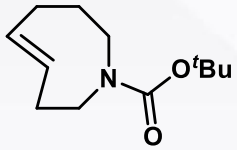
72% (0.72 g)
77% (3.9 g)



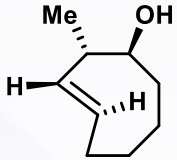
64%
dr: 1.9:1



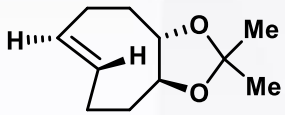
53%
dr: 3.0 : 1



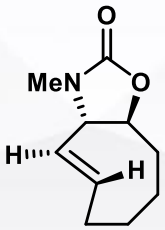
52%



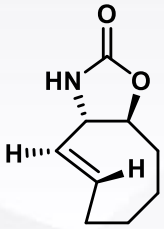
71%
dr: 3.4 : 1



65% (0.65 g)
62% (3.1 g)
dr: 11:1

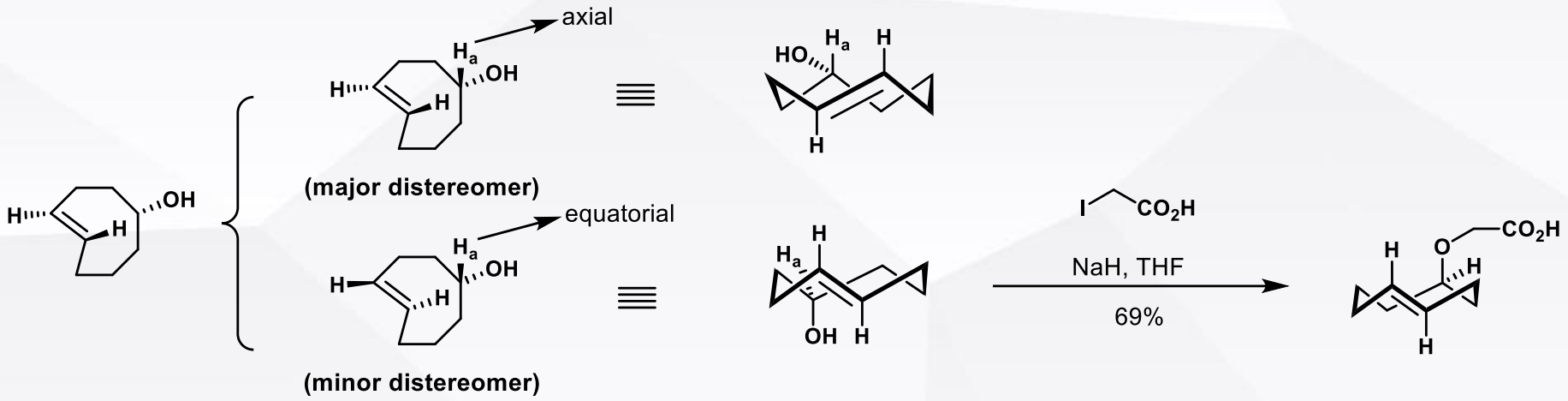


58%
dr: 1:1

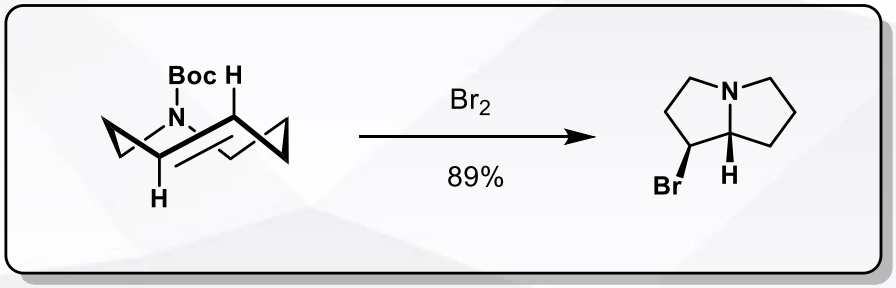


35%
a single diastereomer

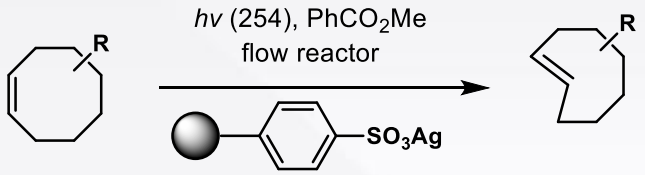
M. Royzen, G. P. A. Yap, J. M. Fox, *J. Am. Chem. Soc.*, **2008**, *130*, 3760

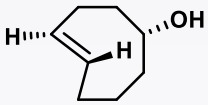


Transannular Cyclization Reaction

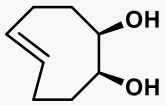


01 New Synthesis Method

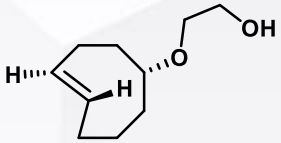




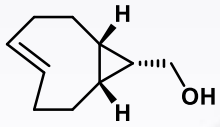
68%
1.5:1 dr
62%
6.2 g product



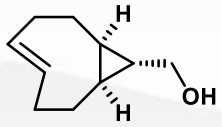
65%



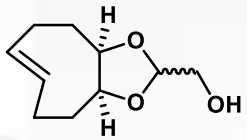
61%
1.1:1 dr



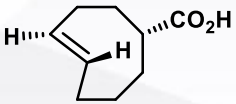
82%



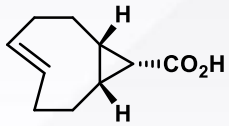
81%



51%



54%
1.5:1 dr



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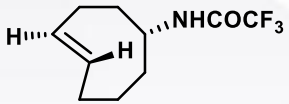


51%
3:1 dr

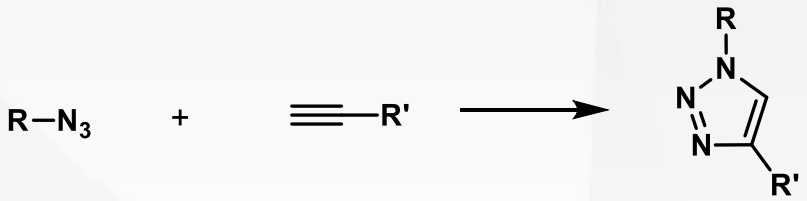
A. Darko, S. J. Boydb, J. M. Fox, *Synthesis*, **2018**, *50*, 4875.

Part 2

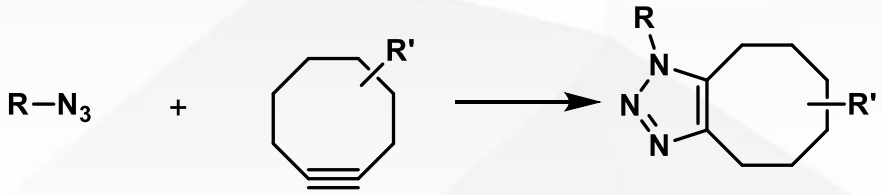
The Reaction of TCO

Bioorthogonal chemistry: Any chemical reaction that can occur inside of living systems without interfering with native biochemical processes.

A. Cu(I)-catalyzed Huisgen cycloaddition ("click" chemistry)



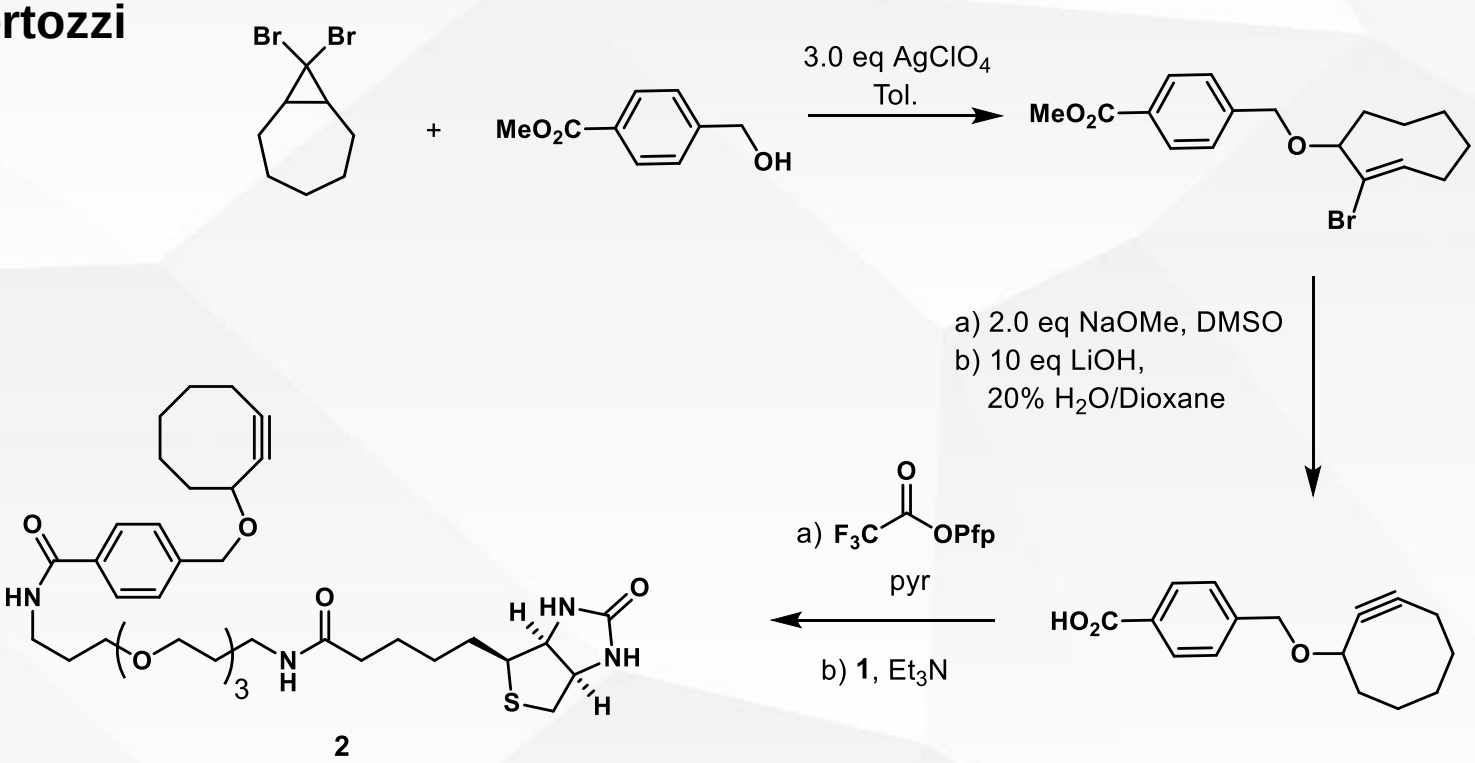
B. Strain-promoted [3+2] cycloaddition of azides and cyclooctynes

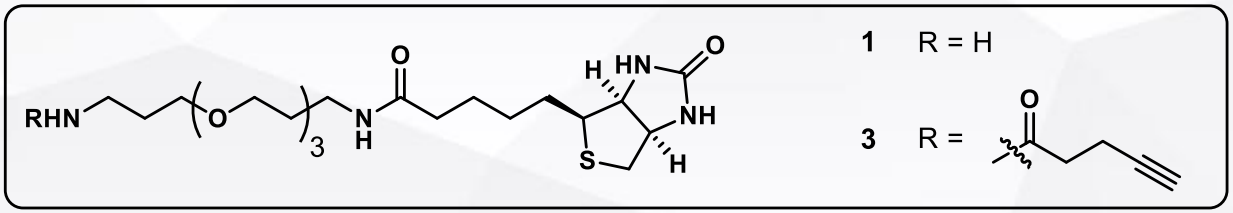


18 kcal/mol of ring strain

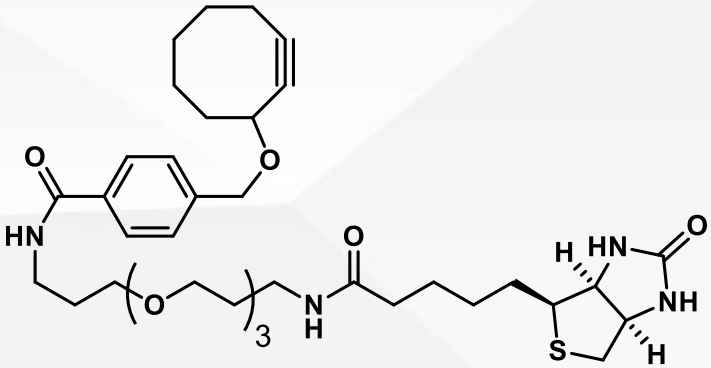
N. J. Agard, J. A. Prescher, C. R. Bertozzi, *J. Am. Chem. Soc.*, **2004**, *126*, 15046.

By Bertozzi

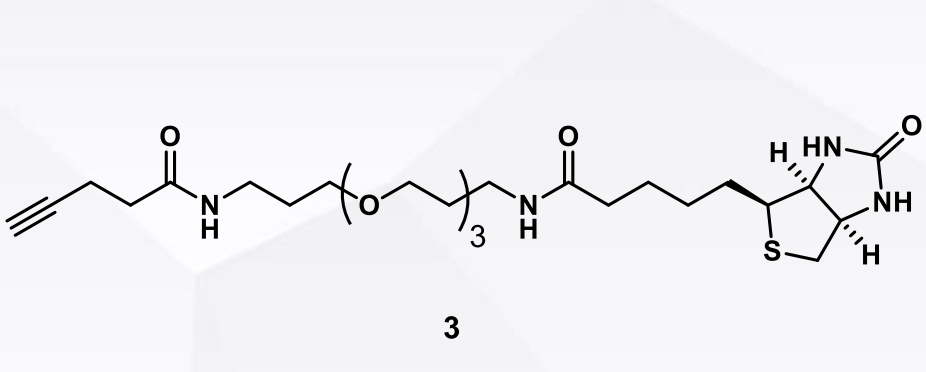

Br
Br
+
MeO2C
OH
3.0 eq AgClO4
Tol.
MeO2C
O
Br
a) 2.0 eq NaOMe, DMSO
b) 10 eq LiOH,
20% H2O/Dioxane
HO2C
O
a) F3C
OPfp
pyr
b) 1, Et3N
HN
O
O
3
N
H
H HN
O
NH
S
H
2


RHN
O
3
N
H
H HN
O
NH
S
H
1 R = H
3 R =
O

02 The Reaction of TCO

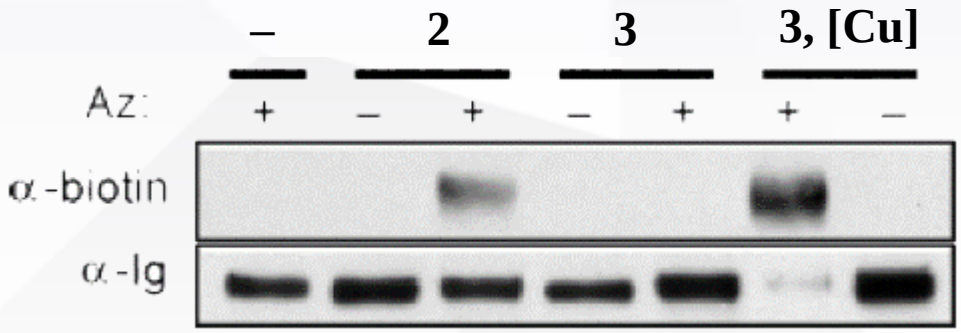


2



3

site: $10^5 \cdot k_2$ (l/mol·s)	
	
cis:	3380
trans:	1270000000
	
2970000	

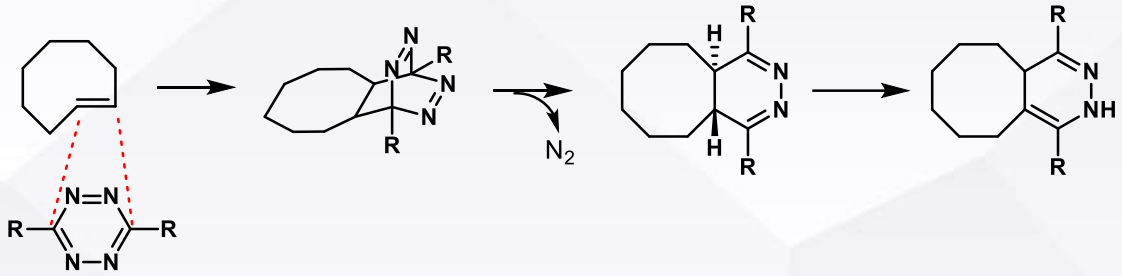


k_2 of SPAAC = 5 $M^{-1}s^{-1}$

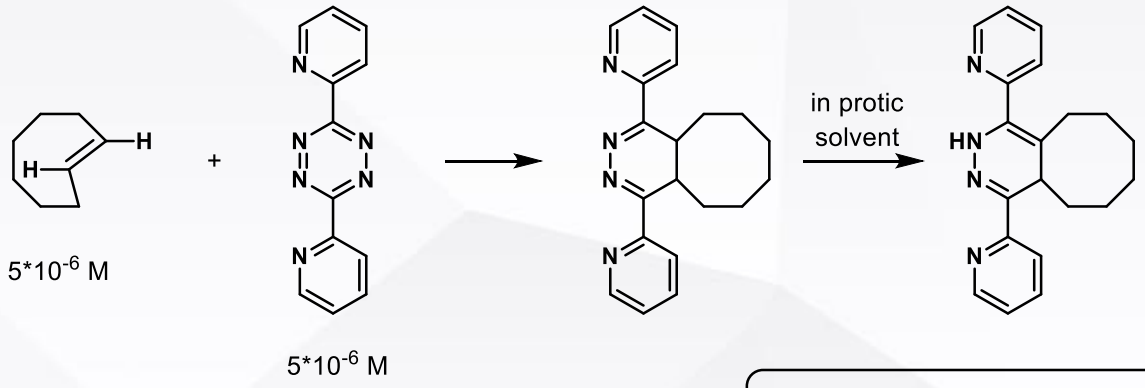
SPAAC = Strain-Promoted Azide-Alkyne Cycloaddition

N. J. Agard, J. A. Prescher, C. R. Bertozzi, *J. Am. Chem. Soc.*, **2004**, *126*, 15046.

Diels-Alder Reactions of Tetrazines with *trans*-Cyclooctene



Fast Reactivity at Low Micromolar Concentrations



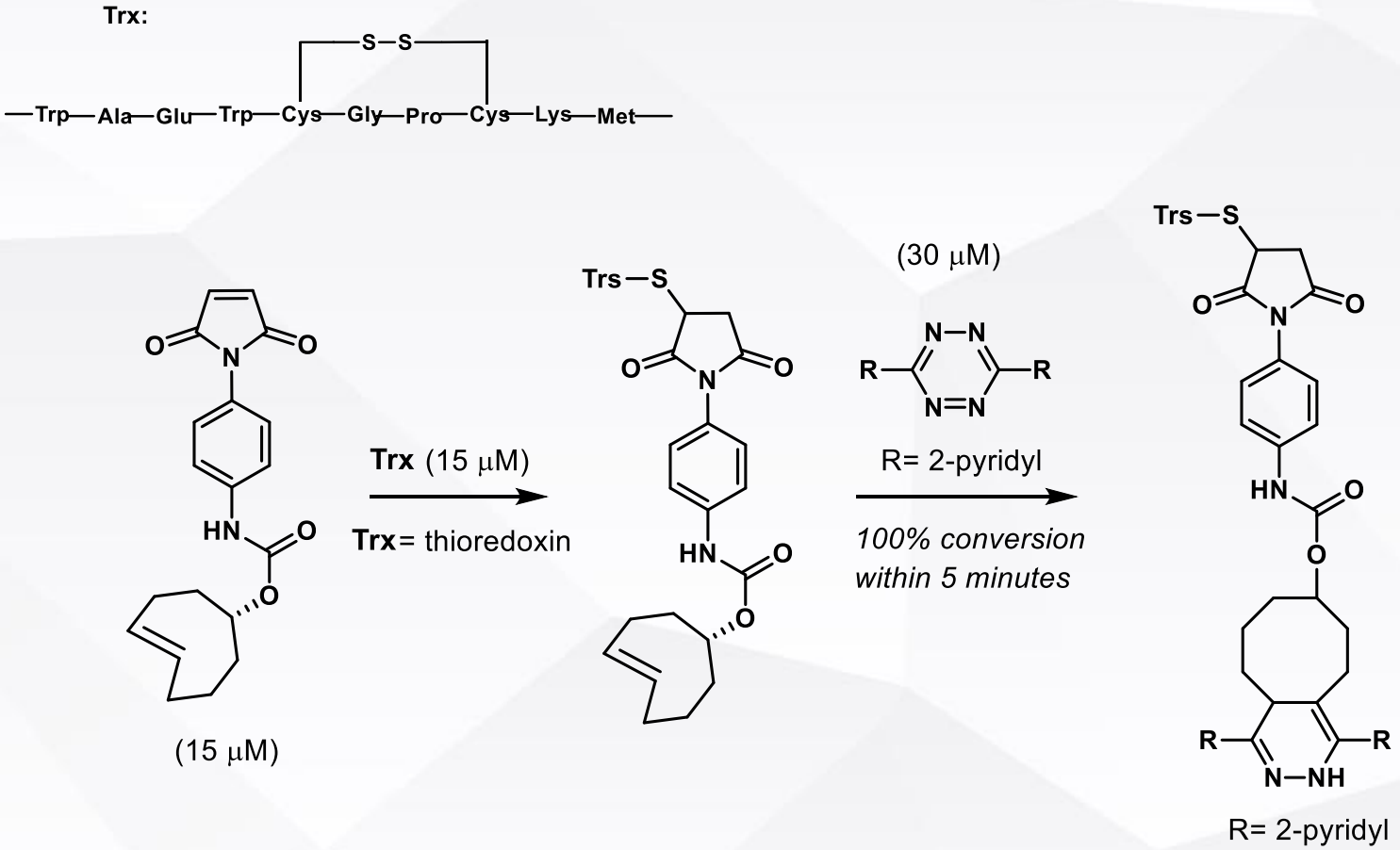
$5*10^{-6}$ M

$5*10^{-6}$ M

- 100% conv. after 40 min at 25 °C at $5 * 10^{-6}$ M
  $t_{1/2}$ = 7s when TCO:Teetrazine = 1:10
- ~quantitative yield with k_2 2000 $M^{-1}s^{-1}$
  (SPAAC = 5 $M^{-1}s^{-1}$)
- Successflu reactivity in organic solvents, water, cell media or cell lysate
- N_2 is the only byproduct

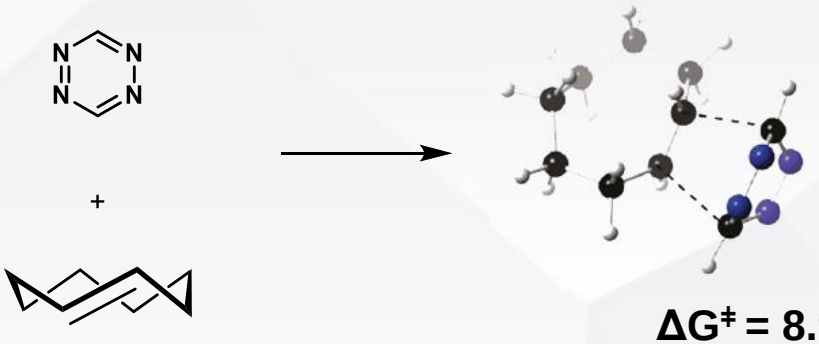
M. L. Blackman, M. Royzen, J. M. Fox, *J. Am. Chem. Soc.*, **2008**, *130*, 13518.

02 The Reaction of TCO



02 The Reaction of TCO

a



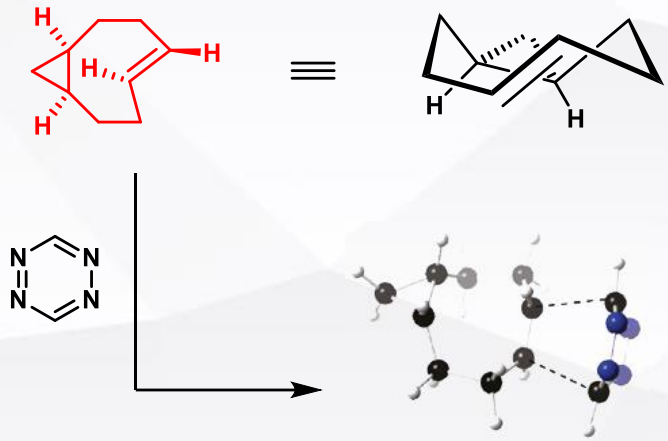
$\Delta G^{\ddagger}$ = 8.92 kcal/mol

b

s-TCO

cis ring

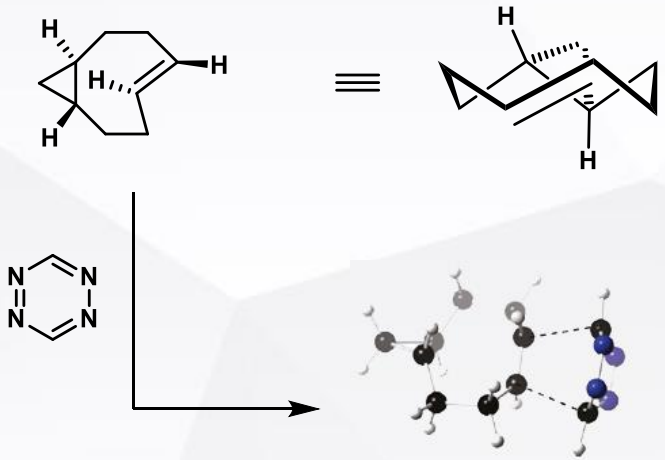
$\Delta G^{\ddagger}$ = 6.95 kcal/mol



c

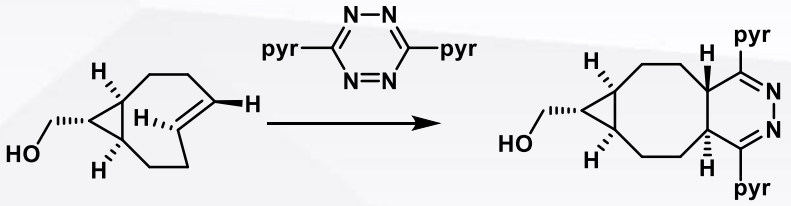
trans ring

$\Delta G^{\ddagger}$ =8.24 kcal/mol

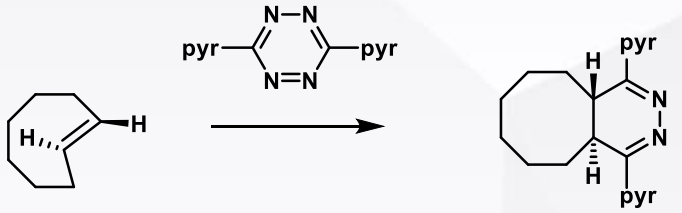


M. T. Taylor, M. L. Blackman, O. Dmitrenko, J. M. Fox, *J. Am. Chem. Soc.*, **2011**, *133*, 9646.

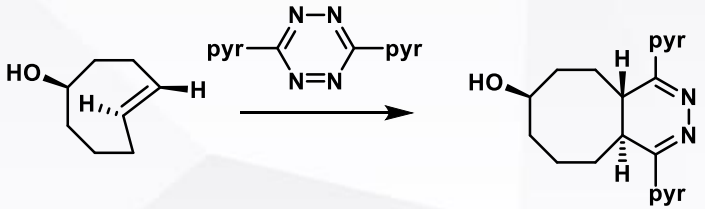
02 The Reaction of TCO



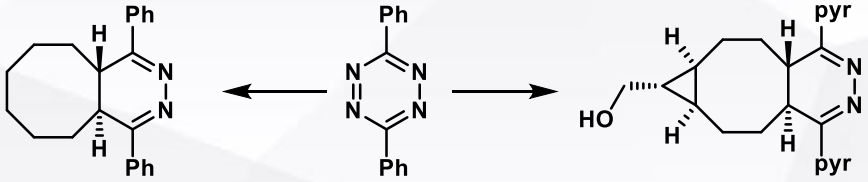
k_2 = 22000 $M^{-1}s^{-1}$



k_2 = 1140 $M^{-1}s^{-1}$



k_2 = 820 $M^{-1}s^{-1}$

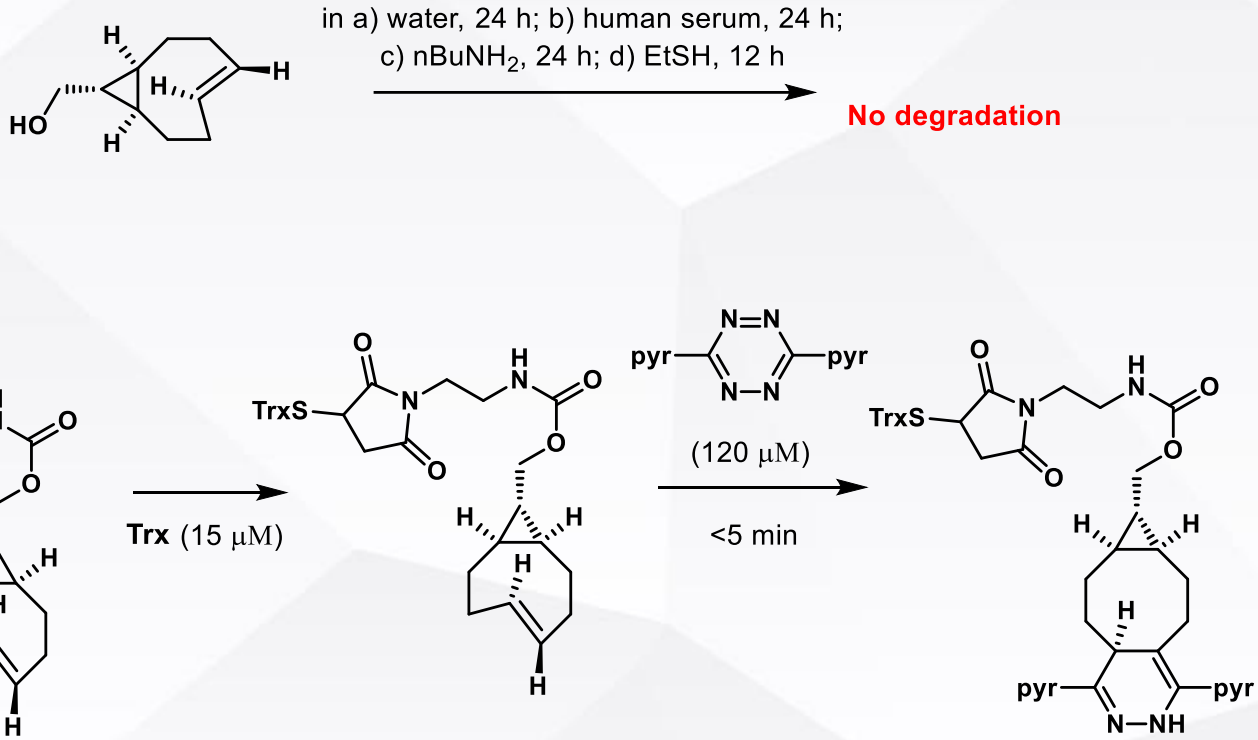


k_2 = 19.1 $M^{-1}s^{-1}$

k_2 = 3100 $M^{-1}s^{-1}$

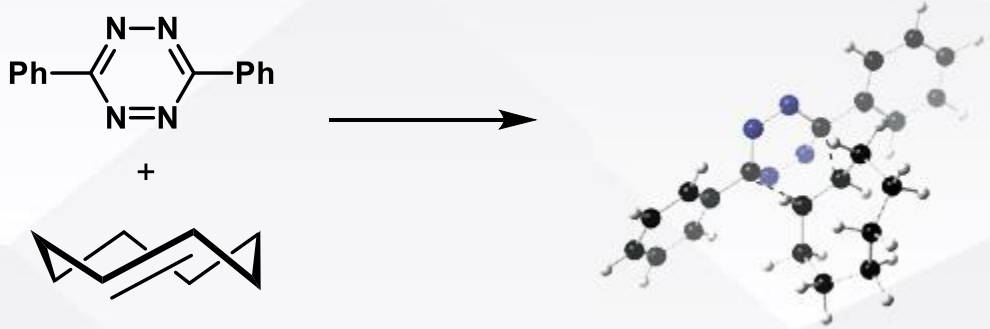
M. T. Taylor, M. L. Blackman, O. Dmitrenko, J. M. Fox, *J. Am. Chem. Soc.*, **2011**, *133*, 9646.

02 The Reaction of TCO



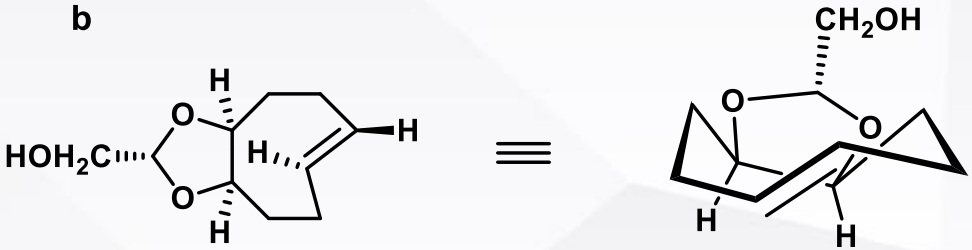
02 The Reaction of TCO

a

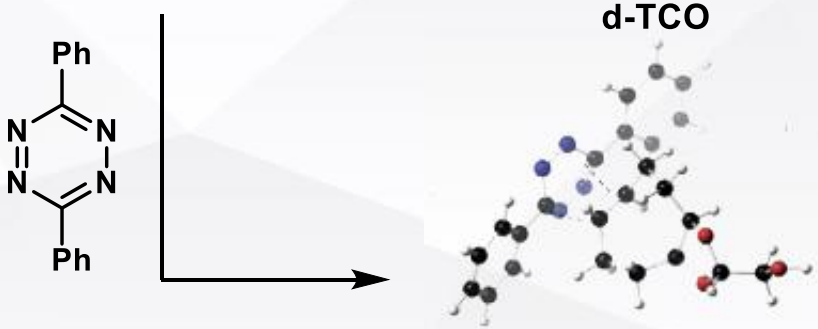


$\Delta G^{\ddagger}$ = 16.09 kcal/mol

b

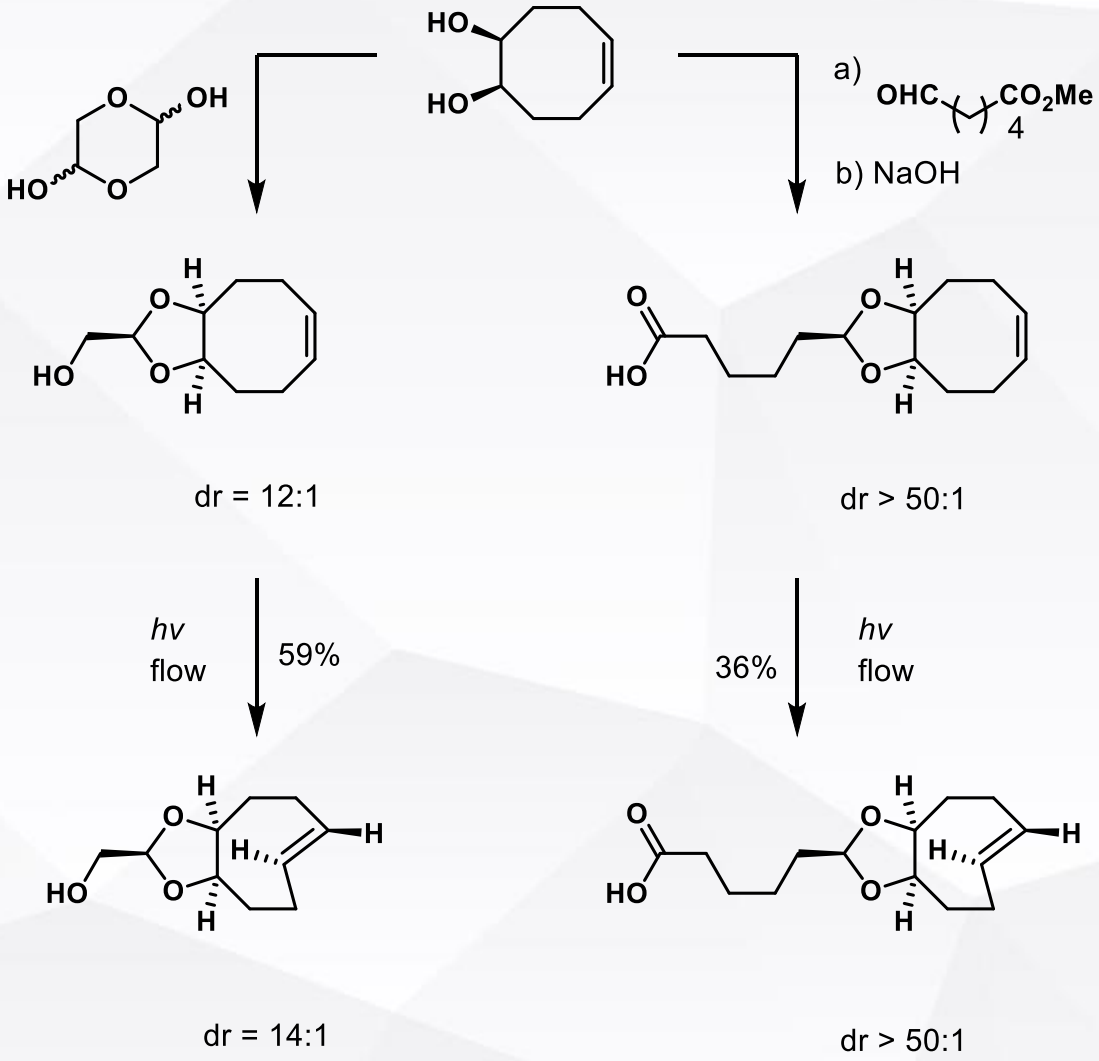


d-TCO

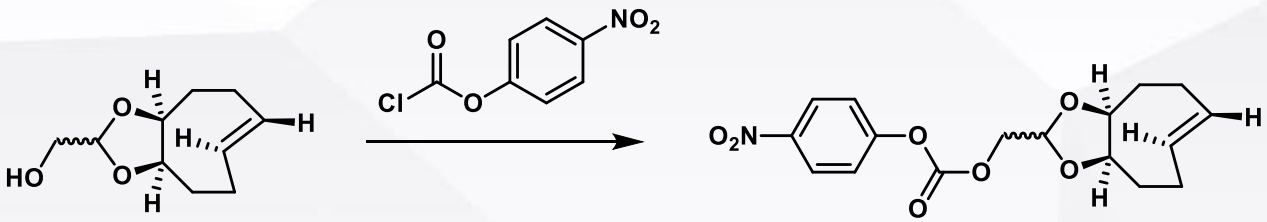


$\Delta G^{\ddagger}$ = 13.27 kcal/mol

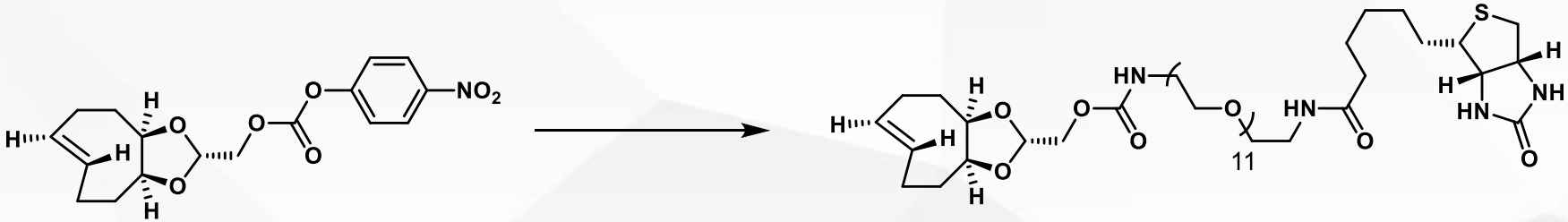
02 The Reaction of TCO



02 The Reaction of TCO



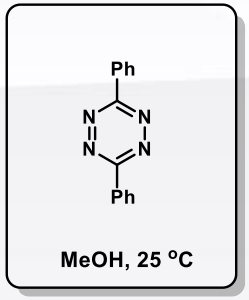
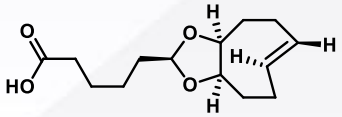
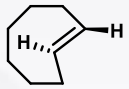
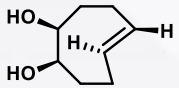
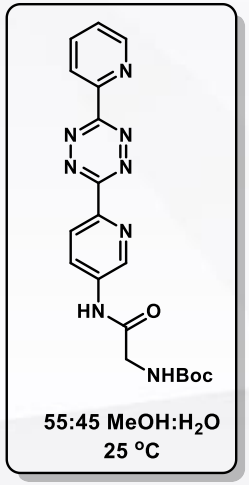
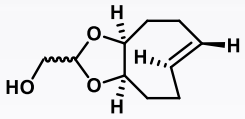
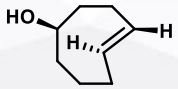
anti:syn = 1.1:1

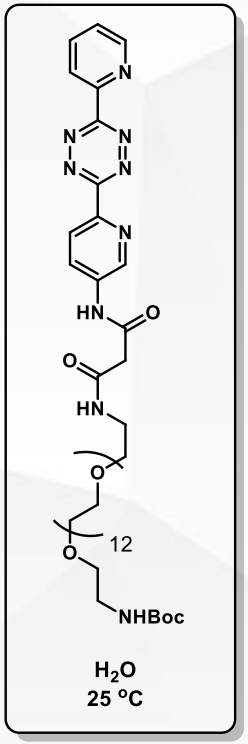
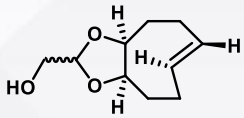
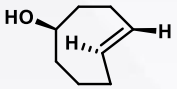
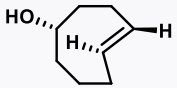
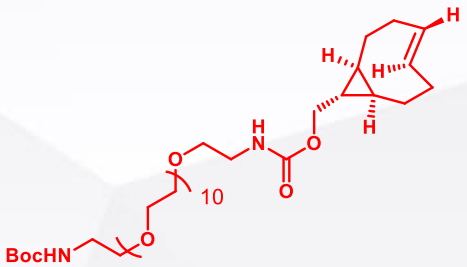


Biotion-mini-PEG derivative

A. Darko, S. Wallace, O. Dmitrenko, M. M. Machovina, R. A. Mehl, J. W. Chinb, J. M. Fox, *Chem. Sci.,* **2014**, *5,* 3770

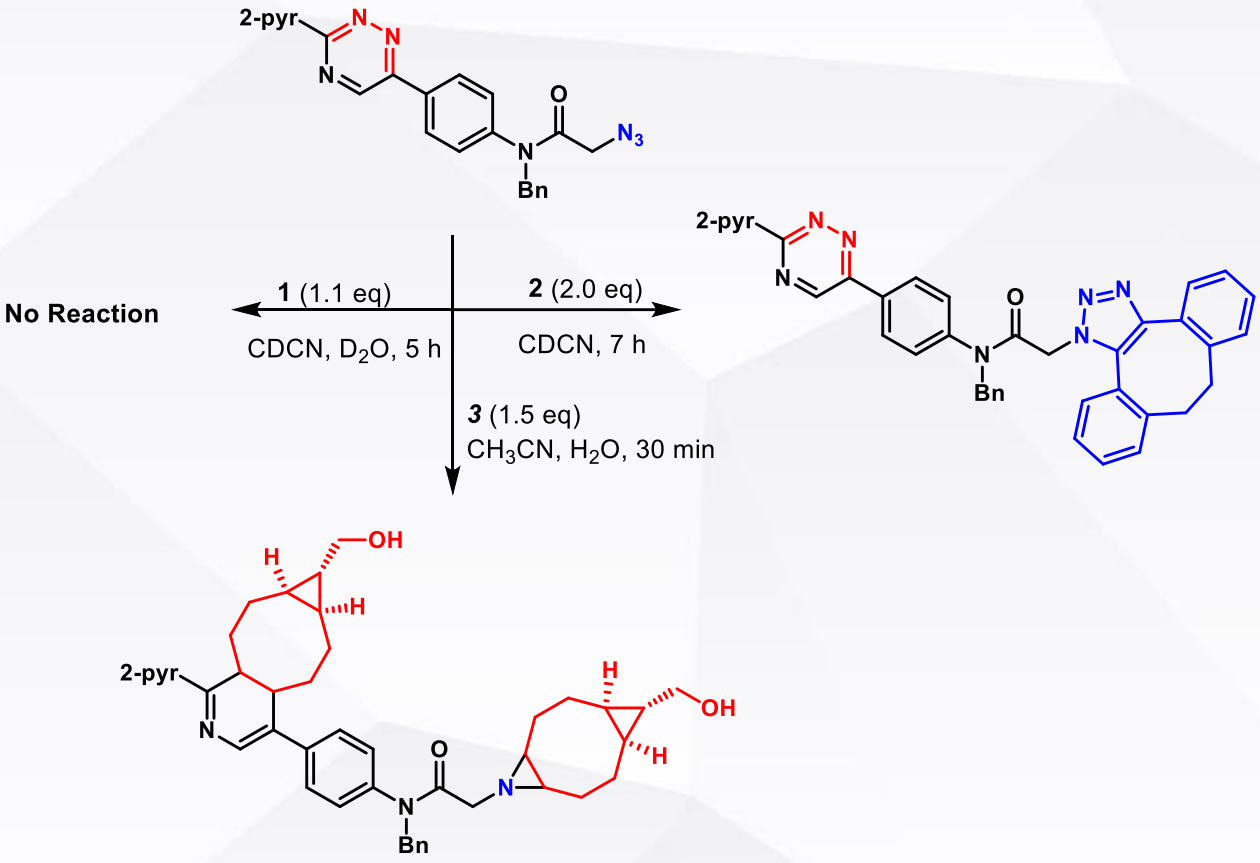
02 The Reaction of TCO

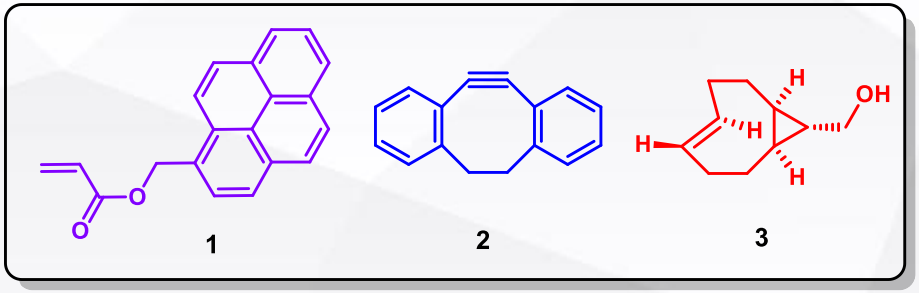
Tz	TCO	k_2 ($M^{-1}s^{-1}$)
		520
		19.1
		41
	 1:1 *syn:anti*	*syn*, *anti* 167000
	 equatorial diasyereomer	5235

Tz	TCO	k_2 ($M^{-1}s^{-1}$)
		*syn* 366000 *anti* 318000
		22600
		80200
		3300000

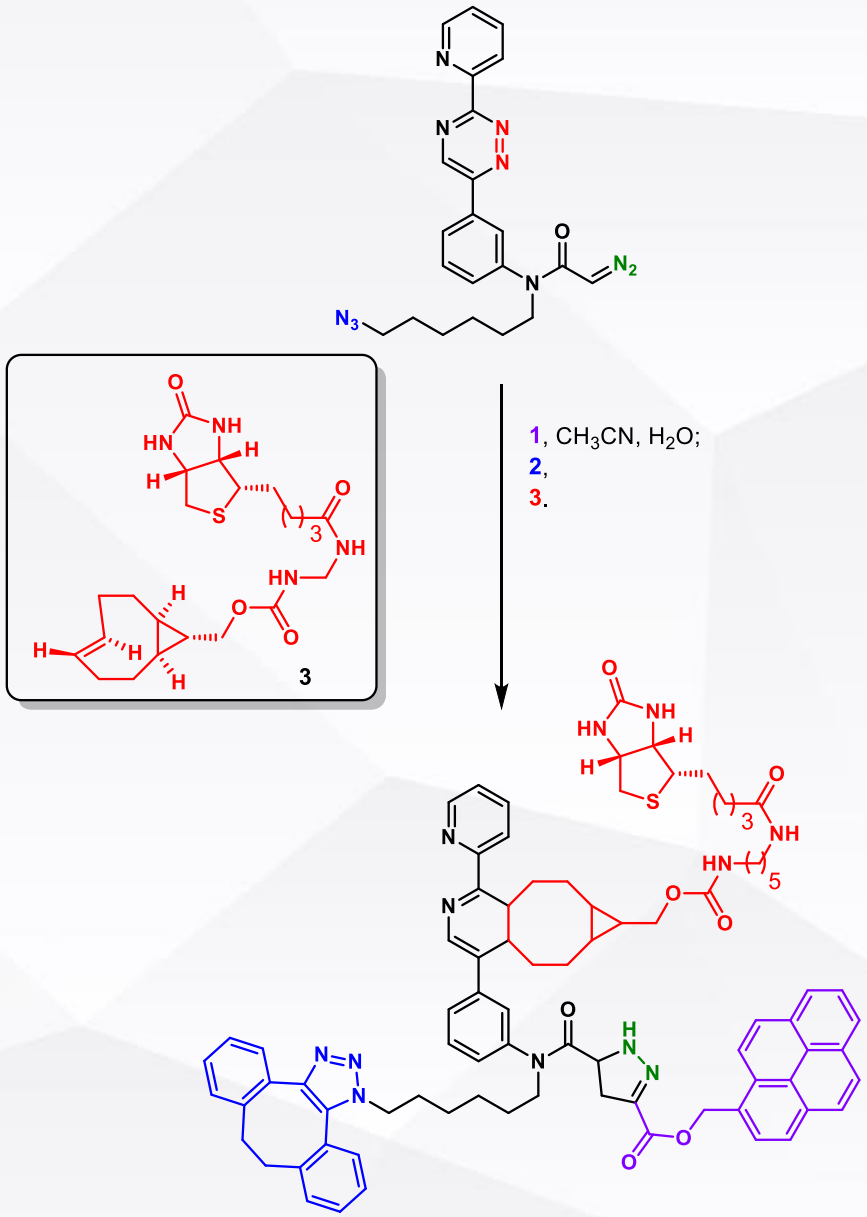
A. Darko, S. Wallace, O. Dmitrenko, M. M. Machovina, R. A. Mehl, J. W. Chinb, J. M. Fox, *Chem. Sci.*, **2014**, *5*, 3770

02 The Reaction of TCO





T. Yokoi, T. Ueda, H. Tanimoto, T. Morimoto, K. Kakiuchi, *Chem. Commun.*, **2019**, *55*, 1891

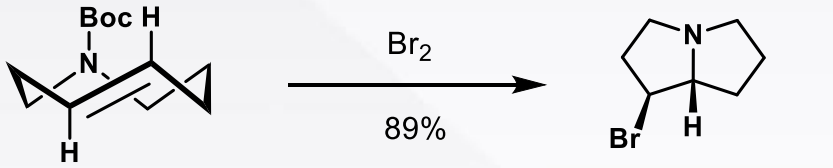

1, CH3CN, H2O;
2,
3.
3

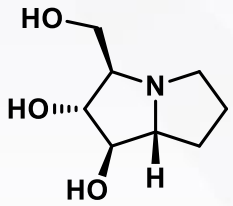
Part 3

Some New Reactions of TCO

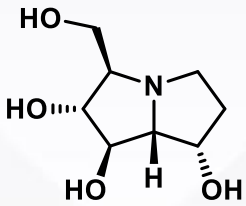
03 Some New Reactions of TCO

Fox 2008

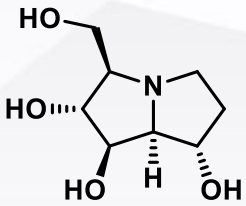




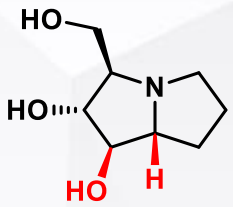
hyacinthacine A_2

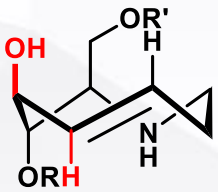


austarline

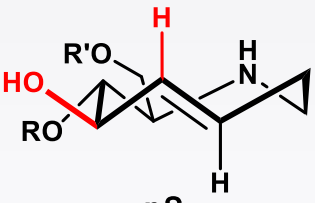


alexine





pR



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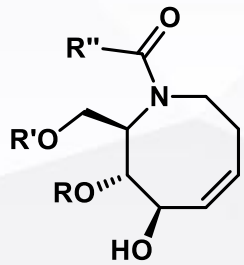
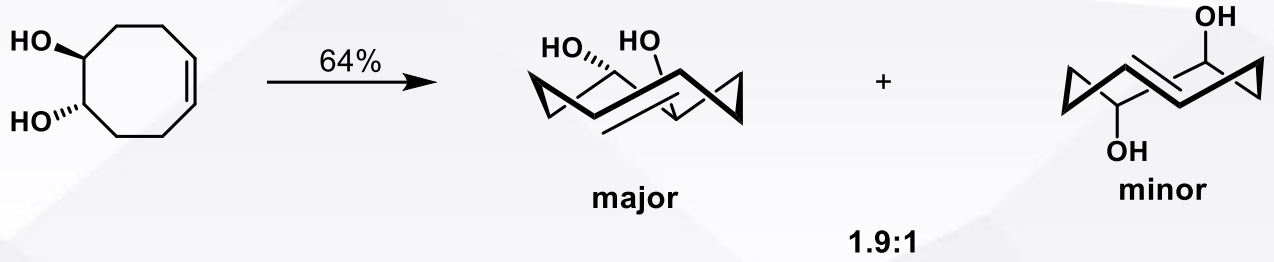
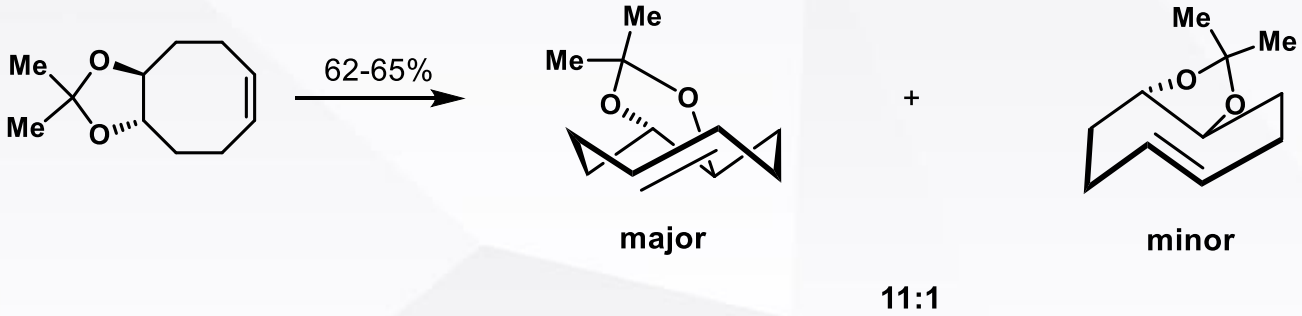
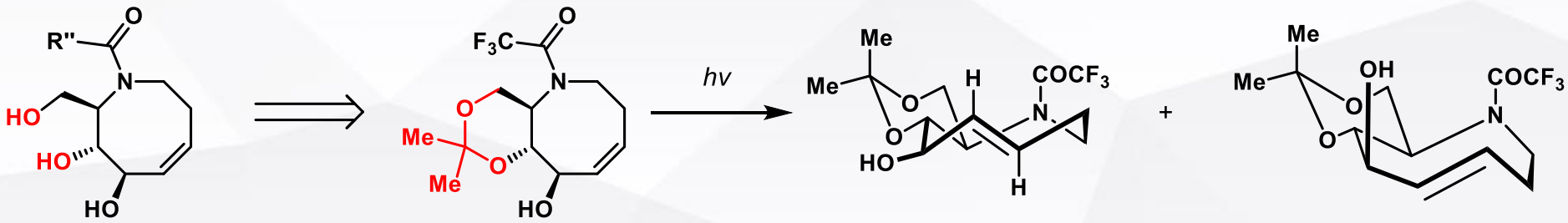


M. Royzen, M. T. Taylor, A. DeAngelis, J. M. Fox, *Chem. Sci.*, **2011**, *2,* 2162 – 2165.

03 Some New Reactions of TCO

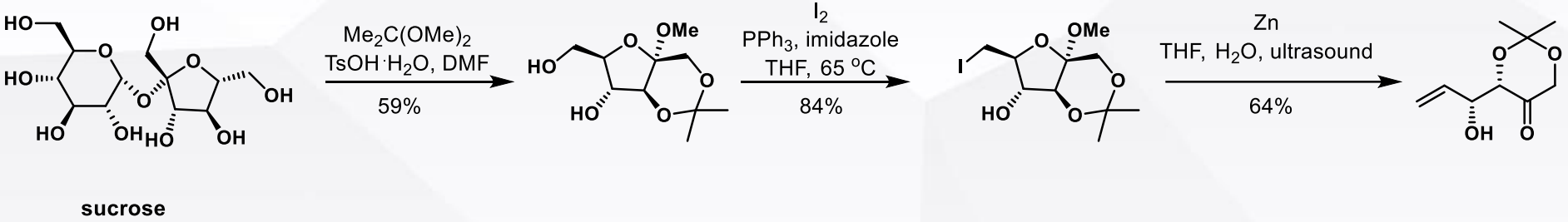


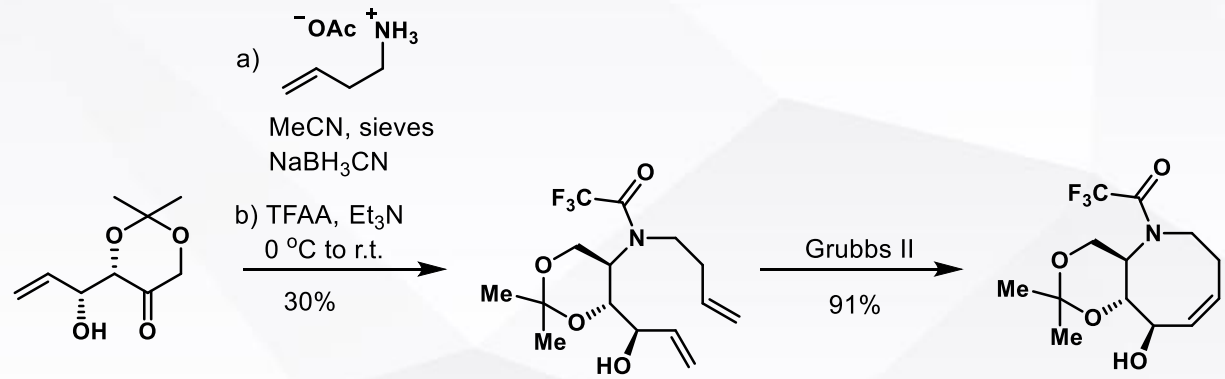




M. Royzen, M. T. Taylor, A. DeAngelis, J. M. Fox, *Chem. Sci.*, **2011**, *2,* 2162 – 2165.

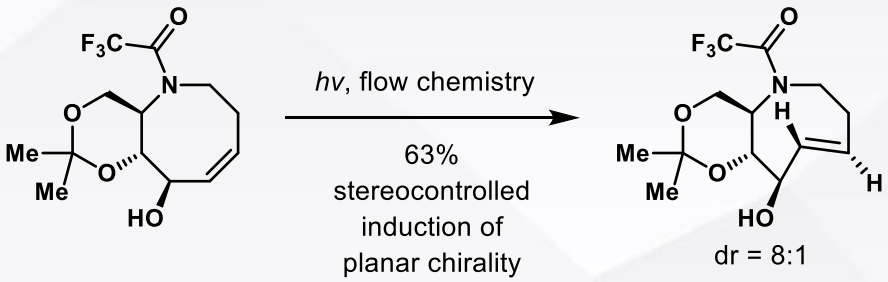
03 Some New Reactions of TCO

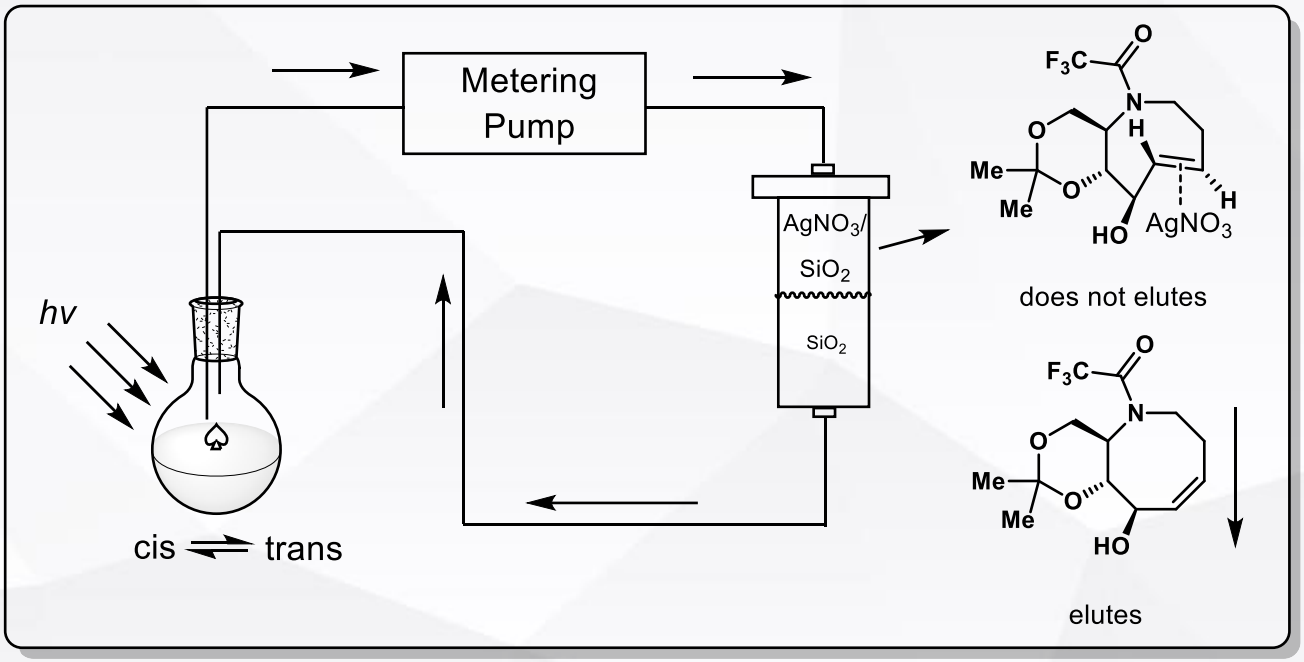




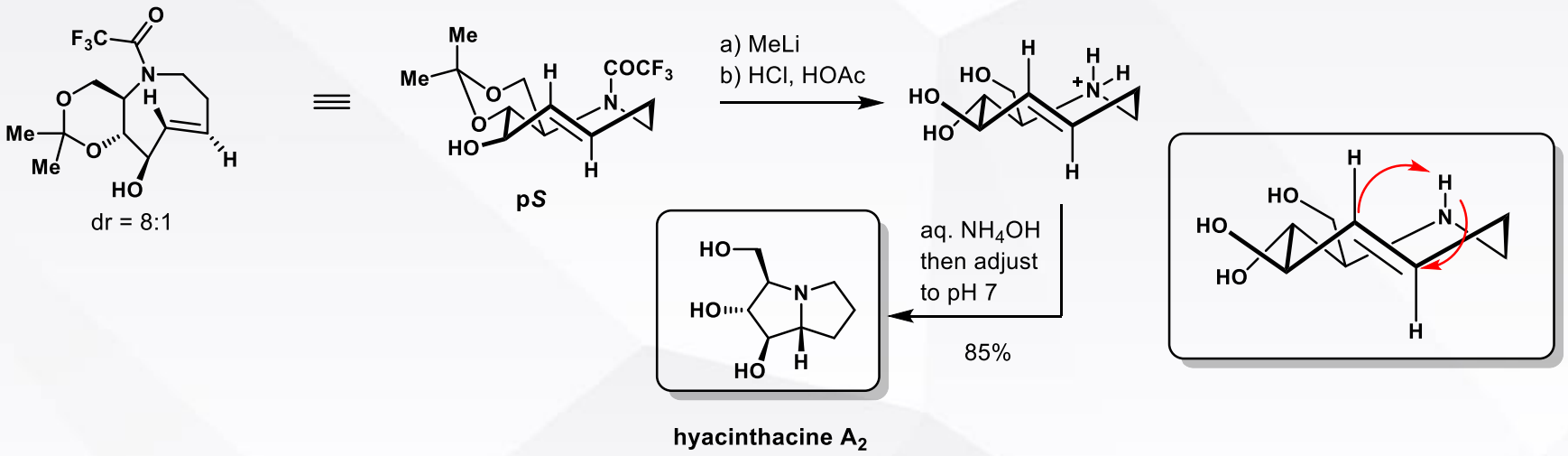
M. Royzen, M. T. Taylor, A. DeAngelis, J. M. Fox, *Chem. Sci.*, **2011**, *2,* 2162 – 2165.

03 Some New Reactions of TCO

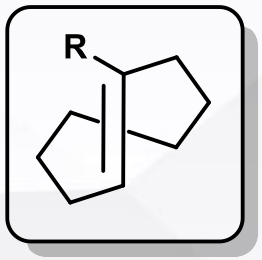




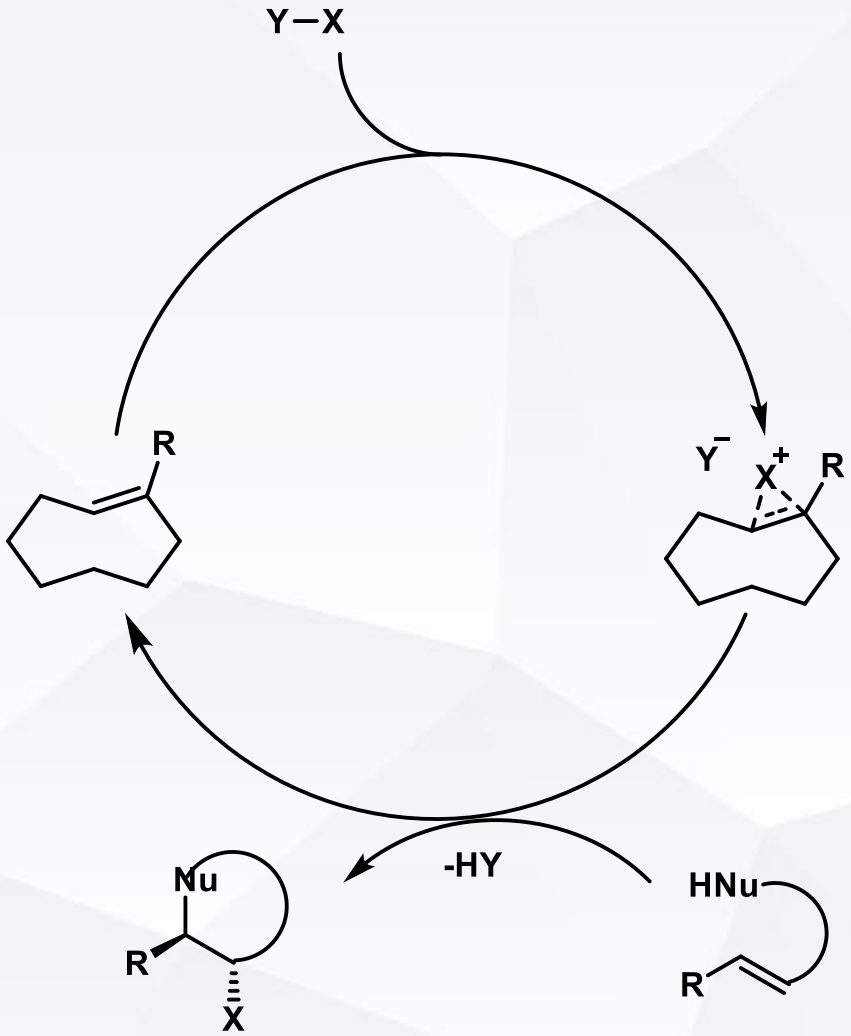
M. Royzen, M. T. Taylor, A. DeAngelis, J. M. Fox, *Chem. Sci.*, **2011**, *2,* 2162 – 2165.


dr = 8:1
pS
a) MeLi
b) HCl, HOAc
aq. NH4OH
then adjust
to pH 7
85%
hyacinthacine A2

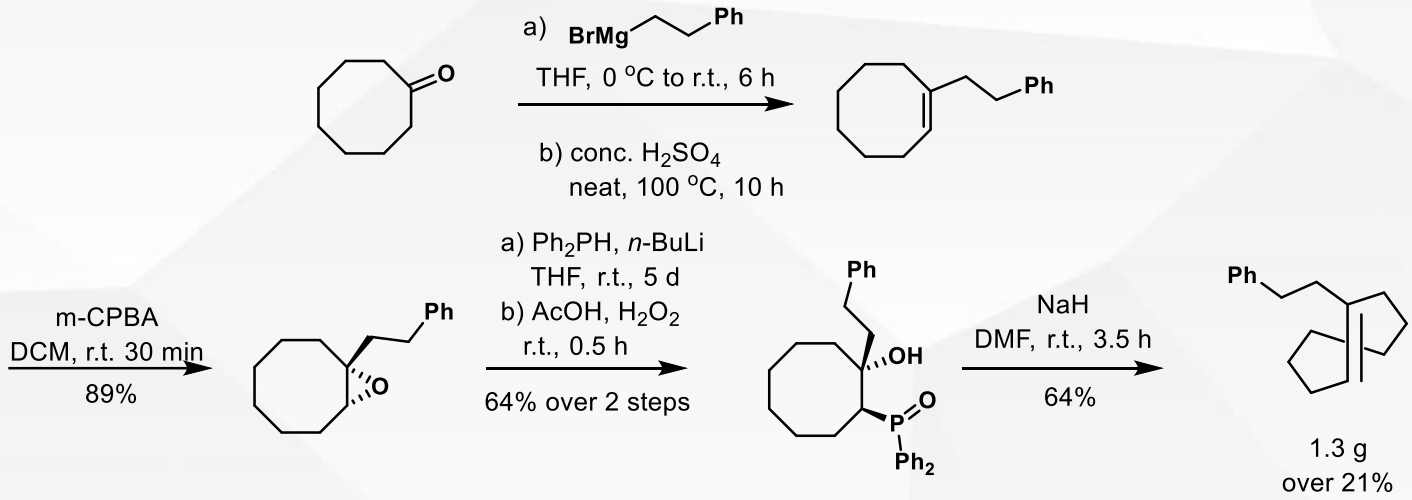
03 Some New Reactions of TCO

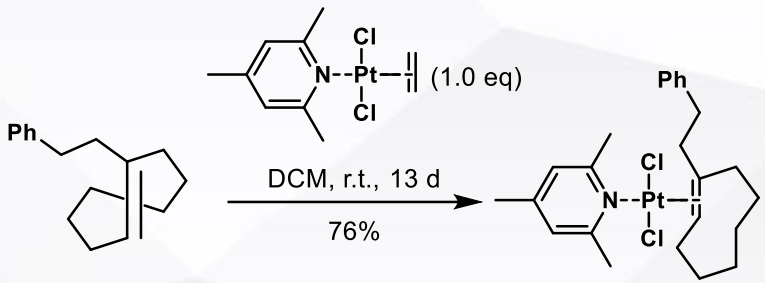


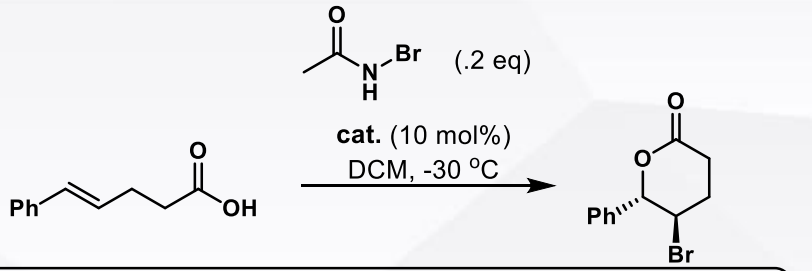
strained olefin

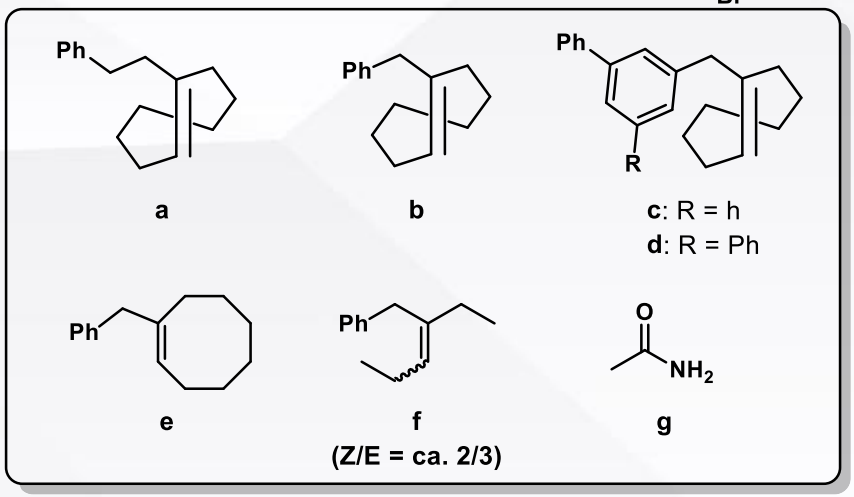


03 Some New Reactions of TCO

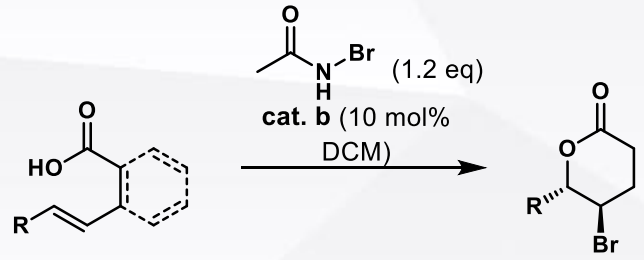


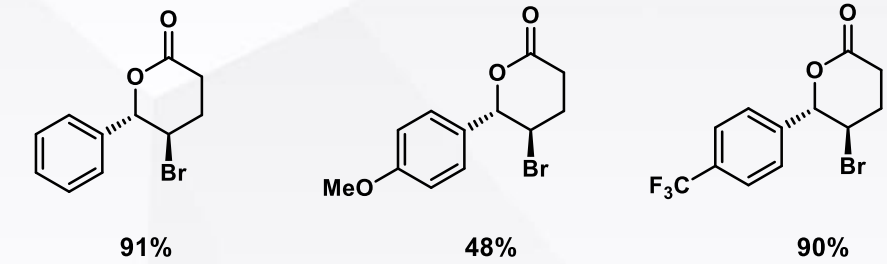


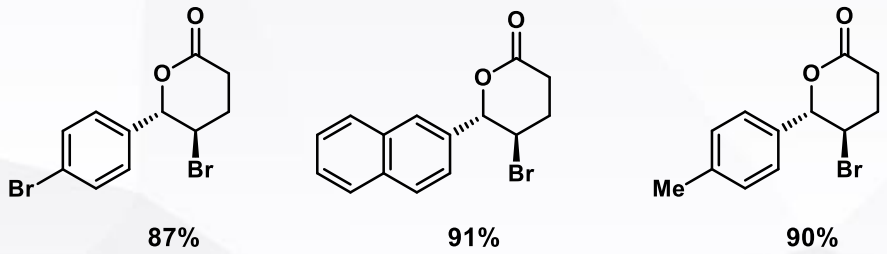


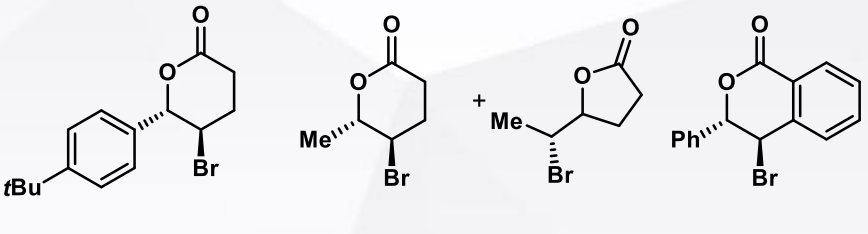


Entry	Cat.	Time [h]	Yiled [%]
1	none	6	3
2	none	48	9
3	**a**	6	2
4	**a**	48	71
5	**b**	6	88
6	**b**	12	99
7	**c**	6	59
8	**d**	6	4
9	**e**	6	1
10	**f**	6	7
11	**g**	6	4
12	**a+g**	6	1

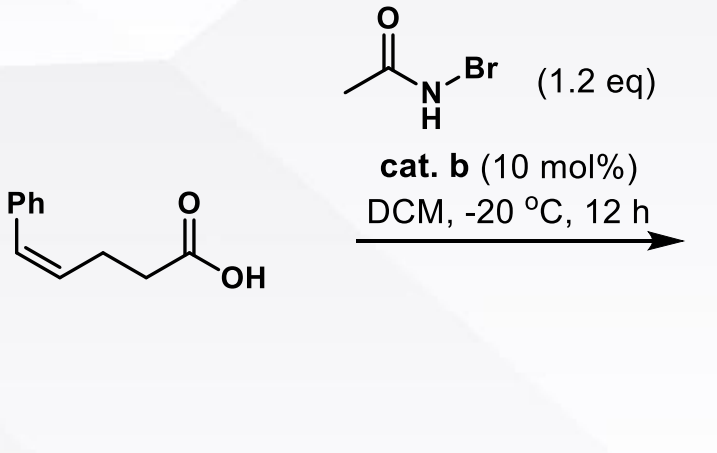


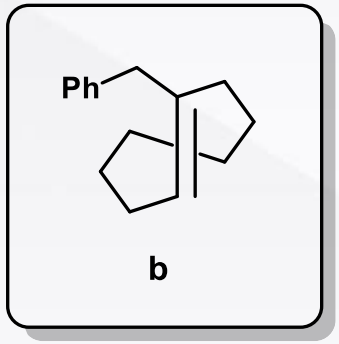






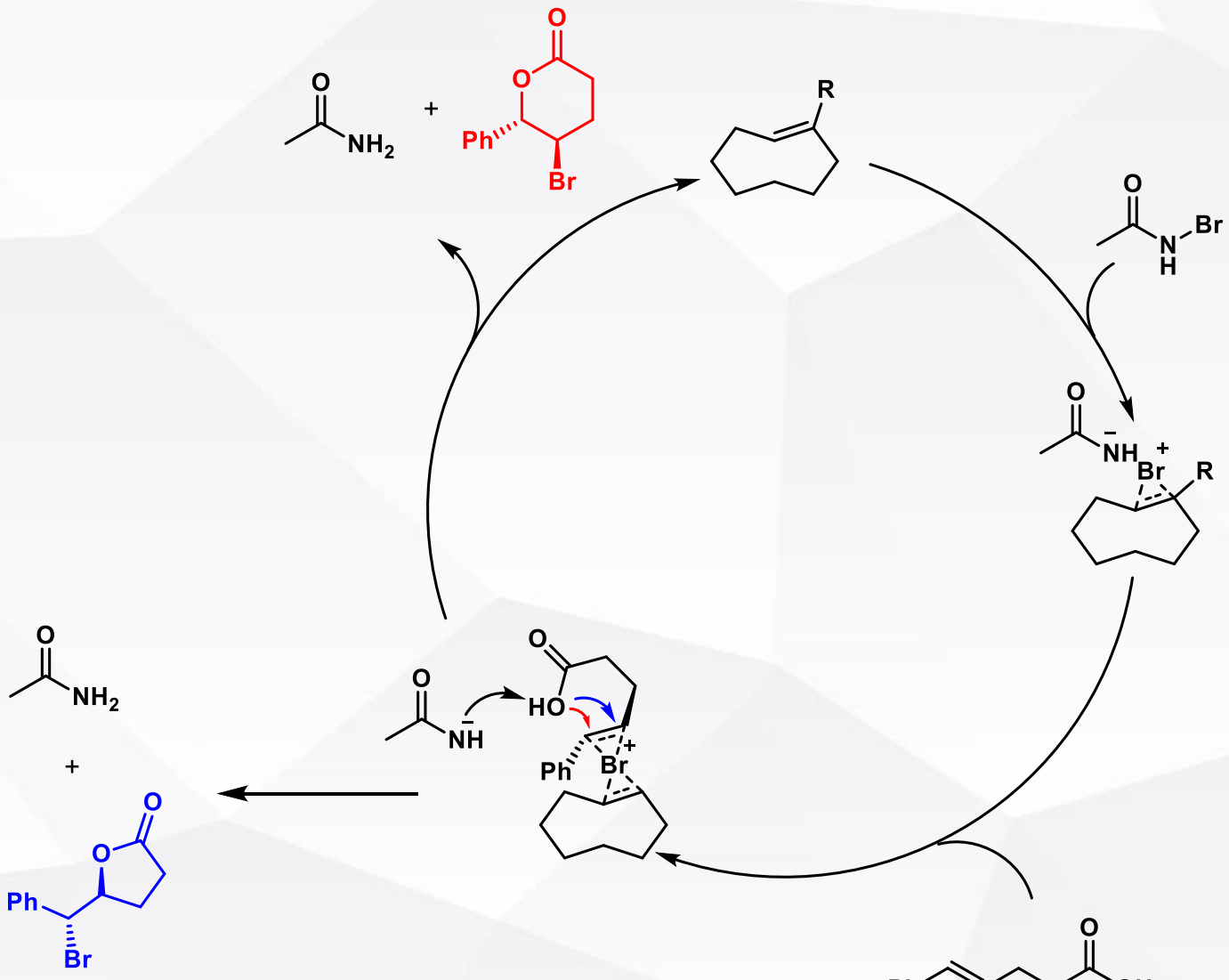
03 Some New Reactions of TCO





	A	B	A:B
with **b**:	26%	71%	1:2.7
without cat.:	<1%	2%	1:>99
with Et_3N:	<1%	99%	1:>99
with PPh_3	15%	69%	1:4.6

03 Some New Reactions of TCO



S. Einaru, K. Shitamichi, T. Nagano, A. Matsumoto, K. Asano, S. Matsubara, *Angew. Chem. Int. Ed.*, **2018**, *57*, 13863 –13867

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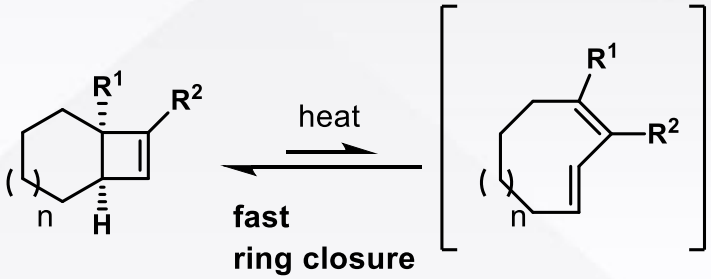
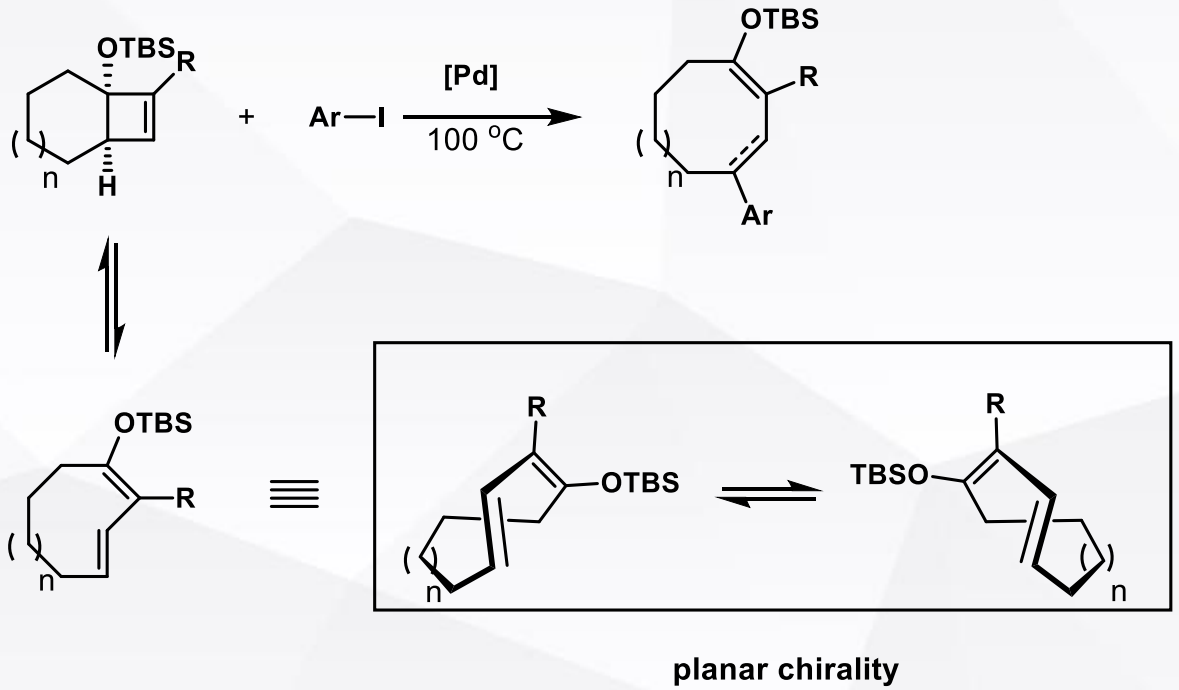
In the past

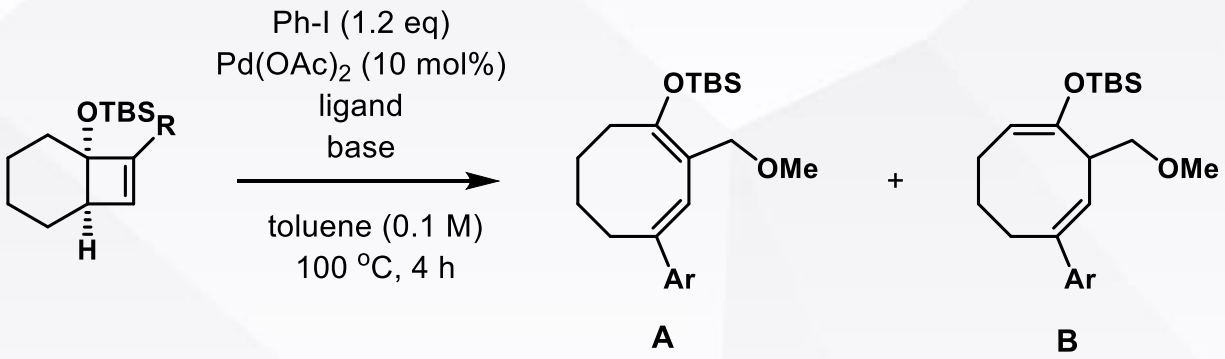


This work



planar chirality

03 Some New Reactions of TCO



entry	base (eq.)	ligand (mol%)	yield (%)	A:B
1	DIPEA (2.0)	PPh_3 (20)	34	>20:1
2	CS_2CO_3 (2.0)	PPh_3 (20)	30	9:1
3	AgOAc (2.0)	PPh_3 (20)	83	8:1
4	Ag_2CO_3 (1.0)	PPh_3 (20)	90	14:1
5	Ag_2CO_3 (1.0)	PCy_3 (20)	64	1:2
6	Ag_2CO_3 (1.0)	dppb (10)	61	1:!

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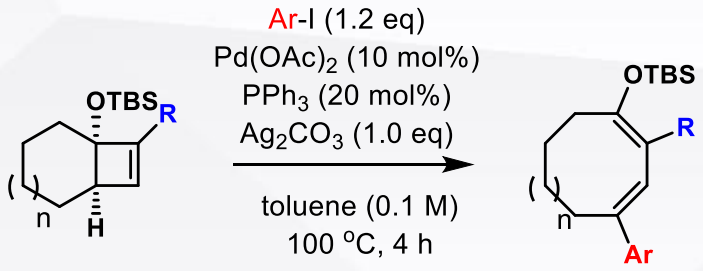
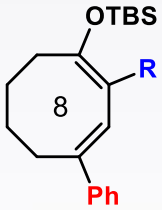
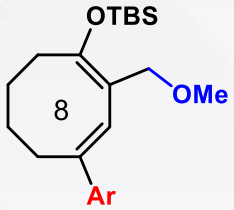
03 Some New Reactions of TCO

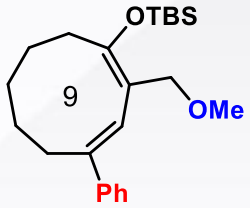




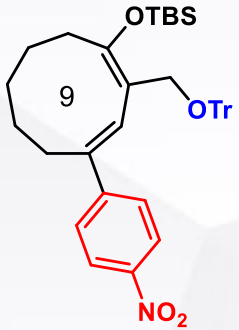
R = Me 83% (12 h)
R = CO_2Et 77% (12 h)



Ar = *m*-$CHOC_6C_4$ 68% (8 h)
Ar = *p*-$MeOC_6C_4$ 67% (8 h)
Ar = 2-thiophenyl 64% (20 h)
Ar = 3-pyridinyl 42% (20 h)



72% (8 h)



78% (13 h)

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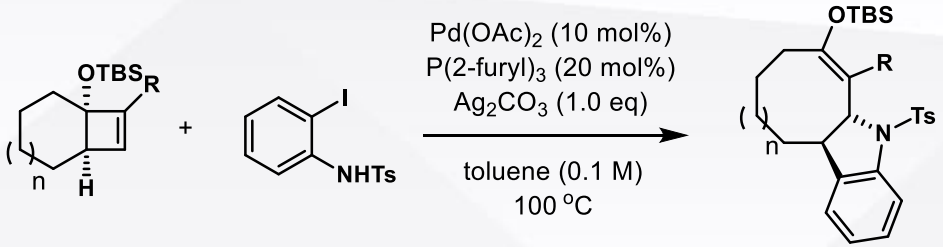
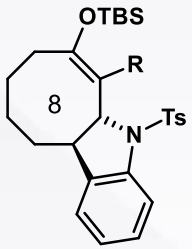
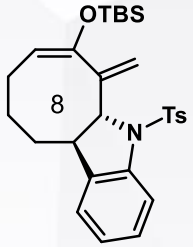
03 Some New Reactions of TCO

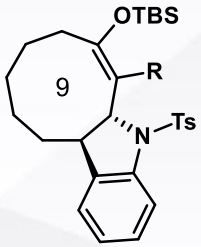




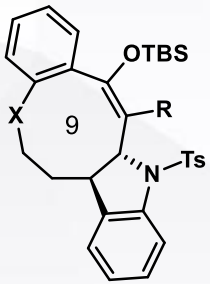
R = CO_2Et 75% (4 h)
R = CH_2NHNs 53% (12 h)



54% (12h)



R = CO_2Et 80% (4 h)
R = CH_2NHNs 64% (6 h)



R = CO_2Et, X = CH_2 74% (10 min)
R = CH_2NHNs, X = CH_2 45% (2 h)
R = CO_2Et, X = O 79% (30 min)

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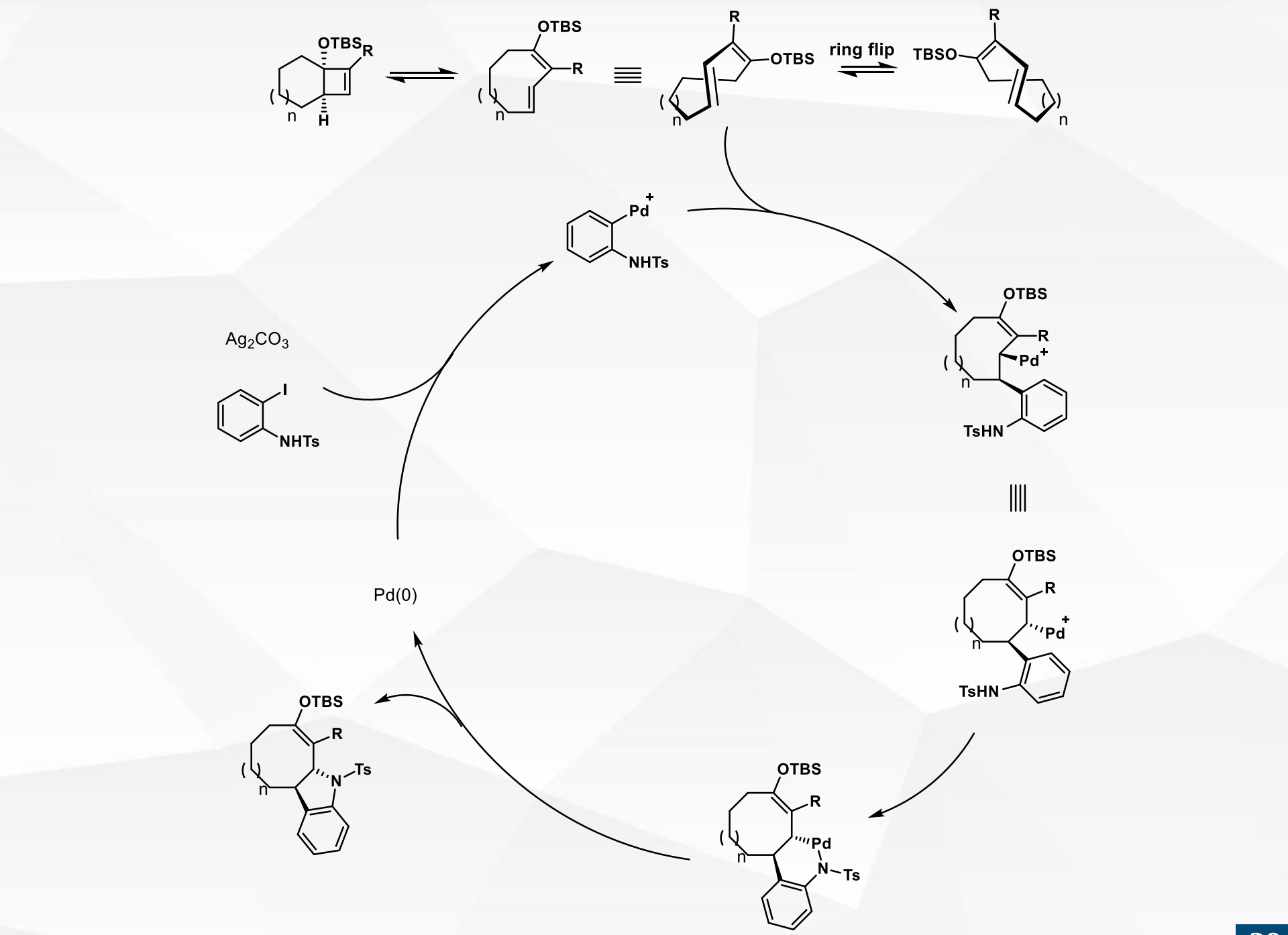
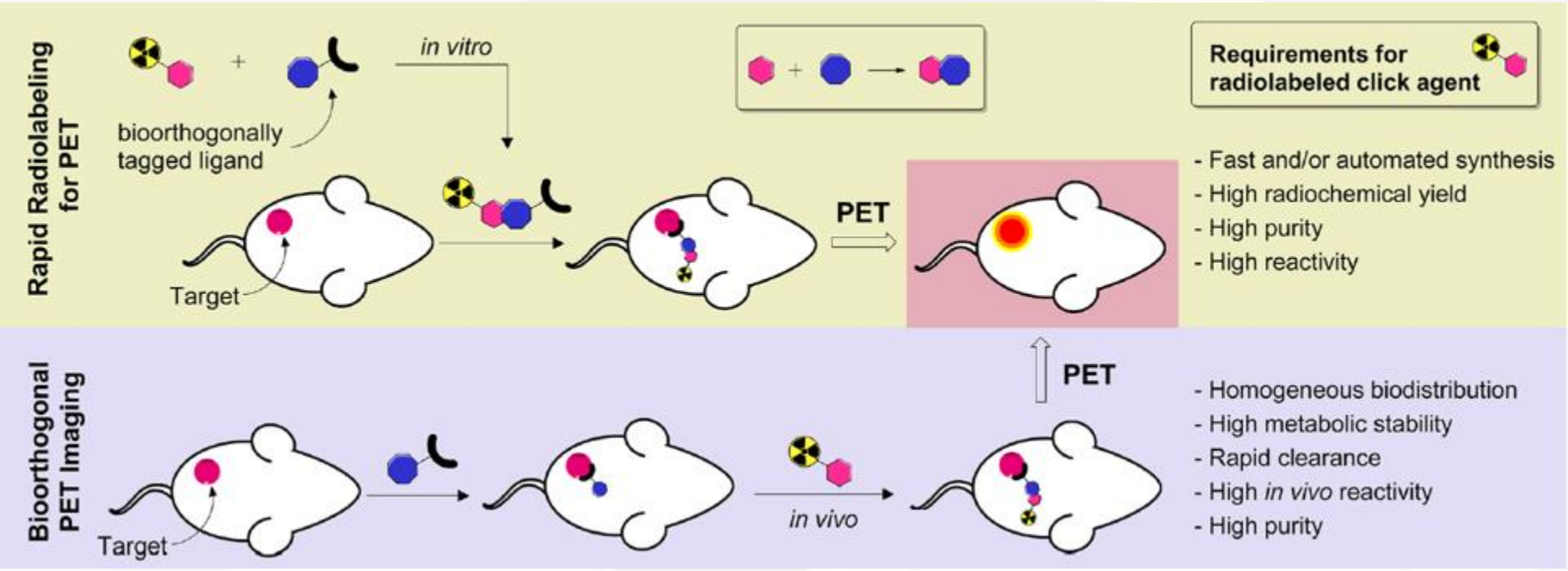


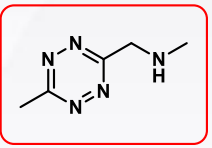
N. Arichi, K. Yamada, Y. Yamaoka, K. Takasu, *J. Am. Chem. Soc.*, **2015**, *137*, 9579.

03 Some New Reactions of TCO

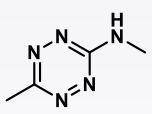


PET: Positron emission tomography

C. Denk,D. Svatunek, J. Stanek, T. Filip, D. Matscheko, C. Kuntner, T. Wanek, H. Mikula, *Bioconjugate Chem*. **2016**, *27*, 1707



1



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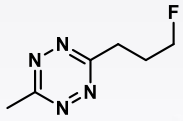

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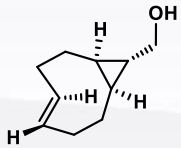

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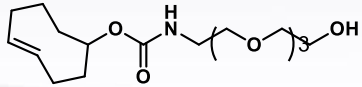

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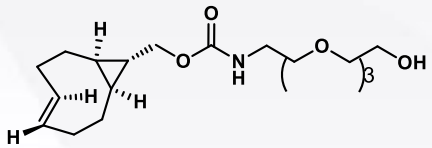


7

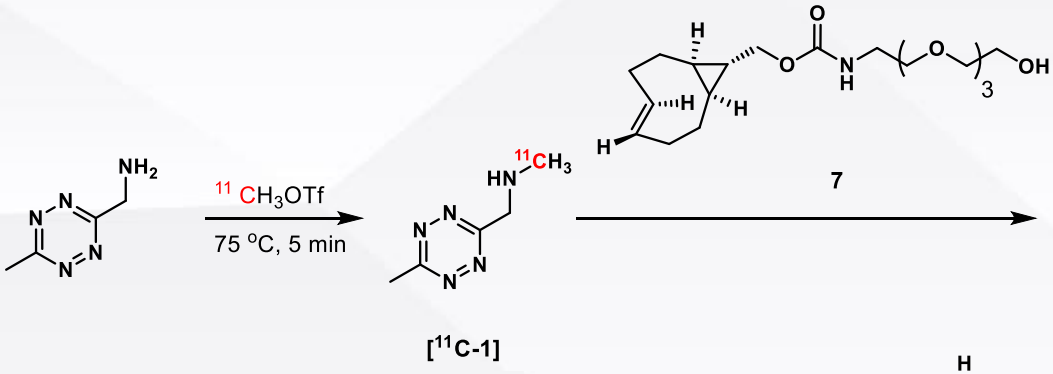
Tz
1-3

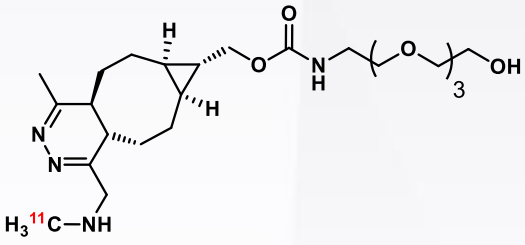
TCO
4-7

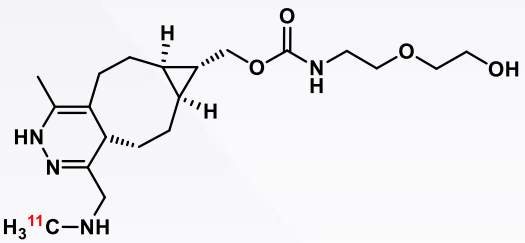
Reaction	k_2 [$M^{-1}s^{-1}$]	calculated realative rate	realative rate
1+4	1.04 ± 0.03[a]	1.32[c]	0.70[c]
2+4	n.d.	0.00009[c]	n.d.
3+4	1.49 ± 0.01[a]	1.00[c]	1.00[c]
1+5	8.95 ± 1.1[a]	1.36[d]	1.05[d]
2+5	n.d.	0.0006[d]	n.d.
3+5	85.5 ± 2.3[a]	1.00[d]	1.00[d]
1+6	175.4 ± 1.2[b]	n.d.	118[c]
1+7	42500 ± 3100[b]	n.d.	497[d]

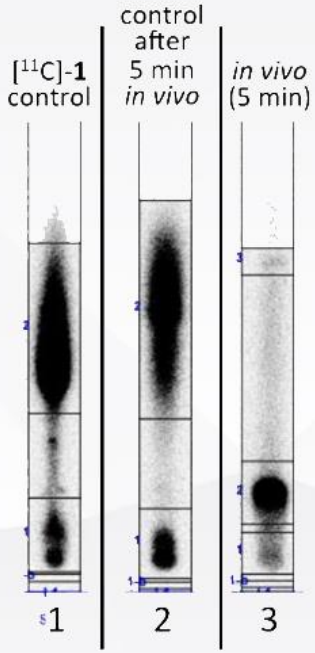
[a]Measured in 1,4-dioxane at 37 °C. [b]Measured in PBS in 37 °C.[c]Relative to the reaction between **3** and **4.** [d]Relative to the reaction between **3** and **5**. n.d. = not determinged

03 Some New Reactions of TCO

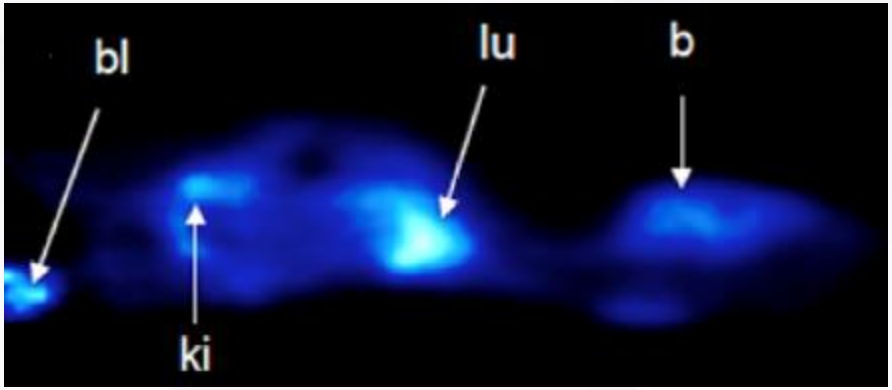








PET Image



b = brain, bl = bladder, k = kidney, lu = lung

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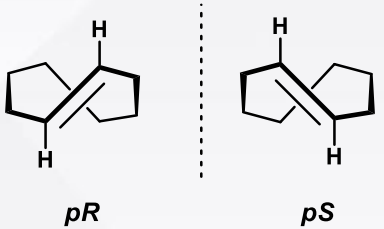
Part 4

Summary

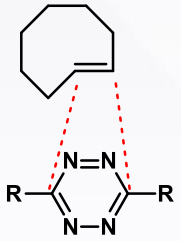
Properties:

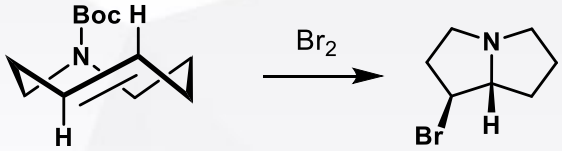
- **Planar chirality**
- **High HOMO energy**
- **High energy of ring strain**



Reaction:

- **IEDDA reaction**
- **Click reaction**
- **Bioorthogonal reaction**
- **Total synthesis**
- **The catalyst of transition metal**





THANKS