

Thiourea, squaramide as H-Bond donor in asymmetric catalysis

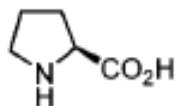
Reporter: Fengjin Wu
Supervisor: *Prof.* Huang
Date: 05. 07. 2018

Outline:

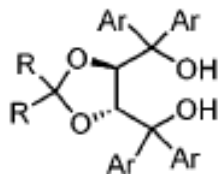
1. Introduction
2. Thiourea as H-bond donor
 - 2.1. monofunctional thiourea
 - 2.2. bifunctional thiourea—cooperative activation
 - 2.3. anion-binding pathway
3. Squaramide as H-bond donor
4. Conclusion
5. Acknowledgement

1. Introduction

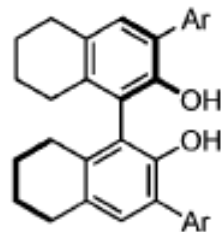
Representative H-bond donor asymmetric catalysts:



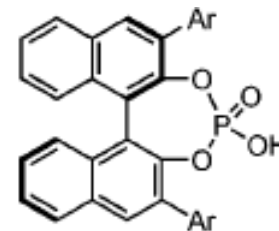
*Hajos, Parrish,
Eder, Sauer, Wiechert, 1970s
Aldol Cyclization*



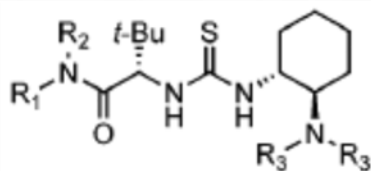
*Rawal, 2003
hetero-Diels-Alder
Cycloaddition*



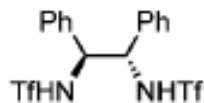
*Schaus, 2003
Baylis-Hillman Reaction*



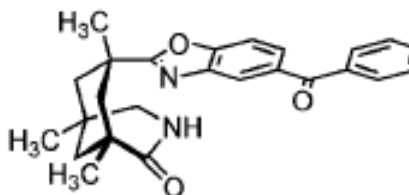
*Akiyama and Terada, 2004
Mannich Reaction*



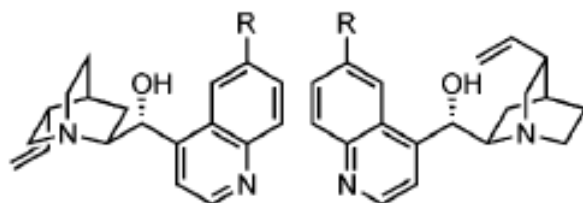
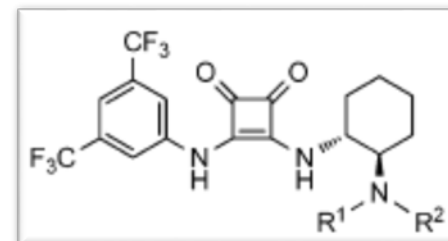
*Berkessel, 2005
Resolution of Azlactones
Jacobsen, 2005
Cyanosilylation of Ketones*



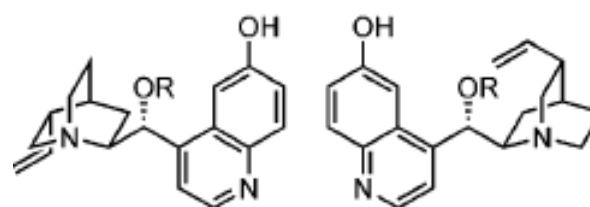
*Mikami, 2005
hetero-Diels-Alder Cycloaddition*



*Bach, 2005
Photocyclization*



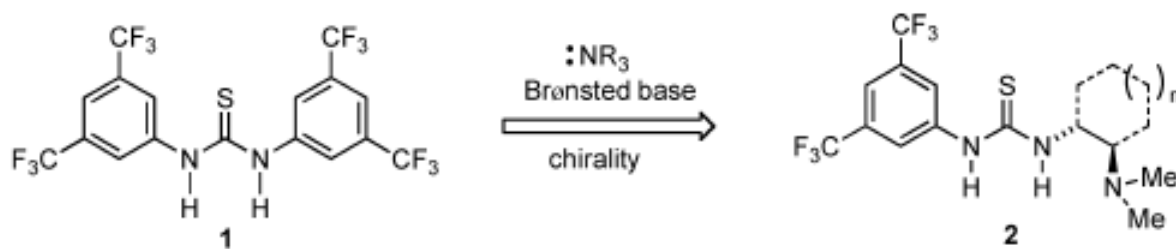
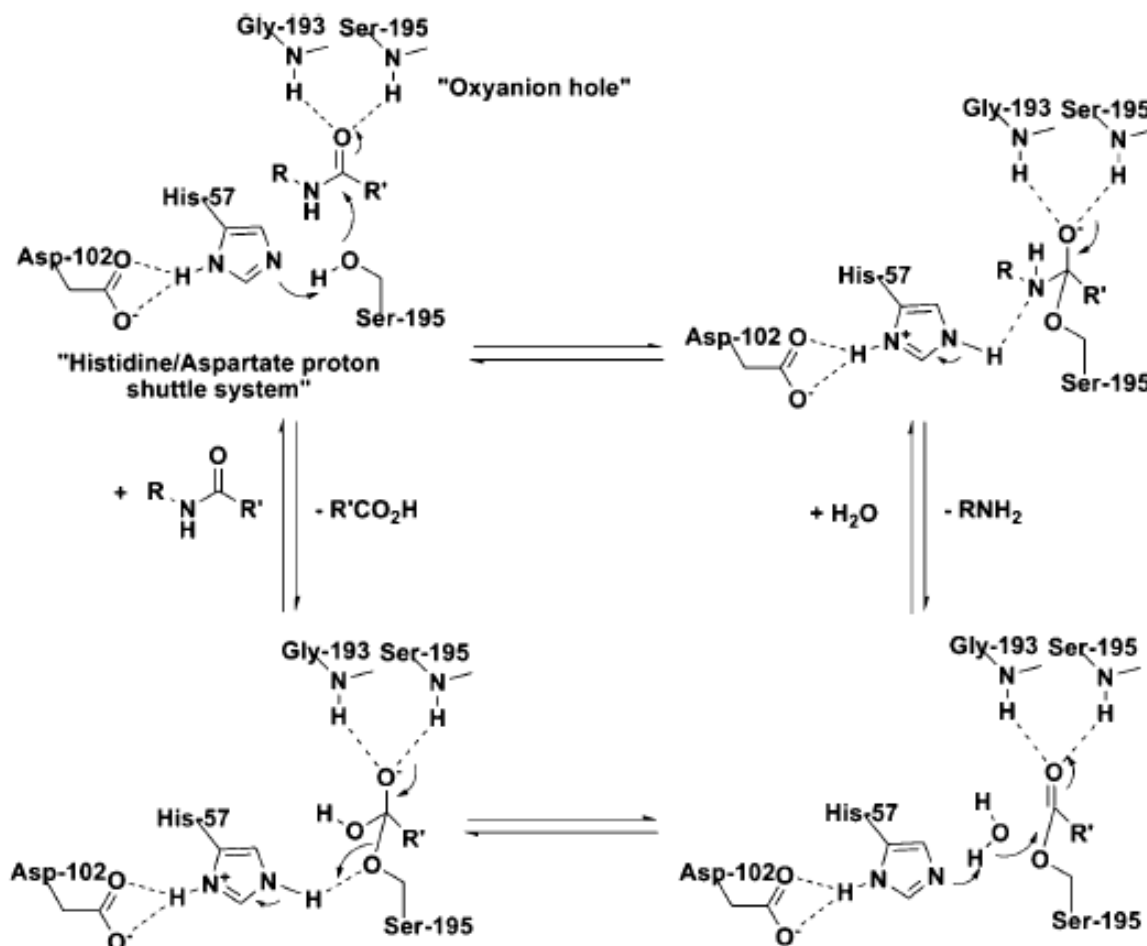
*Wynberg, 1981
Conjugate Addition*



*Deng, 2004
Conjugate Addition*

1. Introduction

Serine protease: Biological process of amide hydrolysis with hydrogen bonding



2. Urea (thiourea) as H-bond donor

2.1. monofunctional thiourea

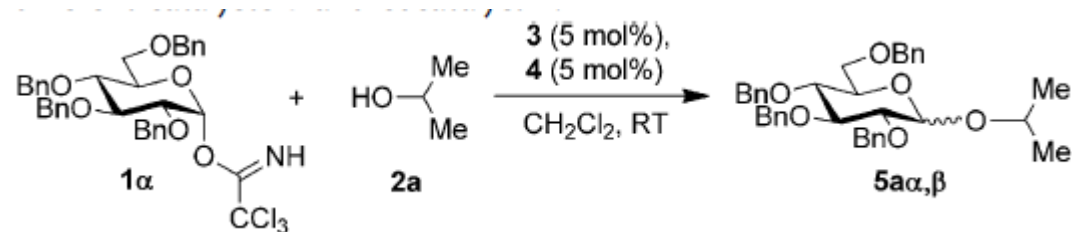
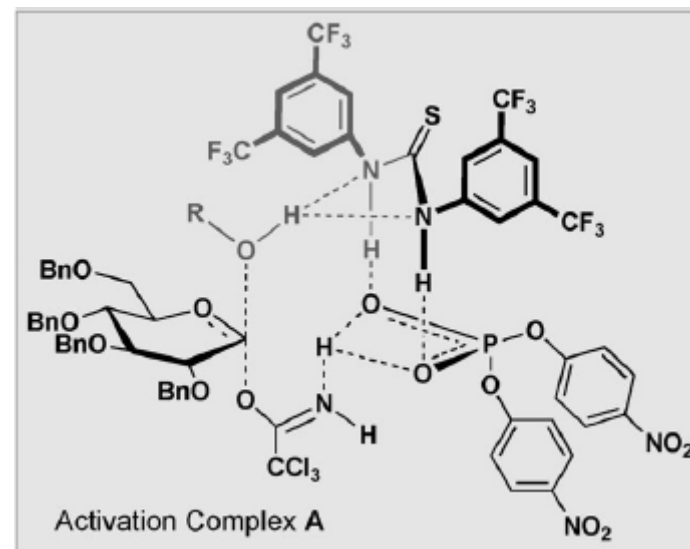


Table 2: Reaction of donor **1α** with isopropanol (**2a**) as acceptor in the presence of TMSOTf as catalyst and **4** as cocatalyst at different temperatures.^[a]

Entry	Addition of 4	Reaction temperature [°C]	Reaction time [min]	5α,β β/α ratio
1	—	0	5	1:1
2	—	−40	10	5:1
3	—	−78	30	12:1
4	+	0	5	1.3:1
5	+	−40	10	11:1
6	+	−78	30	> 20:1 ^[b]

Using TMSOTf as acid can also obtain β-selective product under −78 °C.



Thiourea worked as a relay for proton transfer.

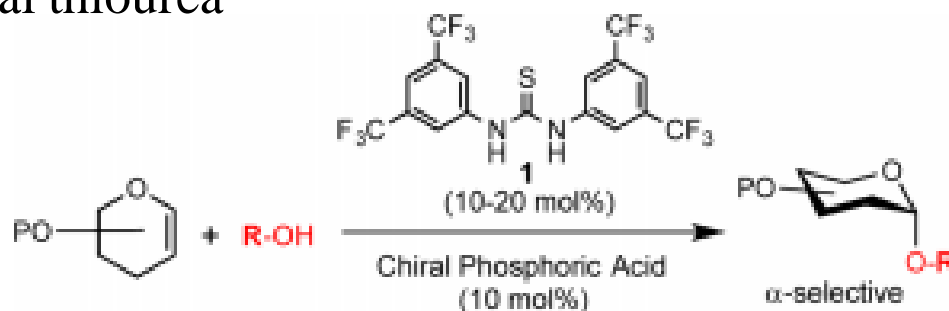
Temperature-dependent ion-pair formation

★ SN2-type reaction at low temperature

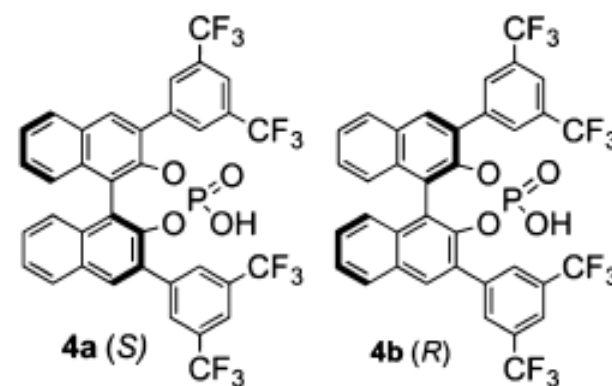
★ SN1-type at high temperature.

2. Urea (thiourea) as H-bond donor

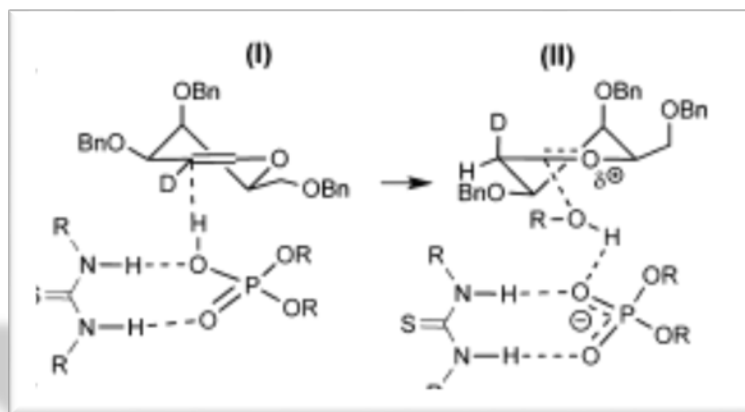
2.1. monofunctional thiourea



entry	acid	time (h)	yield (%) ^c	$\alpha:\beta^c$
1	—	24	0	N/A
2	4a ^a	20	55	9:1
3	4a	3	82	7:1
4	4b ^a	20	70	>30:1
5	4b	3	89	>30:1



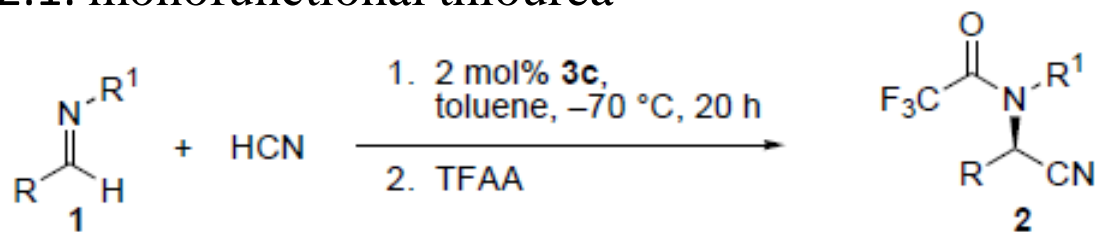
The stereochemistry of CPA have a big effect on selectivity.



an oxonium intermediate

2. Urea (thiourea) as H-bond donor

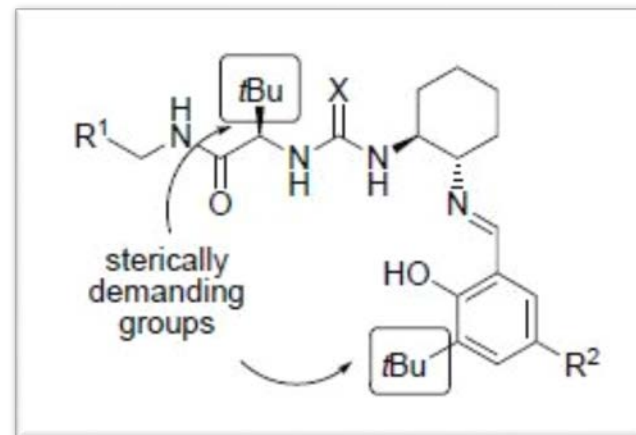
2.1. monofunctional thiourea



3a: $R^1 = \text{Ph}$, $X = \text{S}$, $R^2 = \text{OCH}_3$

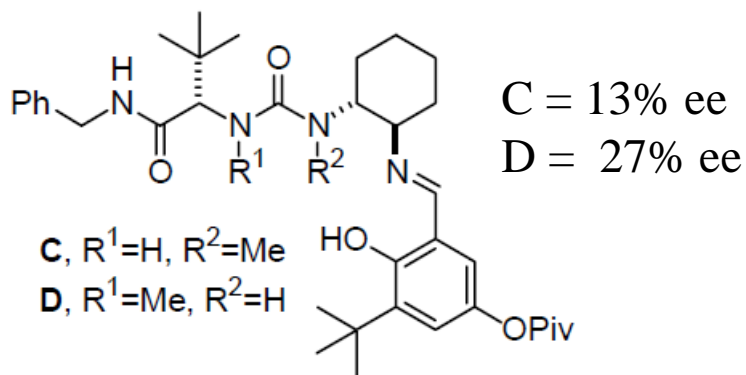
3b: $R^1 = \text{polystyrene}$, $X = \text{S}$, $R^2 = \text{OCO}(t\text{Bu})$

3c: $R^1 = \text{Ph}$, $X = \text{O}$, $R^2 = \text{OCO}(t\text{Bu})$



3b as catalyst, the product was isolated in nearly quantitative yield.
no loss of catalyst reactivity after 10 catalyst cycles.

$K_M = 0.214 \text{ M}$, $k_{\text{cat}}/K_M = 3.8 * 10^{-3} \text{ M}^{-1} \text{ S}^{-1}$ → Reversible formation of an imine-catalyst complex through a hydrogen bond

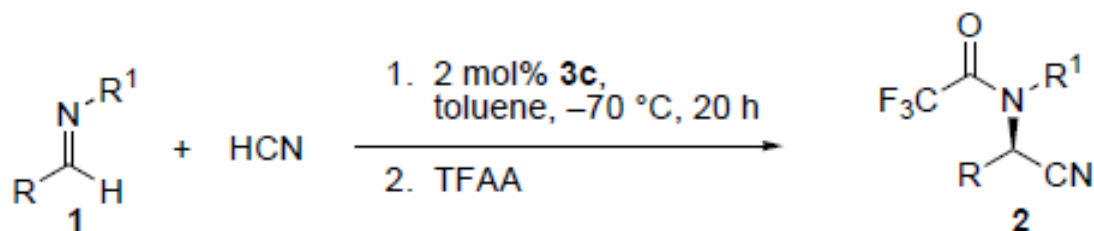


alkylation of the urea led to loss of activity and enantioselectivity

two urea hydrogens were essential for catalyst activity.

2. Urea (thiourea) as H-bond donor

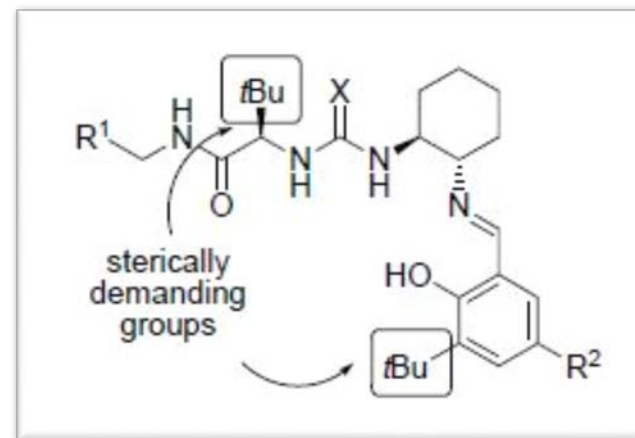
2.1. monofunctional thiourea



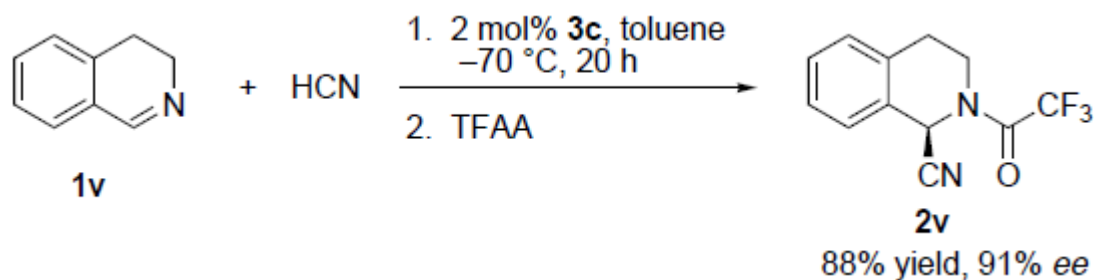
3a: $\text{R}^1 = \text{Ph}$, $\text{X} = \text{S}$, $\text{R}^2 = \text{OCH}_3$

3b: $\text{R}^1 = \text{polystyrene}$, $\text{X} = \text{S}$, $\text{R}^2 = \text{OCO}(\text{tBu})$

3c: $\text{R}^1 = \text{Ph}$, $\text{X} = \text{O}$, $\text{R}^2 = \text{OCO}(\text{tBu})$



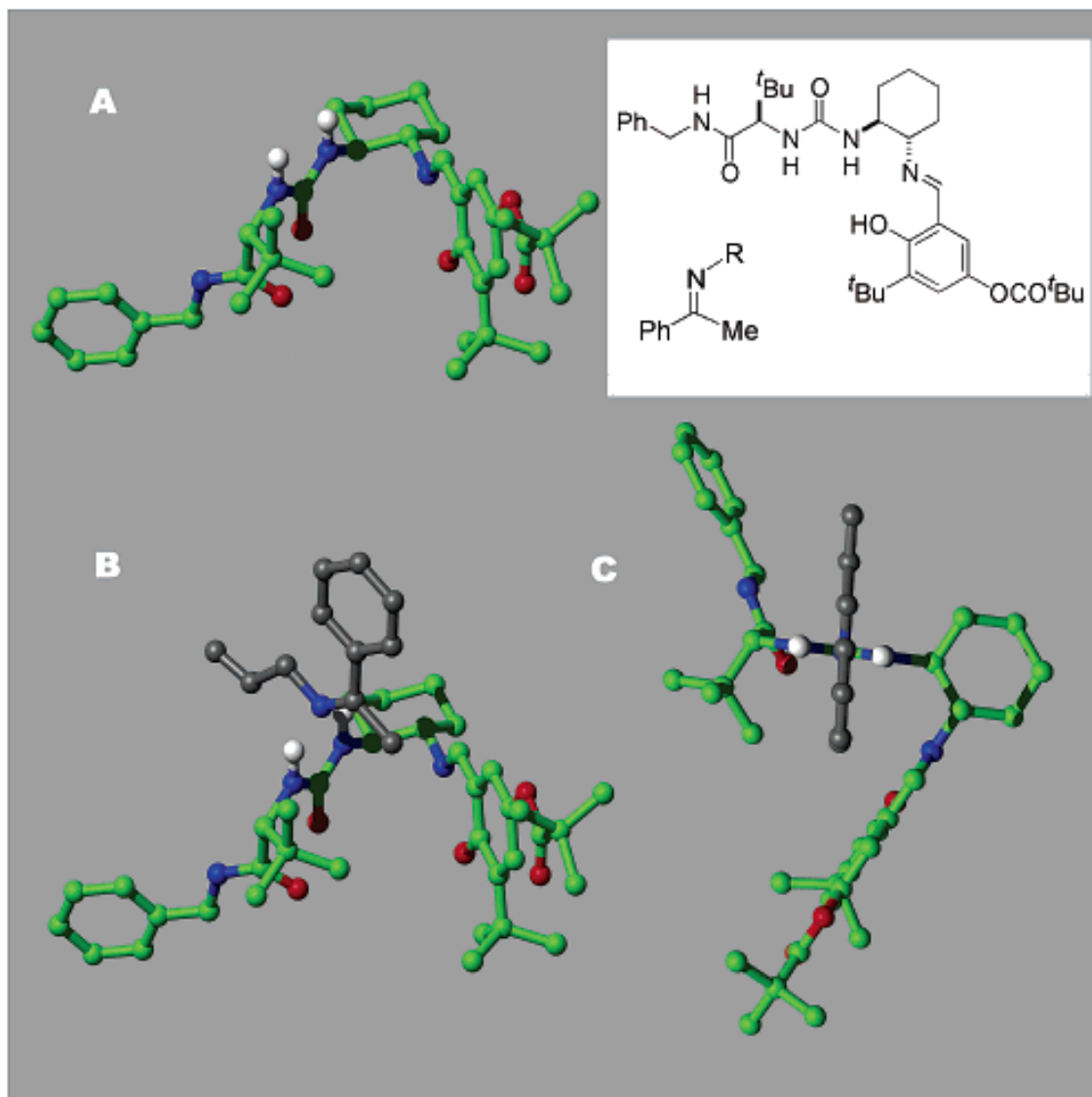
When R group became bigger, the ee value increased.



It was unlikely that lower ee values obtained with unhindered imines are due to the increased amount of Z isomer present in these substrates.

2. Urea (thiourea) as H-bond donor

2.1. monofunctional thiourea



The large group on the imine carbon is directed away from the catalyst

The small group is aimed directly into the catalyst

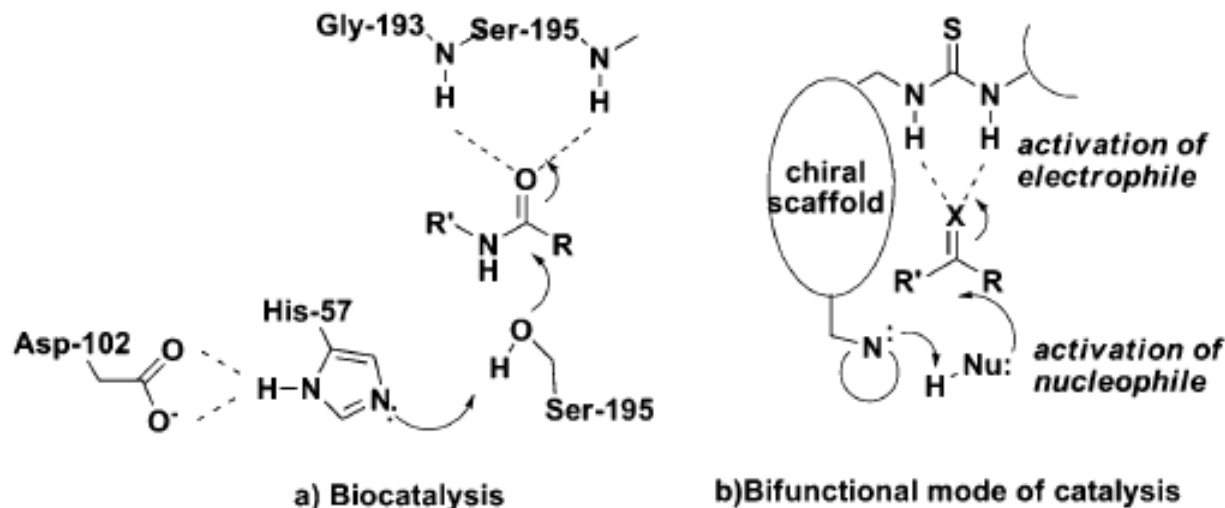
The *N*-substituent is also directed away from the catalyst

➡ 1 involve binding of the imine substrate as the **Z-isomer**.

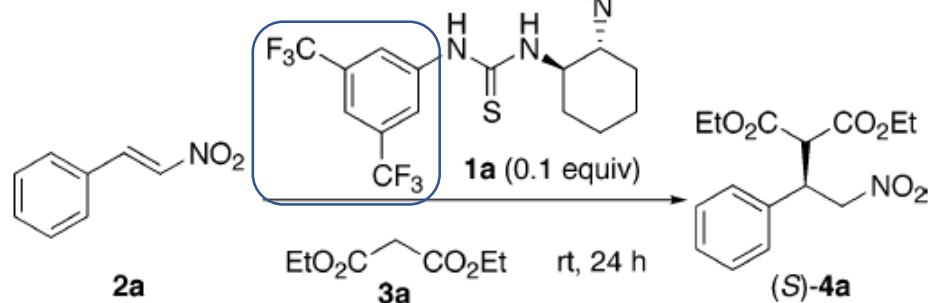
HCN takes place over the diaminocyclohexane portion of the catalyst

2. Urea (thiourea) as H-bond donor

2.2. bifunctional thiourea-amino thiourea



Increase the hydrogen-bond ability

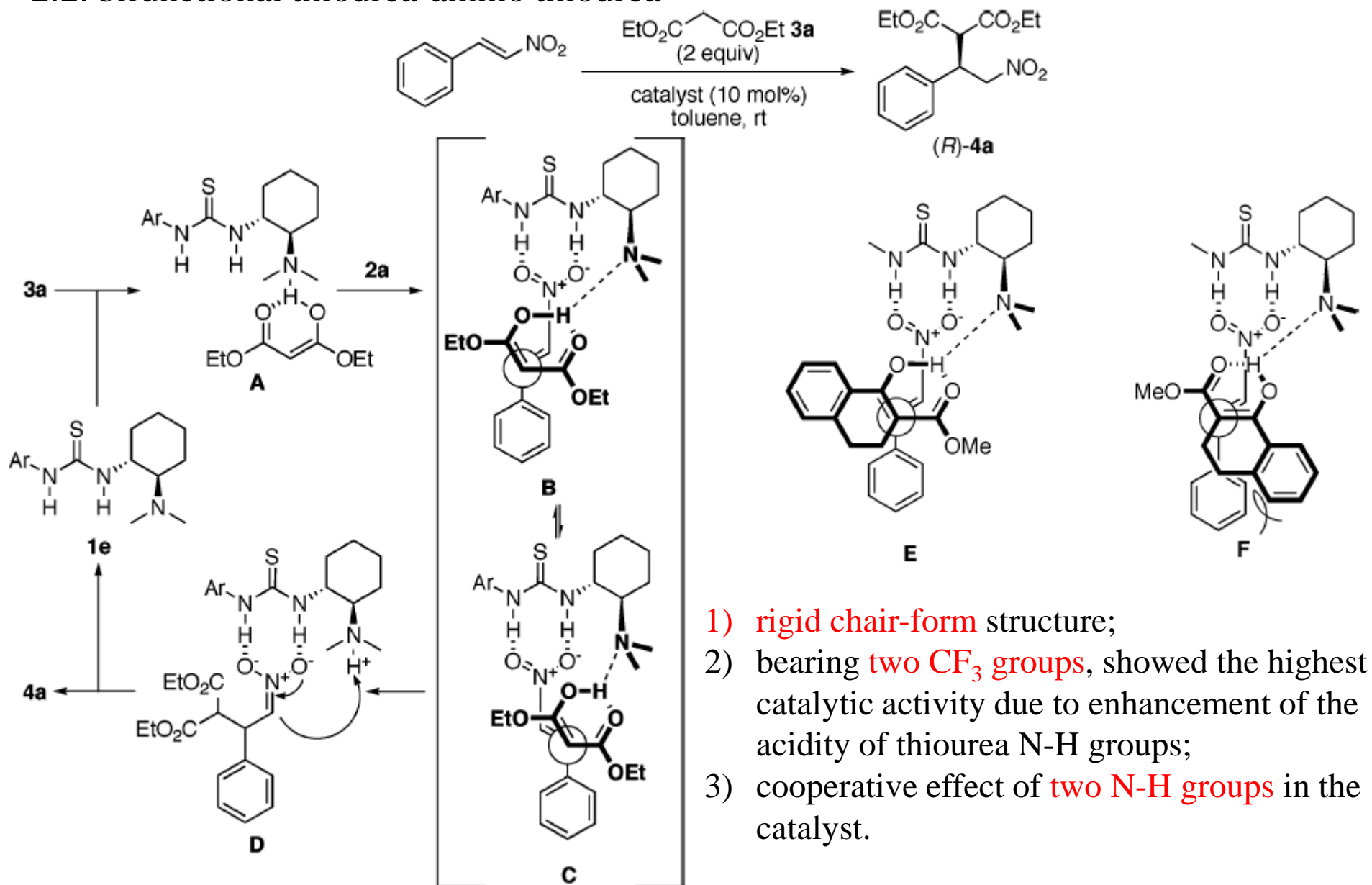


The nitroolefin and the nucleophile are activated.

entry	solvent	3a (equiv)	% yield ^b	% ee ^{c,d}
1	MeOH	1	33	29
2	MeCN	1	47	75
3	THF	1	29	88
4	CH ₂ Cl ₂	1	53	90
5	toluene	1	60	92
6	toluene	2	86	93

2. Urea (thiourea) as H-bond donor

2.2. bifunctional thiourea-amino thiourea

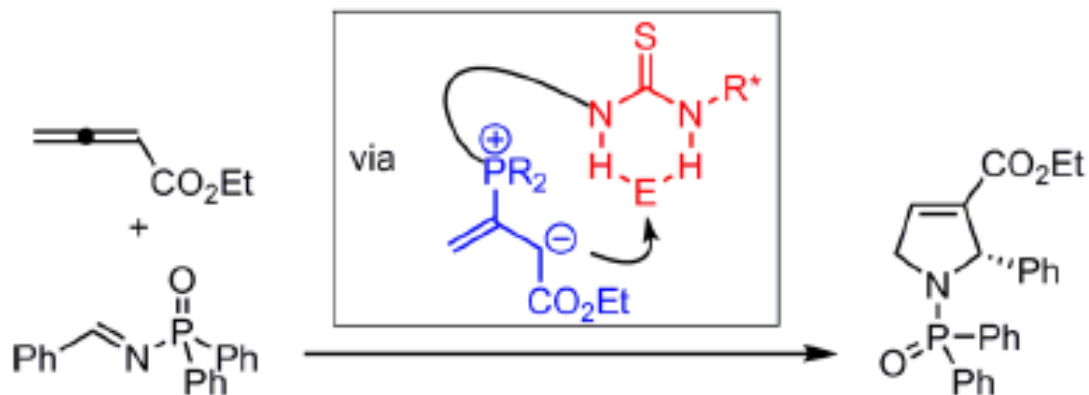


- 1) rigid chair-form structure;
- 2) bearing two CF₃ groups, showed the highest catalytic activity due to enhancement of the acidity of thiourea N-H groups;
- 3) cooperative effect of two N-H groups in the catalyst.

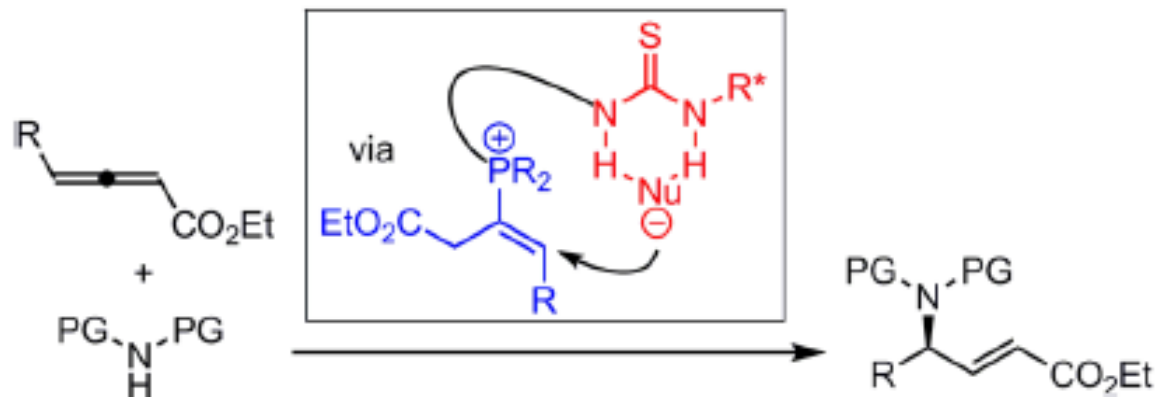
2. Urea (thiourea) as H-bond donor

2.2. bifunctional thiourea---phosphino thiourea

A) Established mode of cooperative activation by phosphinothiourea:
nucleophilic catalysis by phosphine/electrophile activation by thiourea

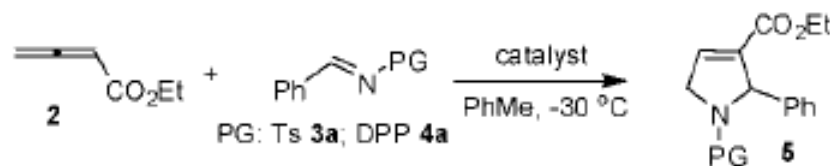


B) Proposed mode of cooperative activation by phosphinothiourea:
nucleophile generation by thiourea/electrophile generation by phosphine

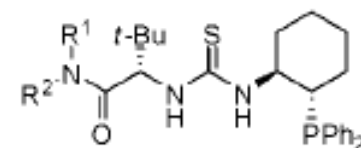


2. Urea (thiourea) as H-bond donor

2.2. bifunctional thiourea---phosphinothiourea

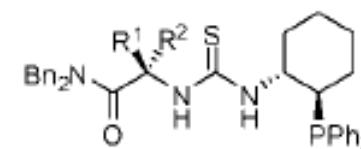


entry	catalyst	additives		time (h)	conversion (%) ^b	ee (%)
		Et ₃ N (mol%)	H ₂ O (mol%)			
1	6b			48	45	93 (<i>R</i>)
2	6b	2		48	70	n.d. ^c
3	6b	5	<i>d</i>	48	70 ^e	n.d. ^c
4	6b	5		24	70	n.d.
5	6b		20	24	86 ^f	n.d.
6	6b	5	20	24	88 ^g	93 (<i>R</i>)
7	7a	5	20	48	100	98 (<i>S</i>)
8	7b	5	20	48	17	87 (<i>S</i>)
9	7c	5	20	48	23	88 (<i>S</i>)
10	8	5	20	48	5	42 (<i>S</i>)



6a: R¹ = R² = 3,4,5-(MeO)₃C₆H₂CH₂

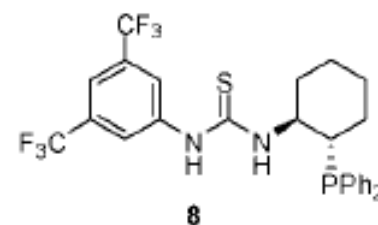
6b: R¹ = R² = 4-PhC₆H₄CH₂



7a: R¹ = Me, R² = H

7b: R¹ = H, R² = Me

7c: R¹ = R² = H



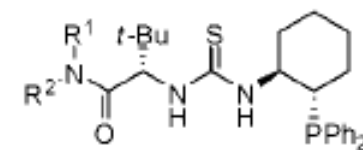
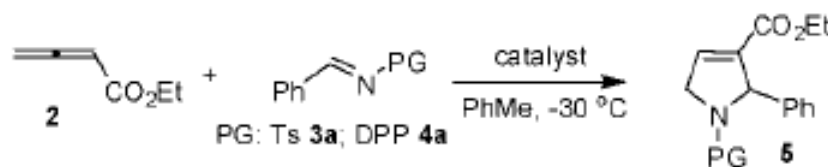
The **amino amide** plays a role relative to enantioinduction;

Et₃N led to improved substrate conversion;

an important beneficial role for water.

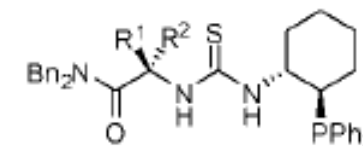
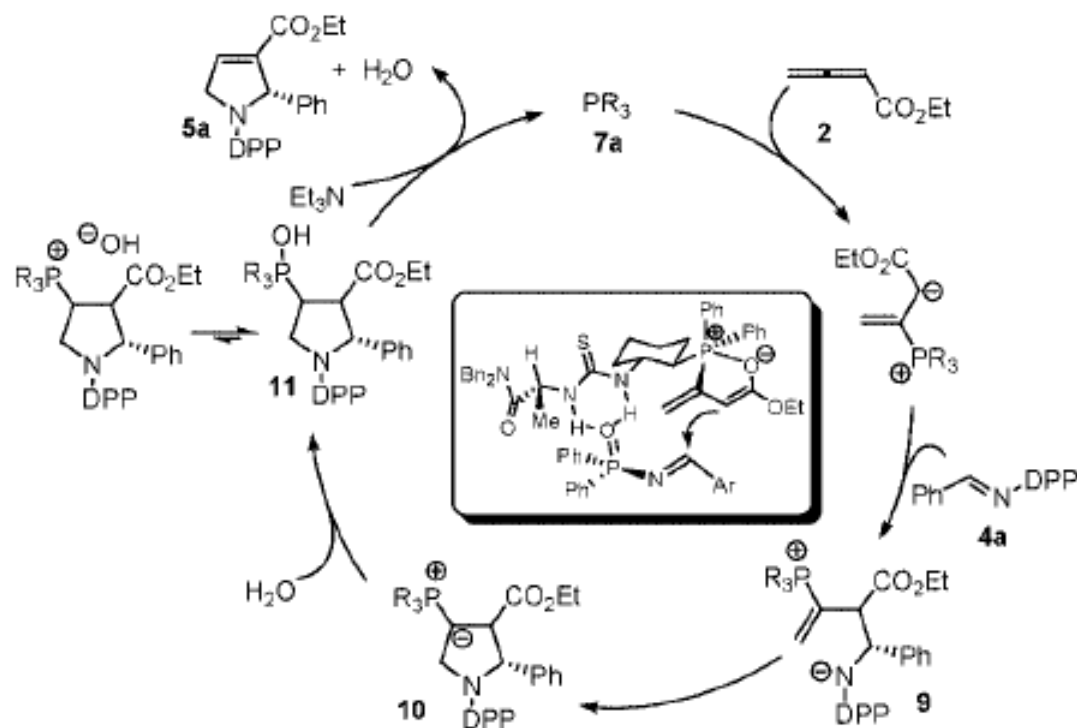
2. Urea (thiourea) as H-bond donor

2.2. bifunctional thiourea-phosphino thiourea



6a: R¹ = R² = 3,4,5-(MeO)₃C₆H₂CH₂

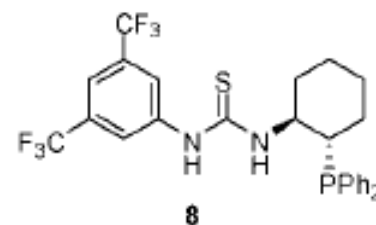
6b: R¹ = R² = 4-PhC₆H₄CH₂



7a: R¹ = Me, R² = H

7b: R¹ = H, R² = Me

7c: R¹ = R² = H

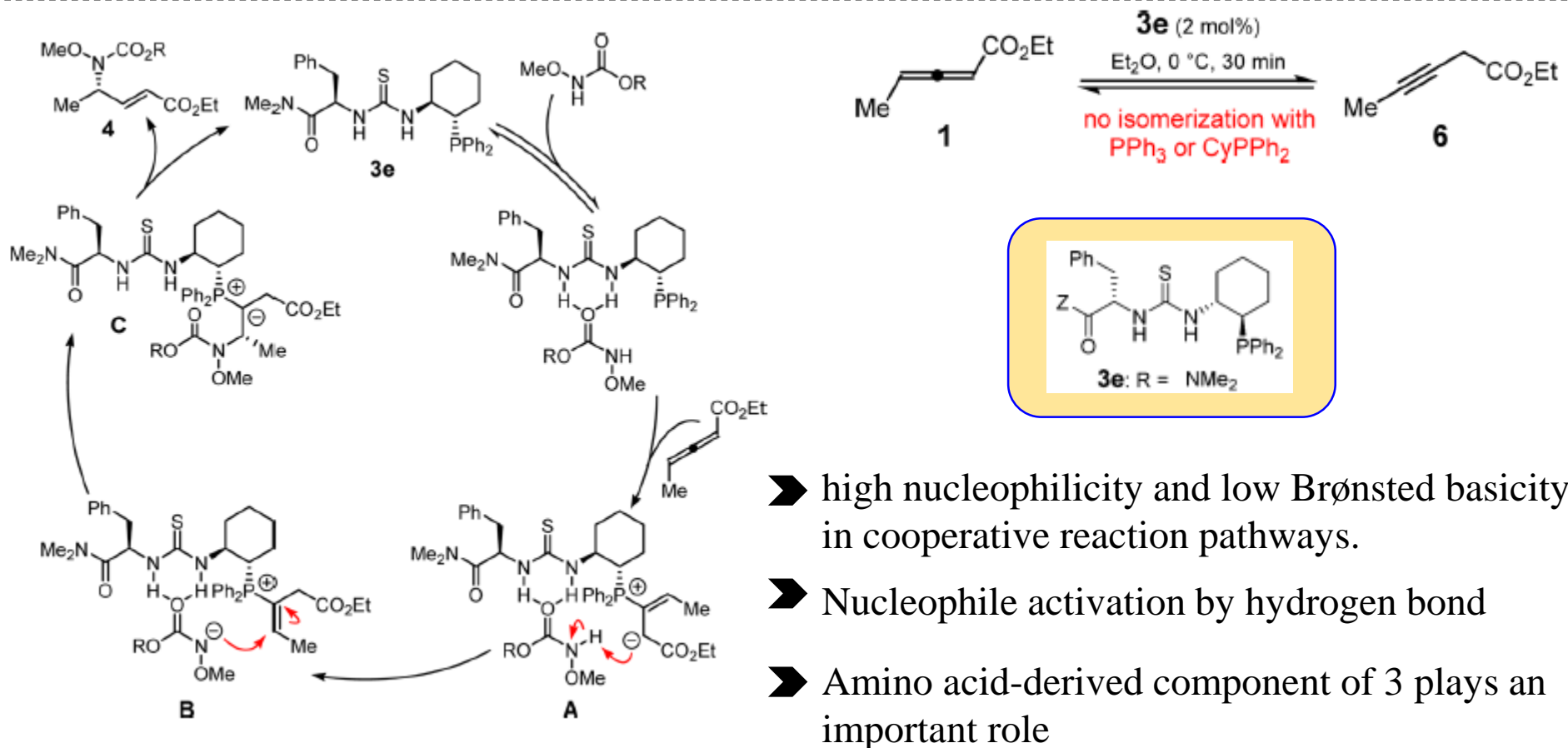
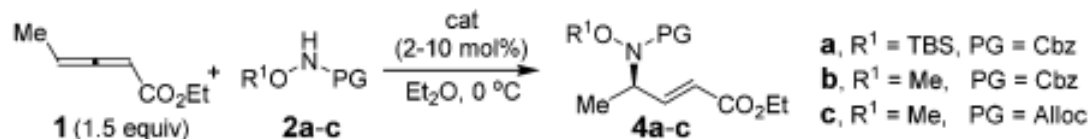


➤ H₂O effects protonation of the basic ylide intermediate 10

➤ Et₃N is likely to promote elimination and liberation of the phosphine catalyst

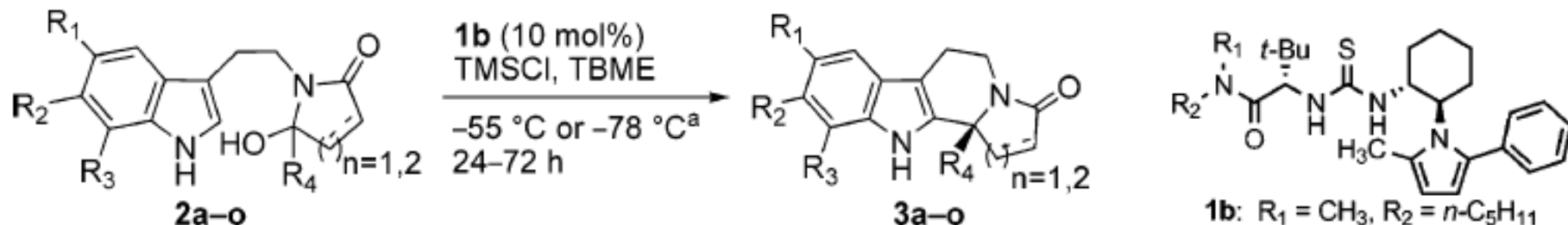
2. Urea (thiourea) as H-bond donor

2.2. bifunctional thiourea-phosphino thiourea

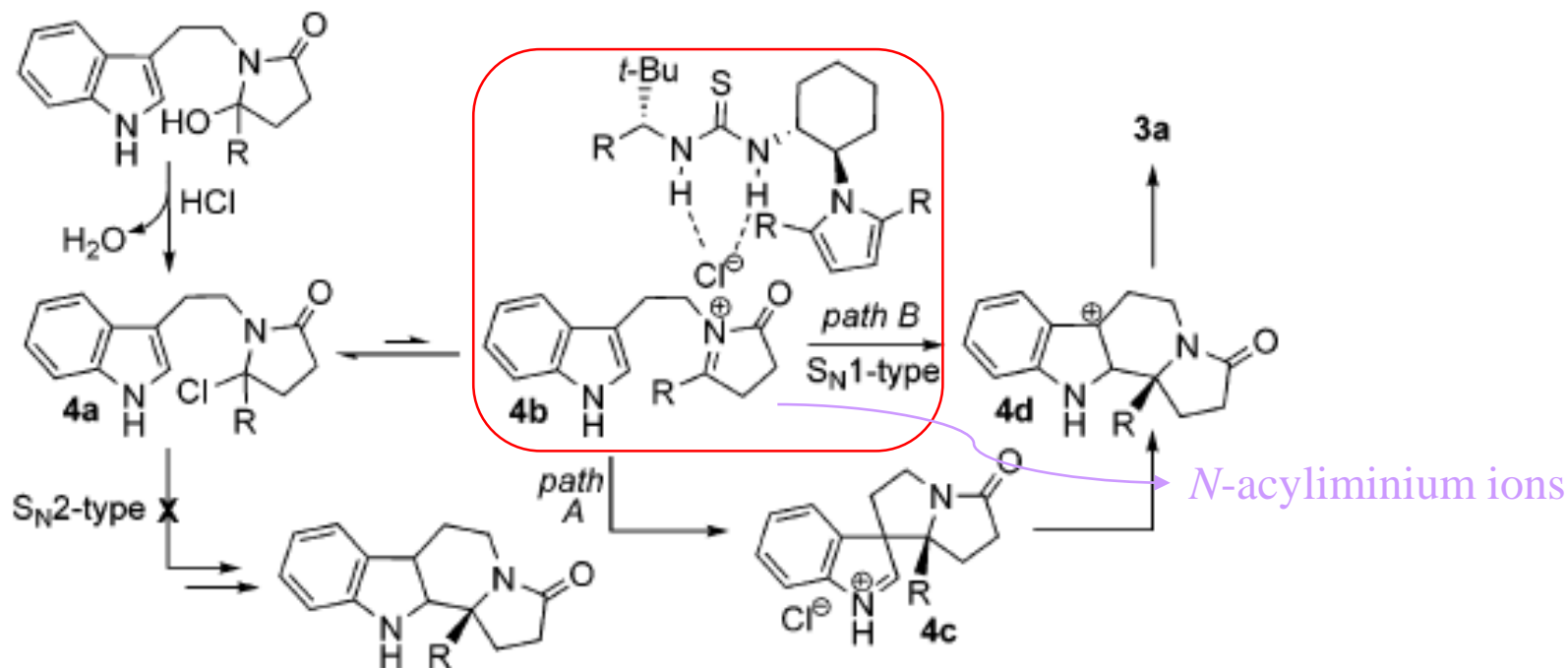


2. Urea (thiourea) as H-bond donor

2.3. anion-binding pathway



The first example of anion-binding pathway using thiourea

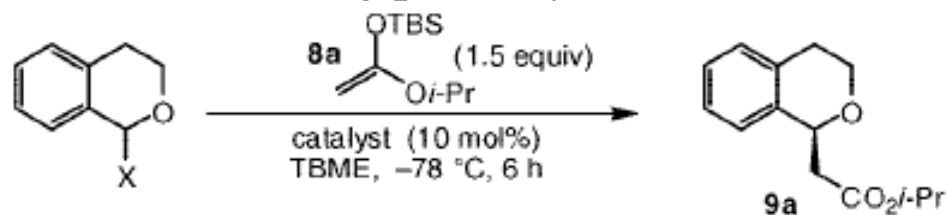


dehydration and formation of the corresponding **chlorolactam** is rapid and irreversible.

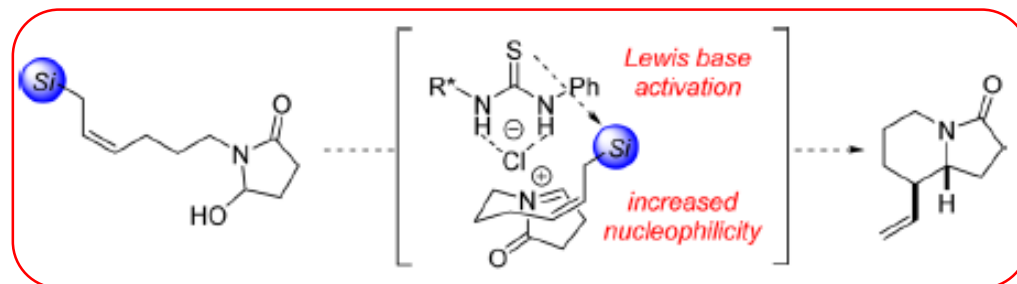
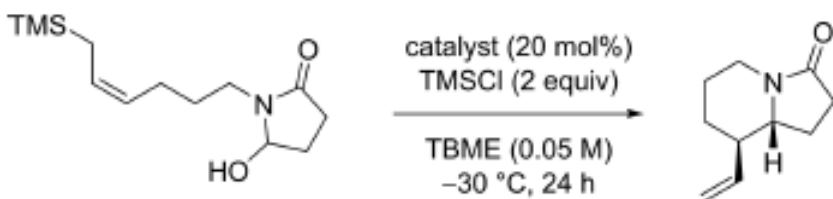
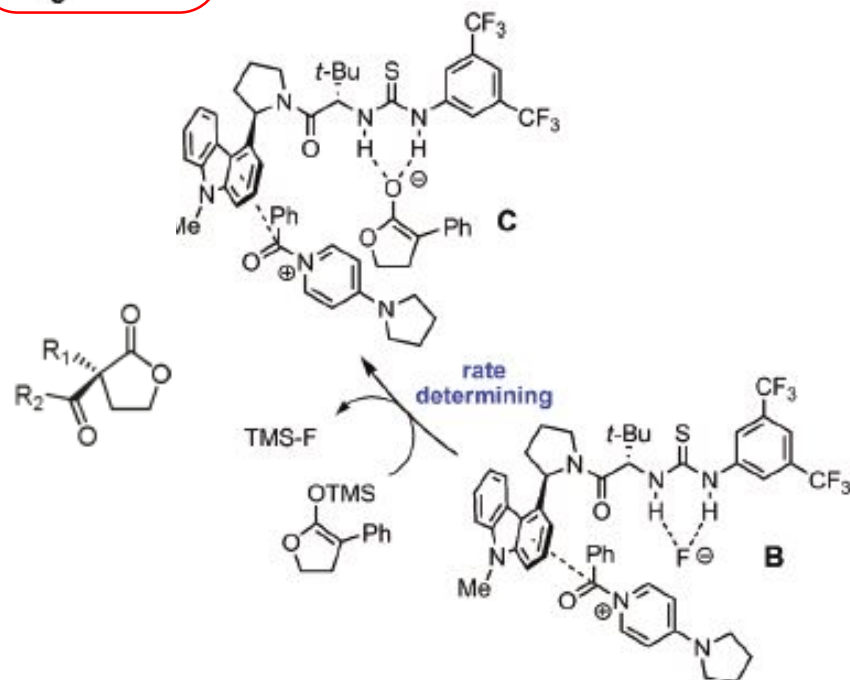
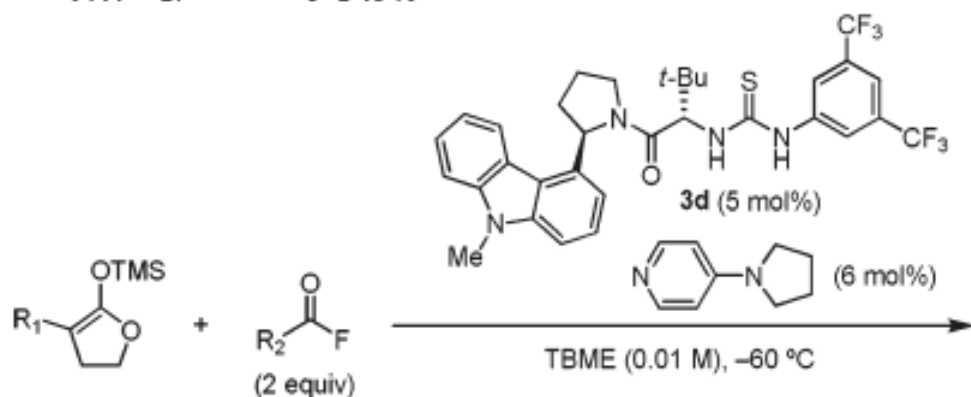
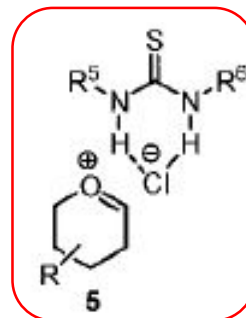
forming a chiral *N*-acyliminium chloride–thiourea complex

2. Urea (thiourea) as H-bond donor

2.3. anion-binding pathway



6: X = OMe $\xrightarrow{\text{BCl}_3, \text{CH}_2\text{Cl}_2}$
 7: X = Cl 0°C to rt



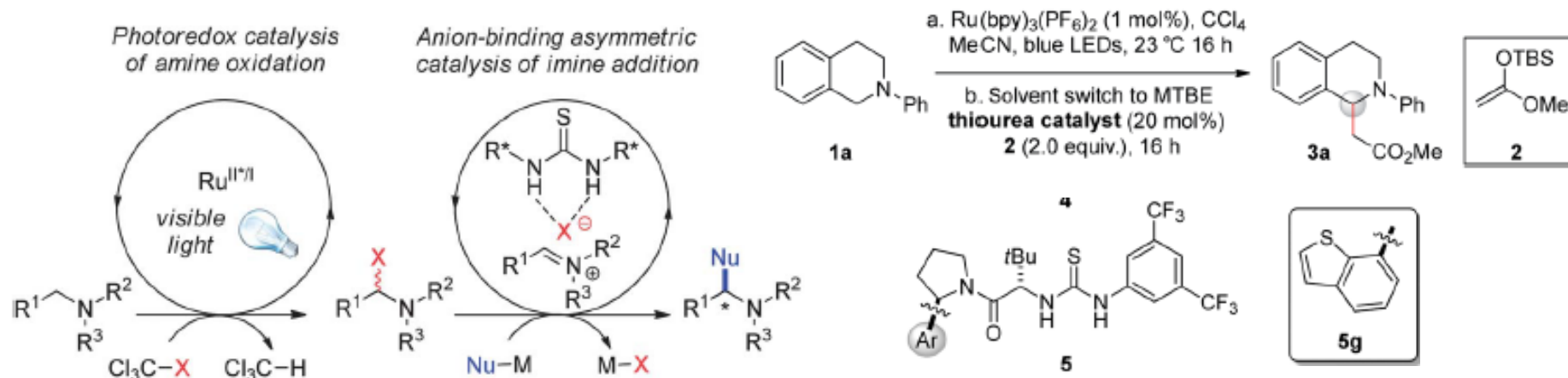
Eric N. Jacobsen, *J. Am. Chem. Soc.*, **2008**, 130, 7198.

Eric N. Jacobsen, *J. Am. Chem. Soc.*, **2011**, 133, 13872.

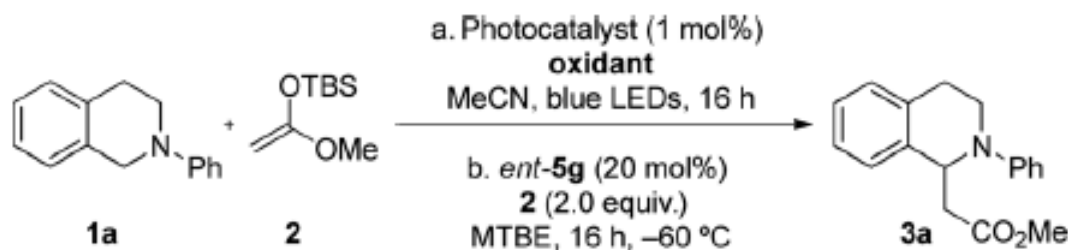
Eric N. Jacobsen, *J. Am. Chem. Soc.*, **2016**, 138, 14848.

2. Urea (thiourea) as H-bond donor

2.3. anion-binding pathway



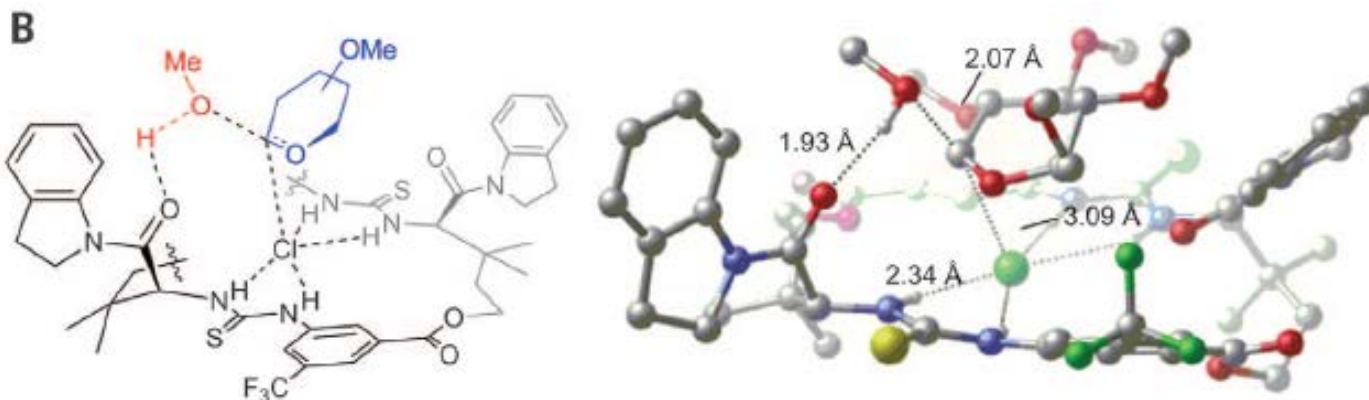
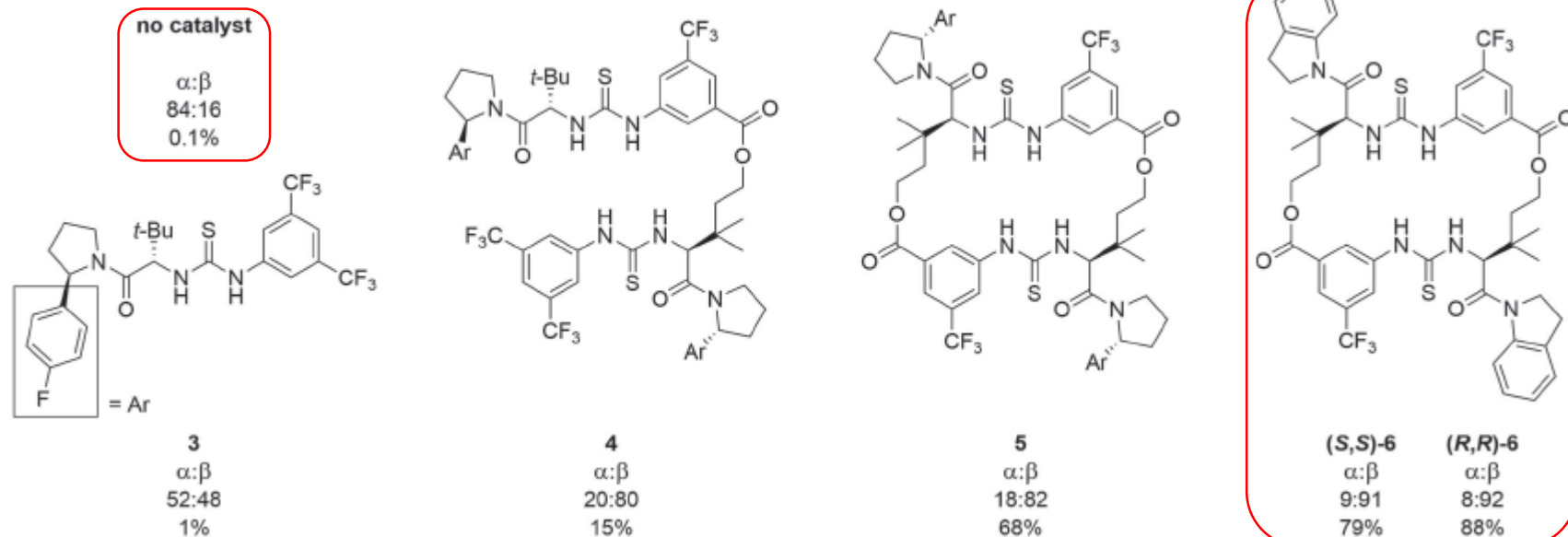
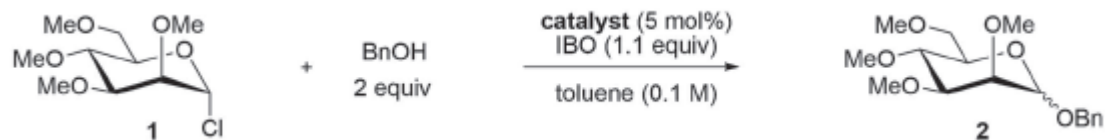
Counterion effects



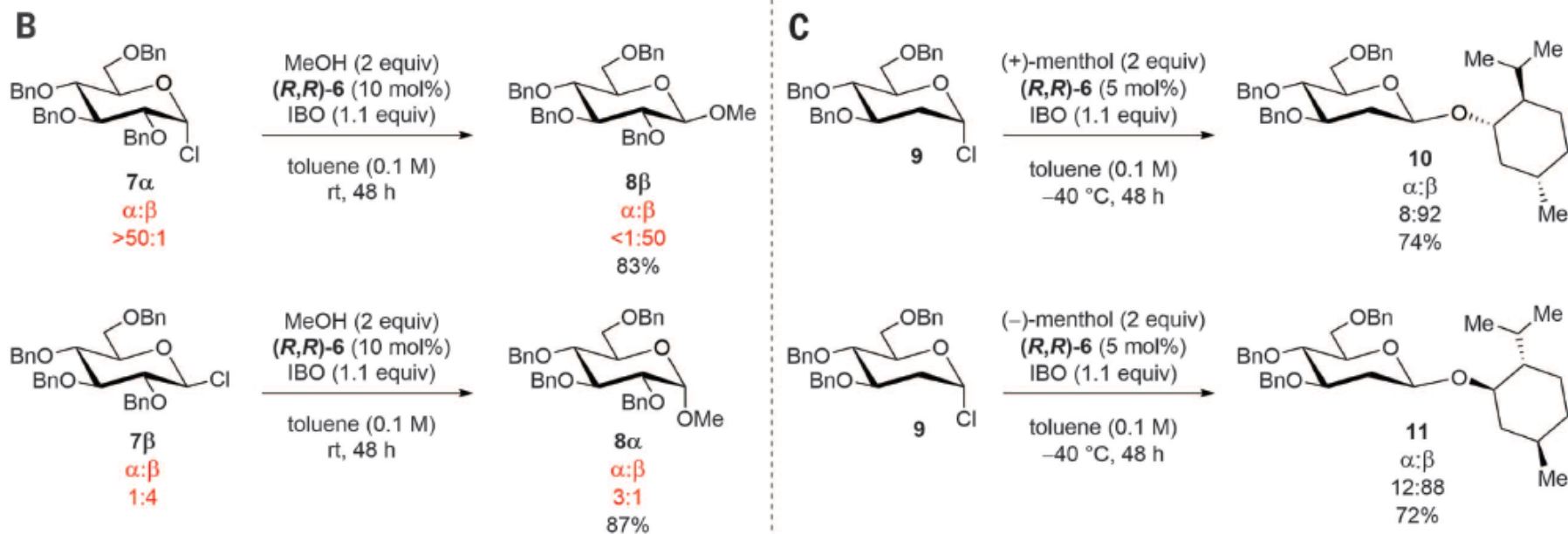
$[\text{Ru(bpy)}_3]^{2+} 2\text{Y}^-$	Y^-	Oxidant	Yield (%)	ee ^a (%)
$\text{Y} = \text{Cl}^- \text{ or } \text{PF}_6^-$	Cl^-	BrCCl_3	65 ^b	79
	PF_6^-	CCl_4	80–95 ^c	61–97 ^d
	Cl^-	CCl_4	69–72 ^b	95–97 ^d

2. Urea (thiourea) as H-bond donor

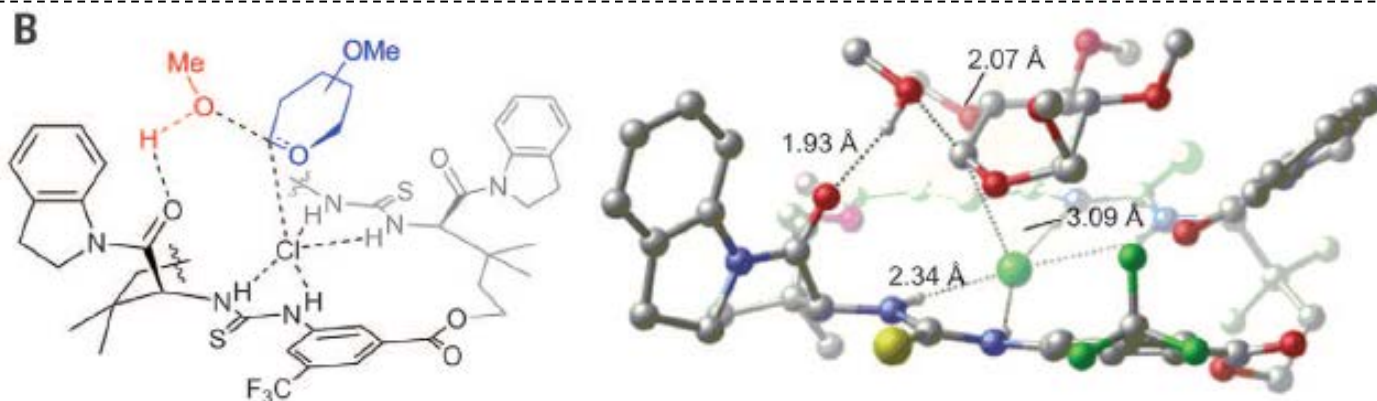
2.3. anion-bonding pathway



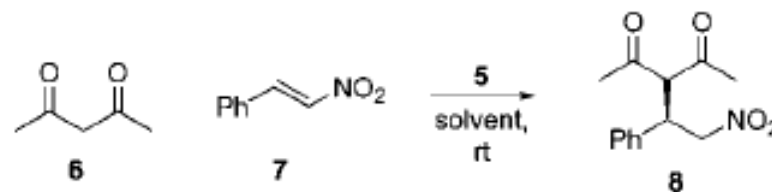
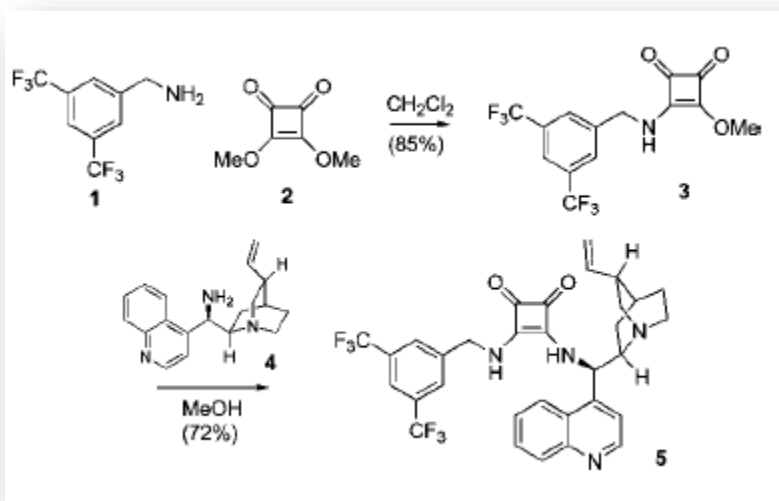
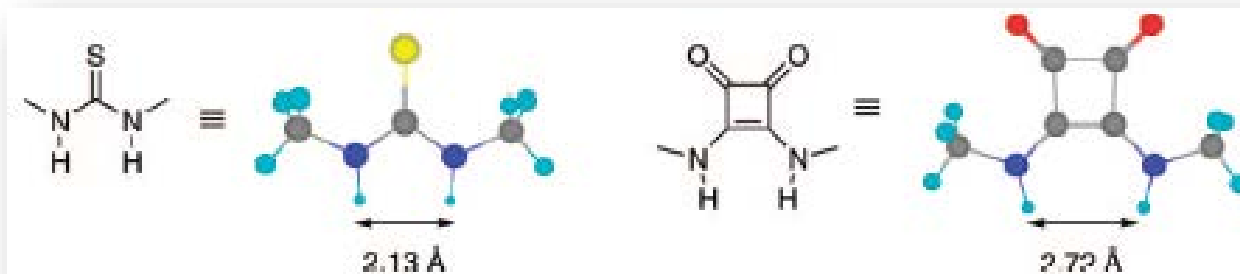
2.3. anion-bonding pathway



The stereochemical outcome depends on the configuration of the electrophilic partner.



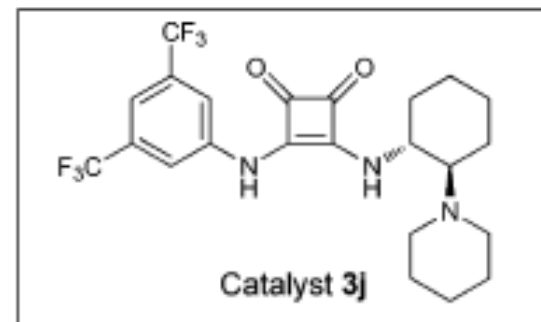
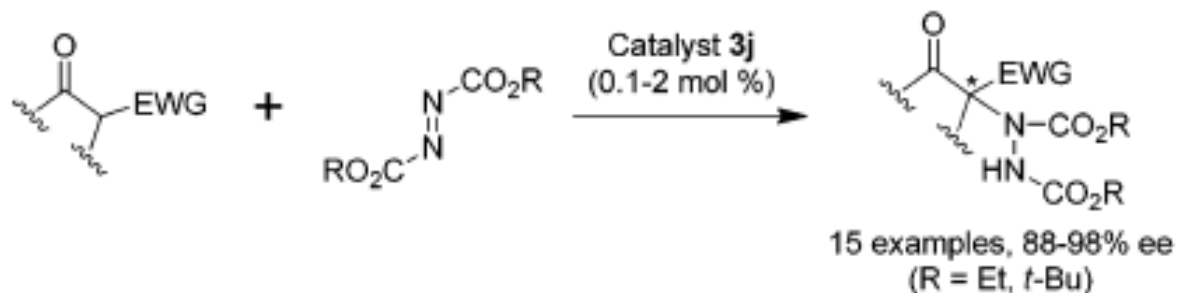
3. Squaramide as H-bond donor



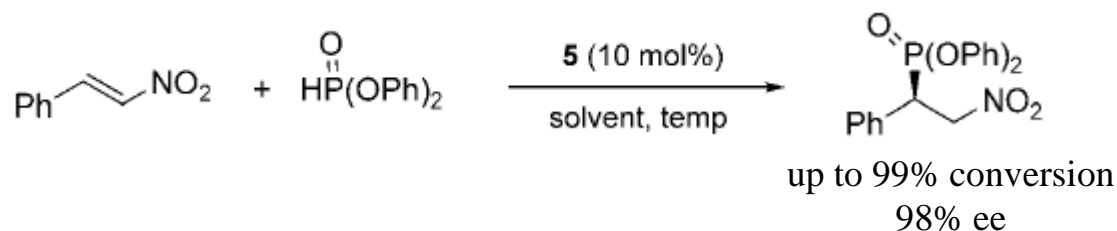
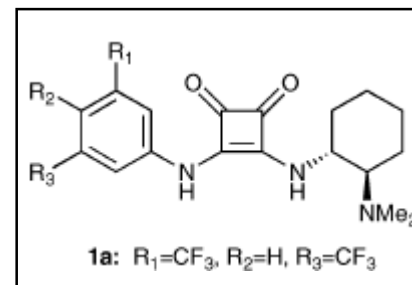
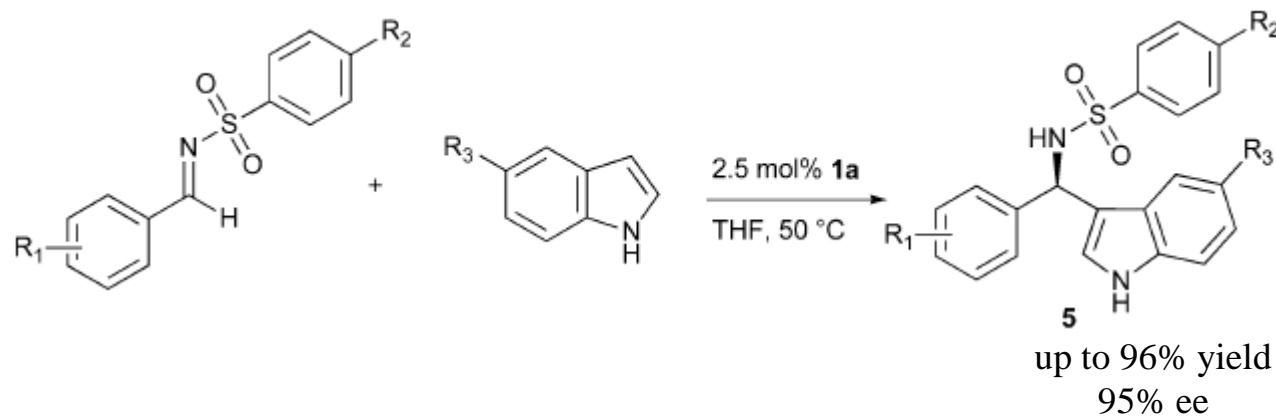
entry	mol % of 5	solvent	time	yield	ee
1	2.0	Et ₂ O	24 h	88%	96%
2	2.0	PhMe	24 h	94%	98%
3	2.0	CH ₂ Cl ₂	7 h	98%	>99%
4	0.5	CH ₂ Cl ₂	8 h	94%	>99%
5	0.1	CH ₂ Cl ₂	20 h	97%	96%

1. The ee value was higher than that using thiourea;
2. The loading of catalyst was lower.

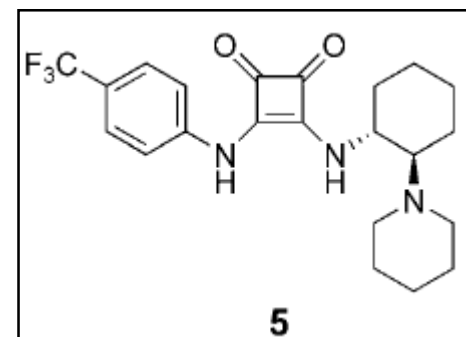
3. Squaramide as H-bond donor



The amino group of **3j** can generate active nucleophilic anion



Alkyl-substituted nitroalkenes can work, with slower rate.

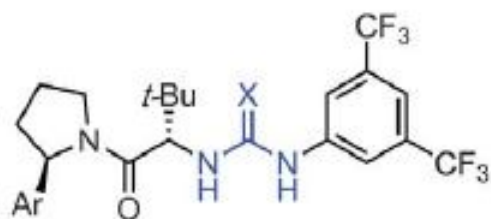
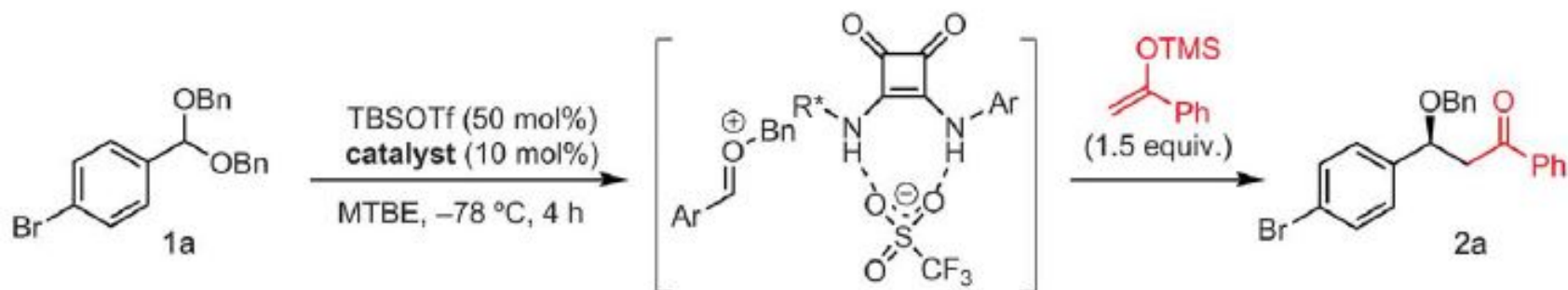


3. Squaramide as H-bond donor

Activation of Silyl Triflates via Anion Abstraction



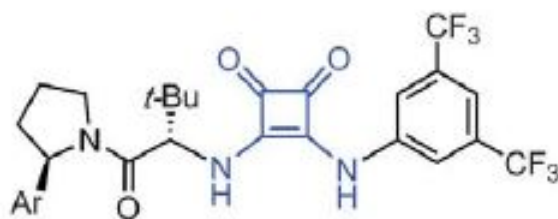
a charge-separated complex



no catalyst: <5% y

3 (X = O, Ar = 9-phenanthryl): <5% y

4 (X = S, Ar = 9-phenanthryl): <5% y



5a (Ar = H): 10% y, 10% e.e.

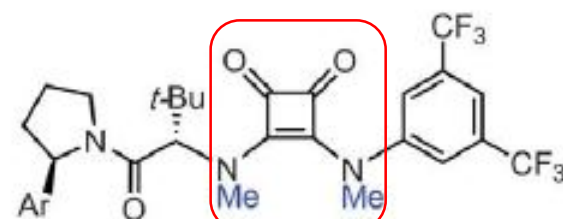
5b (Ar = Ph): 23% y, 42% e.e.

5c (Ar = 1-naphthyl): 31% y, 72% e.e.

5d (Ar = 9-phenanthryl): 100% y, 85% e.e.

5e (Ar = 1-pyrenyl): 100% y, 88% e.e.

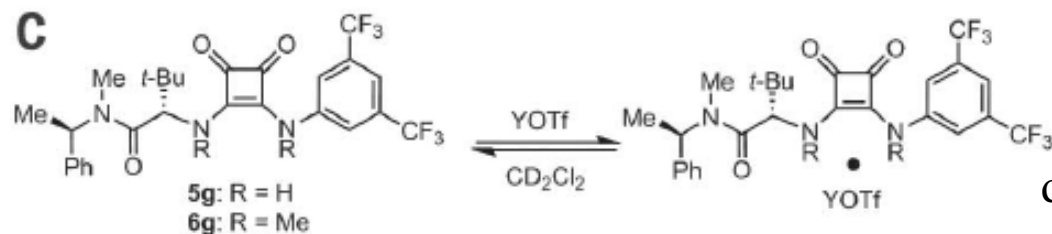
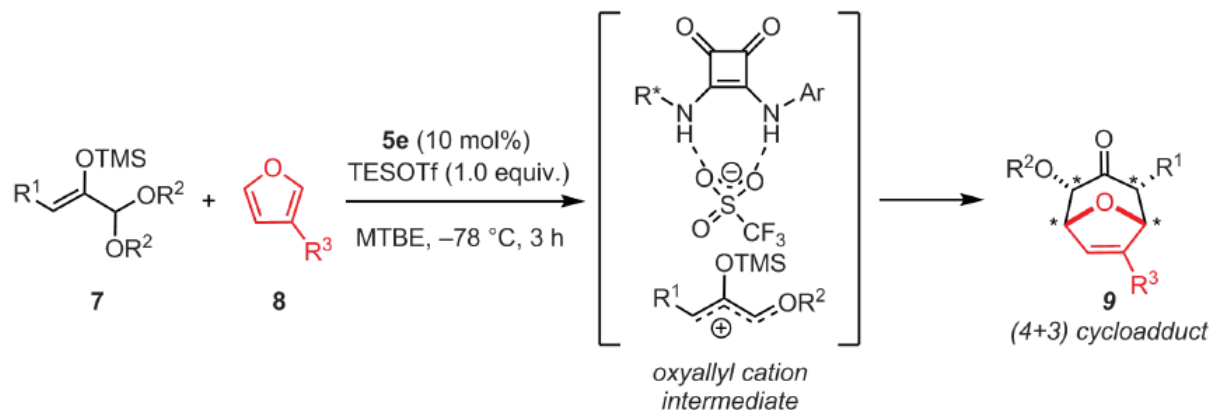
5f (Ar = 1-phenanthryl): 100% y, 87% e.e.



6e (Ar = 1-pyrenyl): 43% y, 2% e.e.

the H-bond donor properties are essential for effective stereochemical control.

3. Squaramide as H-bond donor

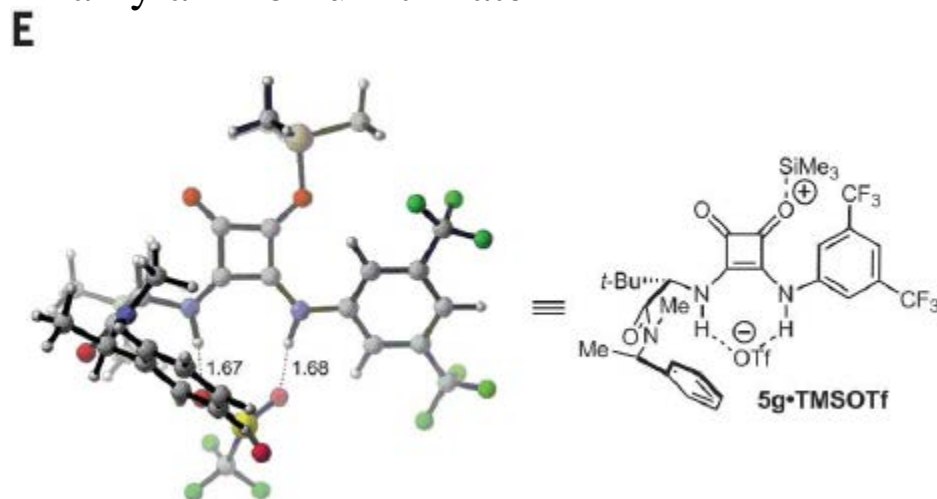


Entry	R	YOTf	$K_{\text{eq}} (\text{M}^{-1})$
1	H	$\text{N}(\text{nBu})_4^+ \text{TfO}^-$	2.0×10^2
2	H	TESOTf	8.0×10^5
3	Me	TESOTf	2.3×10^3

dual interaction mode may account for the enhanced affinity of the squaramide for the silyl triflate relative to tetra-alkylammonium triflate

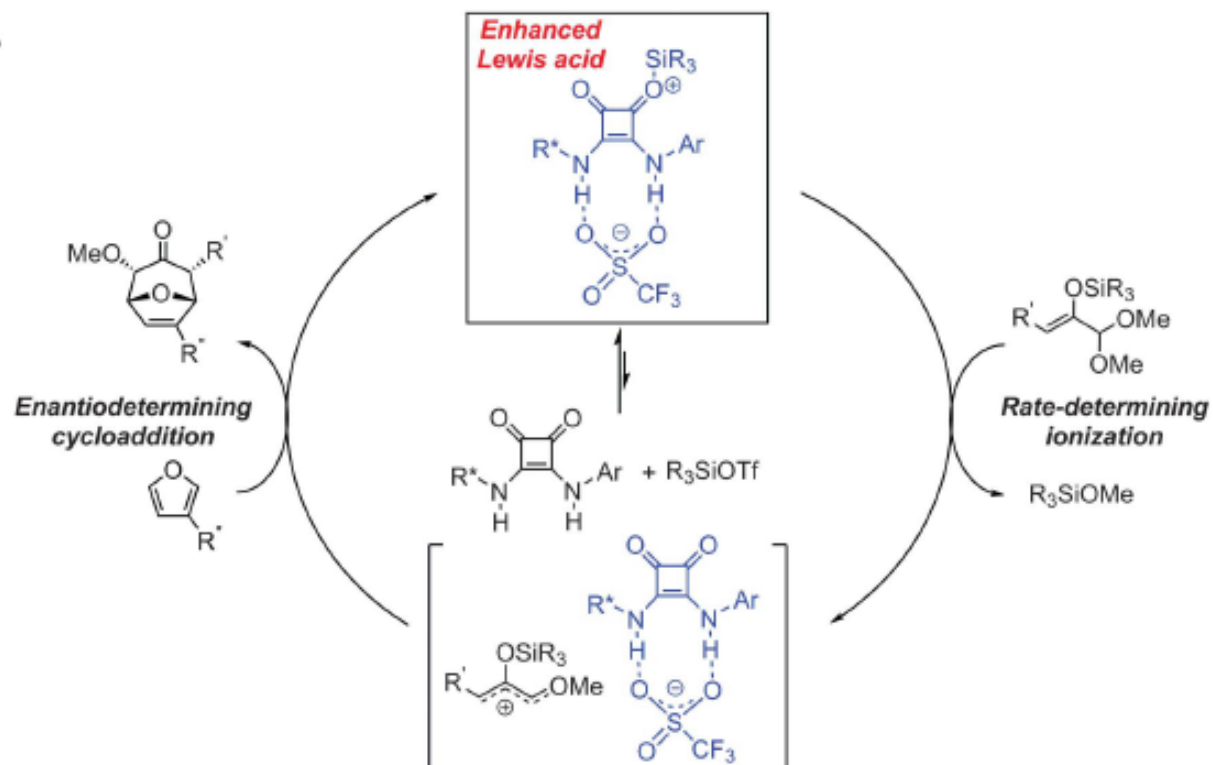
6g which lacks H-bond donor capabilities, forms a complex with TESOTf

simultaneous binding of both the triflate and the trialkyl silyl component may be occurring in the complex

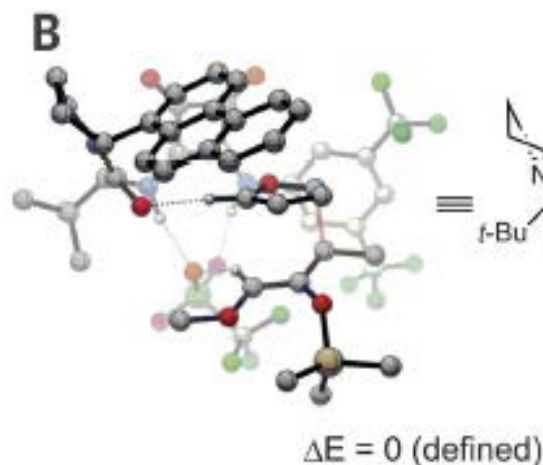


3. Squaramide as H-bond donor

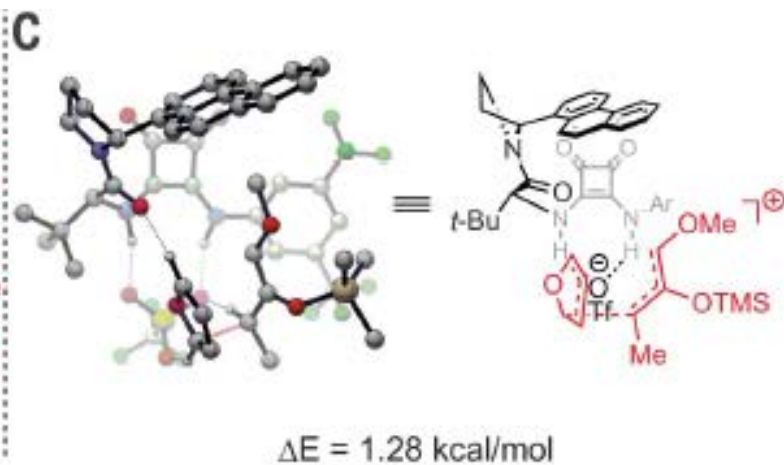
A



B



C



4. Conclusion

1. Using thiourea and Squaramide can achieve high reactivity and enantioselectivity.
2. Common fundamental design feature: a single or dual H-bond donor site flanked by sites for secondary interaction with substrates, such as aromatic, weakly basic or acidic, or strongly basic functionality.
3. Reacting under mild condition demonstrates greater functional group tolerance.

Acknowledgement

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Dr. Chen

All members in E201

Everyone here

Thank you!