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## Development of Anthranilic Acid Based Thiourea Catalysts for the Nitroaldol Reaction

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# Development of Anthranilic Acid Based Thiourea Catalysts for the Nitroaldol Reaction

By

Augie Witkowski

College of Saint Benedict



CAPSTONE THESIS

Submitted in partial fulfillment of the requirements for the Chemistry Major at the College of St. Benedict | Saint John's University, Saint Joseph & Collegeville, Minnesota.

May 1, 2019

# Abstract

Organocatalysis is the use of low molecular weight organic molecules to accelerate chemical reactions. As seen by its rapid growth over the last couple decades, this type of catalysis is attractive to synthetic chemists due to the mild reaction conditions, low cost materials and green chemistry characteristics organocatalysis offers. Thiourea-based organocatalysts promote reactions using reversible and selective, hydrogen bonding, which can be used to activate the electrophile and nucleophile reactants. By modifying the structure, co-catalysts, and other conditions used with these catalysts the activity can be modified and improved for specific products. Using these design principles, a set of thiourea catalysts were synthesized using 3,5-bis(trifluoromethyl)phenyl isothiocyanate and either ortho and para-aminobenzoic acid, or ortho and para-aminophenol. The catalysts were screened for catalytic activity in the Henry Nitroaldol Reaction. As catalytic activity differed with structure this gave insight into optimal motifs and conditions for thiourea catalysts. These catalysts also provide a novel pairing as the thiourea functional group is paired with a carboxylic acid group instead of one of the many basic functional groups commonly paired with it. To further improve both the catalytic activity and recyclability of these catalysts while preserving their initial appealing features a silica surface could be functionalized with these thiourea catalysts.

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# Body of Thesis

## Introduction

Organocatalysis is the use of low molecular weight organic molecules to accelerate chemical reactions. As seen by its rapid growth over the last couple decades, this type of catalysis is attractive to synthetic chemists due to the mild reaction conditions, low cost materials and green chemistry characteristics organocatalysis offers over traditional metal catalysis.<sup>1, 2</sup> Thiourea catalysts are a class within the field of organocatalysis which have been shown effective catalysts in a variety of reactions that produce important pharmaceutical and industrial products. These catalysts encourage the use of mild conditions as a strong base is often no longer needed when a thiourea catalyst is used to activate a reaction. Thiourea catalysts are also favored over other organocatalysts, such as enamine catalysts, due to the fact that they catalyze a reaction by reversibly and selectively hydrogen-bonding to the substrate instead of covalently bonding to the substrate. The structure of thiourea catalysts can easily be modified to promote asymmetric reactions, or increased rates with the addition of a variety of structural motifs.<sup>3</sup>

### A. Electron Withdrawing Groups

A widely used structural motif in thiourea catalysts is the presence of electron withdrawing groups. One of the first, and one of the simpler thiourea catalysts is the Scheiner thiourea, which contains two 3,5-bis(trifluoromethyl) phenyl groups. The presence of these groups pulls electron density away from the nitrogen atoms of the thiourea decreasing the pKa of the protons attached to the nitrogen atoms.<sup>4, 5</sup> The presence of these groups allows for thiourea catalysts to donate in multiple hydrogen bonding interactions, which is key to the overall reactivity. Hydrogen bonding electrophilic activation is one of the common modes of activation observed with the use of thiourea catalysts.

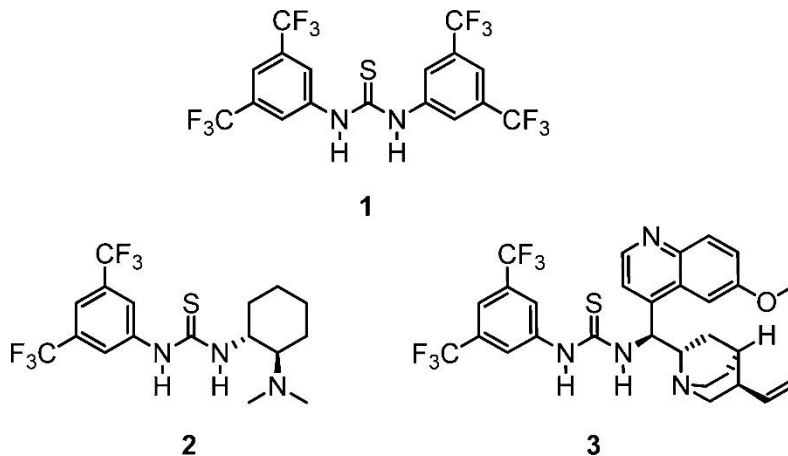


Figure 1. Adapted from Madarász et. al. examples of electron withdrawing groups in thiourea catalysts. N,N'-bis[3,5-bis(CF<sub>3</sub>)phenyl]thiourea (1) (Referred to as Schreiner's Thiourea) and

Two Representatives of Thiourea-Based Bifunctional Amine Catalysts (Takemoto's Catalyst (2) and Epi-quinine Catalyst (3)).<sup>4</sup>

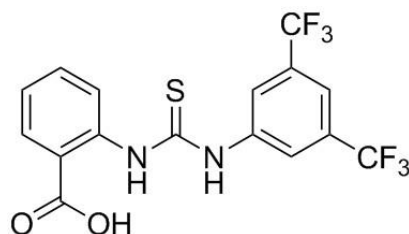


Figure 2. Our group's synthesized p-aminobenzoic acid thiourea catalyst includes the electron withdrawing groups.

### B. Functional Group Pairings

Thiourea catalysts are often bifunctional catalysts, with the thiourea functional group being paired with other functional groups such as primary and tertiary amines, guanidinium ions, cyclopropenium ions, and steroidal structural motifs. The most common bifunctional thiourea catalysts contain a primary amine group which can aid in enantioselectivity by forming the enamine of the nucleophile in a specific orientation next to the thiourea activated electrophile.<sup>6-9</sup> This method was applied to a vinylogous aldol reaction, which increased yields and enantiomeric excesses using reactants that had not previously been used in a enantioselective manner, while increasing the overall reaction rate. The complexes of the catalyst and substrate were detected using mass spectrometry.<sup>7</sup>

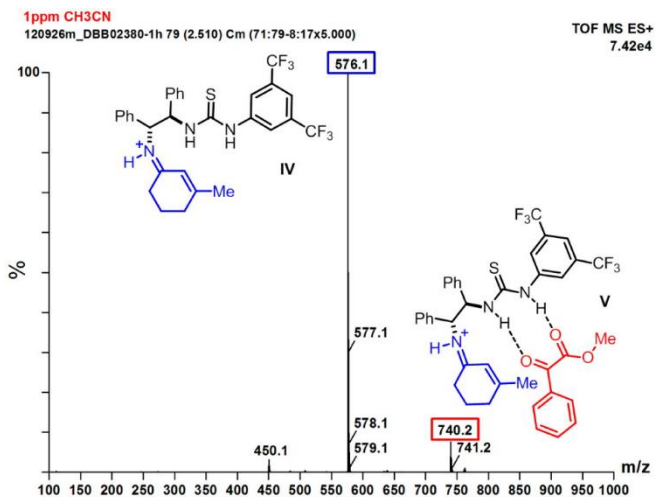


Figure 3. Adapted from Bastida et. al. Intermediates detected by ESI-MS I positive mode of the aldol reaction. This shows the role of the two functional groups in activation.

This structural motif has also been applied to the Diels-Alder reaction to form pharmaceutical intermediates and compounds. Again, in this reaction the enamine catalyzes the nucleophile of the reaction, but the thiourea functional group stabilizes the intermediates of the reaction by bonding to the conjugate base of the acid used in the proton transfer step for the removal of the enamine.<sup>8</sup>

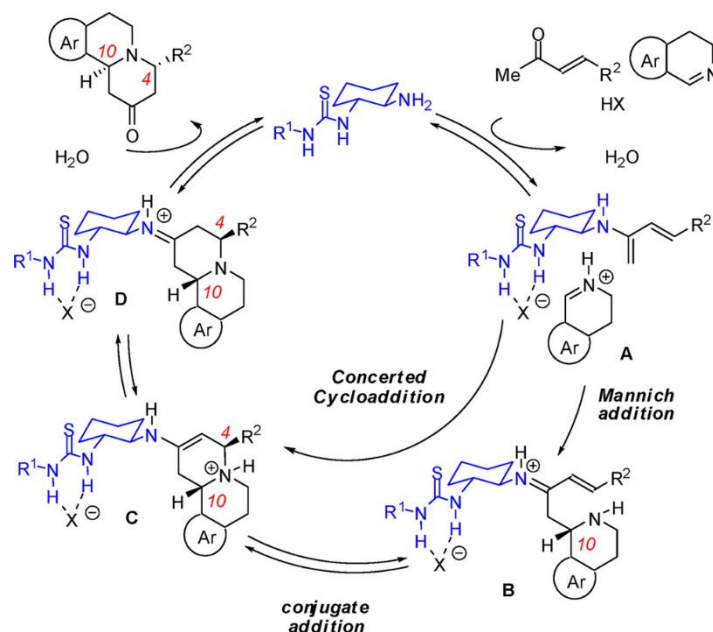


Figure 4. Adapted from Lalonde et. al. Proposed Catalytic Cycle for the Formation of FADA Adducts showing the role of the primary amine and thiourea.<sup>8</sup>

Using this same bifunctionality in conjunction with a chiral scaffold to separate the functional groups produces enantioenriched alcohols in a hydride reduction reaction. These reactions are typically not enantioselective, but with the complexation of the reactants allows forces the reduction on one face of the molecule.<sup>9</sup>

Beyond the common pairing of thioureas with primary amines thioureas have also been paired with tertiary amines, cyclopropenium ions, and guanidinium ions. In order to catalyze an aza-Henry reaction with protected imines a bifunctional thiourea and tertiary amine catalyst was used along with a saccharide group to provide more stereocontrol. Instead of saccharide groups tertiary amine bifunctional catalysts have also been synthesized with large aryl groups which provided enantioselectivity in a Diels-Alder and retro-Nitroaldol reaction.<sup>6, 10</sup>

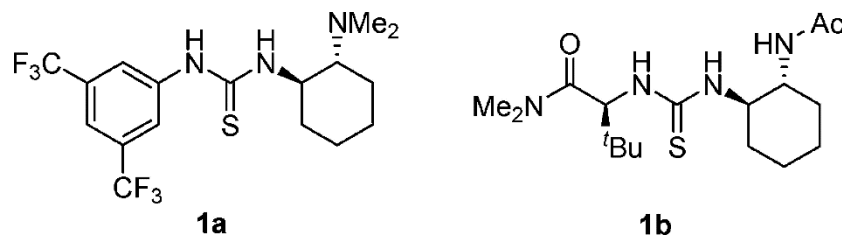


Figure 5. Adapted from Wang et. al. Thiourea catalysts with tertiary and secondary amine functional groups.<sup>6</sup>



The bifunctional cyclopropenium and guanidinium catalysts work in a similar manner by placing a positive charge near the hydrogen bond donating area of the thiourea group, which lowers the pK<sub>a</sub> of the protons. Both of these functional groups also serve to provide activation of the nucleophile through hydrogen bonding.<sup>11, 12</sup>

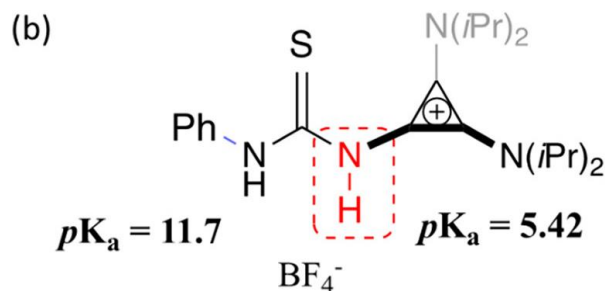


Figure 6. Adapted from Smajlagic et. al. Two-dimensional representation highlighting the computed pK<sub>a</sub> values in DMSO showing the influence of the cyclopropenium ion.<sup>11</sup>

### C. Common Co-catalysts

Thiourea catalysts are often paired with other organic small molecules as co-catalysts for a variety of purposes. The addition of these co-catalysts can increase reaction rates, stereocontrol, and the potential application of thiourea catalysts.<sup>13-16</sup> There are two examples of a thiourea co-catalyst system being used in Pictet-Spengler reactions. Both of these schemes pair benzoic acid with the thiourea to effectively catalyze the reaction of the amines with aldehydes. By using a concentration of the benzoic acid co-catalyst that was less than the thiourea catalyst the Pictet-Spengler reaction proceeding with good yields and large enantiomeric excesses.<sup>15</sup> The use of benzoic acid co-catalyst in these reactions is effective due to the stabilization of the intermediates and transition states of the reaction, which was determined by DFT and KIE studies. It was shown that the thiourea stabilizes the benzoic acid in its deprotonated form through the hydrogen bond donors.<sup>14</sup>

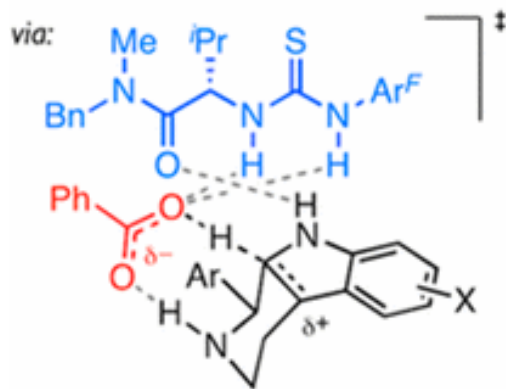


Figure 7. Adapted from Klausen et. al. Example of a transition state stabilized by a thiourea catalyst and benzoic acid co-catalyst in a Pictet-Spengler reaction.<sup>14</sup>

The use of co-catalysts can also expand the reactions that can be catalyzed. The cooperative use of an enamine and thiourea catalyst enables a three-step reaction to be run in one step as the catalysts can activate each consecutive step. The thiourea effectively activates the electrophiles, and the enamine activates nucleophile, acting in a similar way to bifunctional enamine thiourea catalysts. If one of the co-catalysts was not present, then only the first of three reactions was possible.<sup>13</sup>

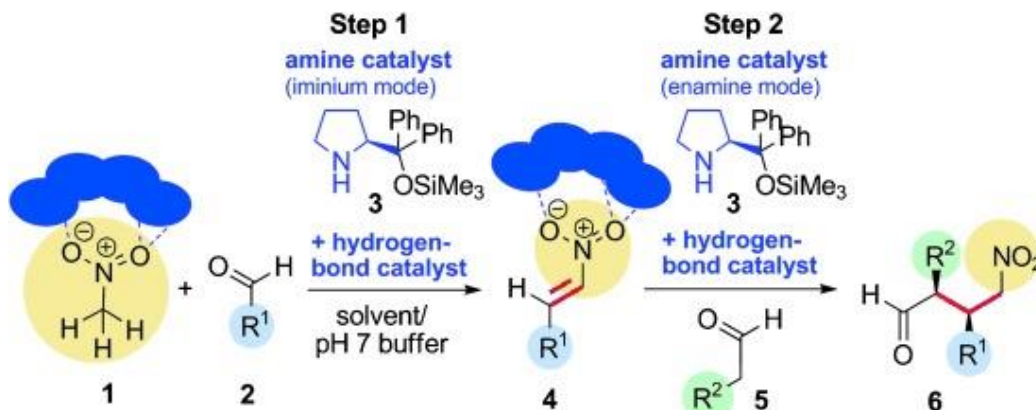


Figure 8. Adapted from Rahaman et. al. A three step reaction sequence with activation of the nitro group by the hydrogen-bond thiourea catalyst.<sup>13</sup>

While the benzoic acid and enamine co-catalysts were necessary in this reaction, a co-catalyst is not always necessary for catalysis itself, but can be used to produce specific results. Joining a thiourea catalyst, and electrophilic catalyst, with the use of 4-dimethylaminopyridine (DMAP), a nucleophilic catalyst, produces kinetic enantiomeric resolution of amines, allowing the effective measurement and study of enantiomeric excess of amine products.<sup>16</sup>

#### D. Hydrogen Bonding Activation

Hydrogen bonding is the most common activation strategy seen in thiourea catalysts, and it can be applied in many variable mechanisms.<sup>17-20</sup> Typically, the thiourea acts as a hydrogen bond donor and activates an electrophile, and often also activates the nucleophile through hydrogen bonding as well.<sup>21</sup>

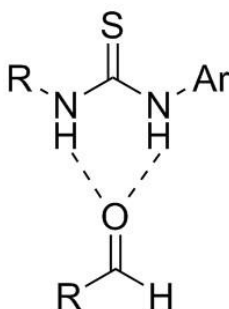


Figure 9. Simplified diagram of the general hydrogen bonding activation mode.

This mode dual activation was observed in a Michal-Henry domino reaction. This study used a cinchona derived catalyst which is a common chiral adduct to offer stereocontrol. This catalyst used a protonated amine to activate the nitro group, and interestingly, even postulated that a hydrogen off of the 3,5-bis(trifluoromethyl)phenyl was involved in this network of hydrogen bonding.<sup>18</sup> The hydrogen bonding motifs of cinchona derived catalysts have been shown to be impacted by solvent though, and can cause the hydrogen bond donors of the catalyst to be decreased to one. This mode of hydrogen bonding was still shown to activate the Henry reaction in an enantioselective manner.<sup>17</sup>

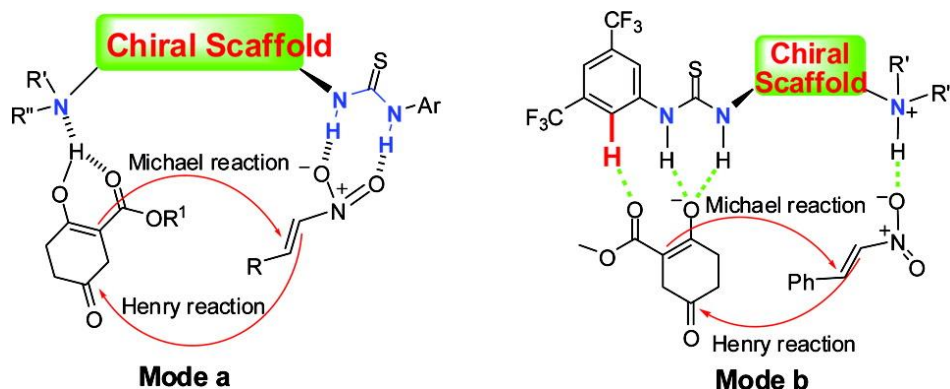


Figure 10. Adapted from Tan et. al. These were the proposed activation modes of the catalyst and substrates before (a) and after (b) the DFT calculations.<sup>18</sup>

Similar hydrogen bonding dual activation has also been observed in another Michael addition reaction. Both the electrophilic enone and the nitroalkyl reactants can form hydrogen bonding complexes with the catalyst, offering a reaction route through whichever reactant bonds.<sup>21</sup> This hydrogen bonding activation has been shown to be key to catalysis through computational studies as well. In the study of various hydrogen bonding complexes that can be formed between thioureas and imines it was shown that this activation mode helps to promote reactions by elongating the bond of the imine promoting the breaking of this bond.<sup>22</sup>

Instead of activation of an electrophile and nucleophile the hydrogen bonding motif has been shown to activate cyclization reactions by stabilizing the anion and cation formed in the reaction. The thiourea essentially acts as a counter ion to both of the reactants in this case through hydrogen bonding and promotes the reaction enantioselectively due to the large chiral aryl group in the structure.<sup>20</sup>

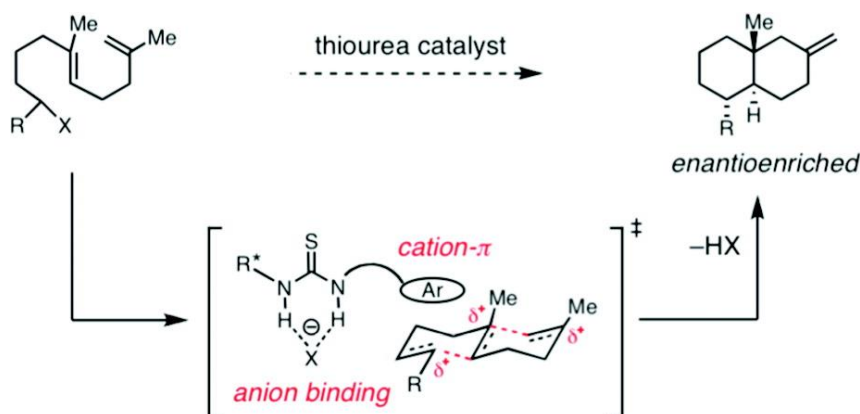


Figure 11. Adapted from Knowles et. al. This was their proposed transition state in the polycyclization reaction showing the simultaneous counter ion effects from the catalyst.<sup>20</sup>

### E. Bronsted Acid Activation

While it has been generally assumed that thiourea catalysts activate reactions by acting as hydrogen bond donors, there are other mechanisms of activation as well. One such mechanism is Bronsted Acid catalysis in which the thiourea catalyst acts as a proton acceptor and deprotonates the nucleophile increasing its reactivity.<sup>4, 11</sup> This mechanism has primarily been observed in variations of pyranylation reactions. The occurrence of this mechanism has been confirmed by both computational and experimental data in these reactions. Instead of hydrogen bonding to the alcohol group the thiourea deprotonates it.<sup>11, 23</sup> This mode of activation is seen due to the extremely electron-withdrawing groups that the thioureas are paired with that lowers the pKa of the thiourea hydrogens drastically, easily causing the two subsequent deprotonations. As many thiourea catalyzed reactions are done in basic conditions this potential mode of activation must be accounted for in the design of the catalysts to lead to the desired activity.

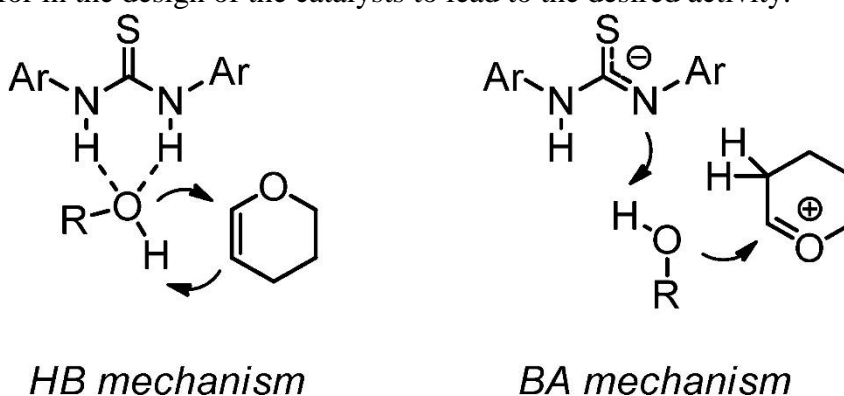


Figure 12. Adapted from Madarasz et. al. showing the expected hydrogen bonding mode of activation and the alternative Bronsted Acid mode of activation.<sup>4</sup>

## F. Design of o-Aminobenzoic Acid Catalyst

With the previous structural and reaction motifs in mind, we synthesized a group of thiourea catalysts. These catalysts include the electron withdrawing 3,5-bis(trifluoromethyl)phenyl structural motif that is seen in Schreiner's thiourea and many others which increases the donating character of hydrogens on the nitrogen atoms of the thiourea moiety. Placed on the opposite side of the thiourea from this group were various benzylic groups. Ortho-aminobenzoic acid and ortho-phenol were catalysts we focused upon, and we compared these reactions with their para positioned counterparts. The inclusion of either the carboxylic acid or hydroxyl group near the thiourea hydrogen bond region was inspired by the common motif of an amine group next to the thiourea.<sup>13, 15</sup> The addition of these functional groups was intended to provide amplified activation of the nucleophile, as is typically seen in enamine catalysis, though without covalently bonding to the reactants. This change could expand the applicability of thiourea catalysts, and we screened these catalysts in the nitroaldol reaction for activity.

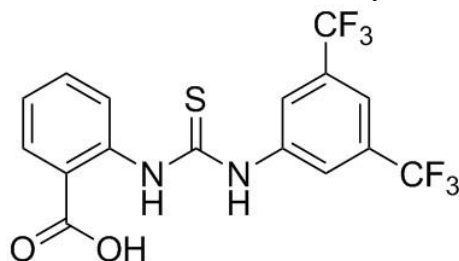


Figure 13. The synthesized o-aminobenzoic acid catalyst which includes common structural motifs of other thiourea catalysts.

## Results and Discussion

Each catalyst was synthesized using 3,5-bis(trifluoro)methyl phenyl and a corresponding amine reactant, either aminobenzoic acid, aminophenol, or aniline stirring in DCM and THF for 24 hours. These products were purified with silica gel chromatography and characterized with HNMR and IR following syntheses of similar thiourea catalysts.<sup>12, 24</sup> The thiourea compounds were screened in the nitroaldol reaction for catalytic activity.<sup>25</sup> The resulting activity gave insight into the impacts of the carboxylate and hydroxyl positions on the catalyst, and how these structural motifs fit in with other common thiourea catalyst structural motifs.

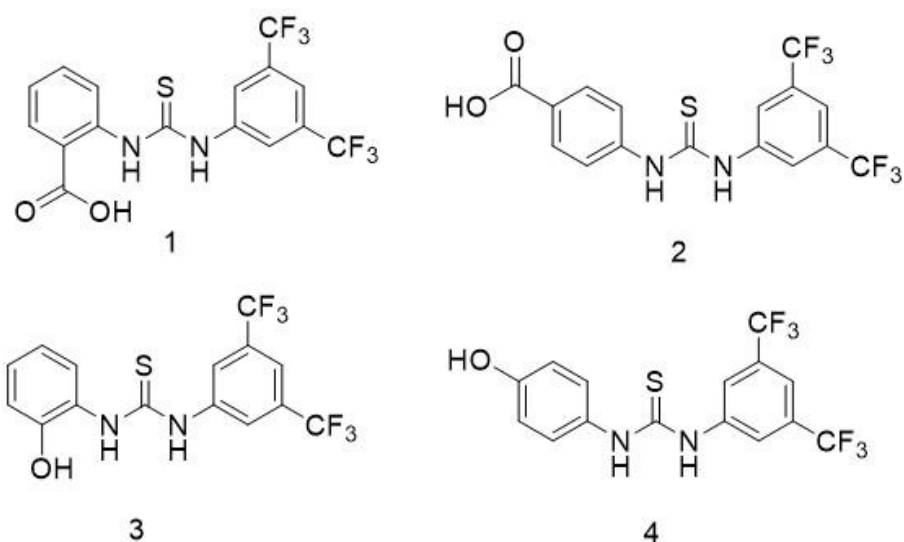
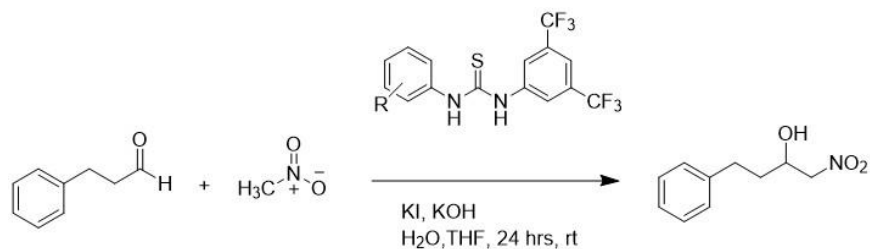


Figure 14. The four thiourea catalysts (1-4) synthesized and screened in the nitroaldol reaction.

Catalyst 1 was found to be the most active in the nitroaldol reaction and produced 83% conversion of the nitromethane to the aldol by HNMR. This activity dropped off substantially when the other catalysts were used. The factors leading to this dramatic decrease in activity were attributed to the structural variations of the catalysts.



Scheme 1. Nitroaldol reaction scheme with catalyst.

Reaction	Thiourea	R	Percent Conversion
1	1	o-COOH	83% +/- 4
2	2	p-COOH	53% +/- 23
3	3	o-OH	34% +/- 24
4	4	p-OH	11% +/- 2
5	-	H	72% +/- 7

Table 1. Percent conversions of the nitroaldol reaction by HNMR in the presence of catalysts 1-4, and the simplest thiourea in entry 5 for comparison.

Beginning with Catalyst 1, the position of the carboxylate on the aryl ring was modified to explore the role of this functional group in catalysis. Catalyst 2 was synthesized with the carboxylate group in the para position instead of the ortho position on the ring and produced variable results in the nitroaldol reaction. Overall, the conversion was reduced to 53% from 83% with the para positioned carboxylate indicating that this group plays a crucial role in catalysis. In the reaction it is proposed that the carboxylic acid is deprotonated quickly to the carboxylate, and

this anionic group helps to form a complex with the hydrogen bond donors of the thiourea that promotes the formation of the nitroenolate.

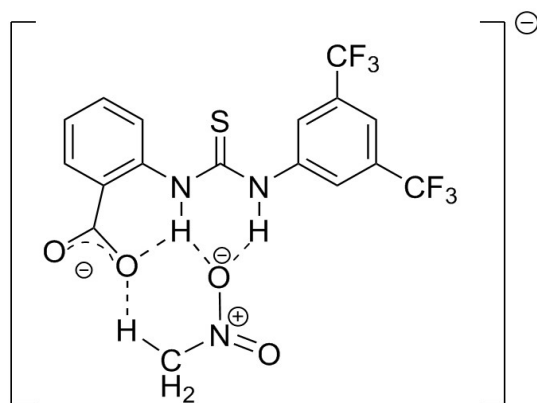


Figure 15. Proposed activation of nitromethane with catalyst 1 showing the role of the carboxylate anion.

This proposed mechanism was further explored with Catalyst 3 and 4. The hydroxyl groups were placed in similar positions as the carboxylate and screened in the nitroaldol reaction to determine if the presence of an intramolecular base was necessary for catalysts. Both of these catalysts produced a lower conversion than the catalysts that contained the carboxylate groups. Catalyst 3 produced a 34% conversion, and catalyst 4 only a 11% conversion. This difference in conversion from the carboxylates could be due to the fact that the hydroxyl group is smaller and may not be able to interact as strongly with the nitromethane in the complex decreasing the initial formation of the nitroenolate.

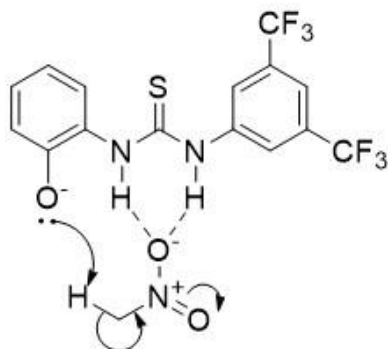


Figure 16. Proposed deprotonation of the nitromethane by catalyst 3.

These two catalysts do reiterate the importance of the location of the intramolecular anion though, as the para positioned hydroxyl group still had a decreased conversion when compared to the ortho hydroxyl group. This decreased activity could potentially also be due to the potential resonance structures of the anion of the complex which decreases the pKa of the hydrogens of the thiourea.

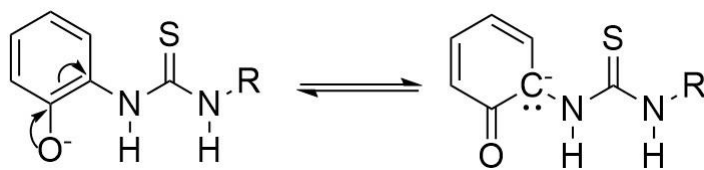


Figure 17. Resonance equilibrium of the deprotonated form of catalyst 3 which leads to decreased catalytic activity.

All of these reactions were compared to a benchmark thiourea catalyst which did not have a carboxylate ion nor a hydroxyl ion present to further emphasize that this intramolecular anion group is necessary for the deprotonation of the nitromethane. This catalyst showed a 72% conversion, which is higher than the hydroxyl group, but still substantially lower than the conversion by catalyst 1 with the carboxylate group. While this conversion still shows modest catalytic activity is taking place the presence of the anion improves the rate.

## Future Work and Research Proposal

### 1. Research Question

Thiourea catalysts have been used in a variety of organic reactions as they can be used in mild conditions and potentially provide stereocontrol of the products. While these catalysts have been proven to be useful in a variety of applications these catalysts are accompanied by a few disadvantages. First, the hydrogen bonding motif that allows these molecules to act as catalysts also interacts with other thiourea catalyst molecules causing the formation of dimers. This dimerization blocks the active site decreasing catalytic activity. Second, the reactions that these catalysts are often applied to have small organic molecules as products which leads to the need for difficult separations to isolate the products.

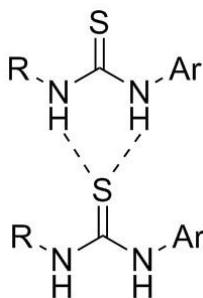


Figure 18. An example of the how the catalyst typically forms hydrogen bond dimers.

To mediate these disadvantages thiourea catalysts could be attached to a surface which could easily be separated from the reaction mixture while still allowing for the selectivity of the catalyst to contribute to the activation of the reaction. This has been done with metal-based homogenous catalysts, such as a ruthenium catalyst for metathesis reactions, and the surface showed little to no degradation over time.<sup>26</sup> The properties of the catalyst were preserved



indicating that this could be applied to other homogenous catalysts provided the functionalization of the surface can be achieved.

## I. Experimental Design

Thiourea catalysts have not been used to functionalize surfaces before, but these catalysts have been added to other forms of heterogenous phases and surfaces have been functionalized with thiols in similar ways. Thus, attaching thiourea catalysts to a hydrocarbon chain tether with a terminal silane functional group could be used to functionalize a silica surface while preserving the properties of the thioureas. Thiol functionalized surfaces do not have the same selectivity as thioureas, but possess similar properties indicating that these catalysts should be successfully bound to a surface. Thiol functionalized silica nanoparticles were added to a membrane and were used to remove metals from wastewater showing that their properties were preserved after functionalization.<sup>27</sup>

Beyond this, thiourea catalysts have been added to other forms of silica and other heterogenous supports before. These catalysts, or other similar ones, have been added to metal-organic frameworks and catalytic activity has been observed. For example, using a primary amide group that extended into the pores of a metal organic framework (MOF) a Friedel-Crafts reaction was catalyzed using a hydrogen bonding motif similar to that of a thiourea group.<sup>28</sup> The catalyst does not even have to be covalently part of the heterogenous structure of the MOF to function either. The thiourea group can be added to the MOF structure by interacting with other group off of the MOF in the pore space, and still perform catalysis on reactions such as the Baylis-Hillman reaction and acetalization.<sup>29</sup> The activity of these catalysts is not impacted with the addition of these MOF structures showing that the addition of these catalysts to a surface should not impact catalytic activity either.

Additionally, nanoparticles have been functionalized with thiourea catalysts. This has been performed with magnetic iron nanoparticles. The catalysts were added to the surface of the particles through thiol linkers and showed effective enantioselectivity and good yields. The magnetic nanoparticles are also easily removed from solutions.<sup>30</sup> This has also been done with mesoporous silica nanoparticles, as thiourea and amine catalysts have been bound separately to the surface of the particles allowing for the same properties as a bifunctional thiourea amine catalyst in a conjugate addition reaction.<sup>31</sup> Building on the idea that silica would be an effective surface for the support of thiourea catalysts there are a few other examples of mesoporous silica functionalized by thiourea catalysts. These materials have been used to form silica gel materials for the adsorption of mercury and for catalysis in the Friedel-Crafts reaction.<sup>32, 33</sup>

These various examples of homogenous organocatalysts being placed onto heterogenous supports could potentially be improved by being placed on a non-porous support, such as a simple silica surface. This would prevent questions of the effects of the pore sizes on the reaction and include the benefits of an easy separation of the catalyst from the reaction. The surface would be covalently functionalized by the catalysts and characterized by techniques such as FT-

IR, SEM, and contact angle measurements. This surface support would also allow for recyclability as the surface could be simply rinsed with a few solvents to clean the surface.

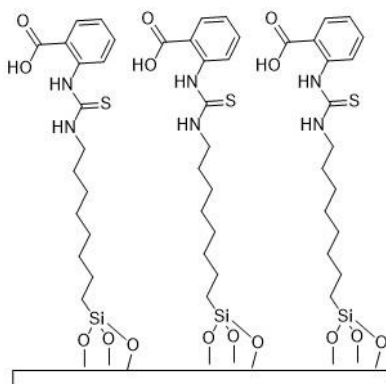


Figure 19. Proposed silica surface functionalized with a modified catalyst X.

## II. Key Technique

The functionalization of the silica surface would be a key technique needed in the potential use of these surfaces for catalysis. First, the catalyst will need to be covalently bonded to the surface to ensure that it is not removed from the surface unintentionally when placed in a reaction mixture. This can be done by placing the catalyst on the surface by first adding a silane functional group to the end of a catalyst molecule. Once synthesized this molecule can be dissolved into solution. A small surface would then be placed within a volume of the catalyst solution and allowed to react for many hours. Other similar surface functionalization techniques take anywhere from a few hours to a few days.<sup>30, 33</sup> Using a long reaction time would allow for the catalysts to organize and bond to the surface, but this reaction time could also be cut down by heating the reaction mixture.

Once the surface had been reacted in the catalyst solution for a sufficient amount of time any excess solvent and catalyst molecules would need to be removed from the surface. This could be done by simply rinsing the surface with a variety of organic solvents that would dissolve and remove any of these excess molecules. The surface would then be dried gently with nitrogen to remove any solvent left from the rinses. This surface could then be characterized and used in a nitroaldol reaction for catalysis.

## Conclusions

Common structural motifs and the reaction conditions of thiourea catalysts were explored. Depending on the structural motifs present thiourea catalysts can either activate the reaction through hydrogen bonding or by acting as a Bronsted Acid. With these commonalities and their effects in mind a group of thioureas was synthesized to study the impact of having a carboxylate or hydroxyl anion in the ortho position to the thiourea or in the para position. The catalysts (1 and 3) with ortho positioned carboxylate and hydroxyl groups produced a higher amount of conversion and catalytic activity when compared to their para-positioned counterparts. The presence of this anion contributes to the deprotonation and activation of the nitromethane into the nitroenolate. These catalysts expand on the current library of thiourea catalysts and provide catalysts that do not require cooperative enamine catalysis.

## Experimental Procedures

### *Synthesis of catalysts 1-4:*

The 3,5-bis(trifluoromethyl)phenyl isothiocyanate (100 mg, 0.369 mmol) was dissolved in dichloromethane (1 mL), and the aminobenzoic acid was added (50.6 mg, 0.369 mmol). Tetrahydrofuran (200  $\mu$ L) was added to ensure the solubility of the aminobenzoic acid. The reaction was stirred at room temperature for 48 hours. The product was concentrated by vacuum. Catalysts 1,3, and 4 were purified by silica gel column with 75/25 hexanes/ethyl acetate. Catalyst 2 was purified with silica column with a variable solvent system increasing from 90/10 hexanes/ethyl acetate to 75/25, to 50/50, and to 100% ethyl acetate. The solvent and product were forced through the column using a pipette bulb.

1-Ortho-aminobenzoic acid catalyst: <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>), 8.16 (1H, d), 7.96 (1H, s), 7.74 (2H, s), 7.37 (1H, t), 7.24 (1H, t), 7.11 (1H, d)

2- para-aminobenzoic acid catalyst: <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>), 8.01 (2H, s), 7.95 (2H, d) 7.75 (2H, d), 7.64 (1H, s)

3-ortho-phenol catalyst: <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>), 8.01(2H, s), 7.65 (1H, s), 7.57 (1H, d), 7.40 (1H, t), 6.95 (2H, m)

4-para-phenol catalyst: <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>), 8.01(2H, s), 7.65 (1H, s), 7.28 (2H, d), 6.70 (2H, d)

5-aniline catalyst: <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>), 8.01(2H, s), 7.70 (2H, d), 7.65 (1H, s), 7.45 (2H, t), 7.15 (1H, t)

### ***General Nitroaldol Reaction Procedure***

Hydrocinnamaldehyde (49.1  $\mu\text{L}$ , 0.373 mmol) and nitromethane (60.7  $\mu\text{L}$ , 1.12 mmol) were dissolved in toluene (1.2 mL) and water (1.2 mL). Potassium iodide (31.0 mg, 0.19 mmol), and the appropriate catalyst was added (15.1 mg, 0.037 mmol). Potassium hydroxide, sodium carbonate, or no base was then added (0.019 mmol) and This was stirred at room temperature for 24 hours. The reaction was stopped by adding saturated aqueous ammonium chloride and extracting with ethyl acetate. It was dried with magnesium sulfate, filtered, and concentrated by vacuum. The product was purified by silica gel column chromatography with a 90/10 hexanes/ethyl acetate solvent system. This procedure was also performed with variable amounts of potassium iodide, potassium hydroxide, benzoic acid, and sodium benzoate.

Nitroaldol product:  $^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ ), 7.38-7.18 (5H, m), 4.44 (1H, s), 4.39 (1H, d), 4.35-4.26 (1H, m), 2.92-2.70 (2H, m), 2.64 (1H, br s), 1.94-1.72 (2H, m).

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