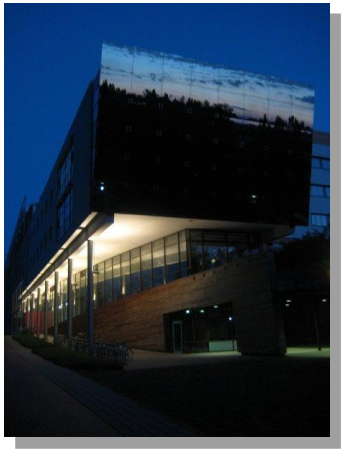
# (Thio)Urea Organocatalyst Equilibrium Acidities in DMSO

A long story short

**Gießen**
**AG Seminar**

03.08.2012

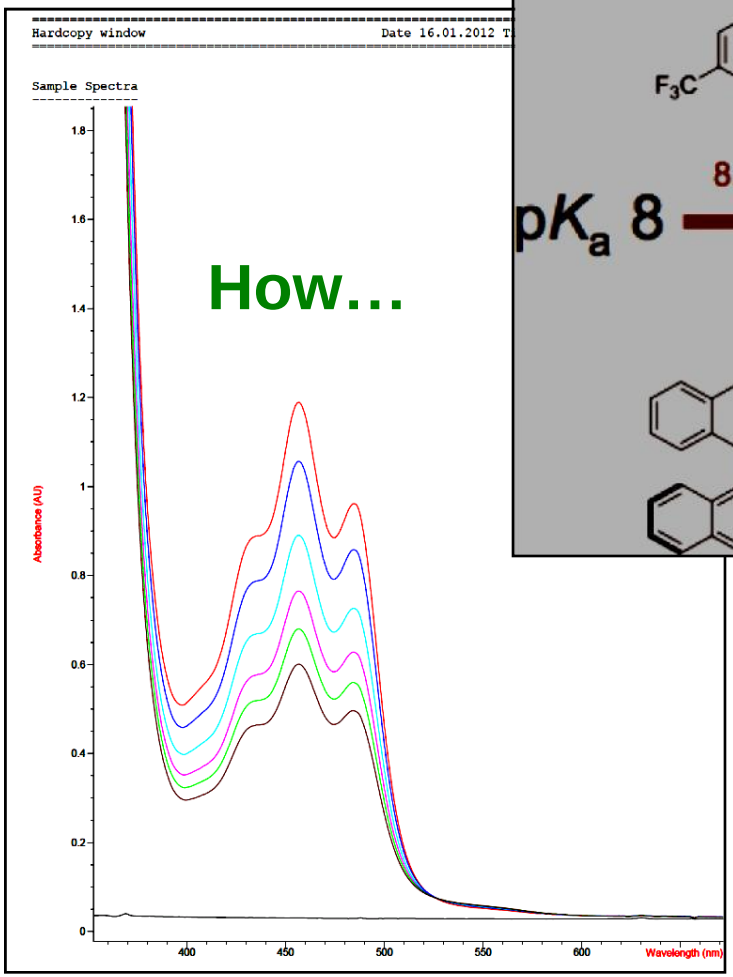



**Gergely Jakab**

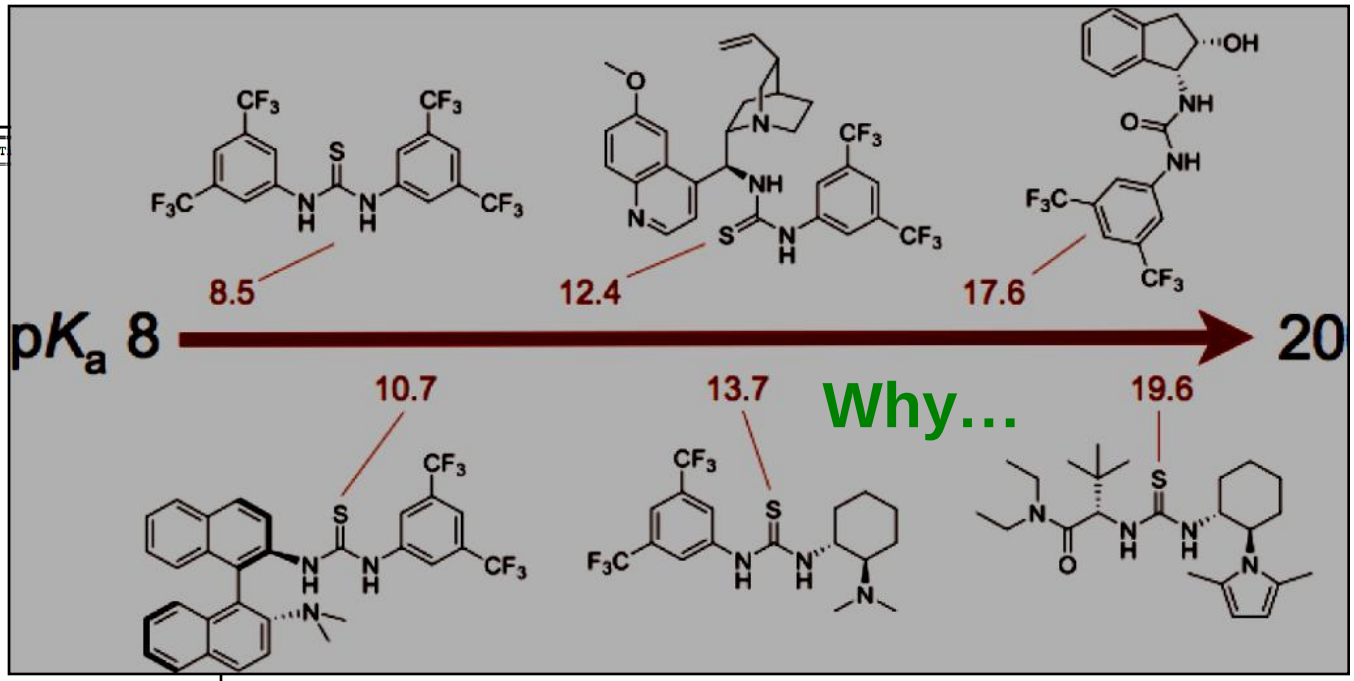
*Institut für Organische Chemie*
*Justus-Liebig-Universität*
*35435 Gießen, Germany*

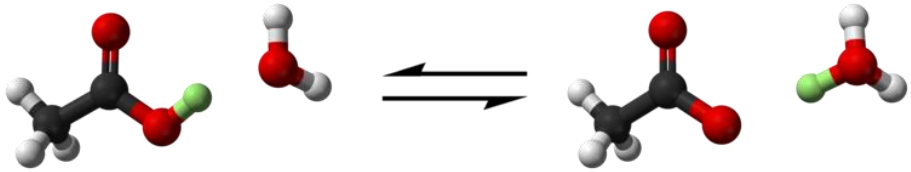
# Introduction

… to determine?




How…

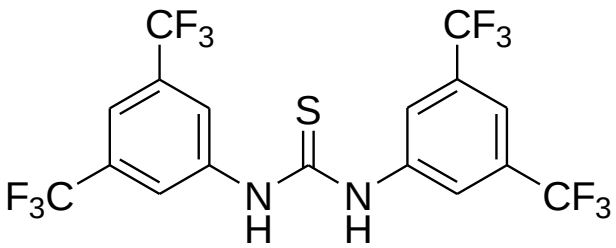


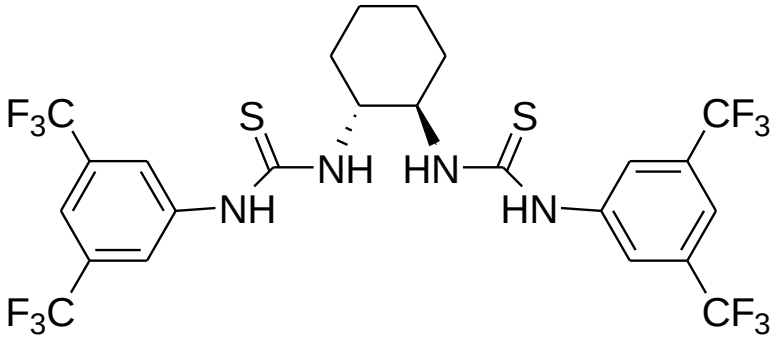



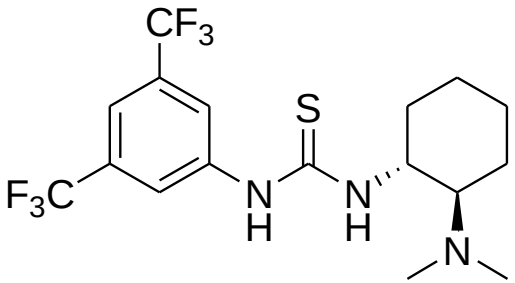
What…

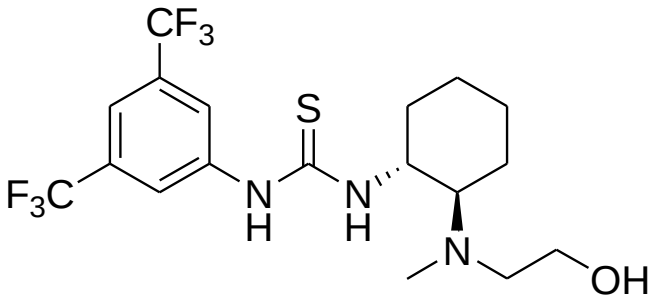
# Thiourea organocatalysts

Overview





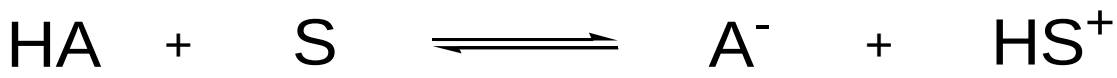





P. R. Schreiner, A. Wittkopp *Org. Lett.* **2002,** *4*, 217.
T. Okino, Y. Hoashi, Y. Takemoto *J. Am. Chem. Soc.* **2003**, *125*, 12672.
Y. Sohtome, A. Tanatani, Y. Hashimoto, K. Nagasawa *Tetrahedron Lett.* **2004**, *45*, 5589.
Y. Yamaoka, H. Miyabe, Y. Takemoto *J. Am. Chem. Soc.* **2007**, *129*, 6686.

# Acidic dissociation

Definitions




$$K = \frac{a_{A^-} \cdot a_{HS^+}}{a_{HA} \cdot a_S} = \frac{[A^-] \cdot [HS^+]}{[HA] \cdot [S]} \cdot \frac{\gamma_{A^-} \cdot \gamma_{HS^+}}{\gamma_{HA} \cdot \gamma_S}$$

$$\frac{d \ln K}{dT} = \frac{\Delta H^0}{RT^2}$$

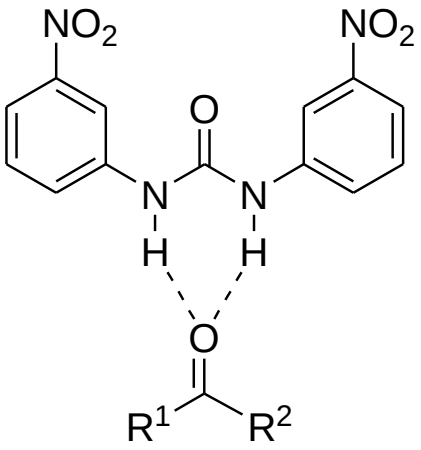
$$K_a = \frac{[A^-] \cdot [H^+]}{[HA]}$$

$$pK_a = -\log K_a$$

- **Solvent effect**
- **Temperature**
- **Ionic strength**

# What is the connection?

H-bond donor aptitude



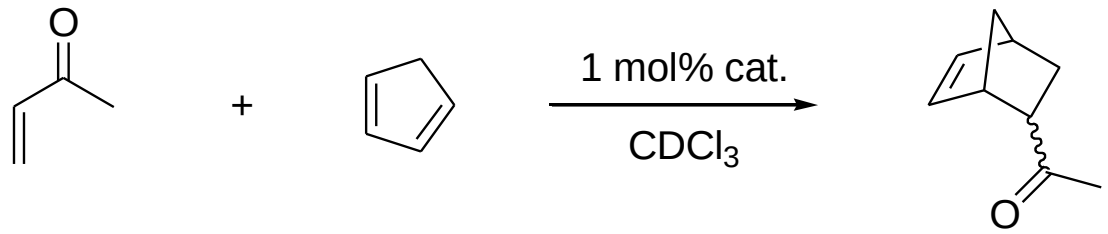

**X-ray and IR evidence**

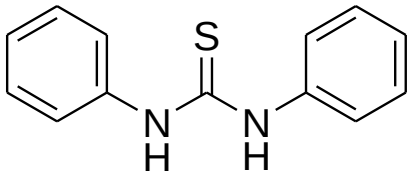
**EWGs are crucial**

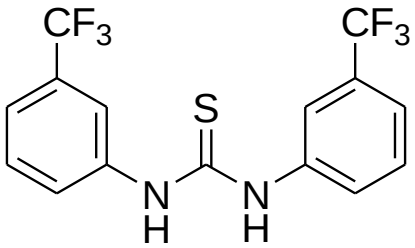
M. C. Etter, Z. Urbanczyk-Lipkowska, M. Zia-Ebrahimi, T. W. Panunto *J. Am. Chem. Soc.* **1990,** *112*, 8415.

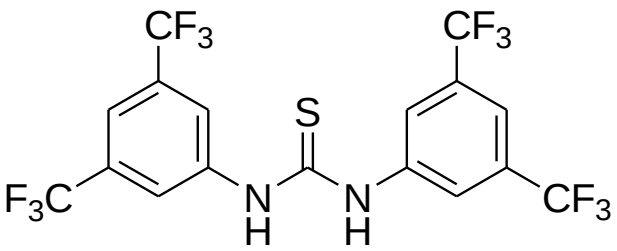
# What is the connection?

H-bond donor aptitude




$k_{rel}$ **1.4** **2.5** **4.8**

A. Wittkopp, P. R. Schreiner *Chem. Eur. J.* **2003,** *9*, 407.

# Acidity scales

Pros and cons

## $H_2O$

- **Buffer solutions**
- **Drug molecules**
- **Stabilizes anions and cations**

- **Effective p$K_a$ range of 2–12 (leveling)**
- **Poor solubility of org. compounds**
- **Side reactions**

## Organic solvents

- **Extended p$K_a$ range**
- **Better solubility of org. compounds**
- **More inert media**

- **Decreased or no H-bonding**
- **Ion pairing**
- **Self association**

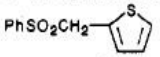
# Acidity in DMSO

The Bordwell scale

**DMSO**

- excellent solvent
- no anion stabilization via H-bonds
- no ion pair formation
- no self association
- p$K_a$ range down to 35
- ~1200 known p$K_a$ values

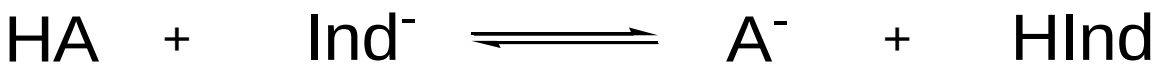
**Table II** (Continued)

| acid | p$K_a$[a] | acid | p$K_a$[a] |
|---|---|---|---|
| oxindole | 18.2[g] | $F_3CSO_2CHMe_2$ | 21.8 |
| $(EtO)_2P(O)NHPh$ | 18.3 | 2-methylindene | 21.8 |
| $p$-$CH_3C_6H_4SO_2CH_2N{=}C$ | 18.4 | $CH_3CONHNH_2$ | 21.8 |
| $CH_3C(=S)NH_2$ | 18.45 | $PhCH_2CN$ | 21.9 |
| | 18.5 | 9-cyano-9,10-dihydrophenanthrene | 21.9 |
| | 18.5[g] | nicotinamide | 22.0 |
| | 18.6 | $CH_3COCH_2SO_2Ph$ | 22.1 |
| | 18.6 | $PhC{\equiv}CCH_2SO_2Ph$ | 22.1 |
| m ion | 18.6 | 4,5-methylenephenanthrene | 22.2 |
| | 18.7 | 2-thiophenecarboxamide | 22.3 |
| | 18.7 | $PhSO_2CHPh_2$ | 22.3 |
| | 18.75 | 2-((phenylsulfonyl)methyl)furan | 22.3 |
| | 18.9 | 9-methylfluorene | 22.3 |
| | 18.9 |  | 22.35 |
| | 19.0 | | |
| | 19.0 | | |
| | 19.1 |  | 22.4 |
| | 19.3 | | |
| | 19.4 | $CH_2{=}CHCH_2SO_2Ph$ | 22.5 |
| | 19.45 | 3-methylindene | 22.5 |
| | 19.45 | $Ph_3PCH_3^+$ | 22.5 |
| | | 2-furancarboxamide | 22.55 |
| | | fluorene | 22.6 |
| | 19.5 | $PhCH_2CO_2Et$ | 22.6 |
| $(PhNH)_2C{=}O$ | 19.55 | phenothiazine | 22.7 |
| $NH_2C(=NH)NHCN$ | 19.6 | $(PhS)_3CH$ | 22.8 |
| pyrazole | 19.8 | pyrrole | 23.0 |
| carbazole | 19.9 | PhCH(Me)CN | 23.0 |
| $PhCH_2SO_3Ph$ | 19.9 | $PhOCH_2CONH_2$ | 23.0 |
| $PhCH_2COCH_3$ | 19.9 | 1-indanone | 23.0[i] |
| 10-cyano-9-methylanthracene | 20.0 | | 29.6[i] (p$K_a^{II}$) |
| indene | 20.1 | $PhSCH_2CONH_2$ | 23.0 |
| $Ph_2C{=}NOH$ | 20.1 | $PhSeCH_2CONH_2$ | 23.1 |
| $PhCH{=}CHCH_2SO_2Ph$ | 20.2 | 2,3,4-trimethylimidazolium ion | 23.2 |
| $PhCOCHF_2$ | 20.2 | 4-aminopyrimidine | 23.3[j] |

W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, N. R. Vanier *J.Am.Chem.Soc.* **1975**, 97, 7006.
F. G. Bordwell *Acc.Chem.Res.* **1988**, *21*, 456.

# Bordwell's method

Principle of measurement




$$K_{eqv} = \frac{[A^-]\cdot[HInd]}{[HA]\cdot[Ind^-]} = \frac{[A^-]\cdot[H^+]}{[HA]}\cdot\frac{[HInd]}{[Ind^-]\cdot[H^+]} = \frac{K_a}{K_{Ind}}$$

$$pK_a = pK_{Ind} - \log K_{eqv}$$

**Known**

- $pK_{Ind}$
- $c^0_{Ind}$
- $c^0_{HA}$

**Determined**

- $A_\lambda$
- $m_{Ind\ solution}$
- $m_{HA\ solution}$

**Calculated**

- [Ind$^-$]
- [HInd]
- [HA]
- [A$^-$]

W. S. Matthews, J. E. Bares, J. E. Bartmess, F. G. Bordwell, F. J. Cornforth, G. E. Drucker, Z. Margolin, R. J. McCallum, G. J. McCollum, N. R. Vanier *J.Am.Chem.Soc.* **1975**, 97, 7006.

# Bordwell's method

Prior to measurement

**DMSO**

$NaNH_2$ + Triphenylmethane

Water content: 7–25 ppm

**K-dimsyl solution**

KH + dry DMSO

Protected from moisture, oxygen and light

Base concentration: 0.2–0.3 mmol/g

**Stock solutions**

Indicator or HA + dry DMSO,

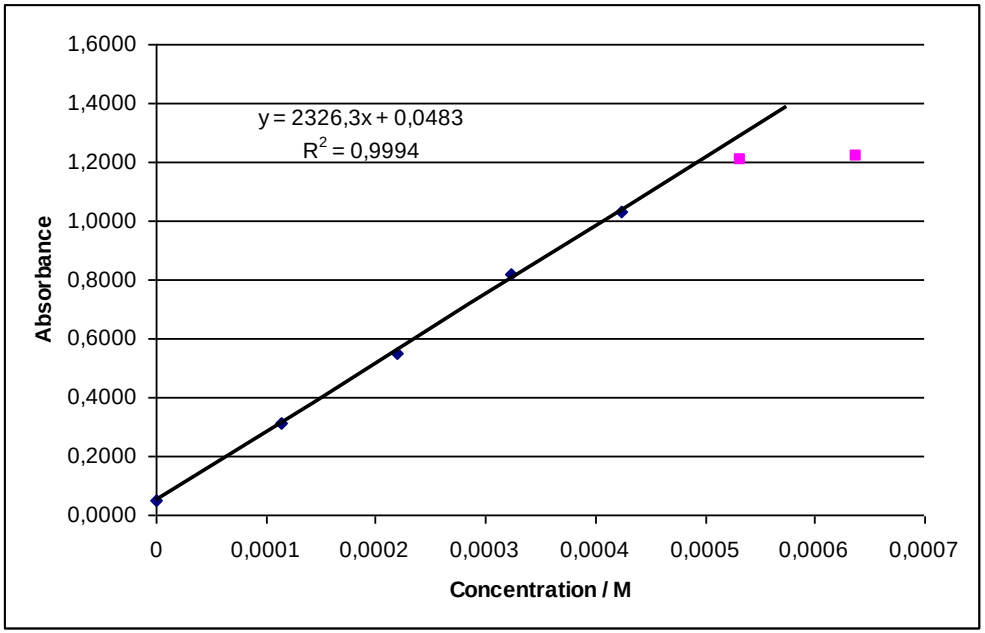
purged with and kept under Ar

# Bordwell's method

Spectrophotometric titration

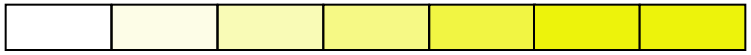

Indicator solution

0.0205 mmol/g




Reaction vessel

- DMSO (3.349 g)
- K-dimsyl solution (11 µl)



$$[\mathrm{Ind}^-] = \frac{A}{\varepsilon \cdot l}$$

$$[\mathrm{HInd}] = \frac{c^0_{\mathrm{Ind}} \cdot m - [\mathrm{Ind}^-] \cdot V}{V}$$

# Bordwell's method

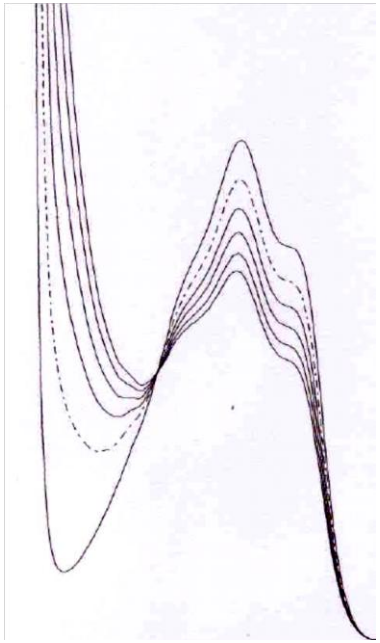
Spectrophotometric titration


Reaction vessel

- DMSO (3.450 g)
- $Ind^{-}$ ($5.02 \cdot 10^{-4}$ M)
- HInd ($1.37 \cdot 10^{-4}$ M)

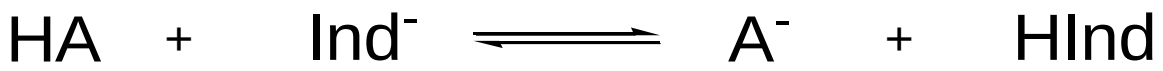
Takemoto's catalyst solution

0.0481 mmol/g



# Bordwell's method

Evaluation




$$[\mathrm{Ind}^-] = \frac{A}{\varepsilon \cdot l}$$

$$[\mathrm{HInd}] = \frac{c^0_{\mathrm{Ind}} \cdot m - [\mathrm{Ind}^-] \cdot V}{V}$$

$$\Delta[\mathrm{HInd}] = [\mathrm{A}^-]$$

$$c^0_{\mathrm{HA}} \cdot m = n_{\mathrm{HA}} + n_{\mathrm{A}^-}$$

| $K_{eqv}$ | 0.0470 | 0.0467 | 0.0468 | 0.0475 | 0.0484 |
|---|---|---|---|---|---|
| p$K_a$ | 13.628 | 13.631 | 13.629 | 13.623 | 13.615 |

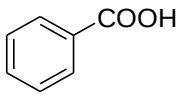
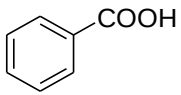
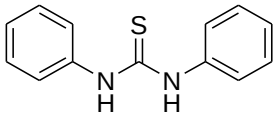
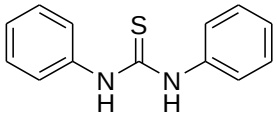
$$K_{\mathrm{eqv}} = \frac{n_{\mathrm{A}^-} \cdot [\mathrm{HInd}]}{n_{\mathrm{HA}} \cdot [\mathrm{Ind}^-]}$$

$$\mathrm{p}K_{\mathrm{a}} = \mathrm{p}K_{\mathrm{Ind}} - \log K_{\mathrm{eqv}}$$

**13.625 ± 0.006**

# Validation

Testing method and manipulations

| Compound | Indicator (p$K_a$) | p$K_a$ Value (lit.) | St. dev. |
|---|---|---|---|
|  | PNP (10.8) | **11.107** (**11.0**) | 0.007 |
|  | MeOOC-FH (10.35) | **11.01** (**11.0**) | 0.02 |
|  | $EtSO_2$-FH (12.30) | **13.306** (**13.4**) | 0.005 |
|  | 2-Br-9-PhS-FH (13.2) | **13.406** (**13.4**) | 0.009 |

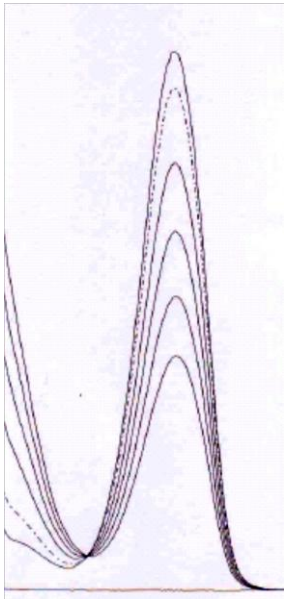
G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner *Org.Lett.* **2012**, *14*, 1724.

# Indicators

What makes them suitable?

**Appropriate indicator**

- obeys Beer's law
- no decomposition or side reaction
- $|pK_{Ind} - pK_a| < 2$



**Indicator is not acidic enough**

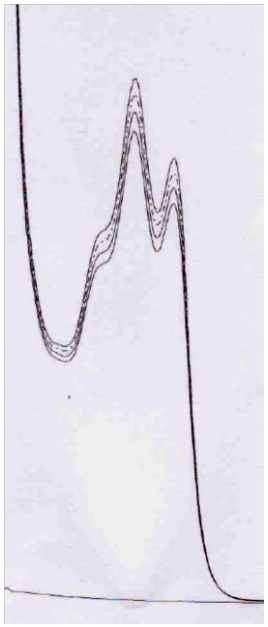
| $pK_a$ | 12.328 | 12.074 | 11.894 | 11.734 | 11.586 |
|---|---|---|---|---|---|

# Indicators

What makes them suitable?

**Appropriate indicator**

- obeys Beer's law
- no decomposition or side reaction
- $|pK_{Ind} - pK_a| < 2$



**Indicator is too acidic**

| | |
|---|---|
| $pK_a$ | n.d. |

# Indicators

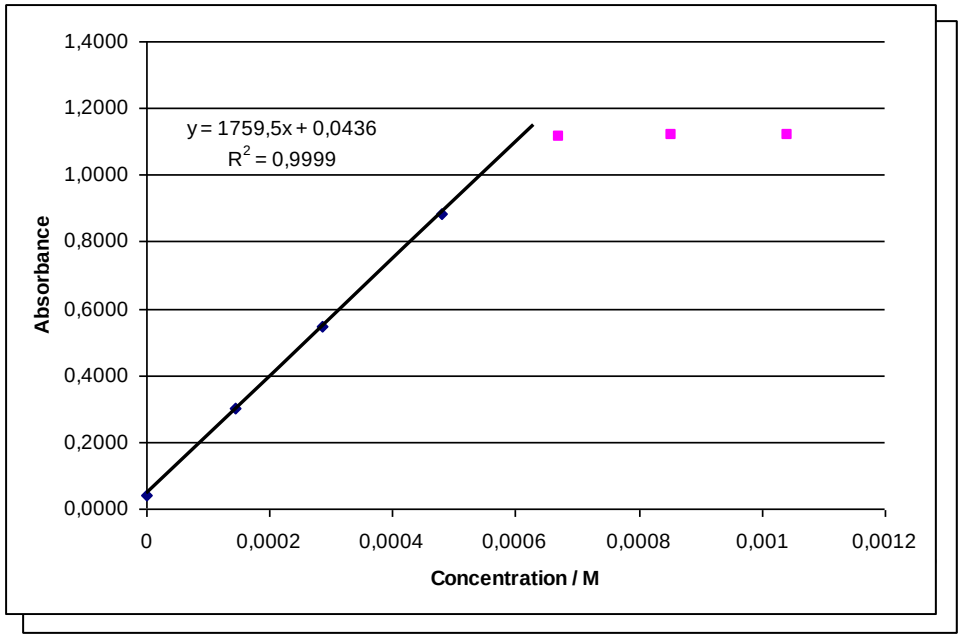
What makes them suitable?

**Appropriate indicator**

- obeys Beer's law
- no decomposition or side reaction
- $|pK_{Ind} - pK_a| < 2$

**Indicator anion is decomposing**

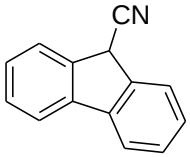
**12.1 ± 0.1** **12.57 ± 0.04**



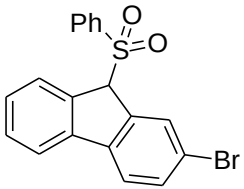

| $pK_a$ | 11.893 | 12.064 | 12.118 | 12.146 | 12.143 |
|---|---|---|---|---|---|

# Indicators

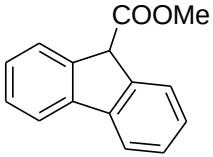
Used in our study



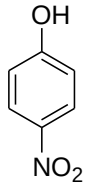

8.3



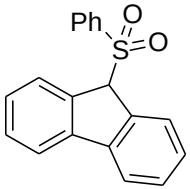

9.6



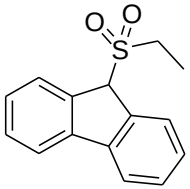

10.35



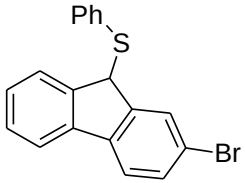

10.8



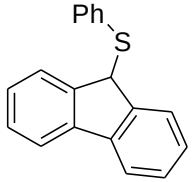

11.55



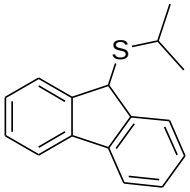

12.30



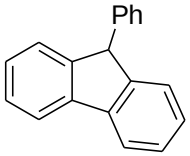

13.2



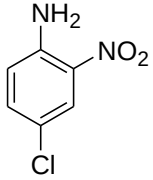

15.4




16.9




17.9




18.9

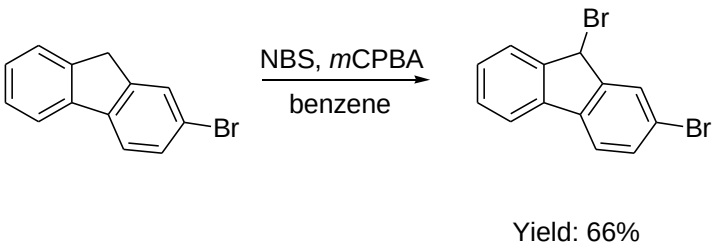
**7** ⟷ **20**

# Indicators

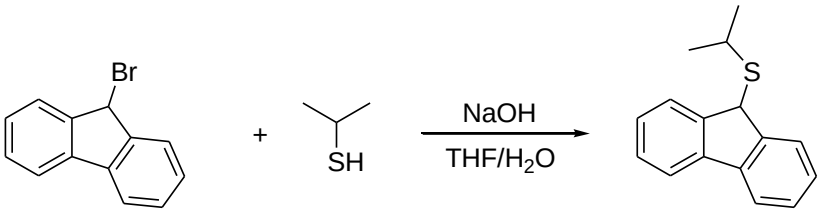
Syntheses

## Starting materials

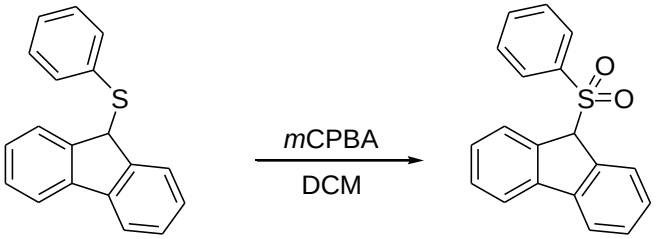
- 9-bromofluorene
- 2-bromofluorene
- 9-carboxyfluorene
- fluorenone
- alkyl-, arylthiols




Yield: 66%




Yield: 45%

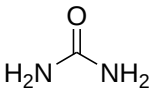



Yield: 47%

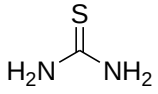
G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner *Org.Lett.* **2012**, *14*, 1724.

# Increasing (thio)urea acidity

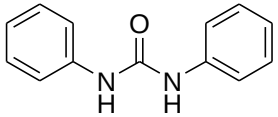
The effect of $CF_3$ groups



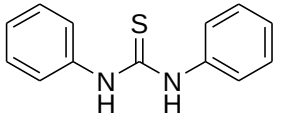

**26.9 ± 0.1**



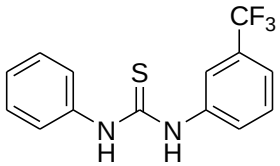

**21.1 ± 0.1**



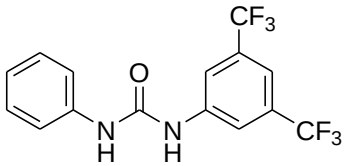

**18.7 ± 0.1**



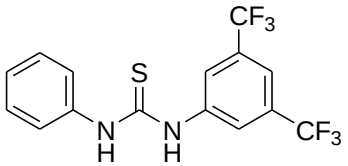

**13.4 ± 0.1**



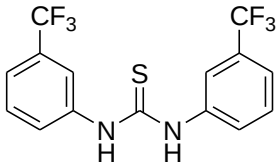

**12.1 ± 0.1**



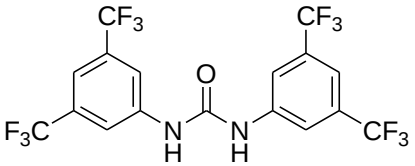

**16.1 ± 0.1**



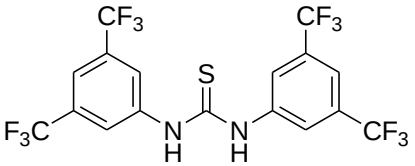

**10.7 ± 0.1**
**(10.8 ± 0.1)**



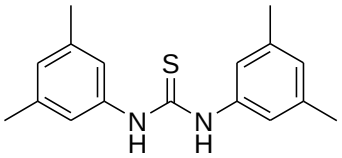

**10.9 ± 0.1**




**Est. 13.8 ± 0.2**




**8.5 ± 0.1**
**(8.4 ± 0.1)**




**13.9 ± 0.1**

**S → O : ~ 5.5**

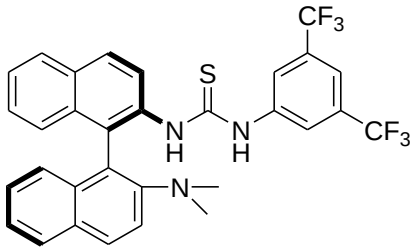
**Aryl : ~ 4**

**H → $CF_3$ : ~ 1.3**

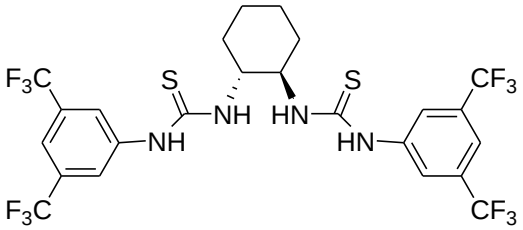

F. G. Bordwell *Acc.Chem.Res.* **1988**, *21*, 456.
X. Li, H. Deng, S. Luo, J.-P. Cheng *Eur.J.Org.Chem.* **2008**, 4350.
G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner *Org.Lett.* **2012**, *14*, 1724.

# (Thio)urea organocatalysts

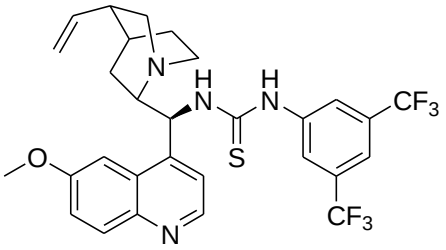
Part 1



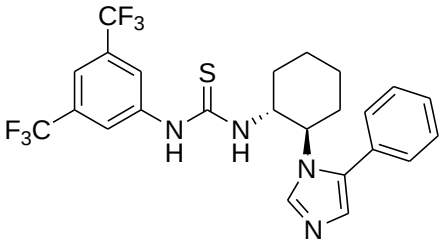
**10.72 ± 0.02**



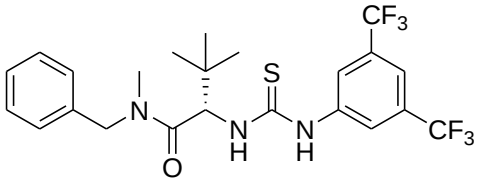
**11.98 ± 0.09**



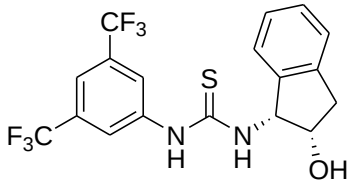
**12.39 ± 0.07**
**(13.2 ± 0.1)**



**12.54 ± 0.07**



**12.57 ± 0.04**

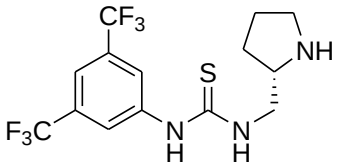


**12.98 ± 0.07**

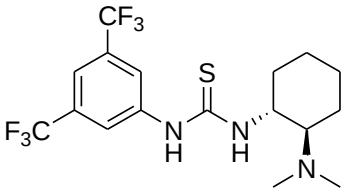
X. Li, H. Deng, B. Zhang, J. Y. Li, L. Zhang, S. Z. Luo, J. P. Cheng *Chem-Eur. J.* **2010**, *16*, 450.
G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner *Org.Lett.* **2012**, *14*, 1724.

# (Thio)urea organocatalysts

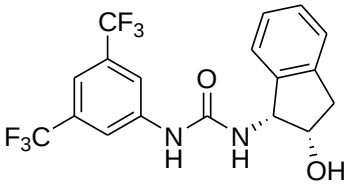
Part 2



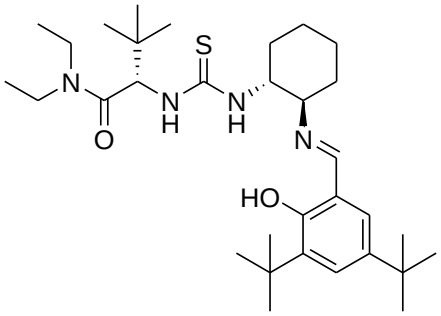
**13.38 ± 0.03**



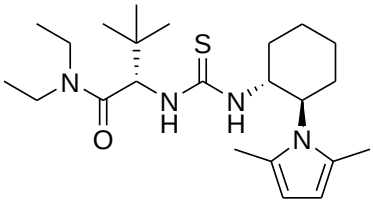
**13.65 ± 0.02**
**(13.8 ± 0.1)**



**17.63 ± 0.07**



**18.3 ± 0.2**

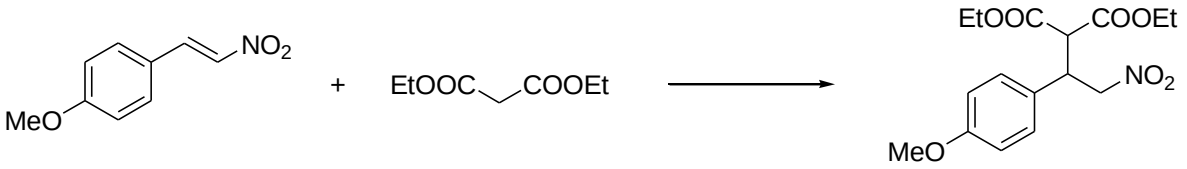


**19.60 ± 0.01**

X. Li, H. Deng, B. Zhang, J. Y. Li, L. Zhang, S. Z. Luo, J. P. Cheng *Chem-Eur. J.* **2010**, *16*, 450.
G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner *Org.Lett.* **2012**, *14*, 1724.

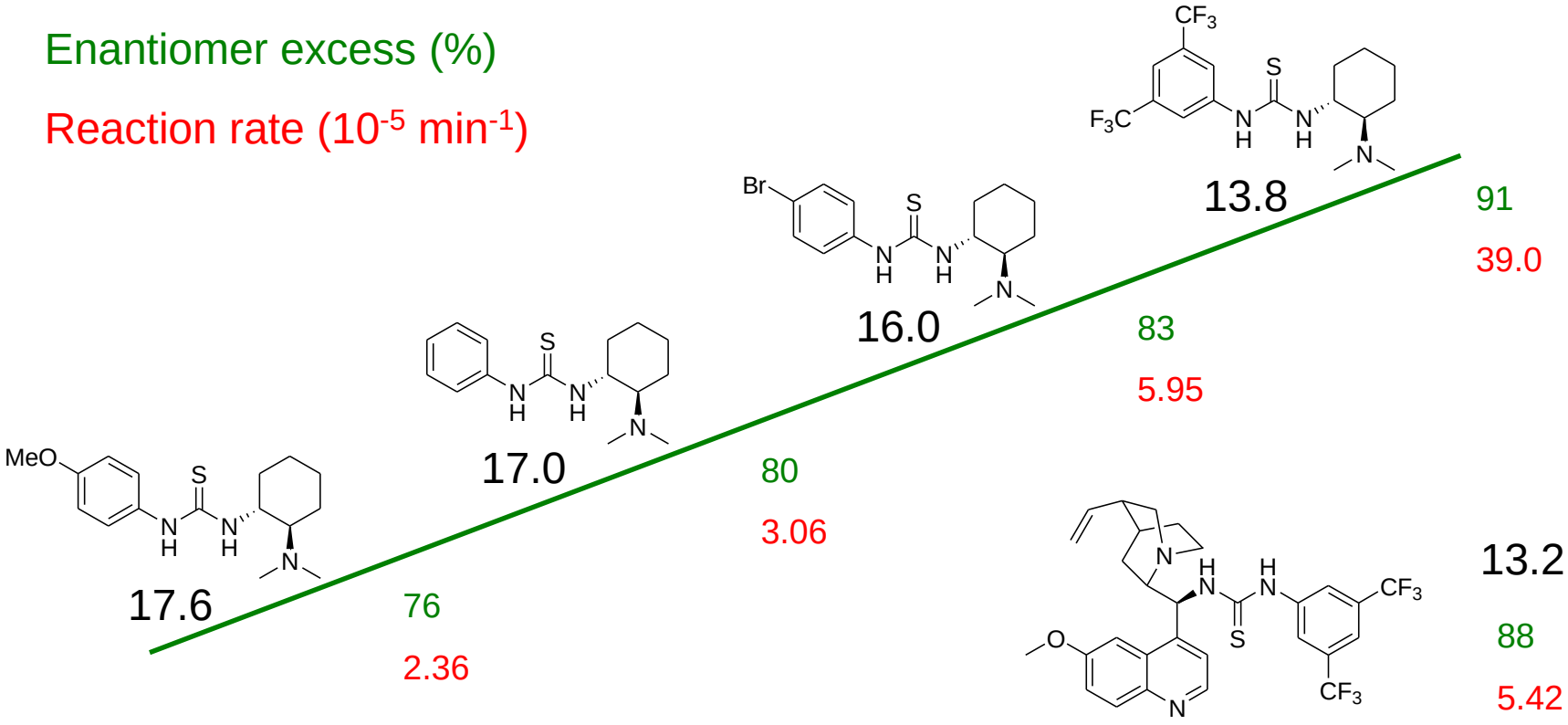
# Acidity and activity

Strong correspondence




Enantiomer excess (%)

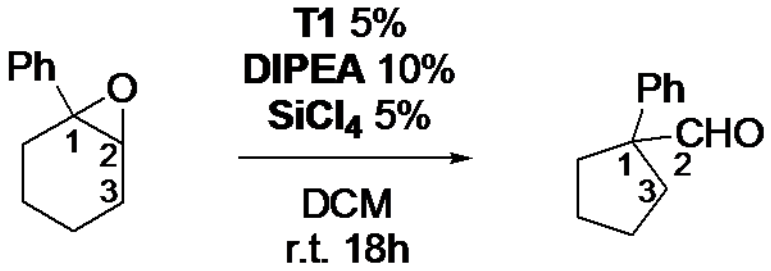
Reaction rate ($10^{-5}$ $min^{-1}$)

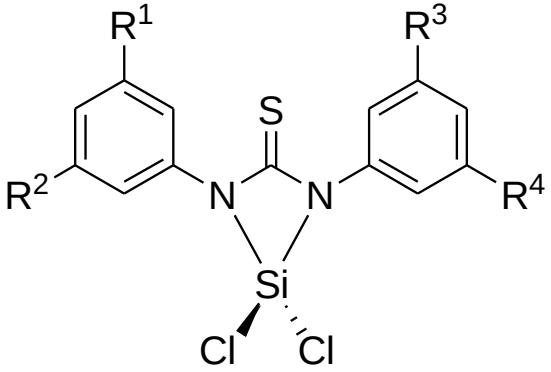



X. Li, H. Deng, B. Zhang, J. Y. Li, L. Zhang, S. Z. Luo, J. P. Cheng *Chem-Eur. J.* **2010**, *16*, 450.

# Acidity and activity

Not only in H-bond mediated reactions



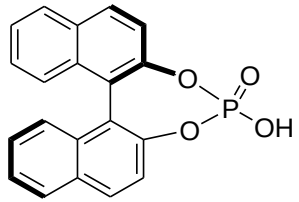




| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Conversion | p$K_a$ |
|---|---|---|---|---|---|---|
| **1** | H | H | H | H | 11% | 13.4 |
| **2** | $CF_3$ | H | H | H | 26% | 12.1 |
| **3** | $CF_3$ | $CF_3$ | H | H | 71% | 10.7 |
| **4** | $CF_3$ | H | $CF_3$ | H | 75% | 10.9 |
| **5** | $CF_3$ | $CF_3$ | $CF_3$ | H | 99+% | nd |
| **6** | $CF_3$ | $CF_3$ | $CF_3$ | $CF_3$ | 99+% | 8.5 |

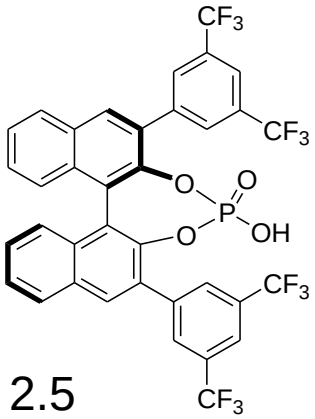

R. Hrdina, C. E. Müller, R. C. Wende, K. M. Lippert, M. Benassi, B. Spengler, P. R. Schreiner *J.Am.Chem.Soc.* **2011**, *133*, 7624.
G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert, P. R. Schreiner *Org.Lett.* **2012**, *14*, 1724.

# Acidity and activity

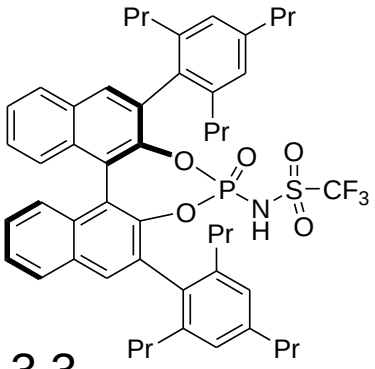
Loose connection



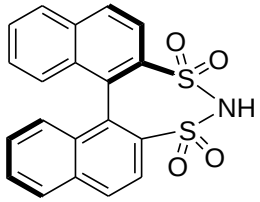
3.3



2.5



3.3



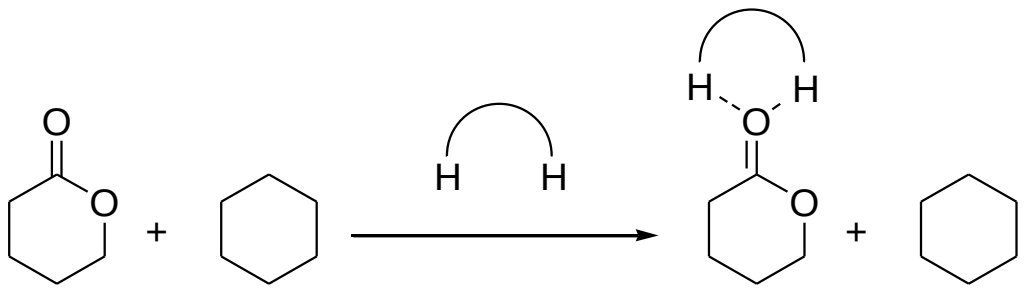
1.8

„*We therefore conclude that for the many catalytic applications of these acids, their relative p$K_a$s may not be the (only) key factor determining catalytic performance.*“

P. Christ, A. G. Lindsay, S. S. Vormittag, J. M. Neudörfl, A. Berkessel, A. C. O'Donoghue *Chem-Eur. J.* **2011**, *17*, 8524.

# Recently...

The Lippert-Rosenberg project




**DOSY-NMR measurements**

0.01 mmol thiourea

0.01 mmol cyclohexane

0.01 mmol δ-valerolactone

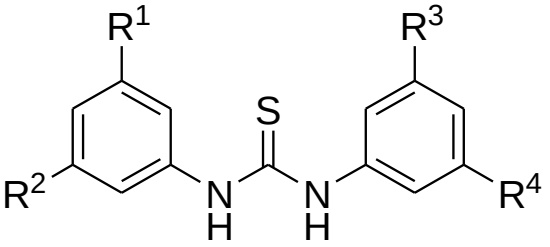
0.75 mL [$d_8$]-toluene

**Hydrodynamic radii of cyclohexane practically unchanged!**

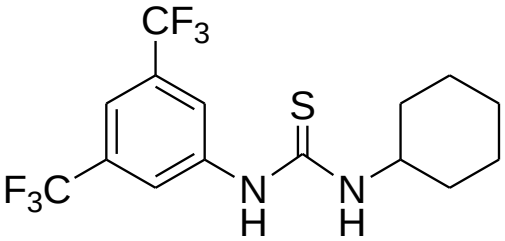
# Recently...

The Lippert-Rosenberg project

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | p$K_a$ | $\Delta R$(h) |
|---|---|---|---|---|---|---|
| **1** | Me | Me | Me | Me | 13.9 | 0.95 |
| **2** | $CF_3$ | H | H | H | 12.1 | 1.11 |
| **3** | $CF_3$ | H | $CF_3$ | H | 10.9 | 1.17 |
| **4** | $CF_3$ | $CF_3$ | H | H | 10.7 | 1.17 |
| **5** | $CF_3$ | $CF_3$ | $CF_3$ | H | nd | 1.36 |
| **6** | $CF_3$ | $CF_3$ | $CF_3$ | $CF_3$ | 8.5 | 1.55 |




**~13.7** **1.15**



# Summary

What we achieved

- Effect of $CF_3$ groups
- p$K_a$ Values of some organocatalysts
- Paper in *Org. Lett.*
- Catalyst library
- Excursion to physical chemistry

# Acknowledgement

Thank you!

**Peter R. Schreiner**

**Hans-Peter Reisenauer**

**Zhiguo Zhang  Carlo Tancon  Katharina M. Lippert**

**NMR and MS Department**

**Whole PRS Group**

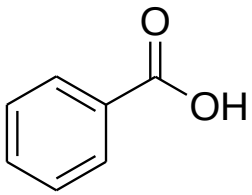
Thank you for your attention!

# Solvent effect on acidic strength

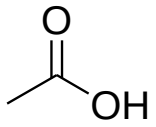
Examples

HCl

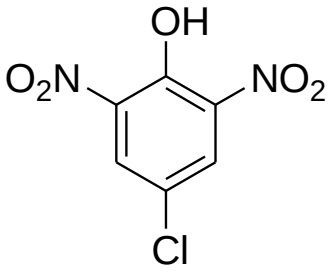
*-8.0* (1.8)



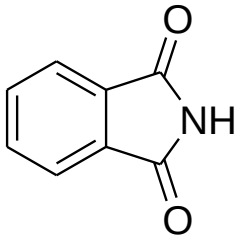

4.2 (11.0)



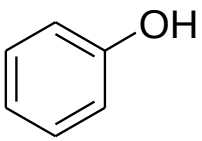

4.76 (12.3)



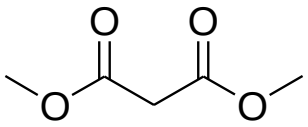

3.0 (3.6)




8.30 (nd)




9.95 (18.0)




13 (15.7)

**$H_2O$ (DMSO)**

C. McCallum, A. D. Pethybridge *Electrochim. Acta* **1975**, *20*, 815.
J. March *Advanced Org. Chem.*, 3rd Ed. **1985**.
F. G. Bordwell *Acc.Chem.Res.* **1988**, *21*, 456.