UC San Diego
UC San Diego Electronic Theses and Dissertations

Title
Progress Towards Synthesis of Novel Aromatic Diisocyanate for Polyurethane Materials

Permalink
https://escholarship.org/uc/item/6pd3g37n

Author
Lerda, Victoria

Publication Date
2023

Peer reviewed|Thesis/dissertation

eScholarship.org Powered by the California Digital Library
University of California

UNIVERSITY OF CALIFORNIA SAN DIEGO

Progress Towards Synthesis of Novel Aromatic Diisocyanate for Polyurethane Materials

A Thesis submitted in partial satisfaction of the requirements
for the degree Master of Science

in

Chemistry

by

Victoria Lerda

Committee in charge:

Professor Valerie Schmidt, Chair
Professor Michael Burkart
Professor Michael Sailor

2023

Copyright

Victoria Lerda, 2023

All rights reserved.

The Thesis of Victoria Lerda is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

2023

DEDICATION

Dedicated to my beloved family,

who has always encouraged and supported my journey as a scientist.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

Å	Angstrom
atm	atmospheres
avg	average
BTX	benzene, toluene, xylene
°C	degrees Celsius
cat	catalytic
calc.	calculated
$CDCl_3$	deuterated chloroform
CFC	chlorofluorocarbon
$CHCl_3$	chloroform
conc	concentrated/concentration
d	day(s) or doublet (NMR)
DCE	dichloroethane
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMSO-D_6	deuterated dimethyl sulfoxide
E. coli	Escherichia coli
equiv	equivalent(s)
ESI	electrospray ionization (MS)
Et	ethyl

EtOAc	ethyl acetate
EtOH	ethanol
EWG	electron-withdrawing group
FTIR	Fourier-transform infrared spectroscopy
GC	gas chromatography
h	hour(s)
HAT	hydrogen atom transfer
HRMS	high-resolution mass spectrometry
IR	infrared (spectroscopy)
L.A.	Lewis acid
LG	leaving group
LRMS	low-resolution mass spectrometry
m	multiplet (NMR)
M	molarity
MDI	methylene diphenyl diisocyanate
Me	methyl
MeOH	methanol
MHz	mega hertz
MS	mass spectrometry
m/z	mass to charge ratio
NCO	isocyanate
NMR	nuclear magnetic resonance
Nuc	nucleophile

OAc	acetoxy
OAT	oxygen atom transfer
OH	hydroxyl
OTf	triflate
Pd/C	palladium on carbon
Ph	phenyl
PhMe	toluene
ppm	parts per million (NMR)
rt	room temperature
s	singlet (NMR)
S_NAr	nucleophilic aromatic substitution
t	triplet (NMR)
^{t}Bu	tert-butyl
TDI	toluene diisocyanate
THF	tetrahydrofuran
TLC	thin-layer chromatography
TOF	time-of-flight (MS)

ACKNOWLEDGEMENTS

I am grateful to my research advisor and Chair, Valerie Schmidt, for her guidance and assistance as I navigated my first years of graduate school in her group. I also thank my committee members, Professor Michael Burkart and Professor Michael Sailor for their willingness to serve on my MS Thesis Committee. Special thanks to Professor Michael Burkart for the inspiration of this project and giving me the opportunity to expand my scientific knowledge at his group meetings as well as the Burkart group members for their guidance. I'd like to recognize and thank the Schmidt group members, both current and former, with special thanks to Anthony Alfaro and Hiya Datta for their unwavering support. I would like to thank American Chemical Society Bridge Program (ACS-BP) for the opportunity to join the graduate program at UC San Diego. I'd like to acknowledge NSF UCSD MRSEC for funding this work, Professor Clifford Kubiak and Professor Seth Cohen groups for FTIR data, Dr. Anthony Mrse with the UCSD NMR Facility, and Dr. Yongxuan Su with the UCSD Molecular Mass Spectrometry Facility. Lastly, I'd like to thank my family, friends, and mentors who have supported me throughout this journey.

ABSTRACT OF THE THESIS

Progress Towards Synthesis of Novel Aromatic Diisocyanate for Polyurethane Materials

by

Victoria Lerda

Master of Science in Chemistry

University of California San Diego, 2023

Professor Valerie Schmidt, Chair

Polyurethanes are versatile organic materials that have transformed modern-day life. Made from polyols and diisocyanates, their versatility is largely determined by the combination of monomers used. In foams, the polyols can be sourced from renewable feedstocks and are diverse in their structures and properties, however, the dominating process for aromatic diisocyanates from fossil fuels has limited the monomers used in polyurethane materials. As society depletes the petroleum resources on this planet, there is an incentive to expand to renewable sources that can further diversify the aryl diisocyanates used in polyurethane

products. Herein, I take inspiration from naturally abundant phenolic compounds to expand the scope of starting materials to access novel aromatic diisocyanates. I explore established synthetic methodologies to prepare the aniline precursor to access novel monomer, 3,5-diisocyanto-1,1’-biphenyl.

Chapter 1

1.1 Background and Significance

Polyurethanes have become essential in modern life due to their wide success in consumer and industrial applications. These diverse and versatile organic materials were first discovered by Otto Bayer in 1937 through the reaction of a diisocyanate and a polyester diol. This discovery launched polyurethane manufacturing for widely successful products such as furniture, shoes, paints, adhesives, coatings, carpet underlay, clothing fibers, and insulation.[1] As the 6th most used polymer, polyurethanes have an estimated yearly production scale of around 18 million tons.[2] The prospect for design and innovation, due to interchangeable building blocks such as polyols and polyisocyanates, have established these materials as commodity products that will continue to grow.

1.2 Polyurethanes

Any polymer that has a repeating urethane group is classified as a polyurethane regardless of having various other functional groups. Synthetically, the urethane linkage is formed through the reaction of diols or polyols with diisocyanates or polyisocyanates (Figure 1-1). While additives like chain extenders, surfactants, and catalysts are incorporated in polyurethane material preparation, this thesis focuses on isocyanates and polyols. The flexible and soft properties of polyurethanes are provided by the polyols whereas the stiffness and hardness come from the isocyanates.

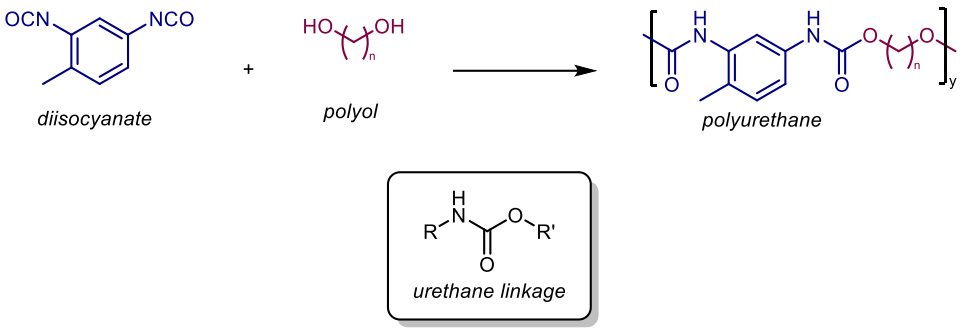


Figure 1-1. Repeating Urethane Linkages Define Polyurethanes

The versatility of polyurethanes stems from the variety of building blocks used in their preparation, most notably, from the diversity in available polyol monomers.[3] Industrially relevant polyols tend to be ether or ester based and can be synthesized with relative ease including some derived from renewable sources.[4] Some bio-based polyols have been upscaled to industrial levels on their way to replace petroleum-based polyols.[5] On the other hand, established industrial methods have dominated the isocyanate industry with limited variability in structure. Derived from petrochemical feedstocks, the range of isocyanates being produced is short, but their insurmountable success in the polyurethane industry has made diversification of these monomers unnecessary. Regardless, the opportunities to pair isocyanates with polyols of varying structures and molecular weight can cause significant changes in physical properties for intended applications.

1.2.1 Foams

Of these polyurethane materials, rigid and flexible foams have had immense success accounting for 67% of the global polyurethane consumption.[6] In flexible foams, when an isocyanate reacts with water, it releases CO_2, giving it an open-cell structure that allows air to flow through the material as it flexes.[7] Roughly 30% of polyurethane market in North America can be attributed to flexible foams where they are most successful in furniture, bedding, transportation, and carpeting.[8] Rigid foams have a closed-cell structure, and they are most successful in insulation,

construction, and automotive applications. This closed-cell structure is usually created when chlorofluorocarbon (CFC) is used as the blowing agent instead of CO_2. Both flexible and rigid foams rely on 2,4- and 2,6-toluene diisocyanate (TDI) and 2,2´-, 2,4´-, and 4,4´-methylene diphenyl diisocyanate (MDI) monomers, as their rigid, bulky, aromatic structure impart firmness and hardness on the foam. These attributes result in foams that exhibit desirable properties such as good tensile strength, load bearing, tear strength, elongation, and resiliency.[9] In rigid foams, the isocyanate serves as the reactant that joins polyol monomers together and builds a highly cross-linked polymer system. Flexible foams use isomeric mixtures of TDI while rigid foams use MDI-based isocyanates.

1.3 Aromatic Diisocyanates and Their Syntheses

MDI and TDI dominate the polyurethane industry constituting roughly 90% of the total diisocyanate consumption.[10] Lesser used aromatic diisocyanates include 1,5-naphthalene diisocyanate (NDI), *para*-phenylene diisocyanate (PPDI), and 3,3´-tolidene 4,4´-diisocyanate (TODI) (Figure 1-2). Aromatic isocyanates serve as the hard segment in polyurethanes and tend to result in the polyurethanes that have higher glass transition, tensile strength, and modulus. While there have been several ways developed to synthesize aromatic isocyanates, the phosgenation of aromatic amines has remained the most common method for their preparation. Alternative methods, including the Curtius, Lossen, and Hofmann rearrangement, have not found much success outside of laboratory settings. Although there are various synthetic routes, the variability in these aromatic monomers used in polyurethanes is fairly limited due to the inherent success of TDI and MDI.

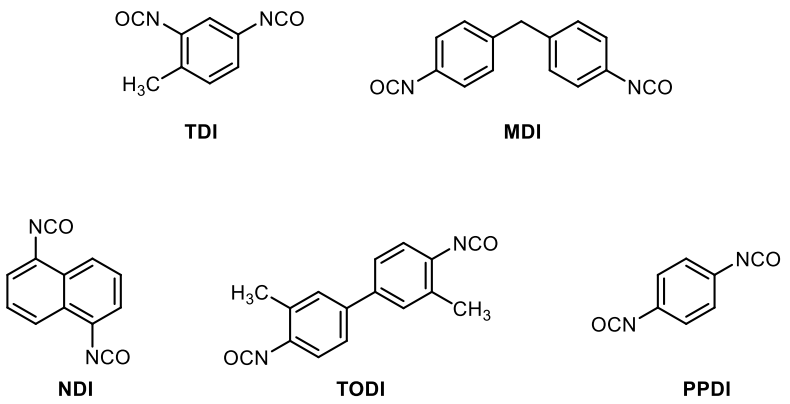


Figure 1-2. Aromatic Diisocyanate Examples

1.3.1 Synthetic Routes of Aromatic Diisocyanates

The general industrial process of preparing these aryl diisocyanates begins from unfunctionalized arenes, particularly benzene, toluene, and xylene (BTX), which are derived from petrochemical feedstocks. Toluene serves as the backbone and starting material for TDI with the first step being nitration with nitric acid and sulfuric acid as a catalyst (Figure 1-3).[11] A mixture of mostly 2,4- and 2,6-dinitro isomers are obtained after the first step which then undergo catalytic reduction under hydrogen pressure to release the diamine that can be treated with phosgene gas to access TDI. When benzene is similarly nitrated and reduced, the resulting aniline serves as the basis for MDI. The condensation of aniline with formaldehyde in acidic conditions produces a mixture of oligomeric diamines and polyamines. The subsequent phosgenation of these amines yields polymeric MDI (PMDI) which can be further purified to separate the isomers.

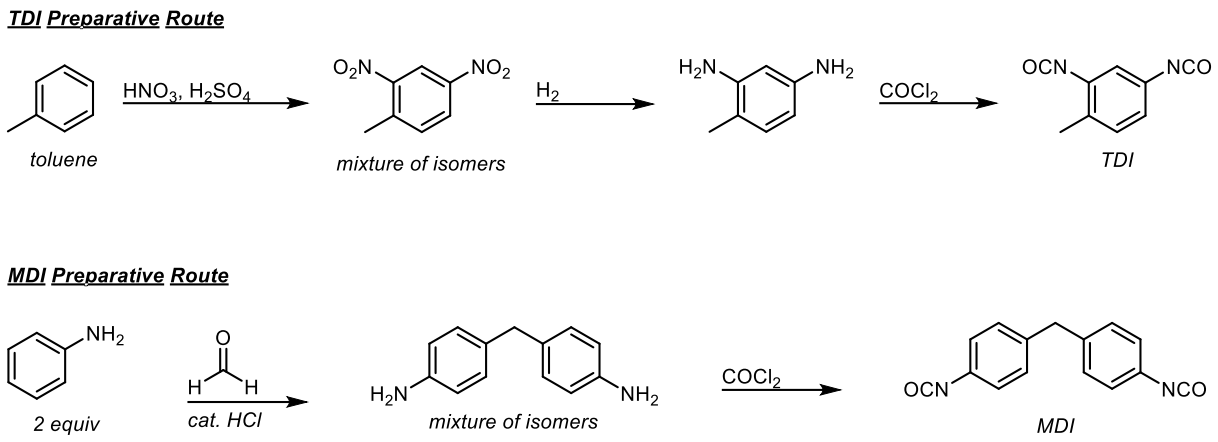


Figure 1-3. Aryl Diisocyanate Industrial Preparative Route

With the annual demand of BTX growing to 108 million metric tonnes, and 90% of all isocyanates being derived from these aromatic feedstocks, it's no surprise that this route has remained the dominant preparative route of aryl diisocyanates.[12] Alternative synthetic pathways have yet to outcompete the successful phosgenation process and this has resulted in limited variability in aryl diisocyanates applied in polyurethane materials. With the growing reliance on fossil fuels, a nonrenewable resource, depletion of this feedstock is expected to occur within 100 years and alternative routes to synthesize existing and novel aryl diisocyanates must be developed.[13]

The Curtius, Lossen, and Hofmann rearrangements are alternative methods to synthesize isocyanates and can be applied to aromatic isocyanates.[14] These rearrangement reactions are typically used to synthesize isocyanates as intermediates that can then be trapped with alcohols or amines to form carbamates or ureas, respectively (Figure 1-4).[15] These rearrangement reactions are used for laboratory scale isocyanate synthesis and not suitable for industrial processes.[16]

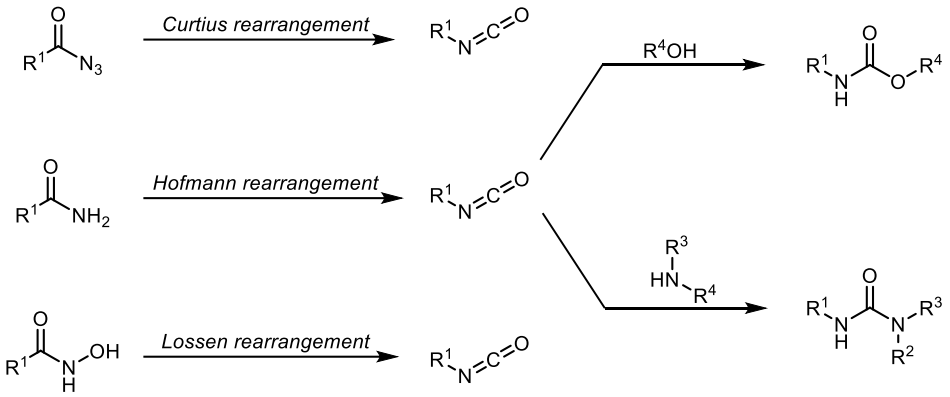


Figure 1-4. Rearrangement Routes to Isocyanates and Further Reactivity

The Curtius rearrangement is a thermal decomposition reaction of an acyl azide that releases nitrogen gas and isocyanate through a concerted mechanism. Isocyanates synthesized through this method are often obtained in high yield at laboratory scale, but the toxicity and explosive nature of the requisite azides and acyl azides renders this process undesirable for industrial applications. The Hofmann rearrangement of amides affords isocyanates that are rapidly trapped with alcohols to yield the corresponding carbamates or degraded to the corresponding amines when reacted with water. Typical reaction conditions require stoichiometric amounts of toxic and corrosive Br_2 and produce a high amount of waste. The Lossen rearrangement of activated hydroxamic acids produces isocyanates which are further reacted to yield ureas, amines, or carbamates and is used less often than the previously mentioned rearrangement reactions. The limited availability and extensive synthesis needed to obtain activated hydroxamic acids as well as the requisite acetic anhydride or acetyl chloride with base have prevented usage in laboratory and industry settings.

Other methods have been explored to synthesize isocyanates, including with renewable resources such as maize and oat husks, but cannot overpower the grasp that industrial routes have over aryl diisocyanate production.[17] As society continues to exhaust our earth's supply of fossil

fuels, we are faced with the challenge of developing new methods to synthesize, upscale production, and expand the diversity of these commodity polyurethane monomers from alternative feedstocks.

1.4 Goals and Summary of Project

With the ever-growing pressure to move away from nonrenewable resources, attention needs to shift towards renewable resources as feedstocks to polyurethane materials that have transformed modern life. Prehistoric plants and organisms have taken millions of years under high pressure to decompose into the natural gases, oils, and coal that polyurethane material productions rely on today.[18] Rather than wait millions of years, it would be opportunistic to exploit biomass as a renewable source to access the aryl monomers required for the expanding demand of polyurethane products. I sought to synthesize a novel aromatic diisocyanate inspired by naturally abundant compounds derived from lignin biomass in hopes that it inspires the future use of renewable resources as feedstock and scaffolds to expand the diisocyanate monomers used in polyurethane materials. This project aims to leverage well-established synthetic methodologies and apply them to access a novel aromatic diisocyanate structure and investigate alternative renewable sources as starting materials which are discussed in Chapter 2.

1.4.1 Inspiration from Natural Products

The current starting materials, BTX, in the well-established phosgenation process for aryl diisocyanate compounds has shown great success from only a handful of monomers used in polyurethane products. This lack of structural diversity offers opportunities to expand the existing library of monomers and offer alternative pathways from different feedstocks.

Aromatic amines, also known as anilines, are the precursors that undergo phosgenation to access diisocyanates and are produced from chemical industries like oil refining, diesel exhaust, and tobacco smoke.[19] They can also be synthesized through well-established cross-coupling

reactions but oftentimes require expensive reagents, designer ligands, and functionalized starting materials derived from the same petrochemical feedstocks.[20]

On the other hand, phenolic compounds derived from lignin biomass are naturally abundant and are not limited in structural diversity.[21] Many naturally occurring phenols share structural similarities with existing aryl diisocyanates and could also serve as inspiration for novel isocyanates (Figure 1-5).[22] Specifically, 3,5-dihydroxy-1,1´-biphenyl offers a unique structure that has an additional aryl unit, like MDI, but functional group linkage similar to TDI. A diisocyanate with this structure has never been reported and could result in polyurethane materials with added rigidity due to the additional aryl group and form crystalline structures.[23] This phenolic compound can be biosynthetically produced from *E. coli* and may offer an alternative pathway utilizing a renewable resource to access the corresponding novel aromatic diisocyanate precursor.[24]

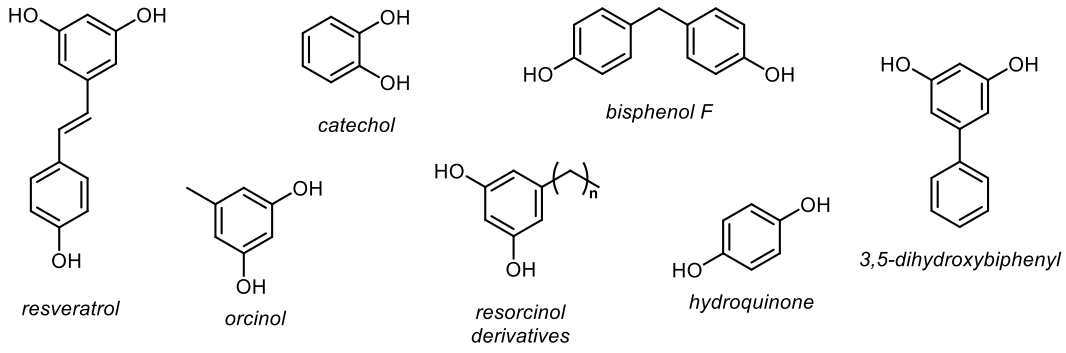


Figure 1-5. Examples of Naturally Abundant Phenols

Although some research has established that phenols can be directly converted to anilines, there has been limited application in expanding the scope of phenolic compounds and applying them in the synthesis of new polyurethane monomers.[25] These naturally occurring phenols can also serve as inspiration to switch to bio-renewable polyurethane building blocks that will lower the environmental footprint.

1.5 REFERENCES

1) Ionescu, M. *Chemistry and Technology of Polyols for Polyurethanes*, Second edition.; Smithers Rapra: Shawbury, 2016.

2) Recycling of Polyurethanes from Laboratory to Industry, a Journey towards the Sustainability. *Waste Manag.* **2018**, *76*, 147–171. https://doi.org/10.1016/j.wasman.2018.03.041.

3) Sonnenschein, M. F. *Polyurethanes: Science, Technology, Markets, and Trends*; John Wiley & Sons, 2021.

4) a) Zeece, M. *Introduction to the Chemistry of Food*; Academic Press, 2020. b) Zeng, H.; Qiu, Z.; Domínguez-Huerta, A.; Hearne, Z.; Chen, Z.; Li, C.-J. An Adventure in Sustainable Cross-Coupling of Phenols and Derivatives via Carbon–Oxygen Bond Cleavage. *ACS Catal.* **2017**, *7* (1), 510–519. https://doi.org/10.1021/acscatal.6b02964. c) Gómez-Jiménez-Aberasturi, O.; Ochoa-Gómez, J. R. New Approaches to Producing Polyols from Biomass. *J. Chem. Technol. Biotechnol.* **2017**, *92* (4), 705–711. https://doi.org/10.1002/jctb.5149. d) Sonnenschein, M. F.; Wendt, B. L. Design and Formulation of Soybean Oil Derived Flexible Polyurethane Foams and Their Underlying Polymer Structure/Property Relationships. *Polymer* **2013**, *54* (10), 2511–2520. https://doi.org/10.1016/j.polymer.2013.03.020.

5) Chiacchiarelli, L. M. 8 - Sustainable, Nanostructured, and Bio-Based Polyurethanes for Energy-Efficient Sandwich Structures Applied to the Construction Industry. In *Biomass, Biopolymer-Based Materials, and Bioenergy*; Verma, D., Fortunati, E., Jain, S., Zhang, X., Eds.; Woodhead Publishing Series in Composites Science and Engineering; Woodhead Publishing, 2019; pp 135–160. https://doi.org/10.1016/B978-0-08-102426-3.00008-4.

6) Gama, N. V.; Ferreira, A.; Barros-Timmons, A. Polyurethane Foams: Past, Present, and Future. *Materials* **2018**, *11* (10), 1841. https://doi.org/10.3390/ma11101841.

7) Zevenhoven, R. Treatment and Disposal of Polyurethane Wastes: Options for Recovery and Recycling. **2004**.

8) *Polyurethane Applications*. American Chemistry Council. https://www.americanchemistry.com/industry-groups/center-for-the-polyurethanes-industry-cpi/applications-benefits/polyurethane-applications (accessed 2023-07-28).

9) a) Jenkines, R. C. Polyurethane Carpet-Backing Process Based on Soft Segment Prepolymers of Diphenylmethane Diisocyanate (MDI). US5104693A, April 14, 1992. https://patents.google.com/patent/US5104693A/en (accessed 2023-07-29). b) Mcgovern, M. J. High Resiliency Polyurethane Foams with Improved Static Fatigue Properties. CA2073584A1, January 18, 1993. https://patents.google.com/patent/CA2073584A1/en (accessed 2023-07-29). c) Favstritsky, N. A.; Rose, R. S.; Borden, D. M.; Honkomp, D. J. Flame Retardant Polyurethane Foam Compositions Containing Polynuclearbrominated Alkylbenzene. US4892892A, January 9, 1990.

https://patents.google.com/patent/US4892892A/sv (accessed 2023-07-29). d) Joubert, M. D. Flexible Polyurethane Foams Having Junction Modifying Particulate Additives. DE3269142D1, March 27, 1986. https://patents.google.com/patent/DE3269142D1/en (accessed 2023-07-29).

10) *MDI and TDI: A Safety, Health and the Environment: A Source Book and Practical Guide*; Allport, D. C., Gilbert, D. S., Outterside, S. M., Eds.; J. Wiley: New York, 2003.

11) Six, C.; Richter, F. Isocyanates, Organic. In *Ullmann's Encyclopedia of Industrial Chemistry*; John Wiley & Sons, Ltd, 2003. https://doi.org/10.1002/14356007.a14_611.

12) Gong, W. H. BTX from Lignin. In *Industrial Arene Chemistry*; John Wiley & Sons, Ltd, 2023; pp 1859–1907. https://doi.org/10.1002/9783527827992.ch60.

13) Shafiee, S.; Topal, E. When Will Fossil Fuel Reserves Be Diminished? *Energy Policy* **2009**, *37* (1), 181–189. https://doi.org/10.1016/j.enpol.2008.08.016.

14) CHATURVEDI, D. Perspectives on the Synthesis of Organic Carbamates. *Perspect. Synth. Org. Carbamates* **2012**, *68* (1), 1, 15-45 [32 p.].

15) Amendola, V.; Fabbrizzi, L.; Mosca, L. Anion Recognition by Hydrogen Bonding: Urea-Based Receptors. *Chem. Soc. Rev.* **2010**, *39* (10), 3889–3915. https://doi.org/10.1039/B822552B.

16) Kreye, O.; Mutlu, H.; Meier, M. A. R. Sustainable Routes to Polyurethane Precursors. *Green Chem.* **2013**, *15* (6), 1431. https://doi.org/10.1039/c3gc40440d.

17) Cawse, J. L.; Stanford, J. L.; Still, R. H. Polymers from Renewable Sources, 1. Diamines and Diisocyanates Containing Difurylalkane Moieties. *Makromol. Chem.* **1984**, *185* (4), 697–707. https://doi.org/10.1002/macp.1984.021850408.

18) Hubbert, M. K. Energy from Fossil Fuels. *Science* **1949**, *109* (2823), 103–109. https://doi.org/10.1126/science.109.2823.103.

19) Pereira, L.; Mondal, P. K.; Alves, M. Aromatic Amines Sources, Environmental Impact and Remediation. In *Pollutants in Buildings, Water and Living Organisms*; Lichtfouse, E., Schwarzbauer, J., Robert, D., Eds.; Environmental Chemistry for a Sustainable World; Springer International Publishing: Cham, 2015; pp 297–346. https://doi.org/10.1007/978-3-319-19276-5_7.

20) a) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116* (19), 12564–12649. https://doi.org/10.1021/acs.chemrev.6b00512. b) Shen, Q.; Ogata, T.; Hartwig, J. F. Highly Reactive, General and Long-Lived Catalysts for Palladium-Catalyzed Amination of Heteroaryl and Aryl Chlorides, Bromides, and Iodides: Scope and Structure–Activity Relationships. *J. Am. Chem. Soc.* **2008**, *130* (20), 6586–6596. https://doi.org/10.1021/ja077074w. c) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. Highly Reactive, General, and Long-Lived Catalysts for Coupling Heteroaryl and Aryl

Chlorides with Primary Nitrogen Nucleophiles. *Angew. Chem. Int. Ed Engl.* **2005**, *44* (9), 1371–1375. https://doi.org/10.1002/anie.200462629. d) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Triflates and Importance of Triflate Addition Rate. *J. Org. Chem.* **1997**, *62* (5), 1268–1273. https://doi.org/10.1021/jo961930x. e) Paul, F.; Patt, J.; Hartwig, J. F. Palladium-Catalyzed Formation of Carbon-Nitrogen Bonds. Reaction Intermediates and Catalyst Improvements in the Hetero Cross-Coupling of Aryl Halides and Tin Amides. *J. Am. Chem. Soc.* **1994**, *116* (13), 5969–5970. https://doi.org/10.1021/ja00092a058. f) Sun, H.-B.; Gong, L.; Tian, Y.-B.; Wu, J.-G.; Zhang, X.; Liu, J.; Fu, Z.; Niu, D. Metal- and Base-Free Room-Temperature Amination of Organoboronic Acids with N-Alkyl Hydroxylamines. *Angew. Chem. Int. Ed Engl.* **2018**, *57* (30), 9456–9460. https://doi.org/10.1002/anie.201802782. g) Chatterjee, N.; Goswami, A. Metal and Base Free Synthesis of Primary Amines via Ipso Amination of Organoboronic Acids Mediated by [Bis(Trifluoroacetoxy)Iodo]Benzene (PIFA). *Org. Biomol. Chem.* **2015**, *13* (29), 7940–7945. https://doi.org/10.1039/C5OB01070E.

21) a) Li, C.; Zhao, X.; Wang, A.; Huber, G. W.; Zhang, T. Catalytic Transformation of Lignin for the Production of Chemicals and Fuels. *Chem. Rev.* **2015**, *115* (21), 11559–11624. https://doi.org/10.1021/acs.chemrev.5b00155. b) Upton, B. M.; Kasko, A. M. Strategies for the Conversion of Lignin to High-Value Polymeric Materials: Review and Perspective. *Chem. Rev.* **2016**, *116* (4), 2275–2306. https://doi.org/10.1021/acs.chemrev.5b00345.

22) a) Koushki, M.; Amiri-Dashatan, N.; Ahmadi, N.; Abbaszadeh, H.; Rezaei-Tavirani, M. Resveratrol: A Miraculous Natural Compound for Diseases Treatment. *Food Sci. Nutr.* **2018**, *6* (8), 2473–2490. https://doi.org/10.1002/fsn3.855. b) Cheng, H. A.; Drinnan, C. T.; Pleshko, N.; Fisher, O. Z. Pseudotannins Self-Assembled into Antioxidant Complexes. *Soft Matter* **2015**, *11* (39), 7783–7791. https://doi.org/10.1039/C5SM01224D. c) Suzuki, Y.; Esumi, Y.; Yamaguchi, I. Structures of 5-Alkylresorcinol-Related Analogues in Rye. *Phytochemistry* **1999**, *52* (2), 281–289. https://doi.org/10.1016/S0031-9422(99)00196-X. d) Mozaffari, P.; Järvik, O.; Baird, Z. S. Vapor Pressures of Phenolic Compounds Found in Pyrolysis Oil. *J. Chem. Eng. Data* **2020**, *65* (11), 5559–5566. https://doi.org/10.1021/acs.jced.0c00675. e) Huang, T.; Danaher, L.-A.; Brüschweiler, B. J.; Kass, G. E. N.; Merten, C. Naturally Occurring Bisphenol F in Plants Used in Traditional Medicine. *Arch. Toxicol.* **2019**, *93* (6), 1485–1490. https://doi.org/10.1007/s00204-019-02442-5. f) Giner, R. M.; Ríos, J. L.; Máñez, S. Antioxidant Activity of Natural Hydroquinones. *Antioxidants* **2022**, *11* (2), 343. https://doi.org/10.3390/antiox11020343. g) Humans, I. W. G. on the E. of C. R. to. Catechol. In *Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide*; International Agency for Research on Cancer, 1999.

23) a) Song, Y. M.; Chen, W. C.; Yu, T. L.; Linliu, K.; Tseng, Y. H. Effect of Isocyanates on the Crystallinity and Thermal Stability of Polyurethanes. *J. Appl. Polym. Sci.* **1996**, *62* (5), 827–834. https://doi.org/10.1002/(SICI)1097-4628(19961031)62:5<827::AID-APP15>3.0.CO;2-P. b) Vasil'ev, V. V.; Tarakanov, O. G.; Dyemina, A. I.; Shirobokova, A. I. Crystallization Study of Polyurethanes. *Polym. Sci. USSR* **1966**, *8* (5), 1031–1038. https://doi.org/10.1016/0032-3950(66)90215-2.

24) Chizzali, C.; Beerhues, L. Phytoalexins of the Pyrinae: Biphenyls and Dibenzofurans. *Beilstein J. Org. Chem.* **2012**, *8* (1), 613–620. https://doi.org/10.3762/bjoc.8.68

25) a) Lardy, S. W.; Luong, K. C.; Schmidt, V. A. Formal Aniline Synthesis from Phenols through Deoxygenative N-Centered Radical Substitution. *Chem. – Eur. J.* **2019**, *25* (67), 15267–15271. https://doi.org/10.1002/chem.201904288. b) Holden, C. M.; Greaney, M. F. Modern Aspects of the Smiles Rearrangement. *Chem. – Eur. J.* **2017**, *23* (38), 8992–9008. https://doi.org/10.1002/chem.201700353. c) Qiu, Z.; Lv, L.; Li, J.; Li, C.-C.; Li, C.-J. Direct Conversion of Phenols into Primary Anilines with Hydrazine Catalyzed by Palladium. *Chem. Sci.* **2019**, *10* (18), 4775–4781. https://doi.org/10.1039/C9SC00595A. d) Cuypers, T.; Tomkins, P.; Vos, D. E. D. Direct Liquid-Phase Phenol-to-Aniline Amination Using Pd/C. *Catal. Sci. Technol.* **2018**, *8* (10), 2519–2523. https://doi.org/10.1039/C8CY00193F. e) Ono, Y.; Ishida, H. Amination of Phenols with Ammonia over Palladium Supported on Alumina. *J. Catal.* **1981**, *72* (1), 121–128. https://doi.org/10.1016/0021-9517(81)90083-X. f) Barker, R. S. Preparation of Aminated Benzenes from Hydroxy Benzenes. US3272865A, September 13, 1966. https://patents.google.com/patent/US3272865A/en (accessed 2023-07-29). g) Becker, M.; Khoobiar, S. Process for the Production of Organic Amines. US3860650A, January 14, 1975. https://patents.google.com/patent/US3860650A/en (accessed 2023-07-29). h) Yasuhara, M.; Matsunaga, F. Preparation of Anilines. US4987260A, January 22, 1991. https://patents.google.com/patent/US4987260A/ko (accessed 2023-07-29).

Chapter 2

2.1 Aryl Carbon – Nitrogen Bond Forming Strategies

Carbon-nitrogen bond forming reactions are paramount in synthetic chemistry. Specifically, aromatic amines are invaluable motifs found in pharmaceuticals, natural products, agrochemicals, and materials for polyurethanes.[1] Anilines, essential precursors to polyurethane monomers, are typically synthesized through the 2-step nitration-reduction sequence, as described earlier. However, there is little structural diversity in naturally abundant aromatic amines. Phenols, a type of aromatic alcohol, on the other hand, are plentiful in nature and can serve as valuable precursors to forge aryl carbon-nitrogen bonds. Direct amination of phenols is the ideal reaction sequence to convert these naturally abundant and diverse oxygenated aromatic building blocks to their respective anilines. While some of these methods are established and used in industry for accessing anilines, they require harsh conditions, are limited in scope, and are challenging to carry-out using non-specialized reaction vessels.[2]

Transition metal-catalyzed cross-coupling reactions are another excellent synthetic strategy for the formation of aryl C-N bonds. While some of these reactions can transform aryl C-O bonds to aryl C-N bonds, there are still limitations in scope and the starting materials are generally derived from petrochemical sources. These bonds can also be formed through intramolecular nucleophilic substitution processes known as the Smiles rearrangement. Radical approaches to forming aryl carbon-nitrogen bonds from aryl carbon-oxygen bonds can also be done through radical Smiles type rearrangements. In this chapter, several well-established aryl C-N bond forming reactions are discussed and then applied to a particular catechol to access a bis-aniline en route to a novel aromatic diisocyanate.

2.1.1 Cross – Coupling Reactions

Aryl C-N bonds can be formed through transition metal catalyzed cross-coupling methods developed by Buchwald, Hartwig, Ullmann, Chan, and Lam which utilize nitrogen-containing nucleophiles with functionalized aryls (Figure 2-1).[3] These functionalized starting materials include aryl halides, pseudo halides, and boronic esters. While these methods have been transformative and useful to forge aryl C-N bonds, the required functionalized aryls are typically accessed via undesirable routes. Aryl halides can easily be formed through the halogenation of the desired aryl compounds derived from petrochemical feedstocks and serve as precursors to aryl Grignard and aryl lithium reagents that further react with trialkyl borates to yield boronic esters.[4]

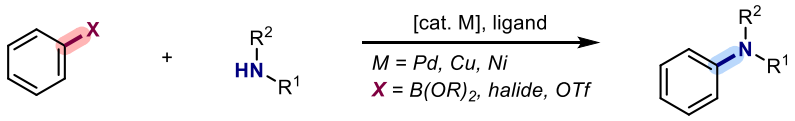


Figure 2-1. General Cross-coupling Reaction to Access Anilines

Many phenol-derived electrophile partners have been successfully used in cross-coupling reactions, however, due to the inherent C-O bond strength and susceptibility of acidic phenolic hydroxyl groups to undergo other transformations, phenols on their own are not suitable in these reactions unless they are converted to activated and nonactivated sulfonate leaving groups.[5] Phenols can be converted to aryl triflates, tosylates, mesylates, as well as esters, carbamates, and ethers. Aryl triflate synthesis requires triflic anhydride or its derivatives and their coupling with amines represents an established method to forge C-N bonds from C-O bonds using transition metal catalysts like nickel and palladium but oftentimes require designer ligands and have a limited scope.[6] Some modifications can be made in nickel-catalyzed aminations, such as using aryl tosylates or aryl methyl ethers, but these methods are further limited in scope as they are not applicable to primary amines or anilines and require excess designer ligand to promote coupling.[7]

Recently, Shi and colleagues reported a rhodium-catalyzed amination of phenols and while this method does not require further functionalization, it suffers greatly when it comes to scope as it is largely limited to secondary and tertiary amines (Figure 2-2).[8] Additionally, the reaction had limited success when additional hydroxyl groups were present. Cross-coupling methods represent an established method to access valuable aryl C-N bonds, but the necessity of petrochemical-derived functional aryls poses another challenge as fossil fuels are a nonrenewable resource. Further research should shift focus to functionalizing naturally abundant phenolic compounds and expand their applicability as cross-coupling partners with amines.

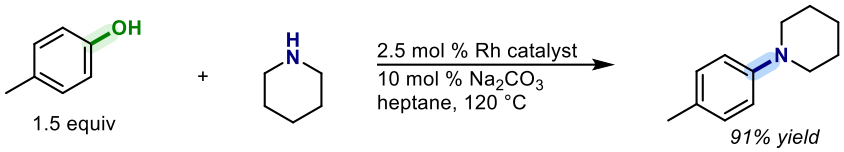


Figure 2-2. Rhodium Catalyzed Amination of Phenols

2.1.2 Direct Amination of Phenols

Since phenolic compounds can be obtained from bio-renewable lignin feedstock, the direct conversion of phenols to anilines would be the ideal preparation for aromatic diisocyanate precursors as it would diminish the reliance on petrochemical feedstocks and further expand the existing library of isocyanate monomers. Ammonolysis of phenols has been a common method used to directly convert phenols to anilines. In 1966, Halcon International Inc published the first process for amination of phenol in the gas phase (Figure 2-3).[9] This method uses Lewis acidic catalysts like SiO_2-Al_2O_3, TiO_2-Al_2O_3, ZrO_2-Al_2O_3, H_3PO_4, WO_3, or H_3PO_4, with up to 20 equivalents of ammonia, requires temperatures up to 600 °C and is applicable to minimally substituted phenols like cresols. A few years later, they reported a modified Al_2O_3 catalyst that expanded the applicability of direct amination to polyphenolic compounds, including naphthols, but still required harsh conditions.[10] In later years, improvements in Lewis acidic catalysts and

incorporation of palladium, niobium, and palladium-gold catalysts increased reaction efficiency by suppressing byproduct formation, lowered the reaction temperature, and in some cases lowered the pressure restrictions, but limited the scope to simple phenols.[11] Despite these advancements, the gas-phase transformation still suffers from the requirement of high temperatures, excess ammonia, and can only be applied to a short range of phenols.

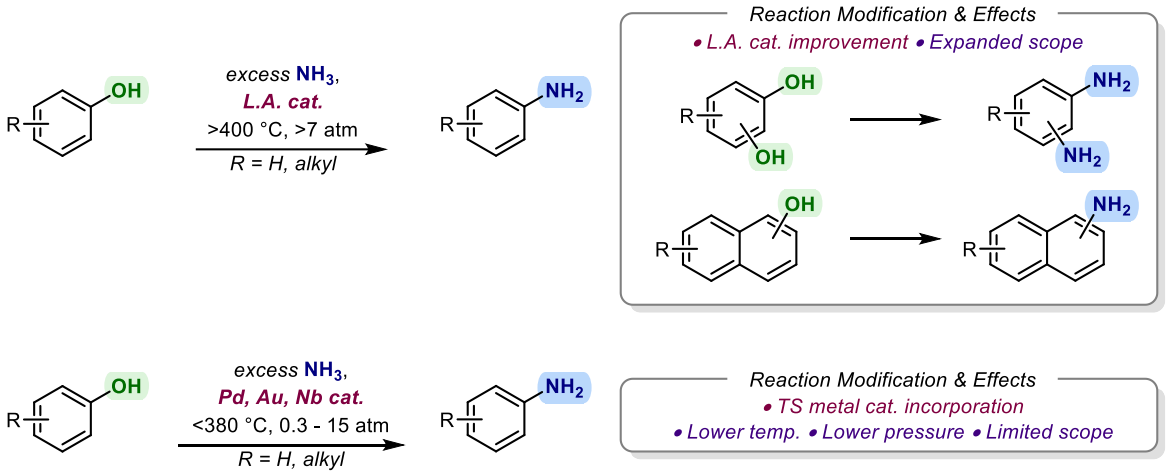


Figure 2-3. Gas-Phase Amination

De Vos was able to access primary anilines through a liquid phase method that directly aminated phenols using ammonia, hydrogen, and a Pd/C catalyst at 200 °C (Figure 2-4).[12] This novel method successfully accessed primary anilines without the significantly higher temperatures necessary to vaporize the phenolic compounds but suffered other drawbacks. To suppress the formation of side products, excess ammonia was crucial, and the substrate scope was only expanded to cresols which had decreased conversion and yield in comparison to phenol.

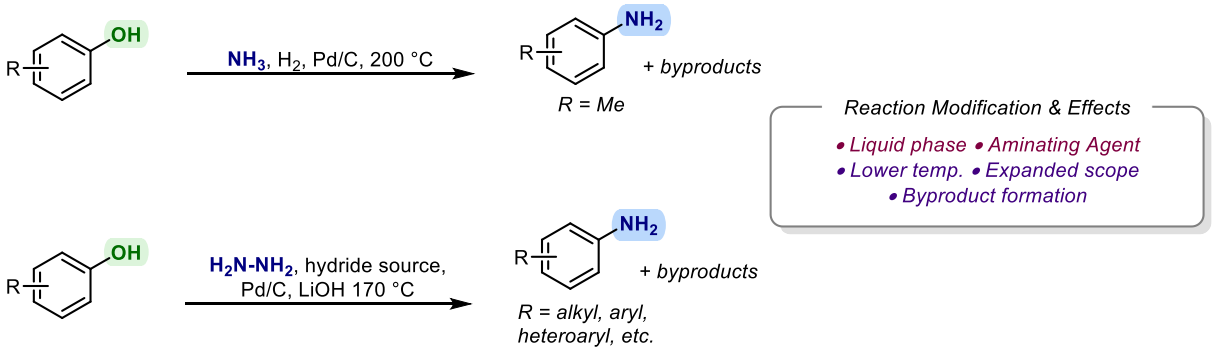


Figure 2-4. Liquid-Phase Amination

In 2019, Li and colleagues were able to overcome some of these hurdles and expand the scope of the reaction.[13] Optimized conditions lowered the reaction temperature to 170 °C, used hydrazine monohydrate as the amine and hydride source, and Pd/C as a catalyst. While this method was an improvement to the previous direct phenol to aniline transformations, their method had limited applicability to compounds with multiple aromatic OH linkages and had no success using lignin monomers as starting material.

2.1.3 Nucleophilic Aromatic Substitution

Nucleophilic aromatic substitutions are reactions in which a nucleophile displaces a leaving group on an aromatic ring. These reactions have historically been used to install aryl-heteroatom bonds, but these reactions have strict requirements to be successful. Strong bases and electron-withdrawing groups that are *ortho* and *para* to the leaving group are crucial.[14] Fluorides have been found to be the best leaving groups for S_NAr but the aryl fluorides accessed through harsh fluorination conditions are often limited in scope and selectivity.[15] Aryl C-N bond forming reactions have been successful when aryl halides with strong electron-withdrawing groups are reacted with strong bases and nucleophilic amines, including liquid ammonia.[16] These strict requirements have thus limited applicability when using oxygenated aromatics to access aryl C-N bonds.[17]

2.1.4 Smiles Rearrangement

Certain base-mediated nucleophilic aromatic substitution reactions, including Smiles rearrangements, offer a pathway to access aryl C-N bonds from phenols and phenol derivatives (Figure 2-5).[18] Smiles rearrangements have historically been exploited to form carbon-carbon or carbon-heteroatom bonds that are otherwise difficult to access if done intermolecularly. Specifically, Smiles rearrangements can undergo intramolecular N-nucleophilic substitution at an aryl C-O bond when done under basic conditions but tend to require electron-poor arenes.[19]

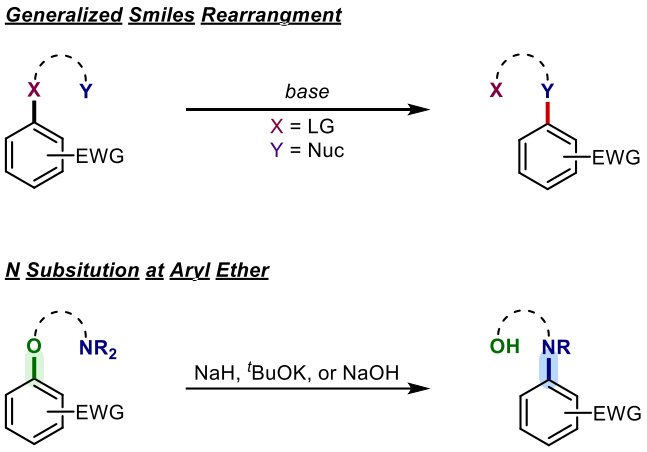


Figure 2-5. Smiles Rearrangement

Smiles-type rearrangements occurring through radical pathways are not as sensitive to electronic demands of the arene, but limited examples demonstrate utilization of N-centered radicals. These include silver or iridium catalysts assisting in facilitating aryl migration through cleavage of a C-C bond to forge a new aryl C-N bond.[20] In both examples of N-centered radical Smiles-type rearrangement, although not required, aryl migration occurred most efficiently with electron-rich arenes. While it is an attractive route to manipulate aryl ethers to access anilines, the strict electronic demands on the aryl ring for base-mediated rearrangements and limited applications through radical pathways suggest additional investigations are necessary.

2.1.5 Sequential Atom Transfer Radical Addition (SATRA)

The Sequential Atom Transfer Radical Addition (SATRA) methodology, previously developed in the Schmidt group, allows for the synthesis of anilines from phenols without the need for expensive reagents, toxic transition metals, or labor-intensive purification methods.[21] This process, mechanistically, starts through thermal radical initiation of the aryl hydroxamic acid **I** which are synthesized from functionalized phenols to produce amidoxyl radical species **II** (Figure 2-6). Through oxygen-atom transfer (OAT) with inexpensive triethyl phosphite, an amidyl radical species **III** is generated. This amidyl radical then undergoes *ipso* aryl ether addition to form the resonance-stabilized radical species **IV** which undergoes selective cleavage of the aryl C-O bond providing phenoxy radical species **V**. The cycle can then be propagated through hydrogen-atom transfer (HAT) between **V** and **I**. The resulting phenol **VI** can then be subjected to acid hydrolysis to release salicylic acid and the desired aniline product **VII**.

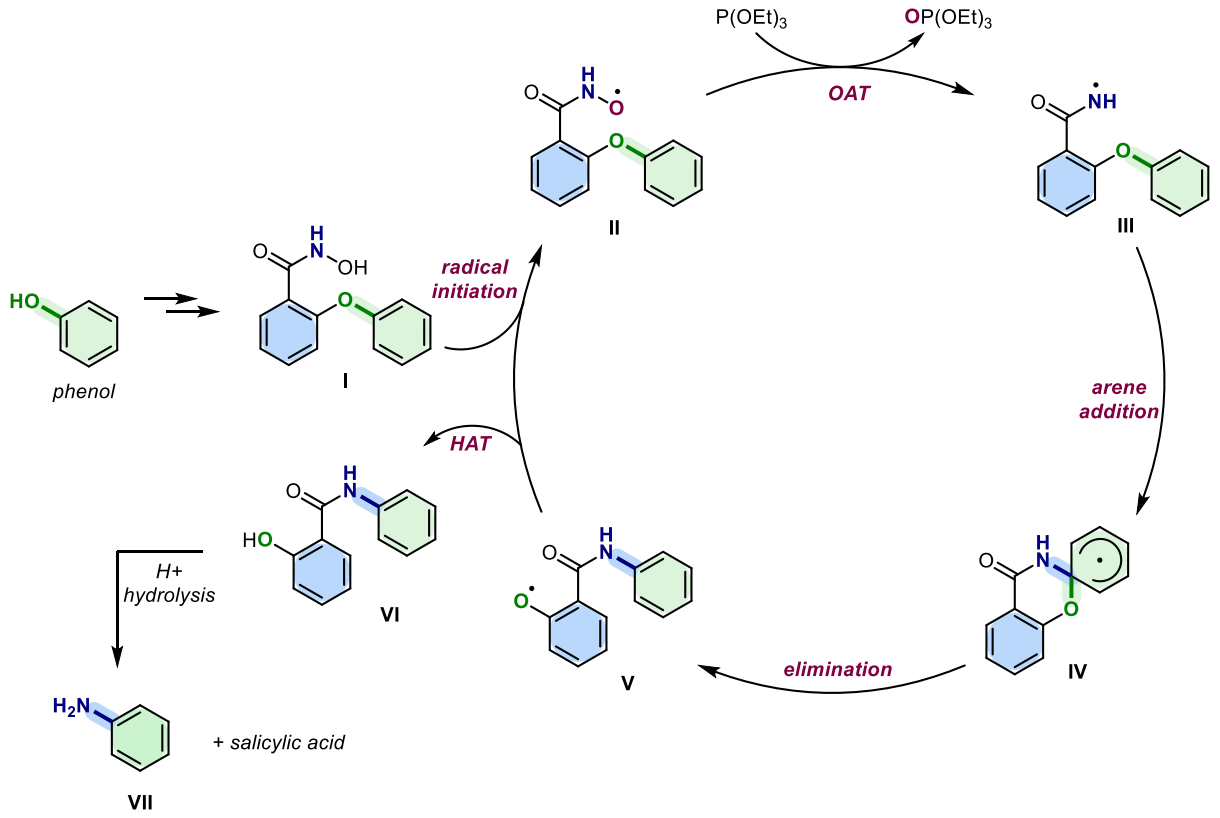


Figure 2-6. SATRA Mechanism

This reaction was found to be unaffected by the electronic demands of the arene, being able to successfully convert both electron-rich and electron-deficient arenes in high yield and could also tolerate polyphenolic substrates. This process, applied to targeted arenes can be implemented to scaleup process from phenol to diisocyanate for polyurethane development.

2.2 Objective of this work

With the current success of MDI & TDI in the polyurethane industry, I hypothesized that similarly structured aromatic diisocyanates have the potential to succeed in the industry. As noted, there is a significant limitation in structures of the currently produced aromatic diisocyanates that are primarily used in the polyurethane industry. The objective of this research looks to leverage already established synthetic methodologies and apply them towards the synthesis of the novel aromatic diisocyanate 3,5-diisocyanto-1,1'-biphenyl (**5**) inspired from bio-sources. I hope this

work encourages further research into using bio-sourced molecules as models and feedstocks to expand the library of aromatic isocyanates used in polyurethane development.

2.3 Results & Discussion

Initial efforts to synthesize **5** first investigated methods to access the precursor 3,5-diamino-1,1'-biphenyl (**4**) that could be subjected to phosgenation to access the isocyanate functionality (Figure 2-7). Ideally, a route to directly convert 3,5-dihydroxy-1,1'-biphenyl (**2**) to its corresponding aniline could limit the requisite synthetic steps and provide an avenue to further expand the application to various naturally abundant polyphenolic compounds. Due to the scalability, applicability, and use of mild inexpensive reagents, SATRA serves as the most attractive route to access the aniline precursor (Route 1, Figure 2-7). Additionally, there are a multitude of established methods to directly aminate phenols, and Li's relatively mild reaction conditions could serve as another avenue to quickly access **4** (Route 2, Figure 2-7). Looking past using **2** as the starting material, the reduction of 3,5-dinitro-1,1'-biphenyl (**3**) would also give access to the precursor (Route 3, Figure 2-7). In each of these cases, triphosgene is used as the safer phosgenation agent substitute to mimic the traditional industrial route which uses phosgene gas to access aromatic isocyanates. Alternatively, Curtius rearrangement of acyl azides can serve as a different pathway to access isocyanate functionality and I envisioned this could also be applied to synthesize **5** (Route 4, Figure 2-7).

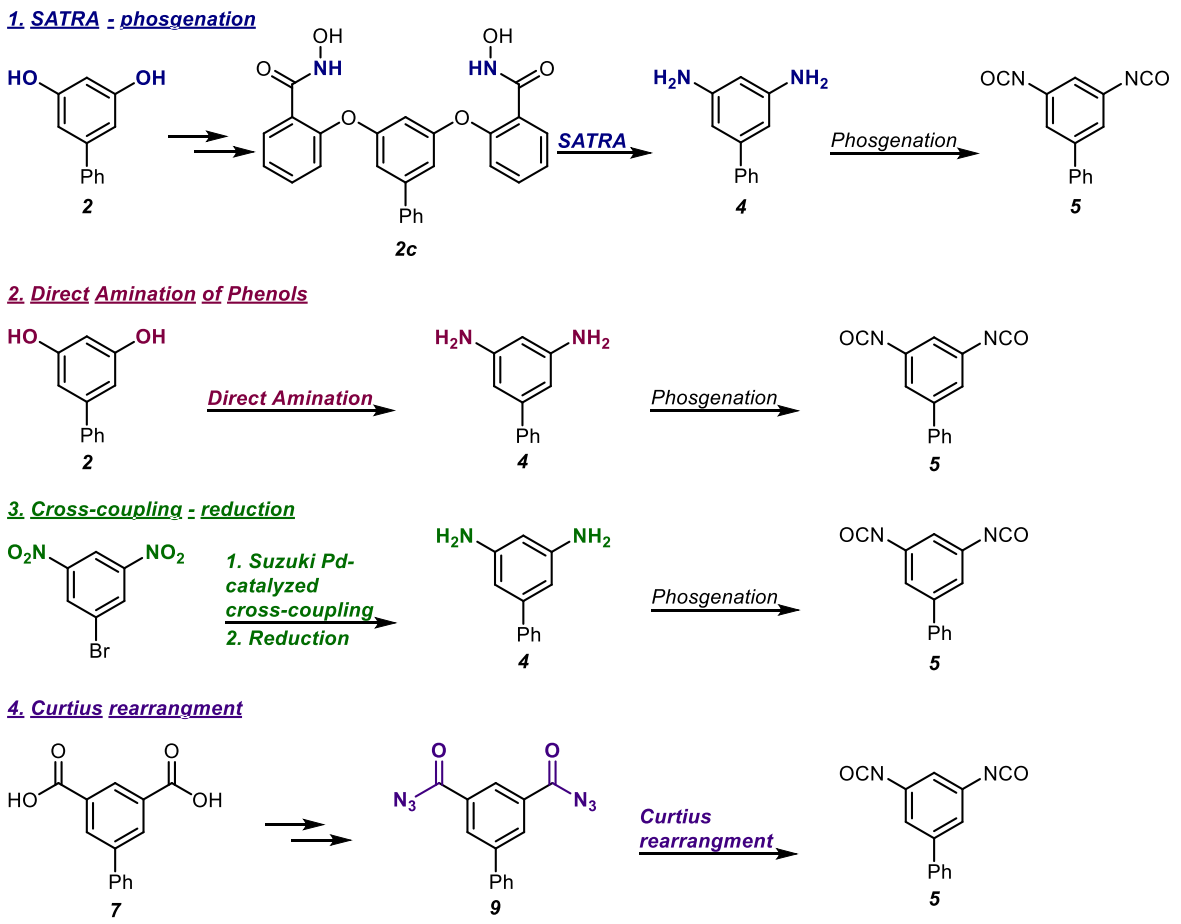


Figure 2-7. Routes to Aromatic Diisocyanate

2.3.1 Route 1: SATRA

Initial investigations were focused on reproducing expected results on bis-phenolic model substrates of resorcinol and orcinol. These model substrates were identified because of the hydroxy moieties in *meta* positions with respect to each other, like the target phenol. Previously, hydroxamic acids were synthesized from the corresponding carboxylic acids. These carboxylic acids were obtained through first, copper-catalyzed cross-coupling reaction of the phenol and 2-iodobenzoic acid, followed by amide bond formation using various *N*-hydroxylamines. Using the model substrates, this synthetic route was modified to eliminate the cross-coupling reaction and instead replace it with a two-step series of reactions: nucleophilic aromatic substitution followed by basic hydrolysis to afford carboxylic acids (Figure 2-8). While these methods increased the

number of reaction steps, it removed the necessity for a copper catalyst while still maintaining high yields. Amide formation was similarly achieved using *N*-phenylhydroxylamine and *N*-hydroxylamine but encountered unfortunate solubility issues in the process. Nevertheless, I was eager to apply these optimized reaction conditions to access the necessary precursors for SATRA with **2**.

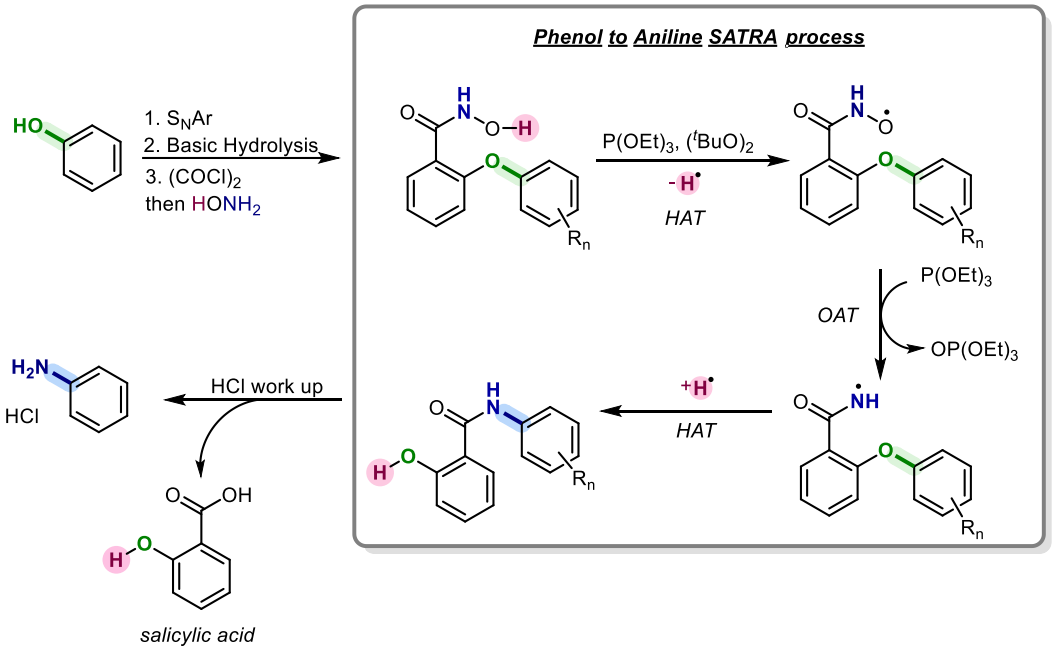


Figure 2-8. SATRA Phenol to Aniline Method

It was found that the target phenol could be synthesized through the dehydrogenative aromatization of the corresponding diketone species 5-phenylcyclohexane-1,3-dione (**1**) (Figure 2-9).[22] This phenolic compound was then subjected to optimized conditions to obtain the corresponding nitrile 2,2'-([1,1'-biphenyl]-3,5-diylbis(oxy))dibenzonitrile (**2a**), carboxylic acid 2,2'-([1,1'-biphenyl]-3,5-diylbis(oxy))dibenzoic acid (**2b**), and hydroxamic acid 2,2'-([1,1'-biphenyl]-3,5-diylbis(oxy))bis(N-hydroxybenzamide) (**2c**). Upon conversion of **2b** to **2c**, similar solubility issues were apparent that made the path forward unviable and while the desired hydroxamic acid was detected by mass spectrometry (MS) it otherwise could not be purified or

isolated. Due to the ongoing challenges in synthesizing the precursors for the following SATRA steps, it was decided to investigate other avenues. While this method has been successfully applied to several other polyphenolic compounds, the intermediates' structures here exhibited tricky solubility profiles that made them unsuitable for this transformation. Regardless, this method could still be utilized with other phenolic compounds to synthesize polyurethane precursors from renewable sources.

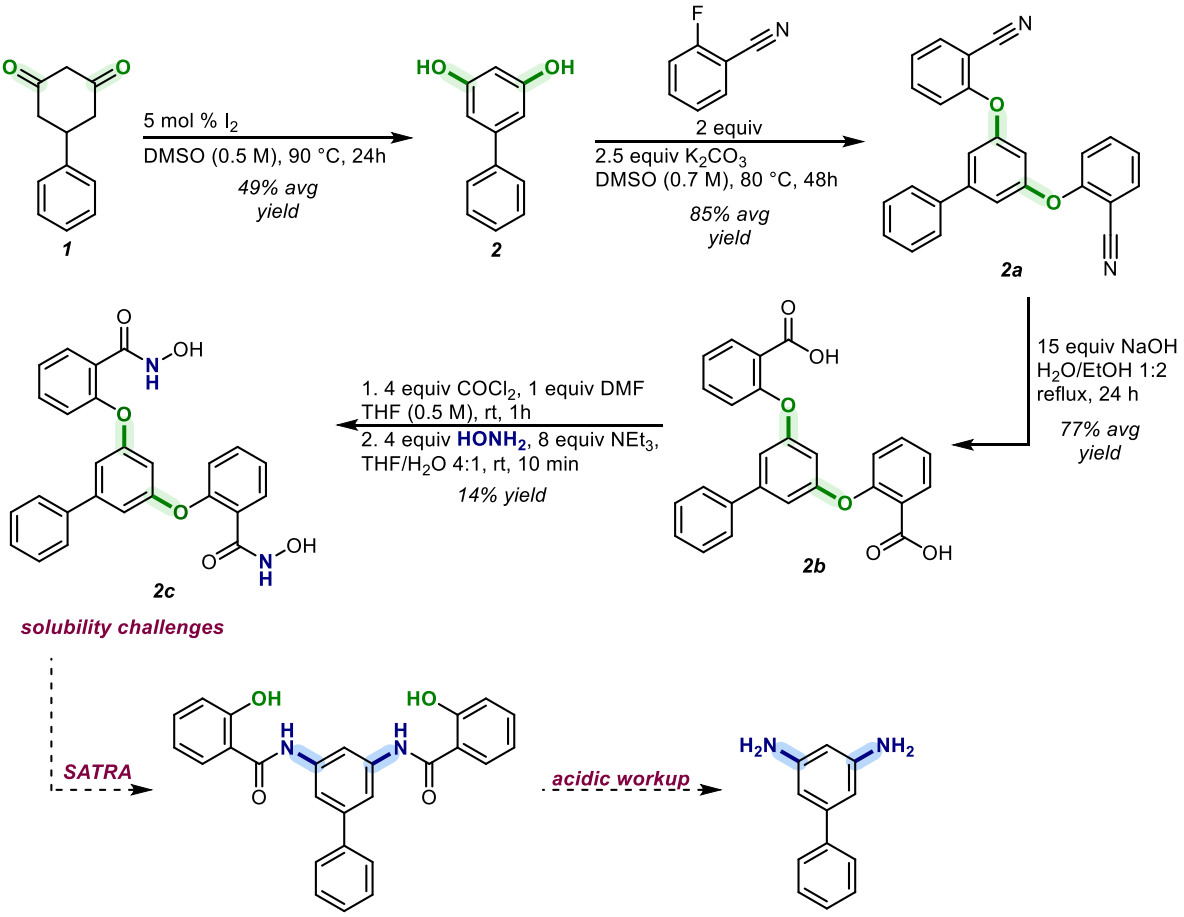


Figure 2-9. Precursor Synthesis for SATRA

2.3.2 Route 2: Replication of Li's Direct Phenol To Aniline Method

Li's published work converting various phenolic compounds to their corresponding anilines with relatively mild conditions, compared to previously developed methods, was an interesting avenue I wanted to investigate on **2**. General optimized conditions (Figure 2-10) use an

excess of hydrazine hydrate, palladium catalyst, lithium hydroxide additive, and heated to 170 °C in an inert environment with molecular sieves to remove any water released in this reaction. **2** was then subjected to similar reaction conditions that were tailored to multi-OH substrates, but no conversion of starting material was observed. Phenol was also subject to these conditions and similarly, no conversion was observed.

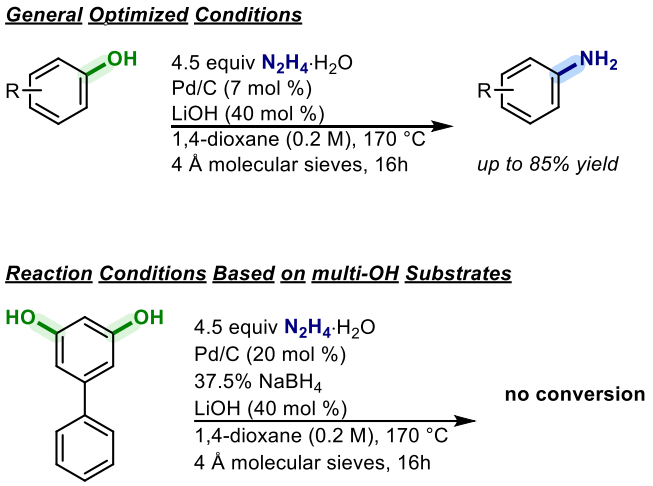


Figure 2-10. Direct Phenol to Aniline Reaction Applied to Target Phenol

Direct phenol to aniline methods have been shown to be difficult reactions unless done under harsh conditions so it is no surprise that this method has proved to be challenging. While these reaction conditions have seen enhancements to less harsh methods and reaction efficiency improved in expanded scopes of phenolic compounds, there is still room for improvement as there are limitations when it comes to phenolic compounds with multiple aryl-OH groups.

2.3.3 Route 3: Accessing Target Aniline Through Traditional Halogenation, Cross-Coupling, and Reduction Methods.

An alternative route that can be used to obtain the desired diamine compound is through reduction of the corresponding nitro compound. It was envisioned that **3** could be obtained through a 2-step reaction sequence initiating from bromination of 1,3-dinitrobenzene to access the requisite aryl halide which could undergo Suzuki-Miyaura palladium-catalyzed cross-coupling with

phenylboronic acid (Figure 2-11).[23] There are a multitude of established reduction reactions of aryl-nitro compounds and after screening multiple different reduction conditions, it was determined that the best condition was with hydrazine monohydrate with Pd/C as a catalyst (Table 2-1).[24]

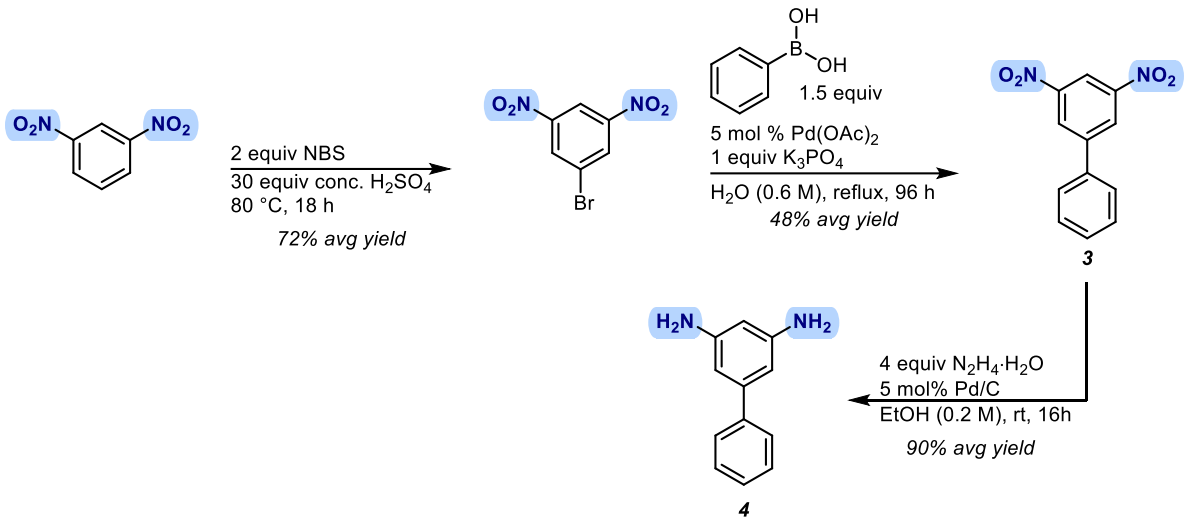
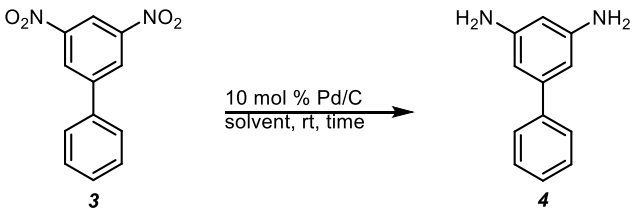


Figure 2-11. Accessing Aniline Through Traditional Synthetic Methods

Table 2-1 Reduction Reaction Screening



Entry	Reducing Agent (equiv)	Solvent (Conc.)	Time	Scale mmol	Isolated Yield
1[a]	H_2	MeOH (0.4 M)	43 h	1.0 mmol	72%
2	NH_4CO_2 (10 equiv)	EtOH (0.17M)	43 h	0.4 mmol	0%
3[b]	$SnCl_2$ (14 equiv)	MeOH (0.1 M)	2 h	0.4 mmol	37%
4	$N_2H_4{\cdot}H_2O$ (4 equiv)	EtOH (0.17 M)	16 h	2.4 mmol	93%

[a] H_2 atmosphere [b]no catalyst, 64 °C

Triphosgene, a phosgenation agent, is a substitute of phosgene gas that has had success at synthesizing isocyanates at laboratory scale.[25] It is a crystalline solid at room temperature and is

easier and safer to transport and store than phosgene gas or liquid diphosgene.[26] With **4** in hand, I began phosgenation reactions to access **5**. Multiple different solvents, including ethyl acetate, dichloromethane, chloroform, and dichloroethane, were screened and reactions were monitored by infrared (IR) spectroscopy to detect formation of the isocyanate functionality. IR spectroscopy revealed a sharp stretch at 2260, consistent with similar aromatic isocyanate NCO stretches, and confirmed product by MS (Figure 2-12).[27] Unfortunately, these reactions revealed numerous byproducts that made isolation and purification of the desired diisocyanate difficult. Analysis of MS data from the crude reaction mixtures identified multiple urea-type byproducts formed as the isocyanates *in situ* reacted with anilines. I hypothesized that the presence of water in the solvents and atmosphere increased the likelihood for decomposition of the isocyanate to form carbamic acids that could then further decompose to reform the aniline and release CO_2.

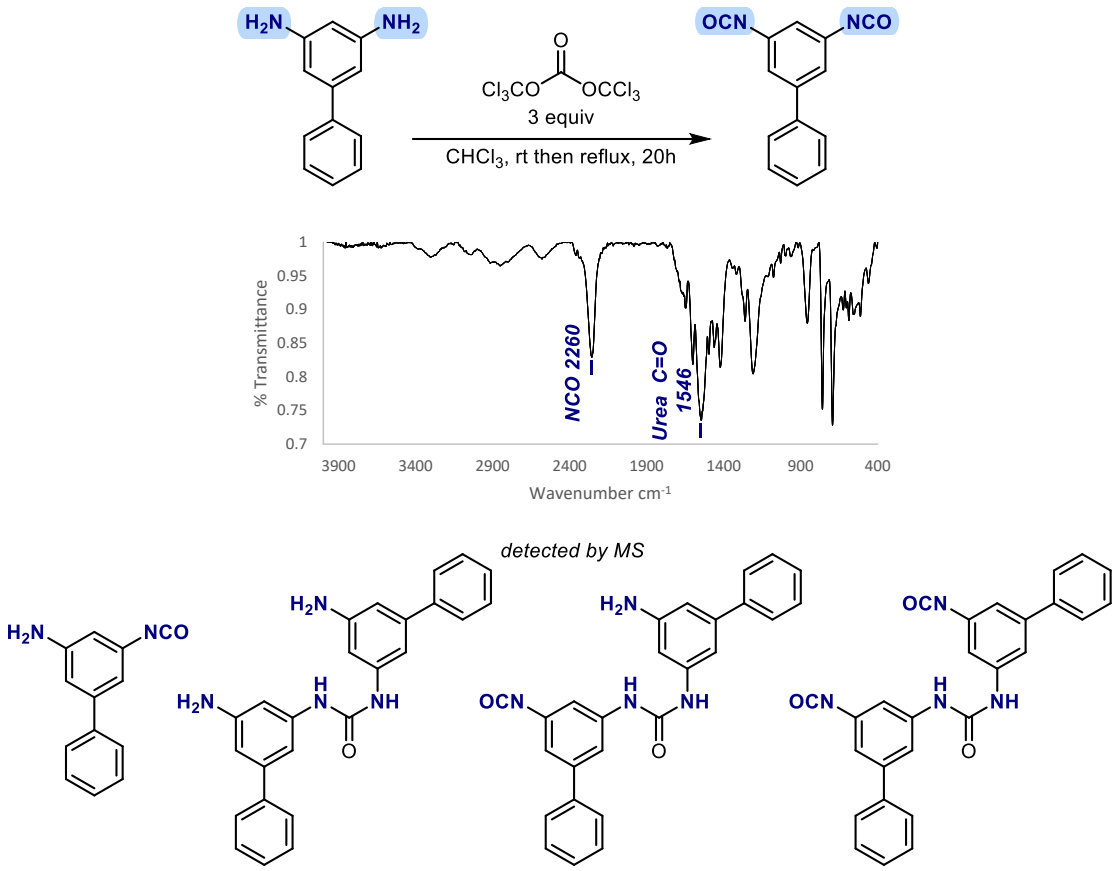


Figure 2-12. Phosgenation of Bis-Aniline and Urea Byproducts

For later phosgenation attempts, solvents were rigorously dried, and reactions were performed under inert conditions, but the formation of urea side products was still present. Other efforts to minimize these intermolecular reactions, such as increasing equivalents of triphosgene, slowing the addition of aniline, dilution of reaction, and performing the reaction at decreased temperatures all failed to limit the formation of byproducts. Phosgene gas may be necessary to rapidly complete the conversion of aniline to isocyanate and minimize the formation of urea side products.[28] While the conversion of **4** yielded the desired novel aromatic diisocyanate **5** successfully, I was unable to isolate, purify, and characterize it. This reaction, done under industrially optimized conditions with phosgene, may provide access to an alternative aryl diisocyanate that could ultimately produce novel polyurethane materials.

2.3.4 Route 4: Curtius Rearrangement

It is evident that urea byproducts are formed rapidly through reaction of the aniline with the isocyanates formed *in situ* so an alternative method may require avoiding starting from the aniline to eliminate that possibility. As mentioned previously, the Curtius, Hofmann, and Lossen rearrangement reactions are all established methods to produce isocyanates from acyl azides, amides, and hydroxamic acids, respectively. Both the Hofmann and Lossen rearrangements are typically used to form isocyanates as an intermediate to carbamates, and because of their requisite reagents, they are not suitable for large scale synthesis and isolation of isocyanates. While the Curtius rearrangement is a clean and high-yielding reaction of isocyanates, it is generally not encouraged to increase the synthetic scale of acyl azides due to the toxic and explosive nature of azide reagents and acyl azide products.[29] Nonetheless, this is the route I decided to pursue because previous work from Burkart and colleagues has shown that various aliphatic and aromatic isocyanates can be prepared at large scale in flow through Curtius rearrangement without isolating the intermediate acyl azide.[30]

Their method prepares acyl azides in a flow reactor through azidination of the more stable dihydrazides which are typically synthesized from the corresponding carboxylic acids. I envisioned **5** could be prepared through a similar process and our efforts initially focused on determining if it could be prepared through Curtius rearrangement at small scale. Synthetically, the requisite acyl azide, [1,1'-biphenyl]-3,5-dicarbonyl diazide (**9**), could be prepared through a multi-step reaction sequence starting from cheap commercially available substrates (Figure 2-13). First, a Suzuki-Miyaura palladium-catalyzed cross coupling reaction between 1-bromo-3,5-dinitrobenzene and phenylboronic acid yields 3,5-dimethyl-1,1'-biphenyl (**6**) in excellent yield.[31] **6** was then oxidized to the corresponding dicarboxylic acid, [1,1'-biphenyl]-3,5-dicarboxylic acid (**7**), with $KMnO_4$. From **7**, in a three-step reaction series, the desired aryl diisocyanate can be

prepared. The acyl chloride, [1,1'-biphenyl]-3,5-dicarbonyl dichloride (**8**), is readily accessed when reacted with a chlorinating agent like thionyl chloride.[32] Without isolation or purification, **8** can be directly converted to the requisite acyl azide **9** with sodium azide. When **9** is subjected to heat, it quickly undergoes Curtius rearrangement to produce the corresponding aromatic diisocyanate **5** as detected by IR (Figure 2-14).

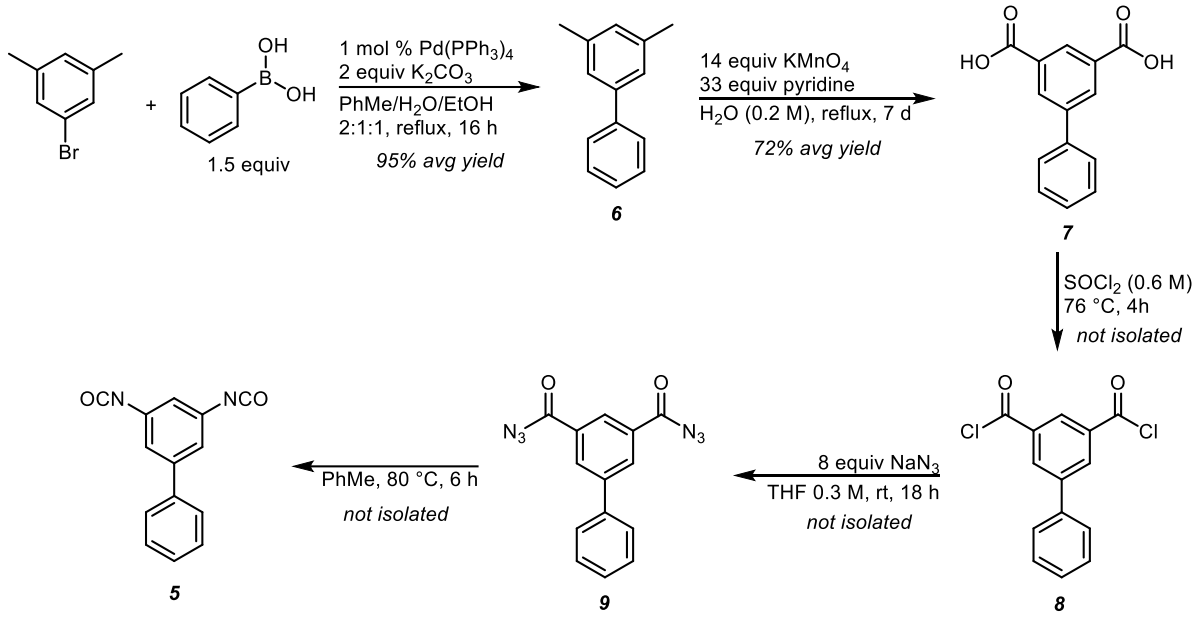


Figure 2-13. Curtius Rearrangement Precursors Synthesis

Unsurprisingly, **5** reacts with residual water and decomposes to the corresponding aniline **4** which ultimately forms urea linkages with another equivalent of **5** or the partial isocyanate. This is confirmed by the complete consumption of the NCO stretch by IR and formation of aniline and urea byproducts detected by MS. The rapid reaction of isocyanates with residual water in Curtius rearrangement reactions are not uncommon and nonetheless, these experiments prove that **5** can be synthesized through other pathways without phosgenation.[33]

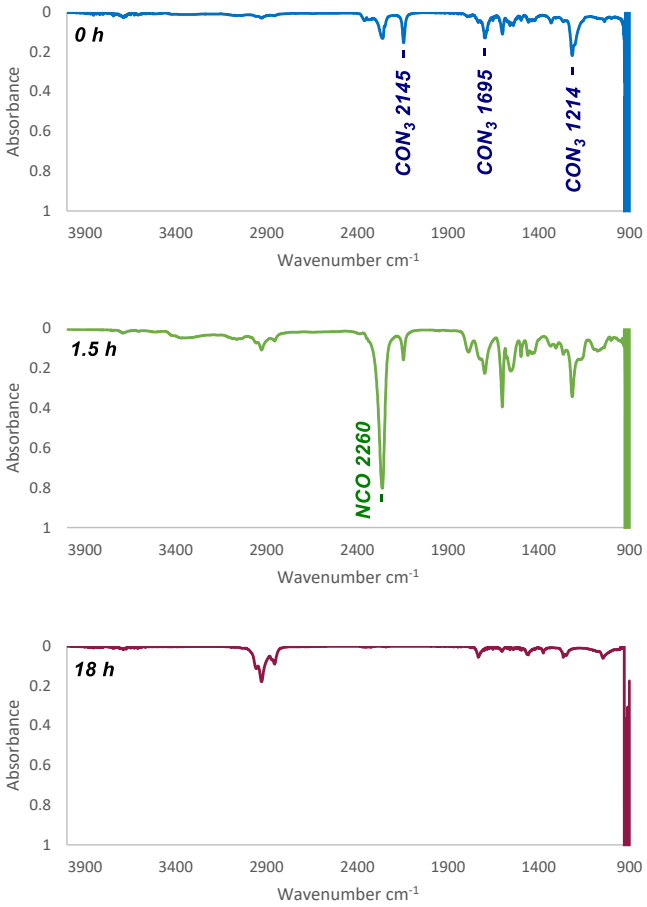


Figure 2-14. IR Spectra for Timed Curtius Rearrangement Reaction

The final step to determine if **9** could serve as an appropriate substrate en route to aromatic diisocyanate in flow was to synthesize the requisite dihydrazide. Dimethyl [1,1'-biphenyl]-3,5-dicarboxylate (**10**) can be obtained through the Fischer esterification reaction of 7 with a 1 molar HCl in methanol solution (Figure 2-15). **10** can then be reacted with hydrazine hydrate to afford [1,1'-biphenyl]-3,5-dicarbohydrazide (**11**) and there are ongoing efforts to focus on the purification and isolation of enough material to be subjected to flow system azidination and Curtius rearrangement.

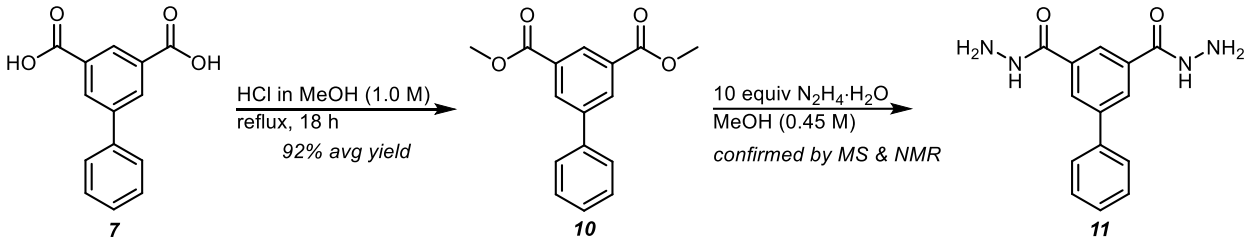


Figure 2-15. Dihydrazide Synthesis from Dicarboxylic Acid

2.4 Summary and Outlook

Herein, I investigated multiple routes to access novel aromatic diisocyanate **5** and demonstrated that it can be accessed through aniline and azide precursors. The inherent reactivity of this aromatic isocyanate prevented isolation, purification, and characterization. Our work originally aimed at directly converting renewable phenolic compound **2** into corresponding aniline and further validated the ongoing challenges in this transformation. Research must advance in direct phenol to aniline conversion methods and phenol-amine cross-coupling reactions if society ever wishes to move away from petrochemical feedstocks. The abundant variety of naturally occurring phenolic compounds should still be exploited to access unique anilines and further transformed into novel aromatic diisocyanates for polyurethane materials.

Alternative methods to synthesize diamine **4** were explored using traditional reductive strategies of nitro-containing arenes and applied to **3**. After exposing **4** to a multitude of phosgenation conditions, it became evident that the inherent reactivity of isocyanates with amines was too overpowering and prevented the isolation and purification of our desired diisocyanate. These results suggest that industrial procedures with phosgene gas are needed to achieve rapid conversion of the aniline and limit the formation of undesired byproducts.

Avoiding phosgene routes and aniline starting material altogether, I demonstrated that **5** could successfully be synthesized at small scale through the Curtius rearrangement of the corresponding acyl azide and synthesized the requisite precursor that can be used for large-scale

synthesis of isocyanates in flow. Unsurprisingly, **5** reacts with residual water and the resulting carbamic acid rapidly decomposes to the corresponding amine which ultimately forms urea linkages with additional equivalents of the isocyanate.

Future works aims at isolating and fully characterizing this novel diisocyanate by subjecting the requisite precursors to Curtius rearrangement conditions using continuous flow chemistry. Additionally, once isolated in large quantities, polymerization reactions with various diols could yield novel polyurethanes to be assessed to determine their properties. Ultimately, I hope this work encourages research into the discovery of unique aromatic diisocyanates through exploitation of abundant phenolic compounds as starting materials.

2.5 Experimental Data

2.5.1 General Experimental Information

All reactions were set-up on benchtop. ^{1}HMNR and ^{13}CNMR spectra were obtained using 400 MHz Varian Spectrometer. High-resolution and low-resolution mass spectrometry were measured using an Agilent 6230 ESI-TOFMS and Agilent 5977B GC-MSD, respectively. Infrared spectra were collected using a Thermo Scientific Nicolet 6700 FTIR and Bruker Alpha-P ATR FTIR. Flash column chromatography was performed using silica (Silicycle SiliaFlash® P60). Solvents (EtOH, MeOH, EtOAc, DMSO, and etc.) were used as received and dried according to literature procedures whenever needed.[34] All commercially available reagents were purchased and used as received.

[1,1'-biphenyl]-3,5-diol (2). The named compound was prepared from 5-phenylcyclohexane-1,3-dione (**1**) (2.560 g, 13.60 mmol, 1 equiv), and iodine (169 mg, 0.666 mmol, 5 mol %) according to a literature procedure.[21] The overall yield was 64% and isolated as a red-brown solid. All spectral and physical data are in correspondence with literature.

General Method for the Preparation of Substrates
Nitrile Synthesis: Method A

To a round bottom flask equipped with a magnetic stir bar, the corresponding catechol (1 equiv) and K_2CO_3 (2.4 equiv) were added. Then 2-fluorobenzonitrile (2.2 equiv) and DMSO (0.73 M) were then added. The reaction was closed off using a rubber septum and topped with a nitrogen filled balloon then heated to 80 °C and stirred for 48 hours. The reaction was monitored by TLC. Once reaction was completed, it was cooled to room temperature, the mixture was further diluted with EtOAc (50 mL) and H_2O (50 mL) and the organic layer was successively washed with 5% NaOH solution, distilled H_2O, and brine. All combined organic layers were dried with Na_2SO_4. After concentrating the organic layer, no further purification was needed.

2,2'-(1,3-phenylenebis(oxy))dibenzonitrile (resorcinol-A). The named compound was synthesized based on Method A from resorcinol (2.531 g, 22.99 mmol, 1 equiv). The reaction reached completion after 16 hours. The overall yield from the synthesis was 96% and was isolated as an off white crystalline solid. All spectral and physical data are in correspondence with literature.[35]

2,2'-((5-methyl-1,3-phenylene)bis(oxy))dibenzonitrile (orcinol-A). The named compound was synthesized based on Method A from orcinol (2.488 g, 20.04 mmol, 1 equiv). The overall yield from the synthesis was 88% and was isolated as a pink crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.4 Hz, 2H), 7.57 – 7.48 (m, 2H), 7.17 (t, *J* = 8.2 Hz, 2H), 6.98 (s, 1H), 6.96 (s, 1H), 6.75 (d, *J* = 3.0 Hz, 2H), 6.60 (s, 1H), 2.35 (s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 21.6, 104.1, 108.5, 116.0, 116.9, 117.8, 123.5, 134.0, 134.5, 142.3, 156.4, 159.1.

HRMS (ESI-TOF) Calc. for [$C_{21}H_{14}N_2O_2$+H^+] = 327.1128, Found 327.1126

2,2'-([1,1'-biphenyl]-3,5-diylbis(oxy))dibenzonitrile (2a). The named compound was synthesized based on method A from **2** (1.009 g, 5.419 mmol, 1 equiv). The overall yield from the synthesis was 93% and isolated as an off white crystalline solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 9.4 Hz, 2H), 7.59 – 7.50 (m, 4H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.1 Hz, 1H), 7.25 – 7.12 (m, 4H), 7.04 (d, *J* = 8.6 Hz, 3H), 6.78 (s, 1H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 104.3, 110.0, 114.9, 115.9, 117.9, 123.7, 127.2, 128.5, 129.1, 134.1, 134.6, 139.2, 145.2, 157.0, 159.0.

HRMS (ESI-TOF) Calc. for $[C_{26}H_{16}N_2O_2+H^+]$ = 389.1285, Found 389.1284

Carboxylic Acid Synthesis: Method A

To a round bottom flask equipped with a magnetic stir bar and the corresponding nitrile (1 equiv), NaOH (14 equiv), H_2O (0.5 M), and EtOH (0.13 M) were added. A reflux condenser was attached to the reaction and then heated to reflux for 18 hours and monitored by TLC. Once reaction was completed, it was cooled to room temperature, acidified to pH 1 with a 1 M HCl solution and then cooled to 8 °C for 1 hour. The resulting precipitate was filtered via vacuum filtration. Crude product was washed with chilled DCM to purify.

2,2'-(1,3-phenylenebis(oxy))dibenzoic acid (resorcinol-B). The named compound was synthesized based on Method A from resorcinol-A (2.073 g, 6.637 mmol, 1 equiv). The reaction reached completion after 48 hours. The overall yield from the synthesis was 99% and was isolated as an off-white powder solid. All spectral and physical data is in correspondence with literature.[33]

2,2'-((5-methyl-1,3-phenylene)bis(oxy))dibenzoic acid (orcinol-B). The named compound was synthesized based on Method A from orcinol-A (3.002 g, 9.198 mmol, 1 equiv). The overall yield from the synthesis was 99% and was isolated as an off-white powder.

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.80 (d, J = 7.7 Hz, 2H), 7.55 (t, J = 7.3 Hz, 2H), 7.26 (t, J = 7.5 Hz, 2H), 7.05 (d, J = 8.2 Hz, 2H), 6.42 (s, 2H), 6.23 (s, 1H), 2.20 (s, 3H).

^{13}C NMR (400 MHz, DMSO-D_6) δ 21.6, 104.9, 112.9, 121.7, 124.8, 125.1, 131.9, 134.1, 141.3, 154.9, 159.1, 166.9.

HRMS (ESI-TOF) Calc. for [$C_{21}H_{16}O_6$-H^+] = 363.0874, Found 363.0881

2,2'-([1,1'-biphenyl]-3,5-diylbis(oxy))dibenzoic acid (2b). The named compound was synthesized based on Method A from **2a** (1.501 g, 3.864 mmol, 1 equiv). The overall yield from the synthesis was 97% and was isolated as a beige powder.

^{1}H NMR (400 MHz, DMSO-D_6) δ 7.83 (d, J = 7.8 Hz, 2H), 7.62 – 7.54 (m, 2H), 7.52 (d, J = 7.0 Hz, 2H), 7.42 (t, J = 7.3 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 6.86 (d, J = 2.2 Hz, 2H), 6.39 (s, 1H).

^{13}C NMR (400 MHz, DMSO-D_6) δ 106.2, 110.5, 122.0, 125.1, 125.2, 127.2, 128.7, 129.6, 132.0, 134.2, 139. 143.6, 154.7, 159.8, 166.9.

HRMS (ESI-TOF) Calc. for [$C_{26}H_{18}O_6$+H^+] = 427.1176, Found 427.1173

Hydroxamic Acid Synthesis: Method A

To a round bottom flask equipped with a stir bar, carboxylic acid (1 equiv), THF (0.5 M), and DMF (1.0 equiv) was added oxalyl chloride (4 equiv) dropwise. The reaction was allowed to stir for 1 hour, after which the corresponding hydroxylamine hydrochloride (4 equiv) and triethyl amine (8 equiv) dissolved in a 4:1 solution of THF:distilled H_2O (0.5 M) was added dropwise. The reaction was allowed to stir for an additional 10 minutes and was quenched by addition of 1M HCl aqueous solution. The organic layer was separated, and the aqueous layer was extracted with DCM. The organic layers were combined, dried over Na_2SO_4, and allowed to cool at 8 °C for 1 hour. The

resulting precipitate was filtered by vacuum filtration and was not further purified due to insolubility of product.

2,2'-((5-methyl-1,3-phenylene)bis(oxy))bis(N-hydroxybenzamide) (orcinol-C). The named compound was synthesized based on Method A from **orcinol-B** (206 mg, 0.565 mmol, 1 equiv). The overall yield from the synthesis was 7% and was isolated as a white powder.

HRMS (ESI-TOF) Calc. for $[C_{21}H_{19}N_2O_6+H^+]$ = 395.1238, Found 395.1234

2,2'-([1,1'-biphenyl]-3,5-diylbis(oxy))bis(N-hydroxybenzamide) (2c). The named compound was synthesized based on Method A from **2b** (505 mg, 1.18 mmol, 1 equiv). The overall yield from the synthesis was 14% and was isolated as a white powder.

HRMS (ESI-TOF) Calc. for $[C_{26}H_{21}N_2O_6+H^+]$ = 457.1394, Found 457.1389

Synthesis of Aromatic Diisocyanate 3,5-diisocyanato-1,1'-biphenyl (5)

General Method A

An adapted procedure from the literature was used to synthesize **5**.[36] To a glass culture tube equipped with a stir bar, a solution of triphosgene (966 mg, 3.26 mmol, 3 equiv) in solvent (EtOAc, DCM, DCE, or $CHCl_3$) (1.4 mL, 0.2 M) was added. A solution of **4** (200 mg, 1.09 mmol, 1 equiv) dissolved in a solvent (1.4 mL, 0.2 M) was added dropwise to the reaction over the course of 30 minutes and stirred at room temperature for 8 hours. The reaction was then heated to reflux for 18 hours. The resulting solid was filtered, washed with hexanes and DCM, and collected as a beige solid. The insoluble solid mixture was analyzed using IR and could not be further purified. The insoluble solid mixture was stirred with methanol to yield the corresponding carbamate product (dimethyl [1,1'-biphenyl]-3,5-diyldicarbamate) and analyzed with MS as a chemical test to confirm **5** as product.

General Method B

An adapted procedure from the literature was used to synthesize **5**.[31] The corresponding acyl azide (**9**) in a round bottom flask was dried under high vac for 1 hour. An oven-dried reflux condenser was attached, and an oven-dried stir bar was added to the round bottom flask. Dry toluene (0.3 M) was added, and the reaction was closed off using a rubber septum and topped with a nitrogen filled balloon then heated to 80 °C and stirred for 6 hours. Periodic monitoring by IR revealed the NCO stretch corresponding to **5**. Once reaction was completed, an insoluble solid mixture was obtained and was stirred with methanol to yield the corresponding carbamate (dimethyl [1,1'-biphenyl]-3,5-diyldicarbamate) and analyzed with MS as a chemical test to confirm **5** as product.

dimethyl [1,1'-biphenyl]-3,5-diyldicarbamate. The named compound was synthesized by both method A and B and collected as a beige solid mixture that could not be further isolated or purified.

LRMS (ESI-MS) Calc. for $[C_{16}H_{16}N_2O_2+H^+]$ = 301.12, Found 301.34

General Method for Preparation of Substrates

1-bromo-3,5-dinitrobenzene. The named compound was prepared from 1,3-dinitrobenzene (3.000 g, 17.85 mmol, 1 equiv), N-bromosuccinimide (6.352, 35.69 mmol, 2 equiv), and concentrated H_2SO_4 (29.74 mL, 535.4 mmol) according to a literature procedure.[22] The overall yield was 84% and isolated as a yellow crystalline solid. All spectral and physical data are in correspondence with literature.

3,5-dinitro-1,1'-biphenyl (3). The named compound was prepared from the 1-bromo-3,5-dinitrobenzene according to a modified procedure from the literature.[23] To a round bottom equipped with a stir bar, 1-bromo-3,5-dinitrobenzene (1.020 g, 4.130 g,1 equiv), phenylboronic acid (657 mg, 5.39 mmol, 1.3 equiv), K_3PO_4 (863 mg, 4.07 mmol, 1 equiv), H_2O (5.2 mL, 0.8 M), diacetoxypalladium (45 mg, 0.20 mmol, 5 mol %) was added. A reflux condenser was attached,

and the reaction was heated to reflux for 96h. Reaction was monitored by ^{1}HNMR with occasional manual disruption of heterogenous clusters in solution. Once the reaction was completed, it was cooled to room temperature, quenched with HCl, and the mixture was filtered through a celite pad. The mixture was then diluted with ethyl acetate (50 mL) and water (50 mL) and the organic layer was successively washed with 5% NaOH solution, distilled H_2O, and brine. All combined organic layers were dried with Na_2SO_4. After concentrating the organic layer, the resulting brown solid was washed with chilled ethyl acetate to yield a beige crystalline solid with an overall yield of 70%. All spectral and physical data are in correspondence with literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.78 (d, *J* = 2.1 Hz, 2H), 7.69 (d, *J* = 6.6 Hz, 2H), 7.62 – 7.48 (m, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 117.2, 127.1, 127.3, 129.7, 130.0, 136.5, 144.9, 149.0.

[1,1'-biphenyl]-3,5-diamine (4). The named compound was prepared from **3** (1.007 g, 4.124 mmol, 1 equiv), hydrazine hydrate (1.222 g, 19.28 mmol, 4.7 equiv), Pd/C (22 mg, 0.206 mmol, 5 mol %) according to a procedure from the literature.[23] The overall yield was 89% and collected as an off-white solid. All spectral and physical data are in correspondence with literature.

HMR (400 MHz, DMSO-D_6) δ 7.45 (d, *J* = 7.1 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 3H), 7.27 (t, *J* = 7.3 Hz, 1H), 6.06 (d, *J* = 2.1 Hz, 4H), 5.83 (s, 1H), 4.82 (s, 4H).

^{13}C NMR (400 MHz, DMSO-D_6) δ 99.7, 102.3, 126.8, 127.3, 129.1, 141.9, 142.4, 150.1.

HRMS (ESI-TOF) Calc. for $[C_{12}H_{13}N_2+H^+]$ = 185.1073, Found 185.1070

3,5-dimethyl-1,1'-biphenyl (6). The named compound was prepared from 1-bromo-3,5-dimethylbenzene (5.6 g, 30 mmol, 1 equiv), phenylboronic acid (5.526g, 45.32 mmol, 1.5 equiv), tetrakis(triphenylphosphine)palladium(0) (383 mg, 0.331 mmol, 1 mol %), and K_2CO_3 (8.336 g, 60.32 mmol, 2 equiv) according to a procedure from the literature.[30] The named compound was

purified by flash column chromatography with hexanes, had an overall yield was 98%, and was collected as a colorless oil. All spectral and physical data are in correspondence with literature.

[1,1'-biphenyl]-3,5-dicarboxylic acid (7). The named compound was prepared from **6** (2.734 g, 15.00 mmol, 1 equiv), $KMnO_4$ (30.82 g, 195.0 mmol, 13 equiv), and pyridine (39.15 g, 495.0 mmol, 33 equiv) in 7 days according to a procedure from the literature.[30] The overall yield was 83% and was collected as a white powder solid. All spectral and physical data are in correspondence with literature.

[1,1'-biphenyl]-3,5-dicarbonyl dichloride (8). The named compound was prepared from **7** (50 mg, 0.21 mmol, 1 equiv) with thionyl chloride (0.34 mL, 0.6 M) according to a procedure from the literature.[31] The named compound was not isolated and was immediately consumed in the next step of the reaction sequence.

[1,1'-biphenyl]-3,5-dicarbonyl diazide (9). The named compound was prepared from **8** (0.21 mmol) with sodium azide (0.11 g, 1.7 mmol, 8 equiv) in THF (0.69 mL, 0.3 M) according to a procedure from the literature.[31] The named compound was not isolated and was immediately consumed in the next step of the reaction sequence.

dimethyl [1,1'-biphenyl]-3,5-dicarboxylate (10). The named compound was prepared from **7** (1.000 g, 4.128 mmol, 1 equiv) with a HCl in MeOH solution (1 M) according to a procedure from the literature.[29] The overall yield was 99% and collected as a white crystalline solid. All spectral and physical data are in correspondence with literature.

[1,1'-biphenyl]-3,5-dicarbohydrazide (11). The named compound was prepared from **10** (150 mg, 0.555 mmol, 1 equiv) with hydrazine monohydrate (352 mg, 5.55 mmol, 10 equiv) according to a procedure from the literature.[29] The named compound was not isolated or purified but identity was confirmed through ^{1}HNMR and LRMS and are in correspondence with literature.

LRMS (ESI-MS) Calc. for $[C_{14}H_{14}N_4O_2+H^+]$ = 271.12, Found 271.33

2.6 REFERENCES

1) Radomski, J. L. The Primary Aromatic Amines: Their Biological Properties and Structure-Activity Relationships. *Annu. Rev. Pharmacol. Toxicol.* **1979**, *19* (1), 129–157. https://doi.org/10.1146/annurev.pa.19.040179.001021.

2) Zeng, H.; Qiu, Z.; Domínguez-Huerta, A.; Hearne, Z.; Chen, Z.; Li, C.-J. An Adventure in Sustainable Cross-Coupling of Phenols and Derivatives via Carbon–Oxygen Bond Cleavage. *ACS Catal.* **2017**, *7* (1), 510–519. https://doi.org/10.1021/acscatal.6b02964.

3) a) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116* (19), 12564–12649. https://doi.org/10.1021/acs.chemrev.6b00512. b) Shen, Q.; Ogata, T.; Hartwig, J. F. Highly Reactive, General and Long-Lived Catalysts for Palladium-Catalyzed Amination of Heteroaryl and Aryl Chlorides, Bromides, and Iodides: Scope and Structure–Activity Relationships. *J. Am. Chem. Soc.* **2008**, *130* (20), 6586–6596. https://doi.org/10.1021/ja077074w. c) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. Highly Reactive, General, and Long-Lived Catalysts for Coupling Heteroaryl and Aryl Chlorides with Primary Nitrogen Nucleophiles. *Angew. Chem. Int. Ed Engl.* **2005**, *44* (9), 1371–1375. https://doi.org/10.1002/anie.200462629. d) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Triflates and Importance of Triflate Addition Rate. *J. Org. Chem.* **1997**, *62* (5), 1268–1273. https://doi.org/10.1021/jo961930x. e) Paul, F.; Patt, J.; Hartwig, J. F. Palladium-Catalyzed Formation of Carbon-Nitrogen Bonds. Reaction Intermediates and Catalyst Improvements in the Hetero Cross-Coupling of Aryl Halides and Tin Amides. *J. Am. Chem. Soc.* **1994**, *116* (13), 5969–5970. https://doi.org/10.1021/ja00092a058. f) Sun, H.-B.; Gong, L.; Tian, Y.-B.; Wu, J.-G.; Zhang, X.; Liu, J.; Fu, Z.; Niu, D. Metal- and Base-Free Room-Temperature Amination of Organoboronic Acids with N-Alkyl Hydroxylamines. *Angew. Chem. Int. Ed Engl.* **2018**, *57* (30), 9456–9460. https://doi.org/10.1002/anie.201802782. g) Chatterjee, N.; Goswami, A. Metal and Base Free Synthesis of Primary Amines via Ipso Amination of Organoboronic Acids Mediated by [Bis(Trifluoroacetoxy)Iodo]Benzene (PIFA). *Org. Biomol. Chem.* **2015**, *13* (29), 7940–7945. https://doi.org/10.1039/C5OB01070E. h) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. Pd Metal Catalysts for Cross-Couplings and Related Reactions in the 21st Century: A Critical Review. *Chem. Rev.* **2018**, *118* (4), 2249–2295. https://doi.org/10.1021/acs.chemrev.7b00443. i) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners. *Chem. Rev.* **2011**, *111* (3), 1417–1492. https://doi.org/10.1021/cr100327p. j) Kohei, T.; Miyaura, N. Introduction to Cross-Coupling Reactions. In *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry; Springer: Berlin, Heidelberg, 2002; pp 1–9. https://doi.org/10.1007/3-540-45313-X_1. k) Munir, I.; Zahoor, A. F.; Rasool, N.; Naqvi, S. A. R.; Zia, K. M.; Ahmad, R. Synthetic Applications and Methodology Development of Chan–Lam Coupling: A Review. *Mol. Divers.* **2019**, *23* (1), 215–259. https://doi.org/10.1007/s11030-018-9870-z.

4) a) Tse, M. K.; Cho, J.-Y.; Smith, M. R. Regioselective Aromatic Borylation in an Inert Solvent. *Org. Lett.* **2001**, *3* (18), 2831–2833. https://doi.org/10.1021/ol0162668. b) Beck, U.; Löser, E. Chlorinated Benzenes and Other Nucleus-Chlorinated Aromatic Hydrocarbons. In *Ullmann's Encyclopedia of Industrial Chemistry*; John Wiley & Sons, Ltd, 2011. https://doi.org/10.1002/14356007.o06_o03. c) Lyday, P. A.; Kaiho, T. Iodine and Iodine Compounds. In *Ullmann's Encyclopedia of Industrial Chemistry*; John Wiley & Sons, Ltd, 2015; pp 1–13. https://doi.org/10.1002/14356007.a14_381.pub2.

5) a) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. Nickel-Catalyzed Cross-Couplings Involving Carbon−Oxygen Bonds. *Chem. Rev.* **2011**, *111* (3), 1346–1416. https://doi.org/10.1021/cr100259t. b) Zarate, C.; Van Gemmeren, M.; Somerville, R. J.; Martin, R. Phenol Derivatives. In *Advances in Organometallic Chemistry*; Elsevier, 2016; Vol. 66, pp 143–222. https://doi.org/10.1016/bs.adomc.2016.07.001.

6) a) Marín, M.; Rama, R. J.; Nicasio, M. C. Ni-Catalyzed Amination Reactions: An Overview. *Chem. Rec. N. Y. N* **2016**, *16* (4), 1819–1832. https://doi.org/10.1002/tcr.201500305. b) Wolfe, J. P.; Buchwald, S. L. Palladium-Catalyzed Amination of Aryl Triflates. *J. Org. Chem.* **1997**, *62* (5), 1264–1267. https://doi.org/10.1021/jo961915s. c) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Triflates and Importance of Triflate Addition Rate. *J. Org. Chem.* **1997**, *62* (5), 1268–1273. https://doi.org/10.1021/jo961930x.

7) a) Gao, C.-Y.; Yang, L.-M. Nickel-Catalyzed Amination of Aryl Tosylates. *J. Org. Chem.* **2008**, *73* (4), 1624–1627. https://doi.org/10.1021/jo7022558. b) Tobisu, M.; Chatani, N. Cross-Couplings Using Aryl Ethers via C–O Bond Activation Enabled by Nickel Catalysts. *Acc. Chem. Res.* **2015**, *48* (6), 1717–1726. https://doi.org/10.1021/acs.accounts.5b00051. c) Tobisu, M.; Yasutome, A.; Yamakawa, K.; Shimasaki, T.; Chatani, N. Ni(0)/NHC-Catalyzed Amination of N-Heteroaryl Methyl Ethers through the Cleavage of Carbon–oxygen Bonds. *Tetrahedron* **2012**, *68* (26), 5157–5161. https://doi.org/10.1016/j.tet.2012.04.005.

8) Chen, K.; Kang, Q.-K.; Li, Y.; Wu, W.-Q.; Zhu, H.; Shi, H. Catalytic Amination of Phenols with Amines. *J. Am. Chem. Soc.* **2022**, *144* (3), 1144–1151. https://doi.org/10.1021/jacs.1c12622.

9) Barker, R. S. Preparation of Aminated Benzenes from Hydroxy Benzenes. US3272865A, September 13, 1966. https://patents.google.com/patent/US3272865A/en (accessed 2023-07-29).

10) Becker, M.; Khoobiar, S. Process for the Production of Organic Amines. US3860650A, January 14, 1975. https://patents.google.com/patent/US3860650A/en (accessed 2023-07-29).

11) a) Ono, Y.; Ishida, H. Amination of Phenols with Ammonia over Palladium Supported on Alumina. *J. Catal.* **1981**, *72* (1), 121–128. https://doi.org/10.1016/0021-9517(81)90083-X. b) Yasuhara, M.; Matsunaga, F. Preparation of Anilines. US4987260A, January 22, 1991. https://patents.google.com/patent/US4987260A/ko (accessed 2023-07-29). c)

Chang, C. D.; Lang, W. H. Aniline or Substituted Aniline from Phenol or Phenolic Compounds. EP62542A1, 1982. d)马建超; **王玲玲**; 陈立功; **董**宪**姝**; **王**丽丽. Bentonite-Based Amination Catalyst Preparation Method. CN103418373A, December 4, 2013. https://patents.google.com/patent/CN103418373A/en (accessed 2023-07-31). e) Mori, Y.; Noro, H.; Hara, Y. Preparation of Aromatic Amines from Phenols. JP06184062A, 1994.

12) Cuypers, T.; Tomkins, P.; Vos, D. E. D. Direct Liquid-Phase Phenol-to-Aniline Amination Using Pd/C. *Catal. Sci. Technol.* **2018**, *8* (10), 2519–2523. https://doi.org/10.1039/C8CY00193F.

13) Qiu, Z.; Lv, L.; Li, J.; Li, C.-C.; Li, C.-J. Direct Conversion of Phenols into Primary Anilines with Hydrazine Catalyzed by Palladium. *Chem. Sci.* **2019**, *10* (18), 4775–4781. https://doi.org/10.1039/C9SC00595A.

14) Pietra, F. Mechanisms for Nucleophilic and Photonucleophilic Aromatic Substitution Reactions. *Q. Rev. Chem. Soc.* **1969**, *23* (4), 504. https://doi.org/10.1039/qr9692300504.

15) Campbell, M. G.; Ritter, T. Modern Carbon–Fluorine Bond Forming Reactions for Aryl Fluoride Synthesis. *Chem. Rev.* **2015**, *115* (2), 612–633. https://doi.org/10.1021/cr500366b.

16) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2006. https://doi.org/10.1002/0470084960.

17) Bernasconi, C. F.; Schmid, P. Base Catalysis of the Reaction of Morpholine with 2,4-Dinitrophenyl Phenyl Ether in 10 Percent Dioxane-90 Percent Water. *J. Org. Chem.* **1967**, *32* (10), 2953–2956. https://doi.org/10.1021/jo01285a003.

18) a) Holden, C. M.; Greaney, M. F. Modern Aspects of the Smiles Rearrangement. *Chem. – Eur. J.* **2017**, *23* (38), 8992–9008. https://doi.org/10.1002/chem.201700353. b) Bunnett, J. F.; Zahler, R. E. Aromatic Nucleophilic Substitution Reactions. *Chem. Rev.* **1951**, *49* (2), 273–412. https://doi.org/10.1021/cr60153a002. c)Truce, W. E.; Kreider, E. M.; Brand, W. W. The Smiles and Related Rearrangements of Aromatic Systems. In *Organic Reactions*; John Wiley & Sons, Ltd, 2011; pp 99–215. https://doi.org/10.1002/0471264180.or018.02.

19) Bayles, R.; Johnson, M. C.; Maisey, R. F.; Turner, R. W. A Smiles Rearrangement Involving Non-Activated Aromatic Systems; the Facile Conversion of Phenols to Anilines. *Synthesis* **1977**, No. 1, 33–34. https://doi.org/10.1055/s-1977-24263.

20) a) Zhou, T.; Luo, F.-X.; Yang, M.-Y.; Shi, Z.-J. Silver-Catalyzed Long-Distance Aryl Migration from Carbon Center to Nitrogen Center. *J. Am. Chem. Soc.* **2015**, *137* (46), 14586–14589. https://doi.org/10.1021/jacs.5b10267. b) Shu, W.; Genoux, A.; Li, Z.; Nevado, C. γ-Functionalizations of Amines through Visible-Light-Mediated, Redox-Neutral C−C Bond Cleavage. *Angew. Chem. Int. Ed.* **2017**, *56* (35), 10521–10524. https://doi.org/10.1002/anie.201704068.

21) Lardy, S. W.; Luong, K. C.; Schmidt, V. A. Formal Aniline Synthesis from Phenols through Deoxygenative N-Centered Radical Substitution. *Chem. – Eur. J.* **2019**, *25* (67), 15267–15271. https://doi.org/10.1002/chem.201904288.

22) Liang, Y.-F.; Song, S.; Ai, L.; Li, X.; Jiao, N. A Highly Efficient Metal-Free Approach to Meta- and Multiple-Substituted Phenols via a Simple Oxidation of Cyclohexenones. *Green Chem.* **2016**, *18* (24), 6462–6467. https://doi.org/10.1039/C6GC02674E.

23) Gude, V.; S. Choubey, P.; Das, S.; N, S. B. B.; Malla Reddy, C.; Biradha, K. Elastic Orange Emissive Single Crystals of 1,3-Diamino-2,4,5,6-Tetrabromobenzene as Flexible Optical Waveguides. *J. Mater. Chem. C* **2021**, *9* (30), 9465–9472. https://doi.org/10.1039/D1TC01841H.

24) a) Richardson, B. G.; Jain, A. D.; Potteti, H. R.; Lazzara, P. R.; David, B. P.; Tamatam, C. R.; Choma, E.; Skowron, K.; Dye, K.; Siddiqui, Z.; Wang, Y.-T.; Krunic, A.; Reddy, S. P.; Moore, T. W. Replacement of a Naphthalene Scaffold in Kelch-like ECH-Associated Protein 1 (KEAP1)/Nuclear Factor (Erythroid-Derived 2)-like 2 (NRF2) Inhibitors. *J. Med. Chem.* **2018**, *61* (17), 8029–8047. https://doi.org/10.1021/acs.jmedchem.8b01133. b) Chen, X.; Zhou, X.-Y.; Wu, H.; Lei, Yi-Zhu; Li, J.-H. Highly Efficient Reduction of Nitro Compounds: Recyclable Pd/C-Catalyzed Transfer Hydrogenation with Ammonium Formate or Hydrazine Hydrate as Hydrogen Source. *Synth. Commun.* **2018**, *48* (19), 2475–2484. https://doi.org/10.1080/00397911.2018.1484924.

25) Ganiu, M. O.; Nepal, B.; Van Houten, J. P.; Kartika, R. A Decade Review of Triphosgene and Its Applications in Organic Reactions. *Tetrahedron* **2020**, *76* (47), 131553. https://doi.org/10.1016/j.tet.2020.131553.

26) Eckert, H.; Forster, B. Triphosgene, a Crystalline Phosgene Substitute. *Angew. Chem. Int. Ed. Engl.* **1987**, *26* (9), 894–895. https://doi.org/10.1002/anie.198708941.

27) a) Stephenson, C. V.; Coburn, W. C.; Wilcox, W. S. The Vibrational Spectra and Assignments of Nitrobenzene, Phenyl Isocyanate, Phenyl Isothiocyanate, Thionylaniline and Anisole. *Spectrochim. Acta* **1961**, *17* (9), 933–946. https://doi.org/10.1016/0371-1951(61)80029-5. b) Bezrodna, T. V.; Ishchenko, A. A.; Kosyanchuk, L. F.; Derevyanko, N. A.; Antonenko, O. I.; Bezrodnyi, V. I. Luminescence Spectral Peculiarities of Polymethine Dye, Bonded Covalently to Polyurethane Matrix. *Mol. Cryst. Liq. Cryst.* **2022**, *748* (1), 90–98. https://doi.org/10.1080/15421406.2022.2067664. c) Vinogradova, E. V.; Fors, B. P.; Buchwald, S. L. Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Triflates with Sodium Cyanate: A Practical Synthesis of Unsymmetrical Ureas. *J. Am. Chem. Soc.* **2012**, *134* (27), 11132–11135. https://doi.org/10.1021/ja305212v.

28) Six, C.; Richter, F. Isocyanates, Organic. In *Ullmann's Encyclopedia of Industrial Chemistry*; John Wiley & Sons, Ltd, 2003. https://doi.org/10.1002/14356007.a14_611.

29) Carnaroglio, D.; Martina, K.; Palmisano, G.; Penoni, A.; Domini, C.; Cravotto, G. One-Pot Sequential Synthesis of Isocyanates and Urea Derivatives via a Microwave-Assisted

Staudinger–Aza-Wittig Reaction. *Beilstein J. Org. Chem.* **2013**, *9* (1), 2378–2386. https://doi.org/10.3762/bjoc.9.274.

30) Phung Hai, T. A.; De Backer, L. J. S.; Cosford, N. D. P.; Burkart, M. D. Preparation of Mono- and Diisocyanates in Flow from Renewable Carboxylic Acids. *Org. Process Res. Dev.* **2020**, *24* (10), 2342–2346. https://doi.org/10.1021/acs.oprd.0c00167.

31) Huang, W.; Jiang, J.; Wu, D.; Xu, J.; Xue, B.; Kirillov, A. M. A Highly Stable Nanotubular MOF Rotator for Selective Adsorption of Benzene and Separation of Xylene Isomers. *Inorg. Chem.* **2015**, *54* (22), 10524–10526. https://doi.org/10.1021/acs.inorgchem.5b01581.

32) Servos, M. A.; Smart, N. C.; Kassabaum, M. E.; Scholtens, C. A.; Peters, S. J. Phenyl Isocyanate Anion Radicals and Their Cyclotrimerization to Triphenyl Isocyanurate Anion Radicals. *J. Org. Chem.* **2013**, *78* (8), 3908–3917. https://doi.org/10.1021/jo4003008.

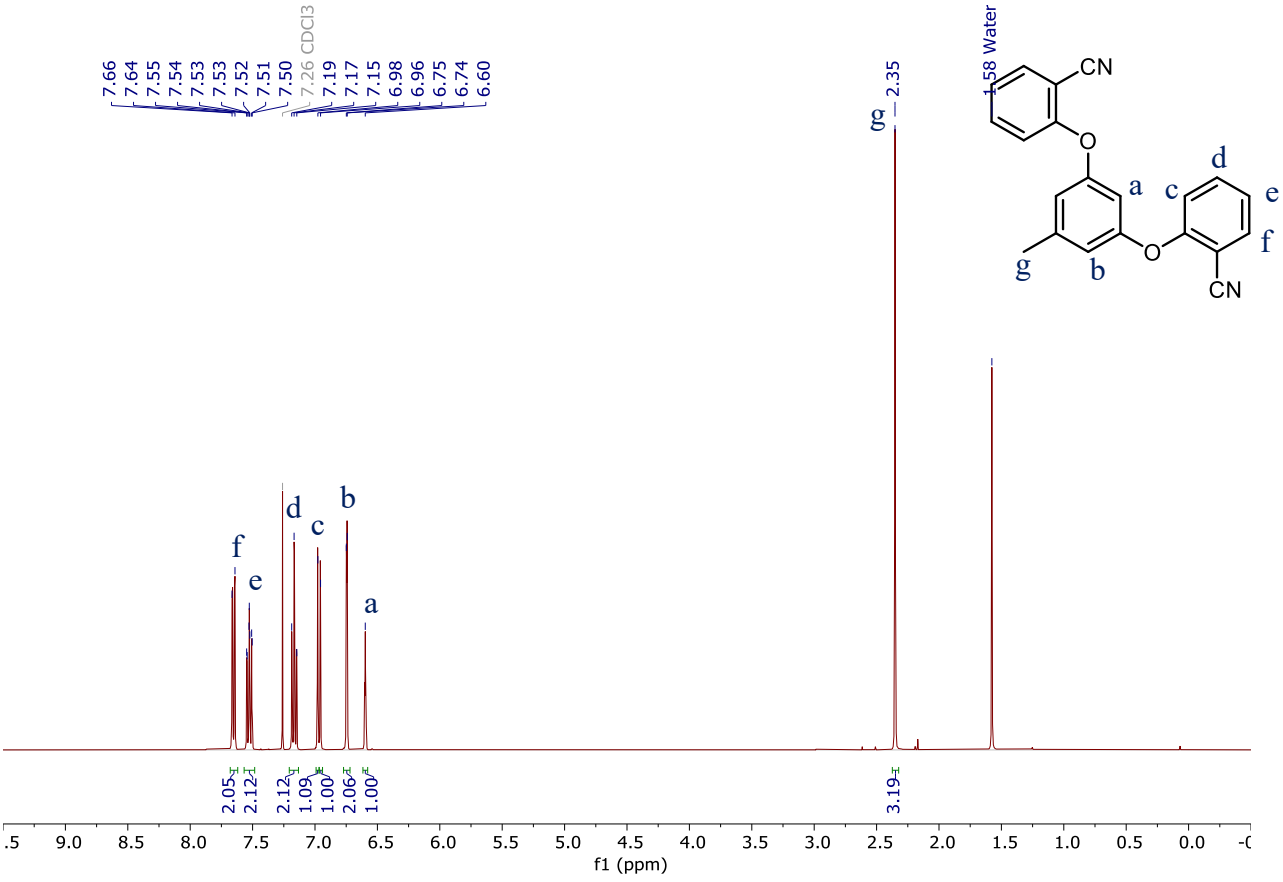
33) Baumann, M.; R. Baxendale, I.; V. Ley, S.; Nikbin, N.; D. Smith, C.; P. Tierney, J. A Modular Flow Reactor for Performing Curtius Rearrangements as a Continuous Flow Process. *Org. Biomol. Chem.* **2008**, *6* (9), 1577–1586. https://doi.org/10.1039/B801631N.

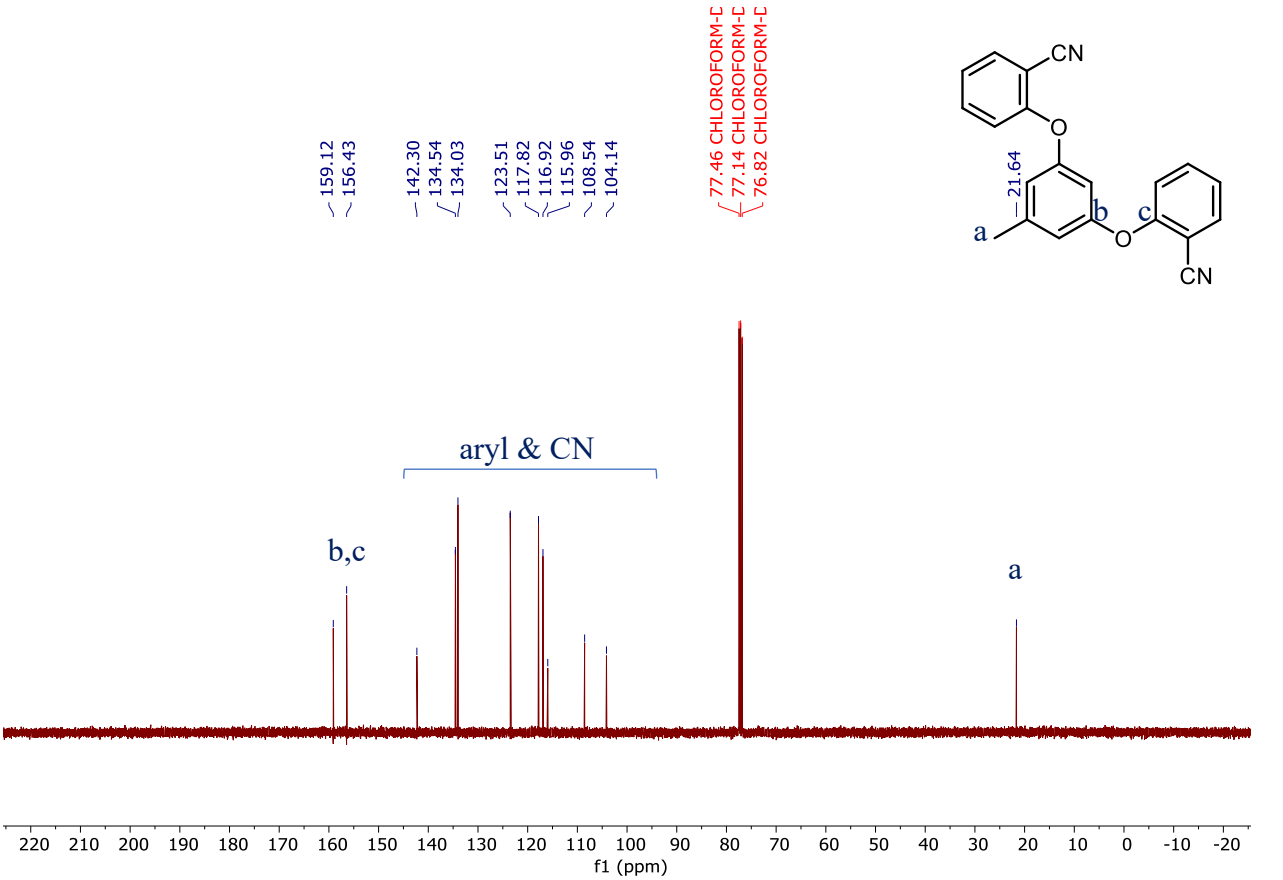
34) Wang, B.; Shao, J.; Xu, T.; Chen, L.; Zhao, J.; Shao, Y.; Zhang, H.-L.; Shao, X. Synthesis of Di- and Trixanthones That Display High Stability and a Visual Fluorescence Response to Strong Acid. *Chem. – Asian J.* **2014**, *9* (11), 3307–3312. https://doi.org/10.1002/asia.201402815.

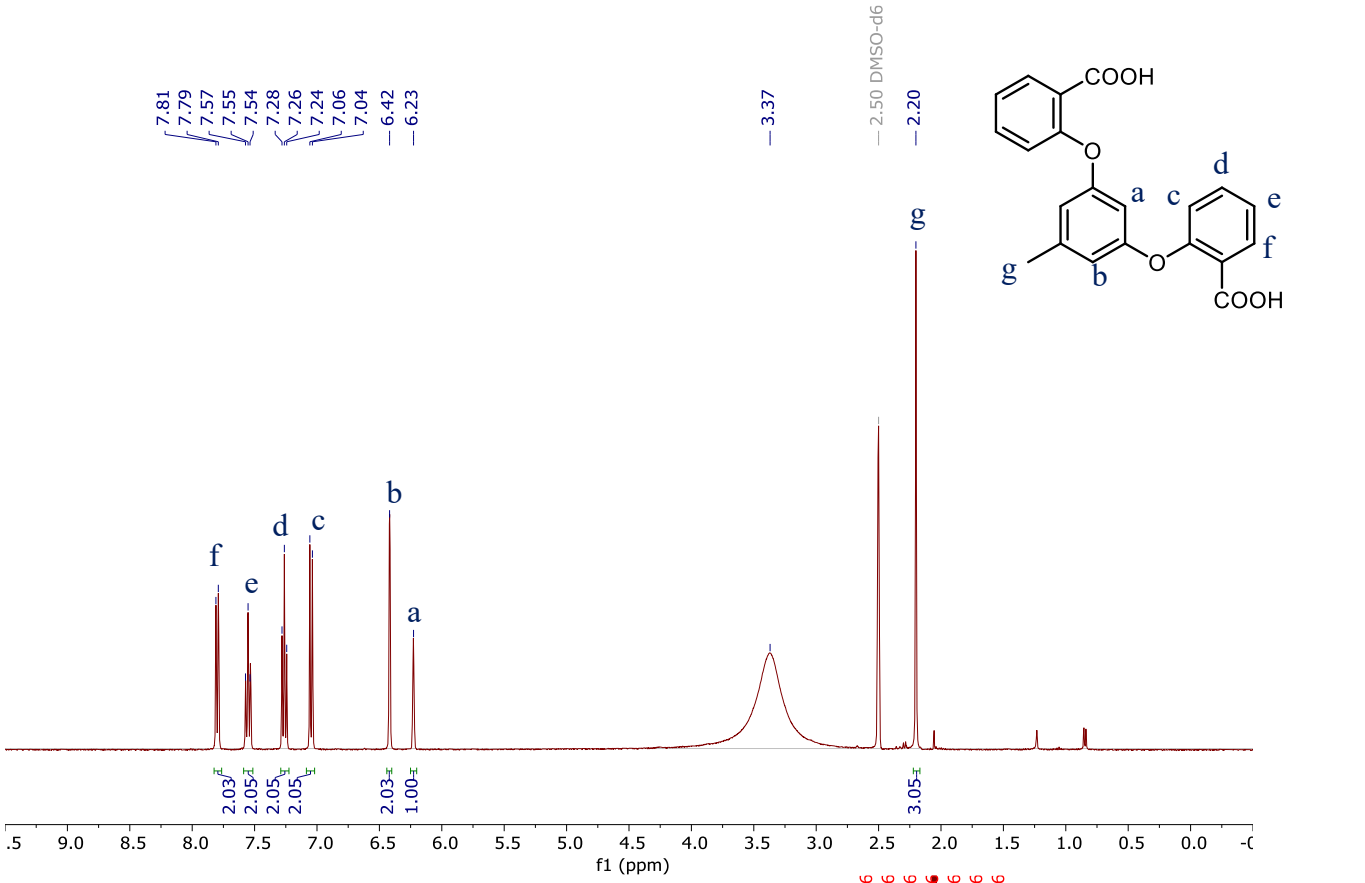
35) Zheng, Z.; Du, D.; Cao, L.; Liu, J.; Chen, X. Synthesis and Antibacterial Activity of Novel 11-[3-[(Arylcarbamoyl)Oxy]Propylamino]-11-Deoxy-6-O-Methyl-3-Oxoerythromycin A 11-N,12-O-Cyclic Carbamate Derivatives. *J. Antibiot. (Tokyo)* **2016**, *69* (11), 811–817. https://doi.org/10.1038/ja.2016.42

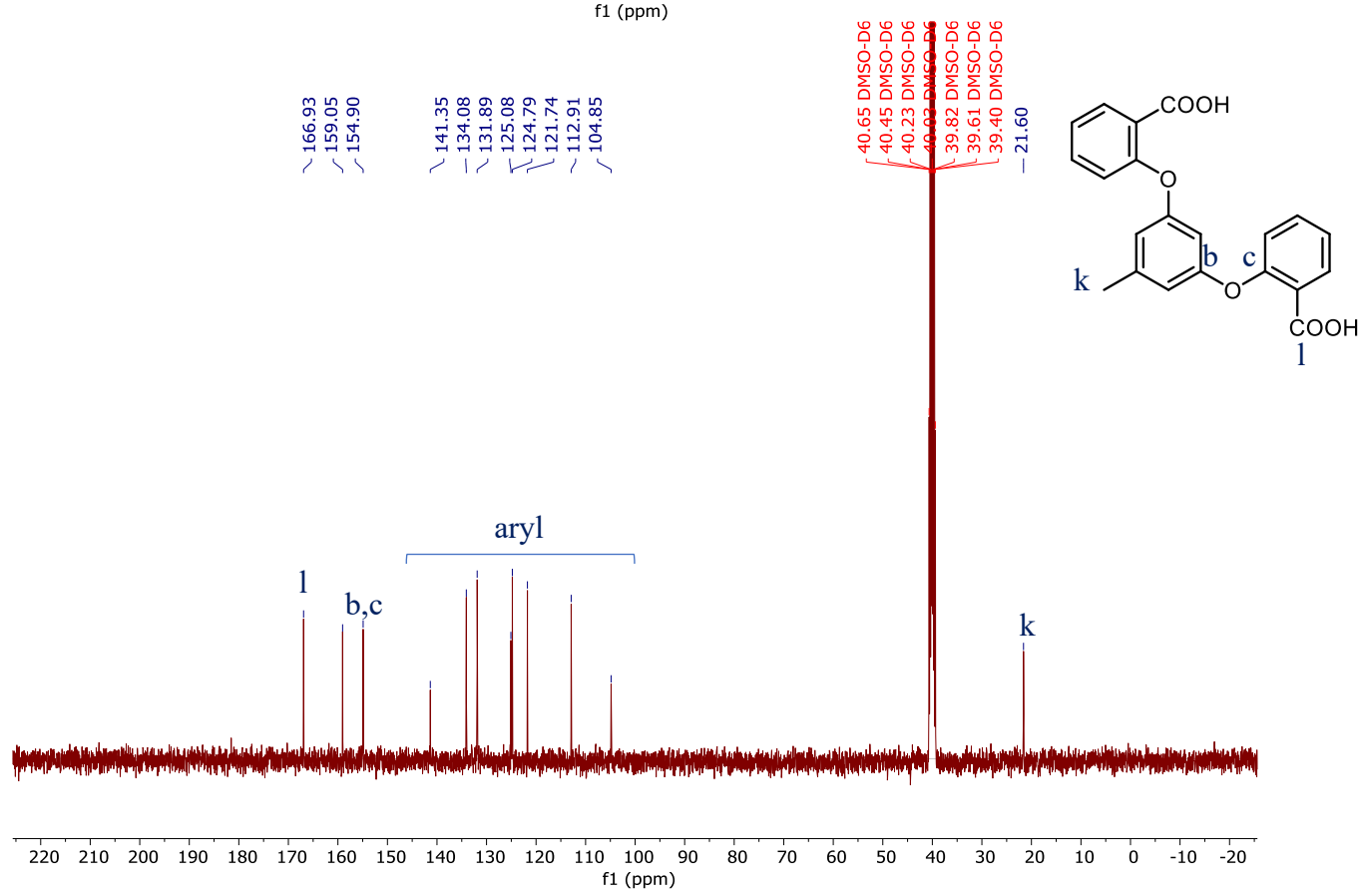
36) Armarego, W. L. F. *Purification of Laboratory Chemicals, 8th Edition*; Butterworth-Heinemann, 2017.

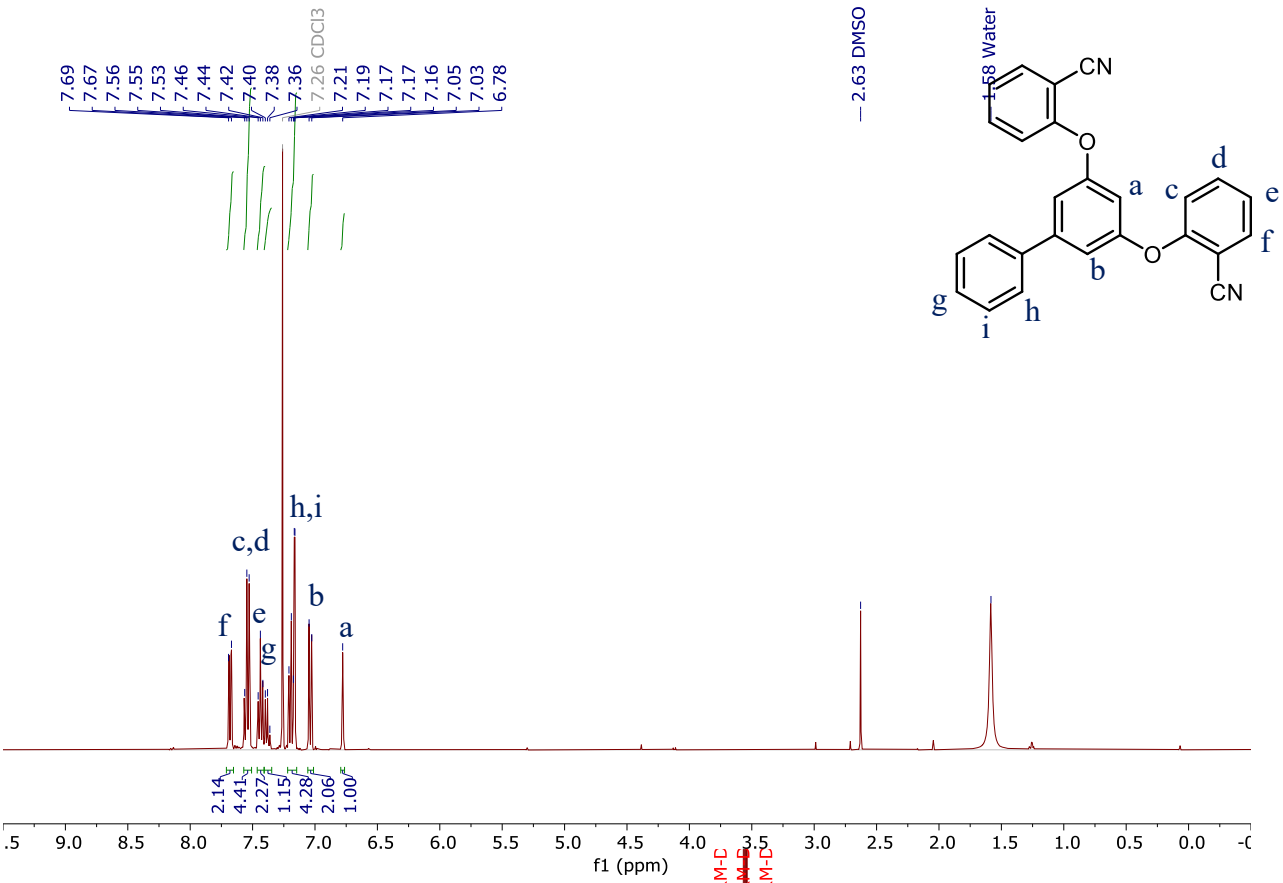
Appendix A: ^{1}H NMR and ^{13}C NMR Spectra of Selected Compounds

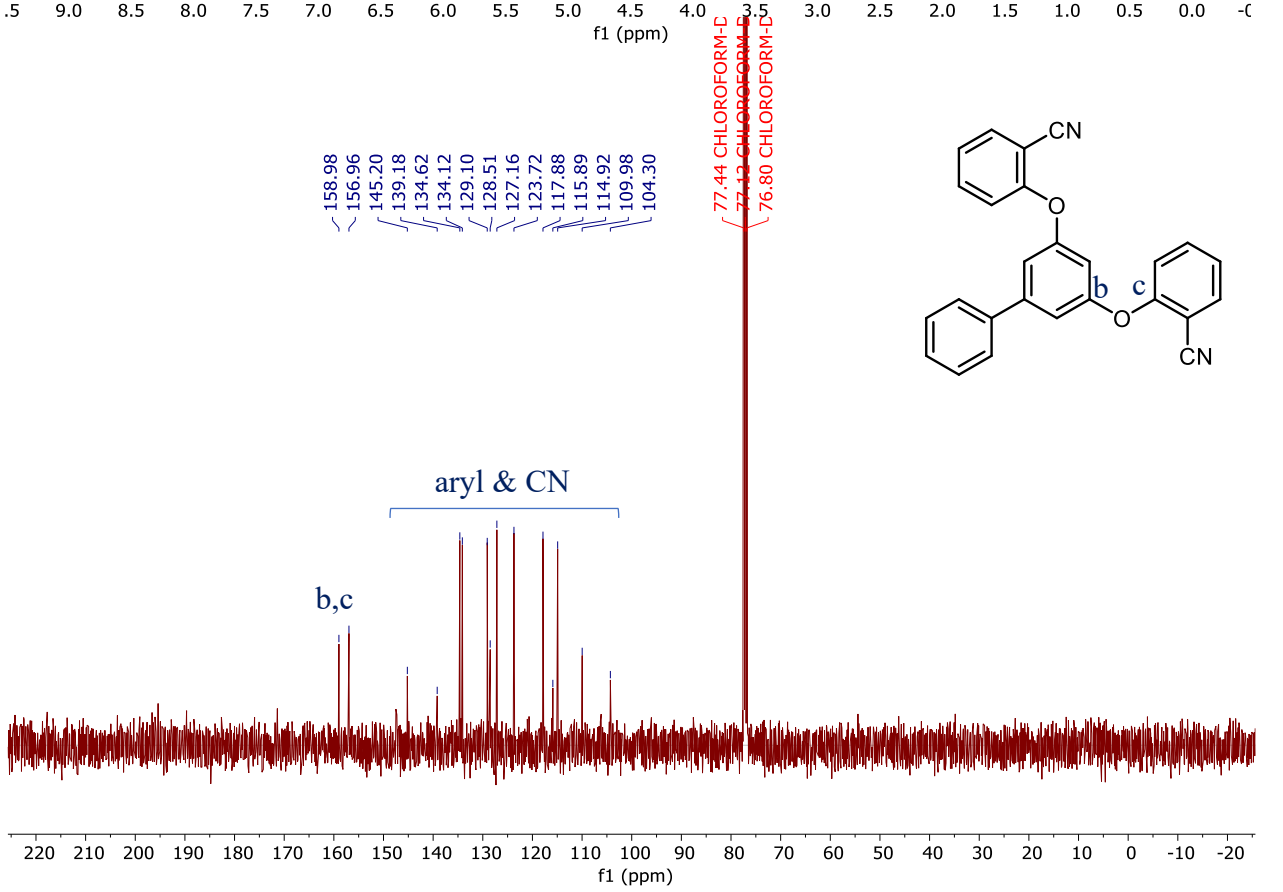

7.66
7.64
7.55
7.54
7.53
7.53
7.52
7.51
7.50
7.26 CDCl3
7.19
7.17
7.15
6.98
6.96
6.75
6.74
6.60
1.58 Water
g 2.35
CN
O
a
c
d
e
f
g
b
O
CN
f
e
d
c
b
a
2.05
2.12
2.12
1.09
1.00
2.06
1.00
3.19
f1 (ppm)

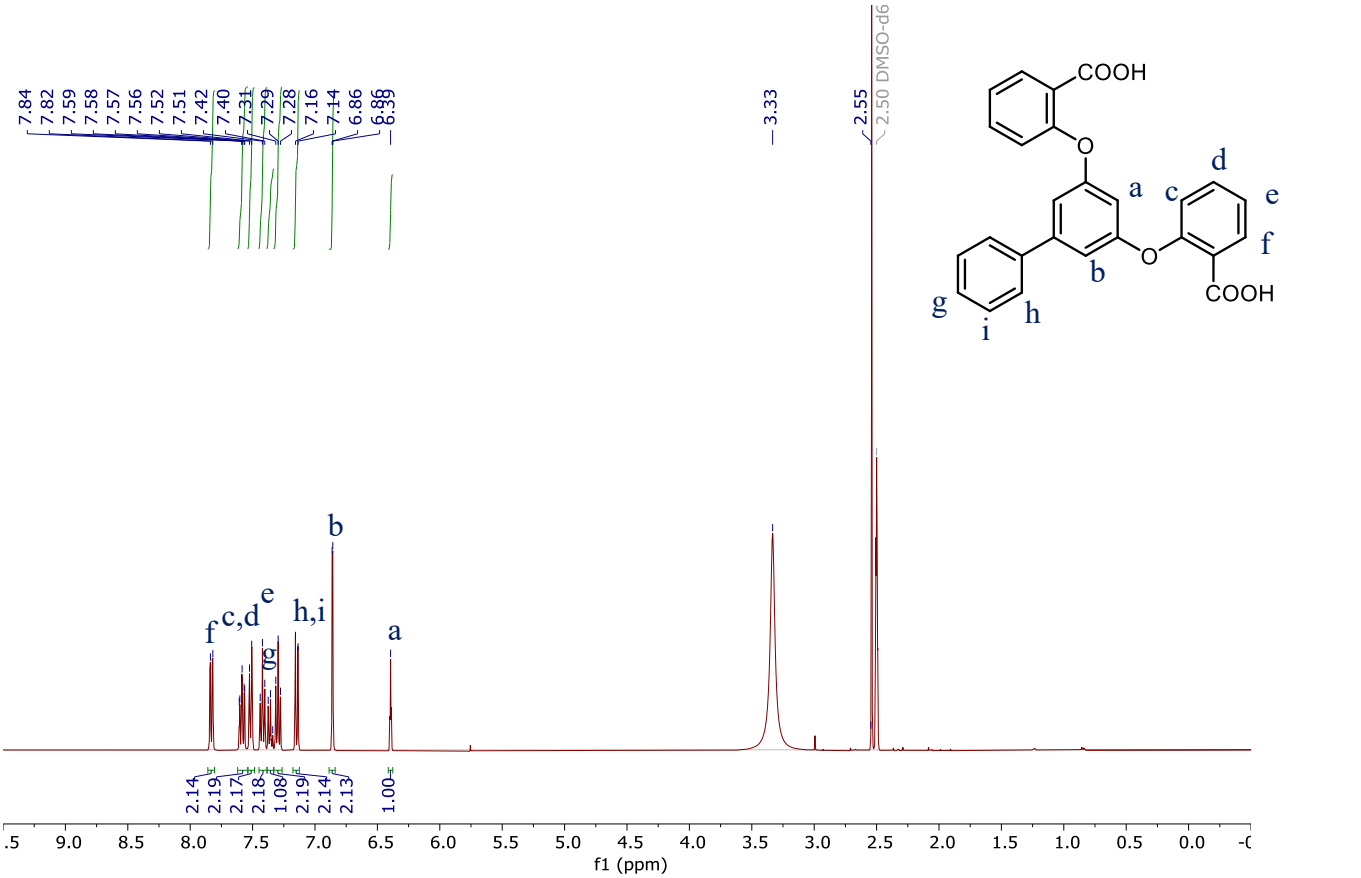

159.12
156.43
142.30
134.54
134.03
123.51
117.82
116.92
115.96
108.54
104.14
77.46 CHLOROFORM-D
77.14 CHLOROFORM-D
76.82 CHLOROFORM-D
CN
O
21.64
a
b
c
O
CN
aryl & CN
b,c
a
f1 (ppm)

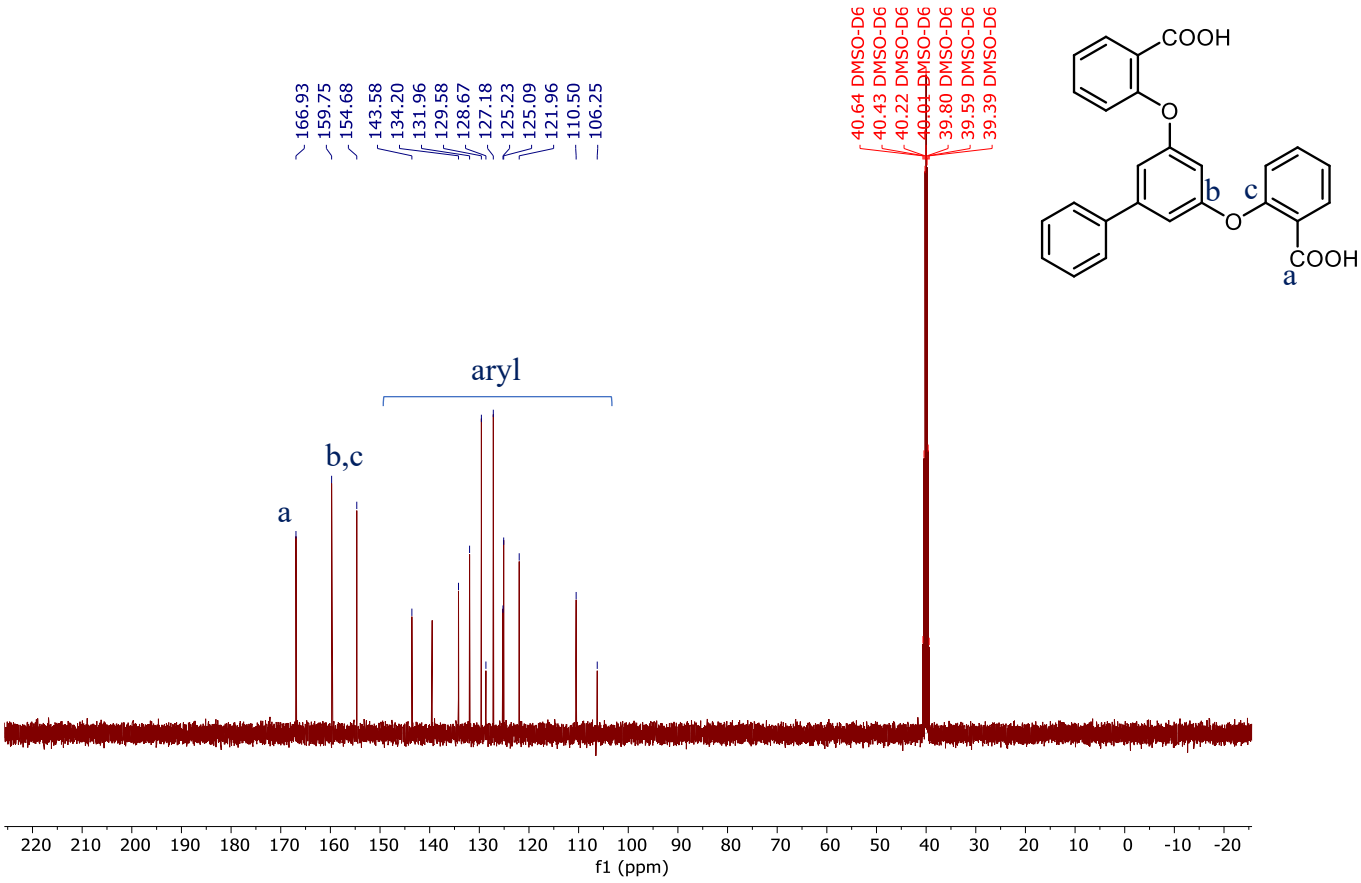

7.81
7.79
7.57
7.55
7.54
7.28
7.26
7.24
7.06
7.04
6.42
6.23
3.37
2.50 DMSO-d6
2.20
COOH
O
a
c
d
e
f
g
b
O
COOH
f
e
d
c
b
a
g
2.03
2.05
2.05
2.05
2.03
1.00
3.05
f1 (ppm)

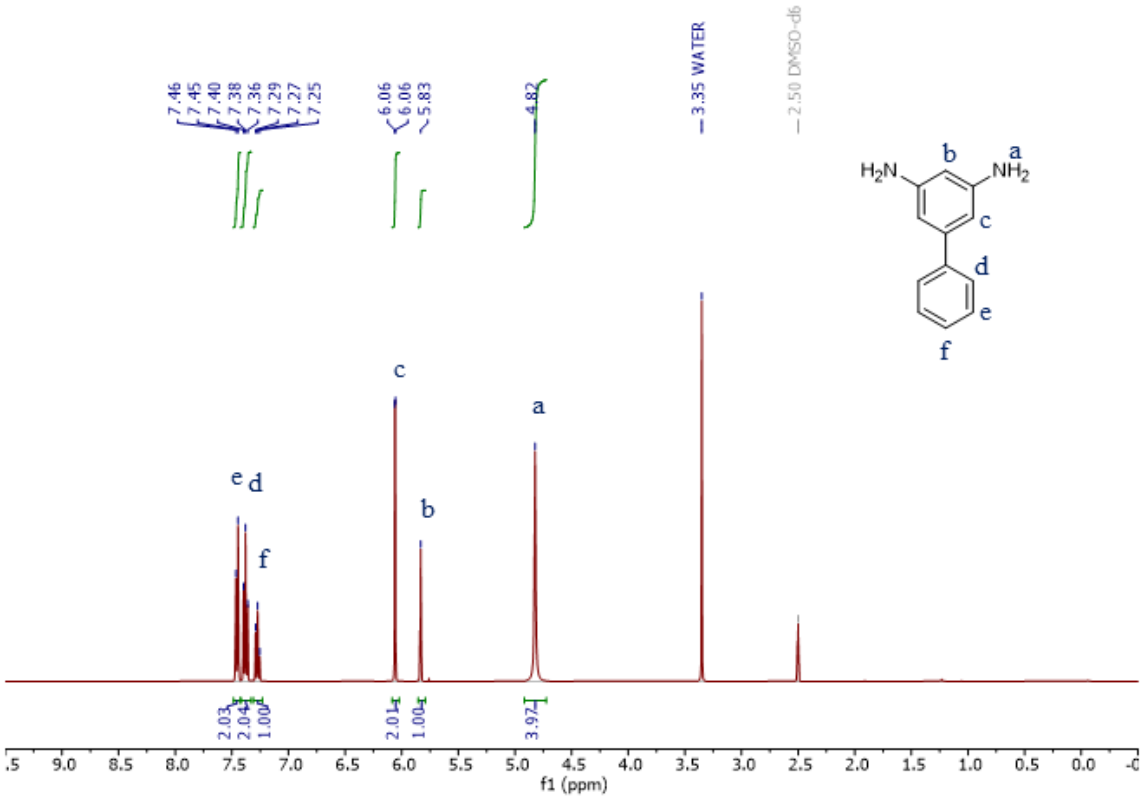

166.93
159.05
154.90
141.35
134.08
131.89
125.08
124.79
121.74
112.91
104.85
40.65 DMSO-D6
40.45 DMSO-D6
40.23 DMSO-D6
39.82 DMSO-D6
39.61 DMSO-D6
39.40 DMSO-D6
21.60
COOH
O
k
b
c
O
COOH
l
aryl
l
b,c
k
f1 (ppm)

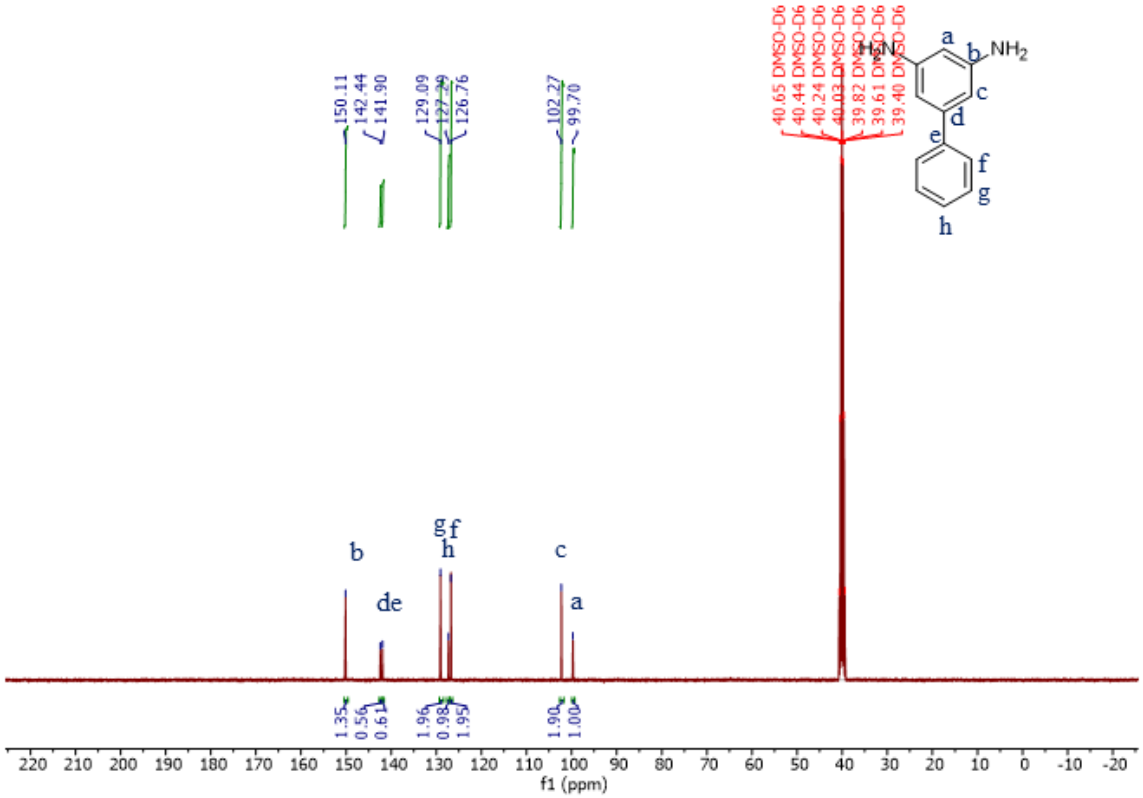

7.69
7.67
7.56
7.55
7.53
7.46
7.44
7.42
7.40
7.38
7.36
7.26 CDCl3
7.21
7.19
7.17
7.17
7.16
7.05
7.03
6.78
2.63 DMSO
1.58 Water
CN
O
a
b
c
d
e
f
g
h
i
O
CN
h,i
c,d
b
a
f
e
g
2.14
4.41
2.27
1.15
4.28
2.06
1.00
f1 (ppm)

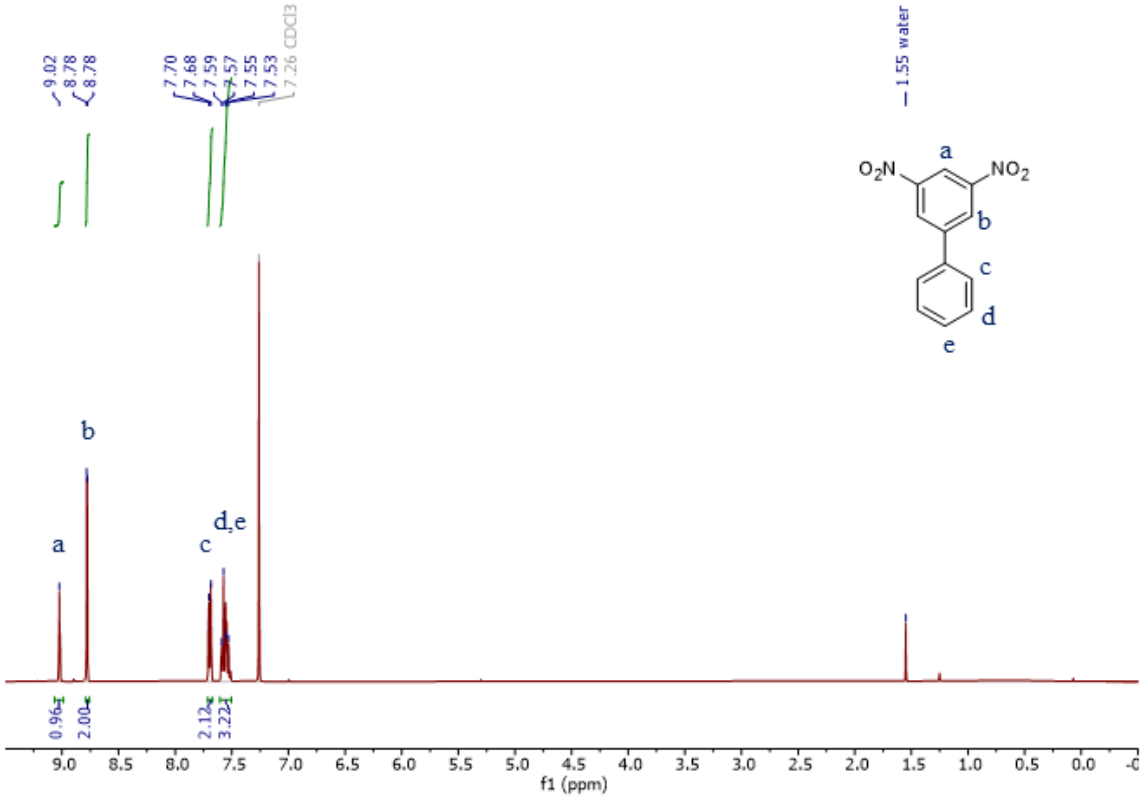

158.98
156.96
145.20
139.18
134.62
134.12
129.10
128.51
127.16
123.72
117.88
115.89
114.92
109.98
104.30
77.44 CHLOROFORM-C
77.13 CHLOROFORM-C
76.80 CHLOROFORM-C
CN
O
b
c
O
CN
aryl & CN
b,c
f1 (ppm)

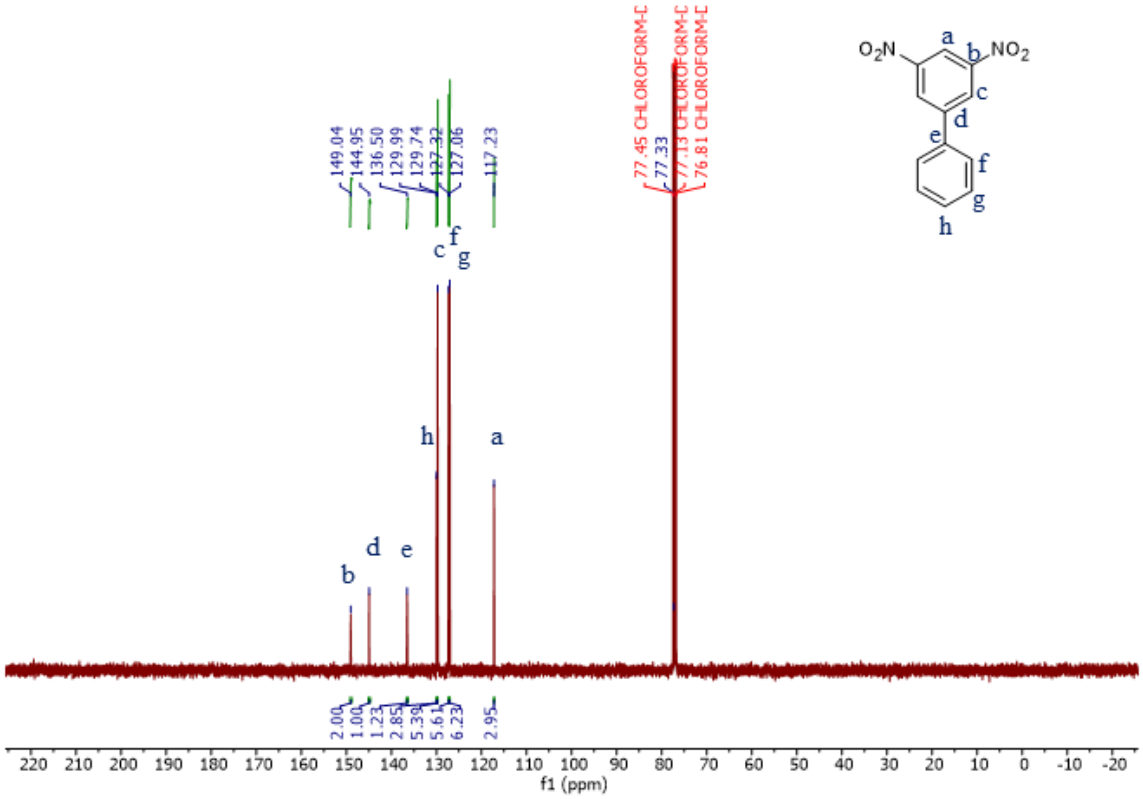

7.84
7.82
7.59
7.58
7.57
7.56
7.52
7.51
7.42
7.40
7.31
7.29
7.28
7.16
7.14
6.86
6.86
6.85
6.85
6.39
3.33
2.55
2.50 DMSO-d6
COOH
O
a
c
d
e
f
b
O
COOH
g
h
i
b
f
c,d
e
h,i
g
a
2.14
2.19
2.17
2.18
1.08
2.19
2.14
2.13
1.00
f1 (ppm)


166.93
159.75
154.68
143.58
134.20
131.96
129.58
128.67
127.18
125.23
125.09
121.96
110.50
106.25
40.64 DMSO-D6
40.43 DMSO-D6
40.22 DMSO-D6
40.01 DMSO-D6
39.80 DMSO-D6
39.59 DMSO-D6
39.39 DMSO-D6
COOH
O
b
c
O
COOH
a
aryl
b,c
a
f1 (ppm)


7.46
7.45
7.40
7.38
7.36
7.29
7.27
7.25
6.06
6.06
5.83
4.82
3.35 WATER
2.50 DMSO-d6
b
a
H_2N
NH_2
c
d
e
f
e d
f
c
b
a
2.03
2.04
1.00
2.01
1.00
3.92
f1 (ppm)


150.11
142.44
141.90
129.09
127.29
126.76
102.27
99.70
40.65 DMSO-D6
40.44 DMSO-D6
40.24 DMSO-D6
40.03 DMSO-D6
39.82 DMSO-D6
39.61 DMSO-D6
39.40 DMSO-D6
a
b
NH_2
H_2N
c
d
e
f
g
h
b
de
g
f
h
c
a
1.35
0.56
0.61
1.96
0.98
1.95
1.90
1.00
f1 (ppm)


9.02
8.78
8.78
7.70
7.68
7.59
7.57
7.55
7.53
7.26 CDCl3
1.55 water
O2N
NO2
a
b
c
d
e
a
b
c
d,e
0.96
2.00
2.12
3.22
f1 (ppm)


149.04
144.95
136.50
129.99
129.74
127.32
127.06
117.23
77.45 CHLOROFORM-D
77.33
77.13 CHLOROFORM-D
76.81 CHLOROFORM-D
O2N
NO2
a
b
c
d
e
f
g
h
h
a
b
d
e
c
f
g
2.00
1.00
1.23
2.85
5.38
5.61
6.23
2.95
f1 (ppm)