Cooperative Catalysis by Tertiary Amino-Thioureas: Mechanism and Basis for Enantioselectivity of Ketone Cyanosilylation

Stephan J. Zuend and Eric N. Jacobsen

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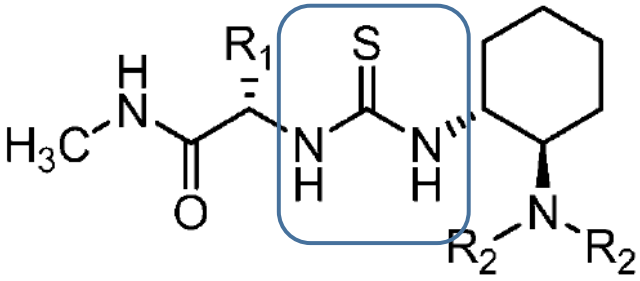
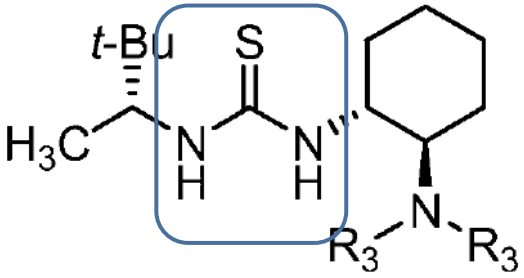
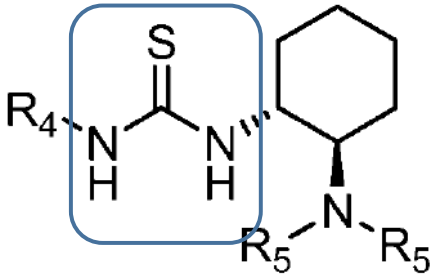
Chiral Thio-Urea catalyst

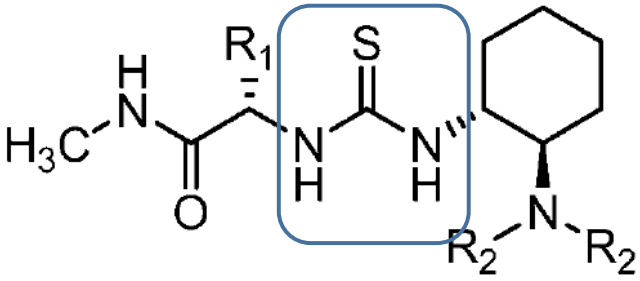


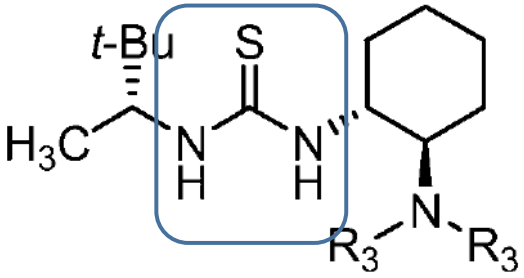


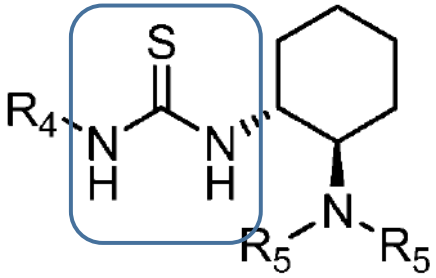


- H-Bond donor
- Cooperative Mechanism

Chiral Thio-Urea catalyst

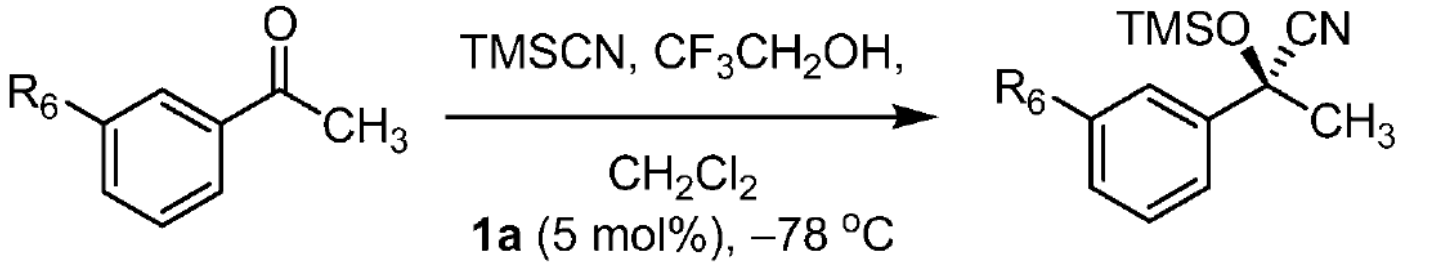






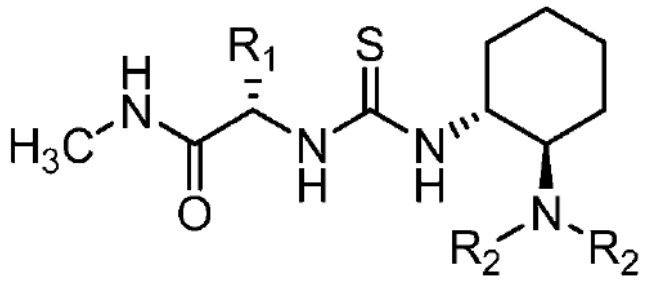
- Activation of electrophile by H-bonding
- Nucleophile binding and activation

Thiourea-Catalyzed Enantioselective Cyanosilylation



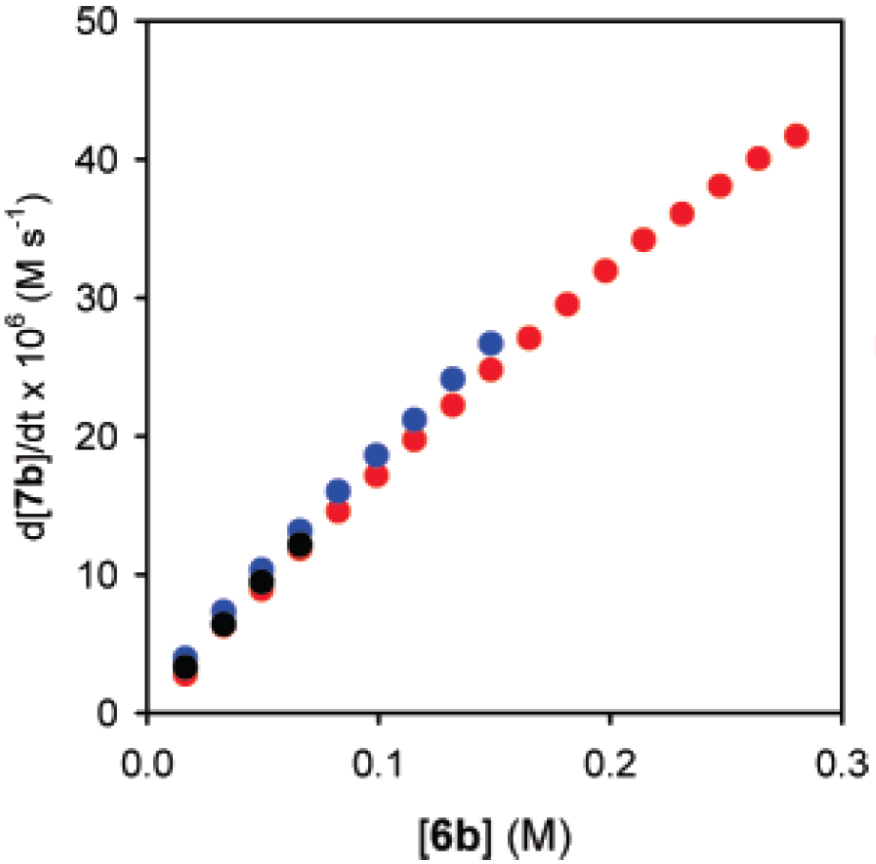
6a: R_6 = H
6b: R_6 = OCH_3

7a: R_6 = H, 97% ee
7b: R_6 = OCH_3, 97% ee



1a: R_1 = *t*-Bu, R_2 = *n*-Pr

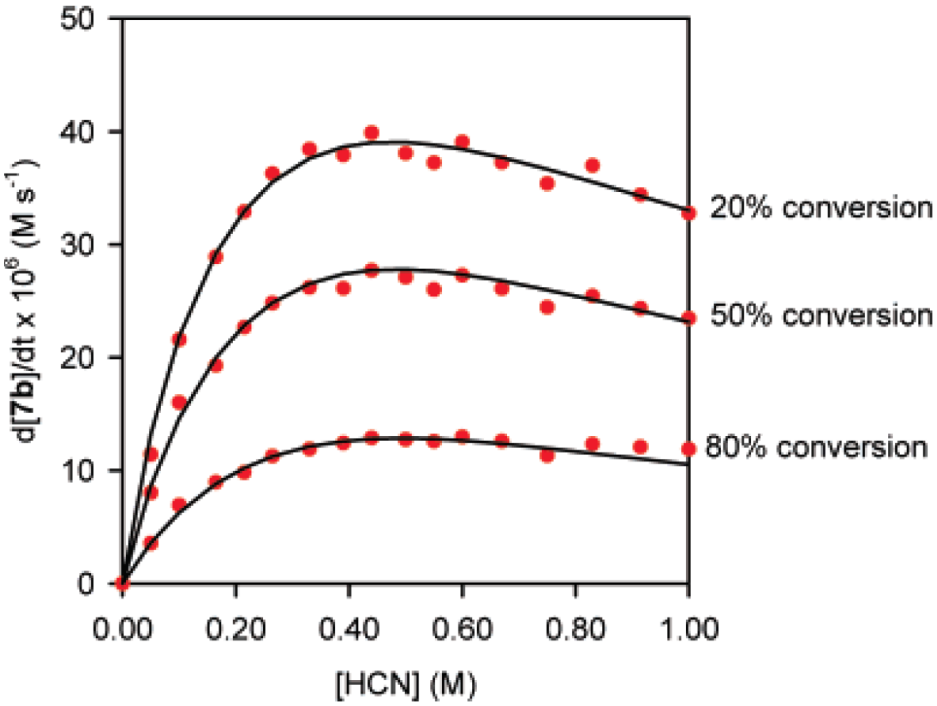
Kinetic Analysis



no appreciable catalyst decomposition or product inhibition occurs over the entire course of the reaction

Figure 1. Rate dependence on [**6b**]. Plot of the rate of cyanosilylation of **6b** with TMSCN ([TMSCN]*i) 0.50 M) catalyzed by HCN (0.33 M) and* **1a** (0.025 M) at different [**6b**]*i. Each set of points represents the results* from a single in situ IR experiment: (red) [**6b**]*i) 0.33 M; (blue) [**6b**]i)* 0.165 M; (black) [**6b**]*i) 0.083 M.*

Kinetic Analysis

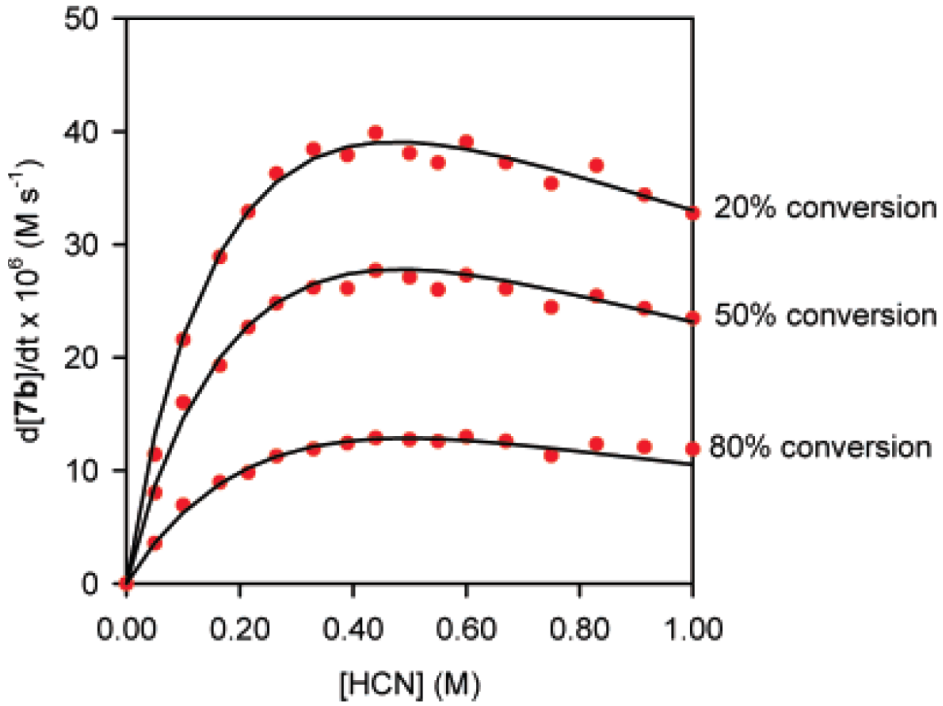


- no reaction occurs without HCN,
- 15 mol % is sufficient to effect >90% substrate conversion.

➢ HCN is a cocatalyst for the ketone cyanation.

Figure 2. 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**.

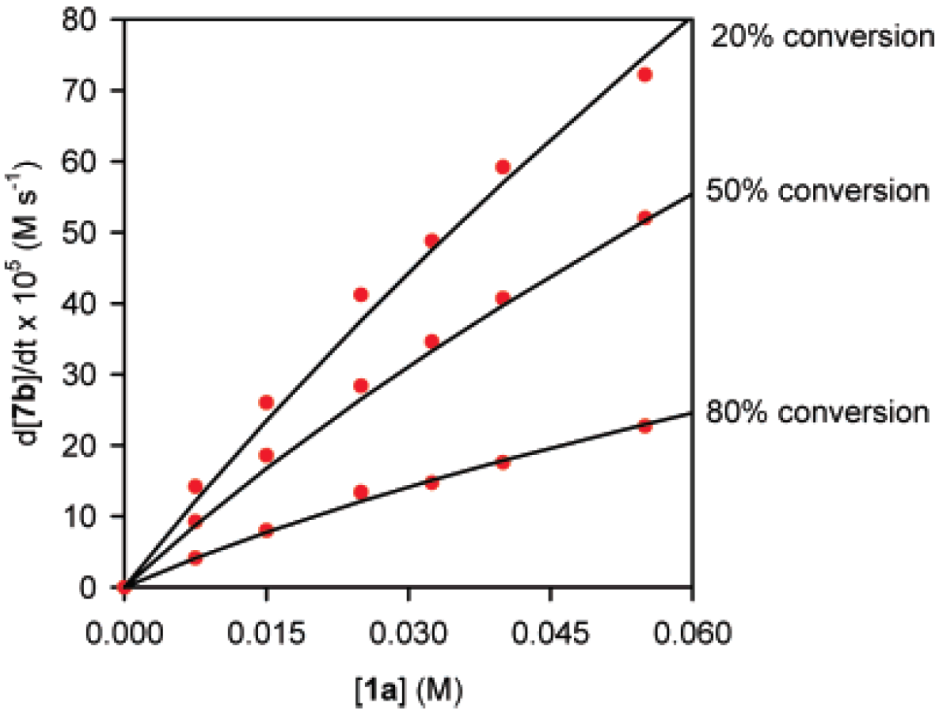
Kinetic Analysis



- Rate inhibition is observed at high [HCN]

Figure 2. 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**.

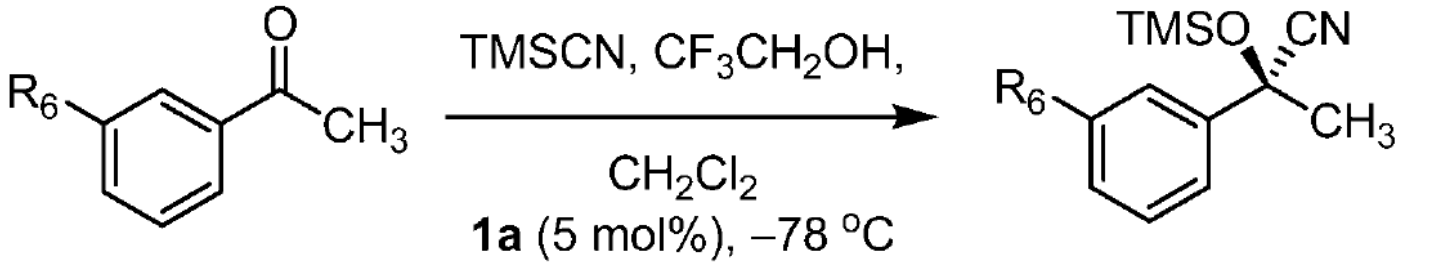
Kinetic Analysis



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

Figure 3. 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.**

Kinetic Analysis



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

7a: R_6 = H, 97% ee
7b: R_6 = OCH_3, 97% ee

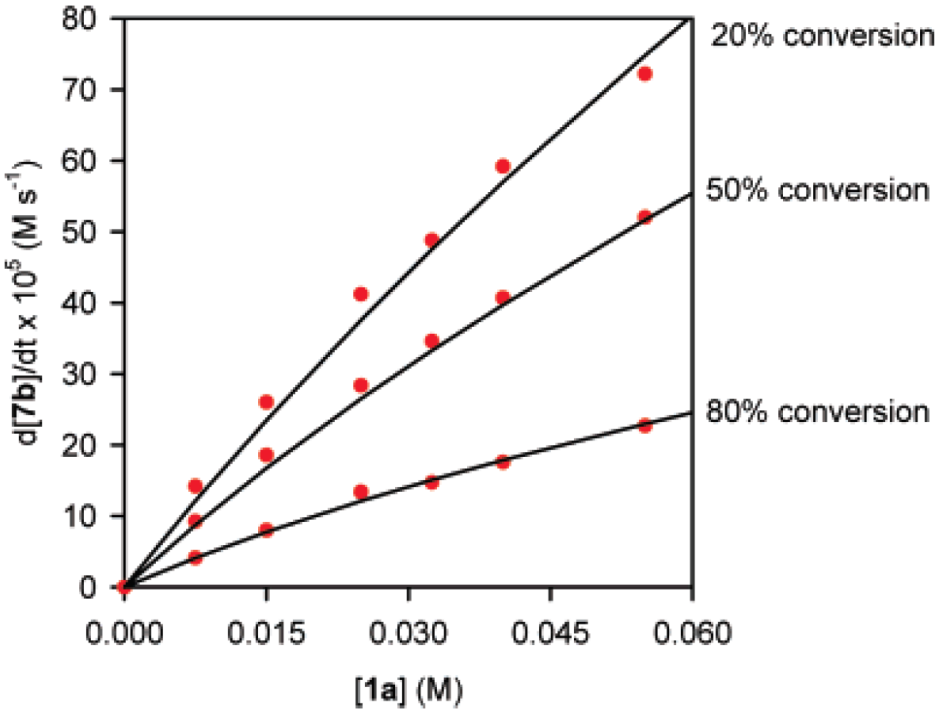
$$\text{rate} = \mathrm{d}[\mathbf{7b}]/\mathrm{d}t = k[\mathbf{1a}]^1[\mathbf{6b}]^1[\mathrm{HCN}]^1[\mathrm{TMSCN}]^0$$

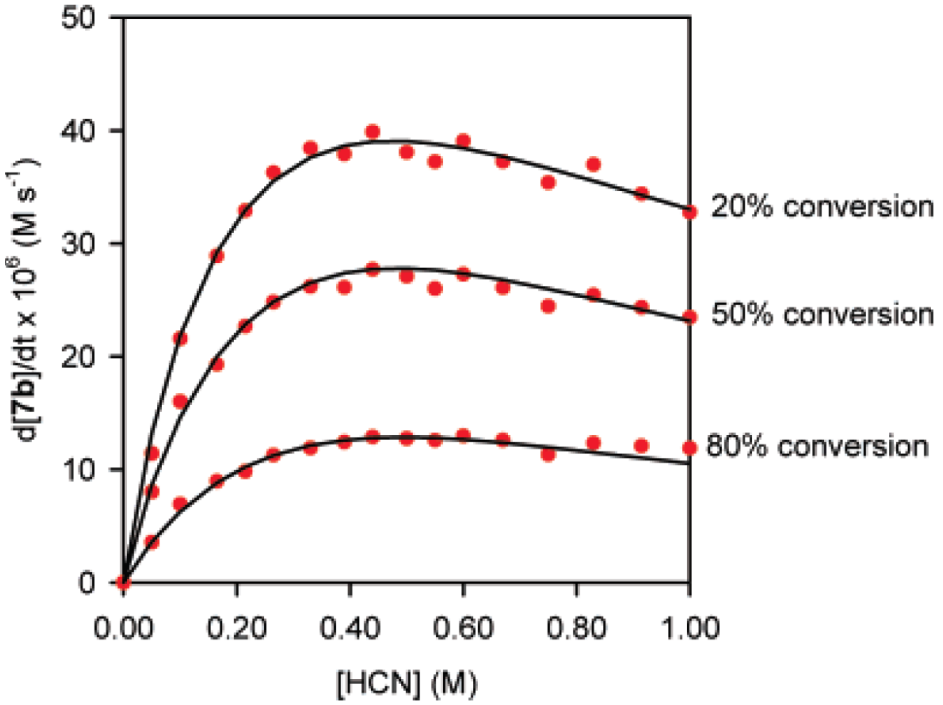
At low concentrations (approximately 0.10 M [HCN], 0.20 M [**6b**], and 0.015 M [**1a**]),

- rate-limiting addition of HCN to **6b** catalyzed by **1a**

- post rate-limiting silylation of an alkoxide or alcohol intermediate to form **7b** and regenerate HCN.

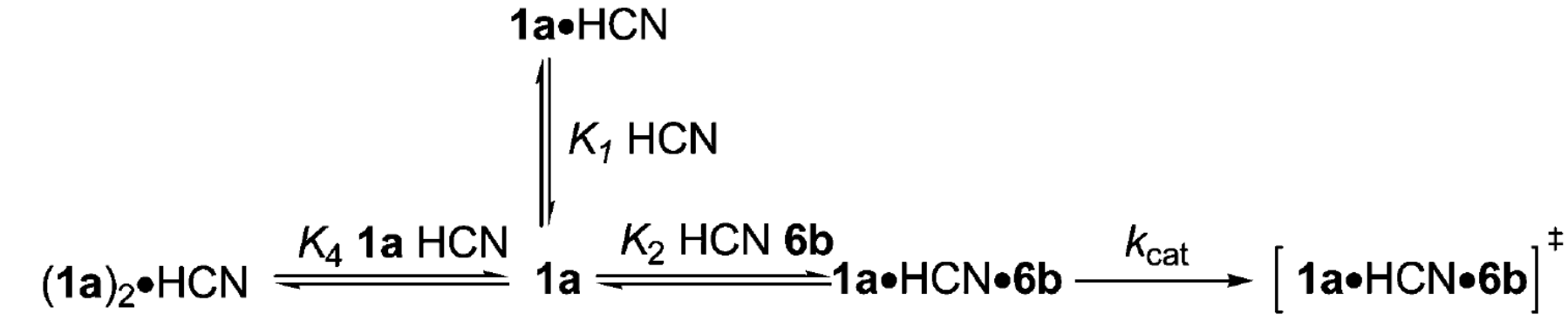
Deviation From First Order Kinetics





deviations from simple first-order kinetic behavior at higher concentrations of catalyst **1a** and **HCN**

Kinetic Parameters for Ketone Cyanation



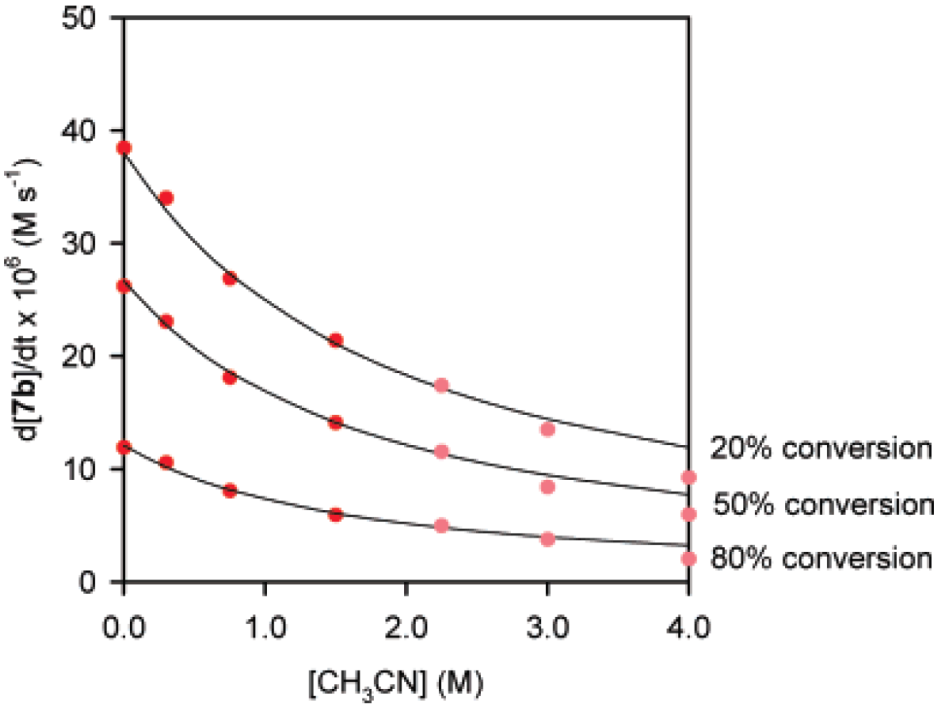
K_1 = 0 (fixed)
K_2 = 11.6 ± 0.5 M^{-2}
K_3 = 5.9 ± 0.1 M^{-2}
K_4 = 58 ± 5 M^{-2}
$K_2 k_{cat}$ = 0.051 ± 0.001 $s^{-1}M^{-2}$

$$\text{rate} = \frac{2K_2k_{cat}[\text{HCN}][\mathbf{6b}][\mathbf{1a}]_{tot}}{1 + K_1[\text{HCN}] + K_2[\text{HCN}][\mathbf{6b}] + K_3[\text{HCN}]^2 + \sqrt{(1 + K_1[\text{HCN}] + K_2[\text{HCN}][\mathbf{6b}] + K_3[\text{HCN}]^2)^2 + 8K_3[\text{HCN}][\mathbf{1a}]_{tot}}} \quad (2)$$

- Uncomplexed catalyst is dominant at low concentrations of all species
- eq 2 simplifies to eq 1

Effect of Added CH_3CN and Pyridine Derivatives

inhibitory effect at high concentrations of HCN : Lewis basic properties



Rate inhibition was observed

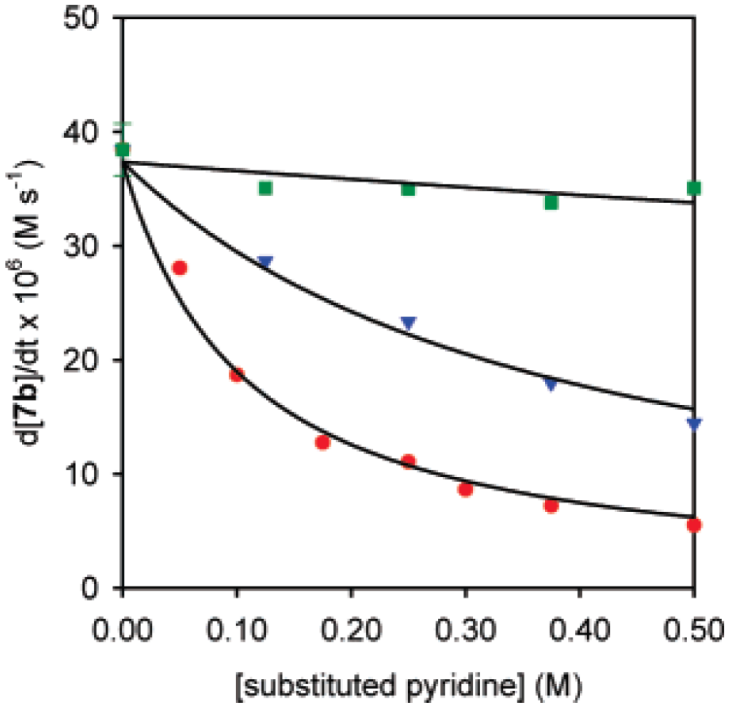
No change in enantioselectivity (97% ee)

Possibilities:

- Specific interaction – sensetive to electronic And steric effect
- Medium effect- inssensetive to steric properties

Figure 4. Rate dependence on [CH3CN]. 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** (0.025 M) in the presence of CH3CN. The curves represent least-squares fits to eq 3 with In $=CH_3CN$

Effect of Added CH_3CN and Pyridine Derivatives



Inhibition rate:
Pyridine > 2,6-lutidine > 2,6-di*tert*-butylpyridine

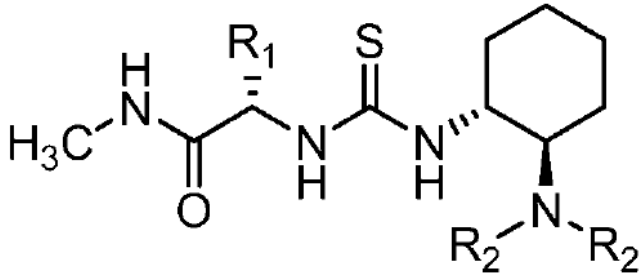
No change in enantioselectivity

Support the direct interaction between Lewis base and catalyst

Figure 5. Rate dependence on [substituted pyridine]. 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** (0.025 M) in the presence of substituted pyridines: pyridine (red), 2,6-lutidine (blue), and 2,6-di*tert*-butylpyridine (green).

Effect of Added CH_3CN and Pyridine Derivatives

Spectral evidence:



less sterically demanding pyridines caused significantly greater changes in chemical shift of both the amide and thiourea protons.

most downfield thiourea proton shows the smallest chemical shift change : internal hydrogen bond to the tertiary amine- maintained upon pyridine binding.

Effect of Added CH_3CN and Pyridine Derivatives : Conclusion

Lewis base binds to thiourea and inhibit ketone cyanation

Constant *ee* – mechanism of productive path-way remains unchanged.

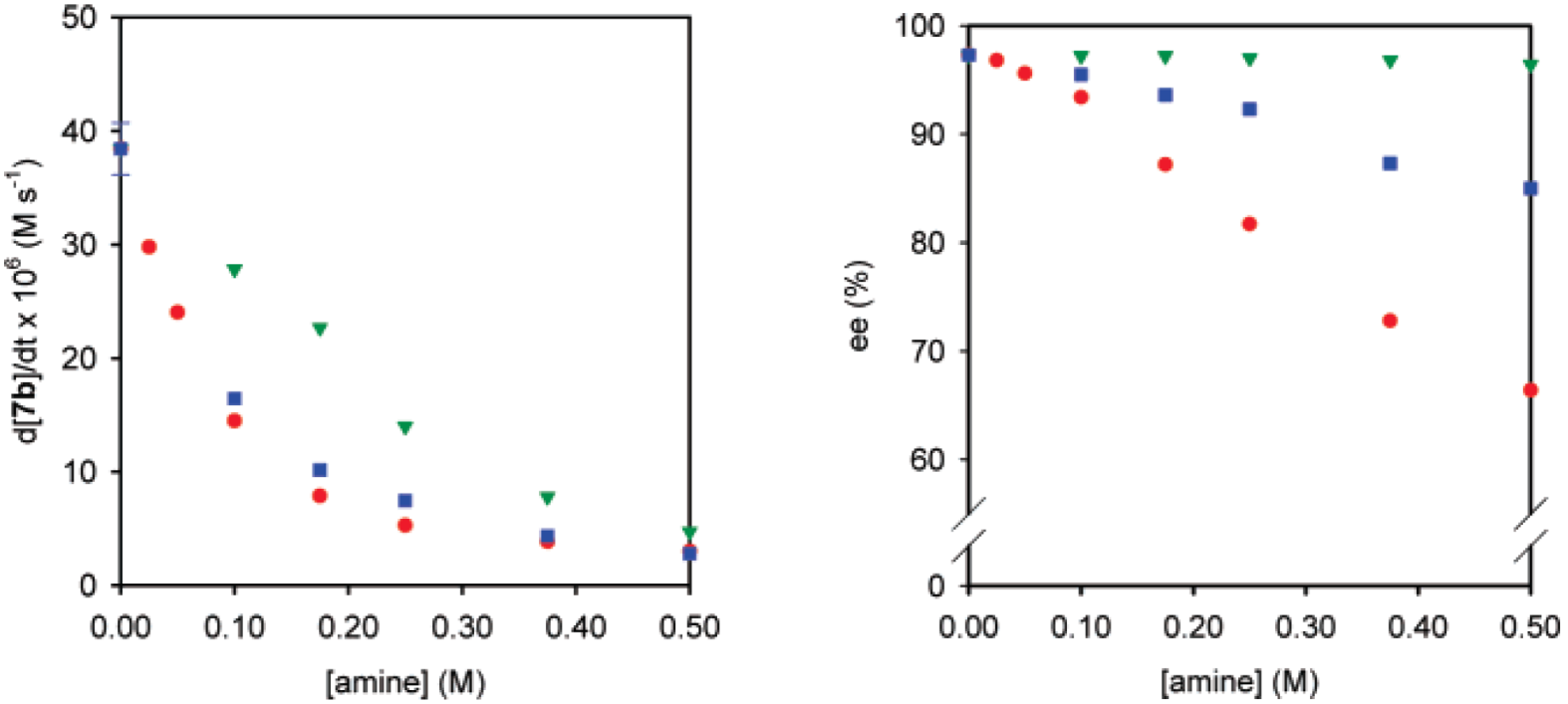
No reaction occurs when inibitor is bound to the catalyst.

Thiourea functionality is involved directly in catalysis of cyanosilylation

data do not reveal how the thiourea is involved in the catalytic mechanism.

Effect of Added Trialkylamines

Determination of productiveor unproductive interactions of HCN with trialkylamine portion catalyst



Effect of trialkylamine on ee and rate. Plot of the rate and enatiomerin excess(%) of cyanosilylation of **6b** **([6b]*i = 0.33 M)*** *with TMSCN* ***([TMSCN]i=0.50*** M) catalyzed by HCN (0.33 M) and **1a** (0.025 M) in the presence of trialkylamines: *i-Pr_2NEt (red), Et_3N (blue), and Me_2NEt (green).*Rate data were obtained at 20% conversion of **6b.**

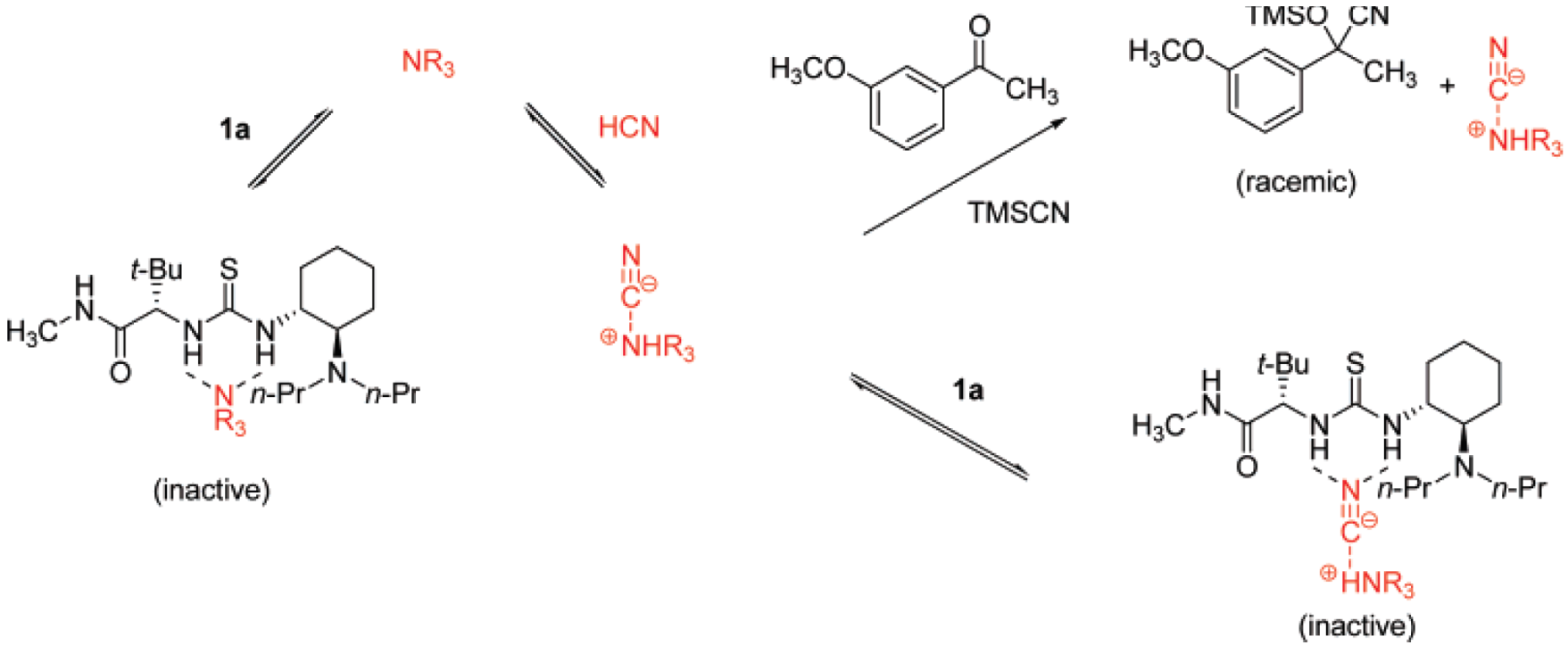
degree of rate inhibition and the decreases in enantioselectivity correlate with the size of the trialkylamine.

Possible Modes of Rate Inhibition and Enantioselectivity Suppression Induced by Trialkylamines

Spectroscopy Data shows same trend as with substituted pyridine.

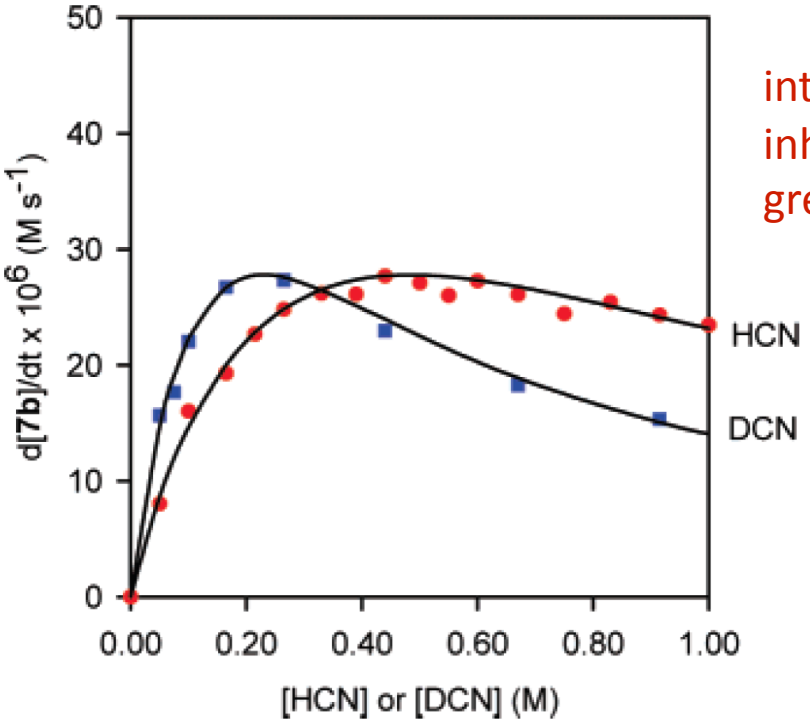
inhibition trends-kinetically and the binding trends- spectroscopically : opposite dependence on the steric properties of trialkylamines,

Brønsted basicity of trialkylamines also correlates with their size



Reaction rate for di-*n-propylamino* catalyst **1a** 20 times faster than dimethylamino **1b**, with slightly higher enantiomeric excess (97% ee versus 95% ee).

Isotope Effects: Comparison of HCN and DCN



intrinsic rate (at low concentrations) and the inhibitory effect (at high concentrations) : greater with DCN than with HCN

(k_H/k_D) of 0.64 ± 0.05.

Posssibility: greater acidity of DCN – deprotonation important for productive or Inhibitory path

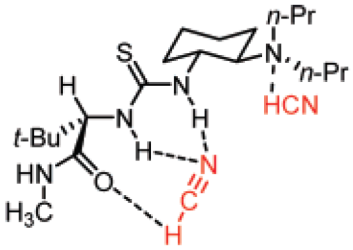
Observation:stronger hydrogen bond in the gas phase between DCN

Rate dependence on [HCN] and [DCN]. 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] or [DCN] at 50% conversion of **6b**.

Mechanistic Possibilities

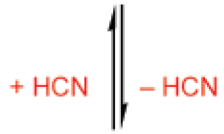
(1) more basic amines :better catalysts and stronger inhibitors (*i*-Pr_2NEt *versus* Me_2NEt)

(2) DCN : more reactive at low concentrations , better inhibitor at high concentrations than HCN

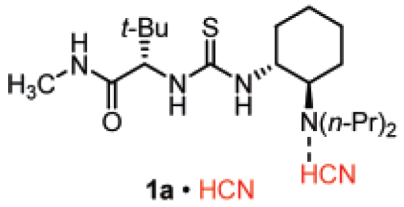


1a • $(HCN)_2$
(inactive)

catalyst inhibition by HCN: formation of a 1:2 complex between **1a and HCN** at high concentrations of HCN



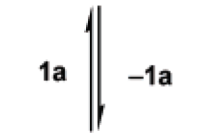
Deprotonation of HCN with trialkylamine: catalysis and inhibition



1a • HCN

catalyst inhibition by trialkylamine: formation of cyanide ion-binds to thiurea.

< first order kinetics at higer [**1a**]: formation of catalyst aggregates.



$(\mathbf{1a})_2$ • HCN
(inactive)

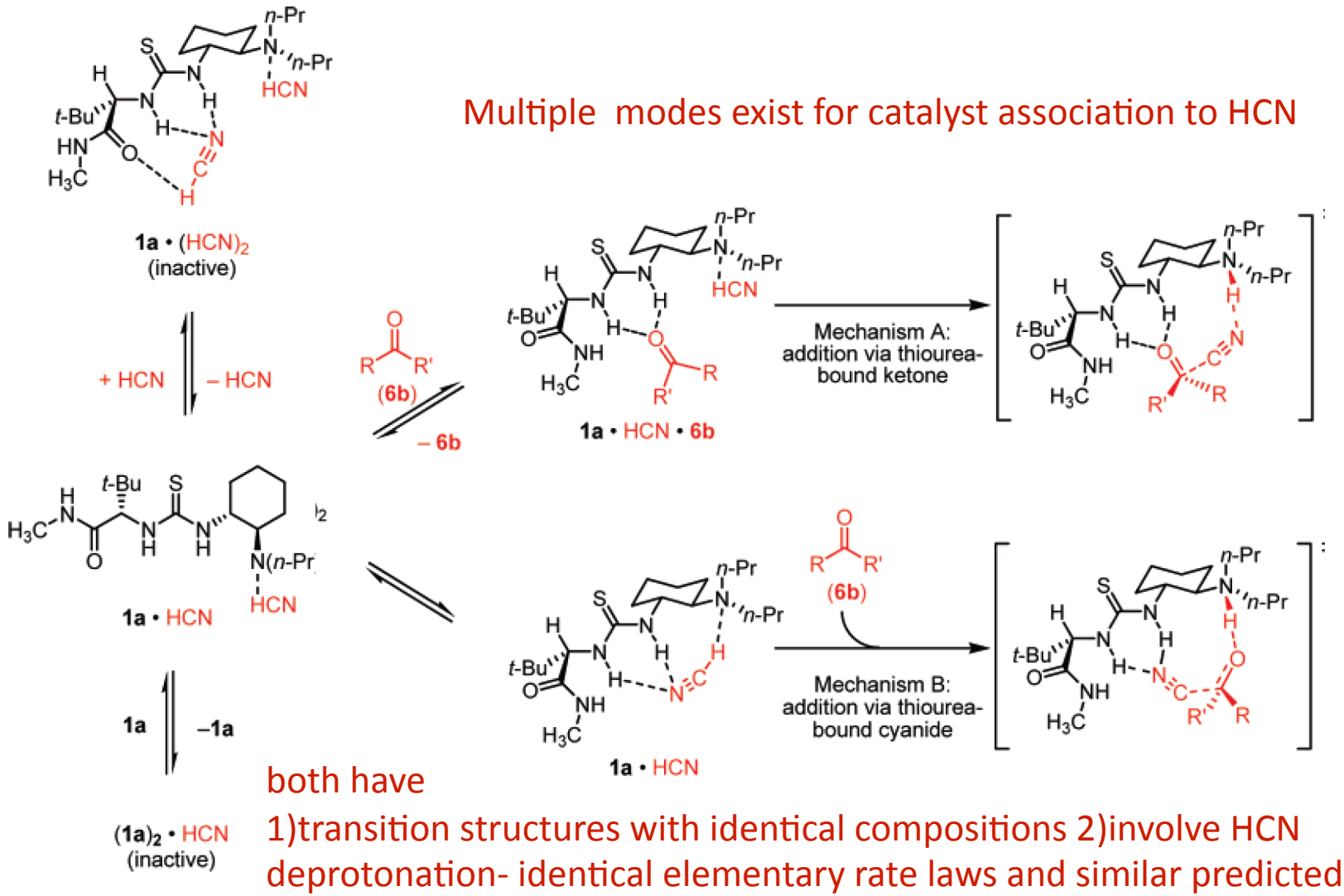
Key finding: tertiary amine activation of HCN is important for catalysis

unproductive binding to the thiourea of **1a** inhibits catalysis-both the thiourea and the trialkylaminefunctions of **1a** are involved directly in the catalytic pathway

Mechanistic Possibilities

(1) more basic amines :better catalysts and stronger inhibitors (*i*-Pr_2NEt *versus* Me_2NEt)

(2) DCN : more reactive at low concentrations , better inhibitor at high concentrations than HCN



Multiple modes exist for catalyst association to HCN

both have

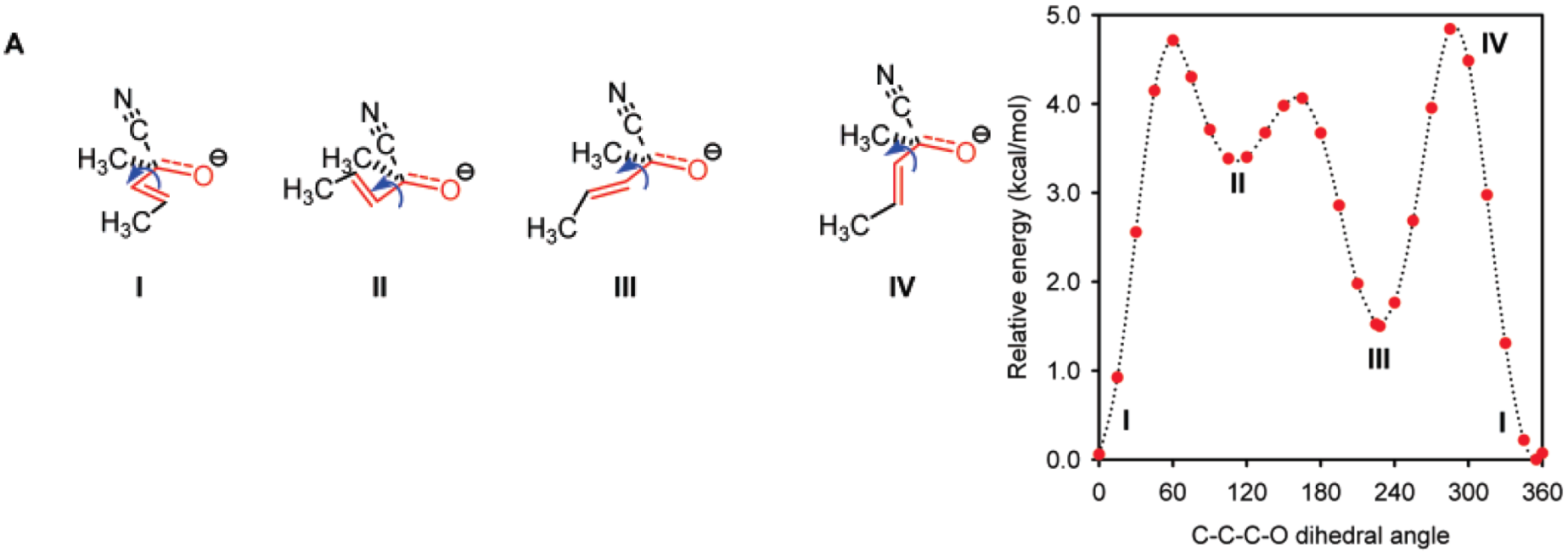
1)transition structures with identical compositions 2)involve HCN deprotonation- identical elementary rate laws and similar predicted isotope effects.

Theoretical Analysis of the Selectivity-Determining Step.

enantioselectivity is independent on reaction conditions:

•same stoichiometry of transition structures leading to the major and minor enantiomer

•selectivity-determining step is the same under all conditions



Variation of C-C-C-O dihedral angles between C=O and C=C (shown in red) in the transition structures for cyanide ion addition to 3-penten-2-one in the absence of catalyst

Theoretical Analysis of the Selectivity-Determining Step.

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•same stoichiometry of transition structures leading to the major and minor enantiomer

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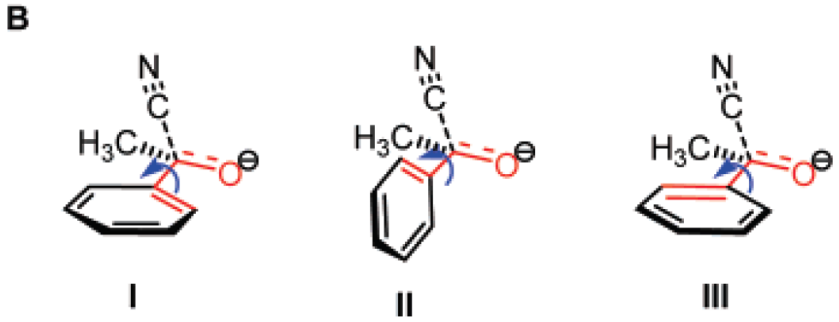
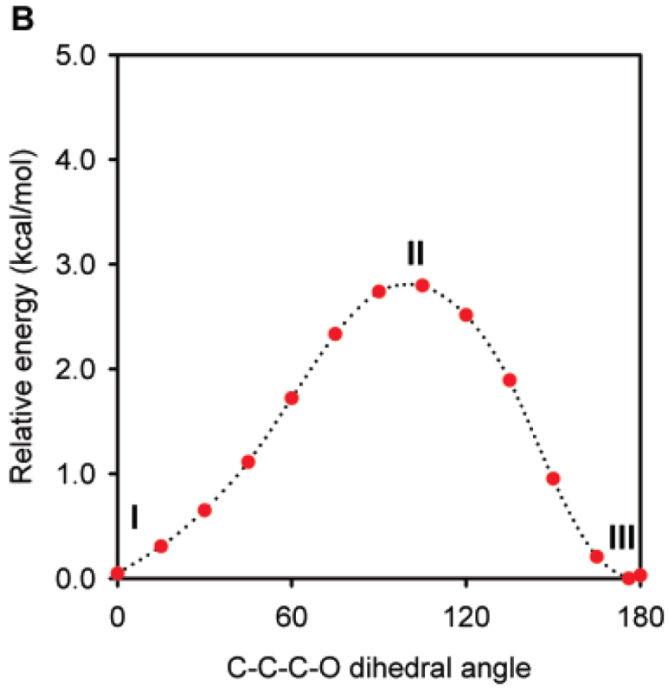




Variation of C-C-C-O dihedral angles between C=O and C=C (shown in red) in the transition structures for cyanide ion addition to acetophenone in the absence of catalyst

Theoretical Analysis of possible Mechanism

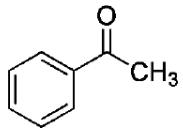
•both mechanisms A and B are energetically accessible mechanism

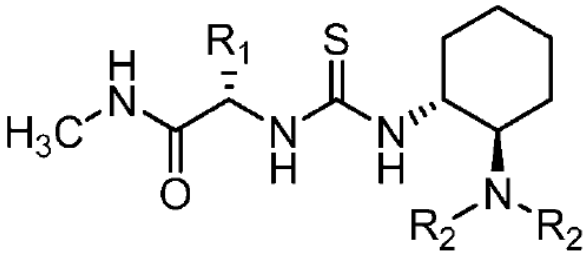
•A is significantly (major enantiomer 4.7 kcal/mol) more favorable.

• calculations of diastereomeric transition states : in mechanism A energy difference between **e**nantiomers *0.9* kcal/mol)

• mechanism B identify no basis for enantioselectivity (energy difference *0.0 kcal/mol)*

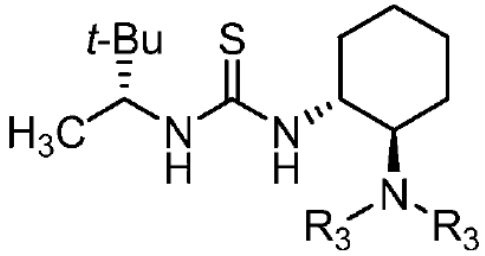
Experimental and Calculated Relative Activation Energies for the Cyanosilylation of Ketone

entry	ketone	catalyst[b]	exp. ee(%)	exp. $\Delta\Delta G^{\ddagger}$ (kcal/mol)	calc. $\Delta\Delta E^{\ddagger}$ (kcal/mol)
1		**1a**	97	1.6	2.7 (2.7)
2		**2a**	90	1.1	1.8 (1.6)
3		**3a**	90	1.1	2.0 (1.6)
4		**4a**	79	0.8	0.9 (1.3)

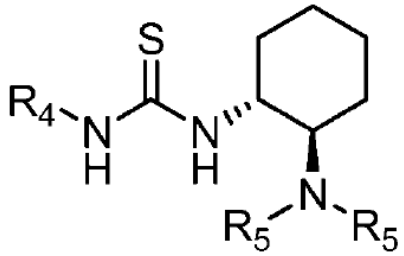


1a: R_1 = *t*-Bu, R_2 = *n*-Pr

2a: R_1 = CH_3, R_2 = *n*-Pr



3a: R_3 = *n*-Pr

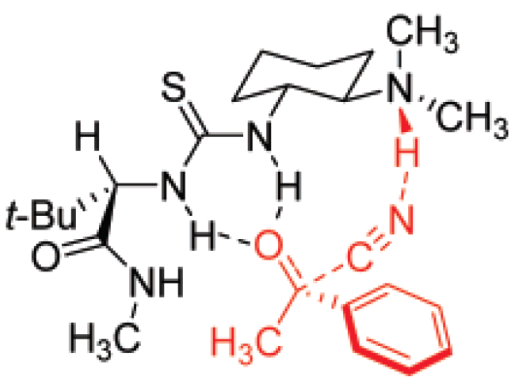


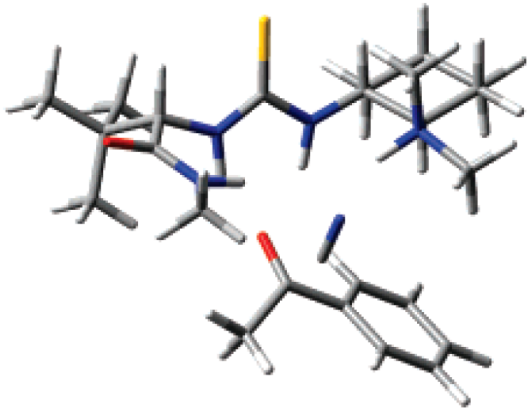
4a: R_4 = *i*-Pr, R_5 = *n*-Pr

both the secondary amide and the *tert-leucine* components of the catalyst play an important role in defining enantioselectivity

Calculated transition structures for the addition of HCN to acetophenone catalyzed by **1b**

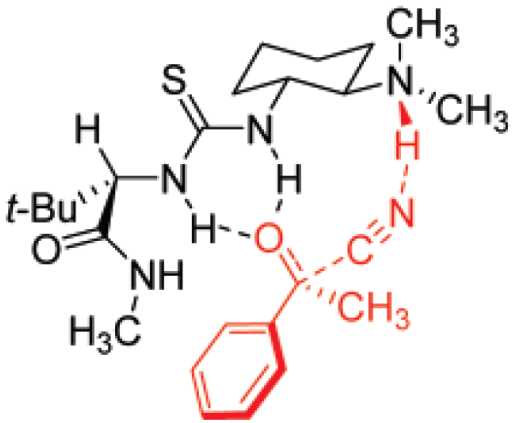
A

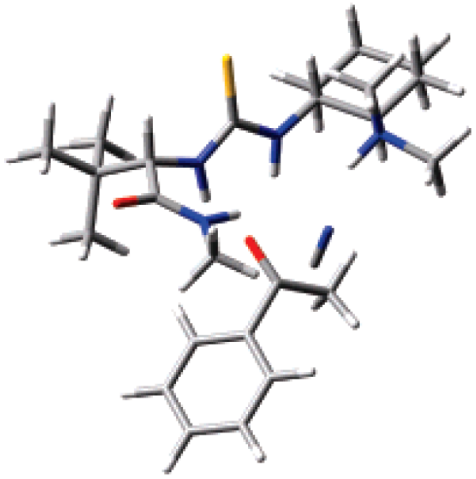




Major

B

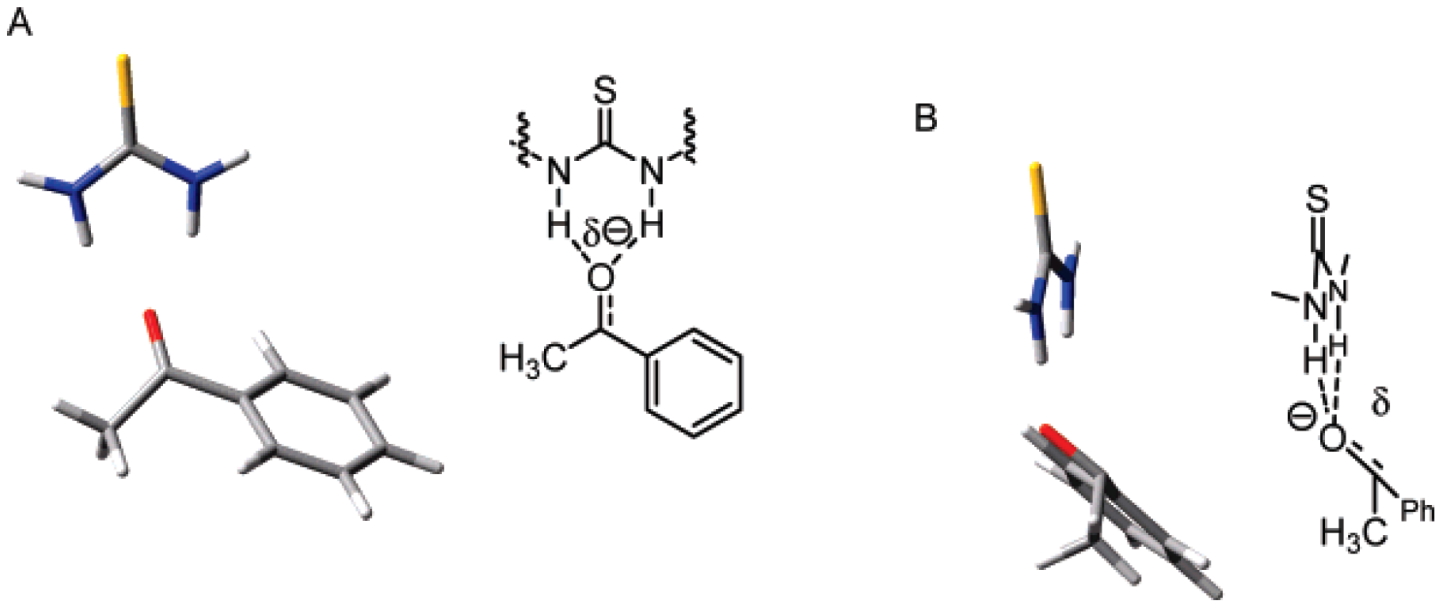




Minor

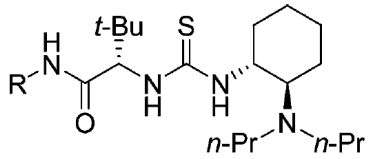
60 X higher reactivity of secondary amide catalysts compared with tertiary amide catalysts: a tertiary amide would block the addition of cyanide by placing an alkyl group

Binding geometry of the ketone-thiourea interaction in the lowest energy calculated transition state

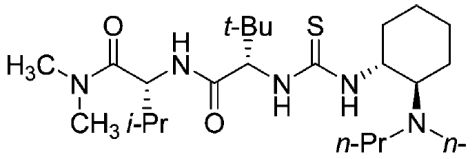


interact through both lone pairs in a nearly symmetrical geometry : enzymatic oxyanion hole

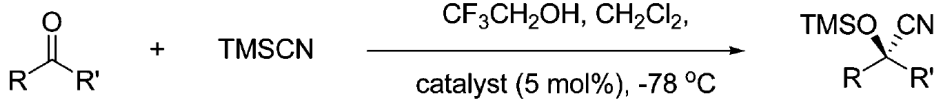
Cyanosilyation of Dialkyl Ketones Using Catalysts with Sterically Demanding Amides

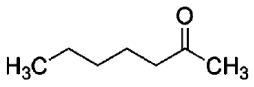
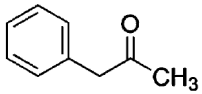


8: R = *i*-Pr
9: R = CH(*t*-Bu)$_2$

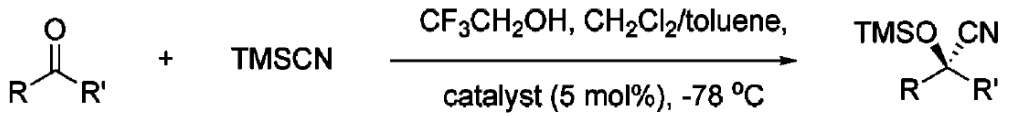


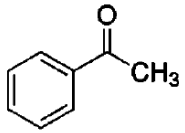
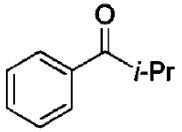
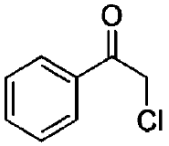
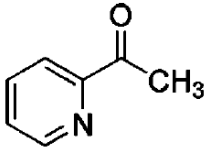
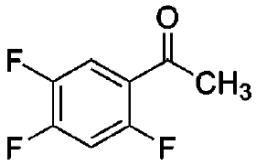
10



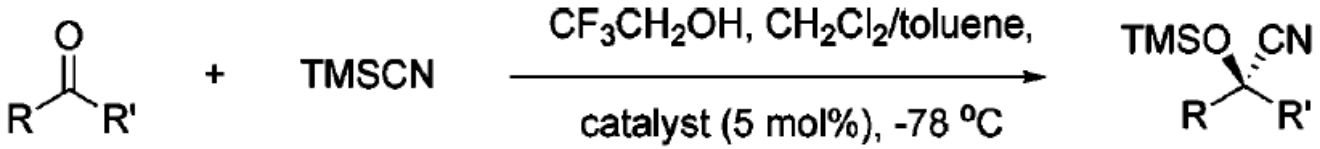
entry	catalyst	ee(%)[a]	
			
1	**1a**	11	8
2	**8**	54	71
3	**9**	63	84
4	**10**	65	85

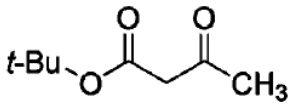
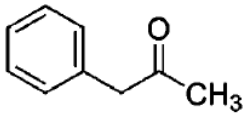
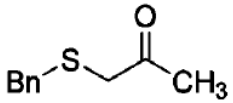
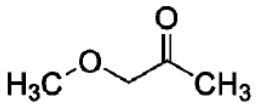
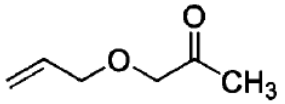
Development of More Highly Enantioselective Catalysts.



entry	ketone	catalyst[a]	time (h)	yield[b] (%)	ee[c] (%)	ee[c] with **1a** (%)
1		**8**	36	88	98	97
2		**8**	60	91	95	86
3		**8**	12	98	92	89
4		**8**	12	97	96	94
5		**8**	12	90	90	78

Development of More Highly Enantioselective Catalysts.



entry	ketone	catalyst[a]	time (h)	yield[b] (%)	ee[c] (%)	ee[c] with **1a** (%)
6		**10**	18	98	92	59
7		**10**	18	95	85	8
8[d]		**10**	12	96	84	51
9[d]		**10**	8	81	88	79
10[d]		**10**	8	91	86	60

2-heptanone gives lower enantiomeric excess than dialkyl ketones bearing *π or lone pair* substituents :direct electronic interactions between substrate and catalyst play an important role in controlling enantioinduction

Conclusions

- amino-thiourea catalyzed ketone cyanosilylation involves simultaneous activation of HCN by the tertiary amine and of the ketone by the thiourea.

- Kinetic analysis : ternary transition structure **1a.**HCN**.6b** and revealed mechanistically significant inhibition effects at elevated concentrations

- Kinetic analysis in the presence of inactive inhibitors and isotopically substituted substrates provides strong evidence that both the thiourea and tertiary amine are involved directly in catalysis.

- Transition state DFT calculations reproduce experimental trends in enantioselectivity- strong evidence for a mechanism of catalysis involving ketone-thiourea rather than cyanide thiourea interactions.

- Analysis of the transition structures : enantioselectivity that involves direct substrate-catalyst interactions and binding through both ketone lone pairs- mode of asymmetric induction with chiral hydrogenbond donors different than with chiral Lewis acids.