

Tandem reactions catalyzed by peptides

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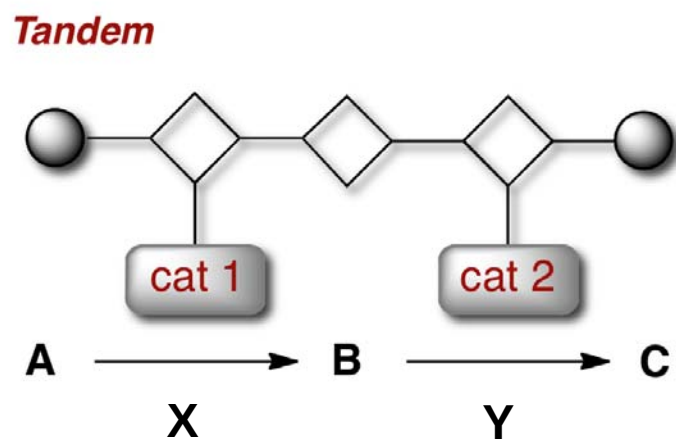
**Institut für organische Chemie, Justus-Liebig Universität
Giessen**

Stand der Forschung, Giessen 2010

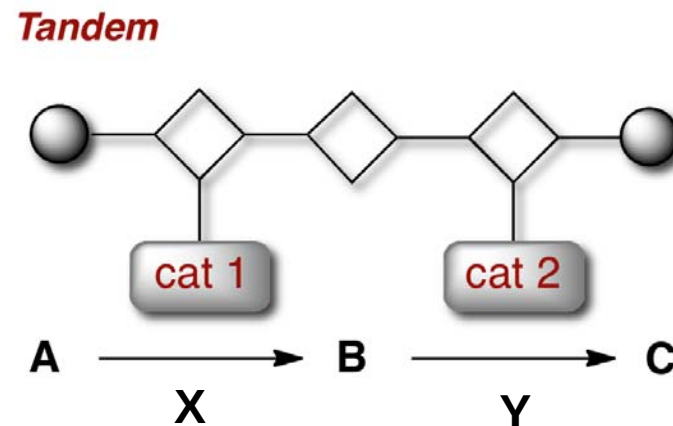


Goal

Development of one-pot sequence reactions



Limitations



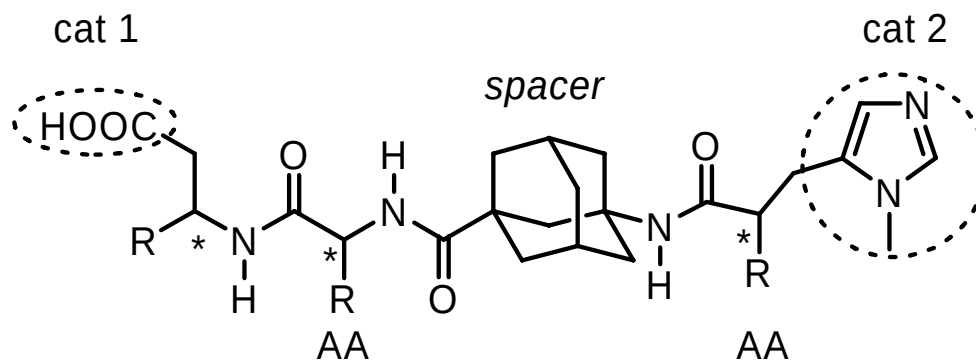
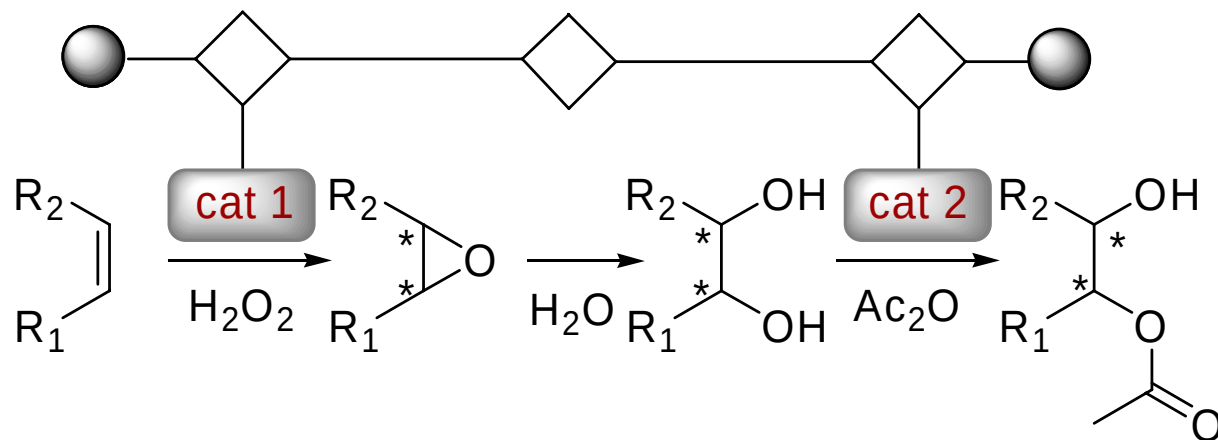
The reactions should be:

- one-pot
- sequentially catalyzed by both reaction centers
- should all be organocatalytic
- mild and easy
- should produce products in good yields as well as purities

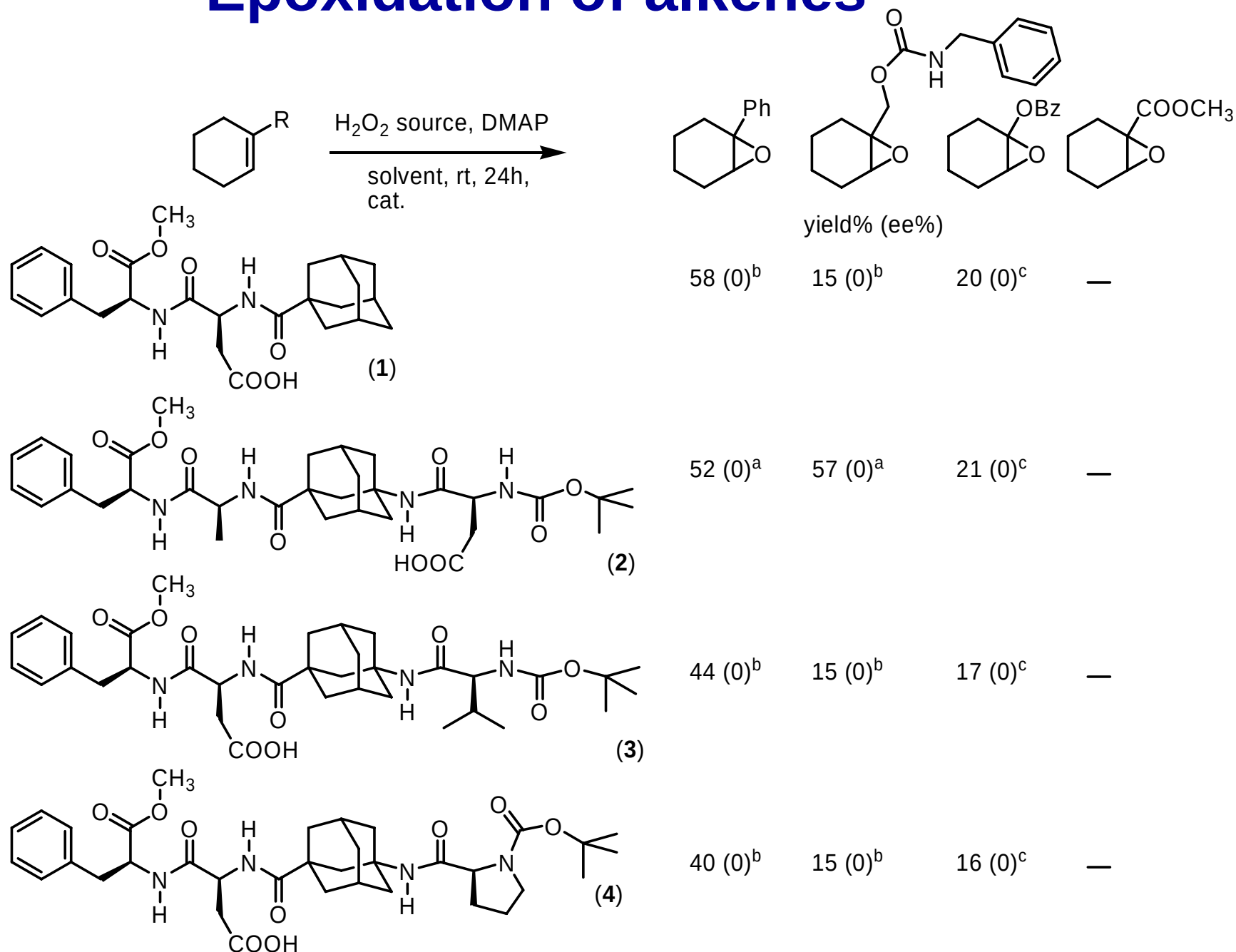
The catalyst should be:

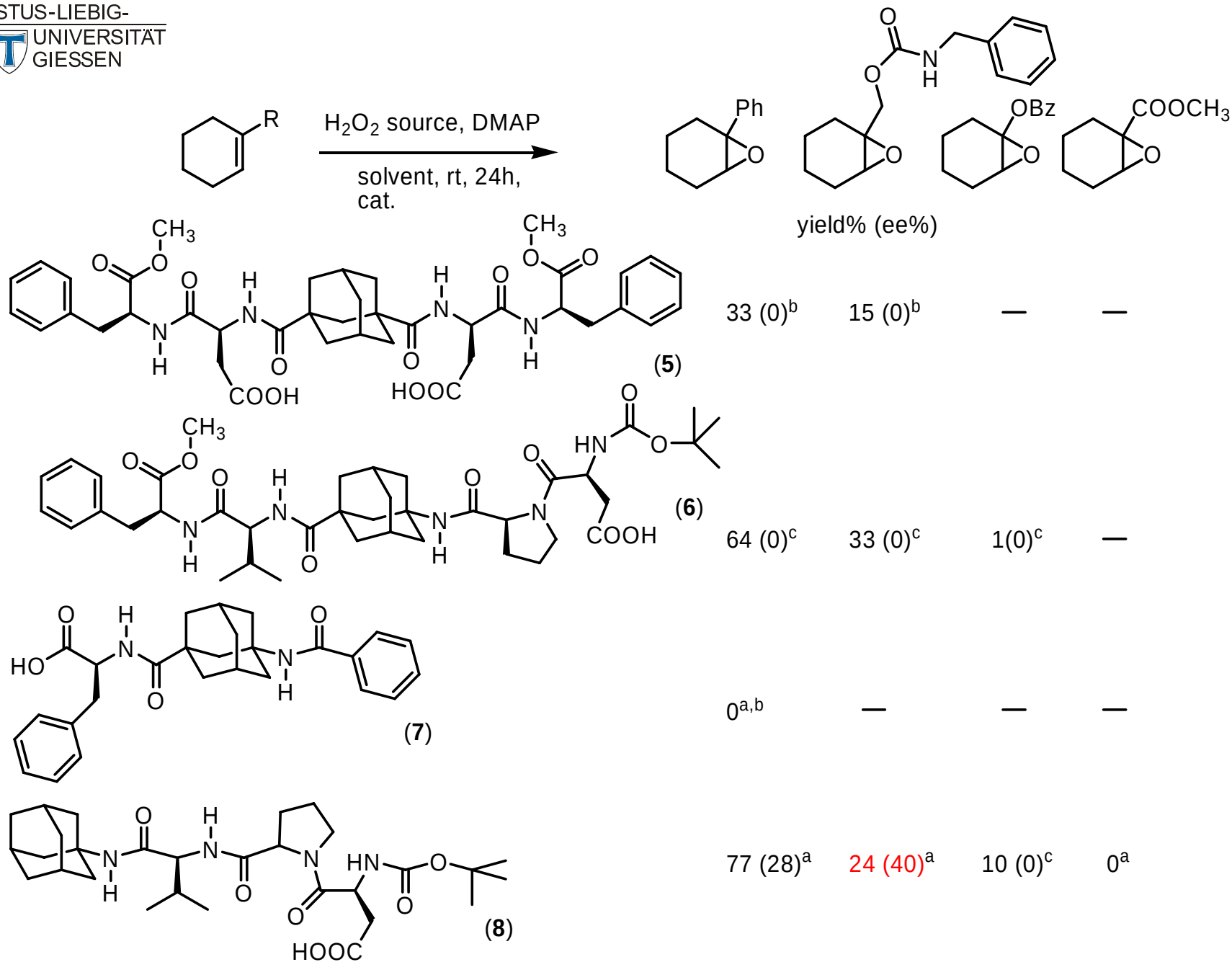
- stable throughout the sequence

The vision



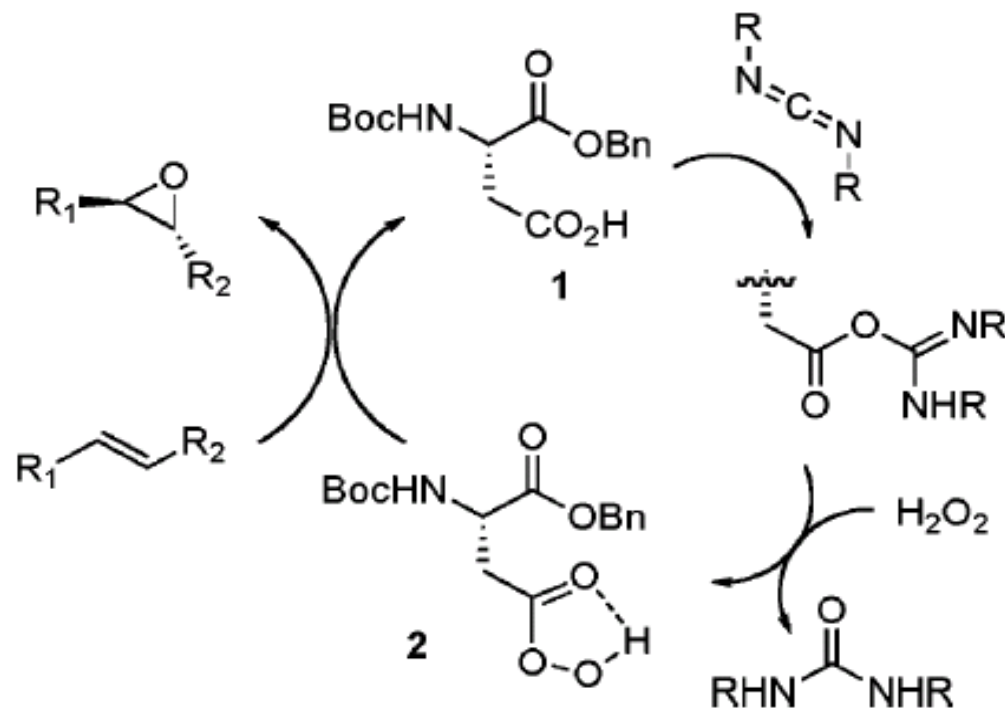
Epoxidation of alkenes





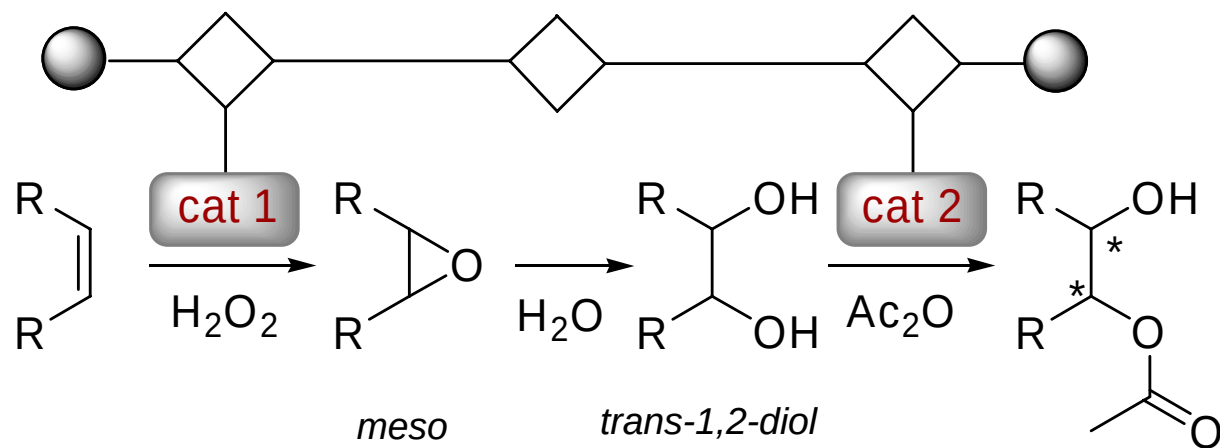
a: 30% H₂O₂ 2.5 eq, DMAP 0.1 eq, DCC 2 eq, 10% cat., toluene, r.t., 24h. b: urea*H₂O₂ 1.1 eq, DMAP 0.1 eq, DCC 1.1 eq, 10% cat., DCM, r.t., 24h. c: 30% H₂O₂ 1 eq, DMAP 0.05 eq, DCC 1.1 eq, 5% cat., toluene, r.t., 24h.

Mechanism of epoxidation ?

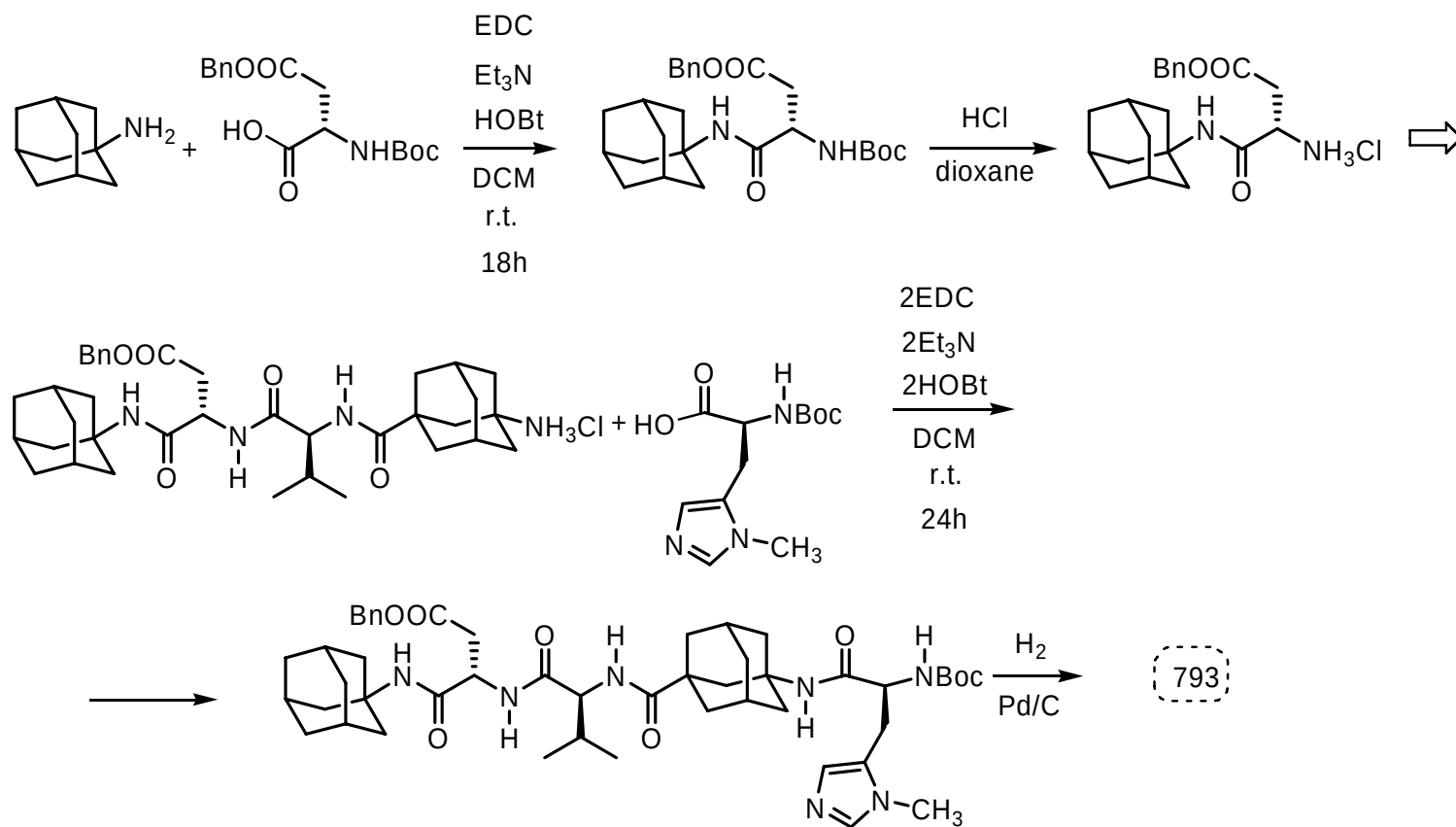
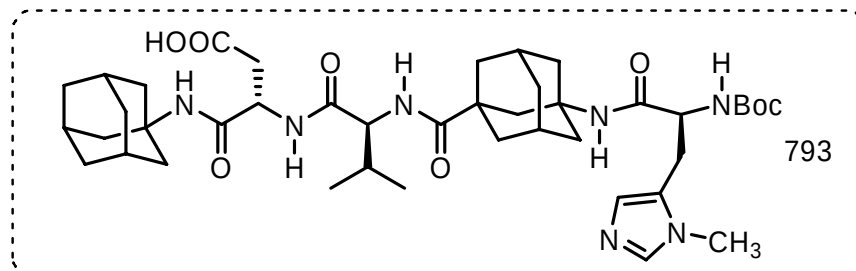


J. AM. CHEM. SOC. 2007, 129, 8710-8711

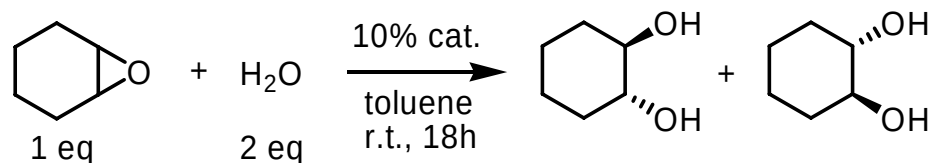
New vision



Synthesis of bifunctional peptides



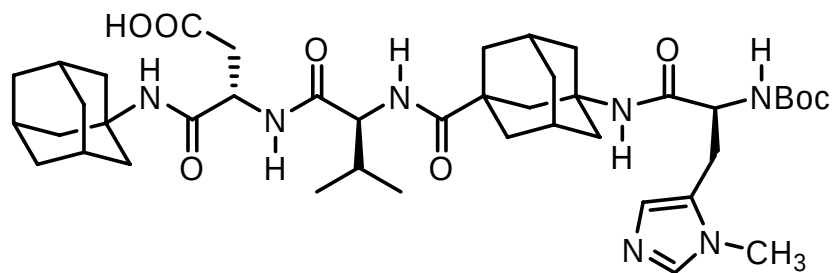
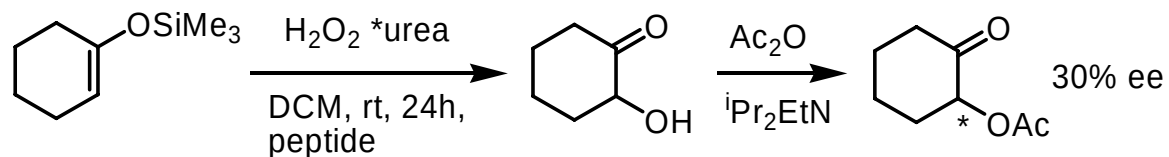
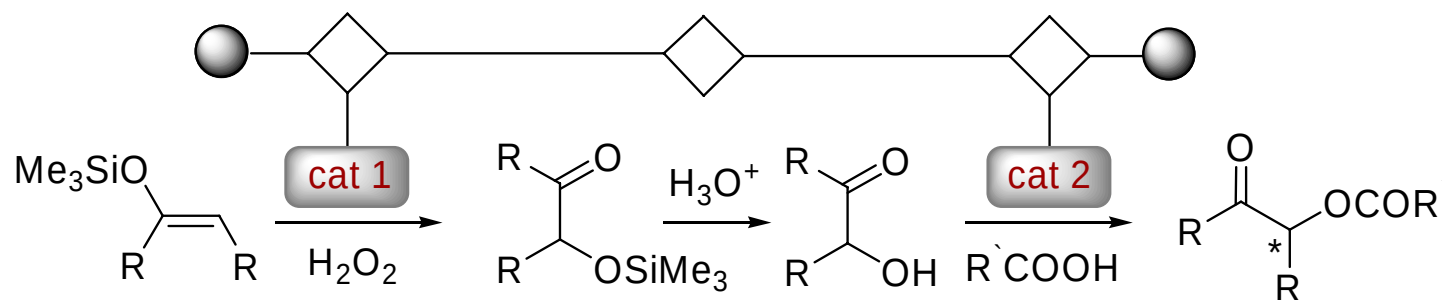
Opening of epoxides by water



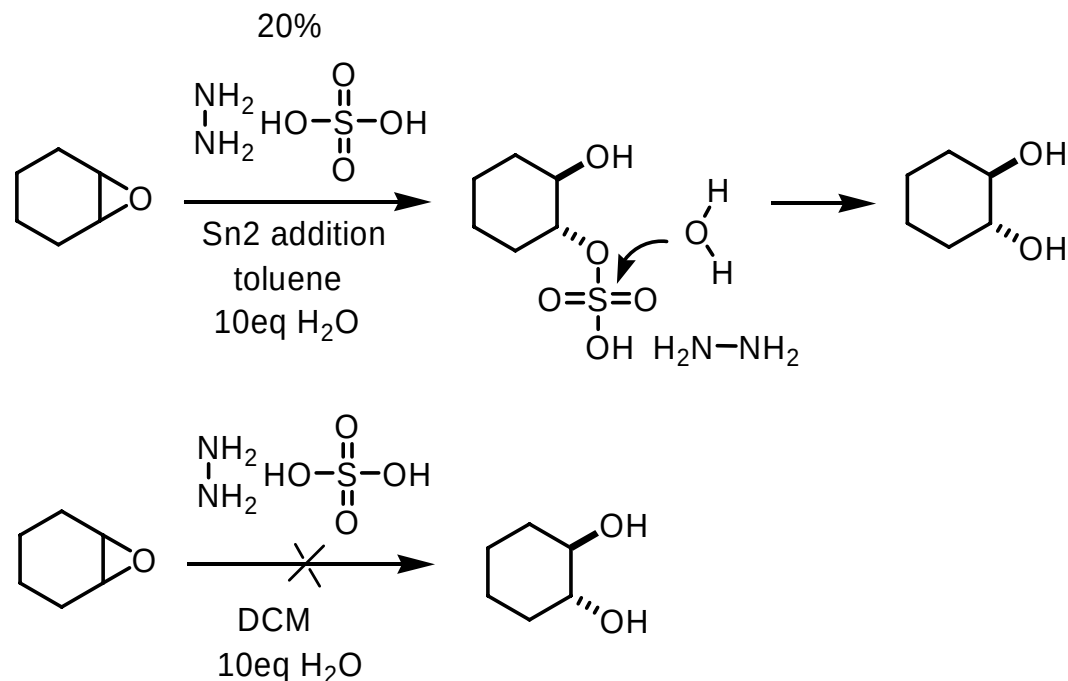
catalyst	yield	catalyst	yield
DMAP	0 %		0 %
NaHCO ₃	0 %		
NaOH	0 %		
CH ₃ COOCOCH ₃	0 %		0 %
CH ₃ COOH	0 %		
<i>p</i> -tolSO ₃ H	0 %		
H ₂ N-CH ₂ -CH ₂ -SO ₃ H	0 %		

First tandem reaction

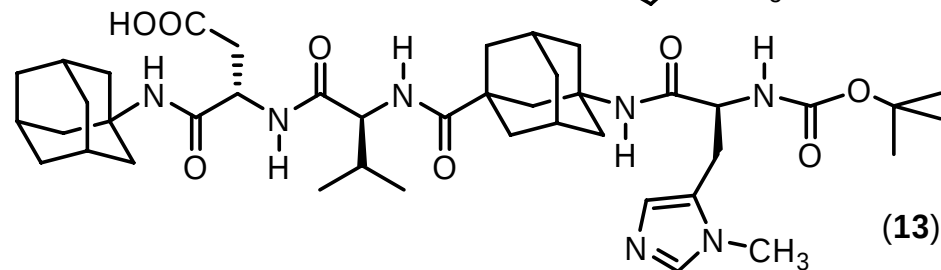
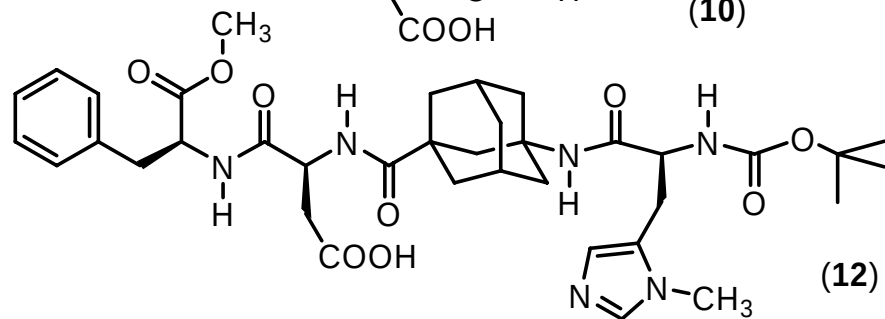
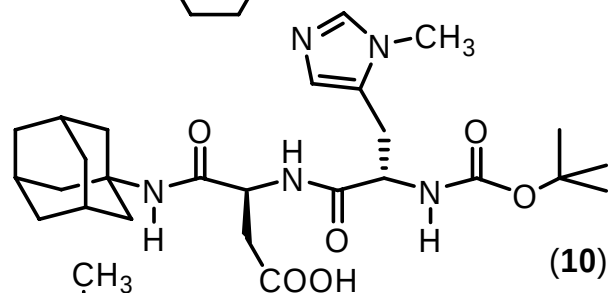
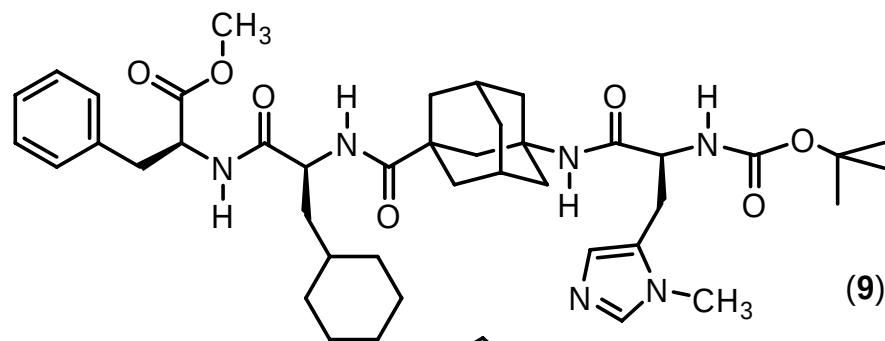
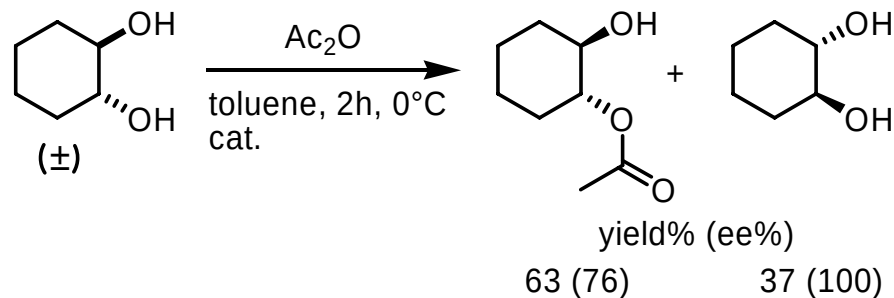
Rubottom oxidation



Mechanism of epoxide opening using hydrazine sulphate as catalyst



Kinetic resolution of *trans*-1,2-diols

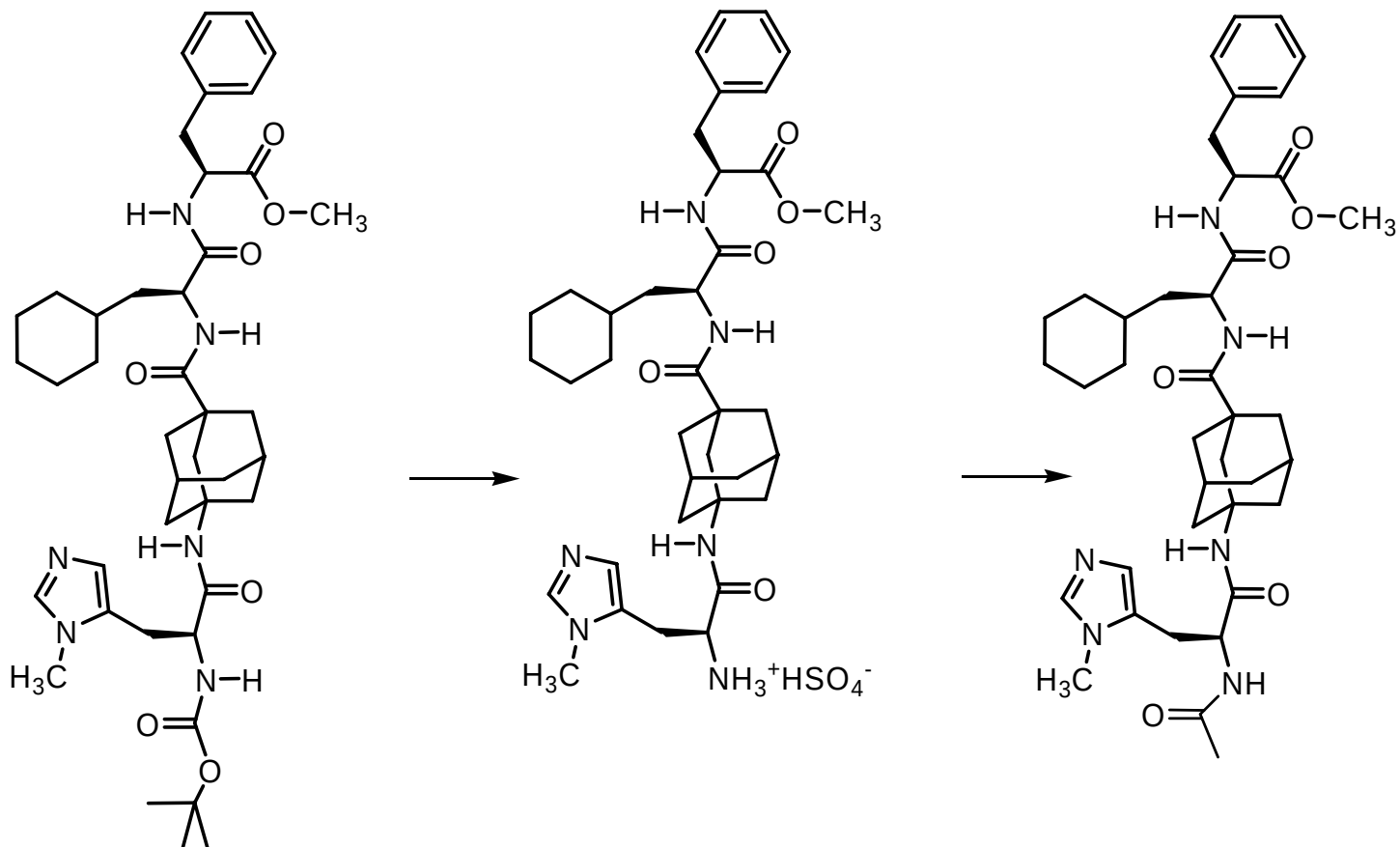
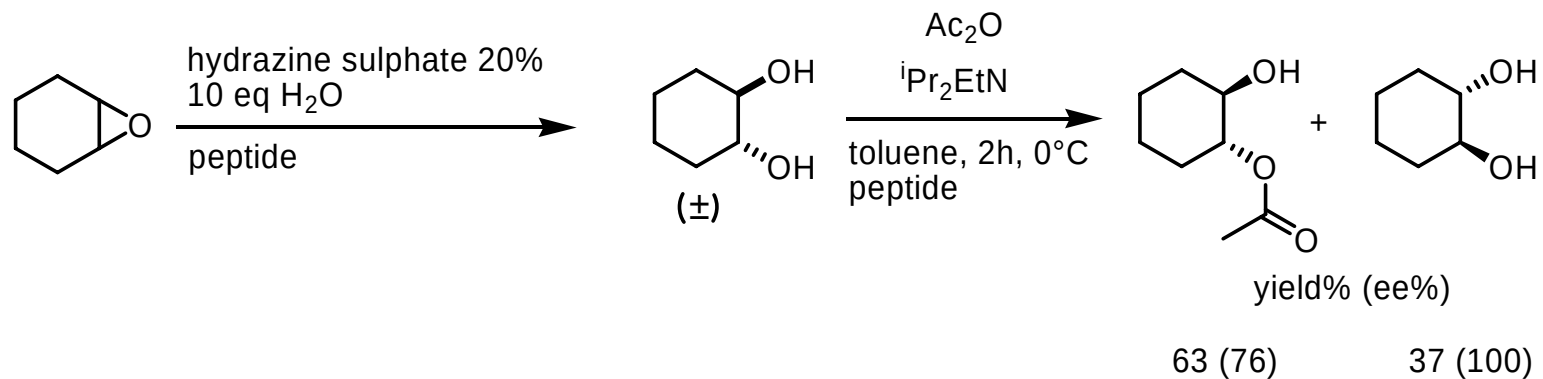


41 (8) 59 (6)

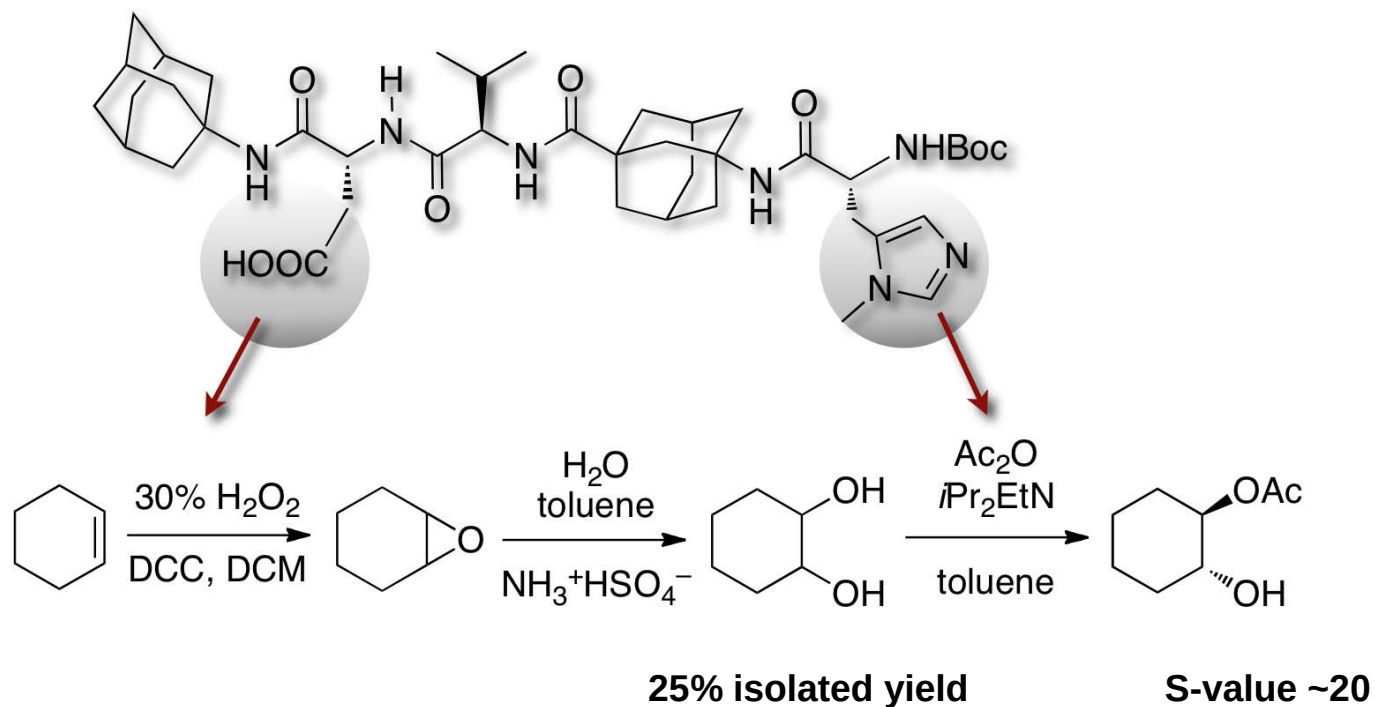
55 (36) 45 (28)

66 (60) 34 (85)

Control experiment

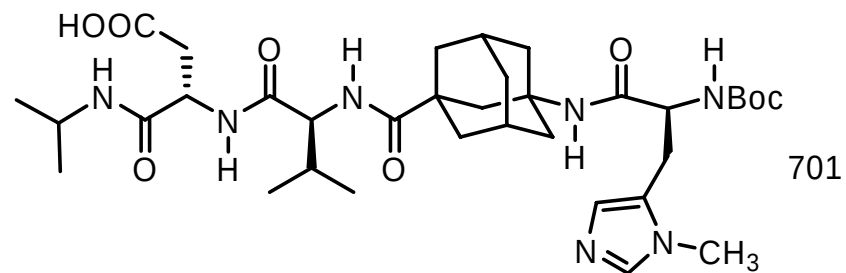
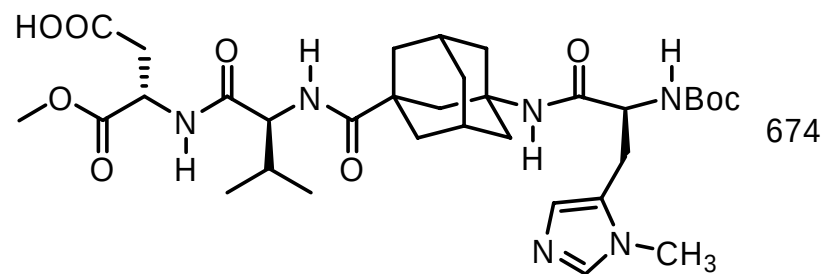
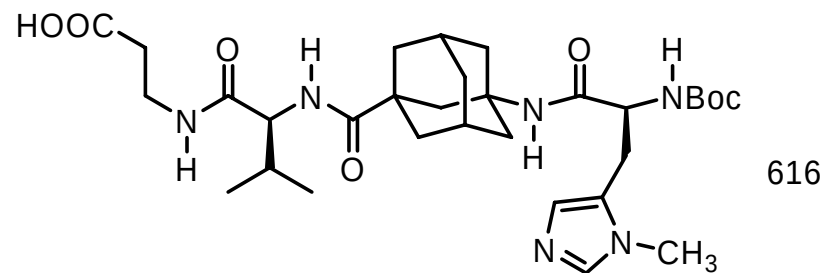
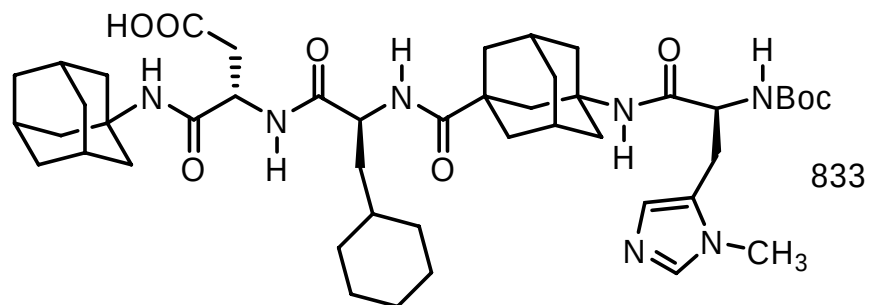
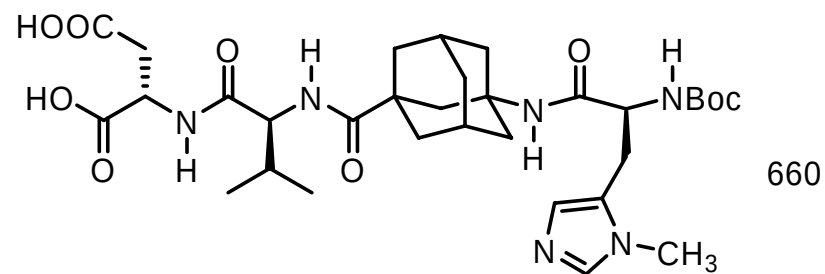
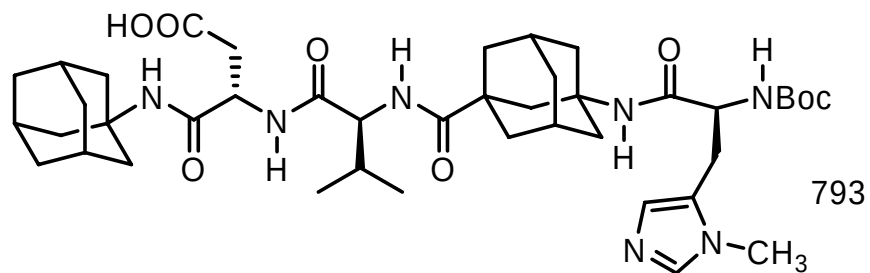


First selective tandem reaction



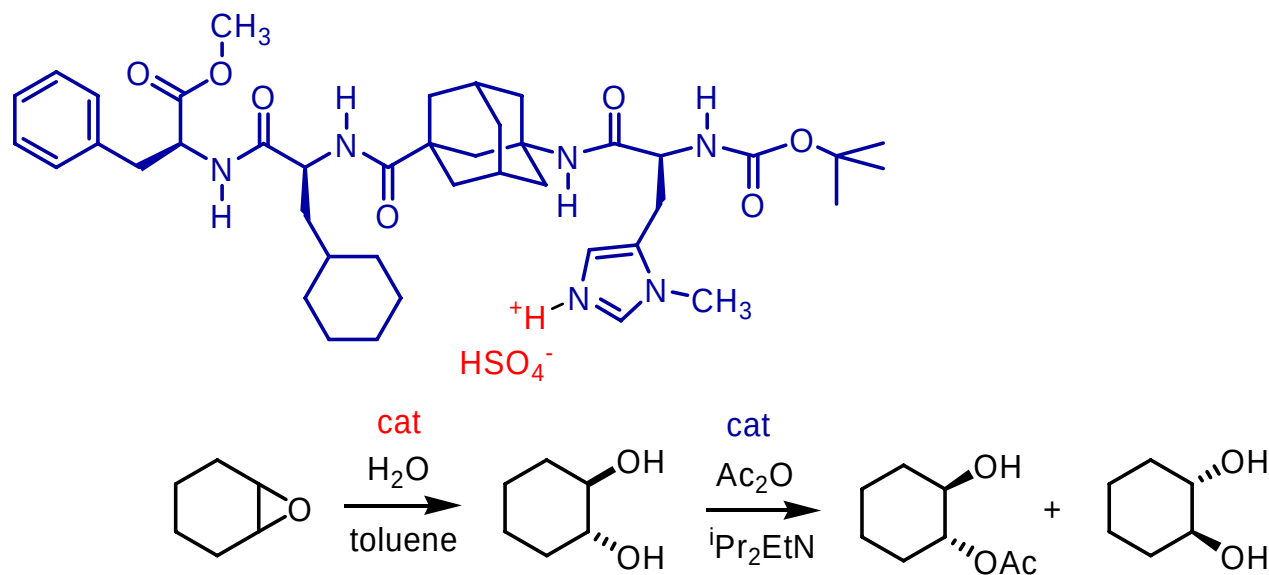
1. 2 eq cyclohexene, 1eq peroxide, 1.2 eq DIC, 5% peptide
2. 10 eq water, 20% hydrazinesulphate, toluene
3. 5 eq Hünig base, 5 eq acetic anhydride

Refining the catalyst

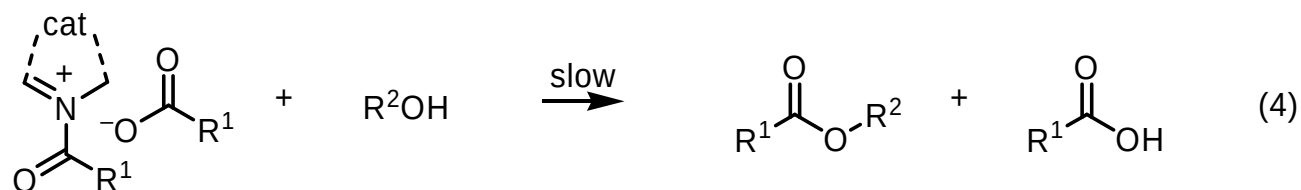
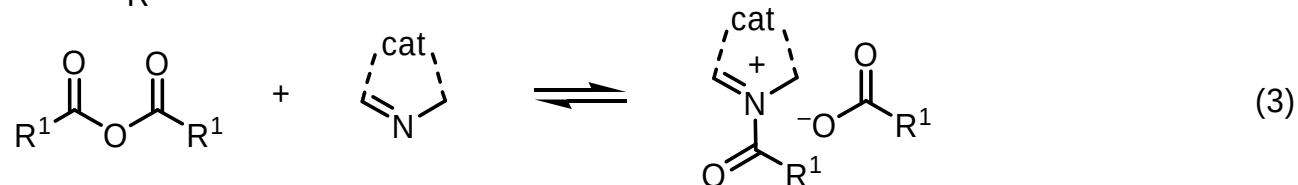
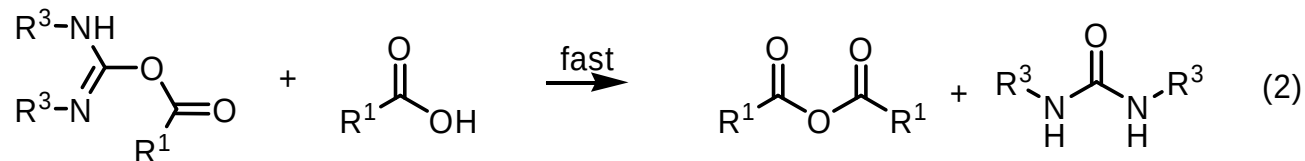
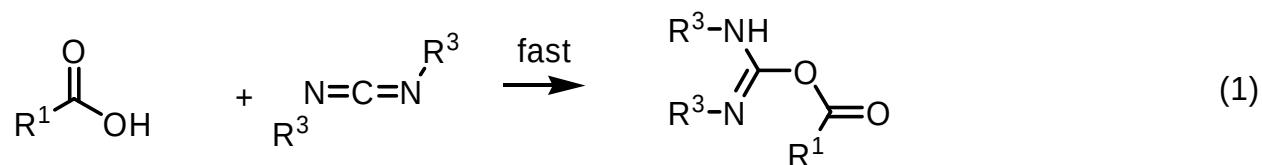


Smart salt

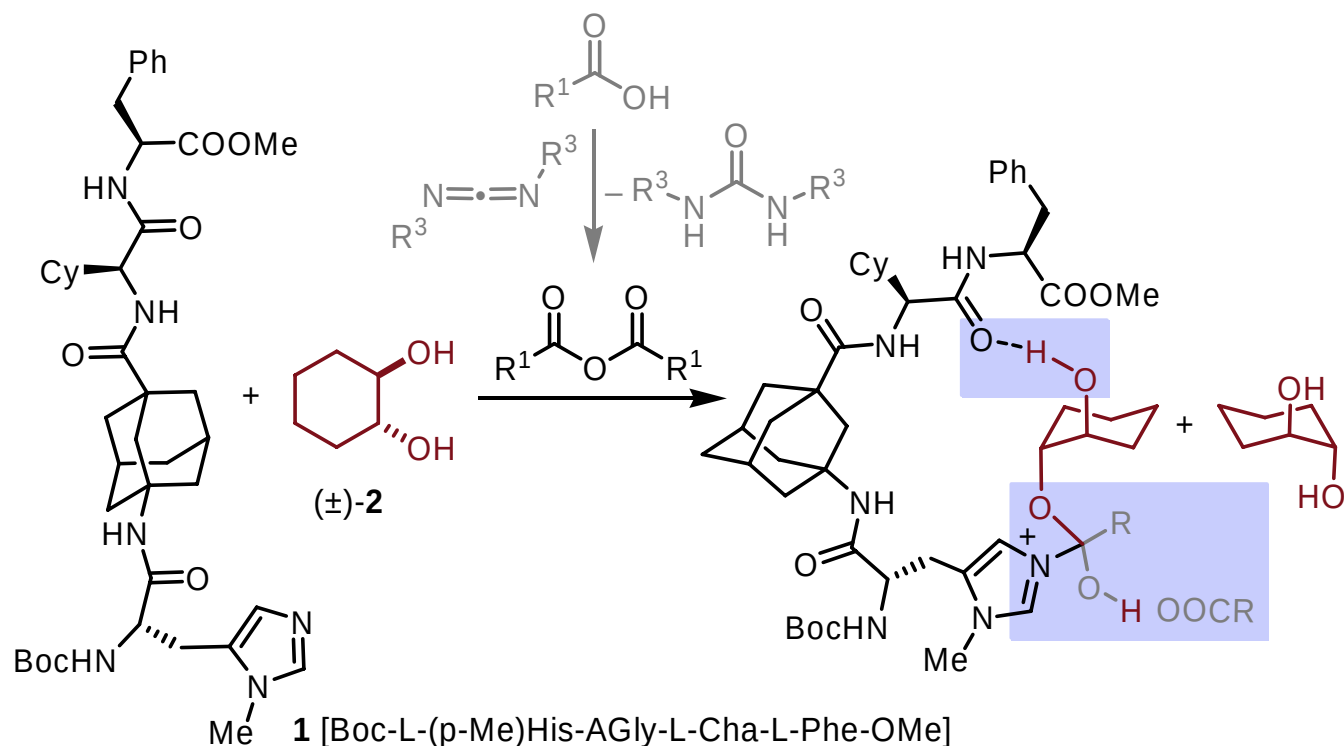
Salt of chiral **week base** and **strong achiral acid**
both parts serve as catalyst



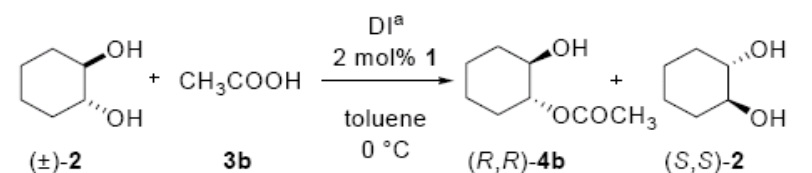
Mechanism of Steglich esterification



Kinetic resolution of *trans*-1,2-diols via Steglich esterification

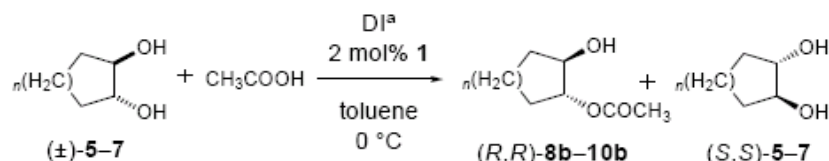


Steglich esterification in use



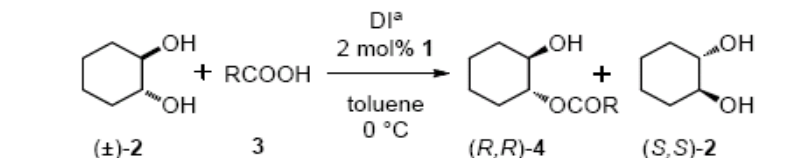
Molar ratio			<i>t</i> (h)	C (%) ^b	<i>ee</i> (%) ^b (<i>R,R</i>)-4b	<i>ee</i> (%) ^b (<i>S,S</i>)-2
(±)-2	3b	DI ^a				
1	1	DCC, 1.0	14	51	87	91
1	1	DIC, 1.0	14	54	83	97
1	1	EDC, 1.0	14	46	89	76
1	2	DIC, 1.2	10	55	81	>99
1	2	DIC, 2.0	7	55	80	>99
1	2	DIC, 1.2	8 ^c	56	76	98
1	2	DIC, 1.2	24 ^d	9	77	8

^aDI = Diimide, eq. given; ^bDetermined by chiral GC; ^cat r.t.; ^din DCM



<i>n</i>	<i>t</i> (h)	C (%) ^b	<i>ee</i> (%) ^b 8b, 32	<i>ee</i> (%) ^b 5 >99
1	10	76	8b, 32	5 >99
3	16	55	9b, 82	6 >99
4	18	55	10b, 81	7 >99

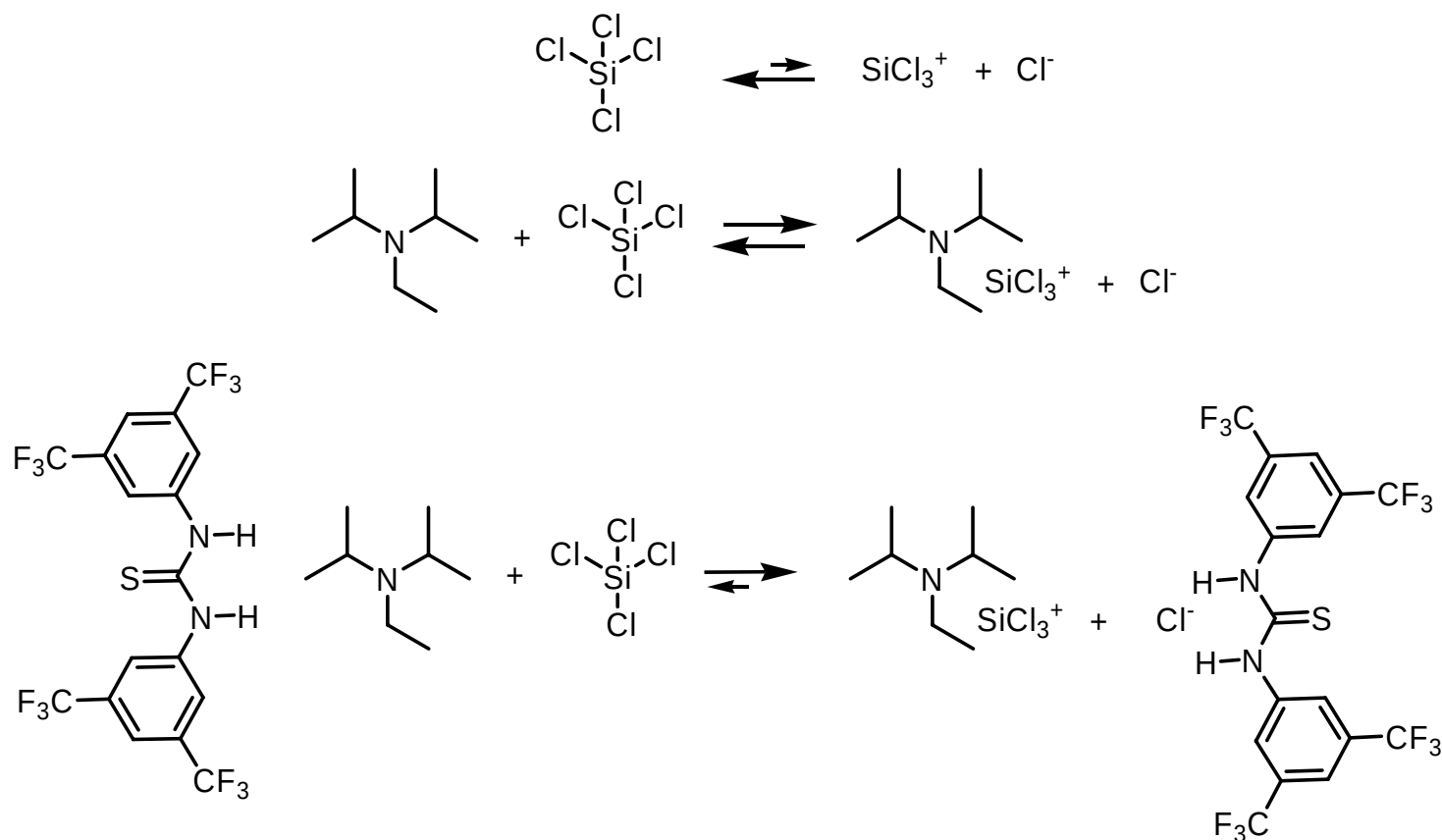
^aDI = diimide; ^bDetermined by chiral GC



	Carboxylic acid	<i>t</i> (h)	C (%) ^b	<i>ee</i> (%) ^b 4	<i>ee</i> (%) ^b 2
3a		7	63 ^d	41	83
3b		15	55	83	>99
		15	(51, 39) ^c	82	98
3c		15	55	83	>99
		41	(48, 43) ^c	90	98
3d		24	54	85	>99
		45	(55, 41) ^c	90	98
3e		48	4 ^e	86	4
3f		48	60 ^e	57	85
3g		2	57	75	>99
		2	(54, 41) ^c	82	>99
3h		48	38 ^e	60	36
3i		48	58 ^e	60	84
3j		48	n. d. ^e	n. d.	3

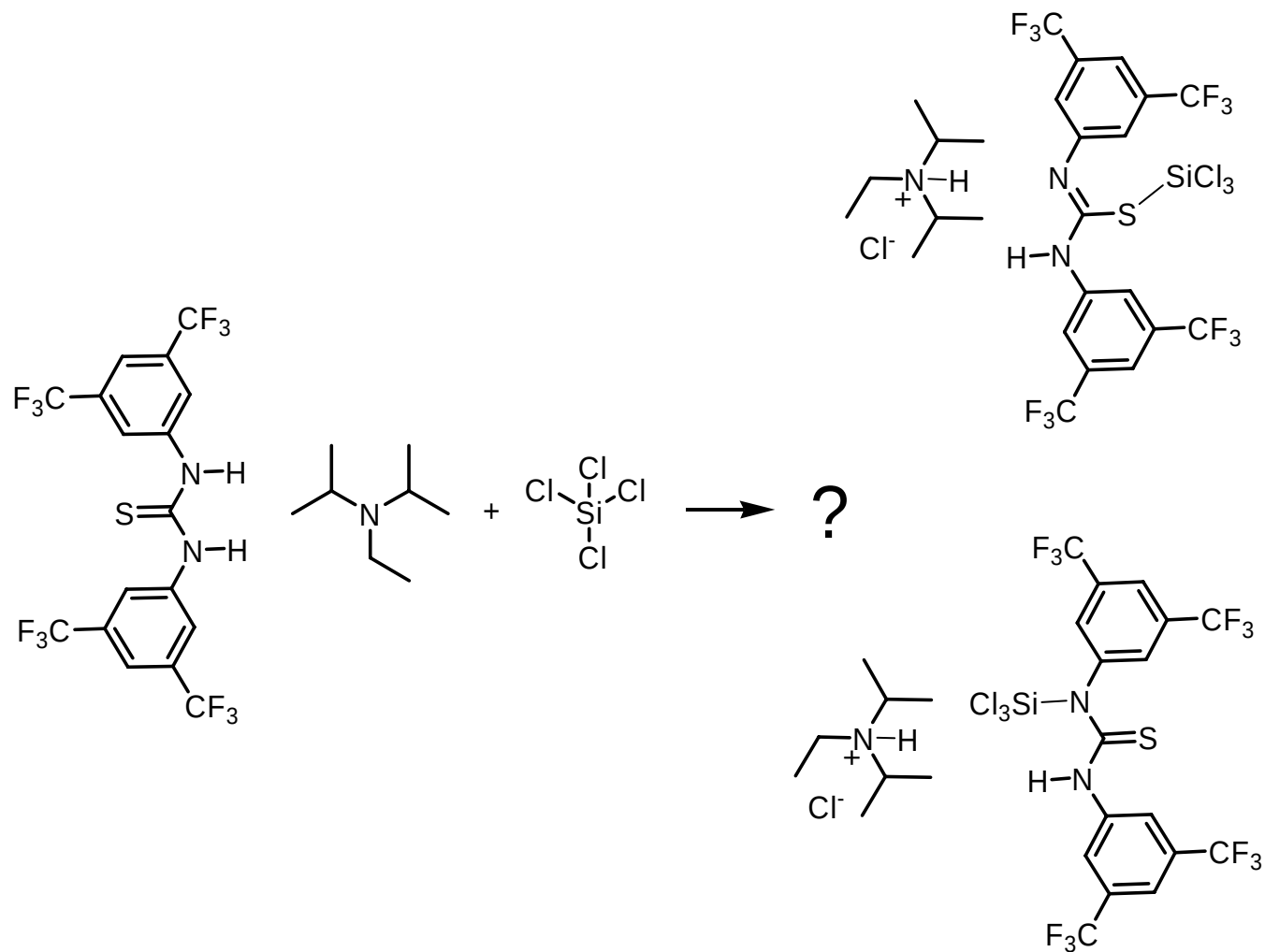
^aDI = diimide; ^bDetermined by chiral GC, ^cpreparative reaction at 1 mmol scale, isolated product yields (yield of 4 in %, yield of the 3 in %), ^ddoubled solvent volume, ^e2 eq. of DIC used

Cooperative organocatalysis: Activation of weak Lewis acid by N-H bond acceptor

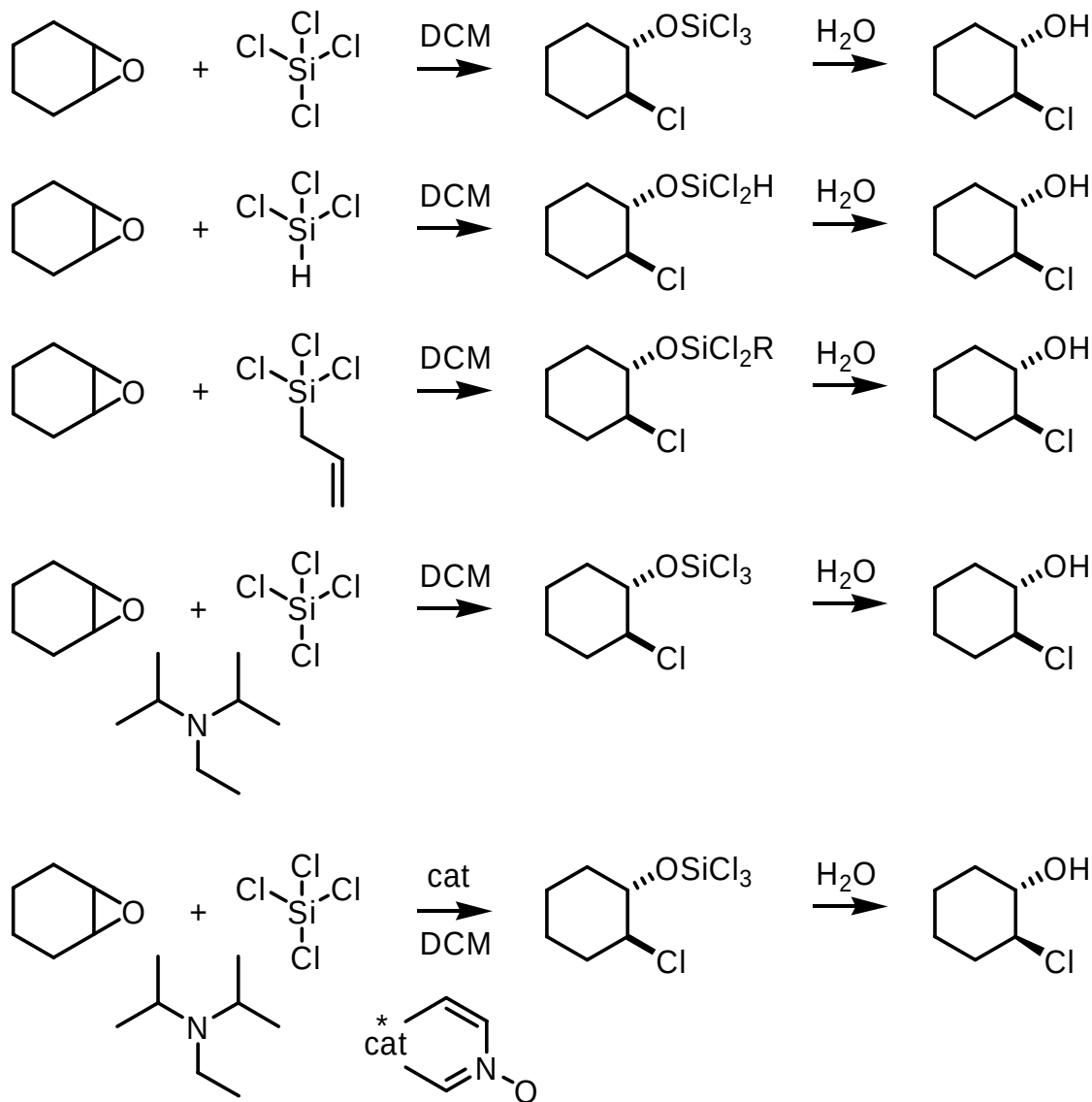


Isn't it a „frustrated system“?

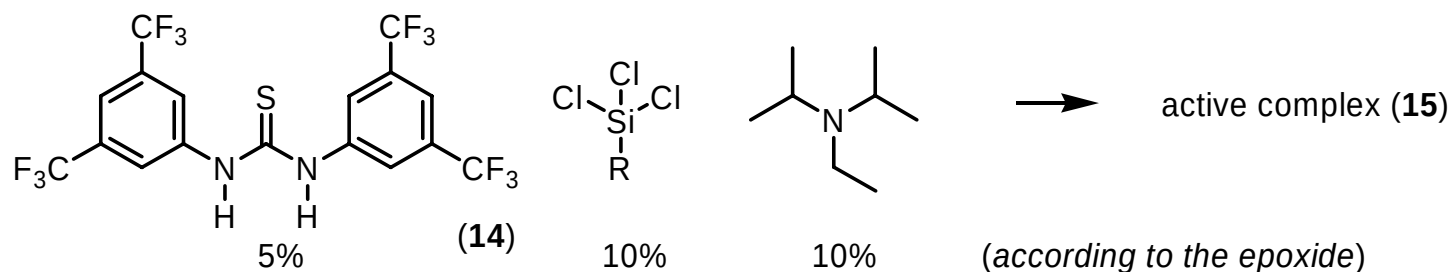
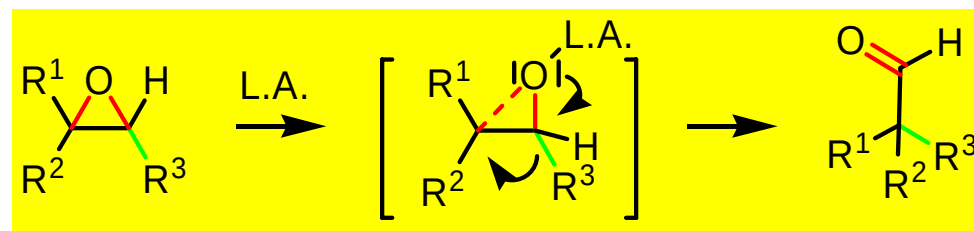
Or covalent compound?



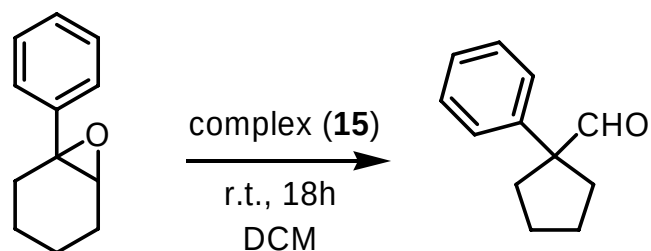
Opening of epoxides by chlorosilanes



Rearrangement of epoxides to aldehydes

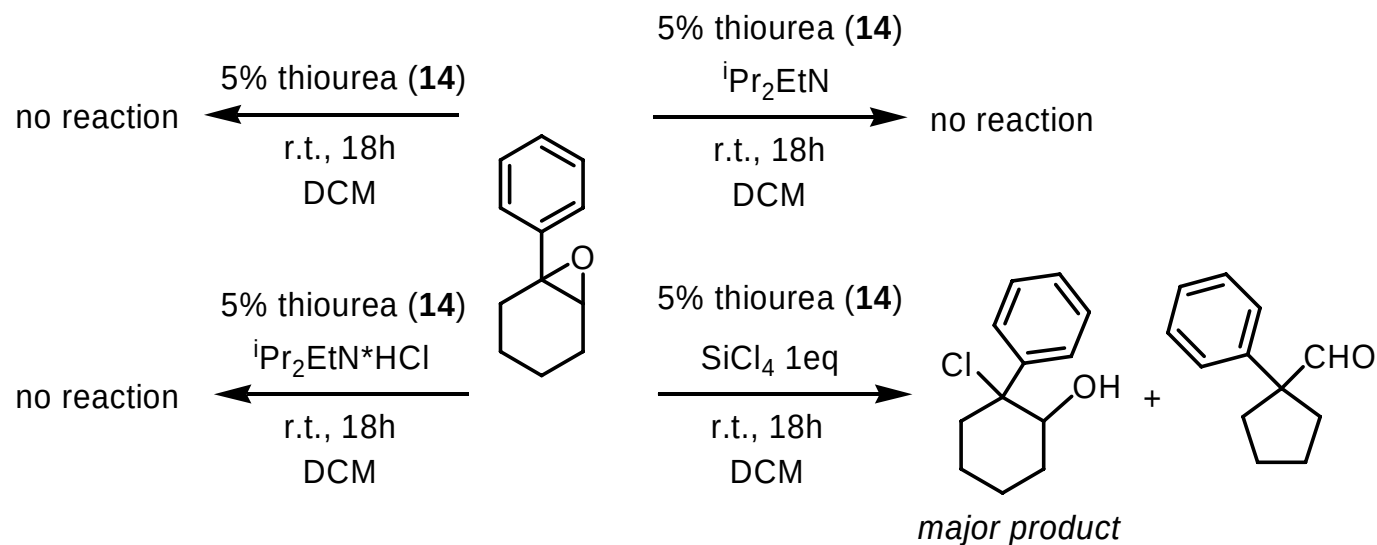


Screening of the chlorosilanes

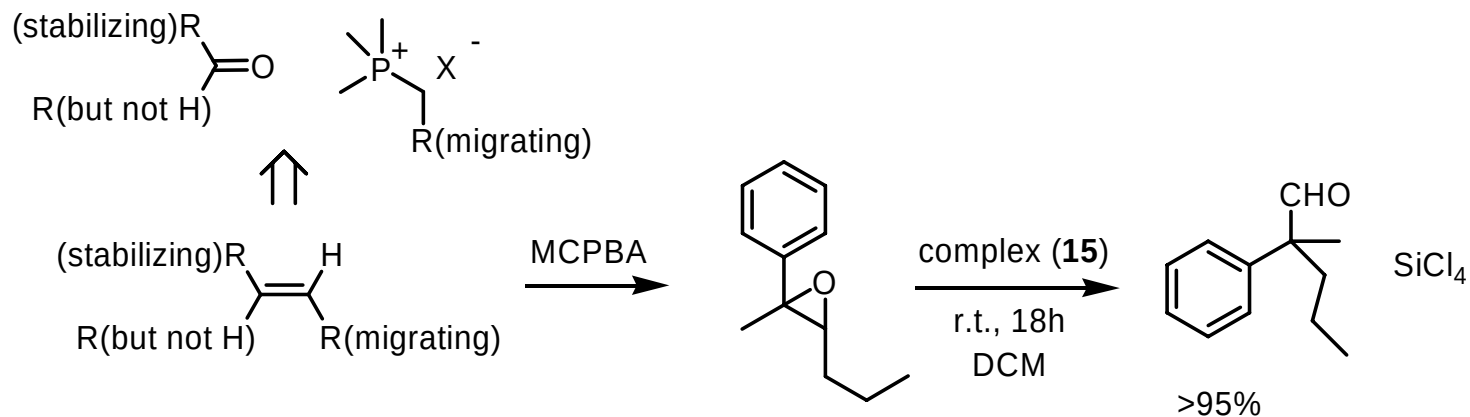


silane	yield
SiCl_4	>95%
PhSiCl_3	86%
Ph_2SiCl_2	24%
Ph_3SiCl	0%
$\text{AllylMe}_2\text{SiCl}$	0%

Control experiments



Substrate scope



Conclusion

1. Approach to the synthesis of compound containing two catalytic centers was developed.
2. It is possible to conduct sequence of three reactions in one pot.
3. Steglich reaction can be used for kinetic resolution of alcohols.
4. Activation of weak Lewis acids *via* anion trapping was exploited in rearrangement of epoxides to aldehydes.

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