Novel Hydrogen Bonding Organocatalysts: Applications in the aza-Morita-Baylis-Hillman Reaction and Anion Sensing

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
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2013

Abstract

Self-assembly is an efficient method for generating large numbers of structurally diverse catalysts for screening. In this work, the method of self-assembly was explored in the construction of bifunctional catalysts, from a chiral aminophosphine, 2-formylphenylboronic acid, and a (thio)urea-containing diol. These catalysts were evaluated by their effect on the asymmetric aza-Morita-Baylis-Hillman reaction. In the second half of this thesis, the hydrogen bonding abilities of different dithiosquaramides were analyzed. As thioureas have been shown to be stronger hydrogen bond donors than ureas, it was hypothesized that dithiosquaramides may also follow a similar trend. Affinities of corresponding squaramides and dithiosquaramides to chloride, sulfate, and tosylate were compared, as well as their abilities to catalyze the Freidel-Crafts alkylation between indole and trans-β-nitrostyrene.
Acknowledgments

My journey through grad school finally comes to an end, and I’m not sure how I made it out alive, but I know I wouldn’t have been able to without the support of many people.

To the Taylor Tots: You guys are very weird. But it is this weirdness that makes it enjoyable to work with all of you. Thank you for all the help you have provided me, and the time you took to listen to all my irrational worries. I may not be able to remember your faces, but I will never forget any of you.

To my parents: Thank you for your patience with me all year, for understanding why I’m almost never home and for letting me continue my work even if it is 4 AM. Thank you to my mom for reminding me not to go crazy – I think I actually needed that.

To Mark Taylor: Finally, I am not an elegant enough writer to be able to convey my appreciation using words typed on a page. Your intelligence is still intimidating, but no matter how many times I’d be given the option to repeat this year, I would always choose to be your student.
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List of Abbreviations

°C  degress Celsius

¹H  proton NMR

¹³C  carbon 13 NMR

app quin  apparent quintet

Ar  aryl

BH  Baylis-Hillman

BINOL  1,1'-bi-2-naphthol

Bu  butyl

d  doublet

DABCO  1,4-diazabicyclo[2.2.2]octane

DCE  dichloroethane

DMSO  dimethyl sulfoxide

DNA  deoxyribonucleic acid

ESI  electrospray ionization

Et  ethyl

EWG  electron-withdrawing group

FG  functional group

HRMS  high resolution mass spectrometry
IR: infrared spectrometry

$K_a$: acid dissociation constant

LBBA: Lewis base-Brønsted acid

M: metal

m: multiplet

$M^+$: parent molecular ion

MBH: Morita-Baylis-Hillman

Me: methyl

mg: milligrams

MHz: megahertz

min: minutes

mL: millilitres

mmol: millimoles

MVK: methyl vinyl ketone

NMP: $N$-methylpyrrrolidone

NMR: nuclear magnetic resonance

Nu: nucleophile

OTf: triflate

Ph: phenyl

$pK_a$: negative logarithm of $K_a$, $-\log K_a$
ppm  parts per million
s  singlet
t  triplet
THF  tetrahydrofuran
TLC  thin layer chromatography
TMSCl  trimethylsilyl chloride
Ts  tosyl
µL  microlitres
Chapter 1

Generating Organocatalysts Via Multicomponent Reactions for the aza-Morita-Baylis-Hillman Reaction

1.1 Introduction

1.1.1 Self-Assembly Catalysts

In organic chemistry, many reactions require catalysts to proceed, including their asymmetric variants. Changing the structure of the catalyst can have a drastic effect on the enantioselectivity. Therefore it is important to be able to discover the optimal catalyst for the reaction in question.\(^1\) This is usually achieved after substantial trial-and-error, in addition to the optimization of other conditions.\(^2\) There has been great progress in developing methods for high throughput screening of catalysts and analysis of results, which now leaves interest in efficient methods to synthesize large numbers of structurally diverse catalysts for the screening process. Self-assembly is a popular method that not only efficiently produces catalysts for screening, but modification of the catalyst simply requires substitution of one of the components.\(^3\)

---

Self-assembly has been used to generate the catalyst itself or ligands for metal catalysts. Breit et al.\(^4\) reported using self-assembly to generate bidentate ligands via hydrogen bonding to catalyze the hydroformylation of functionalized terminal alkenes (Scheme 1). Takacs et al.\(^5\) also generated self-assembled ligands to make chiral heterobimetallic catalysts for asymmetric allylation reactions (Scheme 2).

![Scheme 1](image.png)

**Scheme 1** Catalysis of the hydroformylation of functionalized terminal alkenes using self-assembled bidentate ligands coordinating to Rh by Breit et al.

The work of Chen et al.\(^6\) shows examples of self-assembled organocatalysts, where amino acids and chiral thiourea-functionalized cinchona alkaloid derivatives assemble via ionic interaction. Chen demonstrated the ability of these compounds to catalyze the direct asymmetric vinylogous Michael addition of \(\alpha,\alpha\)-dicyanoolefins and nitroolefins (Scheme 3).

---


Scheme 2 Asymmetric allylation catalyzed by a chiral heterobimetallic complex with a self-assembled ligand by Takacs et al.

Scheme 3 Direct asymmetric vinylogous Michael addition catalyzed by self-assembled L-proline and thiourea-functionalized cinchona alkaloid derivative.

The practicality of self-assembly was tested by applying this concept in screening chiral catalysts for the asymmetric aza-Morita-Baylis-Hillman reaction, which is introduced in the following section.
1.1.2 aza-Morita-Baylis-Hillman Reaction

The Morita-Baylis-Hillman (MBH) reaction, and its variants, is one of the most useful carbon-carbon bond forming transformations.\(^7\) Catalyzed by a Lewis base, this reaction involves the coupling between the \(\alpha\)-carbon of an activated carbon-carbon double bond and an \(\text{sp}^2\) electrophilic carbon.

The original publication came from Morita et al., employing a tertiary phosphine to catalyze the reaction between methyl acrylate or acrylonitrile and various aldehydes (Scheme 4).\(^8\)

![Scheme 4](image)

**Scheme 4** Original reaction by Morita between methyl acrylate or acrylonitrile and various aldehydes, catalyzed by a tertiary phosphine.

Baylis and Hillman developed a similar reaction (BH) in 1972, involving the condensation of activated alkenes, such as \(\alpha,\beta\)-unsaturated esters, amides, nitriles and ketones, with various aldehydes.\(^9\) This reaction could be catalyzed by a tertiary bicyclic amine, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), indolizine, or quinuclidine (Scheme 5).

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\(^7\) Wei, Y.; Shi, M.; *Chem. Rev.* **2013**, *113*, 6659-6690.


Scheme 5 Examples of tertiary amines capable of catalyzing the Baylis-Hillman reaction.

These two reactions are atom economical and have potential to be quite versatile in organic synthesis, but unfortunately, they were ignored by organic chemists for about a decade.

In 1982, Drewes obtained an intermediate of the synthesis of intergerrinecic acid via the BH reaction, by condensing ethyl acrylate and acetaldehyde, employing DABCO as the catalyst (Scheme 6).\(^\text{10}\) Since then, the potential of this reaction in synthetic chemistry has dramatically increased with the discovery of several other variants of the MBH reaction, including a TiCl\(_4\)-catalyzed version,\(^\text{11}\) an intramolecular version,\(^\text{12}\) and the aza-MBH version.\(^\text{13}\) The aza-MBH version, which is the focus of the first half of this thesis, involves the reaction of an imine in place of an aldehyde.

---


Scheme 6 An intermediate of the synthesis of intergerrinecic acid generated by a DABCO-catalyzed Baylis-Hillman reaction.

1.1.3 Mechanistic Considerations

The mechanisms for the amine- or phosphine-catalyzed reaction are similar. Scheme 7 shows the mechanism of the reaction between $N$-benzylidene-4-methylbenzenesulphonamide and methyl vinyl ketone (MVK). Nucleophilic attack of MVK 1-1 by the catalyst forms intermediate A, followed by addition of the $N$-tosyl imine 1-2. There are two different proposed pathways from intermediate B. In the Aggarwal proposal, $^{14}$ hydrogen bonding can occur with a protic solvent, additive, or acidic proton in a multifunctional catalyst, promoting proton transfer via a six-membered ring in intermediate C, which will eliminate to regenerate the catalyst and form the product. The McQuade proposal $^{15}$ involves a second molecule of $N$-tosyl imine combining with intermediate B. This also forms a six-membered ring transition state D, followed by proton transfer and elimination to form the desired product.


1.1.4 Asymmetric Multifunctional Catalysts for the aza-MBH Reaction

Chirality is ubiquitous in nature, as biological functions are intrinsically non-symmetric. The progress in the field of asymmetric catalysis has made a large impact not only in the laboratory,

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but being able to synthesize specific stereoisomers of compounds has also further advanced the pharmaceutical industry and the field of medicine.\textsuperscript{18} Catalytic asymmetric synthesis has been a widely interesting topic for decades.\textsuperscript{19} As the field progressed, an increasing number of chiral catalysts have been reported, where some even have higher catalytic efficiencies than natural catalysts, namely enzymes.\textsuperscript{20} Unfortunately, most are limited in terms of yield and enantioselectivity. The main difference between synthetically asymmetric and nature’s catalysts is that where enzymes activate, for example, both starting materials in a two-substrate reaction, synthetic asymmetric catalysts usually only activate one of the starting materials. This led to the development of the concept of multifunctional catalysis, as described by Shibasaki.\textsuperscript{21} These multifunctional catalysts, as the name suggests, contain multiple functional groups within one molecule that facilitate the reaction.


Multifunctionality can also be applied to organocatalysts.\textsuperscript{22,23} In particular, several multifunctional organocatalysts containing a Lewis base and Brønsted acid (LBBA) have been developed for the aza-MBH reaction. Chiral BINOL-derived bifunctional phosphines are a class of successful catalysts developed by Shi et al. and Sasai et al. (Figure 1a-d).\textsuperscript{24} The phenol group was proposed to stabilize the phosphonium enolate intermediate A in Scheme 7 via hydrogen bonding. Further developments led to replacing these hydroxyl groups with thioureas (Figure 1e), where sterics and electronics of the catalysts were easily modified by changing the substituent of the thiourea. Shi et al. were the first to report the application of these chiral bifunctional thiourea-phosphine organocatalysts for the aza-MBH reaction. They later went on to develop a catalyst bearing multiple phenol groups, increasing the stability of intermediate A (Figure 1f). The group took this one step further and developed a trifunctional phosphine catalyst (Figure 1g) containing a Lewis base, Brønsted acid, as well as a Brønsted base, affording products in good yields and enantioselectivities.\textsuperscript{25}

\footnotesize
\begin{itemize}
  \item \textsuperscript{22} Dalko, P. I.; Moisan, L.; \textit{Angew. Chem. Int. Ed.} \textbf{2001}, \textit{40}, 3726-3748.
  \item \textsuperscript{23} List, B. \textit{Tetrahedron} \textbf{2002}, \textit{58}, 5573-5590.
\end{itemize}
Figure 1 Examples of BINOL-derived multifunctional phosphine catalysts developed by Shi et al. and Sasai et al.
1.2 Results and Discussion

As discussed in section 1.1.4, bifunctional compounds which incorporate both a Lewis base and Brønsted acid (LBBA) can potentially act as catalysts for the asymmetric aza-MBH reaction. Compounds satisfying this requirement can be easily synthesized using three components, a chiral aminophosphine, 2-formylphenylboronic acid (1-4), and a (thio)urea-containing diol via a three-component reaction, simply by heating all three components at 50 °C in degassed chloroform (Scheme 8).26 There are several advantages of incorporating the boronic acid-diol interaction in a self-assembled molecule.27 This interaction is reversible, which is required to ensure that any mistakes in the assembly are undone, and that the thermodynamically most stable structure is always formed. It is directional, which controls the final geometry of the assembly. Lastly, nature provides a diverse and inexpensive pool of diols.

\[
\text{NH}_2\text{PPh}_2^* + \text{CHOB(OH)}_2 + \text{HO}_\text{XNH}N_R \xrightarrow{\text{CHCl}_3, 50 \ ^\circ\text{C}, 30 \text{ mins}} \text{NBO}_XN_HN_R \text{PPh}_2^* \text{X} = S, O \text{R} = \text{alkyl, aryl}
\]

Scheme 8 General reaction scheme for generating potential chiral three-component catalysts for the aza-MBH reaction.


In this complex, the phosphine acts as the Lewis base, and the hydrogen bonding (thio)urea acts as the Brønsted acid. These couplings are quantitative, and the resulting products can be used directly in the aza-MBH reaction. Figure 2 shows all aminophosphine and diol components used in this project.
Aminophosphines 1-7 to 1-9 were used as purchased. Compounds 1-5 and 1-6 were synthesized according to literature (Scheme 9).\textsuperscript{28} Compound 1-6 was recrystallized in hexanes in addition to purification by column chromatography. Diols 1-10 to 1-18, with the exception of 1-15, which is commercially available, were synthesized based on procedures previously published by the group (Scheme 10).\textsuperscript{29}

Scheme 9 Reaction scheme for synthesizing aminophosphines 1-5 (shown) and 1-6.


\textsuperscript{29} Chudzinski, M. G.; McClary, C. A.; Taylor, M. S. \textit{J. Am. Chem. Soc.} \textbf{2011}, \textit{133}, 10559-10567.
Compounds 1-5, 1-4, 1-10 were used to generate 1-19 for the initial experiments catalyzing the reaction between 1-1 and 1-2 (Scheme 11). N-tosyl imine was synthesized based on literature.\textsuperscript{30} Conditions were based on those optimized by Shi.\textsuperscript{31} However, at room temperature with 2 or 5 equivalents of 1-1, no product was observed. Raising the temperature to 60 °C with 2 equivalents of 1-1 yielded 30 % of isolated product in 8 %ee.


Scheme 11 Synthesis of catalyst 1-19 from its individual components.

Under the same conditions, a series of experiments were performed using various solvents (Table 1). Unfortunately, no improvements were seen in yields or enantioselectivities. Hence, CH₂Cl₂ was employed as the solvent for the remainder of the experiments.
Table 1 Reaction performed in various solvents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>30</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>DCE</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>19</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were performed on 0.25 mmol scale of 1-2. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by chiral HPLC analysis (ChiralPak IA; eluent, 80:20 hexane/2-propanol; flow rate, 0.75 mL·min<sup>-1</sup>; detection, 254 nm light).

Each of the three components of 1-19 was then used as a catalyst (10 mol%) in the reaction to determine their influence, if any, on the reaction. Aminophosphine 1-5 generated product in similar yield and enantioselectivity as had been observed using 1-19 (Table 2, entry 1). No product was observed using 1-4 or thiourea 1-10 (entries 2-3).
Table 2 Reaction performed using individual components of catalyst 1-19<sup>a</sup>

![Chemical structure and reaction setup]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-5</td>
<td>37</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>1-4</td>
<td>0</td>
<td>n.d.&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>1-10</td>
<td>0</td>
<td>n.d.&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were performed in CH₂Cl₂ on 0.25 mmol scale of 1-2. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by chiral HPLC analysis (ChiralPak IA; eluent, 80:20 hexane/2-propanol; flow rate, 0.75 mL·min⁻¹; detection, 254 nm light). <sup>d</sup> Not determined.

According to Yuan et al.<sup>32</sup>, catalysts using ureas were inferior to thioureas, giving only trace amounts of product. In this case, switching from thiourea 1-10 to urea 1-11, prepared using the corresponding isocyanate, had no effect on the enantioselectivity. However, it resulted in higher yields than those obtained using the thiourea component (Table 3, entry 1). Based on this result, catalysts incorporating different chiral aminophosphines and urea 1-11 were used (entries 2-5).

---

Table 3 Catalysts generated using combinations of various aminophosphine and urea 1-11<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-19</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>1-20</td>
<td>&lt;5</td>
<td>n.d.&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>1-21</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>1-22</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>1-23</td>
<td>49</td>
<td>9</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were performed in CH<sub>2</sub>Cl<sub>2</sub> on 0.25 mmol scale of 1-2. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by chiral HPLC analysis (ChiralPak IA; eluent, 80:20 hexane/2-propanol; flow rate, 0.75 mL·min<sup>−1</sup>; detection, 254 nm light). <sup>d</sup> Not determined.

Although 1-10 gave higher yields than the other aminophosphines, it required a three-day, low-yielding synthesis to prepare (Scheme 9). Instead, aminophosphine 1-9, which resulted in the
second highest yield of 1-3 from Table 3 and is also commercially available, was used while changing the substitutions on the aryl ring of the urea component (Table 5, entries 2-4). This change in electronics of the urea, hence affecting the hydrogen bonding ability of the N-H protons, did not appear to have any significant consequence on the yield or enantioselectivity.

**Table 4** Catalysts generated using combinations of 1-9 and various urea components

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-9</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>1-24</td>
<td>48</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>1-25</td>
<td>55</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>1-26</td>
<td>44</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1-27</td>
<td>62</td>
<td>3</td>
</tr>
</tbody>
</table>

* Reactions were performed in CH$_2$Cl$_2$ on 0.25 mmol scale of 1-2. * Isolated yields. * Determined by chiral HPLC analysis (ChiralPak IA; eluent, 80:20 hexane/2-propanol; flow rate, 0.75 mL·min$^{-1}$; detection, 254 nm light).
Finally, experiments were performed using catalysts that incorporated an additional chiral centre in the urea component. This chiral component was generated by replacing serinol with either enantiomer of 3-amino-1,2-propanediol and reacting with an iso(thio)cyanate (Scheme 10). However, although there was a slight increase, no profound effect was observed on the enantioselectivity.

Table 5 Catalysis of aza-MBH reaction using combinations of 1-9 and various chiral (thio)urea components

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-28</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>1-29</td>
<td>66</td>
<td>9</td>
</tr>
<tr>
<td>3</td>
<td>1-30</td>
<td>56</td>
<td>16</td>
</tr>
</tbody>
</table>

*a* Reactions were performed in CH$_2$Cl$_2$ on 0.25 mmol scale of 1-2.  
*b* Isolated yields.  
*c* Determined by chiral HPLC analysis (ChiralPak IA; eluent, 80:20 hexane/2-propanol; flow rate, 0.75 mL·min$^{-1}$; detection, 254 nm light).
1.3 Conclusions

The idea of using self-assembly to generate multicomponent catalysts was explored. Twelve structurally different catalysts were generated for the asymmetric aza-Morita-Baylis-Hillman reaction. Unfortunately, these catalysts did not result in any significant preference for one enantiomer of the product. Although attempts at obtaining high enantioselectivities were unsuccessful, it has been demonstrated that self-assembly is an efficient, simple, and useful method in the high throughput screening of catalysts for organic reactions.
Chapter 2
The Role of the Squaramide in Molecular Recognition and Organocatalysis

2.1 Introduction

2.1.1 Squaramides in Molecular Recognition

It is often that an enzyme needs to recognize a specific substrate in order to trigger a biochemical process. Cation recognition was developed around the late 1960s when Lehn first reported accounts of coordination between cations and cryptands.\(^1\) Anion recognition, in comparison, garnered much less attention at the time. Since the 1980s, there have been several different motifs used in synthetic receptors for sensing anions, such as cationic ammonium or guanidinium, neutral calixarenes, amides, ureas, or thioureas.\(^2\)

Shriver and Biallas were the first to report a synthetically developed anion sensor.\(^3\) They demonstrated that a bidentate chelating boron receptor coordinated more strongly to methoxide ions than monodentate boron trifluoride (Figure 3). Shortly after, Park and Simmons also reported the first synthesized macrocyclic anion receptor.\(^4\) They demonstrated the usage of several macrobicyclic ammonium cages for sensing halides via electrostatic interactions and hydrogen bonding.

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Figure 3 Bidentate boron receptor for methoxide ions.

There are several reasons why coordination to anions became a sudden interest. Biological systems consist of several important anions, such as DNA and substrates or cofactors of enzymes. Anions are important for medicine and catalysis, but they also play a role in the environment, such as eutrophication of rivers, due to over-usage of phosphate-containing fertilizers, and carcinogenesis, from metabolism of nitrates. Despite their importance, there are more difficulties in designing an anion receptor in comparison to a cation receptor. Anions are larger than isoelectronic cations, making electrostatic interactions less effective than for cations. Sensitivity to pH must be considered, as the anion may become protonated at lower pH levels. There exist a variety of anion geometries, such as spherical, Y-shaped, or tetrahedral, which in turn requires a higher degree of design of receptors.

Receptors can be organized based on the type of intermolecular non-cova lent interaction involved: electrostatic interactions, hydrogen bonding, metal coordination, hydrophobicity, or a combination of these. The remainder of this thesis will focus on hydrogen bonding interactions.

As hydrogen bonds are directional, it is possible to design receptors that specifically interact with anions of a particular geometry. For example, in 1993, Reinhoudt and coworkers developed a

\[ \text{BF}_2\text{F}_2 \]

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series of acyclic amide-containing tripodal receptors used for binding to tetrahedral anions.\textsuperscript{7} Besides amides, ureas and thioureas are also good hydrogen-bond donors. Kim et al. have demonstrated that the simple ureas (Figure 4a) are good receptors for Y-shaped anions such as carboxylate and nitrate, or tetrahedral anions such as phosphate, phosphonates, and sulfonates, by forming two hydrogen bonds.\textsuperscript{8} Umezawa et al. have also reported binding of dihydrogen phosphate, acetate, and chloride using bis-thioureas (Figure 4b).\textsuperscript{9}

![Figure 4](image_url)  
**Figure 4** a) Urea- and b) thiourea-containing anion receptors.

The group of Philip Gale has extensively studied the potential of ureas and thioureas as transmembrane transporters of important biological anions, such as chloride and bicarbonate.\textsuperscript{10} In addition, they have reported that thioureas are better anion transporters than their urea counterparts.\textsuperscript{11} This is expected as thioureas have a lower pK\textsubscript{a} compared to ureas (21.1 and 26.9


respectively in DMSO), making them stronger acids, and ultimately better hydrogen bond donors.\textsuperscript{12} An example is the comparison of the tris-thiourea and tris-urea derivatives of a tripodal receptor for chloride and bicarbonate, where their results show that the thiourea form is much more significantly capable as an anion transporter (Figure 5).

\textbf{Figure 5} Tris-(thio)urea tripodal receptors for chloride and bicarbonate.

Furthermore, Gale and coworkers also demonstrated recently the use of squaramides as transmembrane anion transporters.\textsuperscript{13} The squaramide motif has been previously used as an anion receptor for chloride, sulfate, and carboxylates,\textsuperscript{14} including work done in this group.\textsuperscript{15,16} Numerous reports confirm that squaramides have higher binding constants to anions than ureas

\begin{equation}
\begin{array}{c}
\text{R} = \text{tBu, Ph} \\
\text{X} = \text{O, S}
\end{array}
\end{equation}


\textsuperscript{16} Rostami, A.; Wei, C. J.; Guérin, G.; Taylor, M. S. \textit{Angew. Chem.} \textbf{2011}, \textit{123}, 2107-2110.
or thioureas. One of the main differences between squaramides and their analogous (thio)ureas is their duality in binding. This means that squaramides not only have the ability to bind to anions via hydrogen bonding, but they are also quite capable of binding to cations, unlike (thio)ureas. This allows squaramides to readily participate in ditopic binding using their acidic protons as well as their oxygens for hydrogen bonding (Figure 6).

(Figure 6 Duality of squaramides.

(Thio)ureas are generally compared to normal (thio)amides, whereas squaramides are closer to vinylogous amides. Delocalization of the nitrogen lone pair through to the carbon-oxygen/sulfur bond is possible for both functionalizations, which restricts the rotation of the C-N bond, making them structurally rigid. In the case of the squaramide, the delocalization is further extended via the cyclobutene ring (Scheme 12). Since the squaramide N-H protons have a lower pK\textsubscript{a} than the


corresponding (thio)urea N-H protons, this increase in acidity may result in stronger binding to anions or activation of substrates in a reaction. The spacing between the N-H groups of (thio)ureas and squaramides also differ, and only in the squaramide is a converging of the N-H bonds found (Figure 7).\textsuperscript{2}

\begin{center}
\begin{align*}
\text{Scheme 12} \ & \text{Comparison of the resonance forms of a) (thio)ureas and b) squaramides.} \\
\text{Figure 7} \ & \text{Comparison of direction and spacing of N-H bonds of N,N'-dimethylthiourea and N,N'-dimethylsquaramide.}
\end{align*}
\end{center}

Squaric acid, from which squaramides are derived, has also been demonstrated to be capable of binding to various transition metals, such as cerium, molybdenum, nickel, palladium, and iron.\textsuperscript{20} Furthermore, Frauenhoff and coworkers illustrated that alkyl dithiosquaramides can form cation complexes with divalent palladium, nickel, or copper in a 2:1 fashion.\textsuperscript{21} This forms a square planar geometry around the coordinating metal centre (Figure 8).

\begin{footnotesize}
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2.1.2 Squaramides in Organocatalysis

In addition to making anion sensors, squaramides have been exploited as bifunctional organocatalysts.² Rawal et al.²² catalyzed the addition of dicarbonyl compounds to nitroalkenes using squaramides, where the acidic N-H protons activated the electrophile via hydrogen bonding and a tertiary amino group activated the nucleophile (Scheme 13). The yields and enantioselectivities were similar to those obtained using analogous thioureas as catalysts, however, catalyst loadings using squaramides could be as low as 0.1 mol%, displaying improved catalyst turnover in comparison to the thioureas. The authors suggested that the enhancement of activity is due to the increased distance between the N-H groups of the squaramide, which in turn improves the fit of the nitroalkene. Other possible factors include the increase in acidity of the N-H protons, greater rigidity of the unit, as well as a more suitable hydrogen-bonding angle.²

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Scheme 13 Applying the bifunctionality of squaramides in organocatalysis.

The squaramide motif has also been used to catalyze the intramolecular Morita-Baylis-Hillman reaction. This work incorporated the squaramide with chiral aminophosphines to easily generate a bifunctional catalyst, yielding excellent enantioselectivities of the desired product (Scheme 14). Additionally, squaramides have been used as organocatalysts in several other reactions including asymmetric Freidel-Crafts reactions of indoles and imines, Michael additions of 4-hydroxycoumarins or 4-hydropyrones to \( \beta,\gamma \)-unsaturated \( \alpha \)-ketoesters, and the 1,4-addition of azlactones, indoles, or dicarbonyl compounds and \( \alpha,\beta \)-unsaturated acylphosphonates.

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Scheme 14 Catalyzing the enantioselective intramolecular MBH reaction using a squaramide-containing aminophosphine.
2.2 Results and Discussion

Based on the data demonstrating that thioureas are better anion binders than ureas, it was hypothesized by the group of Steven Wheeler that dithiosquaramides are superior anion binders than analogous squaramides. In order to test this hypothesis, different squaramides and the corresponding dithiosquaramides were synthesized. Titrations with different anions (as the tetrabutylammonium salt) were performed to determine binding constants.

Three different squaramides with different electronic properties were synthesized. Compounds 2-1 and 2-2 were synthesized using chemistry previously developed in this group, using Zn(OTf)$_2$ as a Lewis acid catalyst (Table 6).

Table 6 Synthesis of bis-squaramides.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R-NH$_2$</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>[Structure]</td>
<td>66</td>
</tr>
<tr>
<td>2-2</td>
<td>[Structure]</td>
<td>88</td>
</tr>
</tbody>
</table>

A third squaramide with two different substituents was also prepared, based on work previously done in this group as well as the group of Butera et al. (Scheme 15).²⁸

![Scheme 15 Synthesis of a squaramide with two different substituents.](image)

Lawesson’s reagent 2-5 was then employed to convert 2-1, 2-2, and 2-4 to the corresponding dithiosquaramides, based on the procedure by Koduri et al. (Scheme 16).²⁹

![Scheme 16 Thiolation of squaramides using Lawesson’s reagent.](image)


Unfortunately, thiolation under these conditions were only successful for compound 2-1 to the corresponding dithiosquaramide 2-6. Although according to the mechanism, each molecule of 2-5 can thiolate both carbonyl groups of one molecule of the squaramide, it was found that having excess of the reagent resulted in better yields (1 equiv.: 42%; 2 equiv.: 67%).

Heating the reaction to 40 °C for the other two squaramides did not show any improvements, so THF was used in place of CH₂Cl₂. Improvement of the solubility of the reagents was also observed in THF. At 70 °C, the reaction only required about 10 minutes before all starting material was consumed, as judged by TLC. The yield of 2-6 using only 1 equivalent of 2-5 was also improved in THF in comparison to in CH₂Cl₂. However, only 10% of 2-8 was isolated, and 2-7 was difficult to isolate by column chromatography due to several side products with similar polarities.

**Table 7**

**Table 7** Thiolation of squaramides using 2-5 in THF.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>x equiv. of 2-5</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-6</td>
<td><img src="image" alt="Structure" /></td>
<td>1</td>
<td>52</td>
</tr>
</tbody>
</table>
Using the obtained 2-6 and 2-8, NMR titration experiments were performed at room temperature in DMSO-$d_6$ with various anions, comparing their binding constants with the corresponding squaramides.

Prior to the titrations, it was observed that there were some unidentified small peaks in the proton NMR spectrum of 2-6. Squaramides can exist as two different conformers in solution, the anti/anti or the anti/syn (Figure 9). The syn/syn conformer has not been observed due to disfavoured steric interaction of the substituents.

The small peaks in the NMR spectrum of 2-6 were confirmed to be a result of a different conformer, likely the more sterically hindered anti/syn conformer, of the product, by running a proton NMR at 60 °C and observing the coalescence of the minor and major peaks. It was determined that, at room temperature, 2-6 exists in a 2:1 ratio of the anti/anti to anti/syn conformations. Therefore, approximately 70 % of 2-6 is in the correct conformer that is capable of hydrogen bonding to anions in DMSO at room temperature.
Figure 9 a) Anti/anti, b) anti/syn, and c) syn/syn conformers of squaramides.

Starting off with 2-1 and 2-6, binding constants with tetrabutylammonium chloride (Bu$_4$NCl) were obtained for each of these compounds. Based on the curve fitting performed using the software OriginLab (see Appendix A), it was determined that the binding constants of 2-1 and 2-6 with chloride were 99 M$^{-1}$ and 205 M$^{-1}$, respectively. This initial result supported the hypothesis that dithiosquaramides are stronger binders to anions than squaramides (Figure 10). The chemical shifts of the peaks corresponding to the anti/syn conformer remained constant throughout the titration, suggesting that it does not participate in hydrogen bonding to the chloride.
Figure 10 Titration curves for the addition of Bu$_4$NCl in DMSO-$d_6$ to 2-1 (open diamonds, $K_a = 99 \pm 17$ M$^{-1}$), 2-6 (solid squares, $K_a = 205 \pm 35$ M$^{-1}$), and 2-4 (open circles, $K_a = 484 \pm 50$ M$^{-1}$). Curve fitting was performed using OriginLab (see Appendix A).

Compounds 2-4 and 2-8 were then titrated with chloride in the same manner. It was observed from the NMR spectrum of 2-4 that it also existed as a mixture of conformers. As expected, 2-4 is a stronger hydrogen bond donor than 2-1 because of the replacement of the donating alkyl group with an electron-withdrawing aryl group, resulting in a $K_a$ of 484 M$^{-1}$. However, when the same experiment was performed on 2-8, no changes were observed to the either of the N-H protons. By NMR spectroscopy, only a single conformer of 2-8 existed in solution, which
suggested that this might be the *anti/syn* conformer. This may be due to the increase in size from the oxygen to the sulfur, which in turn increases the steric interaction between that and the aryl substituent on the neighbouring nitrogen, forcing the adoption of the less stable conformation (Figure 11).

![Figure 11](image)

**Figure 11** Steric interaction between sulfur and the aryl substituent in the *anti/anti* conformation of 2-8.

Titrations were also performed using tetrabutylammonium sulfate and tetrabutylammonium tosylate with 2-1 and 2-6. Since sulfate has a higher pKₐ than chloride (-3.0 versus -9.0 in water), it was expected that the (dithio)squaramides would exhibit stronger binding to sulfate than chloride. However, with both substrates, an accurate binding constant could not be obtained with the data as the N-H proton peak broadened upon addition of sulfate, possibly suggesting deprotonation. With tosylate, chemical shifts of the N-H peaks remained constant throughout the entire titration, suggesting that only the *anti/syn* conformer exists in DMSO at room temperature, and does not participate in hydrogen bonding to the anion.
Based on the results for the binding of 2-1 and 2-6 with chloride, it was hypothesized that 2-6 could be a superior catalyst compared to 2-1 for the Friedel-Crafts alkylation of indole and trans-β-nitrostyrene, as it appears to be a stronger hydrogen bond donor. The Friedel-Crafts alkylation was performed according to the procedure presented by Schneider et al., as shown in Scheme 17.

![Scheme 17 Friedel-Crafts alkylation of indole and trans-β-nitrostyrene.](image)

Crude NMR yields were obtained with reference to mesitylene as the internal standard. Despite the limited solubility of 2-1 in dichloromethane, it resulted in a yield of 20 %, whereas 2-6, which fully dissolved, only resulted in 9 % of product. Even after taking into account that only about 70 % of 2-6 is the anti/anti conformer, this result failed to show that the dithiosquaramide is a better catalyst than the squaramide.

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2.3 Conclusions

The hydrogen bonding ability of different squaramides and dithiosquaramides were explored. It was demonstrated that 2-6, a dialkyl substituted dithiosquaramide, binds more tightly to chloride than its squaramide counterpart, 2-1, as was expected based on previous data on thioureas and ureas. It was also expected and shown that 2-4 binds to chloride more tightly than 2-1, due to the replacement of the electron-donating octyl chain with the electron-withdrawing aryl group. However, no binding to chloride was observed with 2-8, as illustrated by the lack of change in the chemical shifts of the N-H peaks, which was anticipated to be the strongest binder of the four substrates.

Catalysis of the Friedel-Crafts alkylation of indole and trans-β-nitrostyrene was also performed using 2-1 and 2-6. These results did not support the hypothesis that 2-6 would be a better catalyst than 2-1 due to its increased ability to hydrogen bond.
Appendix A

General Procedures. All reactions with air or moisture sensitive reagents were carried out under argon atmosphere. Flash chromatography was performed using neutral silica gel (Silicycle).

Materials. Commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, or TCI and were used as received with the following exceptions: toluene, tetrahydrofuran, and dichloromethane were dried and purified using a solvent purification system (Innovative Technology, Inc.), and handled under argon atmosphere. Chloroform and dichloromethane were degassed by the freeze-pump-thaw method for the aza-MBH reactions. Distilled water was obtained from an in-house supply. Benzaldehyde was distilled before use.

Instrumentation.

Nuclear Magnetic Resonance (NMR): Proton nuclear magnetic resonance ($^1$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Varian Mercury-300 (300 MHz), Varian Mercury-400 (400 MHz), Bruker Avance III 400 MHz, or Agilent DD2 500 MHz. Chemical shifts for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (DMSO: $\delta$ 2.50, DCM: $\delta$ 5.32, CDCl$_3$: $\delta$ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (DMSO: $\delta$ 39.52, CDCl$_3$: $\delta$ 77.16). Data represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, app quin = apparent quintet, m = multiplet), and coupling constants in Hertz (Hz).
**Mass Spectrometry (MS):** High-resolution mass spectra (HRMS) were obtained on a VS 70-250S (double focusing) mass spectrometer at 70 eV or an ABI/Sciex Qstar mass spectrometer.

**High Performance Liquid Chromatography (HPLC):** Enantiomeric excess (e.e.) values were determined by chiral HPLC analysis, using a ChiralPak IA column; eluent, 80:20 hexane/2-propanol; flow rate, 0.75 mL·min⁻¹; detection, 254 nm light.

**Infrared (IR) spectroscopy:** Infrared spectra were obtained on a Perkin-Elmer Spectrum 100 instrument equipped with a single-reflection diamond / ZnSe ATR accessory in the solid state. Spectral features are tabulated as follows: wavenumber (cm⁻¹).

**NMR Titration Procedure:** A host stock solution (Cl: 2 mM, SO₄: 1 mM, OTs: 1 mM) was prepared by dissolving a (dithio)squaramide with DMSO-d₆ in a 5 or 10 mL volumetric flask. The guest stock was prepared by weighing the tetrabutylammonium salt (Cl: 25 mM, SO₄: 6 mM, OTs: 6 mM) into a 2 mL volumetric flask and diluting it with the host stock solution. NMR samples of increasing guest concentrations were prepared. Chemical shifts of the N-H peaks were observed and graphed using Microsoft Excel.

**Curve Fitting:** Binding constants for titrations were determined using OriginLab software, using a non-linear curve fit. Host concentration (H₀) was set to remain constant, as calculated from the experiment, initial dependent value (d₀) was set to 0, and maximum change in N-H chemical shift (d_max) and binding constant (K_a) were allowed to vary.
Literature procedure used. To a 100 mL round-bottomed flask equipped with a stir bar was added $p$-toluenesulfonamide (942 mg, 5.5 mmol) and mixed with dry dichloromethane (25 mL). Distilled benzaldehyde (0.51 mL, 5.0 mmol) and trifluoroacetic anhydride (1.4 mL, 10.0 mmol) was added to the flask. The mixture was refluxed at 60 °C for at 16 h. The reaction was poured into cold water, and extracted 3 x 50 mL with dichloromethane, dried with MgSO$_4$, filtered, and concentrated in vacuo. Pure white crystals were obtained from recrystallization using ether (713 g, 55 %). NMR data were found to be in good agreement with those in literature. IR (neat): 1596, 1574, 1450, 1364, 1215, 1223, 1086, 1022, 999, 866, 802, 781, 754, 704, 689, 669 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.03 (s, 1H, H-1), 7.94-7.87 (m, 4H, H-2), 7.61 (app t, $J = 7.6$ Hz, 1H, H-3), 7.48 (app t, $J = 7.6$ Hz, H-4), 7.34 (d, $J = 8.0$ Hz), 2.43 (s, 3H, CH$_3$). $^{13}$C NMR (100 MHz, DMSO-d$_6$) $\delta$ 170.2, 144.7, 135.3, 135.0, 132.5, 131.4, 129.9, 129.3, 128.2, 21.8.
**Preparation of the self-assembled catalysts:**

To a 1/2 D vial was added 2-formylphenylboronic acid (3.7 mg, 0.025 mmol), diol (0.025 mmol), and a stir bar. To another 1/2 D vial was added aminophosphine (0.025 mmol) under inert atmosphere. Dissolved aminophosphine in degassed chloroform (0.1 mL) was added to the first vial, flushed with argon, and heated at 50 °C for 30 minutes. Solvent was evaporated and the catalyst was used directly in the aza-MBH reaction.

![1-3](image)

Catalyst (0.025 mmol) dissolved in degassed dichloromethane (1 mL) was added to a glass tube containing N-tosyl imine (65 mg, 0.25 mmol), benzoic acid (1.5 mg, 0.0125 mmol), and a stir bar. MVK (42 µL, 0.5 mmol) was added after flushing tube with argon. The tube was capped and stirred at 60 °C for 16 h. After cooling, the reaction was concentrated and purified by column chromatography (15 → 20 % acetone in pentane) to yield a white solid. Racemic material was prepared according to the literature.\(^\text{31}\) IR (neat): 3252, 1663, 1456, 1323, 1250, 1183, 1086, 1060, 958, 930, 850, 809, 741, 702, 664 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.66 (d, \(J = 8.4\) Hz, 2H, H-1), 7.25-7.18 (m, 5H, H-2), 7.09-7.08 (m, 2H, H-3), 6.10 (d, \(J = 6.0\) Hz, 2H, H-4), 5.59 (d, \(J = 8.6\) Hz, 1H, H-5), 5.27 (d, \(J = 8.6\) Hz, 1H, H-6), 2.41 (s, 3H, H-7), 2.16 (s, 3H, H-8). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 199.0, 146.6, 143.5, 139.0, 137.7, 129.6, 128.7, 128.3, 127.8, 127.4, 126.5, 59.1, 26.5, 21.7.
To a 20 mL scintillation vial equipped with a stir bar was added serinol (159 mg, 1.75 mmol) and dry dichloromethane (5 mL). To the mixture was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (320 µL, 1.75 mmol) and was stirred at room temperature overnight. Methanol was added until the precipitate was fully dissolved and the mixture was concentrated and purified by column chromatography (10 % methanol in dichloromethane) to give product as a white solid (479 mg, 75.6 %). IR (neat): 3301, 1525, 1468, 1382, 1274, 1179, 1042, 990, 895, 848, 703, 681 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ 10.2 (s, 1H, H-1), 8.31 (s, 2H, H-2), 7.95 (d, J = 8.0 Hz, 1H, H-3), 7.73 (s, 1H, H-4), 4.86 (s, 2H, H-5), 4.28 (s, 1H, H-6), 3.64-3.61 (m, 2H, H-7), 3.52-3.47 (m, 2H, H-8). ¹³C NMR (125 MHz, DMSO-d₆) δ 180.2, 142.0, 130.3, 130.1, 126.5, 124.4, 122.2, 121.5, 120.0, 115.9, 59.0, 56.8. HRMS (ESI) m/z calcd. for C₁₂H₁₂F₆N₂O₂S [M+H]⁺: 363.0596; found: 363.0599.
To a 20 mL scintillation vial equipped with a stir bar was added serinol (159 mg, 1.75 mmol) and dry dichloromethane (5 mL). To the mixture was added 3,5-bis(trifluoromethyl)phenyl isocyanate (302 µL, 1.75 mmol) and was stirred at room temperature overnight. The precipitate was filtered and washed with dichloromethane to yield a white solid (553 mg, 91%). IR (neat): 3294, 1690, 1572, 1514, 1473, 1385, 1311, 1271, 1183, 1113, 1065, 975, 940, 916, 879, 848, 730, 701, 678 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 9.35 (s, 1H, H-1), 8.02 (s, 2H, H-2), 7.54 (s, 1H, H-3), 6.26 (d, \(J = 8.0\) Hz, 1H, H-4), 4.75 (t, \(J = 5.4\) Hz, 2H, H-5), 3.66-3.59 (m, 1H, H-6), 3.53-3.40 (m, 4H, H-7). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 154.8, 142.8, 126.7, 124.6, 122.4, 120.2, 117.0, 113.3, 62.2, 60.2, 54.6, 52.9. HRMS (ESI) \(m/e\) calcd. for C\(_{12}\)H\(_{12}\)F\(_6\)N\(_2\)O\(_3\) [M+H]\(^+\): 347.0825; found: 347.0828.
Prepared in the manner described for 1-11 using 4-toly isocyanate (221 µL, 1.75 mmol) to yield a white solid (368 mg, 94 %). IR (neat): 3293, 1634, 1594, 1509, 1405, 1311, 1240, 1066, 1033, 975, 813, 778 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ 8.48 (s, 1H, H-1), 7.24 (d, J = 8.4 Hz, 2H, H-2), 7.01 (d, J = 8.4 Hz, 2H, H-3), 5.98 (d, J = 8.1 Hz, 1H, H-4), 4.70 (t, J = 5.2 Hz, 2H, H-5), 3.61-3.56 (m, 1H, H-6), 3.51-3.36 (m, 4H, H-7), 2.20 (s, 3H, CH₃). ¹³C NMR (100 MHz, DMSO-d₆) δ 155.0, 138.0, 129.5, 129.0, 117.4, 60.1, 52.4, 20.3. HRMS (ESI) m/e calcd. for C₁₁H₁₆N₂O₃ [M+H]⁺: 225.1234; found: 225.1237.
Prepared in the manner described for 1-11 using 4-butoxyphenyl isocyanate (317 µL, 1.75 mmol) to yield a white solid (455 mg, 92 %). IR (neat): 3290, 2957, 2869, 1628, 1603, 1515, 1469, 1415, 1384, 1291, 1227, 1176, 1108, 1068, 1037, 973, 879, 837, 810, 793, 755 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆)  δ 8.39 (s, 1H, H-1), 7.24 (d, J = 8.8 Hz, 2H, H-2), 6.79 (d, J = 8.8 Hz, 2H, H-3), 5.93 (d, J = 8.0 Hz, 1H, H-4), 4.70 (s, 2H, H-5), 3.88 (t, J = 6.9 Hz, 2H, H-6), 3.60-3.54 (m, 1H, H-7), 3.50-3.37 (m, 4H, H-8), 1.65 (dt, J = 14.8, 6.9 Hz, 2H, H-9), 1.41 (dq, J = 14.8, 7.4 Hz, 2H, H-10), 0.92 (t, J = 7.4 Hz, 3H, H-11). ¹³C NMR (100 MHz, DMSO-d₆)  δ 155.2, 153.2, 133.6, 119.1, 114.5, 67.3, 63.6, 60.2, 52.4, 30.9, 18.7, 13.7. HRMS (ESI) m/e calcd. for C₁₄H₂₂N₂O₄ [M+H]⁺: 283.1652; found: 283.1656.
Prepared in the manner described for 1-11 using octyl isocyanate (309 µL, 1.75 mmol) to yield a white solid (391 mg, 91 %). IR (neat): 3310, 2960, 2924, 2852, 1623, 1464, 1308, 1237, 1054, 974, 725 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 5.98 (t, \(J = 5.6\) Hz, 1H, H-1), 5.62 (d, \(J = 7.6\) Hz, 1H, H-2), 4.61 (t, \(J = 5.4\) Hz, 2H, H-3), 3.52-3.45 (m, 1H, H-4), 3.43-3.29 (m, 4H, H-5), 2.94 (app q, \(J = 6.4\) Hz, 2H, H-6), 1.34-1.24 (m, 12H, H-7), 0.86 (t, \(J = 6.8\) Hz, 3H, CH\(_3\)). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 158.0, 60.5, 52.7, 31.2, 30.0, 28.7, 28.6, 26.4, 22.1, 14.0. HRMS (ESI) \(m/e\) calcd. for C\(_{12}\)H\(_{26}\)N\(_2\)O\(_3\) [M+H\(^+\)]: 237.2016; found: 247.2018.
A solution of 1-chloro-2,3-propanediol (80 µL, 0.96 mmol) and 30 % NH₄OH (2.5 mL) was stirred in a 2D vial at room temperature overnight. The solution was evaporated until a solid was formed, where saturated aqueous NaHCO₃ (1 mL) and MeCN (1 mL) was added. To this mixture was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (175 µL, 0.96 mmol) and stirred overnight at room temperature. The mixture was extracted with EtOAc (3 x 30 mL), dried with MgSO₄, concentrated, and purified via column chromatography (3.75 → 5 % methanol in dichloromethane) to yield a white solid (235 mg, 68 %). IR (neat): 3228, 1642, 1607, 1553, 1474, 1381, 1273, 1055, 1028, 952, 886, 762, 718, 699, 675 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ 10.2 (s, 1H, H-1), 8.30 (s, 2H, H-2), 8.08 (s, 1H, H-3), 7.72 (s, 1H, H-4), 5.01 (s, 1H, H-5), 4.69 (s, 1H, H-6), 3.77-3.65 (m, 2H, H-7), 3.43-3.30 (overlap with water) (m, 3H, H-8). ¹³C NMR (100 MHz, DMSO-d₆) δ 180.6, 142.2, 126.6, 124.4, 122.3, 121.5, 120.1, 115.8, 69.6, 64.1, 47.5. HRMS (ESI) m/e calcd. for C₁₂H₁₂F₆N₂O₂S [M+H]⁺: 363.0596; found: 363.0598.
Prepared in the manner described for 1-10 using 1-amino-2,3-propanediol (159 mg, 1.75 mmol) under inert atmosphere. Crude product was purified via column chromatography (5 % methanol in dichloromethane) to yield a white solid (599 mg, 94 %). IR (neat): 3230, 1641, 1606, 1552, 1474, 1380, 1273, 1167, 1106, 1055, 1027, 952, 901, 885, 761, 719, 699, 675 cm\(^{-1}\). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 10.3 (s, 1H, H-1), 8.30 (s, 2H, H-2), 8.08 (s, 1H, H-3), 7.72 (s, 1H, H-4), 5.01 (d, \(J = 3.5\) Hz, 1H, H-5), 4.69 (s, 1H, H-6), 3.75-3.66 (m, 2H, H-7), 3.43-3.31 (overlap with water) (m, 3H, H-8). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 180.7, 142.2, 130.5, 130.2, 126.6, 124.5, 122.3, 121.5, 120.1, 115.8, 69.7, 64.1, 47.5. HRMS (ESI) \(m/e\) calcd. for C\(_{12}\)H\(_{12}\)F\(_6\)N\(_2\)O\(_2\)S [M+H]\(^+\): 363.0596; found: 363.0598.
To a 20 mL scintillation vial equipped with a stir bar was added 3-amino-1,2-propanediol (159 mg, 1.75 mmol) and dry dichloromethane (5 mL). To the mixture was added 3,5-bis(trifluoromethyl)phenyl isocyanate (302 µL, 1.75 mmol) and was stirred at room temperature overnight. The precipitate was filtered and washed with dichloromethane to yield a white solid (553 mg, 91 %). IR (neat): 335, 1643, 1572, 1387, 1276, 1175, 1002, 935, 882, 847, 702, 682 cm\(^{-1}\). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 9.35 (s, 1H, H-1), 8.02 (s, 2H, H-2), 7.52 (s, 1H, H-3), 6.38 (t, \(J = 5.5\) Hz, 1H, H-4), 4.86 (d, \(J = 4.5\) Hz, 1H, H-5), 4.60 (t, \(J = 5.5\) Hz, 1H, H-6), 3.54-3.48 (m, 1H, H-7), 3.36-3.26 (overlap with water) (m, 3H, H-8), 2.99 (ddd, \(J = 13.4, 7.1, 5.1\) Hz, 1H, H-9). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 155.4, 142.9, 126.8, 124.6, 122.4, 120.3, 117.2, 117.1, 113.2, 70.7, 64.0, 43.7, 42.8. HRMS (ESI) \(m/e\) calcd. for C\(_{12}\)H\(_8\)F\(_6\)N\(_2\)O\(_3\) [M+H]\(^+\): 347.0825; found: 347.0828.
To a 20 mL scintillation vial with a solution of zinc triflate (95 mg, 0.26 mmol), 3,4-diethoxycyclobut-3-ene-1,2-dione (192 µL, 1.30 mmol), and a stir bar in a 19:1 mixture of toluene/N-methyl-2-pyrrolidone (2 mL) was added octylamine (451 µL, 2.73 mmol). The solution was stirred overnight at 100 °C. Upon cooling to room temperature, a precipitate was formed, which was filtered, washed with toluene, and dried to yield a white solid (288 mg, 66%). IR (neat): 3158, 2954, 2915, 2847, 1803, 1649, 1468, 1385, 1339, 1307, 1292, 1161, 1063, 1030, 864, 834, 757, 721 cm\(^{-1}\). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.26 (br s, 2H, H-1), 3.48 (br s, 4H, H-2), 1.52-1.48 (m, 4H, H-3), 1.27-1.25 (m, 20H, H-4), 0.87-0.84 (m, 6H, H-5). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 43.3, 31.2, 30.8, 28.7, 28.6, 25.8, 22.1, 14.0. HRMS (ESI) \(m/e\) calcd. for \(\text{C}_{20}\text{H}_{36}\text{N}_{2}\text{O}_{2}\) [M+H]\(^+\): 337.2850; found: 337.2853.
Prepared in the manner described for 2-1 using 3,5-bis(trifluoromethyl)aniline (426 µL, 2.73 mmol) to yield a pale yellow solid (615 mg, 88 %). IR (neat): 2928, 1801, 1676, 1562, 1446, 1365, 1273, 1167, 1029, 934, 888, 859, 762, 727, 698, 681 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ 10.6 (br s, 2H, H-1), 7.88 (s, 4H, H-2), 7.69 (s, 1H, H-3). ¹³C NMR (125 MHz, DMSO-d₆) δ 165.8, 140.5, 131.1, 124.1, 122.0, 119.2, 48.5, 30.1, 29.0, 17.2. HRMS (ESI) m/e calcd. for C₂₀H₈F₁₂N₂O₂ [M+H]⁺: 537.0467; found: 537.0464.
To a 20 mL scintillation vial with a solution of zinc triflate (36 mg, 0.1 mmol), 3,4-diethoxycyclobut-3-ene-1,2-dione (148 µL, 1.0 mmol), and a stir bar in ethanol (3 mL) was added 3,5-bis(trifluoromethyl)aniline (156 µL, 1.0 mmol). The solution was stirred at room temperature overnight. The mixture was concentrated and the product was filtered and washed with water to yield a yellow solid (302 mg, 86 %). IR (neat): 3250, 3100, 1815, 1737, 1716, 1555, 1475, 1453, 1407, 1372, 1346, 1327, 1274, 1168, 1100, 1041, 998, 937, 886, 859, 832, 728, 699, 680, 657 cm\(^{-1}\). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 11.2 (s, 1H, H-1), 8.04 (s, 2H, H-2), 7.79 (s, 1H, H-3), 4.80 (q, \(J = 7.2\) Hz, 2H, H-4), 1.42 (t, \(J = 7.2\) Hz, 3H, H-5). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 184.5, 179.3, 140.1, 131.5, 131.3, 130.9, 130.7, 126.3, 124.2, 122.0, 119.5, 119.4, 116.3, 70.1, 15.4. HRMS (ESI) \(m/e\) calcd. for C\(_{14}\)H\(_9\)F\(_6\)NO\(_3\) [M+H]\(^+\): 354.0559; found: 354.0562.
To a 20 mL scintillation vial containing 2-3 (283 mg, 0.80 mmol) and a stir bar in ethanol (4 mL) was added octylamine (145 µL, 0.88 mmol). The solution was stirred at room temperature overnight. The mixture was evaporated and the product was washed with dichloromethane to yield a white solid (249 mg, 71 %). IR (neat): 2930, 1795, 1659, 1627, 1571, 1480, 1426, 1376, 1334, 1297, 1274, 1164, 1001, 931, 912, 884, 836, 734, 701, 681 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ 8.02 (s, 2H, H-1), 7.65 (s, 1H, H-2), 3.61 (s, 2H, H-3), 1.59-1.55 (m, 2H, H-4), 1.30-1.25 (m, 10H, H-5), 0.88-0.83 (m, 3H, H-6). ¹³C NMR (125 MHz, DMSO-d₆) δ 184.8, 180.3, 169.8, 162.2, 141.2, 131.5, 131.3, 126.4, 124.3, 122.1, 117.9, 114.5, 43.9, 31.3, 30.5, 28.7, 28.6, 25.9, 22.1, 13.9. HRMS (ESI) m/e calcd. for C₂₀H₂₂F₆N₂O₂ [M+H]⁺: 437.1658; found: 437.1657.
To a 20 mL scintillation vial of **2-1** (67 mg, 0.20 mmol), Lawesson’s reagent (162 mg, 0.40 mmol), and a stir bar was added dry dichloromethane (4 mL). The mixture immediately turned yellow and was stirred at 40 °C until all solids were completely dissolved to a clear dark red solution. Completion of the reaction was confirmed by TLC. The mixture was concentrated and purified by column chromatography (20 % ethyl acetate in pentane) to yield a bright yellow solid (49 mg, 67 %). IR (neat): 3134, 3000, 2923, 2852, 1608, 1505, 1466, 1378, 1360, 1312, 1249, 1233, 1213, 1189, 1119, 1058, 851, 724 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ 8.41 (t, J = 6.7 Hz, 2H, H₁), 4.02 (q, J = 6.7 Hz, 4H, H₂), 1.64-1.53 (m, 4H, H₃), 1.33-1.24 (m, 20H, H₄), 0.87-0.84 (m, 6H, H₆). ¹³C NMR (125 MHz, DMSO-d₆) δ 203.5, 170.5, 55.2, 42.8, 31.2, 30.5, 28.6, 28.5, 25.8, 22.1, 14.0. HRMS (ESI) m/e calcd. for C₂₀H₃₆N₂S₂ [M+H]+: 369.2393; found: 369.2393.
To a 50 mL round-bottomed flask of 2-4 (349 mg, 0.8 mmol), Lawesson’s reagent (647 mg, 1.6 mmol), and a stir bar was added dry THF (25 mL). The mixture immediately turned yellow and was stirred at 70 °C for 10 minutes. The clear bright red solution was cooled, concentrated, and extracted with ethyl acetate (3 x 50 mL). The crude product was dried with MgSO₄, concentrated, and purified by column chromatography (3 % acetone in pentane) to yield a bright yellow solid (37 mg, 10 %). IR (neat): 3135, 2927, 2858, 1568, 1466, 1437, 1374, 1310, 1279, 1176, 948, 931, 888, 849, 809, 776, 742, 700, 684 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆) δ 11.6 (s, 1H, H-1), 10.4 (s, 1H, H-2), 8.25 (s, 2H, H-3), 7.86 (s, 1H, H-4) 4.02 (q, J = 6.7 Hz, 2H, H-5), 1.63 (app quin, J = 6.9 Hz, 2H, H-6), 1.29-1.23 (m, 10H, H-7), 0.84 (t, J = 7.0 Hz, 3H, H-8). ¹³C NMR (125 MHz, DMSO-d₆) δ 185.0, 183.2, 137.5, 130.1, 129.9, 126.4, 124.2, 123.5, 122.0, 119.8, 117.9, 31.2, 30.1, 28.6, 28.5, 25.7, 22.1, 13.9. HRMS (ESI) m/e calcd. for C₂₀H₂₂F₆N₂S₂ [M+H]^+: 469.1201; found: 469.1204.
Appendix B

$^1$H NMR of 1-2

$^{13}$C NMR of 1-2
$^1$H NMR of 1-3

$^{13}$C NMR of 1-3
$^1$H NMR of 1-10

$^{13}$C NMR of 1-10
$^1$H NMR of 1-11

$^{13}$C NMR of 1-11
$^1$H NMR of 1-12

$^{13}$C NMR of 1-12
$^1$H NMR of 1-13

$^{13}$C NMR of 1-13
$^1$H NMR of 1-14

\[
\begin{aligned}
\text{H} & \text{N} \to \text{O} \\
\text{N} & \text{H} \to \text{O} \\
\text{N} & \text{H} \to \text{O} \\
\text{N} & \text{H} \to \text{O} \\
\text{N} & \text{H} \to \text{O} \\
\end{aligned}
\]

$^{13}$C NMR of 1-14
$^1$H NMR of 1-16

$^{13}$C NMR of 1-16
$^1$H NMR of 1-17

$^{13}$C NMR of 1-17
$^1$H NMR of 1-18

$^{13}$C NMR of 1-18
$^1$H NMR of 2-1

$^{13}$C NMR of 2-1
$^{1}$H NMR of 2-2

$^{13}$C NMR of 2-2
$^1$H NMR of 2-3

$^{13}$C NMR of 2-3
$^1$H NMR of 2-4

\[ \text{Chemical Structure Image} \]

$^{13}$C NMR of 2-4

\[ \text{Chemical Structure Image} \]
$^{1}H$ NMR of 2-6

$^{13}C$ NMR of 2-6
$^1$H NMR of 2-8

$^{13}$C NMR of 2-8