

Enantioselective Silyl Protection of Diol

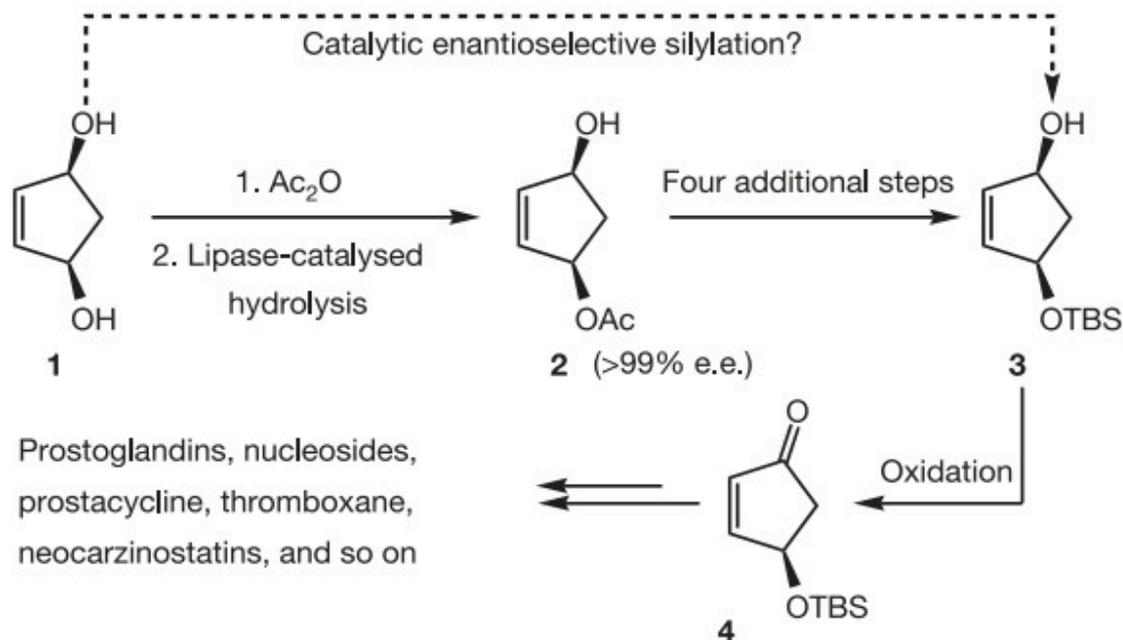
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5-November-2013

Background

How to achieve enantioselective silyl protection ? ? ?

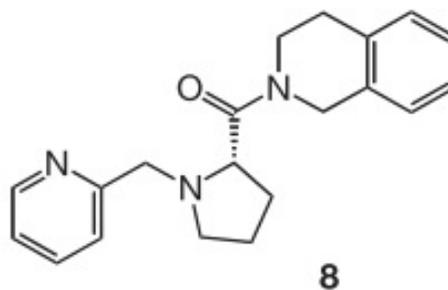
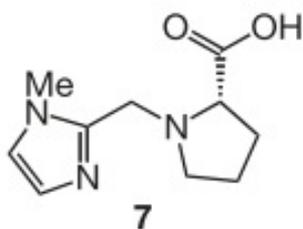
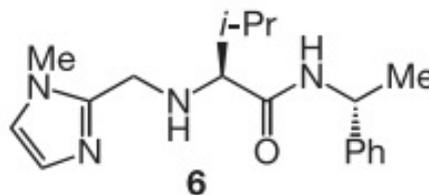
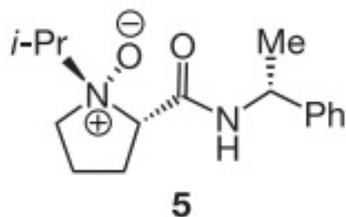
- **Modified guanidines as chiral superbases---less than 50% yield, up to 70 % ee**
- **Cu-catalysed kinetic resolution—Need a stoichiometric chiral silyl PG!**
- **No biomimetic mechanistic blueprint!**

Background



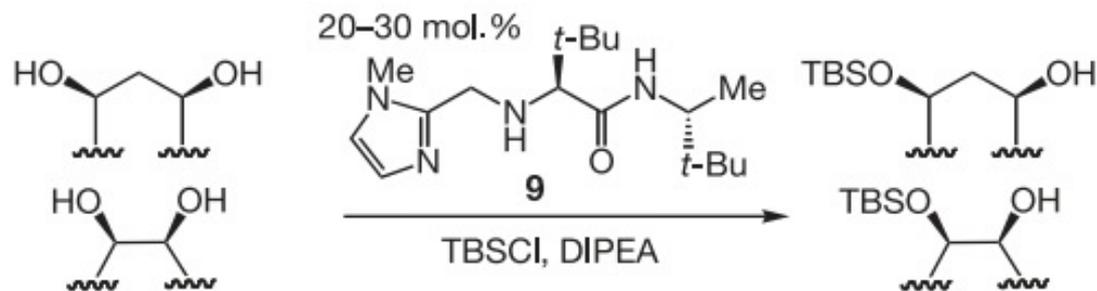
- It takes 6 steps to achieve selective silylation
- The sequence need 10 days---enzymatic deacylation takes a week!

How to design the catalyst?



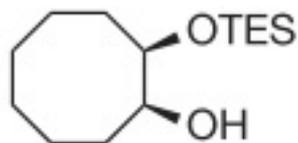
- Lewis basic moiety—increase the electrophilicity of the silyl halide
- H-bonding—establish substrate-catalyst binding
- **6 is found to be active—16 % ee at 25 °C, 48 % ee at -78 °C!**

Results

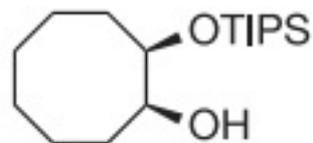


Entry number	Product	Catalyst	Catalyst equivalent	Time (h)	Temperature (°C)	e.r.	e.e. (%)	Yield (%)
8		9	0.3	120	-40	97.5:2.5	95	96
9		9	0.3	72	-40	96.5:3.5	93	80
10		9	0.2	120	-28	95:5	90	84
11		9	0.3	72	-28	96:4	92	67

Results



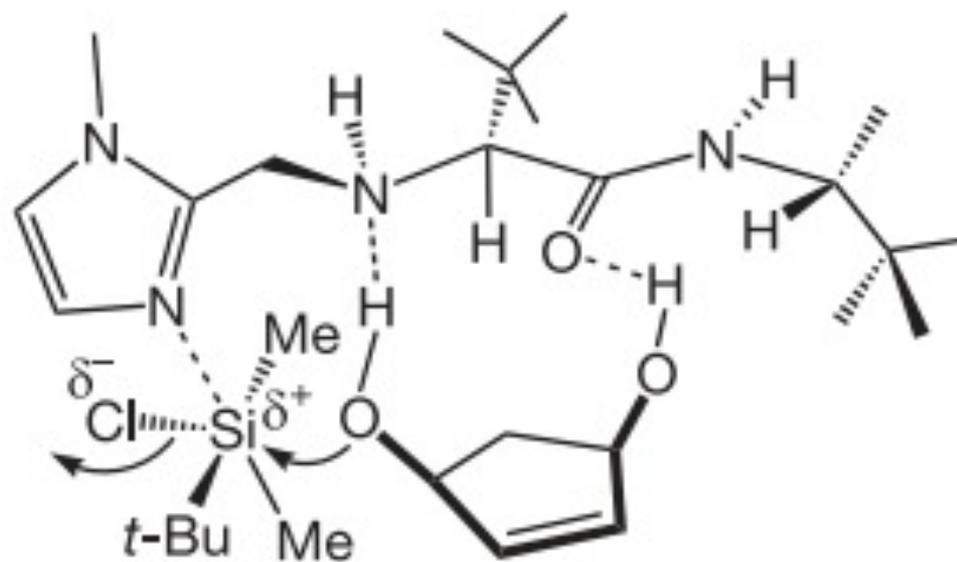
86% e.e., 94% yield
(0.3 equiv. **9**, -40 °C, 48 h)



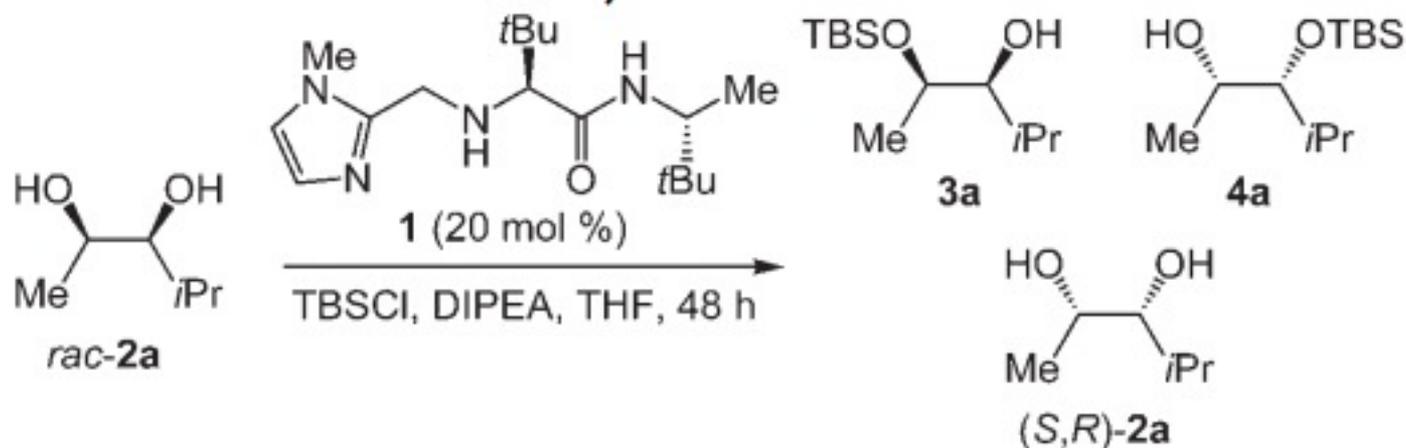
93% e.e., 71% yield
(0.3 equiv. **9**, -10 °C, 120 h)

- The catalyst also works for other silyl PGs
- Catalyst can be easily prepared from commercial chemicals
- High catalyst loading, but 99 % catalyst is recyclable

Proposed Mechanism

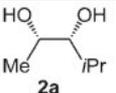
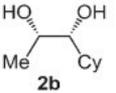
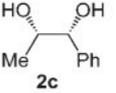
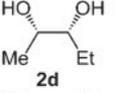
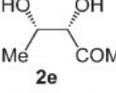
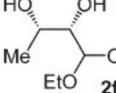
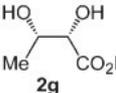
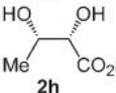


Application-Kinetic Resolution of 1,2-Diol



Entry	T [°C]; Conv. [%] ^[b]	3 a:4 a ^[c]	Recovered 2 a <i>ee</i> [%] ^[c]	Product 3 a <i>ee</i> [%] ^[c]	k_{rel} ^[b]
1	4; 61	> 98: < 2	70	45	5
2	-15; 53	> 98: < 2	82	71	16
3	-30; 30	> 98: < 2	38	88	24
4	-50; 27	> 98: < 2	34	93	35

Application-Kinetic Resolution of 1,2-Diol

Entry	Recovered diol (2)	Equiv. 1 ; Conv. [%] ^[b]	<i>T</i> [°C]; <i>t</i> [h]	3:4 ^[c]	Recovered 2 yield [%] ^[d] ; <i>ee</i> [%] ^[c]	Product 3 yield [%] ^[d] ; <i>ee</i> [%] ^[c]	<i>k</i> _{rel} ^[b]
1		0.3; 55	-50; 72	> 98: < 2	44; 96	48; 81	35
2		0.3; 51	-50; 48	> 98: < 2	48; 91	50; 88	48
3		0.3; 70	-15; 72	> 98: < 2	30; 96	68; 39	8
4		0.3; 57	-40; 48	97:3	36; 98	50; 73	29
5		0.3; 57	-40; 48	98:2	34; 91	45; 71	17
6		0.3; 55	-30; 24	> 98: < 2	44; > 98	52; 80	> 50
7		0.3; 64	-30; 72	86:14	32; 87	34; 78 ^[e]	25 ^[f]
8		0.3; 65	-30; 72	86:14	34; 90	44; 77 ^[g]	25 ^[f]

Application-Kinetic Resolution of 1,2-Diol

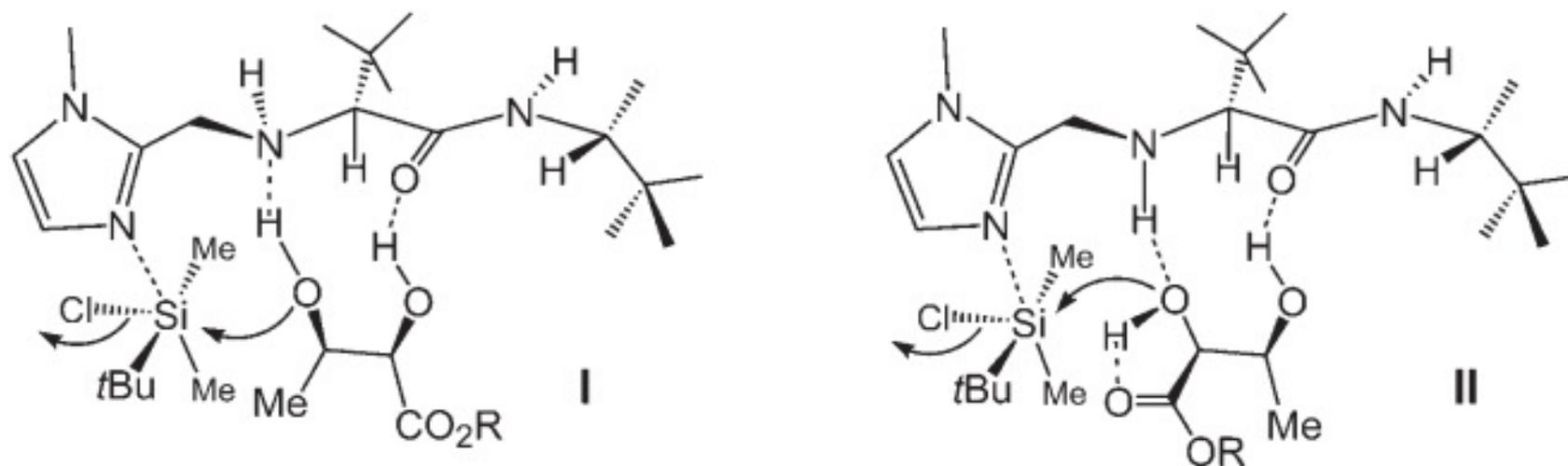
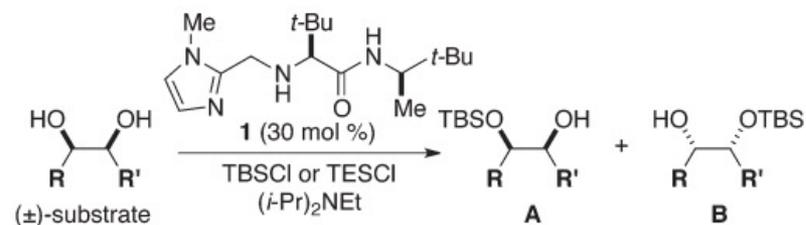
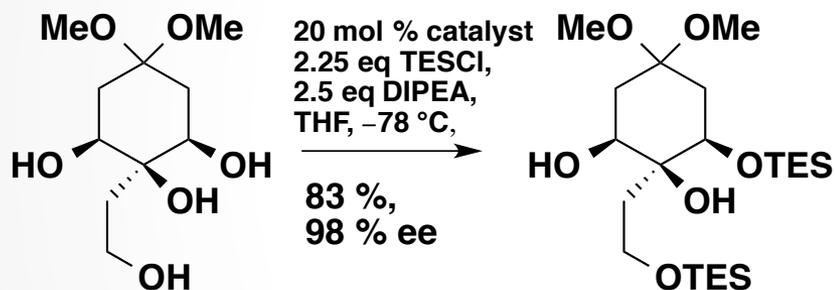


Figure 1. Transition-state models that account for lower site selectivity of ester-containing substrates.

Application-Total Synthesis



entry	substrate	A (ee)	B (ee)	yield (comb.)	ratio A/B
(1)		(88%)	(81%)	92% ^a	50/50
(5)		(85%)	(91%)	75% ^e	52/48
(6)		(83%)	(94%)	50% ^f	52/48

Further Study – Mechanism Revisit

Two significant shortcomings for this reaction are:

- High catalyst loading (20 -30 mol %)
- Long reaction time (2 – 5 days)

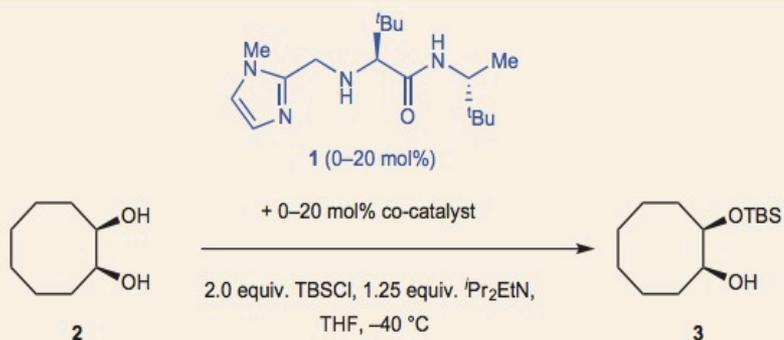
And computational study suggested the catalyst is not bifunctional!

- It is a suitable chiral base for the hydroxyl groups
- It is a bad nucleophilic activator for the silyl chloride

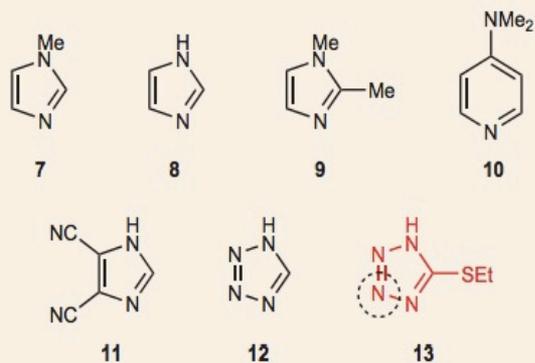
We need a co-catalyst to activate the silyl chloride



Screening of Co-catalyst

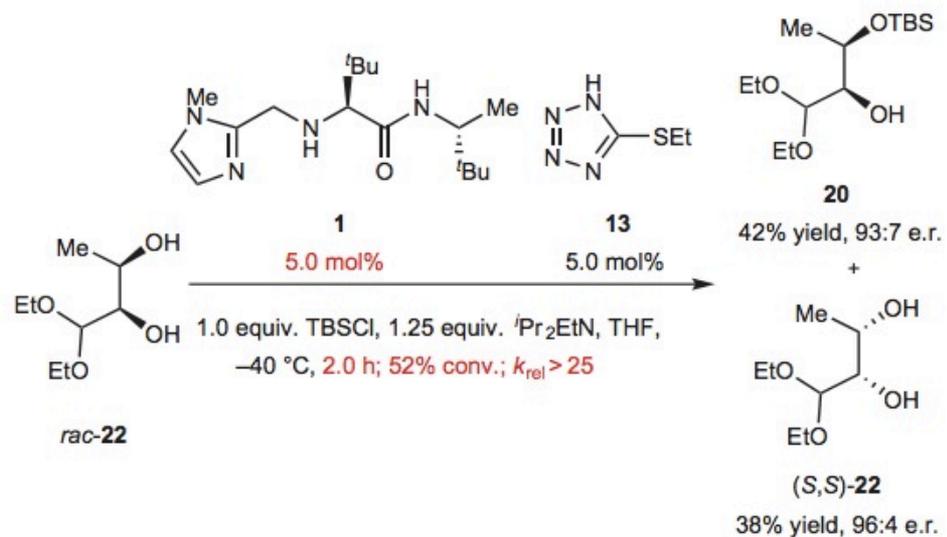
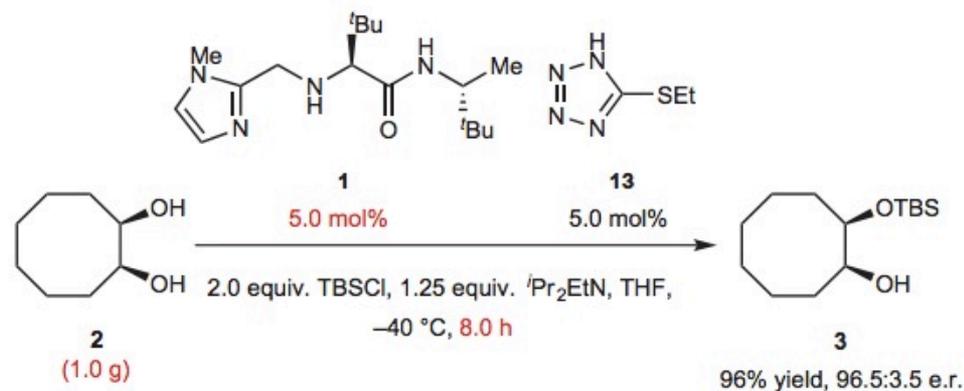


Co-catalysts examined

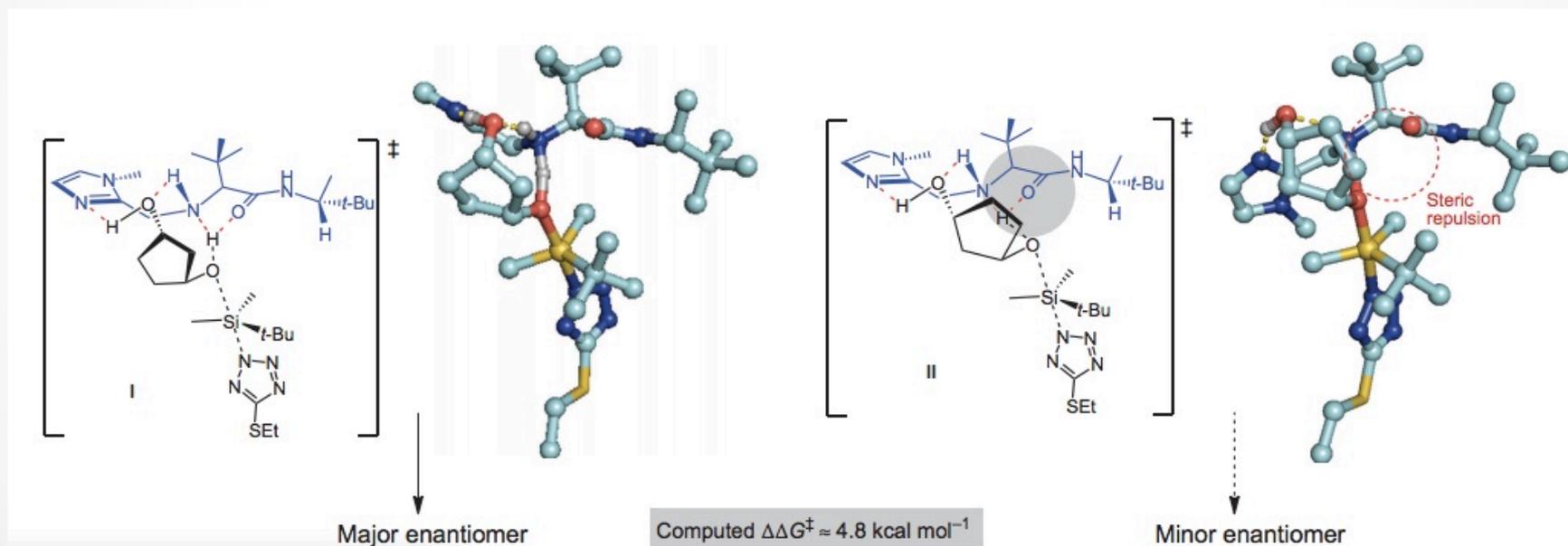


Entry	1 (mol%)	Co-catalyst (mol%)	Time (h)	Conv. (%)*	e.r. [†]
1	20	None; NA	6.0	9	93.5:6.5
2	0	7 ; 20	6.0	69	NA
3	20	7 ; 20	6.0	92	78:22
4	20	7 ; 15	6.0	88	81.5:18.5
5	20	7 ; 10	6.0	79	83:17
6	20	7 ; 7.5	6.0	71	85.5:14.5
7	20	7 ; 5.0	6.0	49	86.5:13.5
8	20	8 ; 7.5	3.0	13	93:7
9	20	9 ; 7.5	3.0	5	90.5:9.5
10	20	10 ; 7.5	3.0	8	86:14
11	20	11 ; 7.5	3.0	47	96:4
12	20	12 ; 7.5	3.0	45	98:2
13	20	13 ; 7.5	3.0	>98	97:3

Result



Mechanism



Reference

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