

Towards Enantioselective Bismuth(III) Lewis Acid Catalysis via Utilization of a Chiral  
Counteranion Method for Asymmetric Induction

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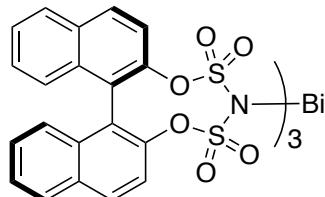
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# Abstract

A bismuth(III) 1,1'-binaphthyl-2,2'-sulfurylimide complex was designed as a Lewis acid catalyst for asymmetric counteranion-directed catalysis (ACDC). This mode of asymmetric catalysis utilizes easily dissociating chiral ligands that are able to provide a chiral environment via an electrostatic interaction with a positive charge on the substrate. It was hypothesized that utilizing an ACDC approach would circumvent two primary difficulties of asymmetric bismuth Lewis acid catalysis: that strongly-binding chiral ligands tend to render the catalyst inactive by reducing the Lewis acidity of the bismuth center, and that more weakly-binding chiral ligands can partially disassociate, compromising the ability of the chiral ligand to induce chirality due to loss of rigidity. The 1,1'-binaphthyl-2,2'-sulfurylimide ligand, dubbed the JINGLE-type ligand, is highly acidic, contains the privilege binaphthyl backbone, and has a facile synthesis. It hence was identified as a promising ligand for ACDC. A bismuth complex capable of catalyzing reactions asymmetrically is of great interest to the green chemistry movement, as bismuth is inexpensive, has low toxicity, and has a low environmental impact. En route to this target bismuth complex, a proof of principle synthesis of bismuth(III) benzenesulfonamide was attempted. A neat reaction between benzenesulfonamide and triphenylbismuth was utilized, with the hypotheses that the reaction would be thermodynamically favorable due to the  $pK_a$  difference between benzenesulfonamide and benzene, and that expulsion of benzene would drive the reaction to completion. It was found that the ligand exchange required temperatures above 150 °C, and that these temperatures likely caused decomposition of the triphenylbismuth. It was hypothesized that the triphenylbismuth was oxidized to bismuth oxide, based upon the general insolubility of the product, IR data, and mass loss equal to three equivalents of bismuth.



Target bismuth(III) JINGLE complex.

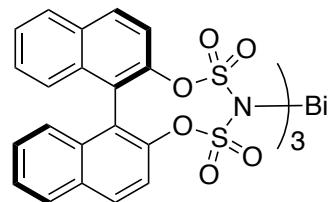


Dedicated to my parents, who provided me with love, encouragement, faith, and lots of free sushi. And life. That one too. Also dedicated to myself, because this thesis represents a major success and also a major failure regarding my ability to pursue something wholeheartedly, despite difficulties. It is from the success that I begin to understand my true capabilities, and it is from the failure and disappointment in myself that I gain a desire to improve myself and concurrently learn how to do so.



# Introduction

This thesis aims to utilize bismuth metal to create a catalyst capable of providing enantioselectivity. The introduction will first describe why bismuth, as a metal center for catalysts, fits particularly well into the green chemistry movement that is attempting to reduce the negative impacts of chemistry, followed by a summary of the origins of bismuth chemistry and the early progress that has allowed bismuth chemistry to recently evolve from a small field to an area of great interest. Second, the electronic properties that allow bismuth to act as a Lewis acid will be examined in detail, as understanding the fundamental properties of bismuth upon which its use as a catalyst is founded is important when considering how to make the most effective bismuth catalyst. Third, Lewis acid catalysis in general, bismuth Lewis acid catalysis, and methods for inducing chirality during Lewis acid-catalyzed reactions will be explored in order to determine how to prepare an effective Lewis acid catalyst, and how a functional asymmetric bismuth catalyst could be developed. Compiling the pertinent conclusions leads to the target bismuth complex (Figure 1), hypothesized to be a strong Lewis acid catalyst capable of chiral induction.



**Figure 1.** Target bismuth(III) 1,1'-binaphthyl-2,2'-sulfurylimide complex.

## The Potential Of Bismuth Metal For Green Catalysis

Synthetic organic chemistry is among the most mature areas of chemistry. One of the original goals was to be able to access any target molecule, and with today's

knowledge this is possible in a majority of cases, though at times with difficulty. Because so much is already known, current research focuses strongly on increasing the efficiency, yield, and selectivity of key reaction pathways, either by optimizing current reactions or by finding new, alternative reactions that are more effective. While this emphasis on methodology is a natural direction to go in, other fields of research have appeared that are quickly being acknowledged as vitally important areas of growth for chemistry, and a prominent one is generally termed “green chemistry”. Green chemistry is a movement recognizing that chemistry uses and produces a great deal of toxic compounds that potentially harm humans and the environment, and the broad goal of the movement is to reduce these negatives in whatever way possible, from using more efficient apparatus and less toxic solvents to dealing with waste and emissions in a cleaner manner. The movement has become well developed, and the goals have been summarized in twelve principles:<sup>1</sup>

1. **Prevent waste:** Design chemical syntheses to prevent waste. Leave no waste to treat or clean up.
2. **Maximize atom economy:** Design syntheses so that the final product contains the maximum proportion of the starting materials. Waste few or no atoms.
3. **Design less hazardous chemical syntheses:** Design syntheses to use and generate substances with little or no toxicity to either humans or the environment.
4. **Design safer chemicals and products:** Design chemical products that are fully effective yet have little or no toxicity.
5. **Use safer solvents and reaction conditions:** Avoid using solvents, separation agents, or other auxiliary chemicals. If you must use these chemicals, use safer ones.
6. **Increase energy efficiency:** Run chemical reactions at room temperature and pressure whenever possible.
7. **Use renewable feedstocks:** Use starting materials (also known as feedstocks) that are renewable rather than depletable. The source of

renewable feedstocks is often agricultural products or the wastes of other processes; the source of depletable feedstocks is often fossil fuels (petroleum, natural gas, or coal) or mining operations.

8. **Avoid chemical derivatives:** Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.
9. **Use catalysts, not stoichiometric reagents:** Minimize waste by using catalytic reactions. Catalysts are effective in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and carry out a reaction only once.
10. **Design chemicals and products to degrade after use:** Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.
11. **Analyze in real time to prevent pollution:** Include in-process, real-time monitoring and control during syntheses to minimize or eliminate the formation of byproducts.
12. **Minimize the potential for accidents:** Design chemicals and their physical forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.

It can be seen that catalysis is a focus, and this is because catalysis allows for more efficient reactions in terms of atom economy, energy usage, and selectivity. A catalyst by definition is a compound that participates in a reaction without being consumed, and useful catalysts generally accelerate a reaction so that it may require less heating or avoid cripplingly slow reaction times. At the most extreme, and most useful, catalysis allows for reactions that are otherwise impossible. A main reason catalysts enable good atom economy is that since the catalyst is not consumed, commonly only a small amount of catalyst is necessary, and it also can often be recovered for future use. Perhaps most interesting, though, is that different catalysts operate utilizing a variety of mechanisms of action, and many of these can be exploited to increase reaction selectivity, forming more of a desired product over undesired side products. These benefits

collectively are why catalysis is one of the most powerful discoveries made in chemistry regarding the design of effective and efficient reactions.

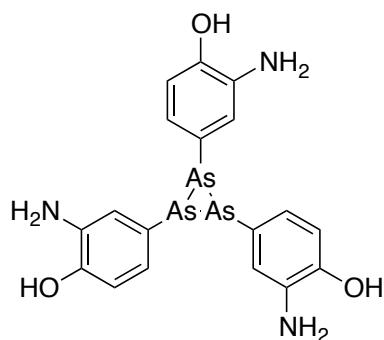
Due to the usefulness of catalysts, the field of catalysis is already one of the largest areas of organic chemistry, and while there are still many challenges, a great number of catalysts have been developed that guide reactions to yields and selectivities approaching perfection. Some of the major current challenges thus deal not with creating more effective catalysts, but with avoiding downsides that have recently come to be more appreciated as important considerations. One such downside is that many of the commonly used catalysts include toxic metals, making them flawed from a green chemistry standpoint. These metals often are also expensive. The latter is a moderate downside in the research laboratory setting, but in the chemical manufacturing or pharmaceutical industries this can render many catalysts unviable. Furthermore, it is these large industries that potentially have the greatest impact on human health and the environment, and thus the prohibitive cost of many catalysts hinder the development of green chemistry where it can be most effective. For green chemistry, it is hence not only catalysis in general that is important, but specifically the development of catalysts that use cheap and nontoxic metals. Regarding this, the metal bismuth presents a promising alternative, as it is nontoxic, environmentally innocuous, and inexpensive.

## **Advantages Of Bismuth**

Perhaps the most important advantage of bismuth is that it is relatively nontoxic, despite being situated on the periodic table among many highly toxic elements, such as mercury, thallium, antimony, and lead.<sup>2</sup> Even compared to elements in its own group, the pnictogens, bismuth shows remarkably low toxicity: whereas organo-antimony and organo-arsenic compounds generally have LD<sub>50</sub>'s (which is the dose fatal to 50% of test subjects) in the range of mg/kg, organo-bismuth compounds generally have LD<sub>50</sub>'s in the g/kg range.<sup>3</sup> Before serious adverse health effects appear, a human hence must ingest several grams of bismuth: a feat that is nearly impossible to do by accident. Indeed, no cases of fatal bismuth poisoning have occurred in the industry or laboratory settings, and in industry, bismuth is considered one of the safest heavy metals. The cases of bismuth

poisoning that have occurred are nearly without exception from large doses of bismuth compounds used during medical treatment.<sup>3,4</sup>

Though cases of bismuth poisoning have occurred during medical treatments, bismuth is still considered to have a remarkably low toxicity in the context of medicine. This low toxicity is exemplified by its continued and common use in medical treatments, primarily for maladies relating to the gastrointestinal tract. The most common bismuth compound in use is bismuth subsalicylate, an antidiuretic. Its toxicity is low enough that it is featured as the active ingredient in the classic over-the-counter medicine Pepto-Bismol, which contains 17.6 mg/mL of bismuth subsalicylate. Bismuth subcitrate has been used to treat peptic ulcers,<sup>5</sup> and various bismuth compounds have been used to combat *Helicobacter pylori*,<sup>6</sup> a bacterium that causes gastritis, peptic ulcers and gastric cancer.<sup>7</sup> Bismuth has also historically been used in the treatment of syphilis due to its low toxicity: in the early twentieth century Salvarsan was used as a treatment for syphilis, but was extremely toxic due the arsenic content (Figure 2), and it was found that replacing the arsenic with bismuth greatly reduced the toxicity of the drug while retaining its potency.<sup>8</sup>



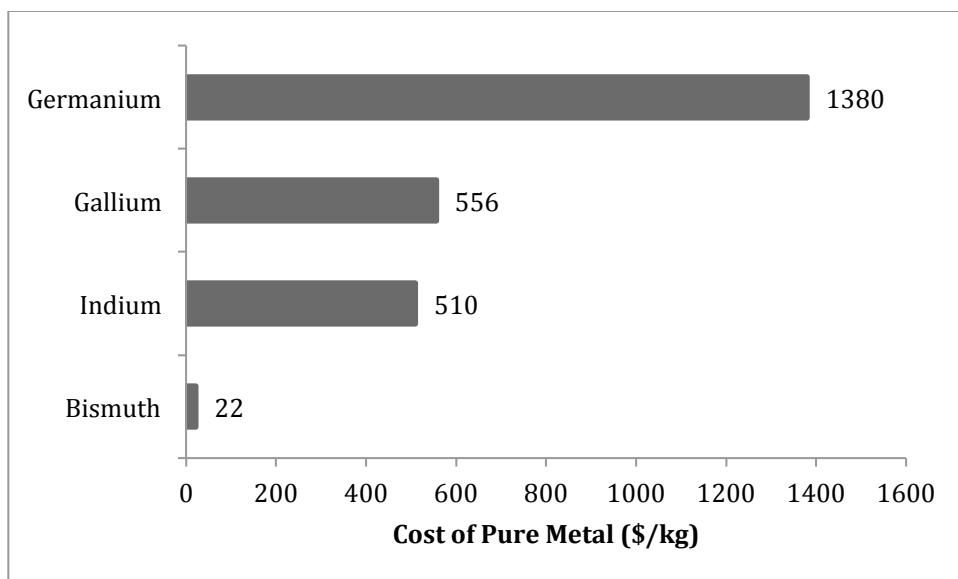
**Figure 2.** Line structure of Salvarsan (arsphenamine trimer).

Most bismuth compounds are insoluble in water, and oral ingestion of water-insoluble bismuth compounds results in low absorption that minimizes its toxicity. Water-soluble bismuth compounds can cause kidney damage, but the damage is generally mild, and these bismuth compounds are quickly eliminated via the urinary tract. Long-term studies of chronic exposure to bismuth in rats show no carcinogenic or other toxic

effects, and there has been no evidence yet for the carcinogenicity, mutagenicity, or teratogenicity of bismuth compounds in humans.<sup>9</sup> However, the toxicity and effects of bismuth compounds have not been thoroughly explored, and so caution must still be exercised when dealing with bismuth compounds.

The impact of bismuth compounds on the environment is similarly thought to be low because of the low toxicity of bismuth and poor solubility of bismuth compounds in water. However, similar to the toxic effects of bismuth on humans, a thorough analysis has yet to be done, and thus the amount of bismuth waste that is allowed into the environment should be minimized.

Bismuth has potential regarding green catalysis because of its low toxicity and environmental friendliness, but if bismuth is not also cost effective, it cannot be a viable alternative. Ranking at 69<sup>th</sup> in elemental abundance, in the range of  $10^{-9}$  kg bismuth per kg of the earth's crust, bismuth is a little more rare than silver and platinum. Despite its rarity, though, bismuth is much less expensive than silver and platinum, as well as metals commonly used for similar catalytic applications (Figure 3).<sup>10</sup> The primary reason for the low cost of bismuth is that bismuth is commonly produced as a byproduct of processing lead, copper, zinc, tin, and silver ores, where its separation is necessary because bismuth impurities compromise the physical properties of the other metals. The cost is further lowered by the general ease of handling of bismuth compounds, due to their low toxicity and sometimes low sensitivity to air and water.



**Figure 3.** Price comparison of bismuth and similar metals, utilizing data from the 2012 U.S. Geological Survey.

Bismuth is a model metal for green chemistry because of these qualities: it has negligible toxicity despite being a heavy metal, making bismuth compounds easy to handle and safe to work with, it is thought to have a low environmental impact, thereby helping to minimize the negative effects of chemistry on the environment, and it is inexpensive, making it viable for wide use in laboratories and industry. Yet, bismuth is only now being incorporated into mainstream methodological and synthetic research. Though bismuth was one of the first metals to be discovered, its unambiguous identification came quite late, and it was generally overshadowed by the transition metals during the rapid growth of organometallic chemistry. Still, work initiated by Frederick Challenger, continued by Sir Derek Barton, and expanded upon by Mokoto Wada and Jacques Dubac ensured that bismuth chemistry was relatively well explored by the time interest in metals for green catalysis arose, allowing for bismuth's potential to be quickly recognized.

# The Development Of Bismuth Chemistry

## The Discovery Of Bismuth

Bismuth is a grey-white metal with a slight red hue. Though it occurs in its native form, its similar appearance to that of lead and tin obfuscated its nature as a separate metal until the necessary analytical techniques were developed in the eighteenth century. It nonetheless seems that older cultures had some notion of bismuth as a substance separate from lead and tin. The handle of a knife discovered at Machu Picchu was determined to be made of a bismuth-bronze-tin alloy containing 18% bismuth.<sup>11</sup> Nearly a thousand analyses of other ancient bronzes showed extremely low or trace amounts of bismuth, demonstrating the consistency of ancient bronze composition and suggesting that the high level of bismuth was purposeful. The bismuth alloy furthermore retained its mechanical properties compared to those of standard bronze while additionally facilitating the casting process, making the new alloy a strict improvement upon the original bronze composition.

The etymology of the name bismuth is unknown, but it boasts a similarity to Arabic, Persian, and German words.<sup>8</sup> Of these, the German words *blei-weiss*, for white lead, and *wismut*, believed to be a shortening of an old mining term for white mass (*weisse masse*), are most often acknowledged as being its probable origins. Germany's apparent historic familiarity with bismuth is likely connected to German mining and alchemic research. Native bismuth metal was referred to by German miners as "tectum argenti," meaning unfinished silver.<sup>12</sup> It was believed that lead eventually turned into silver, and that tin and bismuth were alternate forms of lead that appeared as it underwent this transmutation.

The German monk Basil Valentine was the first to refer to bismuth as *wismut* in text, in his 15<sup>th</sup> century writings,<sup>13</sup> suggesting that by this time bismuth was thought of as a metal potentially separate from lead and tin. *Wismut* was Latinized to *bisemutum* by the German Georgius Agricola, who treated bismuth metal as decidedly separate from lead and tin in his two works: "De Natura Fossilium," published in 1546,<sup>14</sup> and "De Re Metallica", published in 1556.<sup>15</sup> While he believed bismuth was in a family of metals

with lead and tin, he recognized the unique properties of bismuth and detailed how to extract it from bismuth ores.

Despite these early differentiations, the notion that bismuth was some type of lead or that it was a mixture of other compounds continued into the 18<sup>th</sup> century.<sup>16</sup> The 1713 *Proceedings of the French Academy* determined bismuth to be a mixture of sulfur, mercury, arsenic, earth, and mineral, and pharmacopeias of the time included recipes for making “bismuth”. The identity of bismuth as an element was not made absolute until four decades later, in 1753, when the analytic techniques necessary to differentiate it from lead were developed and used by Claude-François Geoffroy in his treatise “The Chemical Analysis of Bismuth”.<sup>17</sup>

## Early Use Of Bismuth In Chemistry

While the inorganic chemistry of bismuth had been explored even before its definitive identification, the use of bismuth in organic chemistry did not begin until the twentieth century. The oxidative properties of pentavalent bismuth compounds were separately discovered first by Fredrick Challenger in 1934,<sup>18</sup> and then by W. Rigby in 1949.<sup>19</sup> Challenger originally researched the synthesis of organobismuth compounds, publishing a series of papers from 1914 to 1924 that systematically explored their syntheses and properties. Challenger focused on trivalent bismuth compounds, commonly with aromatic substituents, but produced pentavalent bismuth compounds as well. In his later 1934 paper, Challenger noted that  $\text{Ph}_3\text{Bi}(\text{OH})_2$  was able to oxidize alcohols—the first demonstration of the potential of organobismuth compounds for use in organic synthesis. In his 1949 paper, W. Rigby reported the oxidative properties of sodium bismuthate,  $\text{NaBiO}_3$ , which he discovered based upon its electronic similarity to lead tetraacetate. He found that sodium bismuthate effects oxidative cleavage of moieties with adjacent functional groups, such as vicinal diols or ketols, in a manner similar to periodic acid or lead tetraacetate, and it soon found use in synthesis for oxidizing glycols and corticosteroids,<sup>20</sup> and was explored in a 1953 synthesis of Vitamin A.<sup>21</sup>

In the late 1970’s, Sir Derek Barton noticed that the potential of pentavalent bismuth compounds for oxidation had remained unexplored despite the discoveries of Challenger and Rigby. Beginning with a paper in 1978 showing  $\mu$ -oxo-

bis(chlorotriphenylbismuth) to be a mild oxidizing agent soluble in common organic solvents,<sup>22</sup> Barton continued and expanded upon this research. Bismuth chemistry became a focus of Barton's throughout the 1980's, leading to the publication of a large series of papers concentrated on oxidation and arylation utilizing pentavalent bismuth compounds. In the late 1990's, Barton also assisted Thomas Arnauld in researching the chemistry of bismuth, again focusing on pentavalent bismuth and its oxidative and arylative properties.

Barton's research into bismuth chemistry led Mokoto Wada to explore bismuth chemistry as well, beginning with a 1985 paper on the metallic bismuth mediated allylation of aldehydes.<sup>23</sup> Wada broke the trend of researching pentavalent bismuth, and in a series of papers published between the mid 80's and early 2000's instead focused on developing the chemistry of trivalent bismuth compounds. Wada demonstrated that trivalent bismuth compounds, at first in catalytic systems with other metals, were effective catalysts for Grignard and Barbier-type allylation reactions, as well as aldol reactions. Wada was accompanied in his research by Jacques Dubac in the early 1990's to the early 2000's, after which both moved on to other research. Dubac similarly investigated the use of trivalent bismuth compounds as catalysts in reactions such as the Mukaiyama aldol reaction, but also expanded their scope compared to Wada's research by employing them as catalysts in Diels-Alder-type reactions<sup>24</sup> and aromatic substitutions.<sup>25</sup>

The research by Barton regarding pentavalent bismuth compounds and by Wada and Dubac regarding trivalent bismuth compounds set precedence for further research in the field of bismuth chemistry, and importantly demonstrated that bismuth is quite promising as a catalyst for a variety of reaction classes. To create effective catalysts utilizing bismuth, however, bismuth chemistry must be understood at a deeper level. Bismuth chemistry can be attributed to its electronic properties, and specifically to the relativistic effects it experiences and to its ability to form hypervalent complexes.

## The Electronic Properties Of Bismuth

Bismuth is a member of the group 15 elements, the pnictogens, and is situated four periods below nitrogen. This position is low enough on the periodic table that

bismuth is found between the transition metals in the *d*-block and the metalloids in the *p*-block, and is hence classified as a post-transition metal. Bismuth has a ground state electron configuration of  $[Xe]4f^{14}5d^{10}6s^26p^3$ . As expected from this configuration, bismuth exists commonly in an unoxidized metallic state, a trivalent bismuth(III) state resulting from the loss of the three electrons occupying the  $6p$  orbitals, or a pentavalent bismuth(V) state resulting from the loss of the three  $6p$  electrons as well as both electrons occupying the  $6s$  orbital.

The lighter pnictogens—nitrogen, phosphorus, and arsenic—tend to form three bonds to satisfy the octet rule, leaving a lone pair of electrons. This lone pair is oriented towards the apex of the pyramidal structure formed by the pnictogen and three substituents, as predicted by VSEPR theory. This lone pair is able to be donated, designating tertiary compounds of the lighter pnictogens as Lewis bases. The strength of the Lewis basicity decreases moving down the group due to *d*-block and lanthanide contractions, and also due to relativistic effects, which will be described shortly. Because of this decrease in Lewis basicity, antimony compounds are generally poor Lewis bases, and bismuth compounds show almost no Lewis basicity. Concurrent with this decreasing Lewis basicity, Lewis acidity increases. Nitrogen shows no Lewis acidity, but phosphorus and arsenic are able to form hypervalent compounds, indicating a greater ability to accept electrons. Antimony and bismuth are both Lewis acids, showing extensive coordination chemistry. As will be discussed after relativistic effects, antimony and bismuth are good Lewis acids because of their ability to form hypervalent complexes, analogous to the hypervalent compounds of phosphorus and arsenic except for the utilization of dative bonds rather than covalent ones.

## Relativistic Effects

The poor Lewis basicity of trivalent bismuth compounds and the oxidative potential of pentavalent bismuth compounds both stem from relativistic effects. The term “relativistic effects” encompasses a variety of effects that arise from the increased mass of electrons that approach the speed of light. Bismuth is a large enough atom that electrons residing in outer electron shells approach significant fractions of the speed of

light, and this high velocity results in electrons with higher energy, and hence higher mass as per  $E=mc^2$ . The general consequence is that electrons experiencing relativistic effects are pulled closer to the nucleus. This orbital contraction occurs classically because the electrostatic attraction exerted by the positive nucleus must be a strong enough centripetal force to keep the electron in orbit. The added mass of the electron means that a stronger force is required, and because the electrostatic force is inversely proportional to distance, the force is increased when the electron is moved closer to the nucleus. This model is not entirely accurate because electrons behave significantly as waves, as described by quantum mechanics, but it is sufficient for conceptualizing the basis of relativistic effects.

While the relativistic mass increase drives all orbitals closer to the nucleus, the final result differs depending on the type of orbital, *s*, *p*, *d*, or *f* (of the same valence), because of electron shielding. The contraction of the *s* orbitals is relatively unimpeded by electron shielding because *s* orbitals place electron density close to the nucleus more than other types of orbitals. Thus, *s* orbitals experience the strongest “direct relativistic orbital contraction”. Due to the *s* orbital experiencing the greatest contraction, electrons residing in the *s* orbital shield electrons in the *p* orbitals by an extra factor. The relativistic orbital contraction is still the stronger effect and so *p* orbitals still contract, but less so. For the *d* and *f* orbitals, the additional repulsive force due to electron shielding from electrons in the *s* and *p* orbitals overcomes the contractive force, and these orbitals experience an “indirect relativistic orbital expansion”.

For bismuth, the energy required to utilize the electrons in the *6s* orbital is large because they are pulled close to the nucleus, leading them to be generally unreactive. This phenomenon is termed the “inert pair effect,” and leads to several notable consequences. The first is that bismuth has difficulty donating these electrons, which is why trivalent bismuth compounds are poor Lewis bases. It is similarly difficult to make pentavalent bismuth compounds, requiring oxidizing agents strong enough to remove the *6s* electrons. The oxidative potential of Bi(V) complexes comes from the energetic favorability of regaining the *6s* electrons as a driving force. This driving force is present in much of the chemistry of Bi(V) compounds, which generally feature trivalent bismuth compounds as leaving groups.

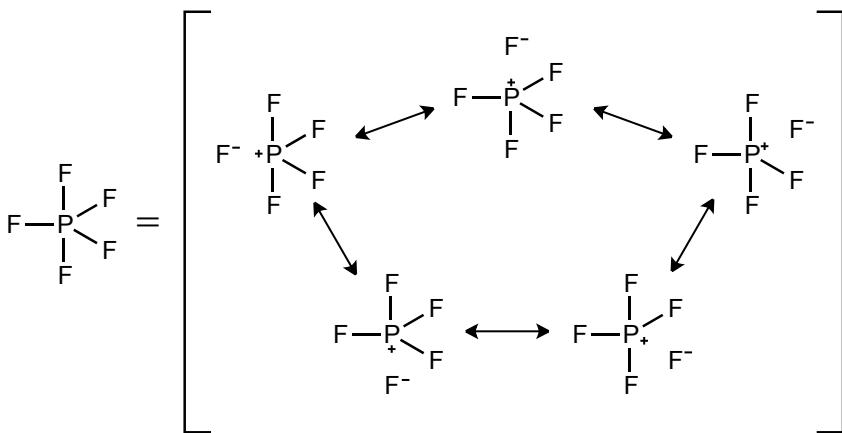
Another result of the inert pair effect is that the  $6s$  orbital of bismuth participates to a negligible extent during bonding. For trivalent bismuth compounds, this means that bismuth forms bonds with ligands utilizing only the  $6p$  orbitals.<sup>26</sup> This is evidenced by the ideal bond angles of trivalent bismuth complexes being near  $90^\circ$ , rather than the  $107.5^\circ$  predicted by the VSEPR model. This ideal is approached by the bond angles of  $\text{BiH}_3$ , which have been determined to be  $90.48^\circ$ .<sup>27</sup> Larger angles arise due to steric interactions. For example, Brenden Murray *et al.* synthesized a trivalent bismuth compound with three highly bulky di(trimethylsilyl)methyl ligands and determined via crystal structure that the bond angles are  $102.9^\circ$ .<sup>28</sup> An interesting consequence of the inability of bismuth to form  $sp^2$  hybrid orbitals is that bismuth compounds do not experience the “nitrogen inversion” that makes chirality about nitrogen difficult to maintain at room temperature, and hence bismuth compounds can be chiral at the bismuth center. Also predicted by the VSEPR model is that the  $6s$  lone pair should occupy some space around the bismuth, directed to minimize interactions with bismuth-ligand bonds. Instead, because of the extremely dominant  $s$  character of the lone pair, the electrons exist in an undirected, spherical space about the nucleus and have little influence on bond angles.

## Hypervalence And Lewis Acidity

Trivalent bismuth compounds consist of a central bismuth atom in the +3 oxidation state coordinated to three ligands. The bonds are dative-covalent in nature due to the metallic character of bismuth, meaning the ligands donate two electrons to form the bond, and bismuth none. The six electrons donated by the ligands and the two electrons of the lone pair in the  $6s$  orbital of bismuth sum to eight, fulfilling the octet rule. Despite the apparent satisfaction of bismuth’s desire for electrons, trivalent bismuth compounds are able to coordinate with up to three additional ligands, for a total of six. If one draws a Lewis structure in which all six ligands form “normal” two-centered two-electron (2c/2e) bonds with the bismuth center, the bismuth will formally have 14 valence electrons. This seemingly violates the octet rule, and strongly so. This phenomenon is referred to as hypervalency, as it was thought for a great deal of time that the central atom must have an extended set of valence orbitals in order to accept the additional electrons.<sup>29</sup>

To see why bismuth is able to be hypervalent, hypervalency in general must be understood. There are two conceptual models used to explain hypervalence, both originally suggested by Linus Pauling. For transition metals, orbital hybrids such as  $dsp^3$  and  $d^2sp^3$  may be formed at the metal center, resulting in the necessary number of appropriately oriented orbitals to form bonds with the ligands surrounding the central atom.<sup>30</sup> Transition metals may do so because their empty valence  $d$  orbitals are energetically accessible. For some time, it was thought that hypervalent compounds of main group elements might also utilize  $d$  orbital hybridization, using higher-level  $d$  orbitals instead because their valence  $d$  orbitals are filled. After thorough computational studies became possible, however, this idea was rejected because it was found that the  $d$  orbitals of the next valence are too high in energy to be accessible for hybridization with valence  $s$  and  $p$  orbitals.<sup>31</sup> Nonetheless, it should be noted that the  $d$  orbitals do appear to be important as polarization functions for theoretical computations, as their inclusion is necessary for quantitative results.<sup>32</sup>

Pauling predicted that hypervalency of compounds involving main group elements would best be explained by highly ionic bonds.<sup>33</sup> Lewis structures of these compounds appear to require the central atom to have an “expanded octet”, but polar bonds between the central atom and its substituents actually draw enough electron density from the central atom that the octet rule is not violated. This can be represented by resonance structures that place positive charge on the central atom and negative charge on the substituents. An example for phosphorus pentafluoride,  $\text{PF}_5$ , is shown below (Figure 4).



**Figure 4.** The resonance structures of  $\text{PF}_5$ .

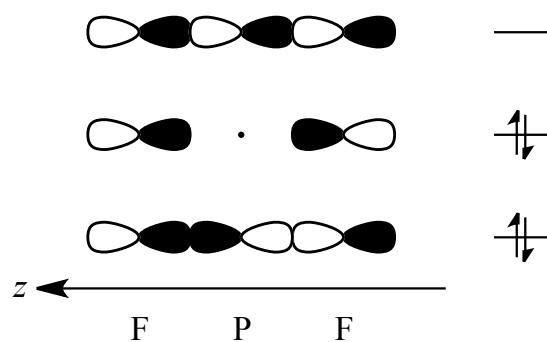
The true character of bonding in  $\text{PF}_5$  is a superposition of the above resonance structures, and this suggests two things: the phosphorus should actually have a partial positive charge and the fluorines partial negative charges, and the bonds between the phosphorus and the fluorines should only be partial bonds. The calculated natural atomic charges for  $\text{PF}_5$  are  $Q_{\text{P}} = +2.63$ ,  $Q_{\text{F}} = -0.51(\text{eq})$ ,  $-0.55(\text{ax})$ ,<sup>34</sup> and the experimentally determined bond lengths are  $1.534 \text{ \AA}$  (eq) and  $1.577 \text{ \AA}$  (ax),<sup>35</sup> which are longer than P-F bonds in normal valence molecules. The data thus agrees with the prediction of weak, polar bonds. Interestingly, it further suggests that the apical bonds are weaker and more polar than the equatorial bonds.

To explain this last observation, one must turn to Molecular Orbital theory. Molecular Orbital theory is a quantum mechanical theory recognizing that in the context of a molecule, electrons reside in molecular orbitals (MO's) that delocalize the electrons across the molecule. These MO's may be described mathematically by linear combinations of the various atomic orbital functions (AO's), obtained from quantum theory, that each atom in the molecule contributes for bonding. For hypervalence, the full descriptive potential of MO theory unfortunately may only be approached computationally,<sup>36</sup> but the general descriptions of hypervalent species obtained by MO theory thankfully can still be described by two conceptual simplifications: orbital hybridization and three-center four-electron (3c/4e) bonds.

For  $\text{PF}_5$  above, in the equatorial plane phosphorus uses its  $3s$ ,  $3p_x$ , and  $3p_y$  AO's to form three  $sp^2$  hybrid orbitals. In other words, because the  $3s$  and  $3p$  AO's of phosphorus

are close in energy, they both contribute significantly to the same MO's. For the equatorial fluorines, this results in the most favorable positions lying in the equatorial plane  $120^\circ$  from each other. The fluorines each utilize one of their  $2p$  orbitals, for the best spatial overlap and energetic match, to contribute to the MO's, resulting in the equatorial bonds being  $2c/2e$  in nature, though highly polar due to the large electronegativity difference between phosphorus and fluorine. Despite the phosphorus  $3p_z$  orbital also being close in energy to the phosphorus  $3s$  orbital,  $sp^3$  hybridization would be ill suited for bonding with five substituents, as it arranges the favorable bonding locations in a tetrahedron about the phosphorus atom, leaving no favorable bonding space for the fifth fluorine.

The phosphorus uses only its  $3p_z$  orbital for the apical P-F bonds. Because the apical bonds are perpendicular to the equatorial bonds and the phosphorus  $3p_z$  orbital has an angular node at the  $xy$ -plane, there is little overlap between the orbitals used for bonding along the  $z$ -axis and those used in the  $xy$ -plane. It is thus acceptable, at the qualitative level, to think of the apical bonding as a separate system of MO's. The two fluorine atoms utilize their  $2p_z$  orbitals (though the same qualitative result would be obtained with their  $2s$  orbitals) because, paralleling the equatorial bonding, they allow for the best spatial overlap and energetic match to the phosphorus  $3p_z$  orbital. These three AO's will produce three MO's, which are represented below (Figure 5).

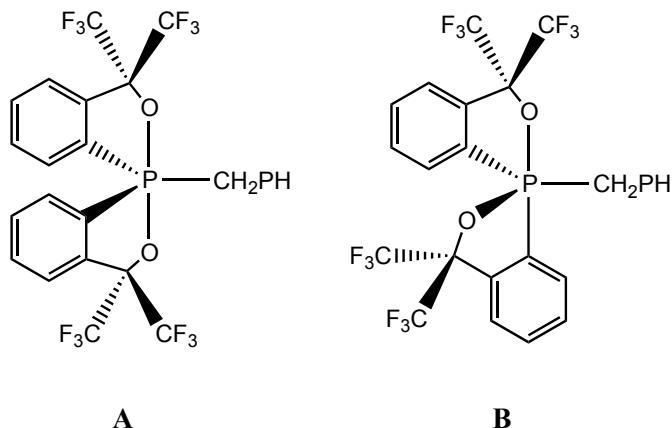


**Figure 5.** The MO's of a  $3c/4e$  bond.

The lowest energy occupied MO is a bonding orbital that distributes the electrons across all three nuclei. Because the fluorines are more electronegative than the

phosphorus, the electron density is not shared equally and instead some will be drawn to the fluorines. The next occupied MO is nonbonding and places almost no electron density around the phosphorus because of the central node, placing it instead upon the fluorines. The third MO is unoccupied and antibonding. These three MO's describe a 3c/4e bond, which was first presented by George C. Pimentel,<sup>37</sup> building upon physical concepts recognized and discussed by R.E. Rundle.<sup>38</sup> Whereas the equatorial 2c/2e bonds have one bonding interaction for one bond, the axial 3c/4e bond has one bonding interaction for two bonds, and the additional electron density is placed on the fluorines. This qualitatively explains the slightly poorer bond strength and higher ionic character of the axial bonds compared to the equatorial bonds. It is important to note that the 3c/4e bonding model only works well for cases involving a *p* orbital of the central atom that has little interaction with the *s* orbital of the same valence. Thus, while this model does a good job of describing many hypervalent bonds, it has difficulty with compounds such as SF<sub>6</sub>, in which none of the 3*p* orbitals can be thought of separately from the 3*s* orbital.

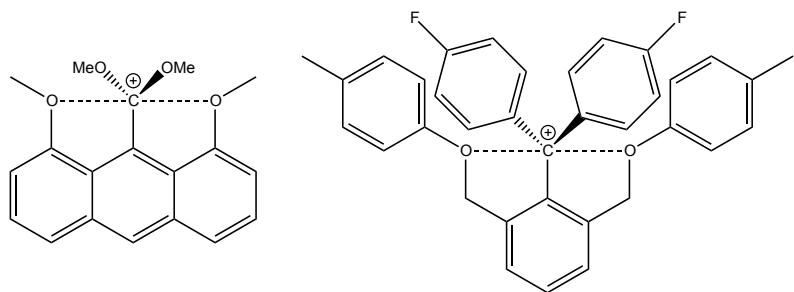
The stability of hypervalent compounds depends mainly on three factors. The first two were implicated in the above discussion: the bonds must be polar, so as to draw electron density away from the central atom, and also the substituents must be able to bear the extra negative charge. The latter requires high electronegativity, or alternatively, in the case of multi-atom substituents, stabilization by inductively or resonantly electron-withdrawing groups. The desire for groups able to bear negative charge can be seen in hypervalent phosphorus compounds, where the most electronegative substituents possess higher apicophilicity. For example, of spirophosphoranes **A** and **B** shown below (Figure 6), **A** is thermodynamically more stable, and applying heat to **B** will cause it to isomerize to **A**.<sup>35</sup> The more electronegative groups are most favorably positioned at the apical sites, as they are better able to bear the additional negative charge. It is worthwhile to note that the bond lengths in **B** follow the trend in bond lengths observed in PF<sub>5</sub>: P-C(eq) = 1.812 Å, P-C(ax) = 1.874 Å, P-O(eq) = 1.661 Å, P-O(ax) = 1.782 Å. The axial bonds, be they P-C bonds or P-O bonds, are longer than the respective equatorial bonds.



**Figure 6.** Positional isomers of a spirophosphorane.

Fluorine is an obvious choice when in need of an electronegative substituent, but it is actually more electron withdrawing than is generally required. Stéphane Noury and Bernard Silvi explored the number of valence electrons around phosphorus in various hypervalent compounds in 2002,<sup>39</sup> utilizing the Electron Localization Function (ELF), originally developed by A.D. Becke and K.E. Edgecombe to easily reveal the electronic structure of simple molecules.<sup>40</sup> They found that in  $\text{PF}_5$ , the valence shell population of P is 5.33, far below an octet. The population increases as the electronegativity of the substituents decreases, yielding values of 7.13 for  $\text{PCl}_5$  and 8.52 for  $\text{PMe}_3\text{CH}_2$ . These electron populations show two things: the first is that hypervalent compounds can be stable with substituents that are only mildly more electronegative than the central atom, and second that the octet rule is not quantitative, but rather qualitatively represents a point of electronic saturation that tends to be near eight valence electrons.

The third, perhaps deceptively simple factor in determining the stability of a hypervalent compound is the size of the central atom. If the central atom is too small, it is difficult to make hypervalence energetically favorable due to steric interactions. This is often the case in attempts to obtain hypervalent compounds of second period elements. Initial attempts at forming a pentavalent carbon compound used an anthracene skeleton to compensate for the unfavorable steric interactions around the carbon. The first unequivocally determined hypervalent carbon compound is shown below and to left (Figure 7).<sup>35</sup> Pentavalent carbon compounds that do not require a rigid backbone have since been developed, and an example is given below and to the right (Figure 7).



**Figure 7.** Hypervalent carbon compounds.

Given the above discussion, it is easy to see why bismuth(III) compounds are Lewis acidic. Residing in the sixth period, the bismuth atom is large enough to coordinate with six ligands. Bismuth also has a Pauling electronegativity of 2.02, allowing for sufficiently polar bonds with elements of the second and third periods, and at times even higher, to form hypervalent compounds. The positive charge the bismuth must bear in a hypervalent compound is not very destabilizing, given its metallic character. The 3c/4e bond model also works exceptionally well for bismuth because the inert pair effect removes the influence of the 6s orbital, allowing each pair of ligands positioned across the bismuth center to be thought of as bonding via a 3c/4e bond. It is because of this that ligands tend to coordinate directly across from another ligand, causing 4-coordinate bismuth(III) compounds to be disphenoidal, 5-coordinate to be square pyramidal, and 6-coordinate to be octahedral.

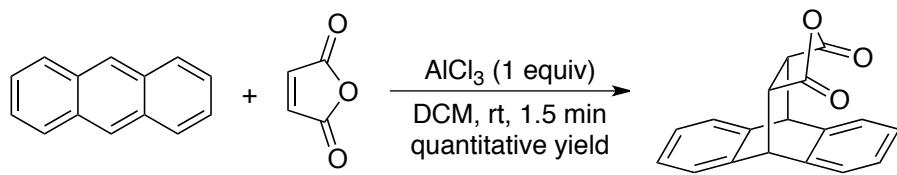
## Lewis Acid Catalysis

The electronic properties of bismuth allow bismuth(III) compounds to catalyze reactions by acting as Lewis acids, meaning that they can activate a reactant by accepting electrons from it. The carbonyl functional group provides a simple example. Uncatalyzed, the oxygen naturally pulls electron density away from the carbon due to the electronegativity difference, and strong nucleophiles such as Grignard reagents and enolates are able to attack the electrophilic carbon. Many interesting and desirable nucleophiles, however, are not strong enough to do so without assistance. Increasing the electrophilic character of the carbonyl carbon by using a Lewis acid to siphon electron

density away via coordination to the oxygen allows many of these weaker nucleophiles to be successfully utilized.

The simplicity of Lewis acid catalysis led to its frequent use even before the concept of Lewis acidity was developed by Gilbert N. Lewis in 1923,<sup>41</sup> making its origin impossible to pinpoint. Understandably, the uses of Lewis acid catalysis were quite limited prior to Lewis' recognition of what Lewis acids are, but Lewis acids came to be used to catalyze an extremely diverse set of reactions once a better understanding of their nature was developed. In addition to activating groups such as carbonyls to nucleophilic attack, Lewis acids are able to promote heterolytic bond cleavage, as in Friedel-Crafts acylation or the formation of Grignard reagents, and can also promote a variety of pericyclic reactions, such as ene reactions, 1,3-dipolar cycloadditions, and Diels-Alder reactions.

The Diels-Alder reaction in particular provides a look at how powerful Lewis acid catalysis can be, despite its simplicity. The Diels-Alder reaction was groundbreaking for its time, earning Otto Diels and Kurt Alder the 1950 Nobel Prize, and is still a core reaction in synthesis for its atom economy and ability create a ring whilst setting multiple stereocenters. A serious downside of Diels-Alder reactions is that they often suffer from cripplingly slow reaction times. The first Diels-Alder reaction to be catalyzed by a Lewis acid utilized aluminum trichloride (Scheme 1).<sup>42</sup> The reaction time was a mere one and a half minutes, whereas the author's extrapolation from the rate curve estimated an uncatalyzed reaction time of over 4800 hours. Hence, the simple addition of aluminum trichloride turned an unusably slow reaction into an extremely quick and efficient one. The requirement of one equivalent of aluminum trichloride here also demonstrates an occasional difficulty of Lewis acid catalysts: namely that the catalyst can remain coordinated to the substrate even after the reaction has completed, rendering it inactive, though recoverable.



**Scheme 1.** The first Diels-Alder reaction catalyzed by a Lewis acid.

In many instances, it is desirable to have the strongest Lewis acid possible in order to accelerate a reaction as much as possible. If there are several possible Lewis acid-catalyzed reactions or if the catalyst remains coordinated to the product, however, it may be necessary to tune the strength of the Lewis acid catalyst employed. While in practice tuning will generally involve an optimization procedure for Lewis acid strength, the relative strengths of Lewis acids can be determined via analysis of the difference in  $^1\text{H}$  and  $^{13}\text{C}$ , or  $^{31}\text{P}$  NMR shifts for specified test substrates alone versus coordinated to the Lewis acid in question.<sup>43</sup>

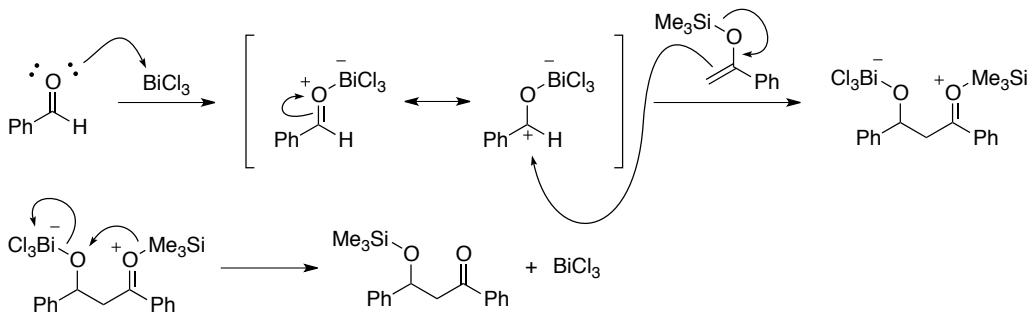
Lewis acidity is effectively governed by the electrophilicity of the metal center. Using a more electrophilic metal will hence yield a more Lewis acidic compound, as will using more weakly coordinating ligands because they donate less electron density. The triflate anion is commonly used as a ligand for this reason: as the conjugate base of a superacid, the triflate anion donates very little electron density to the metal it is coordinating with, thus allowing the metal to approach its maximum Lewis acidity. The triflate anion is also cheap and easy to produce. Current research in the area of bismuth Lewis acid catalysis hence often uses bismuth triflate,<sup>44</sup> which has the additional benefits of being mildly air and water stable. There are ligands that are even less electron donating such as the triflimide ligand, which has been shown to increase the Lewis acidity of metals even more than triflate,<sup>45</sup> but there is far less research that utilizes these ligands.

As mentioned prior, the use of bismuth(III) compounds as Lewis acid catalysts began with research by Wada in 1986 and 1987 using bismuth salts in catalytic systems with other metals, such as zinc, iron, or aluminum, to catalyze allylation reactions.<sup>46</sup> The first reported use of a bismuth salt to catalyze a reaction in the absence of any other reagents was reported in 1988, also by Wada, wherein bismuth trichloride catalyzes the Mukaiyama aldol reaction for a wide variety of silyl enol ethers and receptor carbonyls.<sup>47</sup>

The reactions generally proceeded in good time and yield, with the least substituted reactants yielding the best time and yield (Scheme 2). The reaction mechanism (Figure 8) details how Lewis acids are able to activate carbonyls, and in particular the resonance structures of the carbonyl coordinated to bismuth show how electron density is drawn away from the carbonyl carbon, heightening its electrophilicity.

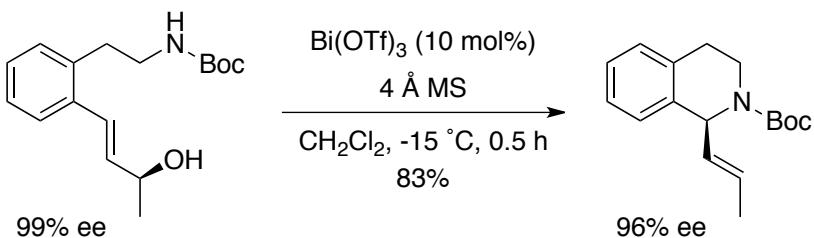


**Scheme 2.** An example reaction catalyzed with bismuth acting as a Lewis acid.



**Figure 8.** Reaction mechanism of the  $\text{BiCl}_3$ -catalyzed Mukaiyama aldol reaction.

The Mukaiyama aldol reaction is a useful test for the capabilities of a Lewis acid catalyst, and hence Wada's research utilizing it shows that bismuth(III) compounds have good potential as Lewis acid catalysts. Since this test reaction, research has shown that bismuth(III) compounds are able to catalyze a wide variety of reactions.<sup>48</sup> An interesting example is provided by Nobuyuki Kawai *et al.*, who use  $\text{Bi}(\text{OTf})_3$  to activate an allylic alcohol towards intramolecular nucleophilic attack from a secondary carbamate nitrogen (Scheme 3).<sup>49</sup> The observed selectivity is hypothesized to be due to the bismuth additionally coordinating to the carbonyl group of the Boc protecting group, directing the amide nitrogen to attack in a *syn* fashion. This case is demonstrative of the ability of many Lewis acids to have secondary bonding interactions that potentially result in stereoselectivity, a useful property.



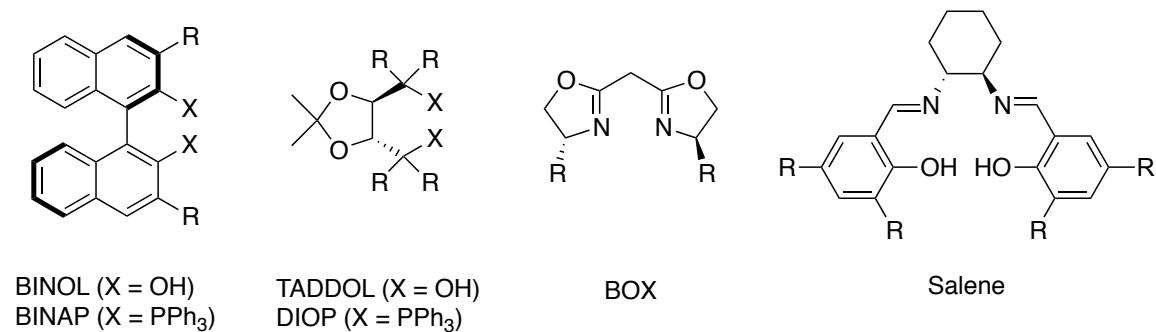
**Scheme 3.** Bismuth triflate catalyzed ring formation and chirality transfer.

## Asymmetric Lewis Acid Catalysis

The bismuth compounds commonly used for Lewis acid catalysis, such as bismuth triflate, are able to mediate reactions that are regio-, chemo-, and diastereoselective, but they are not capable of enantioselectivity. Asymmetric synthesis is an important facet of organic chemistry because many desirable natural products are chiral. Furthermore, drugs often depend upon enantiopurity for their biological activity because at the molecular level the human body is largely chiral. Regarding Lewis acid catalysis, enantioselective reactions are generally obtained by designing a chiral ligand to tightly coordinate to the Lewis acid during the reaction. This puts the chiral ligand close to the reaction site in order to provide a chiral environment that makes formation of one enantiomer favorable over the other.

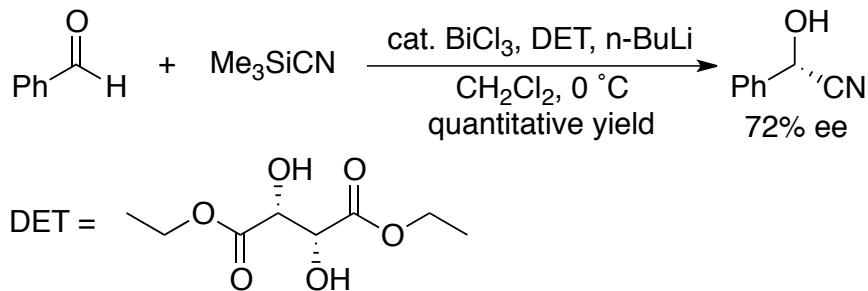
As the field of asymmetric catalysis has developed, several classes of ligands have come to be most commonly used and are referred to as privileged ligands (Figure 9).<sup>50</sup> Through extensive use in a wide variety of reactions, they have been shown to be chemically robust and effective at inducing chirality, and they are easily and cheaply acquired compared to the development of new ligands. They often are also easily modified, allowing for facile steric tuning for specific reactions. Privileged ligands are generally polydentate to ensure tight, rigid binding to the metal center. During a reaction, this rigidity causes the ligand to provide a consistent chiral environment, ideally avoiding conformations that are suboptimal for selectivity. Privileged ligands also generally possess  $C_2$  symmetry, which has proved to be particularly effective at inducing chirality.<sup>51</sup>

The simplicity of the  $C_2$  symmetry yields a binary environment, where the reaction pathway to one enantiomer is substantially hindered and the other is free, while chiral ligands of higher symmetry may allow access to more reaction pathways or secondary conformations that yield poor selectivity.



**Figure 9.** Examples of privileged ligands.

There has been research into chiral bismuth complexes that are capable of inducing chirality during a reaction, but it is a relatively undeveloped field and development is slow because creating bismuth catalysts that are effective and capable of chiral induction is difficult. The first asymmetric reaction involving a bismuth Lewis acid catalyst, reported by Wada in 1997,<sup>52</sup> saw (*2R,3R*)-(+)-diethyltartrate used as a chiral ligand for the asymmetric trimethylsilylcyanation of aldehydes (Scheme 4).

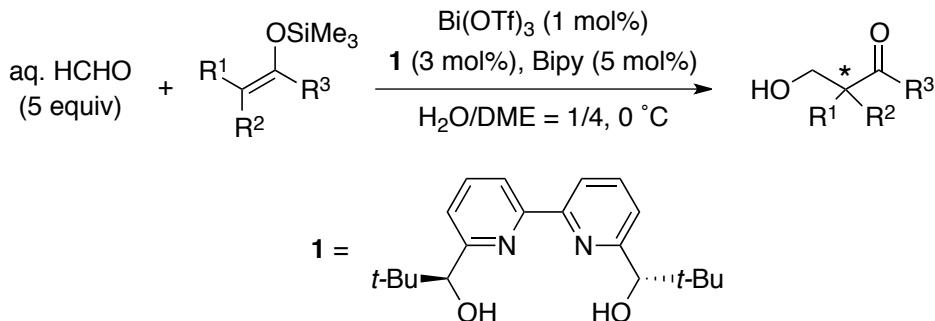


**Scheme 4.** Asymmetric hydrocyanation of an aldehyde, mediated by a chiral bismuth complex.

A wide variety of chiral ligands were screened, and in most cases they either dampened the Lewis acidity of the bismuth, leading to slow reaction times or no reaction,

or showed a low or negligible capability for chiral induction. This introduces two primary difficulties regarding Lewis acid-mediated asymmetric reactions: the first is that for the best induction of chirality, it is desirable to have a polydentate, tightly binding chiral ligand, but this directly contrasts the highly acidic and minimally electron-donating ligands desired for maximizing Lewis acidity. On the other hand, using less tightly binding ligands can result in a second problem: when the metal center coordinates to the substrate, a polydentate chiral ligand that does not bind tightly enough may partially dissociate, resulting in a loss of structural rigidity and thus compromising the ability of the chiral ligand to induce chirality. While generally there is a functional intermediate between a ligand binding too tightly and too loosely, finding this space is difficult when using bismuth, and often bismuth catalysts utilizing chiral ligands are ineffective in one way or another.

Despite these potential difficulties, bismuth(III) compounds utilizing chiral ligands have seen success regarding asymmetric catalysis. In 2005, Shū Kobayashi *et al.* reported that they had asymmetrically catalyzed the Mukaiyama-aldol reaction with a bismuth triflate, chiral bipyridine complex generated *in situ* (Scheme 5).<sup>53</sup> Notably, this catalyst is water-tolerant, suggesting that bismuth has good potential for water-compatible Lewis acid catalysis applications and thus accentuates the potential environmental friendliness of bismuth. This complex was also quickly applied to a catalyzed epoxide ring opening via nucleophilic attack by primary and secondary amines to produce chiral  $\beta$ -amino alcohols.<sup>54</sup> In a more recent screening of potential water-tolerant Lewis acid catalysts utilizing the same chiral bipyridine ligand as above, bismuth yielded the best enantioselectivity,<sup>55</sup> further demonstrating that bismuth shows promise regarding asymmetric Lewis acid catalysis. These were the greatest successes in a number of years, however, and finding a method to make asymmetric bismuth catalysis more facile is imperative in order for bismuth catalysis to be adopted into mainstream chemistry.



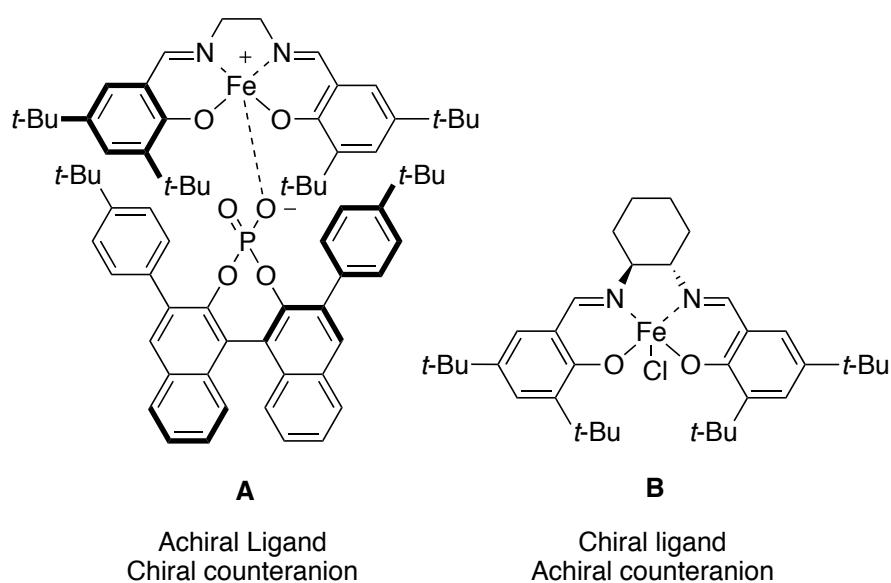
**Scheme 5.** Asymmetric Mukaiyama aldol reaction catalyzed by bismuth with a chiral ligand.

## Asymmetric Counteranion-Directed Catalysis (ACDC)

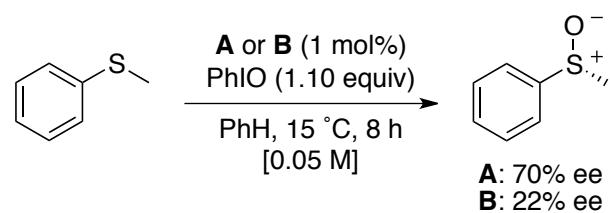
A solution to the difficulties of asymmetric bismuth Lewis acid catalysis outlined above may lie in a recently introduced mode of chiral induction that has seen a great deal of success: asymmetric counteranion-direct catalysis (ACDC). In the opposite direction of using tightly binding ligands to induce chirality, ACDC utilizes weakly binding ligands designed to dissociate and provide a chiral environment as a counteranion.<sup>56</sup> This mode of catalysis is inspired by strong Brønsted acid catalysis,<sup>57</sup> in which a strong Brønsted acid donates a proton to catalyze a reaction,<sup>58</sup> leaving the chiral conjugate base to associate with a positive charge on the substrate and thereby create a chiral environment to induce selectivity. It is important to note that because the counteranion is the conjugate base of a strong acid, its association with the substrate is generally only an electrostatic interaction, rather than a hydrogen bond.<sup>59</sup> A major benefit of ACDC is that easily dissociating chiral ligands will donate very little electron density to the bismuth center, thereby not only preserving its Lewis acidity, but allowing it to approach its maximum Lewis acidity in the same way as the triflate ligand.

Relying on an electrostatic interaction to induce chirality may seem dubious compared to induction via stronger interactions, but ACDC has often yielded results that are as good or even better than those obtained by utilizing chiral ligands, showing that electrostatic interactions are quite effective. A good example has been presented by Saihu Liao and Benjamin List, who studied an asymmetric iron-catalyzed sulfoxidation using

two catalysts (Scheme 6): one with an achiral ligand and a chiral counteranion and the other with a chiral ligand and an achiral counteranion (Figure 10).<sup>60</sup> They found that not only did the catalyst with the chiral counteranion yield a percent conversion comparable to that obtained utilizing the catalyst with the chiral ligand, but it also promoted formation of the chiral sulfoxide over the sulfone to a greater extent and induced much greater selectivity, yielding the sulfoxide in 70% ee, as opposed to 22% ee. Chiral counteranions are also thought to be more generally effective than chiral ligands, as they are able to associate with any positively charged part of a substrate during a reaction, potentially being able induce chirality in reactions where chiral ligands cannot because chiral ligands are relegated to providing a chiral environment only around the site of metal coordination.

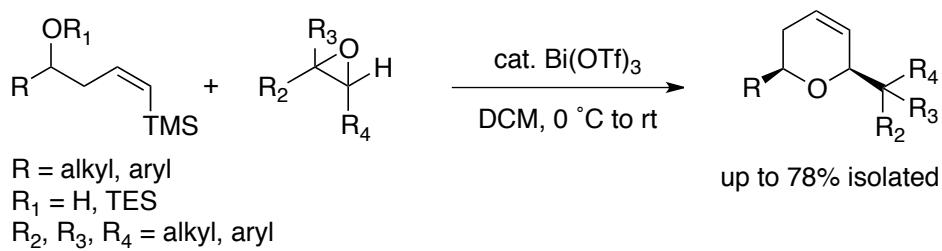


**Figure 10.** Iron catalysts with difference sources of “chiral information”.



**Scheme 6.** Enantioselective sulfoxidation using a traditional chiral ligand vs. ACDC.

ACDC provides another benefit for bismuth catalysis regarding a second difficulty of asymmetric bismuth catalysis: despite the amount of recent research on bismuth Lewis acid catalysis, there is sometimes ambiguity regarding the mechanism of catalysis for bismuth compounds with acidic ligands. In many cases, for example, a reaction catalyzed by bismuth triflate is also catalyzed by triflic acid, introducing the possibility that bismuth triflate is acting as a triflic acid reservoir. R. Frederick Lambert *et al.* explored the role of bismuth triflate in the formation of dihydropyrans (Scheme 7) in depth.<sup>61</sup> They first observed that the reaction could be catalyzed by triflic acid in addition to bismuth triflate, and, as a test, 2,6-di-*tert*-butyl-4-methylpyridine was added to the bismuth triflate-catalyzed reaction as a hindered, non-nucleophilic base. This halted the reaction progress, providing evidence that triflic acid was the catalytic species. However, they also found that addition of water to bismuth triflate was unable to produce detectable amounts of triflic acid, and hence, perhaps ironically, it was concluded that the Lewis acid/Lewis base coordination between the bismuth and the homoallylic alcohol was necessary for the release of triflic acid.



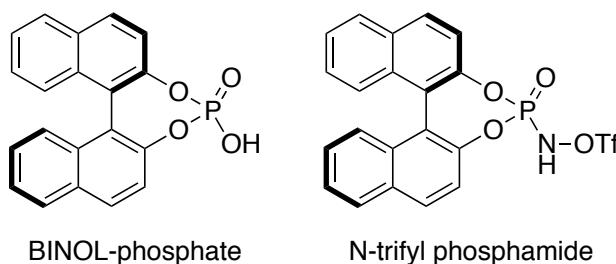
**Scheme 7.** Bismuth triflate-mediated epoxide rearrangement, addition, and intramolecular silyl-modified Sakurai cascade.

Though bismuth triflate may not be the catalytic species for every reaction, the above report shows that even when it is not, it can play a vital role as a particularly effective method of introducing triflic acid to the reaction mixture. For bismuth catalysis in general, this ambiguity is not much of a problem as in either case the reaction is catalyzed using a cheap, relatively nontoxic, and effective catalyst, which is all that is desired from a green chemistry standpoint. For asymmetric catalysis utilizing chiral ligands, however, if the reaction is actually catalyzed by a strong acid, then the bismuth

complex with the chiral ligand will not be in position to provide a chiral environment. Hence, asymmetric bismuth catalysis utilizing chiral ligands is incompatible with the strong acid mode of catalysis. With ACDC, however, the strong acid catalyzing the reaction will be the conjugate acid of the chiral counteranion. Once this acid donates its proton, the chiral counteranion will remain to provide a chiral environment, as desired. Regardless of whether a reaction is Lewis acid-catalyzed or strong Brønsted acid-catalyzed, utilizing an ACDC approach should hence yield an asymmetric reaction.

## Designing A Bismuth Complex To Utilize ACDC

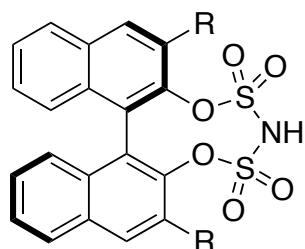
Because the weakly coordinating ligands desired for ACDC will generally be conjugate bases of strong acids, successful chiral strong Brønsted acid catalysts are a promising source for finding potential ligands for ACDC. The 1,1'-binaphthyl ligand backbone has been used extensively in strong Brønsted acid catalysis, with BINOL-phosphates being used often during the development of the strong Brønsted acid catalysis field,<sup>62</sup> and stronger chiral acids such as the N-triflyl phosphoramides commonly being used today (Figure 11).<sup>63</sup> In general, these BINOL-derived strong acids show excellent chiral induction capabilities and facile syntheses, both of which are also highly desirable for ACDC ligands.



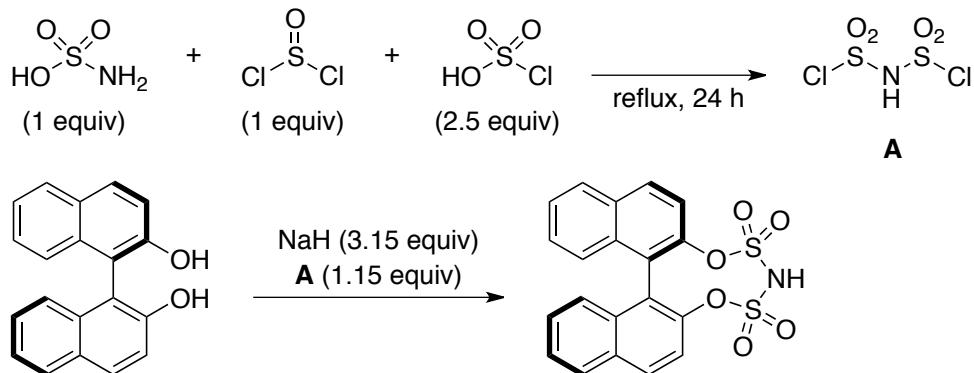
**Figure 11.** Common chiral strong Brønsted acid catalysts.

In 2010, Albrecht Berkessel *et al.* designed and synthesized a new 1,1'-binaphthyl-2,2'-sulfurylimide chiral strong acid, dubbed the JINGLE-type ligand (Figure 12).<sup>64</sup> It has since been demonstrated that the acidity of the JINGLE-type ligand surpasses

common chiral strong Brønsted acids in DMSO<sup>65</sup> and in acetonitrile,<sup>66</sup> making it especially promising for strong Brønsted acid catalysis and ACDC alike. The synthesis of the JINGLE-type ligand is furthermore reported to be facile, differentiating it from BINOL-sulfonamides in particular, which have a longer and more convoluted synthesis. The synthesis is a two-step process (Scheme 8), with imidobis(sulfuryl chloride) first being synthesized by refluxing amidosulfonic acid, chlorosulfonic acid, and thionyl chloride under inert atmosphere.<sup>67</sup> Next, the alcohol groups of the BINOL are deprotonated using sodium hydride, and the imidobis(sulfuryl chloride) is added, undergoing straightforward acid chloride chemistry to yield the JINGLE-type ligand.



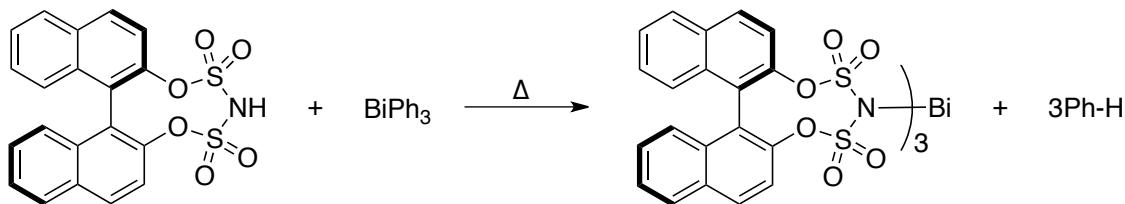
**Figure 12.** A generic JINGLE-type ligand.



**Scheme 8.** Literature synthesis of the JINGLE-type ligand.

After synthesis, the JINGLE-type ligand must be coordinated to bismuth(III). It is predicted that the JINGLE-type ligand will bind through the nitrogen, as it is softer than oxygen, and this softness is accentuated by charge delocalization due to the nitrogen being positioned at the center of the sulfurylimide moiety. There are two common ways

of coordinating ligands to bismuth(III). Trivalent bismuth compounds have successfully been synthesized by mixing a silver salt of the desired ligand with bismuth chloride to utilize precipitation of silver chloride as a driving force for the ligand exchange, as per Le Châtelier's principle.<sup>68</sup> However, a past researcher in the Lalonde group, Adriana Jemison, determined that applying this method to the synthesis of a similar homoleptic bismuth(III) BINOL-phosphate complex yielded multiple products that were difficult to separate or characterize. An alternative procedure is to mix the ligand with triphenylbismuth, either in solution or finely ground together, and to heat the mixture to evaporate benzene as a driving force for ligand exchange (Scheme 9). Because the ligand exchange is fundamentally an acid-base reaction in which the ligand protonates a phenyl group coordinated to bismuth, this method works particularly well for acidic ligands, and thus is well suited for the synthesis of bismuth compounds designed for ACDC. Philip C. Andrews *et al.* in particular observed a great deal of success utilizing this method to synthesize bismuth complexes with a wide variety of sulfuric acid- and acidic sulfonamide-derived ligands.<sup>69</sup>



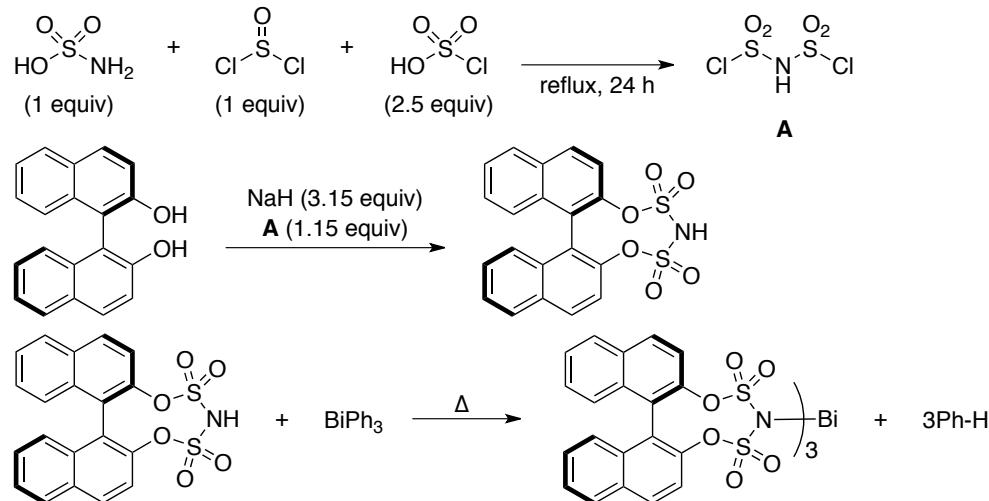
**Scheme 9.** Proposed ligand exchange to form a homoleptic bismuth JINGLE complex.

There is precedence for bismuth(III) coordination compounds involving extremely acidic ligands: the synthesis of bismuth(III) bis(triflimide), reported by Alexandre Picot *et al.* in 2002<sup>70</sup> in particular demonstrates that bismuth is able to coordinate to ligands via highly acidic nitrogens. As JINGLE-type ligands are strong acids predicted to coordinate via the nitrogen, the bismuth triflimide complex thus suggests that a bismuth(III) JINGLE complex is feasible. The ability of the JINGLE-type ligand to coordinate to bismuth is only one of two main concerns pertaining to the synthesis of a bismuth(III) JINGLE complex, however. The other concern is that, sterically, it may be difficult to fit three JINGLE-type ligands around a bismuth center.

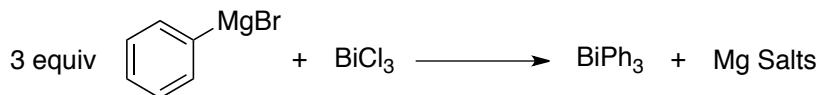
The binaphthyl backbone is quite large, especially considering the ideal bond angles of 90°. Work by Yoshihiro Matano *et al.* on the synthesis of sterically crowded bismuth(III) complexes shows that such steric concerns are valid,<sup>71</sup> but also that bismuth(III) compounds with highly bulky substituents are possible—recalling for a moment the bismuth(III) di(trimethylsilyl)methyl complex introduced during the discussion of relativistic effects.<sup>28</sup> The JINGLE-type ligand also places the site of coordination somewhat far from the bulky binaphthyl backbone, especially compared to the related BINOL-phosphates, phosphamides, and sulfonamides, which ideally will minimize steric conflict. Hence, the steric concerns are predicted to be minor, and by all accounts it is hypothesized that a bismuth(III) JINGLE complex may be synthesized readily.

## Results And Discussion

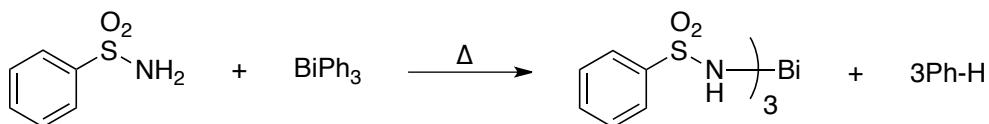
The synthetic plan to form the target bismuth(III) JINGLE complex was first to synthesize the JINGLE-type ligand and second to coordinate three of the ligands to bismuth. The planned synthesis of the JINGLE-type ligand followed the procedure reported in the literature, first making imidobis(sulfuryl chloride) from amidosulfonic acid, thionyl chloride, and chlorosulfonic acid (Scheme 10, top), and second attaching this moiety to BINOL (Scheme 10, middle). It was predicted, based upon literature precedence, that once the ligand was synthesized, a neat ligand exchange reaction with triphenylbismuth would yield a homoleptic bismuth(III) JINGLE complex (Scheme 10, bottom). Also, because in-house synthesis of triphenylbismuth was cheaper than purchasing it, the synthesis of triphenylbismuth via a standard Grignard metathesis was planned (Scheme 11). The synthesis of triphenylbismuth was attempted first, followed by the attempted synthesis of bismuth(III) benzenesulfonamide as a proof of concept (Scheme 12).



**Scheme 10.** Planned synthesis of the bismuth(III) JINGLE complex.

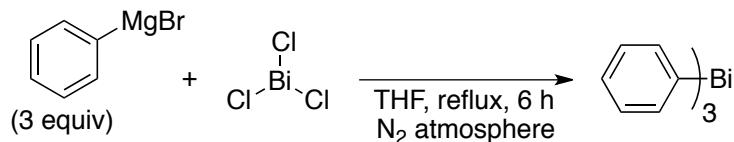


**Scheme 11.** Proposed synthesis of triphenylbismuth.



**Scheme 12.** Proposed synthesis of the proof of concept bismuth(III) benzenesulfonamide complex.

## Synthesis Of Triphenylbismuth



**Scheme 13.** Proposed Grignard metathesis to form triphenyl bismuth.

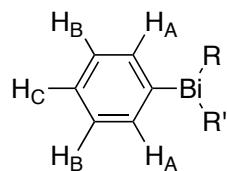
The synthesis of triphenyl bismuth was attempted via a standard Grignard metathesis under inert atmosphere utilizing phenylmagnesium bromide and bismuth trichloride (Scheme 13), as reported in the literature.<sup>72</sup> The reaction was expected to proceed smoothly, resulting in a solution of triphenylbismuth and precipitated magnesium salts. The magnesium salts were expected to solubilize upon addition of acid to neutralize or slightly acidify the solution. There was concern about overly acidifying the solution because triphenylbismuth is known to hydrolyze under acidic conditions, and hence ammonium chloride was chosen as a weak acid to bring the solution to neutral during workup.

A 3 M bottle of phenylmagnesium bromide was purchased from Alfa Aesar. The concentration at the time of the reaction was determined to be approximately 1 M via

titration of salicylaldehyde phenylhydrazone in dry THF with the Grignard solution. Additions of the Grignard solution to bismuth trichloride in dry THF resulted in a cloudy white solution that quickly faded while stirring. Two UV-active compounds, with  $R_f = 0.58, 0.73$  in 5% MTBE/Hex, were observed via TLC during the reaction. In the naïve hope that a greater amount of one product would form after a time, the reaction mixture was refluxed for six hours to yield an extremely sticky, gummy residue.

Workup and concentration yielded a brown residue that crystallized overnight at room temperature, rather than the expected white crystals of triphenylbismuth. The high  $R_f$  UV-active spot was isolated via silica gel column chromatography, eluting with pure hexanes, to yield white crystals upon concentration. The low  $R_f$  spot was not isolated, and could not be found via TLC analysis in the fractions or in the EtOAc column flushes. The isolated product was initially tentatively identified as triphenylbismuth because triphenylbismuth was predicted to be the least polar product of the metathesis, and thus should have eluted first.

While the white crystals of the isolated product matched the appearance of a commercial triphenylbismuth sample obtained from Sigma Aldrich, comparison of the  $^1\text{H}$  NMR spectrum of the top spot (Spectrum 7) to the  $^1\text{H}$  NMR spectrum of the commercial triphenylbismuth (Spectrum 1) revealed that it was not triphenylbismuth (Table 1). Both spectra contained a doublet and two triplets assignable to a mono-substituted phenyl group, but the shifts of the corresponding peaks differed. It was thus hypothesized that the isolated product was the mono- or dichlorinated phenylbismuth complex.

**Table 1.**  $^1\text{H}$  NMR shifts the top spot product and to commercial  $\text{Ph}_3\text{Bi}$ .

Proton	Top spot		Commercial $\text{Ph}_3\text{Bi}$	
	Shift (ppm)	Integration	Shift (ppm)	Integration
$\text{H}_\text{A}$	7.63	2H	7.78	2H
$\text{H}_\text{B}$	7.47	2H	7.42	2H
$\text{H}_\text{C}$	7.38	1H	7.35	1H

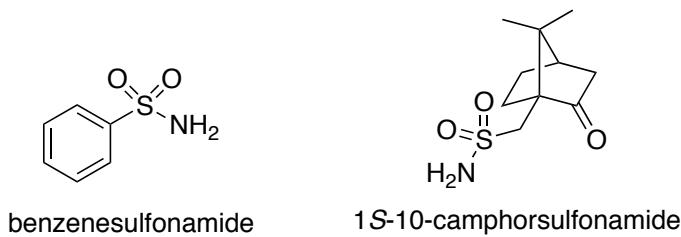
Due to the use of a crude improvised septum, the concentration of the Grignard solution quickly dropped to unusable levels. A bottle, with a septum, of 3 M phenylmagnesium bromide was purchased from Sigma Aldrich. Due to improper sealing technique, the concentration of this bottle also dropped quickly. After a several week hiatus, the concentration was determined in multiple trials to be roughly 0.4 M. No magnesium salts, however, were observed in the bottle, whereas salts had precipitated out of the Alfa Aesar Grignard solution when the concentration approached 1 M and below. It was suspected that the titration procedure was flawed. Due to previous poor sealing technique, it was hypothesized that the THF being used was wet, and upon using a new bottle of THF the Grignard concentration was consistently determined to be approximately 1 M, supporting this hypothesis. The lack of triphenylbismuth formation in the first Grignard reaction hence may have been due to water neutralizing a portion of the Grignard reagent, leaving too few equivalents for three sequential metatheses.

It was also considered that the salicylaldehyde phenylhydrazone might be impure. It was previously determined to be pure via  $^1\text{H}$  NMR, but the color was a light yellow-brown, as opposed to the white color reported in the literature by B. E. Love and E. G. Jones.<sup>73</sup> It also exhibited a sluggish color change during the titration, in contrast to the reported sharp color change. The reagent was recrystallized from boiling chloroform, as suggested by Love and Jones. The recrystallization unexpectedly yielded olive-green crystals, but the rate of color change was much improved.

It was hypothesized that the previous long reflux had caused decomposition. The next attempt was hence run for 1 h at 25 °C, and a fellow researcher also ran it at 25 °C overnight. Addition of the Sigma Aldrich Grignard reagent to bismuth trichloride in dry THF resulted in the immediate formation of a fine black precipitate. After workup, the organic layer was concentrated to yield a small amount of UV-active yellow residue. <sup>1</sup>H NMR showed many unexpected peaks in the alkyl region, suggesting degradation products. The black precipitate was extracted with DCM, but TLC analysis showed no UV-active compounds in the extract, nor in the aqueous layer from the workup. The overnight reaction yielded the same results.

## Proof Of Principle

Due to lack of time, it was decided that triphenylbismuth would be purchased from Sigma Aldrich so that more interesting chemistry could be pursued. It was also decided that before attempting synthesis of the bismuth(III) JINGLE complex, proof of principle bismuth complexes utilizing commercially available ligands should be synthesized. The selected ligands were benzenesulfonamide and 1*S*-10-camphorsulfonamide (Figure 13).



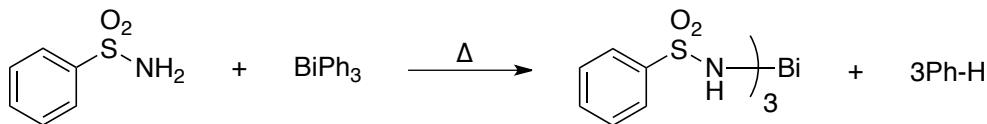
**Figure 13.** Selected commercially available test ligands.

Benzenesulfonamide, having a sulfonamide moiety connected to an aromatic group, is structurally similar to the proposed JINGLE-type ligand, and hence a successful synthesis of bismuth(III) benzenesulfonamide will provide precedence for the formation of the bismuth(III) JINGLE complex. Benzenesulfonamide has a pK<sub>a</sub> of 16.1 in DMSO<sup>74</sup> (10.1 in water),<sup>75</sup> much greater than the pK<sub>a</sub> = 2.11 in DMSO of the JINGLE ligand,<sup>65</sup> and

is lacking as a test ligand in this sense, but the reported synthesis of bismuth triflimide already provides precedence for the formation of an *N*-bond between bismuth and a highly acidic ligand. The ligand exchange reaction also is predicted to still be possible despite the higher  $pK_a$ , as the  $pK_a$  of benzene (43 in water) is much greater yet.

*1S*-10-camphorsulfonamide is a cheap chiral ligand, and thus a bismuth(III) camphorsulfonamide complex is itself interesting, potentially displaying catalytic activity and capability for asymmetric induction. The carbonyl group provides a second coordination site and thus does raise questions about potential modes of coordination, but it is predicted that bismuth will coordinate preferentially to the nitrogen, as the slightly higher polarizability of the nitrogen and the delocalized negative charge (due to being at the center of the sulfonylimide moiety) makes it a softer Lewis base. Andrews *et al.* observed this selectivity with saccharinate, which has a similar selection of coordination sites.<sup>76</sup> It should also be acknowledged that bismuth may coordinate to both sites on the same camphor molecule, forming a seven-membered ring, or on different molecules, forming a polymer. It is unknown what effects this would have on chiral induction, but secondary bonding is predicted to lower the Lewis acidity of the bismuth center, which may undermine its utility as a catalyst.

## Synthesis Of Bismuth(III) Benzenesulfonamide



**Scheme 14.** Proposed ligand exchange to form bismuth(III) benzenesulfonamide.

The synthesis of bismuth(III) benzenesulfonamide was first attempted via a neat reaction used by Philip C. Andrews *et al.* (Scheme 14). Andrews *et al.* synthesized a variety of bismuth(III) complexes with amidosulfonic acid-derived ligands, such as acetosulfame (Scheme 15), by grinding triphenylbismuth and three equivalents of the

desired ligand in a mortar and pestle and heating in a Kugelrohr oven, with the removal of benzene as a driving force as per Le Châtelier's principle.<sup>69</sup> For reactions run cooler than the boiling point of benzene, 80 °C, the reduced pressure allows for use of the expulsion of benzene as a driving force, and for reactions utilizing temperatures over 80 °C, the reduced pressure still assists in the rapid removal of benzene. Because the melting point of triphenylbismuth is just under 80 °C, and also because a melting point depression was predicted, it was hypothesized that running the reaction at 80 °C or slightly above would melt both reactants. While it was predicted that this would accelerate the ligand exchange due to closer interactions between the reactants, it was also predicted that the reaction would proceed in the solid state due to the large  $pK_a$  difference.



**Scheme 15.** Ligand exchange to form bismuth(III) acetosulfame.

Triphenylbismuth and three molar equivalents of benzenesulfonamide were finely ground together and heated to 85 °C at 50 mbar. It was observed that only the triphenylbismuth melted. After one hour, the product mixture was removed from heat, and an NMR sample was prepared in *d*<sub>6</sub>-DMSO. Upon comparison to the <sup>1</sup>H NMR spectra of the starting materials in *d*<sub>6</sub>-DMSO (Spectra 2 and 5), it was found that all peaks in the <sup>1</sup>H NMR spectrum of the product mixture (Spectrum 8) were assignable to the starting materials, and it was concluded that negligible ligand exchange had occurred. It was conjectured that the lack of a melting point depression indicated that the triphenylbismuth and benzenesulfonamide were not interacting readily, and it was further hypothesized that raising the temperature to melt benzenesulfonamide would assist in forming the close interactions necessary for the ligand exchange, thus allowing the reaction to occur.

A melting point apparatus first was used to confirm that a 1:3 molar mixture of triphenylbismuth and benzenesulfonamide would exhibit no melting point depression. As expected of each individually, the triphenylbismuth component melted at 80 °C and the benzenesulfonamide component melted at 150 °C. To expediently test if melting both reagents would enhance reactivity, another melting point sample was left in the apparatus at 165 °C. A white solid formed after roughly one hour, and upon further heating, the solid decomposed somewhere between 340 °C and 400 °C.

The reaction carried out in the melting point apparatus was scaled up by running the ligand exchange reaction in a small vial at 165 °C and open to the atmosphere. The reaction was removed from heat after one hour, and a beige solid was observed to have formed; partial melting point 140-144 °C. FT-IR analysis showed only starting material peaks, indicating that if any reaction had occurred, it was not complete. <sup>1</sup>H NMR data from samples prepared in CDCl<sub>3</sub> (Spectrum 9) showed large starting material peaks, but also several smaller sets of peaks at 8.00, 7.77, and 7.63 ppm. Because the splitting patterns of these new peaks displayed higher-order splitting almost identical to their upfield neighbors, it was hypothesized that the compounds they represented were quite similar to the starting materials, and could be products of the ligand exchange reaction.

The product mixture did not entirely dissolve when preparing the NMR sample in CDCl<sub>3</sub>, and so an NMR sample was prepared in d<sub>6</sub>-DMSO. Undissolved solids were still observed, and because benzenesulfonamide and triphenylbismuth both are soluble in DMSO, it was concluded that a product was either sparingly soluble or insoluble in DMSO. To test whether this insoluble product was the same as the compound responsible for the new peaks, a sample of the product was thoroughly washed with DMSO and the remaining solid was prepared for NMR in d<sub>6</sub>-DMSO. The resulting spectrum showed no peaks other than those corresponding to solvents, signifying that the insoluble material indeed was a second product.

The presence of triphenylbismuth in the NMR spectra suggested that the reaction had not proceeded to completion. Hence, the reaction duration and temperatures were increased in an attempt to drive the reaction further (Table 2). Increasing temperature and duration both resulted in further consumption of triphenylbismuth, as observed by the disappearance of triphenylbismuth peaks in <sup>1</sup>H NMR, and also by increasing mass loss,

tentatively thought to be caused by expulsion of benzene. Unexpectedly, the putative product peaks also disappeared as time and temperature were increased, suggesting this compound was either an intermediate, or was decomposing. Running the ligand exchange reaction at 200 °C for 2 h resulted in total disappearance of triphenylbismuth and putative product peaks (Spectrum 12), as well as a mass loss equal to three equivalents of benzene.

**Table 2.** Ligand exchange reaction summary for various temperatures and durations.

Product	Mass Ph <sub>3</sub> Bi (mg)	Temp (°C)	Time (h)	Equiv BSA <sup>a</sup>	Mass lost (mg)	Ph <sub>3</sub> Bi: BSA <sup>b</sup>	New peak:BSA <sup>c</sup>
3b	51	165	1	3	—	0.4	0.2
3c	39	165	2	3	14	0.1	0.03
3d	41	200	2	3	21	0	0

<sup>a</sup> BSA here is used as a shorthand for benzenesulfonamide.

<sup>b</sup> Via <sup>1</sup>H NMR in *d*<sub>6</sub>-DMSO by relative integrations of the respective *ortho*-hydrogen peaks.

<sup>c</sup> Via <sup>1</sup>H NMR in *d*<sub>6</sub>-DMSO by relative integrations of the *ortho*-hydrogen peak of benzenesulfonamide and the product doublet appearing at 8.00 ppm.

The first reaction run at 200 °C and for 2 hours was run in a small vial with a stir bar. The reaction yielded a beige product, as before, but also a dark brown product at the bottom of the vial where the stir bar had been rotating. The mass loss was equal to 2.5 equivalents of benzene, suggesting an incomplete reaction, but heating for an additional 45 minutes did not change the mass. Furthermore, no triphenylbismuth was observed via NMR. It was thus hypothesized that the dark brown material was a third product, and possibly one due to decomposition of triphenylbismuth. Because the dark brown material had only occurred where the stir bar had been rotating, it was thought that the reactants had been spread too thin in that area. Running a reaction with the same conditions in a conical vial without a stir bar to keep the reactants concentrated in a small volume resulted in no dark brown product.

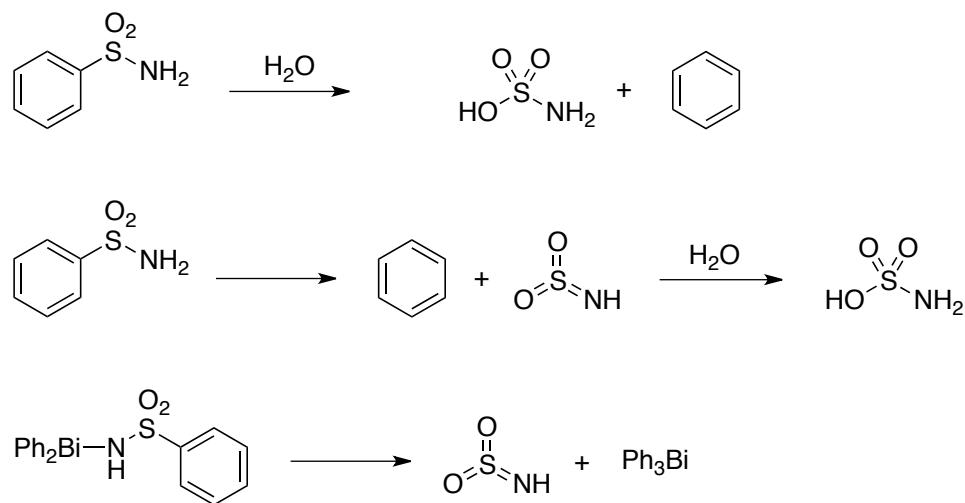
Because the beige product, which appeared to be the main product of these reactions, was difficult to characterize due to insolubility, an effort was made to synthesize the material responsible for the new peaks originally observed. As this product

seemed potentially to be an intermediate, it was tentatively thought that it was the bismuth monobenzenesulfonamide complex, and that increasing the reaction temperature and duration was resulting in its consumption to form bismuth di- and tribenzenesulfonamide. Due to the known solubility problems associated with sulfonamides, the possibility that the di- and tri benzenesulfonamide compounds are insoluble was thought not to be unreasonable.

It was hypothesized that one equivalent of benzenesulfonamide could be mixed with triphenylbismuth and allowed to react at 200 °C for 2 hours to afford the monobenzenesulfonamide. This reaction resulted in the formation of a brittle shell of dark brown material, and beige solid underneath. The mass loss was expected to be equal to one equivalent of benzene, but was found to be equal to 2.7 equivalents of benzene instead. The <sup>1</sup>H NMR spectrum (Spectrum 14) showed only benzenesulfonamide peaks. It was concluded that the dark brown product was almost certainly a decomposition product, the formation of which seemed to be associated to exposure to atmosphere coupled with a lack of multiple equivalents of benzenesulfonamide. Because the insolubility of the products made analysis impossible, because it is known that sulfonamides and triphenylbismuth decompose readily, and because products thought to be due to decomposition were observed, attention was shifted to investigating possible decomposition products.

Possible modes of decomposition of benzenesulfonamide were probed first. Based upon literature, benzenesulfonamide has three likely mechanisms of decomposition. The first would form benzene and amidosulfonic acid via hydrolysis (Scheme 16, top). Philip C. Andrews *et al.* observed sulfate anion in a crystal structure of ligated bismuth and subsequently determined that the sulfate was present due to hydrolysis of the sulfonate ligands.<sup>77</sup> The second possible decomposition pathway is that benzenesulfonamide could undergo thermal decomposition to release sulfonimine, SO<sub>2</sub>NH, and benzene (Scheme 16, middle). Both could evaporate, and the sulfonimine could alternatively be hydrolyzed to amidosulfonic acid. In the same paper by Andrews *et al.* as above, the thermal decomposition of a ligand structurally similar to benzenesulfonamide, 2,4,6-mesitylene sulfonate, was observed via differential scanning calorimetry to undergo thermal decomposition from 80-150 °C, and the release of SO<sub>x</sub> gases was proposed. A third

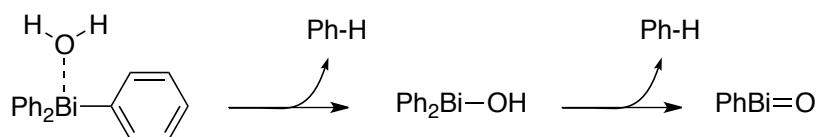
decomposition mechanism, similar to the second, arises in the presence of a metal center: a general procedure for synthesizing organometallic compounds is to form the organosulphinato-metal complex, and subsequently to thermally decompose the compound, releasing  $\text{SO}_2$  gas and yielding the associated organometallic compound.<sup>78</sup> An analogous decomposition could occur to a bismuth benzenesulfonamide complex to release sulfonimine and reform triphenylbismuth (Scheme 16, bottom). While all of these appear reasonable, the consistent strong presence of benzenesulfonamide peaks in NMR and IR spectra suggests that it is primarily not benzenesulfonamide that is decomposing.



**Scheme 16.** Potential modes of decomposition of benzenesulfonamide.

Triphenylbismuth decomposition products were explored as well. Three routes of decomposition were identified: hydrolytic, radical, and oxidative. The ligand exchange is based upon a simple acid/base reaction between benzenesulfonamide and the benzene coordinated to bismuth. It is feasible that water could also act as an acid for ligand exchange, resulting in hydroxy-bismuth compounds. Hydrolysis of a second phenyl group would result in phenylbismuth oxide (Scheme 17). The analogous hydrolytic degradation of bismuth trichloride to bismuth oxychloride is well known.<sup>79</sup> Phenylbismuth oxide is predicted to be soluble in DMSO, however, based upon studies by a fellow researcher. Furthermore, the  $\text{p}K_a$  of benzenesulfonamide is 10.1, nearly six orders of magnitude more acidic than water. If hydrolysis is the primary means of

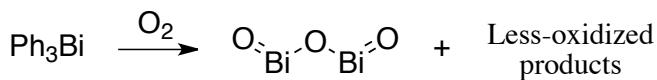
decomposition, then it is expected that the desired bismuth(III) benzenesulfonamide will be formed much more quickly than the hydrolysis product. Though hydrolysis of this complex could occur as well, it appears unlikely based upon the  $pK_a$  difference. It should be noted that this assessment ignores steric effects and the difference between water and benzenesulfonamide concentrations, both factors that could have a significant effect upon the relative rates of these competitive reactions.



**Scheme 17.** Proposed hydrolysis of triphenylbismuth.

Radical decomposition may be possible because bismuth carbon bonds are quite weak, with the triphenylbismuth Bi–C bond dissociation energy being only 46 kcal/mol.<sup>80</sup> Heating a sample of triphenylbismuth could hence potentially provide enough energy for homolytic cleavage of the Bi–C bond. This homolytic cleavage would result in a phenyl radical and a diphenylbismuth radical. It is expected that these radicals would react with all molecules in the reactant mixture, hence with other phenyl groups, benzenesulfonamide, and bismuth centers. Especially because multiple radicals may react with the same molecule, it is expected that this radical chemistry would result in a number of products, predicted to present as a variety of new peaks on IR and NMR. This is not observed, suggesting that radical decomposition does not occur in appreciable amounts.

Lastly, triphenylbismuth could be oxidized by atmospheric oxygen. Alkylbismuth compounds are easily oxidized by air, and in a close study of the oxidation of triethylbismuth undertaken by George Calingaert *et al.*,<sup>81</sup> the observed bismuth-containing oxidation products were  $\text{Et}_2\text{BiOEt}$ ,  $\text{OBiOEt}$ , and  $\text{Bi}_2\text{O}_3$ . While triphenylbismuth is more stable than alkylbismuths, it is hypothesized that oxidation could occur at the high temperatures of the ligand exchange reaction to yield various oxidized benzene derivatives, organobismuth compounds, and bismuth oxide (Scheme 18).



**Scheme 18.** Proposed oxidation of triphenylbismuth.

The formation of bismuth oxide in particular seems to be supported by the results of the ligand exchange reactions. First, bismuth oxide is extremely difficult to solubilize, while less oxidized bismuth compounds are expected to be at least slightly soluble in DMSO. Second, formation of bismuth oxide would result in the expulsion of three equivalents of benzene, causing the mass loss expected of the ligand exchange and a disappearance of triphenyl bismuth from NMR and IR spectra, both of which are observed. Third, formation of bismuth oxide is consistent with the appearance of the two IR peaks just under  $3000 \text{ cm}^{-1}$  observed for the  $200 \text{ }^\circ\text{C}$ , 2 h reaction (Spectrum 13). This analysis is based upon IR data for antimony oxide<sup>82</sup> due to the lack of IR data on bismuth oxide, under the assumption that the IR spectrum of bismuth oxide is similar to that of antimony oxide based upon their analogous molecular and electronic structures. Lastly, bismuth oxide represents a natural endpoint of decomposition, as the products of hydrolysis and any radical decomposition could be oxidized to bismuth oxide, which may be why products of these pathways are not observed.

## Conclusion

The Grignard metathesis to form triphenylbismuth was more difficult than expected, considering that it is commonly reported in the literature. Use of the Alfa Aesar Grignard solution resulted in two UV/active compounds, one of which was isolated and determined to be not triphenylbismuth, but perhaps a mono- or dichloro phenylbismuth complex. It is possible that the unisolated bottom spot was the desired triphenylbismuth. Fellow researchers successfully isolated triphenylbismuth, albeit in low yield, using the same reagents and different reaction conditions, and so it is predicted that optimization of the Grignard reaction will allow triphenylbismuth to be synthesized in good yield. Given time, this should be explored before purchasing triphenylbismuth. Unexpectedly, use of

the Sigma Aldrich Grignard solution resulted in no successful reactions. Research into discovering what was occurring was precluded by a lack of time.

The ligand exchange reaction to form bismuth(III) benzenesulfonamide also proved to be difficult. The reaction was found to require much greater temperatures than those reported in the literature for ligands such as cyclamic acid, and this is thought to be due to the greater  $pK_a$  of benzenesulfonamide. The reactions resulted in at least three products: a product soluble in  $\text{CDCl}_3$  and  $d_6\text{-DMSO}$  that gave several new peaks on  $^1\text{H}$  NMR, an insoluble beige product, and an insoluble dark brown product.

The product responsible for the new NMR peaks disappeared as reaction conditions were adjusted to fully consume triphenylbismuth, suggesting that it is an intermediate or that it decomposes. The dark brown product appeared avoidable when utilizing three equivalents of ligand and running the reaction in a conical vial. The beige solid could not be characterized because it was insoluble in all common solvents, but research into the literature and the presence of two new IR peaks just under  $3000 \text{ cm}^{-1}$  suggest that its identity is bismuth oxide, formed via oxidative decomposition.

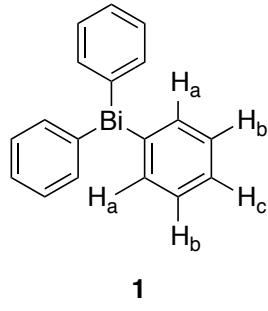
Running the  $200^\circ\text{C}$  reaction in a conical vial for 2 hours again and washing thoroughly with chloroform to remove starting materials is hence expected to give a clean sample of bismuth oxide, which could be characterized via IR, X-ray powder diffraction, and Raman spectroscopy. Running the reaction under inert atmosphere is expected to avoid oxidative decomposition, and could be used as a negative test for the hypothesized formation of bismuth oxide. It is entirely possible, however, that triphenylbismuth or any bismuth complexes formed *in situ* could undergo hydrolytic or radical decomposition in addition to oxidative decomposition, and thus may still decompose in the absence of oxygen. Given this scenario, it may be possible to observe the hydrolytic or radical decomposition products, which would serve to elucidate the mechanism of decomposition. If decomposition occurs in the absence of oxygen, then a lower temperature is required to avoid decomposition. The ligand exchange likely would need to be run for a long duration to compensate for a slow reaction time, but these reaction conditions could result in the desired bismuth(III) benzenesulfonamide complex while avoiding decomposition.

On the other hand, Andrews *et al.* note that the ligand exchange reaction requires greater heat the less acidic the ligand is, which confirms the observed need for higher temperatures when running the ligand exchange reaction with benzenesulfonamide. Andrews *et al.* further note that ligand exchange utilizing carboxylic acid-derived ligands requires temperatures of over 125 °C,<sup>77</sup> and hence it seems entirely possible that ligand exchange utilizing benzenesulfonamide will be impossible at temperatures low enough to avoid decomposition. In this case, the solid-state reaction is unviable, and refluxing the reagents in ethanol may provide a successful alternative. The literature is suggestive of this procedure's effectiveness regarding the synthesis of bismuth(III) benzenesulfonamide, as Andrews *et al.* have successfully used the ethanol reflux procedure to synthesize compounds with ligands structurally similar to benzenesulfonamide, such as saccharin.<sup>76</sup>

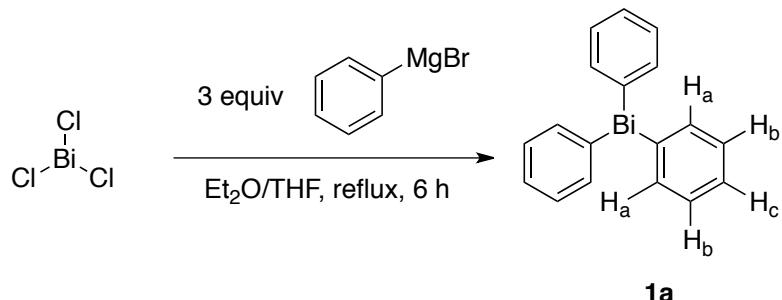


## Experimental Methods

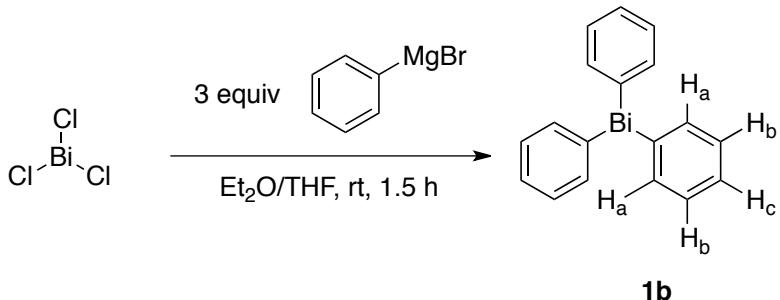
**General.** All starting materials and reagents were purchased from commercial sources and used without further purification. Thin layer chromatography was performed using plastic-backed silica gel plates and was visualized using UV light. Silica gel chromatography was performed using 0.040-0.063 mm EMD silica gel 60.  $^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded using a Bruker AV400 spectrometer with tetramethylsilane (TMS = 0 ppm) or chloroform ( $\text{CDCl}_3$  = 7.26 ppm) as an internal standard. FT-IR spectra were recorded using a Thermo Scientific Nicolet iS5 spectrometer with a flat germanium crystal ATR accessory. Melting point analyses were performed using a Barnstead Thermolyne MEL-TEMP 3.0 capillary melting point apparatus. Abbreviations for solvents include hexanes (Hex), ethyl acetate (EA), dimethyl sulfoxide (DMSO), and dichloromethane (DCM). Abbreviations for NMR include singlet (s), doublet (d), triplet (t), and multiplet (m). Abbreviations for FT-IR include weak (w), medium (m), and strong (s).



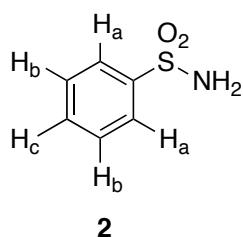
**Characterization of commercial triphenylbismuth (1).**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.74 (m, 2H,  $\text{H}_a$ ), 7.37 (m, 2H,  $\text{H}_b$ ), 7.30 (m, 1H,  $\text{H}_c$ ) ppm.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO):  $\delta$  7.73 (m, 2H,  $\text{H}_a$ ), 7.38 (m, 2H,  $\text{H}_b$ ), 7.30 (m, 1H,  $\text{H}_c$ ) ppm. FT-IR:  $\bar{\nu}$  3057 (w) 3046 (w) 3035 (w)  $\text{cm}^{-1}$ .



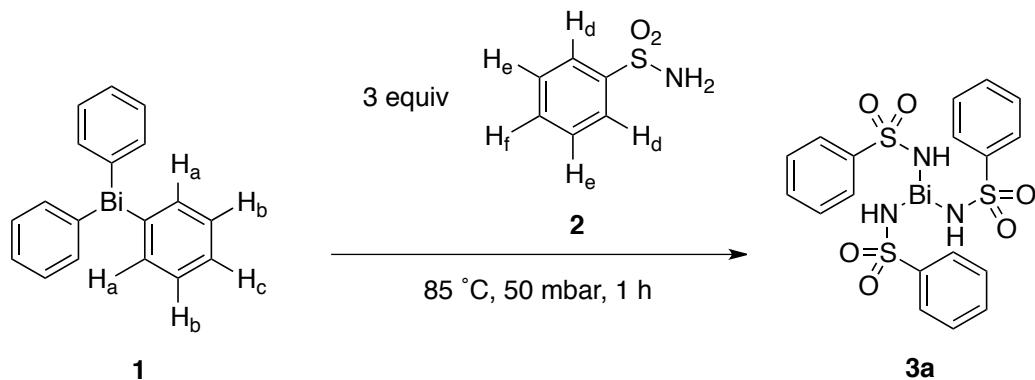
**First attempted synthesis of triphenylbismuth (**1a**).** Salicylaldehyde phenylhydrazone (77 mg, 0.36 mmol) was dissolved in dry THF (5 mL) under N<sub>2</sub>. The solution was titrated with a solution of PhMgBr in diethyl ether, and the endpoint was reached after 0.19 mL, turning the solution red-orange. The PhMgBr concentration was determined to be 1.9 M. This differed from the concentration of 1.0 M determined in several other trials, and it was decided that the 1.0 M concentration would be trusted. Residual H<sub>2</sub>O was removed from BiCl<sub>3</sub> (0.634 g, 2.01 mmol) under reduced pressure, and under N<sub>2</sub> the BiCl<sub>3</sub> was dissolved in dry THF (10 mL). The flask was placed on an ice bath and PhMgBr solution (6.5 mL, 6.5 mmol) was added over 5 minutes. After refluxing under N<sub>2</sub> for 6 h, the flask was placed on an ice bath and the product mixture was quenched with H<sub>2</sub>O (10 mL). The gummy product residue was dissolved in aqueous saturated NH<sub>4</sub>Cl solution (50 mL), H<sub>2</sub>O (25 mL), and hexanes (25 mL). The aqueous layer was extracted with DCM (3 x 50 mL) and the organic fractions were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to yield a brown residue which crystallized overnight (1.472 g). Purification via silica gel chromatography (Hex) yielded white crystals (0.233 g). Absence of the desired product was determined by <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.63 (m, 2H, Ar-H), 7.47 (m, 2H, Ar-H), 7.38 (m, Ar-H) ppm.



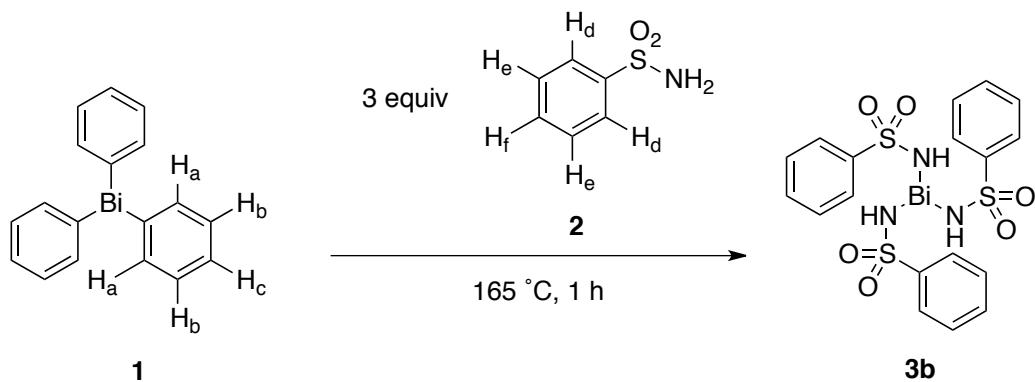
**Second attempted synthesis of triphenylbismuth (1b).** Salicylaldehyde phenylhydrazone (71 mg, 0.34 mmol) was dissolved in dry THF (5 mL) under N<sub>2</sub>. The solution was titrated with PhMgBr in diethyl ether, and the endpoint was reached after 0.33 mL, turning the solution red-orange. The PhMgBr concentration was determined to be 1.0 M. Residual water was removed from BiCl<sub>3</sub> (0.638 g, 2.02 mmol) under reduced pressure, and under N<sub>2</sub> the BiCl<sub>3</sub> was dissolved in dry THF (10 mL). The flask was placed on an ice bath and PhMgBr solution (8.0 mL, 8.1 mmol) was added over 10 min. After stirring under N<sub>2</sub> at room temperature for 90 min, the flask was placed on an ice bath and the product mixture was quenched with H<sub>2</sub>O (10 mL). The pH was brought to neutral with aqueous saturated NH<sub>4</sub>Cl solution (25 mL). DCM (20 mL) was added, and the aqueous layer was extracted with DCM (3 x 20 mL). The organic fractions were combined, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to afford a yellow residue. <sup>1</sup>H NMR in CDCl<sub>3</sub> showed undecipherable alkyl peaks.



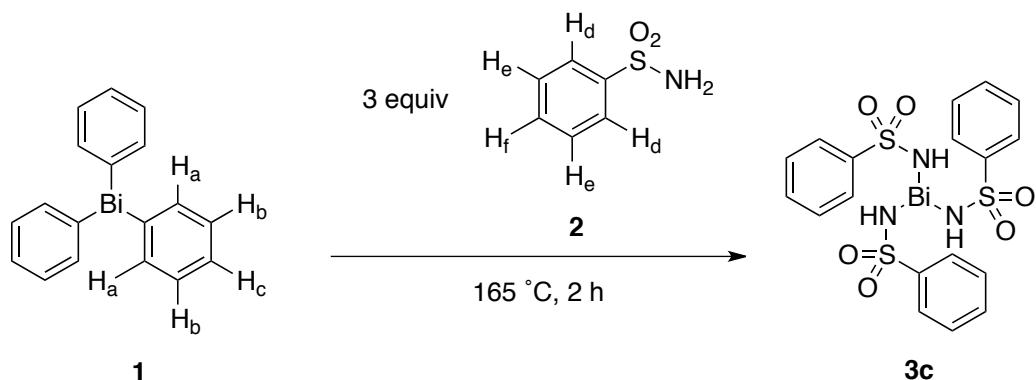
**Characterization of commercial benzenesulfonamide (2).** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.96-7.92 (m, 2H, H<sub>a</sub>), 7.60 (m, 1H, H<sub>c</sub>), 7.53 (m, 2H, H<sub>b</sub>), 4.82 (s, 2H, NH<sub>2</sub>) ppm. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-DMSO): δ 7.84 (m, 2H, H<sub>a</sub>), 7.64-7.52 (m, 3H, H<sub>b</sub> and H<sub>c</sub>), 7.36 (s, 2H, NH<sub>2</sub>) ppm. FT-IR:  $\bar{v}$  3348 (m) 3257 (m) cm<sup>-1</sup>.



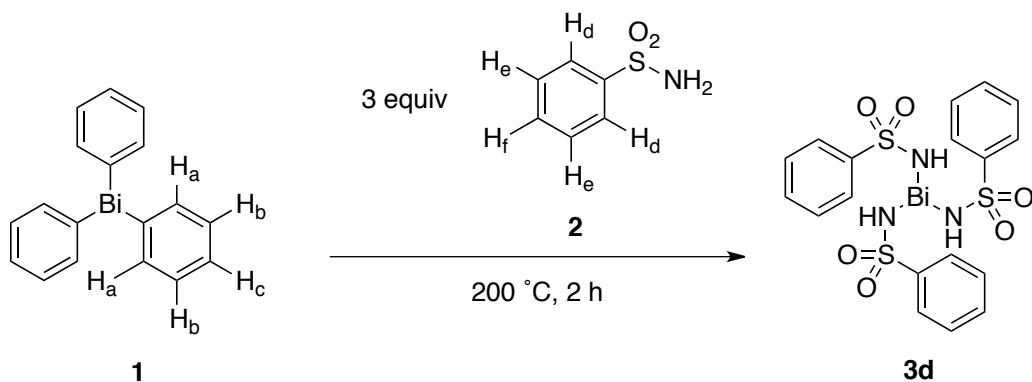
**First attempted synthesis of bismuth(III) benzenesulfonamide (3a).** Ph<sub>3</sub>Bi (0.220 g, 0.501 mmol) and PhSO<sub>2</sub>NH<sub>2</sub> (0.238 g, 1.51 mmol) were ground together using a mortar and pestle. This mixture was heated to 85 °C under vacuum for 1 h to yield a white crystalline solid. Absence of the desired product was determined by <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 7.85 (m, 2H, H<sub>d</sub>), 7.73 (m, 2H, H<sub>a</sub>), 7.63-7.53 (m, 3H, H<sub>e</sub> and H<sub>f</sub>), 7.44-7.34 (m, 4H, H<sub>b</sub> and NH<sub>2</sub>), 7.31 (m, 1H, H<sub>c</sub>) ppm.



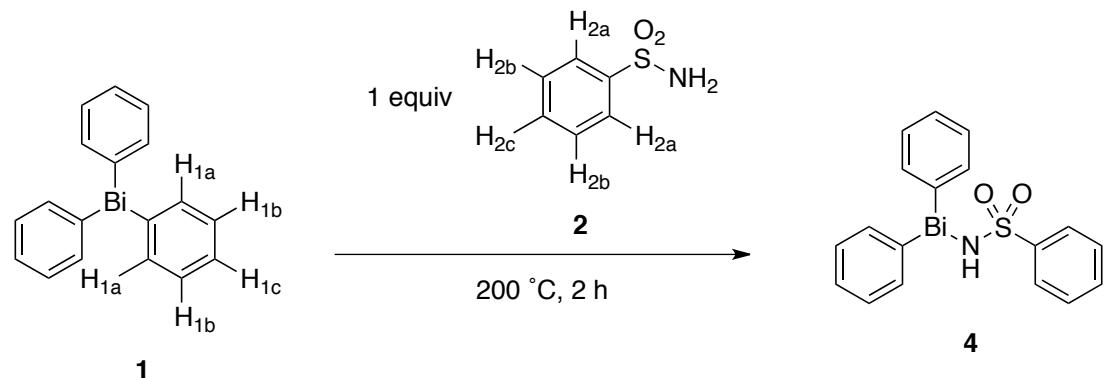
**Second attempted synthesis of bismuth(III) benzenesulfonamide (3b).** Ph<sub>3</sub>Bi (0.051 g, 0.116 mmol) and PhSO<sub>2</sub>NH<sub>2</sub> (0.058 g, 0.370 mmol) were ground together using a mortar and pestle. This mixture was heated to 165 °C for 1 h to yield a beige solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.00 (m) 7.96-7.92 (m), 7.60 (m, 1H, H<sub>c</sub>), 7.77-7.76 (m), 7.76-7.73 (m), 7.64-7.63 (m), 7.63-7.57 (m), 7.56-7.50 (m), 7.42-7.36 (m), 7.36-7.35 (m), 7.34-7.29 (m) ppm. <sup>1</sup>H NMR (400 MHz, *d*<sub>6</sub>-DMSO): δ 8.10 (m), 7.90-7.76 (m), 7.75-7.69 (m), 7.65-7.46 (m), 7.43-7.25 (m) ppm.



**Third attempted synthesis of bismuth(III) benzenesulfonamide (3c).**  $\text{Ph}_3\text{Bi}$  (0.039 g, 0.089 mmol) and  $\text{PhSO}_2\text{NH}_2$  (0.043 g, 0.274 mmol) were ground together using a mortar and pestle. This mixture was heated to 165 °C for 2 h to yield a beige solid.  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO):  $\delta$  8.10 (m), 8.77-7.79 (m), 7.75-7.70 (m), 7.63-7.52 (m), 7.42-7.27 (m) ppm.



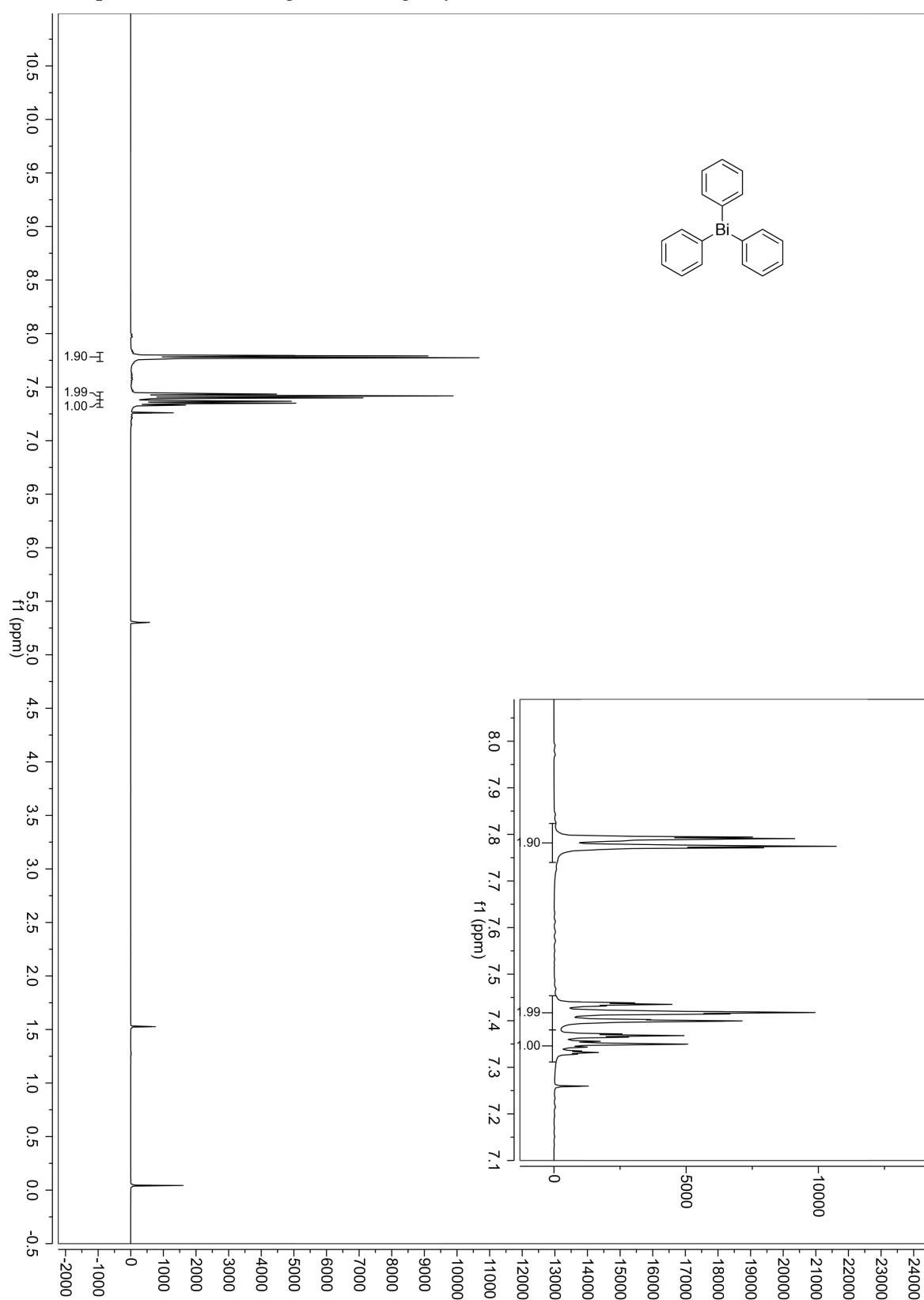
**Final attempted synthesis of bismuth(III) benzenesulfonamide (3d).**  $\text{Ph}_3\text{Bi}$  (0.041 g, 0.092 mmol) and  $\text{PhSO}_2\text{NH}_2$  (0.048 g, 0.302 mmol) were ground together using a mortar and pestle. This mixture was heated to 200 °C for 2 h to yield a beige solid (0.067 g).  $^1\text{H}$  NMR (400 MHz,  $d_6$ -DMSO):  $\delta$  7.83 (m, 2H,  $\text{H}_d$ ), 7.63-7.53 (m, 3H,  $\text{H}_e$  and  $\text{H}_f$ ), 7.33 (s, 2H,  $\text{NH}_2$ ) ppm. FT-IR:  $\bar{\nu}$  3348 (m), 3255 (m), 2988 (m), 2901 (m)  $\text{cm}^{-1}$ .



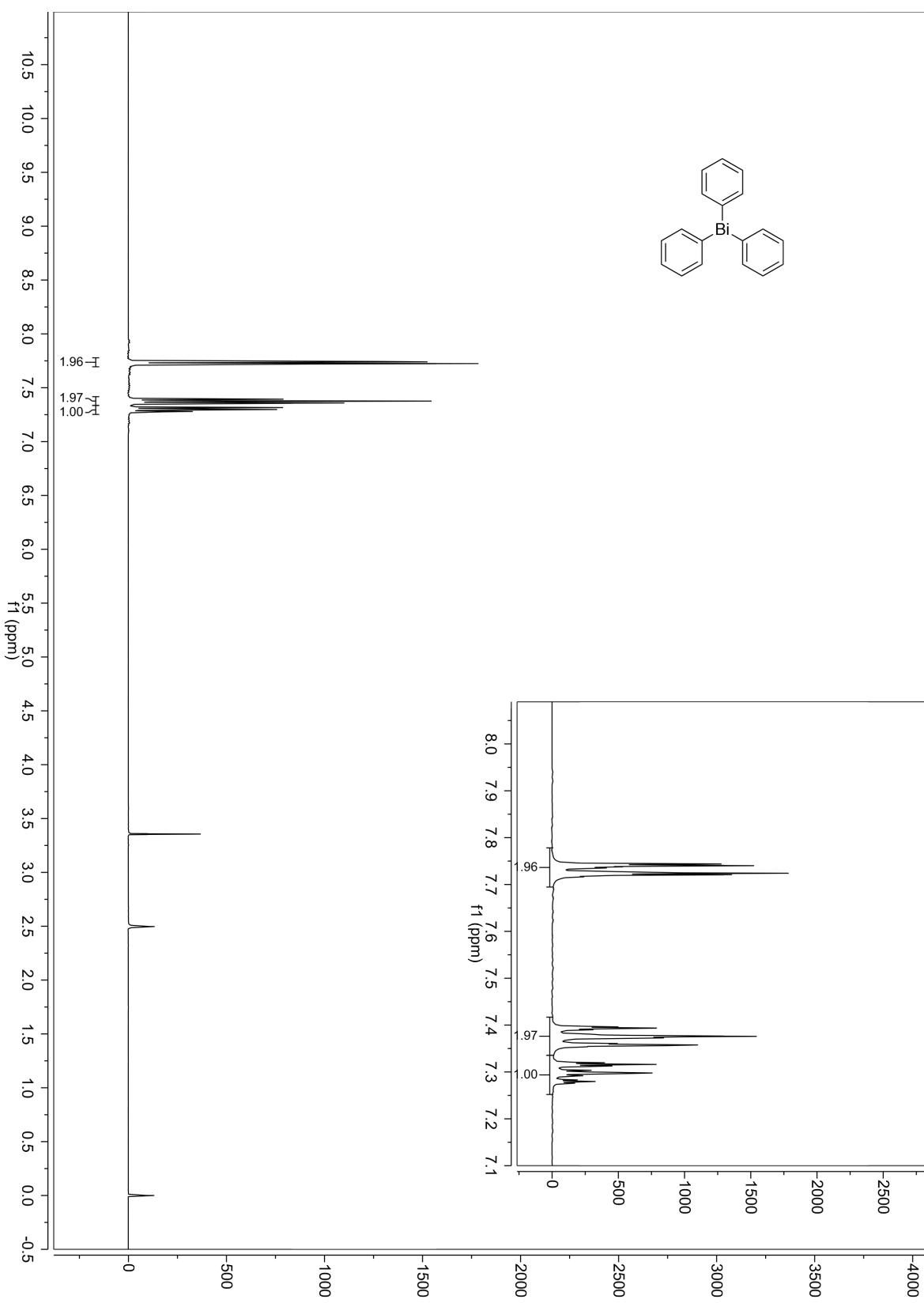
**Attempted synthesis of diphenylbismuth monobenzenesulfonamide (**4**).** Ph<sub>3</sub>Bi (0.055 g, 0.125 mmol) and PhSO<sub>2</sub>NH<sub>2</sub> (0.020 g, 0.125 mmol) were ground together using a mortar and pestle. This mixture was heated to 200 °C for 2 h to yield a beige solid with a separate, dark brown outer layer (0.049 g). Partial degradation was confirmed by <sup>1</sup>H NMR in *d*<sub>6</sub>-DMSO.

## Appendix: Selected Spectra

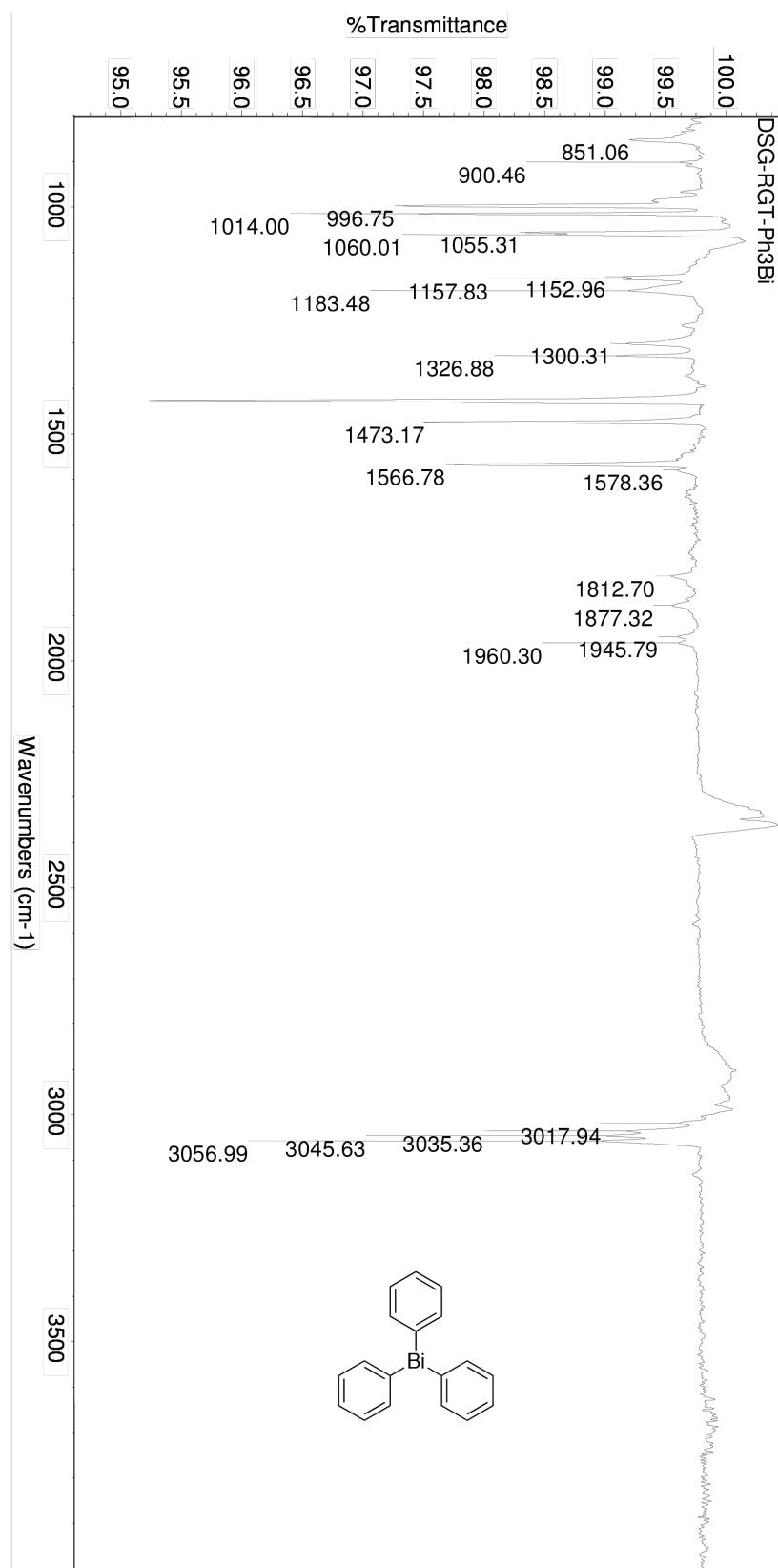
**Spectrum 1.**  $^1\text{H}$  NMR spectrum of triphenylbismuth (**1**) in  $\text{CDCl}_3$ .



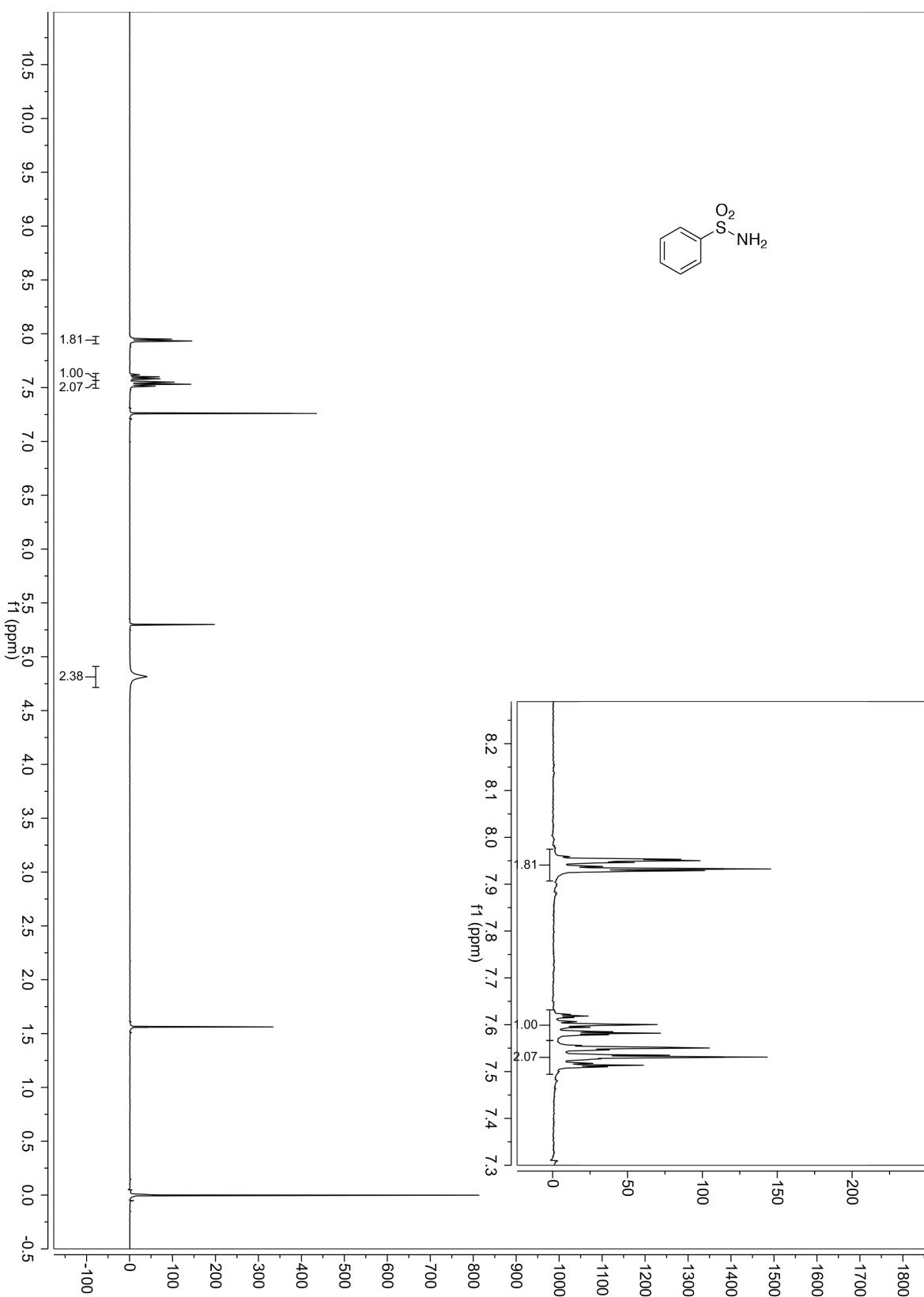
**Spectrum 2.**  $^1\text{H}$  NMR spectrum of triphenylbismuth (**1**) in  $d_6$ -DMSO.



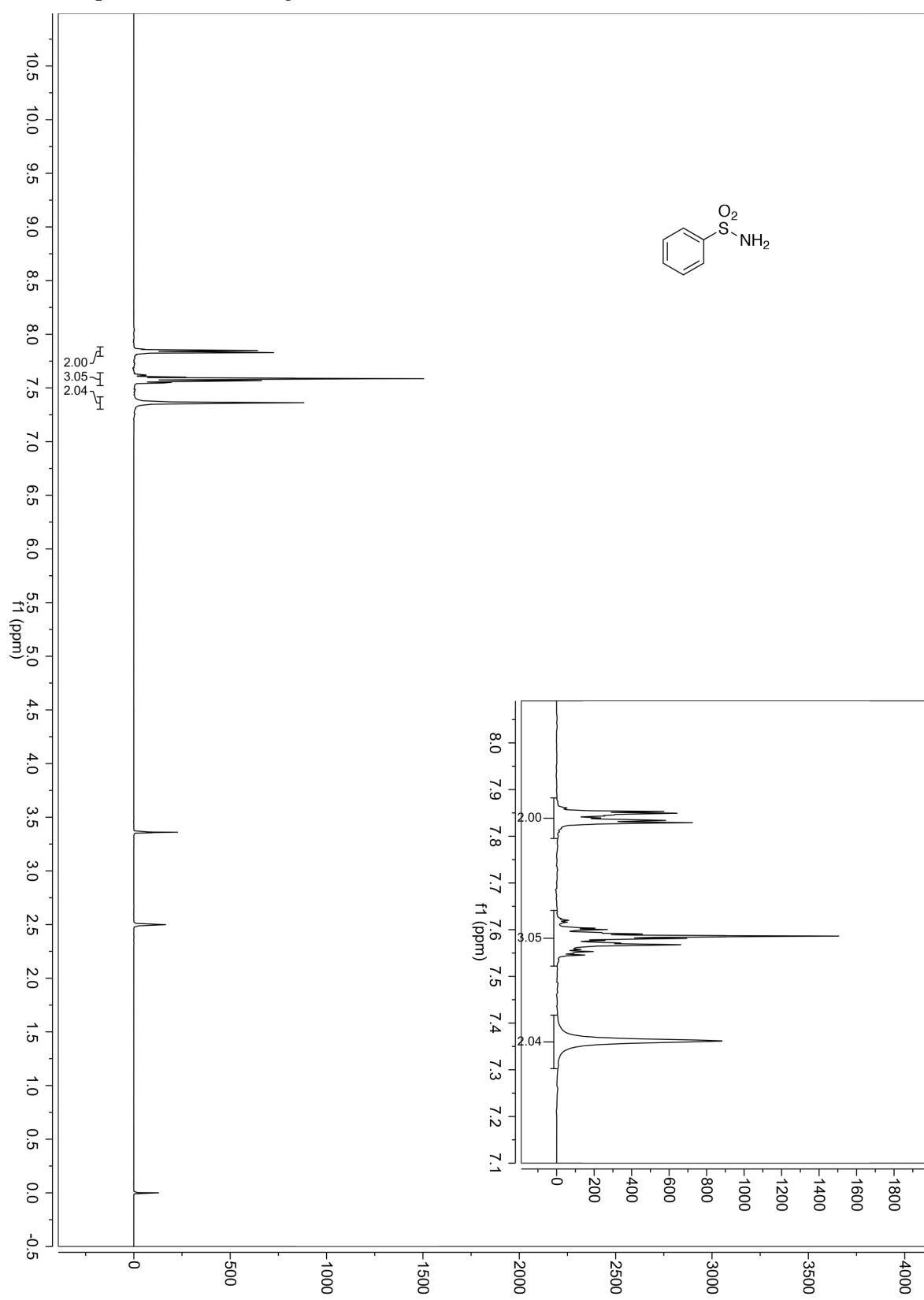
**Spectrum 3.** FT-IR spectrum of solid triphenylbismuth (**1**).



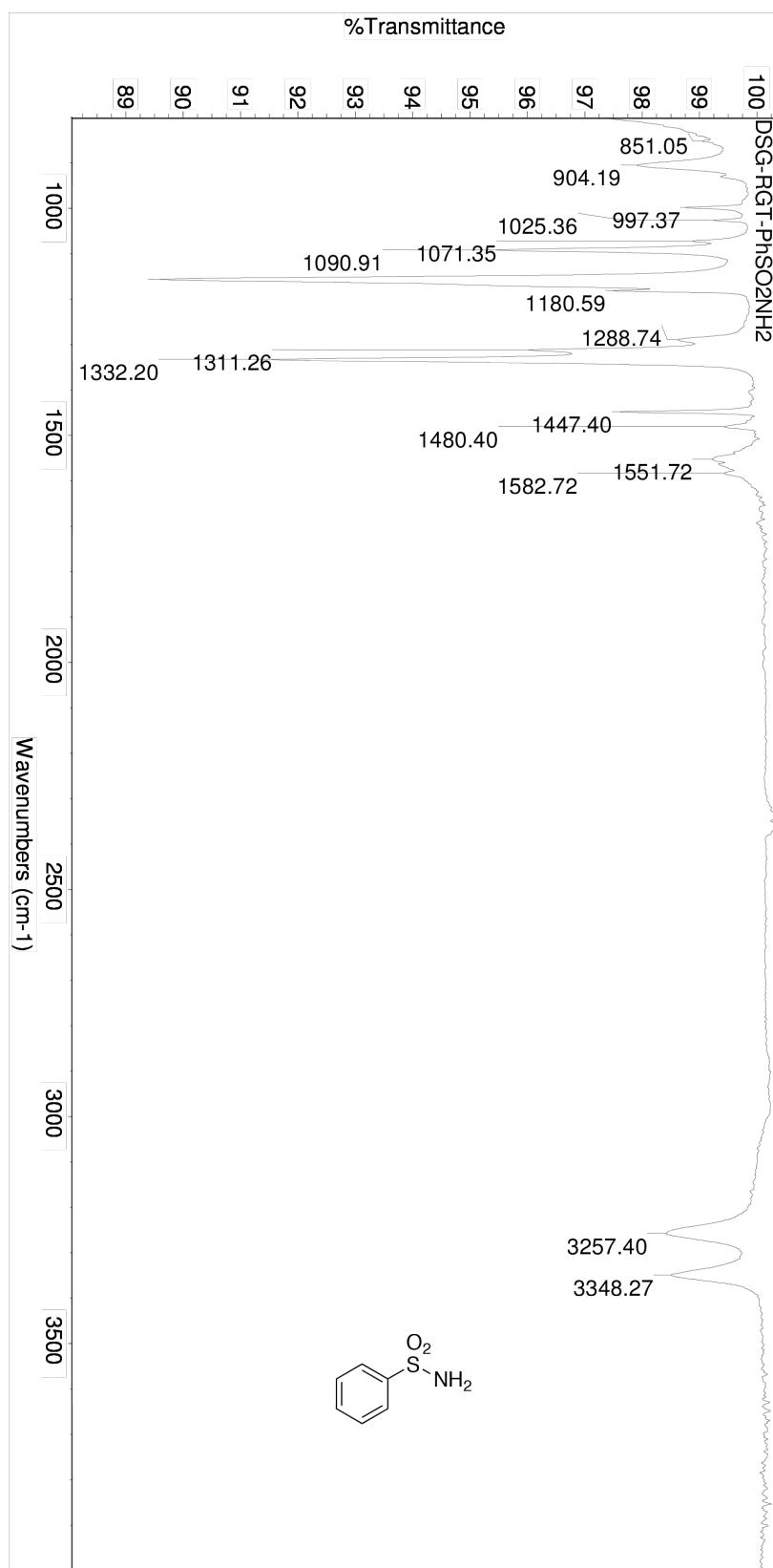
**Spectrum 4.**  $^1\text{H}$  NMR spectrum of benzenesulfonamide (**2**) in  $\text{CDCl}_3$ .



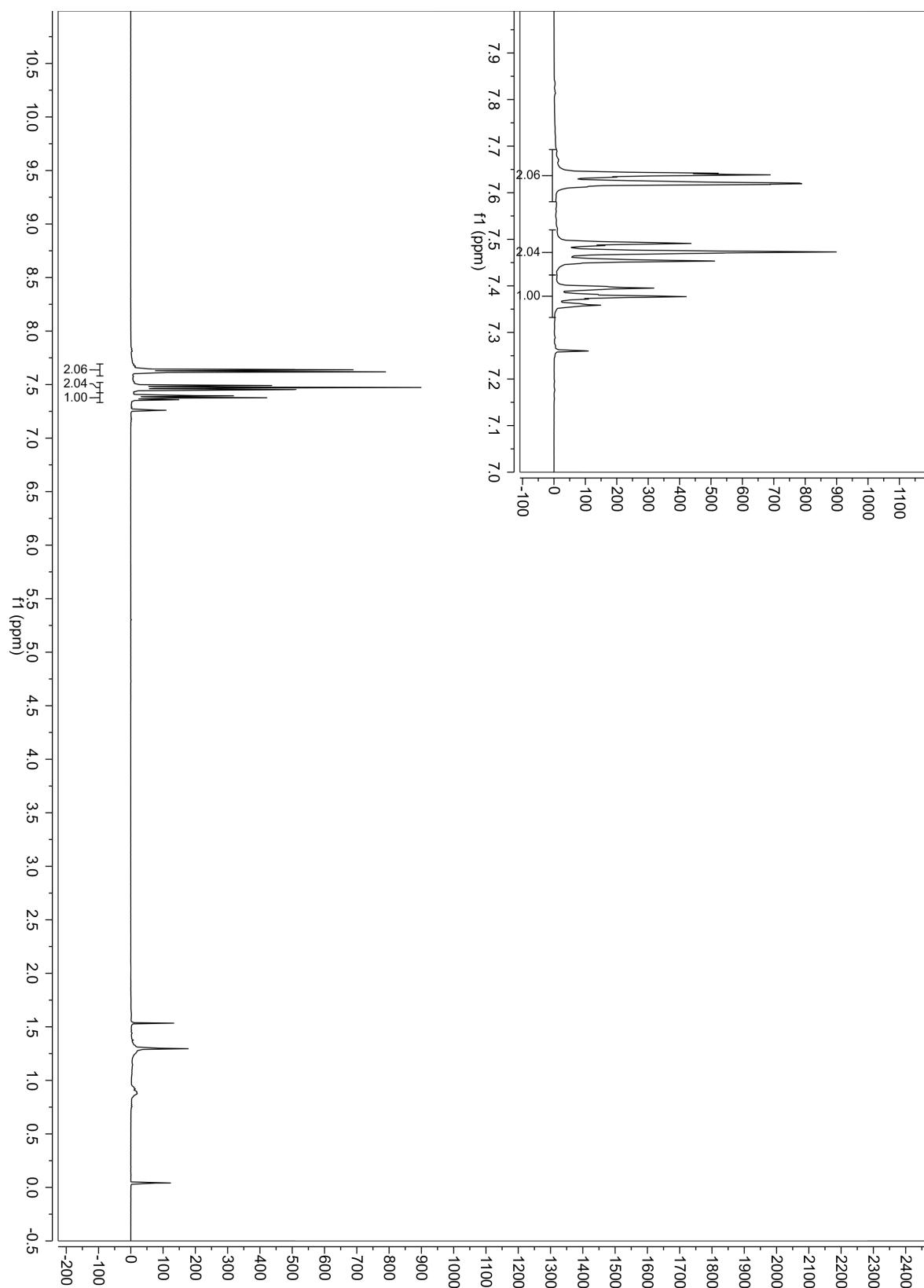
**Spectrum 5.**  $^1\text{H}$  NMR spectrum of benzenesulfonamide (**2**) in  $d_6$ -DMSO.



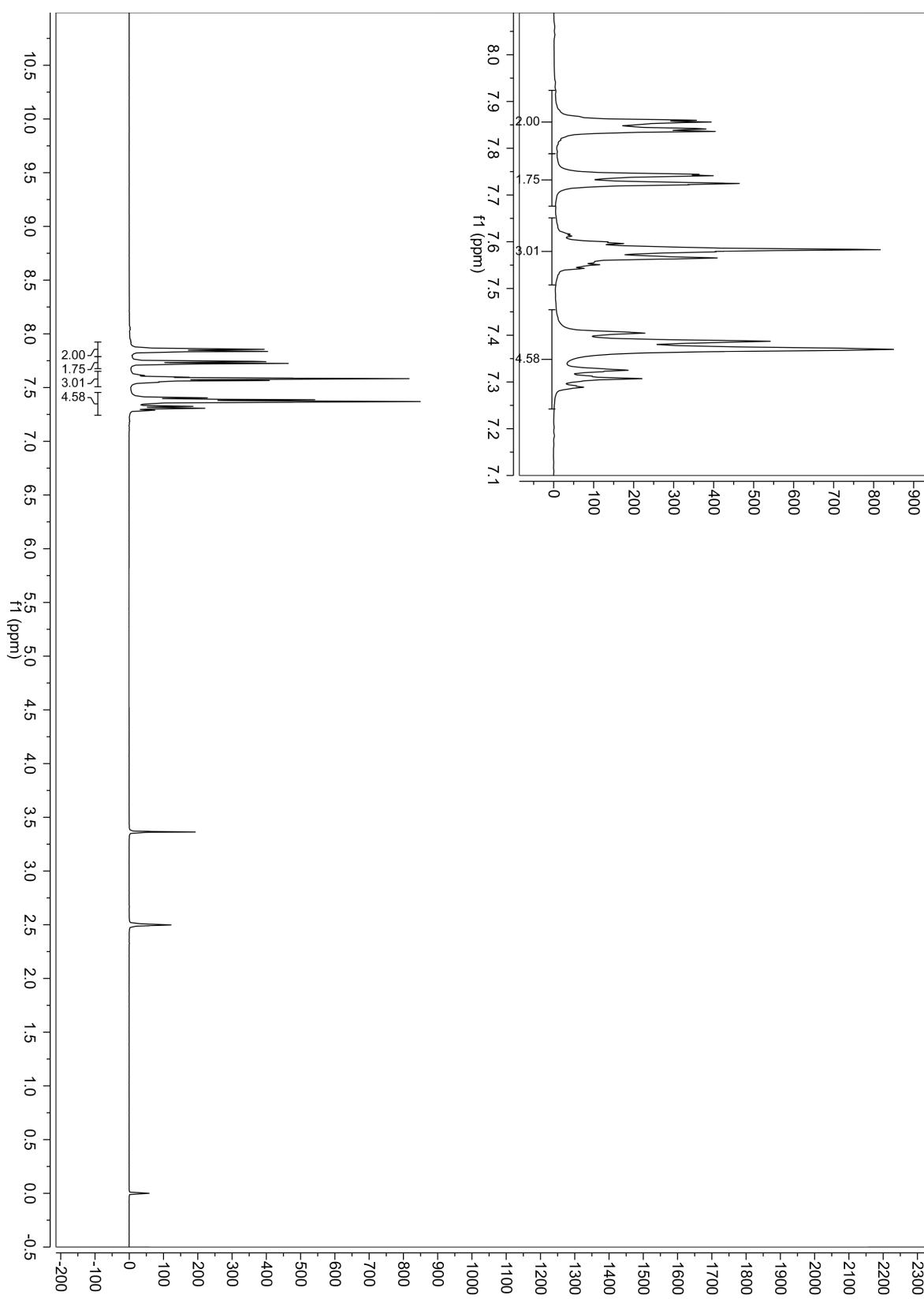
**Spectrum 6.** FT-IR spectrum of solid benzenesulfonamide (**2**).



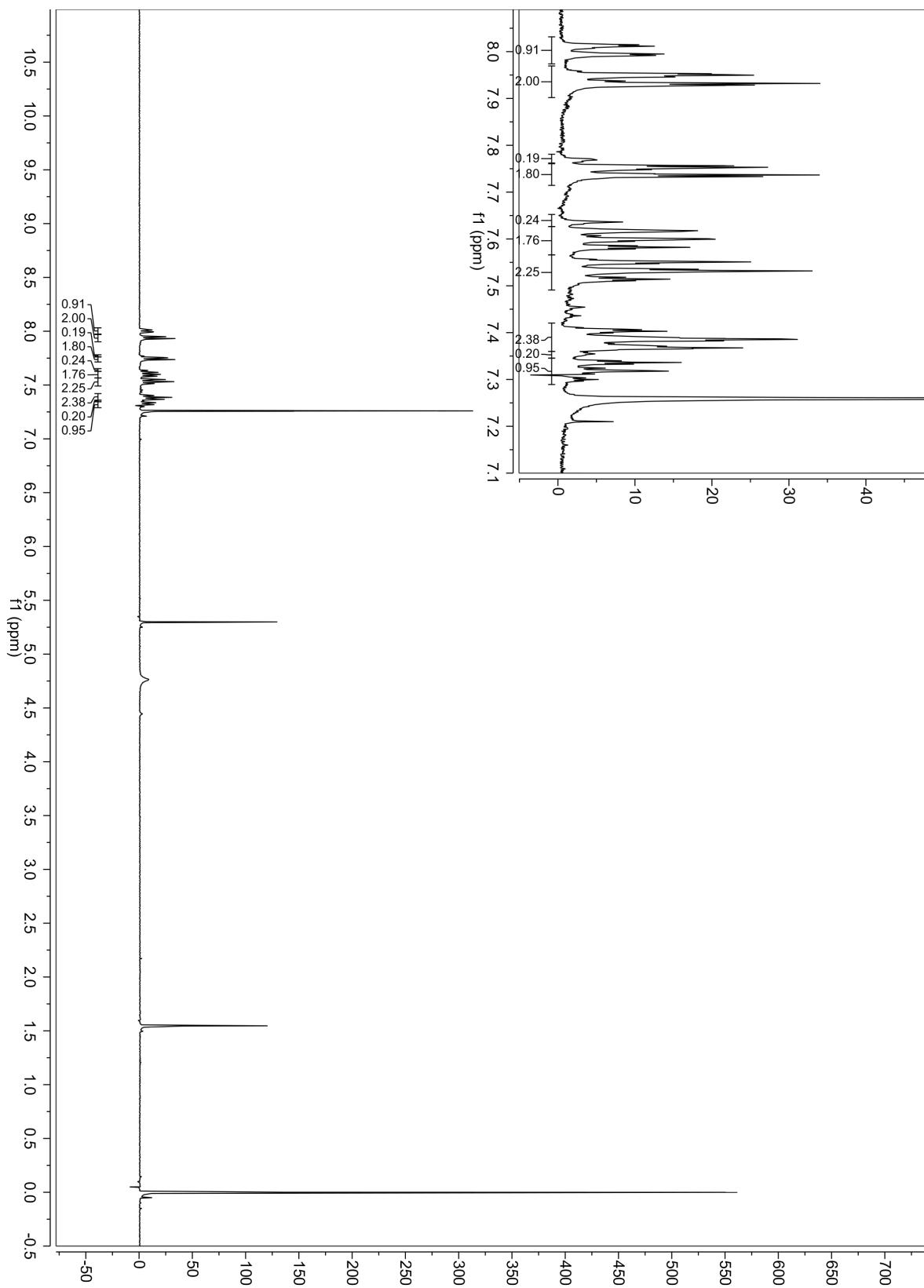
**Spectrum 7.**  $^1\text{H}$  NMR spectrum, in  $\text{CDCl}_3$ , of the isolated product of the Grignard metathesis (**1a**) using the Alfa Aesar Grignard reagent.



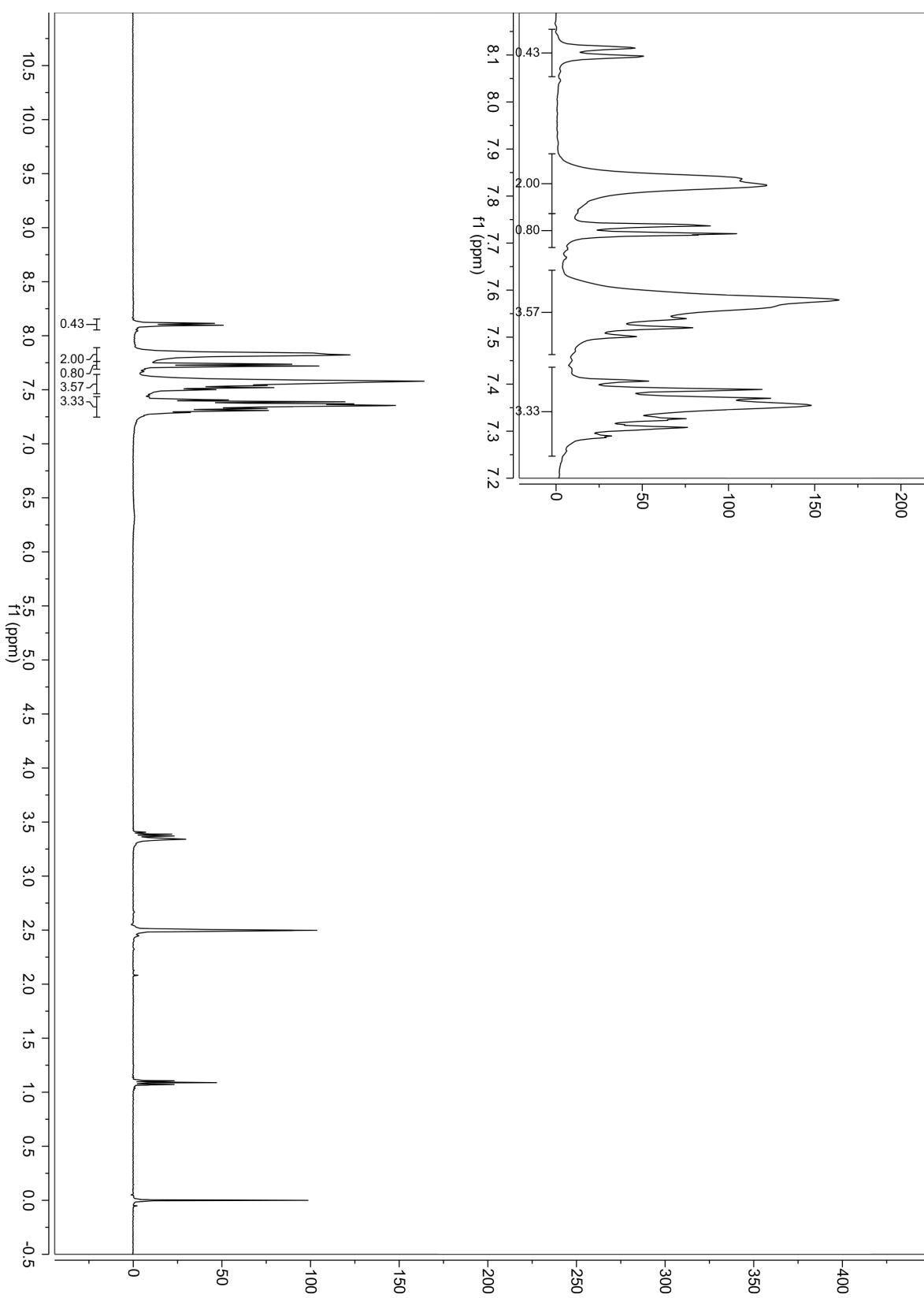
**Spectrum 8.**  $^1\text{H}$  NMR spectrum of the product (**3a**), in  $d_6$ -DMSO, of the ligand exchange reaction run at 85 °C and 50 mbar for 1 h.



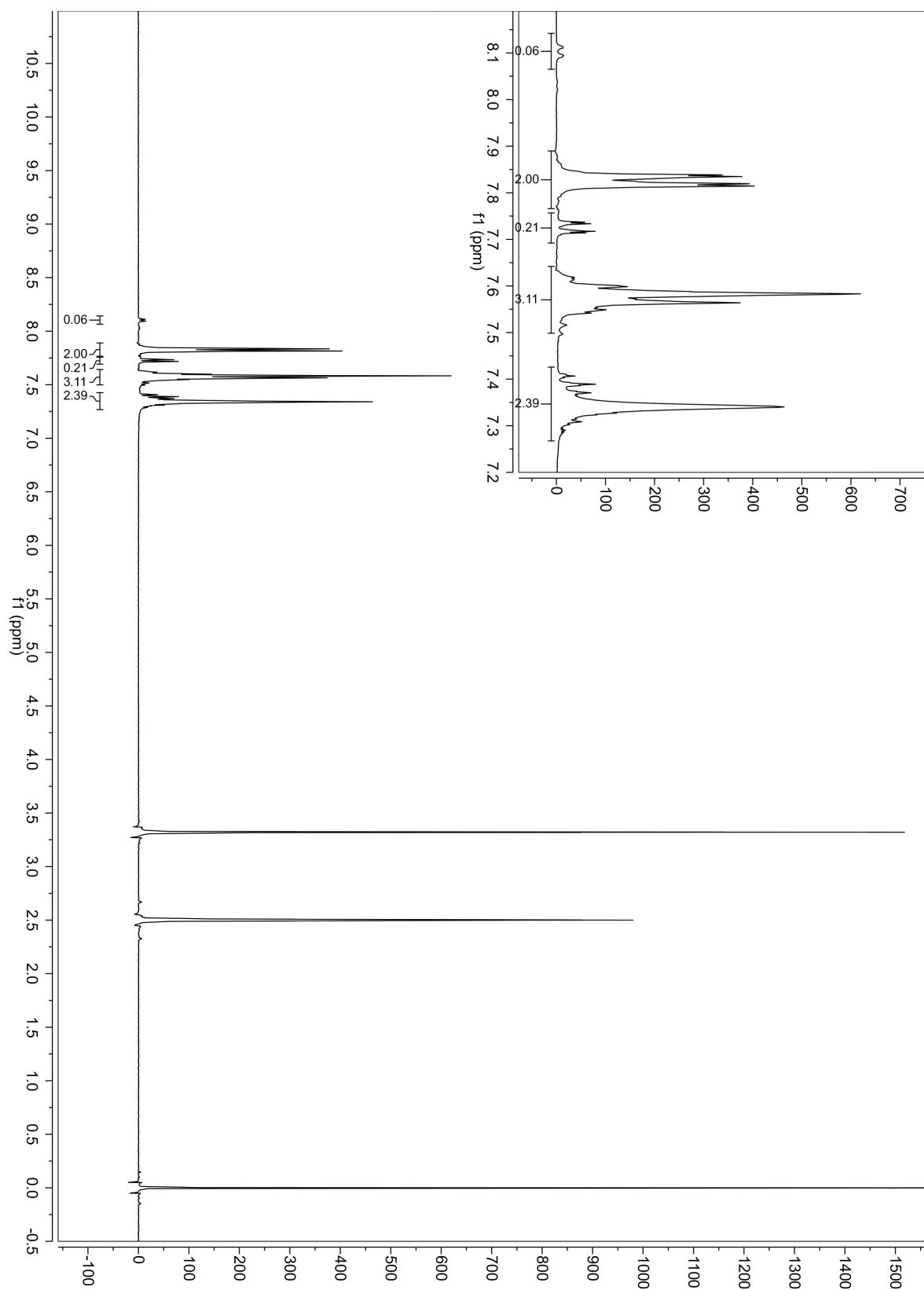
**Spectrum 9.**  $^1\text{H}$  NMR spectrum of the product (**3b**), in  $\text{CDCl}_3$ , of the ligand exchange reaction run at 165 °C for 1 h.



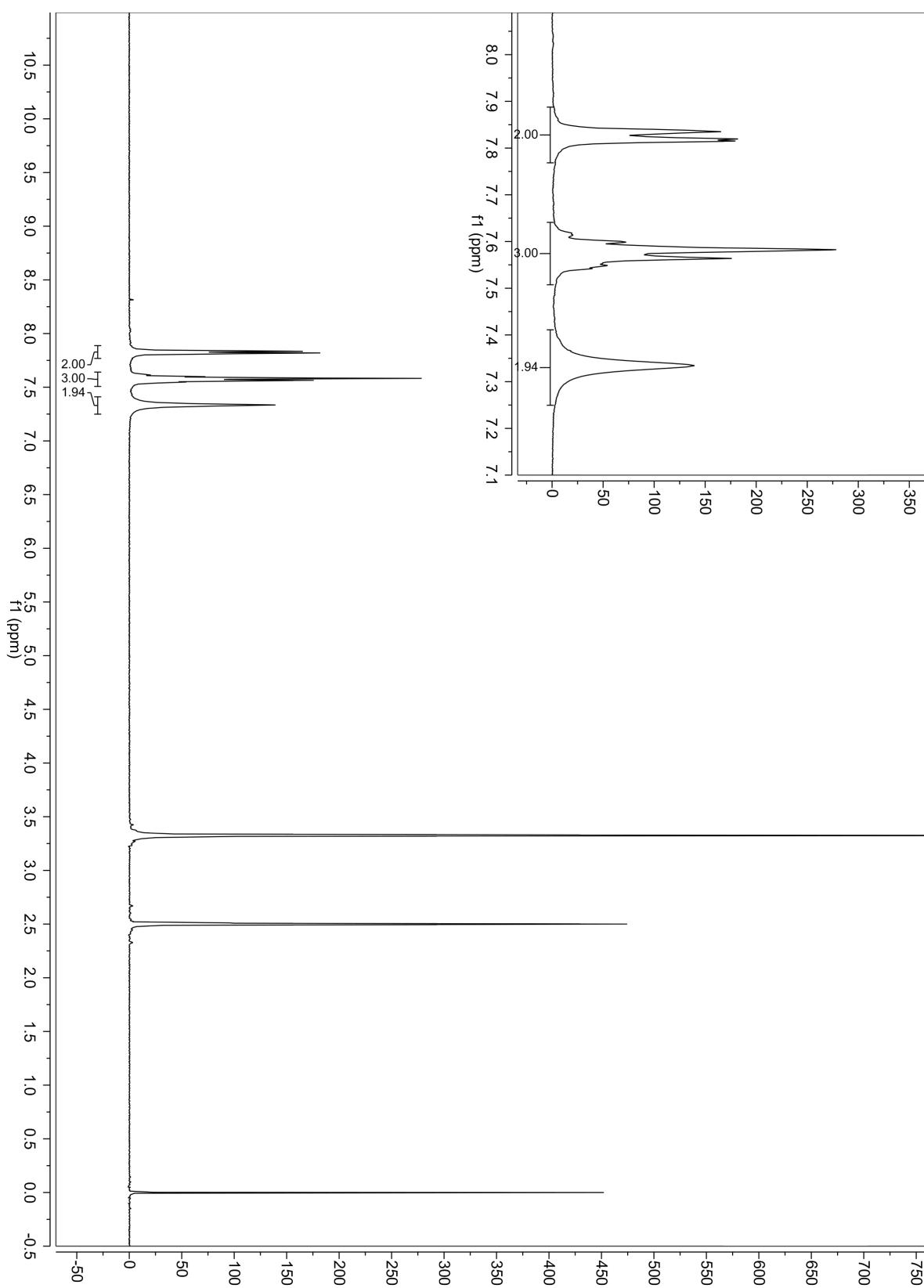
**Spectrum 10.**  $^1\text{H}$  NMR spectrum of the product (**3b**), in  $d_6$ -DMSO, of the ligand exchange reaction run at 165 °C for 1 h.



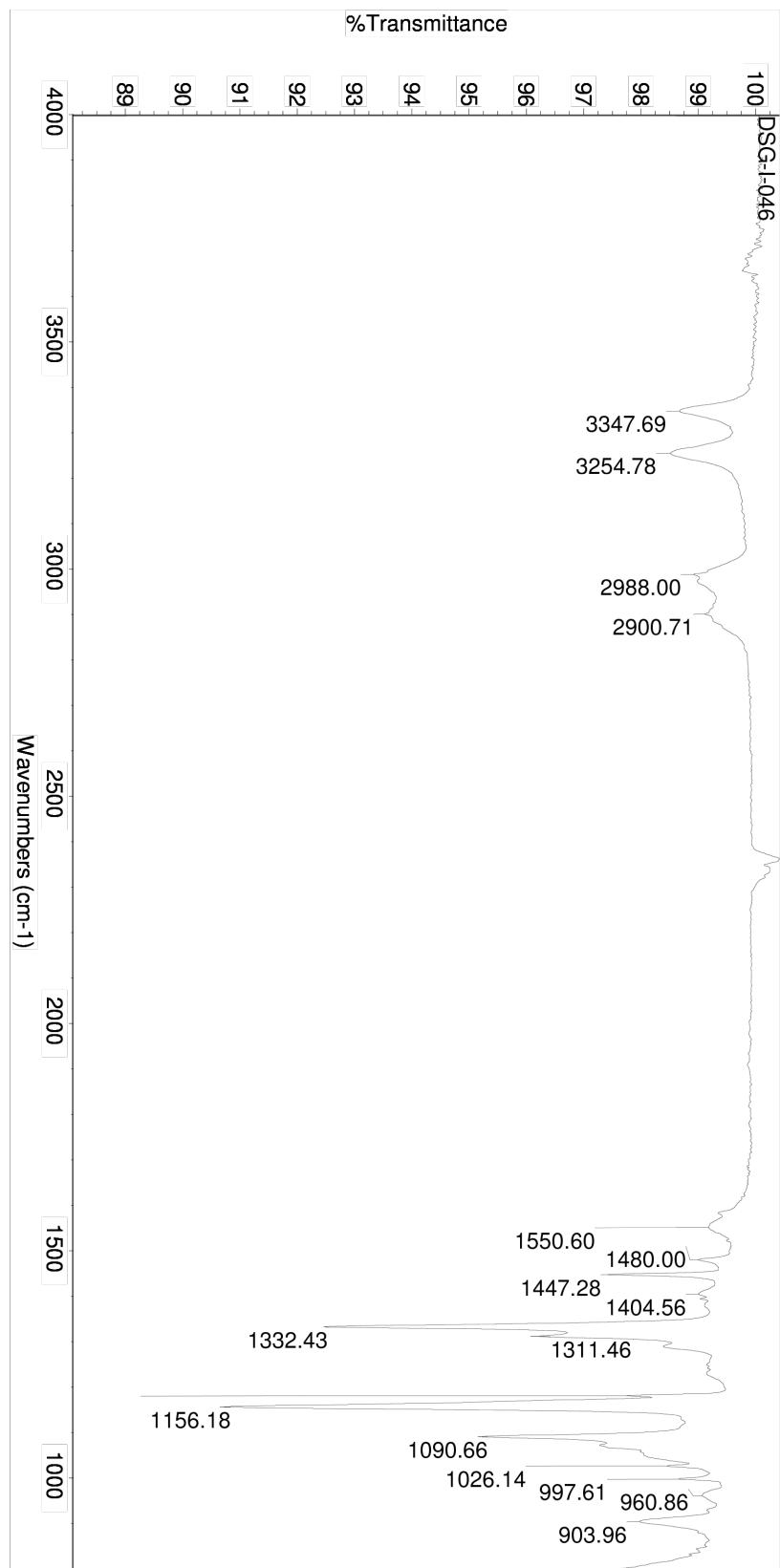
**Spectrum 11.**  $^1\text{H}$  NMR spectrum of the product (**3c**), in  $d_6$ -DMSO, of the ligand exchange reaction run at 165 °C for 2 h.



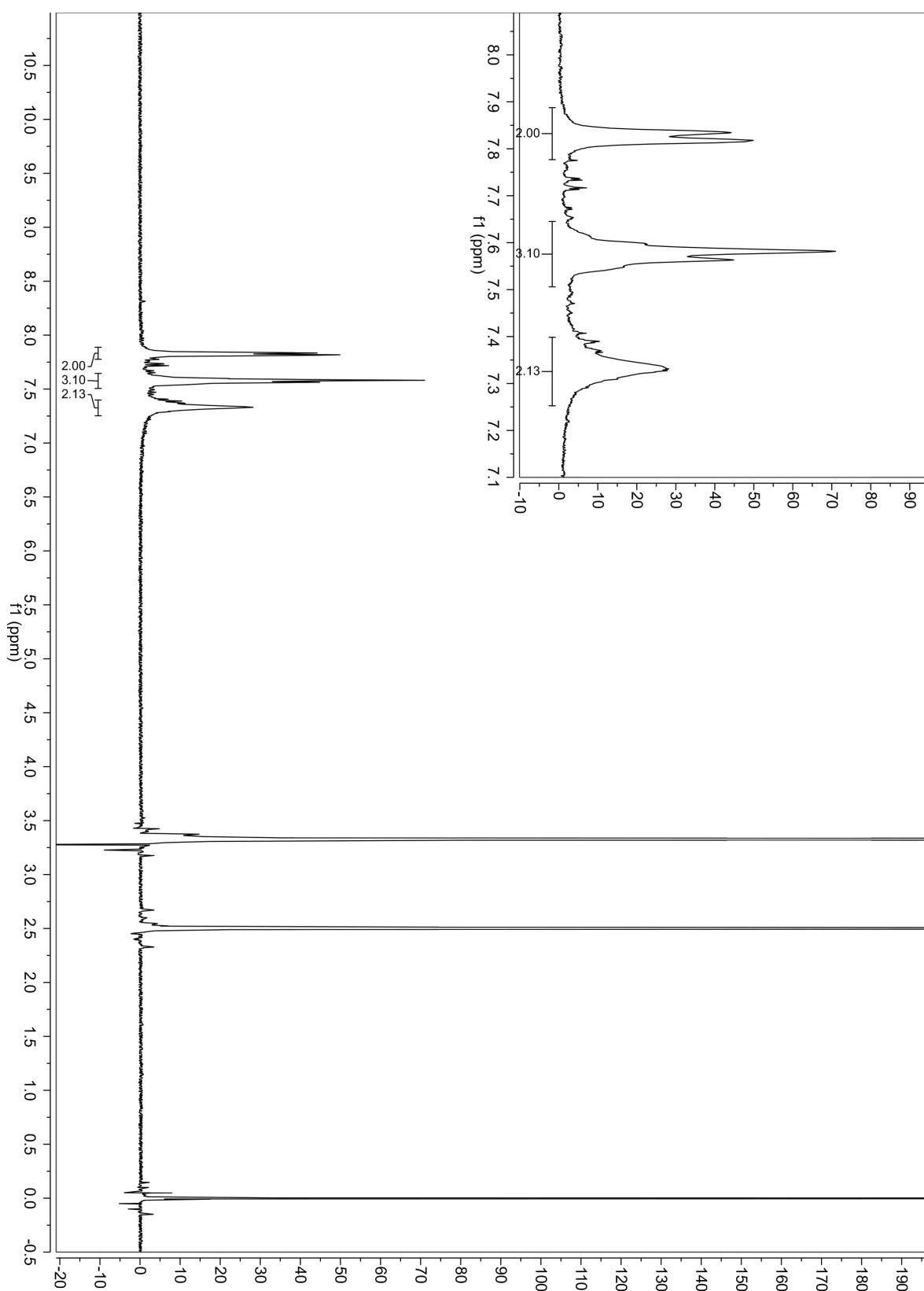
**Spectrum 12.**  $^1\text{H}$  NMR spectrum of the product (**3d**), in  $d_6$ -DMSO, of the ligand exchange reaction run at 200 °C for 2 h.



**Spectrum 13.** FT-IR spectrum of the solid product (**3d**) of the ligand exchange reaction run at 200 °C for 2 h.



**Spectrum 14.**  $^1\text{H}$  NMR spectrum of the product (**4**), in  $d_6$ -DMSO, of the partial ligand exchange reaction run at 200 °C for 2 h.





# Works Cited

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- <sup>2</sup> *Sax's Dangerous Properties of Industrial Materials*. 12 ed.; John Wiley & Sons, Inc.: Hoboken, New Jersey 2012; Vol. 2.
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