Rice University

Development of New Methods for the Synthesis of Novel Biaryls

by

Craig Allen Keene II

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APPROVED, THESIS COMMITTEE

László Kürti, Chair
Associate Professor of Chemistry

K.C. Nicolaou
Professor of Chemistry

Michael Wong
Professor and Chair of Chemical & Biomolecular Engineering

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Abstract

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Craig Keene II

Professor László Kürti

Chapter one of this dissertation gives an overview on the significance of the biaryl motif that is present in thousands of natural products; many of which are used as medicines. This chapter also introduces the concept of axial-chirality and its impact on the synthesis of biaryls. Axially-chiral ligands used in asymmetric catalysis are mentioned as well. Current synthetic strategies are outlined as well as the importance for developing newer, more cost-effective and versatile strategies for their preparation.

Chapters two through five focus on the development of a modular, scalable, transition metal-free approach to 3-substituted-2-nitronaphthalenes, highly stable precursors for the preparation of structurally-diverse $N,N'$-diaryl hydrazines, which are demonstrated to then undergo a $[3,3]$-sigmatropic rearrangement in the presence of a catalytic amount of chiral acid to furnish enantioenriched BINAM derivatives. An organocatalytic synthesis of unsymmetrical biaryls is described as well and the impact of having access to the aforementioned motifs in medicine and chemistry.
Acknowledgements

I would like to thank Professor László Kürti for his encouragement and mentorship since the beginning of my graduate studies in 2011. Within his lab and under his advisement my knowledge of organic chemistry expanded immensely and I attribute much of my chemical understanding to having taken his course and having joined his lab. His steadfast enthusiasm and passion for chemistry will always serve as a source of inspiration.

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Lastly, I would like to thank my parents, Craig and Laura Keene, my sister, Ashely Keene, and my fiancée, Andrea Rodriguez, for their unconditional love and support; without them completing graduate school would have a much more difficult task.
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<td>ee</td>
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<td>$\cdot\text{CH}_2\text{CH}_3$</td>
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CHAPTER 1

Axial-Chirality in Biaryls and their Impact on Society

1.1 The Importance of Biaryls in Medicine

Diazonamide-A, TMC-95A, Biphenomycin, Gossypol, and Vancomycin are just a few examples of well known, biologically active compounds stereoenriched biaryls in medicine.¹

Figure 1.1.1 – Axially-chiral pharmaceutically-active natural products
Biaryls are simply compounds that contain a motif where a $\sigma$ bonds two sp$^2$-hybridized atoms of two aromatic rings together. Though heteroatomic linkages are possible, the most prevalent biaryl bonds in natural products exist between two carbon atoms (Refer to **Figure 1.1**). This simple substructure is also present in stereogenic ligands that happen to be undeniably privileged chiral inductors. These features have generated more attention to this field over the past century into the syntheses of asymmetric compounds containing axially-chiral biaryls such as Vancomycin (**Figure 1.2**), a potent antibiotic used to treat a wide variety of infections caused by Gram-positive bacteria.

**Figure 1.1.2  Structure of Vancomycin**

At the present time our own lab is in the process of developing new methods for the enantioselective construction of biaryls with greater selectivity as well as being able to access a
diverse library of previously inaccessible biaryl molecules for medicinal as well as synthetic applications.

1.2 Axial-Chirality in Biaryls

Axial-chirality refers to a scenario in which H-atoms in the 2- and 6-positions on the aromatic rings of biaryls have been substituted with larger substituents functional groups that raise the activation barrier for rotation about the biaryl axis due to steric repulsion. When the activation barrier becomes significant enough (~22.5 kcal/mol at 27 °C), rotation about the biaryl axis halts, resulting in a pair of atropisomers (enantiomers of axially-chiral molecules). Activation barriers can be overcome by providing enough energy to overcome the rotational barrier either in the form of heat or in some cases irradiation.

Figure 1.2.1 – Central vs. axial chirality
This type of chirality is in stark contrast to central chirality by which interconversion between enantiomers must involve a bond-breaking event followed by new bond formation as shown in Figure 1.2.1.

Some axially-chiral natural products, such as Ancistrocladine, have exceedingly high rotational barriers resulting in the molecule’s decomposition before rotation (racemization) occurs (Shown in Figure 1.2.2.)

![Figure 1.2.2. – Aromatization of (S)-Ancistrocladine with retention of axial-chirality](image)

As is the case with numerous enantiomers bearing central chirality, it is often the case that opposite enantiomers interact differently with their targeted receptors giving them drastically different pharmacological profiles. With the axially-chiral compound Gossypol isolated from the seeds of the cotton plant, seen in Figure 1.1.1, it was found that while the (S)-enantiomer of gossypol exhibited anti-HIV properties when administered to patients, the (R)-enantiomer resulted in male sterility by interfering with spermatogensis.
1.3 Current Methods for the Asymmetric Preparation of Biaryls

Historically, axially-chiral biaryls were prepared by resolving racemic mixtures using diastereomeric resolution. At the beginning of the 21st century major advances in the way of new and chemically-distinct approaches to this important class of molecules had begun to arise. With the growing knowledge of transition metal-catalyzed cross-couplings, many methods using this approach were established with the last decade seeing the most dramatic increase in number of publications describing new syntheses of this class of compounds.

**Scheme 1.3** Summary of new methods used for the synthesis of axially-chiral biaryls

The number of methods to synthesize enantioenriched axially-chiral biaryls also began to increase over the past ten years (See **Scheme 1.3**)
1.3.1 Intermolecular Oxidative Homocouplings

Several efficient Cu, V and Ru-based chiral catalytic systems performing homocouplings of naphthols have been reported at the end of the 20\textsuperscript{th} and 21\textsuperscript{st} centuries. More recently it was demonstrated that aerobic oxidative homocouplings are compatible with air as the terminal, green oxidant.


\textbf{Scheme 1.3.1} Oxidative cross-coupling of 2-naphthols

With enantioselectivity being their primary goal, Luo and Gong designed a new H\textsuperscript{8}-BINOL-based bimetallic oxovanadium complex.\textsuperscript{2} Remarkable enantioselectivity and yields were achieved (See Scheme 1.3.1). Katsuki reported in 2009 a complementary strategy to Luo and Gong’s based on the use of an Fe(salan) catalyst system that was compatible with 2-naphthols bearing non-coordinating substituent at position 3.
1.3.2 Synthesis of Atropisomeric Biaryls from Achiral Starting Materials

In 2014 Sparr reported a chiral tetrazole-catalyzed aldol condensation reaction from \(z\)-ketoaldehydes which undergo dienamine formation. He claimed that rotation about the alkene-aryl bond places the dienamine moiety, formed under the described conditions, in the proper chemical space to facilitate the expected aldol condensation with efficient transfer of stereochemical information during the dehydration step.\(^3\)


\[
\text{OHC} \quad \text{N} = \text{N} \quad \text{CHO}
\]

\[
\begin{array}{c}
\text{N} = \text{N} \\
5 \text{ mol \%}
\end{array}
\]

\[
\text{CDCl}_3, \text{ rt}
\]

74% yield, 98% ee

**Scheme 1.3.2** Atroposelective Intramolecular Aldol Condensation

This transformation affords \(o\)-formyl binaphthyls and proceeds under very mild reaction conditions and gives excellent enantioselectivity and good yields. However, starting materials bearing substituents on either the 2- or 8-position do not undergo the transformation, severely limiting the substrate scope.
1.3.3 Dynamic Kinetic Resolution of Racemizing Chiral Biaryls

Dynamic kinetic resolution has always been considered a very reliable approach toward the synthesis of optically-enriched molecules. One very important example of performing kinetic resolution to access precursors to chiral ligands such as BINAM was shown by Tian, Liu, and Tan.


![Scheme 1.3.3 Kinetic resolution of a BINAM derivative](image)

The role of BINOL-derived scaffolds such as the one used in the catalyst (See Scheme 1.3.3) is to create a chiral environment around the iminium ion intermediate to bias the subsequent reduction with a Hantzsch ester giving a mixture of separable diastereomers. This method of preparation has gained considerable attention and therefore many diverse synthetic approaches have been based on kinetic resolution methodology.
1.3.4 Transition Metal-Catalyzed Aryl-Aryl Coupling

Buchwald showed in 2010 an enantioselective preparation of biaryls phosphine oxides through a Pd-catalyzed Suzuki-Miyaura Reaction. (See Scheme 1.3.4)

Scheme 1.3.4  Suzuki-Miyaura cross-coupling

This is just one demonstration of a number of Pd-catalyzed Suzuki-Miyaura transformations to establish biaryls enantioselectively that have been established over the past decade. Each of these transformations has conditions that have been optimized for a specific substrate scope wherein lies a major limitation for this class of transformations. Also, the reaction is limited to using tri-substituted binaphthyl and biphenyl compounds.
1.3.5 Traceless Central-to-Axial Chirality Exchange via Organocatalysis

Further complementing the above strategies are methods that transfer existing central-chirality into axial-chirality. During a reaction as such, the stereogenic centers present promote an efficient transfer of the chirality thereby delivering atropisomerically-enriched biaryls. One particular example was shown in 2011 by Thompson and collaborators. They were able to demonstrate that sterically-congested bicyclic diones with four stereogenic centers would transfer its existing chirality into enantioenriched biphenols under aromatization conditions (See Scheme 1.3.5).


Scheme 1.3.5 Central-to-axial chirality exchange

Aromatization happens without rotation about the central C-C bond which explains why the chirality is conserved.
1.4 Summary

This chapter illustrates the biological and chemical significance of axially-chiral biaryls in multiple fields of science. From a medicinal standpoint biaryl natural products have enormous potential to eventually become mainstream antibiotics, anti-cancer agents and even anti-HIV drugs. While there have been great strides taken toward the synthesis of axially-chiral biaryls in an enantioselective fashion, in general, most syntheses of axially-chiral biaryls are limited in their substrate scope, creating a need for further synthetic approaches that can achieve the construction of biaryl scaffolds efficiently and selectively without chemo-, regio-, and stereochemical issues arising. While certain axially-chiral biaryl ligands such as BINAM and BINOL have been shown to be widely applicable in asymmetric transformations, further functionalization of these ligands is a lengthy process and necessitating new synthetic methods to be developed making functionalization of the naphthalene subunits of the biaryls simple and efficient. This will allow access to previously unknown axially-chiral biaryls that traditional methods cannot.
1.5 References


CHAPTER 2

An Organocatalytic Atroposelective $[3,3]$-Rearrangement of $N,N'$-Dinaphthylhydrazines to Afford BINAM Derivatives


and


2.1 Introduction

During the past 20 years axially chiral biaryl compounds$^{1-3}$ have played a key role as ligands in the development of many catalytic enantioselective transformations, including transition metal-catalyzed cross-coupling reactions.$^{4-6}$ Without exaggeration it can be stated that axially chiral non-racemic biaryls (e.g., BINAP, BINOL and their derivatives) have become the
most successful class of ligands in history with a wide range of catalytic enantioselective processes, including several that are performed routinely on an industrial scale.\textsuperscript{4,7-11}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ligands.png}
\caption{Examples of axially-chiral biaryl ligands used in asymmetric synthesis}
\end{figure}

Given the abundance of axially chiral biaryl compounds in nature as well as their importance in asymmetric catalysis (See Figure 2.1.1) and materials science, it is surprising that relatively few methods are available for their atroposelective synthesis.\textsuperscript{2,12,13} Current strategies\textsuperscript{14-20} for the synthesis of axially chiral nonracemic biaryls (Figure 2.1.2) include resolution of racemic biaryls, desymmetrization of preformed prohiral biaryls, dynamic kinetic resolution of rapidly racemizing preformed chiral biaryls\textsuperscript{14,20}, transition metal-catalyzed aryl-aryl coupling\textsuperscript{12,15}, \textit{de novo} construction of an aromatic ring\textsuperscript{16} and traceless central-to-axial chirality exchange\textsuperscript{17} (Scheme 2.1).
Scheme 2.1  Proposed mechanism of central-to-axial chirality transfer

The broad scope of reaction conditions tolerated by these ligands and catalysts make them ideal for further exploration. It became apparent that newer and more robust methods should be developed not only to broaden the structural diversity possible but perhaps more importantly to have the ability to create new ligands that existing methods cannot.

Figure 2.1.2  Different approaches toward axially-chiral biaryls construction

I: Traditional resolution or desymmetrization via dynamic kinetic resolution; II: Direct atroposelective biaryl coupling (via metal-catalyzed cross-coupling or oxidation); III: Atroposelective biaryl synthesis by de novo construction of an aromatic ring; IV: Traceless central-to-axial chirality exchange.
While the methods outlined in Figure 2.1.2 are influential, they all have limited substrate compatibility; therefore new and powerful synthetic strategies are needed to complement existing methods. Recently, we became intrigued by the possibility of achieving the first organocatalytic atroposelective biaryl synthesis using $N,N'$-diaryl hydrazines as substrates (Scheme 2.2).

2.2 The Thermal vs. Acid-Catalyzed [3,3]-Sigmatropic Rearrangement of 2,2’-Hydrazonaphthalene

In 1960 Henry Shine began exploring the kinetics of the well-known, yet, still not fully-understood [5,5]-sigmatropic rearrangements of 2,2’-hydrazobenzenes and the [3,3’]-sigmatropic rearrangement 2,2’-hydrazonaphthalenes. His seminal work in understanding the kinetics of the rearrangement gave a breadth of knowledge to the chemical community that ultimately opened up the doors for further exploration into various rearrangements of 2,2’-hydrazoarenes. The thermal or acid-mediated [3,3]-rearrangement of $N,N'$-diaryl hydrazines, a process known for nearly 110 years, leads to the formation of a new C(sp$^2$)-C(sp$^2$) bond between two aromatic rings. This remarkable transformation does not require the use of transition metals, halogen atoms or other replaceable substituents: the two reacting C(sp$^2$)-H bonds are not activated in any way and reactive intermediates (e.g., carbenes, carbon-centered radicals, carbanions or carbocations) are not involved in the process.
A thorough literature search yielded a single report in 1985 by Sannicolo in which an attempted non-catalytic enantioselective rearrangement of 2,2'-hydrazonaphthalene (2.2) to BINAM (2.3), requiring a large excess (3-6 equivalents) of (+)-camphor-10-sulfonic acid (CSA), is described. The observed enantiomeric ratio (er) for BINAM was very low (57.5:42.5). No further studies to render this transformation or any other closely related transformation that furnish biaryls in a catalytic or highly enantioselective fashion have been reported.

It was decided that 2,2'-hydrazonaphthalene would be used as the preferred substrate due to a restricted possibility of only 2 rearrangements possible as the other possible available positions are substituted (See Figure 2.3.)

![Figure 2.3 – The two major expected pathways for the benzidine-type rearrangement](image)

We surmised that with careful screening of catalysts, solvents and temperatures, a set of ideal conditions could be identified that would facilitate the catalytic and highly atroposelective rearrangement of N,N'-biaryl hydrazines to biaryl amines. We chose 2.2 as our preferred
substrate over other $N,N'$-biaryl hydrazines since its substitution pattern allows the formation of only two possible regioisomeric $[3,3]$-rearrangement products (2.3 and 2.31, Figure 2.3); the $[5,5]$- and $[3,5]$-pathways were not expected to compete. Our initial hypothesis was that the ideal catalyst would activate 2.2 by engaging both nitrogen atoms. To maximize the hydrogen bonding between 2.2 and the acid catalyst, toluene was chosen as the solvent and a catalyst loading of 20% was used. Presumably, the greater acidity of the catalyst would promote rate-acceleration of the reaction.\textsuperscript{30}

### 2.3 Preparation of Starting Materials

Synthesis of BINAM and derivatives thereof must begin with the construction of the monomer 2-naphthylamine (2-aminonaphthalene). Copper-catalyzed transformations involving

\[
\begin{align*}
\text{2.01} & \quad \text{NH}_2\text{OH-HCl} (1.1 \text{ equiv}) \\
& \quad \text{NaOAc} (1.2 \text{ equiv}) \\
& \quad \text{MeOH, 50 °C, 8 h} \\
& \quad 99\% \\
\rightarrow & \quad \text{2.02} \\
\text{2.03} & \quad \text{NaOH (4 equiv)} \\
& \quad \text{EtOH/H}_2\text{O (1:1)} \\
& \quad 90 °C, 24 h \\
& \quad 99\% \\
\rightarrow & \quad \text{2.02} \\
& \quad \text{ZnCl}_2 (10 \text{ mol%}) \\
& \quad \text{pTSA (10 mol%)} \\
& \quad \text{MeCN, 80 °C, 16 h} \\
& \quad 81\% \\
\rightarrow & \quad \text{2.1}
\end{align*}
\]

\textbf{Scheme 2.2} Preparation of the 2-aminonaphthalene monomer
a boronic acid in the 2-position of the naphthalene nucleus or a halogen with an aminating agent are well-known methods for 2-naphthylamine preparation.\textsuperscript{31,32}

Alternatively it has been shown that in the presence of catalytic bronsted acids in combination with a catalytic lewis acid such as Zn that ketoximes (2.02) undergo the Beckmann Rearrangement in which the aromatic ring migrates onto the nitrogen followed by trapping by water to give amide (2.03). Hydrolysis under acidic or basic conditions yields the corresponding 2-naphthylamine 2.1 in excellent yields and was scaled up to 0.3 mol.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.8\textwidth]{Scheme2.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.3} Preparation of 2,2’-hydrazonaphthalene from 2-naphthylamine

Once ample quantities of 2-naphthylamine (2.1) had been acquired \textit{via} the synthetic sequence described in \textbf{Scheme 2.2} we turned our attention to the well-known method of converting anilines to their corresponding azoarenes and followed by a Zn-mediated reduction yields diaryl hydrazines (\textbf{Scheme 2.3}). In the case of completely planar azo compounds such as 2.11, purification can become quite difficult due to solubility issues and column chromatography is not a viable solution for this very reason.
2.4 Organocatalytic-Atroposelective Benzidine-Type Rearrangement of 2,2’-Hydrazonaphthalene

Thus we turned our attention to BINOL-derived chiral phosphoric acids as catalysts. Variation of the steric bulk and electronic properties of substituents at the 3- and 3’-positions resulted in dramatic changes both in the reaction rate and the level of asymmetric induction. Catalysts bearing fused aromatic rings or aromatic rings with electron-withdrawing groups as substituents led to faster rearrangements. The presence of CF₃ groups on the aromatic rings in the 3- and 3’-positions led to a dramatic rate enhancement.

Scheme 2.4 Optimized benzidine-type rearrangement of 2,2’-hydrazobenzene to BINAM

Experimental observations showed that when the H⁸-axially-chiral BINOL-derived phosphoric acid (2.3) was employed in catalytic quantities (5 mol%) in toluene a 92:8 er was
achieved. DFT calculations performed indicated that due to the non-polar nature of hydrocarbon solvents such as toluene, tight-ion pairs are promoted due to the low dielectric constant of the non-polar solvent.\textsuperscript{35} With the chiral phosphate ion being in close proximity to the protonated 2,2’-hydrazonaphthalene, higher degrees of enantioselectivity are achieved due to the interaction of the chiral pocket of the ligand with the rearranging 2,2’-hydrazonaphthalene.

The practicality of this powerful catalytic atroposelective method could also be convincingly demonstrated. The optimized procedure performed well on a 2-10 mmol (up to 2.8 g) scale, affording 88-90\% isolated yield of 2.3 with up to 92:8 \textit{er} (Scheme 2.4). Remarkably, the catalysts could be recovered in nearly quantitative yield (99\%) after flash chromatography and, a single recrystallization of the enantiomerically enriched 2.3 from toluene yielded optically pure (>99.5:0.5 \textit{er}) material.
2.5 Transition-State Model for Atroposelective [3,3]-Sigmatropic Rearrangement

To understand the role of the chiral phosphoric acid catalyst and stereoselectivity, we have used M06-2X/6-31G(d,p) density functional calculations in CPCM-toluene solvent to model the rearrangement 2.2→2.3 catalyzed by 2.4. Figure 3 shows TS-3S and TS-3R, which are the lowest energy enantiomeric C-C bond forming transition states leading to the dearomatized intermediate from 2.2. TS-3S has a $\Delta G^\ddagger$ of 20.0 kcal/mol and TS-3R has a $\Delta G^\ddagger$ of 22.2 kcal/mol at 253 K relative to free catalyst and substrate. These $\Delta G^\ddagger$ values are ~14 kcal/mol lower than for uncatalyzed reaction. The model features the phosphoric acid proton fully transferred from the catalyst to one of the N atoms of 2.2 and the phosphate acts as a chiral counterion. This protonation lowers the barrier by charge polarization of the nitrogen-nitrogen bond. Transition states without proton transfer were found to be several kcal/mol higher in energy. After proton transfer the phosphate counterion interacts with protonated 2.2 in a bidentate fashion involving two hydrogen bonding interactions.
Figure 2.4  Transition state models for the 2.4-catalyzed [3,3]-rearrangement of \(N,N'\)-dinaphthyl hydrazine
The free energy difference between \textbf{TS-3S} and \textbf{TS-3R} is 2.2 kcal/mol at 253 K. We have confirmed the in silico predicted preferential formation of the (S)-enantiomer using chiral HPLC. The C-C bond forming step in \textbf{2.2→2.3} is likely a stereo-determining step because rearomatization via phosphate anion deprotonation and proton shuttling to set the axial chirality occurs via amino groups twisting past each other while avoiding naphthyl groups twisting past each other. Stereoselectivity in the C-C bond forming transition states is the result of both steric and electronic effects. The chiral counterion creates a spatial chiral pocket to house one protonated \textbf{2.2} species. In addition, the electron deficient CF$_3$ groups of catalyst (\textit{R})-\textbf{2.4} induce significant C-H bond- and \pi-\pi-aryl interactions that favor \textbf{TS-3S} over \textbf{TS-3R}.

\textbf{2.6 Conclusions}

In conclusion, we have successfully developed the first organocatalytic atroposelective synthesis of biaryl amines, exploiting a facile [3,3]-rearrangement. The demonstration that a catalytic amount of a chiral BINOL-derived phosphoric acid could efficiently catalyze the [3,3]-sigmatropic rearrangement of 2,2’-hydrazonaphthalenes demonstrated the first Organocatalytic aryl-aryl bond formation to construct BINAM. Using density functional calculations of the C-C bond forming step, we can predict the absolute configuration of the axially chiral biaryl products. This approach also allows us to engage in the rational design of more effective catalysts and explore related rearrangements. We are in the process of expanding the scope of this powerful atroposelective method to unsymmetrical diaryl hydrazines, though more diverse methods for
their preparation are needed. The axially chiral and structurally diverse diaryl products are expected to find broad utility in asymmetric catalysis, drug discovery as well as materials science.

During the course of this study it became apparent that the inherent solubility issues of the intermediate azonaphthalenes due to $\pi - \pi$ stacking made it necessary for large quantities of solvents to be used for recrystallization purposes. Another shortcoming was the reality that substituted 2-naphthylamines are not readily available; commercially or synthetically. Specifically it has been shown that BINAM derivatives with substituents in the 3- and 3’-positions typically lead to increased enantio-induction by increasing the chiral space accessible. Literature reports of naphthalene syntheses prompted focus to be drawn to developing a newer streamlined approach to substituted 2-naphthylamines. (See Chapter 3).
2.7 Experimental Details

2.7.1 Materials and Methods

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring unless otherwise indicated. Commercially obtained reagents were used as received. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). $^1$H and $^{13}$C NMR spectra were recorded on Varian Inova-400 or 500 spectrometers. Data for $^1$H NMR spectra are reported relative to chloroform as an internal standard (7.26 ppm) and are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for $^{13}$C NMR spectra are reported relative to chloroform as an internal standard (77.00 ppm) and are reported in terms of chemical shift (δ ppm). Optical rotations were measured on a JAS DIP-360 digital polarimeter. Chiral HPLC analyses were performed on an Agilent 1290 Series system. HRMS data was performed on a Shimadzu LCMS-IT-TOF under the conditions of electrospray ionization (ESI) in both positive and negative mode. Infrared spectra were collected on a Shimadzu IRPrestige- 21 (Fourier Transform Infrared Spectrophotometer) at Shimadzu Center for Advanced Analytical Chemistry, The University of Texas at Arlington. All the catalysts were synthesized and identified with that as literature reported.
2.7.2 Detailed Experimental Procedures

Synthesis of starting materials

**Preparation of (E)-1-(naphthalen-2-yl)ethan-1-one oxime 2.02**

To a 1 L round bottom flask equipped with a magnetic stir bar was added 2-acetonaphthone 2.01 (51.1 g, 0.3 mol) and MeOH (600 mL). Sodium acetate (29.53 g, 0.36 mol, 1.2 equiv) and hydroxylamine hydrochloride (22.93 g, 0.33 mol, 1.1 equiv) was added to the flask before heating the mixture to 50 °C for 8 hours until TLC analysis indicated consumption of the starting material. The flask was allowed to cool to room temperature before the solvent was removed in vacuo followed by dilution with DCM (300 mL). The crude mixture is then poured into a 1 L
separatory funnel and H$_2$O (400 mL) is added. The mixture is then shaken and the organic layer is drained. The aqueous phase in the separatory funnel is extracted with DCM (4 x 150 mL) and the combined organic phases are dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to give 55.0 g of 2.02 as a white solid, 99% isolated yield, which was used in the subsequent reaction (2.02→2.03) without purification. $^1$H NMR (400 MHz, CDCl$_3$): 8.03 (s, 1 H), 7.89-7.83 (m, 4 H), 7.53-7.50 (m, 2 H), 2.43 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$): 183.1, 156.2, 133.5, 133.1, 128.5, 128.2, 127.7, 126.8, 126.4, 126.1, 123.3, 12.2.

**Preparation of N-(naphthalen-2-yl)acetamide 2.03**

A 50 mL round bottom flask, equipped with a magnetic stirrer and reflux condenser, was charged with 55 g oxime 2.02 (0.3 mol), 5.71 g TsOH·H$_2$O (30 mmol, 10 mol%), 4.1 g ZnCl$_2$ (30 mmol, 10 mol%) and acetonitrile (500 mL). The reaction mixture was refluxed for 12 h and then cooled to room temperature. The reaction was then cooled to room temperature and the solvent was removed in vacuo. The crude material was dissolved in 500 mL of DCM and added to a 500 mL separatory funnel with 250 mL H$_2$O. The aqueous phase was extracted with DCM (3 x 75 mL), dried over anhydrous Na$_2$SO$_4$, filtered, concentrated in vacuo. The resulting solid was then recrystallized using 20% EtOAc/hexanes to afford 44.6 g of 2.03 as a white solid with the appearance of glitter, 81% isolated yield. $^1$H NMR (400 MHz, CDCl$_3$): 8.18 (s, 1 H), 7.96 (br s,
1 H), 7.77-7.72 (m, 3 H), 7.48-7.37 (m, 3 H), 2.21 (s, 3 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 168.9, 135.4, 133.7, 130.6, 128.6, 127.6, 127.5, 126.4, 125.0, 120.0, 116.7, 24.5.

**Synthesis of 2-Naphthylamine 2.1**

![2.1](image)

To a 1 L round bottom flask equipped with a magnetic stir bar is added 40 g of 2.03 (0.22 mol), EtOH (220 mL), and H\(_2\)O (220 mL). NaOH 38.4 g (0.96 mol, 4 equiv) was then added to flask along with a reflux condenser. The solution was allowed to reflux at 90 \(^\circ\)C for 24 hours before the yellow solution was allowed to cool. The solution was added to a 1 L separatory funnel and diluted with 300 DCM (degassed with Ar for 30 min). The mixture was extracted with the degassed DCM (3 x 200 mL), the combined extracts dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to afford 30.6 g of 2.1 as a glittery white solid. No further purification was necessary. \(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.69-7.63 (m, 2 H), 7.58 (d, \(J = 8.0\) Hz, 1 H), 7.36 (m, 1 H), 7.23-7.19 (m, 1 H), 6.95-6.90 (m, 2 H), 3.78 (br s, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 144.0, 134.8, 129.1, 127.9, 127.7, 126.3, 125.8, 122.4, 118.2, 108.5.
Preparation of \( N,N'-2,2'-\text{azonaphthalene} \) 2.11

To a vigorously stirred solution of naphthalen-2-amine 2.1 (2.0 mmol) in 5 mL of 1N HCl were added successively H\(_2\)O (100 mL) and concentrated HCl (0.18 mL), then the mixture was cooled to 0 °C. Next, concentrated H\(_2\)SO\(_4\) solution (0.22 mL) in 2.0 mL of water was also added and the suspended amine salt was stirred vigorously and diazotized by slowly adding, below the surface, a cold solution of NaNO\(_2\) (144mg, 2.1 mmol) in 3.0 mL H\(_2\)O. The cold reddish brown solution of the diazonium salt was allowed to stand for 15 min and was then filtered, and the filtrate was transferred into a beaker in an ice-water bath. A cold solution of anhydrous NaOAc (0.68 g) in H\(_2\)O (3.0 mL) was added while the system was kept under 5 °C. A cooled solution of Na\(_2\)SO\(_3\) (320 mg) in H\(_2\)O (20 mL) was slowly added below the surface causing nitrogen evolution and formation of the crude \( N,N'-2,2'-\text{azonaphthalene} \). After the addition was complete, the mixture was stirred for 15 min, and removed from the ice-water bath, then Et\(_2\)O (1.5 mL) was added to induce coagulation. The precipitate was filtered off after over-night standing, washed with water,
and dried in vacuo. A corresponding \( N,N' \)-2,2'-azonaphthalene 2.11 was obtained and it was used in next step without any further purification.

**Synthesis of \( N,N' \)-2,2'-Hydrazonaphthalenes 2.2**

![Diagram of 2.2]

To a solution of \( N,N' \)-azonaphthalene 2.11 (1.0 mmol) in acetone (100 mL) at 0 °C, zinc dust (650 mg, 10 mmol) was added and then the mixture was stirred vigorously at 0 °C. Next, a saturated aqueous solution of NH\(_4\)Cl was added drop-wise until the color of the reaction mixture faded completely. After standing for 20 min in an ice-water bath, the colorless mixture was filtered under argon atmosphere. The filtrate was received in a flask containing a solution of 5% NH\(_3\)H\(_2\)O (200 mL), after stirring for 15 min, removed the solvent (i.e., acetone) under reduced pressure until a colorless solid appeared, then kept the mixture for 3 h at 4 °C, and filtered. The desired \( N,N' \)-2,2'-Hydrazonaphthalene 2.2 was obtained as a colorless solid, 93% isolated yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): 7.70 (d, \( J = 8.4 \) Hz, 4 H), 7.57 (d, \( J = 8.4 \) Hz, 2 H), 7.37-7.33 (m, 2 H), 7.13 (d, \( J = 2.4 \) Hz, 2 H), 7.08-7.05 (m, 2 H), 5.76 (br s, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 146.2, 134.7, 129.4, 128.9, 127.7, 126.5, 126.4, 123.0, 115.4, 106.1.
References


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CHAPTER 3

A New Benzannulation Approach for the Construction of 3-Substituted-2-Aminonaphthalenes

Parts of this chapter have been adapted from: Keene, C.; Kürti, L., “Regiospecific Synthesis of Novel Cyclic Nitrostyrenes and 2-Nitronaphthalenes” *Synthesis* 2013, 45, 1719-1729.

and


3.1.1 Introduction

Our group is pursuing the development of powerful and practical new methods for the synthesis of highly functionalized symmetrical and unsymmetrical biaryls. Given the remarkable track record of axially chiral biaryls as highly efficient ligands in asymmetric synthesis, it is clear that having convenient synthetic access to many structurally diverse and uniquely functionalized biaryls will have a profound impact on the discovery of new chemical reactivity. The first
scalable organocatalytic atroposelective synthesis of BINAM derivatives was recently demonstrated in our laboratory utilizing a remarkably efficient [3,3]-sigmatropic rearrangement of $N,N'$-dinaphthyl hydrazines in the presence of 5 – 20 mol% of chiral acid catalysts (Figure 3.1.1). The required $N,N'$-dinaphthyl hydrazine substrates were prepared from the corresponding substituted 2-naphthylamines in a three-step procedure that involves: (a) diazotization, (b) reduction of the diazonium salt to the corresponding symmetrical azo

![Diagram](image)

**Figure 3.1.1** Representative BINAM preparation from 2-naphthylamine via a [3,3]-sigmatropic rearrangement

compound, and (c) reduction of the azo group with Zn/NH$_4$Cl. However, convenient and readily scalable synthetic access to a wide variety of substituted 2-naphthylamines, especially to 3-alkyl- and 3-aryl-2-naphthylamines, still remains a significant challenge.
3.1.2 A Brief Summary of Naphthalene Synthesis

Three *de novo* synthetic approaches to afford substituted naphthalenes, that rely on tandem 1,4-addition/intramolecular cyclization step, are highlighted in Figure 3.1.2. These methods deliver useful functionalized naphthalene derivatives. However, the aromatic starting materials are highly specialized, the reaction conditions are often harsh and the isolated yields range from low to moderate. With the above mentioned drawbacks we were inspired by these tandem approaches to design a synthesis of 2-nitronaphthalenes.


Makosza, M. *Synthesis* 1994, 3, 264-266


**Figure 3.1.2** Methods for the preparation of substituted naphthalenes
3.1.3 Lack of Accessibility of Substituted 2-Naphthylamines

Traditional routes to substituted 2-naphthylamines begin from a limited selection of 2-acetonaphthones (3.30) or 2-tetralones (3.34) and require three or more steps to prepare the target molecules (Figure 3.1.3); the overall yields are generally low to moderate to (25-50%). A more recent route to substituted 2-naphthylamines involves the transition metal-catalyzed cross coupling of internal alkynes with (2-iodophenyl)acetonitrile (3.32). While the isolated yield and the regioselectivity are generally good, the structural diversity of the products is narrow in scope which limits the usefulness of this approach.\(^{6}\)

![Diagram showing methods for the preparation of 2-naphthylamines](image)

**Figure 3.1.3** Methods for the preparation of 2-naphthylamines

After we had prepared several 2-naphthylamine substrates for previous projects (See Chapter 2) using both the traditional and newer routes, it became clear that a new synthetic
approach had to be developed that addresses the shortcomings of existing methods. In particular, we had difficulties with the preparation of multi-gram quantities of substituted 2-naphthylamines since several steps failed to work efficiently on a larger scale (>10 mmol). Therefore, we decided to develop a convergent route to achieve the rapid and practical synthesis of a variety of 3-substituted-2-naphthylamines.

### 3.2.1 Developing a Protocol for the Preparation of 3-Substituted-2-Naphthylamines

We decided to use the readily available lithiated o-tolualdehyde tert-butyl imine as our starting material. This benzylic lithiated species has been shown by A. Myers to be an excellent nucleophile that easily adds across the carbon-nitrogen triple bond in aromatic nitriles to afford substituted isoquinolines. Our hypothesis was that β-nitrostyrenes/nitroalkenes should also readily react with and upon acidic workup, yield novel cyclic β-nitrostyrenes, though these electrophiles had not been previously reported to undergo this tandem cyclization. Likewise, it appeared reasonable that upon oxidation/aromatization, cyclic nitrostyrenes would furnish the corresponding 3-substituted 2-nitronaphthalenes (See Scheme 3.2.1). We selected β-nitrostyrenes and β-nitroalkenes as coupling partners for
Scheme 3.2.1 Proposed synthesis of 3-substituted-2-aminonaphthalenes

three important reasons: (a) they may be readily prepared from inexpensive precursors in decagram to kilogram quantities; (b) the nitro group will occupy the 2-position in the new bicyclic system and thus perfectly maps onto the structure of 2-aminonaphthalenes; and (c) the nitro group is often referred to as a chemical chameleon due to its extraordinary versatility as a functional group, therefore it will allow the introduction of many other useful substitution patterns on the naphthalene nucleus.

3.2.2 Scalable Synthesis of Novel Cyclic Nitrostyrenes 3.43

Benzylic lithium species 3.41 was prepared from o-tolualdehyde tert-butyl imine based on conditions described earlier: stoichiometric nBuLi is added over 30-40 minutes to a solution of 3.40 and catalytic amounts (15 mol%) of 2,2,6,6-tetramethylpiperidine (TMP) in THF at 0 °C (Table 3.2.2). The resulting lateral-lithated species 3.41 forms a deep-purple solution which is then aged for 45 minutes before cooling to -78 °C. Next, a solution of a particular nitroalkene 3.42 in THF is added over 10 minutes and the reaction mixture is stirred for an additional 30 to 60 minutes. Water is then added to the solution followed by an addition of excess (4 equiv)
concentrated HCl (37%). The acidified reaction mixture is then warmed to room temperature and subsequently neutralized rapidly with 10% sodium carbonate solution. Following extraction and chromatographic purification, cyclic nitrostyrenes 3.43 are isolated as yellow crystalline solids (Table 3.2.2).

The highest yields of cyclic nitrostyrenes 3.43 were achieved when employing electron-rich β-nitrostyrenes as coupling partners to afford cyclic β-nitrostyrenes 3.4303 - 3.4305 while electron-poor β-nitrostyrenes 3.4307, 3.4308 furnished the cyclized products in somewhat lower yields (Table 3.2.2). It is noteworthy that o-nitro-β-nitrostyrene did not undergo the parent transformation to afford 3.4308, the reaction instead led to a complex mixture of inseparable products. Presumably, the presence of two nitro groups leads to many side-reactions that usually take place via complex electron-transfer processes. However, by transmetallating 3.41 with 1 equivalent of CuBr, the 1,4-addition step proceeded more smoothly with fewer side products observed.

We were pleased to observe that nitroalkenes worked well as substrates demonstrating that besides substituted aromatic rings, alkyl substituents can also be introduced at the 3-position on the naphthalene nucleus. When pentafluoro-β-nitrostyrene was used as the coupling partner, in addition to the expected 1,4-addition/cyclization, a nucleophilic aromatic substitution reaction (S_NAr) also took place to furnish 3.4311. We presume that the S_NAr reaction is faster than the tandem 1,4-addition/intramolecular aza-Henry reaction of 1a with 2k. Indeed, we were unable to isolate even trace amounts of the expected C_6F_5-substituted cyclic nitrostyrene product; this
compound, however, does not undergo $S_N$Ar reaction as it is no longer activated for this transformation.

Table 3.2.2  Substrate scope for the synthesis of cyclic nitrostyrenes

The formation of cyclic nitrostyrenes 3.43 from 3.41 and 3.42 is rationalized by a mechanism proposed in Scheme 3.2.2. At low temperatures benzylic lithium species 3.41
rapidly adds to 3.42 in a 1,4-fashion to generate a nitronate intermediate 3.411, which in turn undergoes an intramolecular aza-Henry reaction to form a six-membered carbocycle 3.412.

Scheme 3.2.2 Proposed mechanism for the formation of cyclic β-nitrostyrenes

When the reaction mixture is treated with aqueous acid, the strongly basic nitrogen atom in 3.313 is protonated and a facile elimination of tert-butylamine takes place to afford cyclic nitrostyrene 3.43.

3.2.3 Synthesis of 3-Substituted-2-Nitronaphthalenes 3.44

By securing multi-gram quantities of cyclic nitrostyrenes (3.43, Table 3.2.2), the stage was set for their conversion to the corresponding 3-substituted-2-nitronaphthalenes 3.44. We were surprised to find that these compounds were remarkably stable towards aromatization via
oxidative methods; traditional methods of aromatization (e.g., dehydrogenation mediated by Pd/C, DDQ oxidations, MnO₂ and SeO₂ benzylic oxidations) were largely unsuccessful. Only minimal conversion to the corresponding 2-nitronaphthalenes were observed even after 48 hours at refluxing temperatures in high-boiling solvents (i.e., chlorobenzene, xylenes).

![Chemical structures and reaction conditions](image)

**Table 3.2.3** Aromatization of cyclic β-nitrostyrenes to 2-nitronaphthalenes
We hypothesized that the introduction of a bromine atom at a benzylic position of compounds 3.43 would lead to a reactive intermediate in which HBr elimination would be facile and promote aromatization. We were delighted to find that radical bromination of cyclic nitrostyrenes 3.43 in the presence of catalytic amounts (15 mol%) of dibenzoyl peroxide as the radical-initiator and excess N-bromosuccinamide (1.7 equivalents) at elevated temperatures (> 80 °C) in DCE furnished the corresponding 3-substituted-2-nitronaphthalenes 3.44 in excellent isolated yields (Table 3.2.3). It should be noted that compounds 3.4405 and 3.4412 were not isolated when subjected to the described conditions above. Despite lowering the reaction temperature complex mixtures were obtained in both cases.

3.3 Demonstrating the Synthetic Versatility of Cyclic β-Nitrostyrenes

We explored the synthetic utility of the novel cyclic nitrostyrenes 3.43 and 3-substituted-2-nitronaphthalenes 3.43 by selecting compounds 3.4301 and 3.4401 as representative substrates (Figure 3.3). The 1,4-reduction\textsuperscript{17} of compound 3.43 with NaBH\textsubscript{4} cleanly gave the corresponding cyclic nitroalkane 3.460, while reduction with LiAlH\textsubscript{4} furnished an interesting cyclic amphetamine analog 3.461. Heating 3.43 with NaN\textsubscript{3} in DMSO afforded a previously uncharacterized fused 1,2,3-triazole 3.462 in nearly quantitative yield.\textsuperscript{18-22}

The nitro group is stable towards a variety of oxidizing reagents and conditions, whereas the amino group tends to undergo facile oxidation even when exposed to air. For this reason, 2-
nitronaphthalenes are excellent surrogates to 2-aminonaphthalenes. A mild Pd/C-catalyzed hydrogenation of 3.44 in a mixture of dichloromethane and ethyl acetate gave rise to 3-phenyl-2-naphthylamine 3.451 in high yield; this approach is significantly more effective than those reported involving Boc-protection of the amine functionality followed by a bromination at the 3-position, a subsequent Pd-catalyzed cross-coupling with phenyl boronic acid followed by

**Figure 3.3** Synthetic versatility of cyclic nitrostyrenes 3.43
deprotection of the Boc group to reveal 3.451. Preparation of 3-phenyl-2-naphthol could also be achieved via a highly stable diazonium tetrafluoroborate salt (3.463). Finally, we found that treatment of 3.451 with iron(III)-chloride afforded 3,3’-diphenyl-BINAM 3.121. During the course of examining the synthetic versatility of cyclic β-nitrostyrenes (3.43) we found that the Fe-mediated oxidative homo-coupling of 3-phenyl-2-naphthylamine (3.451) proceeded very cleanly according to TLC analysis. However, liberation of 3.121 from Fe complexes during the workup proved to be a difficult task despite treatment with excess EDTA. No optimized procedures for the de-aggregation of the reagents/substrates resulting from transition metal-promoted oxidative couplings have been reported. This finding further illustrates the need for new methods targeted for construction of 2,2’-diamino-1,1’-dinaphthalenes. It is anticipated that other 3-aryl and 3-alkyl-substituted 2-aminonaphthalenes will undergo similar oxidative dimerization to give rise to 3,3’-disubstituted 2,2’-diaminonaphthalenes.

### 3.4 Summary

In summary we developed a two-step, practical, regiospecific and readily scalable benzannulation method for the preparation of 3-substituted-2-nitronaphthalenes via novel cyclic β-nitrostyrenes 3.43. These products are synthetically versatile as they can be converted to many other valuable compounds such as substituted-2-aminonaphthalenes, BINAMs, 2-naphthols and
fused 1,2,3-triazoles.\textsuperscript{31} In the past, the preparation of substituted 2-aminonaphthalenes was a significant synthetic challenge as the various routes often required several steps, suffered from regioselectivity issues, limited scope of substrates and poor material throughput (i.e.; due to the low overall yields). This novel synthetic approach presented addresses all of these issues effectively. The homo- and hetero-coupling of 3-substituted-2-aminonaphthalenes to the corresponding enantiomerically-enriched BINAM derivatives as well as the efficient conversion of 3.44 and 3.45 to a number of structurally diverse functionalized biaryls is a continuing effort in our laboratory. With a library of new starting materials for biaryl construction we can now investigate alternative methods for the synthesis of symmetrical as well as non-symmetrical axially-chiral biaryls (See Chapter 4).
3.5 Experimental Details

3.5.1 Materials and Methods

All reactions were carried out in oven-dried glassware under an atmosphere of argon with magnetic stirring. All reagents, including the aromatic aldehydes, TMP and nitromethane were purchased from Sigma-Aldrich Co. and used without further purification. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. All reactions were monitored by thin-layer chromatography (TLC) with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel (particle size 0.032 - 0.063 mm) purchased from SiliCycle was used for flash chromatography.

Proton (\(^1\)H) and carbon (\(^{13}\)C) NMR spectra were recorded on a Bruker AV-400 spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei using CDCl\(_3\) as solvent, respectively. Chemical shifts are expressed as parts per million (\(\delta\), ppm) and are referenced to 7.26 (CDCl\(_3\)) for 1H NMR and 77.00 (CDCl\(_3\)) for 13C NMR. Proton signal data uses the following abbreviations: \(s\) = singlet, \(d\) = doublet, \(t\) = triplet, \(q\) = quartet, \(m\) = multiplet and \(J\) = coupling constant. High Resolution Mass Spectrometry was performed on a Shimadzu LCMS-IT-TOF under the conditions of electrospray ionization (ESI) in both positive and negative mode. Infrared spectra were collected on a Shimadzu IRPrestige- 21 (Fourier Transform Infrared Spectrophotometer).
3.5.2 Detailed Experimental Procedures

Preparation of β-nitrostyrenes 3.42

The β-nitrostyrenes used were prepared according to the following procedure.

A 500 mL round bottom flask, equipped with a mechanical stirrer and an internal thermocouple, was charged with benzaldehyde (50.5 mL, 500 mmol, 1 equiv), nitromethane (28.3 mL, 500 mmol, 1 equiv), and reagent grade methanol (100 mL). The resulting solution was then cooled to 0 °C in an ice bath. Next, a solution of NaOH (20 g, 500 mmol, 1 equiv) in water (20 mL) is then added dropwise at a rate so that the internal temperature does not rise above 15 °C. After the addition of the NaOH solution was complete, the resulting thick white paste was stirred for an additional 15 minutes before ice water (200 mL) was added; most of the white solid dissolved as a result. The precipitate was then filtered, washed with water and air dried in vacuo. Recrystallization from EtOH afforded 46.2 g of β-nitrostyrene 3.42 as solid yellow prisms, 62% isolated yield.
(Note: Electron-rich β-nitrostyrenes were prepared by refluxing the benzaldehyde with 7 equiv MeNO₂ in [0.5] AcOH with 1 equiv NH₄OAc for 5 to 6 hours. The reaction was then cooled to room temperature and water was added while stirring until the product precipitated out of solution. The product is filtered, washed with water and recrystallized from MeOH or EtOH.)

**Preparation of o-tolualdehyde tert-butyl imine 3.40**

A 500-mL round bottom flask was charged with 5.96 mL (50 mmol, 1 equiv) of o-tolualdehyde, 11.56 mL (110 mmol, 2.2 equiv) of tert-butylamine and toluene (50 mL). The resulting solution is heated at reflux for 6 hours. The solution is then allowed to cool to room temperature and the solvent was removed in vacuo. Purification was performed by vacuum distillation (70 - 73 °C, 0.6 mmHg) which afforded the title compound as a colorless oil (8.41 g, 96%). \(^1\)H NMR (400 MHz, CDCl₃): δ 8.61 (s, 1 H), 7.89 (dd, \(J_1 = 7.4\) Hz, \(J_2 = 1.7\) Hz, 1 H), 7.32 – 7.22 (m, 2 H), 7.20 – 7.16 (m, 1 H), 2.52 (s, 3 H), 1.35 (s, 9 H); \(^1^3\)C NMR (100 MHz, CDCl₃): δ 153.74, 137.08, 135.13, 130.52, 129.62, 126.95, 126.13, 57.52, 29.75, 19.14. (NMR spectra are in agreement with the published values: *J. Am. Chem. Soc.*, 2006,128 (6), pp 2105-2114).
**General Procedure for the Synthesis of cyclic β-nitrostyrenes 3.4301-3.4312**

α-Tolualdehyde imine 3.40 (3.51 g, 20 mmol, 1 equiv) was mixed with 2,2,6,6-tetramethylpiperidine (0.5 mL, 15 mol.%) and dry THF (20 mL). The solution was then transferred to a flame-dried 100 mL round bottom flask, equipped with magnetic stir bar and an internal thermocouple, and cooled to 0 °C in an ice bath. Next, a solution of 1.6M n-butyllithium in hexanes (13.13 mL, 21 mmol, 1.05 equiv) was added dropwise via syringe pump so that the internal temperature was never allowed to rise above 0 °C. When the addition was complete, the resulting deep-purple solution was allowed to stir at 0 °C for an additional 40 minutes and then cooled to -70 °C in a dry ice/acetone bath. Next, a solution of a particular nitroalkene 3.42 (20 mmol, 1 equiv) in THF (20 mL) was added at -70 °C over 5 minutes. The reaction mixture was stirred for an additional 30 to 60 minutes until the starting materials have all been consumed (as shown by TLC analysis). Water (10 mL, 0.5 mL/mmol of substrate) was then injected into flask rapidly (over 30 seconds) followed by 6.5 mL concentrated HCl (37%) causing a rapid increase in temperature to about -10 °C. The quenched reaction mixture was allowed to warm to room temperature by placing the flask into a Dewar filled with water and the reaction was allowed to stir for an additional 30 minutes. Excess HCl was neutralized with a solution of saturated sodium carbonate (100 mL) and the biphasic reaction mixture was extracted
DCM (4 x 100 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent removed in vacuo. The crude product was purified via column chromatography (EtOAc/hexanes).

(60 mmol), Yellow crystalline needles, 11.3 g, 76% yield, m.p.: 132.6 - 134.6 °C (DCM/hexanes), Rf = 0.2 in 5% EtOAc/hexanes; ¹H NMR (400 MHz, CDCl₃): δ 8.13 (s, 1 H), 7.44 (dd, J₁ = 7.1, J₂ = 1.8 Hz, 2 H), 7.36-7.31 (m, 2 H), 7.22-7.19 (m, 3 H), 7.14-7.11 (m, 3 H), 4.56 (dd, 1 H), 3.65 (dd, 2 H), 3.16 (dd, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 149.77, 139.96, 134.65, 132.28, 131.75, 130.10, 129.72, 128.66, 128.58, 127.44, 127.31, 126.67, 38.20, 37.04; IR (thin film): νmax 1641, 1504, 1492, 1454, 1315, cm⁻¹; HRMS (ESI) m/z calcd for C₁₆H₁₃NO₂ [(M+H)⁺]: 252.1019, found 252.1027.
(20 mmol), yellow solid, 2.53 g, 42% yield, m.p.: 183.2 - 186.5 °C, Rf = 0.2 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.33 (s, 1 H), 8.29 (d, $J_1$ = 8.55, 1 H), 7.90 (d, $J_1$ = 12 Hz, 1 H), 7.71-7.64 (m, 2 H), 7.56 (ddd, $J_1$ = 8.0 Hz, $J_2$ = 6.8 Hz, $J_3$ = 1.1 Hz, 1 H), 7.48 (dd, $J_1$ = 7.20 Hz, $J_2$ = 1.70 Hz, 1 H), 7.30-7.24 (m, 2 H), 7.18 (dd, $J_1$ = 8.20 Hz, $J_2$ = 7.20 Hz, 1 H), 7.01 (dd, $J_1$ = 7.20 Hz, $J_2$ = 1.20 Hz), 6.94 (d, 8 Hz, 1 H), 5.45 (d, $J_1$ = 9.0 Hz), 3.73 (dd, $J_1$ = 8 Hz, $J_2$ = 8 Hz, 1 H), 3.25 (dd, $J_1$ =16.3 Hz, $J_2$ = 1.6 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 149.30, 134.71, 134.50, 133.91, 133.60, 131.73, 130.24, 130.21, 129.60, 129.25, 128.87, 127.98, 127.47, 126.49, 125.67, 125.16, 122.96, 122.78, 36.06, 33.61; IR (thin film): $\nu_{\text{max}}$ 1634, 1568, 1495, 1308, 1227 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{20}$H$_{15}$NO$_2$ [(M+Na)$^+$]: 324.0995, found 324.0981.
(20 mmol), yellow oil, 3.77 g, 67% yield, Rf = 0.15 in 5% EtOAc/hexanes; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 8.08\) (s, 1 H), 7.42 (dd, \(J_1 = 7.0, J_2 = 1.9\) Hz, 1H), 7.37-7.29 (m, 2 H), 7.13 (d, \(J_1 = 8\) Hz, 1 H), 7.04-7.01 (m, 2 H), 6.74-6.71 (m, 2 H), 4.50 (dd, \(J_1 = 8.7, J_2 = 1.7\) Hz, 1H), 3.71 (s, 3 H), 3.05-3.58 (m, 1 H), 3.12 (dd, \(J_1 = 16.4, J_2 = 1.7\) Hz, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 158.76, 150.15, 134.77, 132.07, 131.89, 131.70, 130.05, 129.76, 128.61, 127.76, 127.40, 113.99, 55.06, 37.38, 37.1\); IR (thin film): \(\nu_{max}\) 1549, 1508, 1454, 1329, 1306, 1248, 1179, 1032 cm\(^{-1}\); HRMS (ESI) m/z calcd for C\(_{16}\)H\(_{13}\)NO\(_2\) [(M+Na\(^+\)]: 304.0944, found 304.0932.

(30 mmol), yellow crystalline solid, 8.6 g, 84% yield, m.p. : 115.0 – 115.8 °C (DCM/hexanes), Rf = 0.1 in 10% EtOAc/hexanes; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 8.05\) (s, 1 H), 7.39 (dd, \(J_1 = 7.3, J_2 = 1.5\) Hz, 1H), 7.33-7.24 (m, 2 H), 7.12 (d, 4 Hz, 1 H), 6.29 (s, 1 H), 4.44 (d, \(J_1 = 8.5\) Hz), 3.73 (s, 3 H), 3.62 (s, 6 H), 3.62-3.56 (m, 1 H), 3.12 (dd, \(J_1 = 16.4, J_2 = 1.8\) Hz); \(^13\)C NMR (100
MHz, CDCl$_3$): δ 152.97, 149.86, 136.97, 135.56, 134.82, 132.01, 131.71, 129.82, 129.55, 128.52, 127.38, 103.50, 60.51, 55.66, 38.22, 36.93; IR (thin film): $\nu_{\text{max}}$ 1530, 1472, 1441, 1408, 1348 cm$^{-1}$. HRMS (ESI) m/z calcd for C$_{19}$H$_{19}$NO$_5$ [(M+H$^+$)]: 342.1303, found 342.1296.

(20 mmol), red/yellow oil, 4.84 g, 82% yield, Rd = 0.22 in 10% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.08 (s, 1 H), 7.41 (dd, $J_1 = 7.1$, $J_2 = 1.9$ Hz, 1H), 7.37-7.27 (m, 2 H), 7.13 (d, $J_1 = 7.2$ Hz, 1H), 6.65-6.54 (m, 3 H), 5.85 (q, $J_1 = 1.4$ Hz, 2H), 4.47 (dd, $J_1 = 8.7$, $J_2 = 1.6$ Hz, 1H), 3.60 (ddt, $J_1 = 16.5$, $J_2 = 8.7$, $J_3 = 1.3$ Hz, 1H), 3.11 (dd, $J_1 = 16.4$, $J_2 = 1.7$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 149.82, 147.66, 146.75, 134.61, 133.78, 132.14, 131.81, 130.15, 129.60, 128.60, 127.48, 119.90, 108.34, 107.18, 100.92, 37.86, 37.21; IR (thin film): $\nu_{\text{max}}$ 1263, 731 cm$^{-1}$; HRMS (ESI) m/z calcd for [C$_{17}$H$_{13}$NO$_4^+$ [M+Na]$^+$: 318.0737, found 318.0733.
(20 mmol), yellow crystalline solid, 5.35 g, 62% yield, m.p.: 118.4 - 119.4 °C, (DCM/hexanes) 
Rf = 0.25 in 10% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.43 (dd, $J_1 = 7.2$, $J_1 = 1.7$ Hz, 1H), 7.34 (ddd, $J_1 = 9.5$, $J_2 = 7.0$, $J_3 = 1.4$ Hz, 2H), 7.15-7.11 (m, 1 H), 7.10-7.03 (m, 2 H), 6.91-6.83 (m, 2 H), 4.53 (dd, $J_1 = 8.7$, $J_2 = 1.7$ Hz, 1H), 3.67 – 3.57 (m, 1 H), 3.11 (dd, $J_1 = 16.4$, $J_2 = 1.7$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 161.99 (d, $J_1 = 245.7$ Hz), 149.72, 135.76 (d, $J_4 = 3.3$ Hz), 134.44, 132.31, 131.92, 130.20, 129.61, 128.64, 128.30 (d, $J_3 = 8.1$ Hz), 127.59, 115.62 (d, $J_2 = 21.4$ Hz), 37.51, 37.08; IR (thin film): $\nu_{\text{max}}$ 1639, 1504, 1450, 1331, 1308, 1223, 1155 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{16}$H$_{12}$NO$_2$F [(M+Na$^+$)]: 292.0744, found 292.0750.

(10 mmol), yellow crystalline solid, 1.65 g, 52% yield, m.p.: 123.7 - 124.7 °C, (DCM/hexanes), 
Rf = 0.2 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.24 (s, 1 H), 7.72 (d, $J_1 = 7.7$ Hz, 1 H), 7.51 – 7.46 (m, 1 H), 7.38 – 7.33 (m, 2 H), 7.27 (dt, $J_1 = 21.0$, $J_2 = 7.6$ Hz, 3 H), 7.08
(dd, $J_1 = 5.4$, $J_2 = 3.3$ Hz, 1 H), 6.98 (d, $J_1 = 7.7$ Hz, 1 H), 5.0 (d, $J_1 = 8$ Hz, 1 H), 3.66 (dd, $J_1 = 16.7$, $J_2 = 9.3$ Hz, 1 H), 3.12 (d, $J_1 = 16$ Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 149.09, 138.11, 133.97, 133.60, 133.58, 132.06, 131.97, 129.50, 128.85, 127.66, 127.33, 127.19, 126.88 (q, $J_1 = 5.9$ Hz), 36.71, 34.20, 29.64; IR (thin film): $\nu_{\text{max}}$ 1641, 1499, 1454, 1323, 1267 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{17}$H$_{12}$NO$_2$F$_3$ [(M+Na)$^+$]: 342.0712, found 342.0697.

![3.4308](image)

(25 mmol), yellow crystalline solid, 2.06 g, 56% yield, m.p.: 91.0 - 93.5 °C, Rf = 0.2 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.22 (s, 1 H), 8.00 – 7.88 (m, 1 H), 7.47 (dd, $J_1 = 7.2$, $J_2 = 1.9$ Hz, 1 H), 7.41 – 7.28 (m, 4 H), 7.14 (d, $J_1 = 7.0$ Hz, 1 H), 7.01 – 6.96 (m, 1 H), 5.17 (d, $J_1 = 9.5$, 1 H), 3.74 (dd, $J_1 = 16.9$, $J_2 = 9.4$ Hz, 1 H), 3.30 (d, $J_1 = 17.0$, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 148.47, 134.28, 134.23, 134.02, 134.00, 133.16, 132.33, 130.43, 129.37, 128.93, 128.27, 127.86, 127.80, 125.39, 36.02, 33.25; IR (thin film): $\nu_{\text{max}}$ 1692, 1643, 1599, 1523, 1495, 1355, 1312, 1186 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{16}$H$_{12}$N$_2$O$_4$ [(M+Na$^+$)]: 319.0689, found 319.0677.
(20 mmol), yellow oil, 2.33 g, 54% yield, Rf = 0.35 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.90 (s, 1 H), 7.35 – 7.28 (m, 3 H), 7.26 – 7.19 (m, 2 H), 3.23 – 3.15 (m, 2 H), 3.11 – 3.03 (m, 1 H), 1.85 (td, $J_1 = 6.9$, $J_2 = 5.9$ Hz, 1 H), 0.92 (d, $J_1 = 6.9$ Hz, 3 H), 0.76 (d, $J_1 = 6.8$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 151.17, 136.47, 131.33, 131.30, 129.86, 129.80, 127.92, 127.06, 37.78, 30.63, 30.13, 20.24, 19.17; IR (thin film): $\nu_{\text{max}}$ 1547, 1514, 1454, 1366, 1302 cm$^{-1}$.

(20 mmol), yellow crystalline solid, 2.45 g, 57% yield, m.p.: 57.9 – 59.3 °C Rf = 0.35 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.87 (s, 1 H), 7.33 – 7.25 (m, 2 H), 7.20 (dd, $J_1 = 13.2$, $J_2 = 7.3$ Hz, 2 H), 3.31 – 3.22 (m, 2 H), 3.15 (d, $J = 15.5$ Hz, 1H), 0.78 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 150.40, 137.41, 131.84, 131.27, 129.87, 129.45, 127.32, 126.88,
39.85, 36.84, 30.76, 27.37; IR (thin film): $\nu_{\text{max}}$ 1638, 1501, 1468, 1454, 1308, 1204 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{14}$H$_{17}$NO$_2$ [(M+Na)$^+$]: 254.1152, found 254.1138.

(9 mmol o-tolualdehyde t-butyl imine and 6.83 mmol pentafluoronitrostyrene), 1.13 g, yellow crystalline solid, 57% yield, m.p.: 179.8 – 188.1 °C, Rf = 0.3 in 15% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.27 (s, 1 H), 8.08 (s, 1 H), 7.83 (dd, $J_1$ = 7.6, $J_2$ = 1.7 Hz, 1 H), 7.52-7.38 (m, 4 H), 7.33 (t, $J_1$ = 7.4 Hz, 1 H), 7.18 (d, $J_1$ = 7.5 Hz, 1 H), 7.06 (d, $J_1$ = 7.6 Hz, 1 H), 4.99 (dd, $J_1$ = 9.7 Hz, $J_2$ = 5.0 Hz, 1 H), 4.55 (s, 2 H), 3.60 (dd, $J_1$ = 16.8, $J_2$ = 9.6 Hz, 1 H), 3.20 (dd, $J_1$ = 16.8 Hz, $J_2$ = 4.9 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 192.80, 145.85, 138.89, 134.18, 134.13, 134.12, 133.95, 133.93, 133.53, 132.08, 130.60, 129.65, 129.40, 127.75, 127.34, 34.94, 29.48, 25.10; IR (thin film): $\nu_{\text{max}}$ 1688, 1506, 1479, 1452, 1319, 1198, 1001 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{24}$H$_{18}$NO$_3$F$_4$ [(M+Na)$^+$]: 464.0880, found 464.0880.
(10 mmol imine, 5 mmol nitrostyrene), 891 mg, yellow solid, 42% yield, m.p.: 225–245 °C, Rf = 0.25 in 10% EtOAc/hexanes; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.13 – 7.97 (m, 1 H), 7.50 – 7.19 (m, 5 (7) H), 7.17 – 7.03 (m, 4 H), 6.91 (d, \(J_1 = 3.4\) Hz, 1 H), 4.81 (dd, \(J_1 = 8.8\) Hz, \(J_2 = 6.4\) Hz, 1 H), 4.56 – 4.35 (m, 2 H), 3.70 – 3.50 (m, 1 H), 3.19 – 2.99 (m, 2 H), 1.31 – 0.95 (m, 6 (8) H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 149.67, 140.72, 140.65, 139.21, 139.15, 138.40, 136.04, 134.64, 134.61, 132.21, 132.14, 132.11, 131.85, 131.82, 131.79, 130.13, 130.10, 130.05, 129.63, 129.60, 129.57, 128.69, 128.02, 128.00, 127.73, 127.71, 127.59, 127.46, 127.43, 127.40, 127.27, 127.24, 127.17, 127.12, 127.04, 57.01, 51.00, 45.14, 37.78, 37.71, 37.64, 36.77, 36.68, 30.07, 30.04, 29.98; IR (thin film): \(\nu_{\text{max}}\) 1508, 1314, 758 cm\(^{-1}\); HRMS (ESI) m/z calcd for C\(_{26}\)H\(_{20}\)N\(_2\)O\(_4\) [(M+Na\(^+\)]: 447.1315, found 447.1326.
General Procedure for the synthesis of 3-substituted-2-nitronaphthalenes 3.4401-3.4411

A 100 mL round bottom flask, equipped with a magnetic stir bar, was charged with cyclic nitrostyrene 2 (10 mmol, 1 equiv), benzoyl peroxide (370 mg, 15 mol %), N-bromosuccinimide (3.03g, 17 mmol, 1.7 equiv) and 1,2-dichloroethane (67 mL). The resulting solution was then kept at reflux for the indicated amount of time (See Table 3.2.3). Once the starting material was consumed, the reaction mixture was cooled to room temperature, diluted with DCM (60 mL) and poured into a separatory funnel. Next, 20% aqueous sodium thiosulfate solution (100 mL) was added to neutralize atomic bromine generated during the course of the reaction. The aqueous phase was then extracted with DCM (3 x 100 mL) and the combined organic layers were dried over MgSO₄. The solvent was removed in vacuo and the crude product was purified by column chromatography with EtOAc/hexanes.
(20 mmol), yellow solid, 4.98 g, 99% yield, m.p.: 90.0 – 93.5 °C, Rf = 0.22 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.42 (s, 1 H), 7.98 (dd, $J_1 = 8.2$ Hz, $J_2 = 1.4$ Hz, 1 H), 7.91 (dd, $J_1 = 8.2$ Hz, $J_2 = 1.4$ Hz, 1 H), 7.88 (s, 1 H), 7.70 – 7.61 (m, 2 H), 7.51 – 7.40 (m, 5 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.35, 137.68, 134.26, 132.77, 131.25, 131.03, 129.32, 128.77, 128.55, 127.97, 127.89, 127.86, 127.80, 124.51; IR (thin film): $\nu_{\text{max}}$ 1595, 1522, 1501, 1450, 1348, 1315, 895 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{16}$H$_{11}$NO$_2$ [(M+Na)$^+$]: 272.0682, found 272.0654.

(7 mmol), yellow solid, 2.07 g, 99% yield, m.p.: 144.5 – 155.4 °C, Rf = 0.22 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.68 (d, $J_1 = 11.1$ Hz, 1 H), 8.37 (d, $J_1 = 8.5$ Hz, 1 H), 8.08 (d, $J_1 = 7.4$ Hz, 1 H), 7.96 – 7.85 (m, 3 H), 7.75 - 7.67 (m, 2 H), 7.64 – 7.37 (m, 4 H), 7.30 (d, $J_1 = 7.6$ Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.74, 147.32, 136.46, 136.14, 135.86, 134.50, 134.47, 133.05, 132.48, 131.82, 131.78, 131.54, 131.46, 131.44, 130.59, 130.10,
129.82, 129.60, 129.33, 129.16, 129.08, 128.40, 128.38, 128.22, 127.99, 127.89, 127.87, 127.63, 127.36, 127.27, 126.67, 126.48, 126.46, 125.93, 125.49, 125.22, 125.07, 124.85, 124.78, 123.15;
IR (thin film): $\nu_{\text{max}}$ 1528, 1501, 1423, 1366, 1333 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{20}$H$_{13}$NO$_2$ [(M+Na)$^+$]: 322.0839, found 322.0822.

(10 mmol), yellow solid, 2.07 g, 74% isolated yield, m.p. = 142 143 °C, Rf = 0.2 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.76 (s, 1 H), 8.13 (d, $J_1$ = 2.3 Hz, 1 H), 8.09 – 8.04 (m, 1 H), 7.97 – 7.93 (m, 1 H), 7.69 – 7.62 (m, 3 H), 7.40 (dd, $J_1$ = 8.4, $J_2$ =2.2 Hz, 1 H), 7.06 (d, $J_1$ = 8.4 Hz, 1 H), 4.00 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.85, 144.70, 140.47, 134.38, 134.15, 132.50, 132.19, 130.47, 129.94, 127.81, 126.09, 123.91, 119.82, 111.79, 56.35; IR (thin film): $\nu_{\text{max}}$ 1520, 1495, 1452, 1437, 1356, 1283, 1254, 1055 cm$^{-1}$. 
(6.5 mmol), yellow crystalline solid, 2.16 g, 98% yield, m.p. = 154 – 156 °C, Rf = 0.15 in 10% EtOAc/hexanes; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.80 (s, 1 H), 8.06 (d, \(J = 7.9\) Hz, 1H), 7.92 (d, 8.0 Hz, 1 H), 7.73 – 7.63 (m, 3 H), 4.01 (s, 3 H), 3.95 (s, 6 H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): δ 150.76, 147.10, 145.24, 135.98, 134.84, 131.98, 131.95, 131.63, 129.76, 129.39, 128.29, 128.01, 125.62, 113.93, 61.31, 61.04; IR (thin film): \(\nu_{\text{max}}\) 1530, 1472, 1441, 1408, 1372, 1352, 1086, 1005 cm\(^{-1}\).

(3 mmol), yellow solid, 770 mg, 96% yield, m.p.: 118.8 – 120.0 °C, Rf = 0.27 in 10% EtOAc/hexanes; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 8.41 (s, 1 H), 7.97 (d, \(J_1 = 8.0\) Hz, 1 H), 7.91 (d, \(J_1 = 8.0\) Hz, 1 H), 7.83 (s, 1 H), 7.72 – 7.61 (m, 2 H), 7.37 (dd, \(J_1 = 8.5\) Hz, \(J_2 = 5.4\) Hz, 2 H), 7.14 (t, \(J_1 = 8.6\) Hz, 2 H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)): δ 162.56 (d, \(J_1 = 247.6\) Hz), 147.23, 134.27, 133.75 (d, \(J_3 = 3.5\) Hz), 131.77, 131.32, 131.15, 129.77 (d, \(J_3 = 8.2\) Hz), 129.51, 128.85,
127.97, 127.88, 124.68 (d, $J_4 = 2.0$ Hz), 115.59 (d, $J_2 = 21.7$ Hz); IR (thin film): $v_{\text{max}}$ 1638, 1504, 1450, 1331, 1308, 1223 cm$^{-1}$.

(1 mmol), yellow crystalline solid, 301 mg, 95% yield, m.p.: 78.0 – 80.0 °C, Rf = 0.25 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.73 (s, 1 H), 8.12 – 8.03 (m, 2 H), 7.91 (d, $J_1 = 8.1$ Hz, 1 H), 7.82 – 7.77 (m, 2 H), 7.74 – 7.59 (m, 4 H), 7.53 (dt, $J_1 = 11.7$ Hz, $J_2 = 7.7$ Hz, 2 H), 7.39 – 7.36 (m, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 163.02, 145.94, 137.23 (q, $J_1 = 2.0$ Hz), 134.26, 134.15, 131.83, 131.54, 131.41, 130.91, 130.23, 129.93, 129.73, 129.28, 128.82, 128.23, 127.98, 127.93, 126.01 (q, $J_2 = 5.1$ Hz), 125.36; IR (thin film): $v_{\text{max}}$ 1759, 1601m 1526, 1504, 1337, 1313, 1167 cm$^{-1}$; HRMS (ESI) m/z calcd for for C$_{17}$H$_{16}$NO$_2$F$_3$ [(M+Na)$^+$]: 340.0556, found 340.0531.
(4.5 mmol), yellow crystalline solid, 1.27 g, 95% yield, m.p.: 136.3 – 137.9 °C, (DCM/hexanes), Rf = 0.22 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.82 (s, 1 H), 8.23 (d, $J_1 = 8.2$ Hz, 1 H), 8.07 (d, $J_1 = 7.8$ Hz, 1 H), 7.88 (d, $J_1 = 7.9$ Hz, 1 H), 7.71 (h, $J = 7.3$ Hz, 4 H), 7.61 (t, $J_1 = 7.8$ Hz, 1 H), 7.43 (d, $J = 7.6$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 147.26, 145.42, 134.79, 134.65, 133.44, 131.63, 131.53, 130.41, 130.26, 130.13, 129.52, 128.96, 128.32, 127.82, 125.81, 124.74; IR (thin film): $\nu_{\text{max}}$ 1599, 1517, 1500, 1487, 1346, 1308 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{16}$H$_{10}$N$_2$O$_4$ [(M+Na)$^+$): 317.0533, found 317.0510.

![3.4409](image)

(10 mmol), yellow solid, 2.06 g, 96% yield, m.p.: 73.8 – 75.0 °C, Rf = 0.35 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.26 (s, 1 H), 7.93 – 7.83 (m, 3 H), 7.66 – 7.50 (m, 2 H), 3.55 (td, $J_1 = 6.8$ Hz, $J_2 = 0.6$ Hz, 1 H), 1.39 (d, $J_1 = 6.8$ Hz, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 148.52, 138.84, 134.76, 130.45, 128.82, 128.57, 127.53, 127.10, 126.63, 124.04, 28.52, 23.87; IR (thin film): $\nu_{\text{max}}$ 1524 cm$^{-1}$.

![3.4410](image)
(9 mmol), yellow solid, 1.75 g, 85% yield, m.p.: 73.8 – 75.0 °C, Rf = 0.35 in 5% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): δ 8.81 (s, 1 H), 8.24 (d, $J_1 = 9.1$ Hz, 1 H), 8.04 (d, $J_1 = 8.1$ Hz, 1 H), 7.96 (t, $J = 8.0$ Hz, 2 H), 7.67 (dddd, $J_1 = 26.5$ Hz, $J_2 = 8.3$ Hz, $J_3 = 7.0$ Hz, $J_4 = 1.4$ Hz, 2 H), 1.50 (s, 9 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 145.35, 135.70, 131.79, 129.87, 129.64, 129.41, 127.89, 127.82, 124.50, 119.12, 35.68, 30.89; IR (thin film): $\nu_{\max}$ 1630, 1603, 1526, 1499, 1329 cm$^{-1}$.

(0.6 mmol), yellow solid, 87 mg, 32% yield, m.p.: 57.5 – 60.0 °C, Rf = 0.35 in 15% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): δ 10.32 (s, 1 H), 8.78 (s, 1 H), 8.15 – 8.04 (m, 3 H), 7.95 (d, $J_1 = 6.9$ Hz, 3 H), 7.88 (dd, $J_1 = 7.6$, $J_2 = 1.6$ Hz, 1 H), 7.78 – 7.69 (m, 3 H), 7.64 – 7.35 (m, 6 H), 7.18 (d, $J_2 = 7.4$ Hz, 1 H), 4.70 (s, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 192.93, 171.92, 145.58, 138.90, 134.43, 134.12, 134.03, 133.73, 133.54, 133.40, 132.00, 130.28, 130.11, 129.52, 129.45, 129.21, 129.01, 128.41, 128.12, 127.70, 127.37, 126.35, 25.40; IR (thin film): $\nu_{\max}$ 1688, 1528, 1479, 1325, 1290, 995 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{24}$H$_{13}$NO$_3$F$_4$ [(M+Na)$^+$]: 462.0727, found 462.0724.
Preparation of 2-nitro-3-phenyl-1,2,3,4-tetrahydronaphthalene 3.460

To a 50 mL round bottom flask, equipped with a magnetic stir bar and an internal thermocouple, were added sodium borohydride (645 mg, 3.5 equiv) EtOH (4 mL) and THF (5 mL). Next a solution of 3.4301 (970 mg, 3.86 mmol, 1 equiv) in THF (8 mL) was added dropwise over a period of 15 minutes. During the addition, an internal temperature of 35°C was maintained. After the addition was complete, the reaction was heated to 50°C for 5 hours. The reaction mixture was then diluted with ice water (10 mL) and quenched with 50% AcOH/H₂O (2.3 mL). Next DCM (70 mL) was added, the layers separated and the aqueous phase was extracted with DCM (3x50 mL). The combined organic phases were dried over MgSO₄, filtered, and solvent removed in vacuo. The crude product was purified by column chromatography using 3% EtOAc/hexanes. The product 3.460 was isolated as a white solid, 505 mg, 52% yield, m.p.: 94.6 – 96.7 °C, Rf = 0.2 in 5% EtOAc/hexanes; ¹H NMR (400 MHz, CDCl₃): δ 7.32 – 7.24 (m, 6 H), 7.22 – 7.19 (m, 1 H), 7.14 – 7.10 (m, 2 H), 5.09 (ddd, J = 8.3, 5.5, 3.9 Hz, 1 H), 3.93 (td, J₁ = 5.9, J₂ = 3.9 Hz, 1 H), 3.43 (d, J₁ = 6.0 Hz, 2 H), 3.32 (qd, J₁ = 17.1 Hz, J₂ = 6.9 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 138.45, 134.21, 131.65, 128.97, 128.59, 128.52, 127.76, 127.65, 126.86, 126.49,
84.75, 77.32, 77.00, 76.68, 42.18, 32.71, 29.82; IR (thin film): \( v_{\text{max}} \) cm\(^{-1}\); HRMS (ESI) m/z calcd for C\(_{16}\)H\(_{15}\)NO\(_2\) [(M+Na\(^+\)]: 276.0995, found 276.0985.

**Preparation of 3-phenyl-1,2,3,4-tetrahydronaphthalen-2-amine 3.461**

![Chemical Structure]

A flame-dried 50 mL round bottom flask, equipped with magnetic stir bar, was charged with lithium aluminum hydride (244 mg, 6.42 mmol, 2 equiv) and dry THF (8 mL). The resulting solution was then cooled to 0 °C. Next, a solution of 3.4301 (0.807 g, 3.21 mmol, 1 equiv) in dry THF (8 mL) was added dropwise. After the addition was complete, the reaction mixture was heated at reflux for 12 hours after which it was allowed to cool first to room temperature then to 0 °C in an ice bath. Careful quenching was performed by first adding H\(_2\)O (0.244 mL) dropwise, followed by 15% aqueous NaOH solution (0.244 mL), and more H\(_2\)O (0.73 mL). The resulting slurry was allowed to warm to room temperature and stirred for an additional 30 minutes. The pasty-white mixture was then filtered over Celite to give a yellow-tinted organic phase. The Celite was then washed sequentially with 120 mL EtOAc and 120 mL DCM. The combined organic layers were then evaporated and 5 mL of reagent-grade \( i \)-propyl alcohol was added to the residue. Next, a slight excess of concentrated HCl (37%) was also added, causing heat evolution. Upon cooling, the HCl salt of 3.461 begins to precipitate out of solution. Upon dilution with diethyl ether (10 mL) more solid precipitated and it was filtered, washed with
diethyl ether (50 mL), dried in vacuo to afford 534 mg of a white solid, the HCl salt of 3.461, in 64% isolated yield, Rf = 0.2 in 40% EtOAc/hexanes; $^1$H NMR (400 MHz, (CD$_3$)$_2$SO): δ 8.34 (s, 3 H), 7.51 – 7.14 (m, 9 H), 3.84 (b s, 1 H), 3.67 (b s, 1 H), 3.41 – 3.30 (m, 1 H), 3.18 (ddd, $J_1$ = 21.8 Hz, $J_2$ = 17.1 Hz, $J_3$ = 5.3 Hz, 2 H), 2.88 – 2.77 (m, 1 H); $^{13}$C NMR (100 MHz, (CD$_3$)$_2$SO): δ 140.28, 135.60, 133.35, 129.92, 129.62, 129.52, 129.30, 128.17, 127.56, 127.01, 50.21, 32.67, 31.29, 26.44.

**Preparation of 4-phenyl-4,5-dihydro-3H-naphtho[1,2-d][1,2,3]triazole 3.462**

![Reaction Scheme]

A 10 mL round bottom flask, equipped with magnetic stir bar, was sequentially charged with 3.4301 (439 mg, 1.75 mmol, 1 equiv), DMSO (3.5 mL) and NaN$_3$ (227 mg, 3.5 mmol, 2 equiv). The reaction mixture was then heated at 90 °C for 2 hours until all the starting material was consumed (progress was followed by TLC analysis). The flask was allowed to cool to room temperature before adding water (3 mL) dropwise. The biphasic mixture was then extracted in a separatory funnel with DCM (3 x 30 mL). The combined organic phases were dried over MgSO$_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by column chromatography. Elution with 30% EtOAc/hexanes afforded 415 mg of 3.462 as a white crystalline solid, 96% yield, m.p.: 200 – 205 °C, (DCM), Rf = 0.4 in 30% EtOAc/hexanes; $^1$H
NMR (400 MHz, (CDCl$_3$): δ 13.78 (b s, 1 H, NH), 7.91 (d, $J_1 = 7.4$ Hz, 1 H), 7.35 – 7.17 (m, 8 H), 4.40 (dd, $J_1 = 9.0$ Hz, $J_2 = 6.7$ Hz, 1 H), 3.40 – 3.20 (m, 2 H); $^{13}$C NMR (100 MHz, (CDCl$_3$): δ 141.55, 135.06, 128.55, 128.48, 128.41, 127.57, 127.31, 127.04, 126.95, 122.95, 38.20, 37.95; HRMS (ESI) m/z calcd for C$_{16}$H$_{13}$N$_3$ [(M+H)$^+$]: 248.1182, found 248.1182.

**Preparation of 3-phenynaphthalen-2-amine 3.451**

A flame-dried 100 mL round bottom flask, equipped with a magnetic stir bar, was charged with 10% Pd/C (1.3 g, 0.987 mmol, 15 mol %) and EtOAc (10 mL) that was injected slowly along the inner wall of the flask. Next, the solution of 3-phenyl-2-nitronaphthalene 3.4401 (1.64 g, 6.58 mmol, 1 equiv) in DCM (10 mL) was added. The reaction mixture was then purged with hydrogen gas by means of bubbling it through the solution from a balloon for 15 minutes. Next, a fresh balloon of hydrogen gas was placed atop the flask. The reaction mixture was allowed to stir for 10 hours at which point the starting material was no longer detected by TLC analysis. The reaction mixture was then filtered through Celite and washed with EtOAc (100 mL) and DCM (100 mL). The combined organic solvents were removed *in vacuo* and the residue was purified by column chromatography. Elution with 10% EtOAc/hexanes afforded 1.3 g of 3.451 as a pink oil which solidified upon standing overnight; 90% isolated yield, Rf = 0.27 in 10% EtOAc/hexanes; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.75 (d, $J_1 = 8.2$ Hz, 1 H), 7.67-7.65 (m, 2 H),
7.60 – 7.51 (m, 4 H), 7.47-7.41 (m, 2 H), 7.31 – 7.25 (m, 1 H), 7.10 (s, 1 H), 3.92 (b s, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 142.09, 138.97, 134.34, 130.68, 129.42, 129.19, 128.76, 127.93, 127.68, 127.52, 126.24, 125.31, 122.55, 108.87; IR (thin film): $\nu_{\text{max}}$ 1638, 1609, 1504, 1493, 466, 905, 727 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{16}$H$_{13}$N[(M+H)$^+$]: 220.1121, found 220.1111.

**Preparation of (3-phenynaphthalen-2-yl)-2-(tetrafluoro-λ5-boranyl)diazene 3.463**

A 100 mL round bottom flask, equipped with magnetic stir bar, was charged with 3-phenyl-2-aminonaphthalene 7 (856 mg, 1 equiv) and DCM (39 mL). The solution was then cooled to 0 °C in an ice bath and stirred for 10 minutes. Next, BF$_3$ diethyl etherate (0.578 mL, 4.68 mmol, 1.2 equiv) was added dropwise, followed by the dropwise addition of neat tert-butyl nitrite (0.774 mL, 1.5 equiv) upon which the color of the reaction mixture became brown. The reaction was then allowed to warm to room temperature, the diazonium tetrafluoroborate salt was filtered through a frit funnel and washed with DCM (5 mL) to afford 1.12 g of 3.463 as a yellow solid, 90% isolated yield.
Preparation of 3-phenyl-2-naphthol 3.464

A 10 mL round bottom flask, equipped with magnetic stir bar and gas outlet, was charged with 3.463 (318 mg, 1 mmol, 1 equiv), THF (1.6 mL) and water (1.6 mL). The reaction mixture was then heated at 60 °C for 1 hour until gas evolution ceased. The resulting red solution was diluted with 5 mL CHCl₃ and transferred into a separatory funnel with 30 mL water. The aqueous phase was then extracted with CHCl₃ (3x15 mL), the combined organic layers dried over MgSO₄, filtered, and the solvent was removed in vacuo. Elution with 10% EtOAc/hexanes gave 102 mg of 3.464 as a white solid, 46% isolated yield, Rf = 0.2 in 10% EtOAc/hexanes; ¹H NMR (400 MHz, CDCl₃): δ 7.82 (d, J₁ = 8.3 Hz, 1 H), 7.79 – 7.74 (m, 2 H), 7.62 – 7.59 (m, 2 H), 7.55 (t, J₁ = 8.5 Hz, 2 H), 7.48 (ddd, J₁ = 8.3 Hz, J₁ = 6.9 Hz, J₁ = 1.4 Hz, 2 H), 7.40 – 7.35 (m, 2 H), 5.40 (s, 1 H); ¹³C NMR (100 MHz, CDCl₃): δ 150.69, 136.80, 134.22, 130.39, 129.52, 129.27, 129.16, 128.84, 128.09, 127.72, 126.45, 126.18, 123.84, 110.17.
Preparation of 3,3'-diphenyl-[1,1'-binaphthalene]-2,2'-diamine 3.121

A 50 mL round bottom flask was charged with a finely ground paste of 3.451 (219 mg, 1 mmol, 1 equiv) and iron trichloride hexahydrate (730 mg, 4.5 mmol, 4.5 equiv) that was prepared with a mortar and pestle. Next, water (0.5 mL) was added, the flask was sealed with a septum and heated at 90 °C for 72 h, after which time it was cooled to room temperature and then CHCl₃ (30 mL) was added. The contents of the flask were then transferred into a separatory funnel along with water (30 mL) and the aqueous phase was washed with CHCl₃ (3x40 mL). The combined organic layers were dried over MgSO₄ and solvent was removed in vacuo. The crude material was purified by column chromatography using 4% EtOAc/hexanes to afford 82 mg of 3.121 as a yellow solid, 38% isolated yield, Rf = 0.2 in 10% EtOAc/hexanes. ¹H NMR (400 MHz, CDCl₃): δ 7.74 (d, J₁ = 8.1 Hz, 1H), 7.65 (t, J₁ = 4.2 Hz, 2 H), 7.60 – 7.49 (m, 3 H), 7.47 – 7.38 (m, 2 H), 7.30 – 7.24 (m, 1 H), 7.09 (s, 1 H), 3.92 (s, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 142.10, 138.99, 134.36, 130.71, 129.44, 129.21, 128.78, 127.95, 127.70, 127.54, 126.25, 125.32, 122.57, 108.89; HRMS (ESI) m/z calcd for C₃₂H₂₄N₂ [(M+Na)⁺]: 459.1832, found 459.1815.
3.6 References

CHAPTER 4

Construction of Non-C₂-Symmetrical Atropoisomeric Functionalized Biaryls

Parts of this chapter have been adapted from: Gao, H.; Xu, Q.; Keene, C.; Ess, Daniel H; Yousuffidin, M.; Kürti, L., “Practical Organocatalytic Synthesis of Functionalized Non-C₂-Symmetrical Atropisomeric Biaryls” Angew. Chem., 2015, 55, 566-571.

4.1 Introduction

Hindered rotation about the C-C bond in biaryl compounds renders the biaryl axis stereogenic, which is a key structural motif in a large number of natural products, pharmaceuticals, chiral auxiliaries, ligands and catalysts (Figure 4.1). The magnitude of the rotational barrier is determined by both the size and number of substituents at the ortho-positions flanking the aryl-aryl bond ¹⁻⁴ (See Chapter 1). Among natural products it is common that opposite biaryl enantiomers, formally atropisomers, display completely different biological profiles (e.g., gossypol, Figure 4.1)² and recently it was recognized that controlling the chirality
of unsymmetrical biaryl structures will have enormous implications in the future development of pharmaceuticals.\textsuperscript{5-7}

Figure 4.1 Non C\textsubscript{2}-symmetric axially-chiral biaryls

During the past two decades, both C\textsubscript{2}- and non-C\textsubscript{2}-symmetrical axially chiral biaryl compounds\textsuperscript{1-3} (e.g., BINAP, BINOL, BINAM, NOBIN and their derivatives, Figure 4.1) have played key roles as ligands in the development of metal-catalyzed enantioselective transformations.\textsuperscript{8-17}
A number of synthetic approaches have been developed for the construction of axially chiral biaryl compounds,\textsuperscript{18-26} however, there are a number of biaryl linkages that remain exceedingly difficult to construct in an atom- and step-economical fashion. Synthetic access is further limited for non-C\textsubscript{2}-symmetrical but configurationally stable biaryl diols (e.g., 2,2’-dihydroxy-1,1’-biaryl motif found in certain chiral phosphoric acids) as no general methods are currently available for their preparation.\textsuperscript{27-30} The scarcity of reliable methods is surprising as these atropisomeric, but non-C\textsubscript{2}-symmetrical, biaryldiols have been shown to be excellent ligands or catalysts in many catalytic reactions, especially in those where the C\textsubscript{2}-symmetrical ligands were found to be ineffective.\textsuperscript{15}

### 4.2 Approach to C\textsubscript{1}/C\textsubscript{2}-Symmetrical Atropisomeric Biaryls

As a part of an ongoing program in our group to develop new and practical transition metal-free direct arylation methods for the preparation of highly functionalized symmetrical and unsymmetrical biaryls\textsuperscript{31,32}, we became intrigued by the possibility of using quinone and imino-quinone monoacetals\textsuperscript{33} as arylating agents to access both BINOL and NOBIN-types of functionalized biaryls that are atropisomeric, but non-C\textsubscript{2}-symmetrical, from phenols and naphthols under organocatalytic conditions (Scheme 4.2). The coupling of quinone monoacteals with alkoxyarenes has only been demonstrated in the presence of solid acids such as
montmorillonite (MT) clay.\textsuperscript{34,35} Surprisingly, traditional Brønsted or Lewis acids were found to be completely ineffective in these studies.

Scheme 4.2 Proposed route to unsymmetrical atropisomeric biaryls

We argued that if quinone monoacetals (4.1) were reacted with unprotected naphthols (4.2) in the presence of a strong Brønsted acid catalyst, an acetal exchange would afford the corresponding mixed-acetals (4.101).
4.3 Acid-catalyzed Acetal Exchange and Rearrangement

The mixed-acetal (3) then would undergo a \( [3,3] \)-sigmatropic rearrangement (i.e., Claisen rearrangement) to afford a de-aromatized intermediate (4.102) which, upon rapid re-aromatization, is expected to furnish the corresponding functionalized biaryls (4.3).\(^{36}\) In order to test the hypothesis outlined above we began to look for suitable combinations of strong organic acids (i.e., Brønsted acids) and solvents. We chose quinone monoacetal 1a and 2-naphthol 2a as coupling partners. In the highly polar solvent 2,2,2-trifluoroethanol (TFE), very strong Brønsted acids gave poor results, however, the somewhat weaker acids such as \( p \)-toluenesulfonic acid, trifluoroacetic acid and diphenylphosphoric acid furnished the desired functionalized biaryl products in moderate to excellent yields at room temperature. In order to achieve the highest isolated yield of 5a in the shortest possible time we found that the use of 2 equivalents of 2a and 20 mol\% of the organic acid catalyst were necessary.

4.4 Optimized Conditions for the Formation of Unsymmetrical Biaryls

With the optimization results in hand, we selected two suitable reaction conditions (A: 20 mol\% of TFA in toluene at 100 °C and B: 20 mol\% of DPA in TFE at 25 °C) and initiated an extensive study to determine the scope of substrates. We began with unsubstituted 2-naphthols and reacted them with a variety of quinone and imino-quinone monoacetals.
Varying the structure of the quinone monoacetal coupling partner did not cause any issues and, remarkably an electron-poor 2-naphthols could be coupled with an electron poor quinone monoacetal to afford functionalized 1,2'-biaryldiols 4.4.

Scheme 4.3 Optimized conditions for the preparation of C_1-symmetrical biaryls

2,3-Dihydroxynaphthalene can be coupled twice with quinone monoacetal 4.21 to afford functionalized terphenyl 4.41 in good isolated yield (Scheme 4.4). Intriguingly, only the anti diastereomer was obtained (i.e., racemic form) while the syn diastereomer (i.e., meso form) was not observed. This structural assignment was confirmed by subjecting the exhaustively O-methylated derivative 4.5 to single crystal X-ray diffraction. Nearly all of the

Scheme 4.4 Triaryl synthesis *via* acid catalysis
biaryldiols synthesized are new compounds/structures prepared in an operationally simple and scalable process. Naturally, we also briefly explored the possibility of using chiral BINOL-derived phosphoric acids to catalyze the coupling of 4.3 with 4.2 to afford 4.4 in an enantiomerically enriched form. After testing six popular chiral phosphoric acid catalysts in toluene (10 mol\% catalyst loading) between room temperature and 50˚C, we found that despite achieving moderate to good isolated yields of 4.4 (24-72\%), the level of enantioinduction was very poor (3-10\% ee). Studies are currently ongoing to develop a catalytic enantioselective version of this coupling reaction.

In order to examine the mechanistic feasibility of the proposed mixed acetal/[3,3]-sigmatropic rearrangement sequence (outlined in Scheme 4.2), we conducted M06-2X density functional calculations on a model system. The results of these calculations indicate that the mixed acetal (4.301) can indeed undergo a low-barrier TFA-catalyzed [3,3]-rearrangement (\(\Delta H^\ddagger < 10\) kcal/mol). Subsequent re-aromatization after this rearrangement gives rise to the corresponding biaryl product. Importantly, this mixed acetal/[3,3]-sigmatropic rearrangement reaction pathway is consistent with the nonreactivity of 2-methoxynaphthalene since it cannot generate the mixed acetal intermediate (Scheme 4.5).
4.5 Elucidating the Reaction Mechanism

We also examined alternative reaction pathways (Scheme 4.5). For example, we tested the hypothesis that the H atom on the O of 2-napthol is required for acetal exchange from the oxocarbenium intermediate (4.21a, Scheme 4.5).

Scheme 4.5 Experiments executed to elucidate the reaction mechanism

An S_N2'-type pathway was another possible reactive pathway, however, the observation that 2-methoxynaphthalene did not undergo the transformation was indicative of the proposed
aromatic Claisen-rearrangement. Extensive transition state searching by DFT-calculation also failed to locate a concerted $S_N2'$ transition state.

4.6 Conclusions

In summary, we have developed a practical, external oxidant-free, organocatalytic direct arylation protocol for the regioselective preparation of 1,1′-linked functionalized biaryls. The products are non-$C_2$-symmetrical atropoisomeric biarylols (i.e., BINOL-type) and aminohydroxy biaryls (i.e., NOBIN-type), most of which are novel structures. DFT calculations revealed that the mechanism most likely involves a tandem mixed-acetal formation/3,3/-rearrangement sequence. We anticipate that this transformation may serve as a prototype for related powerful transformations that build molecular complexity rapidly, with exceptional step-economy and in an environmentally-friendly fashion.
4.7 Experimental Details

4.7.1 Materials and Methods

All reactions were carried out in oven-dried glassware under air with magnetic stirring. All phenol and Naphthol compounds were purchased from Sigma-Aldrich Co. and used without further purification. All reactions were monitored by thin-layer chromatography (TLC) with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel (particle size 0.032-0.063 mm) purchased from SiliCycle was used for flash chromatography. Proton ($^1$H) and carbon ($^{13}$C) NMR spectra were recorded on a Bruker AV-400 (or a Bruker DRX-600) spectrometer operating at 400 MHz (or 600 MHz) for proton and 100 MHz (or 151 MHz) for carbon nuclei using CDCl$_3$ [or (CD$_3$)$_2$CO] as solvent, respectively. Chemical shifts are expressed as parts per million ($\delta$, ppm) and are referenced to 7.26 (CDCl$_3$) or 2.05 (CD$_3$)$_2$CO for $^1$H NMR and 77.00 (CDCl$_3$) or 206.26 (CD$_3$)$_2$CO for $^{13}$C NMR. Proton signal data uses the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and $J$ = coupling constant. High Resolution Mass Spectrometry was performed on a Shimadzu LCMS-IT-TOF under the conditions of electrospray ionization (ESI) in both positive and negative mode. X-ray Diffraction Experiment data were measured at 100(2) K on a SMART APEX II CCD area detector system equipped with a Oxford Cryosystems 700 series cooler, a graphite monochromator, and a Mo K$\alpha$ fine-focus sealed tube ($\lambda = 0.71073$ Å). Intensity data were processed using the Saint Plus program. All the calculations for the structure determination were carried out using the SHELXTL package (version 6.14). Initial atomic positions were located by
using XT, and the structures of the compounds were refined by the least-squares method using XL. Absorption corrections were applied by using SADABS. Hydrogen atoms were placed at calculated positions and refined riding on the corresponding carbons.

4.7.2 Detailed Experimental Procedures

Preparation of 4,4-dimethoxy-3,5-dimethylcyclohexa-2,5-dien-1-one 4.21

To a 250 mL round bottom flask equipped with a magnetic stir bar was charged with 3 g of 3,5-dimethylphenol (24.56 mmol) and 123 mL MeOH. The solution was allowed to stir until dissolution of the starting material before 15.82 g PIDA (49.11 mmol, 2 equiv) was added via small portions over a period of 5 minutes. A significant exotherm was observed via an internal thermocouple and the reaction was complete after 30 minutes following the addition of PIDA as indicated by TLC analysis. The resulting solution was allowed to cool to room temperature before removal of the solvent in vacuo. The crude material was dissolved in DCM (100 mL), added to a 250 mL separatory funnel with H₂O (75 mL) and extracted with DCM (3 x 50 mL). The combined organic phases were dried over Na₂SO₄, filtered, concentrated in vacuo and
purified via column chromatography in 20% EtOAc/hexanes to afford 2.1 g of **4.21** as a yellow solid, 47% isolated yield, Rf = 0.5 in 20% EtOAc/hexanes; $^1$H NMR (600 MHz, CDCl$_3$): δ 6.31 (s, 2 H), 3.06 (s, 6 H), 1.93 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 184.88, 155.09, 131.80, 98.06, 50.81, 16.35.

**Preparation of 1,4-bis(6-hydroxy-3-methoxy-2,4-dimethylphenyl)naphthalene-2,3-diol 4.41**

![Chemical reaction diagram]

To a 250 mL round bottom flask equipped with magnetic stir bar was added 1.17 g 2,3-dihydroxynaphthalene (**4.31**, 7.32 mmol), 4 g of quinone acetal **4.21** (3 equiv, 21.95 mmol) and toluene (73 mL). The flask was allowed to stir for 3 minutes before the addition of 0.11 mL (20 mol%, 1.46 mmol) TFA (CF$_3$CO$_2$H). A reflux condenser was then attached and the solution was heated to reflux for 12 h before the flask was removed from heat and allowed to cool to room temperature. The toluene was removed *in vacuo* and the crude material was dissolved in 75 mL DCM and transferred to a 250 mL separatory funnel with 100 mL NaHCO$_3$ (sat.). The aqueous phase was extracted with DCM (3 x 75 mL), dried over Na$_2$SO$_4$, filtered, concentrated *in vacuo*
and purified via column chromatography to afford 1.69 g of 4.41 as a white solid, 50% isolated yield, Rf = 0.25 in 40% EtOAc/hexanes; m.p. 263 - 264 °C; \( ^1H \) NMR (400 MHz, CDCl\(_3\)) δ 7.31-7.24 (m, 4H), 6.77 (s, 2H), 6.02 (br s, 2H), 4.64 (br s, 2H), 3.75 (s, 6H), 2.36 (s, 6H), 1.94 (s, 6H); \( ^13C \) NMR (100 MHz, CDCl\(_3\)) δ 151.0, 149.7, 142.4, 132.9, 131.8, 128.2, 125.3, 124.4, 117.8, 115.4, 115.0, 60.2, 16.3, 13.4; HRMS (ESI): Exact mass calcd. for C\(_{28}\)H\(_{27}\)O\(_6\) [M-H]-: 459.1813, found: 459.1816.

**Preparation of 1,4-bis(3,6-dimethoxy-2,4-dimethylphenyl)-2,3-dimethoxynaphthalene 4.5**

![Diagram](image)

To a 25 mL round bottom flask equipped with magnetic stir bar was added 500 mg 4.41 (1.09 mmol), 1.42 g Cs\(_2\)CO\(_3\) (4.36 mmol, 4 equiv) followed by 11 mL ACS-grade MeCN. The flask was then charged with 0.3 mL MeI (4.5 equiv, 4.91 mmol), sealed with a rubber septum and heated to 50 °C for 12 h. The flask was allowed to cool to room temperature and the crude material was then diluted with 25 mL DCM and added to a separatory funnel along with 25 mL H\(_2\)O, extracted with DCM (3 x 25 mL), dried over Na\(_2\)SO\(_4\), filtered, concentrated \textit{in vacuo} and
purified via column chromatography with 20% EtOAc/hexanes to afford 534 mg of 4.5 as a white crystalline solid, 95% isolated yield, m.p. = 234 - 236 °C, (DCM/EtOAc/hexanes), Rf = 0.5 in 40% EtOAc/hexanes; ¹H NMR (600 MHz, CDCl₃): δ 7.31 (dt, J = 6.3, 3.2 Hz, 2 H), 7.25 (dt, J = 6.5, 3.1 Hz, 2 H), 6.77 (s, 2 H), 3.81 (s, 6 H), 3.76 (s, 6 H), 3.67 (s, 6 H), 2.48 (s, 6 H), 1.98 (s, 6 H); ¹³C NMR (151 MHz, CDCl₃) δ 153.57, 150.93, 149.81, 131.88, 130.33, 130.29, 126.83, 125.24, 124.54, 123.90, 110.85, 60.33, 60.10, 55.82, 16.62, 13.51.
4.8 References


CHAPTER 5

Developing a Versatile Synthesis of Symmetrical and Unsymmetrical Diaryl Hydrazines

Parts of this chapter have been adapted from: Keene, C.; Park, S.; Kürti, L., “Practical Synthesis of Symmetrical and Unsymmetrical N,N'-Diaryl Hydrazines: A New Approach to Functionalized Biaryls and Carbazoles” 2016 (Manuscript in preparation)

and


5.1.1 Introduction

As our lab began to explore alternative possibilities for the construction of axially-chiral biaryls it became apparent yet again that there are relatively few approaches towards N,N'-Diaryl hydrazine synthesis (See Chapter 2). While N,N'-Diaryl hydrazines are highly valuable precursors for diaryl azo compounds, used to prepare dyes for industrial and commercial use, we were more interested in their propensity to rearrange and afford highly sought-after axially-chiral
ligands when \( N,N' \)-dinaphthyl hydrazines are subjected to acidic media giving rise to the privileged 1,1’-binaphthyl-2,2’-diaminonaphthalene structure present in biaryl ligands like BINAM.\(^2\) The problem with current \( N,N' \)-diaryl hydrazine syntheses lies with the inherent side-reactions that lead to inseparable mixtures as well as the oxidatively-sensitive nature of hydrazines.

### 5.1.2 Limitations with \( N,N' \)-Diaryl Hydrazine Synthesis from Nitroarenes and Azoarenes

While the preparation of common diaryl hydrazines such as 2,2’-hydrazonaphthalene often gives consistent results, introducing heteroatoms and various functional groups complicate the reactions even further.\(^3\) The most common problems are the side-reaction/decomposition pathways and over-oxidation of the starting materials, reaction intermediates, and the products.

Scheme 5.1.2 Synthetic routes to \( N,N' \)-diaryl hydrazines
Traditional methods for their preparation involve reductive coupling of nitrobenzenes (5.11) with NaOH and Zn at high temperatures (Scheme 5.1.2).\(^4\) The over-reduction of nitro compounds down to their anilines (5.14) is a common side-reaction and the \(\pi-\pi\) stacking of azoarenes (5.13) makes their handling and preparation less than ideal.

### 5.2 Coupling of Amides: A New Approach for Unsymmetrical \(N,N'\)-Diaryl Hydrazine Synthesis

With limited synthetic methods that yield functionally-diverse \(N,N'\)-diaryl hydrazines it was clear that alternative strategies for their preparation would be of great value to the chemical community. Especially so that unsymmetrical \(N,N'\)-diaryl hydrazine synthesis is not a trivial matter given the lability of the weak nitrogen-nitrogen sigma bond in the presence of acid or heat to be broken and lead to disproportionation products or a number of possible sigmatropic rearrangements depending on the specific substitution pattern on the aromatic rings. It became clear that connecting 2 anilines together would give the desired products but halting the oxidation process at the hydrazine has never been demonstrated given the greater oxidation potential of hydrazines compared to their corresponding anilines.\(^5\)

Alternatively, I contemplated a nitrogen-nitrogen bond formation from \(N\)-aryl amides that would give rise to acylated hydrazine derivatives. Amidyl radicals generated from \(N\)-aryl amides
are well-precendented using metals like Ni(II), Cu(II) and Pb(IV), but have never been shown in the literature to couple at the nitrogen atoms without major side-oxidation products.\textsuperscript{6} An expected limitation to an approach such as this involving intermolecular coupling of two different amides to establish unsymmetrical hydrazine derivatives would inevitably lead to undesirable mixtures.

\textbf{Scheme 5.2.1} New oxidative approach to $N,N'$-diaryl hydrazine synthesis

However, I believed that by tying the amides together (5.3) by a removable tether would suppress or eliminate the possibility of multiple product formation according to the hypothesis that the close proximity of the nitrogen atoms would lead to an intramolecular nitrogen-nitrogen bond forming event that would precede any intramolecular coupling pathway to give rise to 5.4. With the consideration of kinetics a 3, 5, or 6-membered ring system after an intramolecular coupling would be the most facile. A 3-membered ring system would arise from phosgene reacting with anilines but proved to be problematic due to solubility issues of the resulting $N,N'$-diaryl ureas. 6-membered ring systems were attempted using the acid-chloride derivative of phthalic acid but the resulting coupling attempts led to complex, inseparable mixtures of
products. Ultimately, I chose a malonic tether for the formation of a 5-membered ring system. Malonyl dichloride was not used and replaced by the use of 2,2-dimethylmalonyl chloride (5.15) eliminating the possibility of a side-oxidation reaction at the methylene position.

Scheme 5.2.2 Proposed synthesis of pyrazolidine-3,5-diones

I proposed that adding 2 equivalents of an appropriate aniline (5.14) to dimethyl malonyl chloride would lead to product 5.3 by which an intramolecular nitrogen-nitrogen coupling reaction would give rise to pyrazolidine-3,5-dione 5.4. By having the 2-position of a 1,3-diketo compound rendered inactive by the geminal dimethyl substitution of dimethyl malonyl chloride (5.15) the number of oxidative pathways possible is reduced and allows for a greater chance of the desired chemoselective coupling on the nitrogen atoms.
5.3.1 Synthesis of Symmetrical Malonyl Diamides

Though our focus was directed toward synthesizing unsymmetrical $N,N'$-diaryl hydrazines, 4 symmetrical malonyl diamides were prepared (See Table 5.3.1) from the 2 equivalents of the corresponding commercially-available aniline and 1 equivalent of dimethyl malonyl chloride in DCM. For malonyl diamides 5.301, 5.303 and 5.304 purification consisted of filtration after reaction completion with cold DCM and hexanes completion due to the limited solubility of the symmetrical diamides in the reaction solvent DCM. The formation of the malonyl diamides was conveniently scaled up to 14 mmol.

![Chemical Structure]

Table 5.3.1  Scope and preparation of symmetrical malonyl diamides
Purification via column chromatography was performed on malonyl diamide 5.302 due to a number of impurities found in the $^1$H NMR spectra after washing and filtering the crude product. (Note: the success of the following nitrogen-nitrogen bond formation relies heavily on running the reaction with a clean sample).

5.3.2 Making the Nitrogen-Nitrogen Connection through an Intramolecular Amide-Coupling

In order to demonstrate the viability of the proposed method, 5.303, derived from 2-naphthylamine was treated with a variety of well-established N-N bond forming reactions$^{7,8}$ including those from secondary amides but lacked the N-aryl moeity. Traditional metal oxidants either gave no desired product or led to complex mixtures involving decomposition of the starting malonyl diamides. When exposed to halonium species the starting materials underwent ring halogenation via an $S_{NEA}$ mediated pathway or through the elusive Orton rearrangement.$^9$

Given the increasing popularity of hypervalent iodine species such as (diacetoxy)iodobenzene (PIDA) and bis(trifluoromethyl)acetoxyiodobenzene (PIFA) to generate $N$-acyl nitrenium species $in-situ$ to form nitrogen-nitrogen bonds I performed an extensive solvent screen and found that when excess (4 equiv) PIDA was used in MeCN under dilute conditions, [0.01], the reaction proceeded cleanly and selectively with only the nitrogen-nitrogen product being formed. Higher temperatures and higher concentrations led to an increase in over-oxidized side products.
Although it is known that triplet nitrenes are thermodynamically more stable than singlet nitrenes and react in a stepwise manner, we have not been able to elucidate the exact mechanism taking place. An excess of PIDA or PIFA may suggest that two radicals may be formed.

Table 5.3.2  Condensed table of intramolecular amide-coupling optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield of 5.403 (%)</th>
<th>Yield of 5.417 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuCl₂</td>
<td>DCE</td>
<td>23-reflux</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CuOAc₂</td>
<td>CHCl₃</td>
<td>23-reflux</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Pb(OAc)₄</td>
<td>AcOH</td>
<td>23-reflux</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>NXS&lt;sub&gt;x = Cl, Br, I&lt;/sub&gt;</td>
<td>DCM</td>
<td>0-23</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>NXS&lt;sub&gt;x = Cl, Br, I&lt;/sub&gt;</td>
<td>THF</td>
<td>0-23</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Phl(OAc)₂</td>
<td>MeOH</td>
<td>23-50</td>
<td>24</td>
<td>trace</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Phl(OAc)₂</td>
<td>DCM</td>
<td>23</td>
<td>24</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>8&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Phl(OAc)₂</td>
<td>MeCN</td>
<td>50</td>
<td>12</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>9&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Phl(OAc)₂</td>
<td>MeCN</td>
<td>50</td>
<td>12</td>
<td>78</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>di-tert-Bu-diaziridinone, FeBr (10 mol%)</td>
<td>MeCN</td>
<td>23</td>
<td>24</td>
<td>59</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>di-tert-Bu-diaziridinone, CuCl (10 mol%)</td>
<td>MeCN</td>
<td>23</td>
<td>12</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>di-tert-Bu-diaziridinone, CuBr-SMe₂ (10 mol%)</td>
<td>MeCN</td>
<td>23</td>
<td>12</td>
<td>84</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>1</sup>: reaction was performed at [0.1]  
<sup>2</sup>: reaction was performed at [0.01]
simultaneously before a radical termination of species 5.3d (Figure 5.3.1). When PIDA is used with DCM as the solvent a nitrogen-oxygen product is obtained indicating a competing mechanistic pathway. With the observation that MeCN suppressed the formation of nitrogen-oxygen coupled product it is conceivable that the higher dielectric constant of MeCN allows for a radical mechanism to predominate which may explain the observed chemoselectivity.

![Mechanistic Pathways](image)

**Figure 5.3.1** Plausible mechanistic pathways involving hypervalent I(III) reagents

Alternatively, di-tert-butyl diaziridinone, an organic oxidant that has gained popularity due to its wide versatility\(^{10,11}\) was tested as well.\(^9\) We were pleased to find that the diaziridinone led to less decomposition when compared to hypervalent iodine. We also found scalability was significantly improved without any increase in side-oxidation substrates. After testing various
metals it was decided that Cu(1)Br-SMe₂ was best suited as the metal catalyst for this reaction presumably due to Cu higher affinity for nitrogen atom coordination and demonstration of its ability to insert into nitrogen-nitrogen bonds (See Table 5.3.2).⁵,¹⁰,¹¹

**Figure 5.3.2** Proposed catalytic cycle for Cu(I) salts in pyrazolidine-3,5-dione formation

Based on the reactivity of di-tert-butyl diaziridinone 5.16 we believe that the formation of products 5.4 are a result from the proposed catalytic cycle in Figure 5.3.2. Fe(I) salts did
promote the transformation but resulted in lower overall yields and significantly longer reaction times (>7 days).

5.3.3 Proposed Synthesis of Unsymmetrical Malonyl Diamides from Azetidine-2,4-Diones

For the preparation of unsymmetrical malonyl diamides, inevitable mixtures of 5.35, 5.36, and 5.37 were observed when two different anilines (5.141 and 5.142) were added to dimethyl malonyl chloride despite manipulation of reaction temperature, the rate of addition, the order of addition of starting materials and changes in concentration (See Figure 5.3.3).

![Chemical Structures](image)

**Figure 5.3.3** Initial attempts at synthesis of unsymmetrical malonyl diamides
To selectively form unsymmetrical malonyl diamides I became intrigued by the idea that an azetidine-2,4-dione could be prepared from one desired aniline and could then subsequently undergo a nucleophilic ring-opening from another aniline. If carried out this route would prevent the formation of undesired unsymmetrical malonyl diamides (Scheme 5.3.1)

Scheme 5.3.1 Proposed route for the synthesis of unsymmetrical Pyrazolidine-3,5-diones

5.3.4 Azetidine-2,4-Dione Optimization and Substrate Scope

Azetidine-2,4-diones are a well-documented class of molecules and have important uses in polymer, heterocyclic and medicinal chemistry.  While azetidine-2,4-diones have been demonstrated to be useful building blocks for complex substrates, there are scarce methods known for their preparation. Staudinger demonstrated their synthesis from a thermal [2+2]-cycloaddition of ketenes with isocyanates. However, the highly reactive nature of ketenes limited the scope of this approach. In 2006 there was a report of a thermal [2+2]-cycloaddition from isobutyl chloride and phenyl isocyanate in the presence of NEt₃ that was reported to give...
high yields of $N$-phenyl-3,3-dialkyl azetidine-2,4-diones at high temperatures in xylenes although a more extensive substrate scope was not established.\textsuperscript{15} (See \textbf{Scheme 5.3.3})

\begin{align*}
\text{Scheme 5.3.3} & \text{ Azetidine-2,4-dione synthesis from ketenes and isocyanates} \\
\text{Following experimental reports of azetidine-2,4-dione synthesis from the corresponding aniline and malonyl chloride in combination with NEt$_3$ gave inconsistent results with those reported and yielded the symmetrical malonyl diamide as the major product with only trace amounts of the desired azetidine-2,4-dione formed.}^{14} \text{ I observed that without the presence of a trialkylamine base present the only products formed were malonyl diamides. After numerous trials I had recorded a small number of attempts that had led to a significant increase in the yield of the azetidine-2,4-dione 5.201. The obvious alteration made in those experiments compared with the others was that the aniline was added simultaneously with NEt$_3$. This led me to believe that participation of NEt$_3$ gave enhanced reactivity to dimethyl malonyl chloride through generation of an acyl-ammonium species and that was the key to attaining high yields of the 4-membered azetidine-2,4-diones. A screen of acylation reagents was tested and it was found that NEt$_3$ and $N,N'$-dimethylaminopyridine (DMAP) performed equally on most substrates with DMAP having a slight advantage by decreasing reaction time even further (See Table 5.3.2).}
\end{align*}
After a quick optimization it was found that addition of a [1M] solution of the aniline in DCM premixed with DMAP added quickly via syringe to a solution of dimethyl malonyl chloride consistently gave the highest yields. (See Table 5.3.3)

While it comes as no surprise that the less nucleophilic anilines resulted in longer reaction times (5.207 and 5.208), this optimized procedure takes advantage of cheap, commercially available anilines and converts them into azetidine-2,4-diones without external heating in less than 10 minutes in most cases without a decrease in yield as the reaction is scaled up to 14 mmol (Table 5.3.4).
Table 5.3.4  Synthesis of $N$-aryl-3,3-dimethyl azetidine-2,4-diones
5.3.5 Synthesis of Unsymmetrical Malonyl Diamides

After synthesizing a small library of azetidine-2,4-diones (5.2) I began reacting them with a variety of commercially-available anilines. Azetidine-2,4-diones are known to be resistant to ring-opening reactions unless in the presence of strong nucleophiles or under alkali conditions. For this reason it was necessary to perform an irreversible deprotonation on the aryl amine before the addition of the azetidine-2,4-dione to give the highest yield of the corresponding unsymmetrical malonyl diamide.

When electron-deficient anilines such as 3,5-(bis)trifluoromethylaniline were deprotonated with $n$BuLi and mixed with azetidine-2,4-diones no reaction occurred even at elevated temperatures indicating an electronic limitation to this ring opening step. Therefore it was decided that by pairing the more nucleophilic aniline with a more electrophilic azetidine-2,4-dione that the electronic limitation could be overcome to some degree. As shown in Table 5.3.5 the reaction conditions allowed for high yields of the corresponding unsymmetrical malonyl diamides.
Table 5.3.5  Synthesis of unsymmetrical malonyl diamides
5.4.1 Chemoselective Intramolecular Amide Couplings

A variety of malonyl diamides (5.3) were prepared and tested using the optimized conditions and it was determined that the greater oxidative potential of PIFA was sufficient for the transformation when PIDA led to complex mixtures. It was apparent that the thermo-instability of commercially-available hypervalent iodine reagents such as PIDA and PIFA would give a temperature threshold. We were surprised to see that I\textsuperscript{III} reagents tolerated nearly all functional groups with electron-rich diamides resulting in the highest isolated yields of Pyrazolidine-3,5-diones, with the exception of 5.412, which gave an excellent yield. When diaziridinone 5.16 was employed the success of the reaction predictable for the most part. Mildly electron-rich substrates and those with methoxy substituents on the aromatic ring reacted remarkably well.

The reaction with diaziridinone 5.16 was easily scaled to 3 mmol in substrates 5.301, 5.303, 5.304, and 5.306 and 5.307. The inability of the di-tert-butyl-diaziridinone catalyst system to convert the more electron-deficient malonyl diamides to their respective diaryl hydrazines may indicate a shifted equilibrium to the more thermodynamically stable Cu species, one hypothetically bearing the most stable amidyl radical as depicted in the ligand exchange between 5.3g and 5.3h (Figure 5.4.1). This hypothesis is also supported by the observation that the electron-rich malonyl diamides turnover impressively despite the final step being a possible reductive elimination which would favor electron-deficient malonyl diamides.
The suppression of the formation of the nitrogen-oxygen coupled product demonstrates the remarkable chemoselective nature of this transformation under the designed conditions. As predicted, the resulting unsymmetrical diamides performed successfully in the

![Chemical Structure](image)

**Compound, Isolated Yield (%)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>A: Isolated Yield</th>
<th>B: Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.401</td>
<td>85% (3 mmol)</td>
<td>87%</td>
</tr>
<tr>
<td>5.402</td>
<td>N.R.</td>
<td>93%</td>
</tr>
<tr>
<td>5.403</td>
<td>80% (3 mmol)</td>
<td>82%</td>
</tr>
<tr>
<td>5.404</td>
<td>82%</td>
<td>84%</td>
</tr>
<tr>
<td>5.405</td>
<td>N.R.</td>
<td>56%</td>
</tr>
<tr>
<td>5.406</td>
<td>90% (3 mmol)</td>
<td>89%</td>
</tr>
<tr>
<td>5.407</td>
<td>88% (3 mmol)</td>
<td>85%</td>
</tr>
<tr>
<td>5.408</td>
<td>N.R.</td>
<td>54%</td>
</tr>
</tbody>
</table>

**Table 5.4.1** Substrate scope of intramolecular amide-coupling
reaction, tolerating a variety of functional groups and substitution patterns on the aromatic ring.

Table 5.4.2  Substrate scope of intramolecular amide-coupling (continued)
We also utilized the 2-anthracenyl nucleus to successfully synthesize 5.416 using PIDA but were surprised to find that when diaziridinone 5.16 was employed there was no conversion of starting material to product, only slow decomposition of the starting material over a period of days.

As expected, the resulting unsymmetrical diamides performed successfully in the reaction, tolerating a variety of functional groups and substitution patterns on the aromatic rings. We were pleased to find that various substitution patterns and functionalities were tolerated in the synthesis of the unsymmetrical N,N'-diaryl hydrazines with the N-2-naphthyl subunit being an important structural requirement for predicted success with other substrates but the reaction is not limited to such strict structural specifications.

**5.4.2 Intermolecular Variation of the Oxidative Amide-Coupling**

With the success of an intramolecular amide-coupling, we turned our interests to the possibility of an intermolecular variation of this transformation (Refer to Figure 5.4.2). Attempts to synthesize the bis(acylated) N,N'-diaryl hydrazine from N-aryl amides via an intermolecular amide-coupling though were not successful. Employing the optimized conditions from condition (A) yielded only trace amounts of the desired products as was detected on a time-of-flight liquid chromatography/mass spectrometer (TOF LC/MS).
Figure 5.4.2  Attempts at intermolecular amide-couplings using the optimized conditions

With prolonged reaction times TLC analysis indicated decomposition of the starting materials 5.81-5.84. These experimental results along with those that the intramolecular approach was a success led me to believe that an equilibrium between the starting N-aryl amides and the diacylated \( N,N' \)-diaryl hydrazines existed while Cu was present. While the strength of the nitrogen-nitrogen bond of 5.85 is speculative at best, based on the mechanistic understanding of the transformation, the \( N \)-aryl amidyl radical generated by insertion of Cu(I) into the nitrogen-nitrogen bond of 5.85 would inhibit product formation as the activity of the catalytic Cu would be suppressed (See Figure 5.4.1). With consideration that stoichiometric quantities of Cu could drive the reaction forward I varied yet again the reaction concentration, rate of addition and temperature. The addition of larger amounts of Cu only led to a faster rate of decomposition with TLC analysis indicating the formation of various side-products. Despite multiple alterations of the reaction concentration and rate of addition, complex reaction mixtures were formed and unknown species were generated that could not be characterized.
5.5.1 Hydrolysis of Pyrazolidine-3,5-Diones to \(N,N'\)-Diaryl Hydrazines: New Access to Biaryls and Carbazoles

Acidic and basic hydrolysis were attempted using protic solvents EtOH and \(H_2O\) with acids TFA, CSA, TsOH, PTSA, HCl, and \(H_2SO_4\). Alternatively, basic conditions using alkali-hydroxides, \(1^0\) and \(2^0\) amines, hydroxylamine, \(O\)-tBu hydroxylamine, and \(NH_4OH\) buffer solutions were also tested but both so the traditional hydrolytic conditions involving a protic-solvent with a number of acids (TFA, CSA, TsOH, PTSA, HCl, \(H_2SO_4\)) and bases (alkali-hydroxides, \(1^0\) and \(2^0\) amines, hydroxylamine, \(O\)-tBu hydroxylamine, and \(NH_4OH\) solutions) but all attempts gave rise to numerous side-products and decomposition of material throughout the course of the reaction and was thus abandoned. Turning to a more potent nucleophile, it was found that anhydrous hydrazine in toluene cleaved pyrazolidine-3,5-diones 5.3 to their corresponding \(N,N'\)-diaryl hydrazines 5.4 cleanly with the fewest number of side-products formed. With \(N,N'\)-dinaphthyl hydrazine (5.303) prone to rearrange to BINAM (5.6) in the presence of acid I decided to perform an acidic workup thereby removing the step of isolating the

![Scheme 5.5.1](image-url)
hydrazine and attaining BINAM after a quick 10 minute workup with 1 N HCl (See Scheme 5.5.1). Once the diaryl hydrazine has been liberated it can then be isolated or further transformed into biaryls and even carbazoles. In an attempt to isolate the [3,3]- or [5,5]-benzidine-type rearranged product from 5.402, HCl was added to the solution containing the \(N,N'\)-diaryl hydrazine after cleavage of the dimethyl malonyl tether followed by treatment with HCl at refluxing temperatures, however, the anticipated rearranged product was not found in the reaction mixture. Surprisingly, HCl at high temperatures did not promote any rearrangement. Instead, 41% of the symmetrical hydrazine was recovered after silica-gel chromatography indicating a reluctance of this particular \(N,N'\)-diaryl hydrazine 5.51 to rearrange even in the presence of strong acid at high temperatures (Refer to Figure 5.5.1).

![Synthesis and isolation of \(N,N'\)-diaryl hydrazine 5.51](image)

**Figure 5.5.1** Synthesis and isolation of \(N,N'\)-diaryl hydrazine 5.51

There have been some reports where it is speculated that \(N,N'\)-dinaphthyl hydrazines bearing \(\text{NO}_2\) groups on the aromatic ring have a slower propensity to undergo a [3,3]-rearrangement and give lower overall yields.\(^{16}\) More studies into the investigation of substituents stereo-electronic effects need to be carried out in order to better understand these
effects on the rate and efficacy of the [3,3’]- or [5,5’]-sigmatropic rearrangements of \(N,N’\)-diaryl hydrazines.

## 5.6 Summary

In conclusion, we have developed a new method for the preparation of symmetrical and unsymmetrical \(N,N’\)-diaryl hydrazines from commercially available anilines and easily prepared reagents. The current method presents an alternative approach that tolerates a variety of substitution patterns, electronics, and functionalities that existing methods cannot.\(^{17}\) At the current time we are investigating further synthetic transformations of previously inaccessible pyrazolidine-3,5-diones and azetidine-2,4-diones. Further studies are necessary to elucidate the mechanism of this intramolecular amide-coupling.

This approach has allowed us to tap into previously inaccessible symmetrical and unsymmetrical \(N,N’\)-diaryl hydrazines using commercially-available anilines as building blocks with cheap and relatively non-toxic hypervalent iodine reagents as oxidants. Access to large libraries of diaryl hydrazines has now been tapped into and unprecedented structurally-diverse diaryl hydrazines can be synthesized in the lab under mild and relatively safe conditions. Looking to the future, more experimentation needs to be conducted for optimization of the hydrolysis step to relinquish diaryl hydrazines without disproportionation side-products. Further studies on the [3,3]-sigmatropic rearrangement of structurally-diverse diaryl hydrazines in a
variety of solvents should be conducted to further understand the role of stereoelectronics and solvent-effects in this powerful, yet understudied chemical transformation.
5.7 Experimental Section

5.7.1 Materials and Methods

All reactions were carried out in oven-dried glassware under normal atmosphere conditions with magnetic stirring. Most of the reagents, including the aromatic amines, were purchased from Sigma-Aldrich Co. and used without further purification. Procedures for synthesis of select aromatic amines are detailed below. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. All reactions were monitored by thin-layer chromatography (TLC) with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel (particle size 0.032 - 0.063 mm) purchased from SiliCycle was used for flash chromatography. All anilines were purchased commercially from Sigma-Aldrich and Oakwood Chemical except for those synthesized according to the method described in Chapter 3.

Proton (\(^1\)H) and carbon (\(^{13}\)C) NMR spectra were recorded on a Bruker AV-600 spectrometer operating at 600 MHz for proton and 151 MHz for carbon nuclei using CDCl\(_3\) as solvent, respectively. Chemical shifts are expressed as parts per million (\(\delta\), ppm) and are referenced to 7.26 (CDCl\(_3\)) for 1H NMR and 77.00 (CDCl\(_3\)) for 13C NMR. Proton signal data uses the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and J = coupling constant. High Resolution Mass Spectrometry was performed on an Agilent LC/MS-IT-TOF under the conditions of electrospray ionization (ESI) in positive mode. Infrared spectra were collected on a Shimadzu IRPrestige- 21 (Fourier Transform Infrared Spectrophotometer).
5.7.2 Detailed Experimental Procedures

Preparation of 2,2-dimethylmalonyl dichloride 5.15

To a 1 L round-bottom-flask equipped with magnetic stir bar was charged with 25 g of dimethyl malonic acid (189.2 mmol) and DCM (378 ml, [0.5]). The flask was then capped with a septum along with a nitrogen inlet needle and an outlet needle connected to a bubbler. The magnetic stir plate was set to 250 rpm while oxalyl chloride (48 mL, 72 g, 567.7 mmol, 3 equivalents) was added over 5 minutes at 23 °C. 2 drops of DMF were then added in order to initiate the reaction and bubbling was observed immediately. The reaction was allowed to stir for 16 hours under a stream of nitrogen before $^1$H-NMR analysis indicated complete consumption of the starting material. The magnetic stir bar was removed from the flask and the DCM and residual oxalyl chloride were removed in-vacuo at 23 °C until a viscous yellow oil remained. The crude oil was then transferred via glass pipette to a 100 mL round-bottom-flask equipped with magnetic stir bar. The crude material was then reduced under vacuum distillation at which the product was collected as a colorless oil (75 °C / 6 mbar), 72% isolated yield. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.67 (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.93, 69.09, 23.15 $^1$H- and $^{13}$C- NMR spectra were in complete agreement with the reported values.$^{18}$
Preparation of \(N,N'\)-di-\(t\)-butyl diaziridinone 5.16

A 500 mL round-bottom-flask was charged with 30.9 mL of \(t\)-Butyl hypochlorite (prepared as described in \textit{Org. Synth.} \textbf{1969}, \textit{49}, 9; DOI: 10.15227/orsyn.049.0009) (28.2 g, 260.0 mmol) was added dropwise by syringe to a viscous suspension of 1,3-di-\(t\)-butylurea (44.0 g, 255.0 mmol) in dry ether (300 mL) with stirring at room temperature. To the resulting clear pale yellow-green solution was added potassium \(t\)-butoxide (33.2 g, 296.0 mmol) in small portions over a period of 10 minutes. The resulting mixture was stirred at room temperature for 75 minutes until \(^1\)H NMR indicated consumption of the starting material. The reaction was then poured into a 1 L separatory funnel, diluted with pentane (200 mL), washed with water (100 mL x 3) and brine (100 mL), dried over Na\(2\)SO\(4\), filtered, concentrated \textit{in-vacuo}, and distilled under reduced pressure (65 °C/ 5 mmHg) to give di-\(t\)-butyl diaziridinone as a colorless liquid (26.5 g, 155.6 mmol, 61% yield); \(^1\)H NMR (600 MHz, benzene-\textit{d}6) \(\delta\) 1.06 (s, 18H); \(^{13}\)C NMR (151 MHz, benzene-\textit{d}6) \(\delta\) 159.60, 59.55, 27.46; IR (film) 1932, 1879, 1861 cm\(^{-1}\); \(d = 0.871 \text{ g/mL}\) (Greene, F. D.; Stowell, J. C.; Bergmark, W. R. \textit{J. Org. Chem.} \textbf{1969}, \textit{34}, 2254).
Preparation of 3-(4-fluorophenyl)-2-aminonaphthalene 5.141

To an oven-dried 50 mL round bottom flask equipped with magnetic stir bar and septa is purged with argon with an inlet needle and outlet needle piercing the septum. After purging the flask for 5 minutes, the argon line is closed. The septa is removed and 510 mg of 10% Pd/C (10 mol%) is added to the bottom of the flask followed by opening the argon gas line and rinsing any particulate matter with 12 mL DCM. 3-(4-fluorophenyl)-2-nitronaphthalene (prepared as described in Chapter 3)\(^\text{19}\), 1.28 g dissolved in 12 mL EtOAc, was added via syringe to the mixture. A hydrogen balloon equipped with a long needle was inserted into the septa under the surface. An outlet needle was inserted into the septa causing bubbling in the flask. Stirring continued during this time for an additional 10 minutes and then the outlet needle was removed while keeping the hydrogen balloon attached. After 16 hours, TLC analysis showed complete consumption of the starting material. The solution was then poured over a celite filter and rinsed with EtOAc (3 x 50mL). The organic phase is concentrated and purified via column chromatography using 5% EtOAc/hexanes to afford 932 mg of 3-(4-fluorophenyl)-2-naphthylamine as a white solid, 82%, m.p.: 89.0 - 90.7 °C, \(R_f = 0.3\) in 5% EtOAc/hexanes. \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 9.29 (d, \(J = 2.7\) Hz, 2 H), 9.10 (s, 2 H), 8.02 (d, \(J = 11.7\), 2 H), 6.95
(d, J = 9.0 Hz, 2 H), 4.05 (s, 6 H), 1.72 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 171.23, 153.06, 141.53, 127.39, 120.49, 115.27, 109.31, 56.80, 51.84, 23.81; HRMS (ESI) m/z calcd for C$_{16}$H$_{12}$FN [(M+H)$^+$]: 238.0897, found 238.1057.

Preparation of $N_1,N_3$-bis(3,5-dimethylphenyl)-2,2-dimethylmalonamide 5.301

To an oven-dried 50 mL round bottom flask, equipped with a magnetic stir bar, was added 20 mL ACS-grade DCM, and dimethylmalonyl chloride (1.32 mL, 10 mmol, 1.69 g). 3,5-dimethylaniline (2 equiv, 2.49 mL, 20 mmol) was added to the solution via syringe at a rate of 5 mL/min. White precipitate was observed and the solution was allowed to stir for an additional 30 minutes when TLC analysis showed complete consumption of the starting material. 20 mL of hexanes was added to the solution, and the precipitate was filtered and washed with hexanes (3 x 10 mL). The solid was then transferred to a scintillation vial and dried in-vacuo to afford 3.32 g of 5.301 as a white solid, 98% yield, m.p.= 207 – 209 °C, Rf = 0.25 in 10% EtOAc/hexanes. $^1$H
NMR (600 MHz, CDCl$_3$): $\delta$ 8.39 (s, 2 H), 7.17 (s, 4 H), 6.78 (s, 2 H), 2.30 (s, 12 H), 1.66 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 171.45, 138.70, 137.13, 126.48, 118.08, 50.71, 24.18, 21.29; HRMS (ESI) m/z calcd for C$_{21}$H$_{26}$N$_2$O$_2$ [(M+H)$^+$]: 339.2103, found 339.2121.

**Preparation of $N_1,N_3$-bis(2-methoxy-5-nitrophenyl)-2,2-dimethylmalonamide 5.302**

![](image)

To an oven-dried 50 mL round bottom flask, equipped with a magnetic stir bar, was added 20 mL ACS-grade DCM, and dimethylmalonyl chloride (1.32 mL, 10 mmol, 1.69 g). 2-methoxy-5-nitroaniline (2 equiv, 3.36 g, 20 mmol) was added to the solution in one portion followed by the addition of triethylamine (2.2 equiv, 3.07 mL, 22 mmol). The yellow solution was allowed to stir for 2 hours. The solution diluted with 30 mL EtOAc and then transferred to a 250 mL separatory funnel with 100 mL H$_2$O. The organic mixture was then extracted with EtOAc (3 x 100 mL), dried over Na$_2$SO$_4$, filtered, concentrated *in-vacuo* and then purified via column chromatography using 45% EtOAc/hexanes to afford 4.24 g of 5.302 as a yellow solid, 98% isolated yield, m.p. = 217.2 - 219.6 °C, Rf = 0.1 in 40% EtOAc/hexanes. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 9.29 (d, $J = 2.7$ Hz, 2 H), 9.10 (s, 2 H), 8.02 (d, $J = 11.7$, 2 H), 6.95 (d, $J = 9.0$ Hz, 2 H), 4.05 (s, 6 H), 1.72 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 171.23, 153.06, 141.53, 127.39,
120.49, 115.27, 109.31, 56.80, 51.84, 23.81; HRMS (ESI) m/z calcd for C\textsubscript{19}H\textsubscript{20}N\textsubscript{4}O\textsubscript{8} [(M+H)\textsuperscript:+]: 433.1381, found 433.1363.

**Preparation of 2,2-dimethyl-\textit{N},\textit{N}-di(naphthalen-2-yl)malonamide 5.303**

![Diagram of 5.303](image)

To an oven-dried 50 mL round bottom flask, equipped with a magnetic stir bar, was added 20 mL ACS-grade DCM, and dimethylmalonyl chloride (1.32 mL, 10 mmol, 1.69 g). 2-naphthylamine (2 equiv, 2.86 g, 20 mmol) was added to the solution in one portion. White precipitate was observed and the solution was allowed to stir for an additional 1 hour when TLC analysis showed complete consumption of the starting material. 20 mL of hexanes was added to the solution, and the precipitate was filtered and washed with hexanes (3 x 10 mL). The solid was then transferred to a scintillation vial and dried \textit{in-vacuo} to afford 3.67 g of 5.303 as a white solid, 96% yield, m.p.= 211 – 212 °C, R\textsubscript{f} = 0.2 in 20% EtOAc/hexanes. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 8.72 (s, 2 H), 8.24 (s, 2 H), 7.80 (t, \textit{J} = 8.5 Hz, 6 H), 7.51-7.40 (m, 7 H), 1.79 (s, 6 H); 13\textsuperscript{C} NMR (100 MHz, CDCl\textsubscript{3}): δ 171.74, 134.70, 133.70, 130.88, 128.82, 127.70, 127.55, 125.28, 120.14, 117.37, 94.98, 50.95, 24.33; HRMS (ESI) m/z calcd for C\textsubscript{25}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2} [(M+H)\textsuperscript:+]: 383.1761, found 383.1789.
Preparation of 2,2-dimethyl-\(N_1,N_3\)-bis(4-(thiophen-2-yl)phenyl)malonamide 5.304

To an oven-dried 25 mL round bottom flask, equipped with a magnetic stir bar, was added 10 mL ACS-grade DCM, and dimethylmalonyl chloride (0.264 mL, 2 mmol, 338 mg). 701 mg of 4-(thiophen-2-yl)aniline (2 equiv, 4 mmol) was added to the solution in one portion. White precipitate was observed and the solution was allowed to stir for an additional 5 minutes before adding 0.613 mL of NEt\(_3\) (2.2 equiv, 445 mg, 4.4 mmol) in one portion. After 2 hours TLC analysis showed complete consumption of the starting material. The solution was poured into a 125 mL separatory funnel and diluted with 75 mL EtOAc. The organic layer was washed with \(\text{H}_2\text{O}\) (3 x 25), and brine (25 mL). The organic layer was dried over Na\(_2\)SO\(_4\), filtered and washed with EtOAc, concentrated \textit{in-vacuo} and then purified via column chromatography using 80% EtOAc/hexanes to afford 777 mg of 5.304 as a golden solid, 87% yield, m.p.= 211.3 - 211.8 °C, Rf = 0.3 in 40% EtOAc/hexanes. \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 8.53 (s, 2 H), 7.67 – 7.47 (m, 6 H), 7.27 – 7.24 (m, 6 H), 7.09 – 7.01 (m, 2 H), 1.71 (s, 6 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 171.44, 143.71, 136.58, 131.11, 128.03, 126.50, 124.65, 122.89, 120.66, 50.84, 24.26.; HRMS (ESI) m/z calcd for \(\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_2\text{S}_2\) [(M+H)\(^+\)]: 447.1123, found 447.1236.
Synthesis of azetidine-2,4-diones 5.2

**General optimized procedure:**

To an open 250 mL 3-neck round bottom flask equipped with magnetic stir bar is added 80 mL ACS-grade DCM and 1.72 mL dimethylmalonyl chloride 5.15 (13 mmol, 1.3 equiv). The stirring solution is then charged with one syringe containing a premade 1M DCM solution (10 mL) of the appropriate aniline 5.14 (1 equiv, 10 mmol) and 3.16 g of DMAP (26 mmol, 2.6 equiv) over a period of 10 seconds. (An exotherm results after the quick addition but no accidents occurred while carrying out the procedure even on larger scales.) After TLC analysis shows complete conversion of the starting material the solution is transferred to a 250 mL separatory funnel with 100 mL water. The organic phase is then extracted with DCM (3 x 100 mL), dried over Na$_2$SO$_4$, filtered, concentrated and then purified via column chromatography to afford the desired azetidine-2,4-dione 5.2.
Preparation of 3,3-dimethyl-1-(naphthalen-2-yl)azetidine-2,4-dione 5.201

14 mmol scale, 5 minute reaction time. The crude material was purified by column chromatography using 5% EtOAc/hexanes to afford 2.55 g of 5.201 as a white crystalline solid, 76% isolated yield, m.p.= 86 – 87 °C, (DCM/hexanes), Rf = 0.55 in 10% EtOAc/hexanes. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.29 (s, 1 H), 8.00 (d, $J = 8.8$ Hz, 1 H), 7.87-7.80 (m, 3 H), 7.49 (q, 2 H), 1.53 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 172.80, 132.93, 131.71, 131.32, 129.10, 127.82, 127.61, 126.76, 126.08, 117.35, 116.83, 61.66, 17.60; HRMS (ESI) m/z calcd for C$_{15}$H$_{13}$NO$_2$ [(M+H)$^+$]: 240.0946, found 240.0994.

Preparation for 1-(anthracen-2-yl)-3,3-dimethylazetidine-2,4-dione 5.202

6.42 mmol scale, 30 minute reaction time. The crude material was purified by column chromatography using 5% EtOAc/hexanes to afford 1.02 g of 5.202 as a pale-yellow crystalline
solid, 66% isolated yield, m.p. = 207 – 209 °C, (PhMe, MeOH), Rf = 0.2 in 5% EtOAc/hexanes. 

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.43 (d, $J = 9.0$ Hz, 2 H), 8.39 (s, 1 H), 8.04-7.98 (m, 4, H), 7.48 (s, 2 H), 1.56 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 173.05, 132.22, 131.81, 131.32, 130.77, 129.83, 129.53, 128.18, 128.02, 126.57, 126.44, 125.94, 125.71, 117.52, 116.80, 61.89, 17.82; HRMS (ESI) m/z calcd for C$_{19}$H$_{15}$NO$_2$ [(M+H)$^+$]: 290.1103, found 290.1145.

**Preparation for 3,3-dimethyl-1-(pyren-1-yl)azetidine-2,4-dione 5.203**

![5.203](image)

1 mmol scale, 10 minute reaction time. The crude material was purified by column chromatography using 5% EtOAc/hexanes to afford 132 mg of 5.203 as a pale-yellow solid, 42% isolated yield, m.p. = 207 – 209 °C, Rf = 0.4 in 5% EtOAc/hexanes. 

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.21 (d, $J = 7.6$ Hz, 2 H), 8.17 (dd, $J = 10.4$, 8.8 Hz, 2 H), 8.09 (d, $J = 8.9$ Hz, 1 H), 8.03 (t, $J = 7.6$ Hz, 2 H), 7.98 (t, $J = 8.2$ Hz, 2 H), 1.71 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.12, 131.50, 130.96, 130.59, 128.88, 128.39, 126.91, 126.48, 126.06, 125.89, 125.55, 125.14, 124.89, 124.16, 123.79, 122.77, 121.61, 60.81, 18.13; HRMS (ESI) m/z calcd for C$_{21}$H$_{15}$NO$_2$ [(M+H)$^+$]: 314.2113, found 314.2145.
Preparation of 3,3-dimethyl-1-(4-(thiophen-2-yl)phenyl)azetidine-2,4-dione 5.204

1 mmol scale, 5 minute reaction time. The crude material was purified by column chromatography using 5% EtOAc/hexanes to afford 147 mg of 5.204 as a white solid, 54% isolated yield, m.p. = 190 – 191 °C, Rf = 0.3 in 10% EtOAc/hexanes. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.85 (d, $J$ = 8.4 Hz, 2 H), 7.63 (d, $J$ = 8.4 Hz, 2 H), 7.31 – 7.29 (m, 2 H), 7.09 – 7.07 (m, 1 H), 1.50 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 172.65, 143.12, 133.31, 132.76, 128.11, 126.44, 125.26, 123.47, 119.42, 61.80, 17.71; HRMS (ESI) m/z calcd for C$_{13}$H$_{13}$NO$_2$S [(M+H)$^+$]: 272.0667, found 272.0718.
Preparation of 1-(3,5-dichlorophenyl)-3,3-dimethylazetidine-2,4-dione 5.205

![Structure of 5.205](image)

11.11 mmol scale, 5 minute reaction time. The crude material was purified by column chromatography using 5% EtOAc/hexanes to afford 2.01 g of 5.205 as a white crystalline solid, 70% isolated yield, m.p. = 151 – 153 °C, (DCM/hexanes), Rf = 0.4 in 5% EtOAc/hexanes. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.28 (s, 2 H), 7.24 (s, 1 H), 1.49 (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 172.09, 135.75, 135.47, 126.81, 117.33, 62.42, 17.70.; HRMS (ESI) m/z calcd for C$_{11}$H$_9$Cl$_2$NO$_2$ [(M+H)$^+$]: 258.0023, found 258.0057.

Preparation of 3,3-dimethyl-1-(3-nitrophenyl)azetidine-2,4-dione 5.206

![Structure of 5.206](image)

10 mmol scale, 10 minute reaction time. The crude material was purified by column chromatography using 8% EtOAc/hexanes to afford 1.08 g of 5.206 as a white crystalline solid,
46% isolated yield, m.p. = 87 – 89 °C, Rf = 0.3 in 5% EtOAc/hexanes. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.68 (s, 1 H), 8.18 (d, $J = 7.9$ Hz, 1 H), 8.10 (d, $J = 7.8$ Hz, 1 H), 7.60 (t, $J = 8.2$ Hz, 1 H) 1.52 (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.14, 148.46, 134.88, 130.32, 124.47, 121.18, 114.01, 62.51, 17.70.; HRMS (ESI) m/z calcd for C$_{11}$H$_{10}$N$_2$O$_4$ [(M+H)$^+$]: 235.0648, found 235.0686.

**Preparation of 3,3-dimethyl-1-(4-nitrophenyl)azetidine-2,4-dione 5.207**

10 mmol scale, 30 minute reaction time. The crude material was purified by column chromatography using 5% EtOAc/hexanes to afford 984 mg of 5.207 as a white crystalline solid, 42% isolated yield, m.p. = 151 – 153 °C, Rf = 0.25 in 5% EtOAc/hexanes. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.28 (d, $J = 9.0$ Hz, 2 H), 8.05 (d, $J = 9.0$ Hz, 2 H), 1.52 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 172.18, 145.21, 139.19, 125.06, 119.17, 62.58, 17.73.; HRMS (ESI) m/z calcd for C$_{11}$H$_{10}$N$_2$O$_4$ [(M+H)$^+$]: 235.0648, found 235.0685.
Preparation of 1-(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethylazetidine-2,4-dione 5.208

10 mmol scale, 30 minute reaction time. The crude material was purified by column chromatography using 5% EtOAc/hexanes to afford 2.73g of 5.208 as a white crystalline solid, 84% isolated yield, m.p. = 77 - 78 °C, Rf = 0.4 in 5% EtOAc/hexanes. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.31 (s, 2 H), 7.72 (s, 1 H), 1.49 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 171.96, 135.53, 133.19, 132.96, 132.73, 132.51, 125.43, 123.62, 121.81, 120.01, 119.79, 118.82, 62.74, 17.39; HRMS (ESI) m/z calcd for C$_{13}$H$_9$F$_6$NO$_2$ [(M+H)$^+$]: 326.0578, found 326.0586.

Preparation of 1-(2-methoxy-5-nitrophenyl)-3,3-dimethylazetidine-2,4-dione 5.209

3 mmol scale, 30 minute reaction time. The crude material was purified by column chromatography using 10% EtOAc/hexanes to afford 388 mg of 5.209 as a pale-yellow
crystalline solid, 49% isolated yield, m.p. = 134 - 135 °C, Rf = 0.5 in 10% EtOAc/hexanes. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.28 (dd, $J = 9.2$, 2.6 Hz, 1 H), 8.21 (d, $J = 2.6$ Hz, 1 H), 7.07 (d, $J = 9.2$ Hz, 1 H), 3.99 (s, 3 H), 1.53 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 172.58, 159.02, 140.91, 126.10, 122.77, 119.66, 111.64, 60.83, 56.91, 17.86; HRMS (ESI) m/z calcd for C$_{12}$H$_{12}$N$_2$O$_5$ [(M+H)$^+$]: 265.0941, found 265.1026.

**Preparation of 1-(3-(4-fluorophenyl)naphthalen-2-yl)-3,3-dimethylazetidine-2,4-dione 5.210**

3 mmol scale, 5 minute reaction time. The crude material was purified by column chromatography using 10% EtOAc/hexanes to afford 640 mg of 5.210 as a white crystalline solid, 64% isolated yield, m.p. = 190 - 191 °C, (DCM/hexanes), Rf = 0.25 in 10% EtOAc/hexanes. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.86 - 7.84 (m, 4 H), 7.56 (p, $J = 6.7$ Hz, 2 H), 7.41 (dd, $J = 8.0$, 5.5 Hz, 2 H), 7.14 (t, $J = 8.5$ Hz, 2 H), 1.31 (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 173.58, 163.36, 161.72, 136.03, 134.39, 134.37, 133.15, 132.39, 130.50, 130.45, 130.04, 127.80, 127.78, 127.63, 127.06, 126.39, 125.94, 115.43, 115.29, 60.21, 17.26.; HRMS (ESI) m/z calcd for C$_{21}$H$_{16}$FNO$_2$ [(M+H)$^+$]: 334.1247, found 334.1224.
Synthesis of unsymmetrical malonyl diamides

General Procedure:

A 50-mL, flame-dried round bottom flask equipped with magnetic stir bar was placed under Argon atmosphere and charged with 20 mL THF. The appropriate aniline (3 mmol, 1 equiv) is dissolved in 5 mL THF and added to the flask via syringe. The flask was then placed into a dry ice/acetone bath where it was allowed to reach -70 °C. To the flask was added 2.1 mL nBuLi (1.6M, 3.3 mmol, 1.1 equiv) dropwise. After the addition was complete the flask was then placed in an ice bath and allowed to warm to 0 °C for 20 minutes. The flask was placed back into the dry ice/acetone bath and cooled back down to -70°C. At this point the appropriate N-arylazetidine-2,4-dione (5.201-5.210) (3.3 mmol, 1.1 equiv) is dissolved in 5 mL THF and added to the flask via syringe over 10 seconds. After the addition is complete the flask is removed from the dry ice/acetone bath and allowed to warm to room temperature and allowed to react until the starting aniline was no longer visible by TLC analysis (30 minutes – 6 hours). The solution was poured into a 250 mL separatory funnel containing 100 mL of NH₄Cl (sat.). The mixture was extracted with DCM (4x75 mL), washed with brine (75 mL), dried over Na₂SO₄, filtered, concentrated in vacuo and purified via column chromatography to afford the desired unsymmetrical malonyl diamide.
Preparation of 2,2-dimethyl-N1-(naphthalen-2-yl)-N3-(p-tolyl)malonamide 5.305

![Chemical Structure](image)

Prepared from azetidine-2,4-dione 5.201 and p-toluidine

The crude material was purified by column chromatography using 17% EtOAc/hexanes to afford 852 mg of 5.305 as a white solid, 82% isolated yield, m.p. = 179.2 - 180.3 °C, Rf = 0.3 in 20% EtOAc/hexanes. ¹H NMR (400 MHz, CDCl₃): δ 8.91 (s, 1 H), 8.37 (s, 1 H), 8.23 (s, 1 H), 7.78 (d, J = 7.5 Hz, 3 H), 7.49-7.42 (m, 5 H), 7.14 (d, J = 7.9 Hz, 2 H), 2.32 (s, 3 H), 1.72 (s, 6 H); ¹³C NMR (100 MHz, CDCl₃): δ 171.74, 171.50, 134.86, 134.62, 134.59, 133.66, 130.73, 129.45, 128.65, 127.61, 127.47, 126.44, 125.10, 120.60, 120.11, 117.15, 50.74, 24.18, 20.82.; HRMS (ESI) m/z calcd for C₂₂H₂₂N₂O₂ [(M+H)⁺]: 347.1790, found 347.1797.
Preparation of $N_1$(3,5-dimethylphenyl)-2,2-dimethyl-$N_3$(naphthalen-2-yl)malonamide 5.306

Prepared from azetidine-2,4-dione 5.201 and 3,5-dimethylaniline

The crude material was purified using 15% EtOAc/hexanes to afford 962 mg of 5.306 as a white solid, 89% isolated yield, m.p. = 181.3 - 182.6 °C, Rf = 0.25 in 20% EtOAc/hexanes. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.85 (s, 1 H), 8.33 (s, 1 H), 8.40 (s, 1 H), 7.78 (m, 3H) 7.49-7.40 (m, 3), 7.19 (s, 2 H), 6.80 (s, 1 H), 2.31 (s, 6 H), 1.73 (6 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.69, 171.49, 138.74, 136.97, 134.82, 133.68, 130.75, 128.70, 127.65, 127.50, 126.64, 126.48, 125.14, 120.09, 118.18, 117.15, 50.79, 24.23, 21.30; HRMS (ESI) m/z calcd for C$_{23}$H$_{24}$N$_2$O$_2$ [(M+H)$^+$]: 361.1974, found 361.1948.
Preparation of $N_1$-(2,5-dimethylphenyl)-2,2-dimethyl-$N_3$-(naphthalen-2-yl)malonamide

5.307

Prepared from azetidine-2,4-dione 5.201 and 2,5-dimethylaniline

The crude material was purified by column chromatography using 17% EtOAc/hexanes to afford 995 mg of 5.307 as a white solid, 92% isolated yield, m.p. = 179.7 - 181.2 °C, Rf = 0.2 in 20% EtOAc/hexanes. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.96 (s, 1 H), 8.29 (s, 1 H), 8.25 (s, 1 H), 7.81-7.78 (m, 3 H), 7.64 (s, 1 H), 7.51-7.40 (m, 3 H), 7.08 (d, $J$ = 7.7 Hz, 1 H), 6.93 (d, $J$ = 7.6 Hz, 1 H), 2.33 (s, 3 H), 2.23 (s, 3 H), 1.75 (s, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 171.92, 171.57, 136.49, 134.88, 134.84, 133.68, 130.73, 130.32, 128.70, 127.64, 127.49, 126.57, 126.47, 126.42, 125.12, 123.60, 120.06, 117.08, 50.78, 24.28, 21.05, 17.22.; HRMS (ESI) m/z calcd for C$_{23}$H$_{24}$N$_2$O$_2$ [(M+H)$^+$]: 361.1936, found 361.1952.
Preparation of \( N_1\)-(3,5-dichlorophenyl)-2,2-dimethyl-N\(_3\)-(naphthalen-2-yl)malonamide

5.308

Prepared from azetidine-2,4-dione 5.205 and 2-naphthylamine

The crude material was purified by column chromatography using 10% EtOAc/hexanes to afford 975 mg of 5.308 as a white solid, 81% isolated yield, m.p. = 168.5 - 169.7 °C, Rf = 0.25 in 10% EtOAc/hexanes. \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 9.07 (s, 1 H), 8.34 (s, 1 H), 8.17 (s, 1 H), 7.81 – 7.70 (m, 3 H), 7.53 (d, \( J = 1.6 \) Hz, 2 H), 7.48 – 7.42 (m, 3 H), 7.09 (s, 1 H), 1.71 (s, 6 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 172.06, 171.22, 139.30, 135.12, 134.21, 133.55, 130.99, 128.87, 127.64, 127.54, 126.66, 125.48, 124.42, 120.14, 118.40, 117.80, 50.92, 24.16.; HRMS (ESI) m/z calcd for C\(_{21}\)H\(_{18}\)Cl\(_2\)N\(_2\)O\(_2\) [(M+H)\(^+\)]: 401.0795, found 401.0827.
Preparation of 2,2-dimethyl-N₁-(naphthalen-2-yl)-N₃-(3-nitropheryl)malonamide 5.309

Prepared from azetidine-2,4-dione 5.206 and 2-naphthylamine

The crude material was purified by column chromatography using 20% EtOAc/hexanes to afford 725 mg of 5.309 as a white solid; 64% isolated yield, m.p. = 157.9 - 158.7 °C, Rf = 0.15 in 20% EtOAc/hexanes. ¹H NMR (600 MHz, CDCl₃): δ 9.32 (s, 1 H), 8.54 (s, 1 H), 8.33 (s, 1 H), 8.19 (s, 1 H), 7.94 (d, J = 6.8 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.81-7.77 (m, 3 H), 7.48-7.41 (m, 4 H), 1.76 (s, 6 H); ¹³C NMR (151 MHz, CDCl₃): δ 172.17, 171.38, 148.49, 138.70, 134.21, 133.57, 131.02, 129.65, 128.91, 127.66, 127.56, 126.70, 125.69, 125.52, 120.14, 119.08, 117.82, 115.01, 50.94, 24.22; HRMS (ESI) m/z calcd for C₂₁H₁₉N₃O₄ [(M+H)⁺]: 378.1466, found 378.1496.
Preparation of 2,2-dimethyl-N1-(naphthalen-2-yl)-N3-(3-(trifluoromethyl)phenyl)malonamide 5.310

Prepared from azetidine-2,4-dione 5.201 and 3-trifluoromethylaniline

The crude material was purified by column chromatography using 15% EtOAc/hexanes to afford 754 mg of 5.310 as a white solid; 70% isolated yield, m.p. = 162.1 - 162.8 °C, Rf = 0.2 in 15% EtOAc/hexanes. \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 9.02 (s, 1 H), 8.43 (s, 1 H), 7.96 (s, 1 H), 7.81 – 7.77 (m, 3 H), 7.70 (d, J = 7.9 Hz, 1 H), 7.47 (t, J = 7.1 Hz, 2 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.38 (d, J = 7.6 Hz, 1 H), 1.74 (s, 6 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 172.00, 171.41, 138.03, 134.70, 134.37, 133.67, 133.61, 131.70, 131.49, 131.27, 131.06, 130.97, 130.86, 129.45, 128.86, 128.78, 127.66, 127.55, 126.64, 126.55, 125.43, 125.26, 124.68, 123.20, 122.88, 121.20, 121.17, 121.15, 121.12, 120.15, 117.68, 117.40, 117.05, 117.02, 116.99, 116.97, 50.90, 24.2; HRMS (ESI) m/z calcd for C\(_{22}\)H\(_{19}\)F\(_3\)N\(_2\)O\(_2\) [(M+H\(^+\)]: 401.1469, found 401.1510.
Preparation of 2,2-dimethyl-N$_1$-(naphthalen-2-yl)-N$_3$-(4-nitrophenyl)malonamide 5.311

![Chemical Structure](image)

Prepared from azetidine-2,4-dione 5.207 and 2-naphthylamine

The crude material was purified by column chromatography using 20% EtOAc/hexanes to afford 657 mg of 5.311 as a white solid, 58% isolated yield, m.p = 183.8 - 185.2 °C, Rf = 0.1 in 20% EtOAc/hexanes. $^1$H NMR (600 MHz, CDCl$_3$): δ 9.60 (s, 1 H), 8.20-8.16 (m, 4 H), 7.83-7.74 (m, 5 H), 7.49-7.46 (m, 3 H), 1.76 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 172.44, 171.06, 143.63, 143.47, 134.02, 133.57, 131.12, 129.00, 127.69, 127.61, 126.80, 125.66, 124.97, 120.13, 119.49, 118.00, 51.04, 24.29; HRMS (ESI) m/z calcd for C$_{21}$H$_{19}$N$_5$O$_4$ [(M+H)$^+$]: 378.1521, found 378.1485.
Preparation of $N_1$-(3,5-bis(trifluoromethyl)phenyl)-2,2-dimethyl-$N_3$-(naphthalen-2-yl)malonamide 5.312

Prepared from azetidine-2,4-dione 5.208 and 2-naphthylamine

The crude material was purified using 10% EtOAc/hexanes to afford 1.05 g of 5.312 as a white solid; 75% isolated yield, m.p. = 180.7 - 182.9 °C, Rf = 0.4 in 20% EtOAc/hexanes; $^1$H NMR (600 MHz, CDCl$_3$): δ 9.63 (s, 1 H), 8.17 (d, $J$ = 12.7 Hz, 2 H), 8.10 (s, 2 H), 7.83-7.79 (m, 3 H), 7.61 (s, 1 H), 7.50-7.44 (m, 3 H), 1.76 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 172.50, 171.19, 139.13, 133.97, 133.57, 132.65, 132.43, 132.20, 131.98, 131.16, 129.03, 127.71, 127.62, 126.81, 125.76, 125.69, 123.96, 122.15, 120.34, 120.17, 119.75, 118.10, 117.68, 117.66, 117.64, 117.61, 117.59, 50.89, 24.30; HRMS (ESI) m/z calcd for C$_{23}$H$_{18}$F$_6$N$_2$O$_2$ [(M+H)$^+$]: 469.1422, found 469.1397.
Preparation of $N_1$-(2-methoxy-5-nitrophenyl)-2,2-dimethyl-$N_3$-(naphthalen-2-yl)malonamide 5.313

Prepared from azetidine-2,4-dione 5.209 and 2-naphthylamine.

The crude material was purified by column chromatography using 25% EtOAc/hexanes to afford 880 mg of 5.313 as an orange solid; 72% isolated yield, m.p. = 84.8 - 86.6 °C, Rf = 0.1 in 20% EtOAc/hexanes; $^1$H NMR (600 MHz, CDCl$_3$): δ 9.30 (d, $J = 2.5$ Hz, 1 H), 9.04 (s, 1 H), 8.79 (s, 1 H), 8.23 (s, 1 H), 8.01 – 7.96 (m, 1 H), 7.81 – 7.74 (m, 3 H), 7.50 (dd, $J = 8.8$, 2.0 Hz, 1 H), 7.45 (t, $J = 7.4$ Hz, 1 H), 7.40 (t, $J = 7.5$ Hz, 1 H), 6.90 (d, $J = 9.0$ Hz, 1 H), 3.99 (s, 3 H), 1.75 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 172.05, 170.88, 152.97, 141.44, 134.79, 133.64, 130.76, 128.70, 127.60, 127.49, 127.31, 126.48, 125.16, 120.45, 120.09, 117.17, 115.21, 109.25, 56.69, 51.39, 24.05; HRMS (ESI) m/z calcd for C$_{22}$H$_{21}$N$_3$O$_5$ [(M+H)$^+$]: 408.1570, found 408.1593.
Preparation of 2,2-dimethyl-\(N_1\)-(naphthalen-2-yl)-\(N_3\)-(3,4,5-trimethoxyphenyl)malonamide

5.314

Prepared from azetidine-2,4-dione 5.201 and 3,4,5-trimethoxyaniline

The crude material was purified by column chromatography using 40% EtOAc/hexanes to afford 1.17 g of 5.314 as a white solid, 92% isolated yield, m.p. = 189.4 - 190.5 °C, Rf = 0.35 in 50% EtOAc/hexanes. \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 8.60 (s, 1 H), 8.53 (s, 1 H), 8.20 (s, 1 H), 7.79 (s, 3 H), 7.47 – 7.42 (m, 3 H), 6.87 (s, 2 H), 3.86 (s, 6 H), 3.81 (s, 3 H), 1.73 (s, 6 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 171.97, 171.18, 153.30, 134.97, 134.54, 133.65, 133.50, 130.92, 128.83, 127.65, 127.56, 126.63, 125.37, 120.16, 117.54, 97.84, 60.93, 56.12, 50.87, 24.27; HRMS (ESI) m/z calcd for C\(_{24}\)H\(_{26}\)N\(_2\)O\(_5\) [(M+H)]\(^+\): 423.1984, found 423.1965.
Preparation of \(N_1-(3-(4\text{-}fluorophenyl)naphthalen\text{-}2\text{-}yl)\text{-}2,2\text{-}\text{dimethyl}-N_3\text{-}(naphthalen\text{-}2\text{-}yl)\text{malonamide} \text{ 5.315}\)

Prepared from azetidine\text{-}2,4\text{-}dione \text{ 5.210} and 2-naphthylamine (This reaction was performed on a 1 mmol scale.)

The crude material was purified by column chromatography using 30\% EtOAc/hexanes to afford 372 mg of \text{ 5.315} as a white solid, 78\% isolated yield, m.p. = 184.3\ -\ 185.3 \degree C, Rf = 0.1 in 20\% EtOAc/hexanes. \^1\text{H} NMR (600 MHz, CDCl\textsubscript{3}): \(\delta 8.96\ (s,\ 1\ H), 8.83\ (s,\ 1\ H), 8.30\ (s,\ 1\ H), 8.23\ (s,\ 1\ H), 7.88\ (d,\ J = 7.7\ Hz,\ 1\ H), 7.83\ -\ 7.78\ (m,\ 4\ H), 7.71\ (s,\ 1\ H), 7.54\ -\ 7.46\ (m,\ 4\ H), 7.43\ -\ 7.33\ (m,\ 3\ H), 7.18\ (t,\ J = 7.7\ Hz,\ 2\ H), 1.56\ (s,\ 6\ H)\); \(^{13}\text{C} \text{NMR} (151\ MHz, \text{CDCl}_3): 172.11, 170.57, 163.49, 161.84, 134.99, 133.73, 133.37, 133.35, 133.25, 132.17, 131.94, 131.23, 131.18, 130.67, 130.51, 129.31, 128.66, 127.75, 127.65, 127.48, 127.45, 126.70, 126.49, 125.84, 125.06, 119.85, 118.75, 116.72, 116.21, 116.07, 51.14, 23.94. \text{HRMS (ESI) m/z calcd for C}_{31}\text{H}_{25}\text{F}_{2}\text{N}_{2}\text{O}_{2} [(\text{M+H})^+]: 477.2030, \text{found} 477.2011.\)
Preparation of $N_1$-(anthracen-2-yl)-2,2-dimethyl-$N_3$-(3,4,5-trimethoxyphenyl)malonamide

$\text{5.316}$

Prepared from azetidine-2,4-dione $\text{5.202}$ and 3,4,5-trimethoxyaniline

The crude material was purified by column chromatography in 40% EtOAc/hexanes to afford 879 mg of $\text{5.316}$ as a yellow solid, 62% isolated yield, m.p. = 198.9 - 200.2 °C, $R_f = 0.2$ in 40% EtOAc/hexanes. $^1\text{H NMR}$ (600 MHz, CDCl$_3$): $\delta$ 8.62 (s, 2 H), 8.39 (s, 1 H), 8.34 (s, 1 H), 7.95 (s, 3 H), 7.44 (s, 3 H), 6.89 (s, 2 H), 3.85 (s, 9 H), 1.76 (s, 6 H); $^{13}\text{C NMR}$ (151 MHz, CDCl$_3$): $\delta$ 171.98, 171.27, 153.22, 134.89, 133.83, 133.51, 132.09, 131.51, 131.24, 129.23, 129.19, 128.08, 127.83, 126.04, 125.76, 125.60, 125.15, 120.70, 116.67, 97.84, 60.87, 56.03, 50.92, 24.19; HRMS (ESI) m/z calcd for $\text{C}_{28}\text{H}_{28}\text{N}_2\text{O}_5$ [(M+H)$^+$]: 473.2010, found 473.2117.
Synthesis of pyrazolidine-3,5-diones

**General Procedure Using di-tert-butyl diaziridinone (Method A):**

To a 25-mL oven-dried round-bottom-flask equipped with a magnetic stir bar is added 1 mmol of the appropriate malonyl diamide (5.3) followed by the addition of 10 mL ACS-grade MeCN at 23°C. The magnetic stirrer is set to 500 rpm and 21 mg of CuBr-SMe₂ (10 mol%, 0.1 mmol) is added and the flask is sealed with a rubber septum. After stirring for 5 minutes 0.21 mL of di-tert-butyl diaziridinone (5.16) (1.05 equiv, 179 mg, d = 0.871) is added via syringe in one portion. The reaction is allowed to stir at 23 °C until TLC analysis indicates complete consumption of the starting material. The heterogeneous mixture is then poured into a 125 mL separatory funnel and diluted with DCM (50 mL). To sequester the copper present 50 mL NH₄Cl (sat.) is then added to the separatory funnel and shaken. The organic layer at the bottom of the separatory funnel is drained and the resulting aqueous phase is then extracted with DCM (3 x 50 mL), dried over Na₂SO₄, filtered, concentrated *in vacuo*, and then purified *via* column chromatography to afford pyrazolidine-3,5-diones 5.4.
**General Procedure Using PIDA or PIFA (Method B):**

To a 50-mL oven-dried round-bottom-flask equipped with a magnetic stir bar is added the appropriate malonyl diamide (5.3) (0.3 mmol, 1 equiv), followed by the addition of 30 mL of ACS-grade MeCN. The reaction was allowed to stir for 3 minutes before PIDA or PIFA was added in one portion to the stirring solution (1.2 mmol, 4 equiv). The flask was then sealed with a septum, wrapped in foil to prevent the penetration of light, and heated to 50 °C. The mixture was allowed to stir for the appropriate amount of time until the starting material had been consumed by TLC analysis at which point the solution was poured into a separatory funnel containing 50 mL NaHCO₃ (sat.) and extracted with DCM (4x50mL). The combined organic layers were dried over Na₂SO₄, filtered, concentrated *in-vacuo* and purified via column chromatography to afford pyrazolidine-3,5-diones 5.4.
Preparation of (Z)-4,4-dimethyl-2-(naphthalen-2-yl)-5-(naphthalen-2-ylimino)isoxazolidin-3-one 5.417

0.1 mmol scale in DCM with 4 equiv PIDA

Column chromatography in 15% EtOAc/hexanes affords 8 mg of 5.417 as a white solid, 20% isolated yield, Rf = 0.3 in 20% EtOAc/hexanes; \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.10 (s, 1 H), 8.90 (s, 1 H), 8.45 (d, \(J = 9.0\) Hz, 1 H), 8.27 (s, 1 H), 8.20 (d, \(J = 8.6\) Hz, 1 H), 7.81 (q, \(J = 9.0\) Hz, 4 H), 7.60 (t, \(J = 7.7\) Hz, 1 H); 7.53 – 7.39 (m, 4 H), 1.82 (s, 6 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 172.43, 170.86, 134.89, 133.74, 132.06, 131.51, 130.78, 130.58, 128.76, 128.09, 127.70, 127.58, 127.52, 127.49, 126.52, 125.87, 125.16, 123.98, 120.52, 120.05, 119.89, 117.10, 51.42, 24.30; HRMS (ESI) m/z calcd for C\(_{25}\)H\(_{20}\)N\(_2\)O\(_2\) \([(M+H)]^+\): 381.1601, found 381.1598.
Preparation of 1,2-bis(3,5-dimethylphenyl)-4,4-dimethylpyrazolidine-3,5-dione 5.401

Method A: 8 h reaction time (3 mmol scale)

Method B: 4 equivalents PIFA used, 24 h reaction time (0.3 mmol scale)

The crude material was purified using 7% EtOAc/hexanes to afford 858 mg of 5.401, 85% isolated yield (Method A), or 89 mg of 5.401, 87% isolated yield (Method B) as a pale-yellow crystalline solid, m.p. = 151.3 - 154.0 °C, (DCM/hexanes/EtOAc), Rf = 0.3 in 10% EtOAc/hexanes; \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 6.94 (s, 4 H), 6.81 (s, 2 H), 2.25 (s, 12 H), 1.48 (s, 6 H); \(^1^3^C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 174.51, 138.63, 135.96, 128.77, 120.58, 44.28, 21.72, 21.32; HRMS (ESI) m/z calcd for C\(_{21}\)H\(_{24}\)N\(_2\)O\(_2\) [(M+H)+]: 337.1985, found 337.1967.
Preparation of 1,2-bis(2-methoxy-5-nitrophenyl)-4,4-dimethylpyrazolidine-3,5-dione 5.402

Method B: 4 equivalents PIFA used, 72 h reaction time (0.3 mmol scale)

The crude material was purified using 50% EtOAc/hexanes to afford 120 mg of 5.402 as a white crystalline solid, 93% isolated yield, m.p. = 230.7 - 231.9 °C, (DCM/hexanes/EtOAc), Rf = 0.3 in 50% EtOAc/hexanes; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): \(\delta\) 8.24 (dd, \(J = 9.2, 2.8\) Hz, 2 H), 7.92 (s, 2 H), 7.05 (d, \(J = 9.2\) Hz, 2 H), 4.04 (s, 6 H), 1.98 (s, 6 H); \textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}): \(\delta\) 174.70, 160.56, 140.93, 127.73, 127.44, 123.16, 111.99, 56.94, 44.16, 21.60; HRMS (ESI) m/z calcd for C\textsubscript{19}H\textsubscript{18}N\textsubscript{2}O\textsubscript{8} [(M+H)\textsuperscript{+}]: 431.1142, found 431.1125.
Preparation of 4,4-dimethyl-1,2-di(naphthalen-2-yl)pyrazolidine-3,5-dione 5.403

Method A: 12 h reaction time (3 mmol scale)

Method B: 4 equivalents PIDA, 24 h reaction time (0.3 mmol scale)

The crude material was purified using 15% EtOAc/hexanes to afford 913 mg of 5.403, 80% isolated yield (Method A), or 94 mg of 5.403, 82% isolated yield (Method B) as a pale-yellow crystalline solid, m.p. = 186.1 - 187.8 °C, (DCM/hexanes/EtOAc), Rf = 0.2 in 20% EtOAc/hexanes; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.91 (s, 2 H), 7.78 – 7.73 (m, 6 H), 7.51 (d, $J$ = 8.3 Hz, 2 H) 7.45 – 7.42 (m, 4 H), 1.60 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 174.42, 133.43, 132.99, 131.77, 129.11, 127.89, 127.61, 126.75, 126.26, 121.21, 120.41, 44.46, 21.84; HRMS (ESI) m/z calcd for C$_{25}$H$_{20}$N$_2$O$_2$ [(M+H)$^+$]: 381.1525, found 381.1529.
Preparation of 4,4-dimethyl-1,2-bis(4-(thiophen-2-yl)phenyl)pyrazolidine-3,5-dione 5.404

Method A: 1 h reaction time (1 mmol scale) 82%

Method B: 4 equiv of PIDA were used, 4 h reaction time (0.3 mmol scale) 84%

Column chromatography using various eluent systems unfortunately led to an inseparable mixture of 5.404 with di-tert-butylurea. Attempted purification of the crude material using 15% EtOAc/hexanes afforded 506 mg of a 1:1 ratio of 5.404 with N,N’-di-tert-butylurea, 82% yield (Method A), or 155 mg of a 1:1 ratio of 5.404 with N,N’-di-tert-butylurea, 84% yield (Method B) as a yellow solid. Rf = 0.4 in 20% EtOAc/hexanes; $^1$H NMR (600 MHz, CDCl$_3$): δ 7.61 – 7.53 (m, 4 H), 7.37 – 7.35 (m, 4 H), 7.31 – 7.14 (m, 4 H), 7.05 (br s, 2 H), 1.31 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 174.11, 142.95, 134.87, 133.01, 128.06, 126.43, 125.24, 123.49, 122.64, 50.07, 29.58.

Note: The yields reported are based on the 1H NMR spectra that indicate a 1:1 ratio with N,N’-di-tert-butylurea. M.p. was not taken due to the mixture of 2 products present in the sample.
Preparation of 4,4-dimethyl-1-(naphthalen-2-yl)-2-(p-tolyl)pyrazolidine-3,5-dione 5.405

Method B: 4 equiv of PIDA used, 72 h reaction time (0.3 mmol scale)

The crude material was purified using 15% EtOAc/hexanes to afford 58 mg of **5.405** as a yellow oil, 56% isolated yield, Rf = 0.2 in 10% EtOAc/hexanes; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.82 (s, 1 H), 7.76 (s \(br\), 3 H), 7.45 (s \(br\), 3 H), 7.27 (d, \(J = 6.8\) Hz, 2 H), 7.08 (d, \(J = 6.6\) Hz, 2 H), 2.23 (s, 3 H), 1.54 (s, 6 H); \(^1\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 174.35, 174.27, 136.82, 133.47, 133.24, 132.97, 131.75, 129.60, 128.98, 127.88, 127.61, 126.70, 126.22, 122.60, 121.40, 120.62, 44.34, 21.75, 20.87; HRMS (ESI) m/z calcd for C\(_{22}\)H\(_{20}\)N\(_2\)O\(_2\) [(M+H)\(^+\): 345.1616, found 345.1630.
Preparation of 1-(3,5-dimethylphenyl)-4,4-dimethyl-2-(naphthalen-2-yl)pyrazolidine-3,5-dione 5.406

**Method A**: 90% 24 h reaction time (3 mmol scale)

**Method B**: 89% 4 equiv of PIDA used, 72 h reaction time (0.3 mmol scale)

The crude material was purified using 15% EtOAc/hexanes to afford 968 mg of 5.406, 90% isolated yield (**Method A**), or 96 mg of 5.406, 89% isolated yield (**Method B**) as a yellow oil, Rf = 0.35 in 20% EtOAc/hexanes; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.85 (s, 1 H), 7.81 – 7.77 (m, 3 H), 7.50 – 7.43 (m, 3 H), 7.01 (s, 2 H), 6.79 (s, 1 H), 2.23 (s, 6 H), 1.54 (s, 6 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 174.51, 174.41, 138.78, 135.90, 133.47, 133.02, 131.77, 128.99, 128.88, 127.94, 127.62, 126.66, 126.18, 121.18, 120.53, 120.47, 44.36, 21.78, 21.29; HRMS (ESI) m/z calcd for C\(_{23}\)H\(_{22}\)N\(_2\)O\(_2\) [(M+H)\(^+\)]: 359.1771, found 359.1790.
Preparation of 1-(2,5-dimethylphenyl)-4,4-dimethyl-2-(naphthalen-2-yl)pyrazolidine-3,5-dione 5.407

Method A: 24 h reaction time (3 mmol scale)

Method B: 4 equiv of PIDA used, 72 h reaction time (0.3 mmol scale)

The crude material was purified using 20% EtOAc/hexanes to afford 946 mg of 5.407, 88% isolated yield (Method A), or 91 mg of 5.407, 85% isolated yield (Method B) as a yellow oil, Rf = 0.2 in 20% EtOAc/hexanes; \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.78 – 7.76 (m, 4 H), 7.49 – 7.43 (m, 2 H), 7.36 (dd, \(J = 8.8, 2.0\) Hz, 1 H), 7.09 (d, \(J = 7.8\) Hz, 1 H), 7.01 (s, 1 H), 6.93 (d, \(J = 7.8\) Hz, 1 H), 2.44 (s, 3 H), 2.16 (s, 3 H), 1.58 (s, 6 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 174.21, 173.66, 136.59, 134.31, 132.96, 132.38, 132.30, 131.96, 131.18, 129.62, 129.03, 127.93, 127.62, 126.70, 126.40, 125.39, 122.66, 121.29, 44.29, 21.86, 21.60, 20.81, 18.02; HRMS (ESI) m/z calcd for C\(_{23}\)H\(_{22}\)N\(_2\)O\(_2\) [(M+H)\(^+\)]: 359.1771, found 359.1776.

Preparation for 1-(3,5-dichlorophenyl)-4,4-dimethyl-2-(naphthalen-2-yl)pyrazolidine-3,5-dione 5.408
METHOD B : 4 equivalents of PIFA used, 12 h reaction time (0.3 mmol scale)

The crude material was purified using 15% EtOAc/hexanes to afford 65 mg of 5.408 as a yellow solid, 54% isolated yield, m.p. = 175.4 - 176.8 °C, Rf = 0.2 in 20% EtOAc/hexanes; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 9.49 (s, 1 H), 8.11 (dd, \(J = 11.1, 7.8\) Hz, 2 H), 7.85 (s, 1 H), 7.79 (t, \(J = 7.4\) Hz, 1 H), 7.74 (t, \(J = 7.5\) Hz, 1 H), 7.53 (s, 2 H), 7.11 (s, 1 H), 1.72 (s, 6 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \(\delta\) 185.13, 180.68, 173.37, 170.05, 139.51, 139.09, 135.28, 135.11, 133.52, 132.03, 129.84, 126.83, 126.45, 124.71, 118.42, 118.19, 51.91, 23.94; HRMS (ESI) m/z calcd for C\(_{21}\)H\(_{16}\)Cl\(_2\)N\(_2\)O\(_2\) [(M+H)]\(^+\): 399.0644, found 399.0687.
Preparation for 4,4-dimethyl-1-(naphthalen-2-yl)-2-(3-nitrophenyl)pyrazolidine-3,5-dione 5.409

METHOD B: 4 equiv of PIFA used, 12 h reaction time (0.3 mmol scale)

The crude material was purified using 20% EtOAc/hexanes to afford 75 mg of 5.409 as a yellow solid, 67% isolated yield, m.p. = 110.9 - 113.6 °C, Rf = 0.1 in 20% EtOAc/hexanes; $^1$H NMR (600 MHz, CDCl$_3$): δ 9.51 (s, 1 H), 8.92 (s, 1 H), 8.49 (t, $J = 2.1$ Hz, 1 H), 8.10 (t, $J = 8.8$ Hz, 2 H), 7.97 (dd, $J = 9.2$, 1.8 Hz, 1 H), 7.93 – 7.89 (m, 1 H), 7.85 (s, 1 H), 7.79 (t, $J = 8.2$ Hz, 1 H), 7.73 (t, $J = 7.5$ Hz, 1 H), 7.50 (t, $J = 8.2$ Hz, 1 H), 1.75 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 185.16, 180.65, 173.37, 170.32, 148.54, 139.52, 138.48, 135.12, 133.54, 132.00, 129.82, 129.81, 126.82, 126.44, 125.86, 119.34, 118.16, 115.09, 51.94, 23.95; HRMS (ESI) m/z calcd for C$_{21}$H$_{17}$N$_3$O$_4$ [(M+H)$^+$]: 376.1219, found 376.1250.
Preparation of 4,4-dimethyl-1-(naphthalen-2-yl)-2-(3-(trifluoromethyl)phenyl)pyrazolidine-3,5-dione 5.410

Method B: 4 equiv of PIFA used, 12 h reaction time (0.3 mmol scale)

The crude material was purified using 15% EtOAc/hexanes to afford 77 mg of 5.410 as a yellow solid, 64% isolated yield, m.p. = 149.8 - 152.5 °C, Rf = 0.2 in 20% EtOAc/hexanes; $^1$H NMR (600 MHz, CDCl$_3$): δ 9.58 (s, 1 H), 8.67 (s, 1 H), 8.09 (dd, $J = 12.9$, 7.6 Hz, 2 H), 7.89 (s, 1 H), 7.85 (s, 1 H), 7.78 (t, $J = 7.4$ Hz, 1 H), 7.72 (t, $J = 7.7$ Hz, 2 H), 7.44 (d, $J = 14.3$ Hz, 1 H), 7.37 (d, $J = 8.1$ Hz, 1 H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 185.19, 180.66, 173.27, 170.27, 145.36, 139.63, 137.82, 135.81, 135.04, 134.76, 133.48, 132.01, 131.74, 131.53, 131.31, 131.09, 130.85, 130.19, 129.86, 129.83, 129.55, 127.90, 126.79, 126.39, 124.63, 123.29, 122.82, 121.35, 121.32, 121.02, 118.02, 116.99, 51.90, 23.92; HRMS (ESI) m/z calcd for C$_{22}$H$_{17}$F$_3$N$_2$O$_2$ [(M+H)$^+$]: 399.1242, found 399.1287.
Preparation of 4,4-dimethyl-1-(naphthalen-2-yl)-2-(4-nitrophenyl)pyrazolidine-3,5-dione

5.411

Method B: 4 equiv of PIFA used, 48 h reaction time (0.3 mmol scale)

The crude material was purified using 20% EtOAc/hexanes to afford 47 mg of 5.411 as a yellow solid, 42% isolated yield, m.p. = 194.4 - 197.2 °C, Rf = 0.1 in 20% EtOAc/hexanes; 

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 9.44 (s, 1 H), 9.11 (s, 1 H), 8.21 (d, $J = 8.5$ Hz, 2 H), 8.10 (t, $J = 9.9$ Hz, 2 H), 7.85 (s, 1 H), 7.80 – 7.75 (m, 4 H), 1.75 (s, 6 H); 

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 185.08, 180.64, 173.53, 170.15, 143.84, 143.16, 139.39, 135.18, 133.58, 131.99, 129.79, 126.83, 126.46, 125.00, 119.61, 118.30, 52.06, 23.96; 

HRMS (ESI) m/z calcd for C$_{21}$H$_{17}$N$_3$O$_4$ [(M+H)$^+$]: 376.1221, found 376.1239.
Preparation of 1-(3,5-bis(trifluoromethyl)phenyl)-4,4-dimethyl-2-(naphthalen-2-yl)pyrazolidine-3,5-dione 5.412

Method B: 4 equiv of PIFA used, 8 h reaction time (0.3 mmol scale)

The crude material was purified using 15% EtOAc/hexanes to afford 113 mg of 5.412 as a yellow solid, 81% isolated yield, m.p. = 185.1-186.0°C, Rf = 0.3 in 20% EtOAc/hexanes; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}): δ 9.38 (s, 1 H), 9.17 (s, 1 H), 8.12 – 8.09 (m, 4 H), 7.88 (s, 1 H), 7.80 (t, J = 7.5 Hz, 1 H), 7.74 (t, J = 7.5 Hz, 1 H), 7.61 (s, 1 H), 1.76 (s, 6 H); \textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}): δ 185.13, 180.63, 173.66, 170.17, 139.37, 138.90, 135.20, 133.60, 132.73, 132.51, 132.29, 132.07, 132.01, 129.80, 126.86, 126.49, 125.71, 123.90, 122.09, 120.29, 119.90, 119.88, 118.39, 117.97, 117.94, 117.92, 117.89, 117.87, 51.95, 23.96; HRMS (ESI) m/z calcd for C\textsubscript{23}H\textsubscript{16}F\textsubscript{6}N\textsubscript{2}O\textsubscript{2} [(M+H)\textsuperscript{+}]: 467.1095, found 467.1114.
Preparation of 1-(2-methoxy-5-nitrophenyl)-4,4-dimethyl-2-(naphthalen-2-yl)pyrazolidine-3,5-dione 5.413

**Method A**: 24 h reaction time (1 mmol scale)

**Method B**: 4 equiv of PIFA used, 72 h reaction time (0.3 mmol scale)

The crude material was purified using 45% EtOAc/hexanes to afford 288 mg of 5.413, 71% isolated yield (**Method A**), or 97 mg of 5.413, 80% isolated yield (**Method B**) as a yellow solid, m.p. = 184.3 - 186.0°C, Rf = 0.3 in 50% EtOAc/hexanes; $^1$H NMR (600 MHz, CDCl$_3$): 9.68 (s, 1 H), 9.30 (s, 1 H), 9.00 (s, 1 H), 8.11 (dd, $J = 20.9$, 7.1 Hz, 2 H), 8.03 (d, $J = 9.0$ Hz, 1 H), 7.86 (s, 1 H), 7.80 – 7.72 (m, 2 H), 6.95 (d, $J = 9.0$ Hz, 1 H), 4.05 (s, 3 H), 1.74 (s, 6 H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 185.30, 180.66, 172.68, 170.38, 152.91, 141.64, 139.80, 135.00, 133.49, 132.04, 129.93, 127.29, 126.86, 126.34, 120.60, 117.84, 115.35, 109.29, 56.74, 52.31, 23.88; HRMS (ESI) m/z calcd for C$_{22}$H$_{19}$N$_3$O$_5$ [(M+H)$^+$]: 406.1421, found 406.1417.
Preparation of 4,4-dimethyl-1-(naphthalen-2-yl)-2-(3,4,5-trimethoxyphenyl)pyrazolidine-3,5-dione 5.414

Method A: 4 h reaction time (1 mmol scale)

Method B: 4 equiv of PIDA used, 12 h reaction time (0.3 mmol scale)

The crude material was purified using 45% EtOAc/hexanes to afford 374 mg of 5.414, 89% isolated yield (Method A), or 91 mg of 5.414, 72% isolated yield (Method B) as a yellow oil, Rf = 0.3 in 40% EtOAc/hexanes; \( ^1H \) NMR (600 MHz, CDCl\(_3\)): 7.82 – 7.78 (m, 5 H), 7.50 – 7.44 (m, 3 H), 6.62 (s, 2 H), 3.74 (s, 3 H), 3.72 (s, 6 H), 1.55 (s, 6 H); \(^{13}C\) NMR (151 MHz, CDCl\(_3\)): \( \delta \) 174.42, 174.35, 153.28, 136.54, 133.62, 133.04, 131.89, 131.59, 129.23, 127.88, 127.71, 126.90, 126.43, 121.19, 120.48, 100.34, 60.79, 56.12, 44.48, 21.82; HRMS (ESI) m/z calcd for C\(_{24}\)H\(_{24}\)N\(_2\)O\(_5\) [(M+H\(^+\)]: 406.1421, found 406.1417.

Note: The compound was placed in a 0 °C refrigerator to facilitate solid formation but was unsuccessful. It appears that the consecutive trimethoxy aryl moiety has a propensity to
coordinate with EtOAc even after several washings of 5.414 with unstabilized chloroform in order to remove the residual solvent as seen in the $^1$H NMR.

**Preparation of 1-(3-(4-fluorophenyl)naphthalen-2-yl)-4,4-dimethyl-2-(naphthalen-2-yl)pyrazolidine-3,5-dione 5.415**

![Structure of 5.415](image)

**Method A**: 12 h reaction time (0.5 mmol scale)

**Method B**: 4 equiv PIDA used, 48 h reaction time (0.3 mmol scale)

The crude material was purified in 15% EtOAc/hexanes to afford 176 mg of 5.415, 74% isolated yield (Method A), or 80 mg of 5.415, 56% isolated yield (Method B) as a viscous oil, Rf = 0.25 in 20% EtOAc/hexanes; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.07 (s, 1 H), 7.90 (d, $J = 8.4$ Hz, 1 H), 7.76 (d, $J = 8.8$ Hz, 1 H), 7.71 (d, $J = 8.8$ Hz, 1 H), 7.67 – 7.60 (m, 3 H), 7.54 – 7.51 (m, 2 H), 7.44 (d, $J = 4.4$ Hz, 2 H), 7.33 (s, 1 H), 7.31 – 7.23 (m, 2 H), 7.17 (t, $J = 8.5$ Hz, 2 H), 7.07 (d, $J = 8.7$ Hz, 1 H), 1.62 (s, 3 H), 1.49 (s, 3 H); $^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ 175.00, 172.90, 163.55, 161.90, 137.02, 134.47, 134.45, 133.24, 132.66, 132.50, 132.15, 131.41, 130.91, 130.86,
130.84, 130.70, 129.49, 128.66, 127.82, 127.80, 127.71, 127.67, 127.55, 126.93, 126.65, 126.61, 124.45, 122.74, 115.26, 115.12, 44.16, 22.20, 20.91; IR (thin film): \( \nu_{\text{max}} \) 1508, 1314, 758 cm\(^{-1}\); HRMS (ESI) m/z calcd for C\(_{31}\)H\(_{23}\)F\(_2\)N\(_2\)O\(_4\) [(M+H)\(^{+}\)]: 475.1839, found 475.1874

Note: This substrate (5.415) will begin to decompose quickly if left under the conditions outlined in Method A and is thus imperative to quench the reaction after complete consumption of the starting material.

**Preparation of 1-(anthracen-2-yl)-4,4-dimethyl-2-(3,4,5-trimethoxyphenyl)pyrazolidine-3,5-dione 5.416**

![Chemical structure of 5.416](image)

**Method B**: 4 equiv PIDA used, 72 h reaction time (0.3 mmol scale)

The crude material was purified in 40% EtOAc/hexanes to afford 104 mg of 5.416 as a viscous oil, 74% isolated yield, Rf = 0.25 in 40% EtOAc/hexanes; \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 8.37 (br s, 2 H), 7.98 (br s, 4 H), 7.48 – 7.44 (m, 3 H), 6.66 (br s, 2 H), 3.73 (s, 9 H), 1.57 (s, 6 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): \( \delta \) 174.35, 153.29, 136.54, 132.95, 132.16, 131.90, 131.61, 130.72,
129.87, 129.76, 128.17, 127.94, 127.28, 126.39, 126.02, 125.79, 121.13, 120.24, 100.28, 60.79, 56.13, 44.52, 21.84; IR (thin film): $\nu_{\text{max}}$ 1508, 1314, 758 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{28}$H$_{26}$N$_2$O$_5$ [(M+H)$^+$]: 471.1971, found 471.1962.

**Preparation of 1,2-bis(2-methoxy-5-nitrophenyl)hydrazine 5.51**

To an 4 mL vial equipped with magnetic stir bar was added 86 mg of **5.402** (0.2 mmol, 1 equiv), followed by the addition of 2 mL EtOH. The magnetic stirrer was set to 500 rpm and 13 $\mu$L anhydrous hydrazine was carefully added (2 equiv, 0.4 mmol, 12.8 mg) via glass micro-syringe. The flask was then heated to reflux for 2 hours until TLC analysis in 20% EtOAc/hexanes indicated complete consumption of the starting material. The flask was taken off of the heating mantle and allowed to cool to room temperature before being placed in a 0 °C ice bath. 1 N HCl was added dropwise until the pH paper indicated a pH < 2. The mixture was taken out of the ice bath and heated until reflux. The solution was allowed to react for an additional 2 hours before removing the vial from the heat source and allowing it to cool to room temperature. The contents of the vial were rinsed into a 60 mL separatory funnel along with 10 mL H$_2$O. The hydrazine is then extracted with DCM (3 x 15 mL), dried over Na$_2$SO$_4$, filtered and concentrated
in vacuo. The crude material was purified via column chromatography using 10% EtOAc/hexanes to afford 26 mg of 5.51 as a yellow solid, m.p. = 120 °C led to decomposition, Rf = 0.2 in 10% EtOAc/hexanes; \(^1\)H NMR (600 MHz, CDCl\(_3\)): δ 7.69 – 7.65 (m, 2 H), 6.80 (d, \(J = 8.8\) Hz, 2 H), 4.07 (br s, 2 H), 3.95 (s, 6 H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)): δ 151.95, 141.92, 136.53, 114.92, 109.01, 108.94, 56.02; IR (thin film): \(\nu_{max}\) 1508, 1314, 758 cm\(^{-1}\); HRMS (ESI) m/z calcd for C\(_{14}\)H\(_{14}\)N\(_4\)O\(_6\) [(M+H)\(^+\)]: 335.1156, found 285.1262.

**Preparation of [1,1'-binaphthalene]-2,2'-diamine 5.6**

![Chemical Structure](image)

To a 25 mL round-bottom-flask equipped with a magnetic stir bar was added 380 mg 5.303 (1 mmol) followed by 10 mL EtOH. The magnetic stirrer was set to 400 rpm and the flask was then sealed with a rubber septum and fitted with an Argon inlet needle and an outlet needle. Carefully 63 \(\mu\)L anhydrous hydrazine was added (2 equiv, 2 mmol) via glass micro-syringe. The flask was then heated to 50 °C for 2 hours until TLC analysis in 20% EtOAc/hexanes indicated complete conversion of the starting material to the corresponding \(N,N'\)-dinaphthyl hydrazine. The flask was then placed in a 0 °C mL water. The mixture was extracted with DCM (3 x 40 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. 10 mL of degassed EtOH was then added to
the crude material in a round bottom flask equipped with a magnetic stir bar and placed in an ice bath at 0 °C ice bath where 0.1 mL HCL (37%) was added. The flask was then removed from the ice bath and allowed to warm to room temperature over 30 minutes when TLC analysis in 20% EtOAc/hexanes indicated complete conversion of the N,N’-dinaphthyl hydrazine. The solution was then poured into a 125 mL separatory funnel with 50 mL water. The aqueous layer was extracted with DCM (4 x 50 mL), dried over Na₂SO₄, filtered, concentrated in vacuo and then purified on column chromatography using 20% EtOAc/hexanes to afford 239 mg of 5.6 as a white solid, 84% isolated yield, Rf = 0.25 in 20% EtOAc/hexanes. ¹H NMR (600 MHz, CDCl₃): δ 7.82 – 7.80 (m, 4 H), 7.27 – 7.19 (m, 4 H), 7.15 (d, J = 8.8 Hz, 2 H), 7.09 (d, J = 8.1 Hz, 2 H), 3.64 (s, 4 H); ¹³C NMR (151 MHz, CDCl₃): δ 142.40, 133.61, 129.48, 128.49, 128.12, 126.83, 123.92, 122.48, 118.36, 112.74; IR (thin film): νmax 1508, 1314, 758 cm⁻¹; HRMS (ESI) m/z calcd for C₂₀H₁₆N₂ [(M+H)⁺]: 285.1296, found 285.1262.

**Preparation of 7H-dibenzo[c,g]carbazole 5.7**

To an 8 mL vial equipped with magnetic stir bar was added 142 mg of 5.6 (0.5 mmol, 1 equiv), followed by the addition of 1.25 mL H₂O and 1.25 mL EtOH. The magnetic stirrer was set to
500 rpm and 0.272 mL 98% H$_2$SO$_4$ (10 equiv, 5 mmol, 500 mg) was added via syringe. The vial was capped and heated to 90 °C and allowed to react for 12 hours. TLC analysis in 20% EtOAc/hexanes indicated complete consumption of the starting material and the solution was allowed to cool to room temperature. The magnetic stir bar was removed and the mixture was placed into a 60 mL separatory funnel with H$_2$O (20 mL) and DCM (20 mL). The separatory funnel was shaken and once the layer separated the organic layer (bottom) was drained. The mixture was then extracted with DCM (3 x 20 mL), dried over Na$_2$SO$_4$, filtered, concentrated in vacuo and then purified via column chromatography using 15% EtOAc/hexanes to afford 115 mg of 5.7 as a white solid, 86% isolated yield, Rf = 0.3 in 20% EtOAc/hexanes; $^1$H NMR (600 MHz, CDCl$_3$): δ 9.25 (d, $J = 8.4$ Hz, 2 H), 8.62 (s, 1 H), 8.06 (d, $J = 7.9$ Hz, 2 H), 7.86 (d, $J = 8.6$ Hz, 2 H), 7.71 (t, $J = 7.6$ Hz, 2 H), 7.60 (d, $J = 8.6$ Hz, 2 H), 7.55 (t, $J = 7.3$ Hz, 2 H); $^{13}$C NMR (151 MHz, CDCl$_3$): δ 136.11, 129.93, 129.18, 129.16, 126.79, 125.43, 125.15, 123.27, 117.65, 112.56.
5.8 References


APPENDIX A.1

$^1$H NMR and $^{13}$C NMR spectra associated with Chapter 2
APPENDIX B.1

\(^1\)H NMR and \(^{13}\)C NMR spectra associated with Chapter 3
APPENDIX B.2

X-Ray-Crystallography Data for Chapter 3
X-Ray structure for Figure 3.4304

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X-Ray Structure Determination of Compound 3.4407

Audit creation method: SHELXL-97

Chemical name systematic: 2-nitro-3-(2-(trifluoromethyl)phenyl)naphthalene

Chemical melting point: 80°C

Chemical formula sum: 'C17 H10 F3 N O2'

Chemical formula weight: 317.26

Symmetry cell setting: Monoclinic

Symmetry space group name H-M: P2(1)/n
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F3  F  0.9273(7)  0.8662(5)  0.2219(3)  0.0461(12) Uani 0.644(10)  1 d P A 1
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F2A F  0.9939(13)  0.8761(8)  0.0935(4)  0.058(2) Uani 0.356(10)  1 d P A 2
F3A F  0.8853(17)  0.8322(10)  0.2082(8)  0.070(3) Uani 0.356(10)  1 d P A 2
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APPENDIX C.1

$^1$H NMR and $^{13}$C NMR spectra associated with Chapter 4
APPENDIX C.2

X-Ray-Crystallography Data for Chapter 4
X-Ray Structure Determination of Compound 4.5

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  3 -x,1/2+y,1/2-z
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C4 C  0.1126(2)  0.51289(15)  0.19662(7)
C5 C  0.1234(2)  0.60440(15)  0.22385(7)
C6 C  0.2146(2)  0.61571(14)  0.27101(7)
C7 C  0.2196(2)  0.71528(14)  0.30047(8)
H7A H  0.2314  0.7033  0.3395
H7B H  0.1222  0.7523  0.2938
H7C H  0.3084  0.7551  0.2873
C8 C   0.0118(3)  0.50032(19)  0.14674(8)
H8A H  -0.0567  0.5591  0.1428
H8B H  -0.0519  0.4393  0.1504
H8C H   0.0788  0.4944  0.1146
O1 O  0.37705(17)  0.36412(10)  0.28408(5)
C9 C  0.3698(3)  0.26882(14)  0.25760(8)
H9A H  0.2626  0.2428  0.2594
H9B H  0.4408  0.2215  0.2756
H9C H   0.4010  0.2766  0.2195
O2 O  0.03548(19)  0.68605(11)  0.20579(6)
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H32C H 0.6667 0.4405 0.2653

#END
APPENDIX D.1

$^1$H NMR and $^{13}$C NMR spectra associated with Chapter 5
5.314
APPENDIX D.2

X-Ray-Crystallography Data for Chapter 5
X-Ray Structure Determination of Compound 5.201

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O2 O 0.60819(5) 0.4724(3) 0.43537(5)
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C1 C 0.55799(7) 0.3810(4) 0.47517(8)
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C3 C 0.57962(8) 0.3807(4) 0.43953(8)
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H4B H 0.5289 0.6013 0.5042
H4C H 0.5197 0.6471 0.4501
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H5B H 0.5642 0.2594 0.5412
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H24B H 0.6434 0.9075 0.4624
H24C H 0.6823 1.0320 0.4620
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C72 C 0.94093(6) 1.1921(4) 0.79726(8)
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C75 C 0.96968(6) 1.3278(3) 0.69221(8)
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X-Ray Structure Determination of Compound 5.205

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_chemical_formula_weight          258.09
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_cell_length_b                    10.9142(14)
_cell_length_c                    10.2423(14)
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_cell_formula_units_Z             2
_cell_measurement_temperature     296(2)
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_computing_data_reduction         'Bruker SAINT'
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_computing_structure_refinement   'SHELXL-2014/7 (Sheldrick, 2014)'
_computing_molecular_graphics     'Bruker SHELXTL'
_computing_publication_material   'Bruker SHELXTL'
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X-Ray Structure Determination for Compound 5.210

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space_group_name_Hall

-P 2ybc

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_refine_ls_shift/su_mean 0.000

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_atom_site_aniso_U_33
_atom_site_aniso_U_23
_atom_site_aniso_U_13
_atom_site_aniso_U_12
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O2 0.0616(6) 0.0761(7) 0.0292(5) 0.0080(5) 0.0048(5)
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C2 0.0429(5) 0.0478(6) 0.0906(5) 0.0073(4) -0.0031(4)
C3 0.0415(5) 0.0459(6) 0.0033(5) 0.0130(4) 0.0032(4)
C4 0.0575(7) 0.0623(8) 0.0663(8) -0.0046(6) 0.0222(6) 0.0083(6)
C5 0.0541(7) 0.0729(9) 0.0819(10) 0.0071(8) 0.0285(7) 0.0175(7)
C6 0.0383(6) 0.0770(9) 0.0927(11) 0.0179(8) 0.0182(6) 0.0103(6)
C7 0.0353(5) 0.0720(9) 0.0799(9) 0.0056(7) 0.0058(5) -0.0006(5)
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C9 0.0366(5) 0.0570(7) 0.0511(6) -0.0052(5) 0.0019(4) -0.0043(4)
C10 0.0353(5) 0.0459(5) 0.0421(5) -0.0005(4) 0.0054(4) -0.0012(4)
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C13 0.0396(5) 0.0514(6) 0.0457(6) 0.0030(5) 0.0041(4) 0.0002(4)
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C17 0.0667(8) 0.0572(7) 0.0494(6) 0.0021(5) 0.0125(6) 0.0021(6)
C18 0.0729(9) 0.0745(9) 0.0452(6) -0.0024(6) 0.0202(6) -0.0100(7)
C19 0.0442(6) 0.0697(8) 0.0494(6) -0.0199(6) 0.0116(5) -0.0069(5)
C20 0.0571(7) 0.0564(7) 0.0626(8) -0.0068(6) 0.0138(6) 0.0060(6)
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X-Ray Structure Determination for Compound 5.401

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dimethylpyrazolidine-3,5-dione
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_exptl_absorpt_correction_T_max  0.5849  
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_exptl_absorpt_special_details  ?  
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_diffrn_measurement_device_type  'Bruker APEX-II CCD'  
_diffrn_measurement_method  '\textbackslash f and \textbackslash w scans'  
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_computing_cell_refinement 'Bruker SAINT'
_computing_data_reduction 'Bruker SAINT'
_computing_structure_solution 'SHELXS-97 (Sheldrick 2008)'
_computing_structure_refinement 'SHELXL-2014/6 (Sheldrick, 2014)'
_computing_molecular_graphics 'Bruker SHELXTL'
_computing_publication_material 'Bruker SHELXTL'
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X-Ray Structure Determination for Compound 5.402

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_chemical_formula_weight         488.45
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_space_group_name_H-M_alt       'C 2/c' 

_space_group_name_Hall         '-C 2yc' 

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_cell_length_c                  7.4266(8)     
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_cell_angle_beta                93.481(2)    
_cell_angle_gamma               90           
_cell_volume                    2201.4(4)    
_cell_formula_units_Z           4            
_cell_measurement_temperature  296(2)        
_cell_measurement_reflns_used   5478          
_cell_measurement_theta_min     2.83          
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_exptl_crystal_density_method  ?            
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_exptl_transmission_factor_max ?            

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_exptl_absorpt_special_details ?            

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_diffrn_reflns_Laue_measured_fraction_full = 0.999
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_computing_cell_refinement = 'Bruker SAINT'
_computing_data_reduction = 'Bruker SAINT'
_computing_structure_solution = 'SHELXS-97 (Sheldrick 2008)'
_computing_structure_refinement = 'SHELXL-2014/7 (Sheldrick, 2014)'
_computing_molecular_graphics = 'Bruker SHELXTL'
_computing_publication_material = 'Bruker SHELXTL'
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_platon_squeeze_void_average_z
_platon_squeeze_void_volume
_platon_squeeze_void_count_electrons
_platon_squeeze_void_content
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 2 0.500 0.500 -0.025 143 24 
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\_atom\_sites\_solution\_secondary ?
\_atom\_sites\_solution\_hydrogens \ geom
\_refine\_ls\_hydrogen\_treatment \ constr
\_refine\_ls\_extinction\_method none
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\_refine\_ls\_number\_parameters \ 143
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loop
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\ _atom\_site\_type\_symbol
\ _atom\_site\_fract\_x
\ _atom\_site\_fract\_y
\ _atom\_site\_fract\_z
\ _atom\_site\_U\_iso\_or\_equiv
\ _atom\_site\_adp\_type
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\ _atom\_site\_site\_symmetry\_order
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END
X-Ray Structure Determination for Compound 5.403

_audit_creation_method            SHELXL-2014/6
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_chemical_formula_weight         380.43
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_space_group_name_Hall: '-P 2ybc'

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_cell_angle_gamma: 90
_cell_volume: 1940.9(6)
_cell_formula_units_Z: 4
_cell_measurement_temperature: 299(2)
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_cell_measurement_theta_min: 3.01
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