



Published in final edited form as:

Ehrhard, A., Jäger, S., Malm, C., Basaran, S., & Hunger, J. (2019). CF₃-groups critically enhance the binding of thiourea catalysts to ketones - a NMR and FT-IR study. *Journal of Molecular Liquids*, 269: 111829. doi:10.1016/j.molliq.2019.111829.

Link to formal publication: <https://doi.org/10.1016/j.molliq.2019.111829>

Supplemental Information

CF₃-groups critically enhance the binding of thiourea catalysts to ketones - a NMR and FT-IR study

Ehrhard, A., Jäger, S., Malm, C., Basaran, S., & Hunger, J.

1 **CF₃-groups Critically Enhance the Binding of Thiourea Catalysts to Ketones –**
2 **a NMR and FT-IR Study**

3
4 *Amelie Ehrhard, Sebastian Jäger, Christian Malm, Selim Basaran, Johannes Hunger**

5 Max-Planck Institute for Polymer Research, Ackermannweg 10, 55128 Mainz,
6 Germany

7 *email: hunger@mpip-mainz.mpg.de

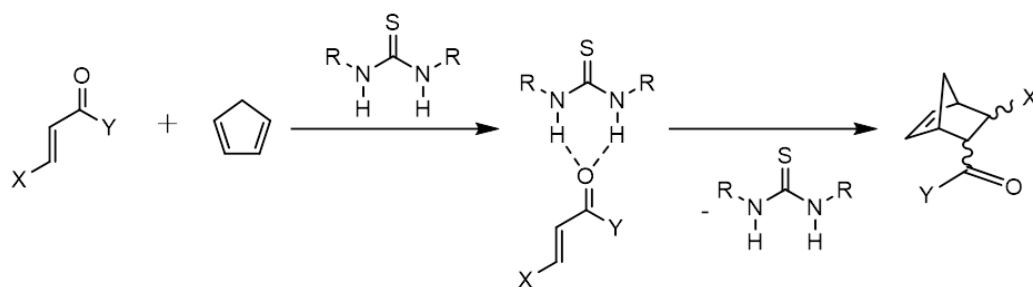
8
9 **Abstract**

10 Substituted phenylthioureas have been established as efficient organocatalysts and
11 substituents containing electron withdrawing CF₃ groups have been shown to enhance
12 catalytic efficiency. The effect of the CF₃ groups on binding of catalysts to substrates in
13 solution has however remained elusive. Here, we report on the effect of CF₃ substituted
14 diphenylthioureas on the association with the substrate 1,3-diphenyl-2-propenone in
15 solution by using a combination of nuclear magnetic resonance (NMR) and Fourier-
16 transform infrared (FT-IR) spectroscopy. We use the ensemble-averaged chemical shift
17 of the thiourea proton as function of substrate concentration to determine the association
18 constants between catalyst and substrate. To experimentally discriminate between free
19 and bound catalyst we use infrared absorption spectra, which show a red-shift of
20 thiourea's N-H stretching vibration upon association with the substrate. With both
21 methods, we find the association constant *K* to increase from ~1 L/mol to ~20 L/mol with
22 increasing number of CF₃ substituents. This enhanced binding can explain the
23 increased reaction rates observed for CF₃ substituted diphenylthiourea catalysts. For
24 the efficient catalyst containing four CF₃-groups (Schreiner's catalyst), the strongest
25 association is observed in toluene as a solvent, while the binding strength is somewhat
26 weaker in dichloromethane, and association to the substrate is not detectable in
27 acetonitrile. Our results thus demonstrate that even weak association between the
28 thiourea catalysts and the ketone can facilitate efficient catalytic conversion. However,
29 the association with the ketone substrates is very susceptible to competing interactions
30 with the solvent.

31
32 **I. Introduction**

33 Hydrogen-bonding donors like thioureas have been established as efficient organo-
34 catalysts.¹⁻¹⁰ In particular, the wide range of catalyzed reactions, including addition,
35 allylation, Strecker, Michael- and Nitro-Mannich reactions,¹¹ renders thioureas
36 promising catalysts, which are available at relatively low costs. In particular, substituted
37 diphenylthioureas, pioneered by Schreiner and co-workers, have been shown to provide
38 fast reaction rates and high stereoselectivity for e.g. Diels-Alder reactions (Scheme 1).¹

² Modified thioureas are since then frequently used as noncovalent organocatalysts.¹²⁻¹⁴



Scheme 1: Reaction scheme of the thiourea catalyzed Diels-Alder cycloaddition. The catalyst hydrogen-bonds to the ketone, which activates the ketone. The catalyst can enhance the reaction rate and the stereoselectivity, which is determined by the electron density of the reactants and the nature of reaction (thermic or photolytic).

Electron-withdrawing groups have been demonstrated to enhance reaction rates and yields in diphenylthiourea catalysis.² In particular, CF₃-groups have been reported to provide highest enhancements (as compared to F or Cl substituents)² and are, as such, frequently used substituents for other thiourea-based catalysts.¹²⁻¹⁴ The enhanced catalytic activity upon CF₃ substitution has been related to an increase in hydrogen-bond donor ability, i.e. a reduction of the pK_a values of thiourea's N-H groups.¹⁵ Indeed, nuclear magnetic resonance (NMR) and infrared (IR) spectroscopy experiments together with mass spectrometry and density functional theory calculations have shown that hydrogen-bonding between thiourea and ketones are the relevant interaction motif for catalysis.¹⁶ Remarkably, not only hydrogen-bond donation of the highly polar N-H group, but also of the ortho-proton of the phenyl group of phenylthiourea was suggested to contribute to the activation of the substrates.¹⁶ Despite the importance of hydrogen-bonding, other contributions including dual activation, secondary interactions, and steric effects have been suggested to affect catalytic activity.¹⁷

Since catalyst-substrate aggregates are the relevant reactive intermediates, which determine amongst others e.g. reaction rates, energetic barriers etc., the binding strength between these thiourea catalysts and the substrates is important for catalytic activity. In principle, an enhanced catalytic activity may originate from stronger binding (substrate activation) or by the formation of more catalyst-substrate complexes. Even though these two effects are not completely independent – stronger hydrogen-bonding results in enhanced complex formation – the formation of catalyst-substrate bonds depends on the solvation of the catalyst, the substrate, and the complexes. For instance, reaction rates have been – rather counterintuitively – shown to be enhanced in hydrogen-bonded water, which has been ascribed to 'hydrophobic hydration'.^{2, 18} Thus, to understand catalytic activity and to allow for a rational catalyst design, it is vital to understand solvation and study binding strength in solution.

73 Here, we report on the association^{19,20} of diphenylthioureas with 1,3-diphenyl-2-
74 propenone, relevant to Diels-Alder cycloaddition (Scheme 1), in solution. To study the
75 effect of electron withdrawing CF₃-groups, we study the association of diphenylthioureas
76 with zero, two, and four CF₃ substituents at the phenyl rings. We determine the rather
77 weak molecular association using the motionally averaged signals of the free and the
78 bound catalyst in the NMR spectra, which shift upon hydrogen-bond formation.²¹⁻²³ The
79 thus obtained association constants are confirmed, using the N-H stretching vibration of
80 the catalyst in the infrared absorption spectra, in which the bound and free catalyst can
81 be spectrally resolved. Our results show, that CF₃-groups indeed enhance the binding
82 to 1,3-diphenyl-2-propenone, however, the association markedly depends on the
83 solvent with rather weak association in toluene and dichloromethane and virtually no
84 interaction between catalyst and substrate in acetonitrile.

85 II. Experimental Methods

86 *Samples*

87 Diphenylthiourea (0CF-DPTU, Fluka, >98%), N,N'-bis[4-(trifluoromethyl)phenyl]-
88 thiourea (2CF-DPTU, TCI, >97%), N,N'-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea
89 (4CF-DPTU, TCI, >98%) and 1,3-diphenyl-2-propenone (Sigma-Aldrich, >98%) were
90 used without further purification. The deuterated solvents used for the NMR experiments
91 dichloromethane (DCM-d₂, Deutero, 99.6%), toluene (toluene-d₈, Aldrich, 99.6%), and
92 acetonitrile (ACN-d₃, Merck, 99.96%) were dried over 4 Å molecular sieves, yielding
93 water contents of ~20 ppm (determined for DCM using Coulometric Karl Fischer
94 titration). To remove solid residuals from the molecular sieves the deuterated solvents
95 were filtered using a 0.2 µm Omnipore membrane filter prior to sample preparation. The
96 non-deuterated solvents dichloromethane (DCM, Fischer Chemical, 99.98%), toluene
97 (Fischer Chemical, 99.8%), acetonitrile (ACN, Fischer Chemical, 99.99%), which were
98 used for infrared experiments, were used without any further purification. Solutions were
99 prepared by weight using an analytical balance, assuming that the solution density is
100 that of the solvent. For the NMR experiments the concentration of the catalyst was kept
101 constant at $c_{\text{cat}}^0 = 0.01$ mol/L ($c_{\text{cat}}^0 = 0.015$ mol/L for 0CF-DPTU) and the concentration
102 of the substrate was varied from $c_{\text{subs}}^0 = 0.005$ mol/L to 0.4 mol/L. For the infrared
103 experiments the catalyst concentration was kept constant at $c_{\text{cat}}^0 = 0.02$ mol/L and the
104 concentration of the substrate was increased from $c_{\text{subs}}^0 = 0.01$ mol/L to 0.4 mol/L.
105

106 *FT-IR Spectroscopy*

107 FT-IR spectra were recorded using a Bruker Vertex 70 and the Nicolet 850 Magna IR
108 spectrometer at a resolution of 4 cm⁻¹. The spectra were collected with a "Specac
109 demountable Omni Cell" with the sample positioned between two CaF₂ windows
110 separated by a 0.5 mm thick spacer.
111

112 *NMR Spectroscopy*

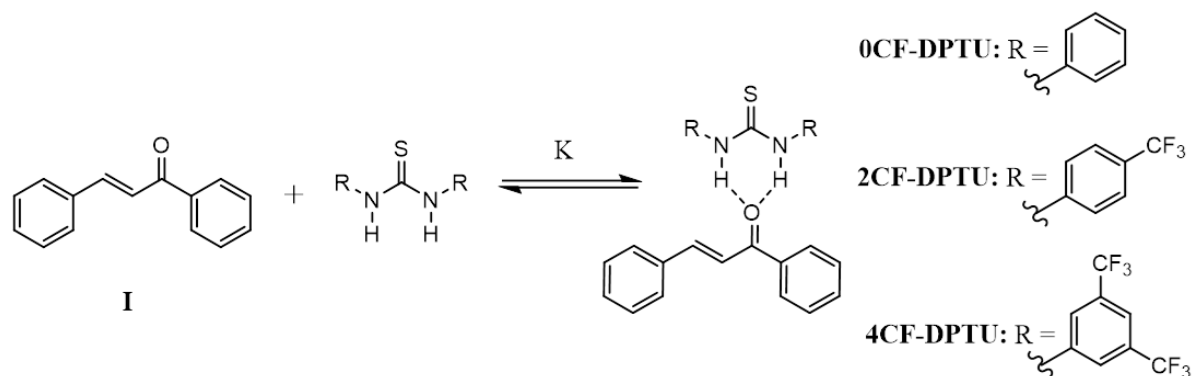
113 To study the strength of interaction between catalyst and substrate, we use NMR-
114 spectroscopy, which provides information about the chemical environment. ¹H-NMR
115

116 spectra were recorded using a Bruker 300 MHz AVANCE III spectrometer. Spectra were
117 referenced to the residual DCM peak at 5.32 ppm, the residual toluene peak at
118 2.09 ppm, or the residual acetonitrile peak at 1.94 ppm. To determine the chemical shift
119 we used the chemical shift value at the peak maximum.
120

121 III. Results and Discussion

122 Molecular association using NMR spectroscopy

123 To study the origin of the different catalytic activities for CF₃ substituted
124 diphenylthioureas, we explore the association of 0CF-DPTU, 2CF-CPTU, and 4CF-
125 DPTU with 1,3-Diphenyl-2-propenone (association equilibria are shown in Scheme 2).
126
127

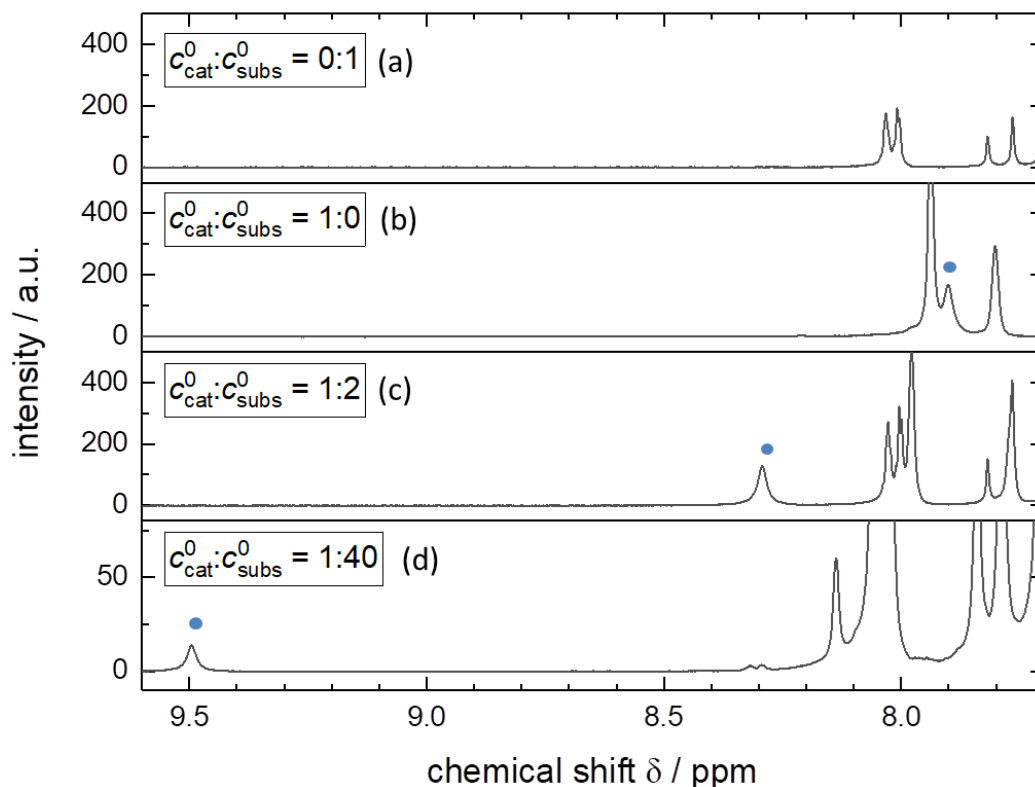


133 **Scheme 2:** Investigated association equilibria between the thiourea catalysts and the
134 substrate, which form a hydrogen-bonded catalyst-substrate complex.
135
136

137 To detect molecular association, we record the ¹H-NMR spectra of solutions with
138 constant thiourea concentration ($c_{\text{cat}}^0 = 0.01$ mol/L) and varying substrate concentration
139 ($c_{\text{subs}}^0 = 0 - 0.4$ mol/L). As can be seen from the NMR spectrum (Fig. 1a) of a solution of
140 only 1,3-Diphenyl-2-propenone, the substrate exhibits four narrow peaks – within the
141 selected range at 7.7 – 8.2 ppm – due to the aromatic protons of the substrate. The
142 spectrum for a solution of 4CF-DPTU contains two narrow peaks (at 7.94 and 7.80 ppm)
143 due to the substituted phenyl groups and a broadened peak at 7.90 ppm due to
144 thiourea's NH protons (Fig. 1b).

145 As can be seen in Fig. 1c,d, also in the ternary mixtures the substrate and catalyst
146 signals are observed, yet shifted with respect to their position in the binary solutions.
147 The NH proton signal undergoes a marked downfield shift in the presence of the
148 substrate. This de-shielding of the NH proton implies a reduction of the average electron
149 density in the vicinity of the NH proton, consistent with hydrogen-bond-formation to the
150 C=O group of the substrate. For all samples we observe a single, motionally averaged
151 proton signal of the NH groups. As such, neither free and hydrogen-bonded NH groups
nor the two NH groups of thiourea can be discriminated via ¹H-NMR spectroscopy at the
ambient temperature. Yet, previous studies have suggested that both NH groups of
thiourea form an intermolecular hydrogen-bond to the substrate's C=O group.¹⁶ We
note, that other protons e.g. of the ortho-proton of the phenyl-substituents undergo only

152 a minor shift (see Figure S1, SI). This marked downfield shift is in line with earlier reports
153 showing that the NH proton is very sensitive to changes in the electronic environment.¹⁶
154



155
156 **Figure 1.** ¹H-NMR spectra for 4CF-DPTU (cat) and 1,3-Diphenyl-2-propenone (subs)
157 mixtures in DCM at 7.7-9.1 ppm: (a) $c_{\text{cat}}^0 : c_{\text{subs}}^0 = 0:1$, (b) $c_{\text{cat}}^0 : c_{\text{subs}}^0 = 1:0$, (c) $c_{\text{cat}}^0 : c_{\text{subs}}^0 =$
158 $1:2$, and (d) $c_{\text{cat}}^0 : c_{\text{subs}}^0 = 1:40$. For visual clarity the NH proton peak is marked with blue
159 filled circle.
160

161 To quantitatively compare the variation of the chemical shift for the studied thiourea
162 catalysts, we analyse the chemical shift of the NH protons as a function of substrate
163 concentration. As can be seen from Fig. 1, the chemical shift of the NH proton is most
164 sensitive to the presence of the substrate. The extracted chemical shifts of the NH
165 protons shown in Fig. 2 exhibit a marked increase with increasing substrate
166 concentration for $c_{\text{subs}}^0 < 0.2$ mol/L, which levels off at higher concentrations of substrate
167 for 4CF-DPTU. For 2CF-DPTU and 0CF-DPTU both the magnitude of the increase is
168 lower and the curvature of the chemical shift as a function of c_{subs}^0 is less pronounced
169 as compared to 4CF-DPTU, indicative of weaker interaction between the thioureas and
170 the substrate. Due to the weaker interaction together with the finite solubility, the
171 chemical shifts as shown in Fig. 2 do not plateau as markedly for 2CF-DPTU and 0CF-
172 DPTU, as compared to 4CF-DPTU. The observed chemical shifts in Fig. 2 are due to
173 the motionally averaged signal of the free and the bonded catalyst. Hence, a change of
174 chemical shift can be either caused by a stronger de-shielding upon hydrogen-bond
175 formation (larger values of the chemical shift of the hydrogen-bonded complexes), or by
176 a higher concentration of hydrogen-bonded complexes.
177

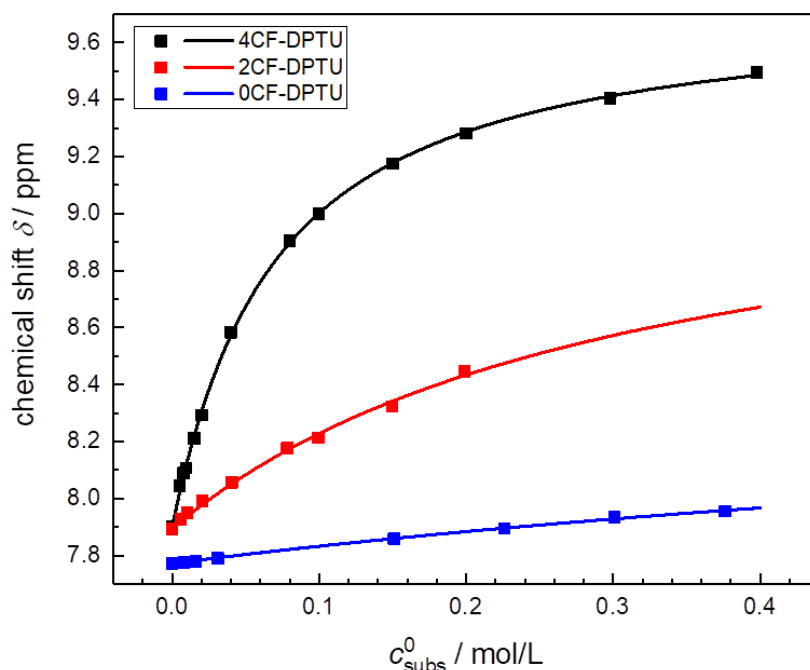


Figure 2. Chemical shift of the NH protons as a function of substrate concentration c_{subs}^0 for 4CF-DPTU (black symbols), 2CF-DPTU (red symbols), and 0CF-DPTU (blue-symbols) in DCM. Solid lines show fits with the association model (eq. 2). The catalyst concentration is kept constant at $c_{\text{cat}}^0 = 0.01$ mol/L for 4CF-DPTU and 2CF-DPTU. For 0CF-DPTU the concentration of the catalyst ($c_{\text{cat}}^0 = 0.015$ mol/L) was higher to enable a better discrimination between the NH signals of the catalyst and the peaks of the substrate.

To disentangle the effect of de-shielding and complex concentration to the observed signals, we fit an association model to the experimental $^1\text{H-NMR}$ data in Fig. 2. To this end, we assume a bimolecular association between the catalyst and the substrate molecule to form a hydrogen-bonded catalyst-substrate complex (scheme 2). The corresponding association equilibrium is given as:

$$K_{\text{NMR}} = \frac{[\text{complex}]}{[\text{cat}][\text{subs}]} \quad (1)$$

where $[\text{cat}]$ and $[\text{subs}]$ are the equilibrium concentrations of the free catalyst and the free substrate, respectively. $[\text{complex}]$ is the concentration of hydrogen-bonded complexes. We assume the observed chemical shift δ to be the concentration weighted average of the chemical shift of the free catalyst, δ_{cat} , and of the chemical shift of the complex δ_{complex} :

$$\delta = \delta_{\text{cat}} \frac{[\text{cat}]}{c_{\text{cat}}^0} + \delta_{\text{complex}} \frac{[\text{complex}]}{c_{\text{cat}}^0} \quad (2)$$

Mass conservation further gives:

$$c_{\text{cat}}^0 = [\text{cat}] + [\text{complex}] \quad (3)$$

We take the value for δ_{cat} from the $c_{\text{subs}}^0 = 0$ samples ($\delta_{\text{cat}}(4\text{CF-DPTU}) = 7.90$ ppm, $\delta_{\text{cat}}(2\text{CF-DPTU}) = 7.89$ ppm, and $\delta_{\text{cat}}(0\text{CF-DPTU}) = 7.77$ ppm). Thus, eqs. (1)-(3) excellently describe the experimental data (see solid lines in Fig. 2) with only two adjustable parameters, K_{NMR} and δ_{complex} . This suggests, that a bimolecular interaction dominates, as opposed to what has been found for other substrates in the solid state²⁴ and for asymmetric thiourea catalysts where different pathways are conceivable for a dual activation of the nucleophile and the electrophile.²⁵

From the fits of eqs. (1)-(3) to the data, we obtain $K_{\text{NMR}}(4\text{CF-DPTU}) = 15.8 \pm 0.7$ L/mol, $K_{\text{NMR}}(2\text{CF-DPTU}) = 3.3 \pm 0.3$ L/mol, and $K_{\text{NMR}}(0\text{CF-DPTU}) = 0.86 \pm 0.03$ L/mol²⁶ and for the chemical shift of the complex $\delta_{\text{complex}}(4\text{CF-DPTU}) = 9.74 \pm 0.02$ ppm, $\delta_{\text{complex}}(2\text{CF-DPTU}) = 9.27 \pm 0.06$ ppm, and $\delta_{\text{complex}}(0\text{CF-DPTU}) = 8.54 \pm 0.02$ ppm,²⁶ respectively. Hence, the observed differences in de-shielding of the NH protons of different catalysts upon substrate addition (Fig. 2) are indeed a result of both, variation of the de-shielding upon complex formation for different catalysts (variation of $\delta_{\text{complex}} - \delta_{\text{cat}}$) and varying complex concentrations. Our results suggest that 4CF-DPTU forms the strongest hydrogen-bonds to the substrate, giving rise to the highest association constant. The thus obtained association constants are also consistent with the variation of the chemical shift of other protons of the catalyst and the chemical shift of the ¹³C carbon of the C=O group of the substrate (see Figs. S2-S3, SI).

Association equilibria from FT-IR spectroscopy

Since the association equilibria as extracted from the NMR chemical shift may be biased by a substrate induced variation of the bulk properties of the solvent,²⁷ in particular for weak variation of the chemical shift (see 2CF-DPTU and 0CF-DPTU),²⁸ we use IR spectroscopy as an independent method to detect association.²⁹ In general, the NH stretching vibrations of the thiourea group are very sensitive to molecular associations, as the N-H stretching markedly red-shifts upon hydrogen-bond formation.³⁰

In Fig. 3 we show the infrared absorption spectra for solutions of 0CF-DPTU (Fig. 3a), 2CF-DPTU (Fig. 3b), and 4CF-DPTU (Fig. 3c) with varying substrate concentration in DCM at frequencies characteristic to the NH stretching modes ($\sim 3150 - 3500$ cm⁻¹). The absorption spectrum of 0CF-DPTU in DCM exhibits two vibrational modes at 3355 cm⁻¹ and 3385 cm⁻¹. For alkyl substituted thioureas the presence of two N-H stretching bands has been explained by the presence of different conformers in solution, with distinctively different vibrational frequencies for the NH stretching mode.^{31, 32} The two N-H stretching modes of N,N-diphenylthiourea (0CF-DPTU) have been suggested to stem from the trans-trans and trans-cis isomers, rather than being a spectroscopic signature of the two NH groups of thiourea.³³ Addition of the substrate hardly affects the NH stretching band in the infrared spectra, except for a minor reduction of the spectral amplitude of the two bands at 3355 cm⁻¹ and 3385 cm⁻¹ and a slight increase of the absorbance at 3180 – 3350 cm⁻¹.

243 The spectrum for a solution of 2CF-DPTU in DCM exhibits a single, yet asymmetric,
244 band at 3370 cm^{-1} (Fig. 3b). The asymmetric band shape, in contrast to the clear double
245 peak structure for 0CF-DPTU, suggests different conformational equilibria and/or faster
246 conformational dynamics³⁴ for 2CF-DPTU, as compared to 0CF-DPTU. Upon addition
247 of substrate to solutions of 2CF-DPTU, the N-H stretching bands at 3370 cm^{-1} decrease
248 in amplitude and a broad absorbance at $3180 - 3350\text{ cm}^{-1}$ appears. Thus, our results
249 indicate that upon addition of substrate, catalyst-substrate complexes are formed.
250 Formation of complexes leads to the reduced concentration of free 2CF-DPTU
251 molecules in solution giving rise to the decrease in the absorbance at 3370 cm^{-1} . A red-
252 shifted NH stretching band due to hydrogen-bonded catalyst-substrate complexes can
253 explain the absorbance at $3180 - 3350\text{ cm}^{-1}$.

254 For solutions of 4CF-DPTU, we observe only a single symmetric absorption band at
255 $\sim 3375\text{ cm}^{-1}$, which suggests that only one catalyst conformation can be detected on the
256 timescale of the infrared experiments. This is consistent with NMR experiments, which
257 have revealed that the trans-trans configuration of 4CF-DPTU prevails at room-
258 temperature and the cis-trans isomer can only be observed at temperatures below
259 190 K .¹⁶ The increasing amplitude of the red-shifted catalyst-substrate band at $3180 -$
260 3350 cm^{-1} with increasing substrate concentration is most pronounced for 4CF-DPTU.
261 Qualitatively, our results are in line with the association constants obtained from NMR:
262 an increasing number of CF_3 groups results in enhanced association of DPTU with 1,3-
263 Diphenyl-2-propenone and the associated complexes give rise to the hydrogen-bonded
264 N-H stretching band at $3180 - 3350\text{ cm}^{-1}$.

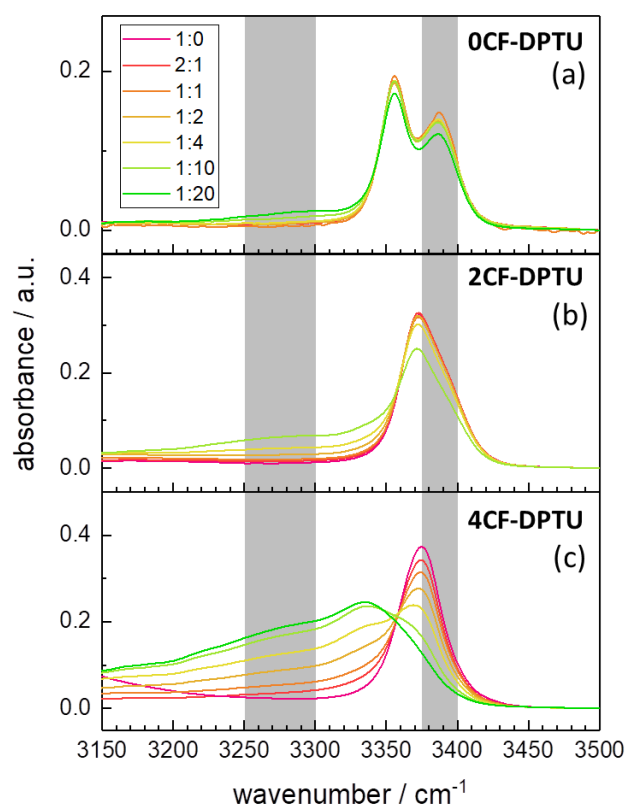


Figure 3: Infrared absorption spectra for solutions of $c_{\text{cat}}^0 = 0.02 \text{ mol/L}$ (a) 0CF-DPTU, (b) 2CF-DPTU, and (c) 4CF-DPTU in DCM for different DPTU:substrate (1,3-diphenyl-2-propenone) ratios. Grey areas indicate the integration ranges used for the determination of the integrated absorbance of the free and the hydrogen-bonded catalyst (see text). The absorbance of the solvent and of 1,3-diphenyl-2-propenone has been subtracted from all spectra (for details see Figure S4, SI).

To quantitatively compare the infrared results to the findings from the NMR chemical shifts, we relate the infrared absorbances to molar concentrations. The absorbance of the free catalyst (A_{cat}) and of the complexes (A_{complex}) can be directly related to their molar concentrations, $[\text{catalyst}]$ and $[\text{complex}]$, via the extinction coefficients of free (ε_{cat}) and bound catalyst ($\varepsilon_{\text{complex}}$):

$$A_{\text{cat}} = \varepsilon_{\text{cat}} \cdot [\text{cat}] \cdot d \quad (4a)$$

$$A_{\text{complex}} = \varepsilon_{\text{complex}} \cdot [\text{complex}] \cdot d \quad (4b)$$

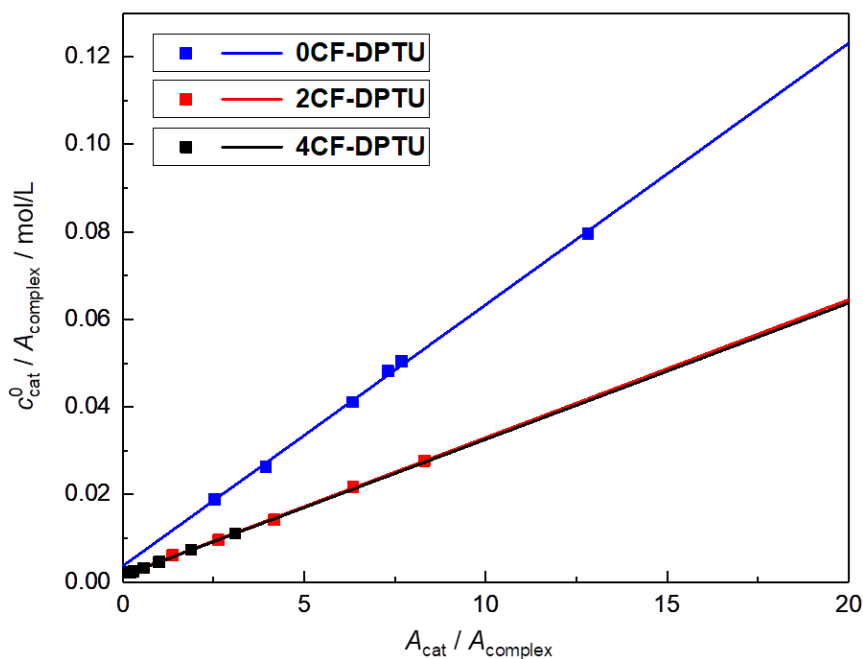
where d is the optical path length of the sample. To obtain the extinction coefficients, we rearrange eqs 3, 4a & 4b such

$$\frac{c_{\text{cat},0}}{A_{\text{complex}}} = \frac{1}{\varepsilon_{\text{cat}} \cdot d} \cdot \frac{A_{\text{cat}}}{A_{\text{complex}}} + \frac{1}{\varepsilon_{\text{complex}} \cdot d} \quad (5)$$

that the inverse extinction coefficients can be obtained from the slope and the intercept of a linear regression ($\frac{c_{\text{cat},0}}{A_{\text{complex}}}$ vs $\frac{A_{\text{cat}}}{A_{\text{complex}}}$). For this analysis, we use the integrated

286 absorbance at 3375-3400 cm^{-1} for A_{cat} and the integrals at 3250-3300 cm^{-1} for A_{complex}
287 (see grey areas in Fig. 3). Note, that these wavenumber ranges do not cover the entire
288 NH stretching bands shown in Fig. 3, in order to omit the spectral range where the
289 contributions of free and bound catalyst overlap. Thus, also the obtained extinction
290 coefficients are characteristic to the selected wavenumber range. In case of 0CF-DPTU
291 the selected wavenumber range only covers the blue-shifted part of the split band. Given
292 that the two bands stem from the presence of different conformers, we assume that the
293 selected wavenumber range is representative of both conformers, which is valid for fast
294 conformational exchange.

295 Using these values for A_{complex} and A_{cat} , the linear relation of eq 5 describes the
296 experimental quantities very well (Fig. 4). We note, that the slopes, which are
297 proportional to the inverse extinction coefficients of the free catalysts, are similar for
298 2CF-DPTU and 4CF-DPTU. For 0CF-DPTU the slope is ~ 2 times higher, which can be
299 explained by the double peak structure of the NH stretching band as this peak splitting
300 results in a reduced apparent extinction coefficient for 0CF-DPTU within the selected
301 wavenumber range.



304
305 **Figure 4:** Linear regression according to eq. 5 to obtain the extinction coefficient of the
306 N-H stretching bands for the bound and the free catalyst.

307
308 With the thus obtained values for ϵ_{cat} and $\epsilon_{\text{complex}}$, we determine the degree of
309 association α (see also Figure S5, SI):

$$\alpha = \frac{[\text{complex}]}{c_{\text{cat}}^0} \quad (6)$$

In line with our NMR results, α increases with increasing c_{subs}^0 and association is stronger with increasing number of CF_3 groups (Fig. 5). For a quantitative comparison to our NMR results we fit the bimolecular association model (eq 1) to the data in Fig. 5, which describes the variation of α with c_{subs}^0 well. The somewhat larger deviations of the data from the model at higher concentrations may stem from the partially overlapping IR bands of the free catalyst and the complex. We thus obtain the association constants K_{IR} , ($K_{\text{IR}}(4\text{CF-DPTU}) = 10.2 \pm 5.2 \text{ L/mol}$, $K_{\text{IR}}(2\text{CF-DPTU}) = 2.0 \pm 0.7 \text{ L/mol}$, and $K_{\text{IR}}(0\text{CF-DPTU}) = 0.7 \pm 0.4 \text{ L/mol}$).²⁶ In contrast to the NMR results (see δ_{complex} values above), we find no evidence for the spectra of the complexes to differ significantly for the three DPTUs (see Figure S6, SI).

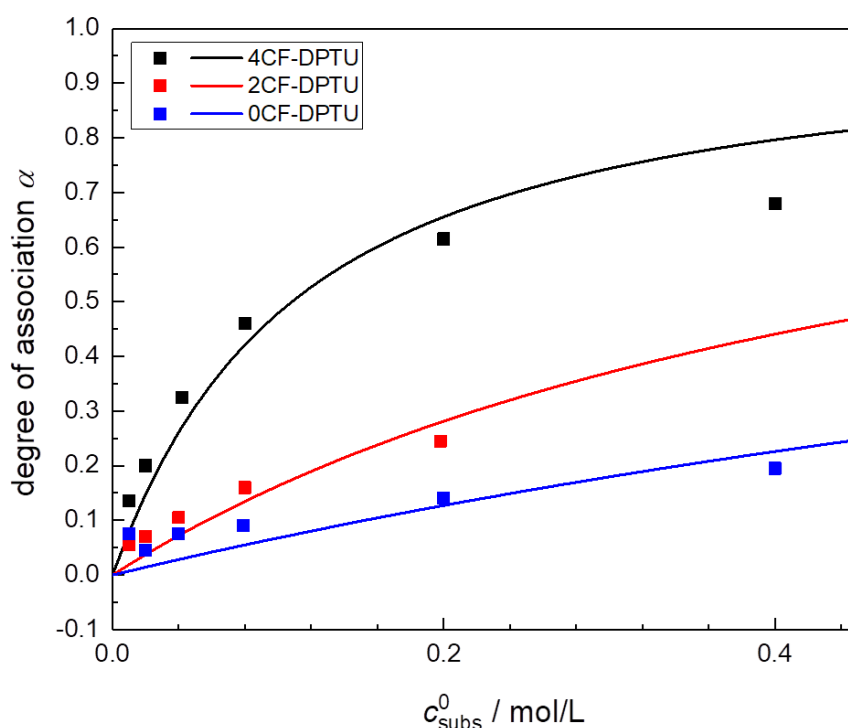
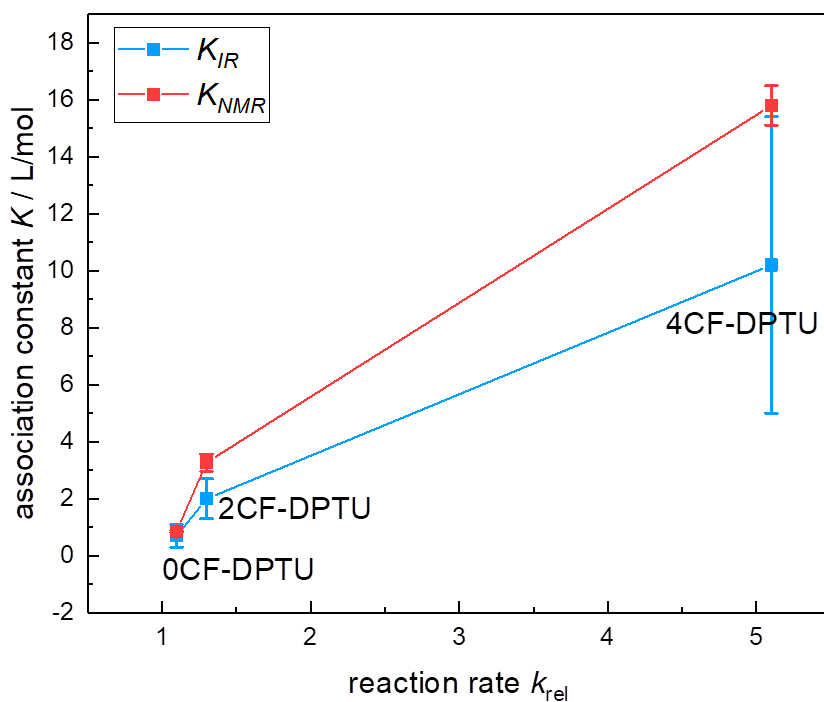


Figure 5: Degree of association α , as obtained from the IR experiments (for details see text) for 4CF-DPTU (black symbols), 2CF-DPTU (red symbols) and 0CF-DPTU (blue symbols) in DCM ($c_{\text{cat}}^0 = 0.02 \text{ mol/L}$). Solid lines show fits using the bimolecular association model (eq 1).

As can be seen in Fig. 6, the association constants determined with both techniques agree well within the experimental error. More importantly, they correlate well with the reaction rates k_{rel} (relative increase of the reaction rate as compared to the absence of a catalyst) reported² for the Diels-Alder reaction of 1,3-diphenyl-2-propenone with cyclopentadiene (10-fold excess) in CDCl_3 catalyzed by 1 mol% 0CF-DPTU, 2CF-DPTU, or 4CF-DPTU. Thus, our results suggest that the enhanced catalytic conversion

333 for CF_3 substituted DPTU catalysts originates from enhanced substrate binding. Our
 334 NMR experiments provide evidence for the enhanced association to originate – at least
 335 in part – from stronger $\text{N-H}\cdots\text{O}$ hydrogen-bonds, as the δ_{complex} , which is predominantly
 336 effected by the local chemical environment, is shifted to higher values with increasing
 337 number of CF_3 groups. However, given the weak association of DPTU with 1,3-diphenyl-
 338 2-propenone, the chemical shift values of the complexes rely on extrapolation and are
 339 as such less certain. In fact, the N-H stretching bands, which are – similar to O-H
 340 stretching band positions³⁵ – also a measure for the hydrogen-bond strength, are little
 341 affected by the presence of the CF_3 groups (see Figure S6, SI), indicative of different
 342 experimental sensitivities of NMR and IR. Nevertheless, the weak variation of the NH
 343 stretching band within the complexes across the studied DPTUs suggests that the
 344 intermolecular hydrogen-bond is not the sole cause for enhanced binding of 4CF-DPTU
 345 to the substrate. Additional, interaction of the ortho-proton of the phenyl group of
 346 phenylthiourea¹⁶ with the substrate can comprise an additional interaction motif (see
 347 also Figure S1, SI) and also reduced solvation of the CF_3 -substituted DPTU molecules
 348 may give rise to enhanced complex formation.



350
 351 **Figure 6:** Association constants K_{IR} and K_{NMR} vs relative rate constants of a Diels Alder
 352 reaction as reported in ref 2. Error bars correspond to K values for which the sum of the
 353 squared deviations increases by 100% when fitting eq (1) to the experimental data.

354 Solvent effects

355 As differences in the solvation of the substrate, catalyst, and complexes in different
 356 solvents may give rise to different association, and thus different catalytic conversion,
 357 we investigate the effect of the solvent on the association: We compare our results for
 358

359 solutions in DCM to the association of DPTUs with 1,3-diphenyl-2-propenone in toluene,
360 which is a commonly used solvent in catalysis, yet with lower polarity. Accordingly, we
361 determine the K_{NMR} values from the $^1\text{H-NMR}$ chemical shifts (see Fig. S7, SI) in
362 toluene.³⁶ As can be seen from the comparison of the determined values of the K_{NMR}
363 (Tab. 1), the association strengths for 0CF-DPTU and 2CF-DPTU in toluene are
364 comparable to those found in DCM. For 4CF-DPTU, however, association is enhanced
365 in toluene as compared to DCM. The enhanced association of 4CF-DPTU with 1,3-
366 diphenyl-2-propenone in toluene as compared to DCM points towards a less favorable
367 interaction between the catalysts NH groups and the solvent in toluene as compared to
368 DCM.

369 Conversely, in the highly dipolar solvent acetonitrile, we find the chemical shift of the NH
370 protons DPTUs of all DPTUs to hardly vary with increasing concentration of 1,3-
371 diphenyl-2-propenone (Fig. S8, SI). Hence, no appreciable association between the
372 DPTUs and the substrate in acetonitrile can be detected, which is further confirmed by
373 the insensitivity of the catalysts NH stretching band to the substrate concentration in
374 infrared absorption experiments (Fig. S9, SI). This suggests that the polarity of the
375 solvent, as for instance determined via the $E_{\text{T}}(30)$ values,³⁷ is a reasonable estimate for
376 the association strength of the DPTUs with ketones in organic (non-hydrogen-bonding)
377 solvents. In general, binding of catalyst and substrate are markedly affected by the
378 solvent, which suggests that solvation of the catalyst and of the substrate plays an
379 important role for the formation of the reactive intermediates in catalysis. This is
380 particularly apparent for 4CF-DPTU, for which association is strongly enhanced in
381 toluene.²³

382
383 **Table 1:** Association constants, K_{NMR} , in DCM and toluene, as obtained from $^1\text{H-NMR}$
384 spectroscopy for the catalysts 0CF-DPTU, 2CF-DPTU and 4CF-DPTU, respectively.

K_{NMR}	4CF-DPTU	2CF-DPTU	0CF-DPTU
CD_2Cl_2	$15.8 \pm 0.7 \text{ L/mol}$	$3.27 \pm 0.3 \text{ L/mol}$	$0.86 \pm 0.03 \text{ L/mol}$
Toluene	$27.7 \pm 1.3 \text{ L/mol}$	$3.06 \pm 0.1 \text{ L/mol}$	$1.65 \pm 0.2 \text{ L/mol}$

385 386 387 IV Conclusions

388 We use two independent techniques, NMR and FT-IR spectroscopy to quantify the
389 association strength of diphenylthiourea-based catalysts with 1,3-diphenyl-2-propenone
390 as a representative substrate in solution. We find bimolecular association to suffice to
391 describe both infrared and NMR experimental findings. Despite the challenges in
392 determining weak association equilibria, the interaction strengths determined by both
393 methods agree very well. We find that with an increasing number of CF_3 substituents
394 from 0CF-DPTU to 4CF-DPTU the association constant increases from $\sim 1 \text{ L/mol}$ to
395 $\sim 20 \text{ L/mol}$. This increase in molecular association correlates well with the reported
396 increased catalytic activity of the DPTU-based catalysts. Our results suggest that the

hydrogen-bond strength of the N-H...O=C bonds in the catalyst-substrate complexes is not the sole origin of the enhanced binding in solution for CF₃ substituted DPTUs but also the solvation of the catalyst, substrate, and the complexes contribute. The relevance of the solvation is supported by the marked dependence of the association equilibria on the solvent, with no detectable binding in solutions of acetonitrile and moderate interactions in toluene and dichloromethane.

Acknowledgements

We thank Mischa Bonn for fruitful discussions. This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement No 714691).

References:

- Schreiner, P. R.; Wittkopp, A., H-Bonding Additives Act Like Lewis Acid Catalysts. *Organic Letters* **2002**, 4 (2), 217-220.
- Wittkopp, A.; Schreiner, P. R., Metal-Free, Noncovalent Catalysis of Diels–Alder Reactions by Neutral Hydrogen Bond Donors in Organic Solvents and in Water. *Chemistry – A European Journal* **2003**, 9 (2), 407-414.
- Schreiner, P. R., Metal-free organocatalysis through explicit hydrogen bonding interaction. *Royal Society of Chemistry* **2003**, 32, 289-296.
- Zhang, Z.; Schreiner, P. R., (Thio)urea organocatalysis—What can be learnt from anion recognition? *Chemical Society Reviews* **2009**, 38 (4), 1187-1198.
- Sigman, M. S.; Vachal, P.; Jacobsen, E. N., A General Catalyst for the Asymmetric Strecker Reaction. *Angewandte Chemie International Edition* **2000**, 39 (7), 1279-1281.
- Sigman, M. S.; Jacobsen, E. N., Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries. *Journal of the American Chemical Society* **1998**, 120 (19), 4901-4902.
- Okino, T.; Hoashi, Y.; Takemoto, Y., Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts. *Journal of the American Chemical Society* **2003**, 125 (42), 12672-12673.
- Takemoto, Y., Recognition and activation by ureas and thioureas: stereoselective reactions using ureas and thioureas as hydrogen-bonding donors. *Organic & Biomolecular Chemistry* **2005**, 3 (24), 4299-4306.
- Custelcean, R., Crystal engineering with urea and thiourea hydrogen-bonding groups. *Chemical Communications* **2008**, (3), 295-307.
- Žabka, M.; Šebesta, R., Experimental and Theoretical Studies in Hydrogen-Bonding Organocatalysis. **2015**, 20 (9), 15500-15524.
- Taylor, M. S.; Jacobsen, E. N., Asymmetric Catalysis by Chiral Hydrogen-Bond Donors. *Angewandte Chemie International Edition* **2006**, 45 (10), 1520-1543.
- Sun, L. F.; Wu, X. W.; Xiong, D. C.; Ye, X. S., Stereoselective Koenigs-Knorr Glycosylation Catalyzed by Urea. *Angewandte Chemie International Edition* **2016**, 55 (28), 8041-8044.

- 440 13. Dubey, A.; Sangwan, R.; Mandal, P. K., N-benzoylglycine/thiourea cooperative
441 catalyzed stereoselective O-glycosidation: Activation of O-glycosyl trichloroacetimidate
442 donors. *Catalysis Communications* **2019**, *125*, 123-129.
- 443 14. Kobayashi, Y.; Nakatsuji, Y.; Li, S.; Tsuzuki, S.; Takemoto, Y., Direct N-
444 Glycofunctionalization of Amides with Glycosyl Trichloroacetimidate by
445 Thiourea/Halogen Bond Donor Co-Catalysis. *Angewandte Chemie International*
446 *Edition* **2018**, *57* (14), 3646-3650.
- 447 15. Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R., (Thio)urea
448 Organocatalyst Equilibrium Acidities in DMSO. *Organic Letters* **2012**, *14* (7), 1724-
449 1727.
- 450 16. Lippert, K. M.; Hof, K.; Gerbig, D.; Ley, D.; Hausmann, H.; Guenther, S.;
451 Schreiner, P. R., Hydrogen-Bonding Thiourea Organocatalysts: The Privileged 3,5-
452 Bis(trifluoromethyl)phenyl Group. *European Journal of Organic Chemistry* **2012**, *2012*
453 (30), 5919-5927.
- 454 17. Walvoord, R. R.; Huynh, P. N. H.; Kozlowski, M. C., Quantification of
455 Electrophilic Activation by Hydrogen-Bonding Organocatalysts. *Journal of the*
456 *American Chemical Society* **2014**, *136* (45), 16055-16065.
- 457 18. Kleiner, C. M.; Schreiner, P. R., Hydrophobic amplification of noncovalent
458 organocatalysis. *Chemical Communications* **2006**, (41), 4315-4317.
- 459 19. H.S, G.; Melavanki, R. M.; D, N.; P, B.; Kusanur, R. A., Binding of boronic
460 acids with sugars in aqueous solution at physiological pH - Estimation of association
461 and dissociation constants using spectroscopic method. *Journal of Molecular Liquids*
462 **2017**, *227*, 37-43.
- 463 20. Banipal, T. S.; Kaur, R.; Banipal, P. K., Interactions of diazepam with sodium
464 dodecylsulfate and hexadecyl trimethyl ammonium bromide: Conductometric, UV-
465 visible spectroscopy, fluorescence and NMR studies. *Journal of Molecular Liquids*
466 **2017**, *236*, 331-337.
- 467 21. Haushalter, K. A.; Lau, J.; Roberts, J. D., An NMR Investigation of the Effect of
468 Hydrogen Bonding on the Rates of Rotation about the C-N Bonds in Urea and
469 Thiourea. *Journal of the American Chemical Society* **1996**, *118* (37), 8891-8896.
- 470 22. Rakipov, I. T.; Petrov, A. A.; Akhmadiyarov, A. A.; Khachatryan, A. A.;
471 Klimovitskii, A. E.; Varfolomeev, M. A.; Solomonov, B. N., FTIR – spectroscopy of
472 intermolecular interactions of pyrrole in solutions: The influence of media and
473 cooperativity of hydrogen bonds. *Journal of Molecular Liquids* **2019**, *277*, 200-206.
- 474 23. Malm, C.; Kim, H.; Wagner, M.; Hunger, J., Complexity in Acid-Base
475 Titrations: Multimer Formation Between Phosphoric Acids and Imines. *Chemistry – A*
476 *European Journal* **2017**, *23* (45), 10853-10860.
- 477 24. Chitra, R.; Das, A.; Choudhury, R. R.; Ramanadham, M.; Lakshmi, S.;
478 Sridhar, M. A.; Prasad, J. S. J. J. o. C. C., Hydrogen bonding in thiourea: diethyl
479 oxalate complex in 2:1 ratio. *Journal of Chemical Crystallography* **2005**, *35* (7), 509-
480 512.
- 481 25. Lutete, L. M.; Miyamoto, T.; Ikemoto, T., Tertiary amino thiourea-catalyzed
482 asymmetric cross aldol reaction of aryl methyl ketones with aryl trifluoromethyl
483 ketones. *Tetrahedron Letters* **2016**, *57* (11), 1220-1223.
- 484 26. The errors were estimated by fixing the chemical shift of the complex to the
485 optimized value of the association model fit. The corresponding association constants
486 to a change of the fitchi value of 100% was then defined as the error. .
- 487 27. Zhang, Y.; Cremer, P. S., Interactions between macromolecules and ions: the
488 Hofmeister series. *Current Opinion in Chemical Biology* **2006**, *10* (6), 658-663.
- 489 28. Lee, F., NMR Methods for the Determination of Protein- Ligand Dissociation
490 Constants. *Current Topics in Medicinal Chemistry* **2003**, *3* (1), 39-53.

- 491 29. Vanderheyden, L.; Zeegers-Huyskens, T., Infrared and Raman study of the
492 interaction between methyl acetate and phenol derivatives. *Journal of Molecular*
493 *Liquids* **1983**, *25* (1), 1-11.
- 494 30. Le Parc, R.; Freitas, V. T.; Hermet, P.; Cojocariu, A. M.; Cattoën, X.;
495 Wadepohl, H.; Maurin, D.; Tse, C. H.; Bartlett, J. R.; Ferreira, R. A. S.; Carlos, L.
496 D.; Wong Chi Man, M.; Bantignies, J.-L., Infrared and Raman spectroscopy of non-
497 conventional hydrogen bonding between N,N'-disubstituted urea and thiourea groups:
498 a combined experimental and theoretical investigation. *Physical Chemistry Chemical*
499 *Physics* **2019**, *21* (6), 3310-3317.
- 500 31. Gosavi, R. K.; Agarwala, U.; Rao, C. N. R., Infrared Spectra and Configuration
501 of Alkylthiourea Derivatives. Normal Vibrations of N,N'-Dimethyl- and
502 Tetramethylthiourea. *Journal of the American Chemical Society* **1967**, *89* (2), 235-239.
- 503 32. Willem M. Nissink, J.; Boerrigter, H.; Verboom, W.; N. Reinhoudt, D.; H. van
504 der Maas, J., An infrared study of host-guest association in solution by substituted
505 resorcinarene cavitands. Part II.1 Comparison of halide complexation by tetrathiourea
506 cavitands and a simple thiourea. *Journal of the Chemical Society, Perkin Transactions*
507 *2* **1998**, (12), 2623-2630.
- 508 33. Russell, R. A.; Thompson, H. W., Vibrational spectra and geometrical
509 isomerism in amides. *Spectrochimica Acta* **1956**, *8* (3), 138-141.
- 510 34. Cohen, B.; Weiss, S., IR lines broadened by chemical exchange. *The Journal of*
511 *Chemical Physics* **1980**, *72* (12), 6804-6804.
- 512 35. Ojha, D.; Karhan, K.; Kühne, T. D., On the Hydrogen Bond Strength and
513 Vibrational Spectroscopy of Liquid Water. *Scientific Reports* **2018**, *8* (1), 16888.
- 514 36. Note, that the solubility of DPTU in toluene is too low to reliably extract K from
515 infrared experiments.
- 516 37. Reichardt, C., Solvatochromic Dyes as Solvent Polarity Indicators. *Chemical*
517 *Reviews* **1994**, *94* (8), 2319-2358.