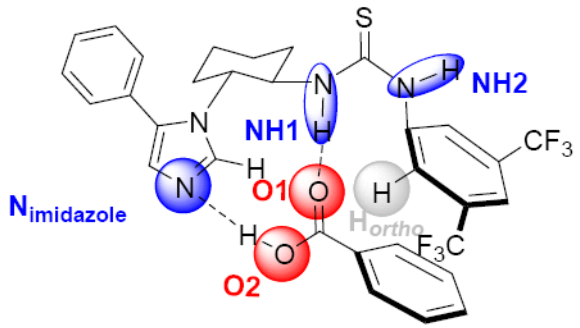
Cooperative Thiourea-Brønsted Acid Organocatalysis: Direct Enantioselective Cyanosilylation of Aldehydes with TMSCN



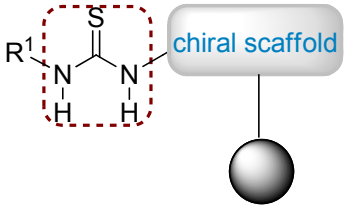
29-04-2011

Zhiguo Zhang and Katharina M. Lippert

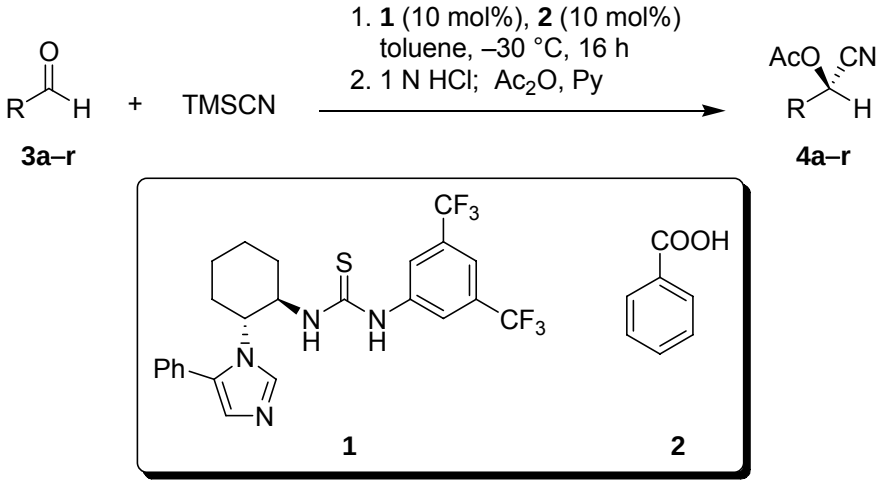
Institute of Organic Chemistry
Justus-Liebig-University
35392 Giessen, Germany

Overview

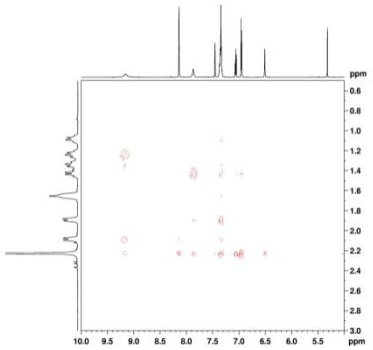
- Introduction

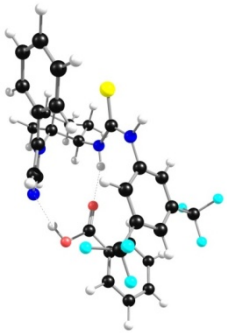


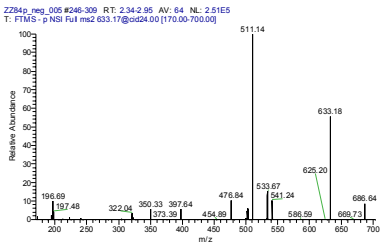
Lewis basic moieties



- Mechanistic Insights

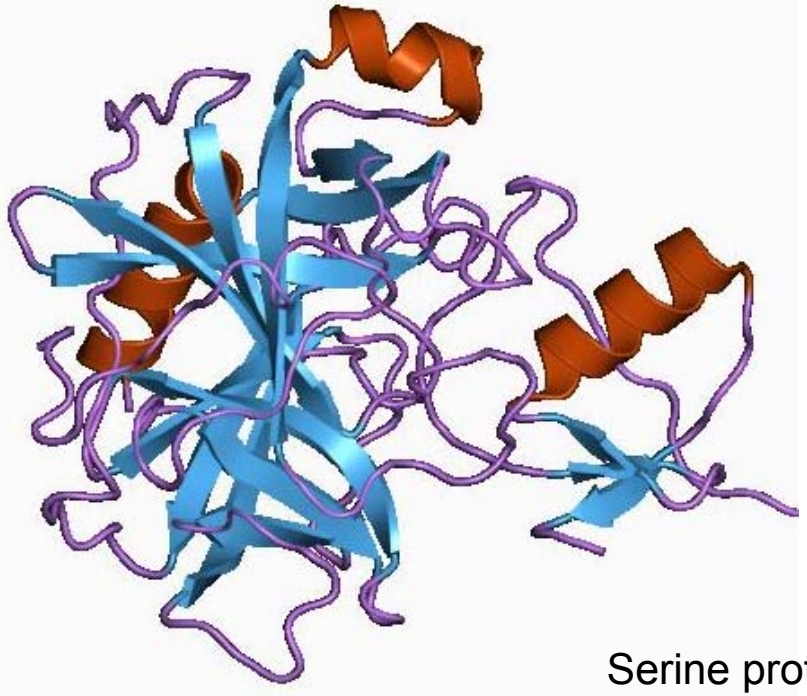


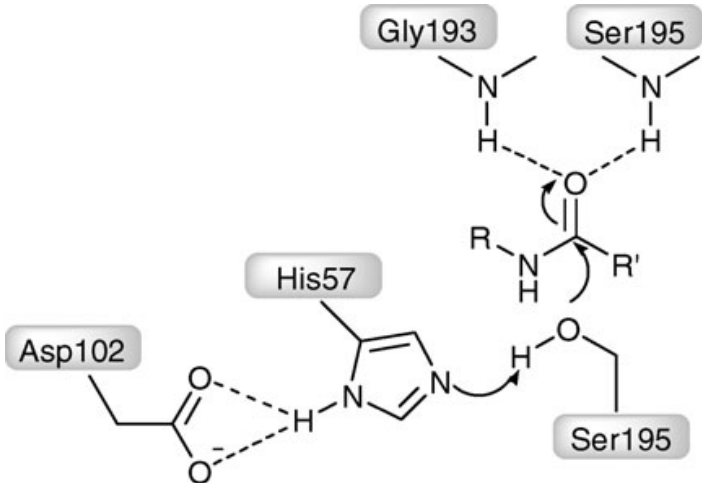




Introduction

- Nature is the master in carrying out chemical transformations with enormous proficiencies and exquisite specificities
- Nature‘s way of catalysis: cooperative activation of two (or more) components
- Hydrogenbonding is a key contributor in a diverse array of enzymatic systems

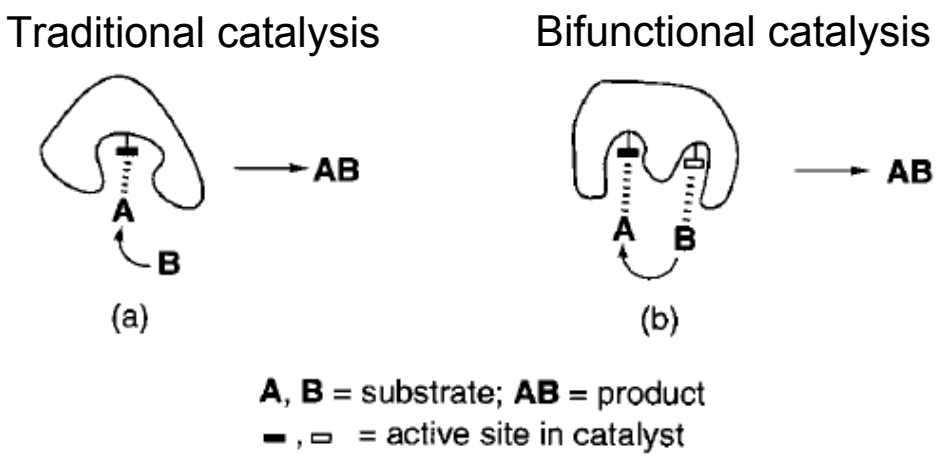




Serine protease

L. Hedstrom, *Chem. Rev.*, 2002, **102**, 4501.
A. Fersht, *Structure and Mechanism in Protein Science*, Freeman, New York, 1999.

Introduction

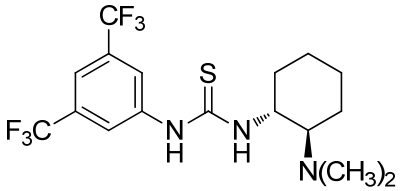


- Single active site
- Activation of one species

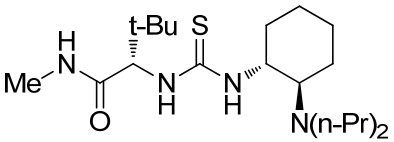
- Two (or more) active sites
- Simultaneous activation of multiple species
- “Artificial enzymes“

M. Shibasaki *et al.*, *Chem. Rev.* **2002**, *102*, 2187

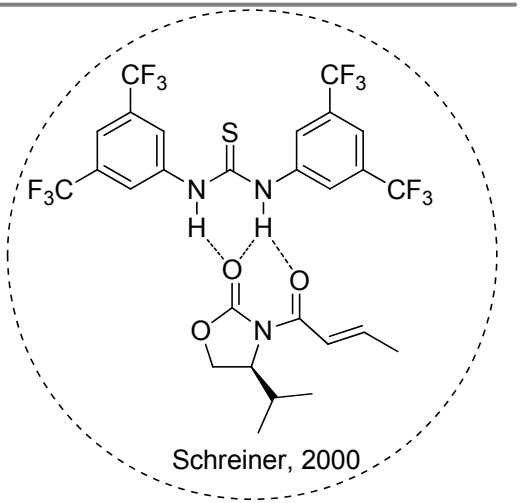
Introduction



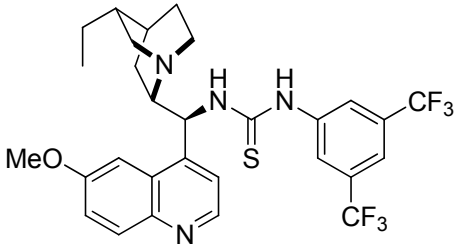
Takemoto, 2003



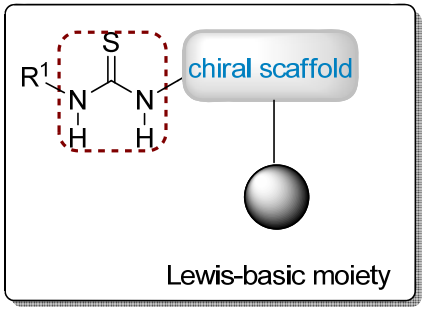
Jacobsen, 2005

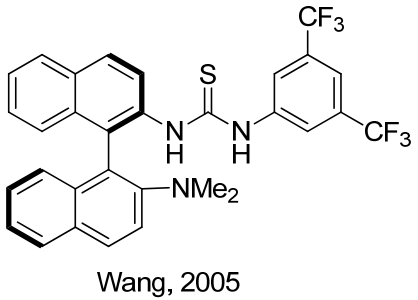


Schreiner, 2000



Soós, 2005



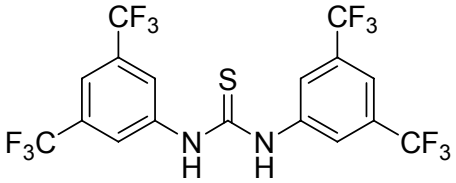


Wang, 2005

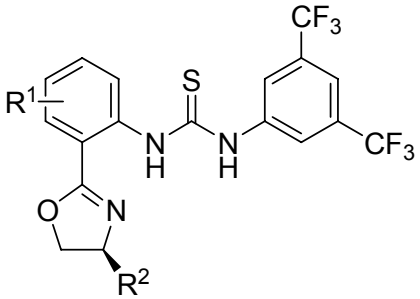
A. Wittkopp, P. R. Schreiner, In *The Chemistry of Dienes and Polymers*, **2000**, 1029.
P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217.
A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407.
P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289.

Introduction

Potential catalysts

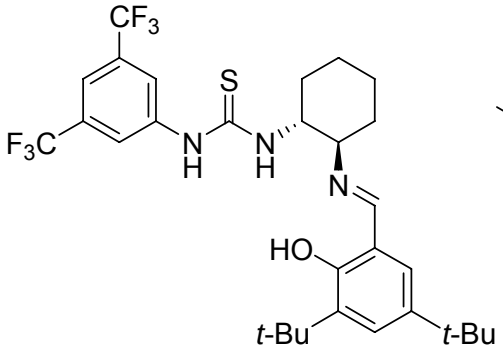


1

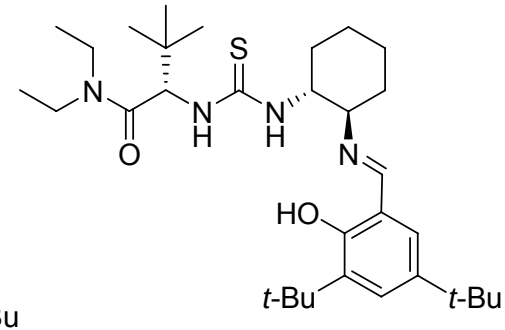


2a-h

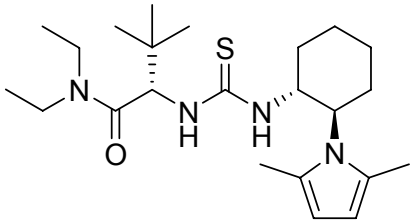
2a: R^1 = H, R^2 = H
2b: R^1 = H, R^2 = Me
2c: R^1 = H, R^2 = *iso*-propyl
2d: R^1 = H, R^2 = benzyl
2e: R^1 = H, R^2 = 2-butyl
2f: R^1 = H, R^2 = 2-*iso*-butyl
2g: R^1 = 3,5-bis(CF_3), R^2 = 2-butyl
2h: R^1 = 3,5-bis(CF_3), R^2 = 2-*iso*-butyl



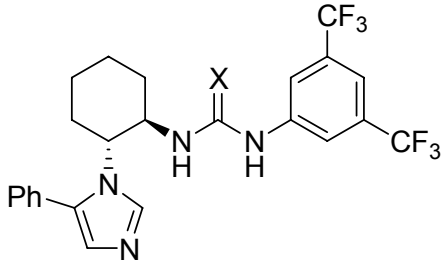
3a



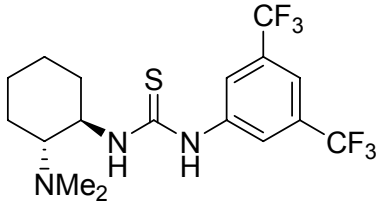
3c



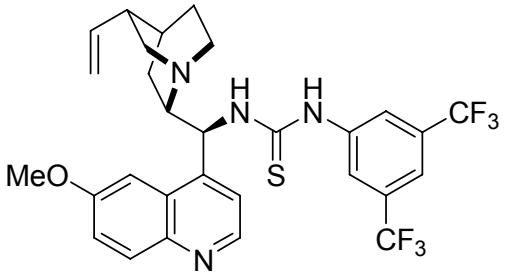
3b



4a: X = S
4b: X = O

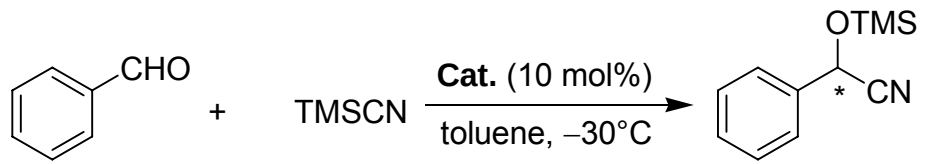


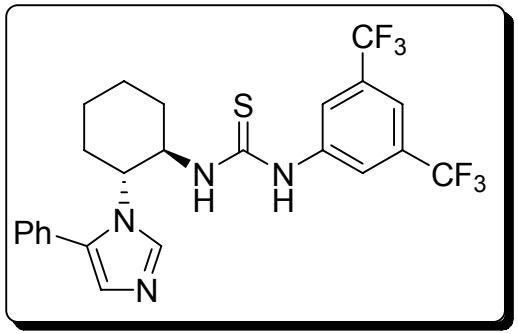
5



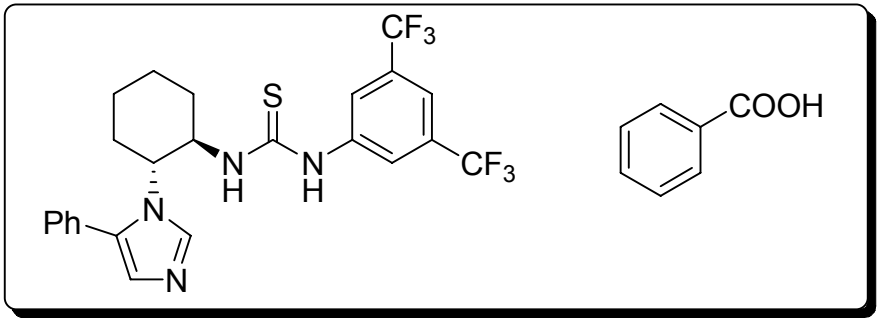
6

Introduction

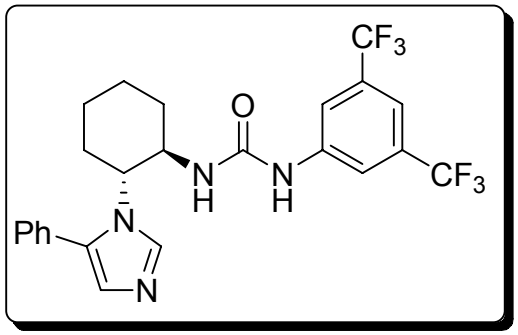




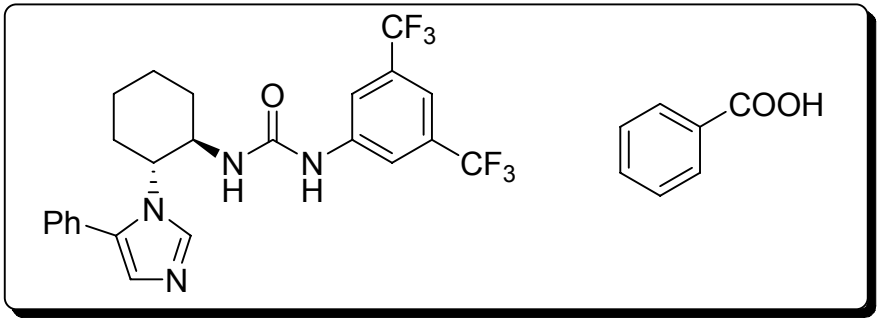
92% conv., 0% *ee*



98% conv., 74% *ee*



96% conv., 0% *ee*

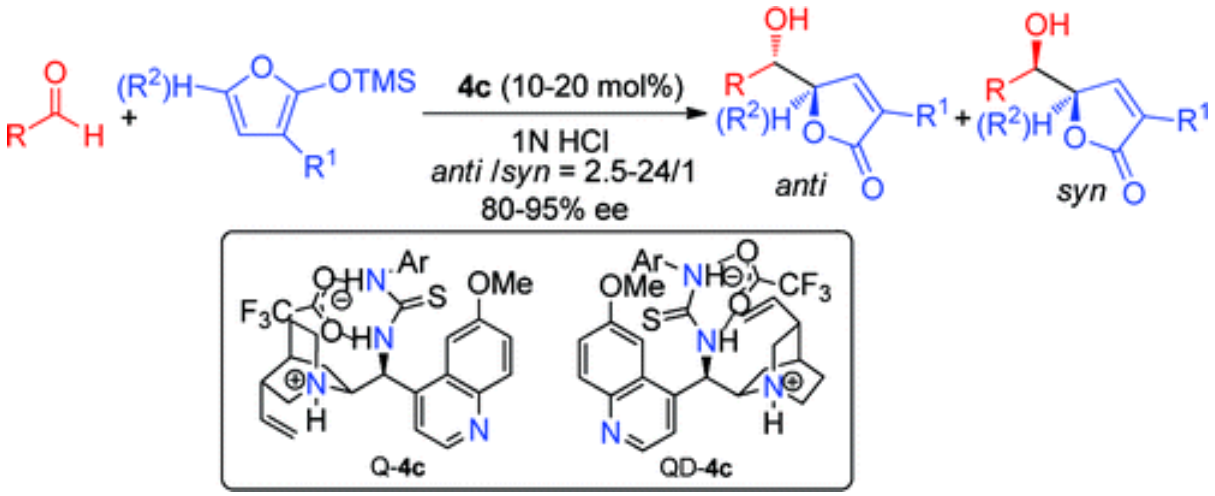


97% conv., 3% *ee*

Introduction

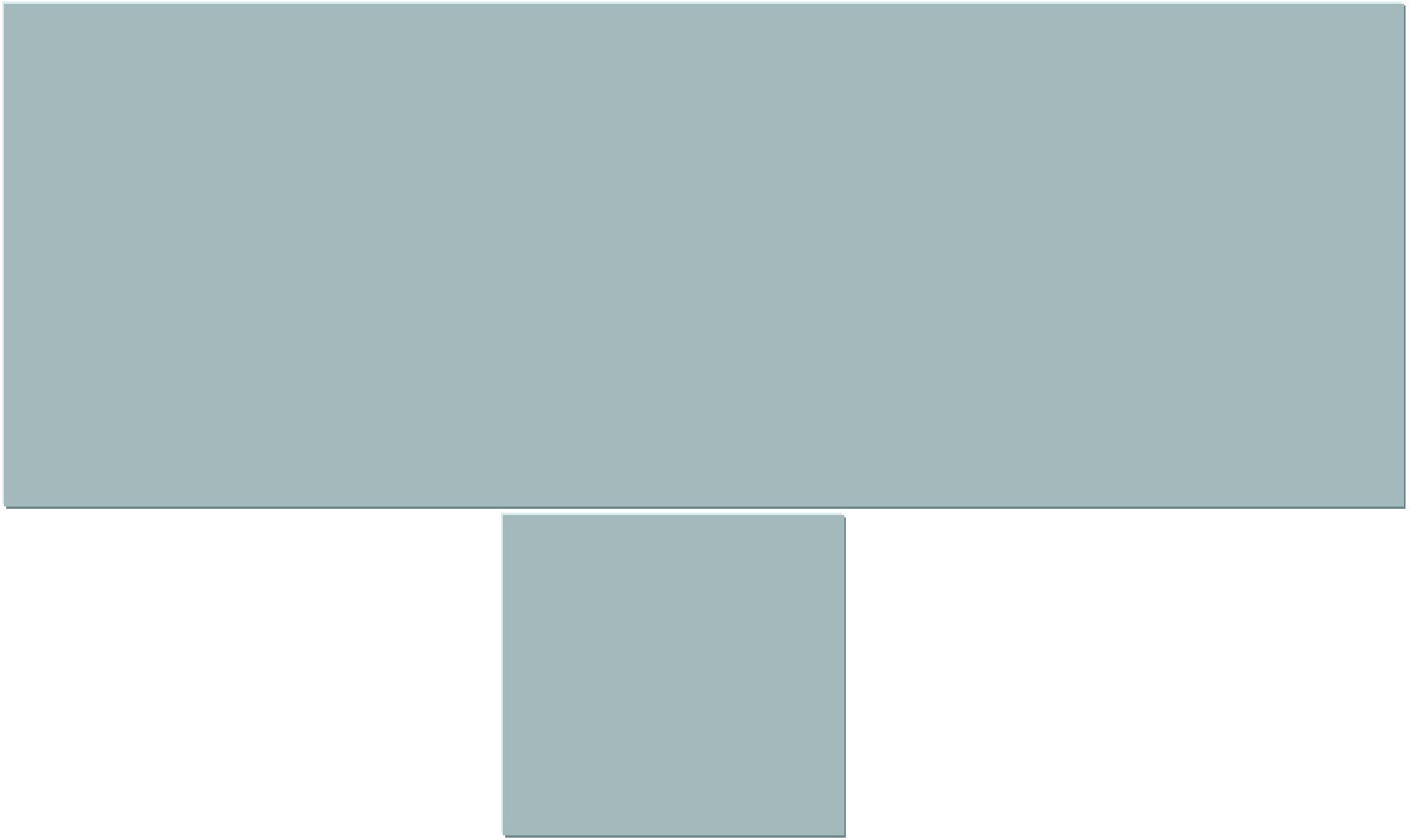
T. Weil, M. Kotke, C. M. Kleiner, P. R. Schreiner, *Org. Lett.* **2008**, *10*, 1513.

Introduction



Singh, R. P., Foxman, B. M., Deng, L. *J. Am. Chem. Soc.* **2010,** *132*, 9558.

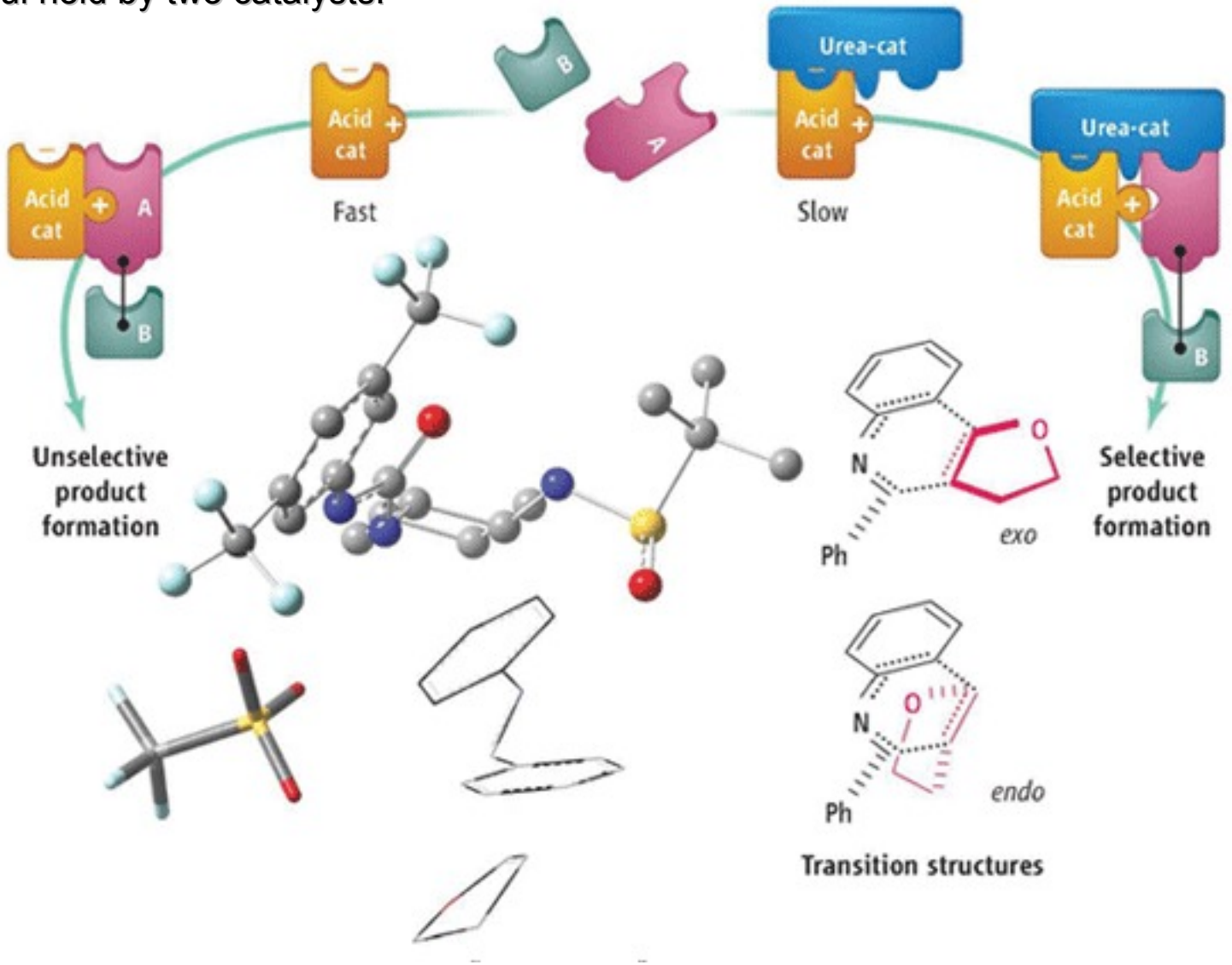
Introduction



H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science*, **2010**, *327*, 986.

Introduction

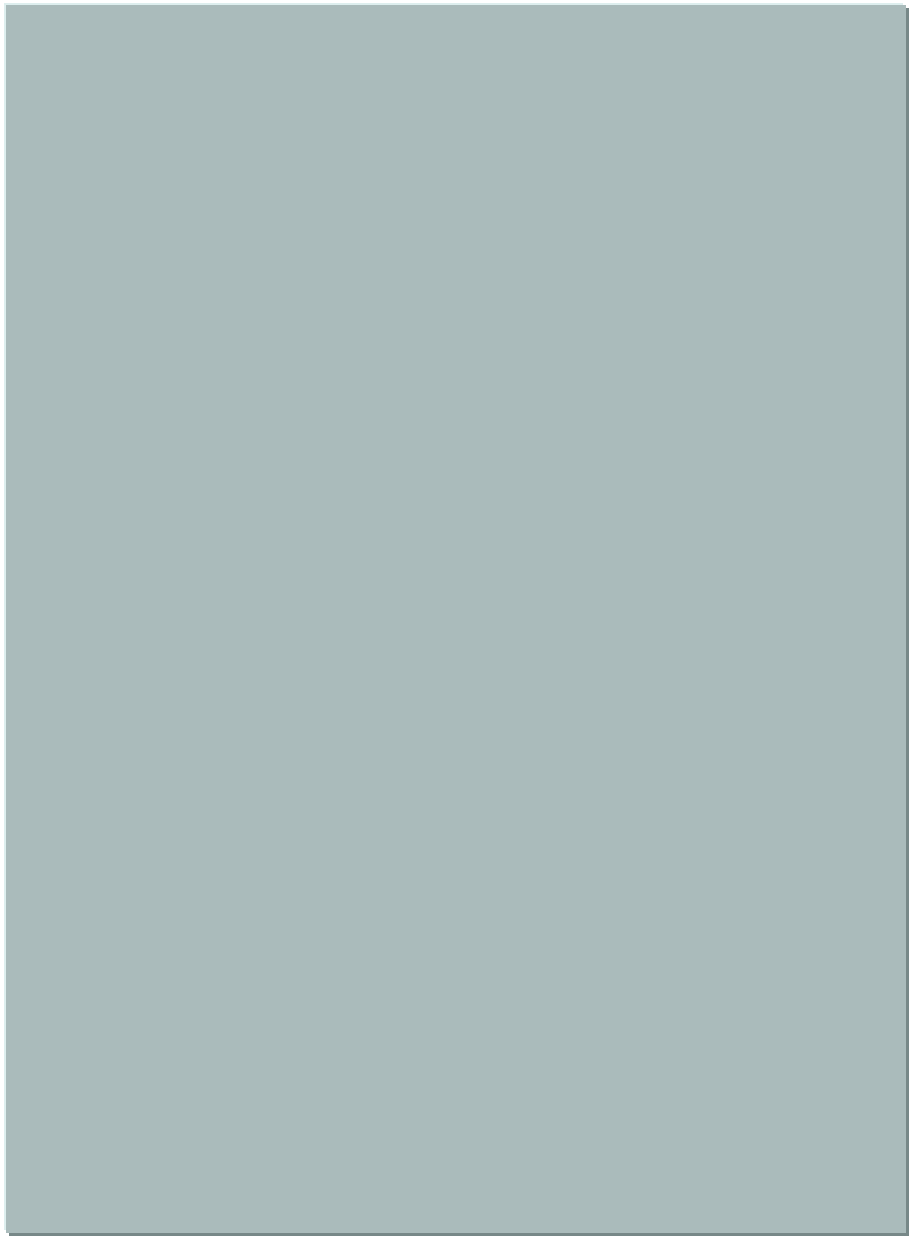
A careful hold by two catalysts.



H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science*, **2010**, *327*, 986.
P. R. Schreiner, *Science*, **2010**, *327*, 965.

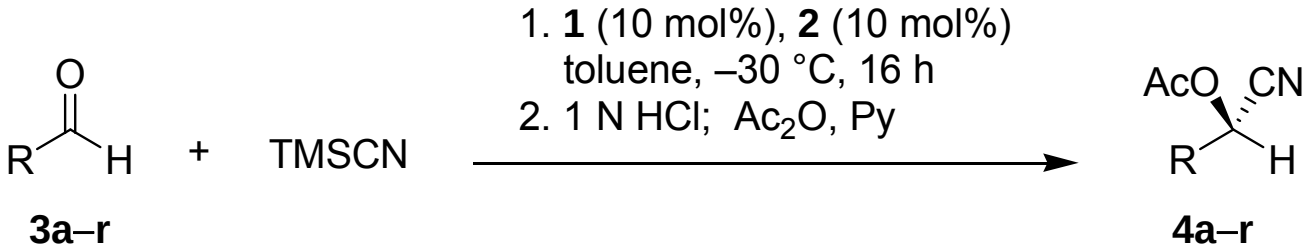
Introduction

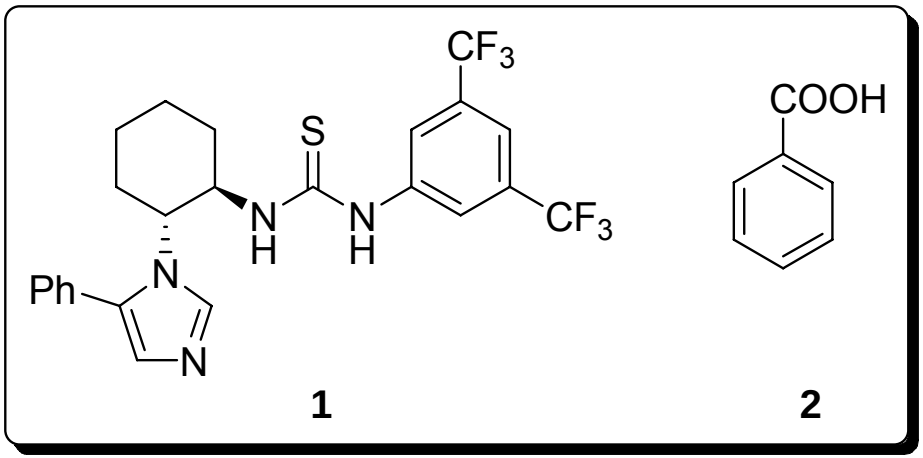
Acids Screening



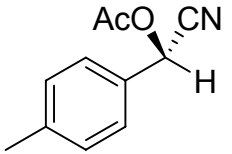
Introduction

Cyanosilylation

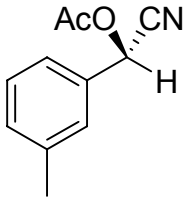




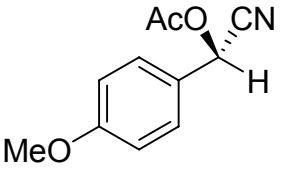
Cyanosilylation



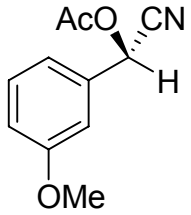
87%, 84% *ee*



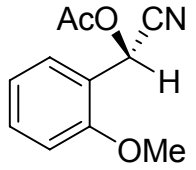
71%, 45% *ee*



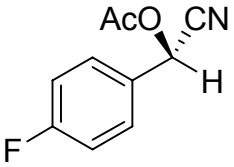
56%, 70% *ee*



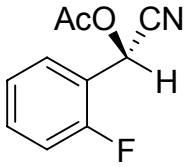
75%, 61% *ee*



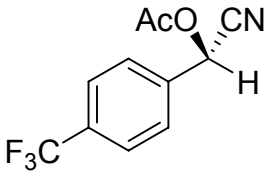
68%, 6% *ee*



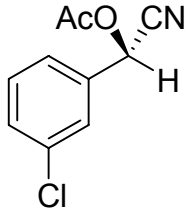
86%, 80% *ee*



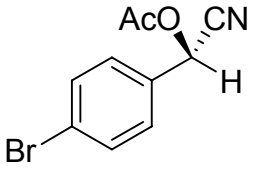
61%, 62% *ee*



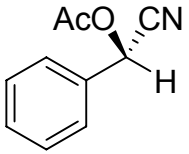
72%, 80% *ee*



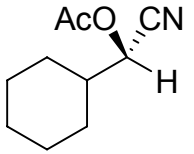
63%, 63% *ee*



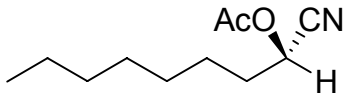
82%, 83% *ee*



73%, 73% *ee*



56%, 7% *ee*



64%, 25% *ee*

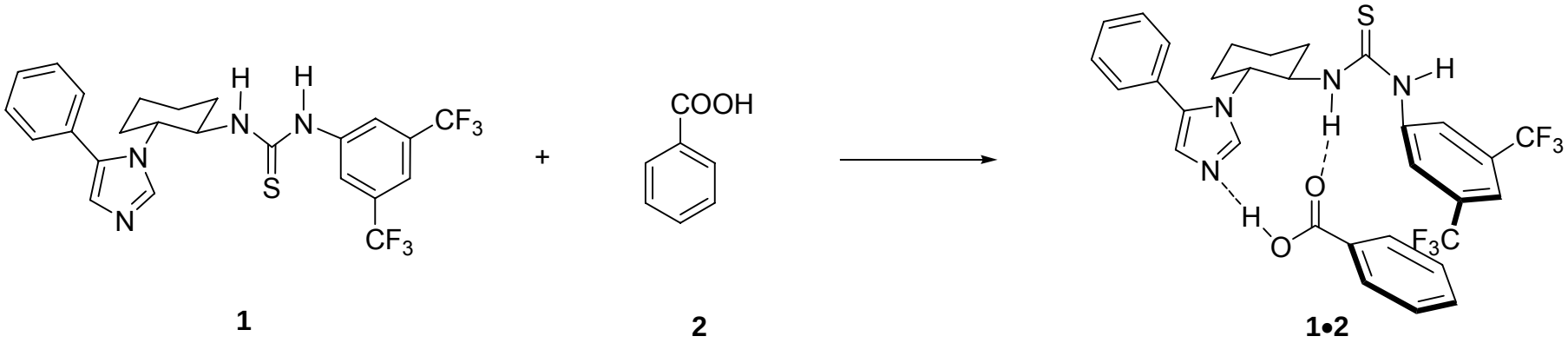
Mechanistic Insights – NMR Studies

- Difficulties due NMR Investigations

  “Free Catalyst is not soluble in benzene
  Additional solvent [d_6]-DMSO needed for higher solubility

- Investigation of binary complex

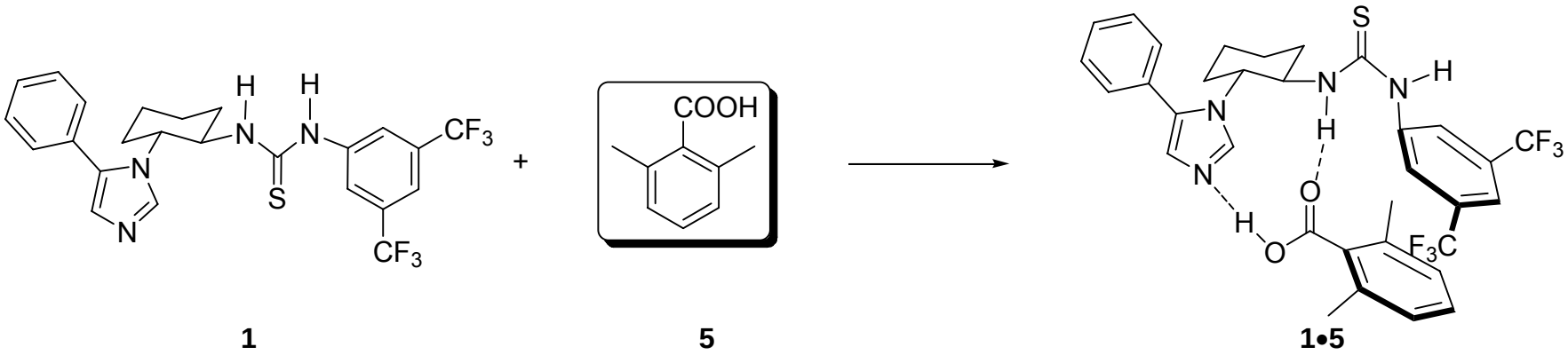
  Difficulties in measuring the NOE-effect: No NOE-effect between bifunctional catalyst and benzoic acid!



1 **2** **1•2**

Mechanistic Insights – NMR Studies

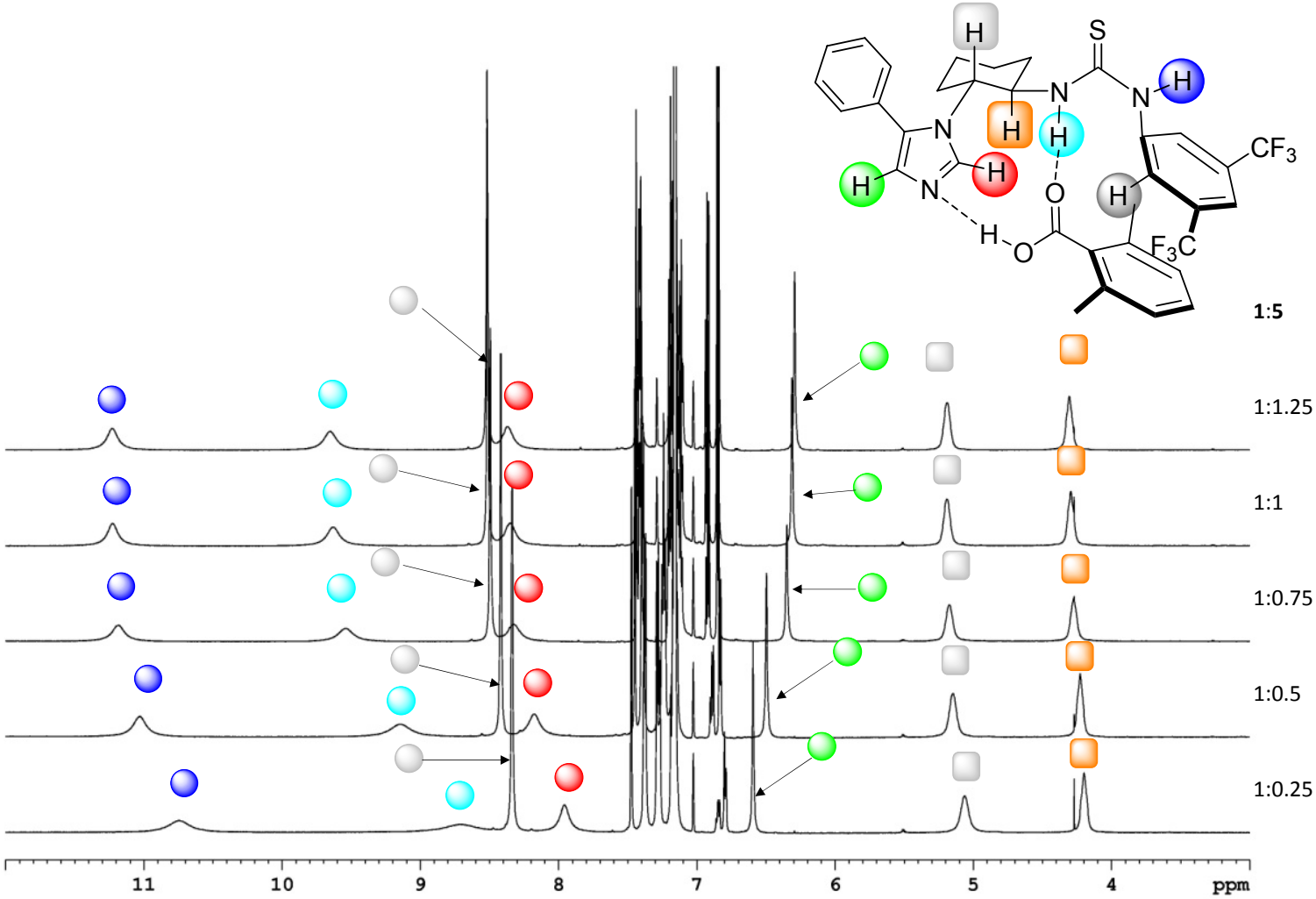
- Investigation of binary complex



1 **5** **1•5**

Mechanistic Insights – NMR Studies

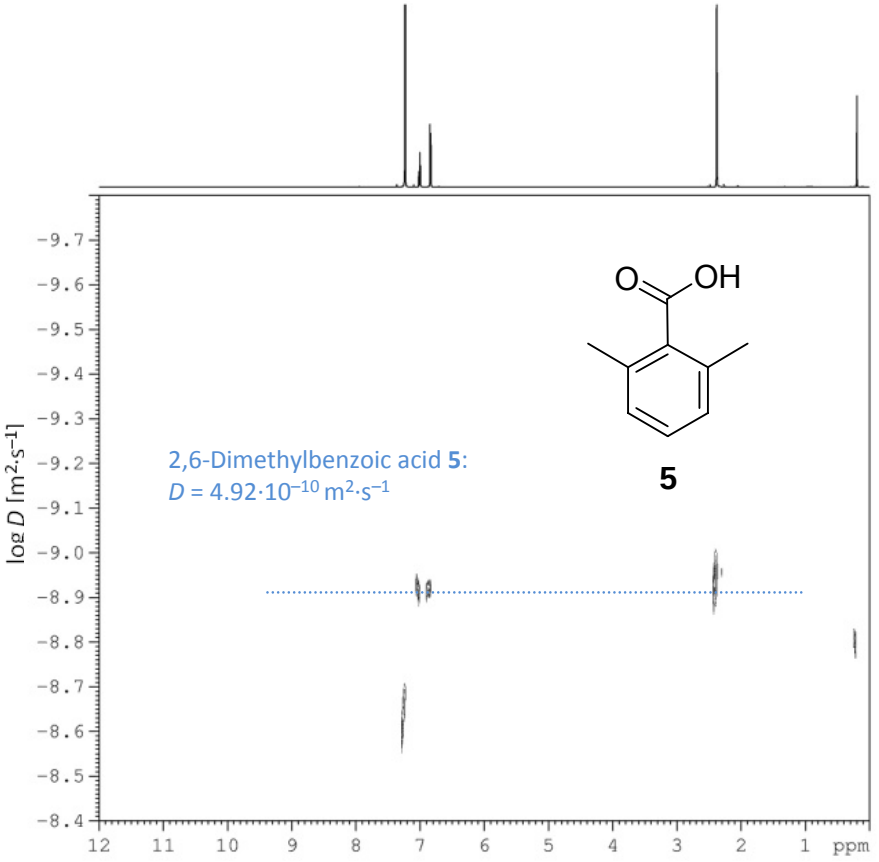
- Titration experiment of catalyst with 2,6-dimethylbenzoic acid in [d_6]-benzene

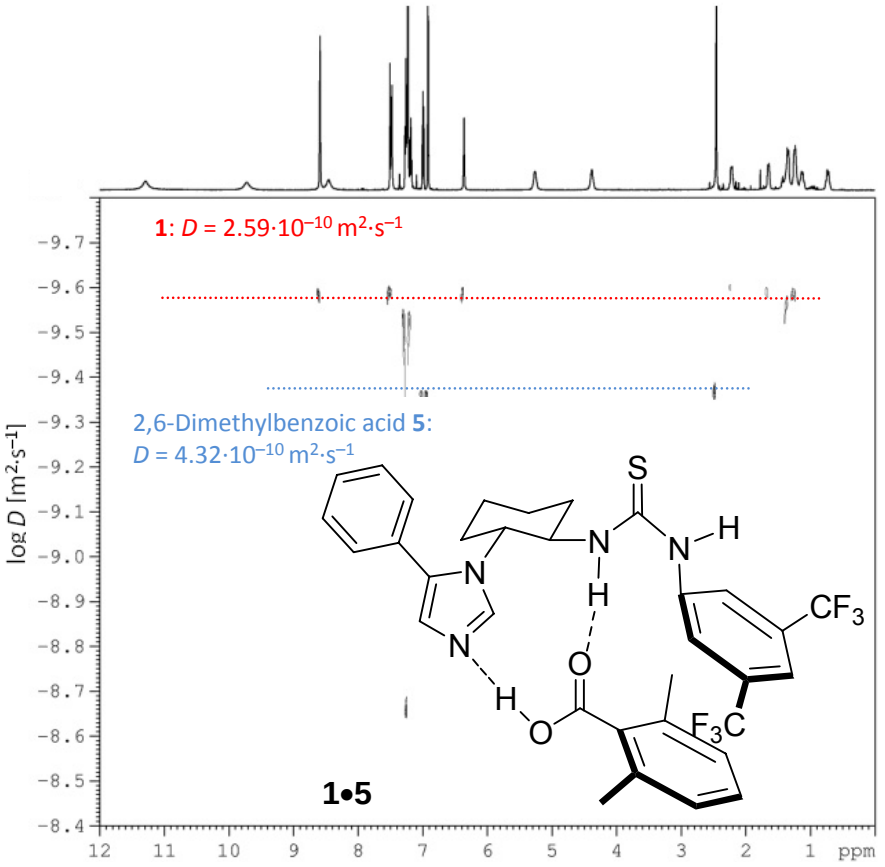


600 MHz, Catalyst (0.01 mmol) with increasing amount of 2,6-dimethylbenzoic acid in [d_6]-benzene

Mechanistic Insights – NMR Studies

- Investigation of binary complex in [d_6]-benzene via ^{1}H DOSY NMR
- ^{1}H DOSY NMR of “free” catalyst is not possible through solubility

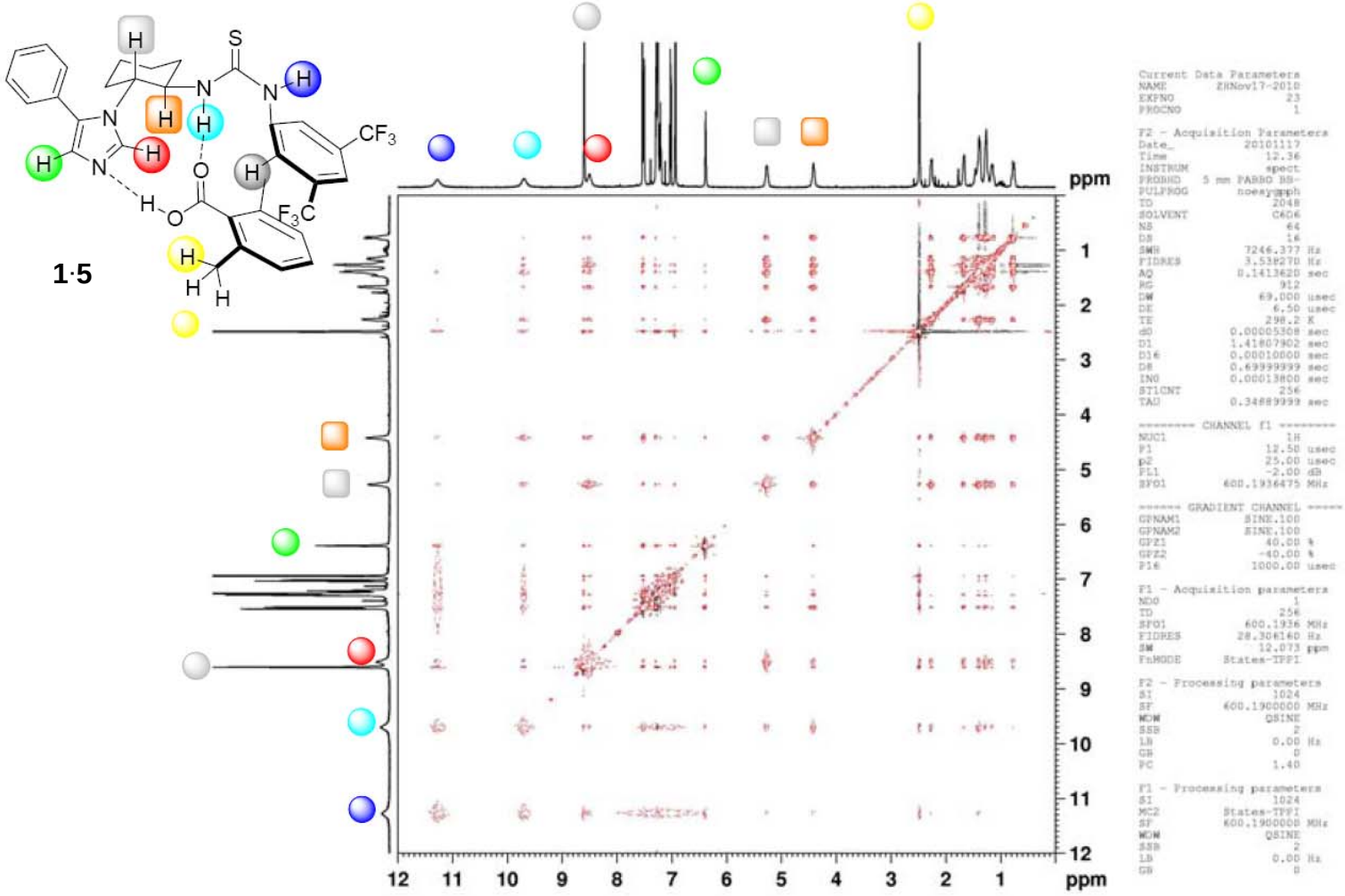




600 MHz, Left: 2,6-Dimethylbenzoic acid (0.01 mmol) in [d_6]-benzene; Right: Catalyst and 2,6-dimethylbenzoic acid (1:1 at 0.01 mmol) in [d_6]-benzene

Mechanistic Insights – NMR Studies

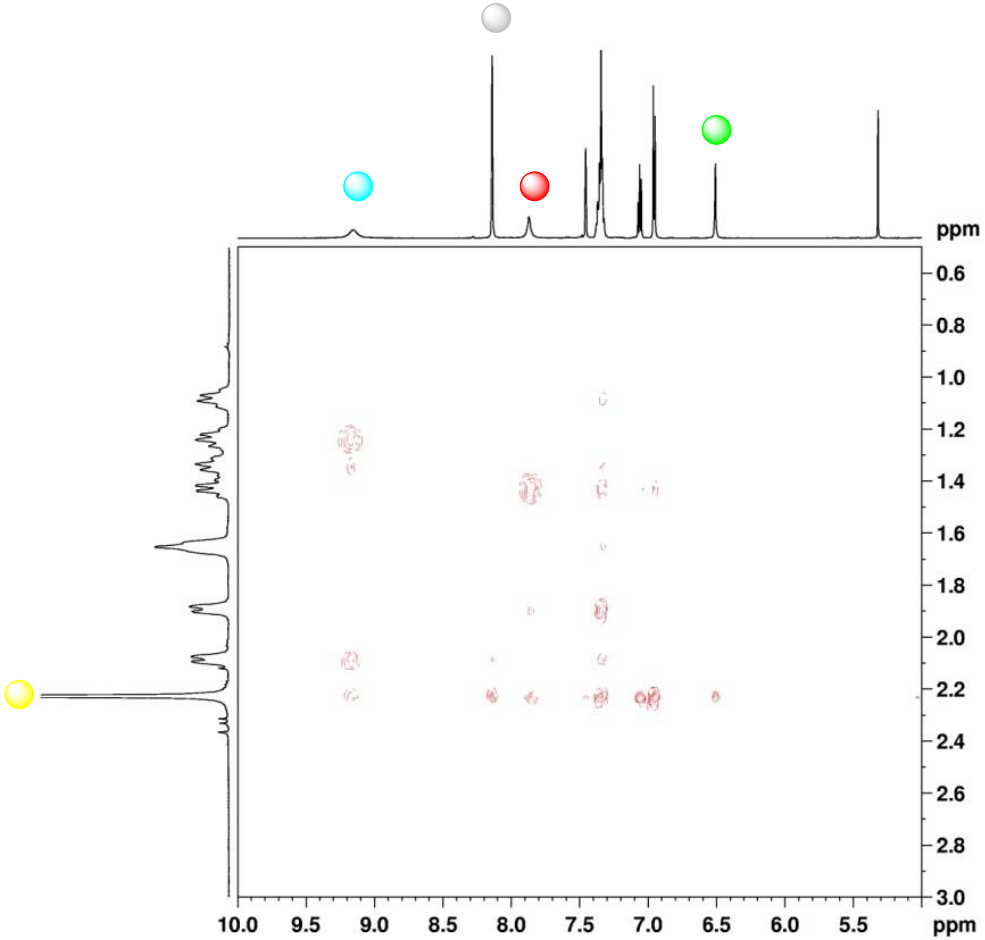
- NOE experiment of catalyst with 2,6-dimethylbenzoic acid in [d_6]-benzene

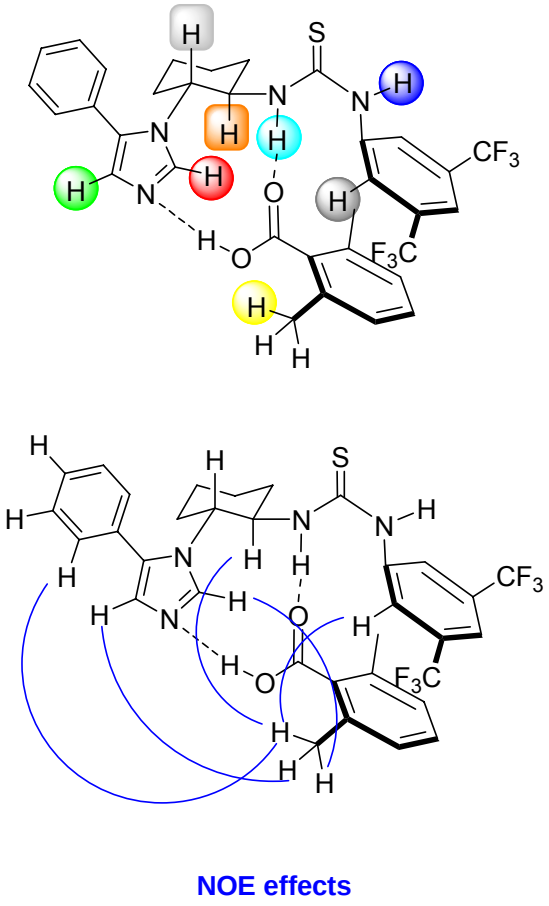


Catalyst and 2,6-dimethylbenzoic acid (1:1 at 0.01 mmol) in [d_6]-benzene

Mechanistic Insights – NMR Studies

- ^{1}H 2D ROESY: NOE experiment of binary complex of catalyst with 2,6-dimethylbenzoic acid in CD_2Cl_2

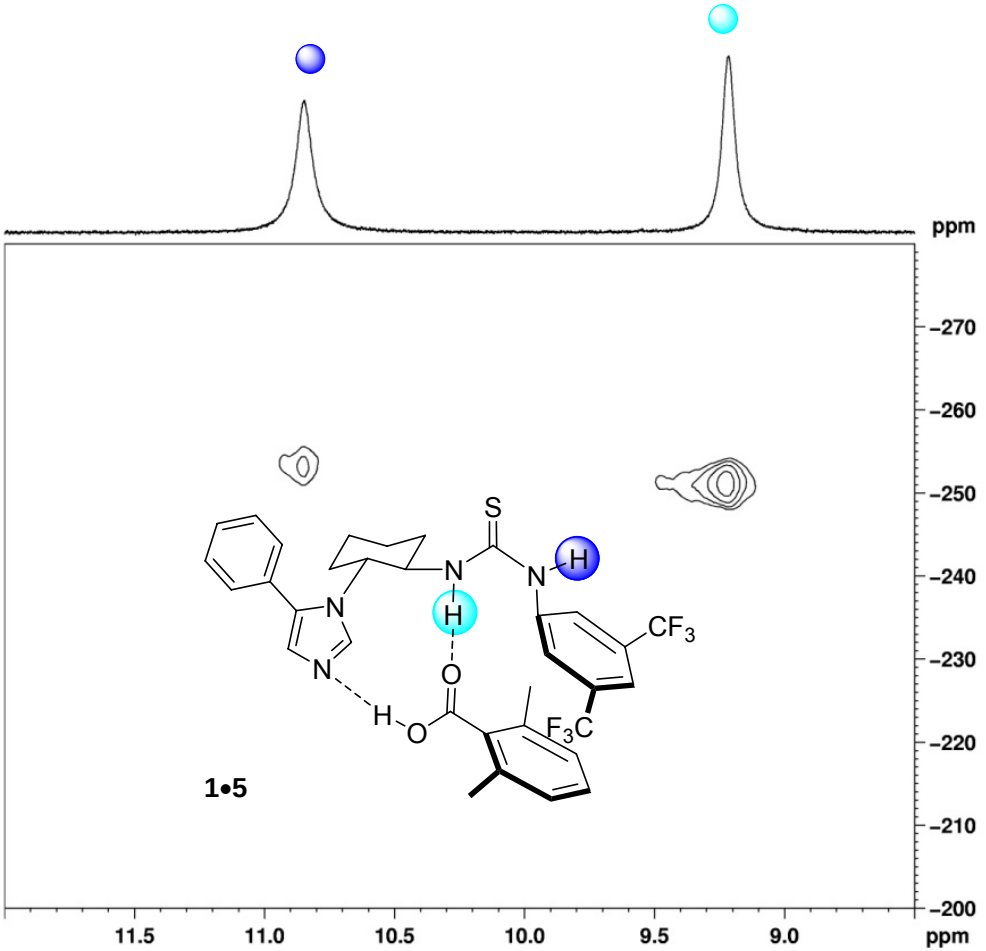




600 MHz, Catalyst and 2,6-dimethylbenzoic acid (1:1 at 0.01 mmol) in CD_2Cl_2

Mechanistic Insights – NMR Studies

- Section of the ^{1}H, ^{15}N-HSQC spectrum of binary complex in CD_2Cl_2

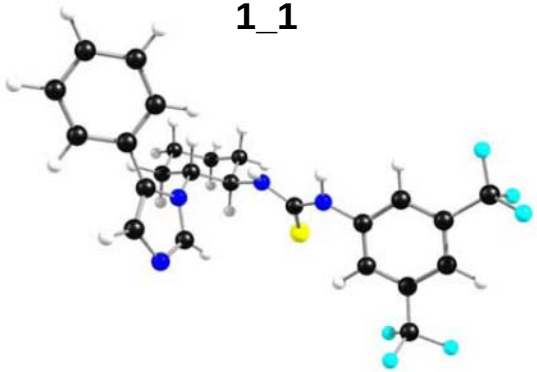


600 MHz, Catalyst and 2,6-dimethylbenzoic acid (1:1 at 0.01 mmol) in CD_2Cl_2

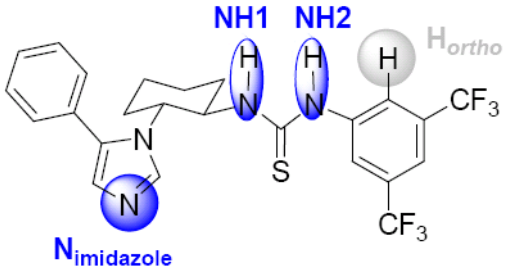
Mechanistic Insights – Computational Studies

- DFT computations of “free” catalyst - conformationally flexible

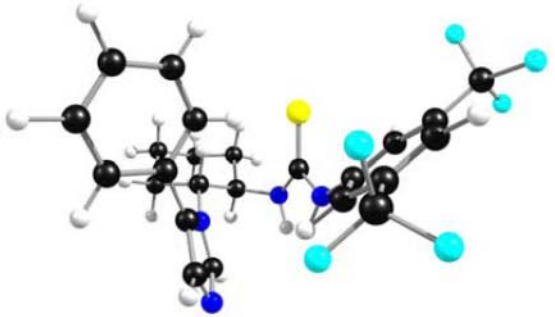
1_1



$\Delta H_0 = 2.4\ (0.7)$, $\Delta G_{298} = -1.5\ (-3.5)$

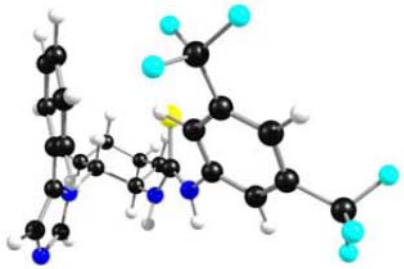


1_2



$\Delta H_0 = 3.8\ (3.3)$, $\Delta G_{298} = 1.8\ (0.7)$
$NH2\cdots N_{imidazole}$ d = 3.072 Å (3.462 Å)
$H_{ortho}\cdots N_{imidazole}$ d = 3.582 Å (4.269 Å)

1_3

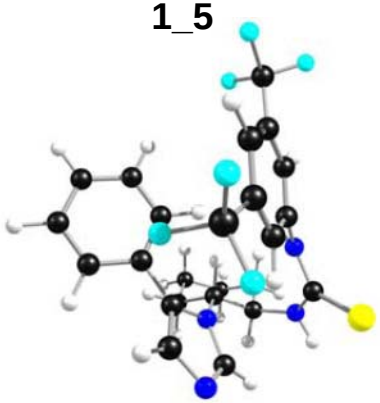


$\Delta H_0 = 0.0\ (0.0)$, $\Delta G_{298} = 0.0\ (0.0)$

1_4

$\Delta H_0 = 0.3\ (-0.5)$, $\Delta G_{298} = -0.8\ (-2.2)$
$H_{ortho}\cdots N_{imidazole}$ d = 3.136 Å (3.251 Å)

1_5



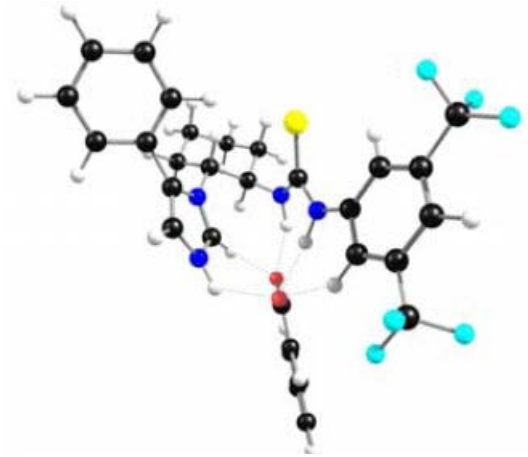
$\Delta H_0 = 4.8\ (3.8)$, $\Delta G_{298} = 4.9\ (2.9)$
$H_{ortho}\cdots N_{imidazole}$ d = 3.174 Å (3.411 Å)

DFT computations (M06/6-31G(d,p)) in the gas phase and solvent model SCRF(benzene). All data in kcal mol^{-1}

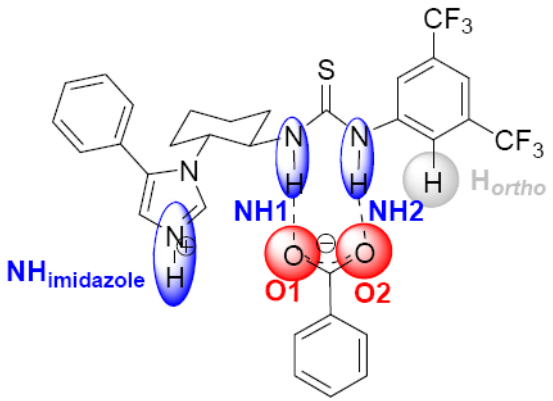
Mechanistic Insights – Computational Studies

- With benzoic acid – stabilization of the conformationally flexible "free" catalyst
- Complex of "protonated" bifunctional thiourea catalyst and benzoate or complex of bifunctional thiourea catalyst and benzoic acid?

1·5_2



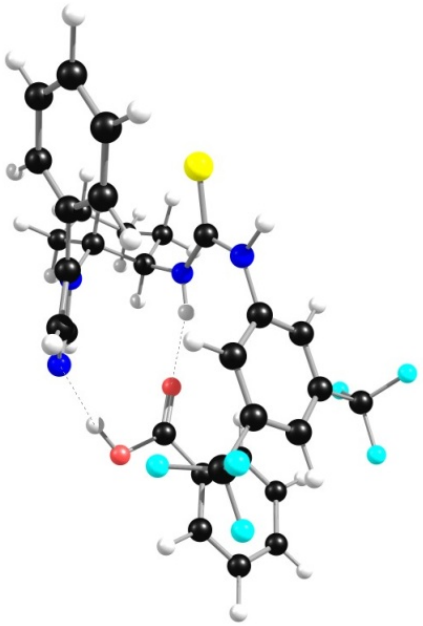
$\Delta H_0 = -2.3$ (1.6), $\Delta G_{298} = -1.7$ (0.7)
$D_0 = 15.2$ (10.4), $D_{298} = 2.3$ (–1.6)
NH1···O1 d = 1.875 Å (1.911 Å)
NH2···O2 d = 1.880 Å (1.797 Å)
H_{ortho}···O2 d = 2.348 Å (2.386 Å)
$NH_{imidazole}$···O2 d = 2.083 Å (2.728 Å)
$CH_{imidazole}$···O1 d = 1.964 Å (2.001 Å)



DFT computations (M06/6-31G(d,p)) in the gas phase and solvent model SCRF(benzene). All data in kcal mol^{-1}

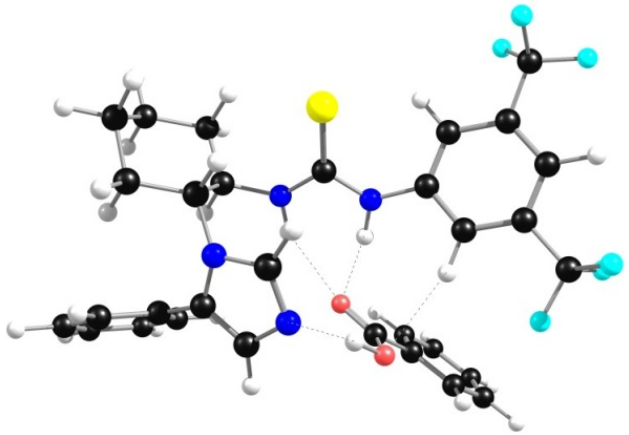
Mechanistic Insights – Computational Studies

- Lowest lying binary complexes
- Left: *Z*,*Z*-orientation versus *E*,*Z*-orientation of the NH-bonds



1·5_7

Distances:
NH1···O1 d = 2.021 Å (2.220 Å)
$N_{imidazole}$···OH2 d = 1.712 Å (1.746 Å)



Distances:
NH1···O1 d = 2.324 Å (2.600 Å)
NH2···O1 d = 1.911 Å (1.897 Å)
H_{ortho}···O1 d = 2.411 Å (3.061 Å)
$N_{imidazole}$···OH2 d = 1.709 Å (1.721 Å)

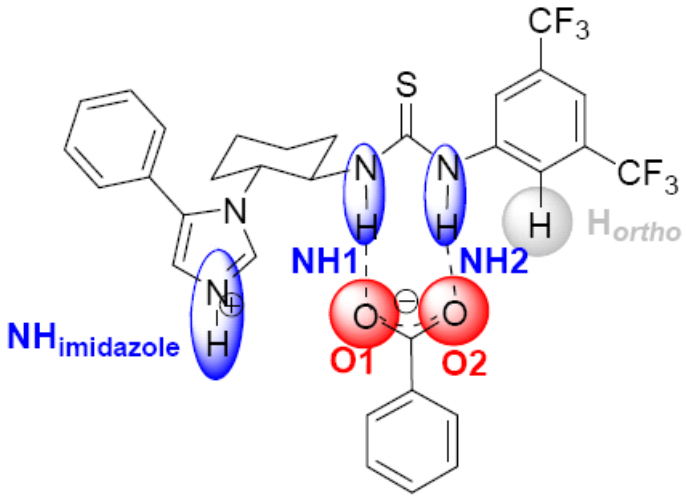
1·5_8

	ΔH_0 (kcal/mol)	D_0 (kcal/mol)	ΔG_{298} (kcal/mol)	D_{298} (kcal/mol)
1·5_7	–14.8 (–9.3)	24.2 (24.2)	–9.3 (–4.4)	7.2 (7.3)
1·5_8	–12.8 (–4.4)	25.7 (16.5)	–10.7 (–2.2)	11.2 (1.3)

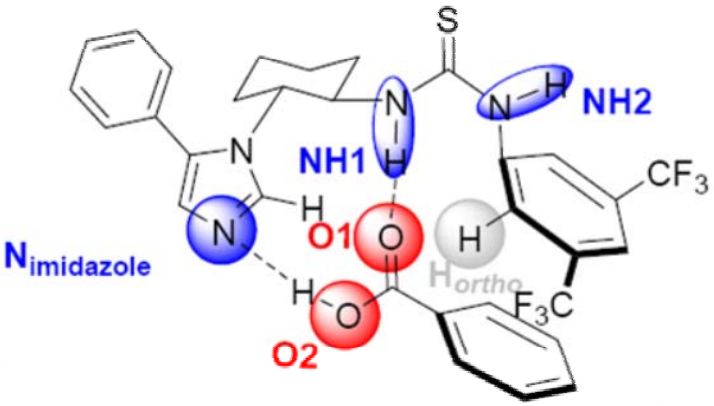
DFT computations (M06/6-31G(d,p)) in the gas phase and solvent model SCRF(benzene). All data in kcal mol^{-1}

Mechanistic Insights – Computational Studies

- With benzoic acid – stabilization of the conformationally flexible "free" catalyst
- Binary complex with benzoic acid not with benzoate!
- *E*,*Z*-orientation of the NH-bonds!



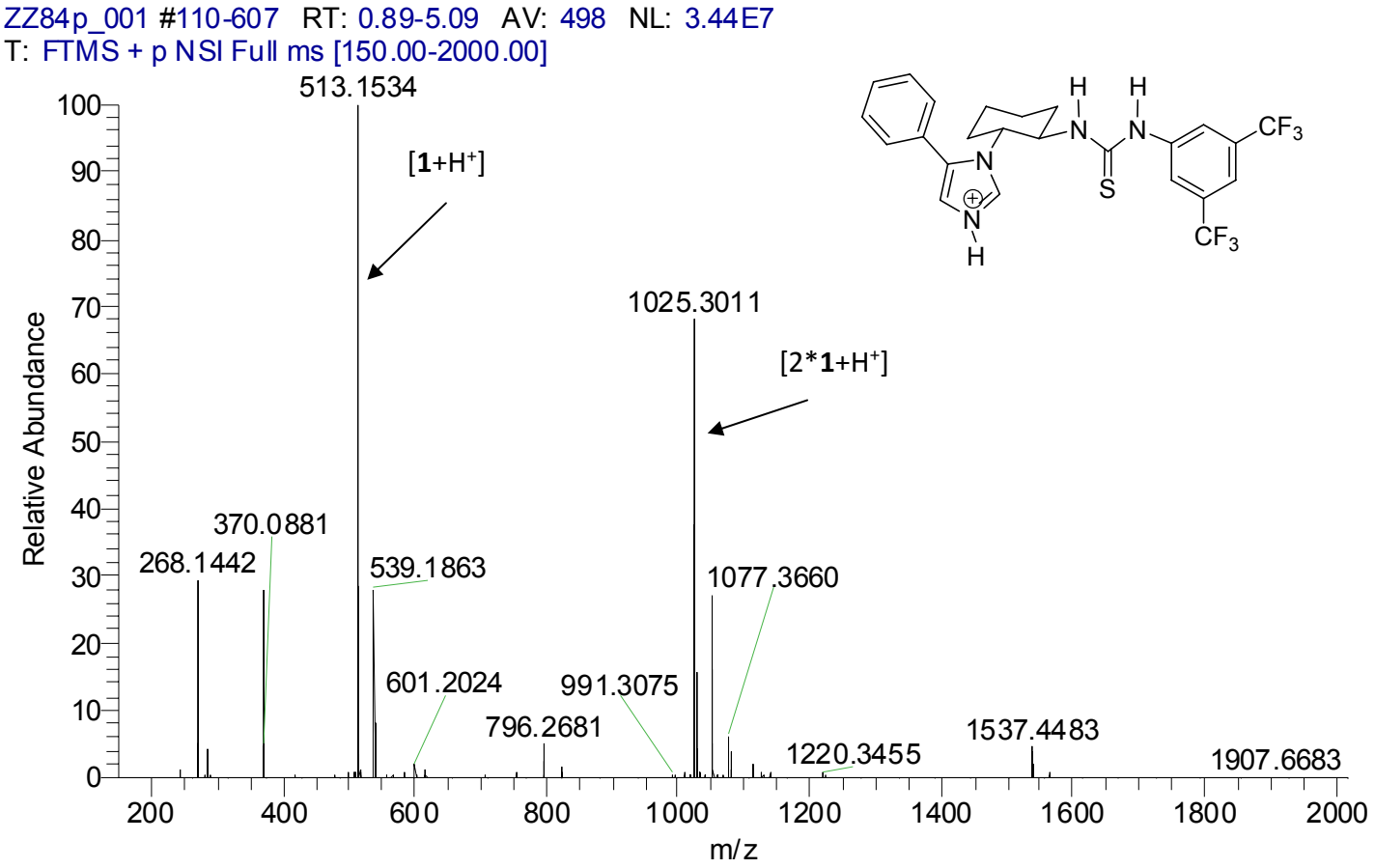
1·5



1·5

Mechanistic Insights – ESI/MS

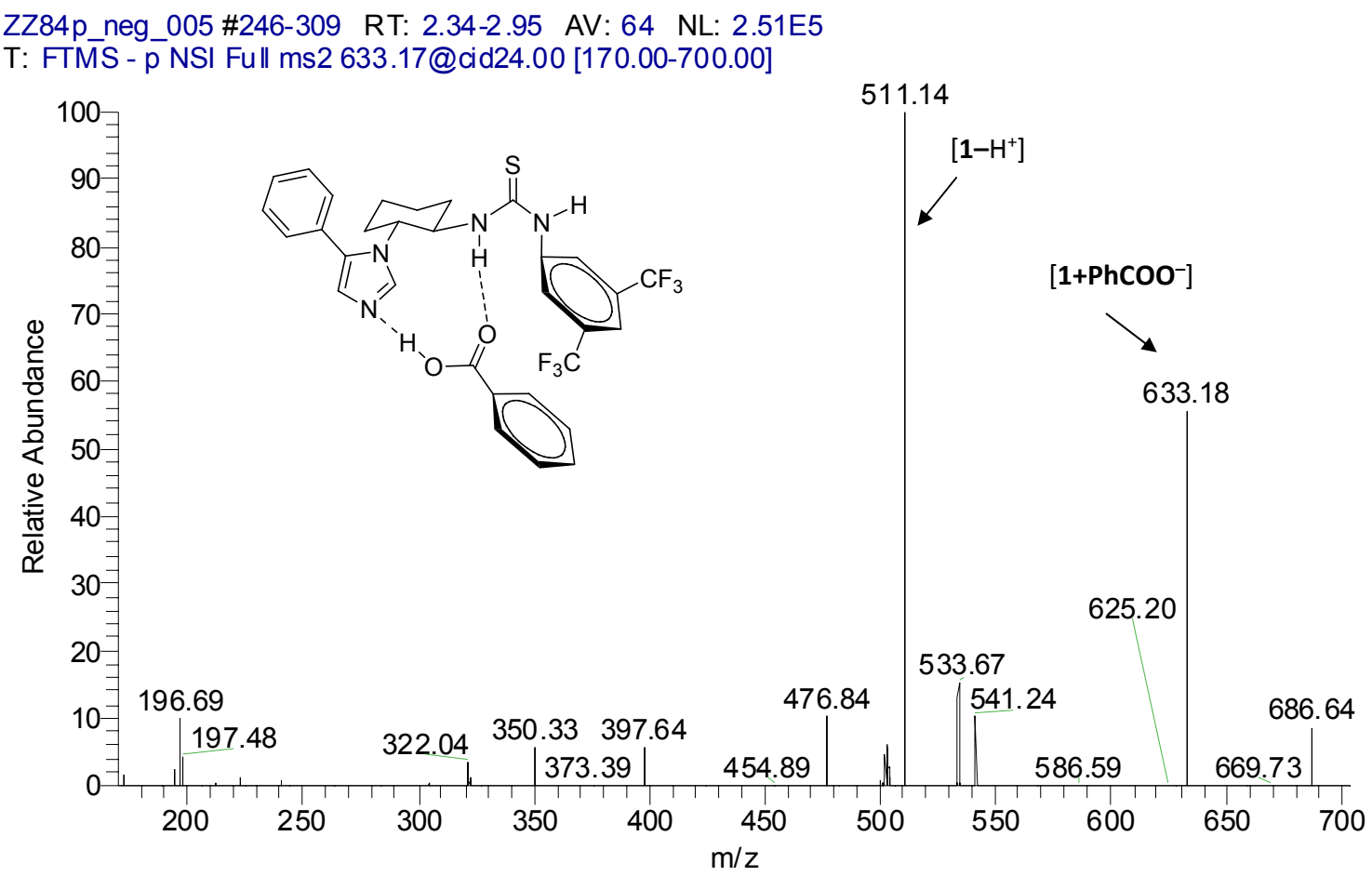
- "Free" catalyst in toluene



ESI/MS, positive mode; catalyst in toluene.

Mechanistic Insights – ESI/MS

- Binary complex of catalyst and benzoic acid in toluene

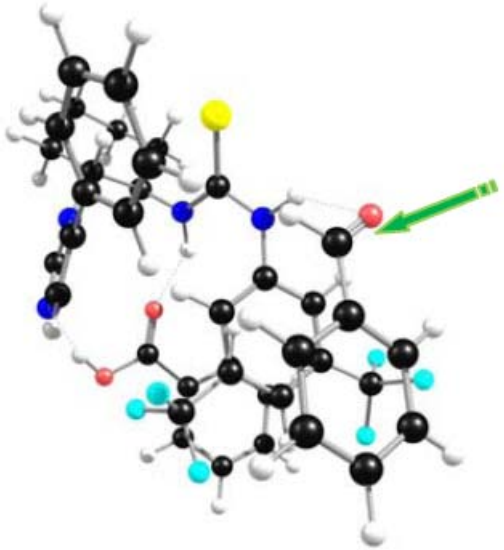


ESI/MS, positive mode; catalyst in toluene.

Mechanistic Insights – Computational Studies

- Ternary complex of bifunctional catalyst and benzoic acid
- ⇢ Nucleophilic attack of TMSCN

ΔH_0 = 0.1 (0.6), ΔG_{298}= 2.1 (1.8)
D_0 = 35.2 (24.3), D_{298}= 5.1 (–7.8)
NH1·· O1 d = 1.953 Å (2.104 Å)
NH2···C=O d = 2.315 Å (2.396 Å)
$N_{imidazole}$···HO2 d = 1.794 Å (1.812 Å)



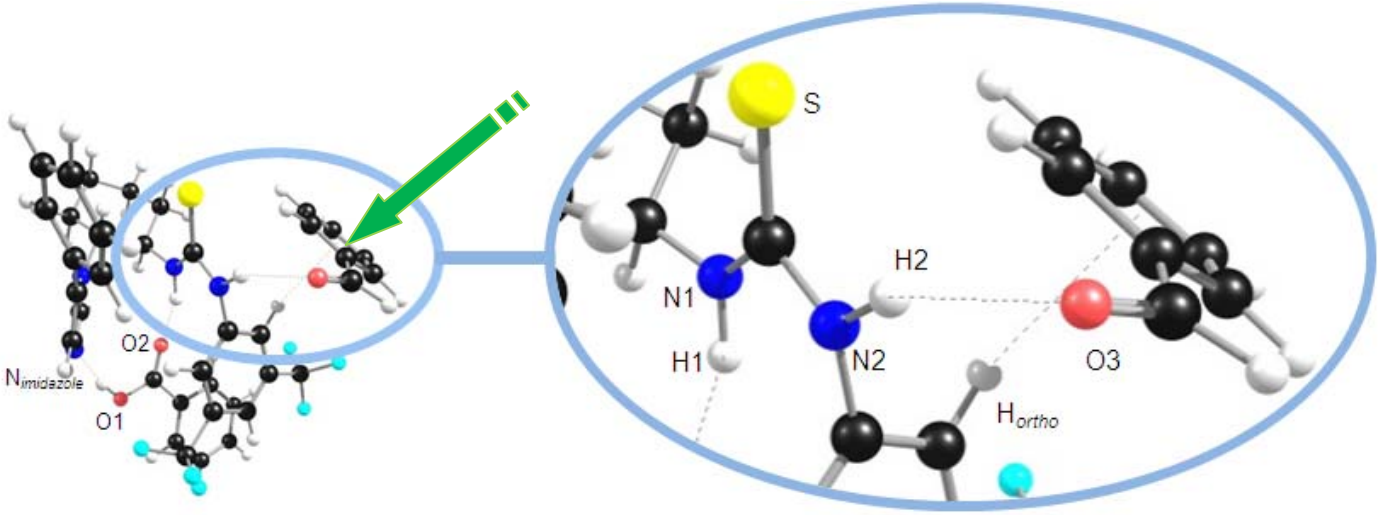
ΔH_0 = –2.1 (5.4), ΔG_{298}= 2.0 (6.0)
D_0 = 37.3 (19.5), D_{298}= 5.2 (–12.0)
NH1·· O1 d = 1.954 Å (2.067 Å)
NH2···O=C d = 2.128 Å (2.172 Å)
N-$H_{imidazole}$ d = 1.812 Å (1.071 Å)
$NH_{imidazole}$···O2 d = 0.997 Å (1.591 Å)

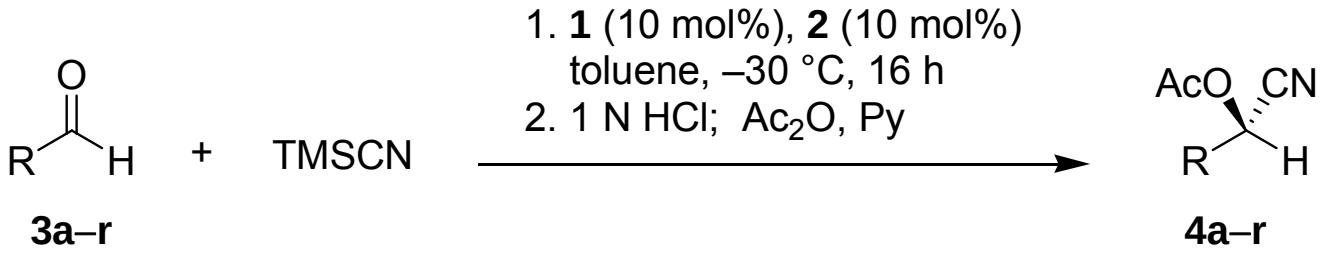
ΔH_0 = 0 (0), ΔG_{298}= 0 (0)
D_0 = 35.2 (25), D_{298}= 7.2 (–6.0)
NH1·· O1 d = 2.044 Å (2.420 Å)
NH2···O=C d = 2.080 Å (2.167 Å)
$N_{imidazole}$···HO2 d = 1.708 Å (1.743Å)

DFT computations (M06/6-31G(d,p)) in the gas phase and solvent model SCRF(benzene). All data in kcal mol^{-1}

Mechanistic Insights – Computational Studies

- *E*,*Z*-orientation of the NH-bonds
- *Re*-facial nucleophilic attack by TMSCN





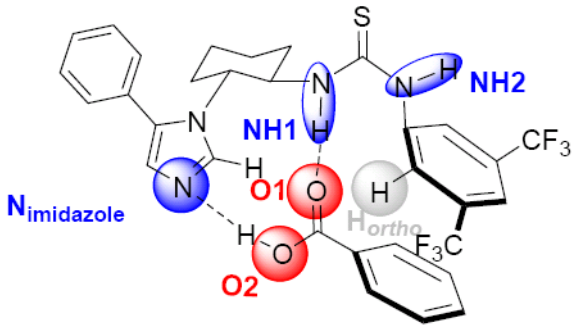
3a–r **4a–r**

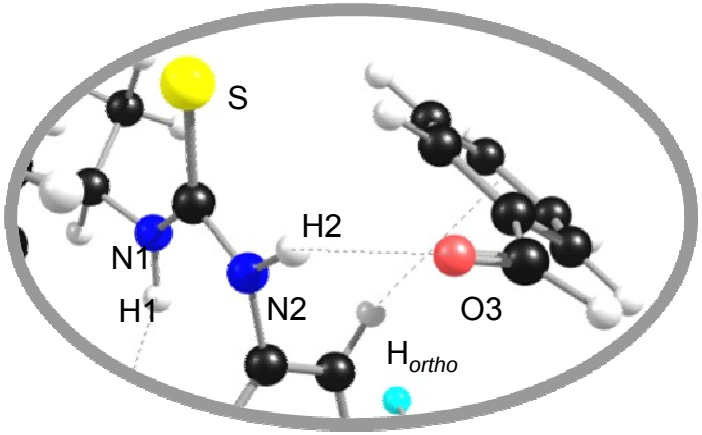
- High enantioselctivities for aromatic aldehydes and low enantioselctivities for aliphatic aldehydes

Distances: NH1···O1 d = 2.044 Å (2.420 Å), NH2···O=C d = 2.080 Å (2.167 Å), $N_{imidazole}$···H-O2 d = 1.708 Å (1.743 Å), NH2···Phenyl-Ring = 2.626 Å (2.585 Å)

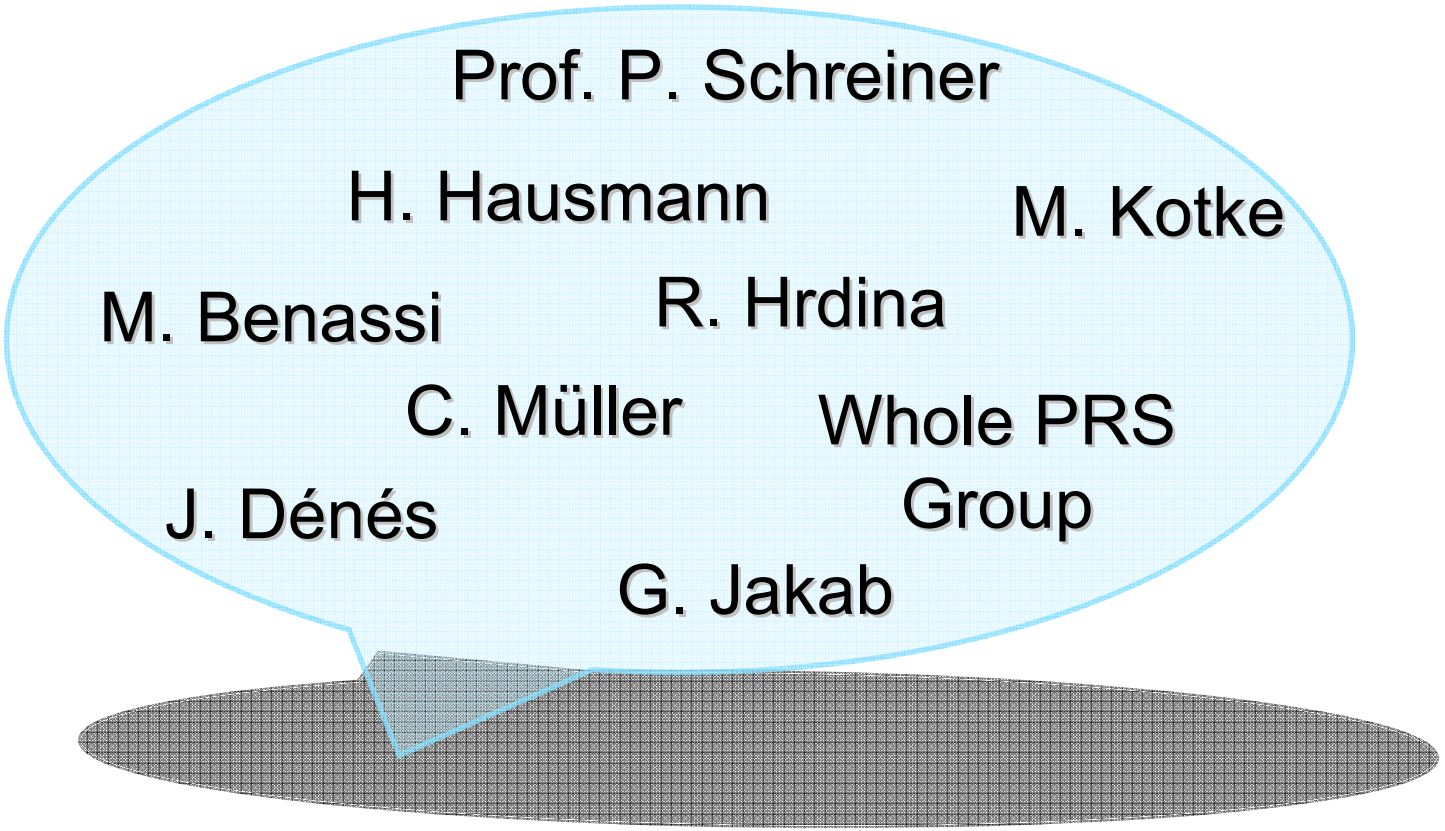
Summary

- Fixation of conformationally flexible catalyst through benzoic acid is critical for the enantioselective cyanosilylation
- Binary complex through hydrogen-bonding of catalyst to benzoic acid underlined by NOE-effect, DOSY, DFT and Nano-ESI/MS
- Ternary complex through hydrogen-bonding of catalyst to benzoic acid as well as to benzaldehyde
- Ternary complex shows an additional T-shaped π-π-interaction of the acidified *ortho*-proton to the phenyl ring of the benzaldehyde
- *Re*-facial nucleophilic attack by TMSCN





Acknowledgement



Thank you for your attention!

600 MHz ^{1}H NMR, Catalyst and 2,6-dimethylbenzoic acid (1:1 at 0.01 mmol) in [d_6]-benzene