2020

# Oxidation of Aldehydes to Nitriles With An Oxoammonium Salt: Preparation of Piperonylonitrile

Nathaniel D. Kaetzel

Kyle M. Lambert
*Old Dominion University*, kmlamber@odu.edu

Christopher B. Kelly



## Original Publication Citation

Kaetzel, N. D., Lambert, K. M., & Kelly, C. B. (2020). Oxidation of aldehydes to nitriles with an oxoammonium salt: Preparation of piperonylonitrile. *Organic Syntheses, 97*, 294-314. https://doi.org/10.15227/orgsyn.097.0294

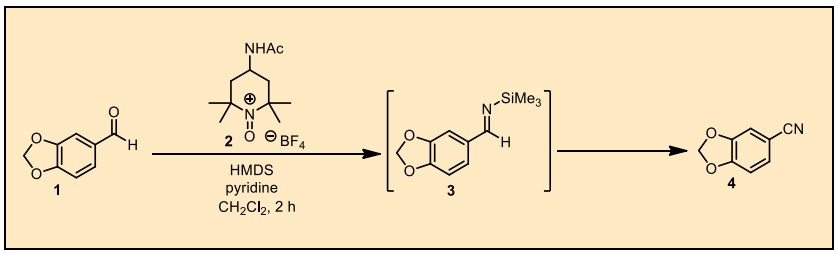
Organic Syntheses

# Oxidation of Aldehydes to Nitriles with an Oxoammonium Salt: Preparation of Piperonylonitrile

Nathaniel D. Kaetzel,† Kyle M. Lambert,[1*‡] and Christopher B. Kelly[2,3*†]

† Department of Chemistry, Virginia Commonwealth University, 1001 West Main Street, P.O. Box 842006, Richmond, Virginia 23284
‡ Department of Chemistry and Biochemistry, Old Dominion University, 4541 Hampton Boulevard, Norfolk, Virginia 23529, United States

*Checked by Charis A. Roberts and Richmond Sarpong*




## **Procedure** (Note 1)

*Piperonylonitrile (**4**).* A 500-mL single-necked, round-bottomed flask (24/40) equipped with a Teflon-coated, oval, magnetic stir bar (2 cm x 2 cm x 4 cm) and is left open to the air. The flask is charged with piperonal (**1**) (10.51 g, 70 mmol, 1 equiv) and dichloromethane (140 mL) (Notes 2 and 3). The flask is placed in a room temperature (26 °C) water bath, magnetic stirring is commenced (Note 4), and the contents of the flask are allowed to stir for 2 min to allow for complete dissolution. Pyridine (6.2 mL, 6.1 g, 77 mmol, 1.1 equiv) (Note 2) is added, followed by the addition HMDS (36.7 mL, 28.2 g, 175 mmol, 2.5 equiv) (Note 2) (Note 5).


DOI: 10.15227/orgsyn.097.0294

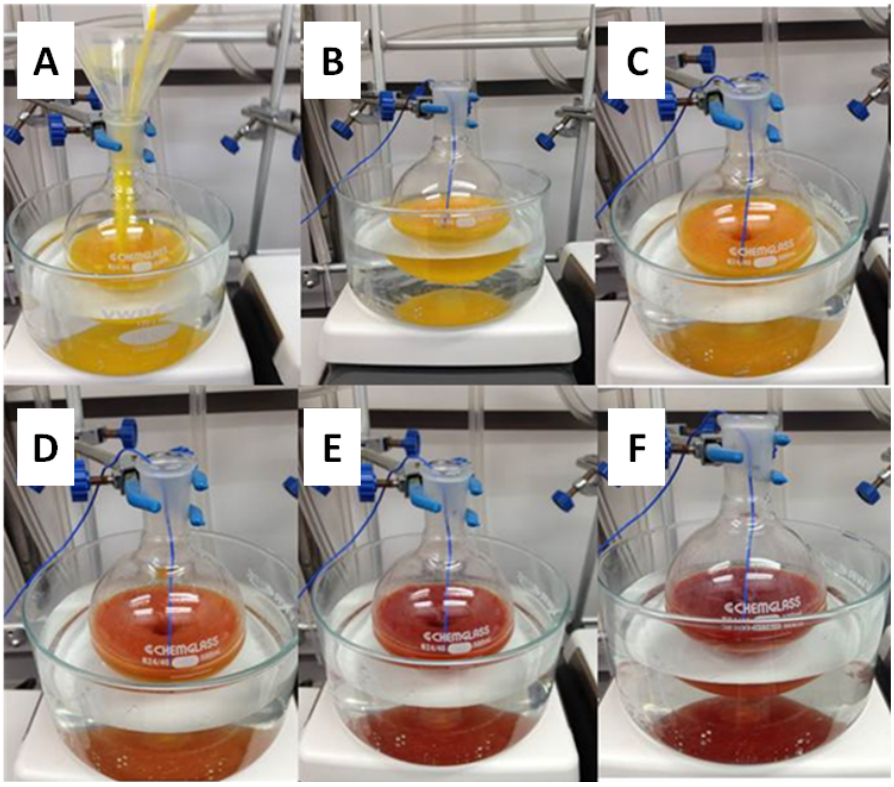



**Figure 1. Progression and observed color change of reaction; (a) Upon initial addition of 2, (b) Upon removal of funnel and addition of temperature probe, (c) 15 Minutes after addition of 2, (d) 30 Minutes after addition of 2, (e) 60 Minutes after addition of 2, (f) Upon completion of reaction 120 minutes after addition of 2 (photos provided by submitters)**

The solution is left to stir at room temperature (26 °C) for five min, at which point the oxoammonium salt (**2**) (52.5 g, 175 mmol, 2.5 equiv) (Note 6) is added to the flask via a plastic powder funnel (OD: 7.5 cm, ID: 1.6 cm) gradually over a two-minute period (Figure 1A). The powder funnel is removed, and a digital temperature probe is inserted to monitor the reaction temperature (Figure 1 B). The reaction is stirred at 26 °C (Note 7) and a color change is noted, starting yellow and progressing through orange until finally reaching a deep red color (Figure 1A–F) (Note 8). After 120 min (Figure 1F), the reaction progress is assessed by crude $^{1}$H NMR and GC/MS (Note 9). At

this time, the solvent is removed *in vacuo* by rotary evaporation (Note 10) (Figure 2A) to give a thick red residue.

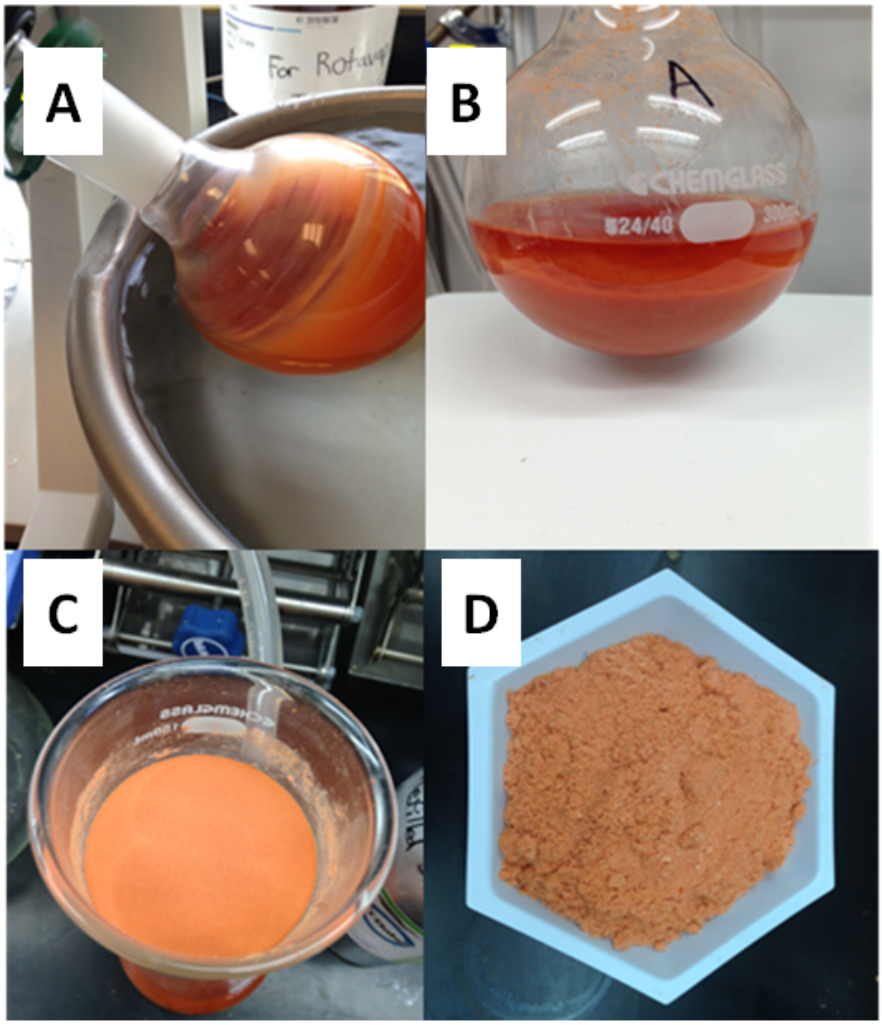



**Figure 2. Work-up of the reaction; (a) Removal of the solvent upon completion of the reaction, (b) Trituration of the thick red residue with diethyl ether to precipitate spent oxidant, (c) Filtration of the spent oxidant, (d) Sample of the recovered spent oxidant after vacuum filtration (photos provided by submitters)**

The residue is triturated by the addition of diethyl ether (200 mL) resulting in a suspension of the spent oxidant. The sides of the flask are scraped with a spatula to release all solid material (Note 11). The flask, which still contains the stir bar, is magnetically stirred (Note 4) to allow for pulverization of the solid, thus maximizing leeching of **4** into the mother liquor. Magnetic stirring is then ceased. A 150-mL, coarse porosity, sintered glass Büchner funnel (7.3 cm diameter) is fitted to a 1-L filter flask, which is prepared for vacuum filtration. The suspension is poured through the filtration set-up to remove the orange precipitate using diethyl ether (50 mL) to ensure complete transfer from the flask. The collected precipitate is then washed with diethyl ether (100 mL) to yield the recovered spent oxidant (Figure 2D) (Note 12). The orange filtrate is then transferred to a 1-L separatory funnel and washed sequentially with 2 M HCl (3 × 150 mL), saturated $NaHCO_3$ (2 × 150 mL), and brine (200 mL) (Figure 3). The organic layer is then dried over anhydrous $Na_2SO_4$ (~ 20 g), which is removed by gravity filtration, and the solvent is removed *in vacuo* by rotary evaporation (Note 10) to yield 9.91 g (96%) of crude piperonylonitrile, 4 (Figure 4A). The nitrile is further purified by recrystallization (Note 13) using a minimal

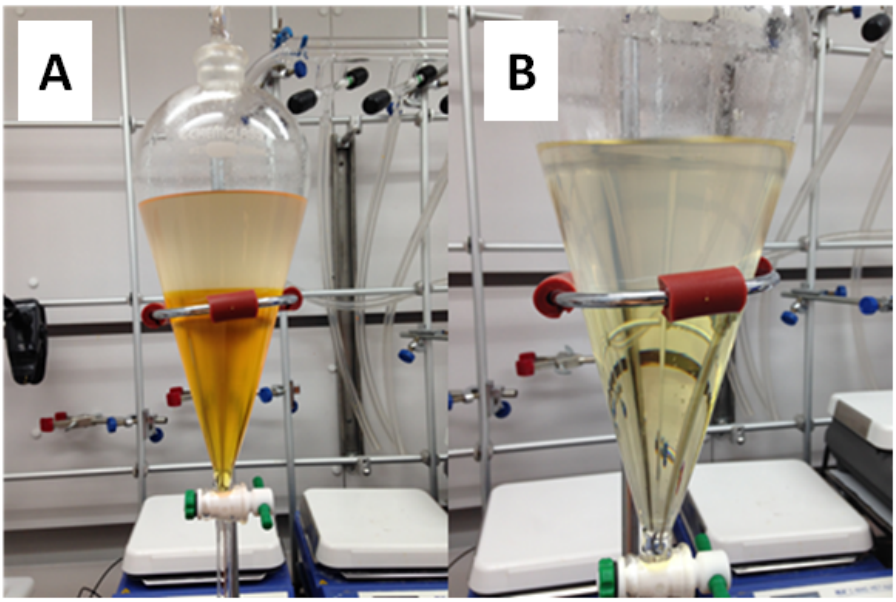



**Figure 3. Extractive work-up of filtrate; (a) Initial wash with 2 M HCl, (b) After 3rd wash with 2 M HCl (photos provided by submitters)**

amount (40 mL) of a hot (~60 °C) 7:3 (v/v) mixture of hexanes/ethyl acetate (Note 14). After full dissolution, the solution is cooled to room temperature for 15 min and then placed in a –4 °C freezer for 2 h. The solid is collected by vacuum filtration through a 60-mL, fine porosity, sintered glass Büchner funnel (5.1 cm diameter) to yield crystalline **2** (8.04 g, 78%) (Figure 4B) (Notes 15, 16, and 17).

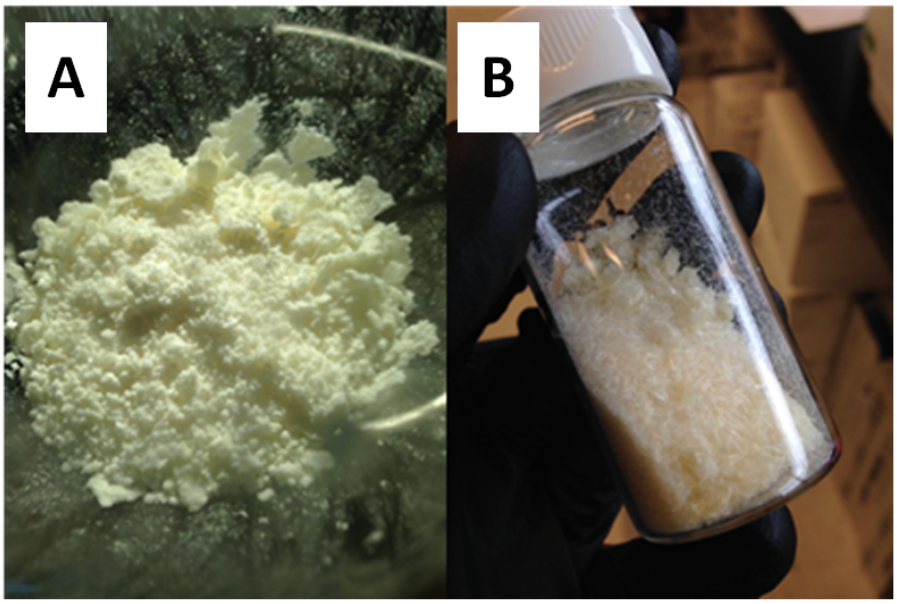



**Figure 4. (a) Sample of 4 isolated after work-up, (b) Sample of 4 isolated after recrystallization (photos provided by submitters)**

## Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at

https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with (piperonal, methylene chloride, 1,1,1,3,3,3-hexamethyldisilazane, pyridine, 4-(acetylamino)-2,2,6,6-tetramethyl-1-oxo-piperidinium tetrafluoroborate, 4-acetamido-2,2,6,6-tetramethylpiperidine 1-oxyl, sodium bicarbonate, sodium sulfate, diethyl ether, ethyl acetate, hexanes, hydrochloric acid, and piperonylonitrile), as well as the proper procedures for (operating a vacuum pump and working with systems under negative pressure, using a rotary evaporator, and working with caustic acids such as 2M aqueous hydrochloric acid).

2. The following reagents were purchased from commercial sources and used without further purification: dichloromethane (Stabilized/Certified ACS, ≥99.5%, Fisher Scientific), pyridine (Certified ACS, ≥99%), 1,1,1,3,3,3-hexamethyldisilazane (98%, Acros Organics), 4-(acetylamino)-2,2,6,6-tetramethyl-1-oxo-piperidinium tetrafluoroborate (97%, Sigma-Aldrich), and piperonal (99%, Sigma-Aldrich).
3. Anhydrous diethyl ether (BHT Stabilized/Certified ACS, ≥99%) was used as received. Hexanes (≥98.5%, Certified ACS, Fisher Scientific) and ethyl acetate (≥99.9%, HPLC grade, Fisher Scientific) were purchased and used as received.
4. The mixture is stirred at 650 rpm throughout the reaction.
5. Rigorous extrusion of air or moisture is not necessary for this reaction. The reaction can be conducted open to air using solvent directly taking from the source bottle without any need for purification.
6. This oxidant can be recrystallized from water. However, there is no observable difference in yield or impurity profile, although the reaction time is slightly longer when the reaction was conducted with recrystallized Bobbitt's salt versus a commercial sample.
7. There appears to be an onset time for the reaction. If a water bath is not used, the temperature of the reaction spikes to near boiling of the solvent

after ~40 minutes then quickly dissipates (Figure 5). On the scale used in the procedure described above, it was necessary to use a cooling bath.

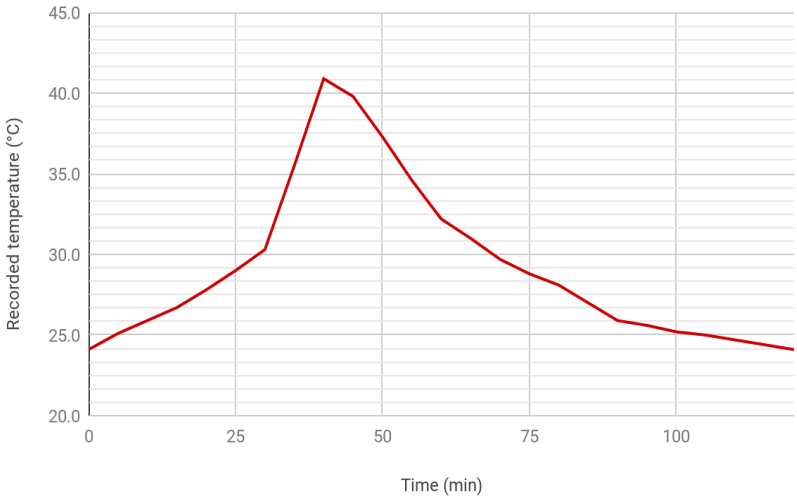



**Figure 5. Temperature profile of reaction without cooling bath on 35 mmol scale**

8. The origin of the red color is from the spent oxidant; 4-acetamido-2,2,6,6-tetramethylpiperidine 1-oxyl (4-AcetamidoTEMPO). The reaction should be dark red at the end of the reaction (Figure 1F).
9. Reaction time does vary slightly (between 2–3 h, thus, reaction monitoring is recommended. The reaction is generally complete around 2 h. The starting aldehyde and nitrile product can co-crystallize if substantial aldehyde remains. Monitoring the reaction by TLC can be challenging due to similar $R_f$ values (Note 17). Monitoring the reaction by NMR is more useful in this case. The characteristic aldehyde peak can be observed at 9.81 ppm and a characteristic aryl C-H bond for the product can be observed at 7.04 ppm in $^1$H NMR spectra of the crude reaction mixture.
10. The rotary evaporator bath temperature was set at 37 °C and was operated at 280 rpm and at an initial pressure of 350 mmHg to avoid bumping of the solution then adjusted to 100 rpm and a pressure of 20 mmHg.

11. It is imperative that sufficient scraping and stirring be performed as the product (**4**) can be trapped in the solid.
12. This crude orange solid can be suspended in boiling ethyl acetate (77 °C), filtered, and recrystallized to give about 80% recovery of the pure 4-acetamido TEMPO (the spent oxidant). This material can then be used to regenerate the oxoammonium salt **2**. See reference 9b for details.
13. Recrystallization is utilized in this procedure to avoid the use of chromatography. Purification can also be accomplished by passage of the crude material over a short pad of $SiO_2$, eluting with a 9:1 (v/v) mixture of hexanes/ether. Chromatography will often give a slightly higher yield of the desired product (c.a. 80%).
14. It is possible to use alternate recrystallization solvents. Listed here are the solubility data for the nitrile product **4** in various organic solvents at room temperature: (a) 0.039 g/mL in $Et_2O$; (b) 0.10 g/mL in toluene; (c) 0.42 g/mL in dichloromethane (d) 0.071 g/mL in methanol. The product is soluble at nearly every concentration for the following solvents: acetone, acetonitrile, THF, ethyl acetate, DMSO, DMF and NMP. The product has virtually no solubility in pentane/hexanes.
15. The product has been characterized as follows: mp 92–95 °C (hexanes/EtOAc, 7:3; uncorrected); $^1$H NMR (500 MHz, $CDCl_3$) δ: 6.07 (s, 2H), 6.86 (d, $J$ = 8.0 Hz, 1H), 7.04 (d, $J$ = 1.6 Hz, 1H), 7.21 (dd, $J$ = 8.0, 1.6 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ: 102.3, 105.1, 109.3, 111.6, 119.0, 128.4, 148.2, 151.7. FTIR (neat): 2912 (vw), 2216 (m), 1486 (m), 1442 (m), 1254 (s), 1026 (s) 917 (vs), 859 (vs), 811 (vs), 612 (vs) $cm^{-1}$.
16. The procedure described will afford the title compound (**4**) in high analytical purity. Quantitative $^1$H NMR analysis (relaxation delay of 60 seconds) showed this product was of 97% purity (average of three runs) (25.4 mg of analyte with 27.9 mg trimethoxy benzene of 99.0% purity purchased from Sigma-Aldrich as a standard. Additional runs of this procedure on half scale reported afforded isolated yields of 87% and 73%.
17. TLC conditions were as follows: 20% EtOAc in hexanes, visualized with a 254 nm UV lamp. The starting material and the products have very similar $R_f$ values, with $R_f$ = 0.33 (**1**) and 0.31 (**4**). (Figure 6)

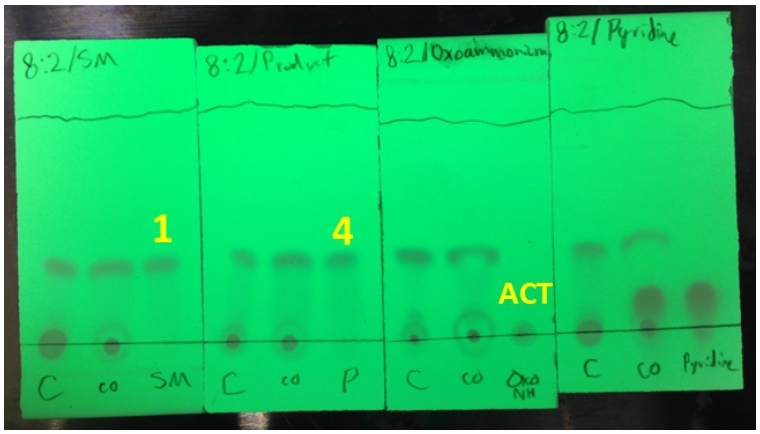



**Figure 6. TLC of reaction components visualized with UV light; C= Crude reaction mixture, Co = Co-Spot, P = Product (photo provided by submitter)**

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

## Discussion

Oxidation processes enable some of the most crucial functional group interconversions in organic synthesis.[4] Definable in numerous ways, oxidation could be as simplistic as the change in oxidation states between an alcohol and a ketone or as complex as asymmetric dihydroxylation, or even lead to the rupture of a molecule via oxidative fragmentation.

Many of the most commonly employed oxidants are transition metal-based. Indeed, textbook examples of oxidation include venerable chromium-based oxidations (e.g. Jones oxidation) as well as the more industrial relevant Wacker process.[5] Other oxidants can facilitate C–H oxidation where oxygen can be used to convert raw petroleum-based products into important oxygen-containing materials (e.g. the Hock process) which are feedstocks for polymer synthesis or building blocks for pharmaceutical agents .[6,7]

Strictly organic oxidants provide an alternative platform for oxidation that often has an inherently "greener", more sustainable profile (Figure 7). Oxidants such as Dess-Martin periodinane (DMP), *m*-CPBA, DDQ, and Selectfluor are not only found in virtually every synthetic chemistry laboratory, but are often the "go-to" reagents to facilitate a particular interconversion (e.g. DMP for alcohol oxidation).[8]

One powerful class of oxidations are those involving oxoammonium cations. Oxoammonium salts (i.e. **2**) and their nitroxide variants (i.e. TEMPO) are highly attractive species because they are safe, inexpensive, environmentally benign, and recyclable. In addition, they are very user-friendly and accomplish a number of oxidative transformations under mild conditions.[9] Both oxoammonium salts and nitroxides can be used catalytically to achieve oxidation on industrial scale using bleach (NaOCl) as the terminal oxidant as in the Anelli process.[10-12]

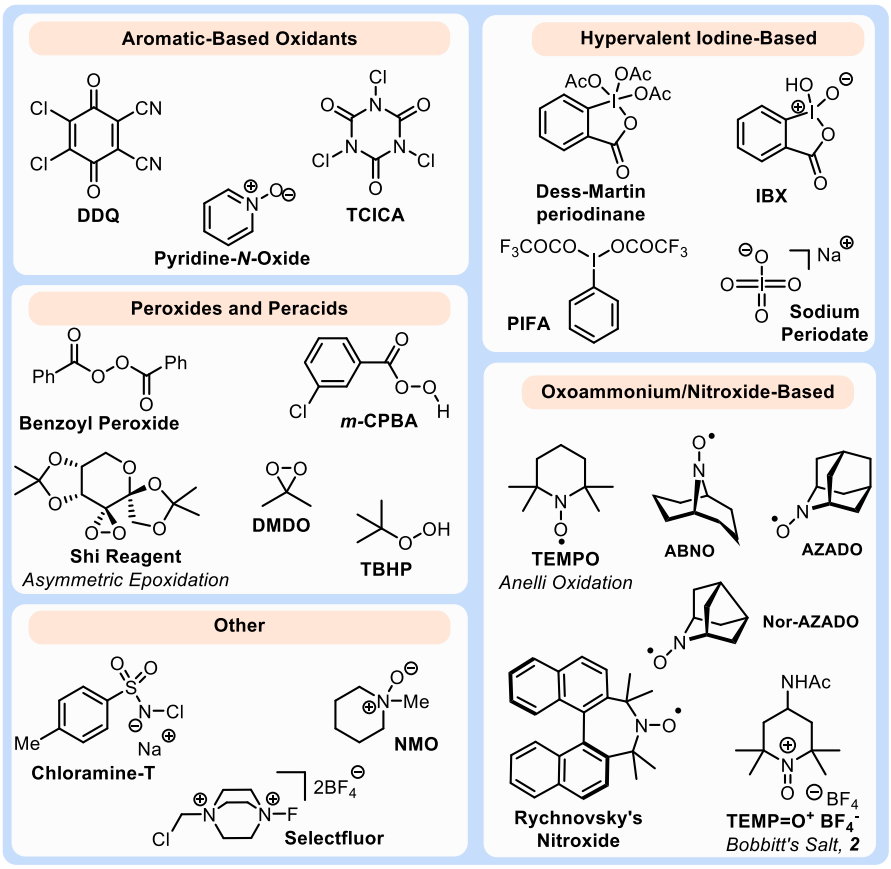



**Figure 7. Common organic oxidants**

Oxoammonium salts have garnered recent attention as practical, versatile stoichiometric oxidants for routine oxidation. In particular, 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate ("Bobbitt's Salt", 4-AcNH-TEMP=O+ BF4-, **2**), a commercially available oxoammonium salt, has been used in an array of oxidative transformations demonstrating its extreme versatility.[9] Bobbitt's salt (**2**) is derived from 4-amino-2,2,6,6-tetramethylpiperidine (a cheap tetramethylpiperidine variant produced from acetone and ammonia)[13] whose physical properties make it an ideal vehicle for tapping into the reactivity of the oxoammonium cation. Bobbitt's salt (**2**) is a robust oxidant that can be prepared in water and the spent oxidant can easily be recovered by precipitation from ether.[9b,14] The

spent oxidant can be used to regenerate the oxoammonium salt, thus making the process inherently recyclable. Until recently, synthetic methods involving this salt focused on the intricacies of the oxidation of alcohols to their corresponding carbonyl compounds.[14] This oxidant is thought to operate via a hydride-transfer mechanism from the α-C-H bond of the carbinol to the electrophilic oxygen of the oxoammonium salt (Figure 8).[15] Under non-base assisted conditions, the transition state is similar to the putative oxocarbenium ion, and thus, the rates of oxidation reflect cation stability. This disparity in rate allows for selective oxidation; secondary alcohols can be selectively oxidized in the presence of primary alcohols under neutral or acidic conditions. Under weakly basic conditions, the hydride transfer and deprotonation events are likely concerted.[15] The key difference is the formation of a pre-oxidation complex that is a direct result of intermolecular hydrogen bonding between the base (typically pyridine-derived) and the alcohol. As such, this process is now under steric control and primary alcohols can be oxidized selectively in the presence of secondary alcohols.[15] Under very strongly basic conditions, steric control is even more pronounced and has been investigated computationally.[15b]

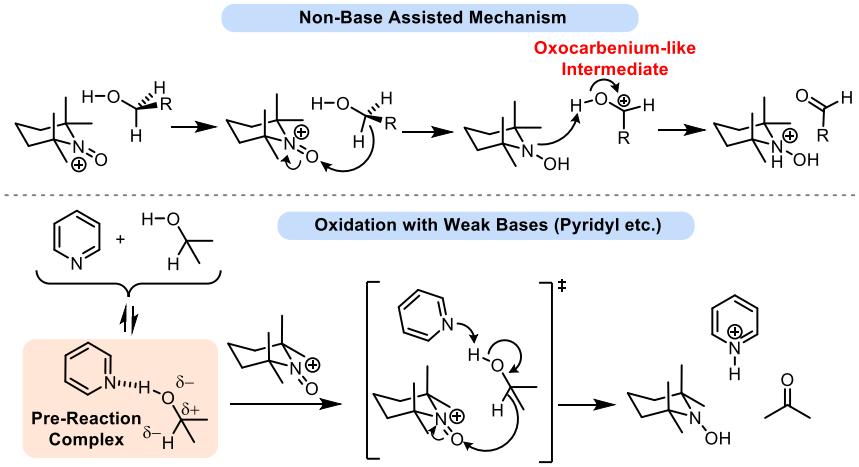



**Figure 8. Mechanism of oxidation of alcohols using 1 under weakly basic and neutral conditions**

Further elaboration of the action of this oxidant has revealed that it can engage in an array of oxidative functionalization processes (Figures 9 and 10). These include methods to perform oxidative esterification,[16a] oxidative

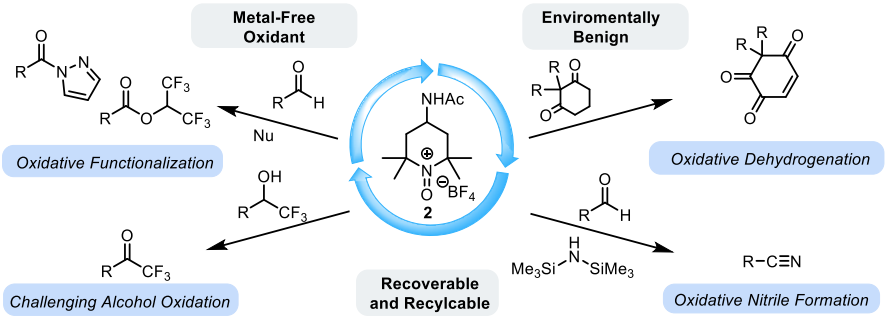



**Figure 9. Recently developed oxidative functionalization using 2**

amidation,[16b] oxidative nitrile formation,[16c] exhaustive oxidation of cyclohexadiones to ene-triketones,[16d] oxidation of α-perfluoroalkyl alcohols,[16e] and dehydrogenation of perfluoroalkyl ketones (Figure 9).[16f] In addition to these applications, the oxoammonium salt can be used to oxidize various functional groups ranging from amines to thiols and can be used to oxidize activated C-H bonds often leading to cleavage (Figure 10).[17]

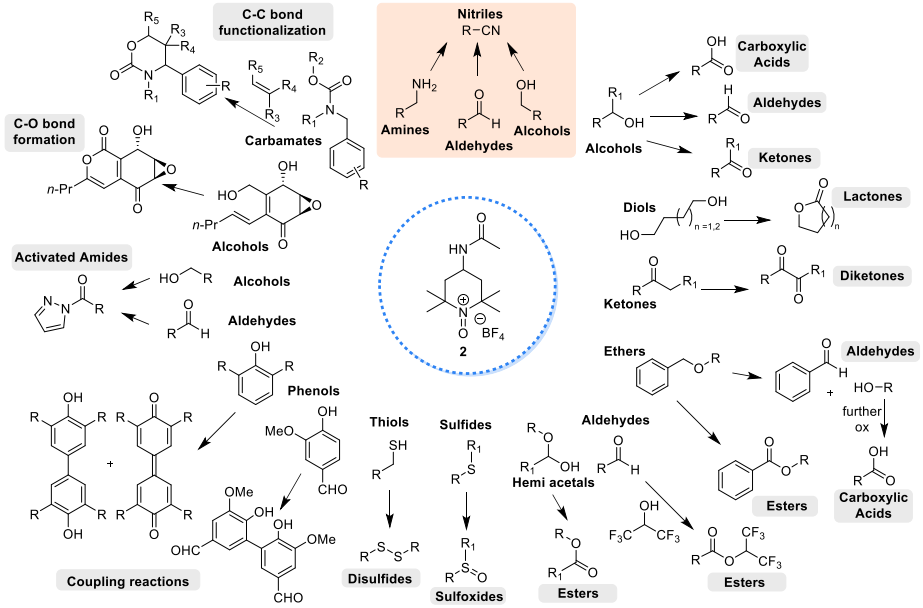



**Figure 10. Applications of 2 as an oxidant for alcohol oxidation and beyond**

In 2014, Bailey and co-workers reported that **2** can be used to directly oxidize primary amines to nitriles under mild conditions.[18] Computational analysis of the mechanism confirmed that aldimine formation was very favorable and revealed the reaction proceeds through a hydride-transfer mechanism. A robust catalytic variant of this process with a wide substrate scope has also been described.[19] Given the importance of nitriles to the medicinal and agrochemical communities, as well as some of the operational challenges of oxidizing amines substrates,[20a] other avenues for the oxidative generation of nitriles were explored.[20b-d] In 2015, a process to convert alcohols and aldehydes into nitriles using **2** was realized and is the subject of the procedure detailed here.[16c]

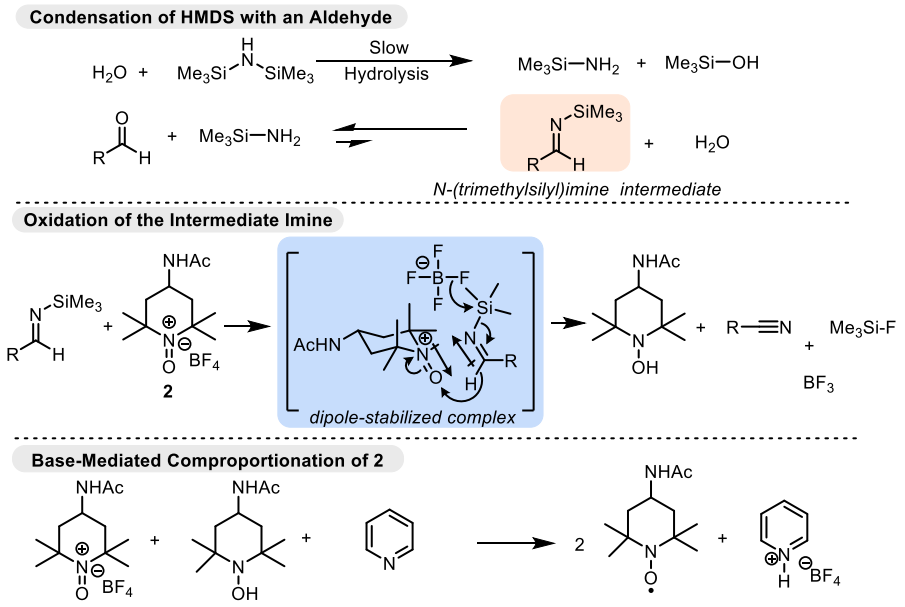



**Figure 11. Mechanism of reaction described in this procedure**

Compared to the typical approach to nitrile installation (e.g. dehydration of amides with $P_2O_5$, substitution of halides with cyanide, etc.),[21] this approach provided an inherently safer and easier platform for constructing nitriles. Although not the first example of this type of interconversion (i.e. aldehyde to nitrile),[22] this reaction is unique as it uses HMDS as the nitrogen source rather than ammonia.

The mechanistic crux of this reaction is the formation of the

*N*- trimethylsilyl imine which can undergo facile oxidation via a through-space hydride transfer to the oxoammonium salt (Figure 12). In addition, the byproduct of this reaction is boron trifluoride which accelerates the initial condensation of HMDS with an aldehyde. Note that the conditions are not rigorously dried, and the mechanism is dependent on the slow hydrolysis of HMDS to the mono-silylated amine.

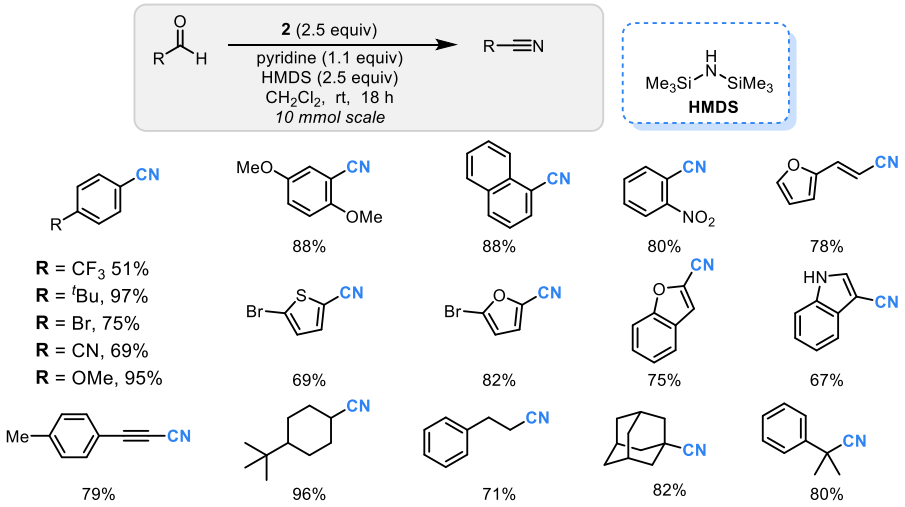



**Figure 12. Scope of oxidative nitrile formation using 2**

The procedure described here can be applied to the conversion of many aldehydes to nitriles, although the means of purification will vary depending on structure (Figure 12). In most cases, purification can be accomplished by passage of the material obtained after work-up over a pad of silica, eluting with a hexanes/EtOAc solvent system. In select cases, the reaction would stall at 92-95% conversion. Given the isopolar nature of the nitriles relative to aldehydes (i.e. Figure 6), purification in these cases required sequestering of the aldehyde by a scavenger. To accomplish this, the crude material is taken up in $Et_2O$ and stirred with SilaBond® amine[23] overnight. Filtration and solvent removal affords the pure nitrile.

Taking advantage of the well-established ability of oxoammonium salts to convert alcohols to aldehydes, a two-step, one-pot approach to the conversion alcohols to nitriles was also realized (Figure 13).[16c, 24] The first step of this process utilizes lutidine to avoid undesired acyl pyridinium formation and hence oxidative dimerization of the resulting aldehyde.[15c] The second

step utilizes the conditions described here and can be initiated without isolation of the aldehyde. Recently, a photoredox version of this process has been described.[25]

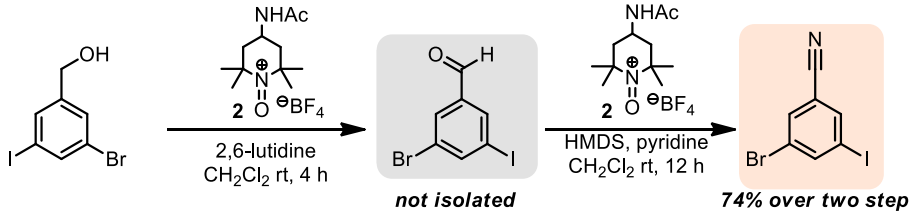



**Figure 13. Two-step, one-pot conversion of an alcohol to a nitrile using 2**

In summary, the oxoammonium salt (**2,** Bobbitt's salt) is a robust reagent for not only routine oxidation, but for oxidative functionalization. Detailed in this procedure is a means to convert aldehydes and alcohols to nitriles under very mild conditions with a broad scope. As a result, this process offers a user-friendly means for the late-stage installation of a nitrile group in advanced systems. The process capitalizes on the inherent electrophilicity of the oxygen of the oxoammonium cation and its ability to readily accept a hydride. Supplementary work in this area has led to the development of a catalytic variant. It is expected that this process will lead to further discoveries using **2**.

## References

1. Department of Chemistry and Biochemistry, Old Dominion University, 4541 Hampton Boulevard, Norfolk, Virginia 23529, United States. Email address: kmlamber@odu.edu (ORCID: 0000-0002-8230-2840). The authors gratefully acknowledge financial support from Old Dominion University.
2. Department of Chemistry, Virginia Commonwealth University, 1001 West Main Street, P.O. Box 842006, Richmond, Virginia 23284-9069, United States.
3. Medicines for All Institute, Virginia Commonwealth University, Biotech 8 737 North Fifth Street, Richmond, Virginia 23219-1441, United States. The authors gratefully acknowledge financial support from Virginia Commonwealth University and the Bill and Melinda Gates Foundation.

Present address for C.B.K.: Janssen Research and Development, LLC, 1400 McKean Road, Spring House, Pennsylvania 19477, United States. E-mail address: ckelly5@its.jnj.com; (ORCID for C. B. K.: 0000-0002-5530-8606); (ORCID for N. D. K.: 0000-0003-3520-8445).

4. Ahluwalia, V. K. Oxidation in Organic Synthesis; CRC Press: United States, **2012**.
5. (a) Muzart, J. *Chem. Rev.* **1992**, *92*, 113–140. (b) Keith, J. A.; Henry, P. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9038–9049. (c) Baiju, T. V.; Gravel, E.; Doris, E.; Namboothiri, I. N. N. *Tetrahedron Lett.* **2016**, *57*, 3993–4000.
6. Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362–3374.
7. Weber, M.; Weber, M.; Kleine-Boymann, M. Phenol. Ullmann's Encyclopedia of Industrial Chemistry, **2004**.
8. (a) Tojo, G.; Fernandez, M. Oxidation of Alcohols to Aldehydes and Ketones; Tojo, G., Ed.; Springer: New York, **2010**. (b) Arends, I. W. C. E.; Sheldon, R. A. In Modern Oxidation Methods; Backvall, J.-E., Ed.; Wiley-VCH Verlag Gmb & Co.: Weinheim, Germany, **2004**.
9. (a) Leadbeater, N. E.; Bobbitt, J. M. *Aldrichimica Acta* **2014**, *47*, 65. (b) Mercadante, M. A.; Kelly, C. B.; Bobbitt, J. M.; Tilley, L. J.; Leadbeater, N. E. *Nat. Protoc.* **2013**, *8*, 666–676. (c) Bobbitt, J. M.; Brückner, C.; Merbouh, N. *Org. React.* **2009**, *74*, 103-424. (d) Bobbitt, J. M.; Merbouh, N. *Org. Synth.* **2005**, *82*, 80–86.
10. Ciriminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2010**, *14*, 245–251.
11. (a) Cao, Q.; Dornan, L. M.; Rogan, L.; Hughes, N. L.; Muldoon, M. J. *Chem. Commun.* **2014**, *50*, 4524–4543. (b) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901–16910.
12. Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987,** *52*, 2559–2562.
13. Lantzsch, R.; Arlt, D. U.S. Patent 4001250 Process for Preparing 4-Amino-2,2,6,6-Tetramethyl Piperidine, **1977**.
14. Bobbitt, J. M. *J. Org. Chem.* **1998**, *63*, 9367–9374.
15. (a) Hamlin, T. A.; Kelly, C. B.; Ovian, J. M.; Wiles, R. J.; Tilley, L. J.; Leadbeater, N. E., *J. Org. Chem.* **2015**, *80*, 8150–8167. (b) Bailey, W. F.; Bobbitt, J. M.; Wiberg, K. B. *J. Org. Chem.* **2007**, *72*, 4504–4509. (c) Bobbitt, J. M.; Bartelson, A. L.; Bailey, W. F.; Hamlin, T. A.; Kelly, C. B. *J. Org. Chem.* **2014**, *79*, 1055–1067.
16. (a) Kelly, C. B.; Mercadante, M. A.; Wiles, R. J.; Leadbeater, N. E. *Org. Lett.* **2013**, *15*, 2222–2225. (b) Ovian, J. M.; Kelly, C. B.; Pistritto, V. A.; Leadbeater, N. E. *Org. Lett.* **2017**, *19*, 1286–1289. (c) Kelly, C. B.; Lambert, K. M.; Mercadante, M. A.; Ovian, J. M.; Bailey, W. F.; Leadbeater, N. E.

*Angew. Chem., Int. Ed.* **2015**, *54*, 4241–4215. (d) Eddy, N. A.; Kelly, C.B.; Mercadante, M. A.; Leadbeater, N. E.; Fenteany, G. *Org. Lett.* **2012**, *14*, 498–501. (e) Kelly, C. B.; Mercadante, M. A.; Hamlin, T. A.; Fletcher, M. H.; Leadbeater, N. E. *J. Org. Chem.* **2012**, *77*, 8131–8141. (f) Hamlin, T. A.; Kelly, C. B.; Leadbeater, N. E. *Eur. J. Org. Chem.* **2013**, 3658–3661.

17. For other applications of this unique oxidant see: (a) Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F. *Org. Lett.* **2006**, *24*, 5485–5487. (b) Wertz, S.; Kodama, S.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11511–11515. (c) Rohlmann, R.; Stopka, T.; Richter, H.; García Mancheño, O. *J. Org. Chem.* **2013**, *78*, 6050–6064. (d) Richter, H.; Fröhlich, R.; Daniliuc, C.-G.; García Mancheño, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 8656–8660. (e) Hayashi, M.; Shibuya, M.; Iwabuchi, Y. *Org. Lett.* **2012**, *14*, 154–157. (f) Shibuya, M.; Osada, Y.; Sasano, Y.; Tomizawa, M.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2011**, *133*, 6497–6500. (g) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 14044–14047. (h) Kelly, C. B.; Ovian, J. M.; Cywar, R. M.; Gossland, T. R.; Wiles, R. J.; Leadbeater, N. E. *Org. Biomol. Chem.* **2015**, *13*, 4255–4259. (i) Loman, J. J.; Pistritto, V. A.; Kelly, C. B.; Leadbeater, N. E. *Synlett* **2016**, *27*, 2372–2377.
18. Lambert, K. M.; Bobbitt, J. M.; Eldirany, S. A.; Wiberg, K. B.; Bailey, W. F. *Org. Lett.* **2014**, *16*, 6484–6487.
19. (a) Lambert, K. M.; Bobbitt, J. M.; Eldirany, S. A.; Kissane, L. E.; Sheridan, R. K.; Stempel, Z. D.; Sternberg, F. H.; Bailey, W. F. *Chem.–Eur. J.* **2016**, *22*, 5156–5159. (b) Lambert, K. M.; Eldirany, S. A.; Bobbitt, J. M.; Bailey, W. F. *Org. Synth.* **2018**, *95*, 60–79.
20. (a) Bartelson, A. L.; Lambert, K. M.; Bobbitt, J. M.; Bailey, W. F. *Chem. Cat. Chem.* **2016**, *8*, 3421–3430. (b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902–7917. (c) Miller, J. S.; Manson, J. L. *Acc. Chem. Res.* **2001**, *34*, 563–570. (d) Pollak, P.; Romeder, G.; Hagedorn, F.; Gelbke, H.-P. in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim, **2012**.
21. (a) Larock, R. C. Comprehensive Organic Transformations, VCH Publishers, New York, **1989**. (b) Yan, G.; Zhang, Y.; Wang, J. *Adv. Synth. Catal.* **2017**, *359*, 4068–4105. (c) Schümperli, M. T.; Hammond, C.; Hermans, I *ACS Catal.* **2012**, *2*, 1108–1117. (d) Ping, Y.; Ding, Q.; Peng, Y. *ACS Catal.* **2016**, *6*, 5989–6005.
22. For some recent examples of this approach see: (a) Hyodo, K.; Togashi, K.; Oishi, N.; Hasegawa, G.; Uchida, K. *Org. Lett.* **2017**, *19*, 3005–3008. (b) Rokade, B. V.; Prabhu, J. R. *J. Org. Chem.* **2012**, *77*, 5364–5370. (c) Noh,

J. H.; Kim, J. *J. Org. Chem.* **2015**, *80*, 11624–11628. (d) Wu, Q.; Luo, Y.; Lei, A.; You, J.; *J. Am. Chem. Soc.* **2016**, *138*, 2885–2888.
23. This is a commercially available scavenger from Silicycle (item number: R52030B) where silica is functionalized with a pendent primary alkyl amine. Condensation of the aldehyde with this amine results in sequestration.
24. (a) Lin, K.; Wiles, R. J.; Kelly, C. B.; Davies, G. H. M.; Molander, G. A. *ACS Catal.* **2017**, *7*, 5129–5133. (b) Lambert, K. M.; Stempel, Z. D.; Wiberg, K. B.; Bailey, W. F. *Org. Lett.* **2017**, *19*, 6408–6411.
25. Nandi, J.; Witko, M. L.; Leadbeater, N. E. *Synlett* **2018**, *29*, 2185–2190.

## Appendix
## Chemical Abstracts Nomenclature (Registry Number)

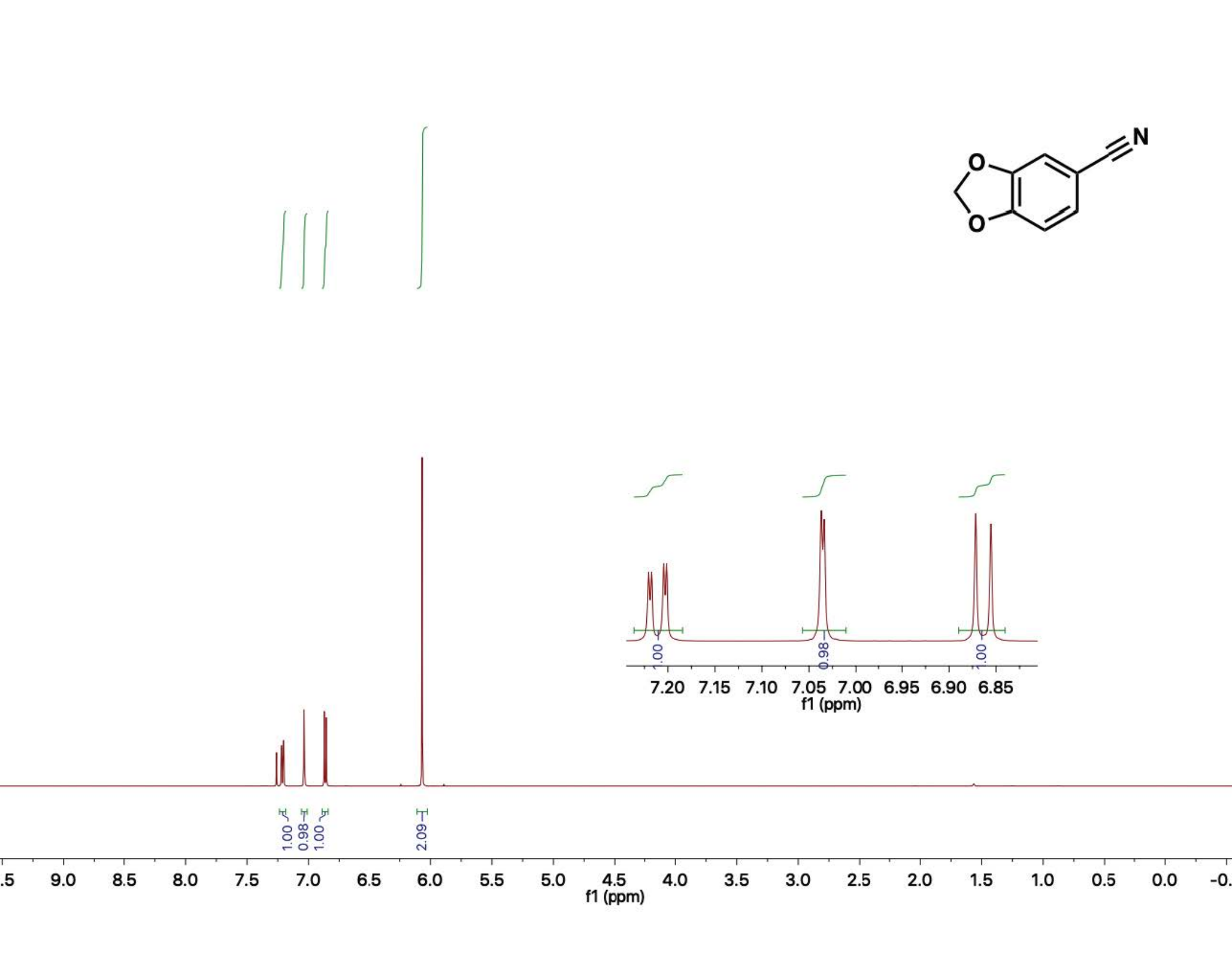
Piperonal: 1,3-Benzodioxole-5-carboxaldehyde; (120-57-0)
1,1,1,3,3,3-Hexamethyldisilazane: HMDS; (999-97-3)
4-(Acetylamino)-2,2,6,6-tetramethyl-1-oxo-piperidinium tetrafluoroborate: Bobbitt's salt; (219543-09-6)
Pyridine; (110-86-1)
Dichloromethane: Methylene Chloride; (75-09-2)

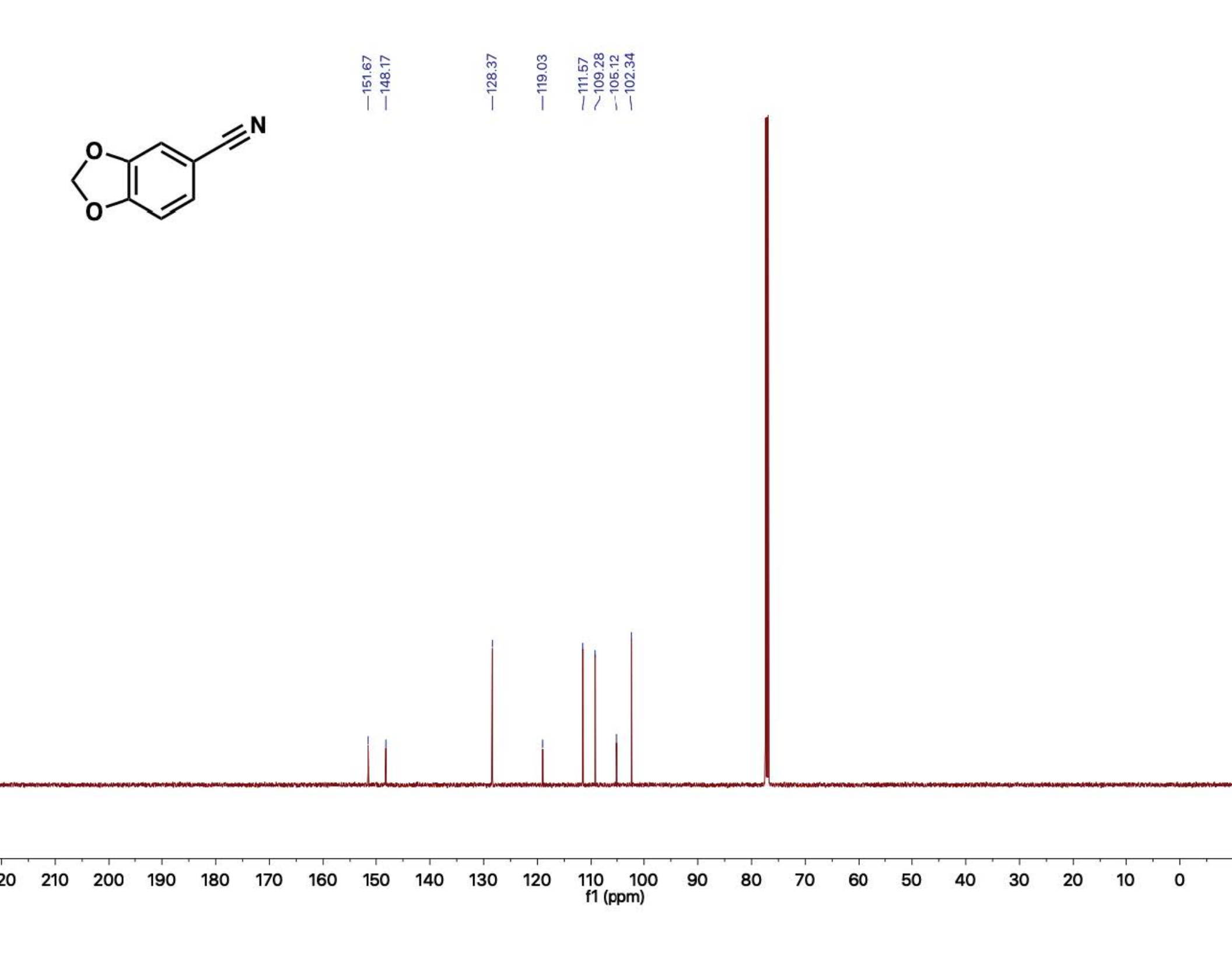
Prof. Christopher B. Kelly studied at Stonehill College in Easton, MA, where he received his B.S. in Biochemistry in 2010. That same year, he joined the University of Connecticut (UConn) where he performed his doctoral studies under the supervision of Dr. Nicholas Leadbeater. While at UConn, he developed new synthetic methods in organofluorine and oxoammonium salt chemistry. After earning his Ph.D. in organic chemistry in 2015, he joined Prof. Gary Molander's group at the University of Pennsylvania as a National Institutes of Health postdoctoral fellow. While at Penn, Chris developed synthetic methods in the arena of photoredox catalysis. In 2018, he began his career initially in academia at Virginia Commonwealth University (VCU) then transitioned to work in industry as a member Janssen's newly formed Discovery Process Research team.

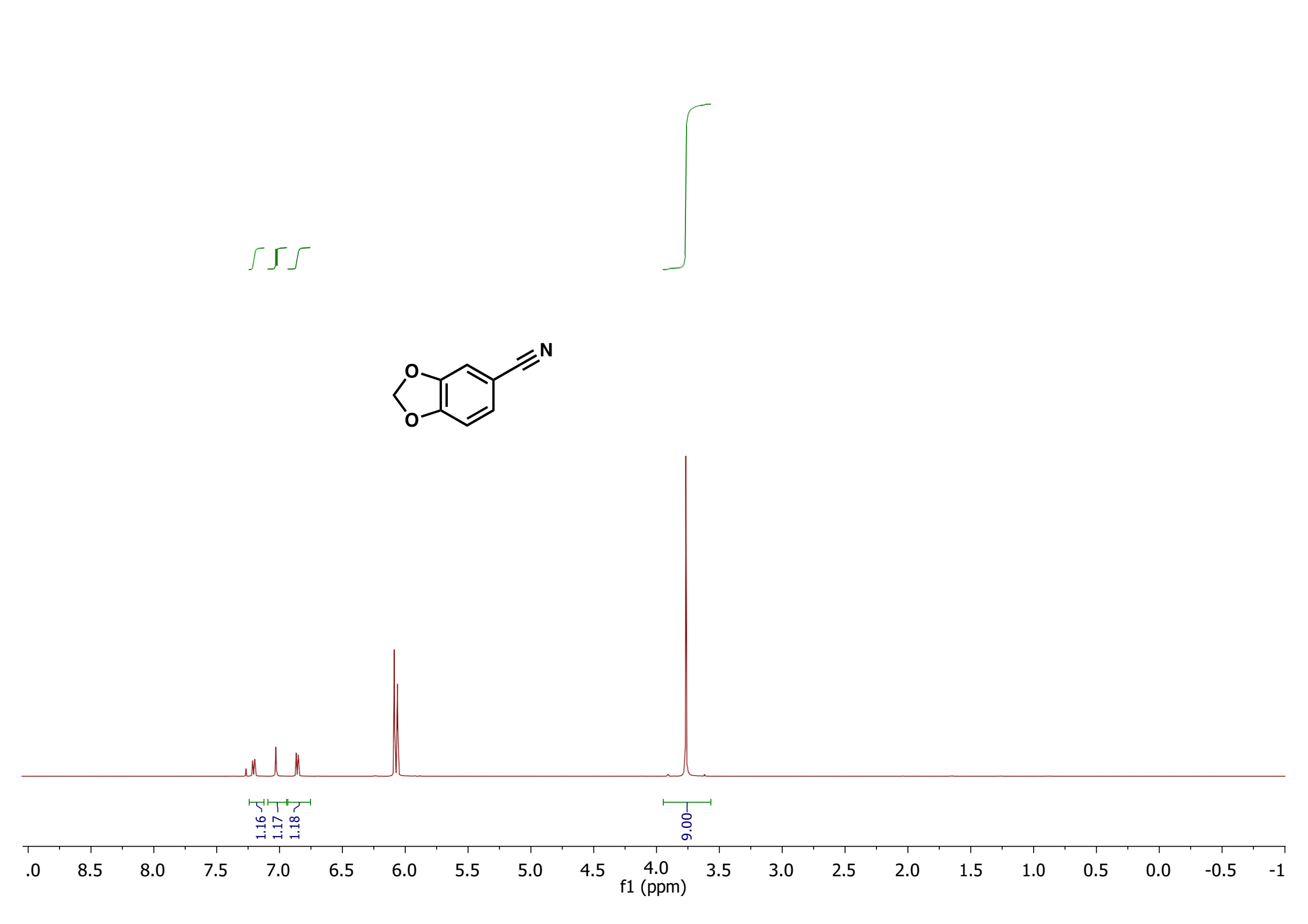
Kyle Lambert received dual B.S. degrees in chemistry and forensic science from the University of New Haven in 2012. He obtained his Ph.D. in 2017 from University of Connecticut while working with Prof. William Bailey. Kyle's doctoral research involved the exploration of oxoammonium salts as selective oxidants, as well as, conformational studies of saturated heterocycles. Following his doctoral studies, Kyle joined Prof. John Wood's group at Baylor University as a National Institutes of Health postdoctoral fellow where he studied natural products synthesis. In 2020, Kyle joined the faculty at Old Dominion University as an Assistant Professor. His new research group's interests are in the development of novel synthetic methods and the total synthesis of biologically relevant natural products.

Nathaniel Kaetzel transferred to VCU in 2018 to pursue chemistry and mathematics. As a high school student, he took an interest in chemistry, enrolled in his first semester of organic chemistry at a local community college, and very soon realized his affinity for the subject. Nathaniel joined Prof. Kelly's laboratory after thoroughly enjoying his CHEM 301 Organic Chemistry I course and has begun his training as an organic chemist.

Charis A. Roberts earned their B.A. in Chemistry from Reed College in 2019, where they studied light-driven isomerization of (hetero)aromatic photochromes with Prof. Sameh Helmy and then later C–H functionalization of saturated aza-cycles with Prof. Rebecca LaLonde. They are currently a graduate student at University of California, Berkeley wherein they study C–H and C–C functionalization methodologies and natural product total synthesis in the laboratory of Prof. Richmond Sarpong.


O
O
N
1.00
0.98
1.00
2.09
7.20 7.15 7.10 7.05 7.00 6.95 6.90 6.85
f1 (ppm)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


151.67
148.17
128.37
119.03
111.57
109.28
105.12
102.34
O
O
N
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
N
1.16
1.17
1.18
9.00
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1
f1 (ppm)