Hydrogen-Bond Donor: Urea/Thiourea

Who discovered hydrogen bond??

Literature Seminar
Haruka Ida
2012.12.17 (Mon.)

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Contents

About Hydrogen bond (H-bond)

Who discovered H-bond??
--T. S. Moore and T. F. Winmill
'The state of amines in aqueous solution'
J. Chem. Soc. Trans. **1912**, *101,* 1635.
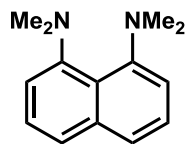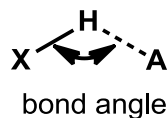H-bond has the 100-year history .

The hydrogen bond is an attractive interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule in which there is evidence of bond formation.
--D. J. Nesbitt, *et al, IUPAC Technical Report*
(http://media.iupac.org/reports/provisional/abstract11/arunan_tr.pdf)

Properties of H-bond.
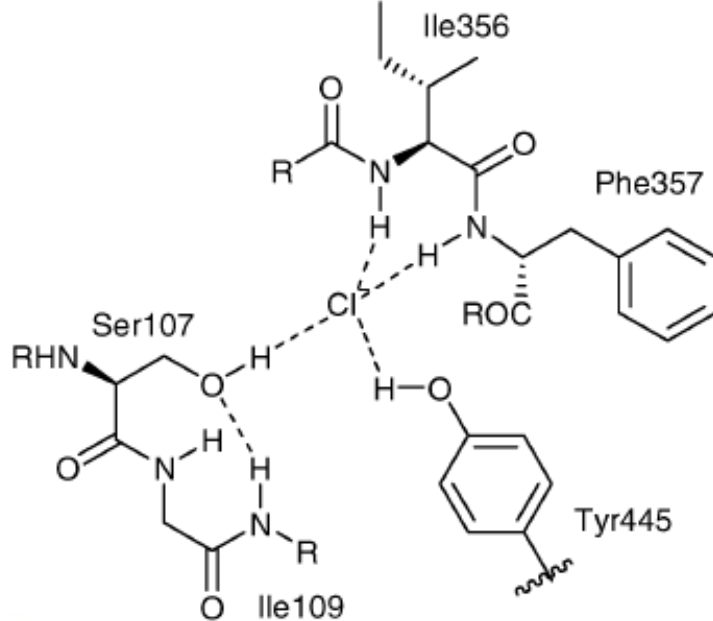
	Strong	Moderate	Weak
type of bonding	mostly covalent	mostly electrostatic	electrostatic
length of H-bond [Å]	1.2–1.5	1.5–2.2	2.2–3.2
bond angles [°]	175–180	130–180	90–150
bond energy [kcal mol^{-1}]	14–40	4–15	< 4
typical example	intramolecular NH···N bond in conjugate acid of proton sponge	NH···O=C bonds in peptide helices and sheets	bonds involving CH donors to N or O acceptors

Urea/Thiourea

bond angle

Mark S. Taylor and Eric N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

H-bond in Nature

CIC chloride channel
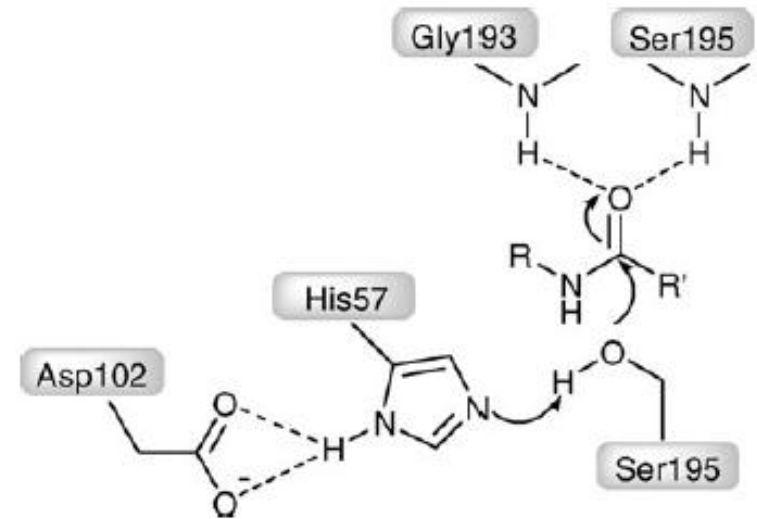

Chloride ion
・regulates membrane potentials.
・is stabilized by electrostatic interactions with α-helix dipoles and by chemical coordination with amino and hydroxyl groups.

serine protease

- A class of enzymes characterized by a uniquely reactive serine side chain cleaving peptide bonds in proteins.
- Stabilizing the oxyanion.

R. MacKinnon, *et al, Nature* **2002**, *415*, 287.
L. Hedstrom, *Chem Rev.* **2002**, *102*, 4501.

Organocatalyst

Organocatalyst
- Consist of elements like carbon, hydrogen, oxygen, nitrogen, sulfur and so on, not including any metal.
- Have low molecular weight.
- Possess the function catalyst.

Advantages:
- The reactions can be performed under an aerobic atmosphere with wet solvents. (Organocatalysts are often more stable than enzymes or metal catalysts.)
- The catalysts are inexpensive.
- They can be anchored to a solid support and reused more conveniently than organometallic/bioorganic analogues, and show promising adaptability to high-throughput screening and process chemistry.

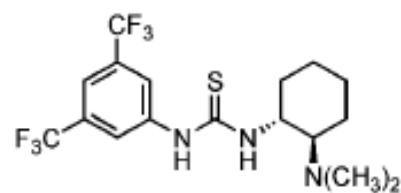Biocatalysis ⇒ Metal Catalyst ⇒ Organocatalyst

Representative H-bond donor catalysts.
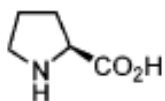
Hajos, Parrish,
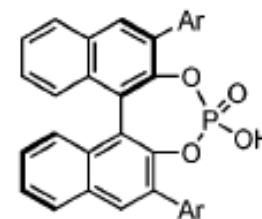Eder, Sauer, Wiechert, 1970s
Aldol Cyclization

Barbas, List, 2000
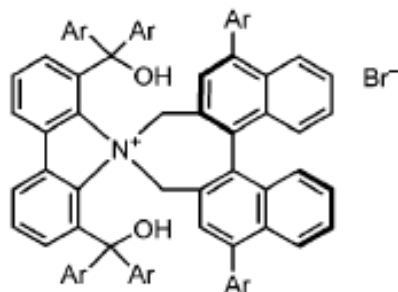Direct Aldol Reaction
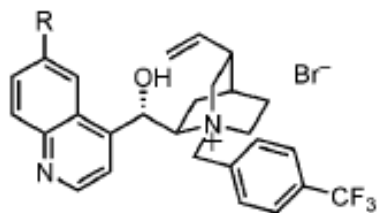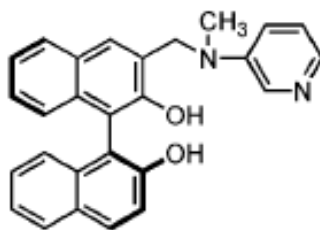
Graboswski, 1984
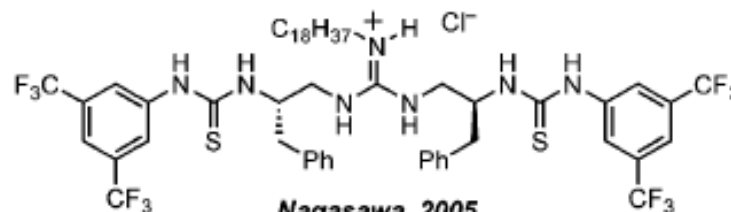Enolate Alkylation

Takemoto, 2003
Nucleophilic Addition to Nitroolefins

Akiyama and Terada, 2004
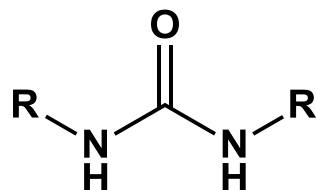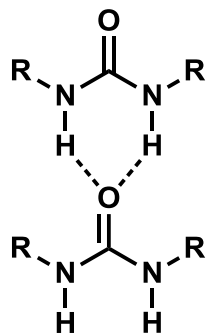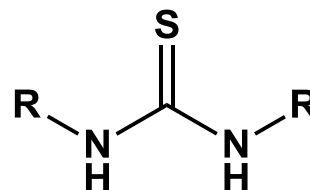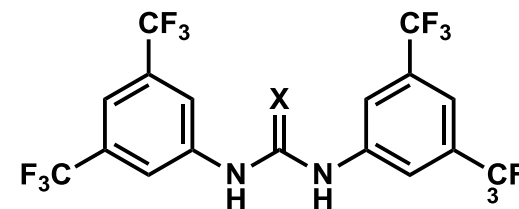Mannich Reaction

Maruoka, 2004
Epoxidation

Sasai, 2005
aza-Baylis–Hillman Reaction

Nagasawa, 2005
Henry Reaction

Mark S. Taylor and Eric N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

About Urea/Thiourea 1

pKa

Urea **Thiourea**

Electronegativity : **O > S**

Tendency to dimerize: Urea > Thiourea

pK$_a$: Urea > Thiourea

Turnover frequency (TOF): Urea < Thiourea
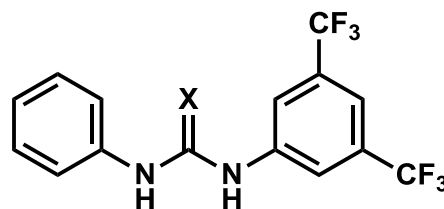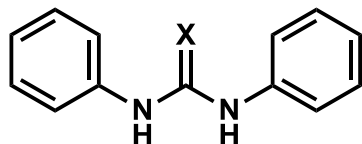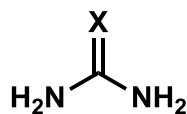
pKa				
X=O	29.6	18.7	16.1	13.8
X=S	21.1	13.4	10.7	8.5

(in DMSO)

cf. Phenol: 9.95

F. G. Bordwell, *et al, J. Am. Chem. SOC.* **1991**, *113*,8398.
P. R. Schreiner, *et al, Org. Lett.* **2012**, *14,* 1724.

About Urea/Thiourea 2

Conformational Preference of *N,N'-diarylurea*

(trans, trans) ⇌ (trans, cis) ⇌ (cis, cis)

strong π–π interaction
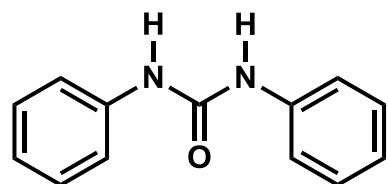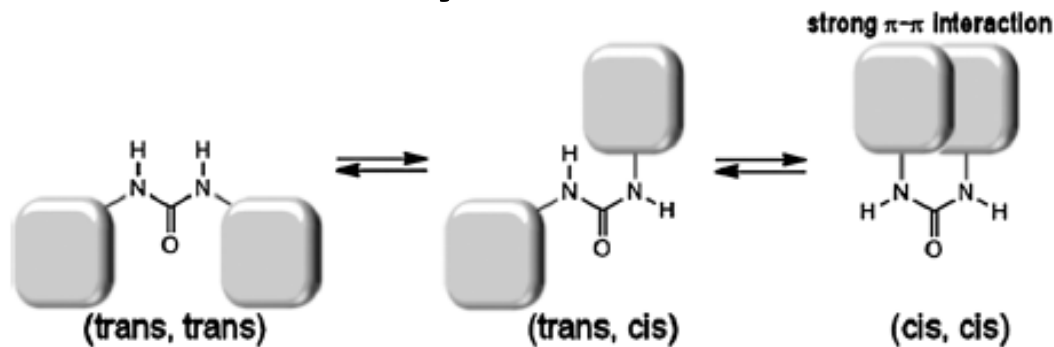
***N,N'*-diphenyl urea**
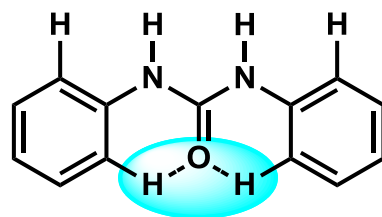
intramolecular hydrogen-bond
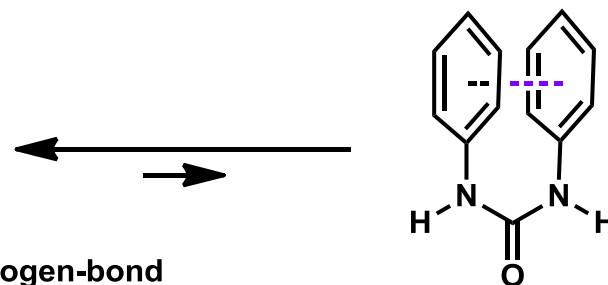
steric hinderance
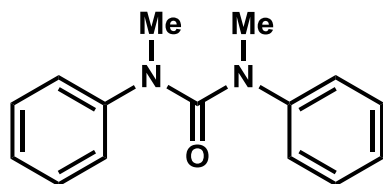
***N,N'*-diaryl-N,N'-dimethyl urea**
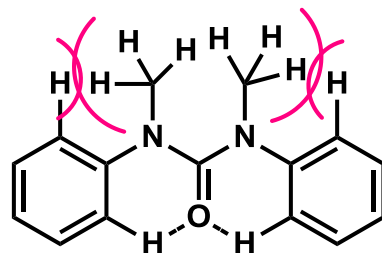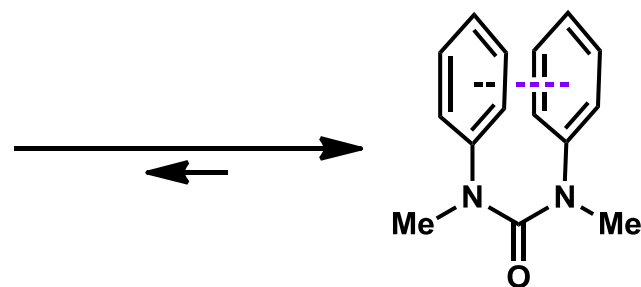
π-π stacking

M. Helliwell, *et al, Phys. Chem. Chem. Phys.* **2010**, *12,* 15064.

Contents

Pioneering Study of Activation of Electrophile Using H-Bond --Hine

Biphenylenediol-Promoted Epoxide-Opening Reaction

PhO $\triangle$ O + Et$_2$NH $\xrightarrow[\text{butanone, 30 °C}]{\text{catalyst (15 mol%)}}$ PhO $\overset{\text{OH}}{\frown}$ NEt$_2$

OH   OH
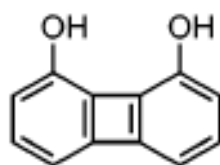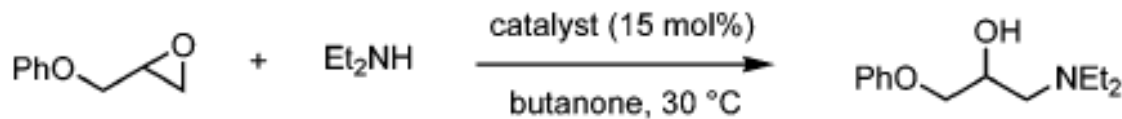
1

catalyst	k_{rel}	pKa
phenol	1.0	9.95
1	12.5	8.00

J. Hine, *et al, JACS* **1985**, *107, 1082.*

<u>1,8-biphenylenediol has two H-bond donor and make oxygen atom negative effectively.</u>
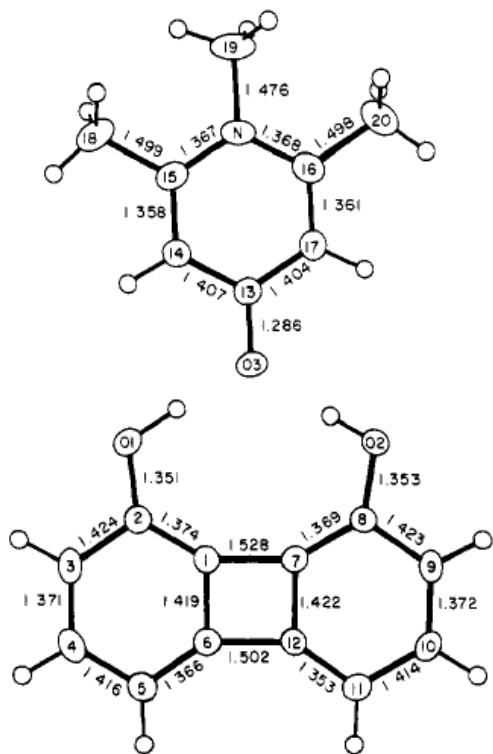
Fig. ORTEP drawing displaying the labeling scheme and bond distances (A) for the 1,8-biphenylenediol-1,2,6-trimethyl-4-pyridone complex with non-hydrogen atoms drawn at the 50% probability level and hydrogen atoms drawn with an artificial radius. The estimated standard deviations on the bond distances are 0.003-0.004 A.

J. Hine, *et al, J. Am. Chem. SOC.* **1984**, *106, 7980.*

Early Example of the Reaction with Recognition of Carbonyl group --Kelly

Diels-Alder Reaction: Rate Acceleration Promoted By A Biphenylenediol

5, Y= H
6, Y= -CH₂CH₂CH₃

pKa 6.1
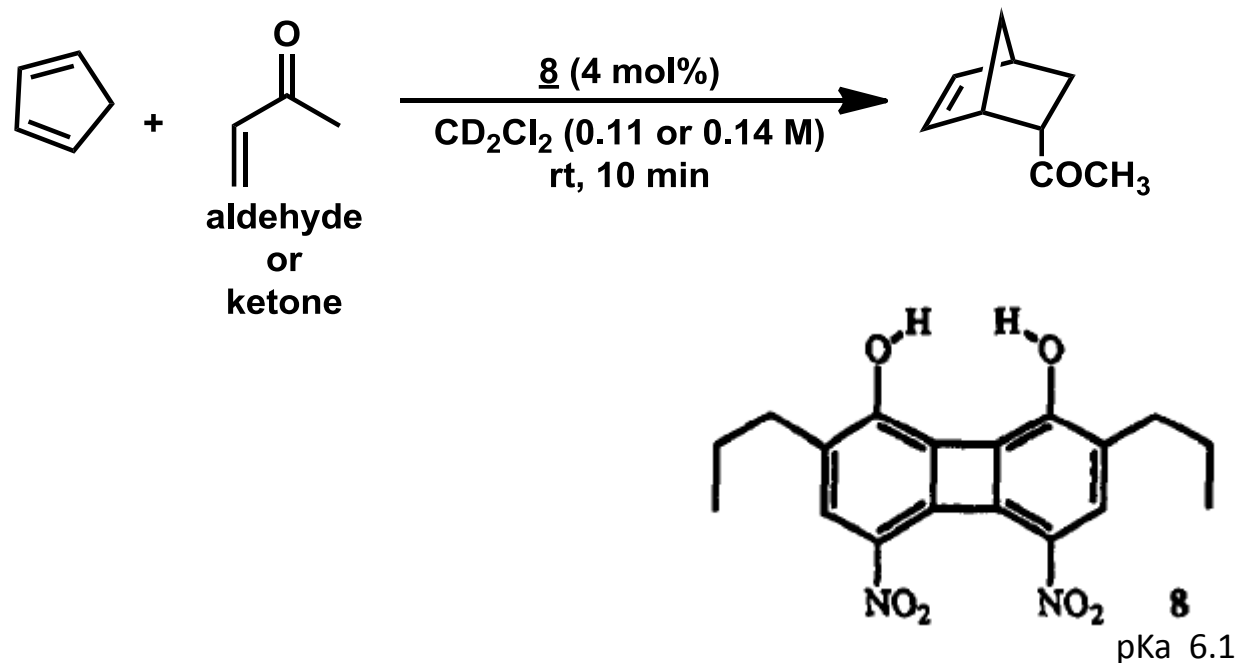
Roles of acids in Diels-Alder Reaction
- Lower LUMO of dienophile and improve the regioselectivity.

Characteristics of **8**
- Superior to acidic monodentate H-bond donor
  (such as p-nitrophenol, 4-nitro-3-(trifluoromethyl)phenol).

pKa 7.2   pKa 6.1

T. R. Kelly, *et al, Tetrahedron Lett.* **1990**, *31,* 3381.
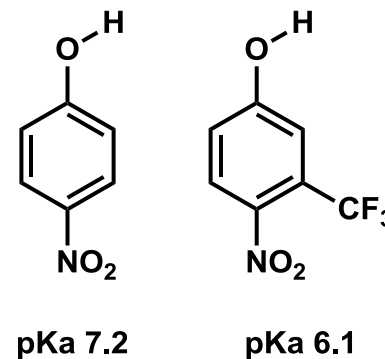
Activation of Dienophile with Thiourea

Diels–Alder Reaction
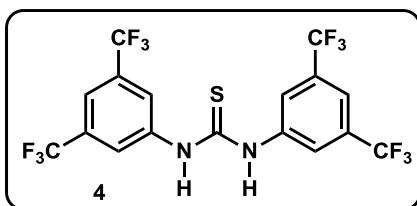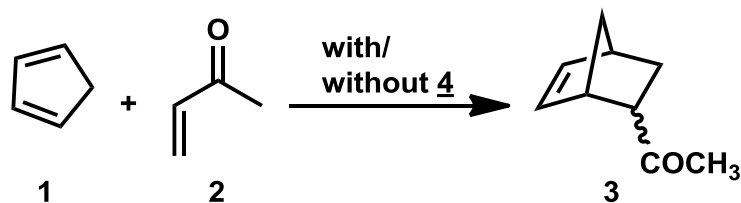
The energy barrier with **4** was smaller than that without **4** by 2 kcal/mol.

P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32,* 289.
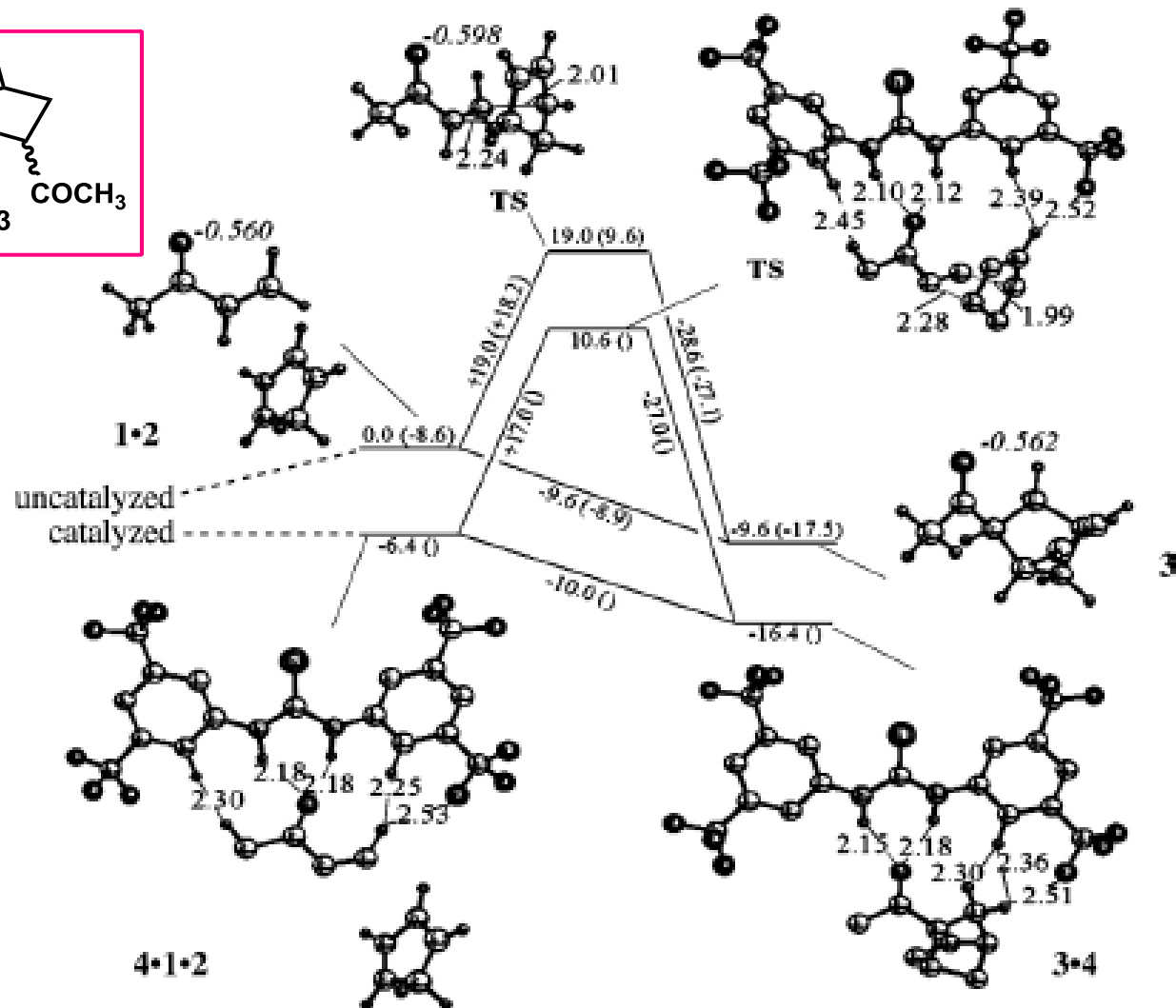
Fig. The Diels–Alder reaction of **1** and **2** uncatalyzed and catalyzed by **4**. The energies at the B3LYP/6-31+G**//AM1 level relative to the starting materials are given in kcal/mol (the SCRF-energies are in parentheses, NBO-charges in italics). Some of the hydrogens were removed for clarity.

Activation and Cyanation of Carbonyl 1

Optimized Catalyst and Equilibrium

6a: R_6 = H
6b: R_6 = OCH_3

7a: R_6 = H, 97% ee
7b: R_6 = OCH_3, 97% ee
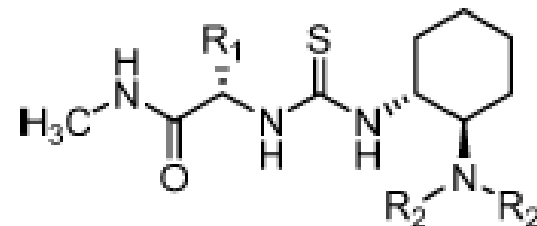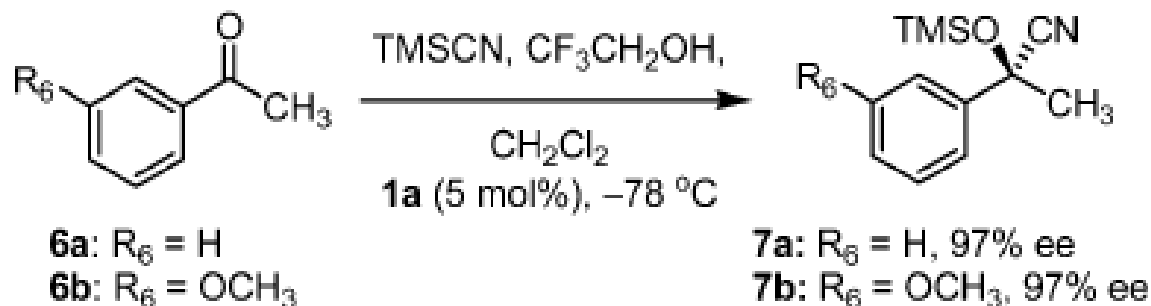
1a: R_1 = t-Bu, R_2 = n-Pr
1b: R_1 = t-Bu, R_2 = CH_3
2a: R_1 = CH_3, R_2 = n-Pr
2b: R_1 = CH_3, R_2 = CH_3

Equilibrium
in ketone cyanosilylation.

K_1 = 0 (fixed)
K_2 = 11.6 ± 0.5 M^{-2}
K_3 = 5.9 ± 0.1 M^{-2}
K_4 = 58 ± 5 M^{-2}
$K_2 k_{cat}$ = 0.051 ± 0.001 $s^{-1}M^{-2}$
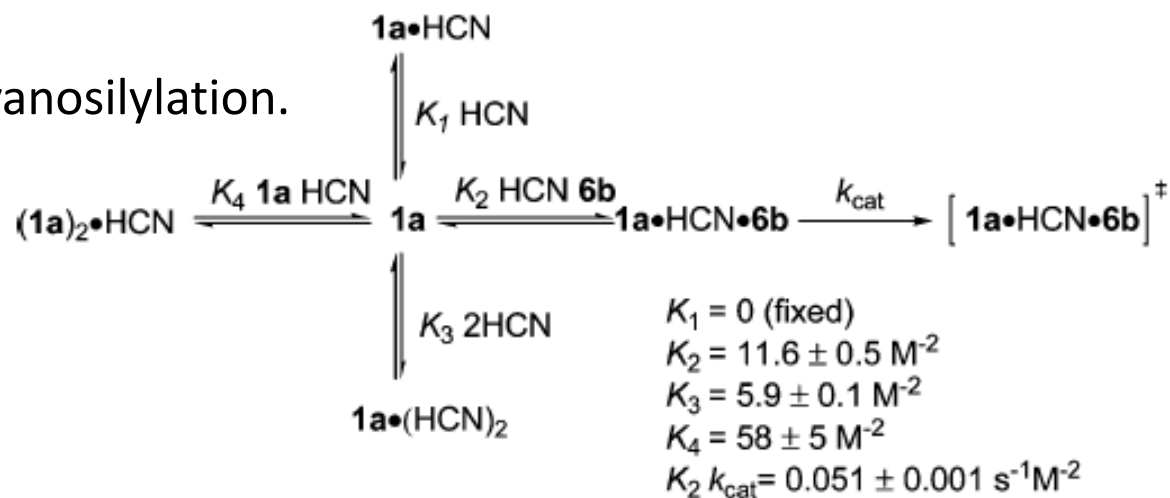
E. N. Jacobsen, *et al, J. AM. CHEM. SOC.* **2005**, *127,* 8964.
E. N. Jacobsen, *et al, J. AM. CHEM. SOC.* **2007**, *129,* 15872. ¹⁴

Activation and Cyanation of Carbonyl 2

Relationship between Reaction Rate and Concentration of HCN

6a: R_6 = H
6b: R_6 = OCH$_3$

7a: R_6 = H, 97% ee
7b: R_6 = OCH$_3$, 97% ee

TMSCN, CF$_3$CH$_2$OH,
CH$_2$Cl$_2$
1a (5 mol%), −78 °C

- Without HCN → No reaction.
- 15 mol% HCN → Sufficient to effect >90% substrate conversion.
- High [HCN] → Rate inhibition.

50% conversion
20% conversion
80% conversion

$d[7b]/dt \times 10^6$ (M s^{-1})

[HCN] (M)

(15 mol%)

Fig. Rate dependence on [HCN].
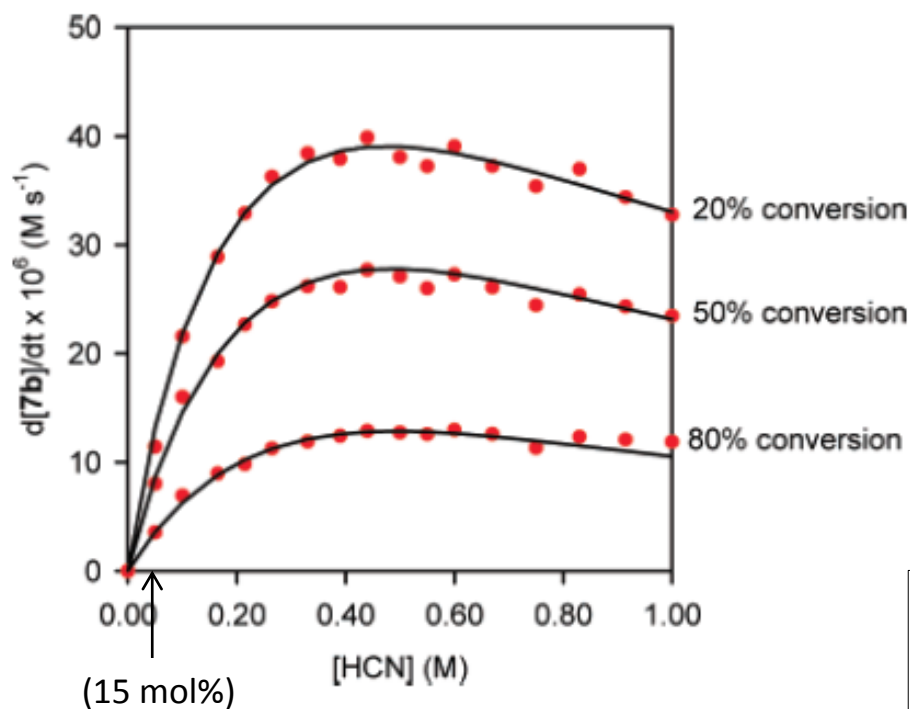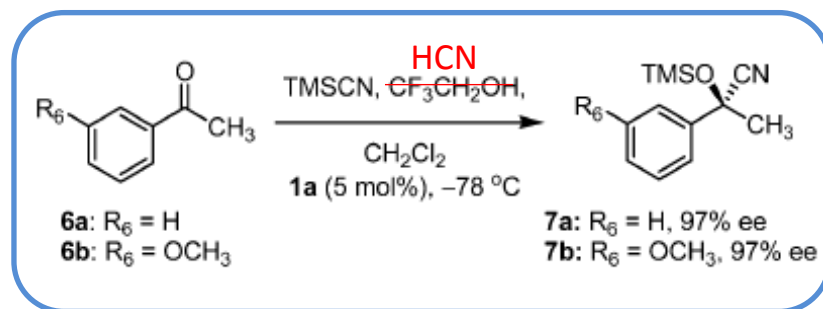Plot of the rate of cyanosilylation of **6b** ([**6b**]i = 0.33 M) with TMSCN ([TMSCN]i= 0.50 M) catalyzed by HCN and **1a** (0.025 M) at different [HCN] and at different conversions of **6b**.

1a•HCN

K_1 HCN

$(1a)_2$•HCN $\xleftarrow{K_4\ 1a\ HCN}$ **1a** $\xrightleftharpoons{K_2\ HCN\ 6b}$ **1a•HCN•6b** $\xrightarrow{k_{cat}}$ [**1a•HCN•6b**]‡

K_3 2HCN

1a•(HCN)$_2$

$K_1 = 0$ (fixed)
$K_2 = 11.6 \pm 0.5$ M^{-2}
$K_3 = 5.9 \pm 0.1$ M^{-2}
$K_4 = 58 \pm 5$ M^{-2}
$K_2 k_{cat}= 0.051 \pm 0.001$ s^{-1}M^{-2}

E. N. Jacobsen, *et al, J. AM. CHEM. SOC.* **2007**, *129,* 15872.

Activation and Cyanation of Carbonyl 3

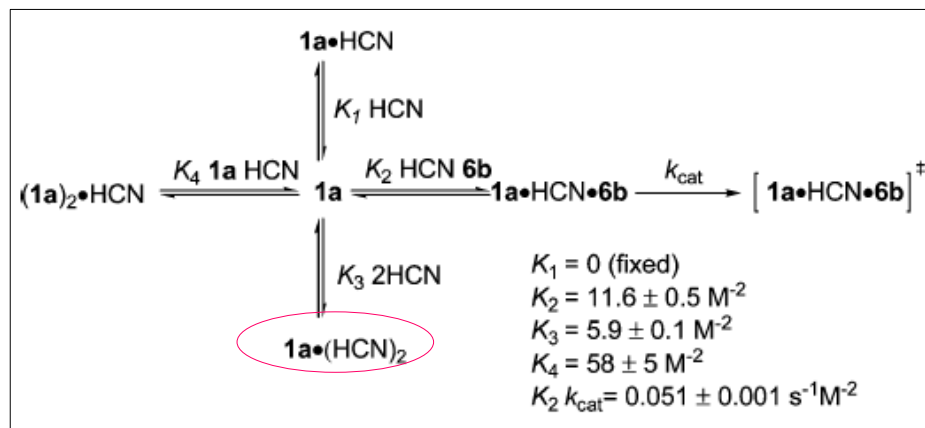## Relationship between Reaction Rate and Concentration of Catalyst

The reaction rate displays a less than first-order dependence on [**1a**] at elevated catalyst concentrations.
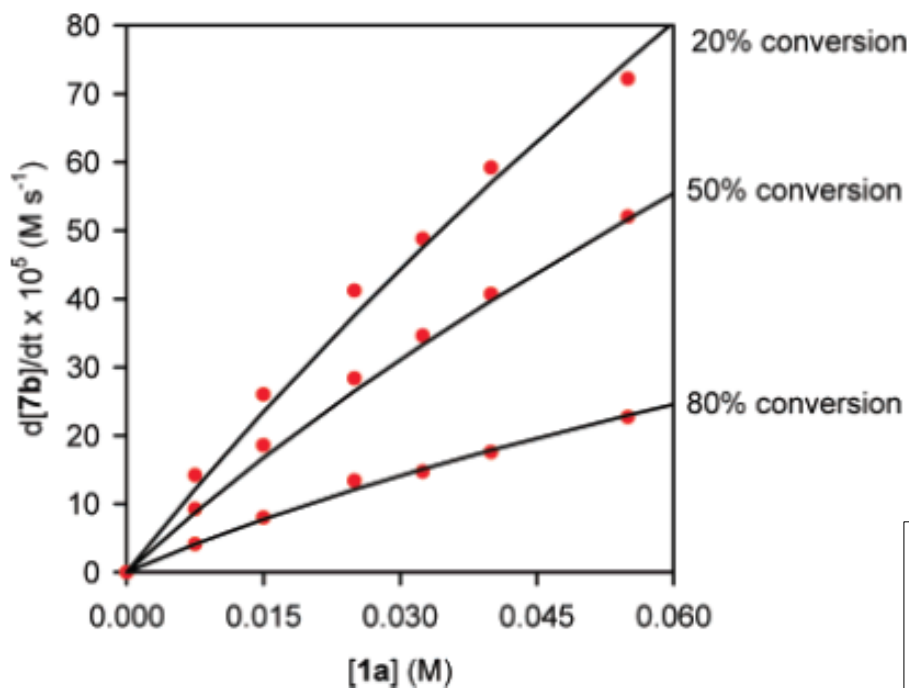

Fig. Rate dependence on [**1a**]. Plot of the rate of cyanosilylation of **6b** ([**6b**]i = 0.33 M) with TMSCN ([TMSCN]i = 0.50 M) catalyzed by HCN (0.33 M) and **1a** at different [**1a**] and at different conversions of **6b**.
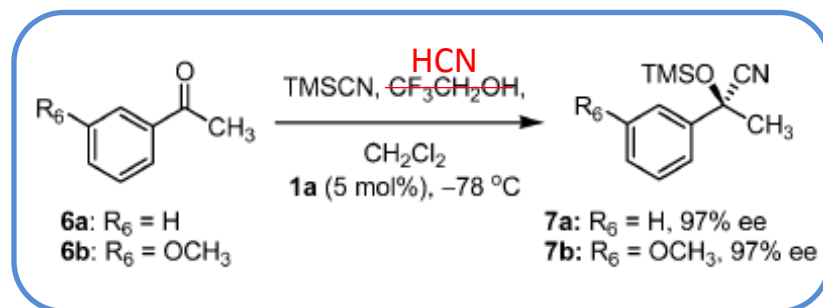
K_1 = 0 (fixed)
K_2 = 11.6 ± 0.5 M^{-2}
K_3 = 5.9 ± 0.1 M^{-2}
K_4 = 58 ± 5 M^{-2}
$K_2 k_{cat}$ = 0.051 ± 0.001 s^{-1}M^{-2}

(*First-order dependence on [**6**])

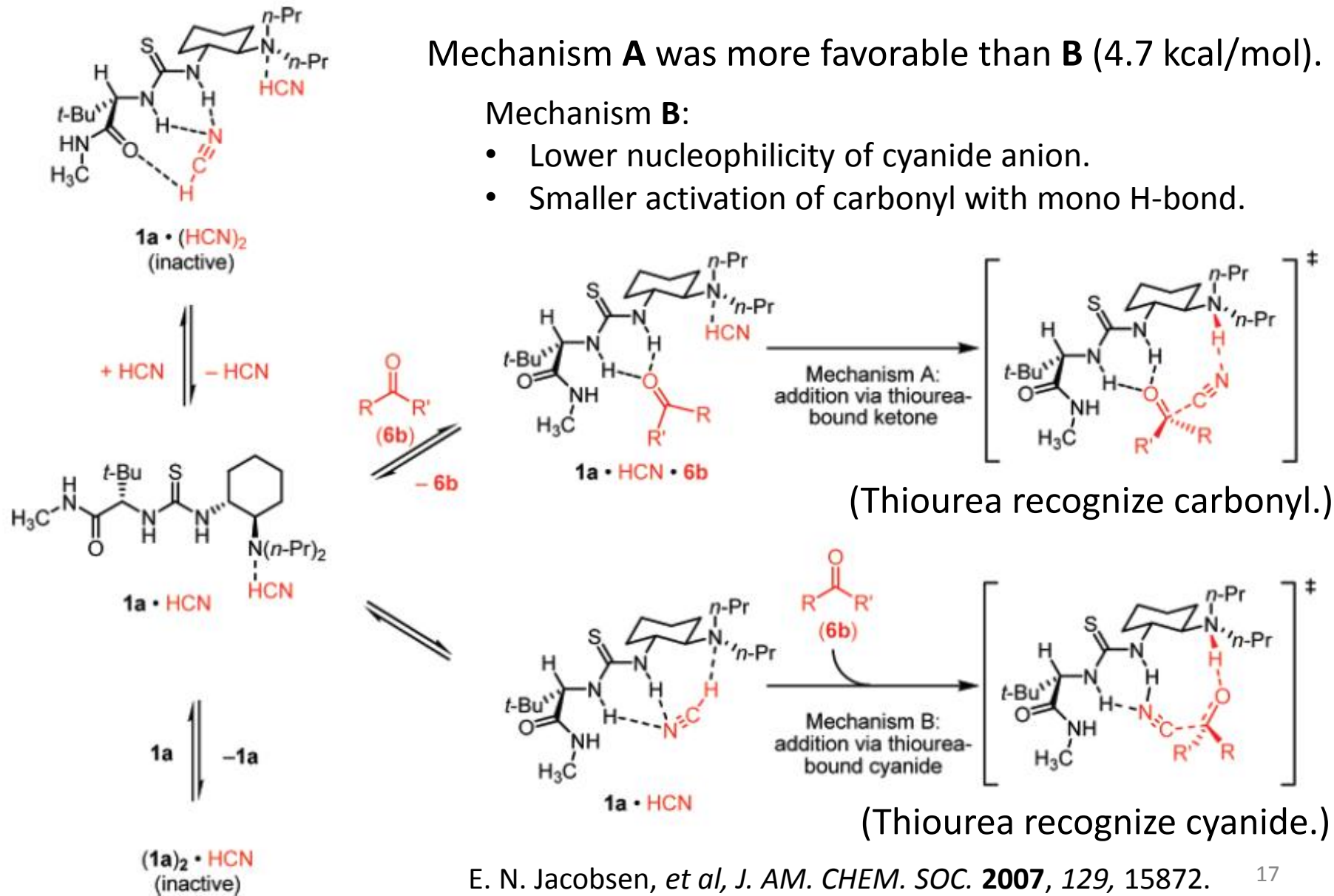E. N. Jacobsen, *et al, J. AM. CHEM. SOC.* **2007**, *129,* 15872.
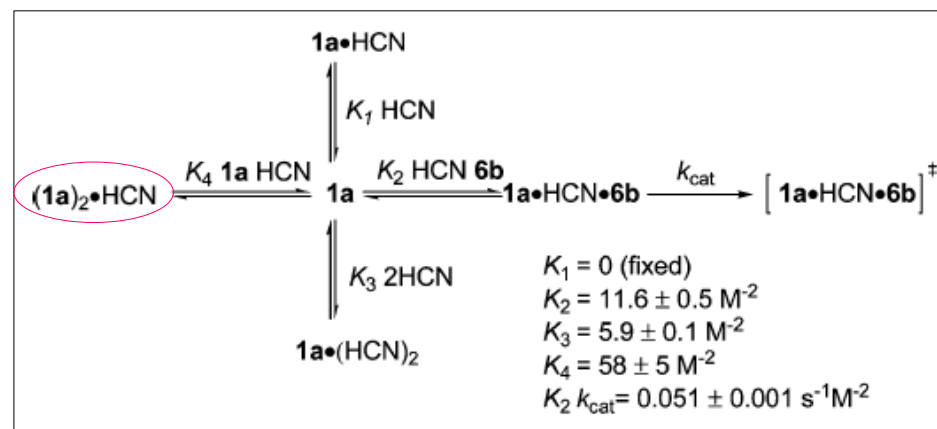
Activation and Cyanation of Carbonyl 4
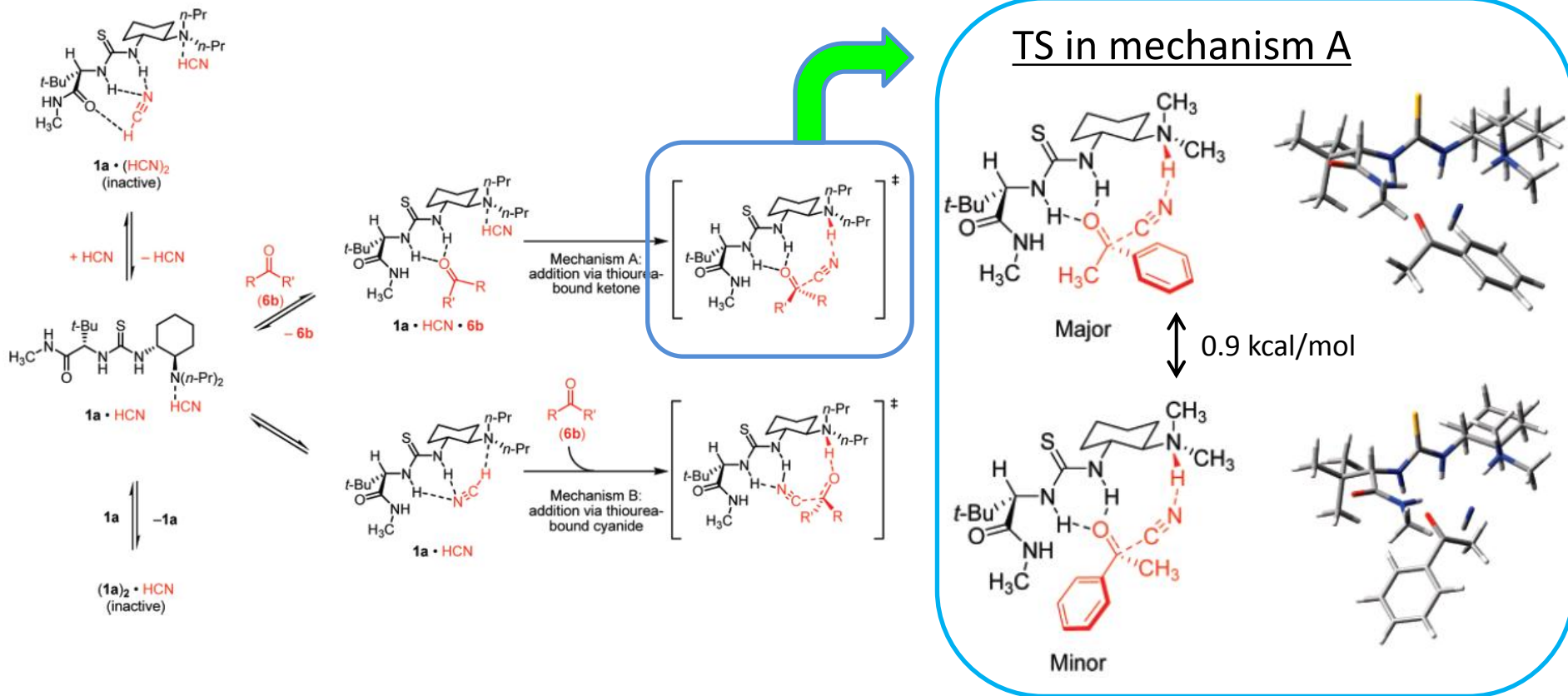
Possible Transition States

Mechanism **A** was more favorable than **B** (4.7 kcal/mol).

Mechanism **B**:
- Lower nucleophilicity of cyanide anion.
- Smaller activation of carbonyl with mono H-bond.

(Thiourea recognize carbonyl.)

(Thiourea recognize cyanide.)

E. N. Jacobsen, *et al, J. AM. CHEM. SOC.* **2007**, *129,* 15872.

Activation and Cyanation of Carbonyl 5

Decision of Steric Configuration

TS in mechanism A

Major

0.9 kcal/mol

Minor

Conclusive factor of the enantioselectivity:

Repulsive interactions between the amide π-system and the substrate π-system.

⇧

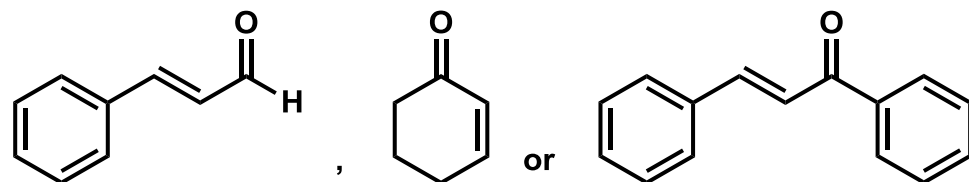Sharp decreases in enantioselectivity were observed when using electrondeficient acetophenone derivatives.

E. N. Jacobsen, *et al, J. AM. CHEM. SOC.* **2007**, *129,* 15872.

Recognition of Nitro Group 1

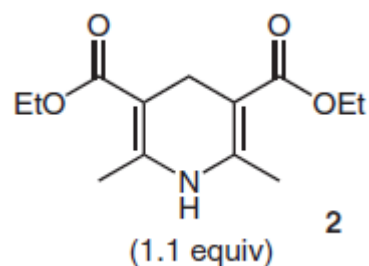**Biomimetic Reduction of Conjugated Nitroalkenes**
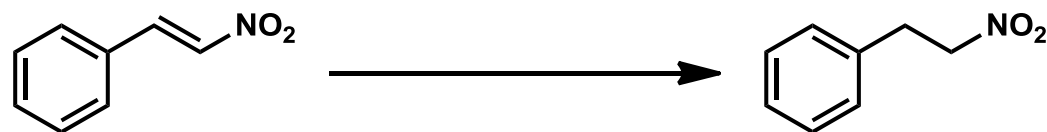
condition:
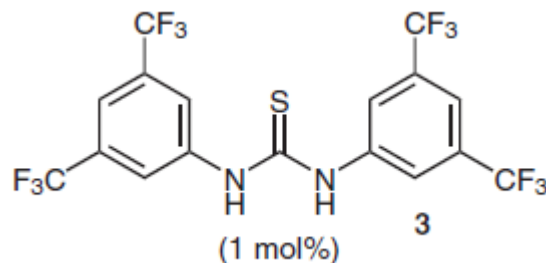**2** (1.1 equiv.), **3** (10 mol%)
CH_2Cl_2, reflux, 24 h

No Reaction.

Only nitrostylene interact with **3** strongly enough to be reduced.
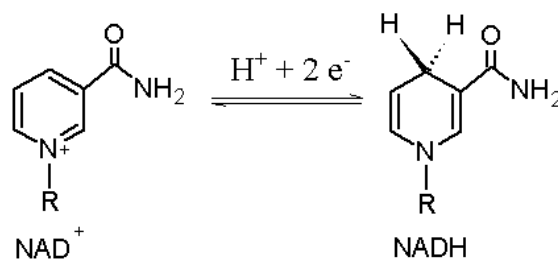

2
(1.1 equiv)

Hantzsch esters

3
(1 mol%)

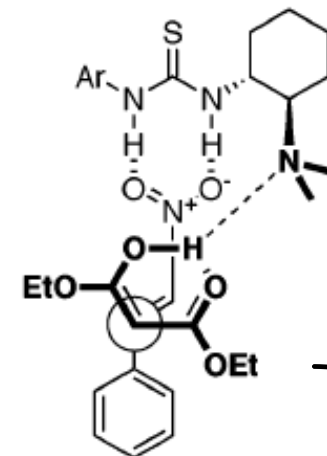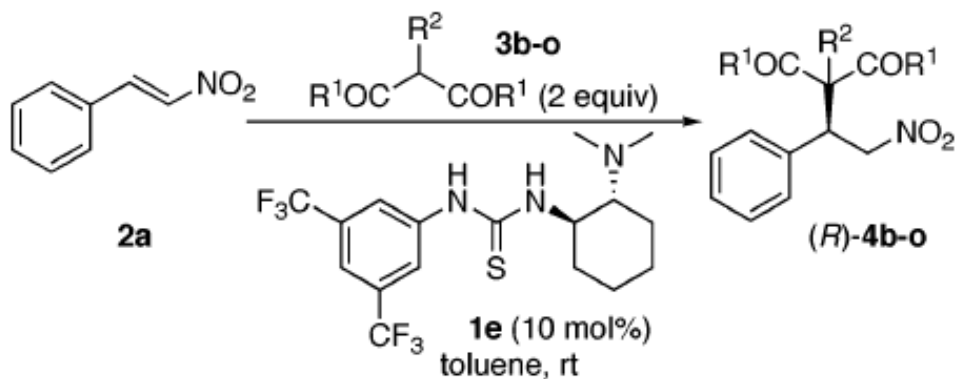Z. Z. Peter R. Schreiner, *Synthesis* **2007**, *16,* 2559.
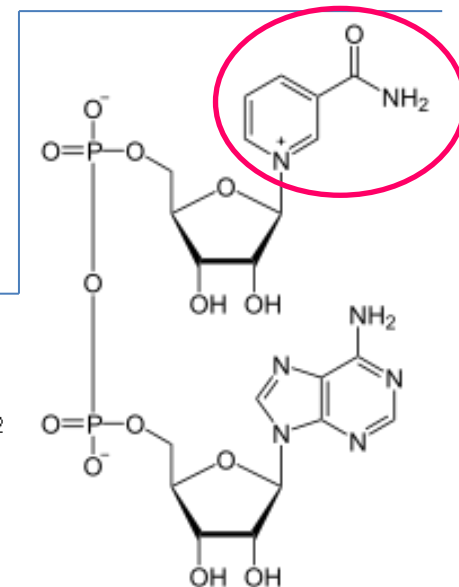
They were inspired by NADH system. Nicotinamide adenine dinucleotide (NADH) is a coenzyme to reduce unsaturated functionalities under very mild conditions.

$$H^+ + 2\,e^-$$

NAD$^+$

NADH

NAD+

19

Recognition of Nitro Group –Michael Reaction 2-1

Substrate Scope

entry	3	R^1	R^2	time (h)	yield^b (%)	ee^{c,d} (%)
1	3b	OMe	H	9	89	86
2	3c	O^{i}Pr	H	48	70	88
3	3d	O^{t}Bu	H	48	trace	–
4	3e	Me	H	1	80	89^e
5	3f	NCCH$_2$CN		0.25	85	25^e
6	3g	OCMe$_2$O	H	24	88	46^f
7	3h	OMe	Me	36	82	93^e
8	3i	OMe	OMe	28	89	94
9	3j	OMe	OMs	1	86	79^e
10	3k	OEt	NHBoc	48	81	82^e
11	3l	OEt	NHAc	24	72	33
12	3m	OMe	Cl	1	>99	89^e
13	3n	OEt	Br	48	nr	–
14	3o	OMe	Ph	48	trace	–

Large R^1 decreased reactivity.

Low ee.
–These cannot form the six-membered TS.
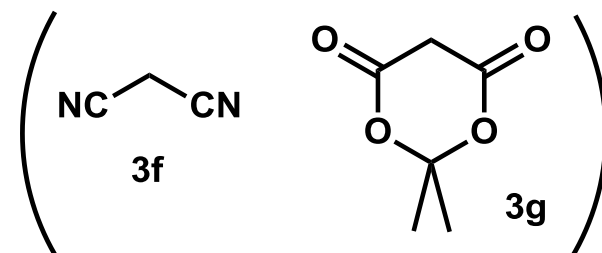
Construct quaternary carbon center.

Y. Takemoto, *et al, J. Am. Chem. Soc.* **2005**, *127,* 119.

Recognition of Nitro Group –Michael Reaction 2-2

Mechanistic Studies

1H-NMR investigation:

2a
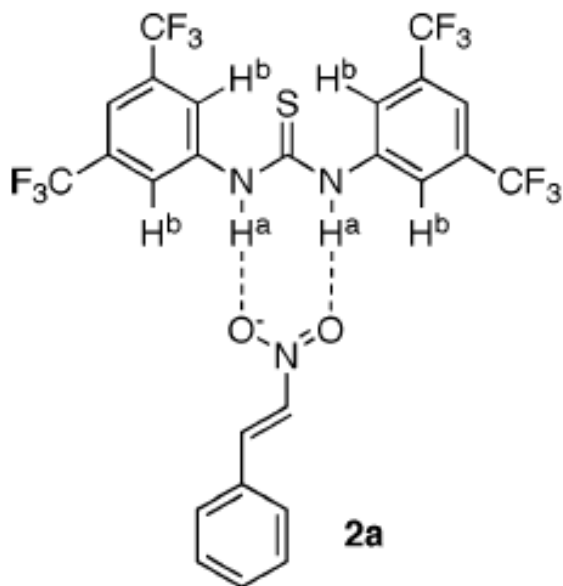
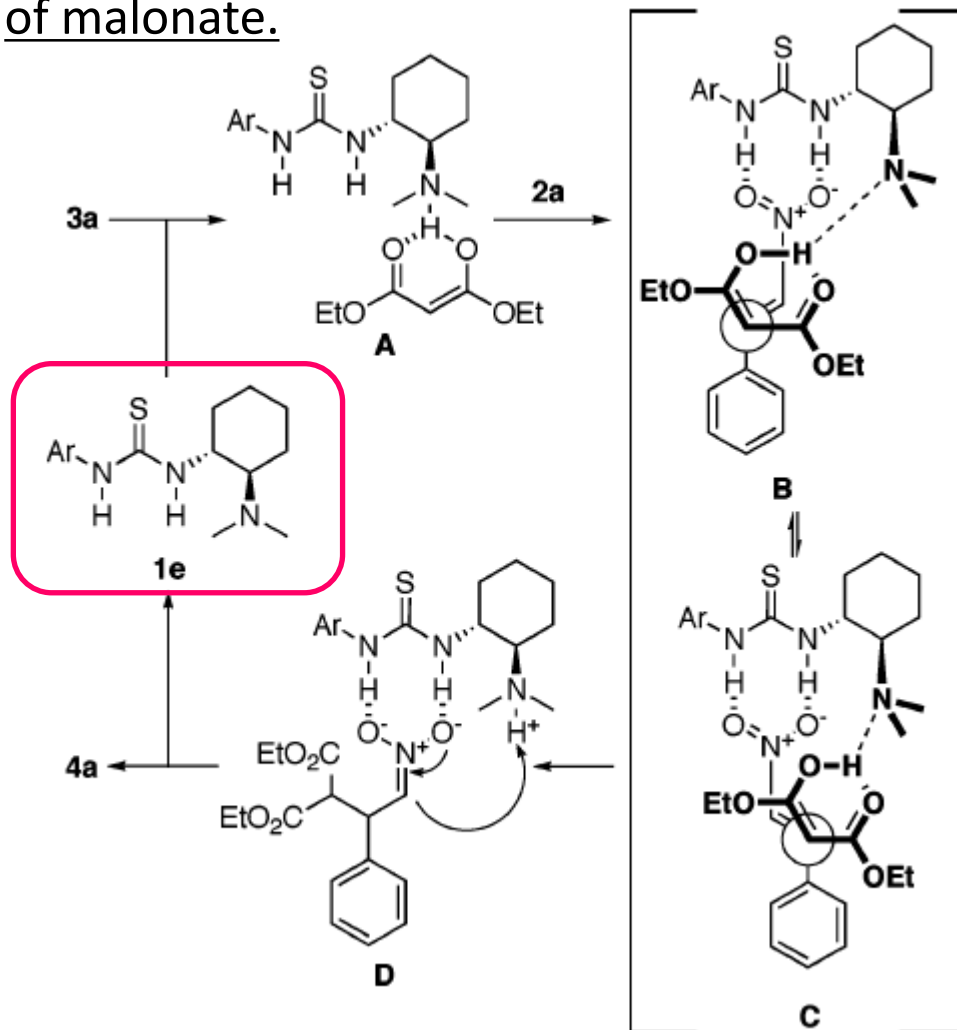H_a: 6.63 to 6.67 ppm
H_b: 7.31 to 7.35 ppm

Kinetic study:
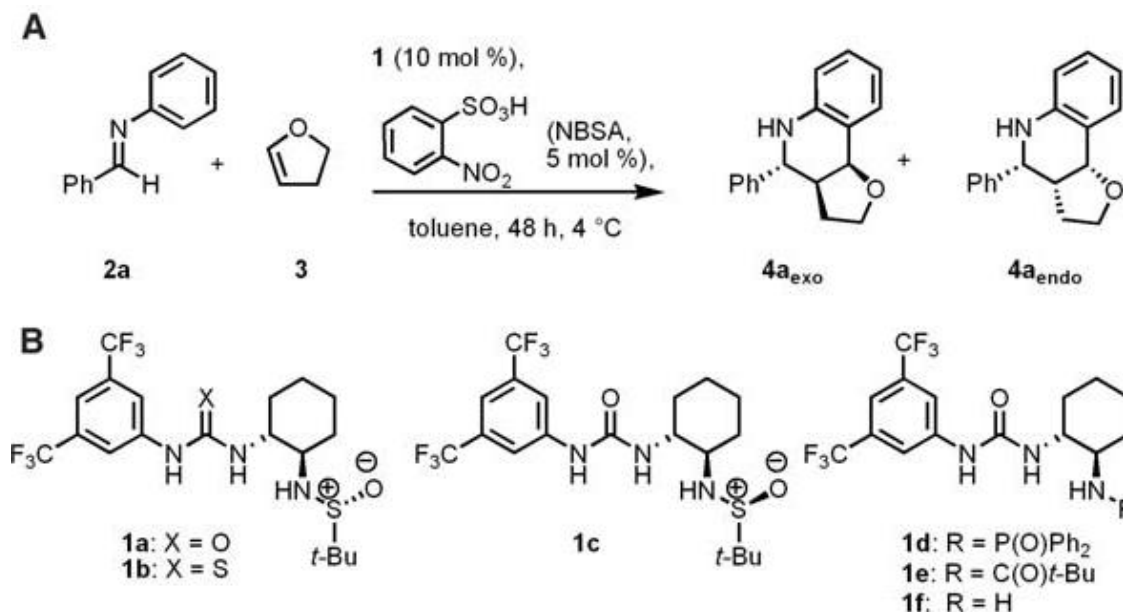The reaction is first-order in catalyst (**1e**), nitrostyrene (**2a**) and maronate (**3a**).

Transition-state models of Michael reactions of malonate.

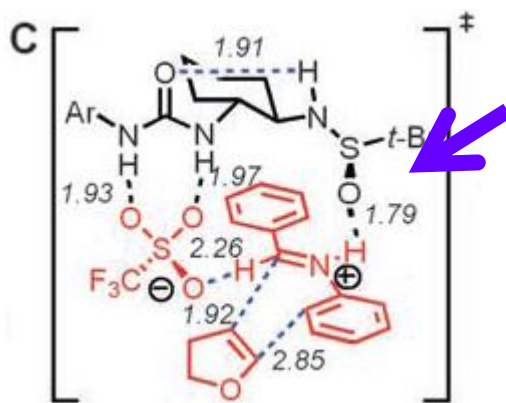

B is favorable to **C** due to the steric hinderance.

Y. Takemoto, *et al, J. Am. Chem. Soc.* **2005**, *127,* 119.

Structure-Reactivity/Enantioselectivity Studies

A

entry	catalyst	conversion (%)	dr ($4_{exo}/4_{endo}$)	4_{exo} ee (%)
1	1a	92	4.0	91
2	1b	95	1.4	83
3	1c	52	0.3	2
4	1d	20	1.0	50
5	1e	8	0.25	<5
6	1f	0	ND	ND

B

1a: X = O
1b: X = S
1c
1d: R = P(O)Ph₂
1e: R = C(O)t-Bu
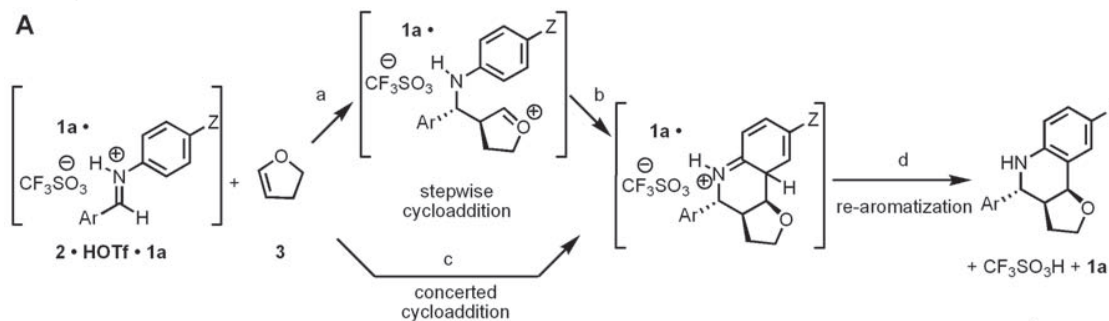1f: R = H

C

- Urea derivative showed better enantio- and diastereo-selectivity than thiourea(catalyst **1a** vs. **1b**).
- The position of sulfonic amide O was important (**1a** vs. **1c**).
- Phosphinic amide urea, pivalamide urea and amino urea induced both low reactivity and selectivity (**1a** vs. **1d**,**1e** and **1f**).

E. N. Jacobsen, *et al, Science* **2010**, *327*, 986. 22

Geometry and energy-minimized structures
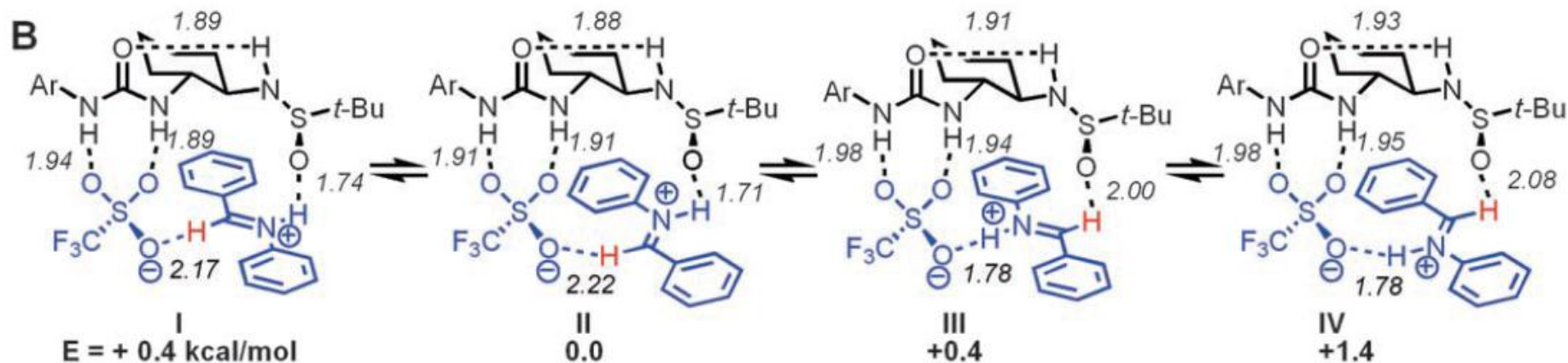
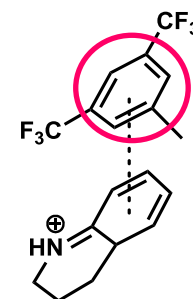**B**: All four intermediates (**I** to **IV**) were expected be energetically accessible.

But nucleophile added, **I'** was predicted to have over 1.3 kcal/mol lower energy than the other complexes. (Because of the π-π interaction (**I'** vs. **II'**) and the room around the reactive sites(**I'** vs. **III'**, **IV'**)).
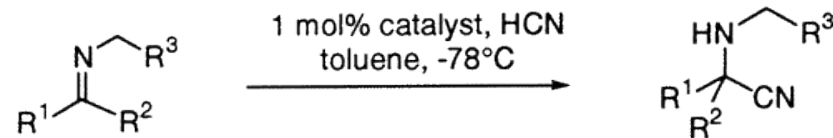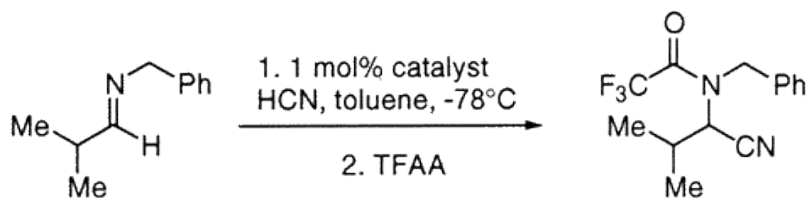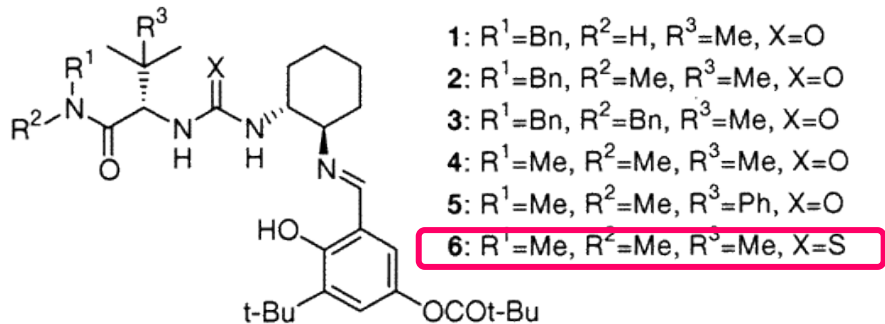
I, II, III and IV + dihydrofurane → I', II', III' and IV'.
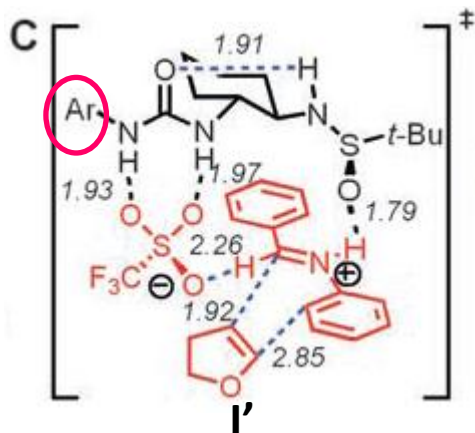
About I' vs. II'

Catalyst Optimization and Comparison Substrates

α-Amino acids are the building blocks of proteins and are widely used as components of medicinally active molecules and chiral catalysts.

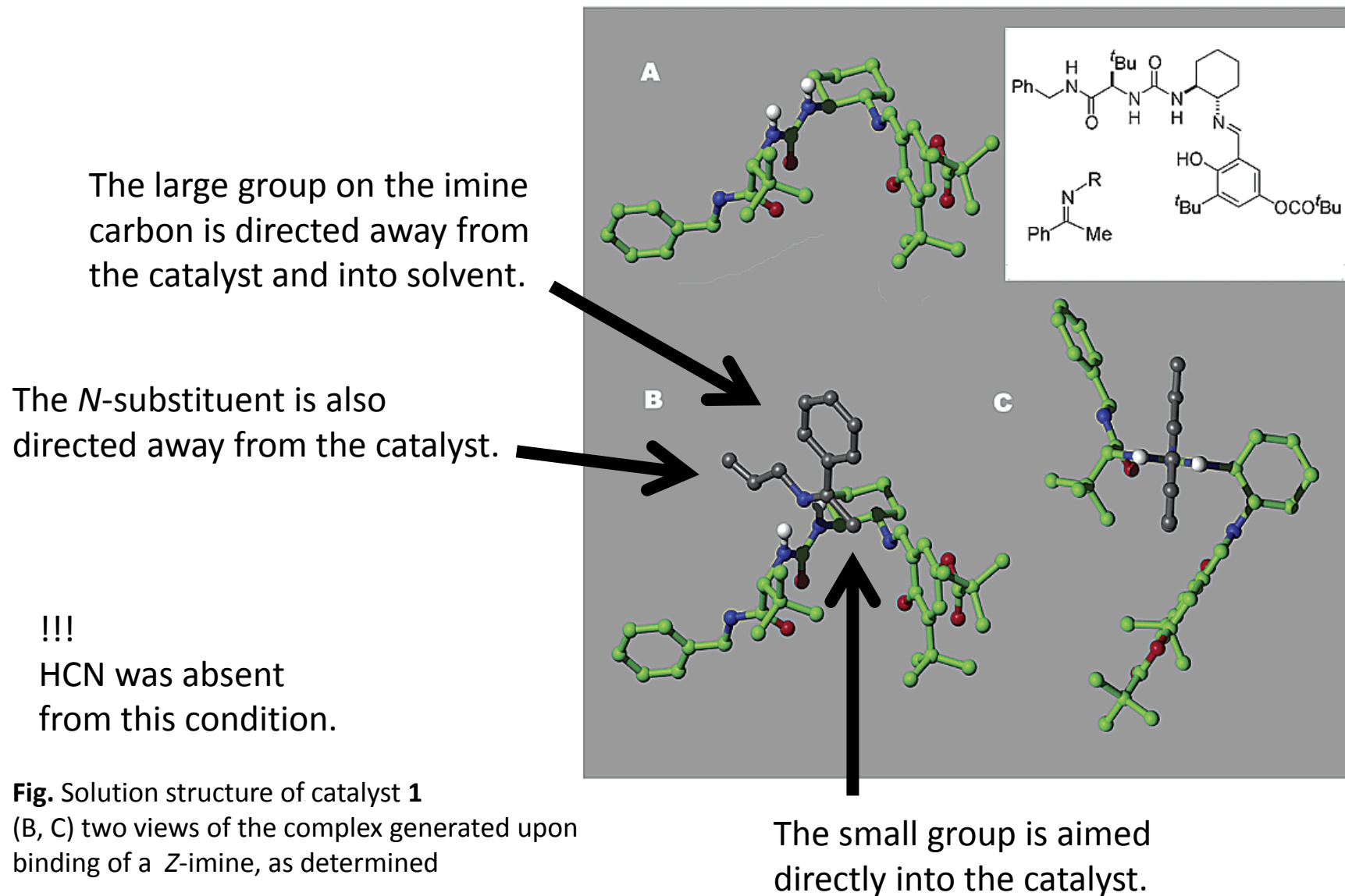1: R^1=Bn, R^2=H, R^3=Me, X=O
2: R^1=Bn, R^2=Me, R^3=Me, X=O
3: R^1=Bn, R^2=Bn, R^3=Me, X=O
4: R^1=Me, R^2=Me, R^3=Me, X=O
5: R^1=Me, R^2=Me, R^3=Ph, X=O
6: R^1=Me, R^2=Me, R^3=Me, X=S

catalyst	ee^a (%)	catalyst	ee^a (%)
1	80.0	4	95.8
2	93.5	5	96.6
3	93.1	6	97.0

1 mol% catalyst, HCN
toluene, -78°C

	substrate			ee^a of product (%)	
entry	R^1	R^2	R^3	catalyst 1	catalyst 6
1	i-Pr	H	Ph	80	97
2	n-Pent	H	Ph	79	96
3	t-Bu	Me	Ph	70	86
4	Ph	Me	p-BrC$_6$H$_4$	92	96
5	t-Bu	H	Ph	96	99.3
6	Ph	H	Ph	96	99.3

P. Vachal and E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012.

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Activation of Hydrogen Cyanide --Strecker Reaction 1-2

Solution structure of Catalyst and Aldimine

The large group on the imine carbon is directed away from the catalyst and into solvent.

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

!!!
HCN was absent
from this condition.

Fig. Solution structure of catalyst **1**
(B, C) two views of the complex generated upon
binding of a *Z*-imine, as determined

The small group is aimed
directly into the catalyst.

P. Vachal and E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012.

Activation of Hydrogen Cyanide --Strecker Reaction 2-1

Improvement in 2009 Nature

Report in 2002:   2009:

o High yield and ee
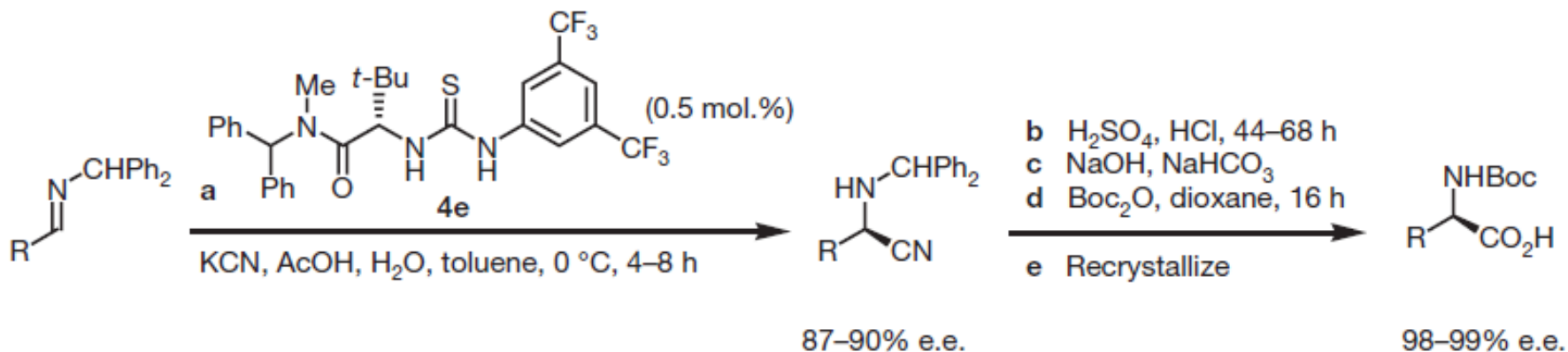
× Cryogenic temperatures ⟶ 0 °C

× Hazardous cyanide source ⟶ KCN/AcOH

× Synthesis of the catalyst requires eight steps. ⟶ Three steps

87–90% e.e.   98–99% e.e.

Fig. Potassium cyanidemediated Strecker synthesis. **a**, Catalyst **4e** (0.5 mol.%), KCN (2 equiv.), acetic acid (AcOH, 1.2 equiv.), H_2O (4 equiv.), toluene, 0 C, 44-68 h. **b**, Aqueous H_2SO_4 and HCl, 120 °C, 44-68 h. **c**, NaOH, $NaHCO_3$. **d**, Di-tert-butyl dicarbonate (Boc_2O, 2.5-3 equiv.), dioxane, 16 h. **e**, Recrystallize directly from hexanes/diethyl ether or as the tert-butylamine (t-BuNH$_2$) salt from tetrahydrofuran/ethanol.

E. N. Jacobsen, *et al, Nature* **2009**, *461*, 968.

Activation of Hydrogen Cyanide --Strecker Reaction 2-2

**(Mechanistic Study)** *Via Cation or Anion ??*
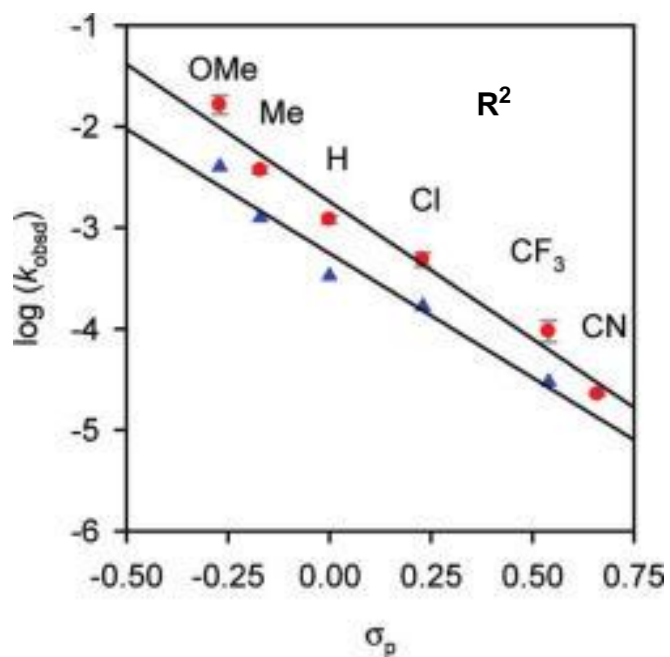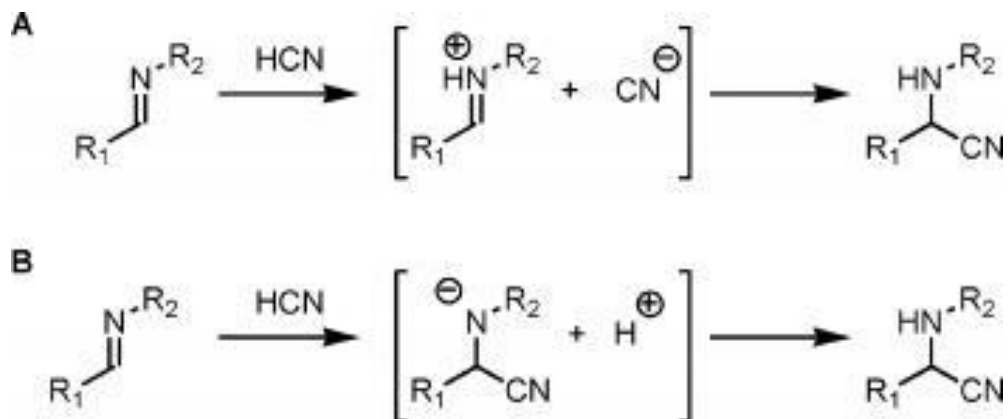
Figure 4. Rate dependence of imine hydrocyanation catalyzed by **4a** or **4b** on substrate electronic properties. Plot of the logarithm of pseudofirst-order rate constant ($\log(k_{obsd})$) versus σ_p for the hydrocyanation of p-substituted imines **2b**-**2g** ($[2]_i = 0.040$ M) by TMSCN/MeOH (0.50 M) mediated by thiourea catalyst **4a** ($[cat]_{tot}$) 0.0020 M, ●) or urea catalyst **4b** ($[cat]_{tot}$) 0.0020 M, ▲) versus σ_p.

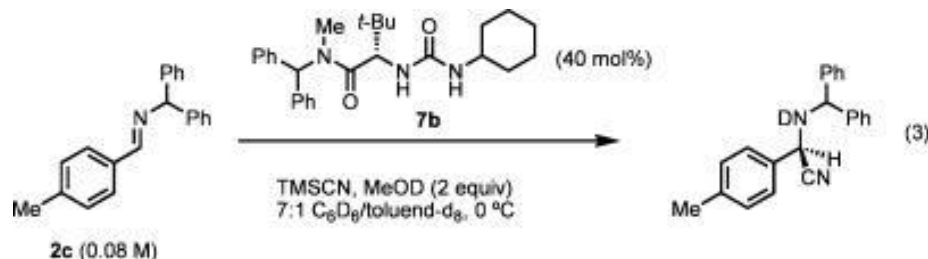X= S (4a)
O (4b)
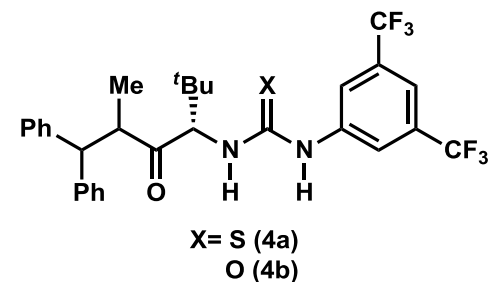
Hydrocyanation proceeded via cation species.

S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358.

Activation of Hydrogen Cyanide --Strecker Reaction 2-3

(Mechanistic Study) *What Protonated Imine??*
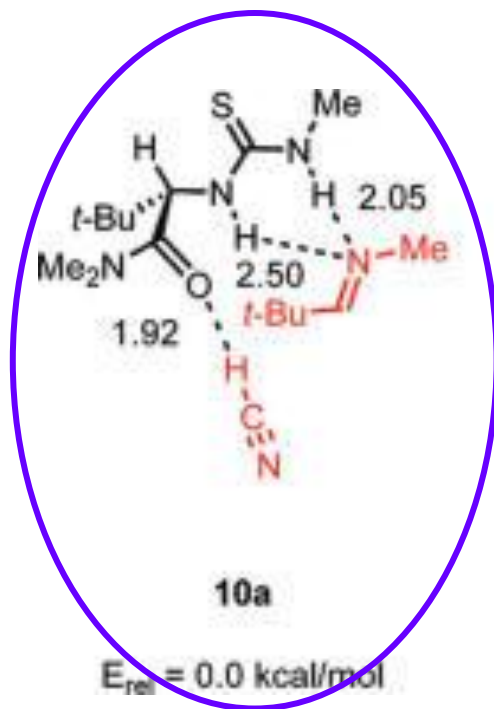
S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358.

(Mechanistic Study) *What Protonated Imine??*

2c (0.08 M)

NH on urea was not exchanged to D.
D was observed on nitrogen in TM.

Urea didn't ptrotonate imine, i. e., to give TM, the interaction between the urea and the substrate was not necessary.
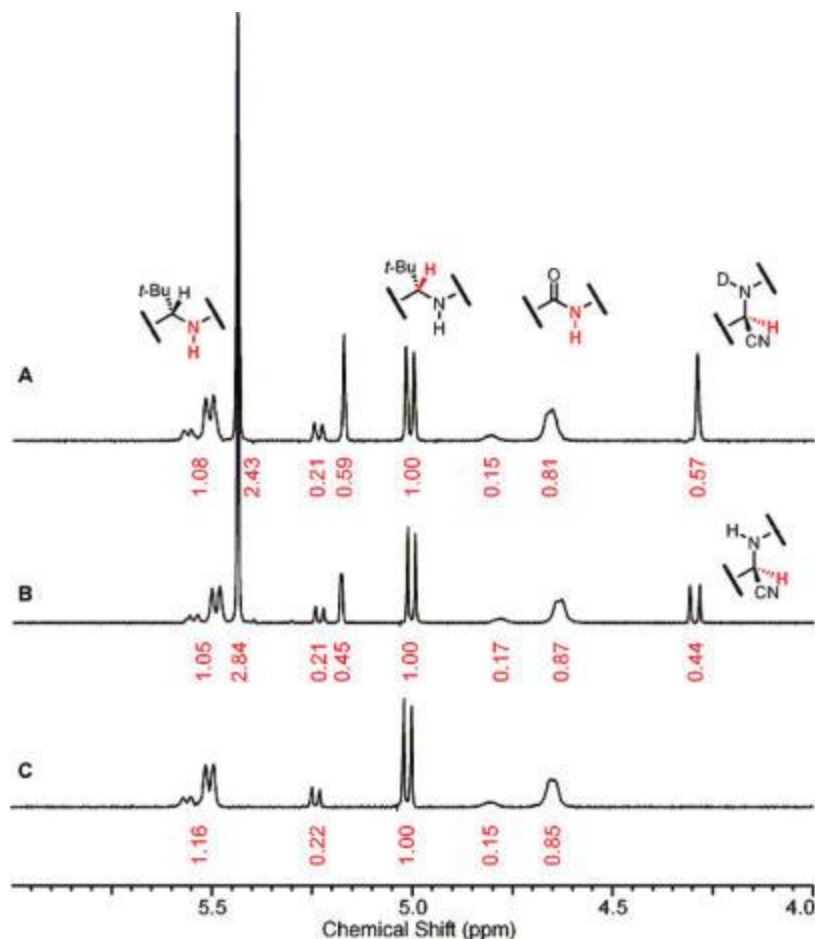
DCN, catalyst **7b**
and imine **2h**

HCN, catalyst **7b**
and imine **2h**

DCN and catalyst **7b**

Figure Partial ^{1}H NMR spectra of reactions depicted in eq 3 after 25 min Data were collected at 32 °C. Under these conditions, the catalyst exists as a 5:1 mixture of amide rotamers. HCN and DCN were generated from TMSCN and MeOH or MeOD. The enantiomeric excess of the α-aminonitrile isolated from these reactions is 84-85%.

S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358.

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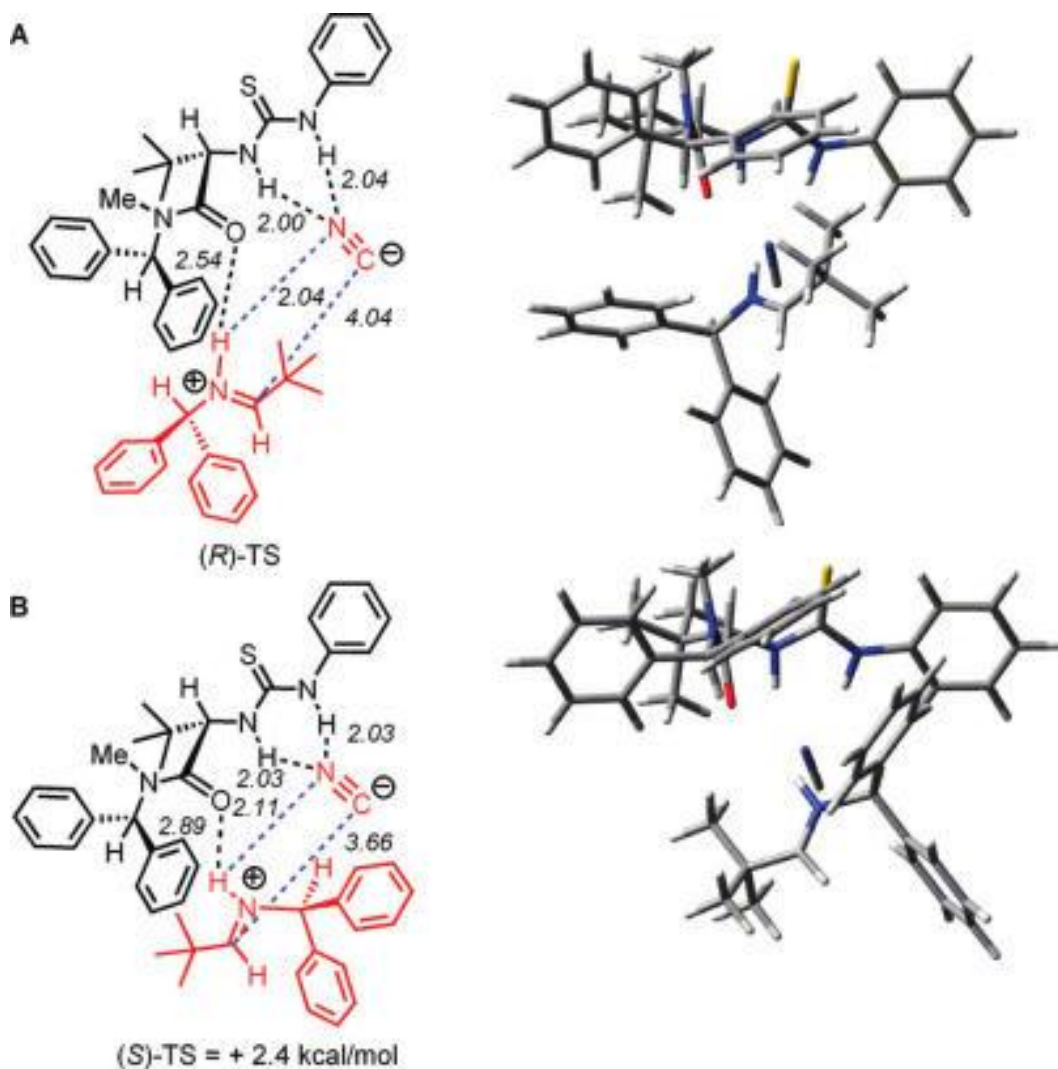**(Mechanistic Study)** *Enantioselectivity-Determining Step*
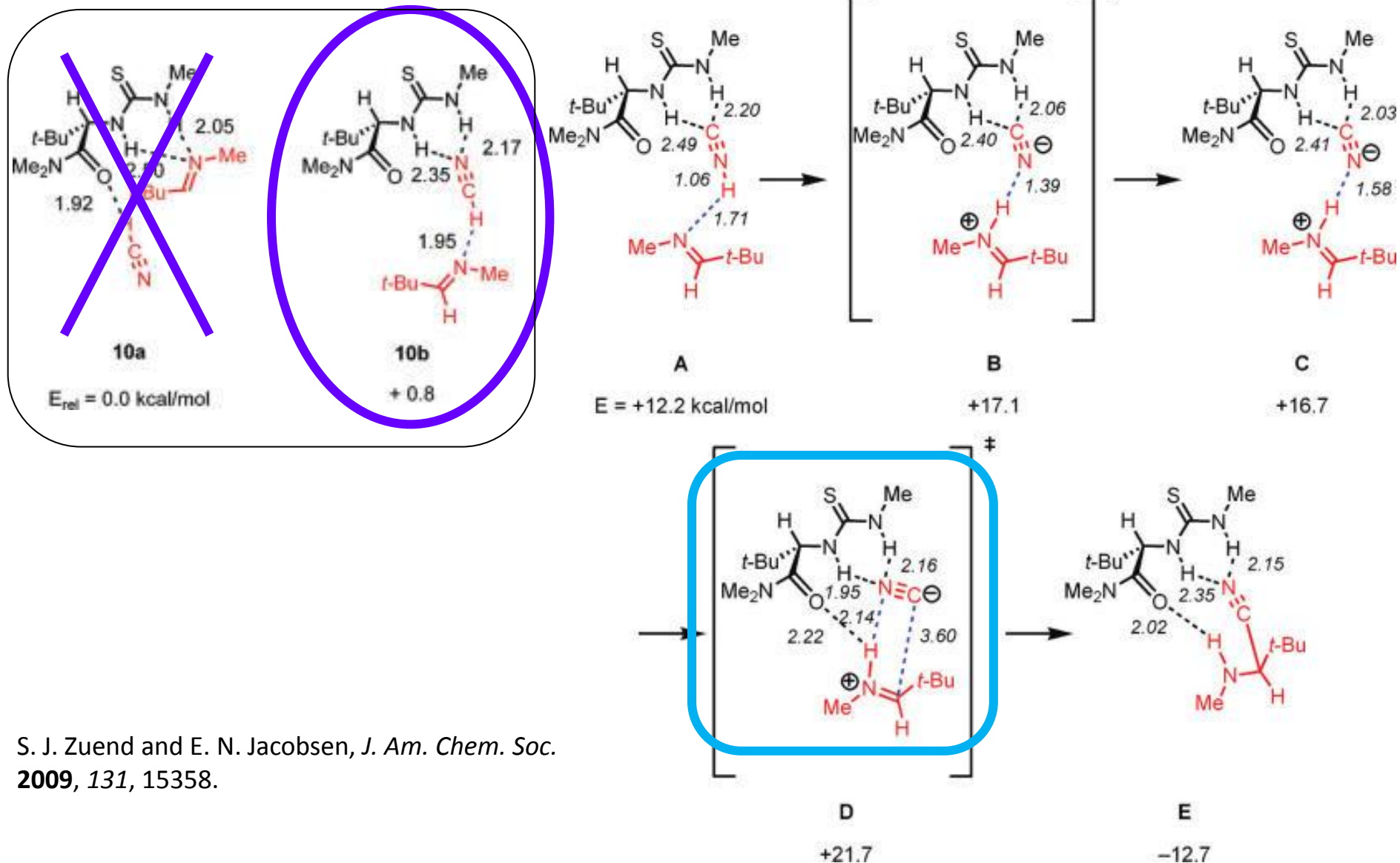
S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358.

Scheme 8. Catalyst-Controlled, HNC-Mediated Imine Hydrocyanation

Activation of Hydrogen Cyanide --Strecker Reaction 2-6
(Mechanistic Study) *Enanthioselectivity*

*Figure 13.* Calculated transition structures for HNC addition to imine **2a** catalyzed by **6a**. Transition structures leading to the (A) major and (B) minor enantiomer are shown.

There are no apparent "steric clashes" that might explain why some transition structures are significantly higher in energy than the one leading to (*R*)-TM with catalyst.

Why **A** is more stable than **B** ??

S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358.

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Activation of Hydrogen Cyanide --Strecker Reaction 2-7

(Mechanistic Study) *Focus on the Distance between Catalysts and Cyanide Anion*

(S)-TS with **6c**

(S)-TS with **6a**

(R)-TS with **6a**

6a-h
(in next slide)
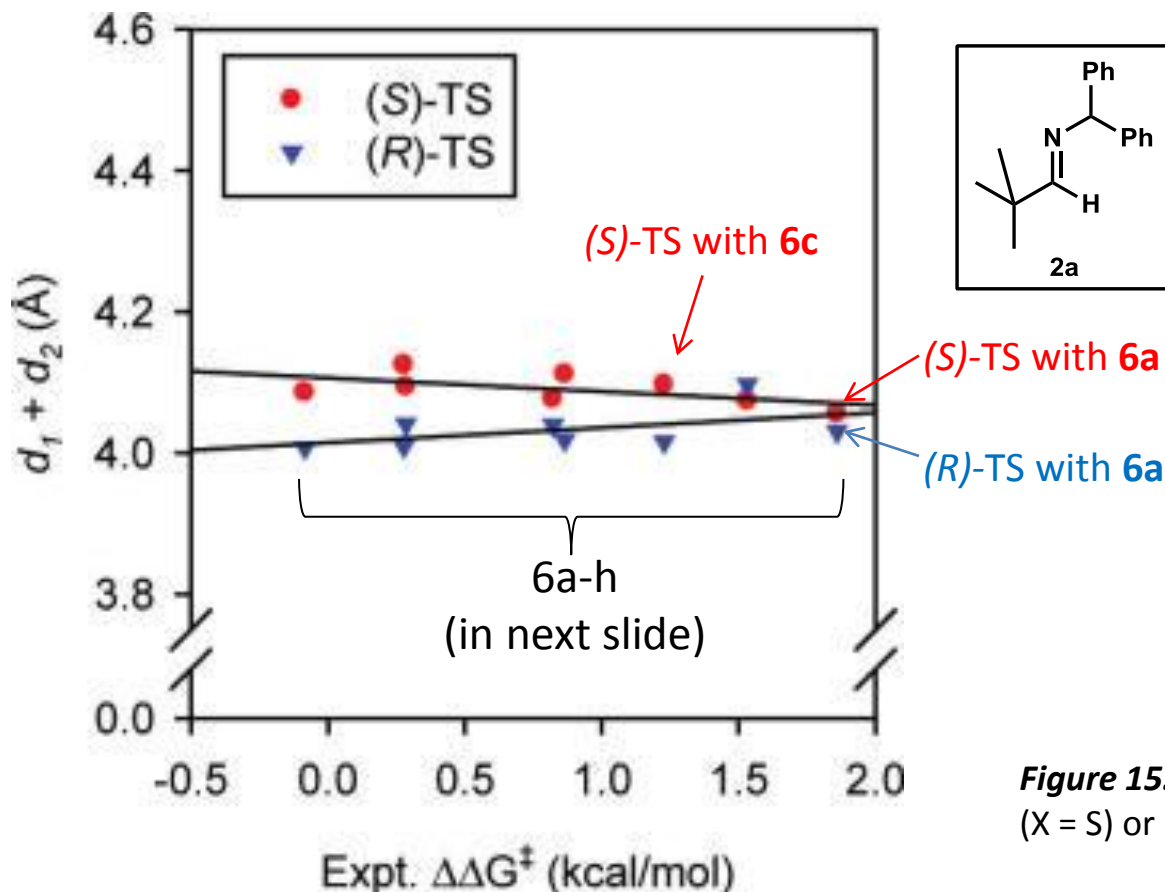
Figure 16. Correlation of transition structure bond length with enantioselectivity for HNC addition to imine **2a**. Plot of the sum of the cyanide-(thio)urea H-bond lengths in B3LYP/6-31G(d) transition structures versus experimental energy difference between (*R*)- and (*S*)-transition states.

$$\Delta\Delta G^{\ddagger} = -RT\ln([R]/[S])$$

2a

catalyst **6**, TMSCN, MeOH
toluene, 0 °C
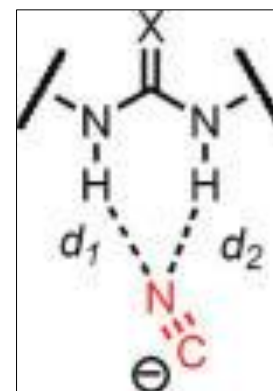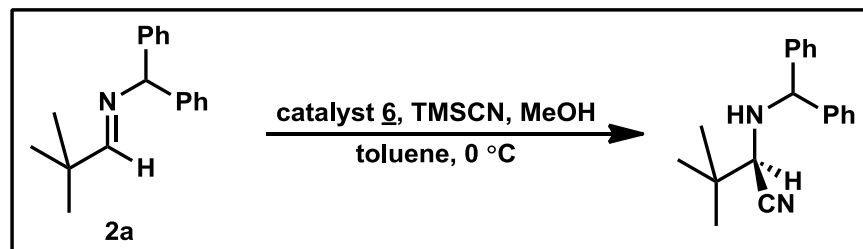
Figure 15. H-bond distances between thiourea (X = S) or urea (X = O) and cyanide anion.

Smaller d1+d2 = More stable complex

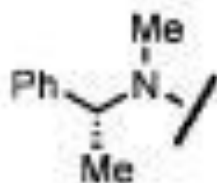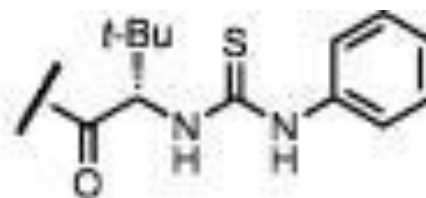There was few difference of the sums (=d1+d2) between (*S*)-TS and (*R*)-TS .

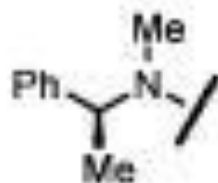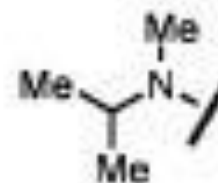S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358.

Structures of 6a - h
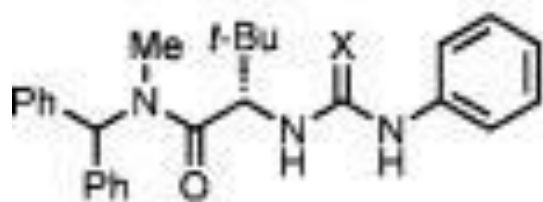
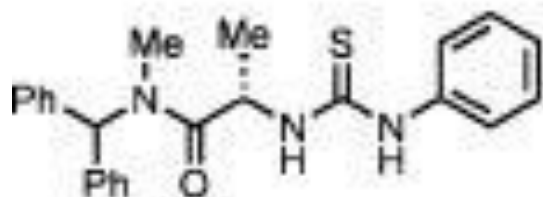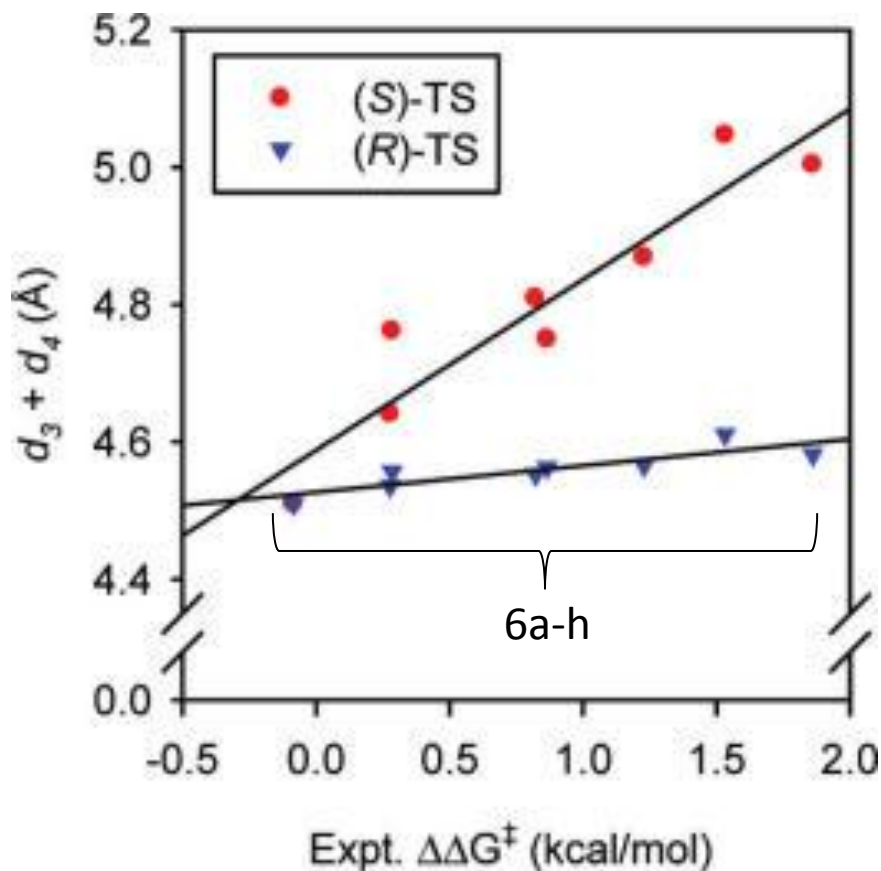
6a: X = S
6b: X = O

6c

6d

6e
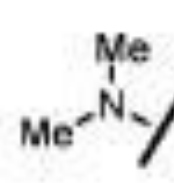
6f
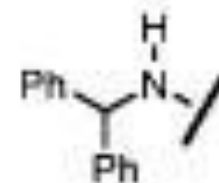
6g

6h

Activation of Hydrogen Cyanide --Strecker Reaction 2-9

(Mechanistic Study) *Focus on the Distance of Another Part of the Complex*

Figure 18. Correlation of transition structure bond length with enantioselectivity for HNC addition to imine **2a**. Plot of the sum of the cyanide *N*-iminium H + amide *O*-iminium H bond lengths in B3LYP/6-31G(d) transition structures versus experimental energy difference between (*R*)- and (*S*)-transition structures.

$$\Delta\Delta G^{\ddagger} = -RT\ln([R]/[S])$$
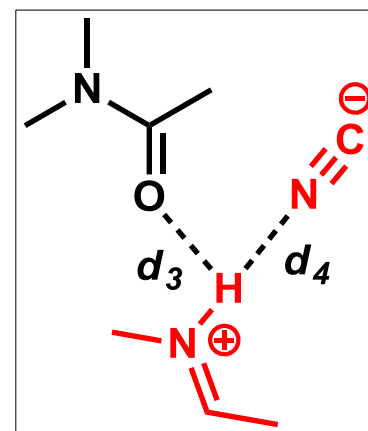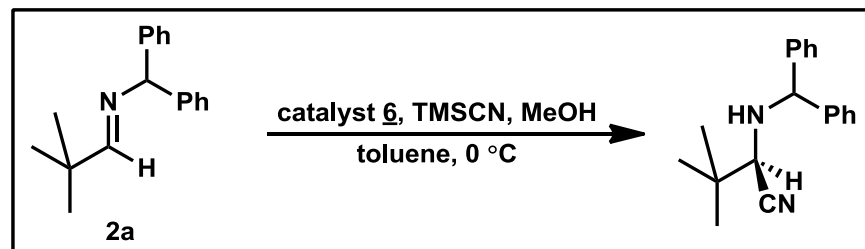
Figure 17. H-bond distances between catalyst and iminiumand between and cyanide anion and iminium.

The basis for enantioselectivity:
<u>Degrees of iminium ion stabilization</u>

S. J. Zuend and E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 15358.

Contents

Gelation using H-bond 1

Structures and Gel/sol images

Compound(s) in MCH at elevated temperature . →Cooling to rt→ Gel or sol ??
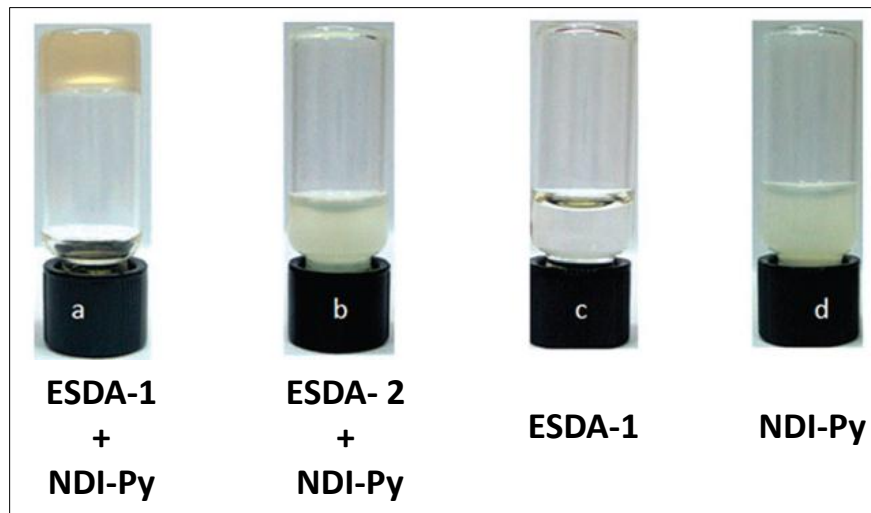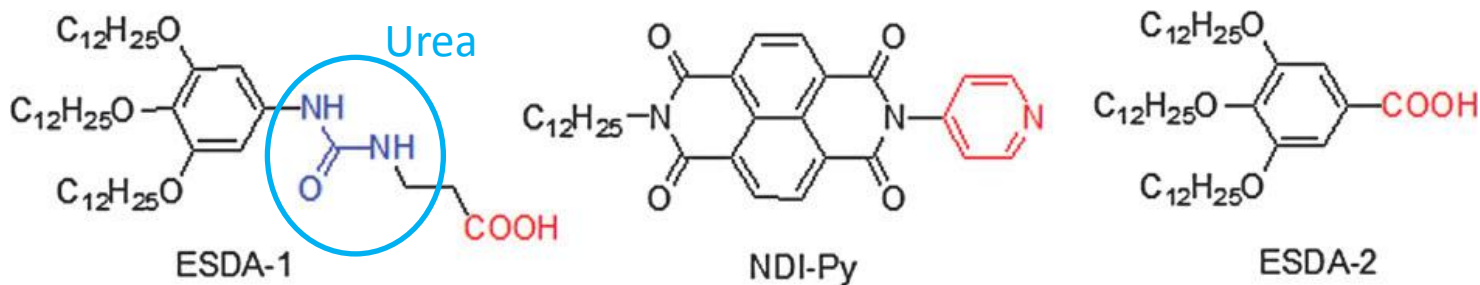
Fig. 1 Structure of the ESDA and the NDI derivatives.

Urea

ESDA-1   NDI-Py   ESDA-2

Fig. 2 Gel/sol images. Total concentration in each case = 0.3 wt%.

ESDA-1 + NDI-Py   ESDA- 2 + NDI-Py   ESDA-1   NDI-Py

ESDA : external structure directing agent
NDI: naphthalene-diimide
MCH: methylcyclohexane

Only ESDA-1 and NDI-Py mixture lead to gelation.

For gelation, both the urea core and the π-conjugated chromophore ware needed.

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Gelation using H-bond 2

Proposed model of gelation

ESDA : external structure directing agent
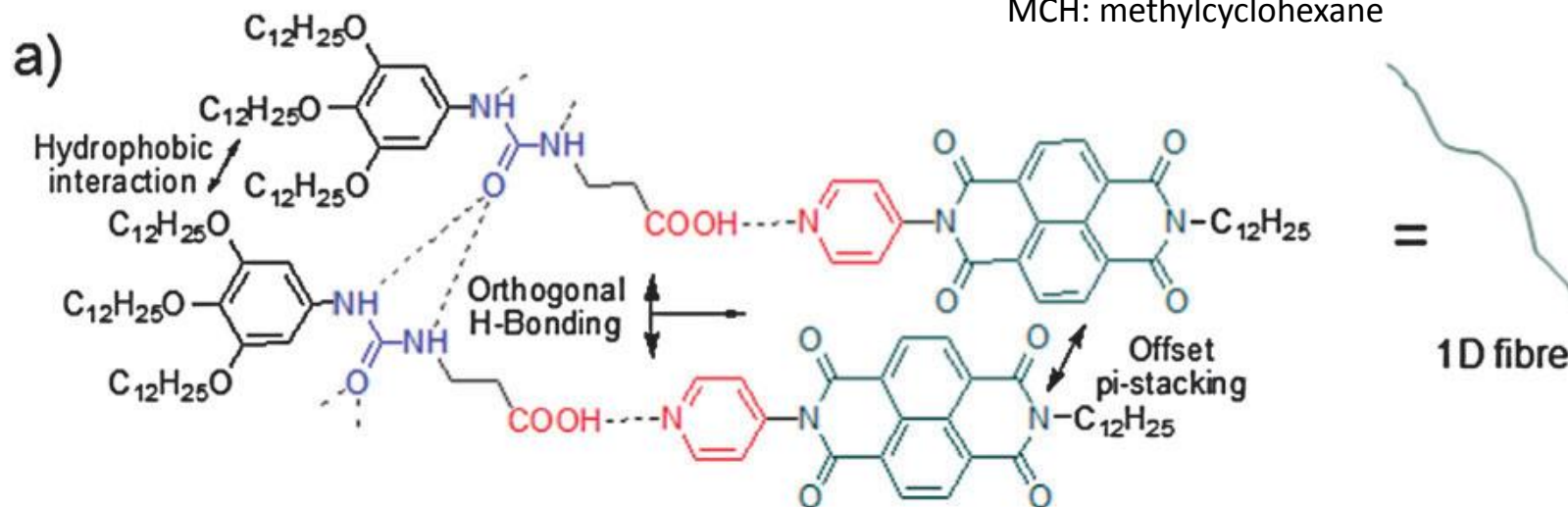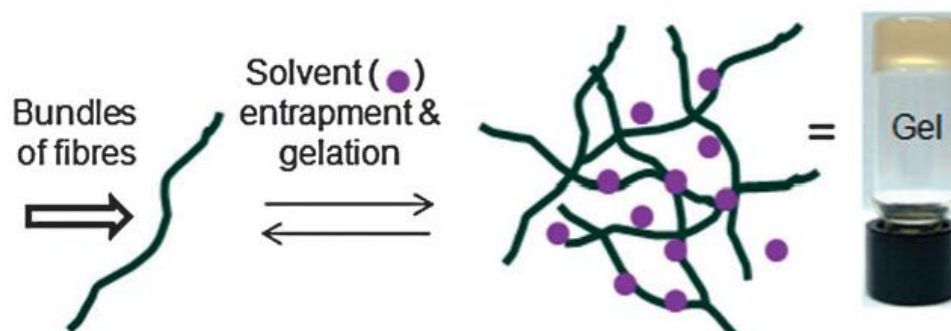NDI: naphthalene-diimide
MCH: methylcyclohexane

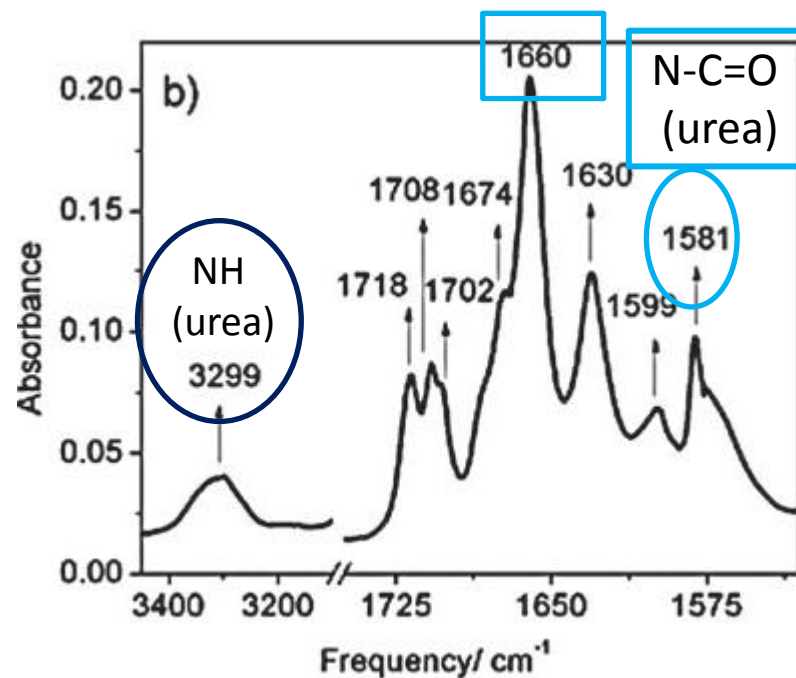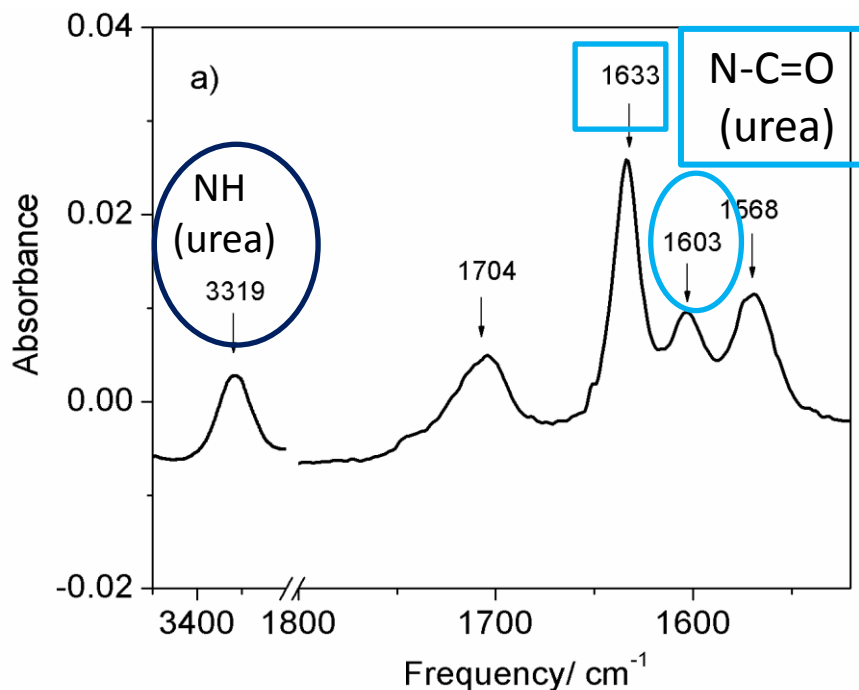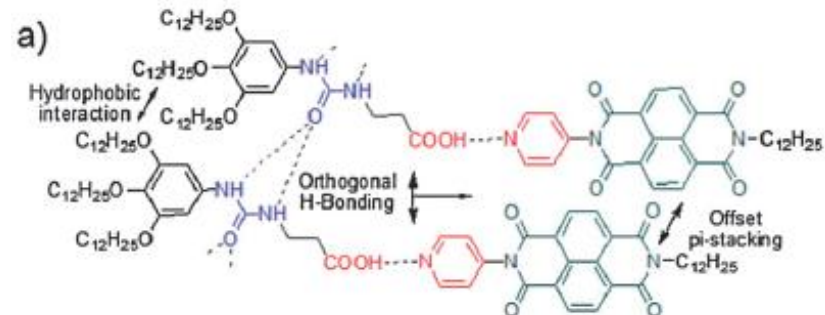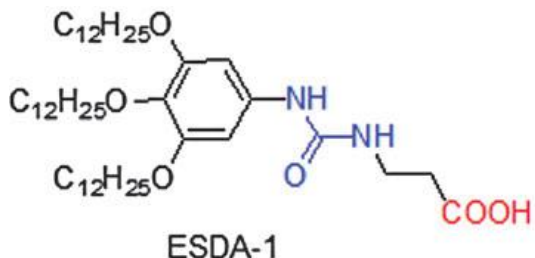**Fig.** (a) Proposed model of gelation by H-bonded assembly of ESDA-1 + NDI-Py.

General characteristics of fibrillar gel:
Superior abilities to transport of charge carriers.
Highly unpredictable photophysical properties.
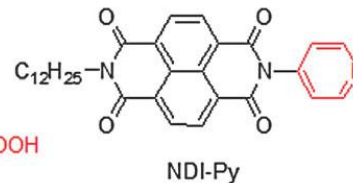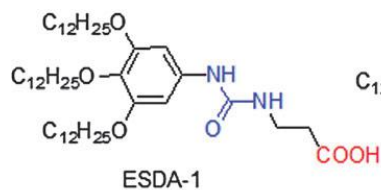
Gelation using H-bond 3

Experiment for Checking H-bond

Fig. Selected region of the FT-IR spectrum of **(a)** ESDA-1 (0.5 wt %), **(b)** ESDA-1 + NDI-Py gel in MCH (1 wt%).

Frequency shift of NH and N-C=O to low energy(right) showed H-bond.

S. Ghoust, *et al, Chem. Comm.* **2012**, asap, DOI: 10.1039/c2cc36536g.

Gelation using H-bond 4

Physical Properties –Molphologgy

ESDA-1   NDI-Py   ESDA-2

ESDA-1 + NDI-Py   ESDA-2 + NDI-Py
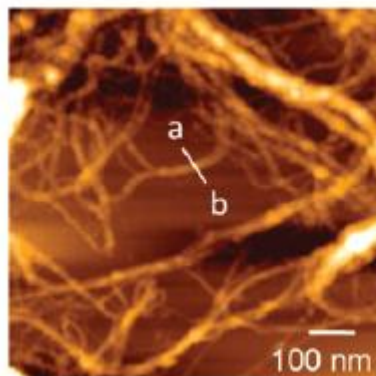
Micrometer long fibers   discontinuous spheres
→Gel   →no Gel
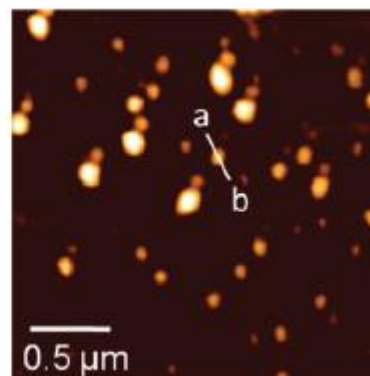
Fig. AFM images.

ESDA-1 + NDI-Py:
H-bonding among the urea groups
and π-stacking among NDI-Py
→ the 1D assembly is too rigid to fold
→ fibrillar morphology

ESDA-2 + NDI-Py:
π-stacking among NDI-Py alone
→ spherical assemblies

S. Ghoust, *et al, Chem. Comm.* **2012**, asap, DOI: 10.1039/c2cc36536g.
S. Ghoust , *et al, Chem. Eur. J.* **2012**, *18,* 9849.

Gelation using H-bond 5

Physical Properties --Photoluminescence

Shift to longer wave length.

Sol ⟶ Gel

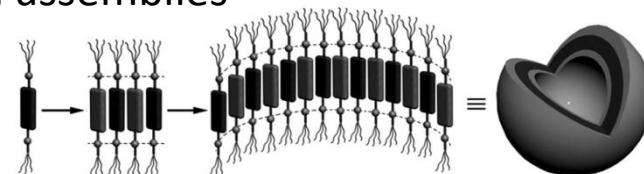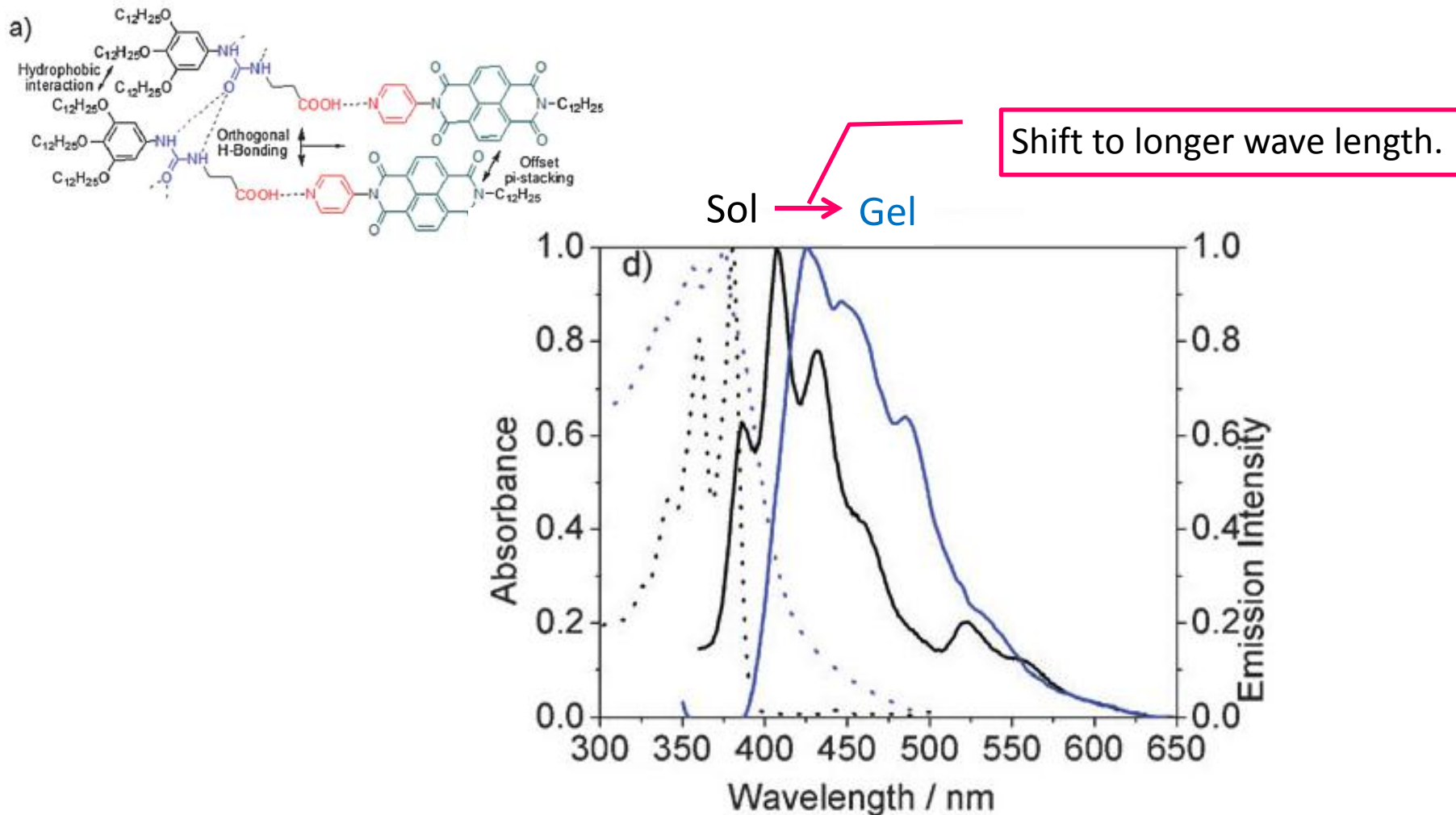**Fig.** Intensity normalized absorption (dashed line) and emission (solid line) spectra of gel (blue) and sol (black). Concentration of each component in gel (MCH) and sol (CHCl3) state=2.0 mM and 0.025 mM, respectively for UV/vis and PL experiments

S. Ghoust, *et al, Chem. Comm.* **2012**, asap, DOI: 10.1039/c2cc36536g.
C. R. S. Moller, *et al, Angew. Chem. Int. Ed.* **2011**, 50, 3376.

Gelation using H-bond 6

Physical Properties --Electrical Conductivity (σ)

ESDA-1 + NDI-Py

$\sigma = 0.19 \times 10^{-4}$ S cm^{-1}

ESDA-2 + NDI-Py

$\sigma = 0.2 \times 10^{-8}$ S cm^{-1}

σ(reported supramolecular polimers)$< 10^{-5}$ S cm^{-1}
σ(distilled water)$= 10^{-6}$ S cm^{-1}
σ(natural rubber)$= 10^{-5}$ S cm^{-1}
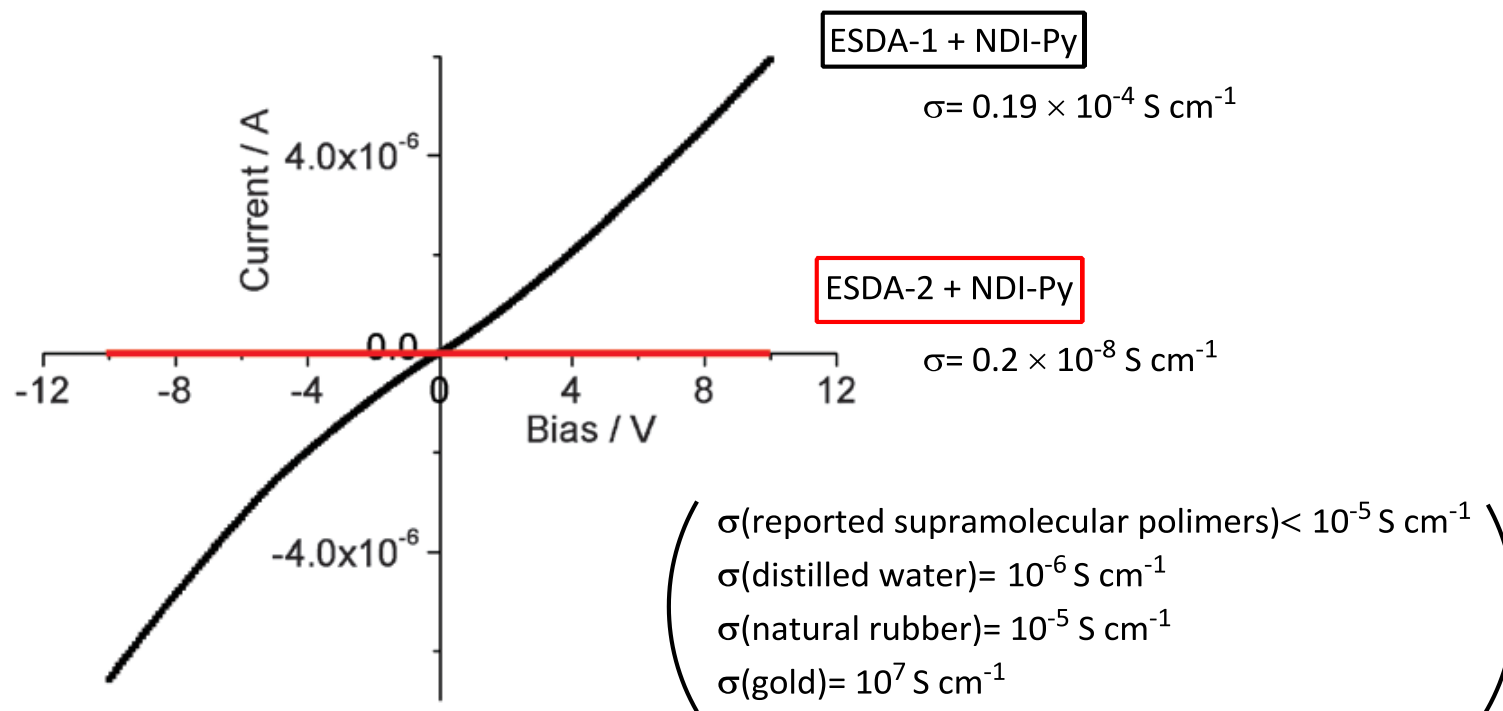σ(gold)$= 10^{7}$ S cm^{-1}

Fig. 4 *I-V* measurement data.

ESDA-1/NDI-Py gel had good electrical conductivity.

S. Ghoust, *et al, Chem. Commun.* **2012**, asap, DOI: 10.1039/c2cc36536g.
S. I. Stupp , *et al, Chem. Commun.*, **2011**, *47,* 5702.

Contents

Anticancer activity using H-bond 1

About *Hedgehog (Hh) Signaling Pathway* and <u>*Medulloblastomas*</u>
(骨髄腫)

Medulloblastomas
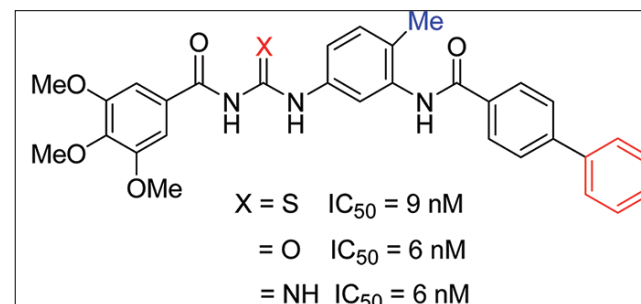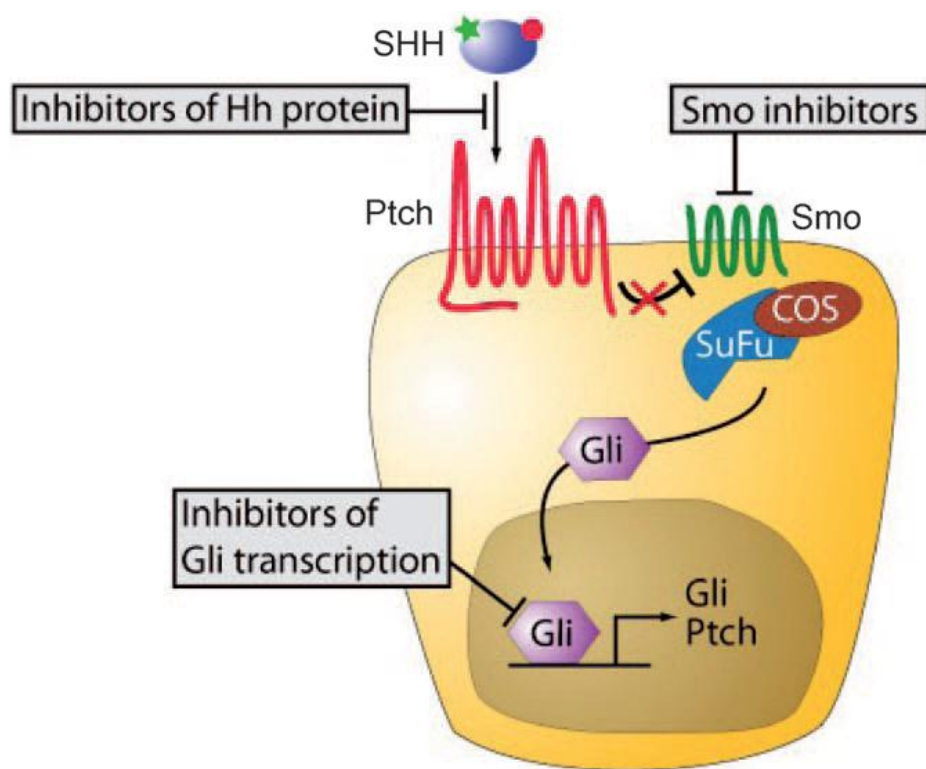
Fig. 1 Components of the Hh signal pathway and molecular sites targeted by Hh pathway inhibitors.

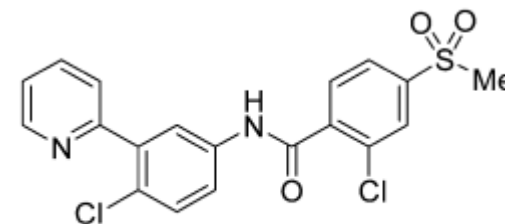K. M. Moslin, *et al, ChemMedChem* **2010**, *5*, 500.

Anticancer activity using H-bond 2

Smo inhibitors
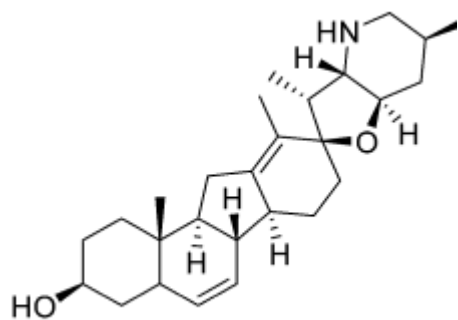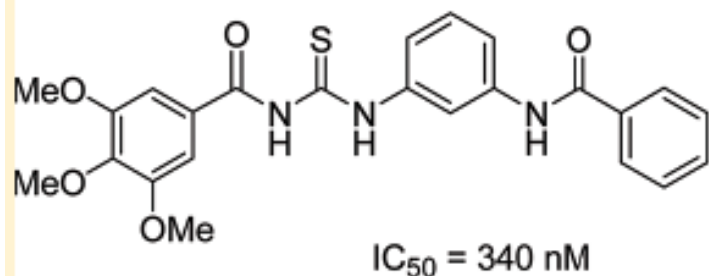

Cyclopamine (IC_{50}= 100 nM)

Isolated from *Veratrum grandiflorum* by T. Hasammune in 1964

GDC-0449

- In clinical trials (Phase II)
- Smo mutation and the resistance was observed in mice.

From virtual screening

IC_{50} = 340 nM

To optimized structures

X = S IC_{50} = 9 nM -(AcTU)
  = O IC_{50} = 6 nM -(AcU)
  = NH IC_{50} = 6 nM -(AcG)
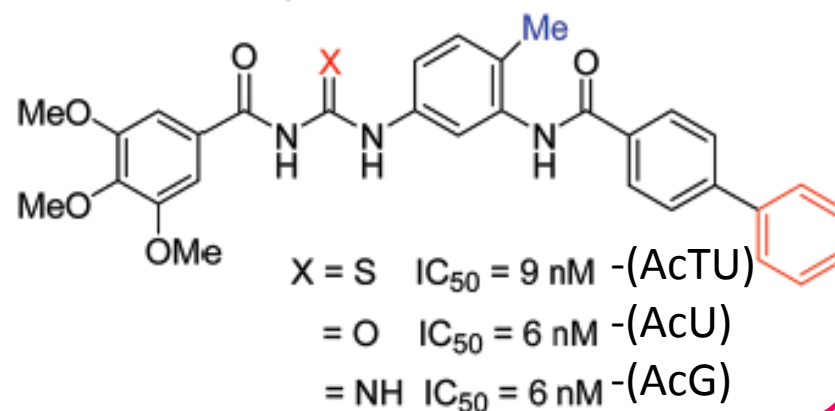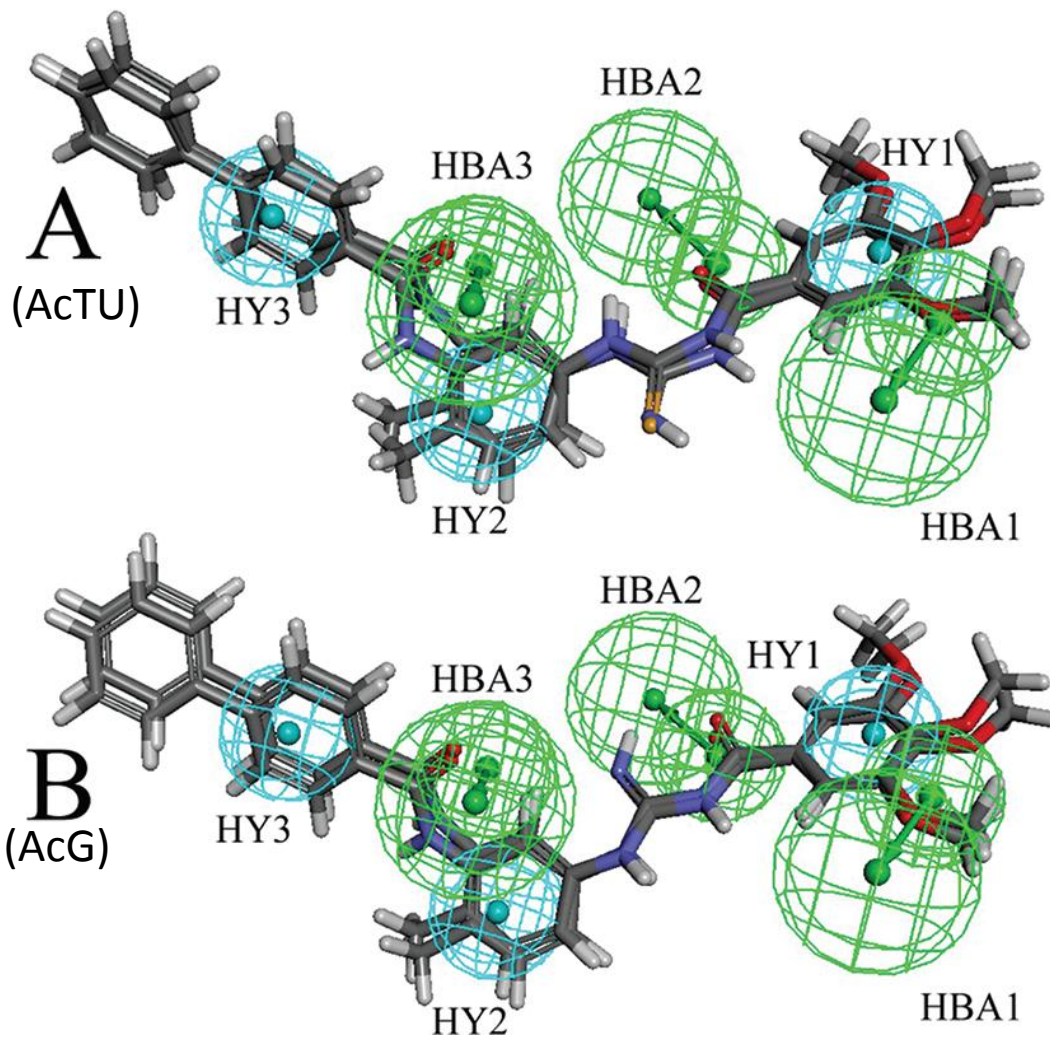
T. Hasammune, *et al, Tetrahedron Lett.* **1964**, *16,* 193.
M. Ruat , *et al, Molecular Pharmacology* **2010**, *78,* 658**.**
M. Ruat , *et al, J. Med. Chem.* **2012**, *55,* 1559.
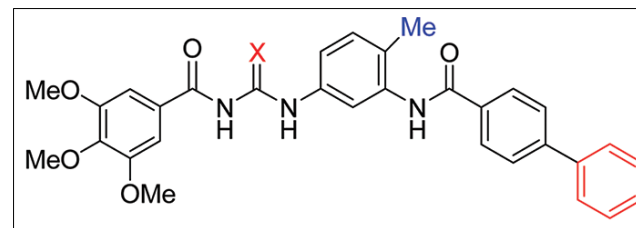
Anticancer activity using H-bond 3

Proposed Fitting Model

A (AcTU)

B (AcG)

AcTU and AcG had the same phrmacophore as the compound reported to be active as Smo inhibitor.

Fig. Compounds in two different conformations layout (**A,B**) with the pharmacophoric model for Smo antagonists. HBA features are constituted by a smaller sphere accommodating the hydrogen bond acceptor group, by a directionality vector represented by an arrow, and by a larger sphere intended to allocate the hydrogen bond donor group of the target macromolecule.

HBA: hydrogen bond acceptor groups
HY: hydrophobic regions

K. M. Moslin, *et al, ChemMedChem* **2010**, *5,* 500.

Anticancer activity using H-bond 4

Involvement of H-bond
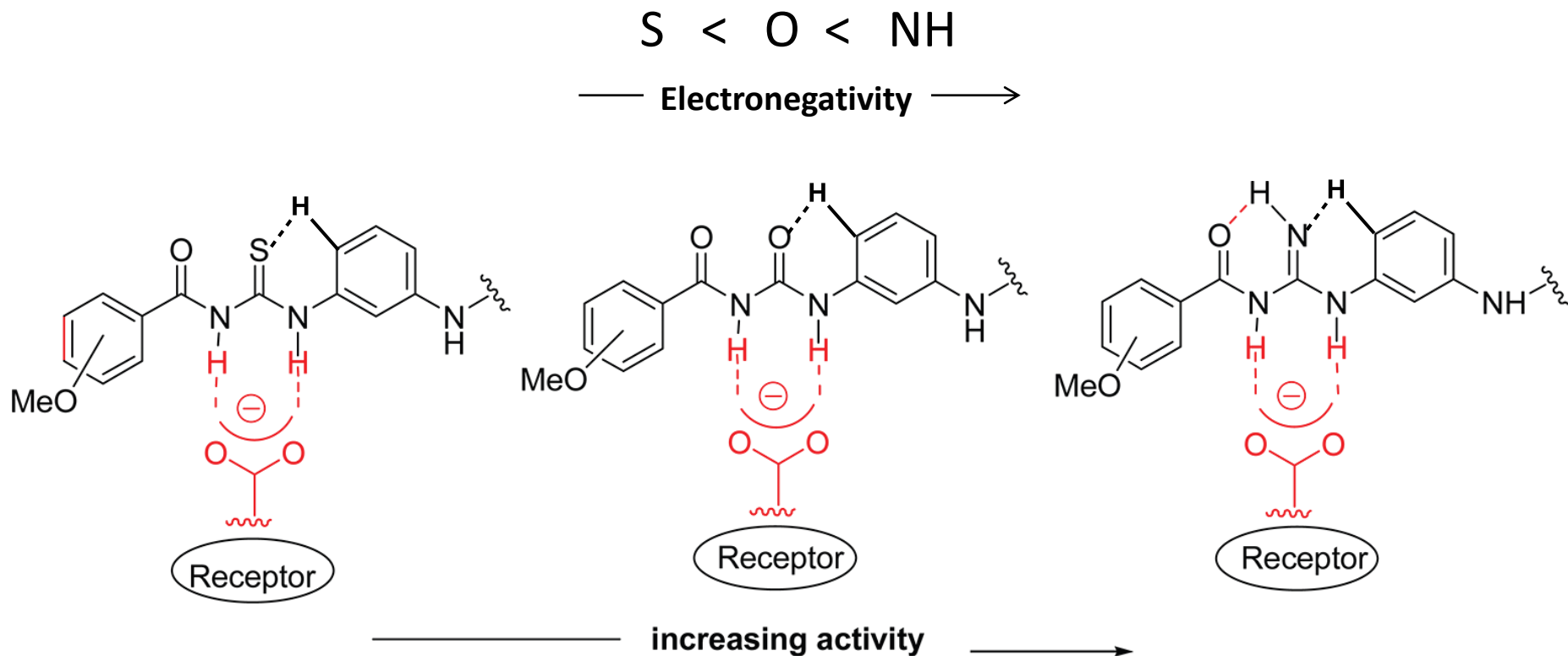
Scheme Proposed H-Bonding Network for the Three Bio-isosteric Structures AcTU, AcU, and AcG towards a Putative Carboxylate Located on Smo (in Agreement with the Conformations of AcTU and AcG Shown in the previous slide).

Summary

1. **Introduction**
   Hydrogen bond
   Organocatalyst
   Urea/Thiourea

<u>Urea has an ability to play important roles in various areas.</u>

2. **Organocatalysis**
   Pioneering Studies
   Recognizing Carbonyl
   Nitro Group
   Sulfonate
   Hydrogen Cyanide

3. **Material**
4. **Bioactive compound**
5. **Summary**

Activation of substrates via oxygen atoms.

Activation of substrates via the ion different from the substrate.

Activation of reagents via nitrogen atoms.

Urea for gel.

Urea for anti-cancer activity.

References
「進化を続ける有機分子触媒」 化学同人　丸岡啓二 [編]
「有機分子触媒の新展開」 シーエムシー出版　監修　柴崎正勝
E. N. Jacobsen, *et al, Chem. Rev.* **2007**, *107,* 5713.
S. J. Connon, *SYNLETT* **2009**, *3*, 354.

Thank you.