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Visible Light-assisted Deconstruction/Refunctionalization of Strained and Unstrained N-Cycloalkylanilines

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Visible Light-assisted Deconstruction/Refunctionalization of Strained and Unstrained *N*-Cycloalkylanilines

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in Chemistry

by

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Abstract

The exploitation of ring strain as a driving force to facilitate chemical reactions is a well-appreciated principle in organic chemistry. Of the strained carbocycles frequently explored in this respect, cyclopropane ring systems have drawn considerably more interest among synthetic chemists than their homolog, the cyclobutane ring systems, even though the strain energy of cyclobutane (26.7 kcal/mol) is similar to that of cyclopropane (27.5 kcal/mol). We have previously developed a [4+2] annulation reaction for the synthesis of aniline-substituted six-membered carbocycles under photoredox catalysis *via* the oxidative cleavage of *N*-cyclobutylanilines. The key reaction involved in this method is a ring-opening process of cyclobutylanilines via single-electron oxidation of the anilines under visible light photoredox conditions to presumably generate distonic radical cation intermediates which possess bimodal reactivity due to the presence of a nucleophilic carbon radical moiety (site Y) and an electrophilic iminium ion moiety (site X) that are spatially separated. We have hitherto successfully achieved orthogonal 1,4-difunctionalization of the two reactive sites by using phenyl allyl sulfone or α-CF₃-styrene as radical acceptor to capture the radical at Y and TMSCN as nucleophile to intercept the iminium ion at X respectively. The first of the three works described in this dissertation further exploits isocyanides (or isonitriles)—"stereoelectronic chameleons" that exhibit dichotomous reactivity—as radical acceptors in the difunctionalization of the bimodal amine distonic radical cations to afford both symmetrical and unsymmetrical *N*-substituted 2,6-diaminopimelonitriles in poor to good yields. This represents the first-ever report of a successful synthetic methodology that exploits the ambivalent reactivities of both distonic radical cations and isocyanides.

Again, we report the development of a novel methodology for the synthesis of aminoalkynes from various *N*-substituted cyclobutane substrates via a sequential visible-light-

assisted ring-opening and distal alkynylation with alkynyl hypervalent iodine (III) reagents. An in situ-generated distonic radical cation intermediate possessing resonance-stabilized iminium ion site mediates the transformation of the substrates into various pharmaceutically important nitrogen heterocycles. This methodology constitutes only the second example of aminoalkyne synthesis employing the cycloalkylamine deconstruction/refunctionalization strategy.

Finally, we report the first-ever aromatization-promoted, visible-light-assisted deconstructive functionalization of unstrained medium-to-large-sized cycloalkanones using diamines as an activator of the ring cleavage for the synthesis of remotely functionalized quinazolinones. The protocol features an amido radical-mediated $C(sp^3)$-$C(sp^3)$ cleavage via an aromatization/radical acceptor-driven ring-opening synergy, without the involvement of transition metals, exogenous oxidants, or chelation assistance. In addition, the reaction exhibits a broad substrate scope, good to excellent product yields, and high regioselectivities.

Acknowledgments

"Great are the works of the LORD, studied by all who delight in them. Full of splendor and majesty is His work, and His righteousness endures forever."—Psalm 111:2-3, ESV. To God alone who gave me the resilience to overcome all the hurdles in the pursuit of this Ph.D. be the glory! During this long but eventful Ph.D. journey, I have myself undergone a "deconstruction and re-functionalization" of sorts (to humorize my dissertation title) and have come away with much experience and maturity. And I dare say that I am the better for it. Thanks be to God!

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Dedication

To my dear parents, Mr. Clement Boateng and Madam Vida Amponsah.

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Chapter 1

Visible Light Mediated Photoredox Catalysis

As the world turns to her scientists to help stall the ominous trends from the adverse effects of industrialization, such as environmental pollution, global warming, and decreased life expectancy, synthetic chemists have been responding to this global call by exploring "greener" and sustainable methods for their syntheses. In their 1998 publication "Green Chemistry: Theory and Practice[1]," Anastas and Warner put forward 12 complementary principles that are widely deemed to delineate the practice of green chemistry, but, essentially, six main goals underlie each of these metrics: waste minimization, avoidance of toxic chemicals, exclusion of unnecessary steps, formation of multiple bonds, achievement of high atom economy, and the usage of abundant and renewable resources.[2] In this regard, light can be considered as a model reagent for "green," environmentally friendly chemical synthesis, because, unlike many conventional reagents, it is not toxic, generates no wastes, and is obtainable from renewable sources such as sunlight.[3] Indeed, it has long been known that light alone could effect unique chemical changes of synthetic significance in organic molecules[4-6] and, a good few examples of chemical transformations utilizing ultraviolet light have been reported in the literature, yet the inability of most organic molecules to absorb the less harmful visible wavelength of light presents a challenge for its use in organic synthesis. Recent research aimed at harnessing the solar energy and sources of visible light for organic reactions have taken advantage of the rich visible light photochemistry of organic dye sensitizers and transition metal complexes—chief among them are the polypyridyl complexes of Ruthenium (II) and Iridium (III)—by employing them as photoredox catalysts to channel energy from visible light into organic molecules.[3, 7, 8] The result is the currently blossoming field of visible light photoredox catalysis with the upsurge of literature showing the utility of this strategy for

achieving ingenious chemical transformations of organic molecules, including expedient works by Yoon,[3, 9-12] Stephenson,[13] MacMillan,[14, 15] Zheng,[16-21] Akita,[22] and others[23] to generate new C-C and C-N bonds in organic molecules.

1.1. Photochemistry

Photochemistry can be defined simply as a chemical reaction triggered by the absorption of light leading to a chemical change. While sunlight-induced photochemistry must have occurred on the planet Earth for billions of years,[6] the chemical changes caused by light have only relatively recently attracted systematic scientific inquiry. In his address to the French Chemical Society on June 8, 1908, Italian chemist Giacomo Ciamician, a pioneering figure of photochemistry and, at the time, a professor at the University of Bologna, presented a comprehensive account of his ongoing work in molecular photochemistry which revealed the rich perspective that photochemistry could offer to synthesis. He reported several reactions and established that these were caused by light alone, not heat. They comprised a large portion of the reaction types presently known, viz., geometrical isomerization of C=C, C=N, and N=N bonds, 2 + 2 cycloaddition of olefins as well as α,β-unsaturated ketones and esters, reactions of ketones such as α-cleavage and intermolecular hydrogen abstraction from alcohols leading to reduction or coupling, inter- and intramolecular reactions of nitro compounds, and photooxygenation reactions.[4, 24] While they were not the first to report a photochemical reaction, the series of 33 photochemical papers published by Ciamician and his research associate Paul Silber between 1900 and 1915 under the title 'Chemical Action of Light' were groundbreaking and gave the most important contribution by a research group to the discovery of new photochemical reactions then and even for many years to

come.[24, 25] Many of Ciamician's photochemical reactions were conducted using sunlight as the source of energy.

In photochemical reactions, absorption of energy as photons from visible and/or ultraviolet light by one component of the reaction produces an electronically excited molecule with the promotion of an electron in the molecule from the ground state singlet (S_0) to a higher energy level singlet excited state. A variety of singlet excited states with various vibrational energies are possible depending on the radiation's energy, though all higher-lying excited states have a tendency to relax within a few picoseconds to the "first" singlet excited state, S_1, which has the lowest energy. A Jablonski diagram, a simplified form of which is shown in **Figure 1.1** below, gives a detailed outline of the subsequent fate of the S_1.
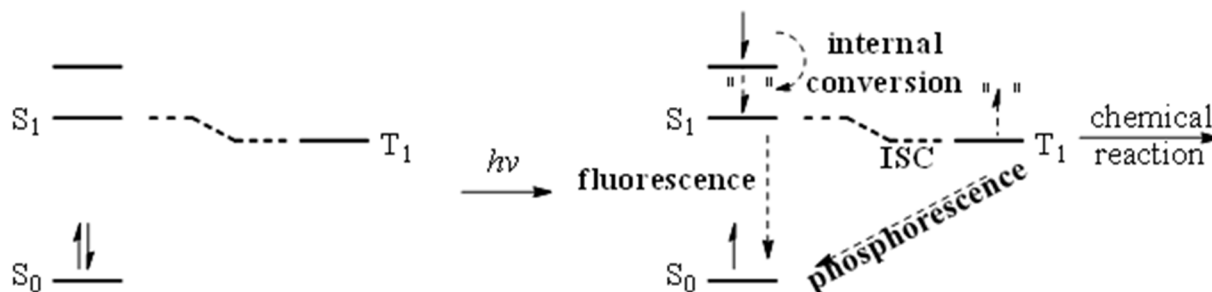
Figure 1.1.1. Photophysical Pathways of Electronically Excited Molecules.

The fate of the singlet excited state S_1 depends on both radiative pathways (via transitions to lower energy states and emission of light) and non-radiative pathways (in which energy is lost as heat). S_1 can return to the ground state S_0 via any of three processes: directly either by the radiative, light-emitting process of fluorescence, or internal conversion IC (a nonradiative transition); or, indirectly, by first proceeding to the lower energy, but longest-living, triplet excited state T_1 via a spin-forbidden, nonradiative process known as intersystem crossing (ISC) en route to S_0. The longer-lived triplet excited state T_1, with a lifetime stretching from a nanosecond to a millisecond,

can either undergo a slow radiative decay to the ground state (a spin-forbidden relaxation) in a process known as phosphorescence, or else be engaged in bimolecular reactions with another component of the reaction through energy transfer (EnT) and electron transfer (ET).[14, 26] The overall process of photoexcitation and electron transfer between an electronically excited state molecule and another molecule in its ground state is what is referred to by the term photoinduced electron transfer, or PET.

1.1.1. Visible Light Photoredox Chemistry

Visible light is the small region of the electromagnetic spectrum (**Figure 1.1.1.1**) spanning wavelengths from 400 nm to 700 nm. In contrast to UV light, visible light has longer wavelengths and is less energetic than light in the accessible range of wavelength (200 to 400 nm) within the entire ultraviolet region (10 nm-400 nm). Thus, numerous photochemical reactions have been performed in the past using short-wavelength UV light,[27] even though these typically require specialized reactors or glass reaction vessels that are transparent to the desired wavelengths, as well as expensive high-intensity UV light sources for irradiation, all of which limit reaction scalability. On the other hand, until recently, the application of visible light for photochemical synthesis had been only sporadic owing to the lack of absorption of visible light by many organic molecules. As a strategy to overcome this limitation, synthetic chemists have employed visible light-absorbing photoredox catalysts and exploited their electron and/or energy transfer processes to sensitize organic molecules to carry out desired photochemical reactions. This approach mimics nature's ability to use visible light-absorbing chromophores to convert solar energy to chemical energy in photosynthesis,[28, 29] and, indeed, the design of photoredox reaction cycles for organic transformations features many of the complex processes also inherent in photosynthesis such as

light harvesting, charge separation, charge transport and charge extinction and the use of sacrificial electron and hole donors.[30]
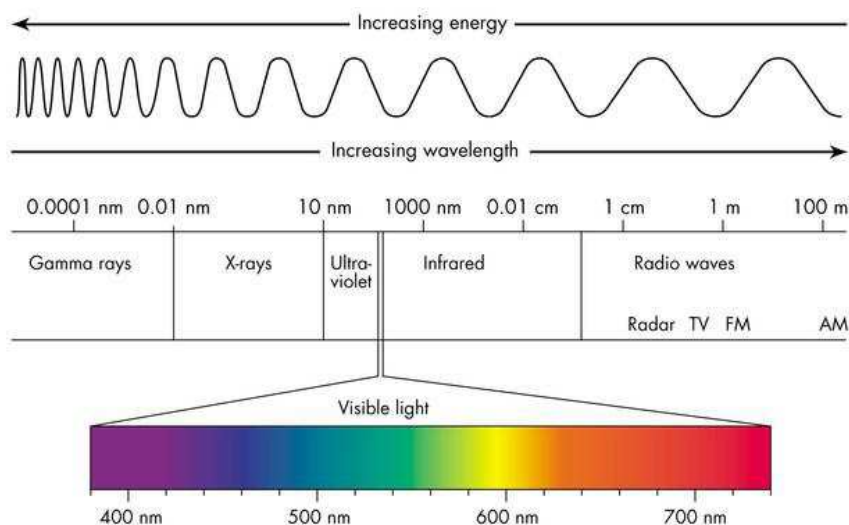
Figure 1.1.1.1 Electromagnetic Spectrum[31]

Although the development of visible light-promoted photocatalytic reactions has evoked interest among synthetic organic chemists since the 1970s,[32-34] only since 2008 have spectacular advancements in the field of visible light photoredox catalysis been achieved. Visible light photocatalysis has been shown to be a powerful tool not only for initiating diverse organic transformations under very mild conditions but also for its ability to help achieve unique bond constructions through the intermediacy of open-shell reactive species which are not possible using established means of chemical catalysis involving polar or two-electron manifolds. Most visible-light-induced photochemical reactions occur through single-electron transfer (SET) process from an excited photocatalyst to an organic substrate or reagent. However, in recent years, a number of visible-light-induced energy-transfer (EnT) reactions have also been reported.[35]
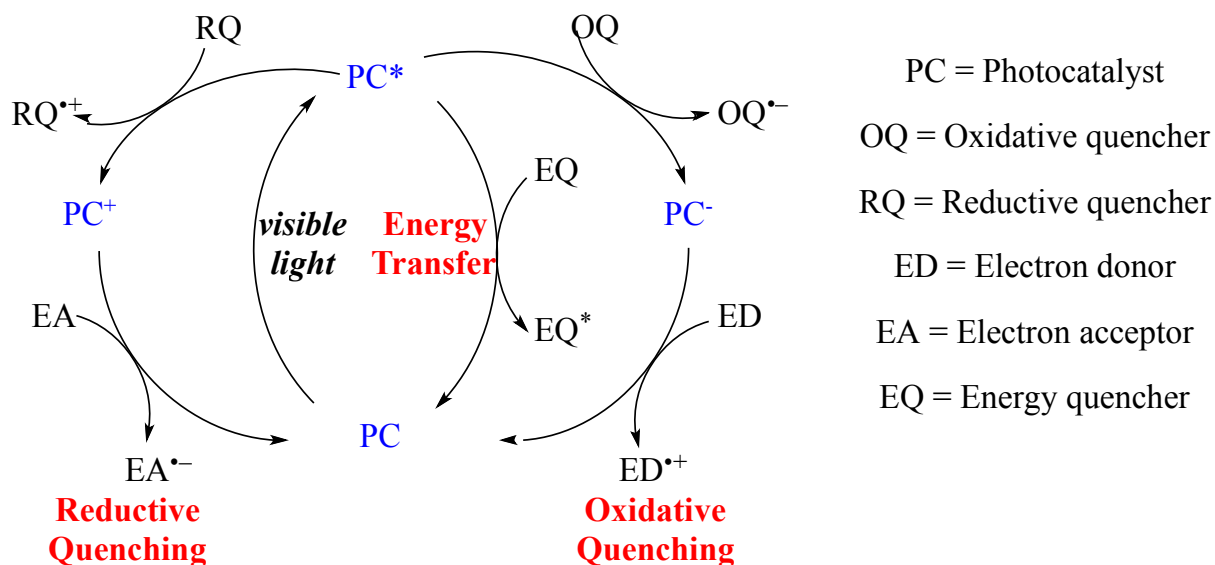
Figure 1.1.1.2. Oxidative Quenching Cycle and Reductive Quenching Cycle

Regarding the SET manifold, two different reaction cycles, namely oxidative quenching and reductive quenching, are often invoked to explain the mechanism of the photoredox catalysis, as illustrated in **Figure 1.1.1.2** above. Either cycle begins with an initial excitation of the photocatalyst (**PC**) by irradiation with visible light, which then undergoes single-electron oxidation or reduction with either an organic substrate or a sacrificial reagent to generate various highly reactive radical or radical-ion species possessing reactivity patterns that are fundamentally different from their electronic ground or excited states.[36] These very reactive species can be harnessed in a controllable manner for accessing many useful compounds. The pathway in which the excited state photocatalyst oxidizes the organic substrate or sacrificial reagent (RQ) and is itself thereby reduced is called reductive quenching cycle, and the converse pathway wherein the photocatalyst is oxidized by the organic molecule is called the oxidative quenching cycle. Photoredox catalysis may be used to achieve overall redox neutral reactions. Since in the same reaction vessel, both oxidants and reductants could be transiently produced, the photoredox

approach could be used to design and perform reactions in which electrons are donated or received by reaction components at different points in the reaction mechanism. Furthermore, only a very low loading of photocatalyst (typically 1 mole % or less) is required typically in visible-light photoredox catalysis, and since organic molecules commonly do not absorb visible light well, deleterious side reactions from photodecomposition of the substrate can be eschewed altogether or significantly suppressed.

1.1.2. Photocatalysts

In photoredox catalysis, an exogenous light-absorbing species, known as the photocatalyst, is used to modulate the redox process and is restored either exactly at or after the final chemical product forming step. Compounds that are typically employed as photocatalysts include the transition metal polypyridyl complexes (such as from ruthenium or iridium) and organic dyes (such as eosin Y, 9,10-dicyanoanthracene, and triphenylpyrylium salts) all of which are capable, in their excited states, of undergoing single-electron transfer (SET) reactions with organic substrates when they are photoexcited with visible light. This is because they have chromophores that can absorb light in the visible region of the electromagnetic spectrum and generate stable photoexcited state species possessing a long enough lifetime (1100 ns for $Ru(bpy)_3^{2+}$) to engage in bimolecular electron-transfer reactions in competition with the undesired pathways which can deactivate them.[37] Representative examples of commonly used photoredox catalysts are shown in **Figure 1.1.2.1**.
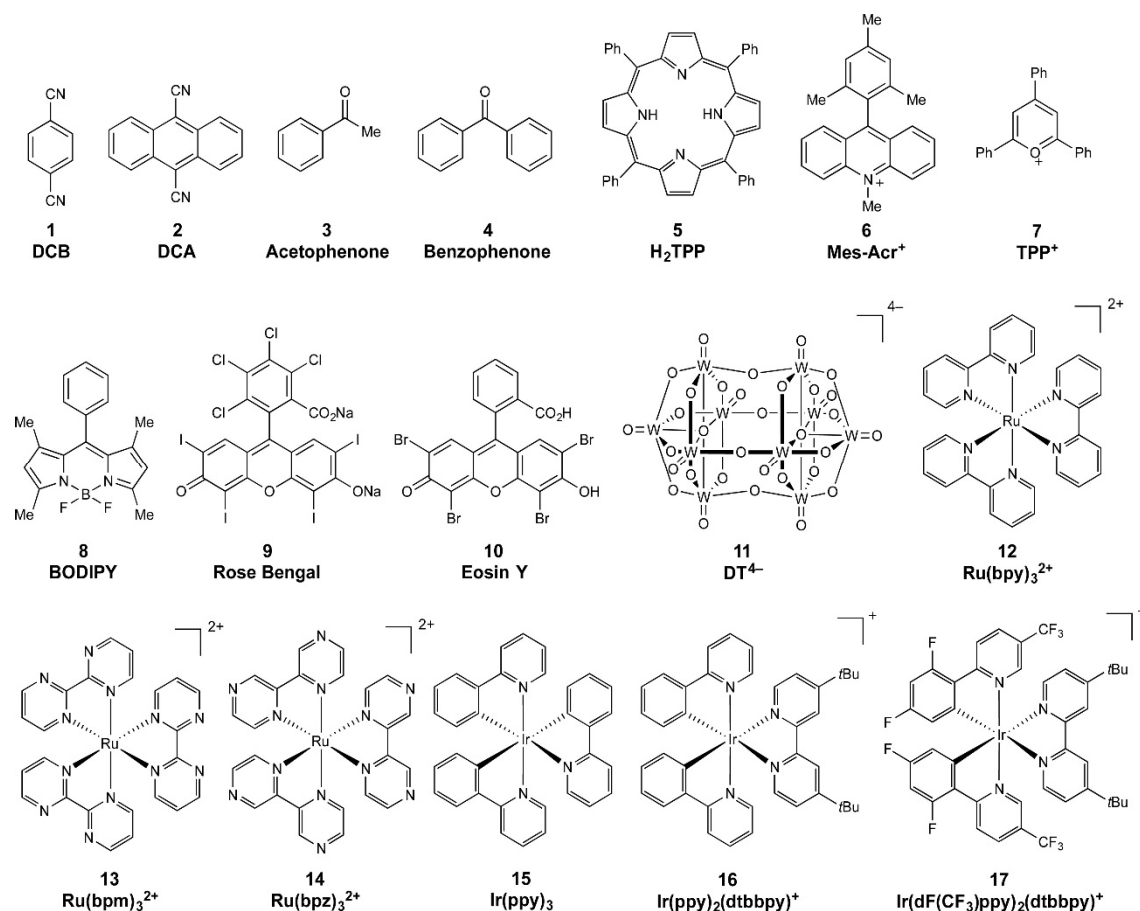
Figure 1.1.2.1. Structures of Commonly Used Photocatalysts[38]

Apart from their recent use in organic synthesis, photocatalysts have been used for other applications in inorganic and materials chemistry, such as splitting of water,[29, 39] carbon dioxide reduction to methane,[40] solar energy storage,[41] photovoltaics[42] and in photodynamic therapy.[43] However, it was not until 2008 when the Yoon group at Wisconsin and the MacMillan group at Princeton published concurrent works demonstrating the use of $Ru(bpy)_3^{2+}$ as a visible light photoredox catalyst to perform a [2 + 2] cycloaddition[10] and α-alkylation of aldehydes[26] respectively, that interest in the utility of these photocatalysts as a theoretically novel approach in synthetic organic reaction development was revived. As already mentioned, an ideal photocatalyst is one that can undergo a redox reaction in the excited state, and an ensuing turnover step allows

them to engage in light-promoted catalytic redox cycles. Organic chemists can design and carry out appropriate reactions by comprehending the underlying processes that control the redox behavior of these photoactive compounds. **Figure 1.1.2.2** shows the photophysical properties and mechanism of action of a prototypical photocatalyst Ru(bpy)$_3$Cl$_2$.
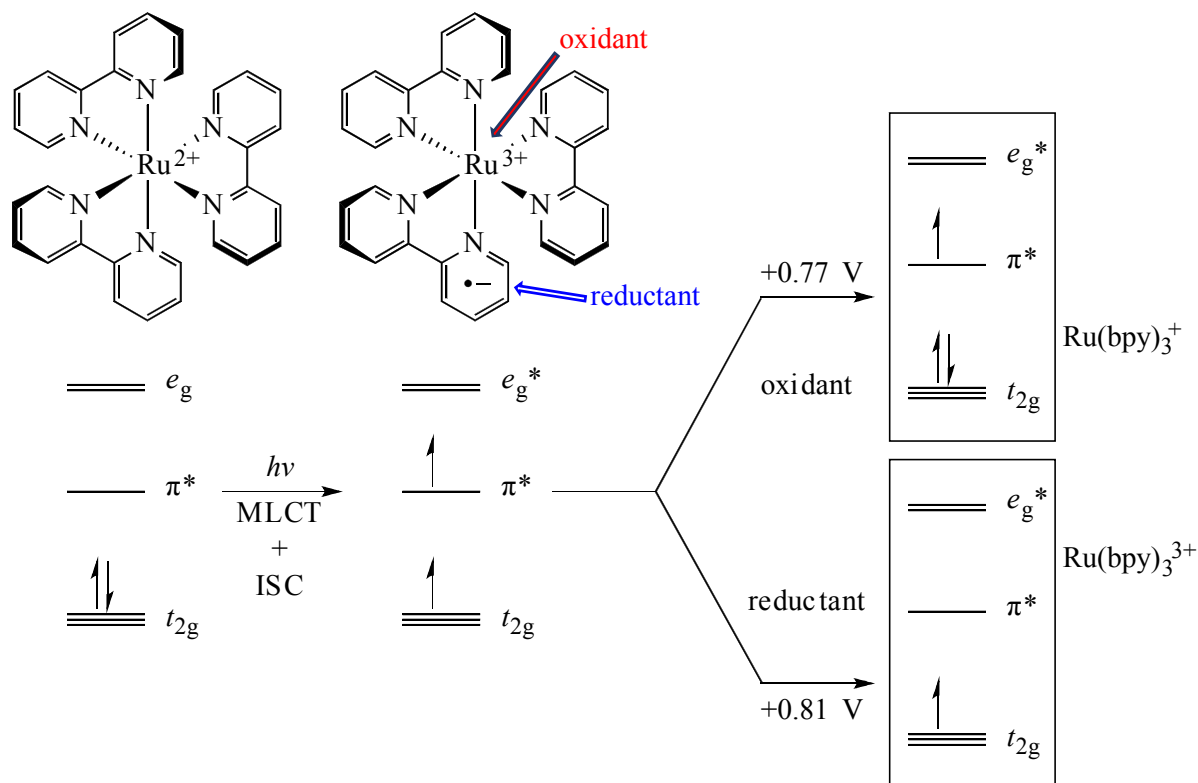
Figure 1.1.2.2. Molecular Orbital Depiction of Ru(bpy)$_3^{2+}$ Photochemistry

As depicted in **Figure 1.1.2.2**, the photoredox action of the photocatalyst Ru(bpy)$_3$Cl$_2$ begins with the absorption of a photon from visible light, causing excitation of an electron from one of the t_{2g} orbitals of the photocatalyst's metal center to the π^* orbital of the aromatic ligand.[44,] [45] This transition, known as metal-to-ligand charge transfer (MLCT), produces a species in singlet excited state in which the metal center has, in effect, undergone single-electron oxidation to the Ru(III) oxidation state while the ligand framework has undergone a single electron reduction to a

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radical anion.[46] This initially occupied singlet MLCT state has a short lifetime, and thus undergoes a rapid intersystem crossing (ISC) to form the lowest-energy triplet MLCT state possessing a longer lifetime. This is because a further decay to the singlet ground state is spin-forbidden. It is this long-lived photoexcited triplet state species that engages in single-electron transfer with an organic substrate or reagent in the reaction. Remarkably, the photoexcited triplet state species is, at the same time, a stronger oxidant and reductant than the ground state analog—its actual redox behavior depending on the reaction partner—and is therefore capable of oxidizing or reducing an organic substrate by single-electron transfer. This electronic duality is nonexistent in conventional redox reaction manifolds, such as electrochemistry, wherein the reaction medium is either oxidative or reductive but never both. Commonly, the photoredox chemistry of $Ru(bpy_3)^{2+}$ is coupled with an oxidative or reductive quenching step that helps to regenerate the Ru(II) resting state of the catalyst.

Since all light-promoted transformations begin with the photocatalyst (PC) absorbing a photon (the Grotthuss-Draper law) to generate a high energy excited state (PC*), the absorption of higher energy visible light (wavelengths 400-475 nm) is desirable as it ensures maximum gain in potential energy without the likelihood of undesired reactivity from direct excitation of organic substrates. Much of the enhanced redox processes available to the photocatalysts is facilitated by this gain in energy. Thus, the ability of the metal-based photocatalysts to absorb such high-energy visible light has significantly promoted them for higher use among synthetic chemists than the photocatalytic organic dyes, despite the advantage of avoiding precious metals in using dyes. For example, the maximum absorbance of $Ru(bpy)_3Cl_2$ is 452 nm, which affords it 0.37 eV more energy to potentially apply to reaction promotion than eosin y having a significantly red-shifted absorbance (λmax (eosin y) = 522 nm).[47] The longer the wavelength of absorption, the lesser will

be the energy possessed by the singlet and triplet excited states. While Ru^{2+} and Ir^{3+} polypyridyl complexes typically possess broad absorption bands, they generally relax initially from various singlet excited states to the lowest spin-allowed metal-to-ligand charge transfer excited state.[45] Rapid intersystem crossing then occurs from this lowest spin-allowed MLCT excited state to the triplet manifold followed by internal conversion to give the long-lived first triplet excited state.

The reactivity of metal-based photocatalysts, such as Ru^{3+} and Ir^{3+} polypyridines, can be tuned for targeted reactions by adjusting the metal and ligand combinations since the redox behavior of these complexes are generally described by oxidations of the metal center and reductions of the ligands. There are two sets of reduction potentials of importance in discussion of redox behavior, namely those associated with the ground states and those on the excited states. In the discussion that follows, the term "reduction potential" is used to refer exclusively to the potential associated with the electrochemical half-reaction (using standard calomel electrode SCE as reference) and it is written to show the more oxidized species being reduced, i.e., $Li^+ + e^- \rightarrow$ Li, $(E_{red}[Li^{1+}/Li] = -3.39$ V).

Figure 1.1.2.3 below shows the electronic effects of ligands on the redox properties of some selected photocatalysts. Considering the Ru^{3+}/Ru^{2+} couple, for example, when ligands that are more electron-donating electronically are used the oxidation becomes more facile, and the reduction potential becomes less positive. An example is the catalyst $Ru(bpy)_2(pz)_2$, which contains two anionic pyrazolo ligands in its structure which makes the reduction potential of the corresponding $Ru(bpy)_2(pz)_2^{1+}/Ru(bpy)_2(pz)_2$ couple substantially less positive ($E_{red} = +0.30$ V)[48] than that of $Ru(bpy)_3Cl_2$ ($E_{red} = +1.26$ V) which has no such ligands in its structure. On the other hand, using a stronger π-accepting ligand, such as 2,2'-bipyrazine, shifts the reduction potential for the $Ru(bpz)_3^{3+}/Ru(bpz)_3^{2+}$ couple to +1.86 V.[49] Similarly, since that the reduction of this kind

of complexes is ligand centered, it can be predicted that the reduction potential of the Ru^{2+}/Ru^{1+} couple will become more negative when electron-rich ligands are involved. By adding methyl substituents, therefore, to the bipyridine ligands the reduction potential of the $Ru(dmb)_3^{2+}/Ru(dmb)_3^{1+}$ couple is shifted to -1.45 V compared with $E_{red}[Ru(bpy)_3^{2+}/Ru(bpy)_3^{1+}]$ of -1.35 V.[50] As expected, the potential of the strongly electron-deficient *mer*-Ru(4-O$_2$N-bpy)$_3^{2+}$/*mer*-Ru(4-O$_2$N-bpy)$^{1+}$ couple bearing nitro groups on the ligands shifts to -0.63 V,[51] making it a strong oxidant towards substrates. In general, making the ligands more electron rich tends to make the metal complex more reducing, whereas making the ligands less electron rich tends to make the metal complex more oxidizing. The ground state reduction potentials have served as the foundation for the entire discussion. The corresponding reduction potentials for catalysts in excited states are normally derived from known cyclic voltammetry (CV) and spectroscopic data because they cannot be measured directly.[52]

Oxidized Complexes (undergoes metal centered oxidation):

Ru(bpy)$_2$(pz)$_2$
E_{red} = 0.30V

Ru(bpy)$_3$
E_{red} = 1.26V

Ru(bpz)$_3$
E_{red} = 1.86V

← electron density of metal center

oxidative power of complex →
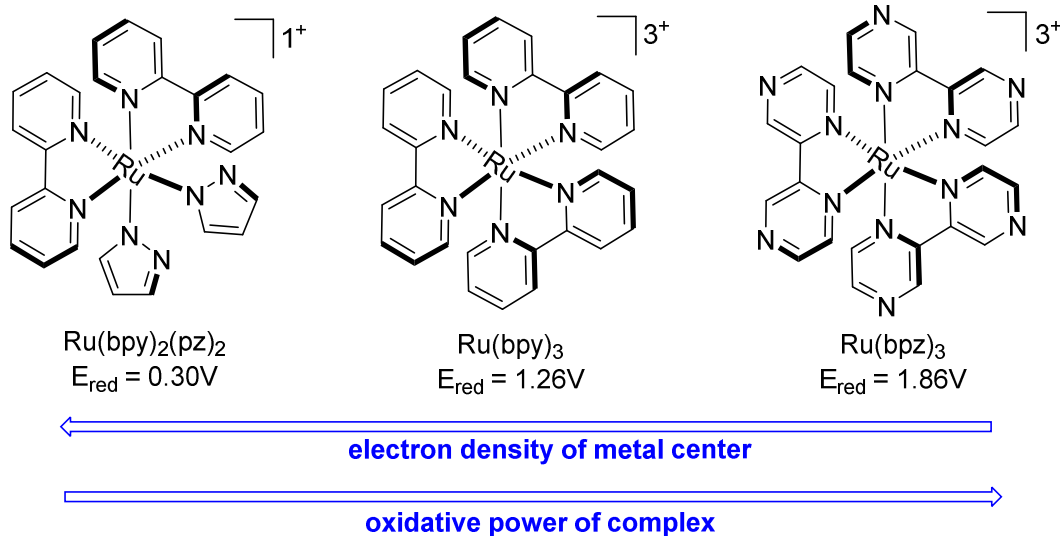
Reduced Complexes (undergoes ligand centered reduction):

Ru(dmb)$_3$
E_{red} = -1.45V

Ru(bpy)$_3$
E_{red} = -1.35V

mer-Ru(4-O$_2$N-bpy)$_3$
E_{red} = -0.63V

← electron density of ligand

reductive power of complex →
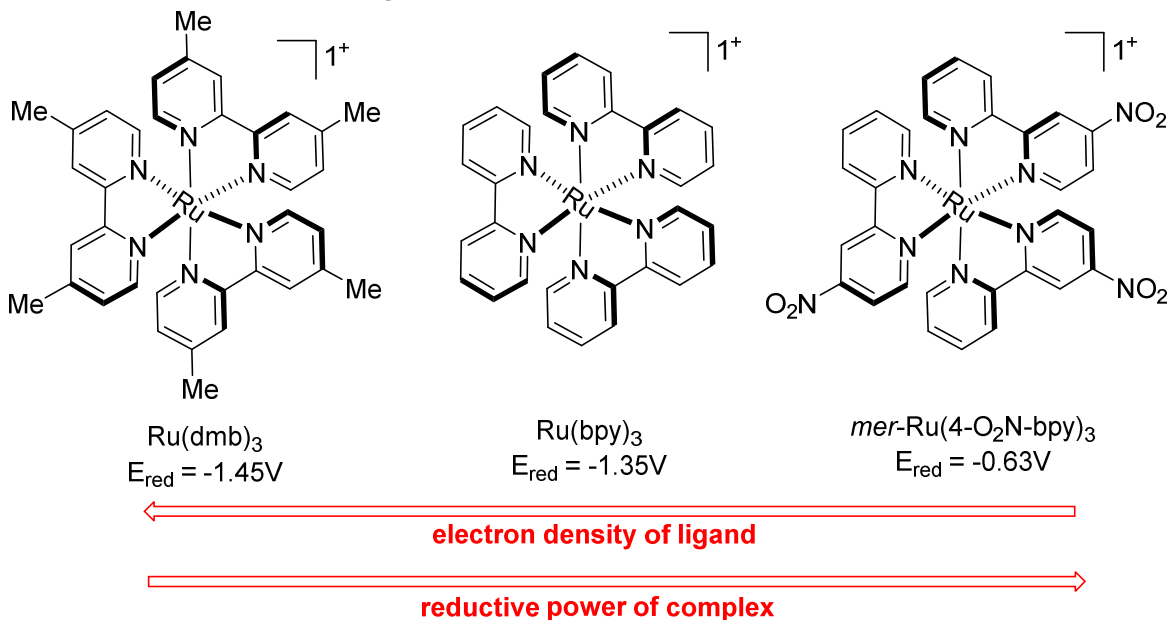
Figure 1.1.2.3. Effect of Ligands on Ground-State Redox Potentials of Photocatalysts

The likelihood of a substrate (**sub**) reacting with a photoredox catalyst (**cat**) in the excited state can be evaluated intuitively using the catalyst's excited state reduction potential E_{red}^*(cat*/cat$^{•-}$) or oxidation potential E_{ox}^*(cat$^{•+}$/cat*) as benchmarks. When the excited state **cat***

is reduced and the substrate in its ground state (**sub**) is oxidized in photoinduced electron transfer (PET), the Gibbs energy of the process is given simply by Equation 1 (i.e. ignoring solvent-dependent energy differences from charge separation):

$$\Delta G_{PET} = -F(E_{red}{}^*(\mathbf{cat}^*/\mathbf{cat}^{\bullet-}) - E_{ox}(\mathbf{sub}^{\bullet+}/\mathbf{sub})) \qquad (1)$$

where $E_{red}{}^*$ is the reduction potential of the excited state **cat** and is calculated by:

$$E_{red}{}^*(\mathbf{cat}^*/\mathbf{cat}^{\bullet-}) = E_{red}(\mathbf{cat}/\mathbf{cat}^{\bullet-}) + E_{0,0} \qquad (2)$$

Here, **cat*** is either the excited state S_1 or T_1, with the corresponding excited state energy $E_{0,0}$ value ($E_{0,0}{}^{S1}$ or $E_{0,0}{}^{T1}$). The subscript "0,0" in $E_{0,0}{}^{S1}$ describes the transition between the lowest energy vibrational states of S_1 and S_0 (i.e. v = 0).

When, on the other hand, a PET involves oxidation of the catalyst's excited state **cat*** and reduction of the ground state substrate **sub**,

$$\Delta G_{PET} = -F(E_{red}(\mathbf{sub}/\mathbf{sub}^{\bullet-}) - E_{ox}{}^*(\mathbf{cat}^{\bullet+}/\mathbf{cat}^*)) \qquad (3)$$

where $E_{ox}{}^*$ which is the excited state oxidation potential of **cat** can be calculated from:

$$E_{ox}{}^*(\mathbf{cat}^{\bullet+}/\mathbf{cat}^*) = E_{ox}(\mathbf{cat}^{\bullet+}/\mathbf{cat}) - E_{0,0} \qquad (4)$$

$E_{red}{}^*$ is positive when a photoredox catalyst is serving as an excited state oxidant, and $E_{ox}{}^*$ is negative when it is behaving as an excited state reductant. Hence, a qualitative estimation of ΔG_{PET} can be used to evaluate the considered PET process. Therefore, equations (1) and (3) together can serve as a simple intuitive framework when deciding on a suitable photoredox catalyst for a desired transformation. For photoinduced oxidation of substrate **sub** to occur, the $E_{red}{}^*$ of photoredox catalyst **cat*** must be more positive than the E_{ox} of substrate **sub**. Similarly, the reduction of substrate **sub** is thermodynamically favorable only when the $E_{ox}{}^*$ of photoredox catalyst **cat*** is more negative than E_{red} of substrate **sub**.

The next few paragraphs are a discussion of how various research groups have achieved targeted transformations by selecting photocatalysts whose ligand electronic properties are fine-tuned for the intended reaction coupling the photocatalyst redox behavior to various photoredox quenching cycles.

1.1.3. Photoredox Quenching Cycles

As was discussed hereinbefore, the long-lived triplet excited state of a photocatalyst is both more oxidizing and more reducing than its ground state and hence can be quenched in either of two quenching cycles—oxidative and reductive—depending on the oxidation or reduction potential of the organic substrate with which it is interacting. In the reductive quenching cycles, the organic molecule is oxidized by the photocatalyst, whereas in the oxidative quenching pathway it is reduced by the catalyst. In both cycles, the photoexcited catalyst engages in single electron transfer (SET) with the substrate. However, due to the relatively high energy of the triplet state of the excited photocatalyst, it can also act as an energy donor, activating an energy acceptor (**EA**) via an energy-transfer (EnT) pathway, a process known as sensitization. In contrast to the SET processes, the reactions that occur via EnT are not constrained by the redox properties of the substrates, but rather depend on the triplet-state energies (E_T) of the organic substrate and the excited photocatalyst. Thus, the EnT strategy provides a complementary approach to photochemical reactions that are unlikely to occur through photoredox (or electron transfer) catalysis. A better understanding of all these catalytic pathways for use in organic transformation is therefore worthwhile to the synthetic organic chemist.

Oxidative Quenching Cycle

As already discussed, in an oxidative quenching cycle, the excited state of the photocatalyst is quenched by donating an electron either to the organic substrate or some oxidant present in the reaction medium, and the turnover step involves the reduction of the generated oxidized catalyst by either the substrate, an external redox-active reagent, or an intermediate species. Thus, single-electron oxidation pathways are typical of photoredox reactions which involve some species present functioning as a stoichiometric electron acceptor. Notable examples feature the single-electron oxidation of very electron-rich functional groups such as arenes and amines. The oxidative quenching cycle can however also be applied in overall redox-neutral transformation.

The first report of a net oxidative photoredox-catalyzed reaction was published in 1984 by Cano-Yelo and Deronzier in which they used aryldiazonium salts as the sacrificial oxidant for the conversion of benzylic alcohols to the corresponding aldehydes employing a ruthenium (II) photocatalyst.[53] Not long after this, they reported the first redox-neutral photoredox-catalyzed transformation, a Ru(bpy)$_3^{2+}$-catalyzed Pschorr reaction which gave quantitative yield of the phenanthrene or substituted phenanthrene product (**Scheme 1.1.3.1**).[54] The reaction was initiated by the reduction of aryl diazonium salts by the excited state of the photocatalyst to generate aryl radical, with the photocatalyst oxidative quenched thereby. The radical undergoes an intramolecular arylation with a pendant arene to give a cyclic radical intermediate which when oxidized by the oxidized form of the photocatalyst produces a carbocation and regenerates the catalyst. Subsequent deprotonation this carbocation furnished the phenanthrenecarboxylic acid. Since then, several photoredox-catalyzed reactions exploiting the oxidative quenching pathway for the generation of various reactive intermediates from different radical precursors have been

reported by many research groups, including works by the groups of Stephenson,[55] MacMillan,[56] Yoon,[11] and others.[57]
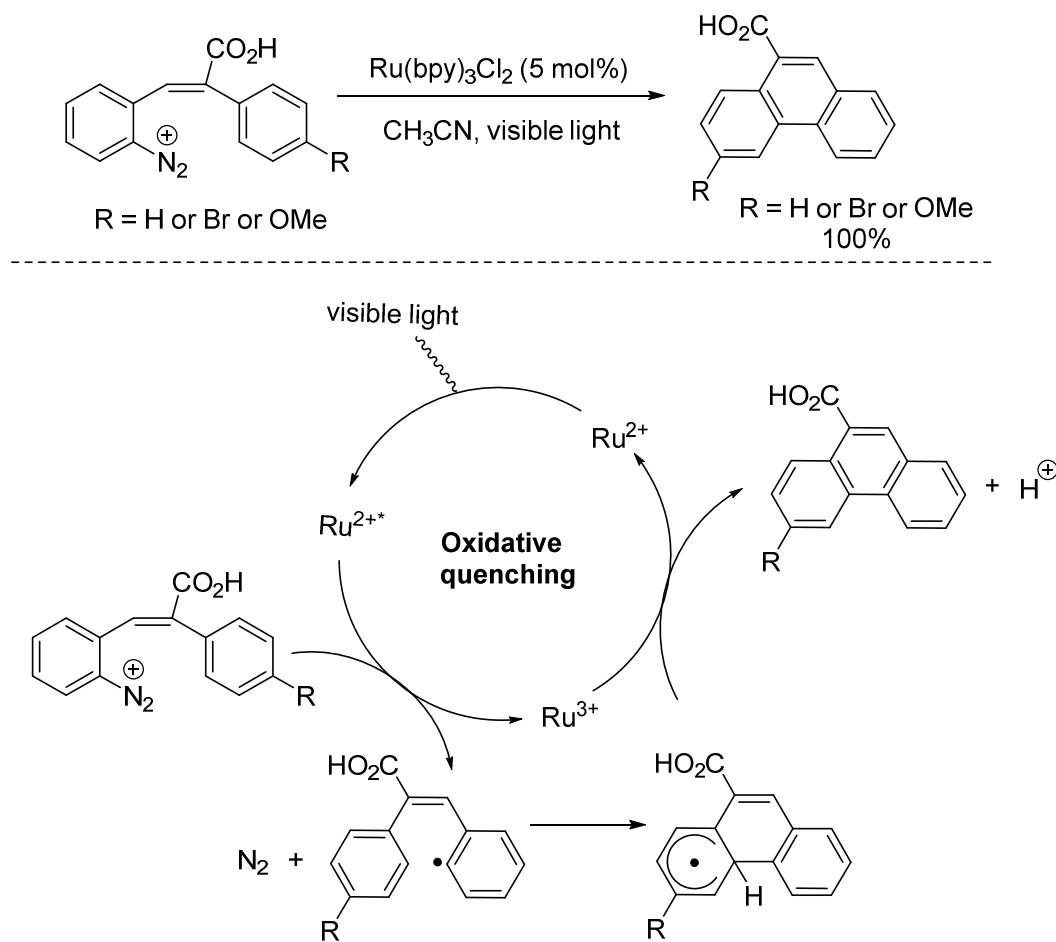
Scheme 1.1.3.1. Photocatalytic Pschorr reaction

One major work by Prof. Yoon and co-workers demonstrating the exploitation of the oxidative quenching cycle in photoredox catalysis was the report in 2010 of the intramolecular [2+2] cycloaddition reactions of styrenyl radical cations generated via oxidation of electron-rich styrenes (**Scheme 1.1.3.2**).[58] In the mechanism of that reaction, the photogenerated excited state Ru^{2+*} donates an electron to the oxidative quencher methyl viologen (MV^{2+}), becoming oxidized to the Ru^{3+} state. The Ru^{3+} subsequently accepts an electron from the electron-rich styrene to

regenerate the ground state catalyst with concomitant formation of a reactive cation intermediate. This intermediate then forms new C–C bonds through radical processes, to furnish the desired bicyclic products eventually in high yields and selectivities.
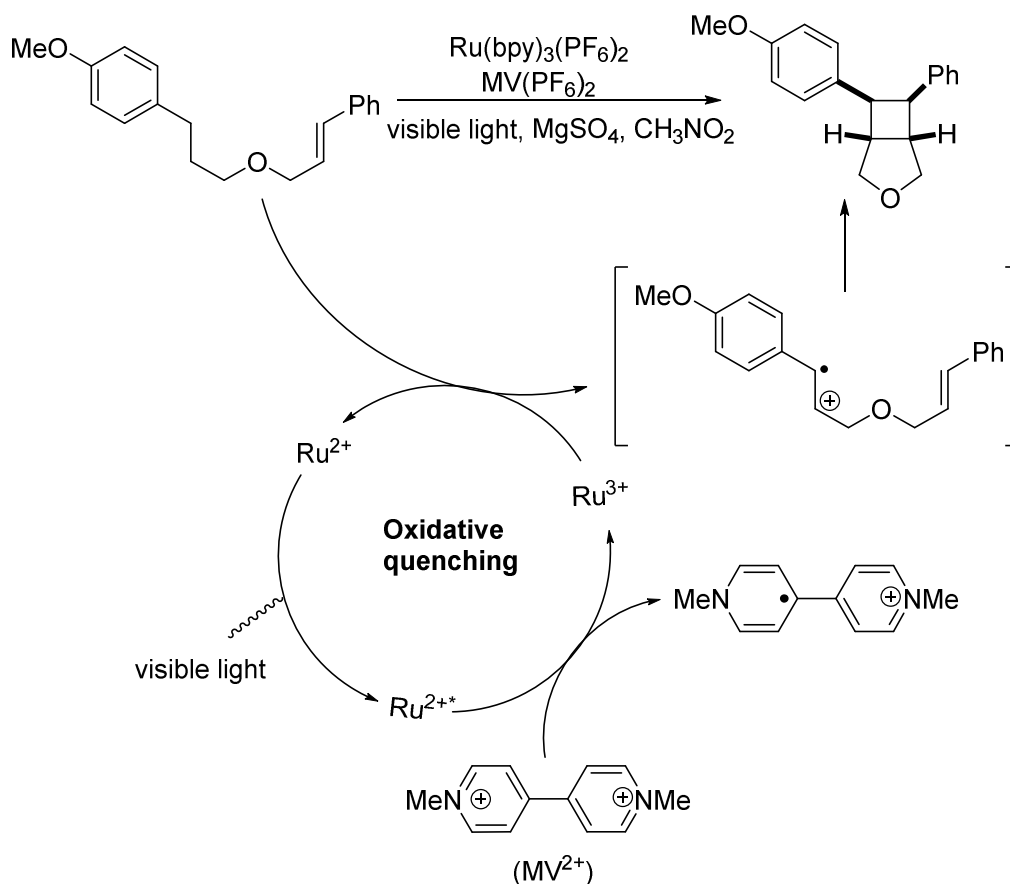
Scheme 1.1.3.2. Photooxidative [2+2] Cycloaddition

Reductive Quenching Cycle

The first reactions in organic synthesis which demonstrated the potential application of visible light photoredox catalysis were net reductive reactions, wherein an electron donor is used as the stoichiometric reductant. Pac and co-workers reported one of the earliest examples of these

types of reactions in 1981, which involved the reduction of electron-deficient olefins in a Ru(bpy)$_3^{2+}$-mediated process.[32] In these studies, 1-benzyl-1,4-dihydronicotinamide (BNAH) was employed as the terminal reductant. This shares the redox-active 1,4-dihydropyridine moiety with the biological reductant 1,4-dihydronicotinamide adenine dinucleotide (NADH). In the proposed reaction mechanism (**Scheme 1.1.3.3**), the sufficiently oxidizing photoexcited state species Ru(bpy)$_3^{2+*}$ ($E_{1/2}^{*II/I} = +0.77$ V vs SCE) generated through visible light absorption by the photocatalyst accepts an electron from BNAH ($E_{1/2}^{red} = +0.76$ V vs SCE), to form a BNAH radical cation and the reduced photocatalyst Ru(bpy)$_3^+$. The catalyst in the reduced state is highly reducing ($E_{1/2}^{II/I} = -1.33$ V vs SCE) and undergoes single electron transfer to dimethyl maleate to give a radical anion with concurrent oxidation of the photocatalyst back to the ground state Ru(bpy)$_3^{2+}$ to complete the photocatalytic cycle. It was proposed that the radical anion so formed would be protonated to yield an α-carbonyl radical which would undergo a second single-electron reduction and protonation to furnish the dimethyl succinate as the final product. The single-electron donor for this step could be either another equivalent of the reduced photocatalyst Ru(bpy)$_3^+$ or the dihydropyridyl radical formed from the deprotonation of earlier formed radical cation which is a strong reductant ($E_{1/2}^{red} = -0.94$ V vs SCE).[59] The dihydropyridyl radical is then converted to the pyridinium form, which is the expected product of two-electron oxidation of BNAH. In addition to reduction of olefins, other reported applications of net reductive reactions include reductive dehalogenation,[60, 61] reductive cleavage of sulfonium and sulfonyl groups, nitrogen functional group reductions,[34, 62, 63] radical cyclizations,[64] reductive epoxide and aziridine opening, and the reduction of labile protective groups.

Scheme 1.1.3.3. Photoredox Reduction of Electron-Deficient Olefins

The reductive quenching cycle has also been exploited for transformations of amines in reactions that are overall redox neutral. An example that amply illustrates this type of transformation is the publication in 2012 by Zheng and coworkers of an intermolecular [3+2] annulation of cyclopropylamines with olefins[16] (**Scheme 1.1.3.4**). They proposed a reaction mechanism in which a cyclopropylamine radical cation was generated *via* reductive quenching of the excited state ruthenium (II) catalyst (i.e by donating a single electron to the catalyst). The amine

radical cation then undergoes fragmentation to give a distonic radical cation, a β-carbon radical iminium ion. The distonic radical cation adds intermolecularly to the olefin to give the adduct as a δ-carbon radical iminium ion species. An intramolecular addition of the radical site to the iminium ion leads to the regeneration of another radical cation, which is then reduced by $Ru(bpz)_3^+$ to afford the final bicyclic product.
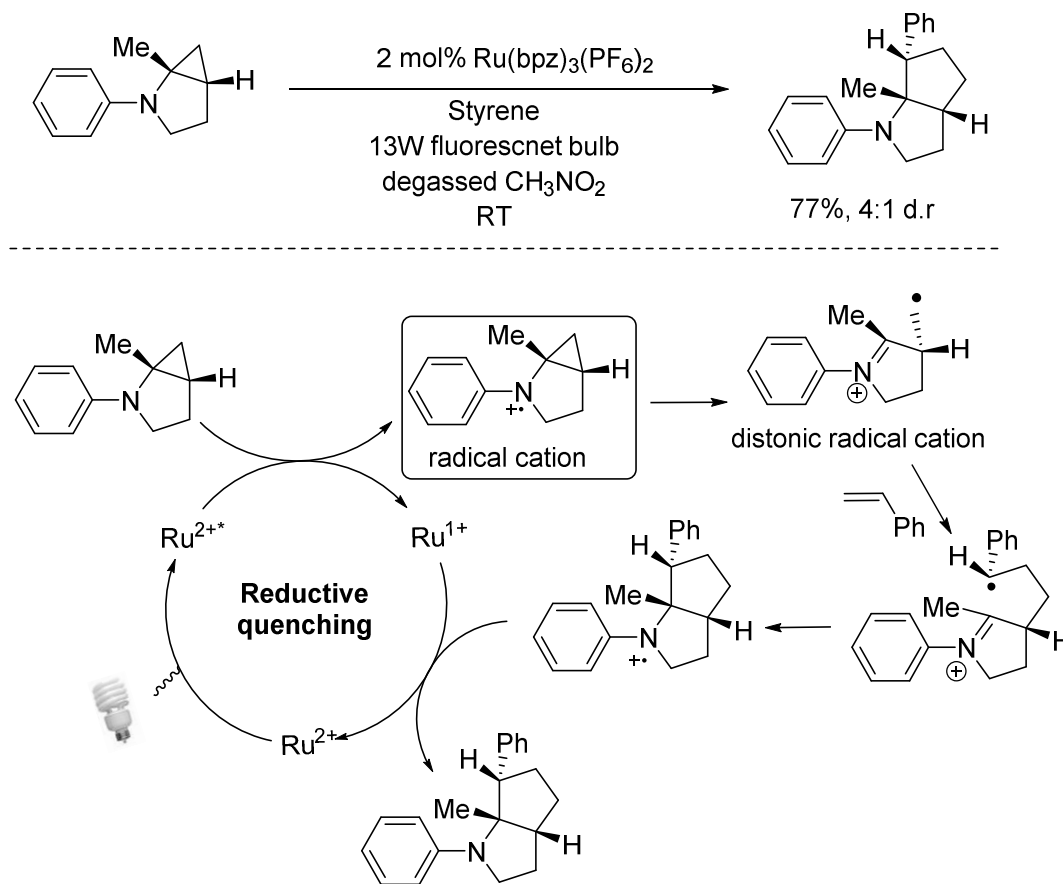
Scheme 1.1.3.4. Intermolecular [3+2] Annulation of Cyclopropylamines with Olefins

Energy Transfer Process

In an energy transfer (EnT) catalysis, the excited state of one molecular entity, the donor D, which could be the photocatalyst, deactivates to a lower-lying state by transferring energy to

another molecular entity (the acceptor A), which is excited thereby to a higher energy state.[65] In a general mechanism, the photocatalyst (**PC**) first absorbs visible light and becomes excited from its ground singlet state (S_0) into the low-lying singlet excited state S_1. Subsequent intersystem crossing (ISC) generates the **PC*** in its long-lived triplet state (T_1). As was explained earlier, the long-lived triplet state may engage in single electron transfer (photoredox) with the substrate if the redox potentials of the latter are compatible with the excited state catalyst, or, it may undergo a facile intermolecular triplet-triplet energy transfer (TTET) with the energy acceptor, **EA**. In the TTET process, the decay of **PC*** from its triplet excited state to its ground singlet state excites the **EA** from its own ground singlet state S_0 to its lowest-energy triplet state T_1 which enables it to participate in a targeted transformation (**Figure 1.1.3.1**). Thus, the EnT is essentially an isoenergetic process in which the photocatalyst or photosensitizer (i.e the energy donor) loses energy while the substrate (energy acceptor) gains energy.
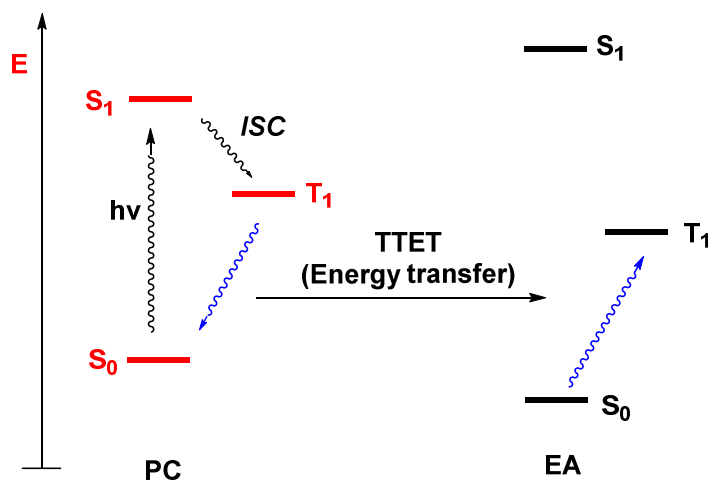
Figure 1.1.3.1. General Mechanism of Triplet-Triplet Energy Transfer

Reports of visible light transformations enabled by triplet-triplet energy transfer are rare in literature. In an early example, the TTET was applied to convert substituted norbornadiene to a

quadricyclene using Ru(bpy)$_3^{2+}$ as photocatalyst (**Scheme 1.1.3.5**).[66] In that transformation, a triplet−triplet energy transfer from Ru(bpy)$_3^{2+*}$ to the norbornadiene excited the substrate to its triplet state, which then underwent bond rearrangement to give the final quadricylene product. This example illustrates the uniqueness of TTET as a mode of activation in contradistinction from photoredox catalysis. Predictably, based on the oxidation (E$_{1/2}$ +1/0 = +1.82 V vs SCE) and reduction potentials (E$_{1/2}$ 0/−1 = −1.39 V vs SCE) of the norbornadiene, both the reductive or oxidative quenching of excited state Ru(bpy)$_3^{2+*}$ would be strictly disfavored, hence a photoredox electron-transfer pathway was not possible in the transformation.

56%
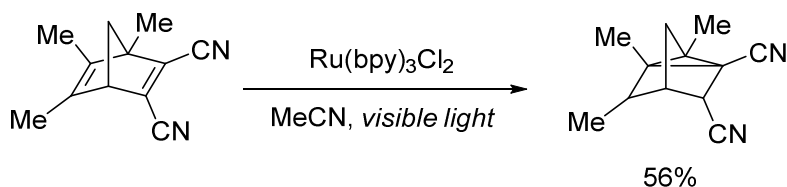
Scheme 1.1.3.5. Transformation of Norbonadiene by Energy Transfer Catalysis

The research groups of Xiao[67] and Yoon[12] recently discovered the visible-light photocatalyzed [2 + 2] cycloadditions independently going through an energy transfer pathway. In Yoon's work, the TTET was exploited to achieve [2 + 2] cycloadditions of styrenyl substrates. It is noteworthy that although this transformation had previously been accomplished via an electron-transfer (photoredox) manifold (see **Scheme 1.1.3.2**), under the earlier photoredox approach, sufficiently electron-rich (mainly methoxy-substituted) styrenes were a *sine qua non* for the single-electron oxidation to the corresponding radical cation to occur. This limitation however was overcome under energy transfer catalysis. The iridium photocatalyst Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)$^+$, with excited-state triplet energy of 61 kcal/mol,[68] was identified by Yoon's group as a potential energy transfer catalyst capable of undergoing energy transfer to styrenes, which have triplet

energies of ~60 kcal/mol.[69] The [2 + 2] cycloaddition of electron-neutral and even highly electron-deficient styrenes occur to furnish in high yield the product containing the cyclobutane ring (**Scheme 1.1.3.6**a). Here too, a single-electron transfer mediation is excluded, as the iridium catalyst ($E_{1/2}*^{III/II}$ = +1.21 V vs SCE) is not oxidizing enough to remove an electron from the styrenyl substrate ($E_{1/2}^{red}$ = +1.42 V vs SCE). Furthermore, as would be predicted, catalysts such as $Ru(bpy)_3^{2+}$ (ET = 46.8 kcal/mol) and $Ru(bpz)_3^{2+}$ (ET = 47.4 kcal/mol), that are more strongly oxidizing than $Ir[dF(CF3)ppy]2(dtbbpy)^+$, but have lower triplet state energies (ET), could not enable the transformation. Additionally, the different products observed from the cyclization of the same electron-rich styrene (**Scheme 1.1.3.6**b,c) illustrate how electron and energy transfer pathways potentially provide access to orthogonal reactivity. For instance, when an electron-transfer pathway is in play, the styrene reacted via a radical cation intermediate to afford the [4 + 2] adduct. However, in the $Ir[dF(CF3)ppy]2(dtbbpy)^+$-promoted cyclization via an energy transfer pathway, the cyclobutane was obtained as the exclusive product.[67]
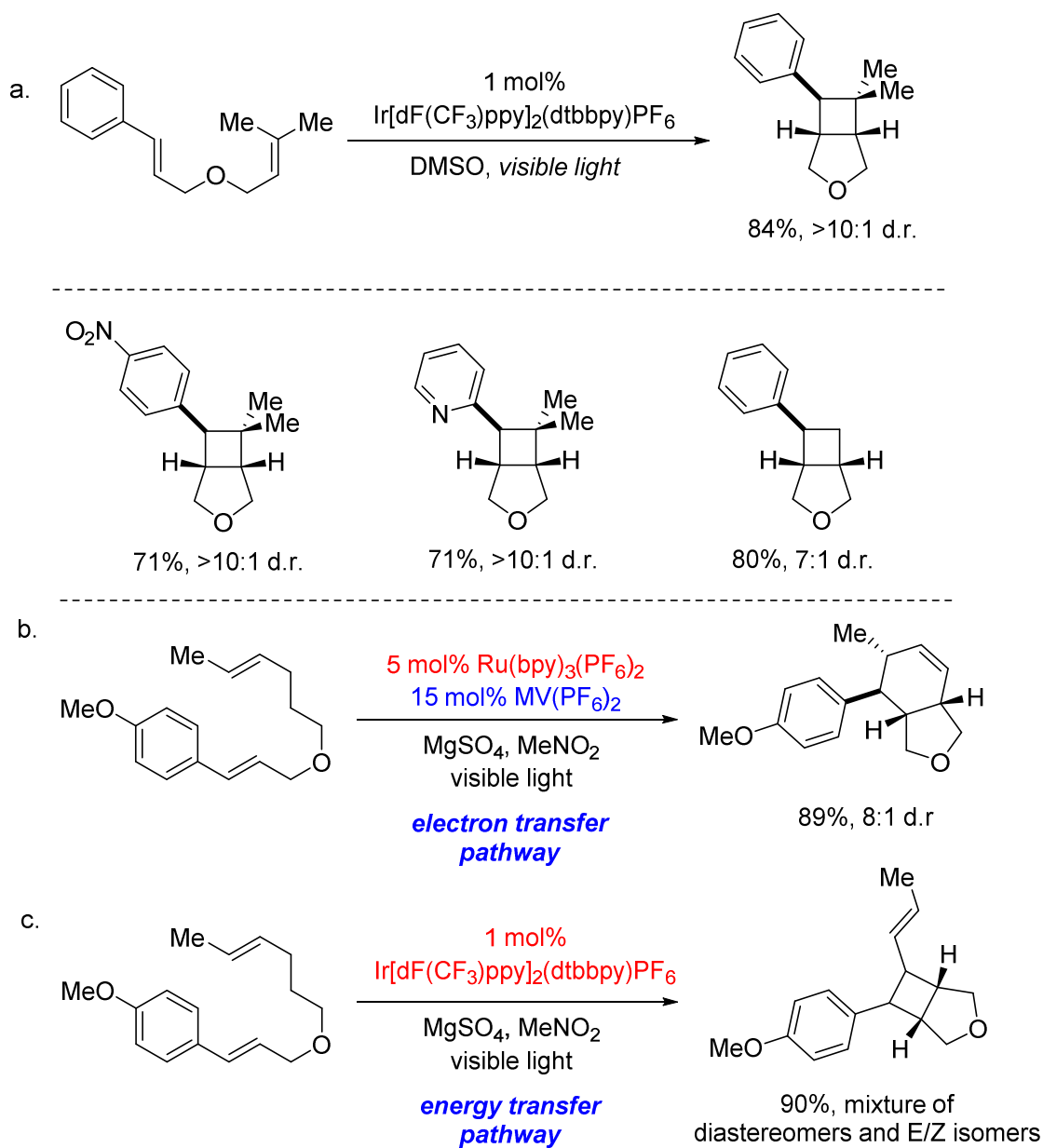
Scheme 1.1.3.6. [2+2] Styrene Cycloadditions Enabled by Energy Transfer

1.2. Nitrogen-centered radicals

Nitrogen-containing compounds abound in natural products, pharmaceuticals, and functional materials, hence transformations in which C-N bonds are formed are crucial in organic synthesis. Compared with closed shell, two-electron (ionic) or transition-metal-catalyzed methods

of C-N bond constructions, such as the palladium-catalyzed Buchwald-Hartwig amination and the copper-catalyzed Ullmann and Goldberg cross-coupling reactions, which employ amines as nucleophiles due to the lone pair of electrons on their nitrogen atoms, the development of practical and efficient radical-mediated reactions for C-N bond formation has been underdeveloped until recently. The reasons for the slow advance, hitherto, of the open-shell, radical-mediated approach can be ascribed to the high reactivity of the nitrogen-centered radical (NCR) species involved, including N-radicals and N-radical ions, which were thought of as being uncontrollable, as well as the lack of convenient methods for their generation.

Historically, these N-radical species have been generated under harsh conditions either by employing stoichiometric amounts of hazardous radical initiators, very high-temperature thermolysis, or high-energy UV photolysis, all of which limit their broad applications in synthetic organic chemistry.[70, 71] However, in recent years, visible light photocatalysis has proven to provide a mild, general method for not only generating NCRs from amine precursors, but also for utilizing them in a controlled way in the synthesis of diversely functionalized N-containing compounds with improved chemoselectivities and functional group compatibility, thereby increasing their synthetic utility. In addition, the flexibility to select from three available photocatalytic quenching/activation cycles—oxidative, reductive, and energy transfer—gives the synthetic chemist more choices in the design of the amine precursor of the NCR for the targeted reaction. Two general types of strategies may be exploited for the generation of the N-centered radical. In the first type, the specific chemical step that generates N-centered radical from the precursor involves a direct homolytic or reductive cleavage of a weak N–X bond, where X is a halogen (except fluorine), a nitrogen, an oxygen, or a sulfur group. In special situations such as with aziridinylmethyl radicals, or in cyclohexadienyl systems where aromatization can provide a

driving force, a strong N-C bond can also be cleaved. Although less common, the N-H bond cleavage from direct oxidation reaction is also possible. In the second type of strategy, the N-centered radical forms in an indirect way after an initial radical addition to an unsaturated nitrogen functionality such as a nitrile, an imine, an oxime, a hydrazone, or an azide.

Based on the charge of the nitrogen atom, NCRs can be classified as neutral amine radicals (aminyl radicals) and amine radical cations (aminium radicals). The former has no charge on the nitrogen atom that bears the radical, whereas the latter has both a radical and a positive charge situated on the same nitrogen atom. Like carbon-centered radicals, NCRs can also be classified as nucleophilic or electrophilic based on their polarity. The nature of the substituents on the nitrogen atom as well as its charge or lack thereof play a deciding role in determining the polarity. For instance, NCRs substituted with two alkyl groups on the nitrogen atom are nucleophilic. Nucleophilic amine radicals are often much less reactive than carbon radicals. They have been known to undergo nonproductive reaction pathways, such as non-selective hydrogen abstraction, dimerization to hydrazines, and disproportionation to Schiff bases and amines, which makes them synthetically ineffective in most cases. In contrast, NCRs that are electron-deficient, such as amine radical cations (due to the positive charge) or sulfonamidyl radicals (due to the electron-withdrawing substituent), are electrophilic. These two classes of radical species are significantly more reactive than the nucleophilic types and are, not surprisingly, commonplace in synthetic applications utilizing nitrogen-centered radicals.
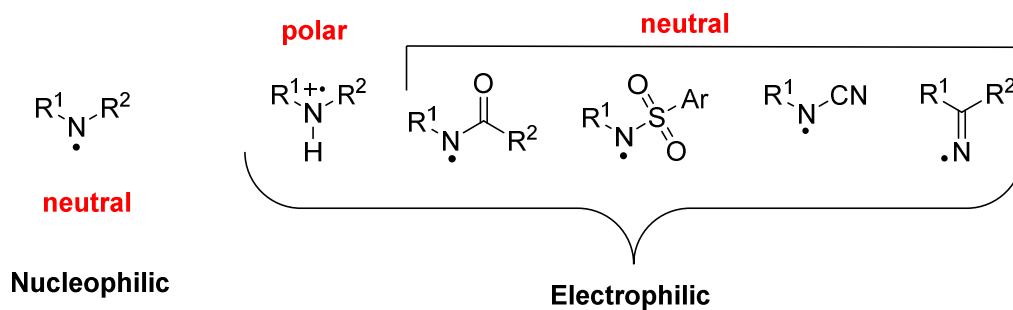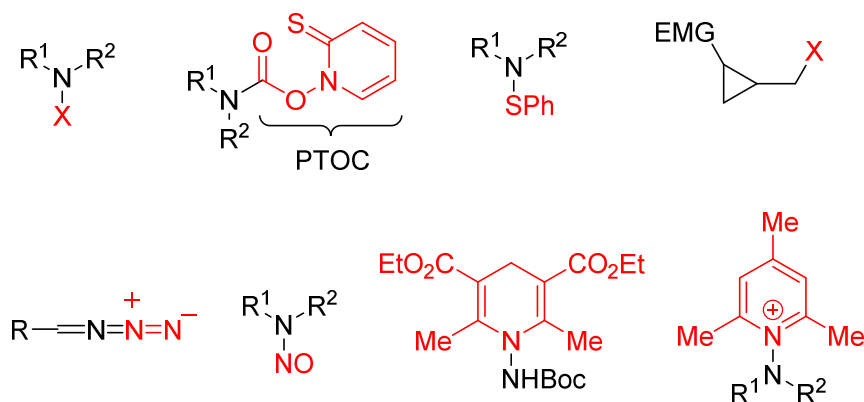
Figure 1.2.1. Representative Examples of *N*-centered Radicals and Radical Precursors

The next few paragraphs are a brief illustration of the visible-light photoredox-catalyzed generation and transformation of some neutral *N*-centered radicals—viz, aminyl radicals, iminyl radicals, and amidyl radicals—and the polar aminium radicals (or amine radical cations) using selected examples from literature. An exhaustive review of the reactivities of NCRs is not in view.

1.2.1. Neutral N-Centered Radicals

Visible light photoredox catalysis has provided a powerful, and convenient avenue for accessing neutral N-centered radicals (NCR) under mild conditions. Various precursors containing N–O, N–S, N–N, and N–X (where X = Cl, Br) bonds have been converted into the corresponding

N-centered radicals *via* a single electron transfer (SET)-facilitated reductive bond homolysis (**Scheme 1.2.1.1**). In contrast, the cleavage of strong or inert N–H bonds to generate NCRs have also been achieved recently *via* SET oxidative processes[72].
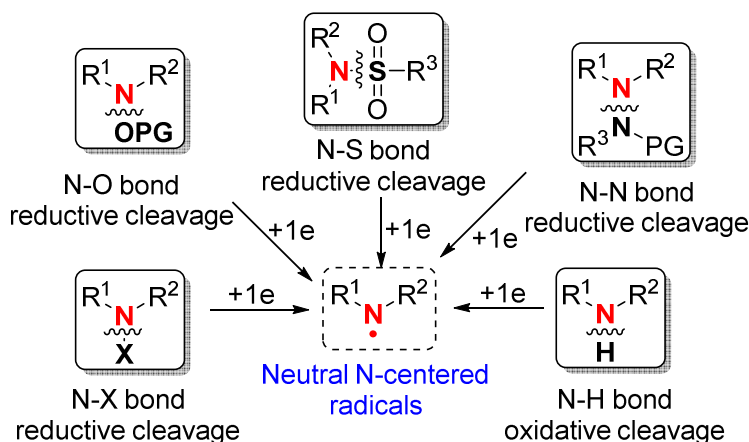
Scheme 1.2.1.1. Generation of Neutral N-centered Radicals

In a 2014 pioneering work by Sanford and coworkers, *N*-acyloxyphthalimides were used as precursors for imidyl radicals, which were accessed *via* single-electron reduction of the weak N–O bond in such compounds (**Scheme 1.2.1.2**).[73] The electron-withdrawing substituents of *N*-acyloxyphthalimides were found to be crucial for the generation of N-radicals as they enhanced the leaving ability of the carboxylate anion significantly. Using *fac*-Ir(ppy)₃ as a photocatalyst under visible light irradiation and trifluoromethylacyloxyphthalimide as the N-radical precursor gave the best results. Electron-rich arenes gave generally high yields while relatively lower yields were obtained with arenes bearing electron-withdrawing groups. These observations therefore confirm the electrophilic nature of these N-radicals. They proposed a mechanism in which the photoexcited Ir^{3+}* is oxidatively quenched by *N*-acyloxyphthalimide *via* an SET process to give the phthalimidyl N-radical. This adds to the arene to form a neutral radical intermediate, which

undergoes an SET oxidation and deprotonation in turns to afford the expected product and the regenerated ground-state photocatalyst.
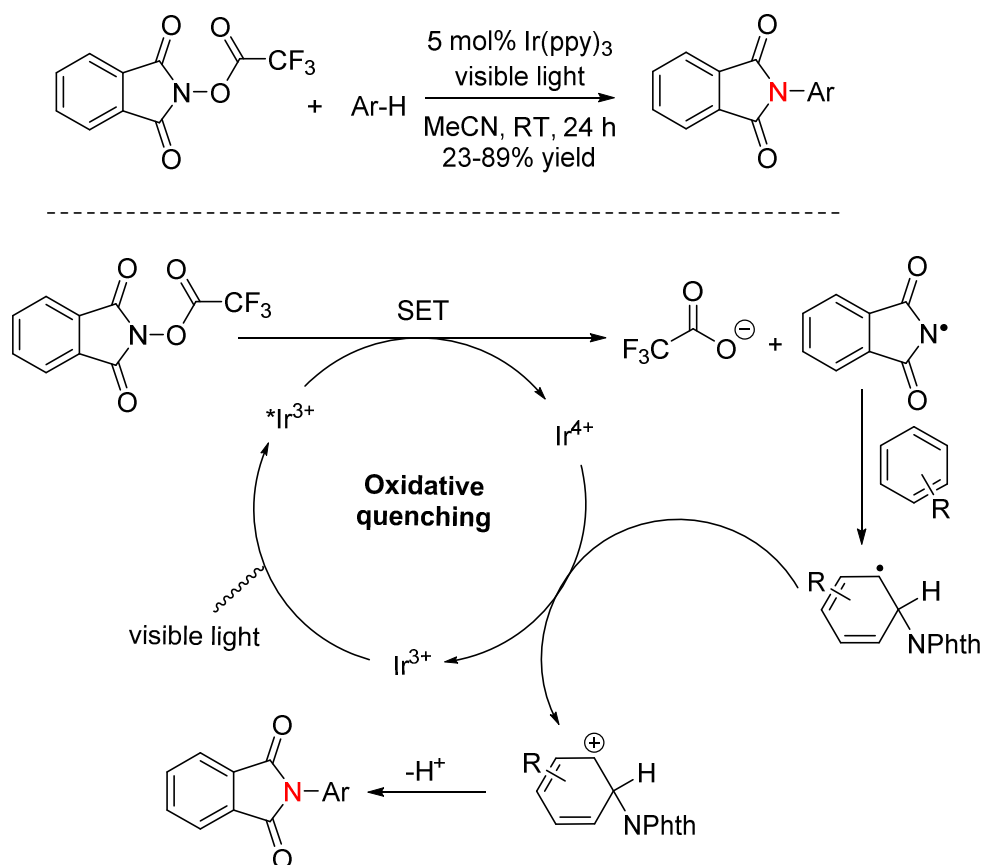
Scheme 1.2.1.2. Photocatalyzed C-H Amination of (Hetero)Arenes with Imidyl Radicals

Shortly thereafter, the group of Yu reported a similar strategy employing a hydroxylamine derivatives as N-radical precursors in the efficient direct C–H bond amination of various heteroarenes under visible light photocatalysis.[74] Like Sanford's work, the key step of this transformation also involved the reductive cleavage of the N–O bond of the hydroxylamine derivative to the N-radical by the excited state catalyst Ir[3+*] and the protecting group of the N-radical precursor had vital influence on this step. Here too, electron-deficient heteroarenes did not work well under the standard conditions. They followed up this work in 2015 by reporting an

efficient catalytic generation of iminyl radicals from the reductive cleavage of N–O bonds of acyl oximes under SET visible light photoredox catalytic process.[75] The intramolecular N-radical-mediated cyclizations of diverse acyl oximes were achieved to furnish various pyridines, phenanthridines, and quinolines in good to high yields. The Leonori group has also reported an analogous photocatalyzed iminyl radical-mediated intramolecular hydroimination and iminohydroxylation of O-aryl oximes using the organic dye eosin Y as the photoredox catalyst,[76] and much recently, hydroamination-cyclization and N-arylation reactions mediated by amidyl radicals.[77, 78] Thus, since Sanford's pioneering work, the reductive N-radical generation from various N-radical precursors such as other hydroxylamine derivatives,[74, 77, 79] sulfonamides,[80] haloamides,[81-83] azides,[84] and N-aminopyridinium salts[85] have been introduced by various research groups and successfully applied to C–H amidation reactions as well as intra- and inter-molecular alkene amidations.[86, 87]

The Studer group disclosed in 2015 an elegant direct amidation of arenes and heteroarenes employing N-aminopyridinium salts as N-radical precursors under visible-light-induced catalysis using Ru(bpy)$_3$Cl$_2$ as photocatalyst (**Scheme 1.2.1.3**).[85] Notably, unlike most N-radical precursors of the type R^{1}R^{2}N-X which are generally unstable, these N-aminopyridinium salts can be prepared on a large scale by a single-step condensation of the very stable commercially available pyrylium salts with hydrazines at room temperature and can be stored at the ambient temperatures for months. While they achieved the amidation of a wide range of electron-rich arenes and heteroarenes in good yields and complete regiocontrol, they found that N–Ac and N-Boc-protected indoles were not suitable for the transformation probably because of their lower activity toward the electrophilic N-radical species. The suggested mechanism (exemplified for the indole amidation) involves an initial oxidative quenching of the excited state of the photocatalyst Ru^{2+}*

by the *N*-aminopyridinium salt to generate the neutral N-radical intermediate via a N–N bond cleavage together with a strongly oxidizing Ru^{3+} species. The N-radical then adds to heteroarene **to** form a C-centered radical **which undergoes** another SET oxidation by the oxidizing Ru^{3+} and deprotonation of the resultant intermediate to produce the final product and regenerate the catalytic cycle.
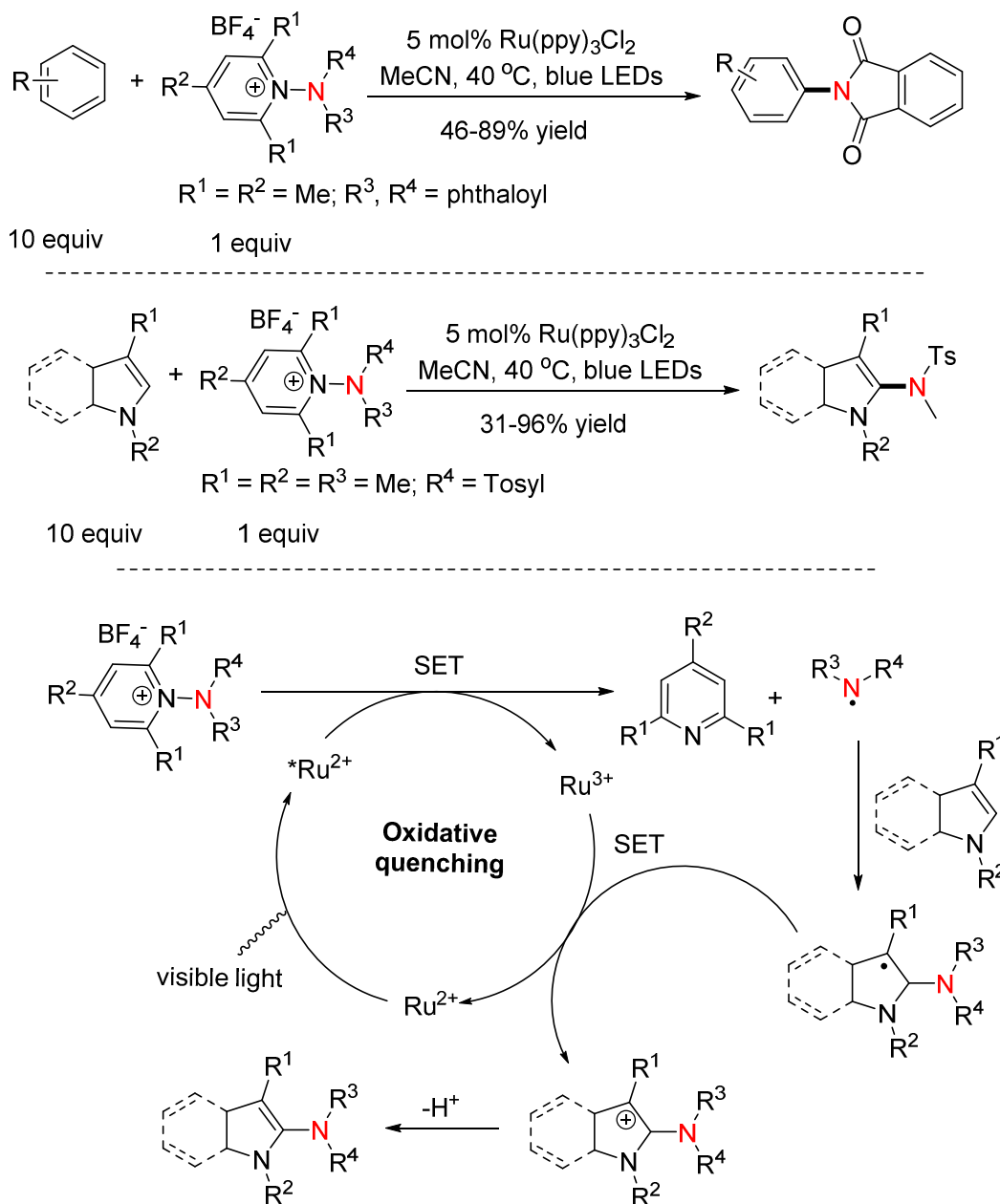
Scheme 1.2.1.3. Direct C-H Amidation of (Hetero)Arenes with N-Aminopyridinium Salts

Owing to their easy preparation and high stability, N–halo compounds, especially N–Cl bonds, have also been often used as precursors to generate N-radicals. In 2014, Lee's group reported an exciting visible light-promoted sp^2 C–H imidation of arenes and heteroarenes using *N*-chlorophthalimide as N-radical precursor, without the requirement of any site-directing group (**Scheme 1.2.1.4**).[82] Oxidative quenching of photoexcited Ir^{3+}* complex by *N*-chlorophthalimide produced the N-centered radical, which undergoes a radical addition/oxidation/aromatization sequence with the arene to deliver the amination products in moderate to good yields, albeit with moderate chemoselectivity. A high functional group tolerance and a broad substrate scope were observed. Additionally, unlike the classical electrophilic amination of arenes, both electron-rich and electron-deficient arenes underwent the imidation to give the desired products. In an analogous reaction by the Xue group, the amination of benzoxazoles was achieved in a photoredox catalytic two-step, one-pot reaction in which various cyclic and acyclic secondary amines were used directly as N-radical precursors, being initially transformed into an N-Cl compound with stoichiometric *N*-chlorosuccinamide.[83] For Xue's reaction, a Ph$_3$N-mediated reductive quenching cycle was proposed in contrast to Lee's work.
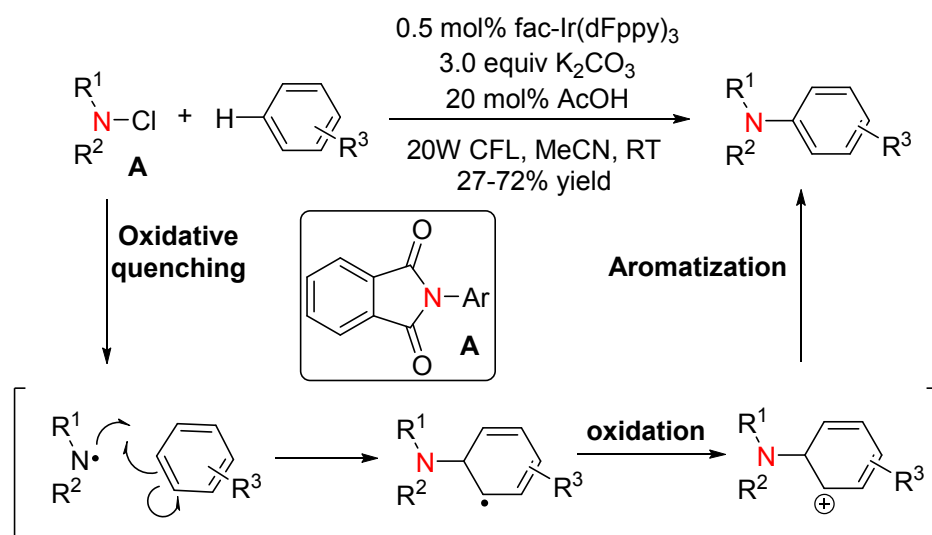
Scheme 1.2.1.4. Photocatalyzed Amination of (Hetero)Arenes with N-chlorophthalimide

33

Although significant advances have been achieved in the development of visible-light-catalyzed $C(sp^2)$–H amination/amidation reactions, the analogous reaction involving inert $C(sp^3)$–H bonds has remained underdeveloped. Yu and coworkers reported in 2015 a photoredox-catalyzed Hofmann–Löffler–Freytag (HLF) reaction[88] of *N*-chlorosulfonamides at room temperature under weakly basic conditions yielding variously functionalized oxazolidines, pyrrolidines, and cyclic benzosulfonamides in good yields (**Scheme 1.2.1.5**).[87] Interestingly, when a lower photocatalyst loading was used, the yield increased substantially and the amount of dechlorination by-product decreased. Also, when the NaOH(s) was excluded from the conditions, the initially chlorinated products could still be isolated in good yields (**Scheme 1.2.1.5**b), thus suggesting that such chlorination products might be the key intermediates in the cyclization reaction.

Based on TEMPO trapping and radical clock experiments it was proposed that the *N*-chlorosulfonamide first quenches the photoexcited Ir^{3+*} oxidatively to generate the N-radical intermediate and an oxidizing Ir^{4+} species. Then, an intramolecular hydrogen atom transfer (HAT) by the intermediate produces a C-centered radical which is oxidized by Ir^{4+} to a cation (path A). The cation can be quickly trapped by chloride ion to produce the chlorination products which, upon subsequent addition of NaOH, are further transformed into the cyclic products. The radical chain propagation pathway is also possible for the formation of the acyclic chlorination product directly from C-radical intermediate (path B).[89]
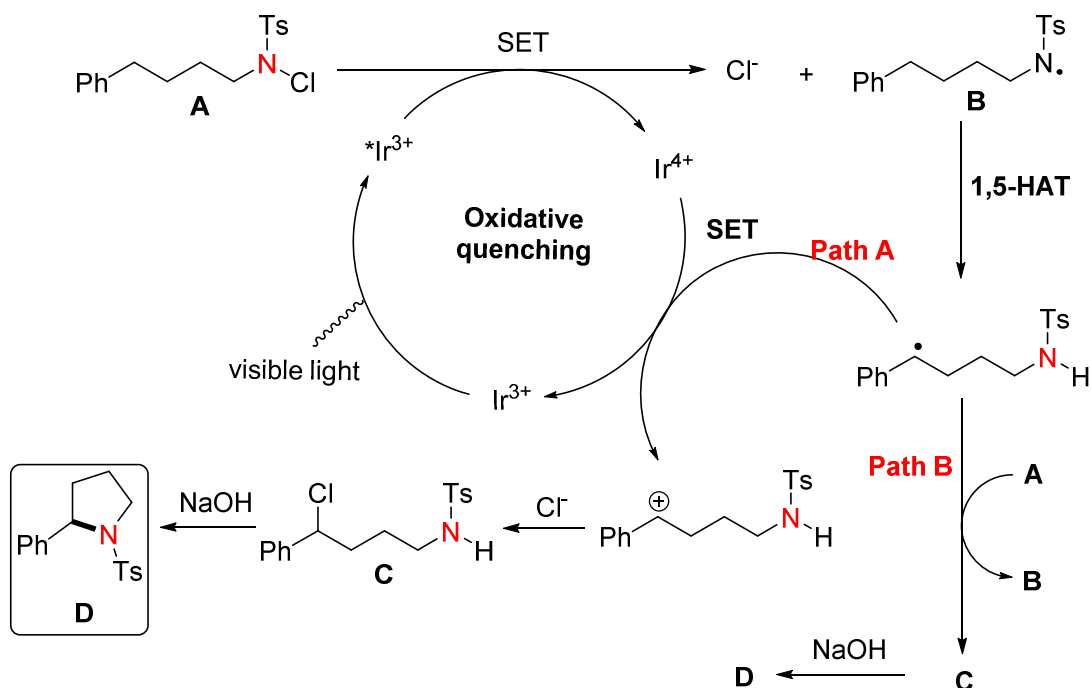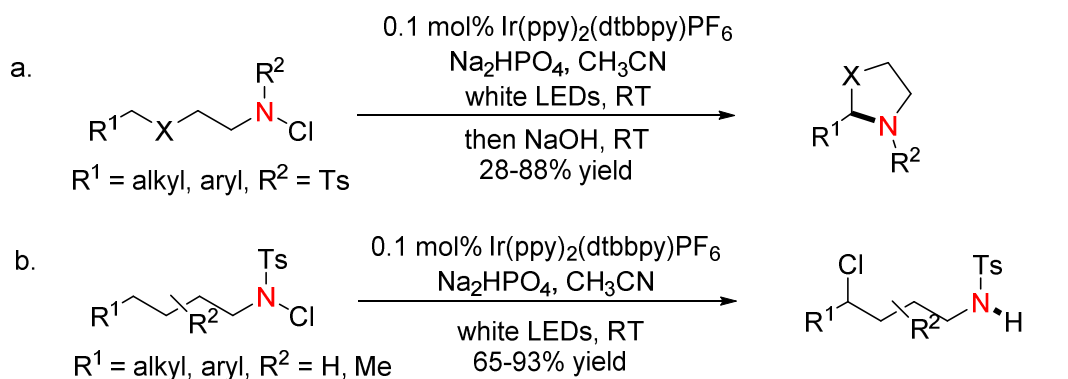
Scheme 1.2.1.5. Photocatalyzed C(sp³)-H Amidation and Chlorination of N-Chlorosulfonamides

A quick SciFinder search will reveal numerous examples of the visible light photoredox-catalyzed reductive approach for N-radical generation from cleavage of weak N-O, N-S, N-N, and N-halo bonds, as well as several reviews detailing the remarkable advances that have been achieved in this area. The oxidative generation of these valuable intermediates under photoredox conditions had however received very little attention generally until recently.[90] The direct

generation of NCRs from amides and sulfonamides by hydrogen atom transfer (HAT) is impossible due to the strength of their N-H bond, hence the development of mild methods for this process is an appealing challenge to the organic chemist. Although pioneering works on direct N-radical generation from N–H bonds by the research groups of Nicolaou,[91] Han,[92] Chiba,[93] Lei,[94] and Li[95] were all achieved by using strong stoichiometric oxidants, these works inspired the first visible-light-induced conversion of N–H bond into N-centered radical that was published by Xiao, Chen, and co-workers in 2014. In that work, the N–H bonds of β,γ-unsaturated hydrazones were converted into N-centered radicals by blue light irradiation at room temperature using $Ru(bpy)_3Cl_2.6H_2O$ as photocatalyst and allowed for the effective intramolecular addition of hydrazonyl radicals to the terminal alkenes to give hydroamination products in good yields.[96] A series of control experiments involving radical trapping, deuterium-labeling, and Stern-Volmer quenching studies suggested that the N-radical generation under the basic conditions occurred through an initial deprotonation of the β,γ-unsaturated hydrazone to an anionic intermediate followed by SET oxidation of the intermediate to the N-radical by the photoexcited Ru^{2+*} complex.

Shortly thereafter, the Knowles group revealed a proton-coupled electron transfer (PCET) strategy for activation of the strong N–H bonds in amides.[97] The strategy involves the cooperative action of a single-electron oxidant (such as the excited state of a photocatalyst) and an appropriate weak base for the homolytic scission of strong amide N–H bonds to generate amidyl radicals, without the need for strong stoichiometric oxidants (**Scheme 1.2.1.6**).
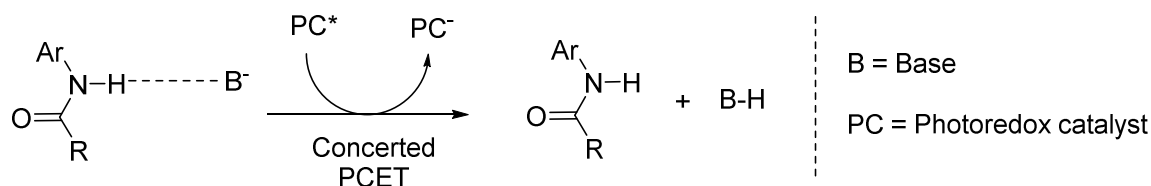
Scheme 1.2.1.6. Amidyl Radical Generation via PCET

The Brønsted base was found to be crucial for the PCET process by adjusting the oxidation potential of *N*-aryl amides through a H-bond interaction, and they successfully generated N-radicals from amides, ureas, carbamates, and thiocarbamates for the carboamidation of unactivated alkenes (**Scheme 1.2.1.7**). NBu$_4$OP(O)(OBu)$_2$, which is a weak phosphate base, was found to be superior to DMAP, lutidine, or NBu$_4$OBz in the PCET-involved transformation. They achieved the amidyl radical-mediated carboamination of various olefin-containing amides to afford the corresponding heterocycles in good yields. Thus, this dual catalytic strategy provides a new avenue for the direct activation of strong amido N–H bonds. Following shortly on this work, the Knowles group applied the PCET strategy to the hydroamination of alkenes by employing thiophenol as polarity-reversal catalyst, acting as H-atom donor.[98]
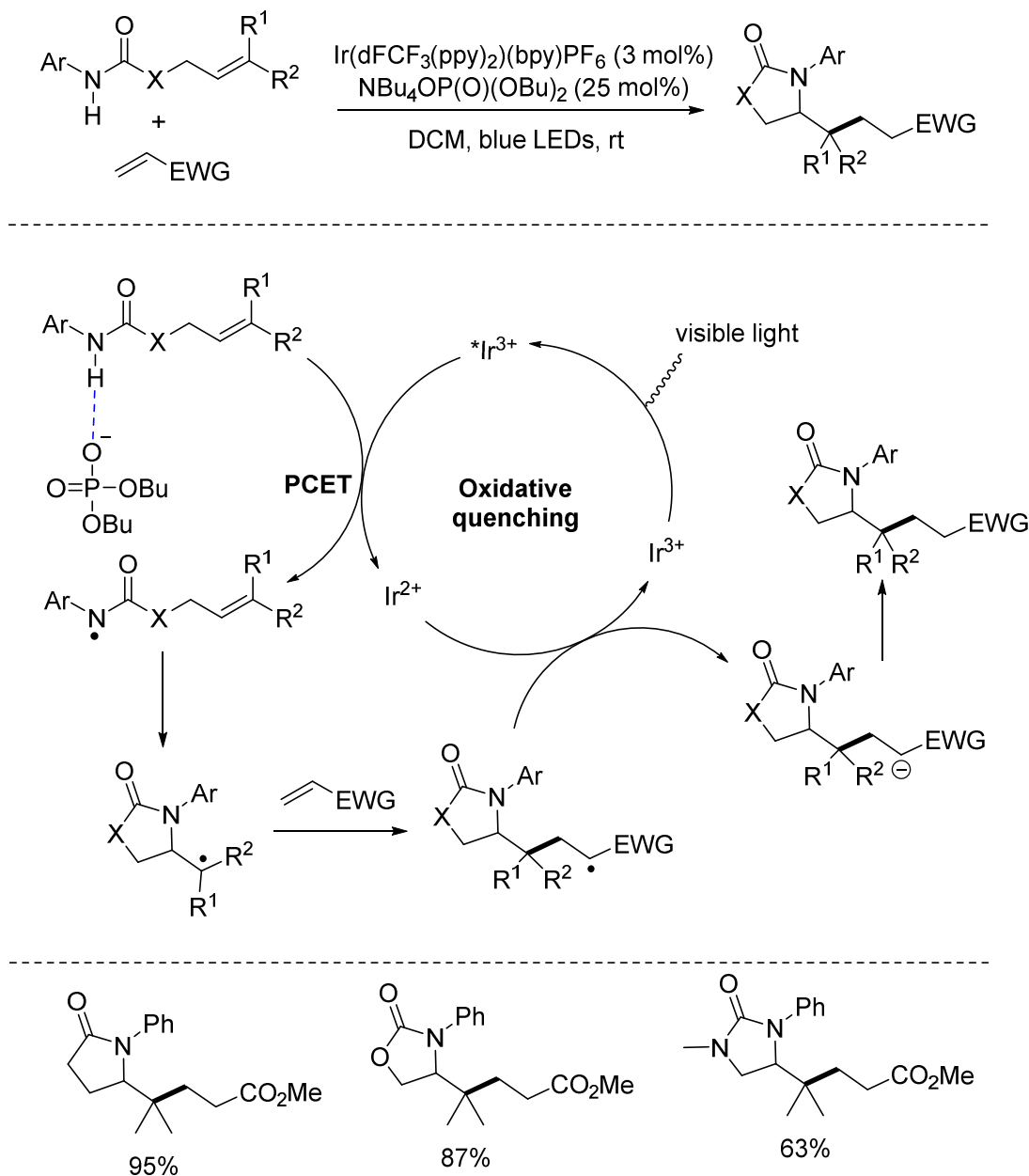
Scheme 1.2.1.7. Carboamidation of Alkenes by PCET

1.2.2. Amine Radical Cations

Amine radical cations (ARCs) (or aminium radical cations) are N-centered radical ions that bear both an unpaired electron and a positive charge on the same nitrogen atom. Though

closely related to the neutral amine radicals (or aminyl radicals), they are however more electrophilic due to their positive charge. Hence, they have been extensively employed as electrophilic aminating species for C−N bond-forming processes with alkenes and arenes. As odd-electron species, amine radicals have been shown to exhibit some unique reactivities that cannot be attained by closed-shell nitrogen species and neutral amine radicals. The Hofmann-Löffler-Fregtag reaction[88, 99] in which an amine radical cation abstracts a hydrogen atom from the δ position via 1,5-hydrogen atom shift to enable remote halogenation at the δ position is one classical synthetic method that involves amine radical cations. Furthermore, ARCs are highly valuable reactive intermediates in amine synthesis.[71, 100, 101]

Traditionally, amine radical cations are produced by homolytic or reductive cleavage of the N-X bond in *N*-haloamines, *N*-haloamides, and hydroxylamine derivatives in the presence of a Brønsted acid or a Lewis acid. However, *N*-nitrosamines, *N*-nitroamines, and 2-tetrazenes have also been identified to undergo bond homolysis leading to the generation of aminium radical cations.[100] The cleavage reaction of the precursors can be achieved by photolytic or thermal conditions, or by treating with a suitable reducing metal salt. Alternatively, amine radical cations can be directly produced via one-electron oxidation of the unfunctionalized parent amines using a suitable chemical or electrochemical oxidant. The latter approach, however, is attended with the problem of electrolytic dealkylations after the anodic oxidation, by the hydrolysis of either the enamine produced in a single-electron process, or hydrolysis of the iminium salt generated in a two-electron process.[102] Finally, ARCs can be generated via single-electron oxidation of a parent amine by the electronic excited states of a photocatalyst or a photosensitized molecule. Recently, the latter method, mediated by visible light, has become an attractive and convenient avenue for accessing and transforming these important reactive intermediates in organic synthesis due to its

"green" characteristics and unique ability to promote unconventional chemical bond formations.[103, 104] Under visible light photocatalysis, ARCs can be generated from amines when they are employed as sacrificial electron donors to quench the photoexcited state of the photocatalyst in the reductive quenching cycle. Ingeniously, Zheng and coworkers, have explored the practicality of using the photogenerated amine radical cation as a useful electrophilic source in synthesis rather than merely as a sacrificial reductant and have reported their successes in achieving the synthesis of various carbocycles and heterocycles by this strategy in a number of publications.[16, 18, 19, 21, 105-110]

Once formed, the amine radical cation can assume either of five modes of reactivity as depicted in **Scheme 1.2.2.1**. The first mode (Path A) is a major side reaction that competes against the other productive downstream reactions, and it involves the radical cation back-donating an electron to the reduced photocatalyst M($n-1$). Either of two approaches, or a combination, can be used to avoid this side reaction: (1) the modification of the structure of the ligand on photocatalyst metal center M to inhibit the back electron transfer, and (2) the design of faster and/or irreversible downstream reactions of the radical cation to obstruct the electron back-donation.[111, 112] The second mode (Path C) involves the abstraction of a hydrogen atom from the aminium radical cation to produce iminium ion, in the presence of a good hydrogen atom acceptor in the reaction. The ability of amine radical cations to act as a source of hydrogen radical has been applied to achieve visible light-mediated reductions such as reductive dehalogenation[61, 113, 114], reductive radical cyclization[64], as well as reduction of activated ketones,[114] of aromatic azides.[63]

The third mode (Path B) involves the α-deprotonation of the amine radical cation to form an α-amino radical, which can be converted to the iminium ion by another single-electron

oxidation. The second one-electron oxidation is facile due to the strongly reducing character of the α-Amino radical.[112, 115] Furthermore, the ARC may undergo C–C bond cleavage α to the nitrogen atom in a fourth mode (Path D), to yield a neutral free radical and an iminium ion. Due to it being an excellent electrophile, whenever an iminium ion is generated in any mode, it can be intercepted by various nucleophiles to directly create a new bond at the position α to the nitrogen atom. On the other hand, the α-amino radical is nucleophilic, and could add to electron-deficient alkenes to form a C–C bond, also at the α position of the nitrogen atom. Finally, the amine radical cation can directly add to electron-rich olefins and arenes to form a C–N bond (Path E).
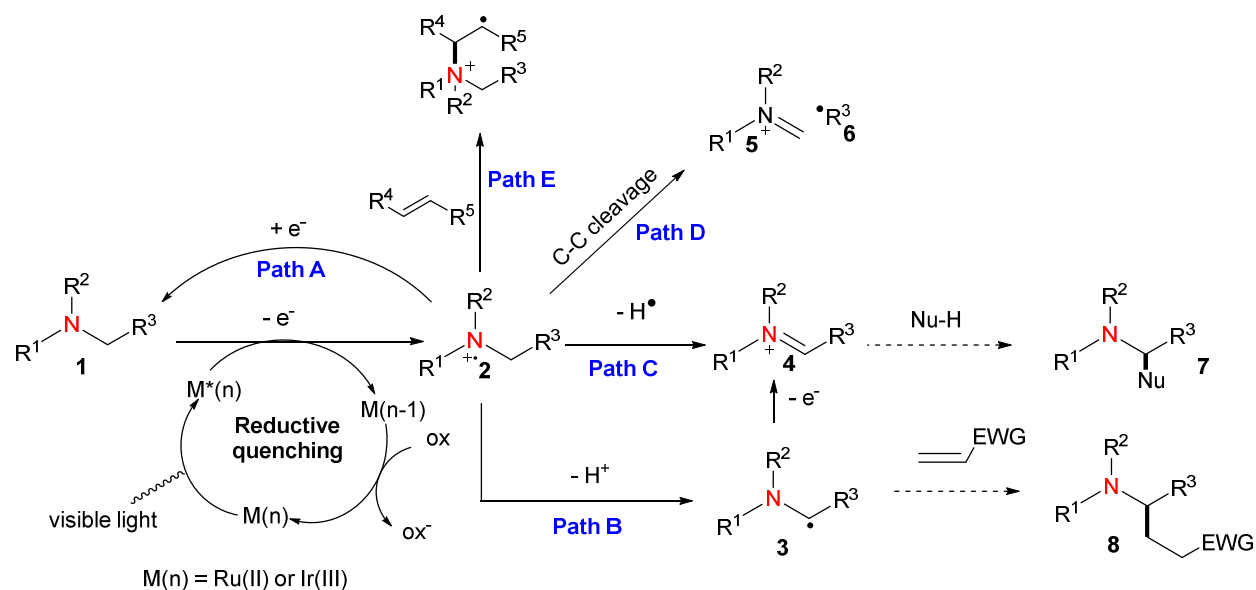
Scheme 1.2.2.1. Mode of Reactivity of Amine Radical Cation

Transformations involving the first two of the productive reaction modes of ARCs (Paths B and C in **Scheme 1.2.2.1**) have recently been reviewed by MacMillan,[7] Xia,[103] Zheng,[116] Lei,[117] and Knowles[118]; and reactions involving the last two modes have been reviewed by Xiao.[119] In addition to the above reactivity modes, photogenerated ARCs of certain amine substrates such DABCO and quinuclidine, whose bridged architecture diminishes their rate of α-deprotonation

(Path B), are known to be useful catalytic mediators of C–H bond abstraction via intermolecular HAT.[120]

1.3. Amine Distonic Radical Cations (ADRC)

In contrast to conventional or classical radical cations, such as amine (aminium) radical cations discussed in the previous section, in which both the radical and the charge are located on the same atom, the charge and radical sites of their isomeric distonic radical cations are not co-localized on the same atomic center but are formally separated.[121, 122] The term "distonic radical cation" was coined by Yates, Bouma, and Radom in 1984 to describe radical ions that can be formed conceptually by the ionization of a zwitterion, a diradical, or a ylide.[121, 123]

Distonic radical cations (DRCs) can be categorized as alpha-, beta-, or gamma-DRCs based on the separation of their charge and radical centers by 0, 1, or 2 atoms, respectively. The α-DRCs, with charge and radical sites on adjacent atoms, are given the special name "ylidion". Structure wise, conventional radical cations possess atom connectivity similar to their parent neutral precursors whereas their distonic counterparts have the atoms of the neutral precursor rearranged into a new structure. Theoretical and experimental results[121, 122, 124] indicate that distonic radical cations, with their spatially separated charge and odd spin sites, are both thermodynamically and kinetically more stable than their isomeric classical forms. This has been attributed to possible long-range stabilizing interaction between the radical and charge sites.[122, 125-127] Generally, due to this spatial and electronic separation of the two sites, they tend to react independently.[126] Some distonic radical cations have been found also to react as bidentate species, i.e., as radicals with inert charge site, or ions with inert radical site, or even both.[128] Hence, DRCs have great synthetic

utility as they can react orthogonally with a nucleophile and radical acceptor at their distinct cationic and radical sites respectively to achieve difunctionalization along their backbone.

Professor Kenttämaa's group have established laboratory approaches to successfully characterize the reactions of DRC species generated in gas phase and distinguish them from their conventional isomers based on their characteristic reactivity with dimethyl disulfide[129], dimethyl diselenide[130], or *tert*-butyl isocyanide[131] in comparison with the reactivity pattern of conventional radical cations toward the same reagents. DRCs (except acidic ones) have been demonstrated to generally react with the first two reagents principally by $CH_3S\bullet$ and $CH_3Se\bullet$ interception respectively at their radical site, in sharp contrast to conventional radical cations which either react by energy transfer or remain unreactive towards them. On the other hand, the behavior of various DRCs towards *tert*-butyl isocyanide, a reagent that can function as a radical acceptor or a nucleophile, illustrates the dual reactivity of DRCs due to their cationic and radical sites, and the potential to tune their dichotomous reactivity through structural modifications for site-selective functionalization. *Tert*-butyl isocyanide was found to react with DRCs preferentially at the electrophilic charge site by a barrierless addition-elimination mechanism involving cyanide-ion transfer (**Scheme 1.3.1**a), by proton transfer, or a by combination (**Scheme 1.3.1**d), depending on the acidity of the cationic site. Cyano-radical transfer to the radical site of DRC is observed only if the charge site of the ion is inert such as in cases of low acidity or coordinative saturation of the charge site (**Scheme 1.3.1**b,c). Reactions at the radical site cannot compete effectively with reactions at the charge site. Thus, cyano-radical abstraction indicates that the charge site is unreactive. An example of a DRC that can undergo a combination of cyanide ion abstraction and proton transfer with *tert*-butyl isocyanide is the distonic cation of methyl formate ion (**Scheme 1.3.1**d), having a highly acidic unsaturated charge site. Consequently, the different reactivities of

various DRCs with *tert*-butyl isocyanide provide a good assessment of the chemical inertness of distonic ions' charge sites.
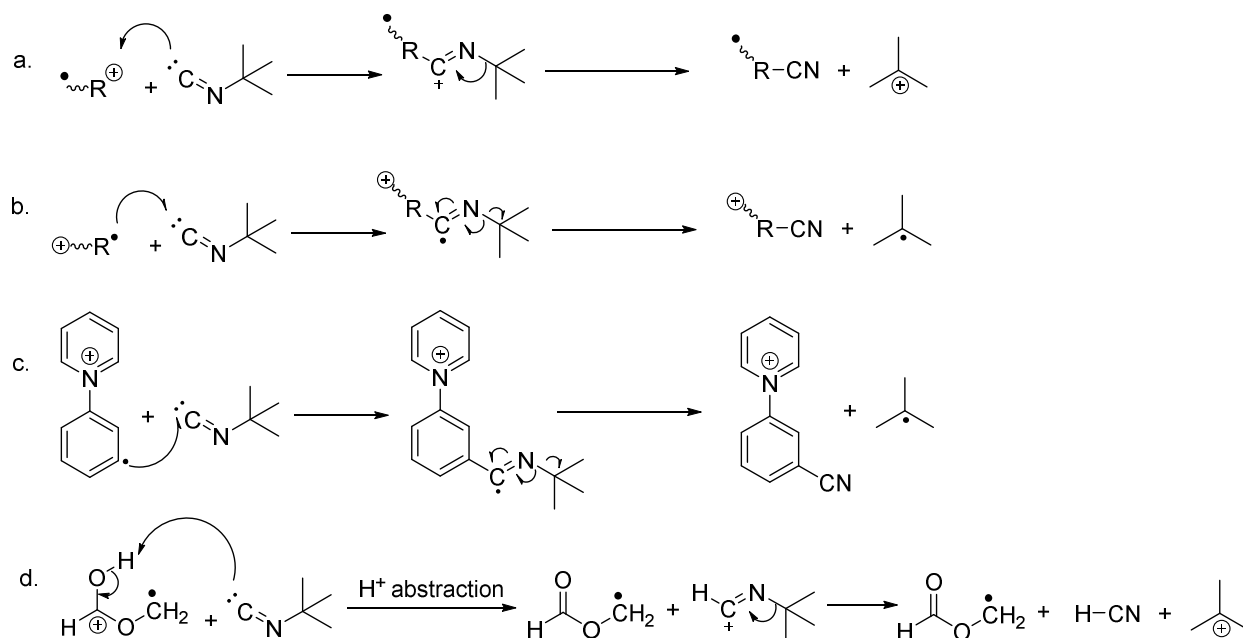
Scheme 1.3.1. Reactivity of Distonic Radical Cation with Tert-Butyl Isocyanide

Curiously, despite the great synthetic potential, at least conceptually, in exploiting amine distonic radical cations (ADRCs) as reactive intermediates for accessing some sought-after N-containing compounds, no characterization of these species, even in gas phase, using any of the reagents discussed above, or others, has been reported in literature as of this writing, to the best of our knowledge. In the studies by the Kenttämaa group, the reactivities of gas-phase-generated conventional radical cations of trimethylamine, aniline, *N-N*-dimethylaniline, and piperidine with $CH_3SeSeCH_3$ were investigated and these species were found to exhibit no reactivity at all, or, in the case of piperidine, to undergo electron transfer with the reagent.[130] However, the reactivities of their distonic radical cationic forms with the reagents were not ascertained, and gaps still remain

thus in our understanding of the reactivity, in biomolecular reactions, of ADRCs generated from ionized neutral amines. The question of whether ADRCs will behave like normal radicals with inert cationic site (e.g. $(CH_3)_2S^+\text{-}CH_2^{\bullet}$ or the distonic radical cation in Scheme 1.5.1c) or will display a preferential reactivity at either of its sites in reactions with certain neutral reagents remains unanswered. An understanding of this will be beneficial for the design of syntheses in which ADRCs are exploited.

In 1986, Williams et al disclosed with ESR evidence (**Scheme 1.3.2**)[132] that the ADRC of cyclopropylamine, generated radiolytically in Freon matrices (e.g. $CFCl_3$ and CF_3CCl_3), exists as the distonic iminium radical **2**, formed *via* a ring opening of the aminium radical cation **1**. The ADRC cannot not be converted by an intramolecular [1,4]-HAT process to the iminyl radical cation **3** but can undergo deprotonation to the imine **5** en route to iminyl radical **6** via a [1,4]-HAT; or it can undergo an intermolecular abstraction from the neutral cyclopylamine precursor. This work establishes the stabilization of the carbon-centered radical by the protonated imine moiety due to the ADRC showing no tendency to isomerize to the iminyl radical cation **3** whiles its conjugate base **5** can readily convert to the nitrogen-centered radical **6**. This ADRC of cyclopropylamines has been implicated as the key reaction intermediates in certain solution-phase transformations of amines by research groups like Zheng's,[17, 105, 108-110, 133-136] Waser's,[137-139] Cha's,[140] Iwata's,[141] and Stephenson's,[142] based on circumstantial evidences from the observed reactivity and reaction products or side products, and have been proposed in the reaction mechanisms.
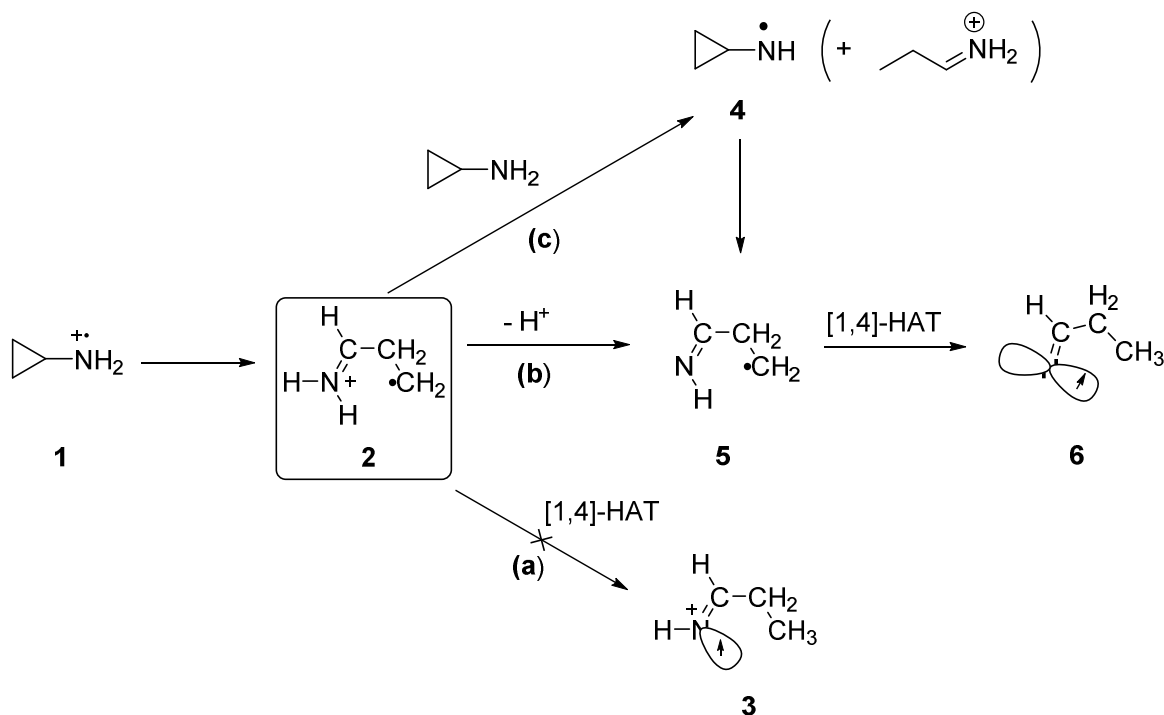
Scheme 1.3.2. Unimolecular Reactivity of the Distonic Radical Cation of Cyclopropylamine

Despite the apparent synthetic value of various distonic radical cations, including amine distonic radical cations (ADRC), and their acceptance as stable, common gas-phase species, the development of methods for their generation and exploitation in solution-phase organic synthesis had until recently been unexplored. The knowledge of their chemical properties was essentially based on the unimolecular reactions of internally excited ions in gas phase, and the several bimolecular reactions of distonic ions that had been examined and published were aimed at structural characterization of the ions rather than investigation of their chemical properties. The available literature on amine distonic radical cations (ADRCs) include several studies[122, 127, 132, 143] in which various α-, β-, and γ-ADRCs have been successfully generated (or modeled *ab initio*) in gas phase and investigated as to their characteristic reactions and fragmentation pathways by the classical routes used for accessing distonic ions, the earliest examples of which are shown in

Scheme 1.3.3. Following ionization of their neutral precursor species by methods like ESI-MS, CAD, ICR, or anodic oxidation, the distonic radical cation species could readily be generated *via* a ring-opening or a [1,n]-shift of a hydrogen or a small substituent. The DRCs can be identified and characterized by ESR spectrometry.

Ion-molecule reactions   **(Gross and McLafferty, 1971)**

$$\triangle^{+\bullet} + NH_3 \longrightarrow {}^{\bullet}CH_2CH_2CH2\overset{\oplus}{N}H_3 \longrightarrow {}^{\bullet}CH_2\overset{\oplus}{N}H_3 \quad (1)$$

1   **2**

Rearrangement-fragmentation   **(Morton and Beauchamp, 1975)**

$$CH_3OCH_2CH_2OH\overset{+\bullet}{C}H2 \longrightarrow CH_3\overset{\oplus}{O}\overset{\bullet}{C}CH_2 + CH_2O \quad (2)$$

3

Ring opening
Ring cleavage   **Corderman et al., 1976)**
                                                                      (Bouma et al., 1978)

$$\overset{O^{+\bullet}}{\triangle} \longrightarrow H_2C{=}\overset{\oplus}{O}{-}\overset{\bullet}{C}H_2 \longrightarrow \quad (3)$$

4
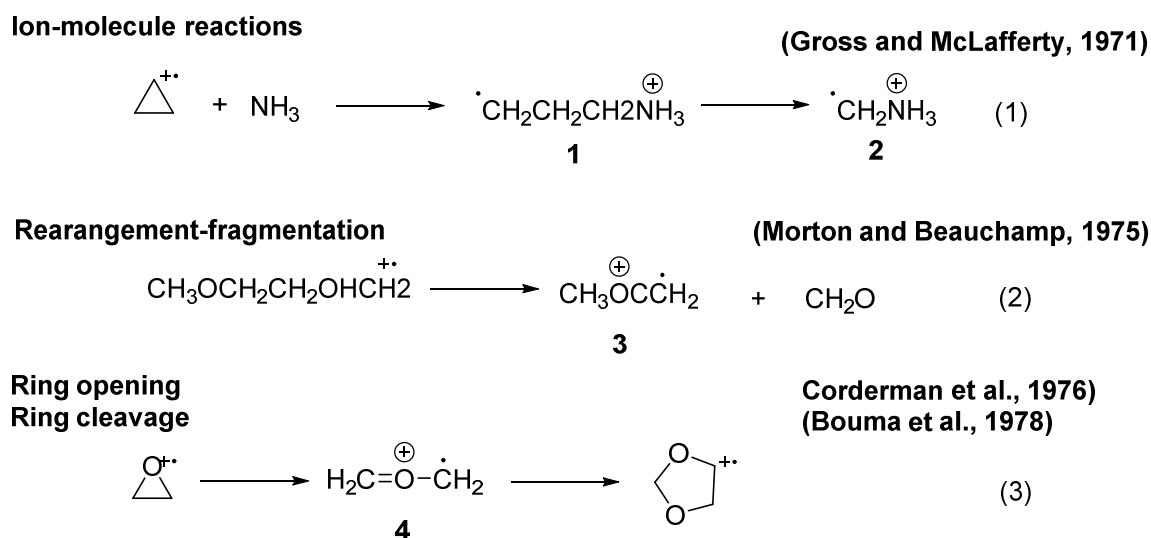
Scheme 1.3.3. Some Early Routes to Various Distonic Radical Cations

In recent times, amine distonic radical cations (ADRCs) have been effectively generated by visible light photoredox catalysis in solution-phase and exploited for the synthesis of interesting N-containing compounds. A common strategy (**Scheme 1.3.4**) is to employ strained small-sized cyloalkylamines, particularly cyclopropylamines and cyclobutylamines, which can undergo photoinduced (single) electron transfer (PET) oxidation to the amine radical cation (ARC), and subsequent strain-releasing ring opening to an amine distonic radical cation (ADRC). This ADRC can then be further functionalized either at the cationic site by addition of a nucleophile, or the radical site (by interception of a radical acceptor), or at both sites (by reaction with both a nucleophile and radical acceptor) to produce mono- and/or di-functionalized products. In the case of cyclobutylamines which is known to undergo a reluctant and potentially reversible ring-opening

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due to having a lesser ring strain, the initial installation of either the nucleophile or radical acceptor

to the distonic radical cation can also serve to facilitate the ring-opening event by inhibiting the

reverse ring-closing to the amine radical cation.
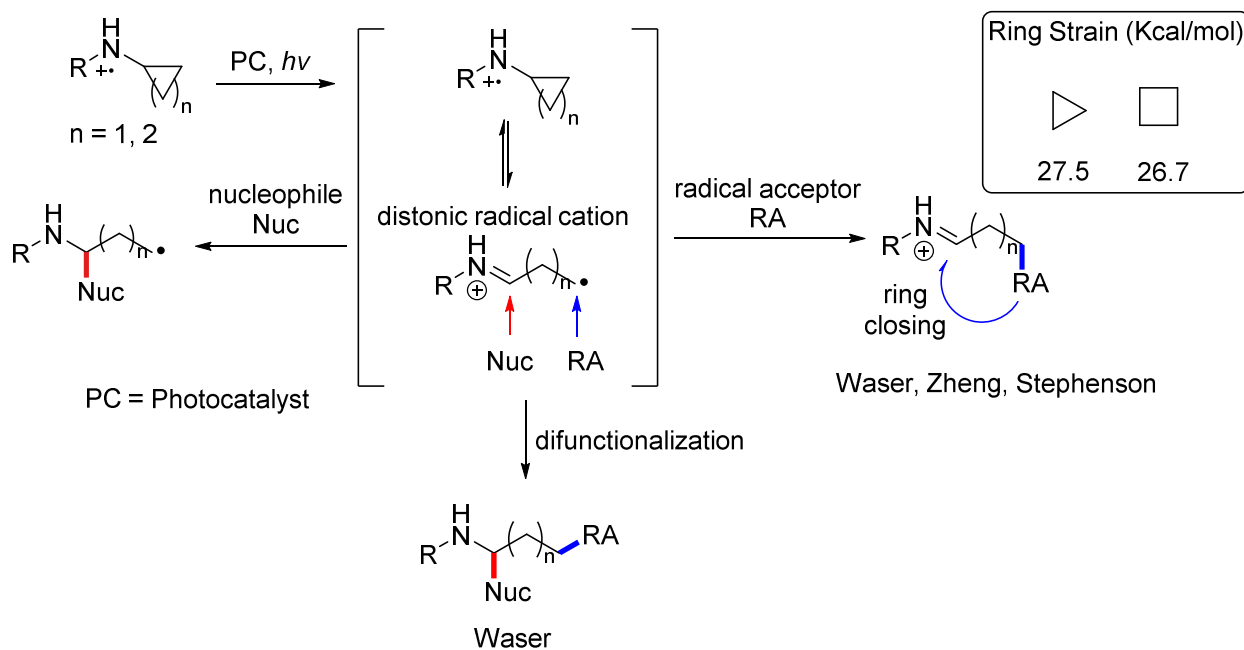
Scheme 1.3.4. Strategies for Functionalizing Photogenerated Amine Distonic Radical Cation

Examples in which this strategy is applied include works by the Zheng's group (**Scheme 1.3.5**) in 2012[16] and 2014[134, 135] involving the [3+2] annulations of cyclopropylanilines with pi bonds, and the analogous [4+2] annulations of cyclobutylanilines with alkynes by the same group in 2015[136] and 2017.[110] In a 2020 collaborative work with the Hao group, they also reported a redox neutral intermolecular [3 + 2] annulation of *N*-cyclopropylanilines and alkenes *via* direct electrolysis in which amine radical cation which underwent the ring-opening was generated in a home-built electrochemistry/mass spectrometry (EC/MS) platform.[144] In the both [3+2] and [4+2] annulation reactions, only one pi bond of alkenes, alkynes, dienes, enynes, or diynes reacts with

both the radical and the cation moiety of the distonic radical cations sequentially to produce an aniline-substituted five-membered and six-membered carbocycle respectively. In addition, the amine played a dual role in these reactions, serving as both an electron donor to reduce the photocatalyst's excited state as well as the neutral substrate from which the amine radical cation is generated by SET oxidation. Although the [4+2] annulation reaction displayed similar scopes with respect to pi bonds as the [3+2] annulations, strongly suggesting that similar reactive intermediate in the two processes—viz, the distonic radical cation—the ring opening process of cyclobutylanilines was found to be slower than that of cyclopropylanilines. Hence, while the latter transformation could be achieved at 23 °C with an optimal catalyst of Ru(bpz)$_3$PF$_6$ in CH$_3$NO$_2$, the slower [4+2] required a higher temperature (50 °C) as well as a different catalyst system comprising Ir(dtbbpy)(ppy)$_2$PF$_6$ in CH$_3$OH. The reaction mechanism of the Zheng's [3+2] annulations has already been discussed using the **Scheme 1.1.3.4**; and the [4+2] equivalent was predicted to proceed by a similar mechanism.
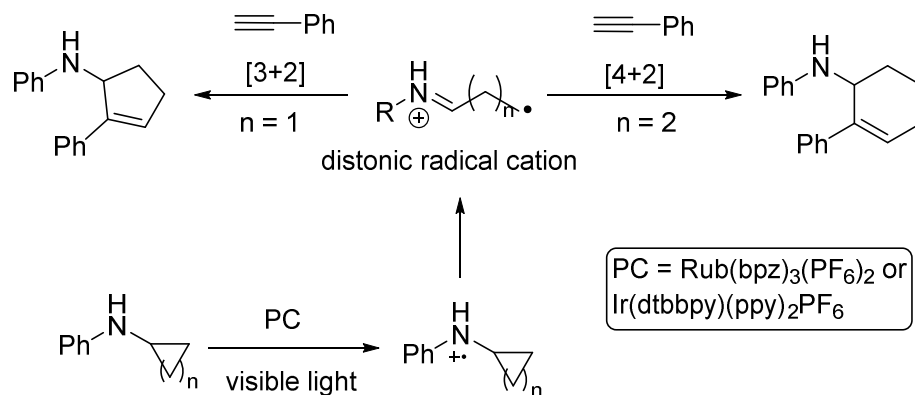
Scheme 1.3.5. Prof. Zheng's [3+2] and [4+2] Annulations of Cycloalkylanilines

In 2018, Wang and coworkers reported a variation of this [3+2] cyclization of arylaminocyclopropanes with alkene derivatives using a dirhodium(II) catalyst which was found

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in mechanistic study to activate the N-H bond of the aminocyclopane substrate by decreasing its bond-dissociation energy (BDE).[145] Also, the Waser group developed in 2019 a variant of the [3+2] strategy by employing cyclopropenes as the radical acceptor,[139] and Stephenson and coworkers later employed a similar strategy to access the medicinally important 1-aminonorbornanes from cleverly designed aminocyclopropanes.[142] In the latter work, they proposed a redox-neutral catalytic cycle to account for the transformation (**Scheme 1.3.6**). A single-electron oxidation of the 1-homoallyl-1-aminocyclopropane by the excited state of the photocatalyst (Ir^{3+}*) generates the amine radical cation, which undergoes a facile β-scission to generate a β-iminium radical, an amine distonic radical cation (ADRC). A subsequent cascade of 6-exo-trig and 5-exo-trig cyclizations produces the radical cation of the product. Reduction of this ARC by reduced state of the photoredox catalyst (Ir^{2+}) yields the final product and regenerates the ground-state photocatalyst (Ir^{3+}). This overall formal [3+2] cycloadditions depict the unique capabilities of amine radical cations located next to a highly strained carbocycle to undergo ring-opening *via* β-scission and react with a π-containing molecule in both inter- and intramolecular fashion.
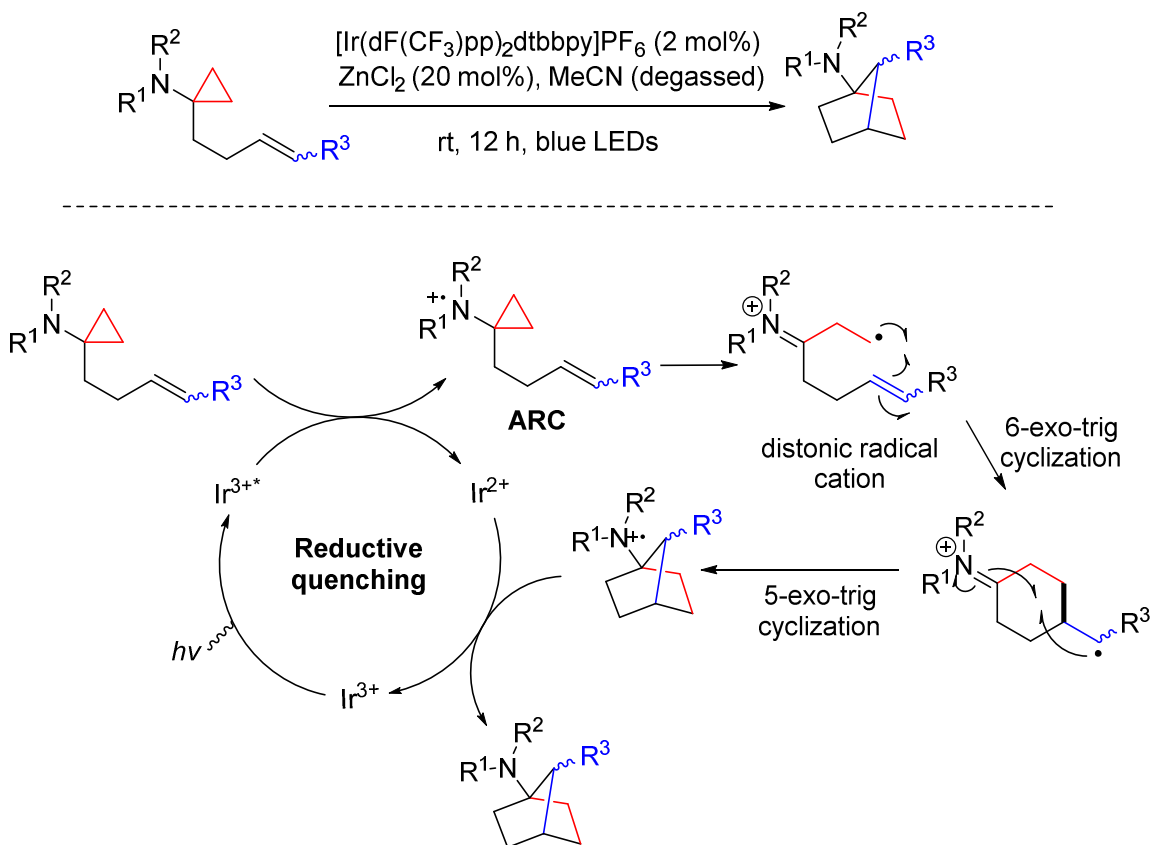
Scheme 1.3.6. Stephenson's 1-Aminonorbanane Synthesis

As already mentioned, ADRCs generated by visible-light PET oxidation have also been exploited to realize the difunctionalization of their strained cycloalkylamine precursors via a ring-opening strategy. A good illustrative example is the 2020 work by the Waser group involving the oxidative fluorination of cylopropylamides and cylobutylamides (i.e N-acylated cyclopropyl- and cyclobutylamines) into fluorinated imines using Selectfluor as both oxidant and fluorination reagent (**Scheme 1.3.7**).[137] The imines were isolated in their more stable hemiaminal form, with selectively installed fluorine atom at the distal γ- or δ-position for the cyclopropylamide or cyclobutylamide substrates respectively. Nucleophilic attack on the hemiaminal moiety using various nucleophiles gives a wide range of fluorinated amines in one pot which are useful building blocks in medicinal chemistry. Due to their high redox potentials, a highly oxidizing excited

photocatalyst was required activate the amide substrates. The authors reported that the reaction could be promoted using either inexpensive benzophenone as the photoredox catalyst with UVA light (365 nm) or organic and inorganic dyes with blue light.
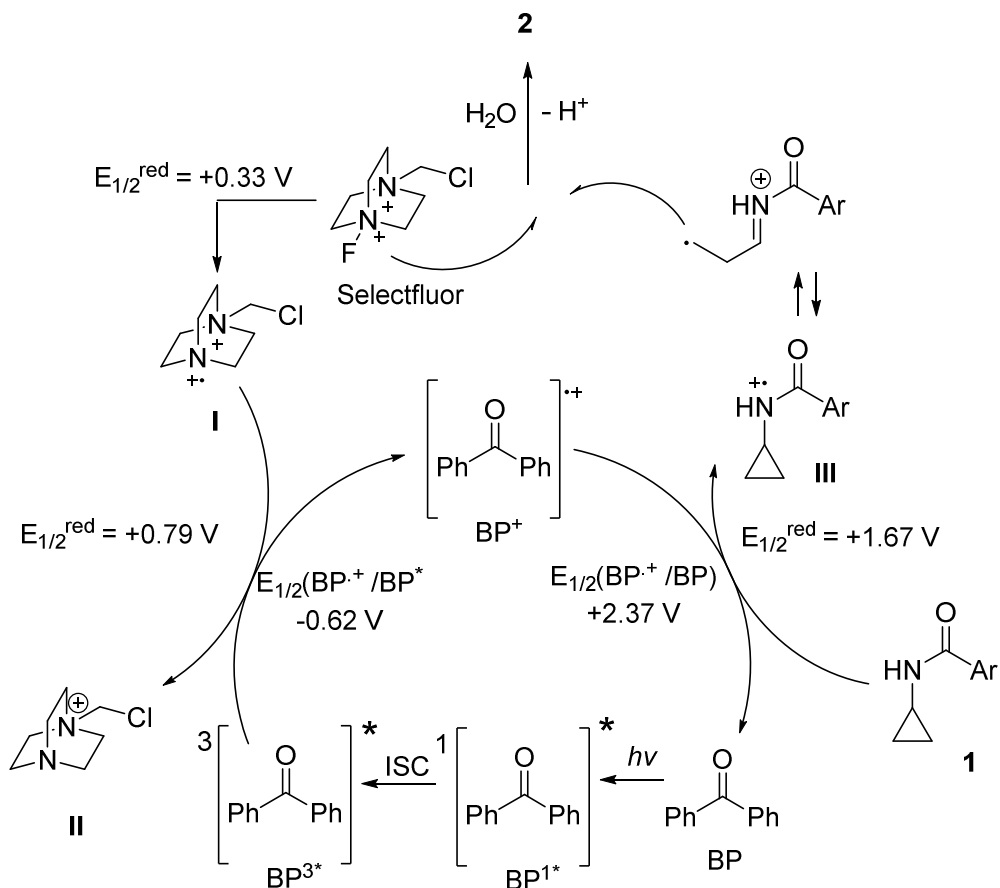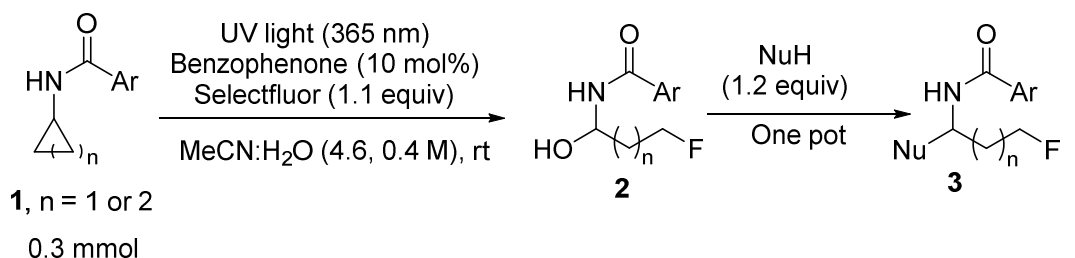
Scheme 1.3.7. Waser's Oxidative Fluorination of Strained Cycloalkylamides

The proposed speculative mechanism for the oxidative fluorination is shown in **Scheme 1.3.7**. Based on the reduction potentials of cyclopropylamide **1** ($E_{1/2}^{red}$=+1.67 V), it cannot be oxidized by Selectfluor ($E_{1/2}^{red}$= +0.33 V) or the triplet-state benzophenone ($E_{1/2}$ BP* /BP⁻= +1.27 V) (BP^{3*}). However, Selectfluor or its radical cation (**I**, $E_{1/2}^{red}$=+0.79 V) can oxidize the benzophenone triplet-state (BP^{3*}, $E_{1/2}$ BP$^+$ /BP^{3*}=−0.62 V) to the benzophenone radical cation BP$^+$, which is sufficiently oxidizing to convert the cyclopropylamide into radical cation intermediate **III** ($E_{1/2}$ BP$^+$ /BP =+2.37 V). A similar catalytic cycle could be proposed when [Ir(dF-CF$_3$ppy)$_2$(dtbbpy)]PF$_6$ is used instead as the photocatalyst, considering its redox properties ($E_{1/2}$ Ir^{3+*} /Ir^{2+}=+1.21 V, $E_{1/2}$ Ir^{3+} /Ir^{4+}=−0.89 V and $E_{1/2}$ Ir^{4+} /Ir^{3+} = +1.69 V). But for the more strongly oxidizing dye Mes-Acr$^+$ ($E_{1/2}^{red}$=+2.06 V), another mechanism may be operative if it is employed. Following the SET oxidation, the generated cyclopropylamide radical cation intermediate **III** undergoes ring-opening to its distonic radical form **IV**, which upon radical fluorination with Selectfluor and nucleophilic addition of water to the iminium site furnishes the initial fluorinated product **2**. By applying appropriate one pot protocols, the hydroxy group could be replaced by the addition of nucleophiles to the reaction mixture to furnish the desired final products **3**. Waser and coworkers were able to access various N,O-, N,S-, and N,N-acetal products in 39-73% yields.

1.4. References

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Chapter 2

Difunctionalization of *N*-Cyclobutylanilines with Isocyanide and TMSCN under

Photoredox Catalysis

2.1. Introduction

Isocyanides (isonitriles) were first discovered by Lieke in 1859 as species with unpleasant odor.[146] Although they have since found use as a useful functional group in a variety of reactions, including free radical additions,[147] coordination chemistry,[148] polymerizations,[149] organometallic transformations,[150] and multicomponent reactions,[151-154] the main drawbacks to their widespread use in organic synthesis have remained their difficulty in accessing them and their (in)famous odor, which makes their synthesis and handling difficult. The chemist Ivar Karl Ugi, named for the famed Ugi four-component condensation (U-4CC) reaction which involves isocyanides as a key reaction one-carbon synthon, admitted: "The development of the chemistry of isonitriles has probably suffered through the characteristic odor of volatile isonitriles, which has been described by Hofmann and Gautier as 'highly specific, almost overpowering', 'horrible', and 'extremely distressing'".[155, 156] However, in recently times, the emergence of more sustainable and widely applicable methods of accessing these compounds have reignited interest in their use in synthesis.[156, 157]

2.1.1. Structure and Reactivity of Isocyanide

Isocyanides have rich and diverse reactivity and display a dichotomy of electronic properties. Structurally, they are isomers of cyanides. Isocyanides exist in two resonance forms (**Scheme 2.1.1.1**) which account for their rich reactivity, namely the carbene-like form **1** (with its terminal carbon atom in a divalent state) and the zwitterionic form **1'** (with negatively charged terminal carbon and positively charged nitrogen atoms). Their characteristic IR absorption at

~2000 cm^{-1} suggests that the zwitterionic form **1'** gives more contribution to their structure. However, computational studies suggest that the carbenoid form is more stable.[158] Some publications refer to isocyanides as carbenes,[151, 152, 159] while others use the zwitterionic form,[160, 161] and still others use both.[162] The question of the best way to define their electronic structure remains open. In the zwitterionic form, the terminal isocyanide carbon is nucleophilic and reacts with electrophiles, whereas in the carbene form it can react with various types of radicals (nucleophilic or electrophilic) as radical acceptor. Both alkyl and aryl isocyanides have been found to undergo isomerization to the cyanides or nitriles under certain thermal and photochemical conditions, and the isomerization is influenced by substituent effects.[163, 164]

$$\left[\quad \underset{\substack{\mathbf{1} \\ \text{50-55\%}}}{\text{R}-\text{N}=\text{C}:} \quad \longleftrightarrow \quad \underset{\substack{\mathbf{1'} \\ \text{24-25\%}}}{\overset{\oplus}{\text{R}-\text{N}}\equiv\overset{\ominus}{\text{C}}} \quad \right]$$
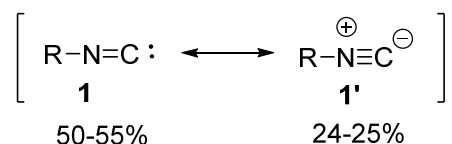
Scheme 2.1.1.1. Resonance forms of Isocyanide

For aliphatic and aromatic isocyanides, the structure of the substrates have little effect on the isocyanide−nitrile rearrangement, and they can isomerize quantitatively at 210−250 °C with within a few hours.[165] Isocyanides bearing heteroatom substituents have a much ambiguous structure−reactivity relationship with silyl isocyanide, for example, being reported exist in equilibrium with its silyl nitrile isomer at room temperature.[166]

Although isocyanides are isoelectronic to alkynes and share many features with them, they display distinctive stereoelectronic features from alkynes. ESP maps of isocyanides, for example, indicate a σ-hole at its C-end. Supramolecular systems' stability and reactivity have been found to be modulated by σ-holes.[167] Due to the difference in electronegativity between carbon and

nitrogen, the π*-orbital of isocyanide is substantially more polarized than its alkyne analog. Also, additions to alkynes and isocyanide produce very distinct results: whiles addition to isocyanides occur in 1,1-fashion in which two new bonds are formed at the isocyanide's terminal carbon, addition to alkynes occur in a 1,2-manner wherein the new bonds are generated at different alkyne carbons (**Scheme 2.1.1.2**). This observed reactivity of isocyanides is in line with their hidden carbene nature.
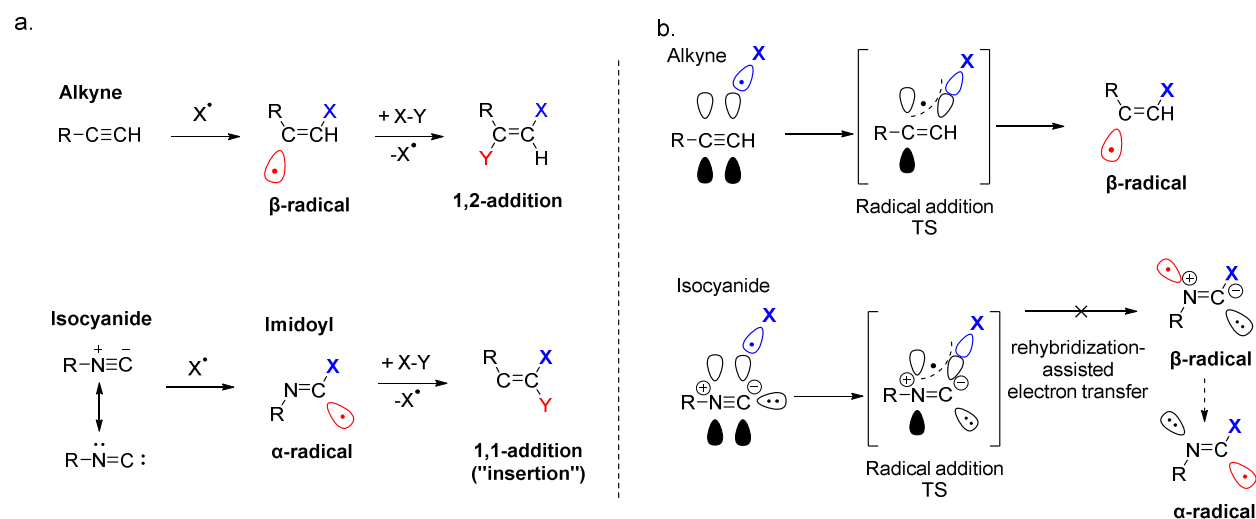
Scheme 2.1.1.2. Comparison of Radical Additions to Alkynes and Isocyanides

Ab initio assessment of the "1,1-addition" to isocyanides by Alabugin and coworkers[168] (**Scheme 2.1.1.2**b) suggest that transition state (TS) of the radical addition is similar to that for alkynes, and that they both proceed initially as an attack at a triple bond in Burgi-Dunitz fashion. Only after the TS does the similarity break. In pre-TS, there is an initial small but noticeable accumulation of spin density at the β-nitrogen atom and less spin density at the terminal carbon (i.e., the α-atom), as would be predicted from classical radical addition to a π-bond. However, after the TS, the radical character of the α-carbon atom gradually increases until it greatly exceeds that of the N. As the C–X bond is created, sp-hybridized carbon-lone pair of the low-energy in

isocyanide begins to rehybridize to a higher-energy sp^2 lone pair.[169] An intramolecular charge transfer from the carbon lone pair to the nitrogen atom's incipient radical orbital occurs, crossing to the electronic state of the imidoyl radical product, which is a key intermediate in isocyanide radical insertion chemistry. In the "rehybridization-assisted" electron transfer event, the developing radical center at the nitrogen atom converts into a lone pair. Alabugin and coworkers found that the phenyl ring of phenyl isocyanide rotates in the process to align itself with the acceptor N=C π-bond rather than the nitrogen lone pair. In consistent manner, the phenyl ring π-system of diphenyl imidoyl radical does not conjugate with the radical center since the latter is already stabilized *via* a 2-center, 3-electron (2c, 3e)-interaction with the nitrogen lone pairs. This is in contradistinction to the case of the isoelectronic phenyl-substituted vinyl radical in which one of Ph rings (i.e. the one adjacent to the radical center) is conjugated with the radical (**Figure 2.1.1.1**). Although an odd-electron density exist at the α-carbon in the imidoyl radical product, the interaction between nitrogen lone pair and carbon radical stays strong and serves as a key source of radical stabilization (i.e., the 2c,3e bond).
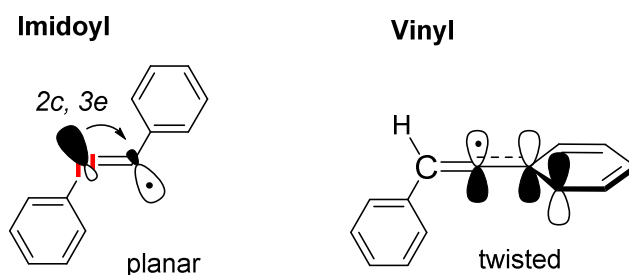
Figure 2.1.1.1. Comparison of Phenyl-substituted Imidoyl and Vinyl Radicals.

Isocyanides have been described as "stereoelectronic chameleons"[170] in supramolecular interactions due to their ability to act as donors or acceptors, depending on the nature of their interacting partner and its approach path for the isocyanide (**Figure 2.1.1.2**). Radicals are

appropriate stereoelectronic partners for isocyanides since their orbitals are half-full and half-empty at the same time, affording them flexibility in their interactions with the former. The preferred interaction pattern between isocyanides and radicals may change depending on whether the radical is electrophilic or nucleophilic, in order for the two interacting species to engage in donor/acceptor interactions in an optimal manner.
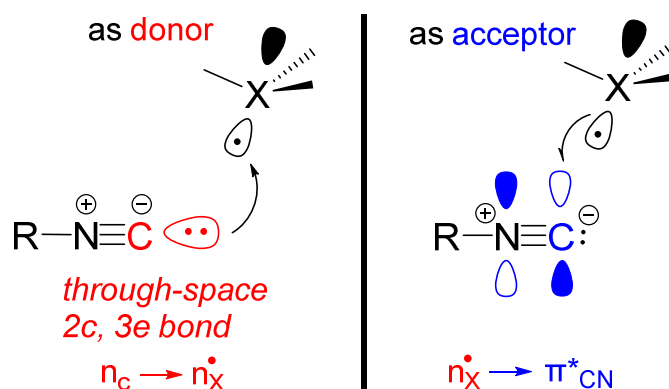
Figure 2.1.1.2. The Donor-Acceptor Dichotomy in Isocyanide Radical Additions

2.1.2. Isocyanide as Radical Acceptor in the syntheses of Nitrogen Heterocycles

Isocyanide's capacity to create two bonds on the same atom is crucial in multicomponent reactions like the Passerini and Ugi reactions.[151, 154, 171] Again, the 1,1-bond formation pattern has allowed for a variety of fascinating radical isocyanide cascades, commonly referred to as "isocyanide insertion" or "insertion of isocyanide". In 1991, Curran and colleagues were the first to use radical addition to isocyanides as one of the critical steps in a radical cascade leading to cyclopenta-fused quinolines such as the antitumor agent camptothecin[172] (**Scheme 2.1.2.1**). The transformation involved a [4+1] radical annulation strategy with the isocyanide serving as the one-carbon synthon. Following that, cyclopenta-fused pyridines and pyrazines were synthesized using the [4 + 1] radical annulation of γ-iodoalkynes or iodonitriles.[173] Nanni and colleagues successfully

synthesized cyclopentaquinoxalines using heteroatom-centered (sulfanyl) radicals.[174] The cyclization of the intermediate imidoyl radical (i.e., 5-exo for the [4 + 1] annulations) determines the size of the new cycle.

Curran
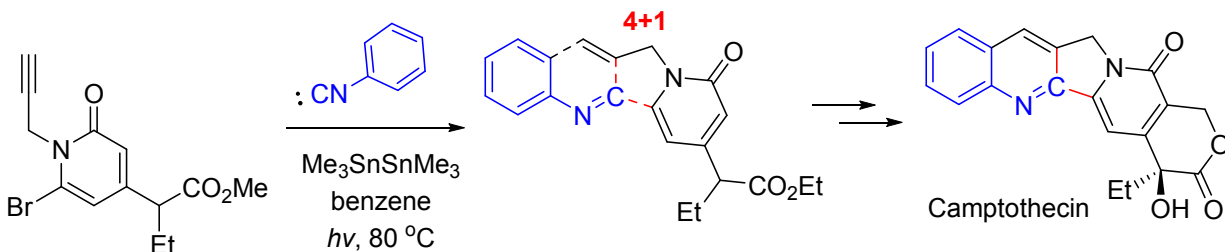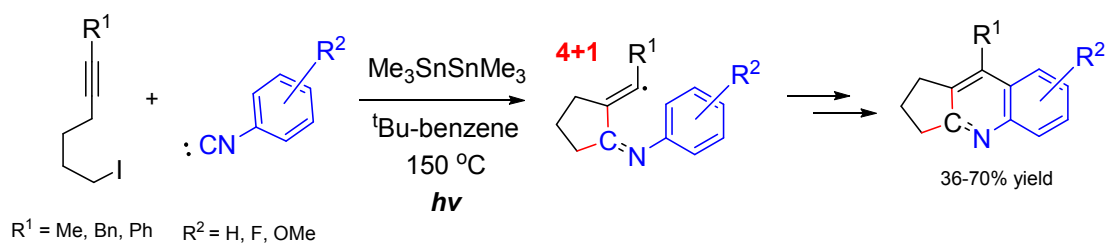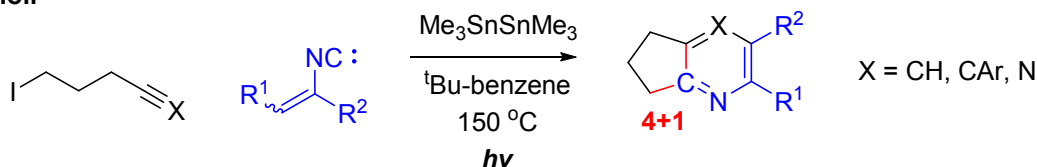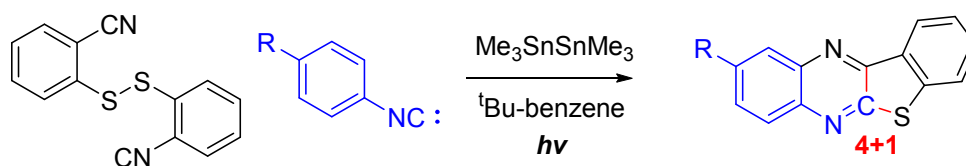
Scheme 2.1.2.1. Seminal Works in [4+1] annulations via "Isocyanide Insertion"[168]

All the above works were catalyzed by light and the annulations proceeded via an imidoyl radical intermediate ($R^1N=C^{\bullet}R^2$). These reactive intermediates were first described by Danen from ESR studies in 1973 as a new class of σ-radicals.[175] They can be generated *via* radical addition to isocyanides/isothiocyanates and homolytic fragmentation of imine precursors. Even though the

first report of their production included homolytic fission, their generation from isocyanides remains a predominant route of occurrence.[176] Reactions of photochemically generated imidoyl radicals have been reviewed by the research groups of Nanni,[177] Zhu,[178] and Sharma.[179] Generally, when the oxidative quenching cycle is operative in the reactions catalyzed by a TM-based photocatalyst, or the reductive quenching cycle in the reactions catalyzed by organic dye or photosensitizer, the generation of the radical from its precursor (electrophiles) occurs in the quenching step. However, the radical-generation typically occurs in the step that regenerates the ground state of the photocatalyst/photosensitizer (i.e. after the quenching step) when the reductive quenching cycle is involved in the reactions catalyzed by TM-based photocatalyst. With the latter reactions, a sacrificial SET reductant (such as a tertiary amine or a carboxylate ion) is typically used to reductively quench the excited state of the photocatalyst to a more reducing state which can facilitate the subsequent radical generation from its precursor electrophile by SET reduction.

Apart from quinoxalines, photo-generated imidoyl radicals have also been exploited for the synthesis of benzothiazoles, isoquinolines, pyridines, and amides. Several groups have reported the successful synthesis of phenanthridine derivatives[180] *via* crucial biphenyl imidoyl radical intermediates generated by adding different radicals to 2-isocyanobiphenyls. In 2012, Chatani (6a) reported the first example of synthesizing 6-aryl/alkyl phenanthridines utilizing aryl/alkyl boronic acids as radical precursors in the presence of 3 equivalents of $Mn(acac)_3$.[181] Studer and colleagues later showed that trifluoromethyl,[182] aroyl,[183] and phosphoryl radicals[184] can react with 2-isocyanobiphenyls to produce C6-substituted phenanthridines. Under photoredox neutral and metal-free conditions, groups of Yu[185] and Zhou[186] reported synthesis of C6-alkylated and C6-trifluoromethylated phenanthridines via imidoyl radical intermediates.

The **Scheme 2.1.2.2** below shows various reaction pathways of the biphenyl imidoyl radical, once generated. A common step proposed in these transformations is the intramolecular homolytic aromatic substitution[187] (HAS, step a) of the biphenyl imidoyl radical on the pendant phenyl ring, to form the cyclohexadienyl radical intermediate. The formation of the phenanthridine products can then proceed in one of two ways. The first is single electron transfer oxidation (SET, step b) to yield the cyclohexadienyl cation, followed by deprotonative aromatization (step c), and the second is deprotonation of the cyclohexadienyl radical first (step d), then SET (step e). When in situ produced diazonium salts are utilized as arylation agents, the SET oxidation of the biphenyl imidoyl radical to biphenyl nitrilium ion (step f) is a competitive pathway to HAS in the arylative cyclization of 2-isocyanobiphenyls. When nitrilium intermediate is generated, it could be trapped by water or some nucleophile to produce amides or imides upon tautomerization and rearrangement, respectively.[188] SET reduction of imidoyl radical to an imidoyl anion has also been reported in the synthesis of amines from electron transfer reduction of nitriles using SmI_2,[189] but this pathway has not been reported in the synthesis of phenanthridines. However, theoretically, a pathway to phenanthridine from biphenyl imidoyl radical can be envisioned in which an imidoyl anion generated from the reduction of the radical undergoes an intramolecular nucleophilic aromatic substitution with the pendant phenyl ring (step h).
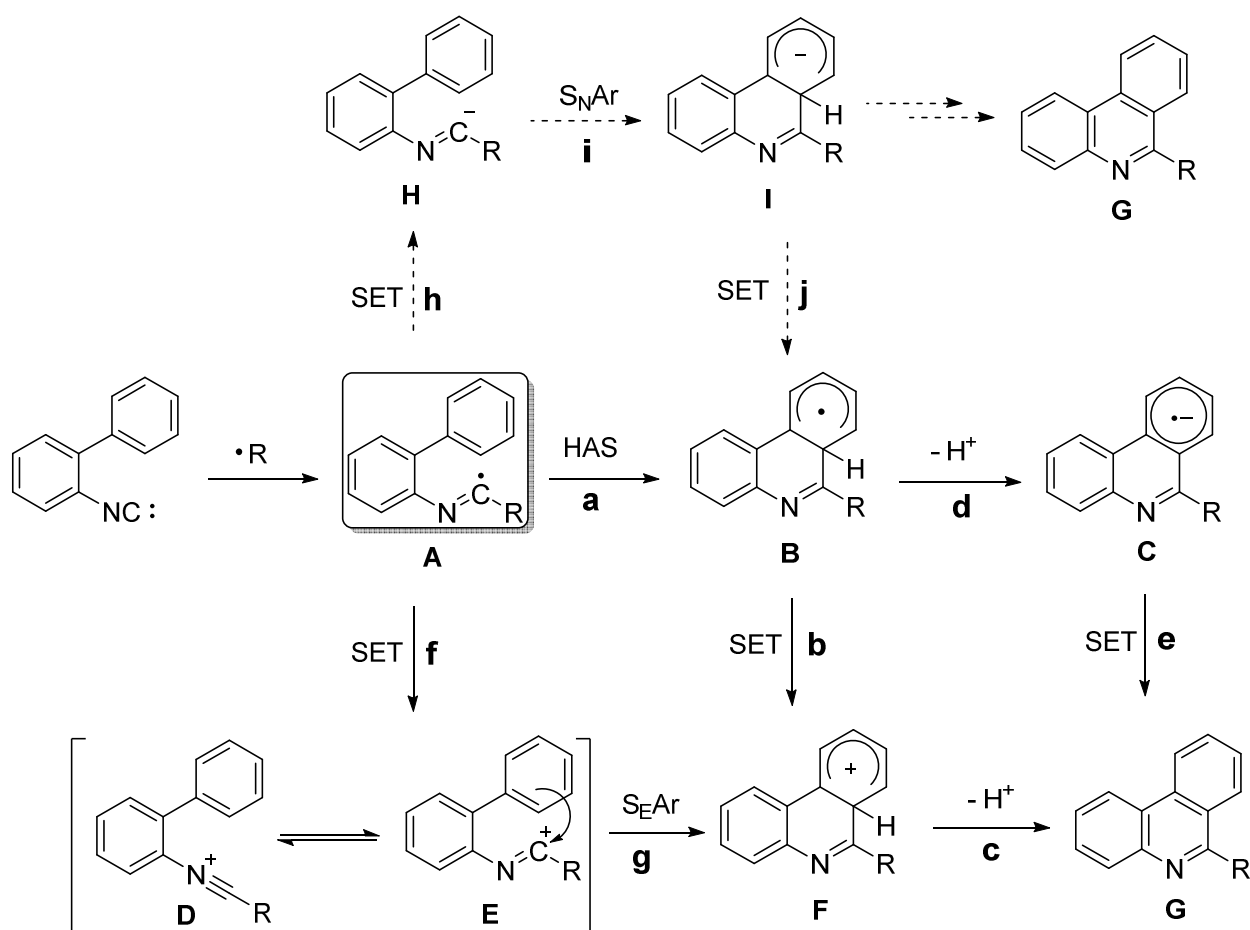
Scheme 2.1.2.2. Pathways of Biphenyl Imidoyl radicals

An illustrative example of phenanthridine synthesis *via* in situ generated biphenyl imidoyl radical is the Wang group's 2014 work employing Umemoto's reagent as the source of trifluoromethyl radical (**Scheme 2.1.2.3**). Under visible-light-induced catalysis using [Ru(bpy)$_3$]Cl$_2$ as the photocatalyst, 2-isocyanobiphenyl **1** was converted to 6-trifluoromethylated phenanthridine derivatives **3**.[190] The photoexcited Ru(II)-complex [Ru(II)*/Ru(III); $E_{1/2}$ =0.81 V vs. SCE] is oxidatively quenched by Umemoto's reagent **2** [$E_{1/2}$ = 0.75 V vs. SCE], resulting in trifluoromethyl radical CF$_3^•$ **4** and Ru(III) species. After that, the CF$_3^•$ radical **4** is added to the isocyanide **1** to produce imidoyl radical intermediate **5**, which is then cyclized to produce cyclohexadienyl radical intermediate **6** [$E_{1/2}$(6/7) = 0.65 V vs. SCE], which is subsequently

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oxidized by Ru(III) species [Ru(III)/Ru(II); $E_{1/2}$ = +1.29 V vs. SCE] to produce the carbocation **7**.

Finally, the product 3 is formed when the carbocation **7** loses a proton.
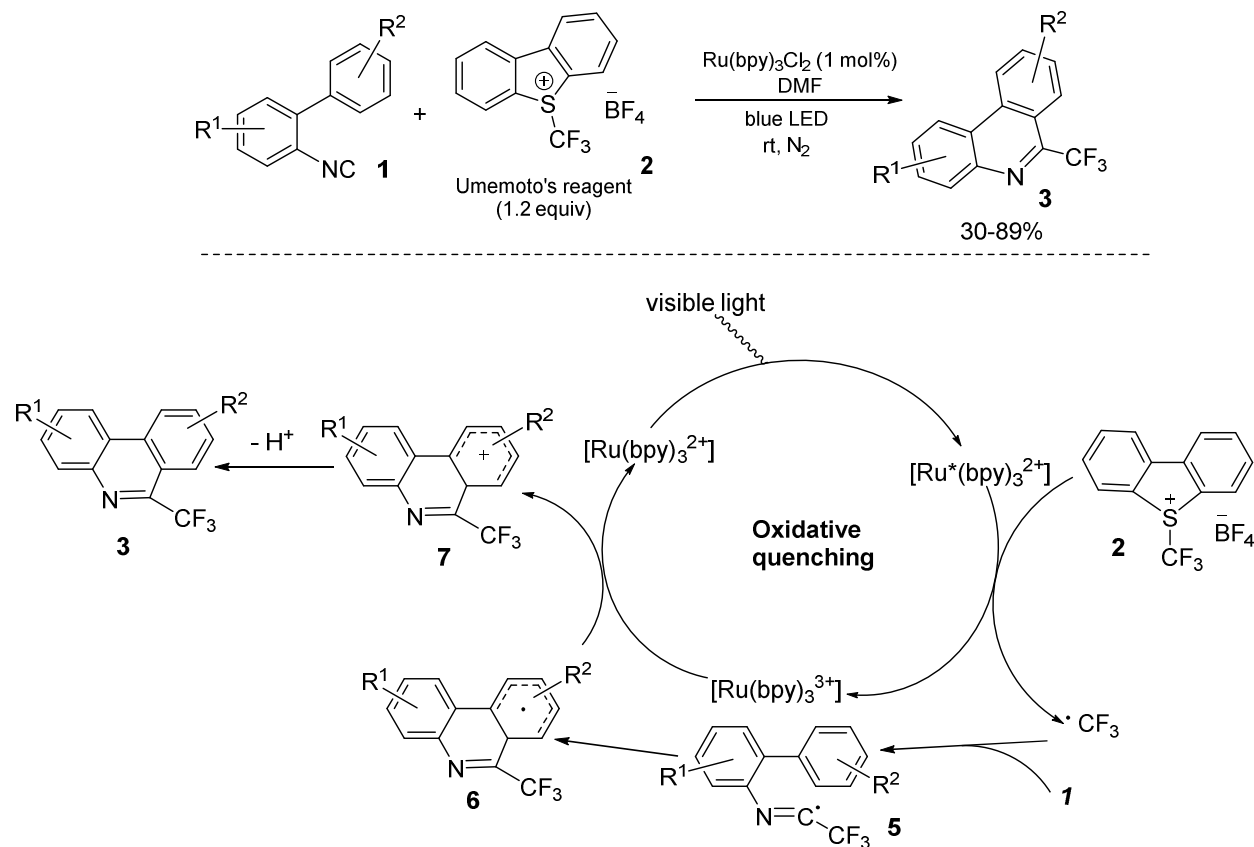
Scheme 2.1.2.3. Wang's Photocatalyzed Phenanthridine Synthesis using Umemoto's Reagent

An illustrative example involving the reductive quenching cycle in a reaction catalyzed by TM-based photocatalyst is the 2016 work by Fu and coworkers using N-hydroxyphthalimide esters of N-protected α-amino acids and peptides as the radical precursors in a [Ru(bpy)₃]Cl₂-catalyzed synthesis of phenanthridines (**Scheme 2.1.2.4**). Photoexcitation of the Ru^{2+} complex to the excited Ru^{2+*} [Ru^{2+*}/Ru^{1+}; $E_{1/2}$ = +0.77 V vs. SCE], followed by reductive quenching by the sacrificial reductant DIPEA [$E_{1/2}$=+0.5 V vs. SCE] gives the Ru^{1+} species. The generated Ru^{1+} species [Ru^{1+}/Ru^{2+}; $E_{1/2}$ = -1.33 V vs SCE] reacts with the *N*-acyloxyphthalide [$E_{1/2}$ = -1.26 V to -1.37 V

vs. SCE] via SET to produce a radical anion with the regenerated Ru^{2+} complex. Following the loss of the phthalimide anion and CO_2 from the carboxyl radical, an α-amino radical is formed which adds to 2-isocyanobiphenyl to generate and imidoyl radical. Intramolecular HAS of the imidoyl radical forms the radical intermediate, which undergoes SET oxidation to a cationic intermediate. The product is finally generated by deprotonation of the cationic intermediate.
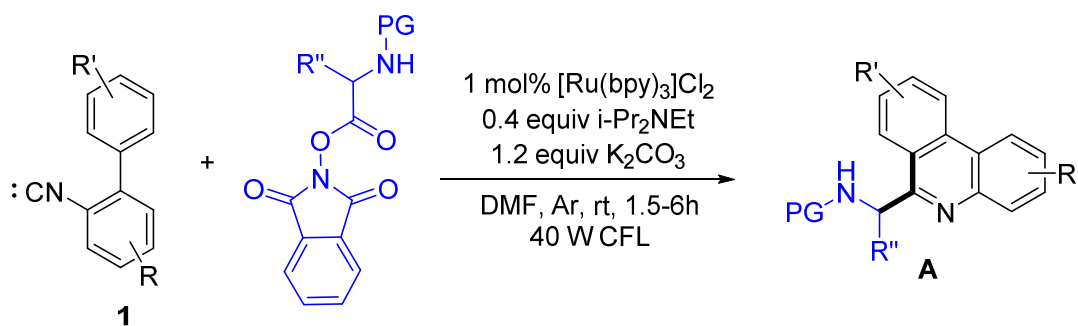
R = 2-Me, 3-Me, 3-Cl
R' = 5-Me, 6-Cl, 7-Me, 7-Cl, 7-OMe, 7-CF$_3$
PG = BocH, Boc, Cbz
R" = Me, iPr, iBu, CH$_2$Ph, CH$_2$-4-PMeC$_6$H$_4$, CH$_2$-OtBu, CH$_2$CO$_2$Me, 1-Boc-2-Pyrrolidinyl
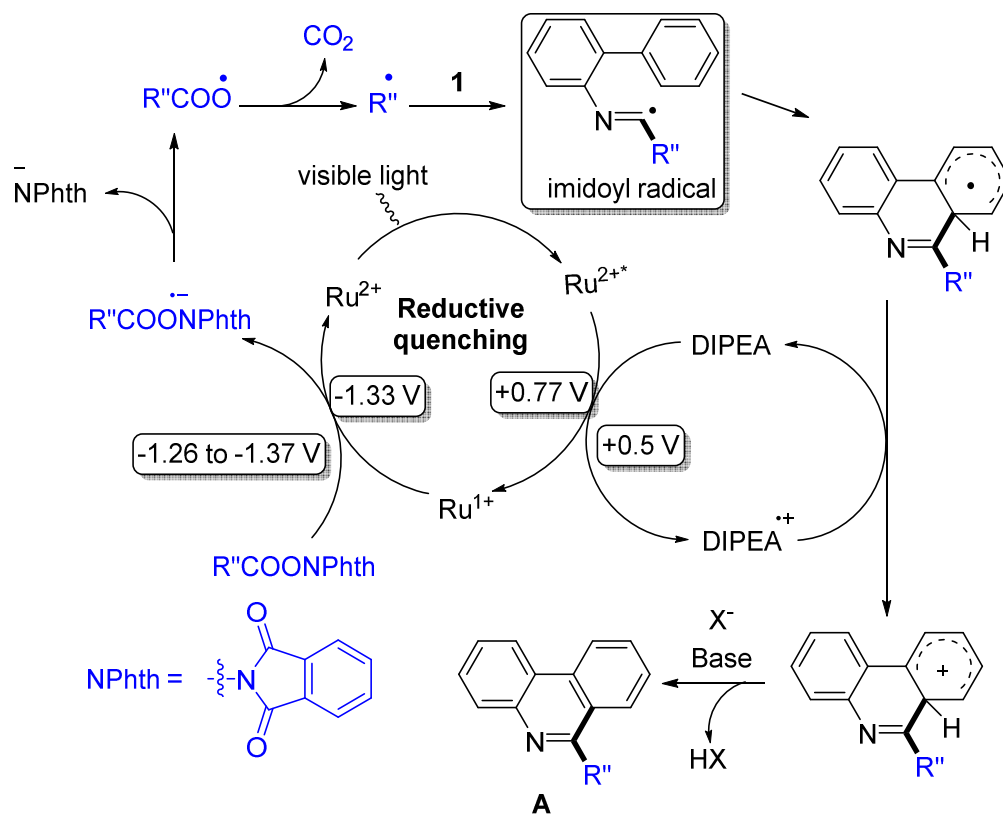
Scheme 2.1.2.4. Synthesis of Phenanthridines Using *N*-Acyloxyphthalimide as Radical Precursor

2.2. Background and significance

Our previous research on photoredox-catalyzed ring opening of easily accessible *N*-cyclopropylanilines and *N*-cyclobutylanilines disclosed a relatively straightforward strategy to

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generate gamma and delta distonic radical cations in solutions. Although the amine distonic radical cations have not detected experimentally by us or other groups, the observed reactivity strongly suggests that they were involved in both the [3+2] and [4+2] annulation reactions (*vide supra,* **Scheme 1.5.5**). The ring opening triggered by photogenerated amine radical cations is the fundamental reaction for accessing gamma- and delta-distonic radical cations like **B** (**Scheme 2.2.0**).

Although current kinetics data[191] from the Tanko group reveal that the ring opening rate of *N*-cyclopropylanilines (~4.1 x 10^4 s^{-1}) when SET mechanism is operative is slower than previously supposed, the indirect experimental evidence from the isolation/detection of their ring-opened products by both our group and others suggest that the ring-opening event that generates β-distonic radical cations from *N*-cyclopropylanilines is still faster than that which generates γ-distonic radical cations from *N*-cyclobutylanilines. For example, whiles the [3+2] annulation of N-cyclopropylanilines with pi bonds was observed to proceed at room temperature, the requirement of higher temperature (50 °C) for the analogous [4+2] annulation involving *N*-cyclobutylanilines hinted that the formation of its gamma-distonic radical ions **B** (**Scheme 2.2.0**, n=1) is likely reversible, favoring the closed amine radical cation form **A**.
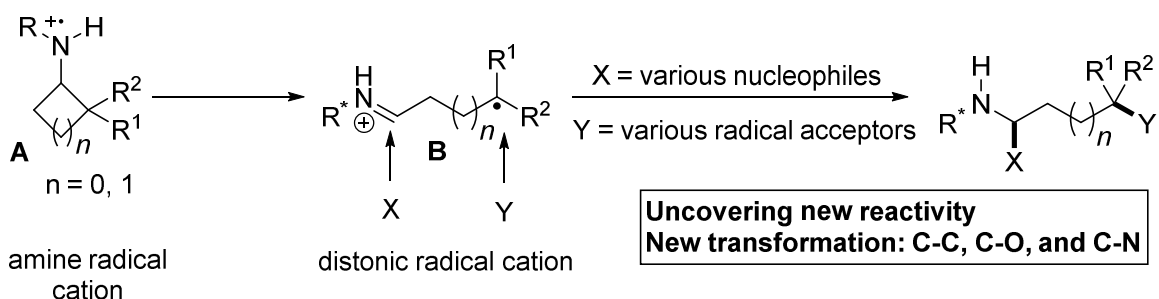
Scheme 2.2.0. Strategy for Difunctionalization of *N*-Cycloalkylamines

The sensitivity of the ring opening process's reversibility towards ring sizes/strain impacts the design of reactions to utilize these species. Howbeit, the proposed distonic radical cation from both *N*-cycloalkyl- and *N*-cyclobutylanilines possesses bimodal reactivity due to the presence of a nucleophilic carbon radical moiety (site Y) and an electrophilic iminium ion moiety (site X). Therefore, in principle, it is possible to orthogonally intercept the two reactive sites by using a suitable radical acceptor Y at the radical site and a nucleophile X at the cationic site, thereby achieving 1,3- or 1,4-difunctionalization along a saturated carbon backbone which is difficult to achieve. Despite the great potential of this difunctionalization strategy for buildup of molecular complexity from small sized cycloalkylamines, to date, only three examples exploiting this strategy for difunctionalization of aminocyclopropanes and aminocyclobutanes have been reported, including works by Waser's research group[137] and unpublished works by us.[192, 193]

Other reported works exist in literature of the 1,3-difunctionalization of strained rings, but most of these either involve no cycloalkylamine substrate,[194-198] and/or no light,[138, 199] with the only exception being a 2021 work by Chen and coworkers[200] involving 1,3- and 1,4-difunctionalization of cyclopropyl- or cyclobutylamides (i.e., "protected cycloalkylamines") with alkynyl hypervalent iodine and suitable nucleophiles.

2.2.1. Previous Photocatalyzed Difunctionalizations of N-Cycloalkylamines in Zheng group
Two successful difunctionalization reactions involving the capturing of the bimodal reactivity of amine distonic radical cations (ADRCs) have already been developed by the Zheng group. The first was achieved by employing TMSCN and allyl phenyl sulfones as the nucleophile/radical acceptor pair and [Ir(ppy)$_2$(dtbbpy)]PF$_6$ as the photocatalyst in degassed CH$_2$Cl$_2$ at room temperature (**Scheme 2.2.1.1**).[192] Optimal reactivity was achieved when TMSCN, which is used extensively in the famed Strecker synthesis, was used as the nucleophile; other

cyanide salts such KCN significantly decreased the yield of the desired difunctionalization product. The cation (TMS) was critical, as in situ NMR investigations revealed that PhSO$_2$TMS[56] was produced, presumably via the capture of sulfinate ion by the TMS cation. Mechanistically, it was proposed that an initial nucleophilic attack by the carbon radicals on the *pi* bond of the allyl sulfone, and subsequent β-elimination of a sulfonyl radical would furnish the allylated product (**Scheme 2.2.1.1**). The resultant sulfonyl radical ($E^{red}_{1/2} = +0.50$ V vs SCE) is sufficiently oxidizing to complete the catalytic cycle by turning over the reduced photoredox catalyst. Competition studies showed the order of reactivity of various types of cyclopropylanilines at 23 °C to be monocyclic cyclopropylanilines **2.3** > bicyclic cyclopropylanilines **2.2** ≈ monocyclic cyclobutylanilines **2.1**. Also, EPR studies showed that at 23 °C, the amine radical cation of a cyclobutylaniline existed as the closed form (amine radical cation) rather than the opened distonic radical cation form, thereby confirming its slow reaction; and control study showed that no reaction occurred with a cyclobutylaniline without TMSCN.
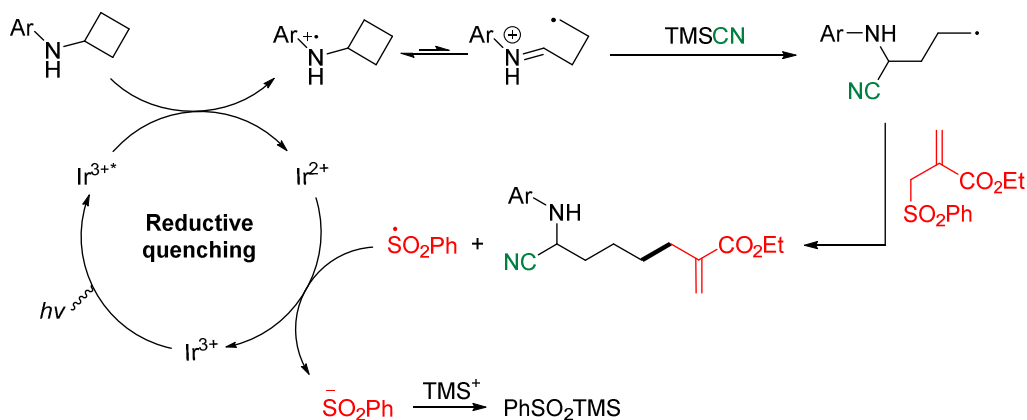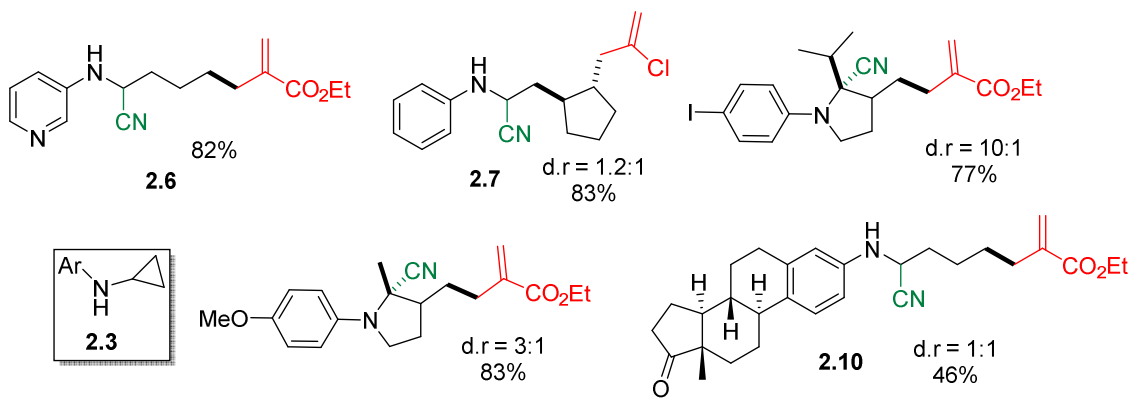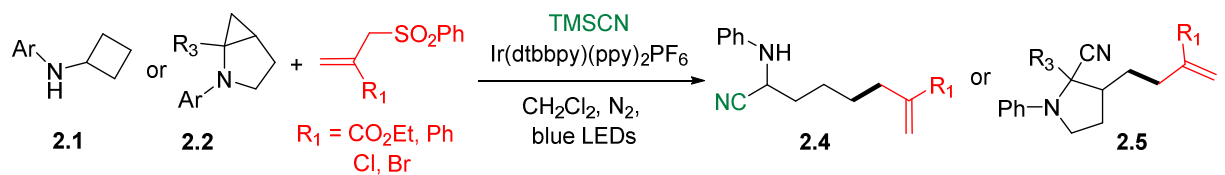
Scheme 2.2.1.1. Difunctionalization of *N*-Cycloalkylanilines with Allyl Sulfone and TMSCN

The second difunctionalization reaction developed by the Zheng group is a variant of the first, employing α-CF3-styrenes which has similar characteristics as phenyl allyl sulfones, as the radical acceptor (**Scheme 2.2.1.2**).[193] This radical acceptor was found to be compatible with a broader scope of substrates, as, in addition to *N*-cycloalkylanilines, 1°, 2°, and 3° *N*-alkyl cyclopropylamines and *N*-alkyl cyclobutylamines which had failed to participate in the difunctionalization involving phenyl allyl sulfone were also amenable to this reaction. Here too,

the radical adduct from the addition to the α-CF3-styrene is highly reducible like the sulfonyl radicals produced in the former reaction. Fluoride ion (F⁻) was produced in the process which can be trapped by the TMS⁺.
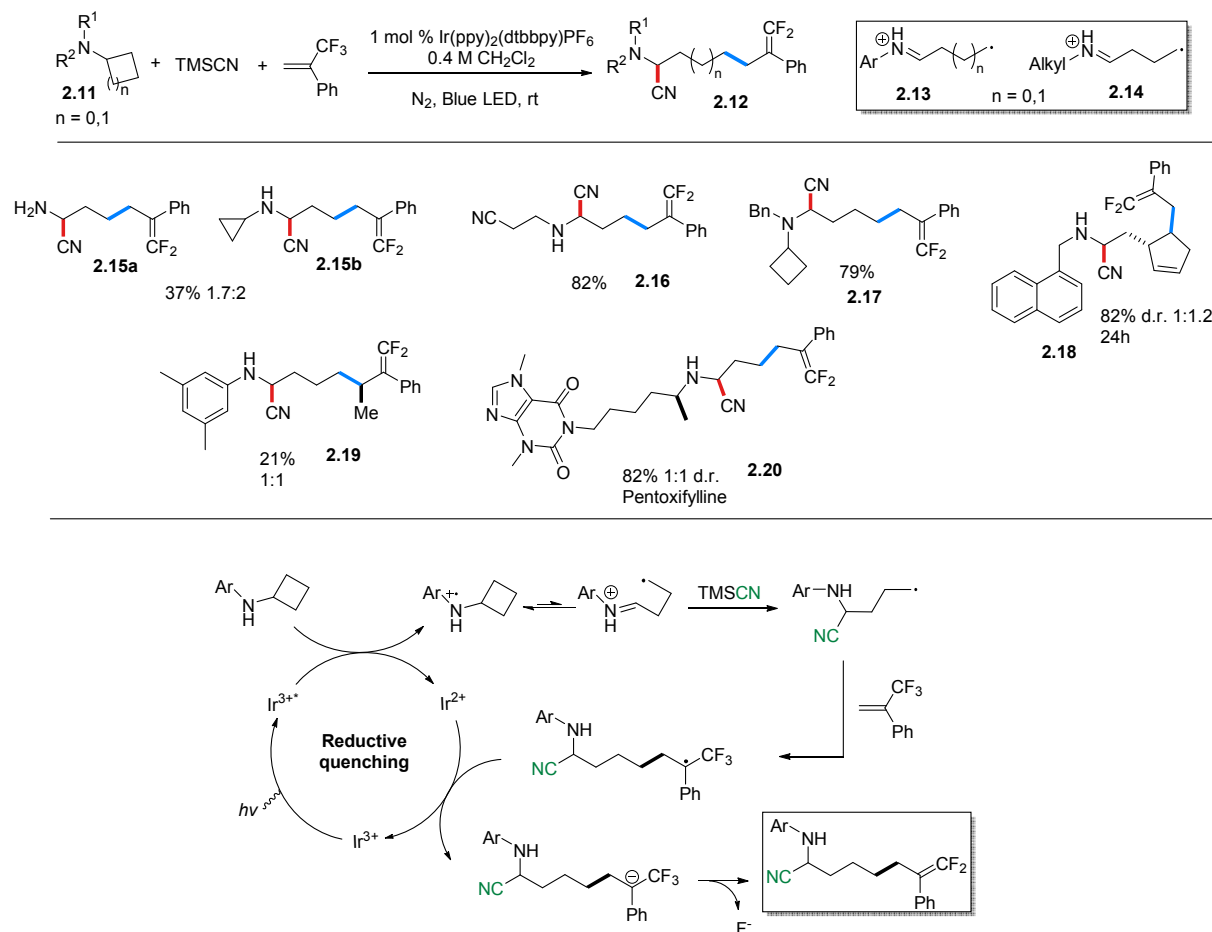
Scheme 2.2.1.2. Difunctionalization of *N*-Cycloalkylanilines with α-CF₃-Styrene and TMSCN

In both of our previously developed difunctionalization of amine distonic radical cation (ADRC), the terminal nucleophilic carbon radical of the ADRC adds to an electron-deficient alkene (i.e. allyl phenyl sulfone and α-CF₃-styrene) in a process which is polarity-matched. This type of radical addition is analogous to that seen in Giese-type reactions. In an analogous work

involving difunctionalization of cycloalkylamides, Chen and coworkers were able to detect by HRMS-ESI the initial imine product formed from the addition of the distal carbon radical of in situ generated imine intermediate to the electrophilic radical acceptor (i.e. an alkynyl hypervalent iodine reagent) prior to the nucleophilic attack of the imine product by the polar solvent (MeOH).[200] This key data established that the interception of the radical preceded the addition of the nucleophile to electrophilic imine moiety. In our developed difunctionalizations, however, the reactive intermediate is an iminium distonic radical cation which is more reactive towards reduction or nucleophilic attack at its electron-deficient site than imines.[201] While a sequence of site functionalizations similar to Chen's is possible in our developed difunctionalizations of *N*-cycloalkylanilines, we hypothesized the reverse sequence of nucleophilic attack/radical interception for the case of our photogenerated ADRC, in which the initial step results in the formation of an neutral α-aminonitrile species bearing a distal nucleophilic carbon radical which is capable of reacting as an ordinary carbon radical in Giese-type reactions. The nucleophilic attack also serves to drive the ring-opening of the lesser strained *N*-cyclobutylaniline by retaining the open-chain form of its ADRC.

2.2.2. This Work: Difunctionalization of N-Cyclobutylanilines with Isocyanide and TMSCN

The results of our previously developed difunctionalization reactions reveal that the ADRCs, possessing the positively charged iminium ion moiety, can be converted to reactive neutral carbon-centered radicals via the interception of the cationic sites by the nucleophile TMSCN. In the current study, we questioned whether this in situ generated carbon-centered radical could subsequently add to the terminal carbon of isocyanides to achieve an overall difunctionalization of both reactive sites of the bimodal ADRC (**Scheme 2.2.2.1**).
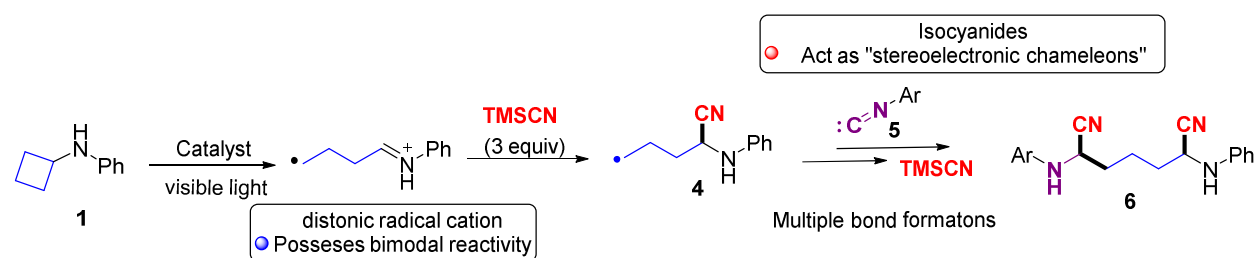
Scheme 2.2.2.1. Difunctionalization of *N*-Cyclobutylanilines with Isocyanide and TMSCN

Comparing with the difunctionalizations involving allyl phenyl sulfone and α-CF$_3$-styrene wherein a reducible intermediate was generated upon the addition to the radical acceptor, we envisioned that the success of the new reaction would hinge on two factors: (1) the proper polarity matching of ADRC, or the neutral carbon-centered radical generated from it, with the isocyanide radical acceptor, and (2) the plausibility of the downstream reduction of initially formed imidoyl radical intermediate to an imidoyl anion by the quenched photocatalyst acting as the reductant. The current transformation involving isocyanide as radical acceptor does not merely extend the scope of radical acceptors that are compatible with ADRCs, as whereas the previously exploited radical acceptors were essentially both electron-deficient alkenes capable of undergoing Giese-type reactions readily, isocyanides on the other hand (as demonstrated specifically with *t*Butyl isocyanide) would be predicted to exhibit ambivalent reactivity towards the charged site and the radical site of distonic radical cations, most likely preferring the former (*vide supra*, section **1.5**). However, it was not clear to us how the isocyanides would react with the amine distonic radical cations (ADRCs), as this work represents the first attempt of this reaction in synthesis. Although Prof. Kenttämaa's work[131] has disclosed both the ambivalent gas-phase reactivity of distonic radical cations (owing to their bimodal character) and of isocyanides (owing to their dichotomous carbene-like and zwitterionic reactivity), and Prof. Alabugin's work[168] has provided computational

understanding of radical addition into the "chameleonic" isocyanides, a practical condensed-phase laboratory synthesis that exploits the reactivities of these two enigmatic species has still been lacking in the literature. This work represents the first attempt to fill this gap.

2.3. Results and Discussion

2.3.1. Development of the Difunctionalization Reaction.

We selected 3,5-Dimethyl-*N*-Cyclobutylaniline **1a** and 2-isocyanobiphenyl **2a** as the standard substrates to investigate the difunctionalization reaction. In quintessential radical insertion reactions of 2-Isocyanobiphenyl that have been reported to date in literature, an in situ generated imidoyl radical typically undergoes arylative cyclization with the pendant phenyl ring to form substituted phenanthridines (see section **2.1.2** hereinbefore), and no report exist of the formation of noncyclized products from this substrate following the radical addition. Thus, if our targeted difunctionalization products are obtained from the reaction of **2a**, it would be the first report of such transformation of **2a** and would establish the robustness of the protocol. Gratifyingly, when a mixture of **1a**, **2a**, TMSCN, and the photocatalyst [Ir(ppy)$_2$(dtbbpy)]PF$_6$ in methanol was irradiated with two 18W white LED bulbs for 24 h (**Scheme 2.3.1.1**a), the desired difunctionalization product **5a** (derivative of 2,6-diaminopimelonitrile) was obtained as a racemate in combined isolated yield of 22%, together with 31% of unsubstituted phenanthridine and only 4% of the substituted phenanthridine product **4a** which would have been predicted based on literature review. X-ray diffraction (XRD) analysis of the isolated difunctionalization product confirmed its structure. Interestingly, when **2a** was substituted with 4-isocyanobiphenyl **6a** which cannot undergo arylative cyclization, a similar isolated yield (18%) of the corresponding difunctionalization product **7a** was obtained under the same reaction conditions (**Scheme 2.3.1.1**b).
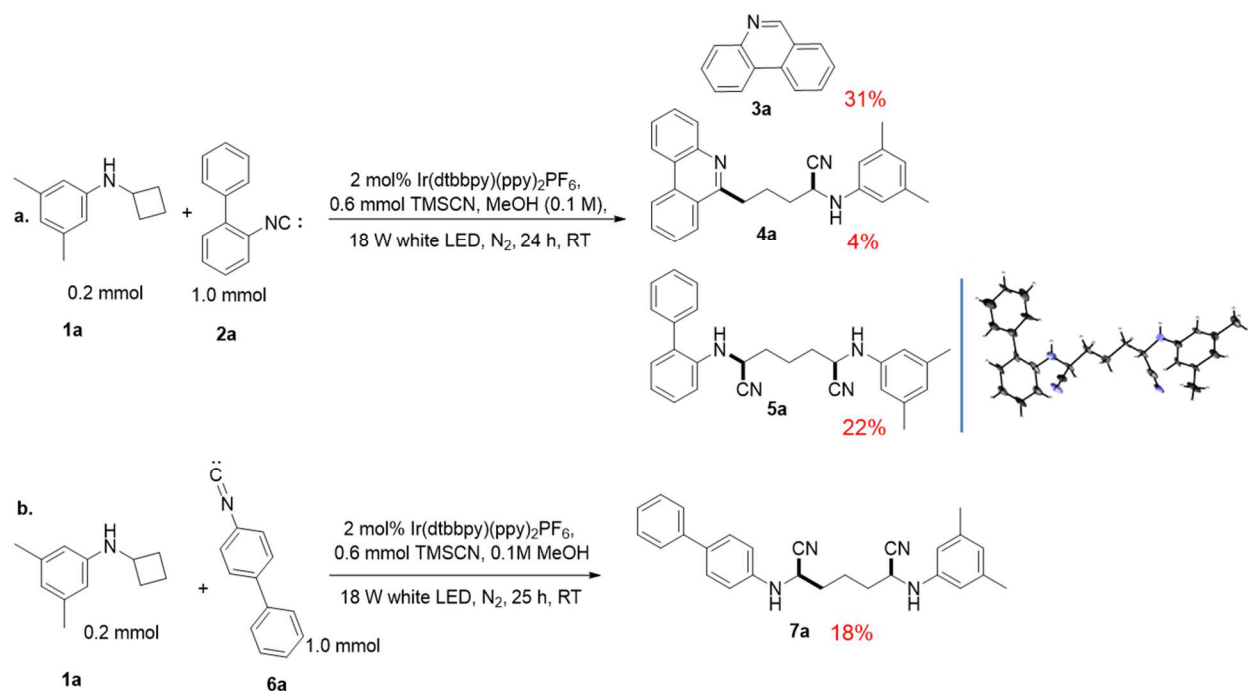
Scheme 2.3.1.1. Initial investigation of the Difunctionalization Reaction

Based on the results of the preliminary investigation, we developed a speculative working model to guide our subsequent optimization studies (**Scheme 2.3.1.2**). We speculated that SET oxidation of the *N*-cycloalkylaniline **1** by the excited state photocatalyst Ir^{3+*} generates the amine radical cation **2** which undergoes a strain-driven ring-opening to an amine distonic radical cation (ADRC). Nucleophilic attack of the ADRC by TMSCN produces a neutral carbon radical **3** which adds to the α-carbon of 2-isocyanobiphenyl to form the imidoyl radical intermediate **5**. Theoretically, intermediate **5** may follow one of two paths to produce an imine en route to the desired difunctionalization product **7**. In one path which do not involve the photocatalyst (path a, **Scheme 2.3.1.2**), it is speculated that the imidoyl radical can undergo hydrogen atom abstraction to directly give the imine **6**, which upon a second nucleophilic attack by cyanide anion delivers the desired product. In the second, and most plausible path, the imidoyl radical **5** undergoes a SET

reduction by the reduced form of the photocatalyst (Ir^{2+}) to an imidoyl anion **8**, which can abstract a proton to produce the imine, together with the regenerated ground photocatalyst Ir^{3+}. A subsequent CN^- trapping of the imine then furnishes the difunctionalization product **7**. The surprising formation of the 6-substituted phenanthridine as minor product **10**, contrary to what would have been predicted based on vastly reported radical insertion reactions of 2-isocyanobiphenyl, may be rationalized in terms of an unfavorable nucleophilic aromatic substitution (S_NAr) step following the reduction of imidoyl radical intermediate to the imidoyl anion (path c).
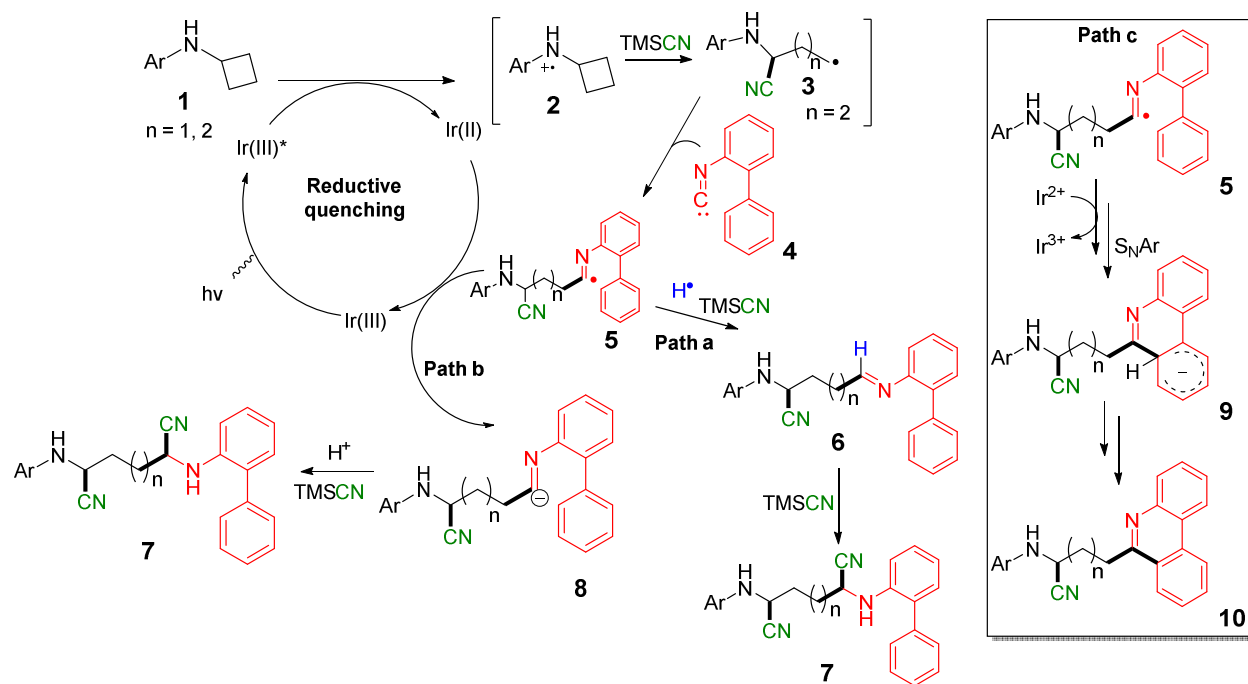
Scheme 2.3.1.2. Working Model for the Difunctionalization Involving Isocyanide

Possible unproductive side reactions that could be anticipated in this difunctionalization strategy is the nucleophilic attack of the iminium ion moiety of distonic radical cation by the isocyanide to give a nitrilium ion intermediate and subsequent CN^- addition to the nitrilium ion,

which is seen in several variants of isocyanide-based multicomponent reactions (e.g., Ugi 4CR, Ugi-azide 4CR, Groebke-Blackburn-Bienaymé 3CR, etc).[154]
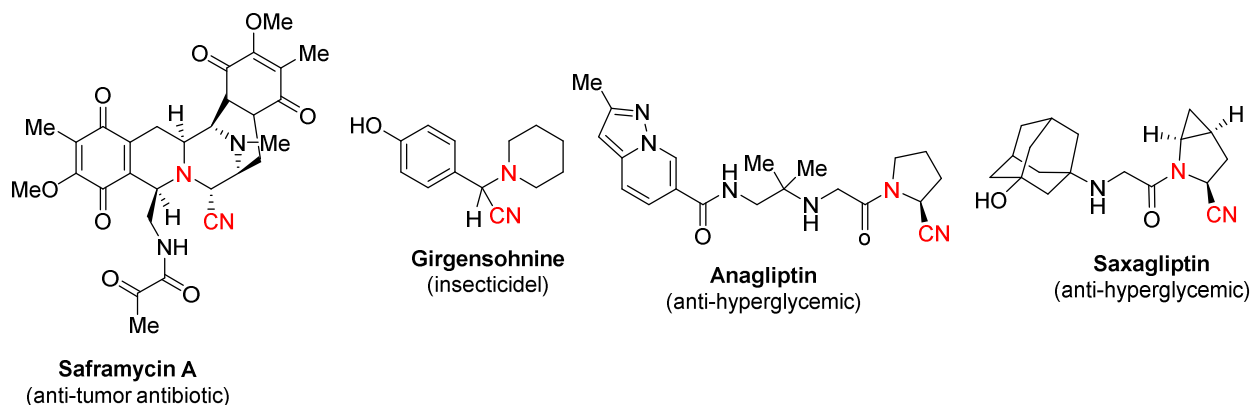
Figure 2.3.1.1. Representative Bioactive Alkaloids and Synthetic Drugs Containing Alpha-aminonitrile group.

Alpha-aminonitriles are essential components of many pharmaceutically relevant bioactive molecules such as saframycin A,[202] girgensohnine,[203] ecteinascidin 743,[204] anagliptin,[205] saxagliptin,[205] and phtalascidin 650,[206] (**Figure 2.3.1.1**) and are also versatile precursors of natural and unnatural α-amino acids, α-amino alcohols, α-amino aldehydes, 1,2-diamines, and synthetically valuable sydnones,[207] mesoionic heterocycles that have been used in 1,3-dipolar cycloaddition reactions. Unsurprisingly, 2,6-Diaminopimelonitriles in the form of bis-alphaaminonitriles are valuable precursors and intermediates in the synthesis of a variety of useful organic compounds and drug candidates or natural products. For example, bis-alphaaminonitriles with identical 2,6-diaminoheptanedinitrile backbone to the difunctionalization products obtained by the method developed herein, can be hydrolysed to 2,6-diaminopimelic acid (2,6-DAP),[208] an important naturally occurring amino acid in the cell wall peptidoglycans of all Gram-negative and some Gram-positive bacteria.[209] Moreover, *meso*-2,6-DAP is the direct biosynthetic precursor of L-lysine in all higher plants, green algae, some lower fungi, and bacteria.[210] Furthermore, bis-

alphaaminonitriles have been converted to bioactive bis-sydnone imines which exhibit antiplatelet and anticoagulant activity *in vitro*.[211] Also, the transformation of bis-α-amino-α-arylacetonitriles derived from the reaction of alkyl dibromides with α-amino-α-arylacetonitriles (as acyl anion equivalents) into convertible symmetrical diketones *via* acid hydrolysis have been reported.[212] Despite the apparent synthetic value of 2,6-diaminopimelonitriles, only few examples of their syntheses have been reported based on imine and/or iminium ion chemistry and the scarce examples have been limited virtually to bis-alphaaminonitriles, typically prepared from either the reaction of the symmetrical aldehyde glutaraldehyde in reaction with an amine or aniline in the presence of a cyanide source (i.e. the Strecker reaction) or the direct hydrocyanation of the preformed imine (i.e., the so-called modified Strecker reaction),[208, 211] or from the reaction of dicyanohydrins of glutaraldehyde with aniline and secondary amines[213] (**Scheme 2.3.1.3**). The novel approach developed herein will be complementary to the foregoing methodologies and provide access to diverse types of both symmetrical and unsymmetrical 2,6-diaminopimelonitriles.
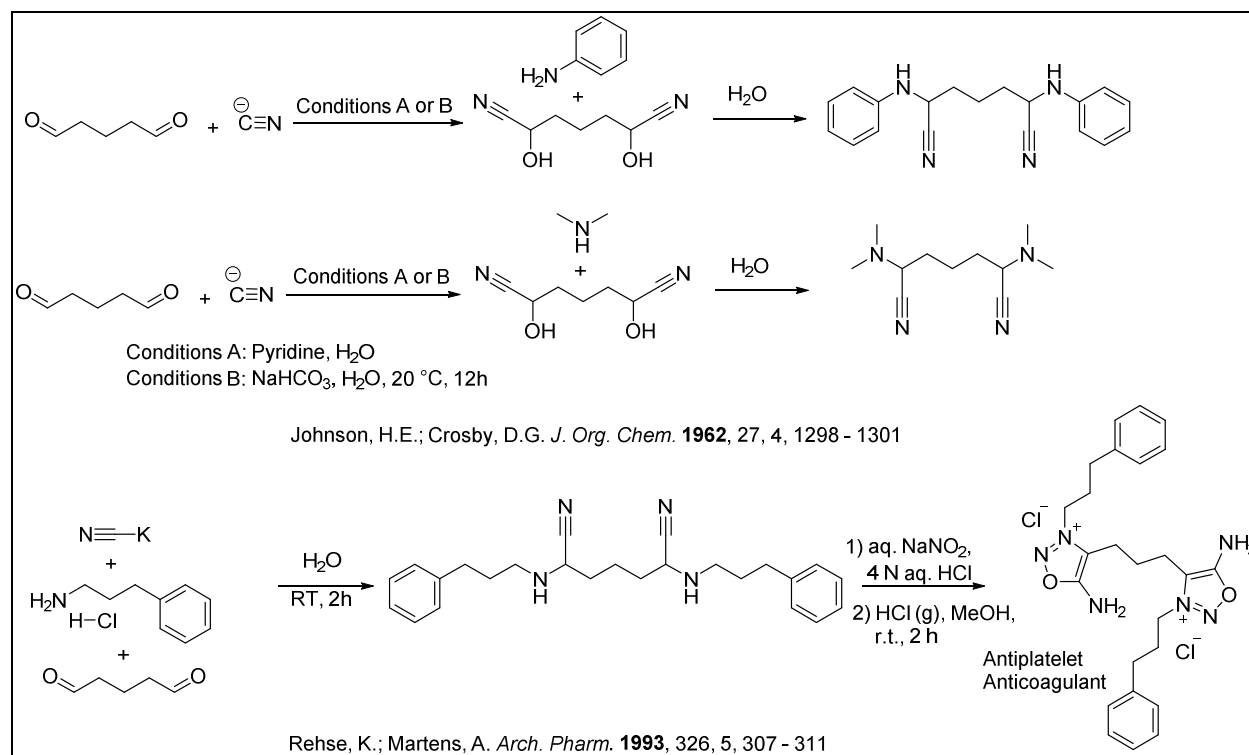
Scheme 2.3.1.3. Representative Examples of 2,6-Diaminopimelonitrile Preparation Reported

2.3.2. Optimization of the Difunctionalization Reaction

Having established a proof-of-concept for our novel reaction from the preliminary investigation, we conducted detailed optimization studies of the reaction involving 2-isocyanobiphenyl **2a** (**Table 2.3.2.1**) using four-row blue LED light bulbs as the source of irradiation. No reaction was observed in the absence of TMSCN, probably because the radical moiety of the photogenerated amine distonic radical cation (ADRC) with unquenched iminium ion site could not react with the divalent isocyano carbon. However, when a degassed mixture of **1a**, **2a**, TMSCN, and Ir(ppy)$_2$(dtbbpy)PF$_6$ (PC1) in methanol was irradiated with blue light for 21 h, the difunctionalization product was obtained in 82% NMR yield. Screening of other solvents (entries 3-8) revealed generally improved yields when alcohols were used as solvent, with 2-

ethoxyethanol (entry 5) giving an optimal 85% NMR yield (70% isolated) of the desired product. An even higher isolated yield (76%) was obtained in a separate reaction employing 5 equivalence of the isocyanide **2a**. Surprisingly, using the more acidic alcohol hexafluoroisopropanol (pka = 9.3) as solvent resulted in a significantly diminished yield. Switching to photocatalysts (**Figure 2.3.2.1**) that are more oxidizing in the excited state than Ir(ppy)$_2$(dtbbpy)PF$_6$ [Ir^{3+*}/Ir^{2+} = +0.66 V; Ir^{3+}/Ir^{2+} = -1.51] led to either poor yields (entries 9 and 10) or no product formation (entries 11 and 12). The inclusion of hydrogen atom donors together with the nucleophile TMSCN did not improve the yields (entries 13-16), and neither acid nor base had a positive impact on the yields (entries 17 and 18). The failure of hydrogen atom donors to improve the reaction efficiency rules out path a (5à8) in our working model (see, **Scheme 2.3.1.2**). Furthermore, the predomination of the dinitrile **7** as major product over the 6-substituted phenanthridine is consistent with our proposed reduction of the imidoyl radical to the anion **6** by the reduced photocatalyst (Ir^{2+}) instead of an oxidation to a nitrilium cation which would have facilitated the formation of **11** *via* electrophilic aromatic substitution (S$_E$Ar). Furthermore, both visible light irradiation and photocatalyst were found to be indispensable for the reaction to produce the desired product (entries 19-20) and no reaction was observed in their absence. Finally, we found that the reaction was slightly influenced by the concentration of the medium: decreased yield was observed when the concentration of the reaction medium was increased from 0.07 M to 0.10 M, or when it was decreased from 0.07 M to 0.05 M (entries 21 and 22).
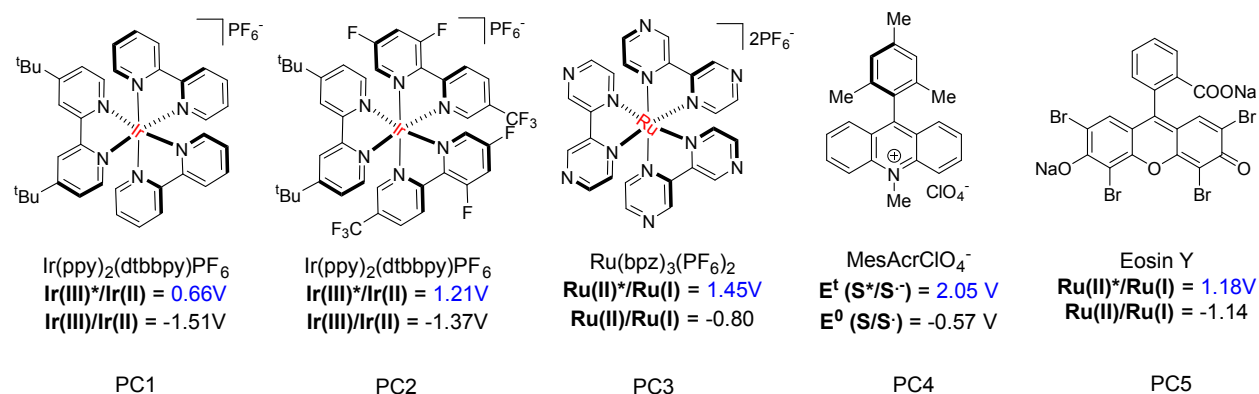
Figure 2.3.2.1. Photocatalysts Screened in the Difunctionalization of *N*-Cyclobutylanilines

Table 2.3.2.1. Optimization of the Difunctionalization reaction

Entry	Catalyst	Solvent	Additives	Time (h)	Yield 3a [%][a]
1	PC1	CH$_3$OH	-	30	Nd
2	PC1	CH$_3$OH	-	21	82 (61)[b]
3	PC1	tBuOH	-	21	75
4	PC1	HFIP	-	21	12
5	PC1	2-ethoxyethanol	-	21	85 (70)[b], (76)[b] [c]
6	PC1	DMSO	-	21	6
7	PC1	CH$_3$NO$_2$	-	21	10
8	PC1	CH$_2$Cl$_2$	-	21	9
9	PC2	2-ethoxyethanol	-	21	25
10	PC3	2-ethoxyethanol	-	21	24
11	PC4	2-ethoxyethanol	-	23	Nd
12	PC5	2-ethoxyethanol	-	20	Nd
13[d]	PC1	2-ethoxyethanol	PhSH	49	Trace
14[d]	PC1	2-ethoxyethanol	Et$_3$SiH	30	(40)[b]
15	PC1	2-ethoxyethanol	9H-fluorene	21	83
16	PC1	2-ethoxyethanol	1,4-cyclohexadiene	21	44
17	PC1	2-ethoxyethanol	*p*TsOH.H$_2$O or ZnCl$_2$	21	Nd

18	PC1	2-ethoxyethanol	K$_2$CO$_3$ (1 equiv)	21	56
19[e]	PC1 (dark)	2-ethoxyethanol	-	21	Nd
20	-	2-ethoxyethanol	-	30	Nd
21	PC1	2-ethoxyethanol (0.10 M)	-	21	(61)[b]
22	PC1	2-ethoxyethanol (0.05 M)	-	21	(59)[b]

Conditions: 1a (0.2 mmol, 1 equiv), 2a (3 equiv), TMSCN (3 equiv), PC (2 mol%) and solvent (3 mL), irradiated with four-strip blue LED light and setup wrapped with aluminum foil to reach an internal temperature of 60-65 °C. [a] 1H NMR yield determined using 1 equiv of CH2Br2 as internal standard. [b] Isolated yield. [c] 5 equiv of 3a was used. [d] Reaction concentration was 0.10 M. [e] Reaction was stirred in an oil bath set to 61 °C in a dark card box. Nd = not detected.

Next, we investigated the sensitivity of the reaction to varying photon flux and light intensities by conducting the reaction with different sources of irradiation (**Table 2.3.2.2**). The optimizations in **Table 2.3.2.1** had been conducted by irradiating the reaction mixture with four-strip blue LEDs and wrapping the reaction setup with aluminum foil to achieve an internal reaction temperature of 60 □C-65 □C. We have determined that irradiating the reaction mixture with two 18 W white LED lamps gives a reaction internal temperature of 60 □C and 34 W blue LED gives 53 □C. As seen in the table below, comparable product yields can be obtained when the reaction is irradiated with four-strip blue LEDs and wrapped with aluminum foil, or when two 18 W white LED lamps are used. Generally, decreasing the temperature also decreased the yield of the desired difunctionalization product **5a** but has no effect on the yield of the substituted phenanthridine side product **4a**.

Table 2.3.2.2. Screening sources of irradiation for the difunctionalization reaction.

100
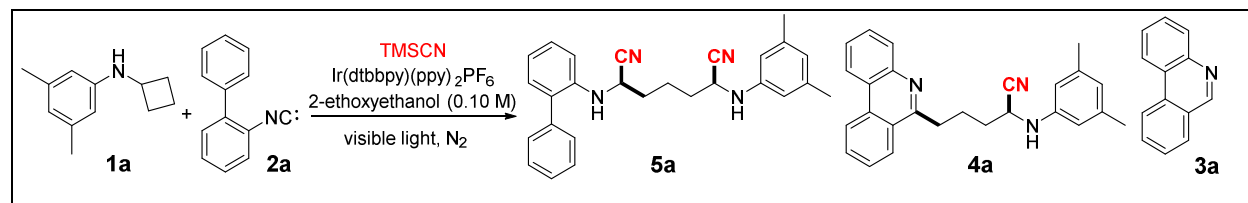
Entry	Light Source	Internal Temp. $\square$C	Time [h]	Yield 5a [%][a]	Yield 4a [%][a]	Yield 3a [%][a]
1	4-strip blue LEDs (reaction setup wrapped with aluminum foil)	62	21	61	2	2
2	Two 18 W white LED lamps	58	29	66	1	8
3	34 W blue LED lamp	52	29	47	3	17
4	2-strip blue LEDs	45-50	29	52	2	25
5	34 W blue LED lamp (with fan blowing down 10 cm from top of test tube)	27	29	15	4	11

Conditions: **1a** (0.2 mmol, 1 equiv), **2a** (3 equiv), TMSCN (3 equiv), Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%) and 2-ethoxyethanol (2 mL), degassed and irradiated with visible light. [a] Isolated yields.

2.3.3. Substrate scope of the Difunctionalization reaction

After the elaborate optimization studies and screenings, the optimal conditions were identified as: *N*-cyclobutylaniline (0.2 mmol, 1 equiv), isocyanide (3 equiv), TMSCN (3 equiv), Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%) and solvent (2 mL or 3 mL), irradiated with four-strip blue LED light with setup wrapped with aluminum foil to achieve an internal temperature of 60-65 °C. With the two sets of optimized conditions in hand (i.e., reaction concentrations of 0.07 M and 0.10 M), we probed the substrate scope of the reaction (**Table 2.3.3.1**).

With respect to metal-isocyanide bonding in coordination chemistry, it is known that by varying the nature of the alkyl/aryl substituent on the isocyano group, it is possible to switch the

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electronic features of isocyanides toward either carbon monoxide-like or cyanide anion-like behaviors.[214] Analogously, in our radical-mediated difunctionalization of ADRCs with isocyanides, we wondered whether by varying the nature of the alkyl/aryl substituent on the isocyano functionality, the substrate scope would reflect a tuning of the electronic features of the isocyanide towards more carbenoid (radical acceptor) character, favoring the desired transformation, or towards zwitterionic (nucleophile) character, disfavoring the desired reaction. Based on the aromatic IR intensities of isocyano substituted benzenes, Katritzky et al. have found that the isocyano group of phenyl isocyanide can act as a resonance donor (+M) or acceptor (-M) depending on whether it is placed para to an acceptor or donor substituent.[215] Certain *ab initio* calculations of the electronic structure of isocyanides, especially the isocyano group, have shown that the $-N \equiv C$ group is a powerful inductive acceptor that also pulls electron density via conjugation[216]; hence, it is a strong π and σ acceptor.[217] A comparison by Juchnovski and Tsenov of the integrated infrared (IR) intensities of the isocyano group, A($N \equiv C$), of substituted phenyl isocyanides with the σ constants of the substituents reveal a weak correlation, but suggests that donors likely favor the stretched carbenoid canonical form of the isocyano functionality (which undergoes radical addition), and withdrawers the contracted, polar zwitterionic canonical form.[218] **Table 2.3.3.1** shows the substrate scope of our difunctionalization reaction with respect to isocyanides.

Table 2.3.3.1. Substrate Scope with respect to Isocyanide.

Ar =

4a
61% (0.10 M)
70% (0.07 M)
59% (0.05 M)
76% (0.07 M, 5 equiv of **2**)

4b
59% (0.10 M)
72% (0.07 M)

4c
43% (0.10 M)
43 % (0.07 M)

4d
Not observed

4e
32% (0.07M)

4f
53% (0.07M)

4g
64% (0.10 M)
67% (0.07 M)

4h
69 % (0.10 M)
66% (0.07 M)
68% (0.07 M, 5 equiv of **2**)

4i
38% (0.10 M)
35 % (0.07 M)

4j
Not observed
(0.10 M or 0.07M)

4k
19% (0.10 M)

4l
25% (0.10 M)

4m
10% (0.10 M)
10% (0.07 M)

4n
Not observed
(0.07 M)

4o
10% (0.07 M)

4p
6% (0.07 M)

4q
7% (0.07 M)

4r
42% desired.
21% [4+2] product
(NMR yields)

Conditions: **1a** (0.2 mmol, 1 equiv), **2** (3 equiv), TMSCN (3 equiv), Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%) and 2-ethoxyethanol (2 mL), degassed and irradiated with four-strip blue LEDs with setup wrapped with aluminum foil. [a] Isolated yields.

Phenyl isocyanides with the strongly electron-withdrawing/ π-accepting substituents CF$_3$ or CN (**4k** and **4l**) or a strongly "resonance donating"/ π-donating substituent (such as **4i**, **4j**, and **4o**) performed poorly in the difunctionalization reaction. On the other hand, those bearing weak π-donors like phenyl (**4a**, **4b**) or alkyl (**4f**, **4g**, and **4h**) groups were well tolerated, affording fair to good yields of the desired product. Also, the difunctionalization reaction tolerated steric hindrance around the isocyano functionality, as phenyl isocyanides **4a** and **4g** bearing ortho substituents gave good yields of the desired product (70% and 67% respectively). Generally, phenyl isocyanides

bearing an -OR group performed poorly in the difunctionalization including the moderately electron-rich isocyanide **4m** which possess a *p*-methoxybenzoate substituent. Much to our surprise, phenyl isocyanide with a methoxy substituent was tolerated when the OMe group was in the para position (**4i**) giving 35-38% of the product, but it was unreactive when it was in the ortho (**4j**) position. Seung has reported that electronegativity (or induction), rather than electron-donating resonance, is the main factor that influences the sensitivity of isocyanide stability to π-donating N-substituents on the isocyanide moeity,[164] but, as was explained earlier, strong electron-withdrawers disfavor carbenoid (carbene-like) canonical form of isocyanide radical acceptor which is able to react to give the desired product. Thus, the strikingly contrasting effects of the para and ortho OMe groups can be rationalized in terms of the strong negative induction (-I) of the proximal ortho OMe group of **4j** on the isocyanide reactivity disfavoring the transformation, compared with a relatively small induction from the more remote para-OMe of **4i**. This would be consistent with our observation that isocyanides bearing substituent groups that exhibit a strong electron-withdrawing effect react poorly or are completely unreactive in the difunctionalization reaction.

In the halide series, the isocyanide was completely unreactive when the most deactivating (and also the weakest π-donating) substituent in the series, i.e. I, was the para substituent on the phenyl ring (**4d**). On the other hand, the more π-donating halogens Br and F were tolerated (**4c** and **4e**) and gave acceptable yields of 42% and 32% respectively. Furthermore, isocyanides with the σ-electron donating alkyl N-substituents, such as TosMIC **4p** and 1-adamantyl isocyanide **4q**, performed poorly in the difunctionalization. These types of isocyanides are very nucleophilic and most likely favor the zwitterionic isocyanide canonical form. Finally, when substrate **4r**, bearing the isoelectronic alkynyl and isocyano groups, was subjected to the reaction conditions, both the difunctionalization product (from the radical reaction at the isocyano site) and the [4+2] annulation

product (from the reaction at alkyne) were obtained in 42% and 21% respectively (2:1). This is consistent with the findings in Prof. Alabugin's computational work in which radical addition to isocyanides was found to have a lower barrier than the addition to alkynes, even though the latter is more thermodynamically favorable than the former (by 6-16 kcal/mol). This was attributed to the presence of the additional transition state (TS) stabilizing effects in the case of isocyanide which lowers the intrinsic barriers in the addition to isocyanides.

Table 2.3.3.2. Substrate Scope with respect to N-cyclobutylaniline.[a]

Conditions: **1a** (0.2 mmol, 1 equiv), **2** (3 equiv), TMSCN (3 equiv), Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%) and 2-ethoxyethanol (2 mL), degassed and irradiated with four-strip blue LEDs with setup wrapped with aluminum foil. [a] Isolated yields.

The substrate scope with respect to *N*-cyclobutylanilines (**Table 2.3.3.2**) similarly revealed a limited functional group tolerance. Here, anilines such as **4g** and **4h** bearing a strongly electron-donating (i.e., OMe), or **4i-4n** and **4t** with strongly electron-withdrawing substitutents (e.g. CF$_3$, CN, pyridyl) on the phenyl ring were unreactive in the difunctionalization reaction. Only anilines with weakly electron-donating groups like Me (**4a**), *i*Pr (**4b**), tBu (**4f**), or Ph (**4c** and **4d**) reacted give to the difunctionalization products in fair to good yields. The very limited functional group tolerance in the difunctionalization involving isocyanide is surprising since all these *N*-cyclobutylanilines uneventfully participated in our previous difunctionalizations involving allyl phenyl sulfones or α-CF$_3$-styrenes, and our reported [4+2] annulation with alkynes. Isocyanide have been reported in literature to preferentially react as a nucleophile with the charged site of distonic radical cations, or as base to deprotonate distonic radical cations bearing an acidic charged site, rather than add to the radical site (see **Scheme 1.5.1** hereinbefore). In some cases of our current scope studies where no desired product was detected, such as in the case of **4i**, **4k** and **4l**, we isolated small amounts of undesired side reaction product corresponding with the aniline N-H addition to the isocyanide carbon without ring-opening, followed by cyanide addition to the resulting imine, and also side product formed from addition of isocyanide to α-position of aniline and subsequent CN trapping by the resulting iminium ion. Therefore, we synthesized cyclobutylanilines **4y** and **4z** which, upon ring-opening, would presumably produce distonic radical cations with inert charged sites (due to resonance or (pre)aromatization), and **4w** with coordinatively saturated or nonacidic charged site, but these also failed to work under the reaction conditions. Surprisingly, when the isocyanide was switched from 2-isocyanobiphenyl to 3,5-

dimethylphenylisocyanide, p-methoxycyclobutylaniline **4g** which was completely unreactive with the former isocyanide now reacted to give 56% yield of the expected product (**Table 2.3.3.3**). EDGs like OMe are known to lower the oxidation potential of anilines, after initial SET oxidation, by stabilizing the amine radical cation through resonance, while also slowing the rate of ring-opening.[219] Thus, the utilization of the less sterically hindered 1-isocyano-3,5-dimethylbenzene as radical acceptor for **4g** probably helped to drive the ring-opening, thereby favoring the products. In addition, the yields obtained with the new isocyanide were generally improved for the same anilines probed with 2-isocyanobiphenyl.

Table 2.3.3.3. Surprising results in the Difunctionalization reaction
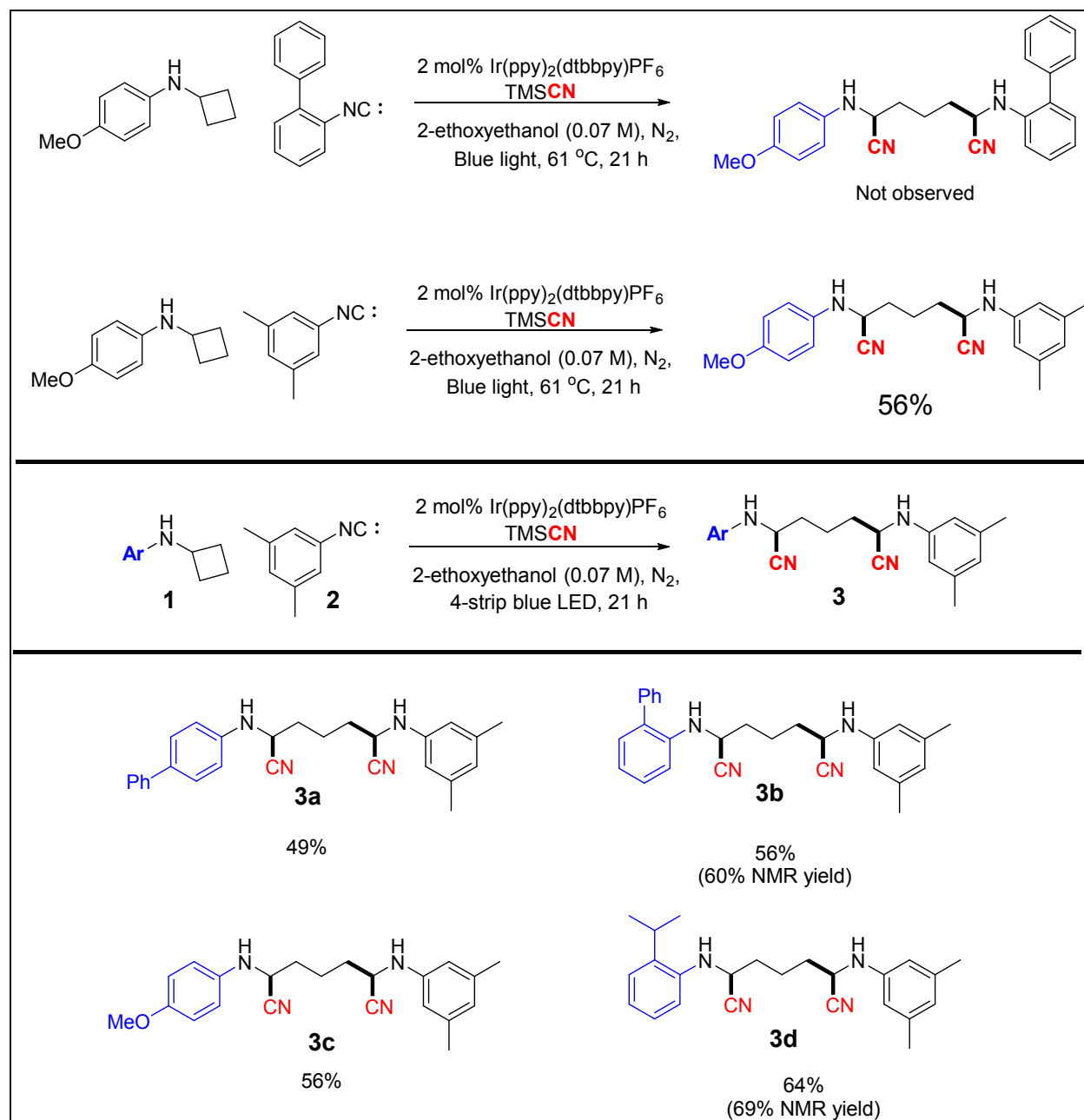
Conditions: **1** (0.2 mmol, 1 equiv), **2** (3 equiv), TMSCN (3 equiv), Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%) and 2-ethoxyethanol (3 mL), degassed and irradiated with four-strip blue LEDs with setup wrapped with aluminum foil. [a] Isolated yields.

Control Studies

We investigated the curious lack of reactivity of the *N*-cyclobutylanilines bearing moderately and strongly electron-donating or electron-withdrawing substituents on their phenyl ring by conducting control experiments in the absence of the isocyanide reaction partner (**Scheme 2.3.3.1**). Interestingly, various anilines bearing electron-donating, electron-withdrawing, and electron-neutral substituents could undergo the ring-opening/cyanide trapping to give the corresponding alphaaminonitriles, consistent with their behavior in our previous difunctionalizations and [4+2] annulation. The aniline with the weakly EDG substituent (i.e., methyl groups) on phenyl ring reacted to give NMR yield of 88%, and all the other anilines probed gave good yields (ca. 58%) of the aminonitrile, except for the very electron-difficient *N*-cyclobutylpyridin-2-amine which failed to undergo the ring-opening even in the absence of isocyanide. The results suggest that when present, isocyanide does inhibit the ring-opening of some anilines, probably by converting the amine radical cation to an iminium ion *via* α-deprotonation.[100, 118, 220] This is possible as isocyanides RNC: have been reported to have higher proton affinities (PA ≈ 199-207 kcal/mol) than even the corresponding cyanides RCN, regardless of the identity of R.[221] Ionic reactions of this type are presumably rapid and preclude the reactions at the radical site.[131]

Based on the foregoing rationalization, it can be supposed that a negative inductive effect (-I) on the HN$^{+\bullet}$ moiety of the radical cation, such as in the cases of Cl, CN, CF$_3$, or pyridine as substituent on the aniline, will render the α-C-H bond more acidic and thus susceptible to the deprotonation by isocyanide. On the other hand, a positive induction (+I) on the HN$^{+\bullet}$ of the radical cation, such as in the case of alkyl substituents, would stabilize the radical cation by reducing its electrophilicity and consequently decreasing the acidity of the α-C-H, thus rendering the α-

deprotonation less likely. Also, the ability of *N*-cyclobutylanilines with phenyl substituent to undergo the difunctionalization can be rationalized in terms of negative mesomeric effect (-M) of Ph which renders the nitrogen atom of its distonic radical cation coordinatively saturated when formed, thus allowing the radical site to react as normal C-centered radical with isocyanide.
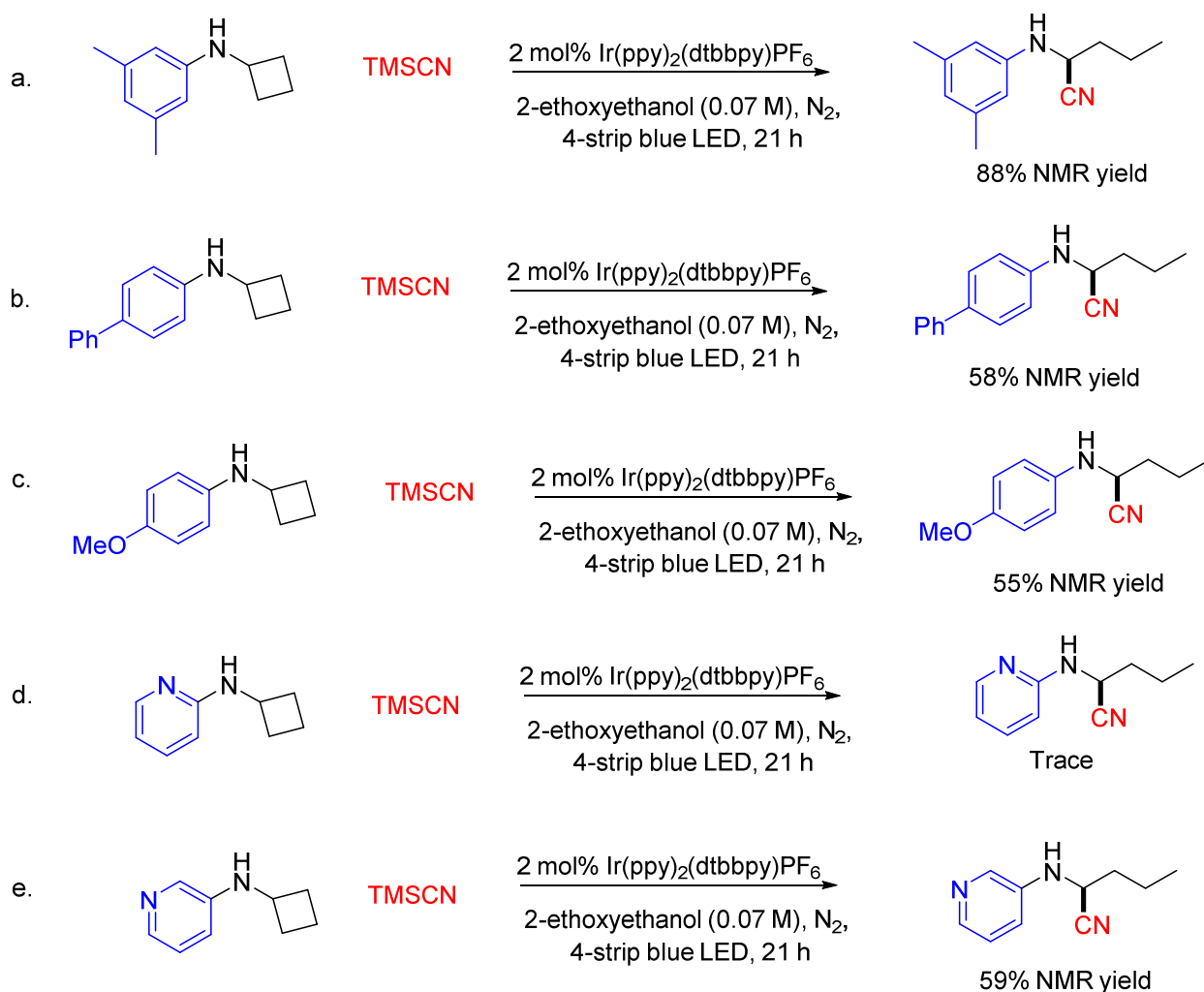
Scheme 2.3.3.1. Control Studies: Investigating the Ring-opening in Absence of Radical Acceptor

A summary of the results for the difunctionalization of *N*-cyclobutylanilines with isocyanide and TMSCN is illustrated in **Table 2.3.3.4**. The results reveal the inferior reactivity

isocyanide as radical acceptors compared with allyl phenyl sulfones and α-CF₃-styrenes used in our previously developed difunctionalization reactions as certain anilines which reacted effortlessly in the previous reactions to produce the desired products in decent yields failed to react at all in the current difunctionalization involving isocyanide. Also, limited substrate scope of the current difunctionalization strategy illustrates the unique challenge involved in exploiting the dichotomous reactivities of the two chemical species—namely amine distonic radical cations and isocyanides—in synthesis.

Table 2.3.3.4. Summary of results for the difunctionalization with Isocyanide and TMSCN

Cyclobutylaniline	Isocyanide	Yield
Strong EWG	Strong EDG	?
Strong EWG (2-pyr)	Strong EWG (4-CF3)	7%
Strong EDG (4-OMe)	Strong EWG (4-CF3)	15%
Strong EDG	Strong EDG	?
Strong EDG (4-OMe)	Weak EDG (3,5-diMe)	56%
Strong EWG (2-Pyr, 3-pyr)	Weak EDG (3,5-diMe, 2-Ph)	No reaction, 16% NMR
Weak EWG (4-Cl)	Weak EDG (2-Ph)	No reaction
Weak EWG (3,5-diMe)	Strong EDG (4-OMe)	35% NMR
Weak EDG (3,5-diMe)	Weak EWG (4-Br, 4-I, 4-F)	43%, 32%, 0%
Weak EDG (3,5-diMe)	Strong EWG (4-CF₃)	19%
Weak EDG (3,5-diMe)	Strong EDG (4-OMe, 2-OMe)	38%, 0%
Weak EDG	Weak EDG	
(3,5-diMe)	(3,5-diMe)	69%, 56%, 49%, 64%
(2-Ph)	(2,6-diMe)	64%,
(4-Ph)	(2-Ph)	70%, 24%, 12%, 31%
(iPr)	(4-Ph)	65%,
	(2-OAc)	10%,

2.4. Future work

The experimental data obtained in the difunctionalization of *N*-cyclobutylanilines with TMSCN and isocyanide delineates the substrate scope as well as provide some mechanistic insights for the reaction. It is clear, for example, that anilines with strongly electron-donating and strong electron-withdrawing substituents on the phenyl ring do not react in the difunctionalization reaction. Further work on this chemistry is needed to better understand how the radical acceptor may be inhibiting the ring-opening of some types of the *N*-cyclobutylanilines. This can be accomplished this through Stern Volmer fluorescence quenching studies.

Also, we suspect that two main factors account for the challenging difunctionalization involving isocyanides: 1) the isocyanide interacts with the amine radical cation (ARC) prior to the ring-opening and a competitive α-deprotonation may convert the ARC to an iminium ion which cannot undergo the ring-opening; 2) the reduction of imidoyl radical to the imidoyl anion is more challenging than the reduction of sulfonyl radical or the radical adduct with α-CF$_3$styrenes. To overcome the issue of α-deprotonation, a new type of substrates, namely *N*-cyclobutylbenzamides and *N*-cyclobutylsulfonamides, can be employed together with a weak base (such as K$_3$PO$_4$ or *Bu$_4$N*[*OP*(O)(OBu)$_2$]) to generate the desired carbon-centered radicals via PCET-assisted, amidyl radical-mediated ring-opening (**Scheme 2.4.1**a). Since amides have higher oxidation potential, a more strongly oxidizing photocatalyst may also be required. For the 2nd issue, we envision that the addition of oxidants such as persulfates or Cu(II) salts to oxidize the imidoyl radical intermediate to the corresponding imidoyl cation, which will then be intercepted by the CN$^-$ to give the difunctionalization product or undergo arylative cyclization with ortho phenyl ring to produce the 6-substituted phenanthridine product which is well precedented in literature.
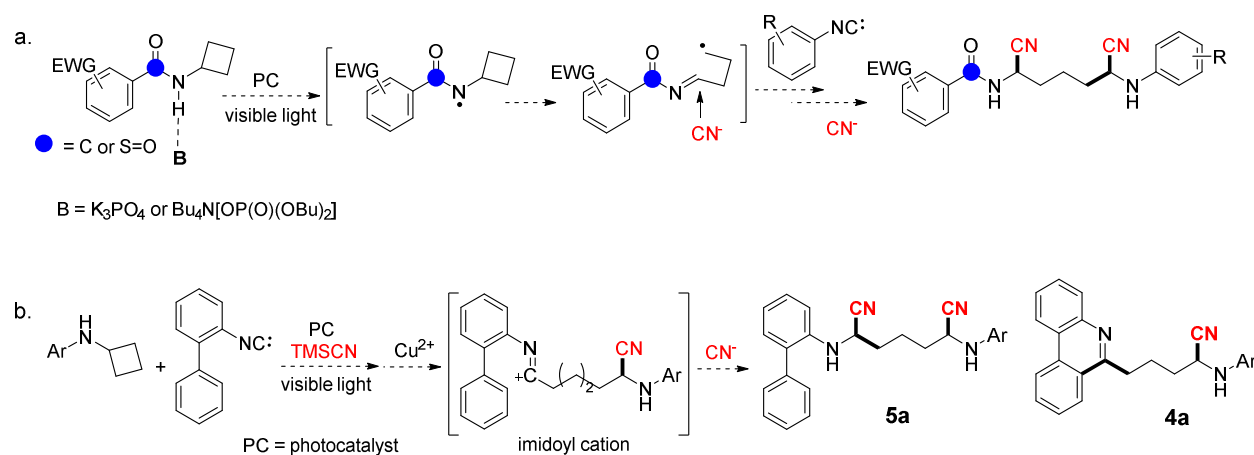
Scheme 2.4.1. Future Work on the Difunctionalization of N-cyclobutylanilines with Isocyanide and TMSCN.

2.5. References

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Chapter 3

Resonance-Assisted Deconstruction/Distal Alkynylation of Strained *N*-Cycloalkane Rings Using Hypervalent Iodine (III) Reagents under Photoredox Catalysis

3.1. Introduction

3.1.1. Deconstructive Distal functionalization of Strained N-cycloalkane Rings

Although seemingly counterproductive, the strategy of breaking apart aliphatic rings present in biomolecules followed by selective functionalization is a highly attractive approach for scaffold hopping[222-224] and the building up of molecular complexity in organic synthesis. The key step of this strategy involves the selective cleavage of inert C-C single bonds, a feat which presents a difficult challenge to organic chemists due to the high bond dissociation energies of the C-C bond. Compared with direct Sp^3 C functionalizations involving the selective activation/functionalization of $C(sp^3)$-H bonds,[225] ring deconstruction/functionalization strategies have the ability to unmask latent functional groups in the substrates as well as introduce two new functional groups at predefined distances along the open chain, dictated by the size of the original ring.

The pioneering approaches to $C(sp^3)$-$C(sp^3)$ cleavage, beginning with Eschenmoser[226] in the 1950s, and followed by Grob,[227] Beckmann, and others,[228] involved heterolytic fragmentation and were noncatalytic. Later, transition metal-catalyzed activation and cleavage of C-C bond in strained rings emerged as efficient means for straightforward access to structurally diverse molecular motifs with varying degrees of complexity.[229] The C-C cleavage mediated by TMs can occur either via direct oxidative addition[225, 230] (involving strain release of small rings, and chelation assistance, decarbonylation, etc, in the case of unstrained rings[231]) or by β-carbon

elimination.[232] While significant progress has been made in this area, these methods usually require harsh reaction conditions and their application for C-C bond cleavage in deconstructive functionalizations usually suffer from poor selectivity due to competitive C-H bond activations.

Recently, radical-mediated C-C bond cleavage has emerged as a powerful disconnection approach for achieving selective ring deconstruction and functionalization under mild conditions.[195, 233-235] Since the Schaafsma and coworkers disclosed in the 1960s that Cu^{2+}- and Fe^{3+}-promoted one-electron oxidation of cyclopropanols could produce ring-opened free-radical intermediates,[236] several works involving the $C(sp^3)$-$C(sp^3)$ cleavage of both strained and unstrained cycloalkanols *via* TM-assisted homolysis of the strong O-H bond for achievement of remote functionalization of the alcohols have reported by the groups of Nasaraka,[237, 238] Murakami,[239] Zhu,[196, 197, 240] Loh,[241] Duan,[242, 243] Zhang,[244] Lopp,[245] Orellana,[246] Chiba,[237, 247] and others.[196] In these reactions, sub-stoichiometric amounts of the various TM catalysts allow for the homolysis of O-H bonds of the cycloalkanols to generate reactive alkoxy radicals which mediate the C-C cleavage to give distal keto-radicals, and diverse distal functionalizations of the deconstructed alcohols have been achieved, including halogenation, olefination, alkynylation, allylation, alkoxylation, amination, azidation, sulfurylation, etc. Also, TM-catalyzed reductive fragmentation and functionalization of strained and/or unstrained cycloketone oxime derivatives *via* iminyl radical-mediated C-C cleavage have also been reported by the groups of Selander,[248] Shi,[249] Guo,[250] Liu,[251] Yu,[252] and Wang.[253]

Much recently, visible-light photoredox catalysis has become attractive avenue for C-C bond activation and controllable radical-mediated cleavage in organic synthesis owing to its characteristically mild reaction conditions, unique selectivities, great functional group tolerance, and general environmental friendliness. It has been applied to the deconstructive functionalization

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of strained and/or unstrained cyclic alcohols by the groups of Leckta,[254] Chen,[255] Knowles,[256] Xia,[257] Zuo,[258] and others,[259] and of cycloketone oxime derivatives by the groups of Chen,[260] Xiao,[261] Zhou,[262] Leonori,[263] Waser,[264] and others.[223, 265, 266] The conversion of the comparatively weak C-O (BDFE ≈ 105 kcal/mol) and C=N (BDFE ≈ 147 kcal/mol) bonds of highly reactive cycloalkoxy and cycloalkyliminyl radical intermediates into the much stronger C=O (BDFE ≈ 178 kcal/mol) and C≡N (BDFE ≈ 213 kcal/mol) bonds respectively, serves as additional thermodynamic driving force for the ring opening. Visible-light assisted deconstructive functionalization of cycloalkanamines *via* cycloalkyl aminium or aminyl radical-mediated ring-opening processes have also been reported by the research groups of Zheng[16, 18, 19, 21, 105, 107, 109] and Waser,[138] but these have been limited to strained three- and four-membered rings. In the deconstruction of strained cycloalkanols, cycloalkanone oximes, and cycloalkanamines, a strain relief-driven C-C bond activation provides the main thermodynamic driving force for the ring opening. In all these reactions, the ring-opening event generates a reactive distal sp^3 C radical which can be quenched by suitable radical acceptors to afford diverse γ- and δ-functionalized products, bearing an unmasked functional group at the α-position in the case of alcohols and cycloketone oxime substrates.
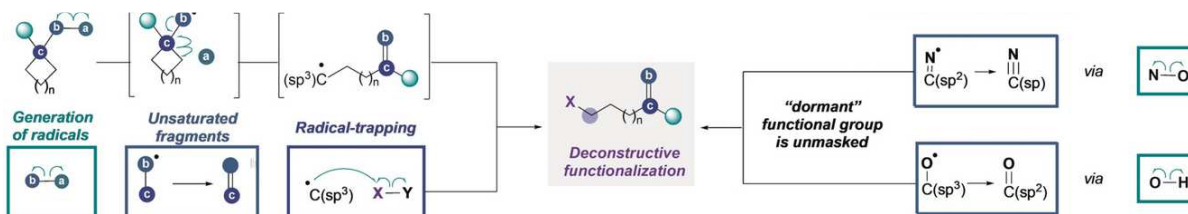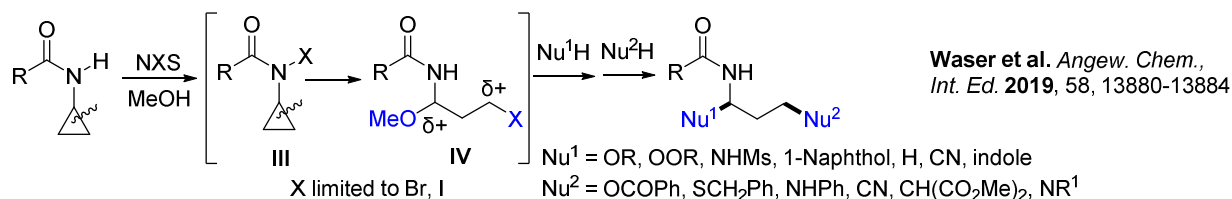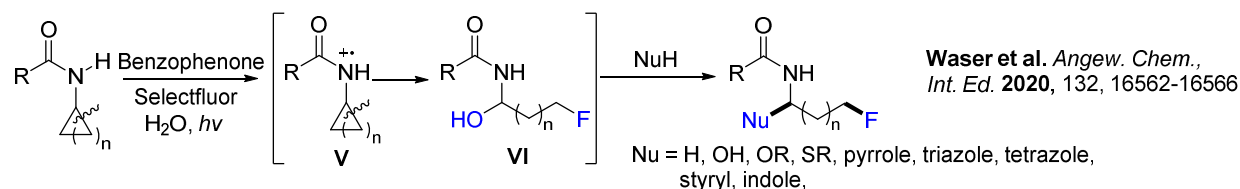

Figure 3.1.1.1. Deconstructive Functionalization via Alkoxy, Iminyl, and Aminium Radical-mediated Ring-opening (Adapted from: Morcillo, S.P. *Angew. Chem. Int. Ed.* 2019, 58, 40, 14044-14054. Copyright 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim)
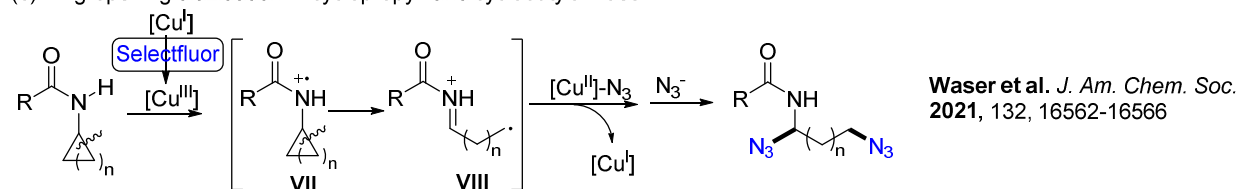
(a) HLF reaction-inspired ring-opening halogenation of cyclopropylamides

Waser et al. *Angew. Chem., Int. Ed.* **2019**, 58, 13880-13884

Nu^1 = OR, OOR, NHMs, 1-Naphthol, H, CN, indole
Nu^2 = OCOPh, SCH$_2$Ph, NHPh, CN, CH(CO$_2$Me)$_2$, NR^1

X limited to Br, I

(b) Oxidative ring-opening fluorination of cyclopropyl- and cyclobutylamides

Waser et al. *Angew. Chem., Int. Ed.* **2020**, 132, 16562-16566

Nu = H, OH, OR, SR, pyrrole, triazole, tetrazole, styryl, indole,

(c) Ring-opening diazidation of cyclopropyl- and cyclobutylamides

Waser et al. *J. Am. Chem. Soc.* **2021**, 132, 16562-16566

(d) Ring-opening alkynylation of cyclopropyl- and cyclobutylamides with Iodine(III)-alkynes

Chen et al. *ACS Catal.* **2021**, 143, 31, 11969-11975

BI'-OAc
non-covalent activation

BI'-OAc

Nu = OH, OR, SR, CN, indole, naphthol
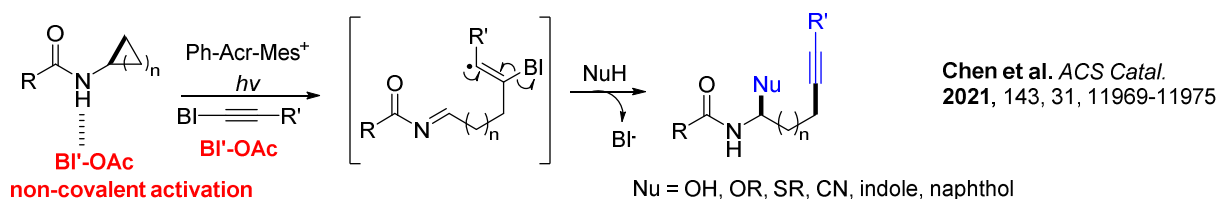
Scheme 3.1.1.1. Reported Ring-opening/Distal functionalizations of Strained Aminocycloalkanes

Whilst with cycloalkoxy and cycloalkyliminyl radical-mediated ring-opening derivatizations, diverse distal functionalizations have been achieved, the earlier reports of deconstructive distal functionalizations of strained cycloalkylamines *via* aminyl or aminium radical intermediates by Waser's group were limited to halogenations (i.e., bromination,[138] iodination,[138] and fluorination[137]), and the introduction of unsaturated functional groups at the distal position of a ring-opened cycloalkylamine was unexplored. The ring-opening/distal brominations and iodinations (**Scheme 3.1.1.1**b) were inspired by the Hofmann–Löffler–Freytag

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(HLF) reaction, and the use of the halogenation reagents *N*-bromo and N-iodo succinamides (NBS and NIS) enabled the conversion of the N-H bond of cyclopropylamide to an N-X bond. This weak bond undergoes homolytic cleavage at room temperature to afford the N-centered radical which mediates the C-C bond activation and cleavage to produce a highly reactive 1,3-dielectrophilic imine with the distal C-centered radical, instead of undergoing the HAT typical of the HLF reaction. Following the interception of X• at the distal radical site, the imines could either be isolated in high yields in its more stable N,O-acetal form, or converted to diverse α,γ-difunctionalized amines through a sequence of nucleophilic addition and SN$_2$ reactions. On the other hand, the ring-opening fluorination reaction proceeded by the photo-induced oxidative ring-opening of cyclopropyl- and cyclobutylamides *via* an aminium radical intermediate (**Schemes 3.1.1.1**c and **1.3.7** hereinbefore). The recently developed ring-opening difunctionalization reactions of N-cyclopropyl- and N-cyclobutylanilines by the Zheng group (discussed under **section 2.2** hereinbefore) involving allyl phenyl sulfones, α-CF$_3$-styrenes, and isocyanides as radical acceptors are also examples of deconstructive/refunctionalization of strained aminocycloalkanes mediated by aminium radicals (or amine radical cations).

In August 2021, Waser and coworkers reported the aminium radical-mediated, Cu-catalyzed oxidative ring-opening diazidation/nucleophilic substitution sequence for the synthesis of 1,3- and 1,4-diamines from cyclopropyl- and cyclobutylamides respectively under non-photo conditions (**Scheme 3.1.1.1**d).[267] In the strategy employed, the amine group of the starting material played a dual role: first, as an activating group promoting the diazidation of an adjacent σ C-C bond, and, second, to promote the azide dissociation at the aminal position allowing for introduction of various nucleophiles. This work was followed immediately by Chen and coworkers' report of the first visible-light-catalyzed selective C(sp^3)-C(sp^3) cleavage/distal

alkynylation of cyclopropyl- and cyclobutylamides (i.e. protected amines) for the synthesis of aminoalkynes which involved the transfer of an alkynyl functional group to the distal position of the deconstructed aminocycloalkane (**Scheme 3.1.1.1**e).[200] In Chen's work, catalytic amounts of the cyclic iodine(III) reagent BI'-OAc was used to facilitate the one-electron oxidation and ring-opening *via* non-covalent activation of the amide N-H bond, and alkynyl hypervalent iodine reagents (AHIRs) were employed to transfer the alkyne group as an electrophile. This is the first and only example of a deconstruction/distal alkynylation of a strained cycloalkanamine to date. The research groups of Zheng and Stephenson have previously reported photocatalyzed ring-deconstruction/refunctionalization reactions of strained aminocycloalkanes with unsaturated functional groups (i.e., alkenes or alkynes), but these proceeded by cycloaddition and the loss of a degree of unsaturation in the functional group, and in none of the cases was the unsaturated functional group transferred whole to the deconstructed aminocycloalkane in the product (**Scheme 3.1.1.1**a).[16, 18, 19, 21, 107, 109, 142, 192, 193, 268] In these reactions, cyclopropyl- and cyclobutylanilines underwent photoinduced SET oxidation to the aminium radical, which upon ring-opening to the amine distonic radical cation (ADRC), adds to the alkene or alkyne to generate an alkyl radical (in the reaction involving alkenes) or an alkenyl radical (in the reaction involving alkynes). This is then trapped intramolecularly by a highly reactive iminium radical moiety of the ADRC to afford formal cycloaddition products instead of a distally olefinated or alkynylated amine product.

3.1.2. Cyclic Alkynyl Hypervalent Iodine(III) Reagents in Photocatalyzed Ring-opening/Alkynylation of Strained Cycloalkane Rings.
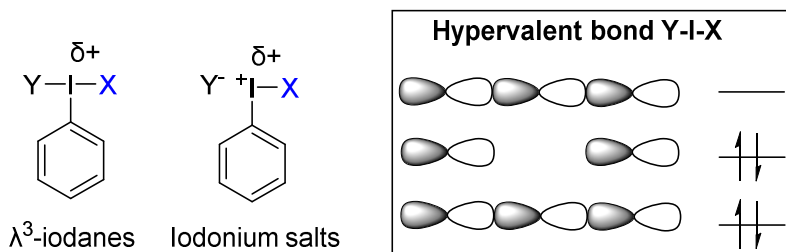
Alkynes are versatile functional groups in organic synthesis, and they are common building blocks in medicinal chemistry, materials science, and synthetic chemistry. Thus, the development of new methods for adding them into organic molecules is highly desirable.[269] Traditionally,

alkynes have been added as nucleophiles to organic compounds. However, hypervalent iodine reagents have been found to provide a unique possibility for the development of electrophilic alkyne synthons by inverting the normal polarity of the alkyne functional group (i.e., so-called the concept of Umpolung introduced by Seebach). Alkynyliodonium salts have been widely utilized to alkynylate nucleophiles, particularly soft carbon nucleophiles and heteroatoms, since 1985 (**Figure 3.1.2.1**a). They have had a particularly big impact on the production of very valuable ynamides. Despite this, their use has been restricted due to their instability. Since 2009, in a number of transformations, the more stable cyclic alkynyl hypervalent iodine(III) reagent, viz., ethynylbenziodoxol(on)e (EBX) reagents, have been found as improved electrophilic alkyne synthons. These are readily prepared and have shelf-stableness.[270] They can be used to alkynylate acidic C–H bonds using transition metal catalysts or aromatic C–H bonds utilizing bases.[271] They have also been very successful for the functionalization of radicals and in transition metal-catalyzed domino reactions. First synthesized by the Ochiai group,[272] they have been explored extensively by the Waser group[264, 271, 273-276] and others[63, 200, 277-279] for their use in electrophilic alkynylation reactions. They have been used to successfully alkynylate a wide range of heteroatoms such as N,[280] O,[281] S,[282, 283] and P.[284]

(a) X⁻ Examples of nucleophiles for functional group transfer

Heteroatoms		C1 synthons	Larger C nucleophiles
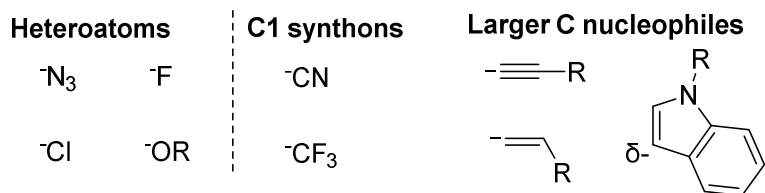
(b) X⁺ Low stability hypervalent iodine reagents for reactivity Umpolung

λ³-iodanes   Iodonium salts

Hypervalent bond Y-I-X

(c) X⁺ via benziodoxol(on)es: Enhanced stability for broad applications

Z = O, (CH₃)₂
(CF₃)₂

Ochiai 1991
Zhdankin 1996

Zhdankin
1994-1996
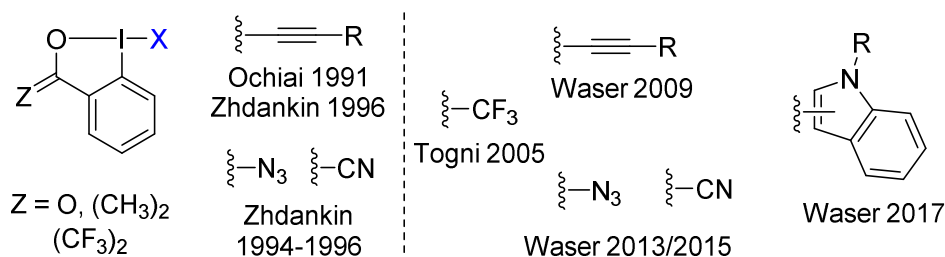
Togni 2005

Waser 2009

Waser 2013/2015

Waser 2017

Figure 3.1.2.1. Classical Reactivity and Umpolung with Hypervalent Iodine Reagents[276]

Structurally, the bonding of iodine compounds differs from that of the light main-group elements due to the high size of the iodine atom. Interatomic π-bonding, which is common in light p-block element compounds, is absent in iodine compounds. Instead, the overlap of the 5p orbital on the iodine atom with the orbitals on the two ligands L forms a linear three-center-four-electron (3c-4e) bond (L–I–L). A "hypervalent bond" is the moniker given to the 3c-4e bond.[285] The presence of a weak, highly polarized hypervalent bond explains the unique structural characteristics and reactivity pattern of polyvalent iodine compounds.[286] The hypervalent bond comprising four electrons on three atoms is fascinating not only from a theoretical point of view,

but also in practical synthesis because it confers an exceptional reactivity to these reagents, allowing them to imitate more toxic and expensive late transition metals. The high reactivity of hypervalent iodine reagents can result in instability in the presence of strong bases, transition metals, or when heated. However, the incorporation of the iodine atom into a heterocycle in cyclic hypervalent iodine compounds such as ethynylbenziodoxol(on)e (EBX) tend to impacts enhanced stability to such compounds.[287] Additionally, aryl λ^3-iodanes ArIXY (where X, Y = heteroatom ligands and others) assume a T-shape geometry with near linear X-I-Y triad; thus *trans*-effect in the hypervalent bond which places more electron density at the ends (X, Y) than at the center also helps to stabilize these λ^3-iodanes.[288] Finally, structural modifications or the use of additives can be used to further modulate reactivity (**Figure 3.1.2.2**).[276, 289]
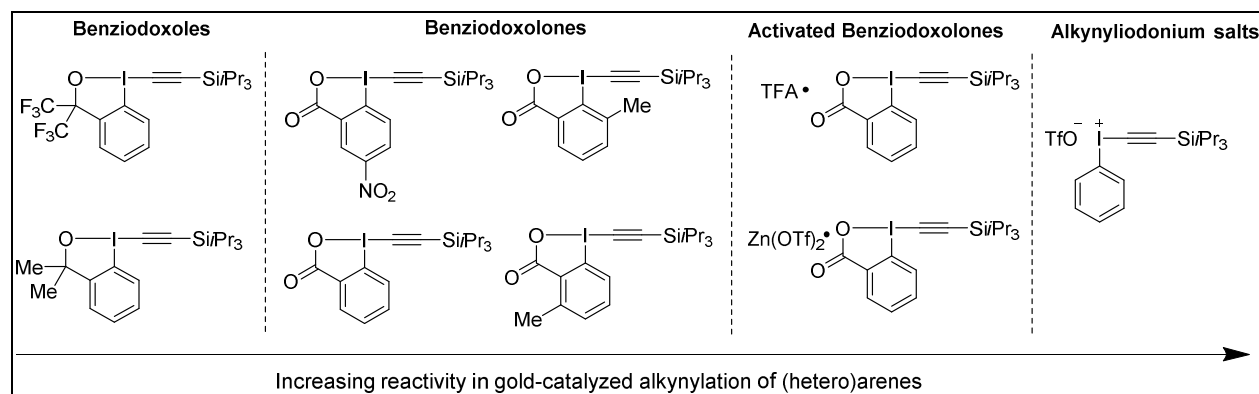
Figure 3.1.2.2. Modulating the Reactivity of EBX Reagents by Structural Modifications and Use of Additives[276]

As efficient group transfer reagents, akynyl hypervalent iodine reagents (AHIRs) have been employed as radical acceptors in the visible-light-promoted deconstructive distal alkynylation of strained/less strained cycloalkanols,[255] cycloketone oximes,[264] cyclic thioeters,[275] and, much recently, cycloalkylamides.[200]

The Duan group reported in 2015 an efficient $Na_2S_2O_8$-promoted tandem ring-opening/alkynylation of tertiary cycloalkanols with alkynyl hypervalent iodide reagents for the synthesis of β-, γ-, and δ-alkynylated ketones under thermal conditions.[243] In 2016, Chen and coworkers combined photocatalysis and cyclic iodine(III) reagent (CIR) catalysis under blue LED irradiation to establish a new and powerful technique for alkoxyl radical production. This reaction tolerated a variety of strained cyclopropanols, cyclobutanols, and even linear alcohols, demonstrating the protocol's versatility. An SET approach is used to convert alcohol-BI, which is produced in situ from the benziodoxole (BI-OAc)/alcohol complex, to the alkoxyl radical. The alkyl radical is then formed by β-C–C bond fragmentation of the photogenerated alkoxyl radical, which reacts with the alkynyl carboxylate-bound benziodoxole to furnish the desired distal alkynylation product. The Duan group later developed a practical, photocatalyst-free C3-ketoalkylation of quinoxaline-2(1H)-ones by oxidative ring-opening of cycloalkanols based on this technique.[290]
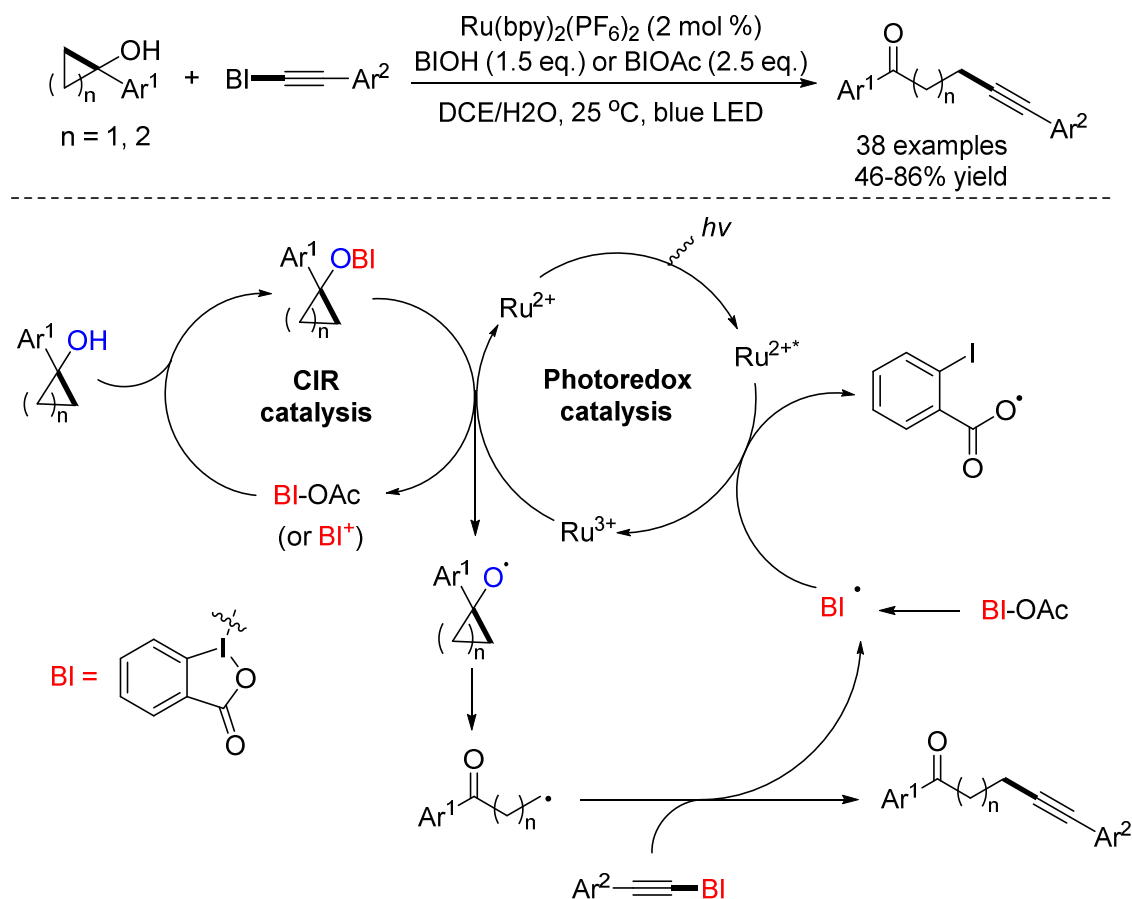
Scheme 3.1.2.3. Dual CIR/Photoredox-Catalyzed Alkynylation

In 2018, Waser and coworkers demonstrated metal-free alkynylation of alkyl nitrile radical **IV**, which was generated via oxidative ring-opening fragmentation of cyclic alkyl ketone oxime ethers at room temperature. The catalyst system was finely tuned 4ClCzIPN in combination with blue LEDs. A variety of functionalized alkynyl nitriles was readily accessed with this protocol from both four- and five-membered cyclic oxime ethers. The reaction begins with the excited state PS* of the organic dye oxidizing the potassium carboxylate ($E_{1/2} = +1.48$ V vs. SCE in DMF) to produce carboxyl radical **I** and the reduced state PS$^{•-}$. After acetone extrusion, the α-oxy radical **II** is released, which can either proceed to iminyl radical **III** or be

directly trapped by EBX reagents. The iminyl radical **III** fragments into the nucleophilic alkyl nitrile radical **IV**, which interacts with EBX. A concerted process *via* transition state **TS1** can be envisioned for this step to provide the necessary alkynylnitrile and radical **V**. Depending on the migratory aptitude, a β-addition followed by a 1,2-shift of the EBX substituent is also possible. Final reduction of **V** then regenerates the ground state photocatalyst PS, and generates the carboxylate.
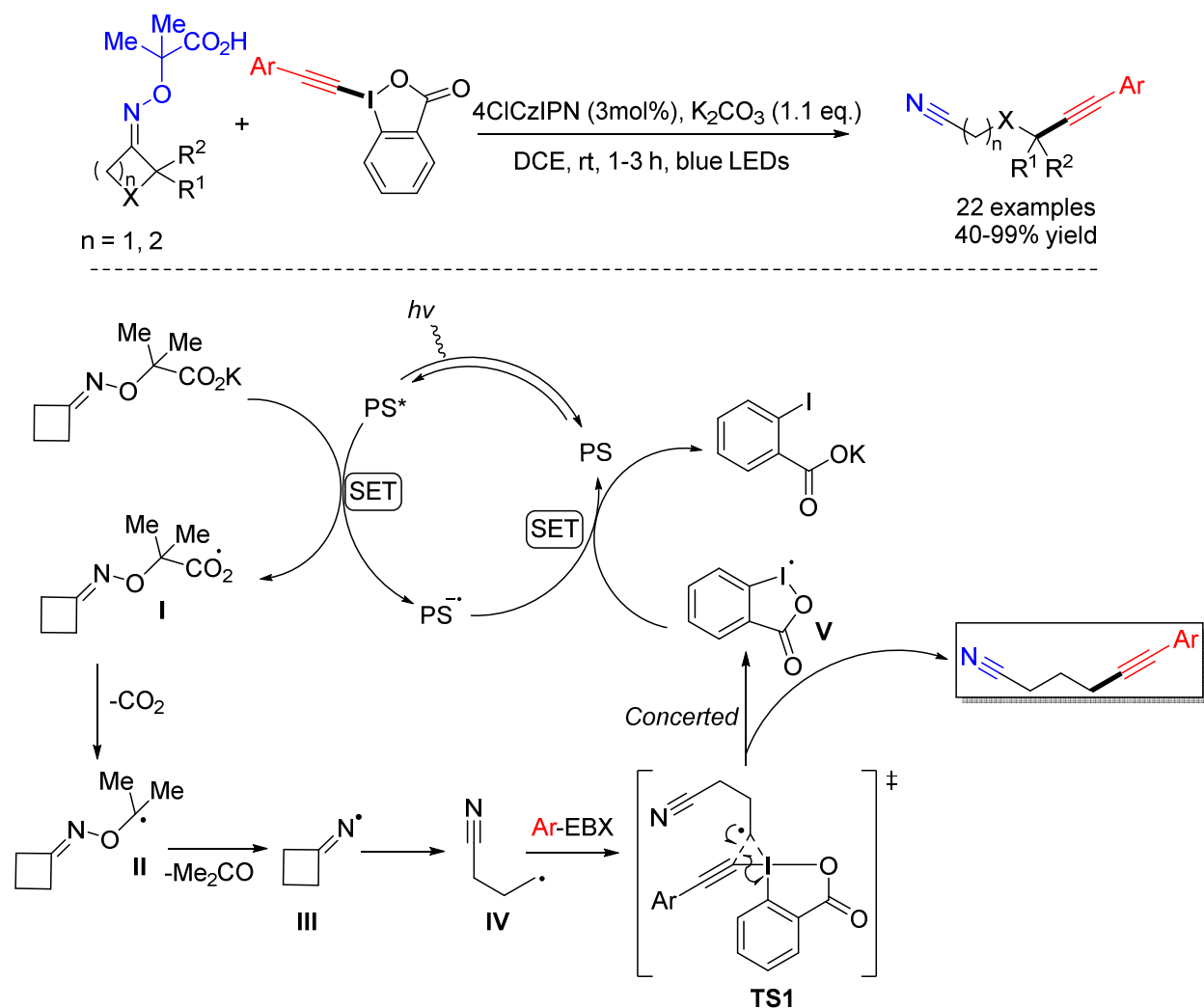
Scheme 3.1.2.4. Visible Light-Induced Alkynylation Cascades of α-Imino-Oxy Acids

The Waser group also reported in 2020 a copper-catalyzed ring-opening/alkynylation of thiiranes and thietanes with EBX reagents under non-photo conditions[291] as well as a photocatalyzed oxidative deconstructive ring-cleavage/alkynylation of less-strained cyclic and acyclic thioethers leading to the formation of thio-alkynylated aldehydes for the first time.[275] Regarding the latter work (**Scheme 3.1.2.5**), only moderate yields of α-alkynylation had been previously reported with other methods.[292] The products contain two highly valuable functionalities, an aldehyde and a thioalkyne, which can readily be transformed into thioesters[293] or engage in a variety of cycloadditions.[283, 294] Phenylglyoxylic acid was found to be an ideal photoinitiator to promote the reaction. $PhCOCO_2H$ (**4a**) is excited to the singlet state **4a^{1*}** after irradiation, followed by intersystem crossing to triplet phenylglyoxylic acid (**4a^{3*}**). $PhCOCO_2H$ photodecomposes to benzaldehyde or diphenyltartaric acid in THF via homolytic cleavage of triplet excited $PhCOCO_2H$ from benzoyl radicals **III** and **I**, respectively. In other solvents (*i*PrOH), homolytic cleavage only produces radical **I** or benzoyl radical **III**. An α-radical **IV** is generated when one of the radicals formed by irradiating $PhCOCO_2H$ (**I** or **III**) abstracts a hydrogen (HAT) from the thioether. After HAT, radical **IV** might theoretically react with oxygen in the reaction mixture to form peroxide **VIII**. The peroxide **VIII** would then disintegrate into thiol radical **IX** and a hydroxy radical. Iodanyl **VI** would result from **IX** reacting quickly with **2a**. This mechanism, however, does not account for water's critical part in the reaction. Thus, the authors proposed that the removal of peroxide instead produces sulfonium **X**, which can be trapped by water to produce thio-hemiacetal **XI**, which is in equilibrium with free thiol **XII**. HAT from **XII** to **IX** is expected to be quick in the presence of many radical intermediates. Other routes to intermediate **X** include SET oxidation of the sulfur atom of tetrahydrothiophene to yield radical cation **XIII**, followed by conversion to **X** *via* a second oxidation process associated with

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proton loss. This could happen through recombination with triplet oxygen, followed by HAT and

hydrogen peroxide loss, for example. Sensitization of triplet oxygen by **4a³*** could also produce

singlet oxygen, which interacts quickly with thiophene to produce intermediate **XV**. Peroxide

elimination would then result in **X**.
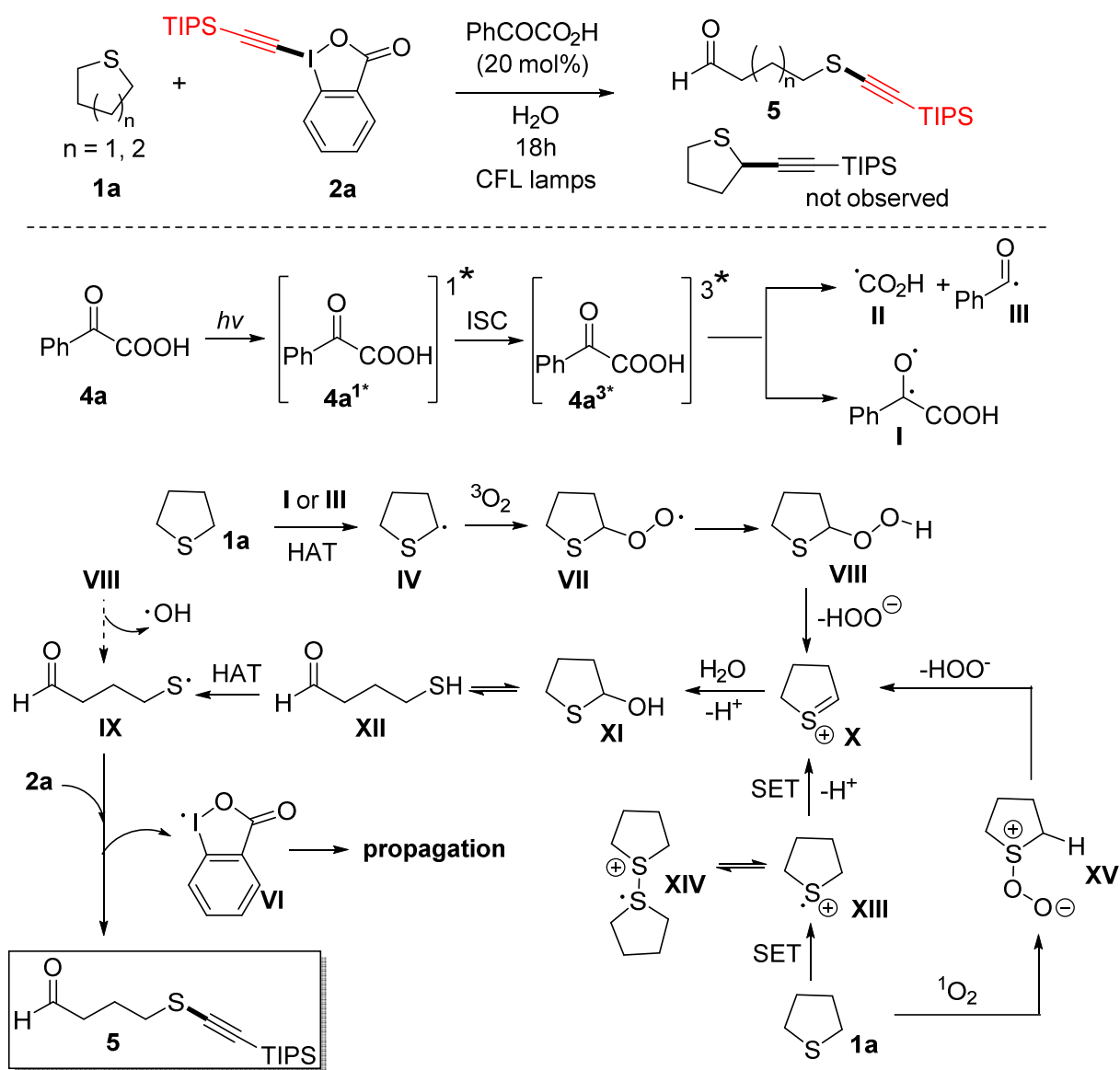
Scheme 3.1.2.5. Oxidative Deconstructive Alkynylation of Cyclic Thioethers with EBX reagents

Finally, in August 2021, Chen and coworkers reported the selective C(sp³)-C(sp³) cleavage and alkynylation of cycloalkylamides for aminoalkyne synthesis under mild photoredox catalysis conditions (**Scheme 3.1.2.6**). γ- and δ-Aminoalkynes with a variety of alkyne and amine substituents could be accessed easily from reaction of cyclopropylamides and cyclobutylamides with hypervalent iodine(III) reagents *via* amidyl radicals. The single-electron oxidation and ring-opening alkynylation of the cycloalkylamides to the amidyl radicals were aided by the use of catalytic quantity of the cyclic iodine(III) reagent BI'-OAc.
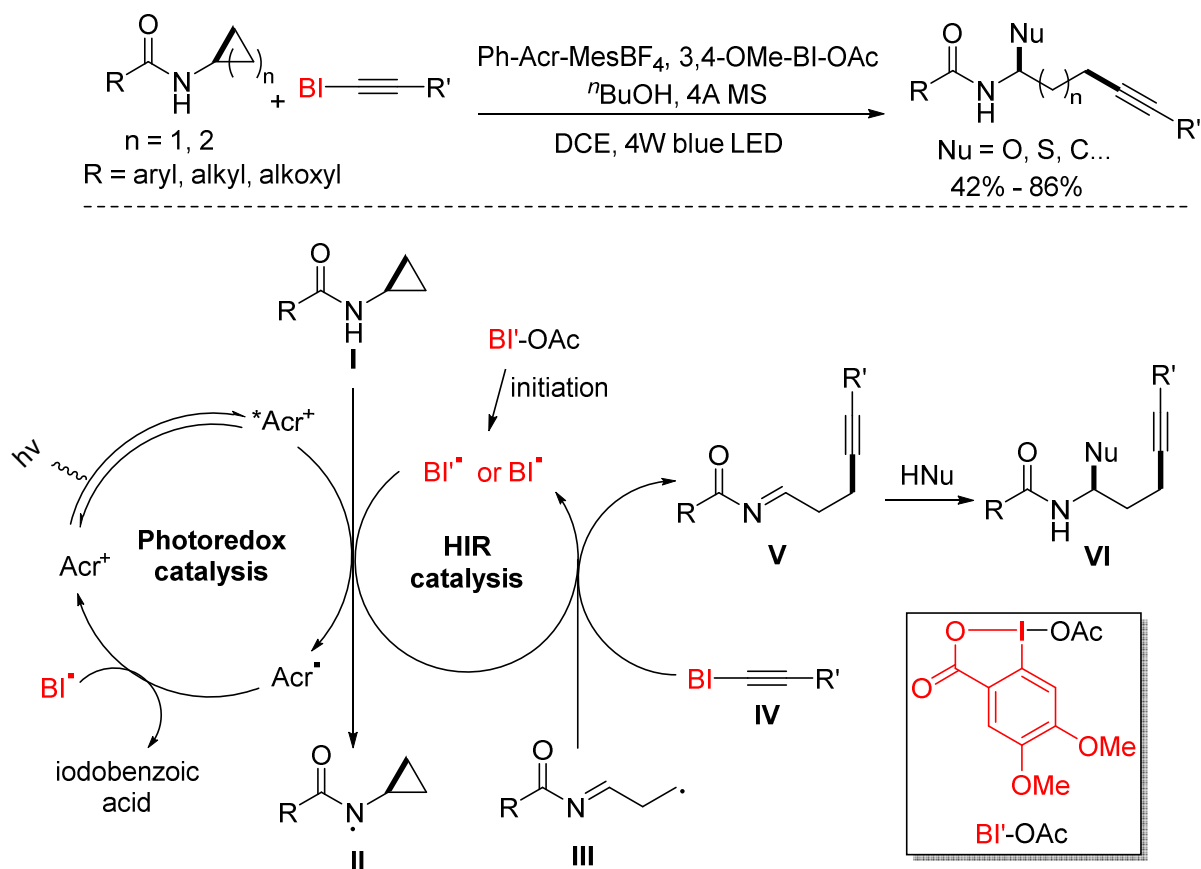
Scheme 3.1.2.6. Deconstructive Distal Alkynylation of Cycloalkylamides with EBX reagents

3.2. Background and significance

Stephenson's group and ours have independently reported the [3+2] annulations of strained *N*-cycloalkylanilines with olefins. Also, we have previously reported the cycloaddition reactions of cyclopropylanilines and cyclobutylanilines with alkynes. All of these reactions proceeded with the loss of a degree of unsaturation in the alkene or alkyne functionality upon the addition to photogenerated amine distonic radical cations (ADRCs), and in none of these reactions was the functional group transferred whole to the deconstructed aminocycloalkane chain or restored in the final product (**Scheme 3.2.1**a). Presumably a fast 5-exo-trig cyclization following the addition of the ADRC to the alkene or alkyne (in the case of cyclopropylanilines) or a 6-exo-trig cyclization (in the case of cyclobutylanilines) precludes the restoration of the functional group in the final product. Thus, the distal installation of these unsaturated functional groups to deconstructed cycloalkylamines remains a challenge.
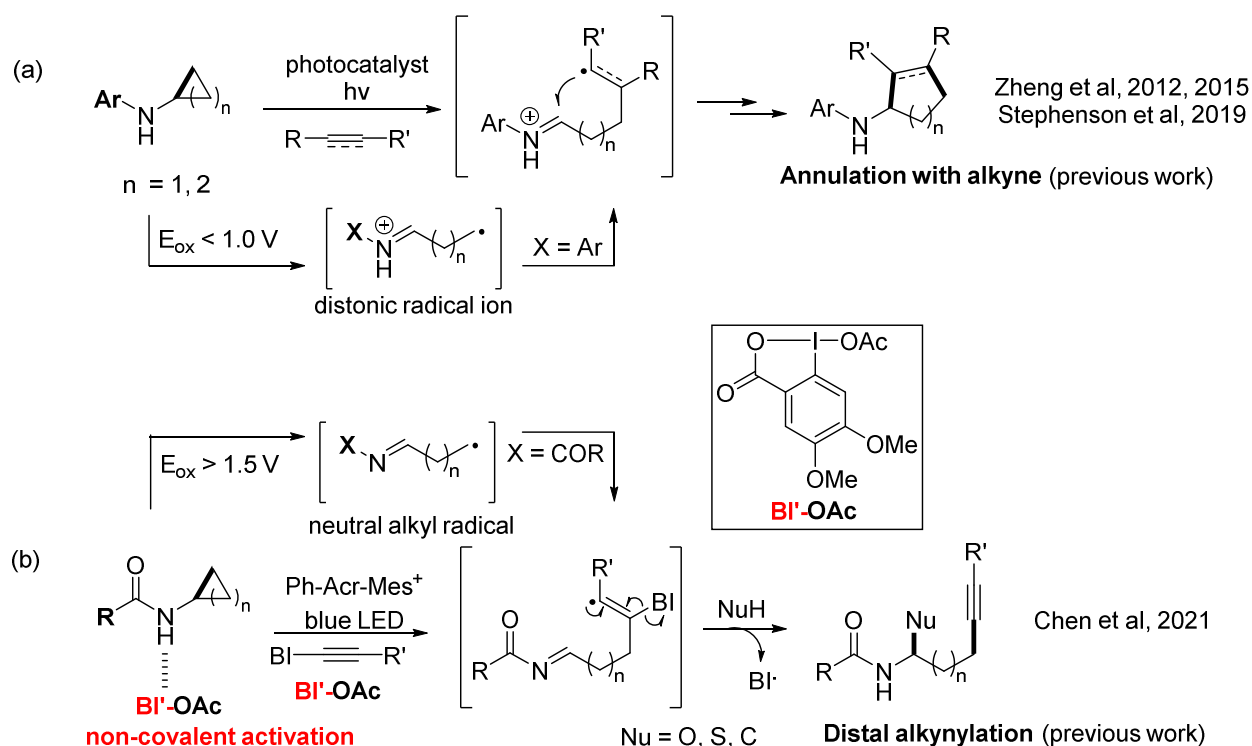
Scheme 3.2.1. Reported Ring-opening/Alkynylation of Strained N-cycloalkane Rings: (a) Ring-opening of Cycloalkylaniline for Annulation with Alkynes (b) Ring-opening of Cycloalkylamide for Distal Alkynylation.

Alkenes and alkynes are versatile functional groups for late-stage modifications in organic synthesis, hence the development of methods to transfer these groups whole to targeted sites in organic molecules is an attractive challenge in the synthetic organic chemistry community. For example, the successful transfer of alkynes to deconstructed aminocycloalkanes will furnish aminoalkynes, important bifunctional building blocks that can be readily derivatized [161, 295] to bioactive fused azacycles like indolizidine found in natural products such as rosettacin, lycorine, and oxypalmatine.[296] The existing synthetic methods to aminoalkynes rely on the Gabriel or N–H Mitsunobu reactions, which have harsh reaction conditions and supplementary protection/deprotection steps that limit their synthetic use and functional group compatibility. Photocatalyzed radical-mediated ring-opening/distal alkynylation of aminocyclopropane and

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aminocyclobutanes is a conceptually attractive approach for accessing aminoalkynes under mild, environmentally sustainable reaction conditions, but the practical realization of this strategy is nontrivial. To date, the only example in the literature exploiting this strategy to access distally alkynylated amines is the 2021 report by Chen and coworkers of γ- and δ-aminoalkyne synthesis involving the non-covalent activation of the strained cycloalkylamide and cycloakylcarbamate substrates with hypervalent iodine reagents, which allowed for the selective $C(sp^3)$-$C(sp^3)$ cleavage and subsequent alkynylation with cyclic alkynyl hypervalent iodine reagents (or alkynylbenziodoxolones, BI-alkyne) (**Scheme 3.2.1**b).

In Chen's work, they hypothesized that a facile BI elimination following the radical addition to cyclic alkynyl hypervalent iodine (III) reagents which regenerates the alkyne triple bond functionality, could switch the annulation cascade to the aminoalkyne synthesis.[278, 297] Also, the use of cyclopropyl- and cyclobutylamides as substrates, rather than cycloalkylanilines, allowed for more flexible derivatizations as various oxygen-, sulfur-, and carbon-based nucleophiles could readily add to the in situ generated imine to give diverse α,γ- and α,δ-difunctionalized aminoalkynes, despite the fact that amides require strongly oxidative conditions due to their high oxidation potentials ($E_{ox} > +1.5$ V). We wondered whether their more strongly electron-rich counterparts, viz. cycloalkylanilines ($E_{ox} < + 1.0$ V), could likewise undergo the ring-opening/distal alkynylation with alkynyl hypervalent iodine reagents (AHIR) under even milder reaction conditions upon PET oxidation to their amine radical cation form.

We anticipated that being electron-rich, cycloalkylanilines would be more prone to the PET oxidation. However, it was not clear to us how the amine distonic radical cation (ADRCs) would react with the hypervalent iodine reagent when formed—i.e., whether ADRCs would add to BI-alkyne like a normal carbon-centered radical, in an identical fashion to the neutral carbon radical

generated in the case of cycloalkylamides. Our studies on ADRCs over the years suggest that the charged iminium ion moiety of ADRCs likely affects the reactivity of the radical site. Their radical reactivity appears more pronounced when the charge site is inactive such as when it is quenched with by nucleophile like TMSCN, or when it is stabilized by a π-donating group or through resonance (**Scheme 3.2.2** hereinafter). Also, in functionalization reactions, their reactivity is impacted by the compatibility with and/or effectiveness of both the nucleophile and the radical acceptor. They can exhibit reactivities towards certain reagents that deviate from normal carbon-centered radicals' reactivities towards the same reagents. Thus, whereas *N*-cyclobutylaniline **1** is unreactive towards TEMPO **3**, DIAD **4**, and some other radical acceptors even in the presence of the nucleophile TMSCN (**Scheme 3.2.2**), the spirocyclic dihydroquinazoline **2**, whose ADRC cationic site is stabilized *via* resonance, reacts with the first two reagents to give quantitative yield of the corresponding adduct. Data from our previously developed [3+2] and [4+2] annulations of cyclopropylanilines and cyclobutylanilines with alkynes as well as from our developed difunctionalization reactions (section **2.2.1** *vide supra*) suggest the ring-opening of cyclobutylanilines upon PET oxidation is both slow and reversible. Thus, we surmised, and have confirmed in ab initio computational studies, that when the radical acceptor is incompatible with the nature of the distonic radical cation produced from cyclobutylaniline, the ADRC can undergo the reverse 4-exo-trig cyclization back to the closed amine radical cation form. Based the foregoing data from our previously developed chemistries involving strained cyclobutylanilines, we envisioned that the success of our targeted deconstruction/distal alkynylation with alkynyl benziodoxolones (BI-alkyne) would hinge on the choice and tunability of the amine substrate.
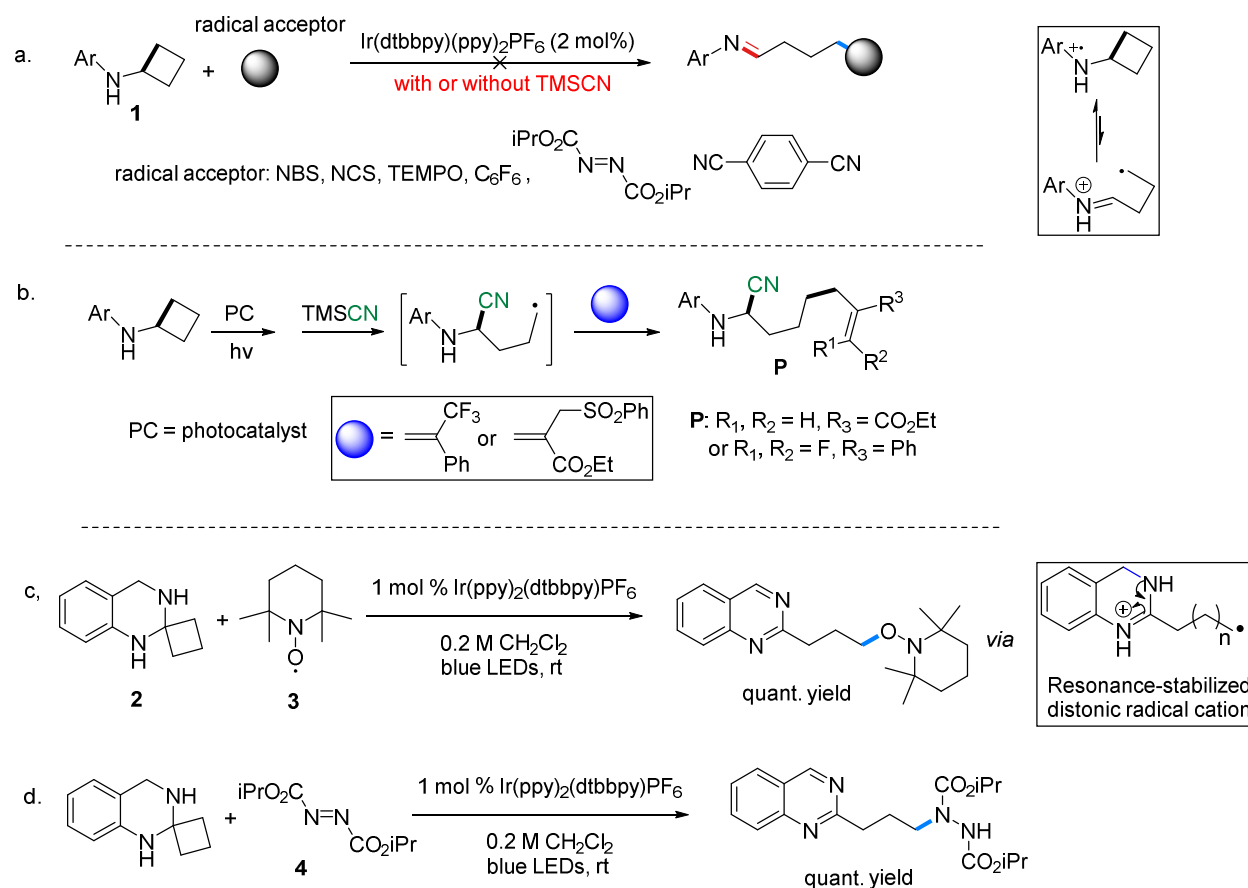
Scheme 3.2.2. Comparison of the Reactivities of Distonic Radical Cations with Structurally Different Iminium Ion Moieties

In our developed difunctionalization reactions, a nucleophile, TMSCN, was used to intercept the iminium site of ADRC and convert the distonic ion into a normal neutral carbon radical that is able to add readily to radical acceptor (**Scheme 3.2.2**b). However, in the current work, we explored *N*-cyclobutane substrates that are structurally similar to the dihydroquinazoline **2** in **Scheme 3.2.2** which upon SET oxidation and ring-opening, would produce distonic radical cations with the cationic sites stabilized through resonance to render it inactive, thus favoring the reactivity of the radical site with alkynyl hypervalent iodine reagents (**Scheme 3.23**).

This work: Resonance-assisted ring-opening cyclobutylaminals for distal alkynylation

Y = CH$_2$, C=O

Resonance-stabilized distonic radical cation

Distal alkynylation
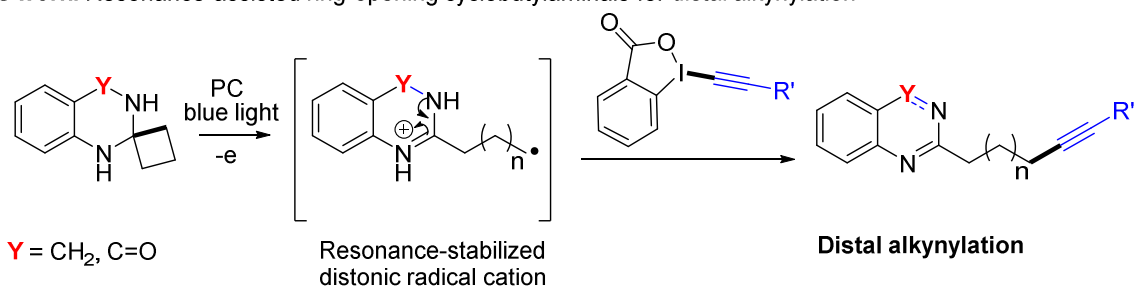
Scheme 3.2.3. Distal Alkynylation of N-cyclobutane Rings via Resonance-Stabilized DRC.

3.3. Results and Discussion

3.3.1. Development of the Ring-opening/Distal Alkynylation Reaction

The initial results in our investigation of the deconstructive/distal alkynylation strategy is summarized in **Scheme 3.3.1.1** below. We began our study by examining the reaction of the secondary cyclobutylaniline **3.1** with trimethylsilylethynylbenziodoxolone TMS-EBX, **3.2**. Upon irradiating a degassed methanol mixture of the cyclobutylaniline, TMS-EBX, TMSCN, and Ir(dtbbpy)(ppy)$_2$PF$_6$ with two-strip blue LEDs for 10 hours, the undesired N-alkylated cyclobutylaniline **3.4** was obtained in 39% yield, and the desired distal alkynylated product was not detected. Presumably, the hypervalent iodine (III) reagent **3.2** oxidized the solvent methanol to formaldehyde, which condensed with cyclobutylaniline to form the iminium ion. The obtained desired product results from the interception of the iminium ion by TMSCN. Changing the solvent from methanol to dichloromethane, led to a complex reaction mixture (as observed on tlc) and evidence of aniline decomposition in the crude NMR spectra. The cyclobutylaniline also failed to undergo ring-opening/azidation or cyanation with the hypervalent iodine reagents **3.8** and **3.9** respectively.
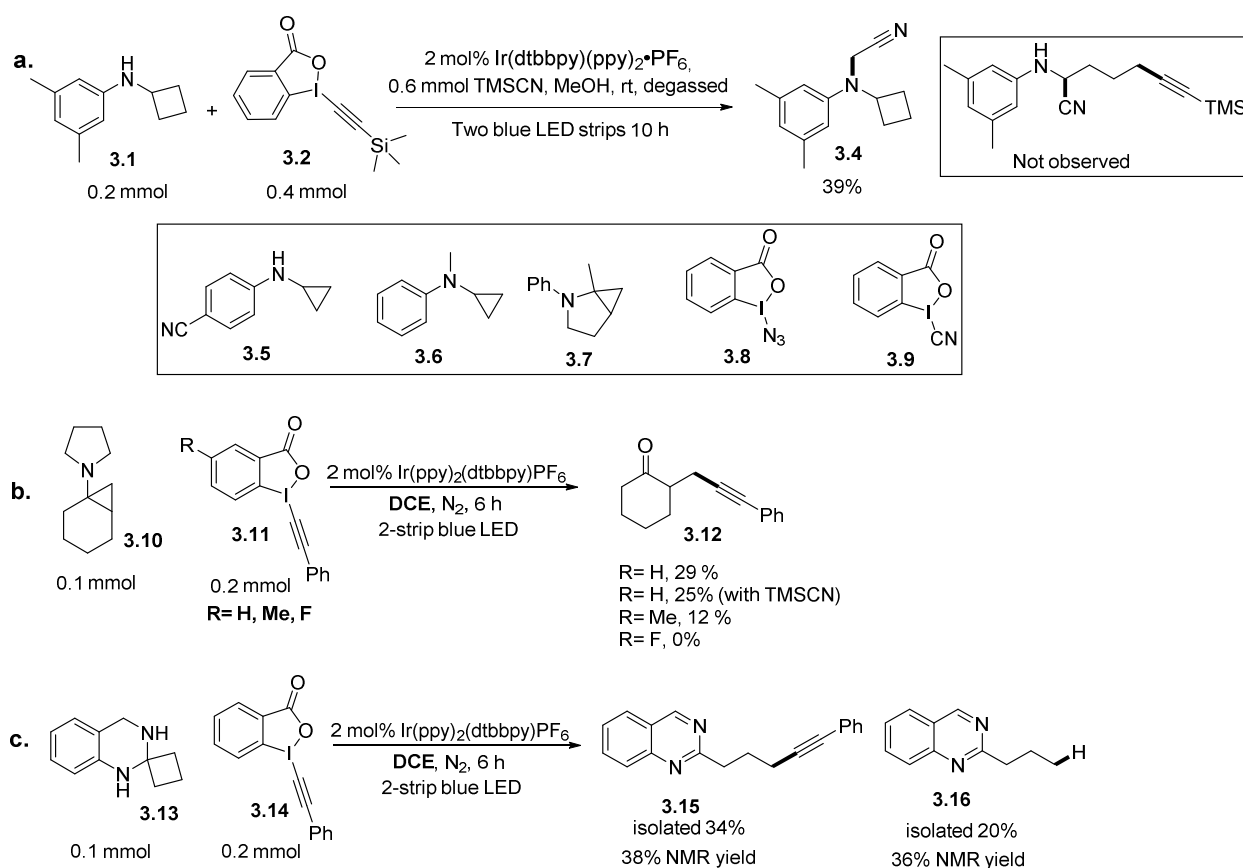
Scheme 3.3.1.1. Initial Results of the Ring-opening/Distal Alkynylation with Hypervalent Iodine (III) Reagents

The failure of the secondary amine to afford ring-opening products led us in a search of tertiary amines capable of undergoing ring-opening process upon PET oxidation. Based on our previous studies on [3+2] annulation reactions wherein tertiary cyclopropylaniline **3.6** failed to undergo the ring opening under the reaction conditions, we prepared tertiary bicyclic cyclopropylamine **3.10** that was expected to be more disposed to the ring-opening. By switching the iodine (III) reagent to Ph-EBX **3.14**, with its more stable phenyl substituent (compared with the labile trimethylsilyl group of **3.2**)[298], and also changing the solvent to 1,2-dichloroethane (DCE), the photocatalyzed reaction furnished the expected ring-opening/distal alkynylation

product **3.12** in 29% isolated yield (**Scheme 3.3.1.1**b). Notably, TMSCN was not added to the iminium ion presumably due to steric hindrance at the tetrasubstituted iminium ion. Tuning the PhEBX electronic behavior with electron-donating (Me) or electron-withdrawing (F) substituents decreased the yield of the alkynylation product. When cyclobutylaniline **3.1** and **3.5** were subjected to the improved reaction conditions they still proved unsuccessful with evidence of aniline decomposition in the crude NMR spectra. Without irradiation, **3.10** failed to give the expected product. In hindsight, given the strong oxidizing ability of hypervalent iodine (III) compounds and the susceptibility of cyclopropylanilines and cyclobutylanilines to oxidation, these obstacles are unsurprising.

In our initial investigations, we employed a strategy in which TMSCN was used to drive the ring opening of the amine radical cation by interception of the iminium ion of any generated distonic radical cation (DRC). This would also inactivate the cationic site of the DRC making it react more as a normal nucleophilic carbon radical. We envisioned an alternative strategy wherein the ring-opening could be favored owing to stabilization of the iminium ion of the DRC when produced which would also render the charged site inert. To test this hypothesis, we synthesized cyclobutylaniline **3.13** bearing an aminal moiety by condensation of 2-aminobenzylamine with cyclobutanone and subjected it to the improved conditions for the distal alkynylation with PhEBX, albeit without TMSCN. This substrate is more stable than our successful bicyclic cyclopropylamine **3.10** and have been found to react with various radical acceptors without facilitation of the external nucleophile TMSCN (**Scheme 3.2.2** hereinbefore). To our delight our expected remote alkynylation product **3.15** was obtained in 38% NMR yield together with side product **3.16** (36%) which results from the ring-opened cyclobutylaniline undergoing a hydrogen atom abstraction instead of acetylene transfer from PhEBX (**Scheme 3.3.1.1**). The two have

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identical polarities and the complete separation by flash column chromatography proved difficult. Both ^{1}HNMR and LCMS of the isolated mixture confirmed the two products. Notably, the reaction proceeded with aromatization of the ring containing the aminal moiety in the product, similar to what pertained in its reaction with the oxidants TEMPO and DIAD. Next, we conducted optimization studies of the reaction involving the aminal by screening various solvents and additives with the aim of suppressing the side product **3.16**.

3.3.2. Optimization and Substrate Studies of the Ring opening/Alkynylation Reaction

Table 3.3.2.1 shows the results of the optimization studies conducted for spirocyclic dihydroquinazoline cyclobutane substrate. Surprisingly, the amount of the undesired side product **3.16** persisted, and was even increased, when the reactions were conducted in solvents like benzene and chlorobenzene that are neither protic nor good hydrogen atom donors (entries 3 and 5) or when it was conducted in deuterated dichloromethane (entry 7). This suggests that the H$^{\bullet}$ was not supplied by the solvent used for the reaction. The addition of cyclic iodine(III) hydroxybenziodoxole (BI-OH), which has been reported to activate selective cycloalkanol C-C cleavage[200, 278] as well as enable C(sp^3)-C(sp^2) coupling of alkyl radicals with vinyl carboxylic acids,[279] did not improve the yield (entry 10), and noncyclic phenyliodine(III) diacetate (PIDA) led to decomposition of the substrate (entry 9). Also, the addition of a base decreased the yield of the desired product (entry 8).

Table 3.3.2.1. Optimization of the Ring-opening/Distal Alkynylation of 3',4'-dihydro-1'H-spiro[cyclobutane-1,2'-quinazoline].

| Entry	Deviations from standard conditions	NMR Yield 3.15 [%][a]	NMR Yield 3.16 [%][a]
1	-	38 (34)[b]	36 (20)[b]
2	DMF as solvent	27	14
3	Benzene as solvent	19	53
4	DCM as solvent	31	27
5	PhCl as solvent	27	50
6	MeOH as solvent	12	10
7	CD_2Cl_2 as solvent	32	48
8	1 equiv $NaHCO_3$ added	19	29
9[c]	1 equiv PIDA added	-	-
10	BI-OH added	32	48

Conditions: **3.13** (0.1 mmol, 1 equiv), **3.14** (2 equiv), Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%) and 1,2-dichloroethane DCE (1 mL), degassed and irradiated with two-strip blue LEDs. [a] ^{1}H NMR yield determined using 1 equiv of CH_2Br_2 as internal standard. [b] Isolated yields are in parentheses. [c] ^{1}H NMR of the crude showed that the substrate decomposed under the reaction conditions.

We proposed a mechanism in which the abstraction of the weak benzylic H of the quinazoline by the resonance-stabilized distonic radical cation intermediate aromatizes the quinazoline ring as well as produces the side product in a radical chain process (**Scheme 3.3.2** and

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Scheme 3.3.3). Upon single electron oxidation of the quinazoline cyclobutane substrate **3.13** by the excited state of the Ir^{3+} photocatalyst, the amine radical cation **3.16** is formed which undergoes ring-opening to give a distonic radical cation (DRC) with a resonance-stabilized iminium ion moiety. Addition of the radical site of the DRC to the BI-Alkyne **3.14** at the position alpha to the iodine affords the adduct **3.17** containing a vinyl radical and a pendant dihydroquinazolinium moiety; although addition to the β position followed by a 1,2-shift or a concerted mechanism cannot be ruled out at this stage.[274, 299] A subsequent β-elimination of BI• **3.19** from the adduct affords the remotely alkynylated dihydroquinazolinium product **3.18**. The ground state Ir^{3+} catalyst can be regenerated *via* the reduction of BI• to 2-iodobenzoate anion **3.20** which can abstract a proton from the dihydroquinazolinium product **3.18** to convert it to its neutral form (**Scheme 3.3.2**). Upon re-excitation, the regenerated photocatalyst can then initiate the further transformation of the deprotonated **3.18** *via* an SET oxidation/HAT/deprotonation relay to finally furnish the desired distally alkynylated product **3.15** with the ring which contained the aminal moiety in the initial substrate now fully aromatized (**Scheme 3.3.3**). In the HAT step of the product-forming relay, the ADRC abstracts the benzylic H of **3.18** en route to the side product formation *via* a relay identical to that which produces the major product.
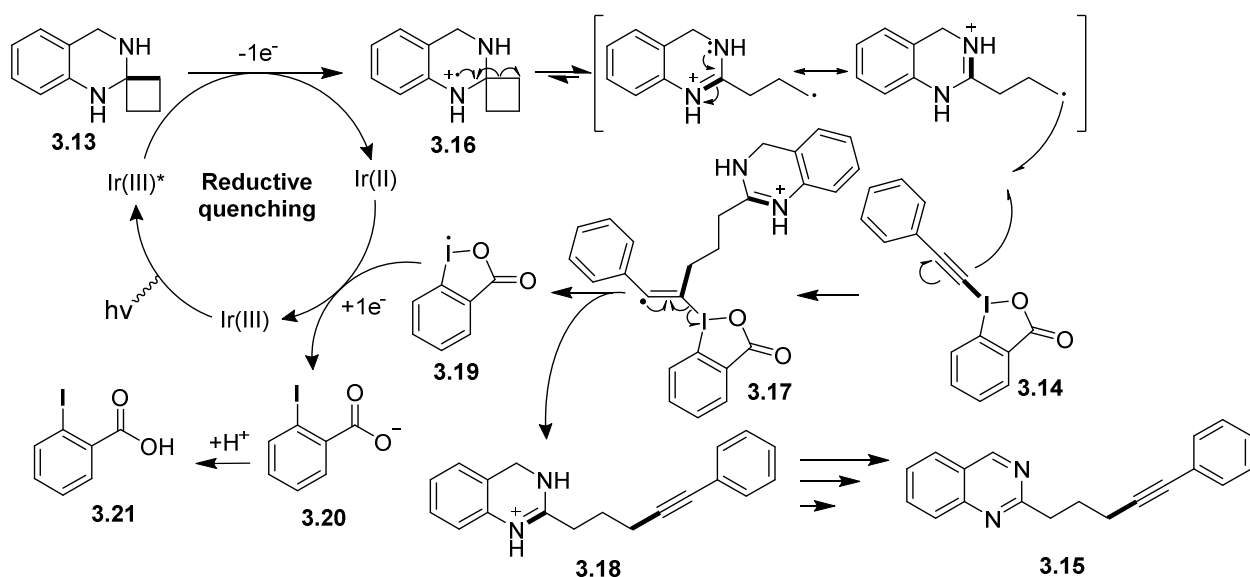
Scheme 3.3.2. Proposed General Mechanism of the Ring-opening/Distal Alkynylation of 3',4'-dihydro-1'H-spiro[cyclobutane-1,2'-quinazoline]
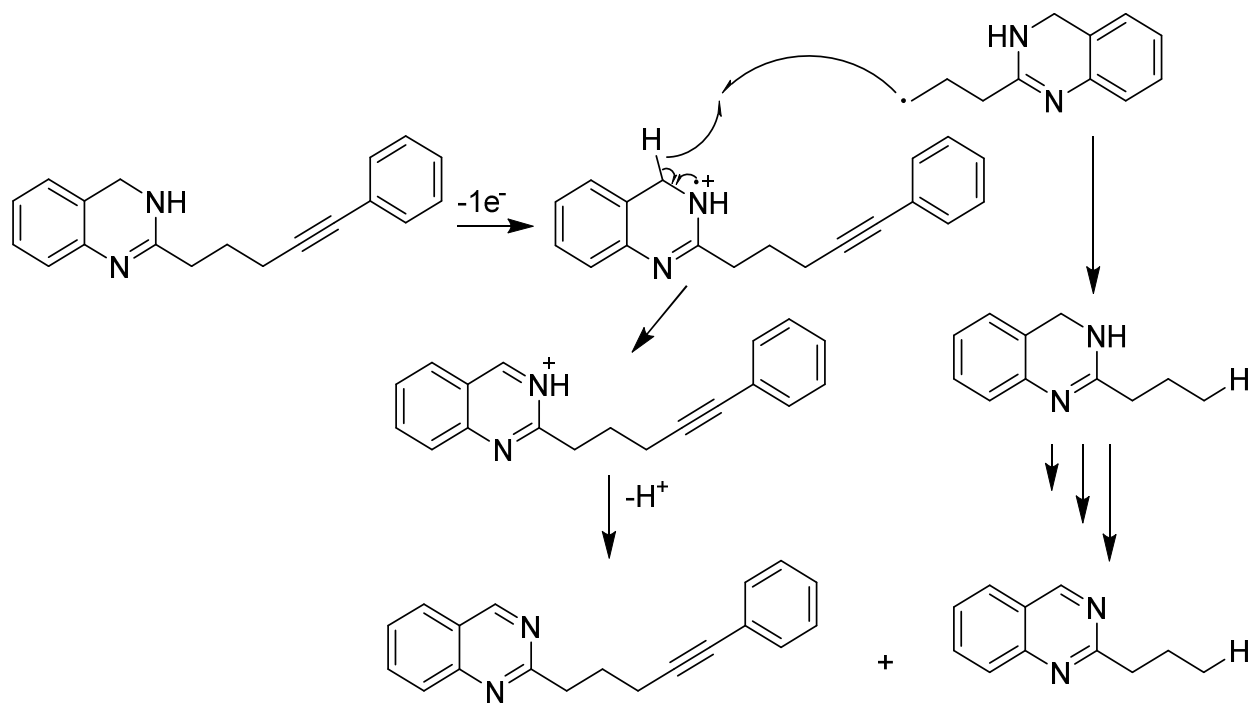
Scheme 3.3.3. Proposed SET/HAT/Deprotonation Relay for the Product and Side Product Formation in the Deconstructive/Distal Alkynylation of 3',4'-dihydro-1'H-spiro[cyclobutane-1,2'-quinazoline

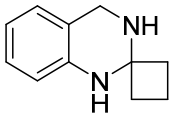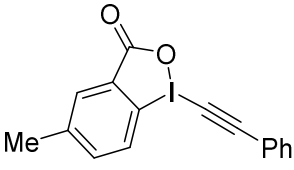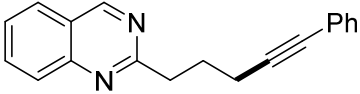**Table 3.3.2.2. Screening of Amines and Alkynyl Hypervalent Iodine Reagents (AHIR)**
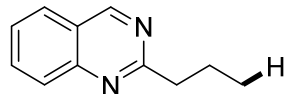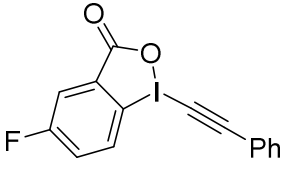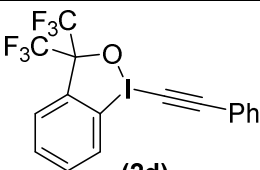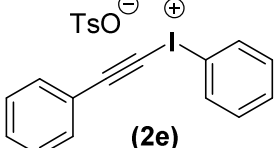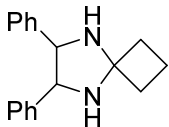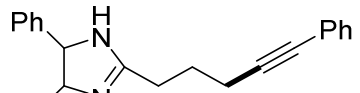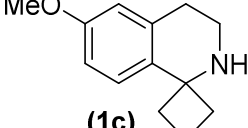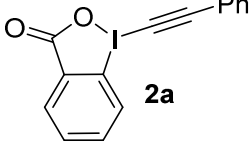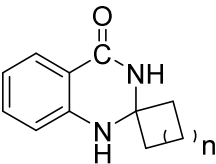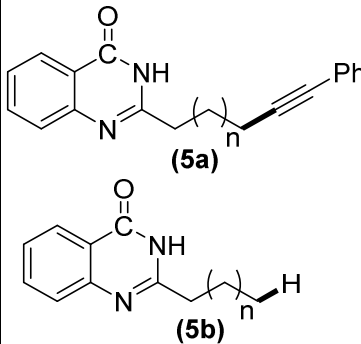
Entry	Amine	AHIR	NMR Yield [%][a]
1	(1a)	(2b)	(3a) 23% (3b) 14%
2	1a	(2c)	(3a) 17 (3b) 25%
3	1a	(2d)	(3a) 22% (3b) 21%
4	1a	(2e)	No product
5	(1b)	2e	(4a) 10%
6	(1c)	2a	No product

Table 3.3.2.2 (Cont.)

Entry	Amine	AHIR	NMR Yield [%][a]		
7	n= 1 **(1d)** n= 2 **(1e)**	**2a**		n = 1	n = 2
			(5a)	69%	14%
			(5b)	8%	2%

Conditions: Amine (0.1 mmol, 1 equiv), alkynyl hypervalent iodine reagent (2 equiv), Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%) and 1,2-dichloethane DCE (1 mL), degassed and irradiated with two-strip blue LEDs. [a] ^{1}H NMR yield determined using 1 equiv of CH$_2$Br$_2$ as internal standard.

Our optimization of the dihydroquinazolinyl cyclobutane reaction (**Table 3.3.2.1**) revealed that the solvent was not the origin of the hydrogen atom that was abstracted by the distonic radical cation en route to forming the side products. More likely, the substrate itself supplied the H atom from its benzylic position. We considered two strategies for overcoming the persistent benzylic H atom abstraction: (1) by tuning the electronic properties of the alkynyl hypervalent iodine reagent (AHIR), it could more effectively intercept the distonic radical cation and outcompete the hydrogen atom abstraction from the benzylic position of the substrate, and/or (2) by modifying the structure of the amine, the side reaction from the HAT could be eliminated or considerably suppressed. To probe the test the first strategy, we reacted the original dihydroquinazoline cyclobutane substrate with alkynyl hypervalent iodine reagents of various electronic properties based on structure and/or substituents on the benziodoxolone ring. The results of this study are summarized in **Table 3.3.2.2** above. Although the ratio of product/side product was improved in the reaction with AHIR bearing the electron-releasing 5-Me substituent (entry 1), the yield of

desired product (i.e., 23%) was significantly lower than that obtained in the reaction of the original unsubstituted PhEBX (i.e., 38%). An electron-withdrawing 5-F substituent on the benziodoxolone ring (entry 2) led to a poorer product/side product ratio; and neither the selectivity for the product nor the yield improved in the reaction involving iodine(III) reagent F_6-PhEBX (**2d**) bearing geminal trifluoromethyl groups in place of C=O at the 3-position (entry 3). These results suggest that the functionalization of the hypervalent iodine reagents at the benzylic position could have a profound effect on the reaction efficiency. Finally, the use of the noncyclic AHIR (**2e**) which is strongly oxidizing led to decomposition of the substrate and none of the desired remote alkynylation product.

To test the second strategy, we synthesized three new amine substrates and examined them in reaction with PhEBX. The amines **1b** and **1d** were synthesized by condensations of 1,2-diphenylethane-1,2-diamine or 2-aminobenzamide with cyclobutanone, respectively, and **1c** was obtained by a Pictet-Spengler reaction of 2-(3-methoxyphenyl)ethylamine with cyclobutanone. Whereas **1b** and **1c** failed to give satisfactory results in the ring-opening/alkynylation reaction with BI-alkyne, the spirocylic cyclobutane quinazolinone **1d** reacted to give the desired distal alkynylation product **5a** in 69% NMR yield, with only 8% of side product **5b** resulting from hydrogen atom abstraction by the distonic radical cation. As in the reaction of the original substrate, the products from the reaction of **1d** also had ring that contained the aminal moiety fully aromatized. Whiles the side product was significantly suppressed, it was curious that any was formed at all since the substrate **1d** has no benzylic H. On the other hand, we hypothesized that the aromatization of the ring could provide a driving force for the cleavage of larger cycloalkane rings. To our delight, when the cyclopentane equivalent of this compound (**1e**) was synthesized and subjected to the reaction conditions, 14% of the alkynylation product was produced along with

2% side product. This reaction represented the first successful realization of our long-sought aim of a deconstructive functionalization of unstrained *N*-cycloalkane rings and would inspire the development of our later chemistries in this area.

3.4. Future Work

The current study has identified the limitations and challenges of the ring-opening/distal alkynylation reaction of strained *N*-cyclobutane rings. We have found that, compared with the analogous transformation involving cycloalkylamides, the reactions employing strained-ring anilines are more challenging owing to the susceptibility of anilines to decomposition under the reaction conditions involving both hypervalent iodine reagent and photocatalyst. By tuning the structure of the amine substrate, we have identified a suitable substrate (**1d**) for the current strategy which can be easily synthesized from commercially available precursors, is stable under laboratory ambient conditions, and, more important, is able to suppress the side products which was a major challenge with the earlier substrates. Further studies to optimize the reaction involving the newly discovered substrate will be needed to assure of a broad substrate scope. **Scheme 3.4.1** shows an elaborate plan that can be pursued to complete the study on the developed strategy for publication.
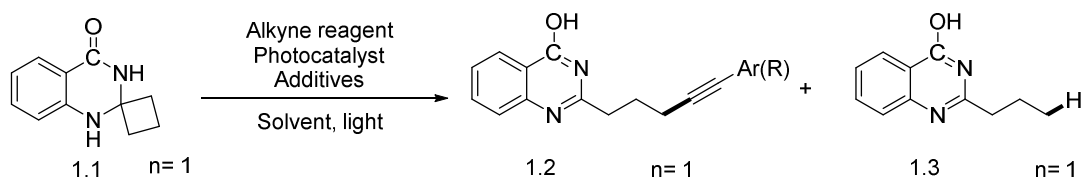
Screen:

1. Photocatalysts: Ir(ppy)$_2$(dtbbpy)PF$_6$, Ir(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$, [Ru(bpy)$_3$](PF$_6$)$_2$, Ph-Acr-MesBF$_4$, Ir[dF(CF$_3$)ppy]$_2$(5,5'-dCF$_3$bpy)(PF$_6$), 4CzIPN, Eosin Y, etc.
(*Also, perform reaction without light, in dark).
2. Solvents: DMF, DMSO, DMA, MeOH, Acetonitrile, etc.
3. Additives: bases (K$_3$PO$_4$, Na$_2$CO$_3$, collidine, Bu$_4$N[OP(O)(OBu)$_2$], etc); co-catalysts (e.g. BI-OAc; phenyliodine(III) diacetate (PIDA); 3,4-F-BI-OAc; 3,4-OMe-BI-OAc, K$_2$S$_2$O$_8$).

Scope based on aniline
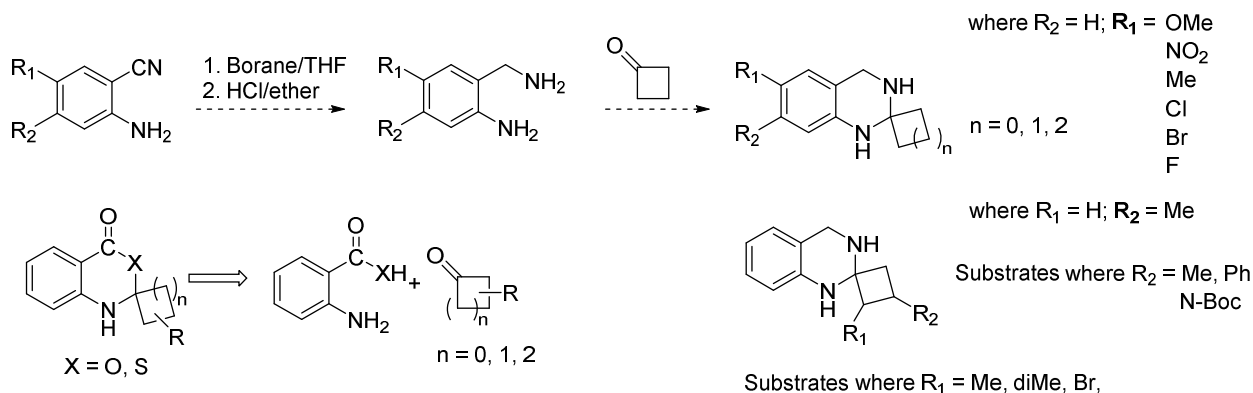
Scope based on alkyne

Mechanism studies:

To probe origin of H atom

- Stern Volmer fluorescence quenching studies.
- Probing the radical mechanism with TEMPO or 1,1-diphenyl ethylene..
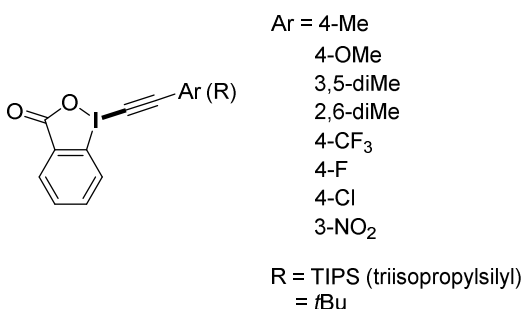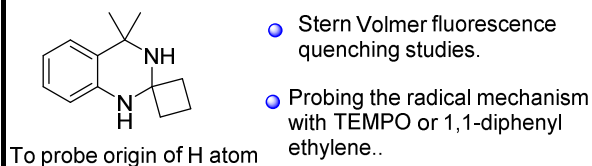
Scheme 3.4.1. Future Works on the Resonance-Assisted Deconstruction/Distal Alkynylation of Strained N-Cyclobutane Rings.

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3.5. **References**

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Chapter 4

Visible Light-mediated Aromatizative Deconstruction/Refunctionalization of Unstrained Cycloalkanones Using Diamines as Activating Groups
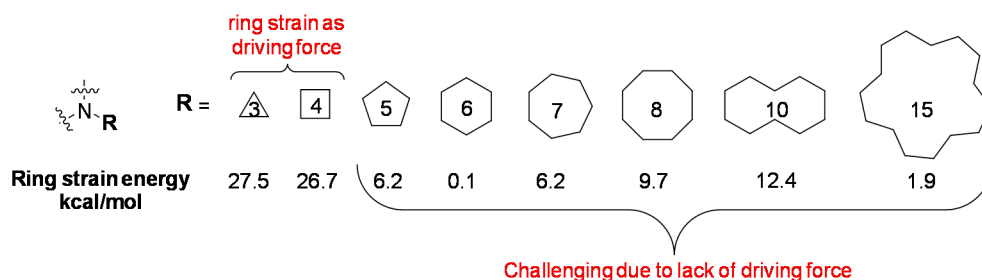
This project was undertaken in collaboration with my lab colleague Enoch Kudoahor.

4.1. Introduction

The development of strategies for the activation of the inert carbon-carbon (C-C) single bonds in aliphatic rings, especially unstrained carbocycles, towards their cleavage and functionalization remains an interesting challenge to synthetic chemists. Aliphatic rings are ubiquitous in pharmaceutical drugs, natural products, and functional materials.[300] Thus, strategies aimed at deconstructing such frameworks in molecules can provide fascinating opportunities for streamlining the synthesis of complex molecules, as they enable unconventional installations of multiple functionalities simultaneously[301] and the rapid buildup of molecular complexity. Whereas several examples of radical-mediated ring-opening functionalizations of strained cyclopropane and cyclobutane rings have been reported based on strategies exploiting the thermodynamic driving force provided in the release of their inherent ring strains for the ring-opening event, the analogous reaction involving unstrained rings remains a nontrivial challenge to chemists due to lack of driving force for the ring-opening. Five-, six-, and seven-membered rings, as well as large-sized rings, have a lower ring strain energy,[302] making these scaffolds less reactive (**Figure 4.1.1**a), and for the last several decades, the ring-opening functionalization of unstrained molecules has received little attention. One promising strategy that has been used to achieve C–C bond cleavage in unstrained rings takes advantage of the high reactivity of oxygen- and nitrogen-centered radicals in the form of cycloalkoxy and cycloalkyliminyl radicals to facilitate the deconstruction of medium- and large-sized cyloalkanols[303] and cycloalkanones respectively under both photo and

thermal conditions. Alkoxy radicals have much greater ring-opening rates than reverse cyclization rates (see **Figure 4.1.1**b, $k_{open} \approx 10^8$ s$^{-1} \gg k^{-1}_{cyclization} \approx 10^4$ s^{-1} 5-membered ring and $k_{open} \approx 10^7$ s$^{-1} \gg k^{-1}_{cyclization} \approx 10^5$ s^{-1} for 6-membered rings), therefore their ring-opening process is both thermodynamically and kinetically favorable.[304] Significant advances have been realized in the cleavage of unstrained rings of alcohols and ketones employing this approach, especially the former, and these have been reviewed by Morcillo[223] in 2019 and also by the research groups of Bi[235] and Zhu[234] in 2019, Zhou[198] in 2020, Zeng[305] in 2020, and Xiao[265, 306] in 2020 and 2021. On the other hand, the radical-mediated C-C bond cleavage/editing of cycloalkanamines is underdeveloped, and the scarce reports have been limited almost entirely to strained rings wherein ring-strain release serves as the thermodynamic driving force of the ring-opening.[16, 21, 105, 107, 138] This is attributable to the high reverse 5-exo cyclization rate constants of nitriles and imines for unstrained cycloalkanamines, particularly for 5- and 6-membered cycloalkanamines (**Figure 4.1.1**b, $k^{-1}_{cyclization} \approx 10^7$ s^{-1}).[307] Sarpong's research group have demonstrated the transition metal-catalyzed deconstruction/functionalization of unstrained 3° alicyclic amines having the nitrogen atom as part of the ring framework,[224, 308] but only in 2020 was the first work involving the cleavage/functionalization of unstrained cycloalkanamines reported by Han's group,[304] employing aromatization as both a dynamic and thermodynamic driving force to promote the ring-opening.

a. Ring-opening thermodynamic driving force

ring strain as driving force

R =	3	4	5	6	7	8	10	15
Ring strain energy kcal/mol	27.5	26.7	6.2	0.1	6.2	9.7	12.4	1.9

Challenging due to lack of driving force

b. Rate constants of radical-mediated ring-opening and its reverse cyclization

K_{open} s^{-1}

10^2 10^3 10^4 10^5 10^6 10^7 10^8 10^9 $K^{-1}_{cyclization}$ s^{-1}
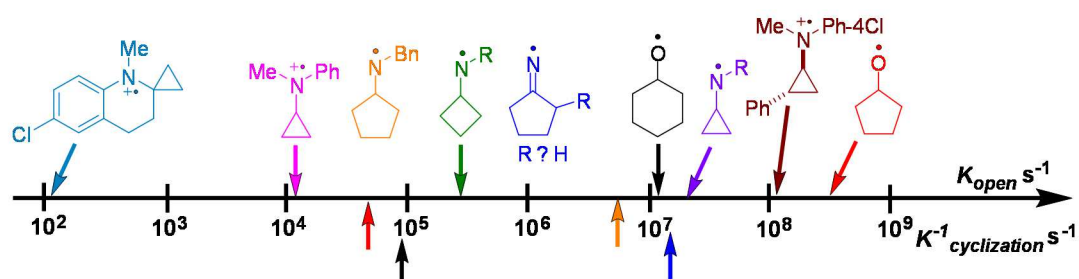
Figure 4.1.1. Ring Strain energies and Rate Constants of Ring-opening and Reverse Cyclizations

Although the aromatization has been exploited as a thermodynamic driving force for C-C bond activation as far back as 1972[309] assisted by transition metals, this strategy had been unappreciated until recently.[310, 311] A major limitation to the application of aromatization as driving force for chemical transformations is the difficulty in generating pre-aromatic substrates in situ due to the tedious prefabrication usually required.[312, 313] Various types of reactions have been developed by exploiting aromatization as a thermodynamic driving force for cleavage of unstrained C-C bonds. Between 2017 and 2019, the groups of Molander,[314] Melchiorre,[315] and Chen[316] independently reported aromatization-driven C-C bond cleavage of 4-alkyl-1,4-dihydropyridines for intermolecular C-H alkylation reactions (**Scheme 4.1.1**a). Also, the Ma group reported the pioneering work on 1,2-migration of Pt- and Au-carbene intermediates driven by aromatization (**Scheme 4.1.1**b).[311, 317] The aromatization-driven C-C bond activation strategy has also been

applied in ring-expansion reactions. For example, the research groups of You,[318] as well as others,[319] have reported the synthesis of polycyclic indoles via an aromatization-driven acid-mediated ring-expansion and re-aromatization of spiroindolenines. Again, the aromatizative ring-cleavage/cyclization of spirocyclic dienone to the phenol has been reported (**Scheme 4.1.1**c).[320] In 2003, Kotsuki's group developed an unprecedented hydrothermal reaction protocol for the condensation of *o*-phenylaniline or 2-isopropenylaniline with cycloalkanones to afford substituted phenanthridines and quinolines at elevated temperatures (250-300 °C)[321] (**Scheme 4.1.1**d). Following the condensation of the aniline with the cyclic ketone, the reaction was proposed to go through an aza-triene-type 6π-electrocyclization and a subsequent irreversible cycloalkane ring fission with possible further [1,3]-migrative ring expansion in the case of cyclobutanone and cyclopentanone reactions. A final aromatization in air then furnishes the desired product. This innovative work exploited the use of an activator (i.e., the hydrochloride of *o*-phenylaniline and its homologues) for the cleavage of both strained and unstrained cycloalkanones *via* the aromatization of an *in situ*-formed pre-aromatic intermediate.

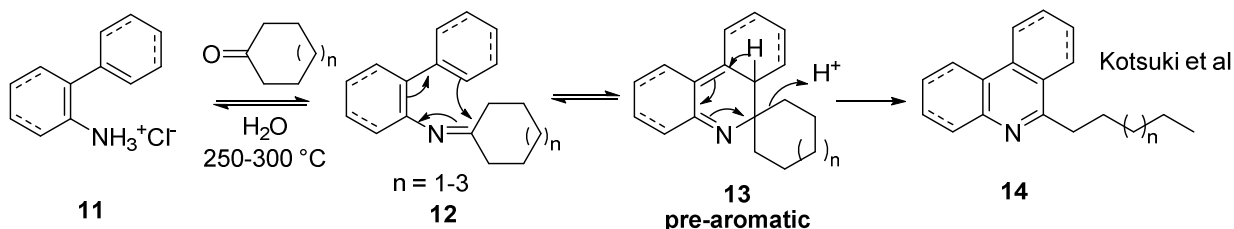a. Aromatization-driven C-C bond cleavage for C-H alkylations

R
EtO$_2$C   CO$_2$Et

Me   N   Me
      H
1
pre-aromatic

+   **acceptor**
      2

→

EtO$_2$C   CO$_2$Et

Me   N   Me
3

+   R
      4

Melchiorre, Molander, Chen
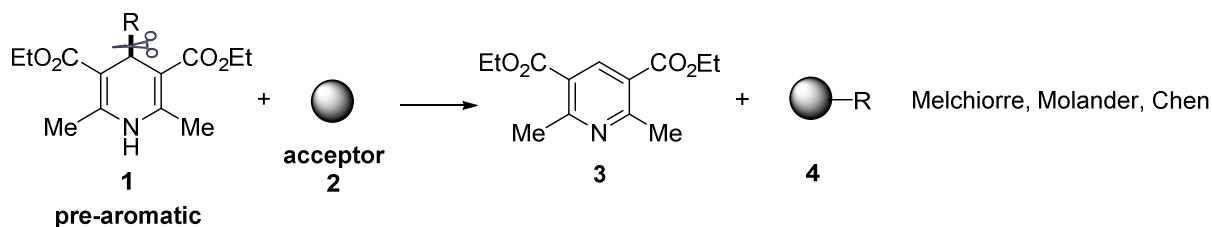
b. Aromatization-driven 1,2-migration of Pt- or Au-carbene intermediates

R^2

R^3
R^3

N
R^1
OH
5

[Pt] or [Au] →

R^2 M$^{\ominus}$
              R^3
         $\oplus$ R^3

N   H
R^1
pre-aromatic

→

R^2 R^3

              R^3

N   R^3
R^1

Ma et al
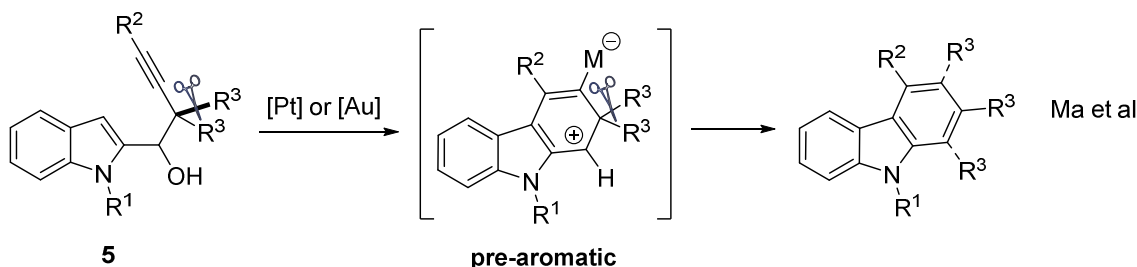
c. Aromatization-driven ring expansion of spirocycles

( )$_n$

N
7
pre-aromatic

acid
n = 1, 2
→

( )$_n$

N
R^1
8

You et al

O

9
pre-aromatic

acid →

OH

10

Yoshida et al
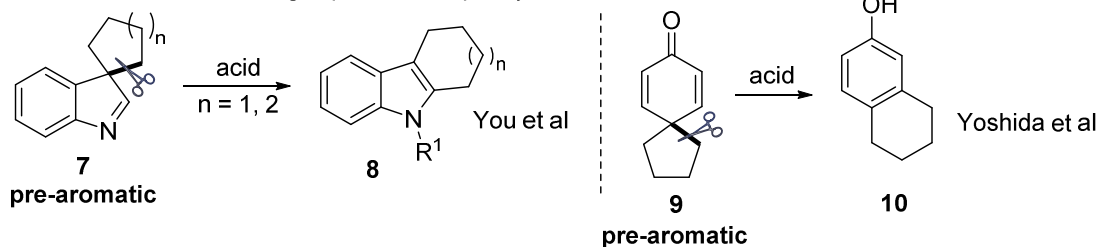
d. Aromatization-driven ring-opening of unstrained aliphatic rings

NH$_3^+$Cl$^-$
11

O   ( )$_n$

H$_2$O
250-300 °C
⇌

N   ( )$_n$
n = 1-3
12

⇌

H

N
13
pre-aromatic

H$^+$ →

N   ( )$_n$

14

Kotsuki et al

Scheme 4.1.1. Representative Examples of Aromatization-driven C-C Bond Cleavage Reactions

In addition to the deconstructive ring-expansion reactions described above, aromatization-driven ring-cleavage/remote functionalization reactions of unstrained cycloalkane rings have also been reported (**Scheme 4.1.2**). Except for Han's work involving the aromatization-driven cleavage and functionalization of unstrained primary cycloalkanamines, all the reported examples applying this strategy involved cycloalkanones. In typical reported reactions of this type, the cyclic ketone

or amine is condensed with a suitable activator to generate the pre-aromatic intermediate or substrate which undergoes aromatizative ring-opening to a generate distal carbon radical with a tethered fully aromatized heterocycle moiety. This carbon radical can be further transformed *via* oxidation to a carbonyl functionality or terminated by a HAT process (**Scheme 4.1.2**a). Although the radical could intuitively also be functionalized *via* interception with radical acceptors, no example involving unstrained cycloalkanones or cycloalkanamines has yet been reported.

a. Dong et al, 2019: Transition metal-catalyzed aromatizative ring-opening/functionalization of cyloalkanones

b. Fan et al, 2017: Transition metal-catalyzed aromatizative ring-opening/functionalization of cyloalkanones

c. Han et al, 2020: Thermochemical aromatizative deconstruction/functionalization of unstrained cycloalkanamines
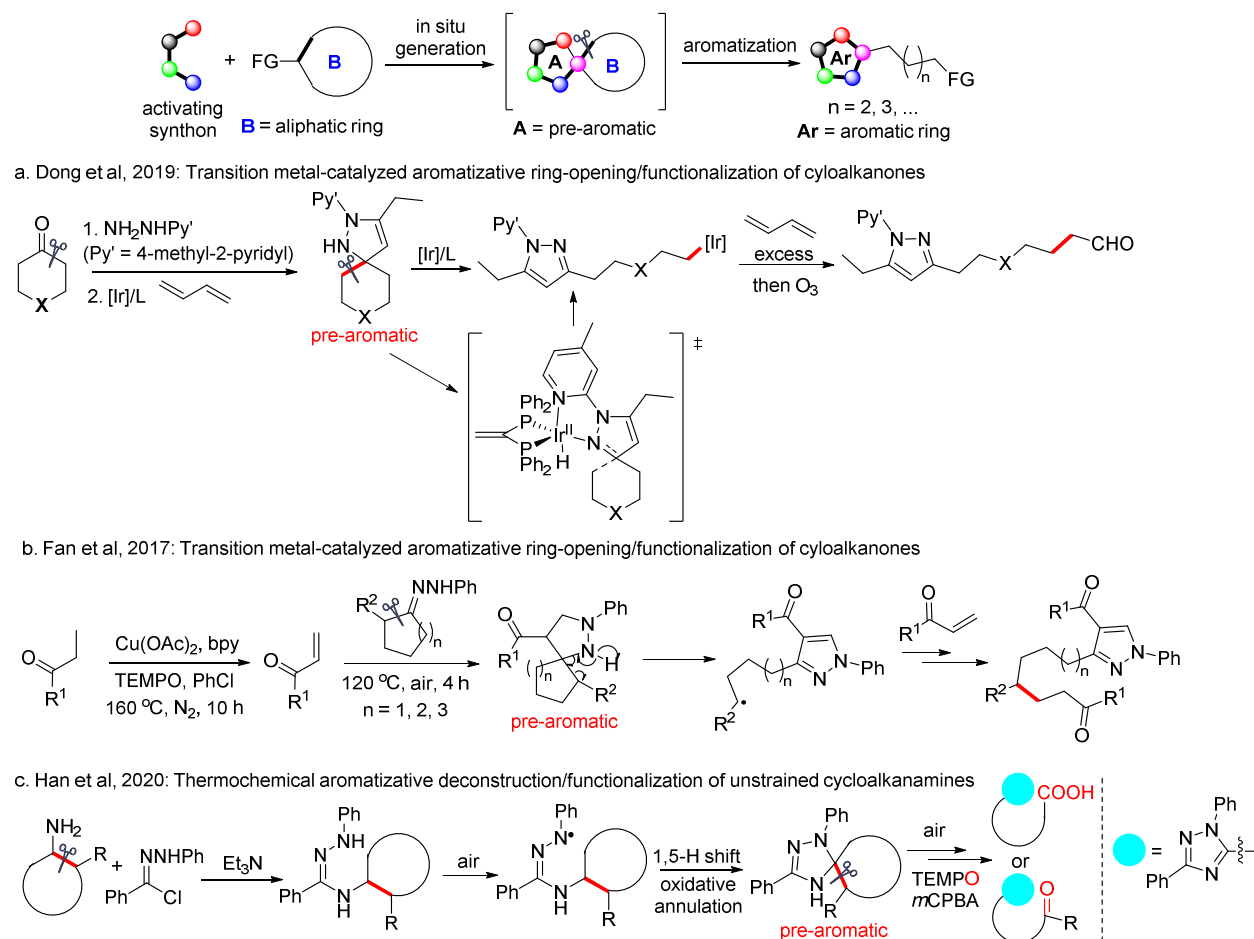
Scheme 4.1.2. Activator-assisted Aromatization-Driven Cleavage/Remote Functionalization Reactions of Unstrained Cycloalkanones and Cycloalkanamines.

Selective and catalytic C-C bond activation and cleavage in unstrained cycloalkanones for the introduction of chemical functionality is not trivial and only a few examples have been

reported. In a 2001 seminal work, Jun's group disclosed the rhodium(I)-catalyzed ring-opening of medium to large cycloalkanone imines for accessing ketones with various editing along their aliphatic chains.[322] Dong's group has made outstanding contributions to this research area employing transition-metal catalysis in the C-C bond activation/cleavage of unstrained cycloalkanones with the assistance of in situ-formed directing groups.[323] Much recently, in 2019, they reported an efficient radical-mediated C-C activation/refunctionalization of unstrained cycloalkanones, using aromatization as driving force (**Scheme 4.1.2**a).[312] An iridium catalyst mediates/facilitates the homolytic C-C bond cleavage in the transition state. In this deacylative transformation, a three-component coupling of a ketone, a 1,3-diene, and a substituted hydrazine produces a dihydropyrazole intermediate, i.e. the pre-aromatic intermediate, which then undergoes aromatization-driven C–C cleavage to produce an activated alkyl-Ir species bearing a tethered fully aromatized pyrazole moiety. Subsequent C-H reductive elimination or coupling with excess 1,3-diene followed by oxidation furnishes the corresponding products. Acylic ketones could also be transformed in the reaction. In a preceding 2017 publication, Fan and coworkers revealed a variant reaction which involved the Cu(I)-catalyzed reaction of unstrained cyclic ketone hydrazines with acyclic ketones (**Scheme 4.1.2**b). Oxidation of the ketone produces an enone which undergoes a [3+2] cyclization with the unstrained cyclic ketone hydrazone en route to the pre-aromatic intermediate. An aromatizaton-driven C-C bond fission and radical re-organization produces the distal carbon radical which be intercepted by and another equivalence of the enone and then undergo an HAT to result in the product bearing a tethered aromatized pyrazole moiety.

The exploitation of aromatization as driving force for C-C cleavage in unstrained rings have also been applied to cycloalkanamines. In 2020, Han and coworkers reported the first and only aminyl-radical-mediated ring-opening functionalization of unstrained primary cycloalkanamines

to date by employing aromatization as both kinetic and thermodynamic driving force (**Scheme 4.1.3**c).[304] Here, a different activating heterocyle moiety, a dihydrotriazole group, facilitates the aromatizative deconstruction/functionalization of the pre-aromatic intermediate. The nucleophilic substitution between the cycloalkanamine and hydrazonyl chloride produces hydrazonamide, which is auto-oxidized by air to yield an aminyl radical. The key isolable pre-aromatic spiro heterocycle is formed when radical undergoes a tandem 1,5-hydrogen atom shift/further oxidation/annulation process. The spiro heterocycle is oxidized by air to produce the cyclic amino radical intermediate. The aromatic 1,2,4-triazole is then produced as a result of aromatization, which acts as a driving force for the radical C–C bond breaking. TEMPO quickly intercepts the produced distal alkyl radical connecting aromatic 1,2,4-triazole, resulting in the ring-opening product. Treatment of by *m*CPBA produces the final product by oxidation/Cope-elimination sequence.

4.2. Background and significance

Ketones are ideal targets for chemical innovation due to their broad utility as chemical precursors,[324] the variety of methods for their synthesis, and their prevalence in medicinal and commercial chemicals. Common synthetic manipulations of ketones usually focus on the latent polarity of their electrophilic C=O bonds or the nucleophilicity of related enolates, but the selective and catalytic C-C bond cleavage of ketones, especially unstrained cyclic ketones, as avenues for installing new chemical functionality remains a challenge and only few methods have been reported. Compared with strained cyclic ketones, the development of strategies for the cleavage and functionalization of unstrained cycloalkanols is especially challenging due to the lack of driving force in the ring-opening event.

The C–C bond activation and cleavage of strained cycloalkanones in the form of cycloalkanone oximes have been achieved by taking advantage of the high reactivity of the resulting iminyl radical from homolysis of the weak N-O bond of the oxime (BDE ≈ 50 kcalmol^{-1}) and the additional driving force provided by the generation of the stronger C≡N bond (BDFE ≈ 213 kcalmol^{-1}) in the ring-opening product (**Scheme 4.2.1**a). Ring-opening of strained cycloalkyliminyl radicals is favorable due to the release of ring strain as a thermodynamic driving force, and by installing substituents at the α-position, the β-scission of unstrained five- and six-membered rings to produce distal cyano alkyl radicals can also been achieved.[198, 223, 234, 235, 265, 305] The C-C bond cleavage of unstrained cycloalkylaminyl radicals has also be realized at elevated temperatures. Although significant advances have been made in iminyl-radical-triggered deconstruction/re-editing of unstrained cycloalkanones under photo and thermal conditions with and without the involvement of TMs, all of these reactions still require prior transformation of the ketone into the iminyloxy precursor which decreases the overall reaction step-economy.

a. Iminyl-radical-mediated C-C bond cleavage/distal functionalization of cycloalkanones

n = 1, 2, 3, ...
X = C, N, O

TM = transition metal, µW = microwave
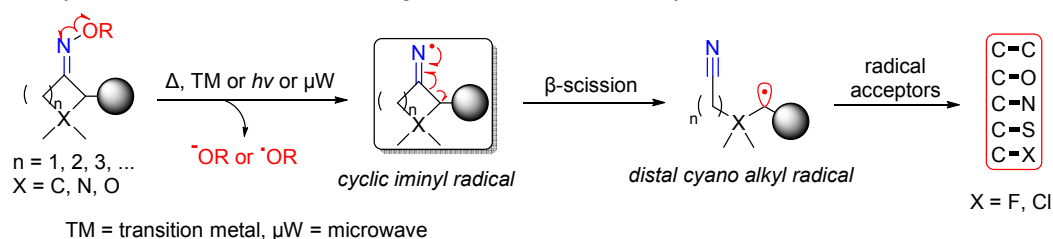
b. LMCT-promoted deconstructive functionalization of cycloalkanones (Zuo et al)
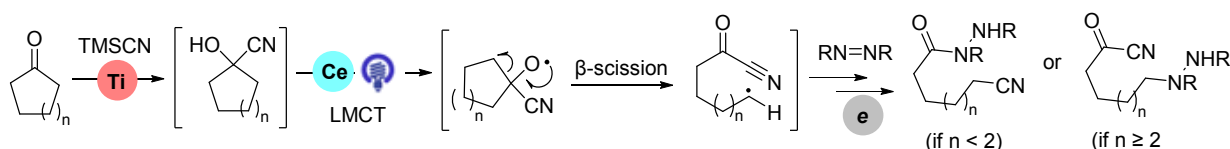
c. Transition metal-catalyzed aromatizative ring-opening/functionalization of cyloalkanones (Dong et al)
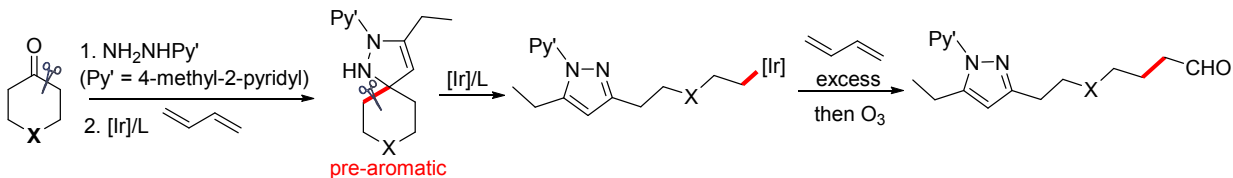
Scheme 4.2.1. Reported Methods for Radical-mediated Cycloalkanone Ring-cleavage/functionalizations

Zhuo and coworkers have reported a cooperative Lewis acid/LMCT catalyzed, visible-light-assisted, Norrish I-type C–C bond cleavage/functionalization of unstrained cycloketones. Although the straightforward but uncoventional way of harvesting visible light for the C-C bond cleavage of the unstrained cycloalkanones was effective, the complex cerium-based LMCT excitation and reaction system presents a drawback to its broad use (**Scheme 4.2.1**b).

An effective but relatively less explored strategy for the deconstruction/functionalization of unstrained cycloalkanones exploits aromatization of an *in-situ*-formed pre-aromatic fused spirocyclic intermediate as the thermodynamic driving force of the ring-opening. However, the couple of examples by the groups of Dong[312] and Fan[325] which applies this strategy both involved elevated temperatures and required the use of transition metal/ligand combinations to promote the

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generation of the *in situ* pre-aromatic substrate (*via* a hydrazone intermediate) and/or mediate the subsequent aromatization-driven C-C bond cleavage (**Scheme 4.2.1**c). The complex reaction protocols involved in these works depict the major challenge associated with the use of this strategy for the deconstructive functionalization of unstrained cycloalkanones, viz., the difficulty of generating pre-aromatic substrates *in situ*. Thus, the development of milder and efficient methods of generating the pre-aromatic substrates or intermediates would enable the wider use of this strategy. Meanwhile, easily accessible benzo-fused heterocycles such as ketone-derived 2,2-disubstituted benzimidazolines,[326] benzothiazolines,[327-329] and dihydroquinazolinones (DHQZs)[330-333] have been reported to undergo aromatization-driven α C-C cleavage under thermal or photochemical conditions to generate alkyl radicals which can be intercepted by radical acceptors. In this way, these pre-aromatic compounds have potential synthetic value as complementary precursors of alkyl radicals to the traditional reagents like 4-alkyl-substituted Hantzsch esters or nitriles[334] and Katritzky salts.[335] For example, 2,2-dialkyl-benzothiazolines, synthesized from condensation of acyclic ketones with *o*-aminothiophenol, have recently been used to successfully produce acyl and alkyl radicals for formal alkylation, alkenylation and alkynylation reactions under photochemical conditions,[328] and the formal hydroalkylation and hydroacylation of electron-deficient olefins under photocatalytic conditions.[329] Furthermore, 2,2-disubstituted DHQZs, derived in one step from acyclic ketones, was used in a 2020 report by Zhu's group as alkyl radical precursors for intermolecular conjugate addition to Michael acceptors for the construction of diverse vicinal quaternary carbon centers under visible light irradiation in the presence of photosensitizer (**Scheme 4.2.2**a),[330] and in a 2022 report by Martin's group as adaptative $C(sp^3)$ handles in cross-coupling with aryl and alkyl bromides under metallophotoredox catalysis.[331]

Based on the foregoing reports, we envisioned that the analogous spiro-cycloalkane-dihydroquinazolinones, obtained from the one-step condensation of *o*-carbamoylaniline and various unstrained cyclic ketones, would likewise undergo the α C-C bond cleavage to give a distal carbon radical tethered to a fully aromatized quinazolinone moiety. The carbon radical could then be trapped with various radical acceptors to afford the deconstruction/refunctionalization products. Quinazolinones are considered a "privileged structure" for drug discovery and development[336, 337] and are prevalent in biologically active compounds and a variety of natural products,[338] including tryptanthrin,[339] rutaecarpine,[340] luotonin A, B, E, and F,[341] (**Figure 4.2.1**). Thus, synthetic quinazolinone scaffolds have been in high demand due to their promising biological and therapeutic capabilities, which include antibacterial,[342] anti-inflammatory,[343, 344] anticancer,[344, 345] and antihypertensive[346] effects. Under visible-light photoredox catalysis, we anticipated that the ring-opening functionalization of the spirocyclic aminal would occur under mild conditions following PET oxidation. To the best of our knowledge, no photocatalytic aromatization-driven deconstruction/re-functionalization of unstrained cyclic ketones has been reported as of this writing. Furthermore, this represents the first systematic synthetic effort towards organic reaction development using cycloketone-derived dihydroquinazolinones.

2-methyl-4(3H)-quinazolinone	**rutaecarpine**	**tryptanthrin**	**luotonin A, B, E**
Antibacterial Anti-fungal Anti-inflammatory	Anti-thrombotic Anti-cancer Anti-inflammatory Anti-obesity	Anti-inflammatory Anti-cancer Anti-mycobacterial Anti-allergic	Anti-tumor Anti-inflammatory Anti-rheumatism Anti-cancer
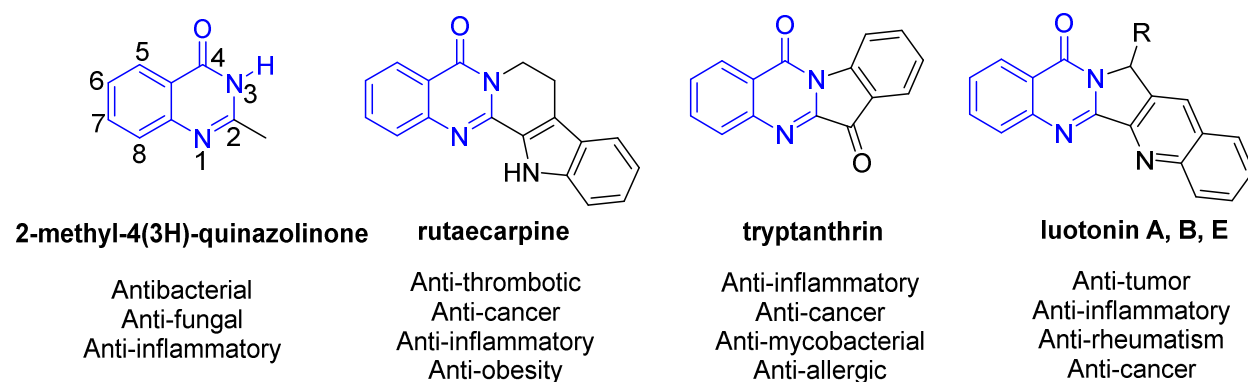
Figure 4.2.1. Natural Products Containing the Quinazolinone Skeleton

We report herein the first visible-light-assisted aromatizative deconstruction/refunctionalization of unstrained cycloalkanones in the form of spirocylic aminals employing o-carbamoylaniline (2-aminobenzamide) as activator of the C-C bond cleavage (**Scheme 4.2.2**b). Our protocol features readily accessible spirocyclic pre-aromatic substrates derived from the condensation of the 2-aminobenzamide activator and cyclic ketones and proceed *via* an amido-radical-mediated ring cleavage facilitated by both aromatization and the action of radical acceptors in a "push-pull" synergy.

a. *Zhu et al, 2020*: Visible-light-assisted aromatizative cleavage/functionalization of acyclic ketones
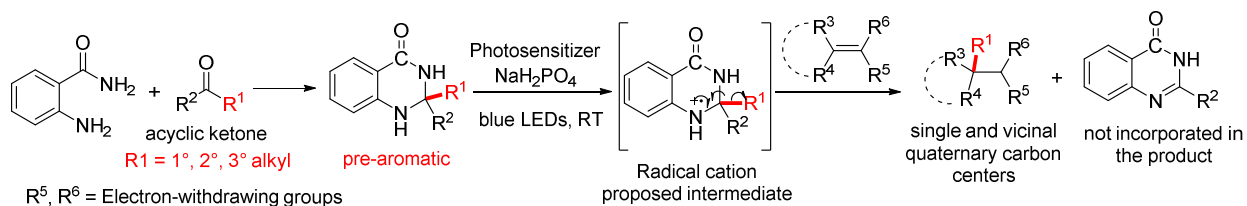
b. *This work*: Visible-light-assisted aromatizative deconstruction/functionalization of unstrained cyclic ketones
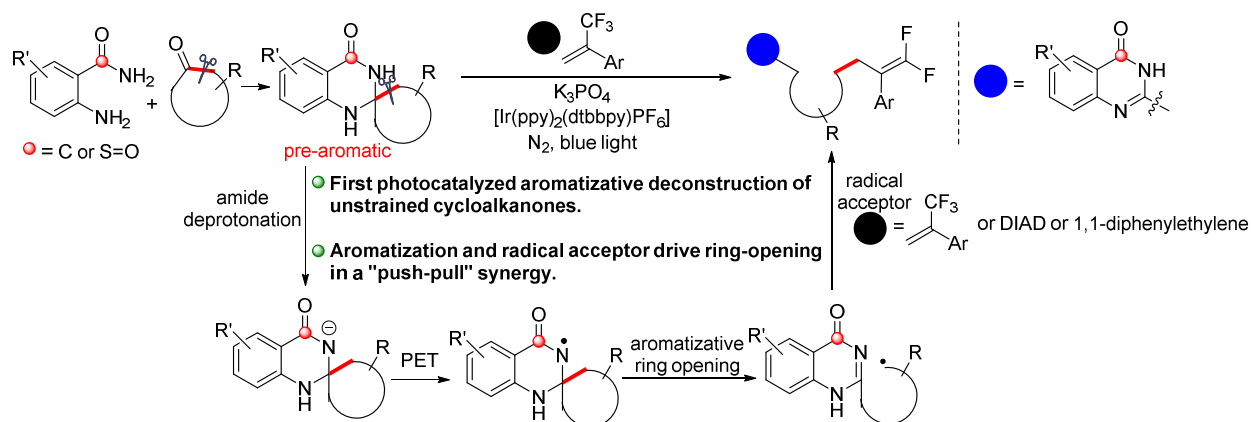
Scheme 4.2.2. Current Work: Visible Light-mediated Deconstruction/Refunctionalization of Unstrained Cycloalkanones Using Diamines as Activating Groups

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4.3. Results and Discussion

4.3.1. Development of the Aromatizative Deconstruction/Functionalization of Unstrained Cycloalkane Rings

We hypothesized that the pre-aromatic spiro-cycloalkane-dihydroquinazolinones would undergo aromatizative α C-C cleavage upon photoinduced oxidation to produce a distal carbon radical bearing a tethered aromatized quinazolinone moiety which could be intercepted by radical acceptors to furnish a remote functionalization product. Thus, we began our investigation with the search of suitable or compatible radical acceptors capable of intercepting the carbon radical. **Scheme 4.3.1.1** shows a summary of our initial successful results from the reactions of both spiro-cyclopentane-dihydroquinazolinone **1** and spiro-cyclohexane-dihydroquinazolinone **6** and it indicates that the compatibility and/or reactivity of the radical acceptor impacts the observed ring-opening of the unstrained ring.

Gratifyingly, irradiating a degassed 1,2-dichloroethane mixture of **1** (0.1 mmol), Ir(ppy)$_2$(dtbbpy)PF$_6$ (2 mol%), and phenylethynylbenziodoxolone **2** (2 equiv) as the radical acceptor for 18 h under blue light irradiation yielded 14% of the desired deconstruction/distal functionalization product and 2% of side product resulting from the hydrogen atom abstraction by the generated carbon radical, together with lots of unreacted starting material (**Scheme 4.3.1.1**a). Modification of the reaction conditions by employing 1:1 DCE/H$_2$O as solvent system and/or adding additives like hydroxybenziodoxole BI-OH or base (Na$_2$CO$_3$) neither improved the reaction yield nor eliminated the side product. Switching the radical acceptor to 1,1-diphenylethylene **3** (5 equiv) and the solvent to DMF led to enhanced reaction of **1** affording 68% of the desired ring-opening functionalization product and still 3% of the side product (**Scheme 4.3.1.1**b). The use of diisopropylazodicarboxylate **4** (DIAD) as radical acceptor improved the reaction further giving

77% of the corresponding product (**Scheme 4.3.1.1**c). To our delight, the radical acceptor α-CF$_3$-sytrene **5** which was employed by us in our previous difunctionalization of strained cycloalkylanilines involving TMSCN proved to be efficient also in the current reaction in the presence of the base K$_3$PO$_4$ and the drying agent Na$_2$SO$_4$, affording 93% isolated yield (and quantitative NMR yield) of the ring-opening/distal functionalization product from **1** (**Scheme 4.3.1.1**d). Intrigued by this result, we subjected the lesser strained spiro-cyclohexane-dihydroquinazolinone **6** to the same conditions and obtained 43% of the corresponding product (**Scheme 4.3.1.1**e). **Scheme 4.3.1.1** also shows radical acceptors which proved unsuccessful when probed in reaction with **1** resulting in the recovery of the starting material.

Having established a proof-of-concept with the initial investigations and identified an ideal reaction (i.e., **Scheme 4.3.1.1**d,e) we selected the reaction involving the lesser reactive spiro-cyclohexane-dihydroquinazolinone **6** for the subsequent optimization studies (see section **4.3.2** hereinafter). We synthesized **6** on a gram scale and conducted an elaborate, systematic optimization studies of the reaction.

Scheme 4.3.1.1. Initial Successful results of the Deconstructive Functionalization of Unstrained Cycloalkane Rings

Table 4.3.2.1. Optimization of the reaction conditions.[a]

Entry	Solvent	Photocatalyst	Base	Temp, Time	Yield 3a [%][b]
1	DMF	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	-	50 °C, 17 h	nd
2	DMF	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	K$_3$PO$_4$	50 °C, 17 h	51
3	DMF	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	K$_2$HPO$_4$	50 °C, 17 h	9
4	DMF	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	Bu$_4$N[OP(O)(OBu)$_2$]	50 °C, 17 h	3
5	DMF	Ru(bpy)$_3^{2+}$ PF$_6$	K$_3$PO$_4$	50 °C, 17 h	4
6	DMF	Mes-Acr$^+$ ClO$_4^-$	K$_3$PO$_4$	50 °C, 17 h	nd
7	DMF	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	Na$_2$CO$_3$	50 °C, 17 h	31
8	DMF	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	K^{t}OBu	50 °C, 17 h	7
9[c]	DMA	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	K$_3$PO$_4$	50 °C, 17 h	18
10[d]	CHCl$_3$	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	K$_3$PO$_4$	50 °C, 17 h	11
11[e]	MeOH	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	K$_3$PO$_4$	50 °C, 17 h	7
12	DMF	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	K$_3$PO$_4$	50 °C, dark, 17 h	nd
13	DMF	-	K$_3$PO$_4$	50 °C, 17 h	nd
14	DMF	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	K$_3$PO$_4$	50 °C, 36 h	76 (55)[f]
15	DMF	[Ir(ppy)$_2$(dtbbpy)]PF$_6$	K$_3$PO$_4$	60 °C, 24 h	83 (51)[f]

[a] Conditions: **1a** (0.2 mmol, 1 equiv), **2a** (5 equiv), [Ir(ppy)$_2$(dtbpy)]PF$_6$ (2 mol%), K$_3$PO$_4$ (2 equiv) and DMF (2 mL), irradiated for 36 h with a four-strip blue LED light (425 nm) under N$_2$, or wrapped with aluminium foil and irradiated for 24 h with four-strip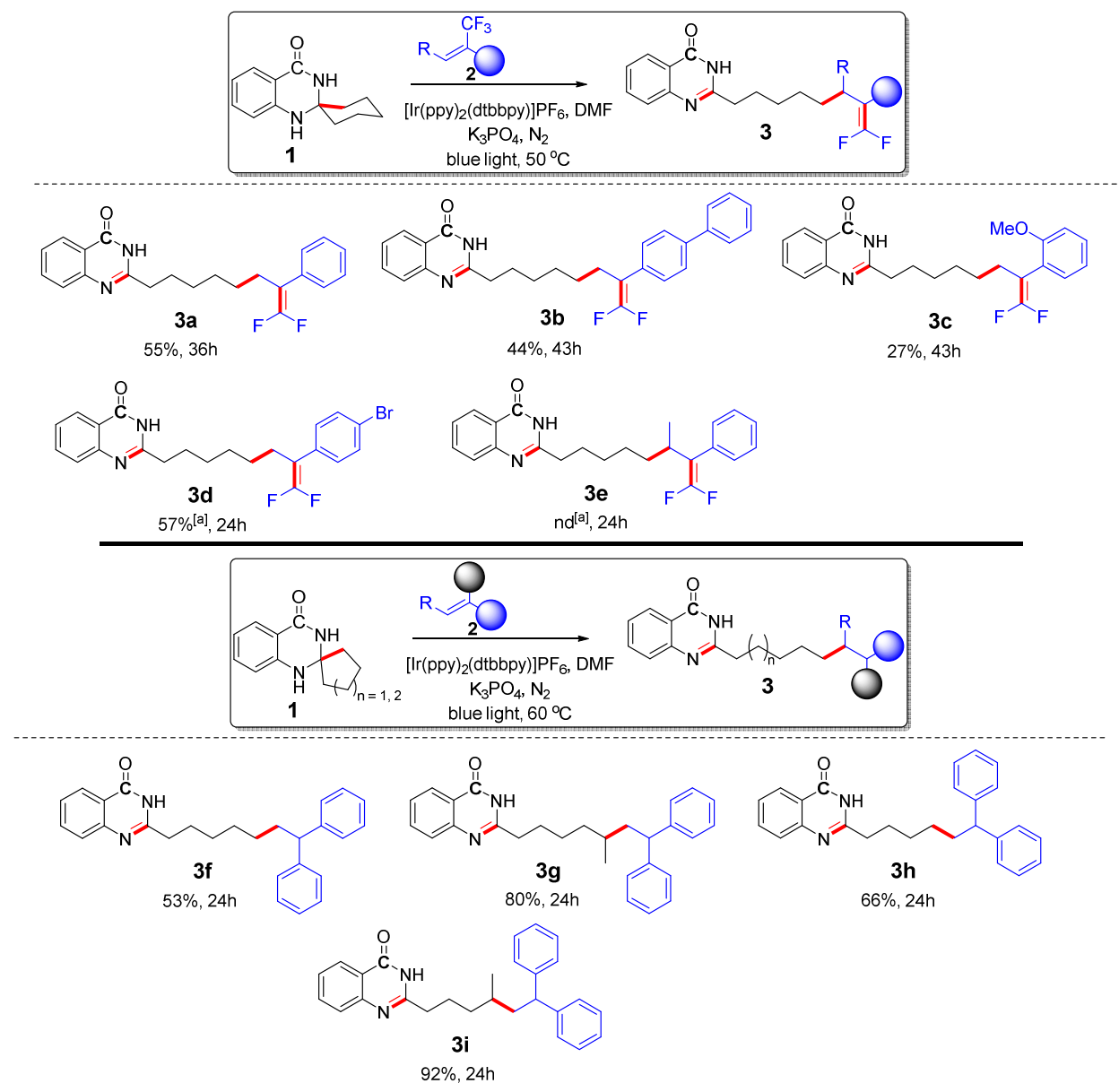 blue light to reach an internal temperature of 58-60 °C. [b] ^{1}H NMR yield determined using 1 equiv of CH$_2$Br$_2$ as internal standard. [c] N,N-dimethyl acetamide (DMA) as solvent. [d] CHCl$_3$ as solvent. [e] MeOH as solvent. [f] Isolated yield. nd = not detected.

Table 4.3.2.1 above shows a summary of the results of the optimization studies. When a degassed DMF mixture of 1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one **1a** (0.2 mmol), α-CF$_3$-styrene **2a** (5 equiv), and the photoredox catalyst [Ir(ppy)$_2$(dtbbpy)]PF$_6$ [Ir(III)*/Ir(II) = 0.66V, Ir(III)/Ir(II) = -1.51V] was irradiated with blue light for 17 h, the substrate remained

unreacted and the expected product **3a** was not detected in crude NMR analysis of the reaction mixture (entry 1). Adding K_3PO_4 afforded 51% NMR yield of the desired product (entry 2) whereas K_2HPO_4 and KH_2PO_4 decreased the yield of **3a** (entry 3), thus demonstrating the importance of a suitable base in the transformation. Suspecting that a PCET step is possibly involved in the reaction, we tested the oft-used PCET Brønsted base $Bu_4N[OP(O)(OBu)_2]$ in the reaction (entry 4) but this decreased the yield significantly, thereby excluding a concerted PCET process in the reaction pathway. The use of Na_2CO_3 (entry 7) or the much stronger base K^tOBu (entry 8) also hindered the reaction probably by quenching the excited state of the photocatalyst. Switching the solvent to DMA (entry 9), $CHCl_3$ (entry 10), or MeOH (entry 11) also lead to decreased yields. Furthermore, both visible light irradiation (entry 12) and photocatalyst (entry 13) were indispensable for the transformation, and no product was detected when these were excluded. With the reaction conducted at 50 °C, doubling the reaction time improved the NMR yield to 76% (entry 14), whereas 83% NMR yield was observed after 24 h when the reaction was carried out at 60 °C (entry 15). Thus, we applied both conditions (entries 14 and 15) for the subsequent scope studies.

4.3.3. Substrate Scope of the Reaction

With the two sets of optimized conditions in hand (i.e., the conditions at 50 °C and 60 °C) the substrate scope of the reaction was evaluated (**Table 4.3.3.1**). We achieved the ring opening/functionalization of diverse spirocyclic dihydroquinazolinones of medium-to-large cycloalkane ring sizes in decent to excellent yields. As shown in **Table 4.3.3.1**, a large variety of unstrained monocylic (**1a-1l**), bicyclic (**1o**), heterocyclic (**1p**, **1r**), bridged (**1o**), and benzofused (**1s**, **1u**) cycloalkanone-derived dihydroquinazolinones underwent the transformation with

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different levels of efficiency. Generally, higher yields and shorter reaction time were observed at 60 ºC than at 50 ºC.

Table 4.3.3.1. Substrate Scope with respect to Cycloalkane Rings
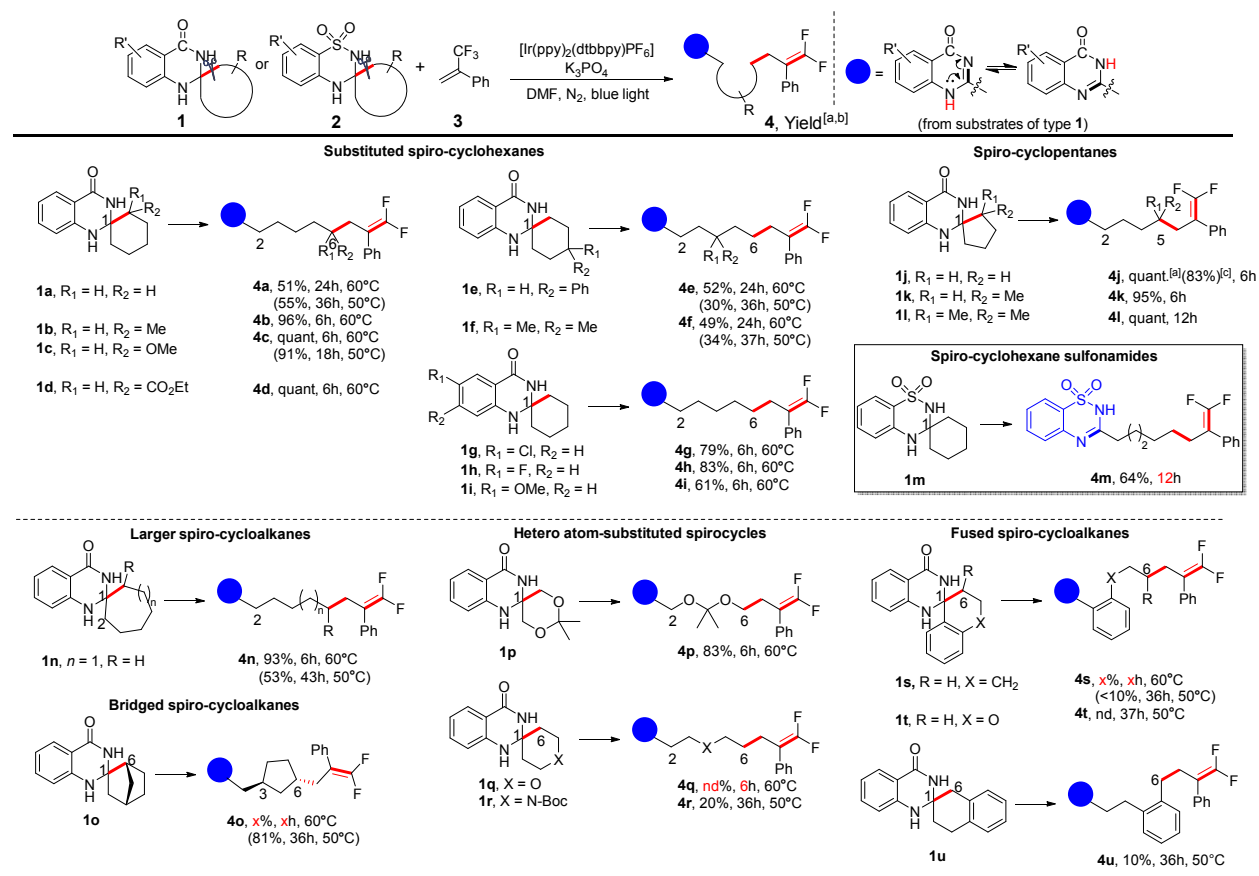
[a] Yields of isolated products. [b] Reaction conditions: Aminal (0.2 mmol, 1 equiv), α-CF$_3$-styrene (5 equiv), [Ir(ppy)$_2$(dtbpy)]PF$_6$ (2 mol%), K$_3$PO$_4$ (2 equiv) and DMF (2 mL), irradiated for 36 h with a four-strip blue LED light (425 nm) under N$_2$, or wrapped with aluminum foil and irradiated for 24 h with four-strip blue light to reach an internal temperature of 58-60 °C. [c] No base was used.

Unsubstituted spiro-cycloalkane-dihydroquinazolinones such as **1a** and **1j**, as well as dihydroquinazolinones **1e-1f** and **1k-1l** with substitution on the cyclohexane or cyclopentane ring underwent the transformation to give the desired ring-opening/functionalization products in good to excellent yields. Introducing either an electron-releasing group such as OMe (**1i**) or electron-

withdrawing groups such as the halides Cl and F (**1g** and **1h**) on the benzene ring of the dihydroquinazoline moiety improved the reactivity of the cyclohexane substrate. Substrate **1n** with a cycloheptane ring also could also undergo the transformation to yield the product in 53% at 50 ºC or 93% at 60 ºC. The alpha C-C bond cleavage was found to be regioselective, occurring preferentially at the more substituted carbons of dihydroquinazolinones **1b-1d** and **1k-1l** bearing substitution at the 2-position of the cyclohexane and cyclopentane rings respectively, or at the α-position of heteroatoms such as in substrates **1p** and **1r**. Near quantitative or quantitative yields of the desired products were achieved with both an electron-releasing group such as OMe (**1c**) and electron-withdrawing substituent such as CO_2Et (**1d**) at the 2-position of the cycloalkane ring, although no improvement in the yield was observed with substitution at the 4-position (**1e** and **1f**). Heterocyclic substrates **1q**, **1r**, and **1t** bearing an O or N in the ring cycloalkane ring performed poorly; however, acetal **1p** possessing a *gem*-dimethyl group reacted effortlessly to give 83% of the corresponding product. For the benzofused cycloalkane systems, β-tetralone-derived substrate **1u** gave 10% of the product while the analogous α-tetralone-derived substrate **1s** afforded even less product. Predictably, the bridged spiro-cyclohexane-quinazolinone **1o** underwent ring-cleavage at the more substituted carbon to give the corresponding product in 81% yield at 50 ºC. Finally, the ring-disconnection/refunctionalization could be achieved successfully in 64% yield with substrate **1m** derived from the condensation of cyclohexanone with 2-aminobenzenesulfonamide (*o*-sulfanilamide).

Next, the scope of the reaction with respect to radical acceptors was examined (**Table 4.3.3.2**). With α-CF_3-styrene as radical acceptor, in comparison with the yield from standard unsubstituted substrate **3a** (55%), the yield was not improved with a weakly electron-donating group such as Ph (**3b**) or a weakly deactivating group Br (**3d**) as substituent on the para position,

giving 44% and 57% respectively. When the phenyl ring was substituted with the strongly activating group OMe at the ortho-position **3c**, the yield dropped to 27% and the desired product was not detected when tri-substituted α-CF$_3$-styrene **3e** was used. The significantly diminished reactivity of the radical acceptor in these cases can attributed to the steric hindrance around the C=C bond. In the scope with respect to 1,1-diphenylethylene, the yield of the desired product was improved from 53% to 80% when the dihydroquinazolinone substrate was substituted at the 2-position of the 2-position of the cyclohexane ring, and from 66% to 93% for the reactions conducted with the cyclopentane equivalents.

Table 4.3.3.2. Substrate Scope with respect to Radical Acceptors

3a
55%, 36h

3b
44%, 43h

3c
27%, 43h

3d
57%[a], 24h

3e
nd[a], 24h

3f
53%, 24h

3g
80%, 24h

3h
66%, 24h

3i
92%, 24h

[a] Reaction was conducted at 60 ºC. nd = not detected.

4.4. Mechanistic Study

The structures of our pre-aromatic spiro-cycloalkane-dihydroquinazolinone substrates contain an anilino N-H group as well as an amido N-H group. The aromatization-driven α C-C bond cleavage of the analogous acyclic ketone-derived 2,2-dialkyl-dihydroquinazolinones have

previously been reported by the groups of Tang,[332] Zhu[330] and Martin,[331] to occur *via* an amine radical cation intermediate generated by SET oxidation of the aniline group in the substrate's structure. However, theoretically, the cleavage *via* an amido radical intermediate generated from the activation of the N-H bond of the amide functionality by a concerted base-promoted PCET or a stepwise PT/ET is also possible in the presence of a suitable base. To gain insight into the possible mechanism of our deconstruction/refunctionalization reaction, a set of control and mechanistic experiments were conducted (**Scheme 4.4.1**).

In our earlier optimization studies, spiro-cyclohexane-dihydroquinazolinone **1** was completely unreactive in the reaction conducted without the base K_3PO_4, based on analysis of the crude ^{1}HNMR of the reaction mixture (**Table 4.3.2.1**, entry 1 or **Scheme 4.4.1**a). Curiously, when its smaller homolog spiro-cyclopentane-dihydroquinazolinone **3** was subjected to the same conditions, the desired ring-opening/functionalization product was obtained in NMR yield of 80%, down from the quantitative yield when a base was involved (**Scheme 4.4.1**b), thus begging the question of what mechanistic differences exist (if any) between the ring-opening events of these two substrates which possess similar structures. Substituting the amido H in the structure of **1** with a methyl group resulted in no reaction (**Scheme 4.4.1**c). Together with the observed drop in reactivity or the lack thereof in the absence of a base, this result suggests the direct involvement of the amide N-H bond in the aromatizative ring-opening event and rules out oxidative cleavage *via* amine radical cation intermediate from SET oxidation of the aniline group. Moreover, the significant decrease in the yield observed when the PCET Brønsted base $Bu_4N[OP(O)(OBu)_2]$ was used in the reaction (**Table 4.3.2.1**, entry 4) excludes a concerted PCET pathway process in the reaction mechanism. Still, when the structure of the substrate was modified to remove the pre-aromaticity in the substrate such as by substituting a methylene group for the aniline N-H (**Scheme**

4.4.1d), removing the fused benzene ring (**Scheme 4.4.1**e), or substituting a methylene group for the amide C=O group, no reaction was observed.
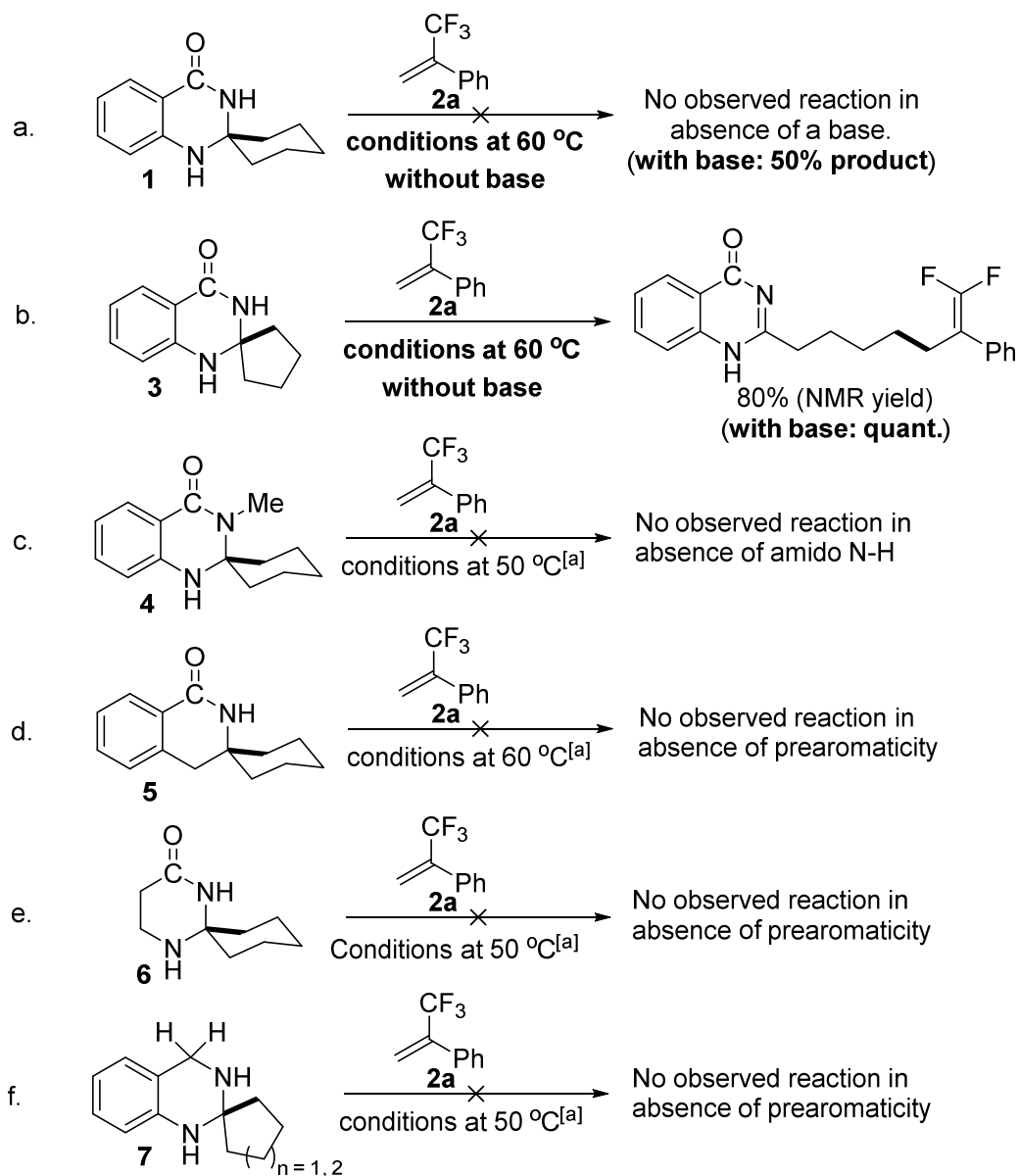
Scheme 4.4.1. Control Studies: Investigation of the Structural Requirements for Ring-opening of Unstrained N-Cycloalkane Rings

Thus, based on the foregoing discussion, we surmise that the aromatization-driven ring-opening proceeds *via* a stepwise PT/ET manifold in which the amide is initially deprotonated by the K_3PO_4 base to an amido anion, followed by photoinduced single-electron oxidation to an amido radical by the excited state Ir^{3+} catalyst which mediates the α C-C bond cleavage.

In addition to the control studies above, we performed ab initio computations to further understand the difference in reactivity between the spiro-cyclohexane-DHQZ **1** and spiro-cyclopentane-dihydroquinazolinone **3** (**Figure 4.4.1**). Our ab initio DFT-B3LYP-6-31G* energy calculations of the gas and solution-phase ground state equilibrium geometries using Spartan'18 reveal that the ring-opening *via* an amido radical intermediate is more exergonic, and hence more favorable, for both **1** and **3** ($\Delta E_{polar\ solvent} \approx$ -8.52 kcalmol^{-1} and -6.63 kcalmol^{-1} for **1** and **3** respectively) than the analogous process mediated by an amine radical cation which is endergonic ($\Delta E_{polar\ solvent} \approx$ +9.90 kcalmol^{-1} and +7.05 kcalmol^{-1} for **1** and **3** respectively). This suggests that an identical species, namely an amido radical, mediates the ring-opening of both substrates following photoinduced oxidation, and the striking difference may be rationalized in terms of the much higher cyclopentane ring strain energy of **3** compared with the negligible cyclohexane ring strain of **1** (6.2 kcalmol^{-1} vs 0.1 kcalmol^{-1}) which presumably provides, in the case of the former, an extra driving force for the ring-opening in addition to the aromatization. However, these determinations do not account conclusively for the prerequisite of a base for reactivity in the one case but not in the other and further investigation is warranted.
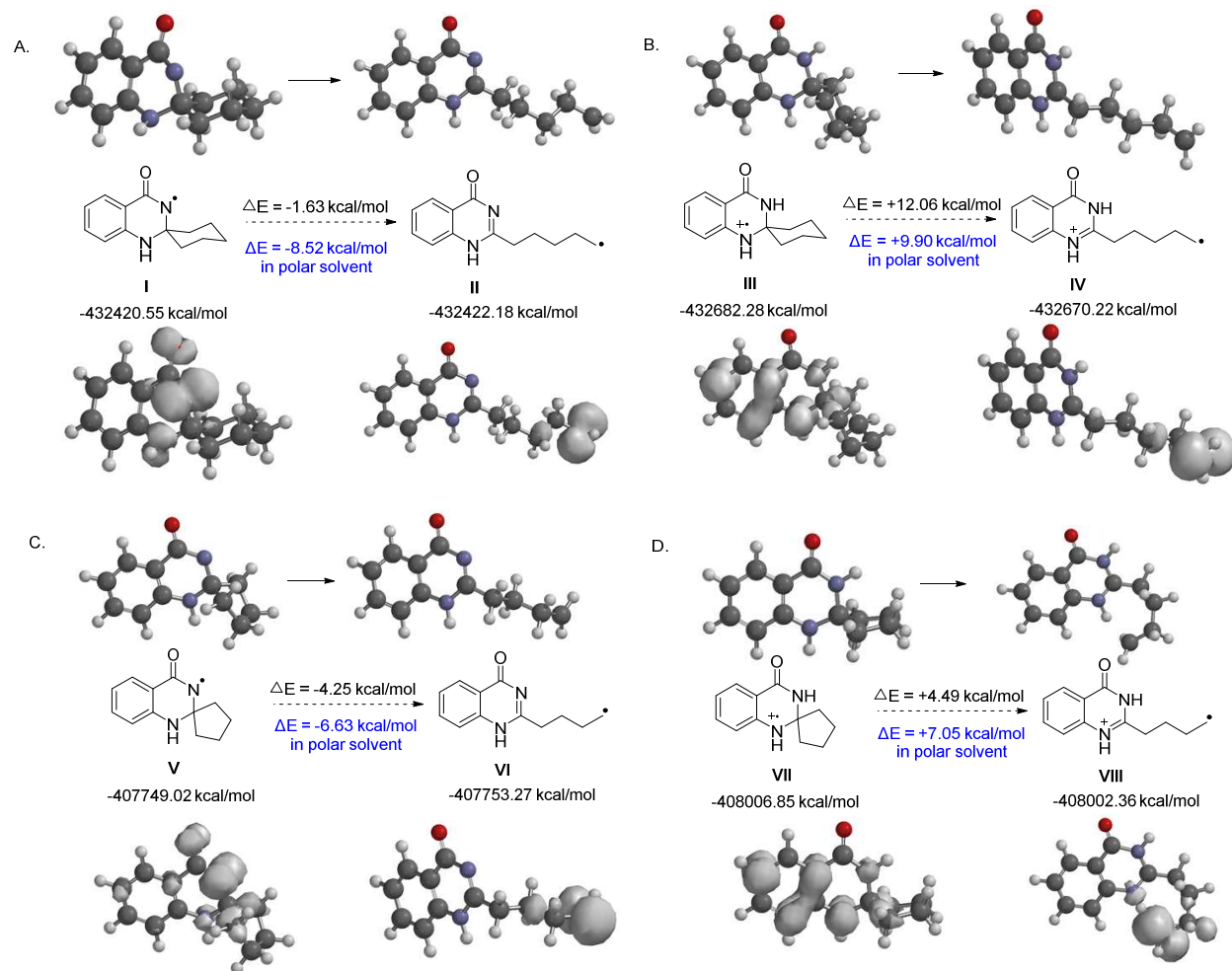
Figure 4.4.1. DFT-B3LYP-6-31G* Ground State Equilibrium Geometries and Spin Densities in Gas Phase

Proposed Mechanism:

Our proposed mechanism for the aromatizative deconstruction/refunctionalization of unstrained cycloalkanones in the form of spiro-cycloalkane-dihydroquinazolinones is shown in **Scheme 4.4.2** below. As described earlier, a deprotonation of the amide N-H followed by single-electron oxidation of the resulting amido anion by the excited state of the photocatalyst generates the reduced form of the photocatalyst Ir^{2+} together with amido radical intermediate **III**. An alpha

C-C bond scission mediated by **III** achieves the ring-opening of the cycloalkane ring to afford a distal carbon-centered radical **IV** bearing a tethered fully aromatized quinazolinone moiety. **IV** has four other possible tautomers, two of which are indicated in **Scheme 4.4.2**. Addition of the tautomer **V** of this radical to the α-CF₃-styrene **2a** produces the transient α-trifluoromethyl radical **VII** which is transformed *via* a reductive radical-polar crossover (RRPCO)[347] to the carbanion intermediate **VIII** whiles also regenerating the photocatalyst. Finally, β-fluoride elimination readily occurs to furnish the target product **3a** bearing a terminal *gem*-difluoroalkene group.[348-350] *Gem*-difluoroalkenes are structural motifs found in a wide range of substances, including pharmaceuticals and pesticides (**Figure 4.4.3**). In the case of alkenes such as 1,1-diphenylethylene as radical acceptor, a direct protonation of corresponding carbanion intermediate following the RRPCO affords the 1,1-diphenyl distal functionalization product.[350]
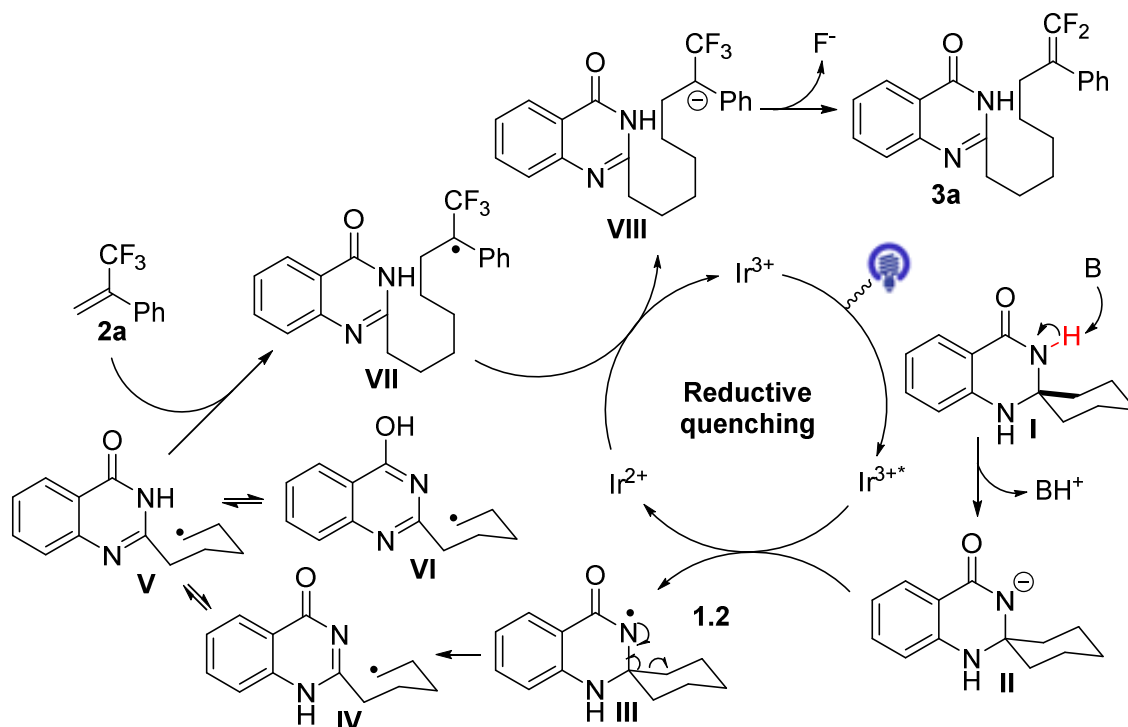
Scheme 4.4.2. Speculative Mechanism of the Deconstructive Functionalization of Unstrained N-Cycloalkane Rings

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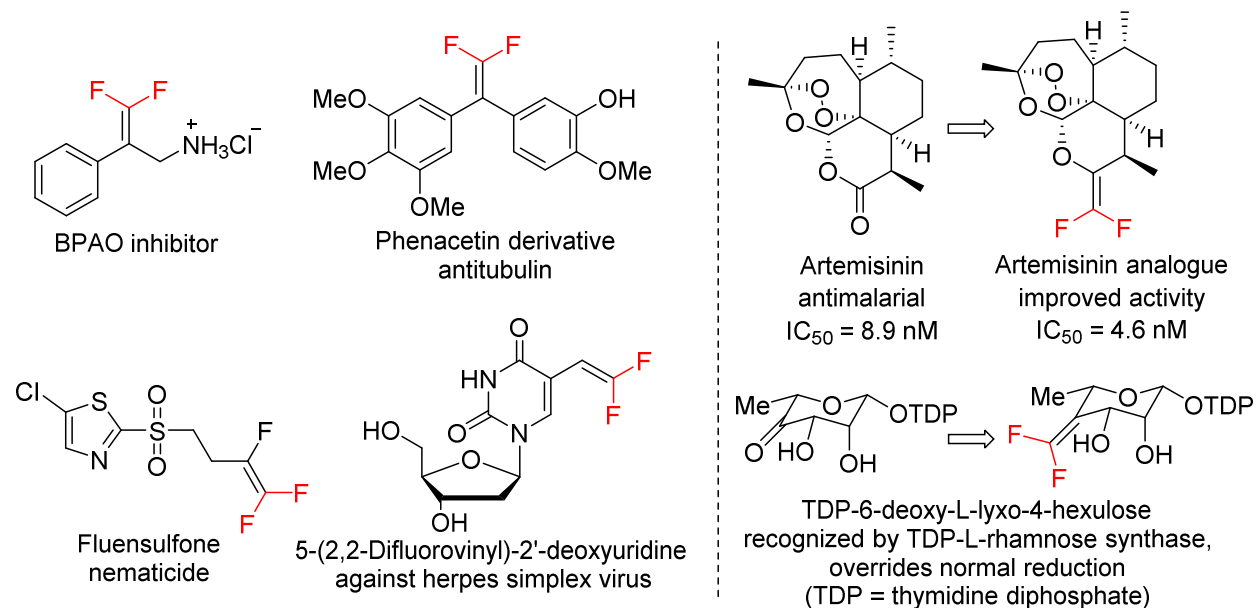
Figure 4.4.3. Examples of Biologically Active Gem-difluoroalkenes[349]

4.5. Future Work

We have successfully developed the first photocatalyzed aromatizative deconstructive functionalization of unstrained cycloalkanones in the form of spiro-cycloalkane-dihydroquinazolinones (DHQZs). The control experiments as well as the examples contained in the substrate scopes delineate the nature of substrates that are amenable to the reaction. DFT calculations suggested that the ring-opening of both the DHQZs containing spiro 5- and 6-membered rings likely proceed via an amido radical intermediate. However, to further probe why a base was required for reactivity of the latter but not the former in control studies (**Scheme 4.4.1**), and to definitively determine whether the two types of substrates possibly react by different mechanisms, we intend to methylate the amido N-H of the spiro-cyclopentane-dihydroquinazolinone and subject it too to the standard reaction conditions. A successful transformation of this substrate would infer that the ring-cleavage of this substrate, which has a

comparably higher strain than the larger 6-membered ring homolog, proceeds via an amine radical cation intermediate from SET oxidation of the anilino group in contradistinction from that of its larger homolog which have established to proceed via an amido radical from deprotonation/SET oxidation of the amide group in the substrate. Also, we will conduct Stern-Volmer fluorescence quenching studies to further understand the reaction mechanism. Further, we will apply the developed protocol to druglike compounds such estrone containing convertible unstrained cycloketone moieties to demonstrate the utility of the developed reaction for late-stage modification of important bioactive compounds. Finally, we will explore approaches for the challenging ring-degradation[336] of the quinazolinone moiety present in the products in order to unmask an aldehyde or carboxylic acid functionality. This will demonstrate another synthetic utility of the developed method in which *o*-aminobenzamide effectively serves as an activator of the ring-cleavage of the unstrained ring and the dihydroquinazolinone moiety as a masked carbaldehyde or carboxylic acid.
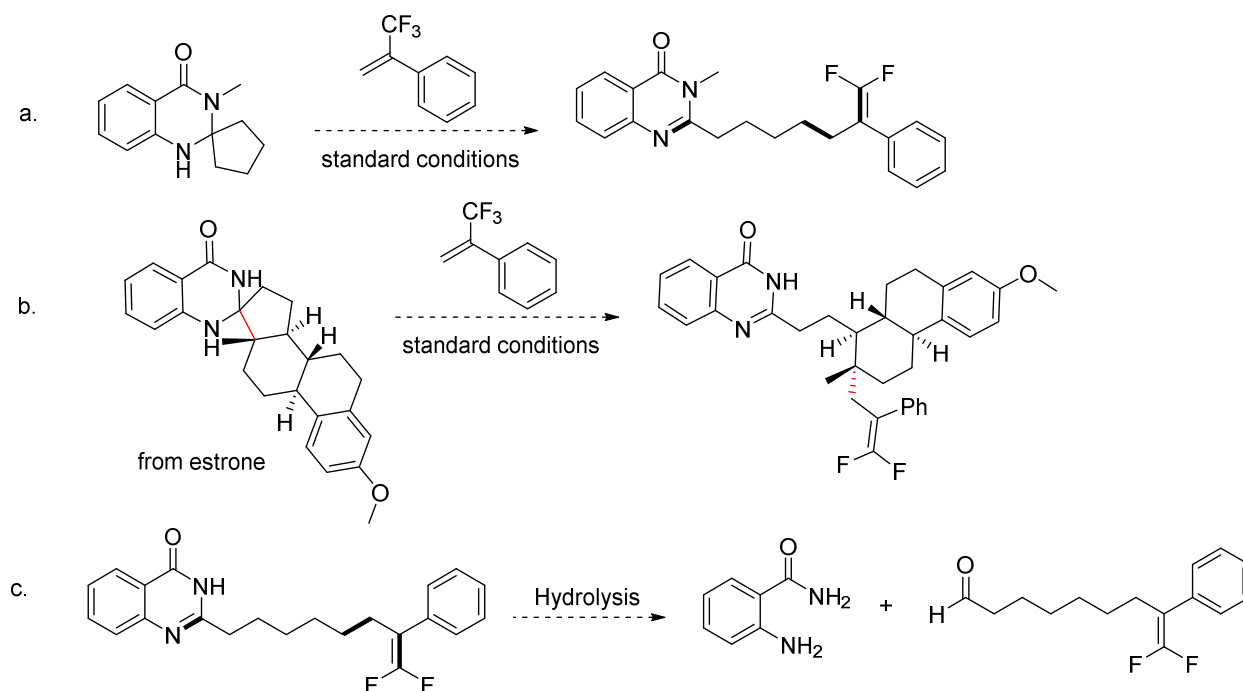
Scheme 4.5.1. Representative Further Reactions on the Deconstructive Functionalization of Unstrained Cycloalkanone Rings

4.6. References

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Appendix A

Experimental Data for Chapter 2—Difunctionalization of *N*-Cyclobutylanilines with

Isocyanide and TMSCN under Photoredox Catalysis

General Considerations

Unless stated otherwise, all reactions were carried out under a nitrogen atmosphere. Acetonitrile (CH_3CN) was pre–dried over molecular sieves. Toluene and THF were collected under argon from a solvent purification system. Column chromatography was performed using silica gel (230–400 mesh) or neutral alumina gel flash grade 32–63u. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, high–resolution mass spectroscopy (HRMS) or gas chromatography/mass spectroscopy (GC/MS), melting point (when applicable), and (in most cases) IR spectroscopy. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance DPX–300 and Bruker Avance DPX–400. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual proton or carbon signals in $CDCl_3$ (7.27 ppm, 77.23 ppm), CD_2Cl_2 (5.32 ppm, 54.0 ppm), and DMSO–d_6 (2.50 ppm, 39.51 ppm) at room temperature. 2D NMR experiments were performed on some of the new compounds to establish their structure, including relative configuration. Diastereomeric ratios were determined using ^{1}H NMR of crude products. IR spectra were recorded (thin film on NaCl plates) on a PerkinElmer Spectrum 100 series instrument. High Resolution Mass spectra were recorded on either a Bruker Ultraflex II TOF/TOF mass spectrometer or a Bruker Apex–Qe mass spectrometer with an ESI source (Fourier Transform Mass Spectrometry). Gas chromatography/mass spectroscopy analyses were performed on an Agilent 6890N Network GC System/5973 inert Mass Selective Detector. Gas chromatography analyses were performed

using a Shimadzu GC–2010 Plus instrument. When applicable, melting point ranges (m.p.) were recorded using a Stuart SMP10 Melting Point Apparatus and were uncorrected.

A1. General Procedure GPA1: Preparation of Aryl Isocyanides Using 2-Isocyanobiphenyl as Representative Example

A two-step approach published by Zhou et al was adapted for the synthesis of aryl isocyanides.[186]
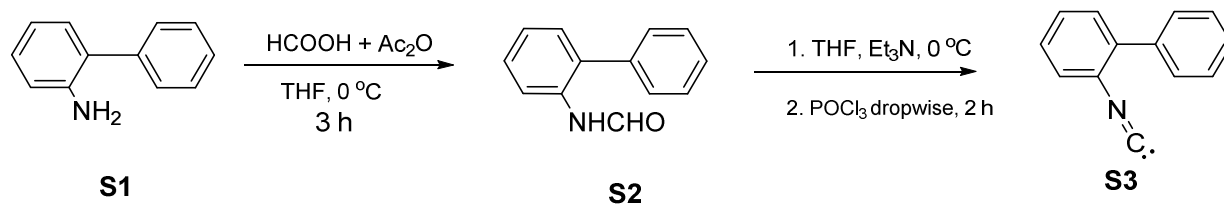
Scheme A1.1. Synthesis of 2-Isocyanobiphenyl

N-(2-phenylphenyl)formamide (S2): Acetic formic anhydride was freshly prepared under nitrogen atmosphere from the reaction of acetic anhydride (48 mL, 506 mmol) with formic acid (21 mL, 1.1 equiv) at 55 □C for 2 h in a 3-necked round-bottomed flask equipped with a magnetic stir bar, and fitted to a Vigreux condenser capped with a rubber septum. ^{1}H NMR analysis of crude reaction aliquots was done to determine the quantity of acetic formic anhydride in the reaction mixture (formic anhydride was also present). 2-Aminobiphenyl **S1** (3 g, 17.7 mmol) dissolved in 35.5 mL THF was added to a flask and cooled to 0 □C. 14.8 mL of the prepared acetic formic anhydride was added dropwise into the solution of **S1** at 0 □C. After the addition, the mixture was warmed to room temperature and stirred for 1 h. Then the mixture was treated with saturated NaHCO$_3$ and extracted with ethyl acetate three times. The extract was dried over anhydrous MgSO$_4$ and concentrated in vacuo to give the crude formamide **S2** as a brown, viscous liquid which crystallizes upon standing at room temperature. This was purified by flash column chromatography eluting with 2:1 Hexanes:EtOAc to give an off-white solid (2.8 g, 79 %). ^{1}H NMR

analysis of the purified compound shows a mixture of rotamers of the title compound. The material was used in the subsequent dehydration step. NB: In the reported work, the crude was used in the next step without any purification. ^{1}H NMR (300 MHz, CD$_2$Cl$_2$) δ: 8.55 (d, 1H), 8.23 (d, 1H), 8.15 (s, 1H), 7.39 – 6.85 (m, 19 H).

2-isocyanobiphenyl (S3): Compound **S2** (5.6 g, 28.5 mmol), THF (70 mL), and trimethylamine (20.3 mL, 146 mmol) and were added to an oven-dried round-bottom flask under N$_2$ atmosphere. After cooling the reaction mixture to 0 °C with an ice bath, POCl$_3$ (9.6 mL, 88.5 mmol) was added dropwise via syringe pump over 2 h. After the addition was completed, the resulting mixture was stirred at 0 °C for an additional 1 h, with regular monitoring of the reaction by TLC. Upon completion of the reaction, the mixture was quenched by adding dropwise to a chilled saturated NaHCO$_3$ solution with careful control of the temperature (0 °C) and pH (~9) of the reaction mixture (the reverse addition of NaHCO$_3$ to a chilled reaction mixture which was reported in the adapted work was found to repeatedly lead to hydrolysis of the product back to **S2**, as observed on TLC and confirmed by GCMS). The quenched mixture was extracted with methylene chloride and dried with anhydrous MgSO$_4$, followed by solvent removal in vacuo to give the crude product of **S3** as a brown, viscous liquid. The pure product was isolated in 86% yield as a green liquid (with a piercing odor) by silica gel column chromatography with 20:1 Hexanes:EtOAc. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.38 – 7.24 (m, 4H), 7.24 – 7.08 (m, 5H); ^{13}C NMR (300 MHz, CDCl$_3$) δ: 166.59, 138.85, 137.04, 130.62, 129.60, 129.02, 128.60, 128.41, 128.19, 127.88, 124.61.
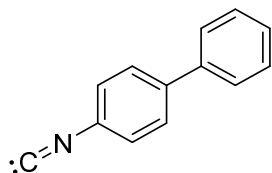
4-isocyanobiphenyl: Following the procedure **GPA1** described for **S2** with 4-aminobiphenyl (3g, 17.7 mmol), acetic formic anhydride (14.8 mL, 187 mmol) and 35 mL THF.

The crude formamide product was obtained as a pale brown solid (2.4 g, 69 %) which was used in the subsequent dehydration step without further purification. In previous attempts of this synthesis, the crude product was either purified by silica gel column chromatography or recrystallized from EtOAc before being used in the next step, but the NMR of purified product did not differ significantly from that of the crude. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.75 (d, 1H), 8.42 (s, 1H), 7.72 – 7.51 (m, 12H), 7.50 – 7.39 (m, 5H), 7.35 (q, 2H), 7.15 (d, 3H); ^{13}C NMR (300 MHz, CDCl$_3$) δ: 162.72, 159.22, 140.52, 140.18, 138.57, 137.93, 136.29, 136.04, 129.09, 129.01, 128.60, 127.92, 127.82, 127.65, 127.44, 127.06, 120.49, 129.44, 119.29.

Step 2: The procedure described for the synthesis of the 2-isocyanobiphenyl **S3** was adapted for the synthesis of 4-isocyanobiphenyl using 2.4 g (12 mmol) of formamide obtained from the first step, 33 mL THF, triethylamine (8.5 mL, 61.7 mmol), POCl$_3$ (3.5 mL, 37.5 mmol). Purification of the crude by flash column on silica gel (7:1 Hexanes:EtOAc) afforded 4-isocyanobiphenyl as yellowish crystals (1.6 g, 72 %). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.75 – 7.51 (m, 4H), 7.50 – 7.41 (m, 5H); ^{13}C NMR (300 MHz, CDCl$_3$) δ: 142.42, 139.37, 129.03, 128.21, 128.04, 127.12, 126.79.

Figure A1.1 shows the structures of the various literature-reported aryl and alkyl isocyanides used in the current study. Isocyanides **5a-5l** and **5n-5r** (except **5p**) were synthesized by following **GPA1** above. The ^{1}H NMR and ^{13}C NMR data matches with that reported in literature.[186, 351] Isocyanide **5p** was obtained commercially from Sigma-Aldrich. The synthesis of isocyanide **5m** by a different method is described below.[352]
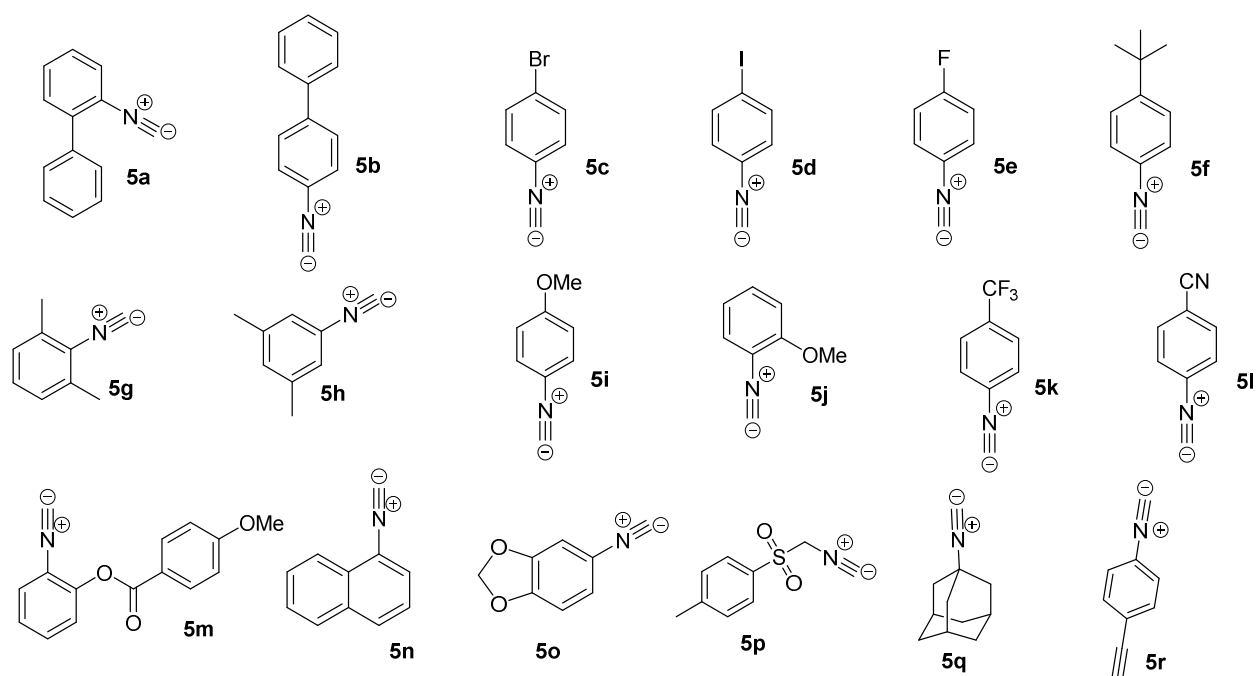
Figure A1.1. Isocyanides used in the Difunctionalization of N-Cyclobutylanilines

Synthesis of 2-isocyanophenyl 4-methoxybenzoate **(5m)**[352]
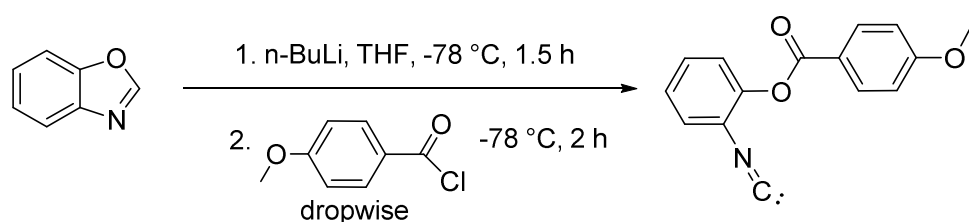
Scheme A1.2. Synthesis of 2-isocyanophenyl 4-methoxybenzoate

2-isocyanophenyl 4-methoxybenzoate was synthesized following a procedure reported in 2006 by Pirrung and Ghorai.[352] Benzoxazole (1.2 g, 10 mmol) was charged to a flask and THF (20 mL) was added. The mixture was cooled to -78 °C for 5 minutes, then n-BuLi (6.6 mL, 10.5 mmol) was added. The mixture was stirred at -78 °C for 1.5 h then the acid chloride (1.4 mL, 10.5 mmol) was added dropwise to the solution and was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was then quenched by pouring into a mixture of ether and saturated NaHCO$_3$ solution at 0 °C. The organic layer was washed with water, dried over anhydrous MgSO$_4$ and the

concentrated in vacuo to give a fluffy, pale yellow solid. This resulting residue was purified by silica gel flash column chromatography (4:1 Hexanes:EtOAc) to yield the pure product as a slightly off-white crystals in (1.6 g, 61 % yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 8.21 (d, 2H), 7.46 (t, 2H), 7.40 (d, 1H), 7.32 (t, 1H), 7.02 (d, 2H), 3.92 (s, 3H).

A2. General Procedure GPA2: Synthesis of *N*-cyclobutylanilines

Method 1:[21]
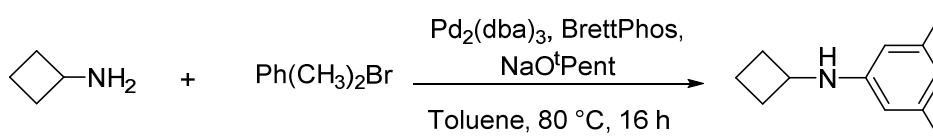
Scheme A2.1. Synthesis of 3,5-Dimethyl-N-cyclobutylaniline by Buchwald-Hartwig Amination.[21]

To an oven-dried Schlenk tube equipped with a stir bar were added Pd$_2$(dba)$_3$ (45.6 mg, 0.05 mmol) and BrettPhos ligand (80.2 mg, 0.15 mmol) or (R)-Tol-BINAP ligand (10.2 mg, 3 mol%). Glove box was used to add NaO^{t}Pent (826 mg, 7.5 mmol), followed by aromatic halide (0.68 mL, 5 mmol), cyclobutylamine (0.48 mL, 5.5 mmol), and 15 mL of toluene were then added to the reaction mixture and heated at 80 $^\circ$C for 16 h. The reaction mixture was cooled to room temperature, diluted with diethyl ether, filtered over a short pad of silica gel, and concentrated in vacuum. Purification by flash chromatography on silica gel with 30:1 Hexanes:EtOAc afforded 3,5-Dimethyl-*N*-cyclobutylaniline as a yellow liquid (715 mg, 82 %). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.42 – 6.33 (m, 1H), 6.26 – 6.17 (m, 2H), 4.33 – 3.46 (m, 2H), 2.49 – 2.33 (m, 2H), 2.24 (s, 6H), 1.91 – 1.71 (m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 147.46, 138.92, 119.46, 111.09, 49.13, 31.49, 21.63, 15.37.

Method 2:[353]
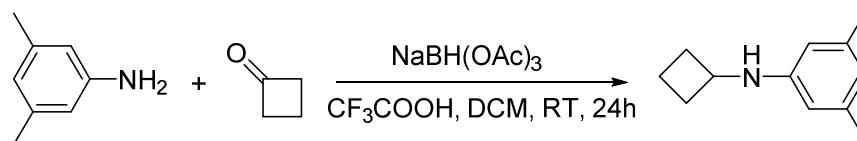
Scheme A2.2. Synthesis of 3,5-Dimethyl-N-cyclobutylaniline by Reductive Amination. [353]

3,5-dimethylaniline (3.8 mL, 30 mmol) and cyclobutanone (4.5 mL, 60 mmol) were mixed in DCM (75 mL) and then treated with sodium triacetoxyborohydride (9.5 g, 60 mmol) portionwise. Trifluoroacetic acid (11.5 mL, 150 mmol) was then added dropwise and the mixture was stirred at rt under a N_2 atmosphere for 24 h or until the reactants were consumed as determined by TLC analysis. Next, the reaction mixture was quenched by adding 1 N NaOH, and the product was extracted with ether. The organic extract was then washed with brine and dried with anhydrous $MgSO_4$. The solvent was removed in vacuo to give the crude. Purification by flash chromatography on silica gel with 20:1 Hexanes:EtOAc afforded 3,5-Dimethyl-*N*-cyclobutylaniline as a yellow liquid (4.2 g, 79%).

Figure A2.1 below shows the structures of *N*-cyclobutylanilines investigated in the difunctionalization with isocyanide and TMSCN. We have previously reported the syntheses and characterization of compounds **5s-5zh**.[108, 136]
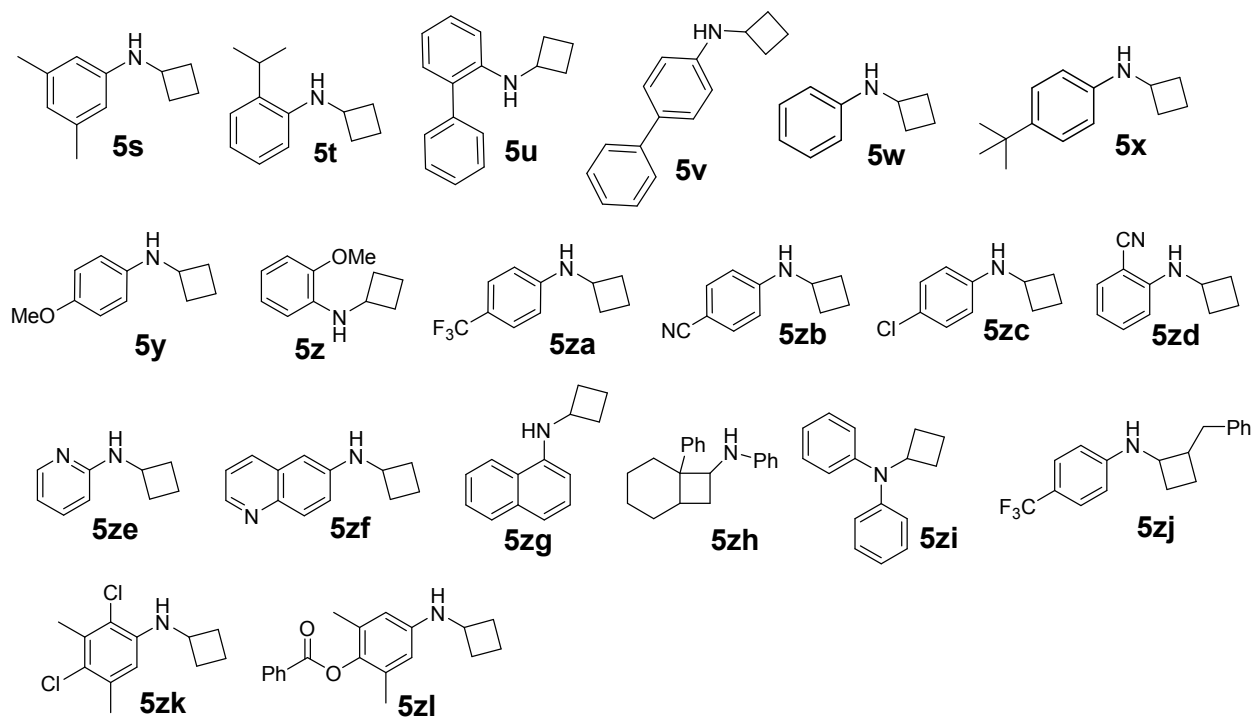
Figure A.2.1. *N*-Cyclobutylanilines Investigated in the Difunctionalization Reaction

***N*-cyclobutyl-N-phenylaniline, 5zi**: Following **GPA2** Method 2 using diphenylamine (1.7g, 10 mmol) and cyclobutanone (1.5 mL, 20 mmol), **5zi** was obtained as a viscous colorless liquid after flash column chromatography with silica gel stationary phase. Complete conversion of the amine was observed on TLC; however most of the pure product was spilled in transfer to vial after column leaving only 34%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34 – 7.18 (m, 4H), 7.01 (ddt, *J* = 1.2, 1.2, 7.3, 8.5 Hz, 2H), 6.93 – 6.79 (m, 4H), 4.30 (ttd, *J* = 0.9, 7.1, 7.1, 9.2, 9.2 Hz, 1H), 2.36 – 2.15 (m, 2H), 2.00 – 1.77 (m, 2H), 1.75 – 1.52 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 129.3, 122.9, 122.1, 54.5, 30.5, 14.9. IR υ$_{max}$ (cm^{-1}) 3439, 3063, 3029, 2981, 2938, 2866, 1591, 1491, 1447, 1381, 1342, 1314, 1290, 1256, 1227, 1171, 1122, 1070, 989, 888, 874, 750, 697, 654, 612, 531, 521, 482, 439. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{16}$H$_{17}$N 224.1434; found 224.1438.
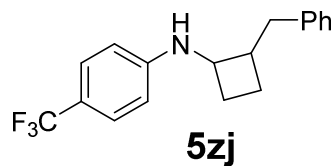
N-(2-benzylcyclobutyl)-4-(trifluoromethyl)aniline, 5zj: Following **GPA2** Method 2 using 4-(Trifluoromethyl)aniline (2.2 mL, 18 mmol) and previously prepared 2-benzylcyclobutanone (1.4 g, 9 mmol), **5zj** was obtained as a yellow liquid after flash column chromatography with silica gel stationary phase (20:1 Hexanes:EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (d, J = 8.3 Hz, 2H), 7.38 (t, J = 7.3, 7.3 Hz, 2H), 7.31 (d, J = 6.9 Hz, 1H), 7.25 (d, J = 7.4 Hz, 2H), 6.57 (d, J = 8.4 Hz, 2H), 4.07 (s, 1H), 3.72 (q, J = 7.6, 7.6, 7.8 Hz, 1H), 3.00 (dd, J = 6.5, 13.6 Hz, 1H), 2.87 (dd, J = 8.2, 13.6 Hz, 1H), 2.55 – 2.41 (m, 2H), 2.11 – 1.97 (m, 1H), 1.78 – 1.53 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 150.1, 140.3, 128.8, 126.8, 126.4, 112.2, 54.3, 46.6, 41.3, 28.8, 21.9. IR υ_{max} (cm^{-1}) 3416, 3072, 3019, 2976, 2937, 2857, 1610, 1529, 1495, 1457, 1414, 1314, 1529, 1494, 1452, 1414, 1318, 1276, 1190, 1156, 1103, 1061, 1008, 941, 826, 750, 697, 636, 592, 502, 478, 463. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{18}$H$_{18}$F$_3$N 306.1464; found 306.2459.
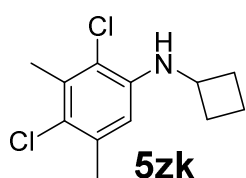
2,4-dichloro-N-cyclobutyl-3,5-dimethylaniline, 5zk: 5zk was obtained serendipitously in an attempt to chlorinate the N atom of the corresponding *N*-cyclobutylaniline by adapting the procedure reported by Gassman and Gruetzmacher.[354] To a vigorously stirred solution of *N*-cyclobutyl-3,5-dimethylaniline (876 mg, 5 mmol) in DCM at -65 ºC was added *tert*-butylhypochlorite (0.6 mL, 5 mmol) dropwise. The reaction was stirred for 25 minutes, warmed to RT, and stirred for additional 4 hours (mixture turns dark brown in color). TLC analysis of the reaction mixture showed lots of unreacted aniline. An additional equivalence of *tert*-butylhypochlorite was added and the reaction was stirred overnight. The mixture was concentrated and the crude purified by flash column chromatography on silica gel stationary phase (50:1 Hexanes:EtOAc) to give **5zk** as a yellow liquid in 41% (507 mg). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.34 (s, 1H), 4.42 (s, 1H), 3.93 (p, J = 7.7, 7.7, 8.2, 8.2 Hz, 1H), 2.55

– 2.48 (m, 2H), 2.47 (s, 3H), 2.31 (s, 3H), 1.99 – 1.75 (m, 4H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 141.52, 135.13, 134.11, 134.11, 111.10, 48.93, 31.39, 31.27, 21.41, 18.54, 15.50. IR υ_{max} (cm^{-1}) 3421, 2976, 2929, 2852, 1586, 1486, 1452, 1400, 1381, 1332, 1276, 1242, 1223, 1180, 1075, 1037, 993, 826, 755, 721, 668, 640, 615, 587, 458.
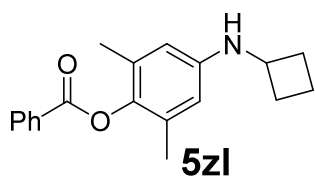
4-(cyclobutylamino)-2,6-dimethylphenyl benzoate, 5zl: Compound **5zl** was obtained serendipitously in the attempt to benzoylate the N atom of the starting *N*-cyclobutylaniline using a published procedure.[355]

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.27 (d, 2H), 7.74 – 7.61 (m, 1H), 7.54 (t, *J* = 7.6, 7.6 Hz, 2H), 6.31 (s, 2H), 3.92 (p, *J* = 7.2, 7.2, 7.7, 7.7 Hz, 1H), 2.56 – 2.36 (m, 2H), 2.12 (s, 6H), 1.91 – 1.70 (m, 4H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 165.26, 145.24, 140.04, 133.54, 130.95, 130.31, 129.86, 128.74, 113.00, 49.43, 31.48, 16.85, 15.44. IR υ_{max} (cm^{-1}) 3402, 2995, 2919, 2848, 1730, 1271, 1204, 1180, 1142, 1089, 1065, 1027, 764, 750, 707, 458. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{19}$H$_{21}$NO$_2$ 296.1645; found 296.1649.

A3. General Procedure GPA3: Difunctionalization Reaction Photochemistry

(a) Setup with blue LED strips   (b) At end of reaction   (c) Setup with LED lamps

Figure A3.1. Setup of the Photochemical Reaction

An oven-dried test tube equipped with a stir bar was charged with the cyclobutylaniline (0.2 mmol), Ir(dtbbpy)(ppy)$_2$PF$_6$ or photocatalyst (2 mol%), isocyanide (0.6 mmol, 3 equiv), trimethylsilyl cyanide (TMSCN) (0.6 mmol, 3 equiv) and 3 mL 2-ethoxyethanol (or solvent) . The test tube was capped with a Teflon screw cap and the mixture was degassed using several Freeze-Pump-Thaw (FPT) cycles. The reaction mixture was then backfilled with nitrogen and irradiated using blue light by placing the test tube in the center of a circle of four-row blue LEDs and wrapping the setup with aluminum foil (**Figure A3.1**a; the internal reaction temperature was measured at the end of the reaction and found to be in the range of 58 ºC - 61 ºC). Alternatively, two white LED lamps (each 18 watts) can be used as the source of irradiation wherein the lamps are positioned 6 cm from mid-point of the test tube (**Figure A3.1**c). After 21 hours, the reaction mixture was diluted with diethyl ether and filtered through a short pad of silica gel. The filtrate

was concentrated and the corresponding products were isolated by flash chromatography using silica gel as stationary phase.
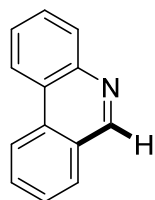
Phenanthridine: Isolated as a pale brown solid in varying yields (2%-25%) from different reactions. NMR data corresponds with that reported in literature.[356] ^{1}H NMR (CDCl$_3$): δ, 9.32 (s, 1H), 8.65 (d, 1H), 8.61 (dd, 1H), 8.22 (d, 1H), 8.08 (d, 1H), 7.72 (m, 2H), 7.62 (m, 2H); ^{13}C NMR (CDCl$_3$): δ, 153.4, 144.3, 132.3, 130.8, 130.0, 128.5, 127.3, 126.9, 126.2, 123.9, 122.1, 121.7.
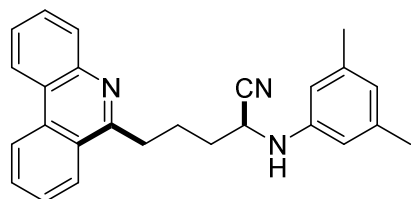
2-((3,5-dimethylphenyl)amino)-5-(phenanthridin-6-yl)pentanenitrile: Isolated as a pale brown liquid in varying yields (1%-4%) from different reactions. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.68 (d, J = 8.3 Hz, 1H), 8.58 (dd, J = 1.4, 8.1 Hz, 1H), 8.25 (dd, J = 1.3, 8.3 Hz, 1H), 8.15 (dd, J = 1.4, 8.1 Hz, 1H), 7.87 (ddd, J = 1.3, 7.0, 8.3 Hz, 1H), 7.79 – 7.63 (m, 3H), 6.52 (s, 1H), 6.38 (s, 2H), 4.37 (q, J = 7.2, 7.2, 7.2 Hz, 1H), 4.16 (d, J = 8.9 Hz, 1H), 3.52 (t, J = 7.2, 7.2 Hz, 2H), 2.39 – 2.29 (m, 3H), 2.27 (s, 6H), 2.16 (dt, J = 6.9, 6.9, 9.8 Hz, 3H). ^{13}C NMR (300 MHz, CDCl$_3$) δ: 160.23, 145.18, 139.25, 133.01, 130.59, 129.55, 128.77, 127.51, 126.67, 125.83, 125.17, 123.70, 122.66, 122.01, 121.77, 119.76, 111.89, 45.98, 34.21, 32.77, 29.70, 24.33, 21.48. IR υ_{max} (cm^{-1}) 3282, 2962, 2919, 2852, 1596, 1462, 1195, 1113, 1075, 822, 764, 736, 697, 616. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{26}$H$_{25}$N$_3$ 380.2121; found 380.2122.
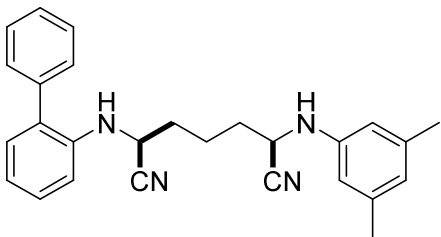
2-([1,1'-biphenyl]-2-ylamino)-6-((3,5-dimethylphenyl)amino)heptanedinitrile: was isolated as off-white-to-pale yellow crystals (58 mg, 71% yield) and the structure was confirmed by X-ray single crystal analysis (as shown in the inset). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 – 7.44 (m, 2H), 7.41 (d, J = 7.4 Hz, 3H), 7.34 (t, J = 7.8, 7.8 Hz, 1H), 7.19 (dd, J = 1.6, 7.5 Hz, 1H), 6.98 (t, J = 7.5, 7.5 Hz, 1H), 6.87 – 6.81 (m, 1H), 6.56 (s, 1H), 6.34 (s, 2H), 4.31 – 4.09 (m, 2H), 3.95 (d, J = 9.4 Hz, 1H), 3.61 (dd, J = 5.5, 9.9 Hz, 1H), 2.28 (s, 6H), 2.02 – 1.87 (m, 4H), 1.80 (dtt, J = 4.1, 4.1, 8.4, 8.4, 17.4 Hz, 2H). ^{13}C NMR (300 MHz, CDCl$_3$) δ: 144.65, 141.58, 139.38, 138.39, 130.82, 129.60, 129.33, 129.19, 128.95, 127.81, 122.38, 120.21, 119.24, 119.16, 112.50, 112.23, 45.84, 45.68, 32.85, 32.77, 32.69, 32.64, 22.06, 21.98, 21.49. IR υ_{max} (cm^{-1}) 3383, 3358, 3058, 3019, 2924, 2862, 1596, 1486, 1438, 1337, 1309, 1247, 1185, 1127, 831, 769, 750, 692, 616, 549, 478. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{27}$H$_{28}$N$_4$ 409.2387; found 409.2385.
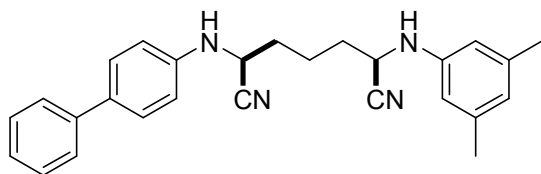
2-([1,1'-biphenyl]-4-ylamino)-6-((3,5-dimethylphenyl)amino)heptanedinitrile: Isolated as a brown solid (55 mg, 65%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 – 7.50 (m, 5H), 7.46 – 7.39 (m, 4H), 6.81 (dd, J = 2.0, 8.7 Hz, 2H), 6.56 (s, 1H), 6.36 (s, 2H), 4.29 (ddtt, J = 3.7, 3.7, 7.1, 7.1, 9.5, 16.6 Hz, 2H), 3.84 (dd, J = 3.8, 9.7 Hz, 1H), 3.64 (dd, J = 3.5, 10.1 Hz, 1H), 2.28 (s, 6H), 2.15 – 2.02 (m, 4H), 2.01 – 1.87 (m, 2H). ^{13}C NMR (300 MHz, CDCl$_3$) δ 144.63, 143.90, 140.51, 139.42, 133.62, 128.75, 128.31, 127.17, 126.69, 126.56, 122.45, 119.18, 115.82, 114.59, 112.26, 47.25, 45.74, 32.97, 32.16, 29.70, 29.36, 29.00, 22.64, 22.23, 21.82, 21.46. IR υ_{max} (cm^{-1}) 3407, 3373, 3038, 2923, 2856, 1600, 1524, 1500, 1476,

1457, 1318, 1300, 1276, 1251, 1195, 1108, 826, 764, 692,497, 420. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{27}$H$_{28}$N$_4$ 409.2387; found 409.2386.
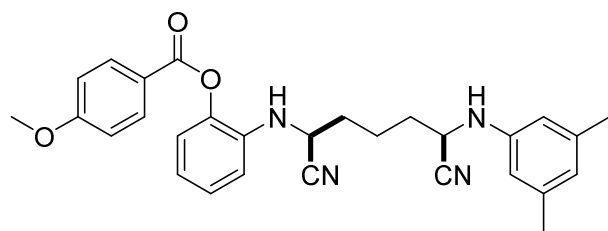
2-((1,5-dicyano-5-((3,5-dimethylphenyl)amino)pentyl)amino)phenyl 4-methoxybenzoate: Isolated as a pale yellow liquid (25 mg, 26%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.25 – 8.09 (m, 2H), 7.24 (td, J = 1.5, 7.7, 7.7 Hz, 1H), 7.16 (dt, J = 1.3, 1.3, 8.0 Hz, 1H), 7.05 – 6.98 (m, 2H), 6.95 (td, J = 1.4, 7.7, 7.7 Hz, 1H), 6.90 (dt, J = 1.7, 1.7, 8.1 Hz, 1H), 6.54 (s, 1H), 6.32 (d, J = 4.0 Hz, 2H), 4.33 – 4.18 (m, 1H), 4.00 (d, J = 9.4 Hz, 1H), 3.90 (d, J = 1.4 Hz, 3H), 3.74 (d, J = 9.7 Hz, 1H), 2.27 (s, 6H), 2.04 – 1.85 (m, 4H), 1.85 – 1.70 (m, 2H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 164.47, 164.32, 144.79, 139.29, 139.15, 137.01, 132.46, 127.01, 122.95, 122.18, 121.05, 120.34, 119.33, 119.03, 114.19, 113.83, 112.19, 60.43, 55.60, 32.69, 32.60, 21.91, 21.47, 21.07, 14.22. IR υ_{max} (cm^{-1}) 3383, 3010, 2929, 2862, 1730, 1605, 1505, 1462, 1442, 1318, 1261, 1185, 1161, 1065, 1027, 831, 764, 746,697, 631, 578, 511, 463, 421. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{29}$H$_{30}$N$_4$O$_3$ 483.2391; found 483.2396.
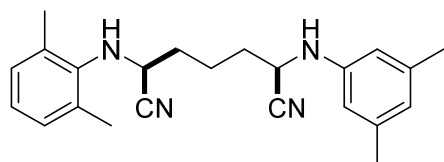
2-((2,6-dimethylphenyl)amino)-6-((3,5-dimethylphenyl)amino)heptanedinitrile: Obtained as a brown solid (48 mg, 67%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.07 (d, J = 7.5 Hz, 2H), 6.97 (dd, J = 6.8, 8.2 Hz, 1H), 6.57 (s, 1H), 6.38 (s, 2H), 4.27 (dt, J = 4.6, 4.6, 9.7 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.71 (s, 1H), 3.38 (s, 1H), 2.34 (s, 6H), 2.30 (s, 6H), 2.06 (dt, J = 7.1, 7.1, 14.0 Hz, 4H), 1.95 (qt, J = 3.1, 3.1, 7.9, 9.4, 9.4 Hz, 2H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 144.74, 141.82, 139.38, 130.76, 129.30, 124.32, 122.33, 120.19, 119.41, 112.23, 49.29,

45.75, 33.79, 33.14, 22.13, 22.08, 21.50, 18.31. IR υ_{max} (cm^{-1}) 3368, 3019, 2924, 2862, 2231, 1605, 1524, 1510, 1476, 1332, 1261, 1218, 1190, 1098, 1027, 831, 764, 687, 554, 482. HRMS (ESI) m/z [M+H]$^+$, calc'd for $C_{23}H_{28}N_4$ 361.2387; found 361.2382.
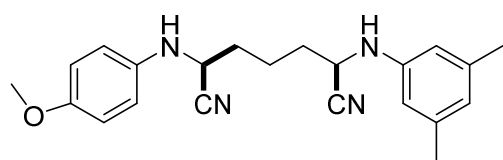
2-((3,5-dimethylphenyl)amino)-6-((4-methoxyphenyl)amino)heptanedinitrile: Brown solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.90 – 6.79 (m, 2H), 6.77 – 6.65 (m, 2H), 6.56 (s, 1H), 6.35 (s, 2H), 4.24 (ddt, J = 4.6, 4.6, 7.1, 10.1 Hz, 1H), 4.20 – 4.09 (m, 1H), 3.78 (s, 3H), 3.65 (dd, J = 4.3, 9.3 Hz, 1H), 3.49 (s, 1H), 2.28 (s, 6H), 2.03 (t, J = 7.2, 7.2 Hz, 4H), 1.96 – 1.81 (m, 2H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 154.34, 144.65, 139.39, 138.40, 122.39, 119.42, 119.31, 116.59, 115.09, 112.24, 55.67, 47.24, 45.75, 32.90, 22.05, 21.46. IR υ_{max} (cm^{-1}) 3397, 3373, 3344, 3034, 3000, 2958, 2924, 2862, 2231, 1605, 1505, 1462, 1442, 1337, 1237, 1190, 1118, 1027, 822, 764, 692, 583, 554, 516, 473, 421. HRMS (ESI) m/z [M+H]$^+$, calc'd for $C_{22}H_{26}N_4O$ 363.2179; found 363.2171.
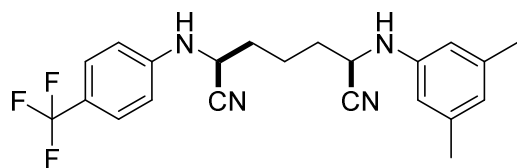
2-((3,5-dimethylphenyl)amino)-6-((4-(trifluoromethyl)phenyl)amino)heptanedinitrile: Brown solid (15 mg, 19%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (d, J = 8.3 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 6.57 (s, 1H), 6.36 (s, 2H), 4.30 (dtd, J = 3.3, 6.7, 6.9, 13.6 Hz, 2H), 4.10 (dt, J = 4.1, 4.1, 9.5 Hz, 1H), 3.64 (d, J = 10.8 Hz, 1H), 2.28 (s, 6H), 2.17 – 2.02 (m, 4H), 2.01 – 1.87 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 147.3, 144.6, 139.6, 127.2, 122.8, 122.3, 119.4, 118.6, 117.9, 113.7, 112.3, 46.1, 45.1, 33.0, 33.0, 32.8, 29.8, 22.2, 22.2, 21.6, 21.6. IR υ_{max} (cm^{-1}) 3449, 3392, 3014, 2924, 2862, 1625, 1600, 1529, 1510, 1491, 1457,

1419, 1323, 1276, 1195, 1171, 1108, 1065, 1008, 826, 769, 746, 697, 587, 505, 478421. ^{19}F NMR (400 MHz, CDCl$_3$) δ -61.85. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{22}$H$_{23}$F$_3$N$_4$ 401.1948; found 401.1950.
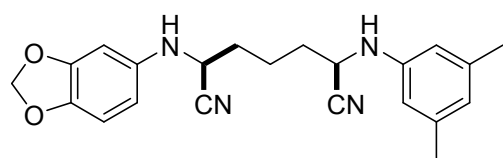
2-(benzo[d][1,3]dioxol-5-ylamino)-6-((3,5-dimethylphenyl)amino)heptanedinitrile: Brown liquid (7.8 mg, 10%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.72 (d, J = 8.3 Hz, 1H), 6.56 (s, 1H), 6.35 (d, J = 2.4 Hz, 2H), 6.34 (s, 1H), 6.19 (dd, J = 2.4, 8.3 Hz, 1H), 5.92 (s, 2H), 4.24 (qd, J = 6.5, 8.7, 8.7, 8.9 Hz, 1H), 4.17 – 4.04 (m, 1H), 3.72 – 3.60 (m, 1H), 3.58 – 3.46 (m, 1H), 2.28 (s, 6H), 2.09 – 1.98 (m, 4H), 1.97 – 1.79 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 148.8, 144.8, 142.3, 140.0, 139.5, 122.5, 119.4, 112.4, 108.9, 107.2, 101.2, 98.3, 52.3, 47.4, 45.9, 33.0, 33.0, 29.8, 29.6, 22.2, 21.6. IR υ$_{max}$ (cm^{-1}) 3358, 2962, 2924, 2857, 2379, 1681, 1600, 1500, 1486, 1462, 1442, 1337, 1261, 1199, 1122, 1032927, 826, 764, 750, 692, 420. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{22}$H$_{24}$N$_4$O$_2$ 377.1972; found 377.1973.
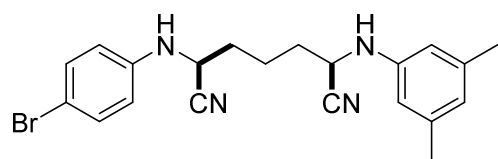
2-((4-bromophenyl)amino)-6-((3,5-dimethylphenyl)amino)heptanedinitrile: Brown liquid (35.7 mg, 43%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.31 (m, 2H), 6.60 (dd, J = 2.3, 9.1 Hz, 2H), 6.56 (d, J = 1.9 Hz, 1H), 6.35 (s, 2H), 4.31 – 4.12 (m, 2H), 3.83 (dd, J = 4.2, 9.6 Hz, 1H), 3.73 – 3.58 (m, 1H), 2.28 (s, 6H), 2.12 – 1.97 (m, 4H), 1.90 (td, J = 5.2, 8.8, 9.1 Hz, 2H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 144.59, 143.64, 139.43, 132.44, 132.03, 122.47, 119.30, 118.78, 116.72, 115.87, 115.86, 112.47, 112.26, 112.24, 45.71, 45.68, 45.65, 32.89, 32.83, 32.70, 32.64, 22.04, 22.00, 21.48. IR υ$_{max}$ (cm^{-1}) 3392, 3024, 2924, 2866,

2236, 1596, 1495, 1404, 1337, 1313, 1290, 1256, 1127, 1070, 998, 817, 769, 750, 692, 573, 549, 502, 473, 425. HRMS (ESI) m/z [M+H]$^+$, calc'd for $C_{21}H_{23}BrN_4$ 411.1179, 413.1159; found 411.1183, 413.1157.
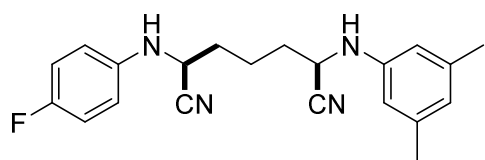
2-((3,5-dimethylphenyl)amino)-6-((4-iodophenyl)amino)heptanedinitrile: Brown viscous liquid (29.3 mg, 32%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.02 – 6.93 (m, 1H), 6.73 – 6.63 (m, 1H), 6.55 (s, 1H), 6.34 (s, 1H), 4.30 – 4.20 (m, 1H), 4.19 – 4.10 (m, 0H), 3.73 – 3.56 (m, 1H), 2.27 (d, J = 0.7 Hz, 3H), 2.04 (dddd, J = 2.1, 3.8, 6.9, 10.5 Hz, 2H), 1.97 – 1.83 (m, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 158.8, 156.4, 144.7, 141.0, 141.0, 139.5, 122.6, 119.5, 119.4, 119.2, 119.2, 116.5, 116.3, 116.0, 115.9, 112.4, 46.7, 46.7, 45.9, 33.1, 33.0, 33.0, 32.9, 22.2, 22.2, 21.6. ^{19}F NMR (376 MHz, CDCl$_3$) δ -124.1, -124.1, -124.5, -124.7. IR υ$_{max}$ (cm^{-1}) 3383, 3358, 3029, 2919, 2862, 2231, 1605, 1504, 1476, 1332, 1314, 1285, 1223, 1195, 1127, 1032, 822, 764, 697, 602, 549, 516, 434. HRMS (ESI) m/z [M+H]$^+$, calc'd for $C_{21}H_{24}FN_4$ 351.1985; found 351.1982.
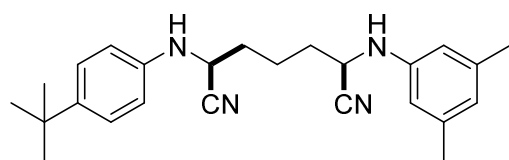
2-((4-(tert-butyl)phenyl)amino)-6-((3,5-dimethylphenyl)amino)heptanedinitrile: Brown solid (41.3 mg, 53%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 (d, J = 8.6 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 6.57 (s, 1H), 6.37 (s, 2H), 4.24 (t, J = 7.4, 7.4 Hz, 2H), 3.70 (s, 2H), 2.29 (s, 6H), 2.15 – 1.97 (m, 4H), 1.97 – 1.82 (m, 2H), 1.31 (s, 9H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 144.82, 143.54, 142.31, 139.56, 126.61, 122.56, 119.54, 119.52, 119.50, 119.48, 114.31, 112.42, 112.41, 46.16, 45.92, 34.24, 33.13, 33.07, 33.06, 31.63, 22.26, 22.22, 21.64. IR

υ_{max} (cm^{-1}) 3392, 3349, 3019, 2962, 2862, 2317, 2231, 1600, 1519, 1505, 1471, 1457, 1366, 1337, 1266, 1195, 1132, 1108, 826, 755, 692, 544, 516. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{25}$H$_{32}$N$_4$ 389.2700; found 389.2701.
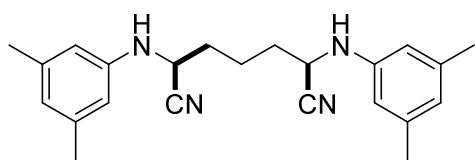
2,6-bis((3,5-dimethylphenyl)amino)heptanedinitrile: Brown viscous liquid (49.6 mg, 69%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.57 (s, 1H), 6.36 (s, 2H), 4.33 – 4.15 (m, 1H), 3.71 (dd, J = 4.8, 9.3 Hz, 1H), 2.30 (s, 6H), 2.01 (dd, J = 6.1, 8.7 Hz, 2H), 1.95 – 1.81 (m, 1H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 144.90, 139.54, 122.50, 119.59, 112.39, 45.87, 33.03, 21.59. IR υ_{max} (cm^{-1}) 3344, 3014, 2919, 2862, 2231, 1596, 1524, 1505, 1476, 1462, 1380, 1185, 1118, 1037, 960, 869, 826, 788, 692, 626, 578, 511, 449. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{23}$H$_{28}$N$_4$ 361.2387; found 361.2385.
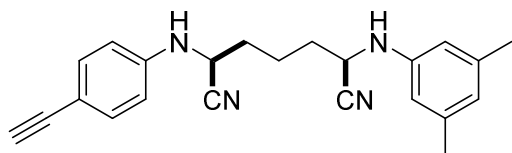
2-((3,5-dimethylphenyl)amino)-6-((4-ethynylphenyl)amino)heptanedinitrile: Pale brown viscous liquid (19.1 mg, 27%). NMR yield = 42%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (d, J = 8.6 Hz, 1H), 6.65 (d, J = 8.6 Hz, 1H), 6.57 (s, 1H), 6.36 (s, 1H), 4.31 – 4.18 (m, 1H), 3.98 (dd, J = 5.1, 9.4 Hz, 1H), 3.72 – 3.60 (m, 1H), 3.02 (s, 1H), 2.29 (s, 4H), 2.15 – 1.98 (m, 3H), 1.98 – 1.86 (m, 1H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 145.05, 144.75, 139.60, 133.87, 127.76, 122.65, 119.46, 118.85, 113.90, 113.71, 112.42, 83.86, 76.06, 45.89, 45.43, 45.41, 33.06, 33.01, 32.88, 32.82, 22.21, 22.17, 21.64, 21.64. IR υ_{max} (cm^{-1}) 3368, 3287, 3029, 2924, 2862, 2236, 2102, 1600, 1510, 1457, 1323, 1295, 1256, 1185, 1127, 826, 760, 750,

697, 654, 583, 531, 444. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{23}$H$_{24}$N$_4$ 357.2074; found 357.2076.
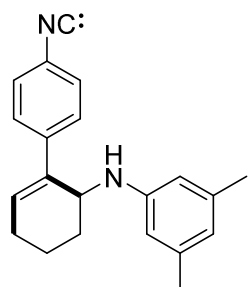
N-(3,5-dimethylphenyl)-4'-isocyano-2,3,4,5-tetrahydro-[1,1'-biphenyl]-2-amine: Pale brown viscous liquid (6.2 mg, 10%). NMR yield = 20%. NMR yield = 42%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (d, J = 8.6 Hz, 2H), 7.28 (d, J = 4.3, 4.3 Hz, 3H), 6.40 (d, J = 2.4 Hz, 2H), 6.27 (s, 2H), 4.43 (s, 1H), 3.65 (s, 1H), 2.45 − 2.03 (m, 9H), 1.80 − 1.58 (m, 3H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 181.68, 146.79, 141.76, 139.32, 136.20, 130.95, 126.55, 126.50, 119.56, 110.97, 47.88, 29.89, 27.47, 26.22, 21.72, 17.04. IR υ_{max} (cm^{-1}) 3402, 3034, 2924, 2857, 2823, 2121, 1596, 1505, 1466, 1410, 1342, 1261, 1195, 1171, 1113, 1075, 1037, 993, 917, 846, 822, 741, 692, 583, 525, 458. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{21}$H$_{22}$N$_2$ 303.1856; found 303.1862.
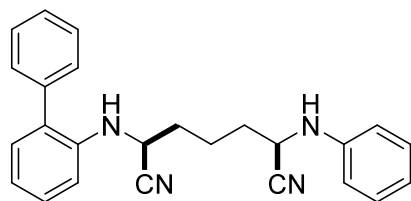
2-([1,1'-biphenyl]-2-ylamino)-6-(phenylamino)heptanedinitrile: Isolated as a viscous pale brown liquid (13.7 mg, 18%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 − 7.45 (m, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.37 − 7.31 (m, 0H), 7.20 (dd, J = 1.6, 7.5 Hz, 1H), 6.98 (t, J = 7.5, 7.5 Hz, 1H), 6.91 (t, J = 7.4, 7.4 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 4.30 − 4.16 (m, 1H), 3.95 (d, J = 9.4 Hz, 1H), 3.73 (dd, J = 5.5, 9.7 Hz, 0H), 2.03 − 1.89 (m, 2H), 1.87 − 1.75 (m, 1H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 144.75, 141.74, 138.55, 130.98, 129.83, 129.81, 129.49, 129.34, 129.11, 127.98, 120.62, 120.41, 119.31, 119.30, 119.23, 119.21, 114.46, 112.70, 46.02, 45.99, 32.98, 32.91, 32.87, 32.83, 22.22, 22.16, 14.39. IR υ_{max} (cm^{-1}) 3397, 3358, 3058, 3034, 2929, 2866, 2240, 1605, 1581, 1433, 1366, 1314, 1280, 1261, 1127, 1070, 1008,

912, 874, 822, 750, 707, 592, 568, 544, 516, 487, 449. HRMS (ESI) m/z [M+H]⁺, calc'd for C₂₅H₂₄N₄ 381.2074; found 381.2076.
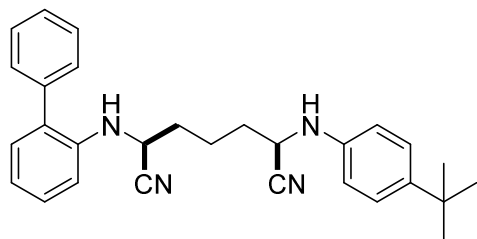
2-([1,1'-biphenyl]-2-ylamino)-6-((4-(tert-butyl)phenyl)amino)heptanedinitrile: Pale brown viscous liquid (51.3 mg, 58%). ¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.45 (m, 2H), 7.44 – 7.38 (m, 3H), 7.37 – 7.32 (m, 1H), 7.32 – 7.29 (m, 2H), 7.20 (dd, J = 1.6, 7.5 Hz, 1H), 6.99 (t, J = 7.4, 7.4 Hz, 1H), 6.85 (dt, J = 1.3, 1.3, 8.2 Hz, 1H), 6.71 – 6.65 (m, 2H), 4.25 (t, J = 6.9, 6.9 Hz, 1H), 4.18 (t, J = 7.0, 7.0 Hz, 1H), 3.95 (s, 1H), 3.66 (s, 1H), 1.95 (dtd, J = 4.5, 8.2, 8.5, 13.6 Hz, 4H), 1.85 – 1.73 (m, 2H), 1.32 (s, 9H). ¹³C NMR (400 MHz, CDCl₃) δ 143.45, 142.37, 141.79, 138.58, 130.99, 129.80, 129.78, 129.50, 129.36, 129.12, 127.99, 126.60, 120.38, 120.36, 119.53, 119.38, 114.29, 112.70, 46.08, 45.98, 34.25, 32.80, 31.66, 22.23, 22.17. IR υ_max (cm⁻¹) 3397, 3358, 3057, 3029, 2958, 2866, 1610, 1581, 110, 1486, 1438, 1366, 1323, 1305, 1261, 1175, 1142, 1056, 903, 836, 773, 746, 697, 544, 487, 449. HRMS (ESI) m/z [M+H]⁺, calc'd for C₂₉H₃₂N₄ 437.2700; found 437.2698.
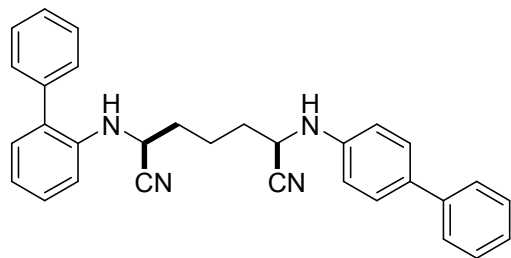
2-([1,1'-biphenyl]-2-ylamino)-6-([1,1'-biphenyl]-4-ylamino)heptanedinitrile: Isolated as a pale brown viscous liquid (10.6 mg, 12%). NMR yield = . ¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.49 (m, 4H), 7.48 – 7.43 (m, 3H), 7.40 (ddd, J = 3.0, 4.0, 8.6 Hz, 5H), 7.31 (dq, J = 1.9, 1.9, 2.2, 8.2 Hz, 2H), 7.18 (dd, J = 1.6, 7.5 Hz, 1H), 6.97 (tt, J = 1.0, 1.0, 7.4, 7.4 Hz, 1H), 6.84 (dt, J = 1.4, 1.4, 8.1 Hz, 1H), 6.80 –

6.74 (m, 2H), 4.24 (td, J = 3.2, 6.5, 6.6 Hz, 2H), 3.95 (t, J = 7.8, 7.8 Hz, 1H), 3.79 (d, J = 9.1 Hz, 1H), 2.05 – 1.89 (m, 4H), 1.88 – 1.74 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 144.0, 141.7, 140.8, 138.5, 133.6, 130.9, 129.8, 129.4, 129.3, 129.1, 128.9, 128.4, 127.9, 126.8, 126.7, 120.4, 119.3, 119.1, 114.7, 112.7, 46.0, 46.0, 45.8, 32.9, 32.8, 32.8, 29.8, 22.2, 22.1. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{31}$H$_{28}$N$_4$ 457.2387; found 457.2393.
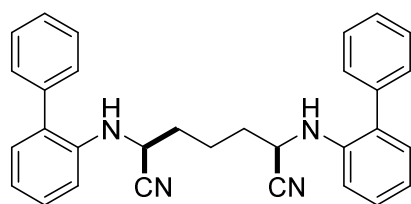
2,6-bis([1,1'-biphenyl]-2-ylamino)heptanedinitrile: Isolated as a pale brown solid (29 mg, 32%). NMR yield = 48%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (td, J = 3.5, 6.9, 7.6 Hz, 4H), 7.38 (dd, J = 2.1, 8.7 Hz, 5H), 7.33 (td, J = 1.7, 7.7, 7.8 Hz, 2H), 7.18 (dd, J = 1.6, 7.5 Hz, 2H), 7.04 – 6.91 (m, 2H), 6.82 (d, J = 8.1 Hz, 2H), 4.18 (dt, J = 7.0, 7.0, 9.7 Hz, 2H), 3.95 – 3.80 (m, 2H), 1.85 (qt, J = 5.3, 5.3, 9.9, 9.9, 9.9 Hz, 4H), 1.71 (q, J = 7.3, 7.3, 7.4 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 141.9, 138.7, 138.7, 131.1, 131.1, 130.0, 130.0, 129.6, 129.5, 129.5, 129.3, 128.1, 120.6, 120.6, 119.4, 119.4, 112.9, 112.9, 46.2, 46.2, 33.0, 33.0, 22.4, 22.3.
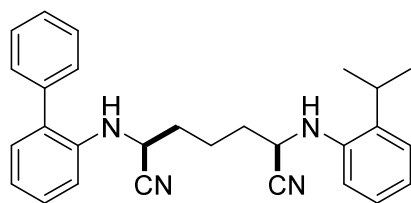
2-([1,1'-biphenyl]-2-ylamino)-6-((2-isopropylphenyl)amino)heptanedinitrile: Brown viscous liquid (26.5 mg, 31%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 – 7.43 (m, 2H), 7.43 – 7.36 (m, 3H), 7.36 – 7.29 (m, 1H), 7.22 (dd, J = 1.6, 7.7 Hz, 1H), 7.21 – 7.15 (m, 2H), 6.97 (tt, J = 1.0, 1.0, 7.4, 7.4 Hz, 1H), 6.93 (td, J = 1.2, 7.5, 7.5 Hz, 1H), 6.84 (dt, J = 1.7, 1.7, 8.1 Hz, 1H), 6.74 (dd, J = 1.2, 8.1 Hz, 1H), 4.23 (tdd, J = 5.0, 8.1, 16.2, 16.2 Hz, 2H), 3.94 (d, J = 9.4 Hz, 1H), 3.77 – 3.62 (m, 1H), 2.85 (pt, J = 3.5, 3.5, 7.1, 7.1, 7.1, 7.1 Hz, 1H), 2.02 (ddd, J = 1.8, 7.2, 8.4 Hz, 2H), 1.99 – 1.91 (m, 2H), 1.88 – 1.75 (m, 2H), 1.27 (dd, J = 1.4, 6.8 Hz, 3H),

1.24 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 141.7, 141.5, 138.5, 134.4, 130.9, 129.8, 129.7, 129.4, 129.3, 129.3, 129.0, 127.9, 127.1, 125.8, 120.7, 120.4, 119.4, 119.4, 119.2, 119.2, 112.8, 112.6, 46.1, 46.1, 46.0, 45.9, 33.2, 33.2, 32.9, 32.8, 27.4, 22.8, 22.6, 22.3, 22.2, -12.5. IR ν_{max} (cm^{-1}) 3378, 3067, 3029, 2962, 2924, 2862, 2236, 1605, 1581, 1510, 1486, 1438, 1361, 1309, 1280, 1256, 1166, 1132, 1070, 1037, 108, 907, 750, 697, 549, 478, 421. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{28}$H$_{30}$N$_4$ 423.2543; found 423.2550.
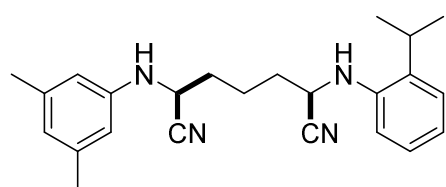
2-((3,5-dimethylphenyl)amino)-6-((2-isopropylphenyl)amino)heptanedinitrile: Pale brown solid (28.6 mg, 38%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23 (dd, J = 1.5, 7.7 Hz, 1H), 7.19 (td, J = 1.4, 7.5, 7.7 Hz, 1H), 6.93 (t, J = 7.5, 7.5 Hz, 1H), 6.76 (dt, J = 1.5, 1.5, 8.0 Hz, 1H), 6.56 (s, 1H), 6.35 (s, 2H), 4.25 (ddp, J = 3.4, 3.4, 4.1, 4.1, 6.9, 10.6 Hz, 2H), 3.78 (dd, J = 2.7, 9.4 Hz, 1H), 3.69 (dd, J = 4.1, 9.6 Hz, 1H), 2.88 (hept, J = 6.8, 6.8, 6.8, 6.8, 6.8, 6.8 Hz, 1H), 2.28 (s, 6H), 2.16 – 1.97 (m, 4H), 1.97 – 1.86 (m, 2H), 1.28 (dd, J = 1.3, 6.8 Hz, 3H), 1.25 (d, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 145.0, 141.7, 139.7, 134.6, 134.6, 127.3, 126.1, 122.7, 120.9, 119.8, 119.8, 119.7, 119.7, 113.0, 112.6, 46.3, 46.3, 46.1, 46.1, 33.5, 33.4, 33.2, 33.2, 27.6, 23.0, 22.8, 22.5, 22.5, 21.8. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{24}$H$_{30}$N$_4$ 375.2543; found 375.2539.
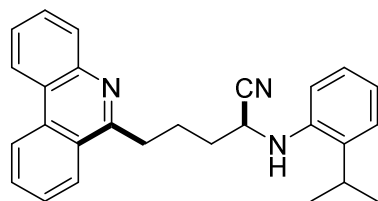
2-((2-isopropylphenyl)amino)-5-(phenanthridin-6-yl)pentanenitrile: Obtained as a viscous brown liquid (6.8 mg, 9%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.67 (ddt, J = 0.5, 0.5, 1.2, 8.2 Hz, 1H), 8.61 – 8.51 (m, 1H), 8.24 (ddd, J = 0.6, 1.3, 8.3 Hz, 1H), 8.13 (ddd, J = 0.5, 1.4, 8.1 Hz,

1H), 7.86 (ddd, *J* = 1.3, 7.0, 8.3 Hz, 1H), 7.72 (dddd, *J* = 1.3, 7.0, 8.2, 10.8 Hz, 2H), 7.65 (ddd, *J* = 1.4, 7.0, 8.4 Hz, 1H), 7.24 – 7.10 (m, 2H), 6.94 – 6.83 (m, 1H), 6.82 – 6.73 (m, 1H), 4.41 (q, *J* = 7.4, 7.5, 7.5 Hz, 1H), 3.90 (d, *J* = 9.0 Hz, 1H), 3.52 (t, *J* = 7.1, 7.1 Hz, 2H), 2.87 (p, *J* = 6.7, 6.7, 6.8, 6.8 Hz, 1H), 2.45 – 2.29 (m, 2H), 2.30 – 2.15 (m, 2H), 1.23 (dd, *J* = 6.7, 15.8 Hz, 7H).

A.4. References

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A.5. NMR Spectra for Chapter 2

BED600-III_p112_10-24-2020.1.fid
BED600-III_p112_10-24-2020_N,N-diphenylcyclobutylamine check

2.14 2.18 1.33 2.15 2.01 0.96 1.02 1.07 1.11 2.10 1.16 2.21

8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

129.26 122.93 122.10 54.50 30.52 14.90

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

229

230
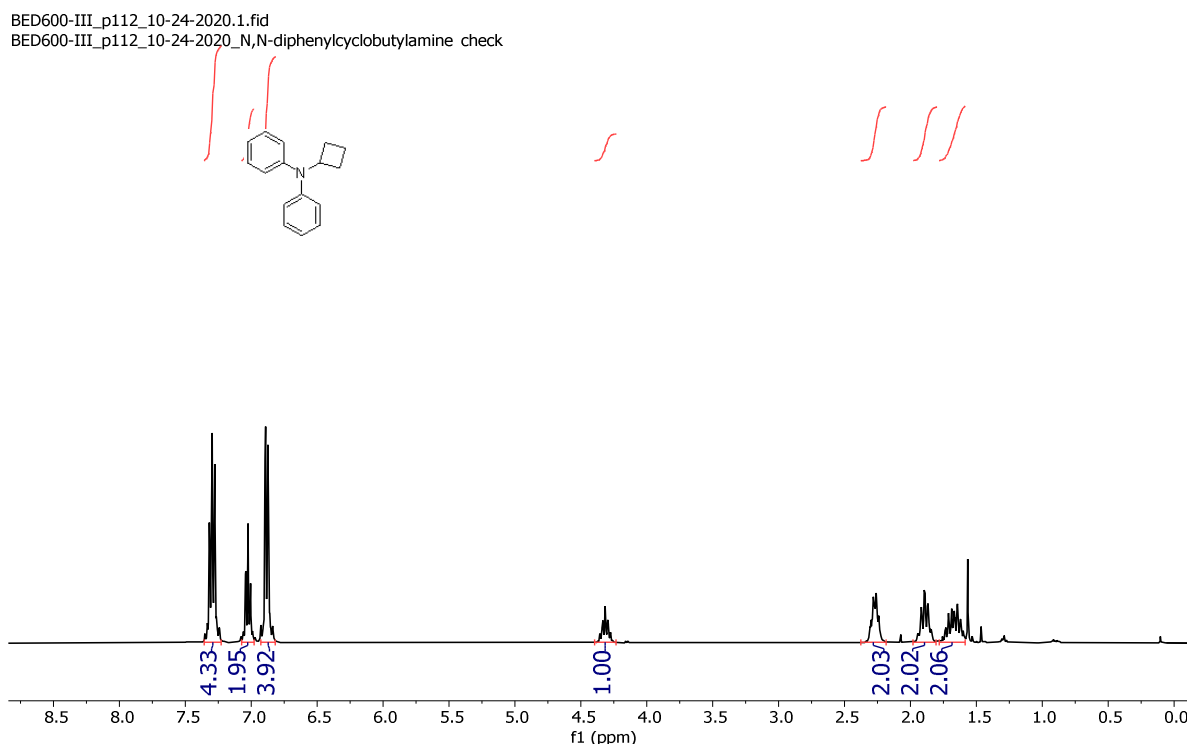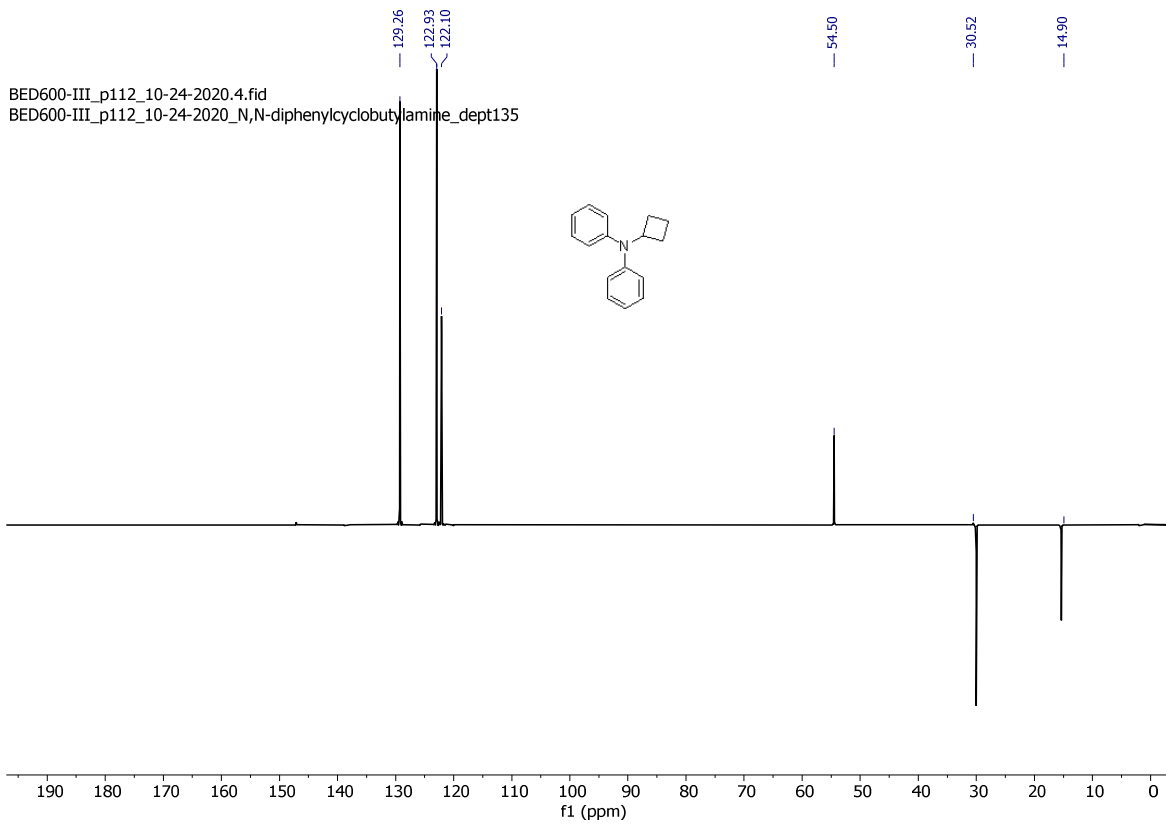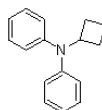
BED703-III_p179_3-1-2021.4.fid
BED703-III_p179_3-1-2021_N-2Benzylcyclobutyl-p-CF3aniline_ check_dept135

128.90
126.60
126.20
112.06
53.46
46.38
41.09
28.59
21.71

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
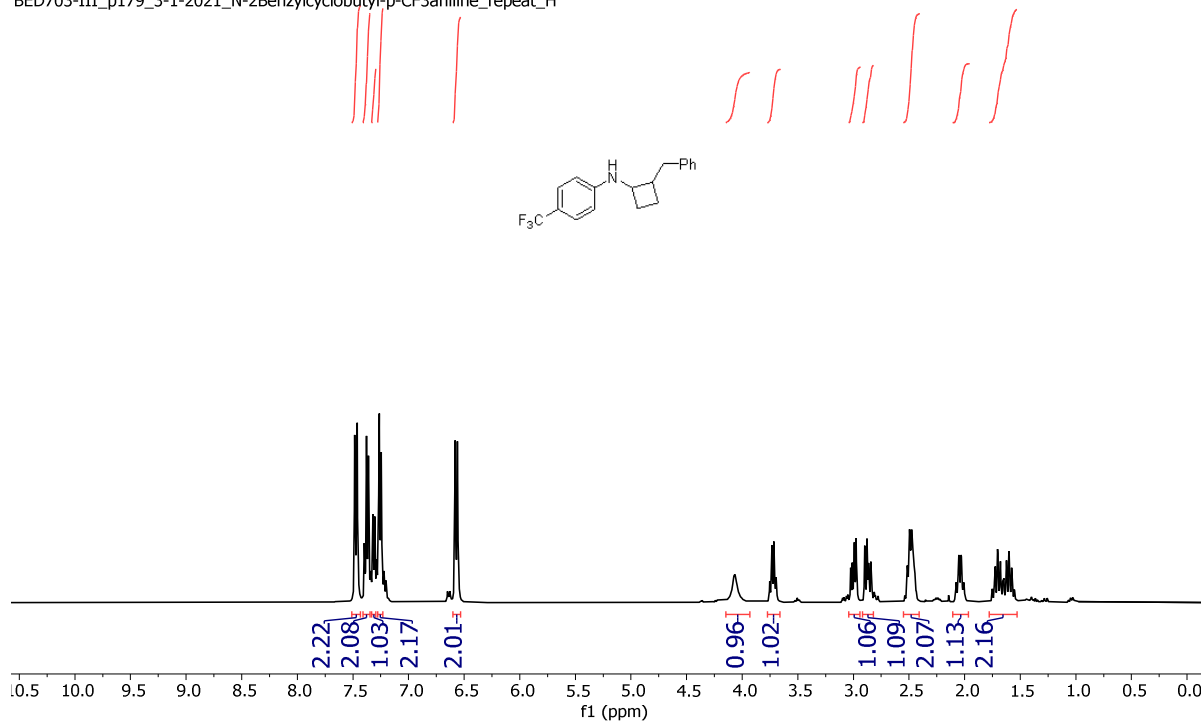
BED617-III_p123_11-9-2020.1.fid
BED617-III_p123_11-9-2020_N-Cl-3,5-dimethylcyclobutylaniline_H check

0.78 0.92 0.94 1.68 3.09 2.60 4.00

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

231

141.52
135.13
134.11
122.84
117.07
111.10
48.93
31.39
31.27
21.41
18.54
15.50

BED617-III_p123_11-9-2020.2.fid
BED617-III_p123_11-9-2020_N-Cl-3,5-dimethylcyclobutylaniline check_C13

150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)

110.92
48.75
31.21
31.10
21.24
18.36
15.33

BED617-III_p123_11-9-2020.3.fid
BED617-III_p123_11-9-2020_N-Cl-3,5-dimethylcyclobutylaniline_dept135

50 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0
f1 (ppm)

BED616-III_p122_11-8-2020.1.fid
BED616-III_p122_11-8-2020_4-OBz-3,5-dimethylcyclobutylaniline_spot 4 check

1.73 0.88 1.83 1.70 1.01 2.01 5.68 3.84

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

165.26 145.24 140.04 133.54 130.95 130.31 129.86 128.74 113.00 49.43 31.48 16.85 15.44
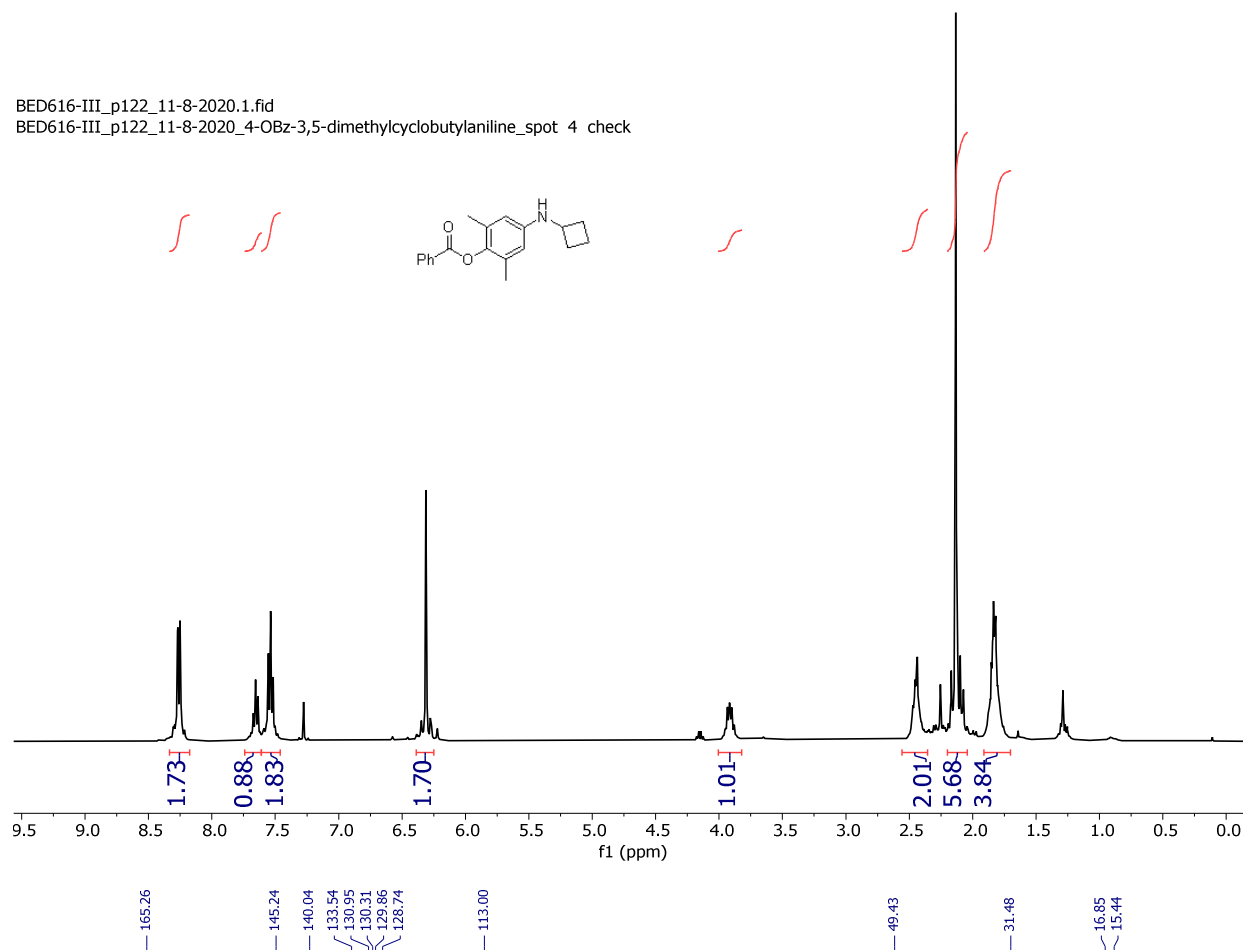
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BED616-III_p122_11-8-2020_4-OBz-3,5-dimethylcyclobutylaniline rxn spot 4_C13

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

233

BED616-III_p122_11-8-2020.3.fid
BED616-III_p122_11-8-2020_4-OBz-3,5-dimethylcyclobutylaniline_dept135

133.37
130.14
128.57
112.83
50.10
31.40
16.68
15.18

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED110_F14-19_2-iso-tmscn-Et3SiH-2-ethoxyethanol-photochem_4-6-17.1.fid
BED110_F14-19_2-iso-tmscn-Et3SiH-2-ethoxyethanol-photochem_4-6-17 H

1.86
2.79
1.11
0.94
0.95
0.94
0.83
1.87

2.07
0.92
0.92

6.00
3.86
1.92

.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

234

144.65
141.58
139.38
138.39
130.82
129.60
129.33
129.19
128.95
127.81
122.38
120.21
119.24
119.16
112.50
112.23

45.84
45.68

32.85
32.77
32.69
32.64

22.06
21.98
21.49

BED043_F53-61_2-iso-tmscn-photochem-7-20-16.1.fid
BED043_F53-61_2-iso-tmscn-photochem-7-20-16

160   150   140   130   120   110   100   90   80   70   60   50   40   30   20   10   0
f1 (ppm)

130.82
129.33
129.19
128.95
127.81
122.37
120.21
112.49
112.22

45.00

34.12
32.64

21.98
20.38

BED043_F53-61_2-iso-tmscn-photochem-7-20-16.2.fid
BED043_F53-61_2-iso-tmscn-photochem-7-20-16

160   150   140   130   120   110   100   90   80   70   60   50   40   30   20   10   0
f1 (ppm)

235

236

BED043_F53-61_2-iso-tmscn-photochem_7-20-16 HMBC

F1 [ppm]

F2 [ppm]

BED036_F21-25_bottomcombo_2-iso-tmscn-photochem-7-8-16-300nmr.1001.fid
BED036_F21-25_bottomcombo_2-iso-tmscn-photochem-7-8-16

f1 (ppm)

EDB-BED036 C13_F21-25_2-iso-tmscn-bottomcombo photochem-7-9-16.101.fid
BED036 C13_F21-25_2-iso-tmscn-bottomcombo photochem-7-9-16

160.24
145.18
139.26
132.58
130.59
129.55
128.77
127.91
126.67
125.84
125.19
123.48
122.67
122.01
121.78
120.22
111.89
45.37
35.00
32.27
30.02
23.58
21.48

f1 (ppm)

BED036_F21-25_2-iso-tmscn-photochem_8-3-16.1.ser
BED036_F21-25_2-iso-tmscn-photochem_8-3-16 HSQC

f2 (ppm)

f1 (ppm)

BED036_F21-25_2-iso-tmscn-photochem_8-3-16.2.ser
BED036_F21-25_2-iso-tmscn-photochem_8-3-16 COSY

BED036_F21-25_2-iso-tmscn-photochem_8-3-16.3.ser
BED036_F21-25_2-iso-tmscn-photochem_8-3-16 HMBC

BED115_F42-50_isocyanobenzoate-tmscn-2-ethoxyethanol_4-28-17.1.fid
BED115_F42-50_isocyanobenzoate-tmscn-2-ethoxyethanol_4-28-17 H
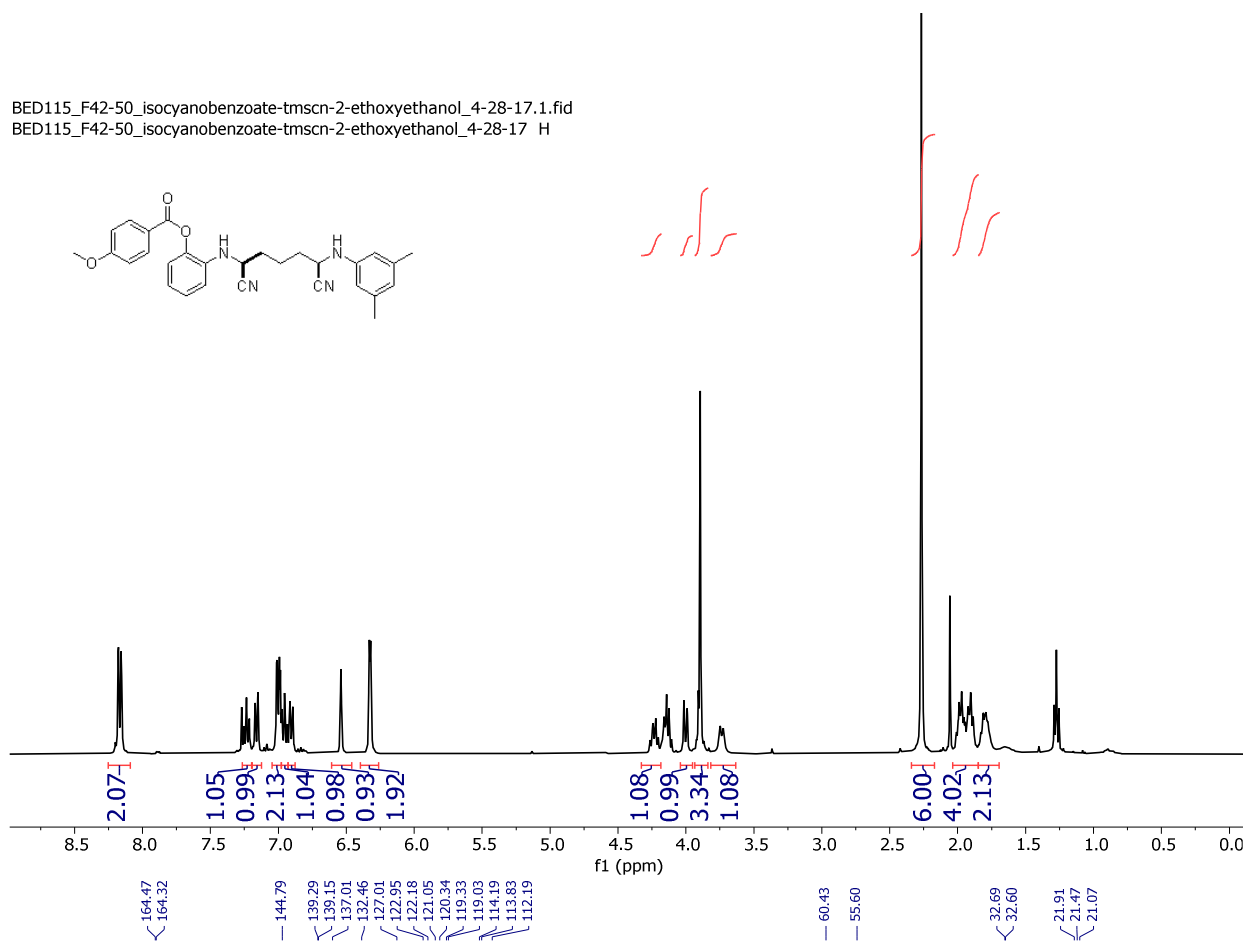
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BED115_F42-50_isocyanobenzoate-tmscn-2-ethoxyethanol_4-28-17 C13

240

132.46
127.02
122.93
122.19
120.35
114.19
113.82
112.15
55.61
45.67
45.37
32.69
32.60
21.95
21.47

f1 (ppm)

BED115_F42-50_isocyanobenzoate-tmscn-2-ethoxyethanol_4-28-17.5.ser
BED115_F42-50_isocyanobenzoate-tmscn-2-ethoxyethanol_4-28-17 COSY

f2 (ppm)

f1 (ppm)

241

BED115_F42-50_isocyanobenzoate-tmscn-2-ethoxyethanol_4-28-17.6.ser
BED115_F42-50_isocyanobenzoate-tmscn-2-ethoxyethanol_4-28-17 HSQC

f1 (ppm)

f2 (ppm)

BED379-II_p274_1-21-19.5.fid
BED379-II_p274_1-21-19_cyclobut-2,6-diMePhisocyanide-tmscn spot 4 H

f1 (ppm)

BED365-II_p260_12-17-18.2.fid
BED365-II_p260_12-17-18_p-isocyanoanisole-cyclobut-tmscn-4strip-2-ethoxy spot 5 H

1.97 2.00 0.86 1.73 1.00 1.27 3.30 1.05 0.80 5.67 4.40 2.07

f1 (ppm)

154.34 144.65 139.39 138.40 122.39 119.42 119.31 116.59 115.09 112.24 55.67 47.24 45.75 32.90 22.05 21.46
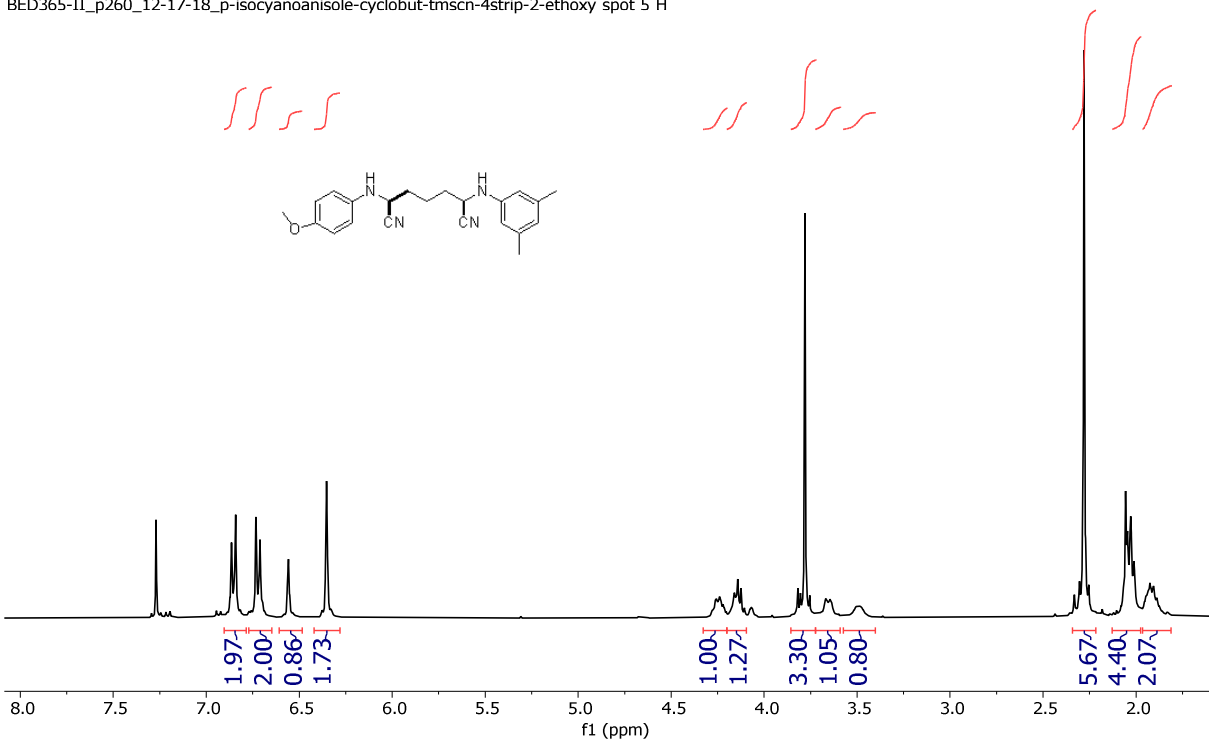
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BED365-II_p260_12-17-18_spot 5 C13

f1 (ppm)
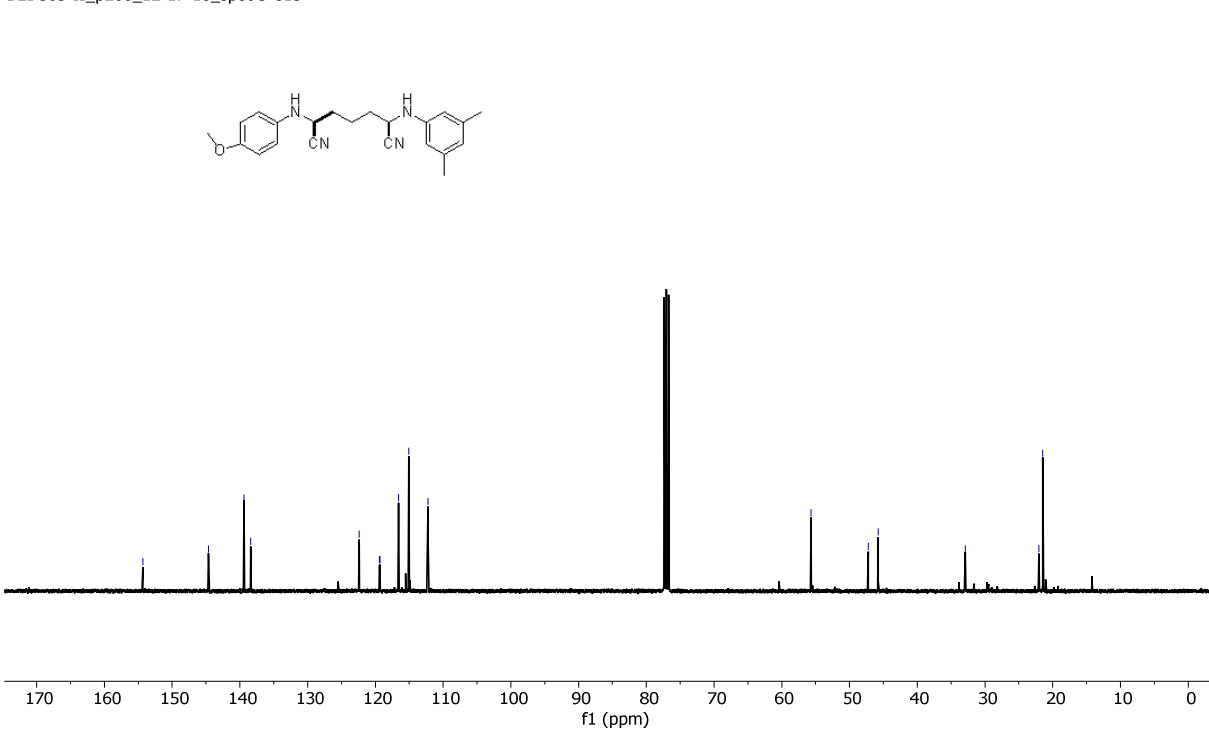
BED365-II_p260_12-17-18.8.fid
BED365-II_p260_12-17-18 spot 5 dept 135

122.39
117.05
114.90
112.23
55.66
46.81
45.74
32.90
22.05
21.47

f1 (ppm)

BED365-II_p260_12-17-18.9.ser
BED365-II_p260_12-17-18 spot 5 HSQC

BED365-II_p260_12-17-18.10.ser
BED365-II_p260_12-17-18 spot 5 COSY
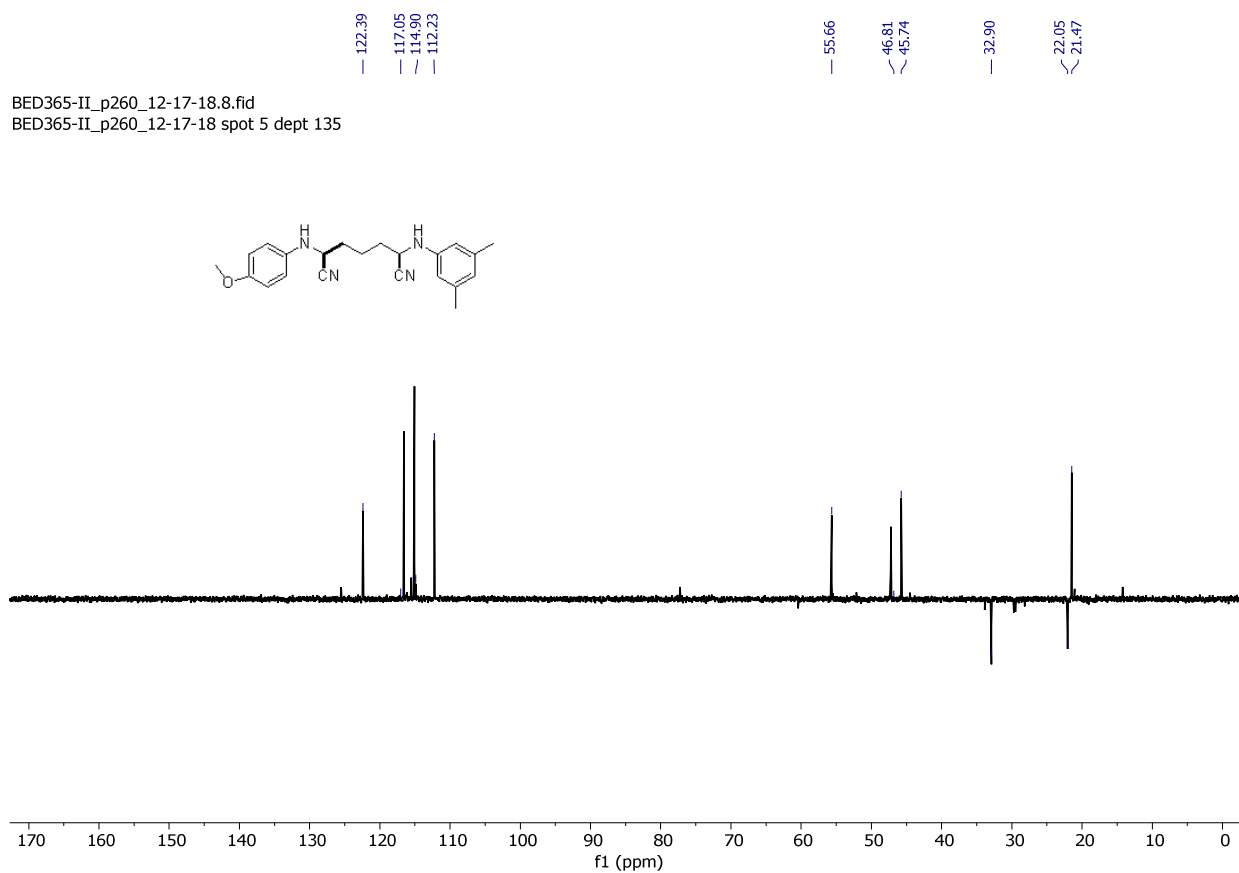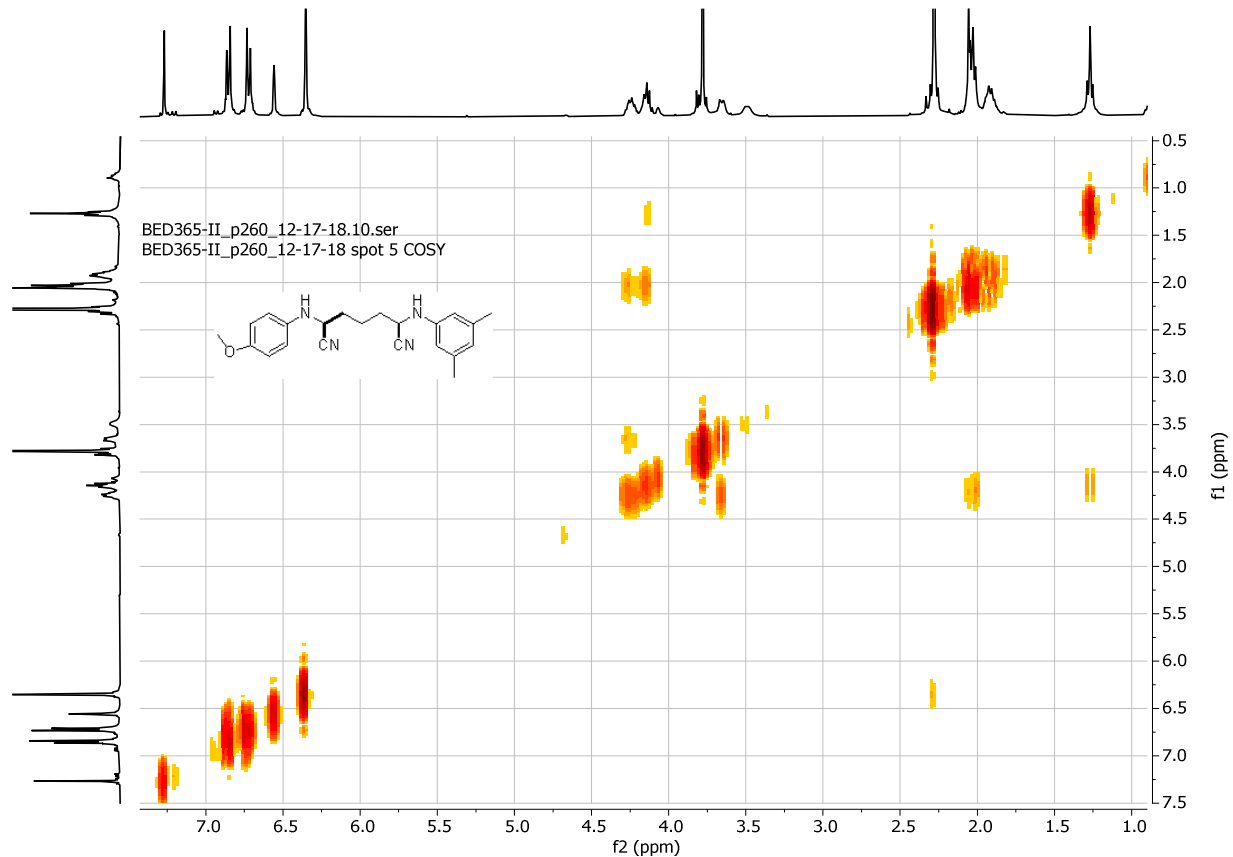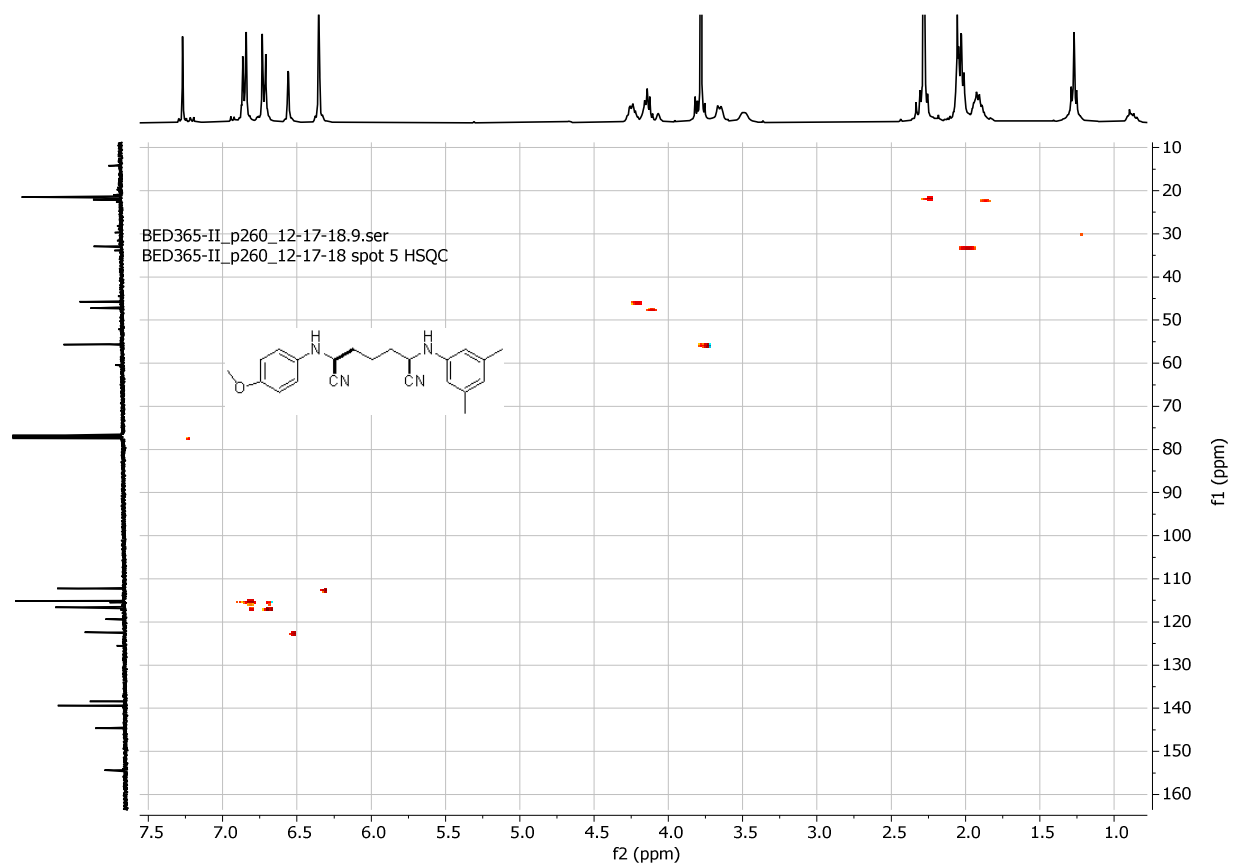
BED395-II_p284_2-1-19.6.fid
BED395-II_p284_2-1-19_cyclobut-4-CF3phenylisonitrile-tmscn spot 3 H
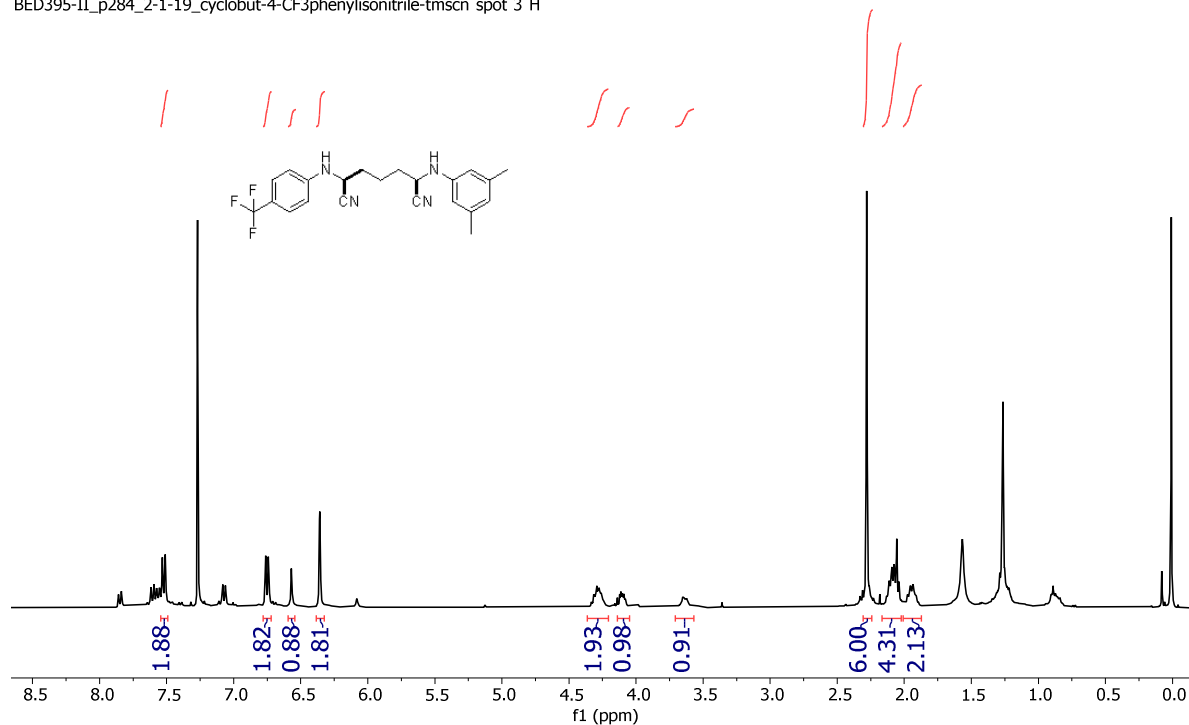
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BED395-II_p284_2-1-19_p-CF3 phenylisocyanide-cyclobut-tmscn spot 3 F
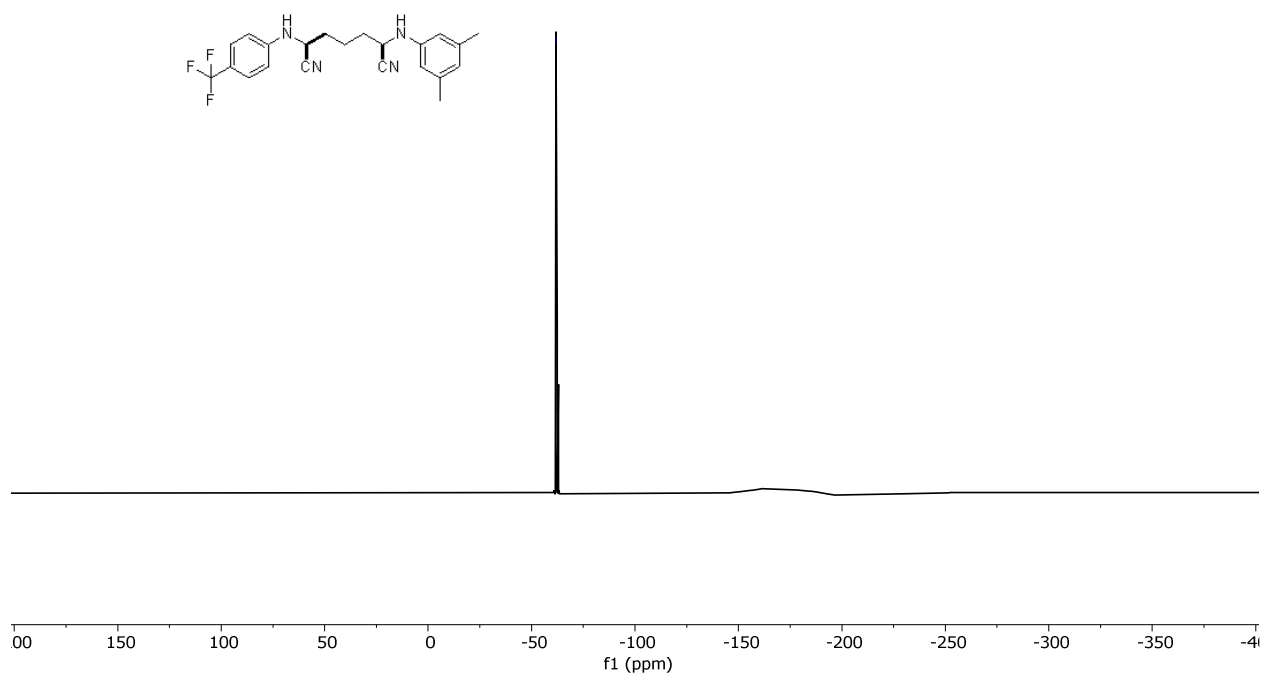
127.62
123.15
121.86
117.06
113.95
112.21

46.28
44.13

33.21
31.84
29.65

21.93
21.39

BED395-II_p284_2-1-19.10.fid
BED395-II_p284_2-1-19_cyclobut-4-CF3phenylisonitrile-tmscn spot 3_Dept135
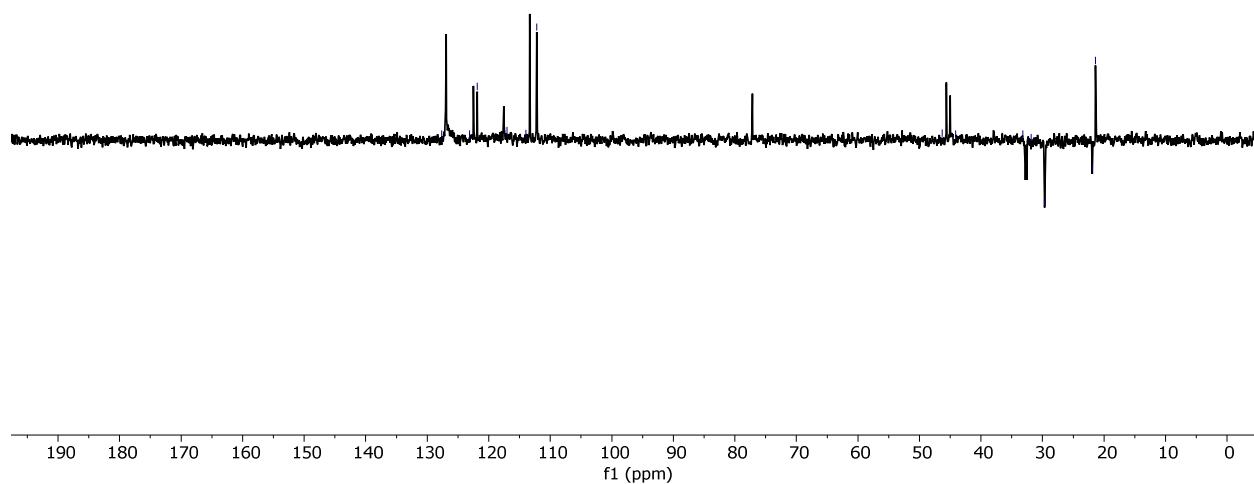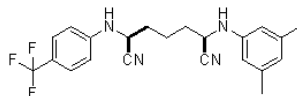
190   180   170   160   150   140   130   120   110   100   90   80   70   60   50   40   30   20   10   0
f1 (ppm)

—61.85

BED395-II_p284_2-1-19.5.fid
BED395-II_p284_2-1-19_p-CF3 phenylisocyanide-cyclobut-tmscn spot 3 F

:00   150   100   50   0   -50   -100   -150   -200   -250   -300   -350   -4(
f1 (ppm)
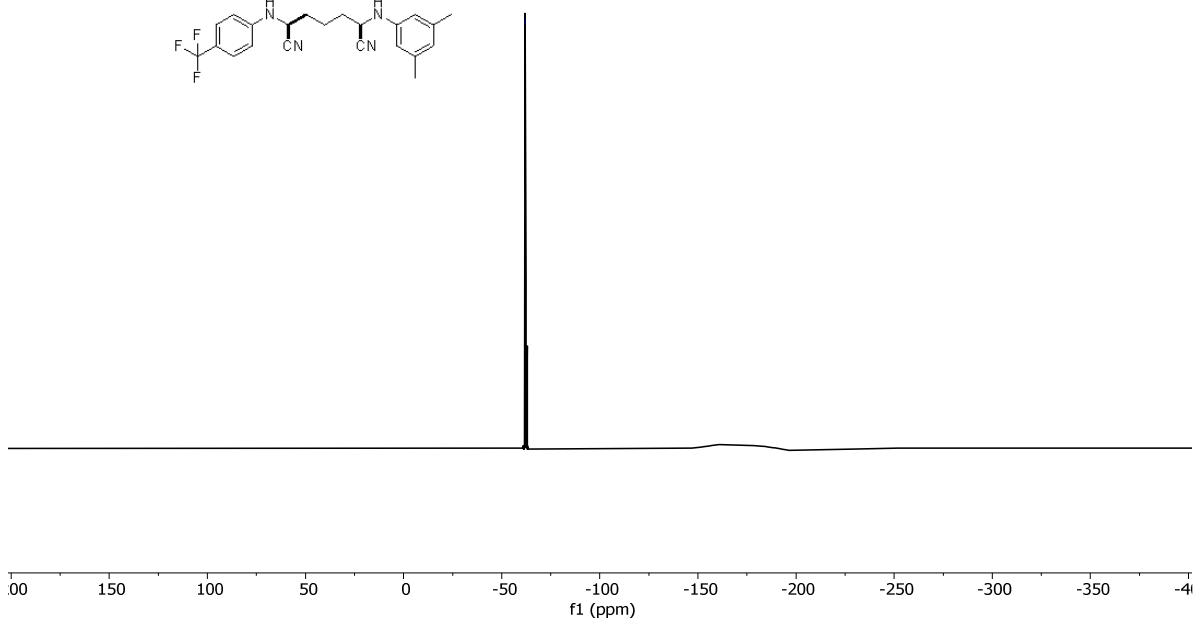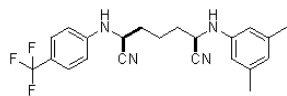
BED439-III_p10_3-12-19.2.fid
BED439-III_p10_3-12-19_cyclobut-3,4-dioxyiso-tmscn spot 4 H
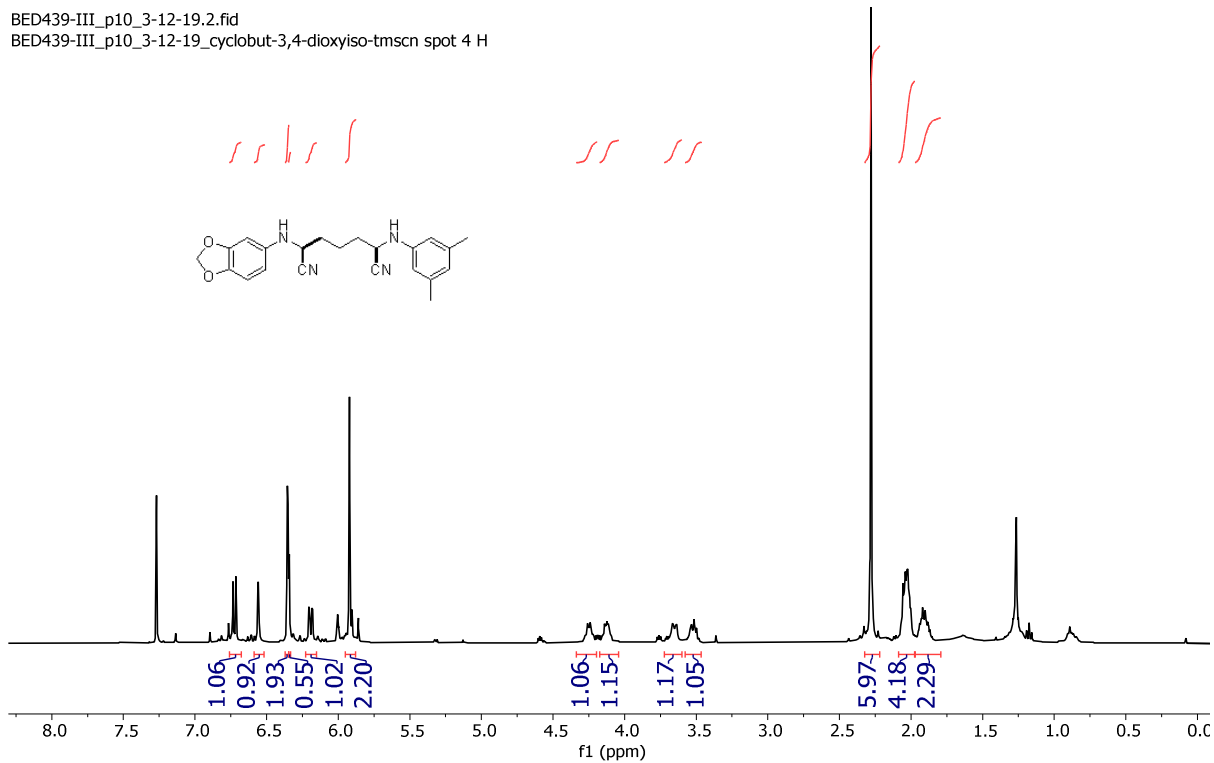
BED380-II_p274_1-21-19.2.fid
BED380-II_p274_1-21-19_cyclobut-4-BrPhisocyanide-tmscn spot 4 H

122.34
112.16
109.30
106.41
101.04
98.03
52.07
47.14
45.65
32.82
29.65
29.38
21.99
21.40

f1 (ppm)

1.84
1.71
1.01
1.82
1.95
0.89
1.13
6.00
3.90
2.02

f1 (ppm)

BED380-II_p274_1-21-19.3.fid
BED380-II_p274_1-21-19_ spot 4 C13

144.59
143.64
139.43
132.44
132.03
122.47
119.30
118.78
116.72
115.87
115.86
112.47
112.26
112.24
45.71
45.68
45.65
32.89
32.83
32.70
32.64
22.04
22.00
21.48

f1 (ppm)

BED380-II_p274_1-21-19.4.fid
BED380-II_p274_1-21-19 spot 4 dept135

132.44
132.03
122.47
116.72
115.86
112.25
112.23
45.70
45.64
32.88
32.82
32.69
32.63
22.04
21.99
21.48

f1 (ppm)

251

BED380-II_p274_1-21-19.5.ser
BED380-II_p274_1-21-19 spot 4 HSQC

BED380-II_p274_1-21-19.6.ser
BED380-II_p274_1-21-19 spot 4 COSY

f1 (ppm)

5.28 3.85 2.24 0.75 1.69 2.05 0.93 1.03 5.85 4.32 2.38

144.74 140.99 140.97 139.55 122.56 119.46 119.44 119.22 119.20 116.48 116.25 116.01 115.93 112.37 46.75 46.72 45.86 33.05 32.99 32.96 32.91 29.84 29.50 22.20 22.15 21.60

f1 (ppm)

253

BED484-spot 5-III_p32.4.fid
BED484-spot 5-III_p32_3,5-cyclobut-4-iodo-isocyanide-tmscn_Dept135

122.35
116.27
116.04
115.79
115.71
112.15

46.52
45.16

32.77
32.35
28.88

21.97
21.39

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

-124.06
-124.08
-124.46
-124.71

BED484-spot 5-III_p32.2.
BED484-spot 5-III_p32_3,

_ F19

00 150 100 50 0 -50 -100 -150 -200 -250 -300 -350 -4
f1 (ppm)

254

255

EDB-BED047_C13 actual-4-isoc-tmscn-photochem-7-22-16.1.fid
BED047_C13 actual-4-isoc-tmscn-photochem-7-22-16

144.63
143.90
140.51
139.42
133.62
128.75
128.31
127.17
126.69
126.56
122.45
119.18
115.82
114.59
112.26

47.25
45.74

32.97
32.16
29.70
29.36
29.00
22.64
22.23
21.82
21.46

f1 (ppm)

128.75
128.31
126.68
126.56
122.45
116.10
115.20
112.66

47.25
45.38

32.96
31.93
29.70
29.00
22.09
21.60
21.46

| 80 | 170 | 160 | 150 | 140 | 130 | 120 | 110 | 100 | 90 | 80 | 70 | 60 | 50 | 40 | 30 | 20 | 10 | 0 |

f1 (ppm)

1.70
1.76
0.90
1.67
1.75
1.69
5.71
4.00
2.03
8.96

f1 (ppm)

127.59
122.39
121.55
114.14
112.24
45.97
45.74
32.93
32.89
31.46
22.05
21.48

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED660-III_p149_1-9-2021.11.ser
BED660-III_p149_1-9-2021_cyclob-p-tButphenisocy-tmscn-2-ethoxyethanol_spot 5 after heat drying_ HSQC

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f2 (ppm)

f1 (ppm)
20 30 40 50 60 70 80 90 100 110 120 130 140
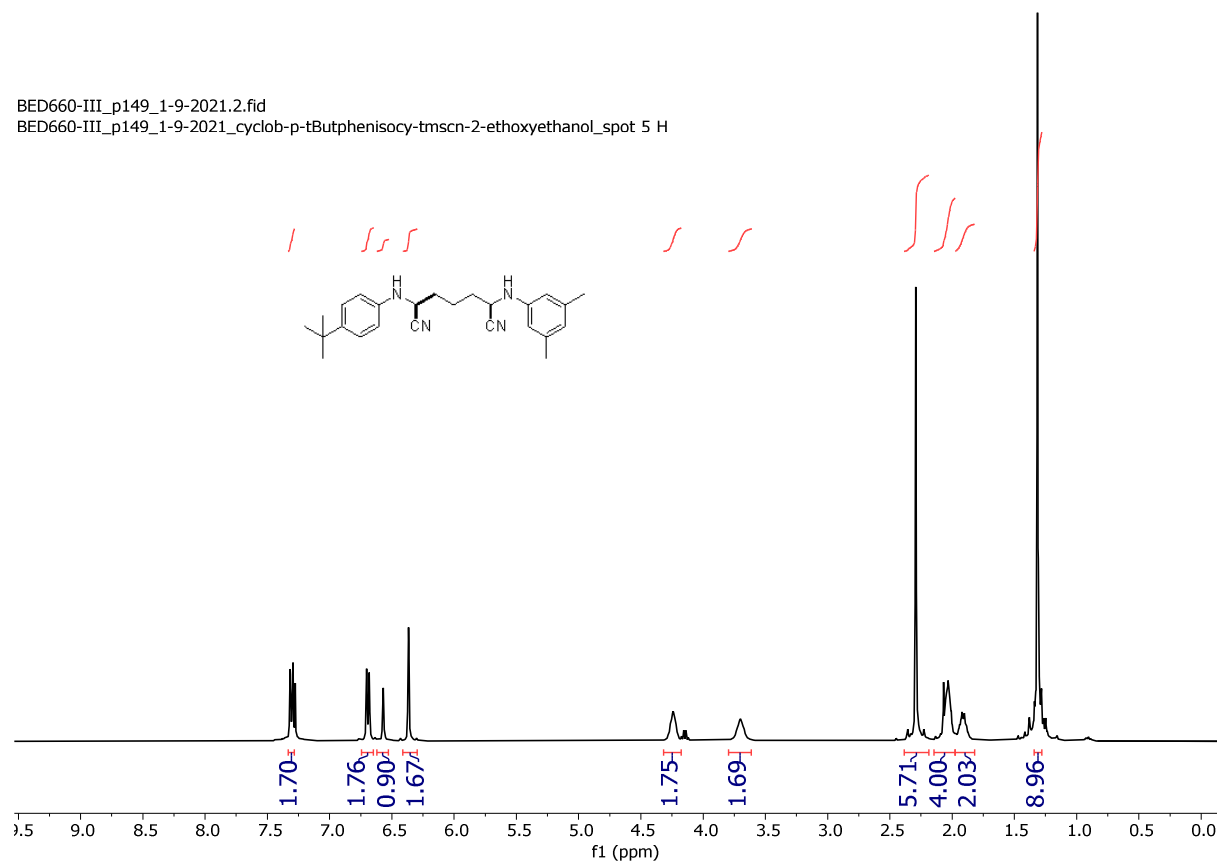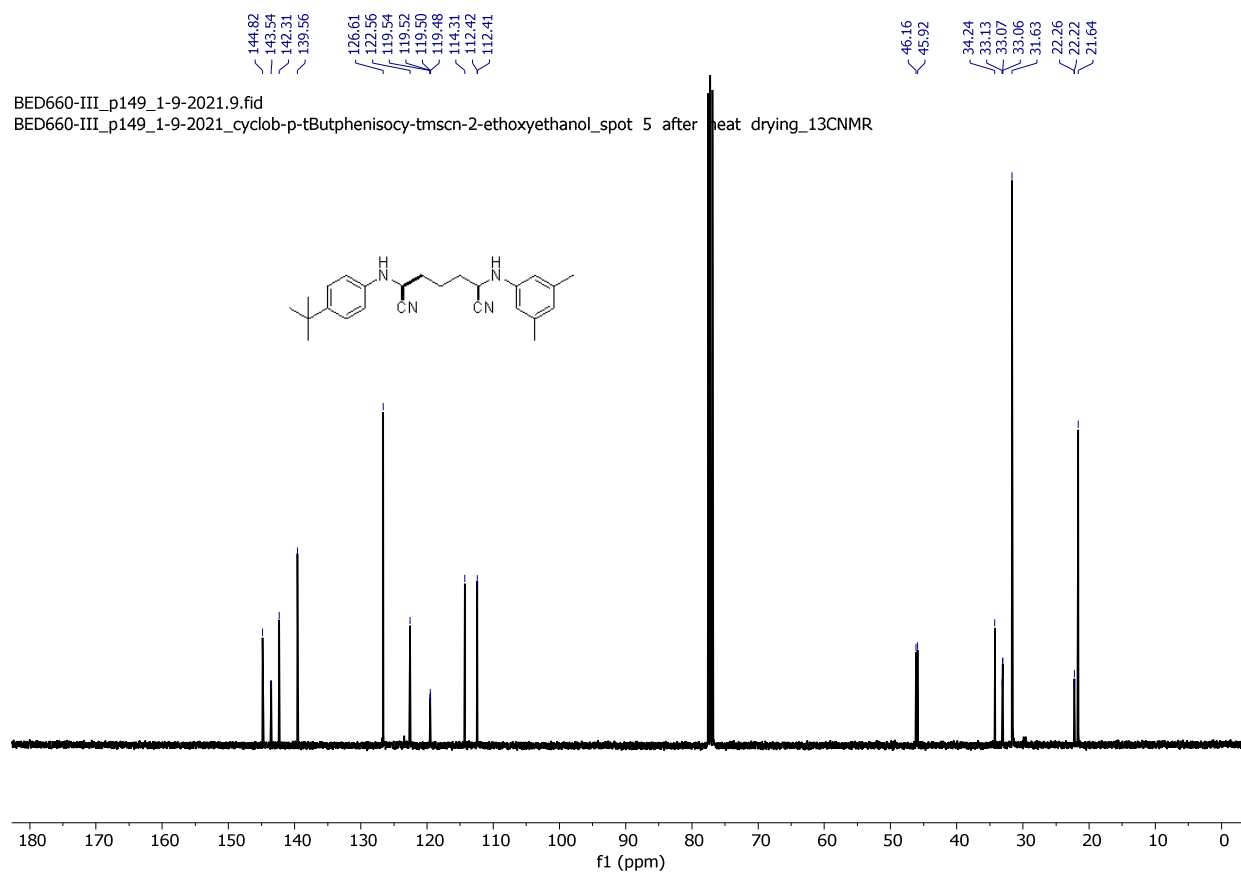
BED660-III_p149_1-9-2021.6.ser
BED660-III_p149_1-9-2021_cyclob-p-tButphenisocy-tmscn-2-ethoxyethanol_spot 5_ COSY

BED660-III_p149_1-9-2021.7.ser
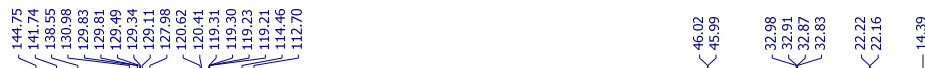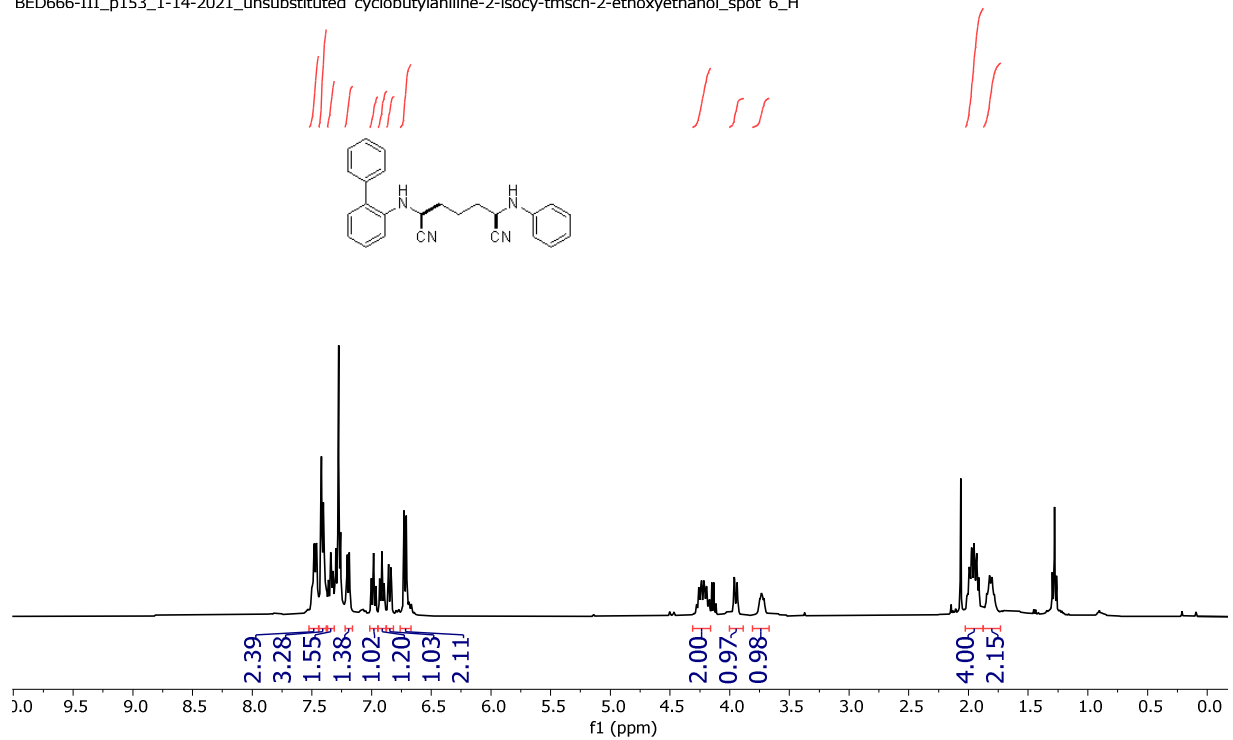BED660-III_p149_1-9-2021_cyclob-p-tButphenisocy-tmscn-2-ethoxyethanol_spot 5_HMBC
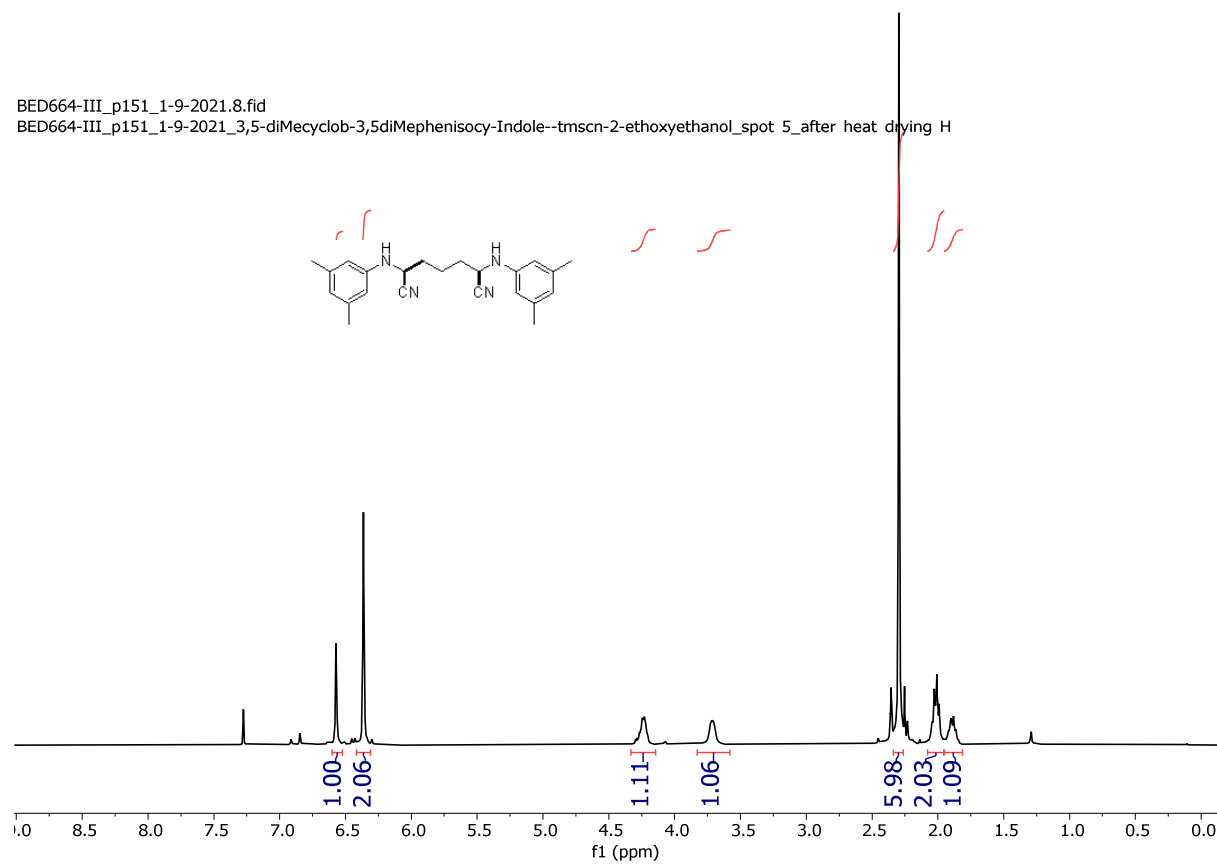
BED664-III_p151_1-9-2021.9.fid
BED664-III_p151_1-9-2021_3,5-diMecyclob-3,5diMephenisocy-Indole--tmscn-2-ethoxyethanol_spot 5_after heat drying_ C13

144.90
139.54
122.50
119.59
112.39
45.87
33.03
21.59

f1 (ppm)

BED664-III_p151_1-9-2021.10.fid
BED664-III_p151_1-9-2021_3,5-diMecyclob-3,5diMephenisocy-Indole--tmscn-2-ethoxyethanol_spot 5_after heat drying_Dept135
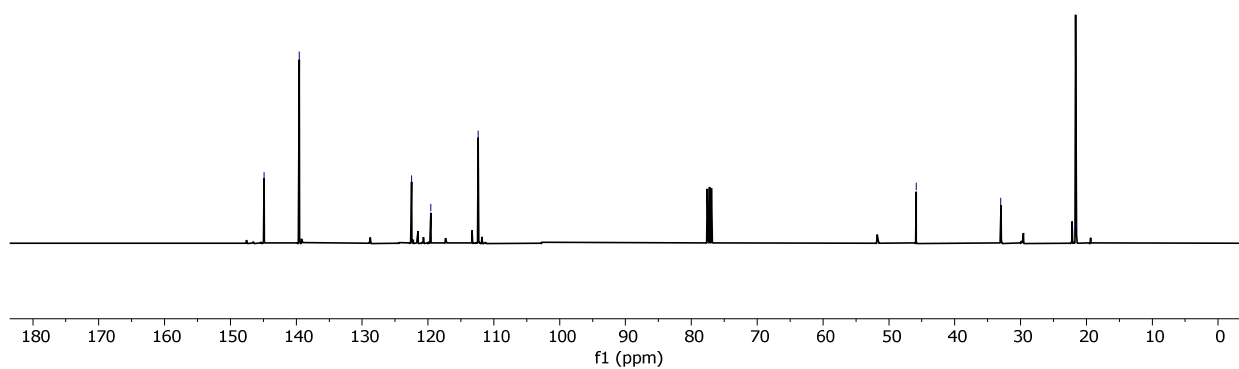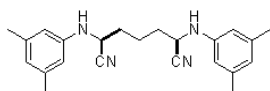
122.32
112.22
45.69
32.85
22.06
21.50

f1 (ppm)

263

BED664-III_p151_1-9-2021.11.ser
BED664-III_p151_1-9-2021_3,5-diMecyclob-3,5diMephenisocy-Indole--tmscn-2-ethoxyethanol_spot_5_after_heat_drying_ HSQC

BED664-III_p151_1-9-2021.12.ser
BED664-III_p151_1-9-2021_3,5-diMecyclob-3,5diMephenisocy-Indole--tmscn-2-ethoxyethanol_spot_5_after_heat_drying_ COSY
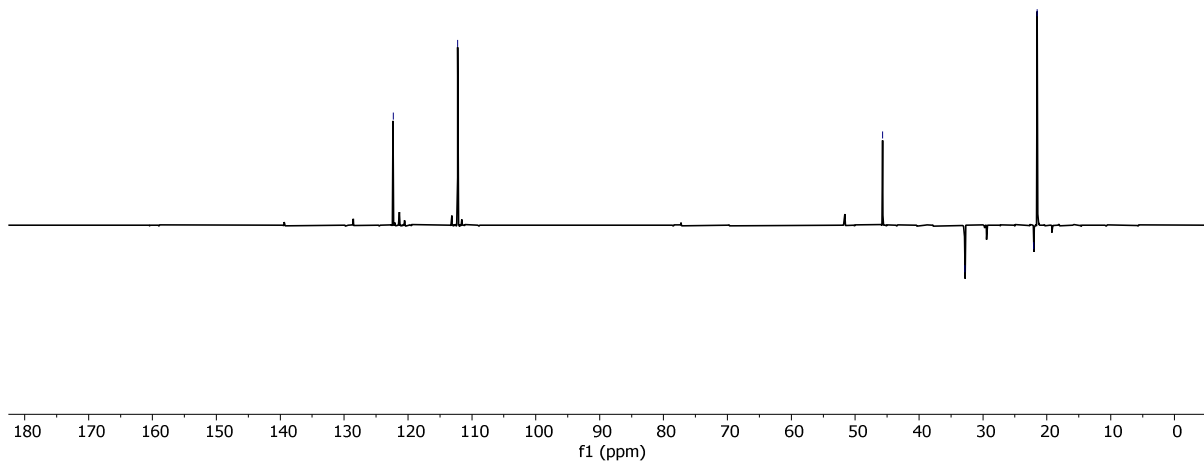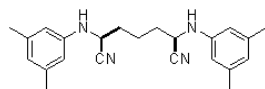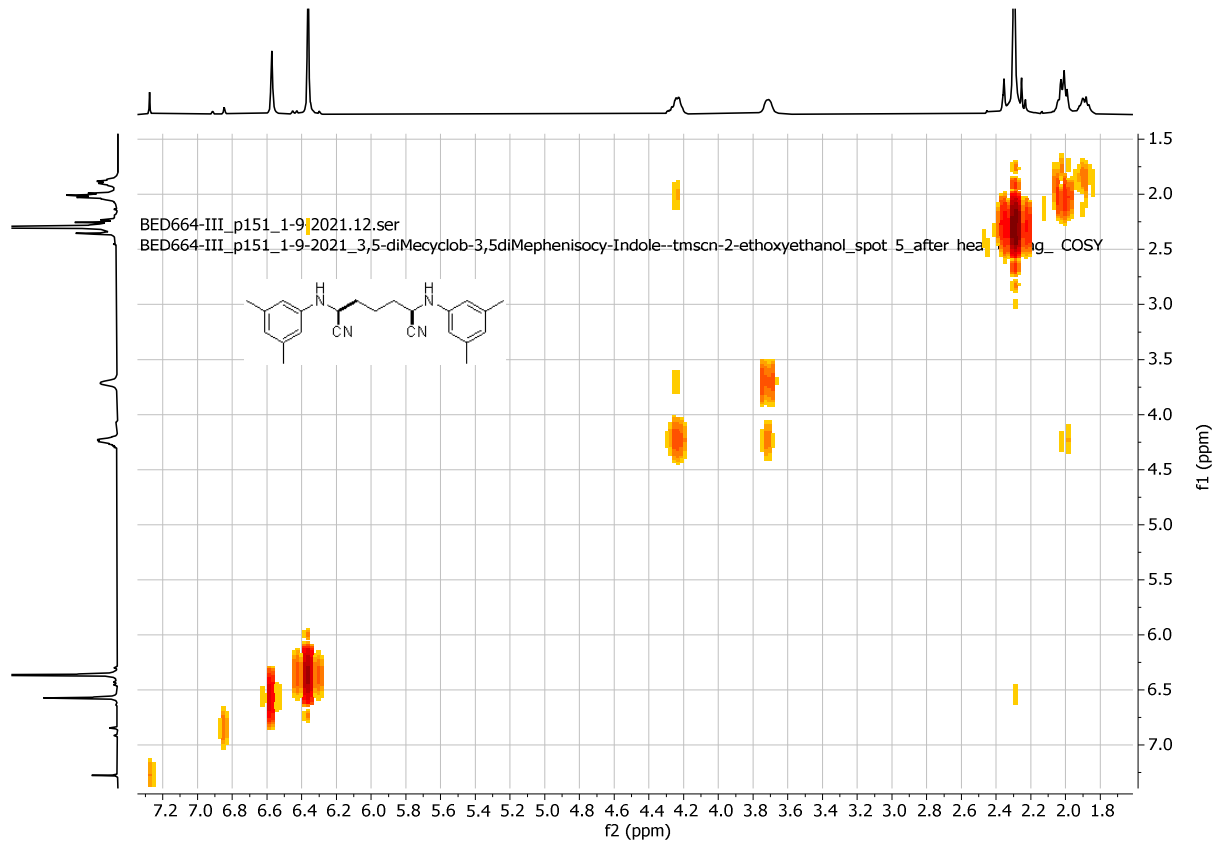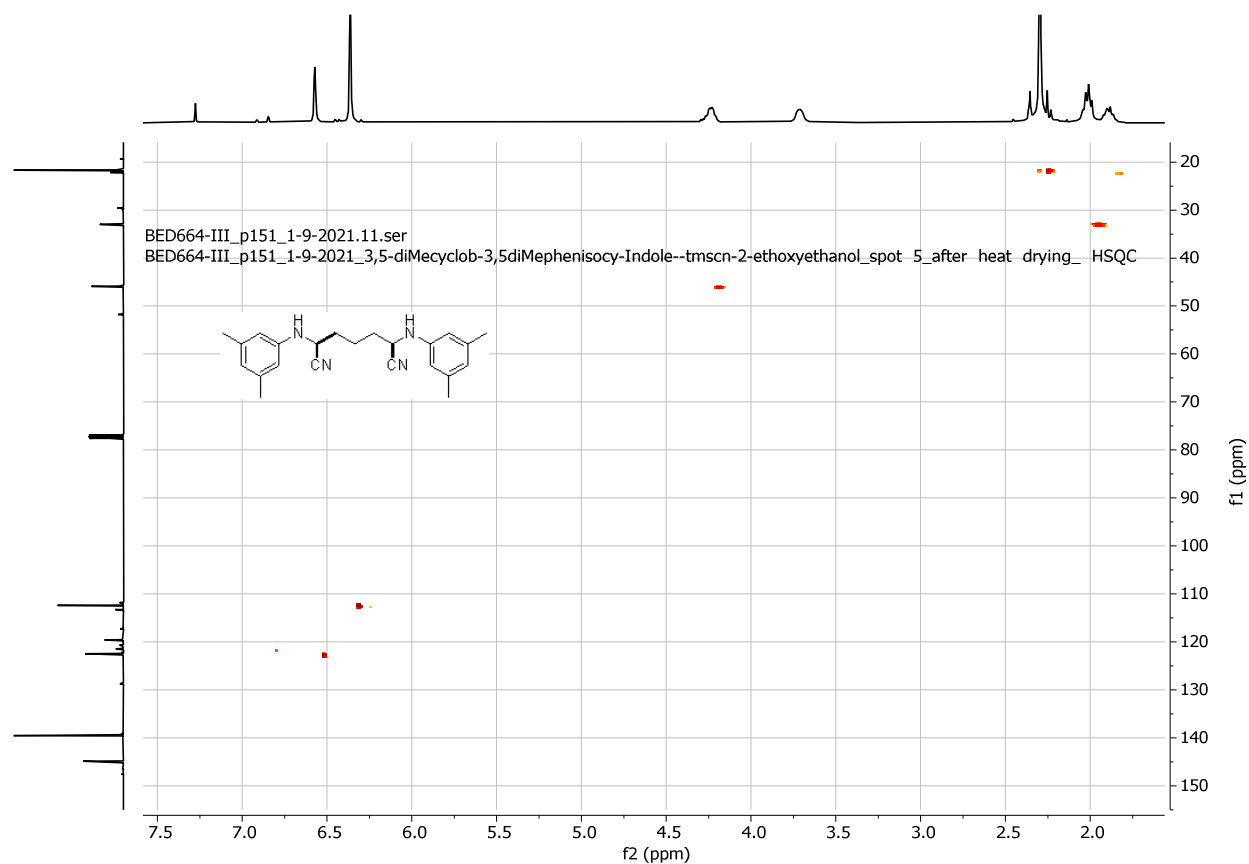
BED666-III_p153_1-14-2021.2.fid
BED666-III_p153_1-14-2021_unsubstituted cyclobutylaniline-2-isocy-tmscn-2-ethoxyethanol_spot 6_H

2.39
3.28
1.55
1.38
1.02
1.20
1.03
2.11

2.00
0.97
0.98

4.00
2.15

f1 (ppm)

144.75
141.74
138.55
130.98
129.83
129.81
129.49
129.34
129.11
127.98
120.62
120.41
119.31
119.30
119.23
119.21
114.46
112.70

46.02
45.99

32.98
32.91
32.87
32.83

22.22
22.16

14.39

BED666-III_p153_1-14-2021.3.fid
BED666-III_p153_1-14-2021_unsubstituted cyclobutylaniline-2-isocy-tmscn-2-ethoxyethanol_spot 6_ C13

f1 (ppm)
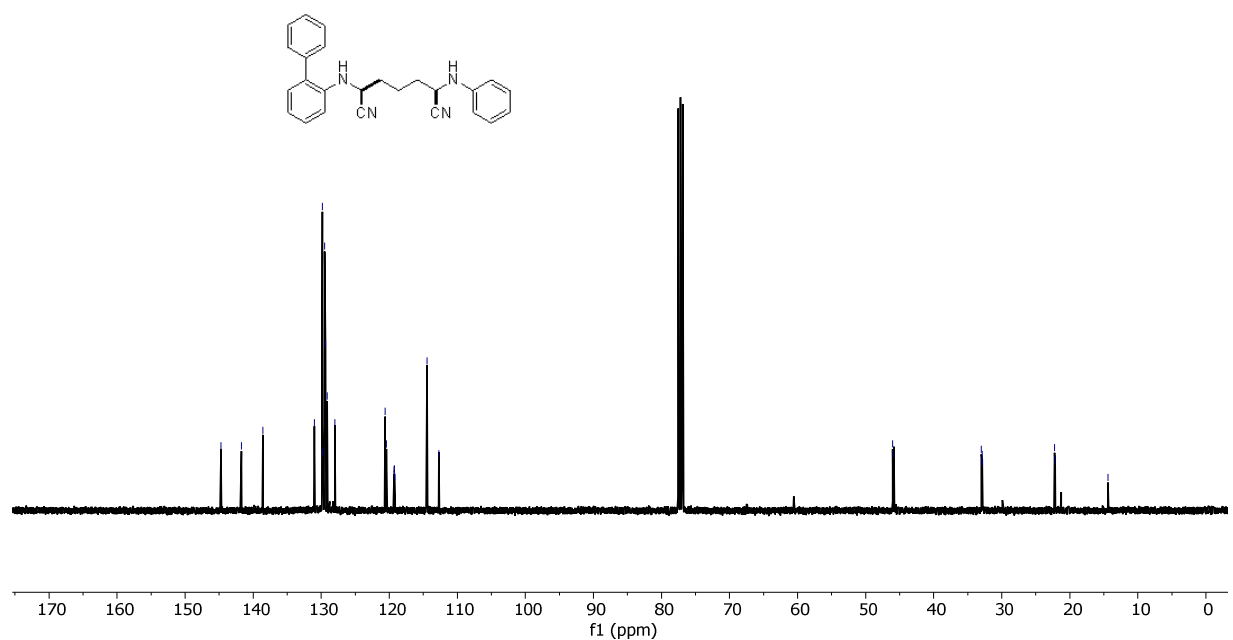
130.81
129.64
129.31
129.18
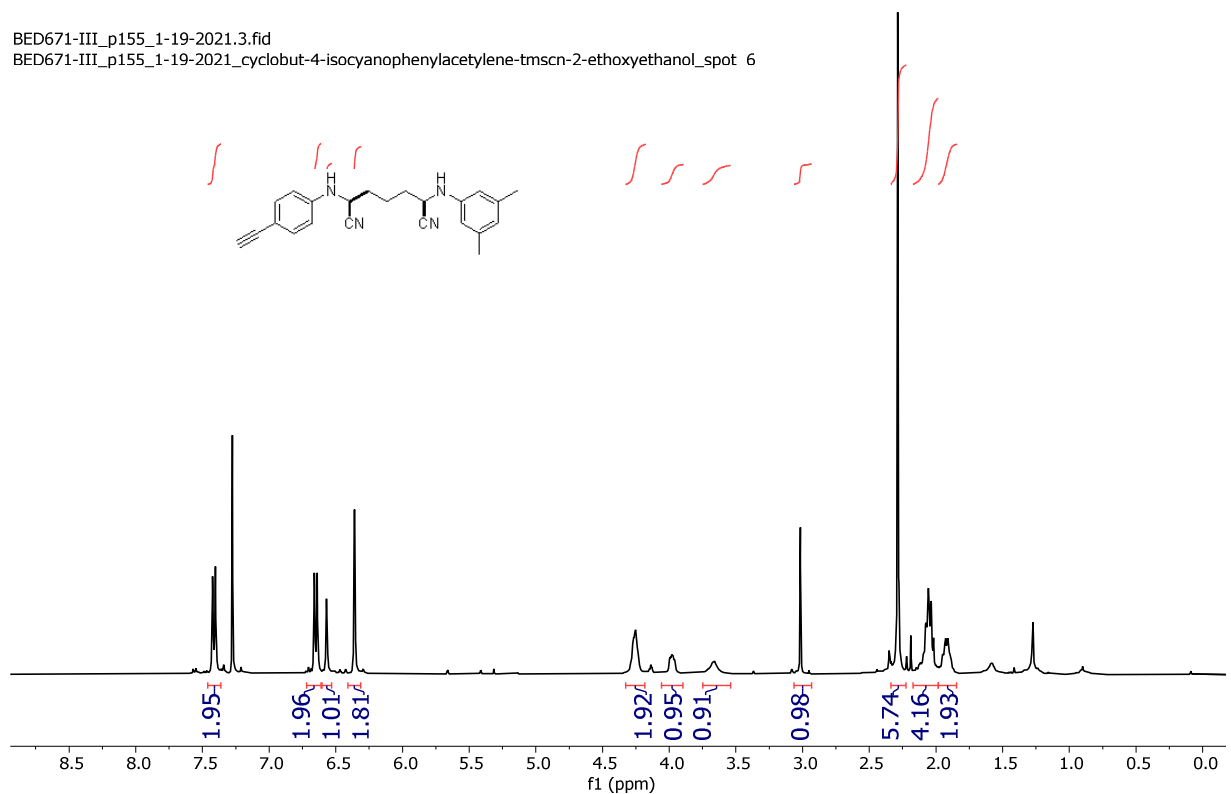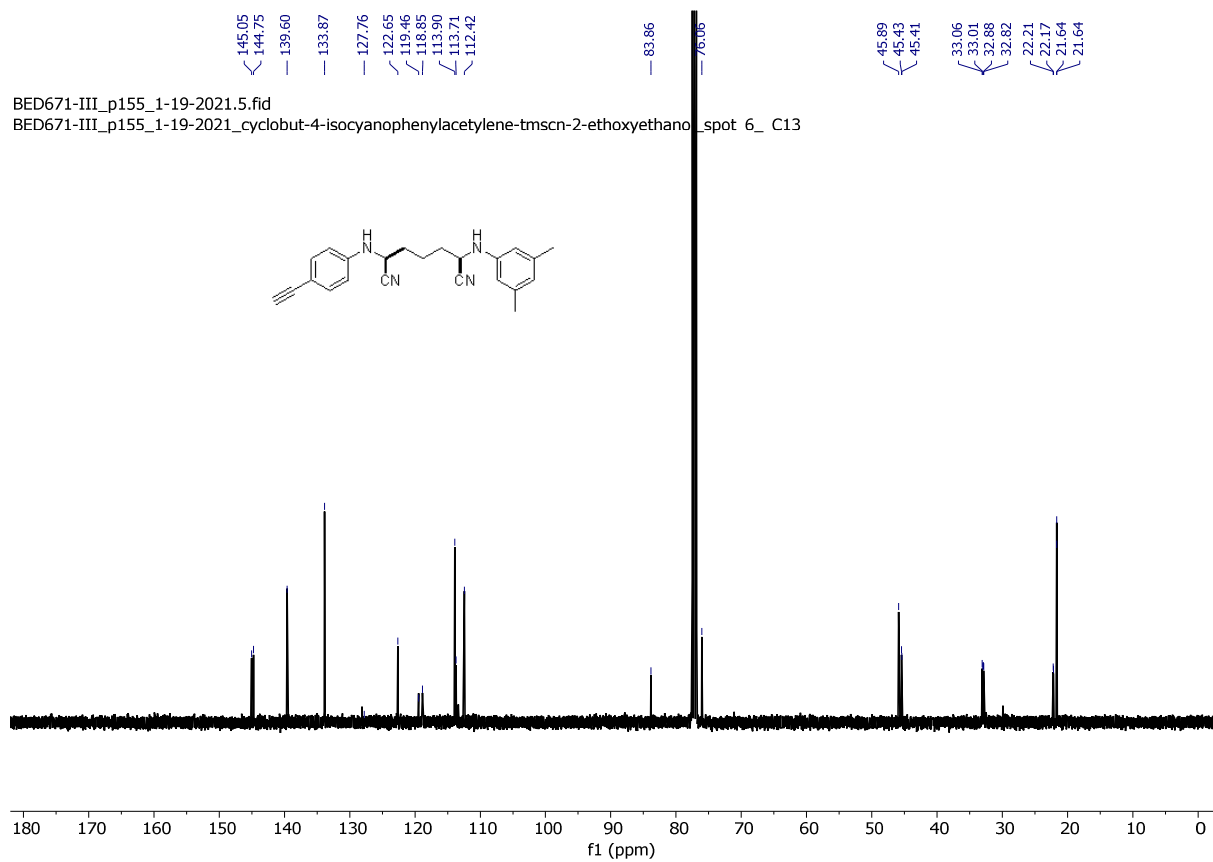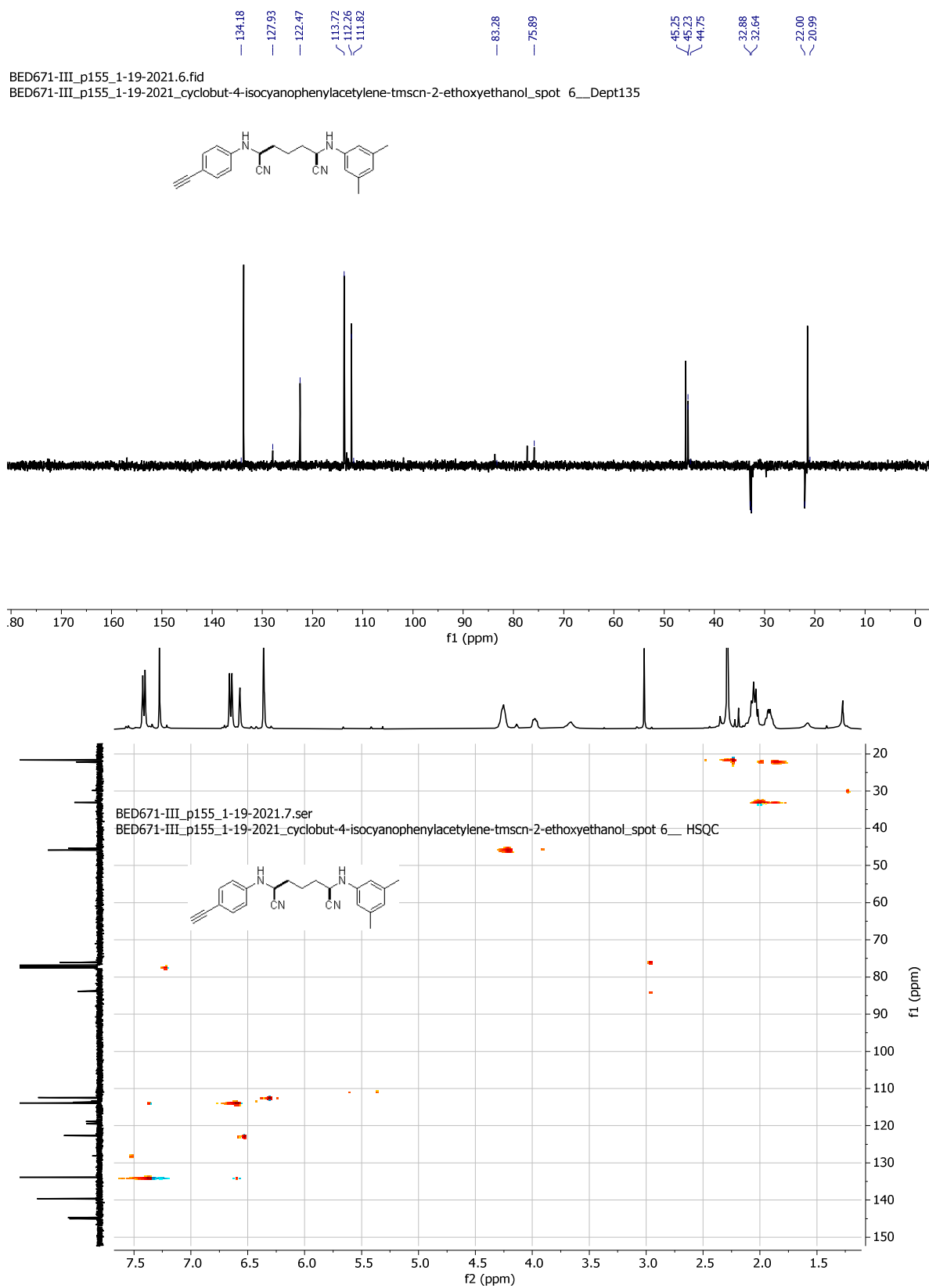128.94
127.81
120.44
120.24
114.28
112.51

45.84
45.66

32.80
32.73
32.69
32.65

22.05
21.99

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED666-III_p153_1-14-2021.5.ser
BED666-III_p153_1-14-2021_unsubstituted cyclobutylaniline-2-isocy-tmscn-2-ethoxyethanol_spot 6__ HSQC

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
f2 (ppm)

f1 (ppm)
20
30
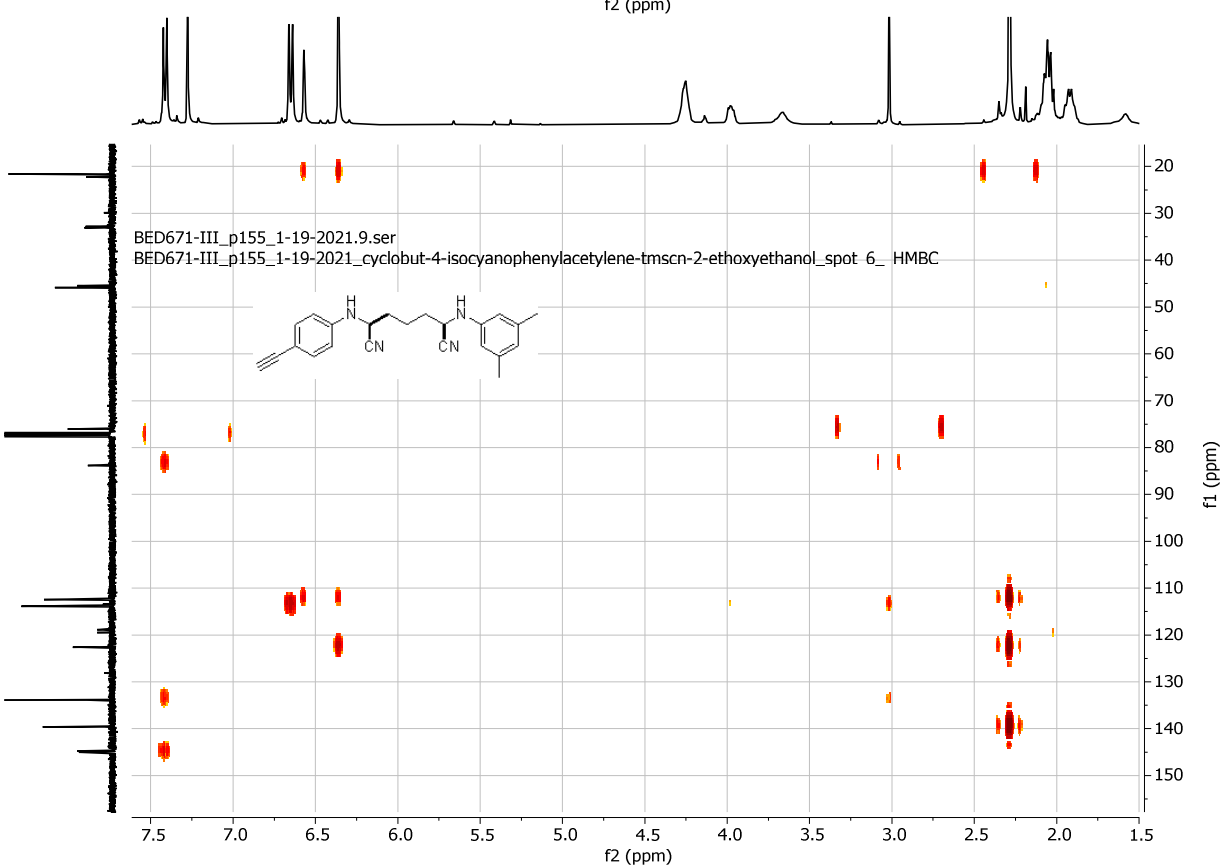40
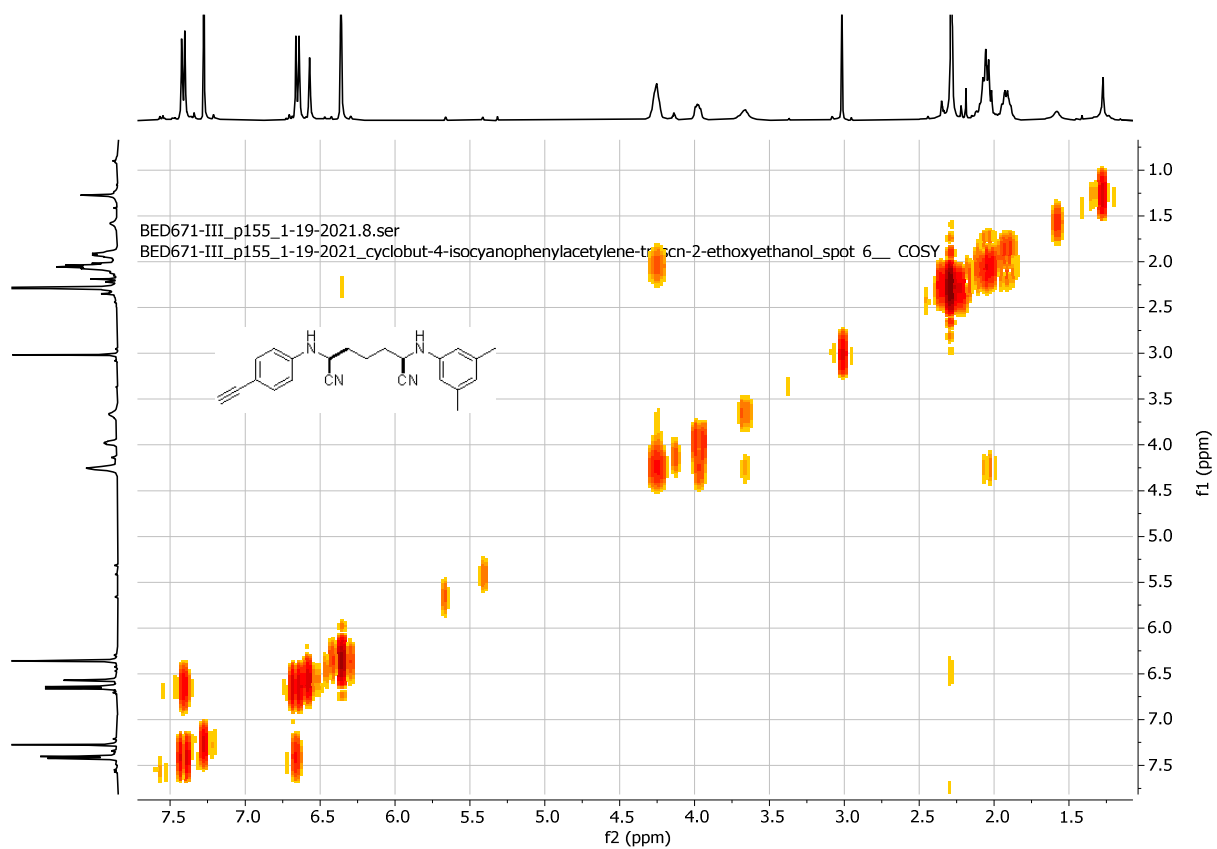50
60
70
80
90
100
110
120
130
140

266

BED666-III_p153_1-14-2021.6.ser
BED666-III_p153_1-14-2021_unsubstituted cyclobutylaniline-2-isoy-tmscn-2-ethoxyethanol_spot 6__ COSY

f1 (ppm)

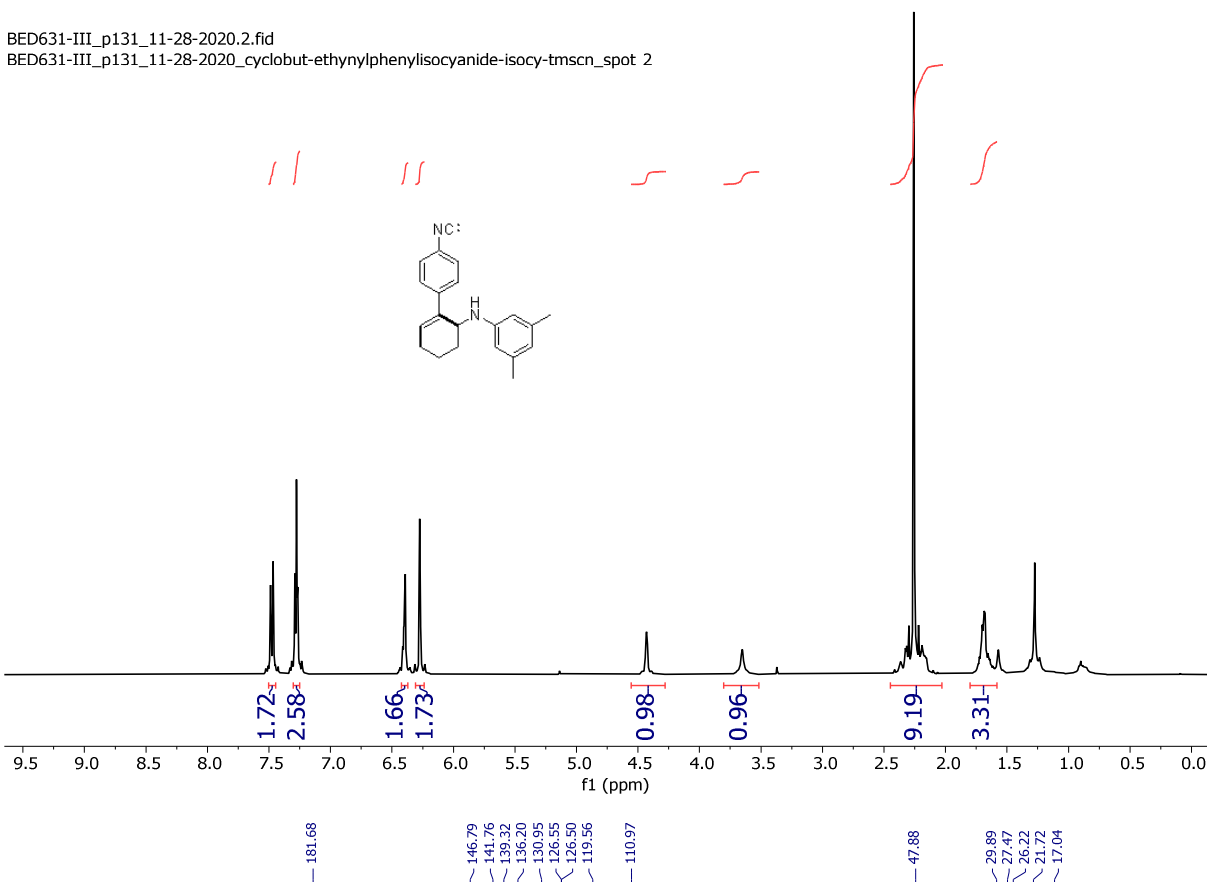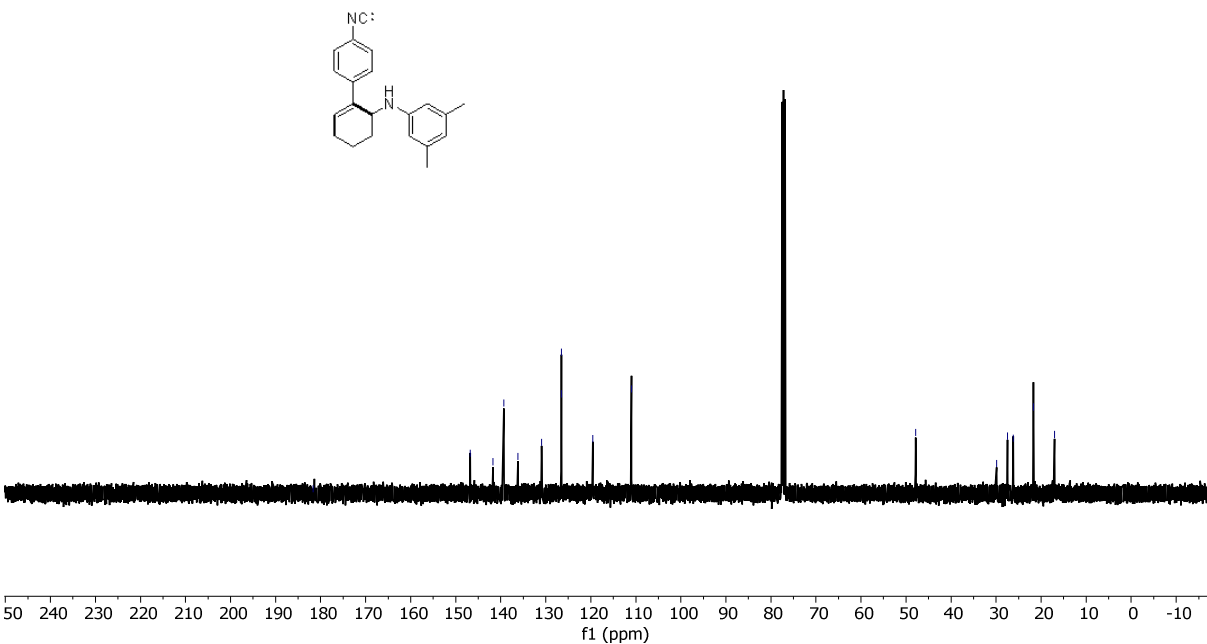f2 (ppm)

BED671-III_p155_1-19-2021.3.fid
BED671-III_p155_1-19-2021_cyclobut-4-isocyanophenylacetylene-tmscn-2-ethoxyethanol_spot 6

1.95
1.96
1.01
1.81
1.92
0.95
0.91
0.98
5.74
4.16
1.93

f1 (ppm)

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

134.18 127.93 122.47 113.72 112.26 111.82 83.28 75.89 45.25 45.23 44.75 32.88 32.64 22.00 20.99

BED671-III_p155_1-19-2021.8.ser
BED671-III_p155_1-19-2021_cyclobut-4-isocyanophenylacetylene-tmscn-2-ethoxyethanol_spot_6___ COSY

BED671-III_p155_1-19-2021.9.ser
BED671-III_p155_1-19-2021_cyclobut-4-isocyanophenylacetylene-tmscn-2-ethoxyethanol_spot_6_ HMBC

270

BED631-III_p131_11-28-2020.2.fid
BED631-III_p131_11-28-2020_cyclobut-ethynylphenylisocyanide-isocy-tmscn_spot 2

1.72
2.58
1.66
1.73
0.98
0.96
9.19
3.31

f1 (ppm)

181.68

146.79
141.76
139.32
136.20
130.95
126.55
126.50
119.56

110.97

47.88

29.89
27.47
26.22
21.72
17.04

BED631-III_p131_11-28-2020.4.fid
BED631-III_p131_11-28-2020_cyclobut-ethynylphenylisocyanide-isocy-tmscn_spot 2 C13

f1 (ppm)

271

130.79
126.38
118.22
110.79
48.10
29.73
27.30
26.05
21.55
17.76

50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -
f1 (ppm)

BED631-III_p131_11-28-2020.6.ser
BED631-III_p131_11-28-2020_cyclobut-ethynylphenylisocyanide-isocy-tmscn_spot 2 HSQC

f1 (ppm)

7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
f2 (ppm)

BED631-III_p131_11-28-2020.7.ser
BED631-III_p131_11-28-2020_cyclobut-ethynylphenylisocyanide-isocy-tmscn_spot 2 COSY
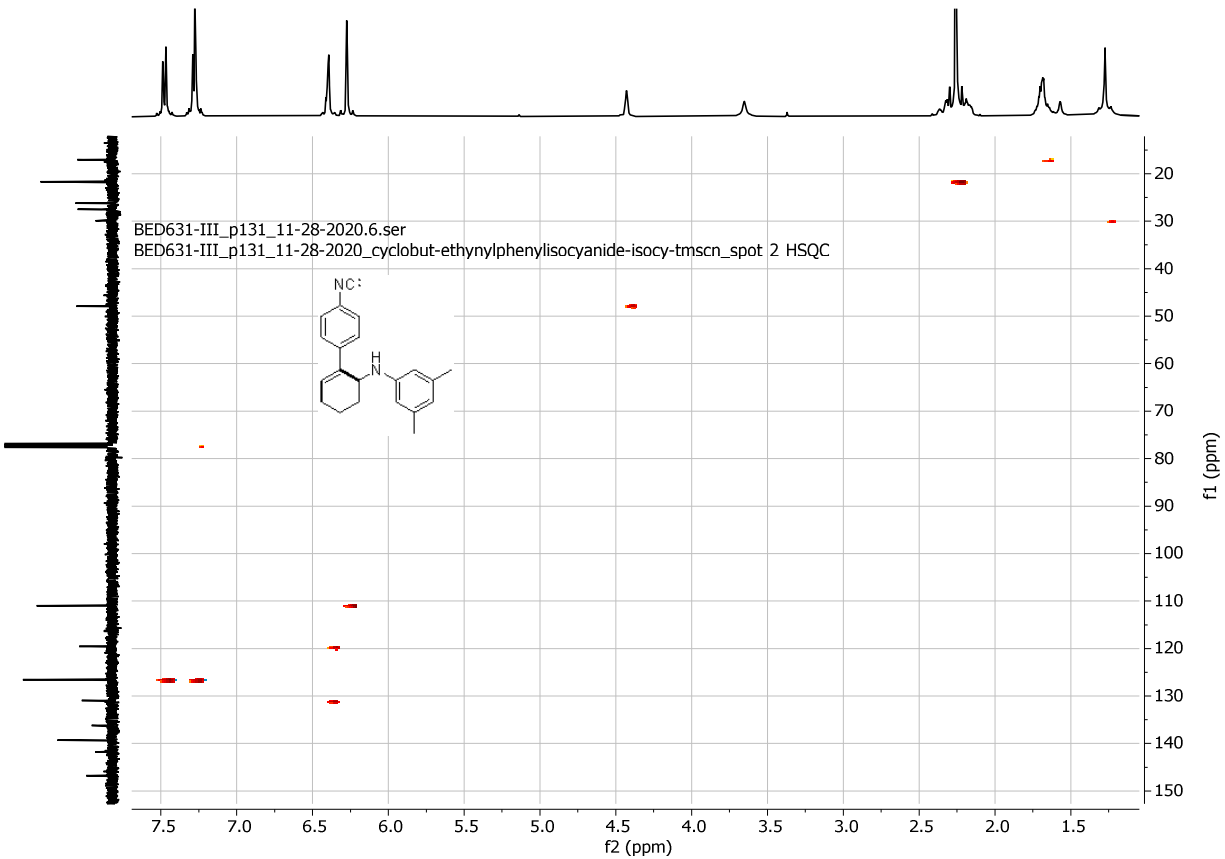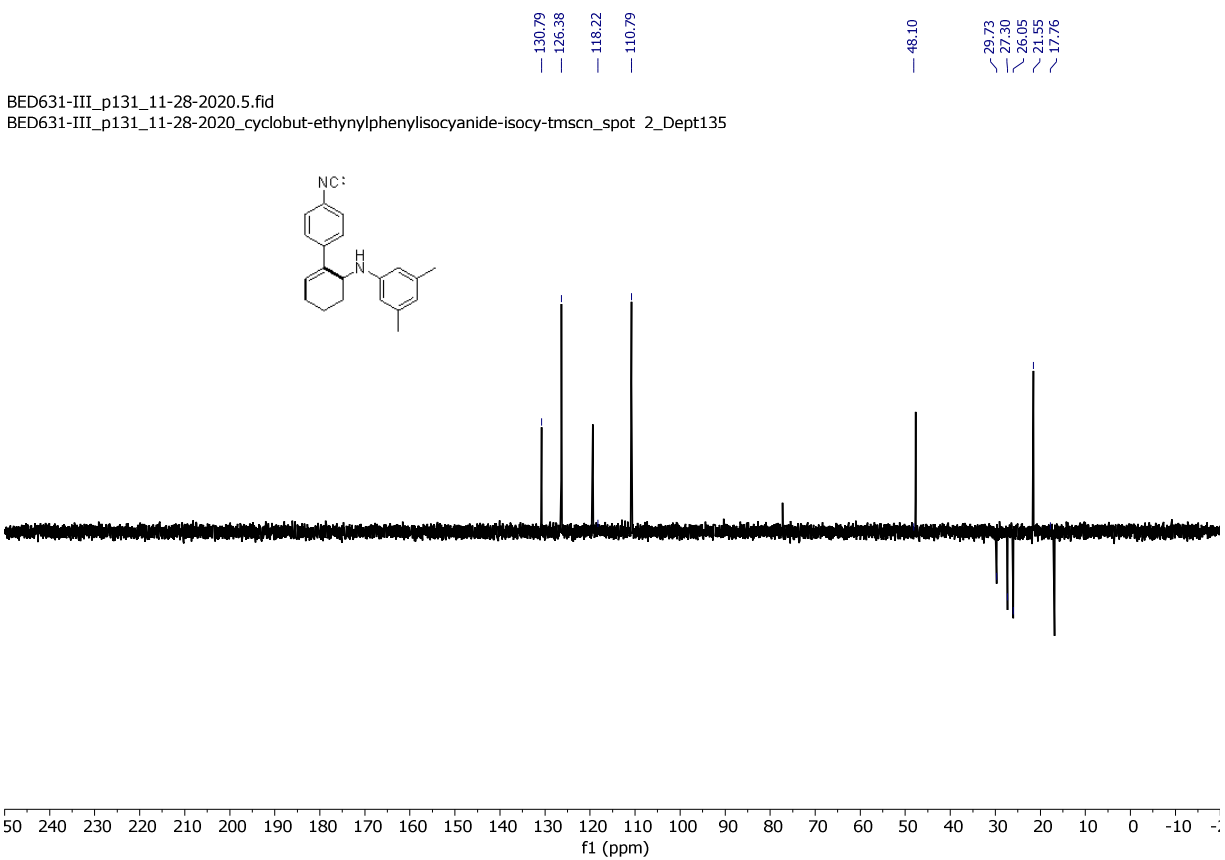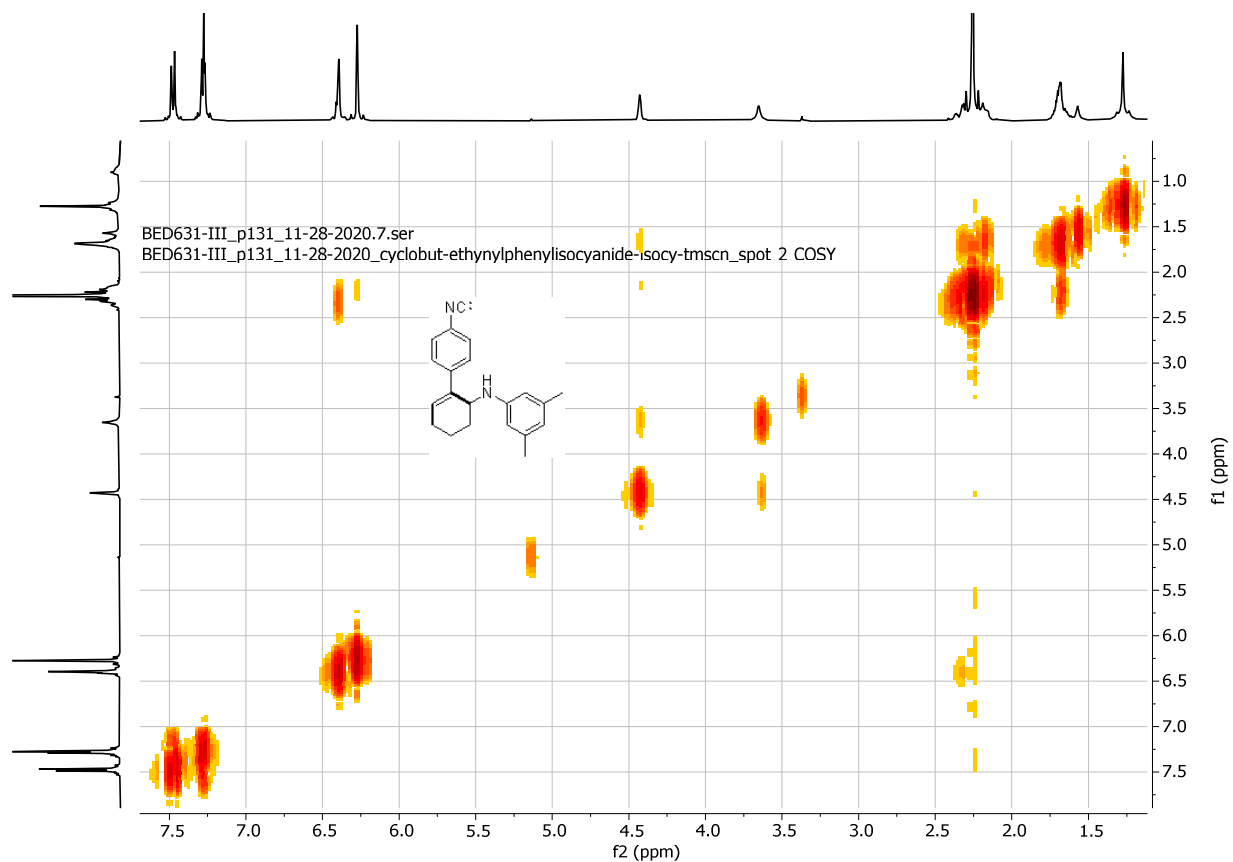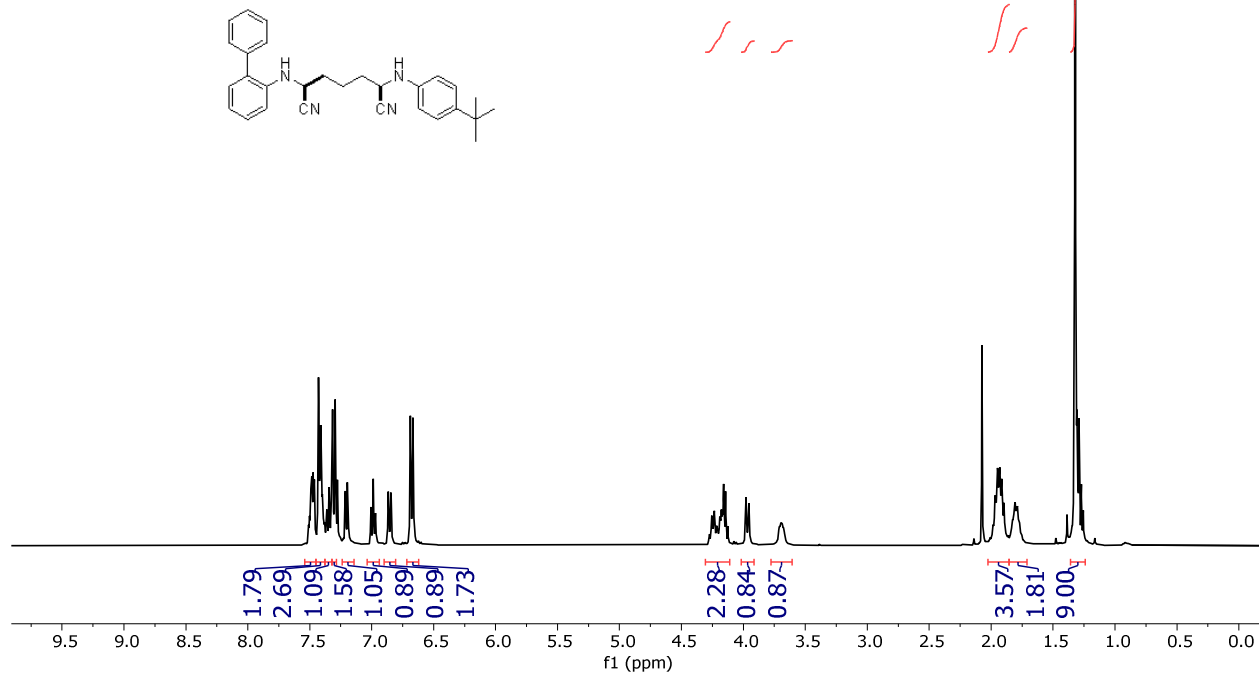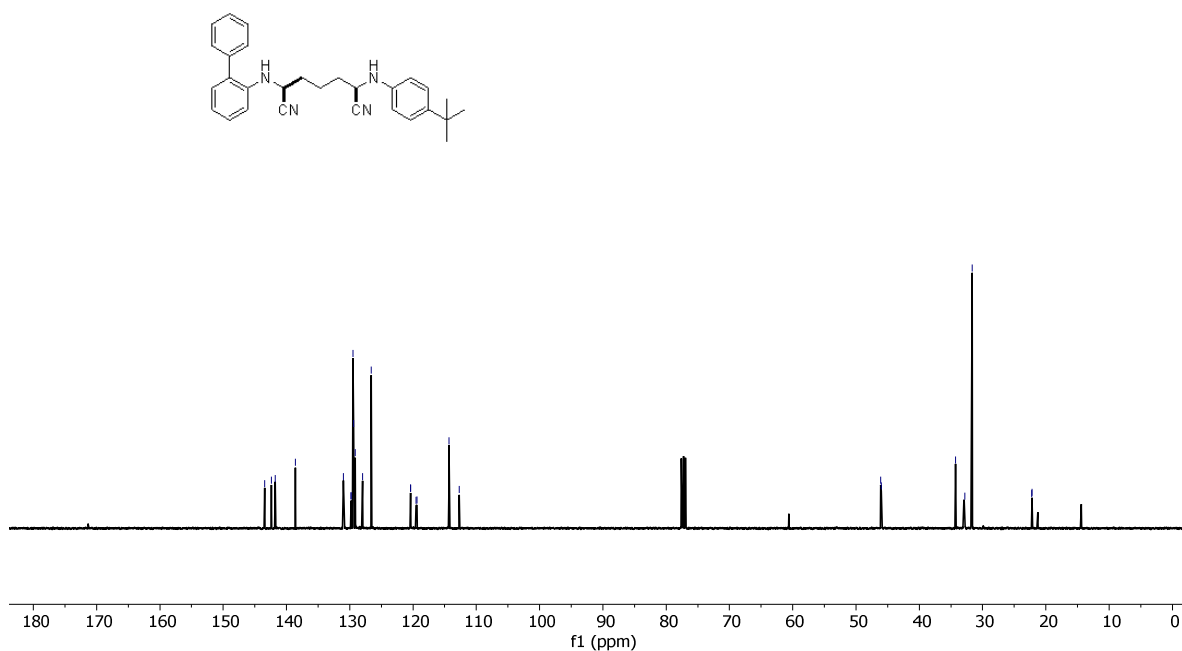
BED653-III_p145_12-23-2020.8.fid
BED653-III_p145_12-23-2020_p-tBu-cyclob-2-iso-tmscn-2-ethoxyethanol_spot 6_after heat drying H
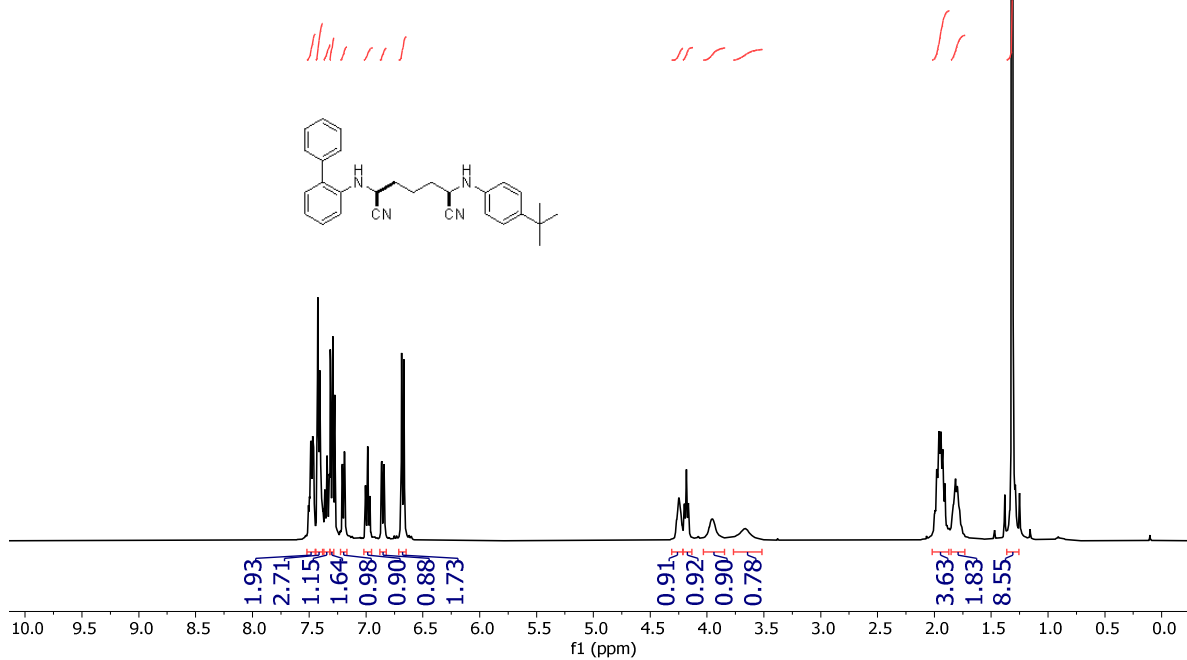
BED653-III_p145_12-23-2020.2.fid
BED653-III_p145_12-23-2020_p-tBu-cyclob-2-iso-tmscn-2-ethoxyethanol_spot 6 H

1.79
2.69
1.09
1.58
1.05
0.89
0.89
1.73

2.28
0.84
0.87

3.57
1.81
9.00

f1 (ppm)

143.45
142.37
141.79
138.58
130.99
129.80
129.78
129.50
129.36
129.12
127.99
126.60
120.38
120.36
119.53
119.38
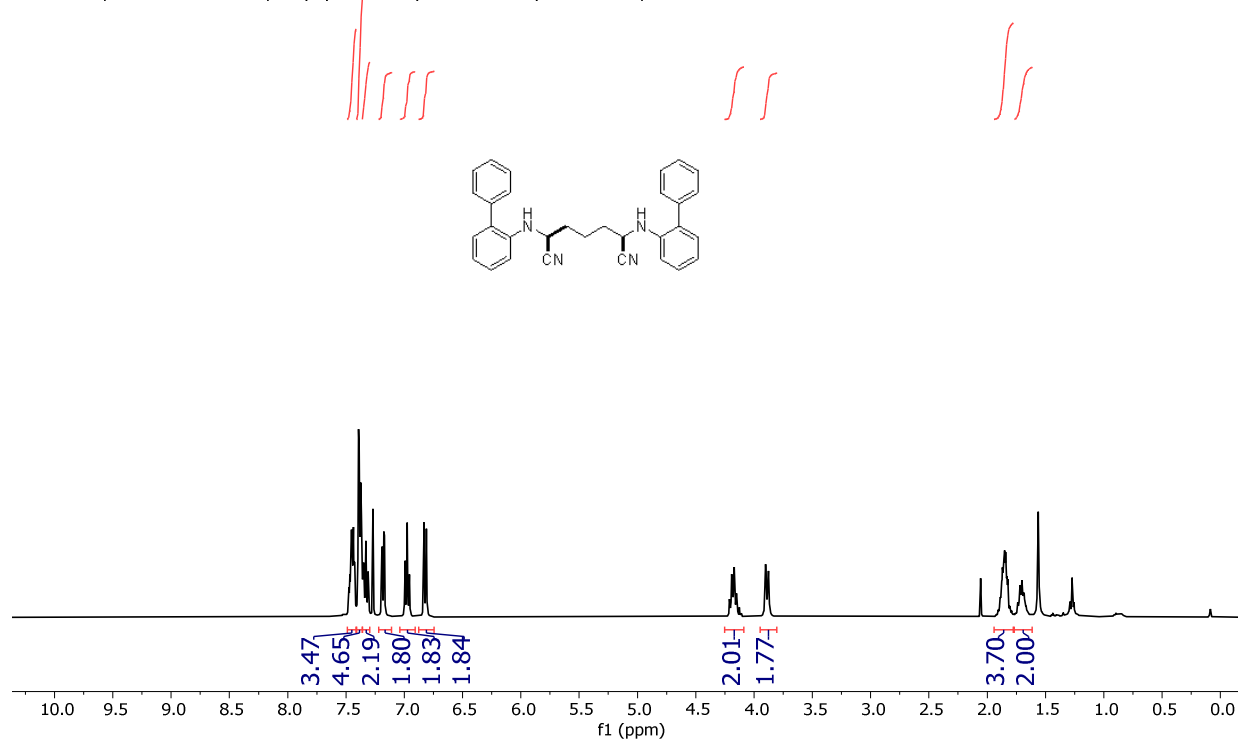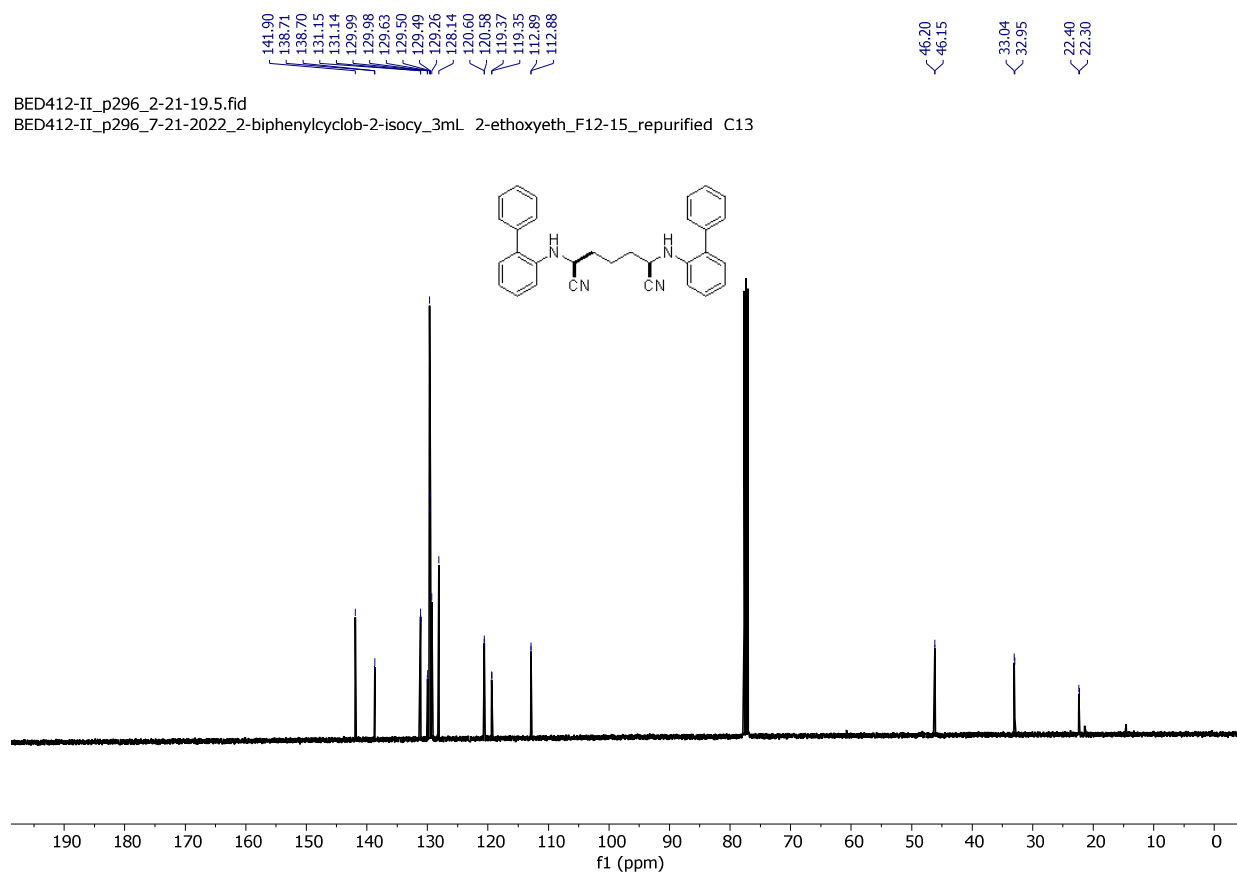114.29
112.70

46.08
45.98

34.25
32.80
31.66

22.23
22.17

BED653-III_p145_12-23-2020.3.fid
BED653-III_p145_12-23-2020_p-tBu-cyclob-2-iso-tmscn-2-ethoxyethanol_spot 6_ C13

f1 (ppm)

130.82
129.33
129.20
128.95
127.81
126.43
120.21
120.19
114.12
112.52
112.50

46.59
45.80

32.79
32.06
31.02

22.06
21.99

f1 (ppm)

BED653-III_p145_12-23-2020.6.ser
BED653-III_p145_12-23-2020_p-tBu-cyclob-2-iso-tmscn-2-ethoxyethanol_spot 6_ COSY

f2 (ppm)

f1 (ppm)

275

BED653-III_p145_12-23-2020.5.ser
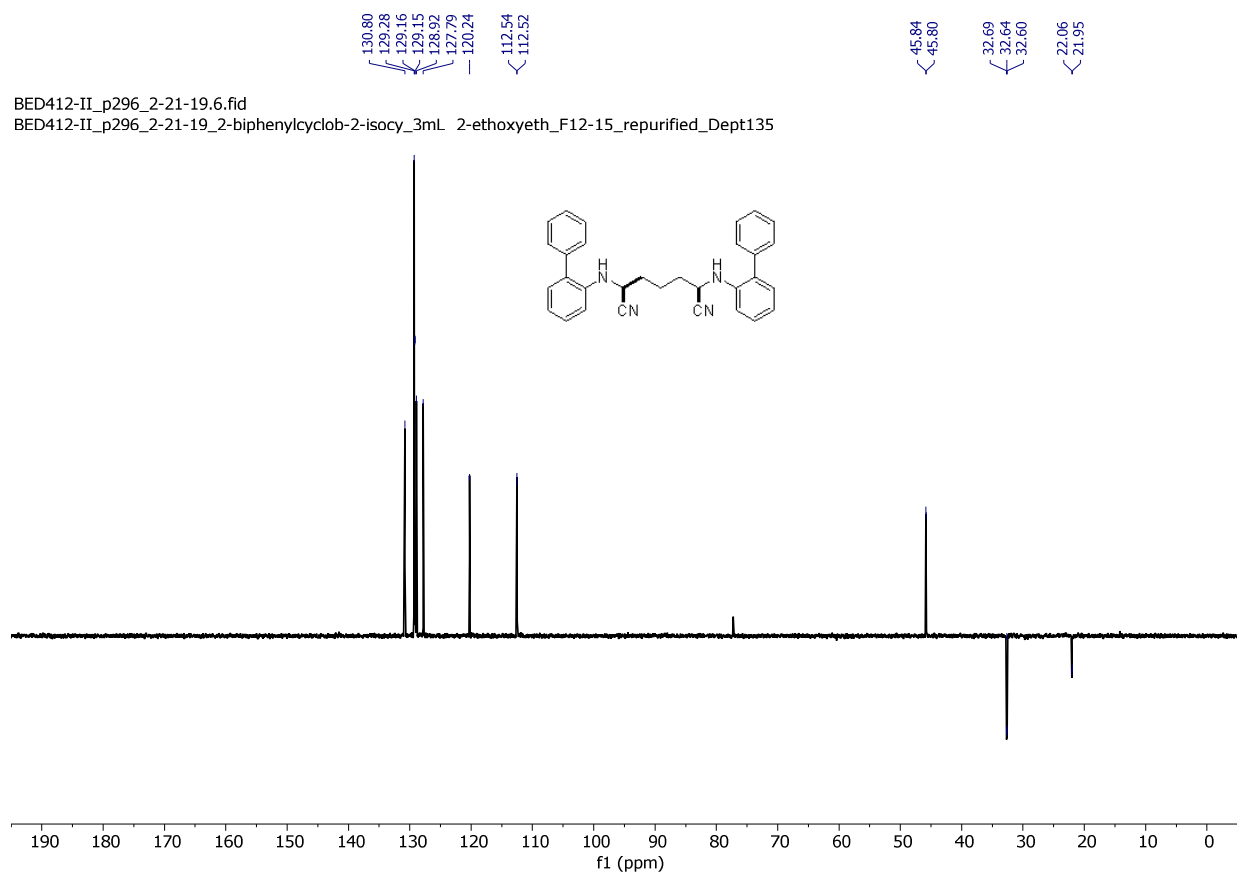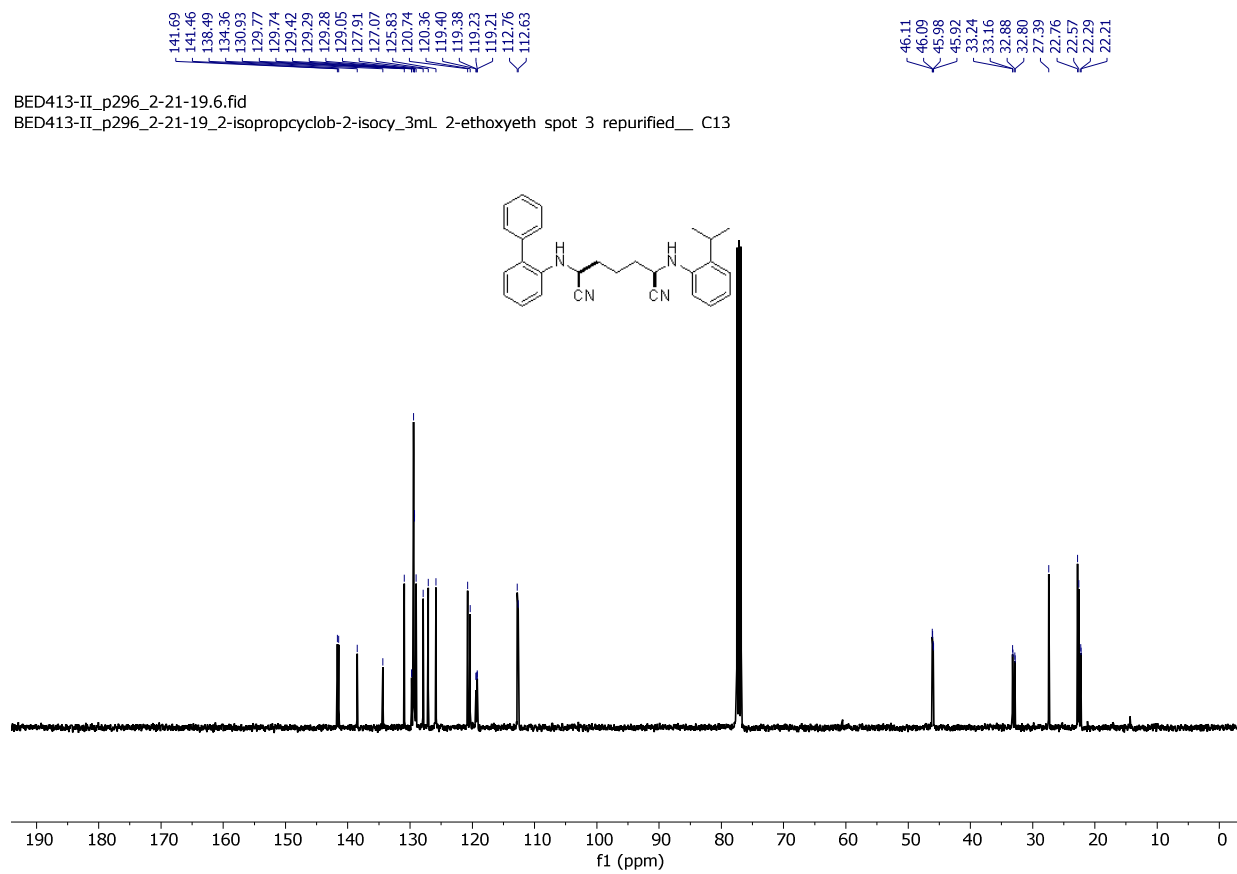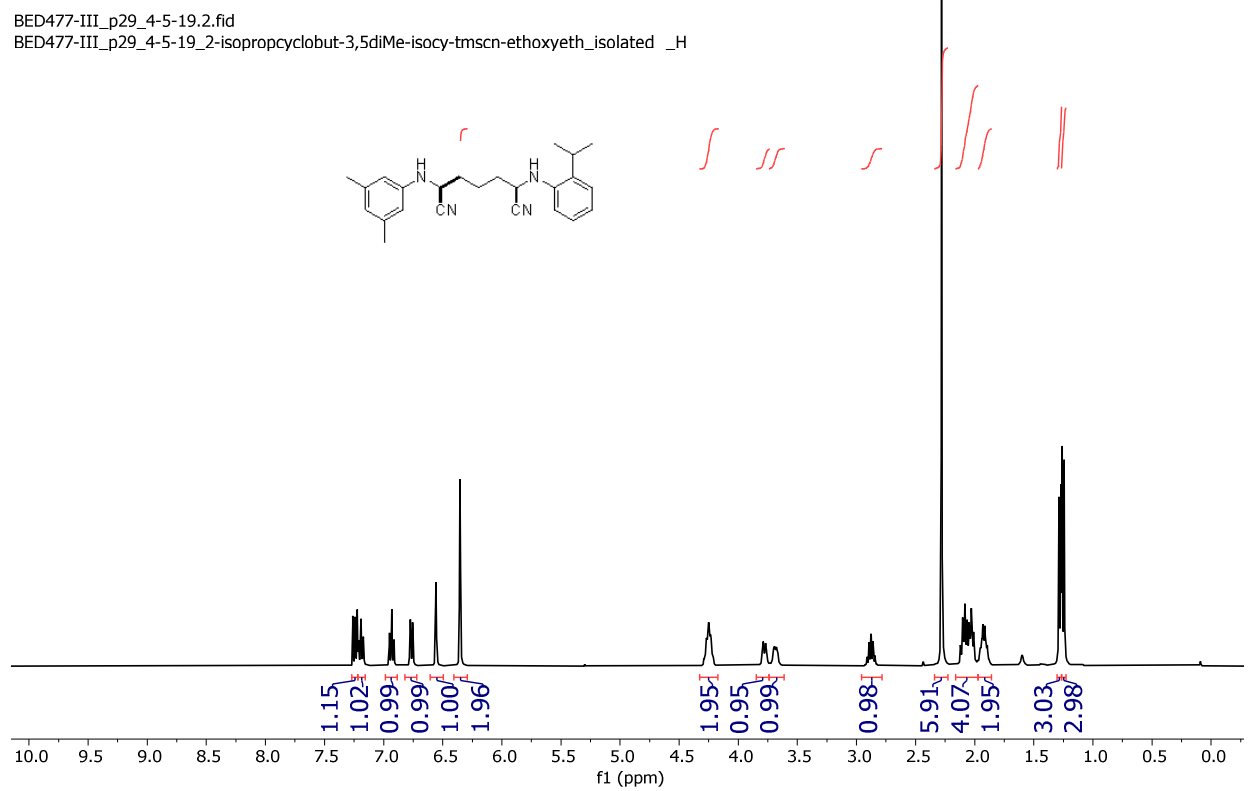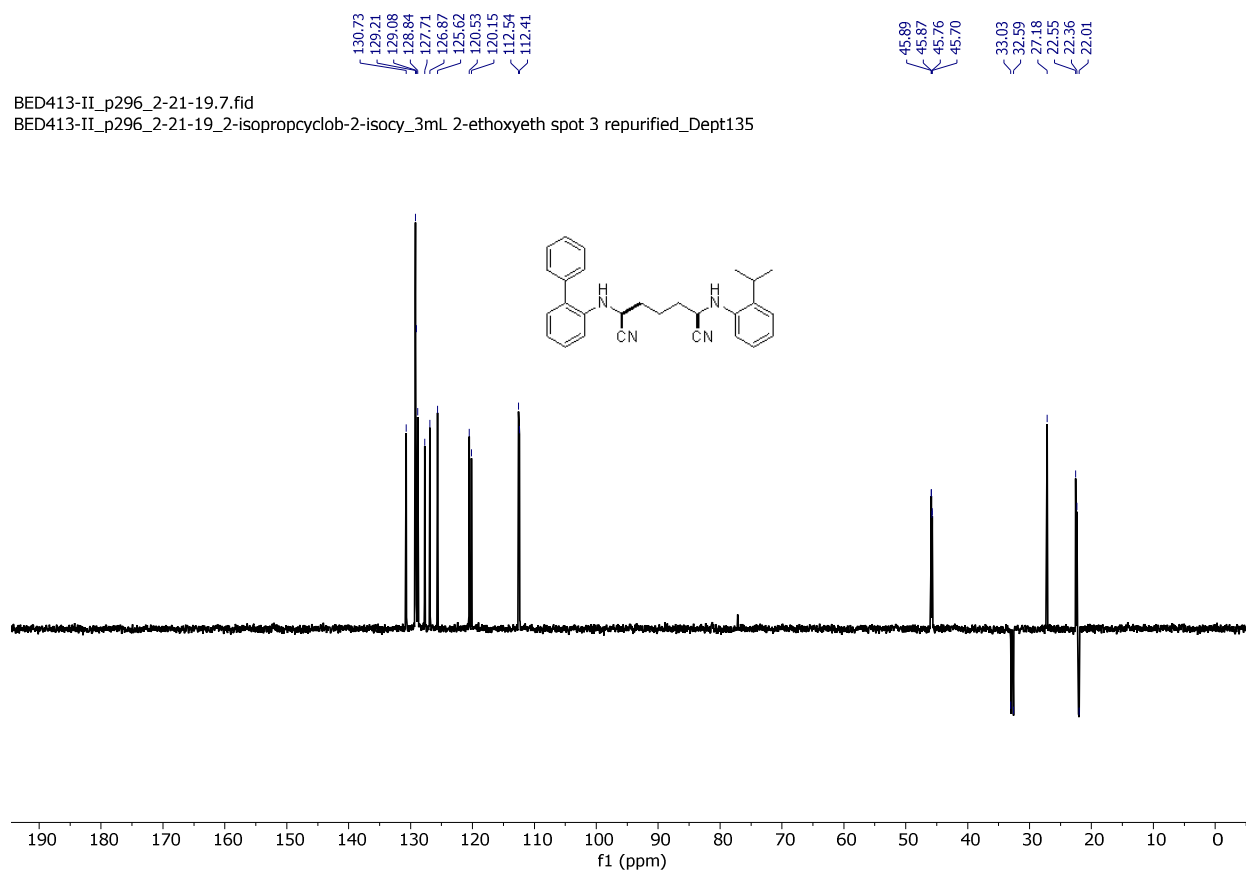BED653-III_p145_12-23-2020_p-tBu-cyclob-2-iso-tmscn-2-ethoxyethanol_spot 6_ HSQC
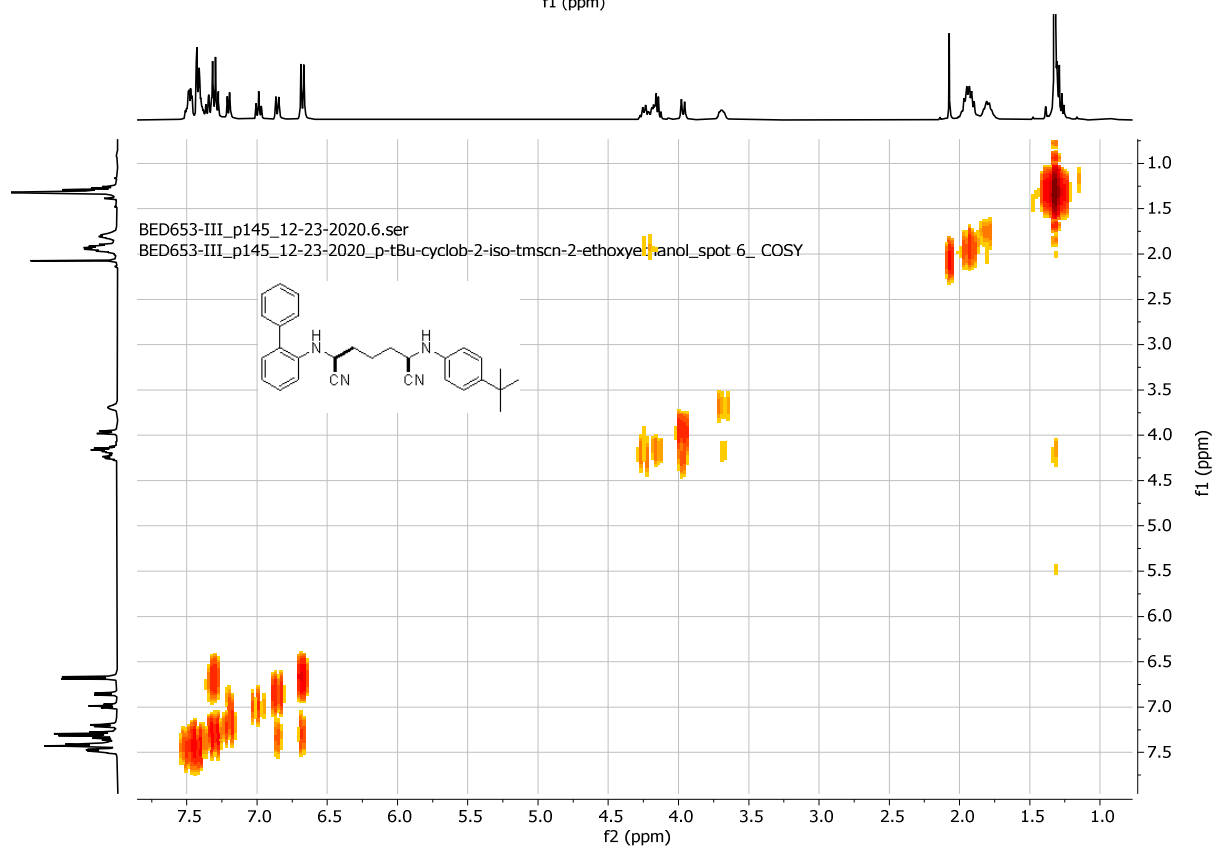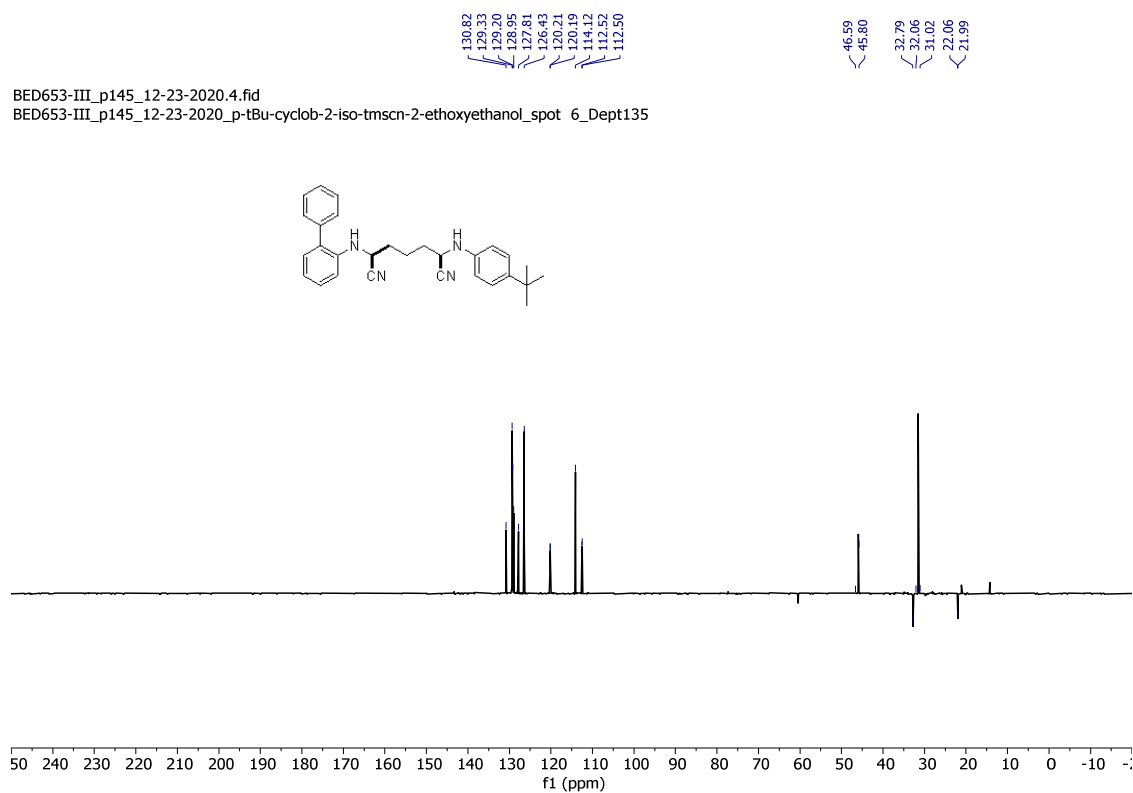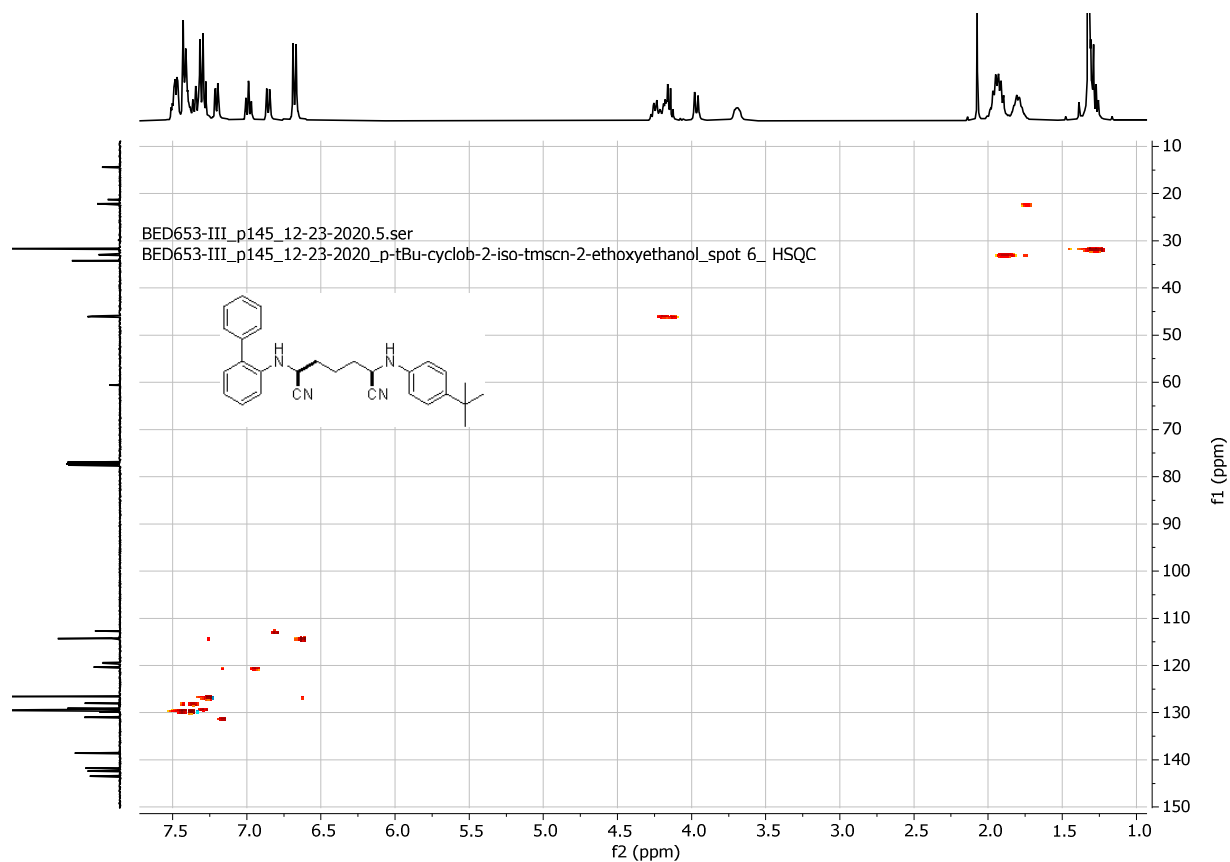
BED412-II_p296_2-21-19.4.fid
BED412-II_p296_7-23-2022_2-biphenylcyclob-2-isocy_3mL 2-ethoxyeth_F12-15 pure_H

141.90
138.71
138.70
131.15
131.14
129.99
129.98
129.63
129.50
129.49
129.26
128.14
120.60
120.58
119.37
119.35
112.89
112.88

46.20
46.15

33.04
32.95

22.40
22.30

f1 (ppm)

BED412-II_p296_2-21-19_2-biphenylcyclob-2-isocy_3mL 2-ethoxyeth_F12-15_repurified_Dept135

130.80
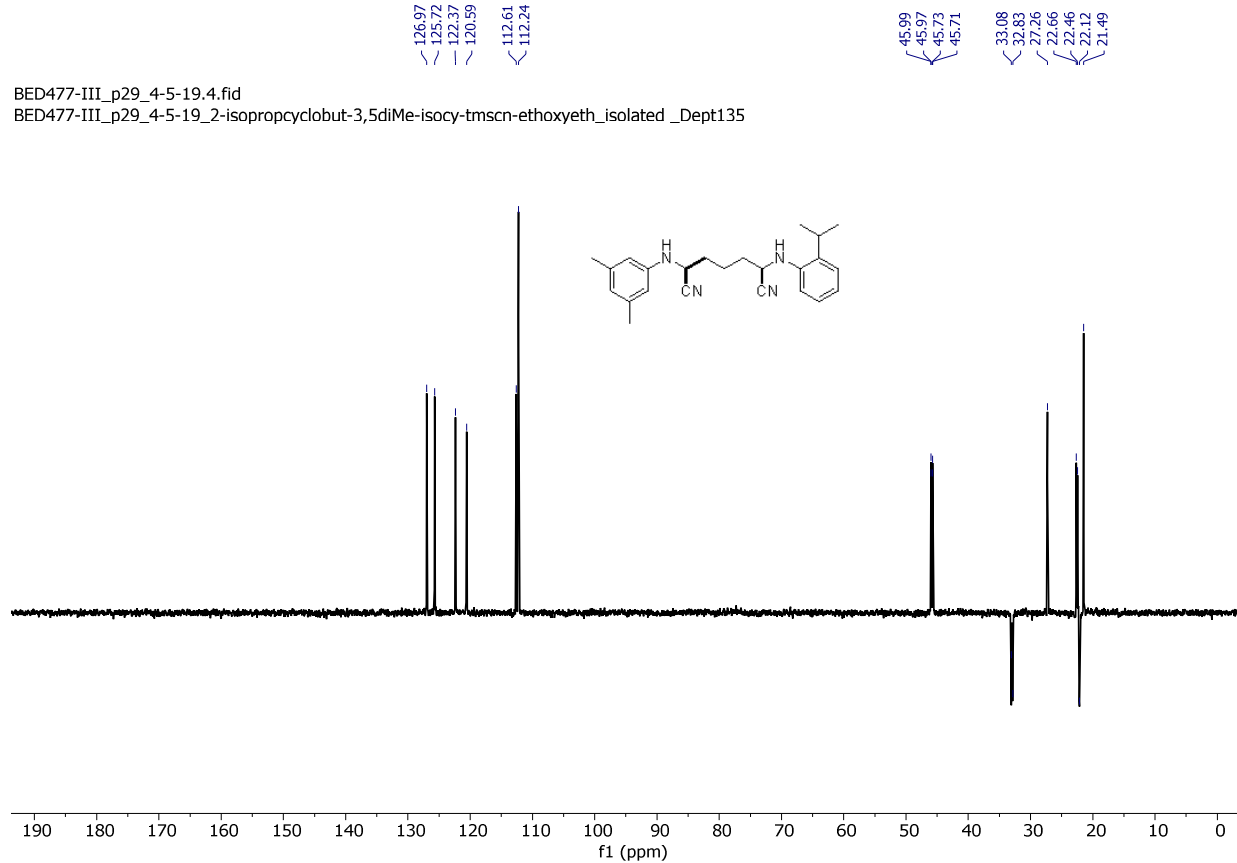129.28
129.16
129.15
128.92
127.79
120.24
112.54
112.52
45.84
45.80
32.69
32.64
32.60
22.06
21.95

f1 (ppm)

BED413-II_p296_2-21-19.5.fid
BED413-II_p296_2-21-19_2-isopropcyclob-2-isocy_3mL 2-ethoxyeth spot 3 repurified_H

1.87
2.79
1.11
0.95
1.98
0.94
1.00
1.00
1.00

2.00
1.00
0.97

1.01

1.72
1.98
2.00
3.15
3.33

f1 (ppm)

278

141.69
141.46
138.49
134.36
130.93
129.77
129.74
129.42
129.29
129.28
129.05
127.91
127.07
125.83
120.74
120.36
119.40
119.38
119.23
119.21
112.76
112.63

46.11
46.09
45.98
45.92
33.24
33.16
32.88
32.80
27.39
22.76
22.57
22.29
22.21

279

130.73
129.21
129.08
128.84
127.71
126.87
125.62
120.53
120.15
112.54
112.41

45.89
45.87
45.76
45.70

33.03
32.59
27.18
22.55
22.36
22.01

f1 (ppm)

1.15
1.02
0.99
0.99
1.00
1.96

1.95
0.95
0.99

0.98

5.91
4.07
1.95

3.03
2.98

f1 (ppm)

BED477-III_p29_4-5-19.3.fid
BED477-III_p29_4-5-19_2-isopropcyclobut-3,5diMe-isocy-tmscn-ethoxyeth_isolated _ C13

145.04
141.74
139.73
134.63
134.61
127.31
126.07
122.71
120.93
119.81
119.79
119.73
119.70
112.96
112.59

46.34
46.32
46.08
46.06
33.45
33.41
33.24
33.18
27.61
23.01
22.81
22.52
22.47
21.84

f1 (ppm)

126.97
125.72
122.37
120.59
112.61
112.24

45.99
45.97
45.73
45.71
33.08
32.83
27.26
22.66
22.46
22.12
21.49

BED477-III_p29_4-5-19.4.fid
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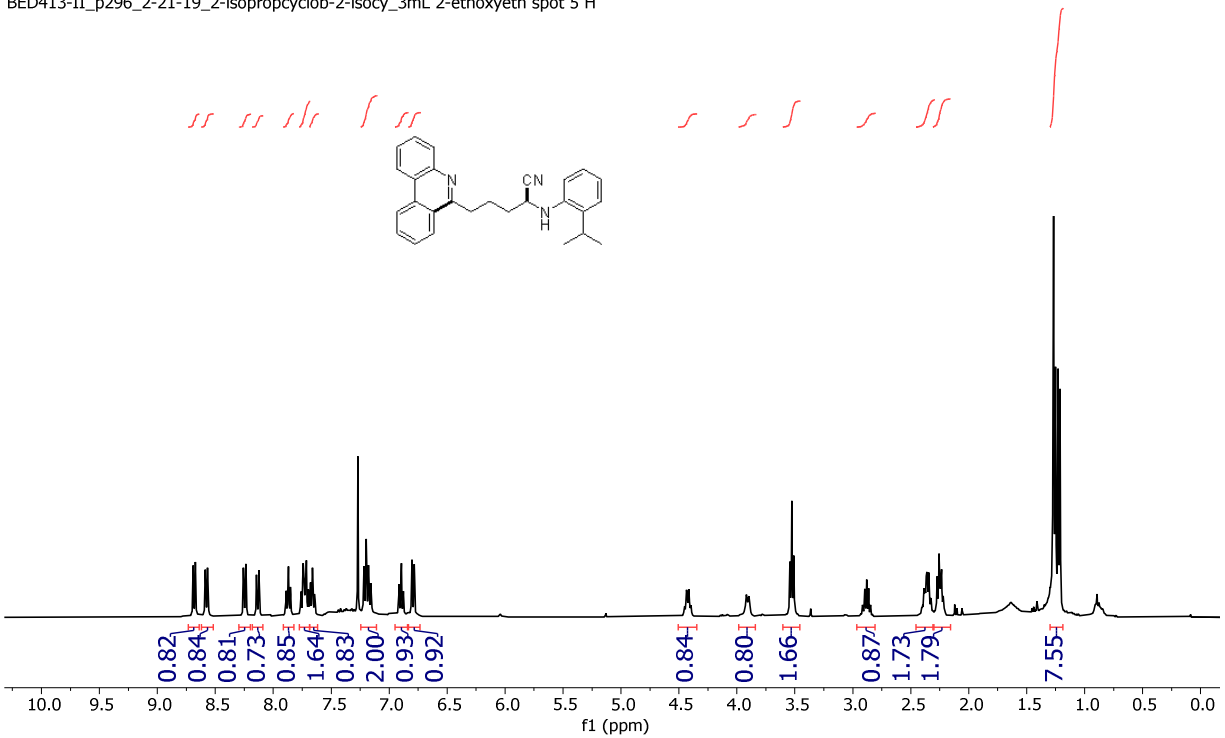

f1 (ppm)

281

BED413-II_p296_2-21-19.4.fid
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0.82
0.84
0.81
0.73
0.85
1.64
0.83
2.00
0.93
0.92
0.84
0.80
1.66
0.87
1.73
1.79
7.55

f1 (ppm)

BED421-III_p1_2-28-19.2.fid
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4.41
2.73
4.37
2.81
1.15
1.08
1.18
1.79
1.79
0.88
0.86
3.74
2.00

f1 (ppm)

282

BED421-III_p1_2-28-19.4.fid
BED421-III_p1_2-28-19_4-Phcyclob-2-isocya-tmscn_ C13

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED421-III_p1_2-28-19.5.fid
BED421-III_p1_2-28-19_4-Phcyclob-2-isocya-tmscn_Dept135

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

283
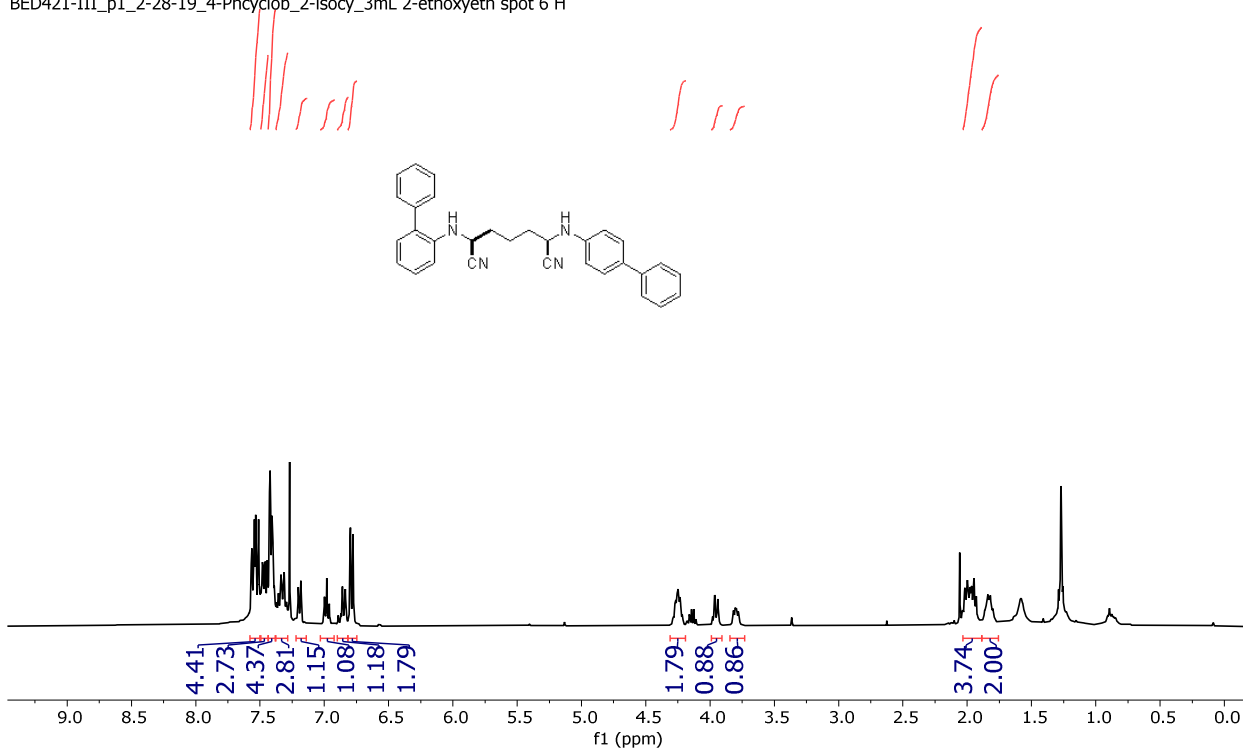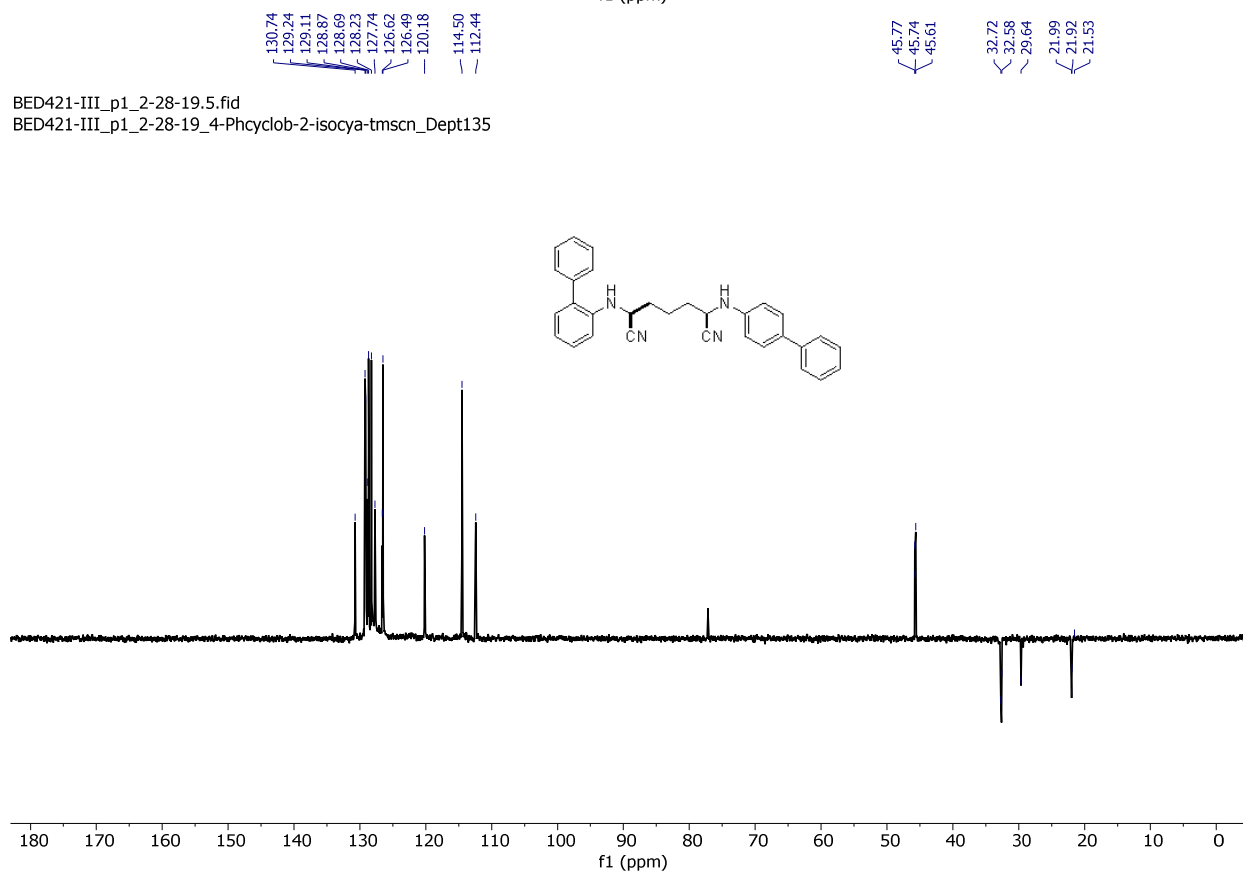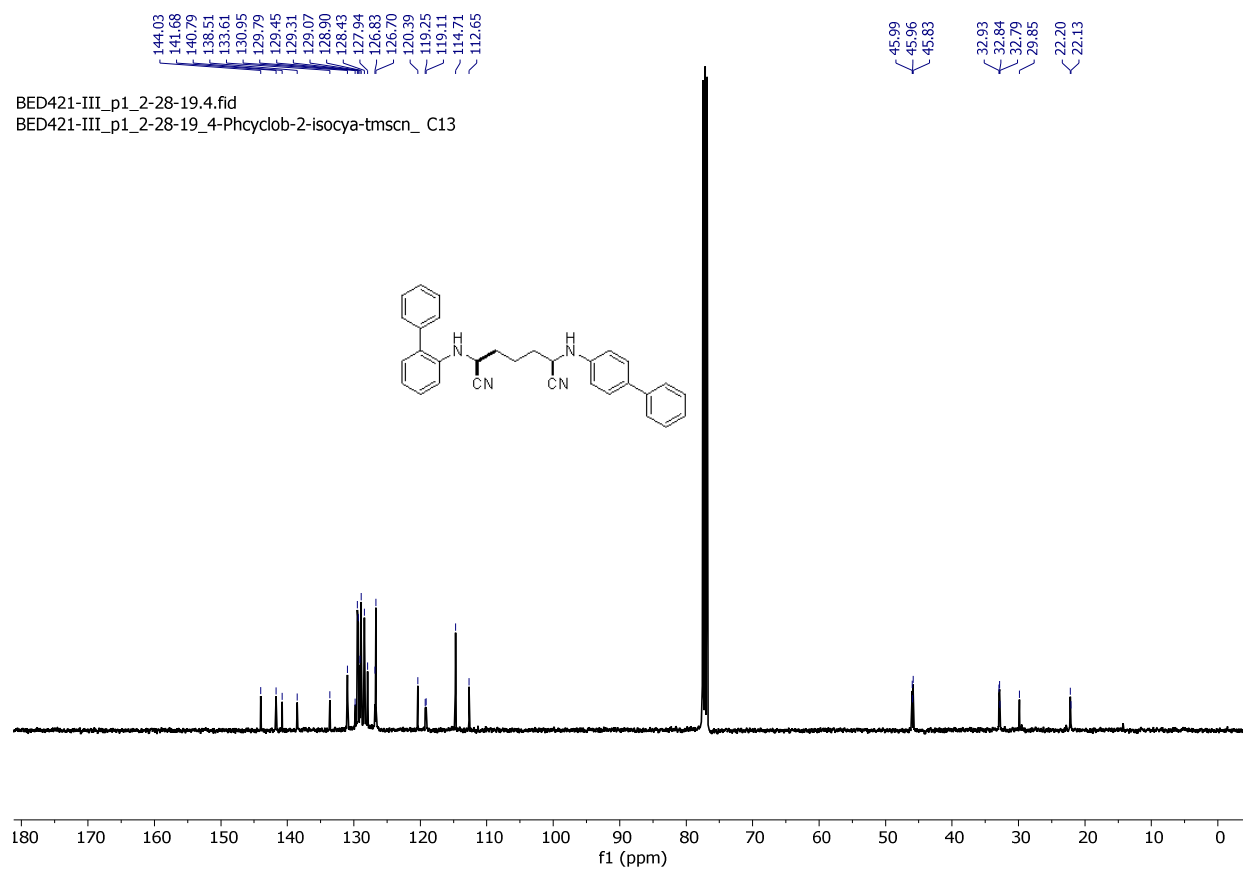
Appendix B

Experimental Data for Chapter 3—Resonance-Assisted Deconstruction/Distal Alkynylation of Strained *N*-Cycloalkane Rings Using Hypervalent Iodine (III) Reagents under Photoredox Catalysis

General Considerations

Unless stated otherwise, all reactions were carried out under a nitrogen atmosphere. Acetonitrile (CH₃CN) was pre–dried over molecular sieves. Toluene and THF were collected under argon from a solvent purification system. Column chromatography was performed using silica gel (230–400 mesh) or neutral alumina gel flash grade 32–63u. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, high–resolution mass spectroscopy (HRMS) or gas chromatography/mass spectroscopy (GC/MS), melting point (when applicable), and (in most cases) IR spectroscopy. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance DPX–300 and Bruker Avance DPX–400. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual proton or carbon signals in CDCl₃ (7.27 ppm, 77.23 ppm), CD₂Cl₂ (5.32 ppm, 54.0 ppm), and DMSO–d₆ (2.50 ppm, 39.51 ppm) at room temperature. 2D NMR experiments were performed on some of the new compounds to establish their structure, including relative configuration. NMR yields were determined using ^{1}H NMR of crude products. IR spectra were recorded (thin film on NaCl plates) on a PerkinElmer Spectrum 100 series instrument. High Resolution Mass spectra were recorded on either a Bruker Ultraflex II TOF/TOF mass spectrometer or a Bruker Apex–Qe mass spectrometer with an ESI source (Fourier Transform Mass Spectrometry). Gas chromatography/mass spectroscopy analyses were performed on an Agilent 6890N Network GC System/5973 inert Mass Selective Detector. Gas chromatography analyses were performed using

a Shimadzu GC–2010 Plus instrument. When applicable, melting point ranges (m.p.) were recorded using a Stuart SMP10 Melting Point Apparatus and were uncorrected.

B1. Synthesis of the Amines and Hypervalent Iodine Reagents Used

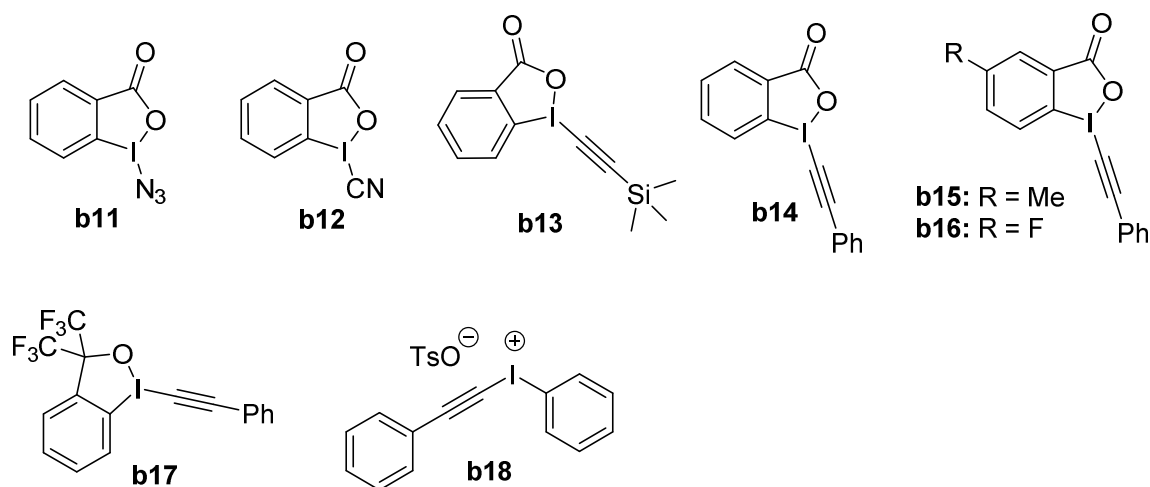**Amines investigated:**
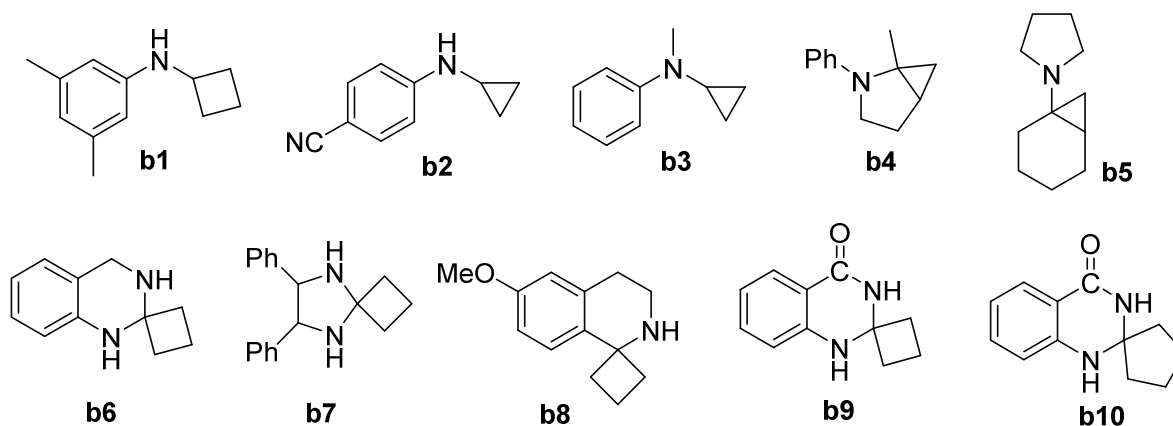
Hypervalent iodine reagents used

Figure B1.1. Structures of Cycloalkylamines and Hypervalent Iodine Reagents Investigated

Figure B1.1 above shows the structures of the substrates used in the titled study in Chapter 3. All the amine substrates are already known compounds and were synthesized using procedures reported in literature. The spectroscopic/spectrometric data (^{1}H NMR, ^{13}C NMR, MS) matched

with those reported in the relevant adapted works. We previously reported the syntheses and characterization of compounds **b1-b4** in our earlier works.[16, 18, 21, 134] Compound **b5** was synthesized by following the reported method of enamine cyclopropanation by Yan and coworkers using dichloromethane as electrophilic carbene equivalent via a $CH_2Cl_2−TiCl_4−Mg$ system.[357] The spirocyclic aminals **b6** and **b7** were accessed via condensation of cyclobutanone with *o*-aminobenzylamine and 1,2-diphenylethylenediamine respectively.[358] Substrate **b8** was synthesized by adapting the procedure published by Fujioka and coworkers.[359] Spiro-cycloalkane-dihydroquinazolinones **b9** and **b10** were obtained by condensing *o*-aminobenzamide with cyclobutanone and cyclopentanone respectively under reflux in the presence of *p*-toluenesulfonic acid. The spectroscopic data of **b10** corresponds with that reported in literature.[360, 361] The synthesis of **b9** is described below. The alkynyl hypervalent iodine reagents (AHIRs) were also synthesized by following reported procedures and the spectroscopic data of the already reported ones (i.e. **b11-b14** and **b17-b18**) matched with those reported in the relevant publications.[278, 362] The syntheses of AHIRs **b15** and **b16** by adapting the procedure[278] reported for the preparation of unsubstituted PhEBX are described hereinafter.

Synthesis of 1'H-spiro[cyclobutane-1,2'-quinazolin]-4'(3'H)-one (b9):
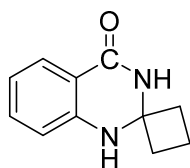
A round-bottom flask containing 2-aminobenzamide (2.0 g, 14.7 mmol), cyclobutanone (1.32 mL, 17.6 mmol) and catalytic amount of *p*-toluenesulfonic acid monohydrate (16.5 mg, 0.5 mol%) in chloroform (36 mL) was fitted to a water condenser and refluxed at 75 ºC for 4 hours. Upon the completion of the reaction, as monitored by TLC, the mixture was concentrated to give a solid, filtered over filter paper, and washed with water and ethyl acetate to form an off-white solid. Recrystallization of the crude solid product with methanol afforded the desired product **b9** as a shiny off-white crystals (1.7 g, 61.2%).

^{1}H NMR (400 MHz, DMSO) δ 8.49 (s, 1H), 7.57 (dd, J = 1.6, 7.8 Hz, 1H), 7.33 − 7.20 (m, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.65 (t, J = 7.4, 7.4 Hz, 1H), 2.25 (dddd, J = 6.5, 8.9, 11.9, 35.4 Hz, 4H), 1.86 − 1.60 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 163.7, 147.5, 133.9, 127.8, 117.6, 115.2, 115.2, 70.5, 38.4, 12.1. HRMS (ESI) m/z [M+H]$^+$, calc'd for $C_{11}H_{12}N_2O$ 189.1022; found 189.1024.

General Procedure GPB1: Synthesis of Substituted Phenyl Ethynyl Benziodoxolones b15 and b16:
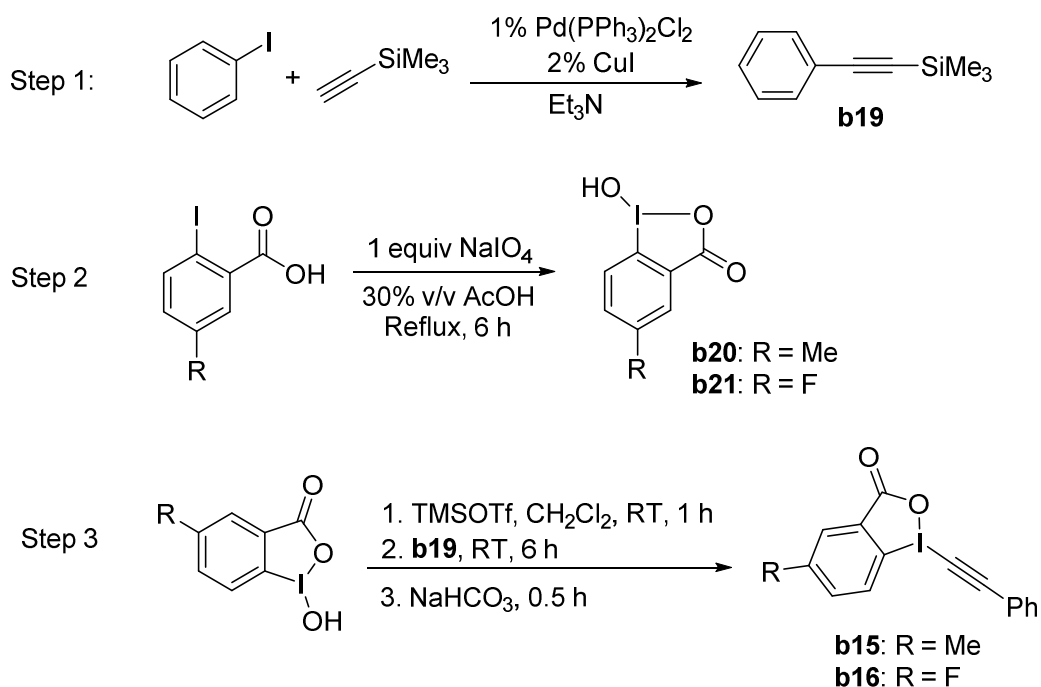

Scheme B1.1. Preparation of Substituted Phenyl Ethynyl Benziodoxolones

Compounds **b15** and **b16** in **Scheme B1.1** above were synthesized in 3 steps as follows:

Step 1: A solution of trimethylsilyl acetylene (10.5 mL, 75 mmol) was added dropwise by cannula to a mixture of phenyl iodide (5.6 mL, 50.0 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (350 mg, 0.5 mmol), and copper(I) iodide (190 mg, 1.0 mmol) in of triethylamine (120 mL, 75 mmol). The reaction mixture was stirred at room temperature for 1-3 hours, after which it was concentrated and purified using column chromatography to obtain the desired trimethylsilyl alkyne **b19** as a yellow oil (6.2 g, 72%). The ^{1}H and ^{13}C NMR data were consistent with that reported in literature.[278]

Step 2: NaIO$_4$ (2.5 g, 9 mmol, 1.0 equiv.) and 5-substituted-2-iodobenzoic acid (2.5 g, 9 mmol, 1.0 equiv.) were suspended in 30% (v:v) aqueous AcOH (23 mL). After the reaction mixture was stirred vigorously and refluxed for 4 h, protecting from light, cold water (60 mL) was then added and allowed to cool to RT. After 1 h, the crude solid product was collected by filtration, washed with ice water (3 x 15 mL) and then with acetone (3 x 15 mL). After air-drying in the dark, the corresponding 5-substituted hydroxybenziodoxole **b20** or **b21** (BI-OH) was obtained as a white solid. The spectroscopic data of the product were consistent with that reported in literature.[278]

Step 3: Hydroxybenziodoxole (BI-OH, 1.0 equiv.) was suspended in CH$_2$Cl$_2$ at room temperature, and then trimethylsilyl triflate (1.1 equiv.) was added. Trimethylsilyl alkyne was added after the resulting yellow liquid had been stirred for one h (1.1 equiv.). Saturated NaHCO$_3$ (100 mL) was added after the liquid had been stirring for 6 h at room temperature. The mixture was then stirred vigorously for 30 minutes. Next, it was filtered to give a solid residue, and the filtrate was washed with saturated NaHCO$_3$, and dried over anhydrous Na$_2$SO$_4$. The organic layers were combined and concentrated in vacuo to give a second batch of solid which was added to the previously obtained solid and recrystallized in CH$_3$CN.
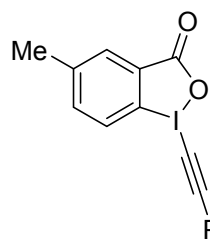
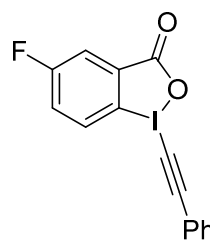**5-methyl-1-(phenylethynyl)-1l3-benzo[d][1,2]iodaoxol-3(1H)-one (b15):**

Obtained as pale yellow crystals (1.5 g, 49%). Mp 153-155 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.21 (d, J = 2.2 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.65 – 7.52 (m, 3H), 7.52 – 7.34 (m, 3H), 2.49 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.0, 142.5, 135.9, 133.1, 132.9, 131.3, 130.8, 128.8, 126.2, 120.7, 112.6, 106.3, 50.1, 20.8. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{16}$H$_{11}$IO$_2$ 362.9877; found 362.9875.

5-fluoro-1-(phenylethynyl)-1l3-benzo[d][1,2]iodaoxol-3(1H)-one (b16):

Obtained as off-white crystals (890 mg, 28%). Mp 147 ºC (lit.,[363] 147-152 ºC). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.20 (dd, J = 4.2, 9.0 Hz, 1H), 8.13 (dd, J = 2.9, 8.0 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.55 – 7.41 (m, 4H). ^{19}F NMR (400 MHz, CDCl$_3$) δ -110.02.

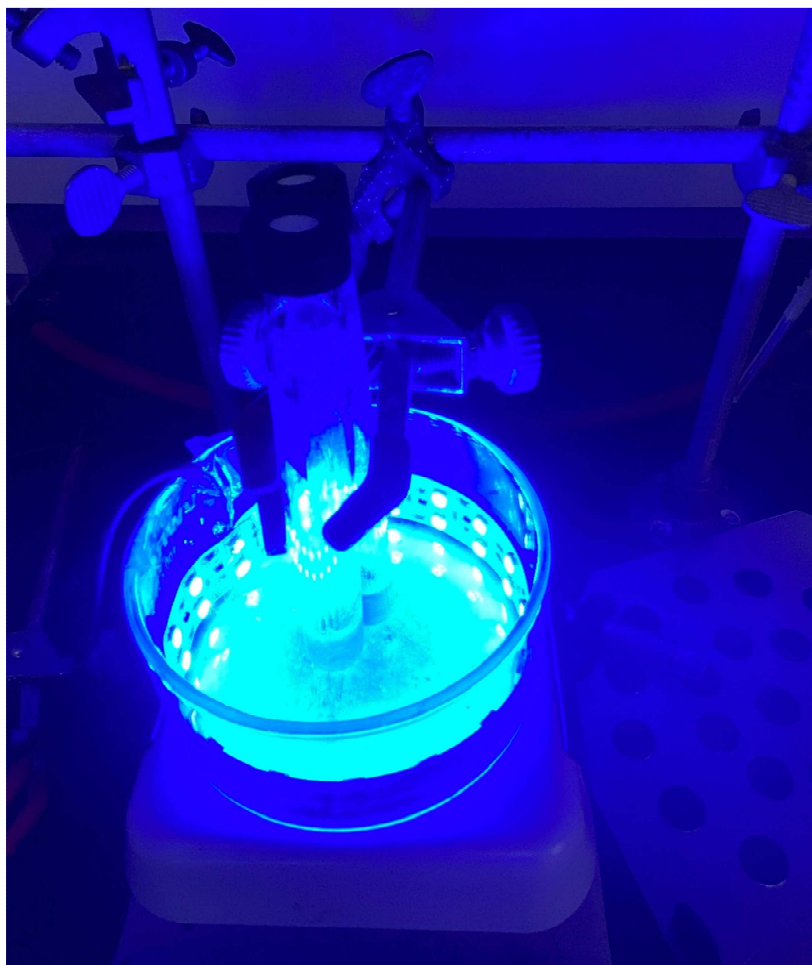**B2. General Procedure GPB2: Resonance-Assisted Deconstruction/Distal Alkynylation Photochemistry**


Figure B2.1. Setup of the Photochemistry for Ring-opening/Distal Alkynylation Reaction

Procedure: An oven-dried test tube equipped with a stir bar was charged with Ir(dtbbpy)(ppy)$_2$PF$_6$ (1.8 mg, 2 mol%), the amine substrate (0.1 mmol), alkynyl hypervalent iodine reagent (0.2 mmol), and 1 mL 1,2-dichloroethane or suitable solvent. The test tube was capped with a Teflon screw cap and followed by degassing by Freeze-Pump-Thaw cycles several times. The reaction mixture was then irradiated with two-strip blue LEDs. The test tube was positioned at the center of the circle of blue LED strips as shown in Figure **5.6.1** above. After reaction was complete, as

monitored by TLC, the mixture was diluted with diethyl ether and filtered through a short pad of silica gel. The solution was concentrated and the residue was purified by silica gel flash chromatography to isolate the product(s).
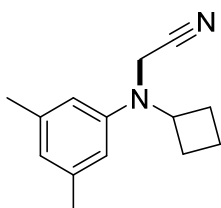
2-(cyclobutyl(3,5-dimethylphenyl)amino)acetonitrile: Following **GP5B2** with 3,5-dimethyl-*N*-cyclobutylaniline (35.1 mg, 0.2 mmol), trimethylsilylethynylbenziodoxolone TMS-EBX (0.4 mmol), and trimethylsilyl cyanide TMSCN (0.8 mL, 0.6 mmol), the titled product was isolated as colorless liquid (16.6 mg, 39%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 6.6 (s, 1H), 6.50 (s, 1H), 4.10 (s, 2H), 3.91 (quin, 1H), 2.31 (s, 8H), 2.01 (quin, 2H), 1.81-1.70 (m, 2H); ^{13}C NMR (400 MHz, CDCl$_3$) δ: 146.95, 138.88, 123.80, 116.45, 116.11, 53.93, 39.03, 28.65, 21.60, 14.22. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{14}$H$_{18}$N$_2$ 215.1543; found 215.1545.
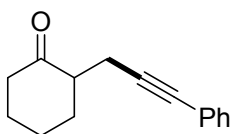
2-(3-phenylprop-2-yn-1-yl)cyclohexan-1-one: Obtained as a pale yellow liquid (14.6 mg, 35%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 (dddd, *J* = 1.5, 2.6, 3.9, 6.7 Hz, 2H), 7.33 – 7.18 (m, 3H), 3.09 (tdd, *J* = 2.8, 4.5, 7.0, 7.0 Hz, 1H), 2.83 – 2.77 (m, 2H), 2.66 (ddd, *J* = 3.5, 9.4, 16.3 Hz, 1H), 2.53 (dddd, *J* = 1.0, 3.1, 8.1, 16.2 Hz, 1H), 2.07 – 1.88 (m, 3H), 1.85 – 1.64 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 212.5, 131.0, 128.4, 128.1, 123.4, 91.1, 83.6, 49.1, 43.6, 36.4, 28.0, 27.5, 24.1. The spectral data corresponds to that reported in literature.
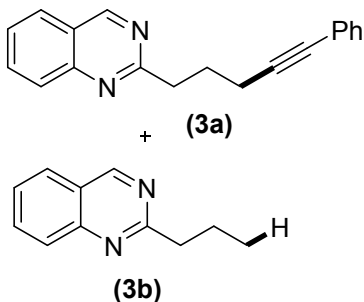
3a + 3b: Mixture of the desired product **3a** and the side product **3b** was isolated in the ratio **3a:3b** = 1.8:1 from the reaction conducted in DCE without additives. ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.42 (s, 1H), 9.41 (s, 1H), 8.14 (dd, 1H), 8.04

(dd, 2H), 7.92 (tt, 3H), 7.62 (m, 2H), 7.49 (m, 1H), 7.35 (qd, 3H), 7.25 (m, 2H), 3.34 (t, 3H), 3.15 (m, 1H), 2.60 (t, 2H), 2.28 (m, 3H), 1.98 (m, 1H), 1.05 (t, 2H). LCMS (ESI) *m/z* [M+H]$^+$, calc'd for $C_{11}H_{12}N_2$ (**3b**) 172.1 (retention time 2.12 mins), found 173.1; LCMS (ESI) *m/z* [M+H]$^+$, calc'd for $C_{19}H_{16}N_2$ (**3a**) 272.1 (retention time 3.60 mins), found 273.2.
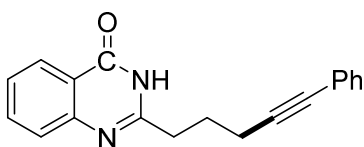
2-(5-phenylpent-4-yn-1-yl)quinazolin-4(3H)-one: Pale brown solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.97 (s, 1H), 8.25 (m, 1H), 7.76 (m, 2H), 7.41 (m, 3H), 7.25 (m, 3H), 3.03 (t, 2H), 2.66 (t, 2H), 2.25 (p, 2H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 170.63, 164.57, 142.05, 135.30, 133.37, 131.94, 128.54, 128.53, 128.33, 128.04, 126.98, 126.71, 123.97, 120.79, 89.05, 82.21, 34.97, 26.52, 19.44. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for $C_{19}H_{16}N_2O$ 289.1335; found 289.1137.
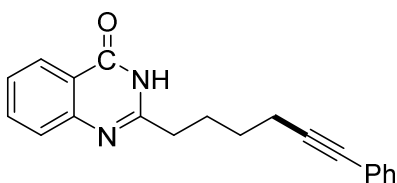
2-(6-phenylhex-5-yn-1-yl)quinazolin-4(3H)-one : Pale brown solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.21 (s, 1H), 8.31 (d, 1H), 7.79 (m, 2H), 7.49 (m, 1H), 7.38 (m, 2H), 7.26 (m, 3H), 2.88 (m, 2H), 2.54 (m, 2H), 2.10 (m, 2H), 1.83 (m, 3H). HRMS (ESI) *m/z* [M+H]$^+$, calc'd for $C_{20}H_{18}N_2O$ 303.1492; found 303.1493.
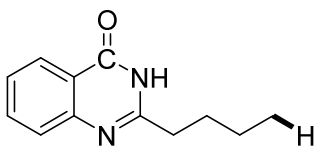
2-butylquinazolin-4(3H)-one: White solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.38 (s, 1H), 8.29 (dd, J = 1.5, 8.0 Hz, 1H), 7.88 – 7.63 (m, 2H), 7.48 (td, J = 1.3, 6.9, 7.5 Hz, 1H), 2.80 (t, J = 7.9, 7.9 Hz, 2H), 1.88 (dq, J = 7.6, 7.6, 7.7, 9.3 Hz, 2H), 1.50 (dt, J = 7.4, 7.4, 14.8 Hz, 2H), 1.01 (t, J = 7.3, 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.22, 157.15, 149.69, 135.17, 127.51, 126.77, 126.61, 120.89, 36.02, 30.05, 29.94, 22.73, 14.11. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for $C_{12}H_{14}N_2O$ 203.1179; found 203.1178.

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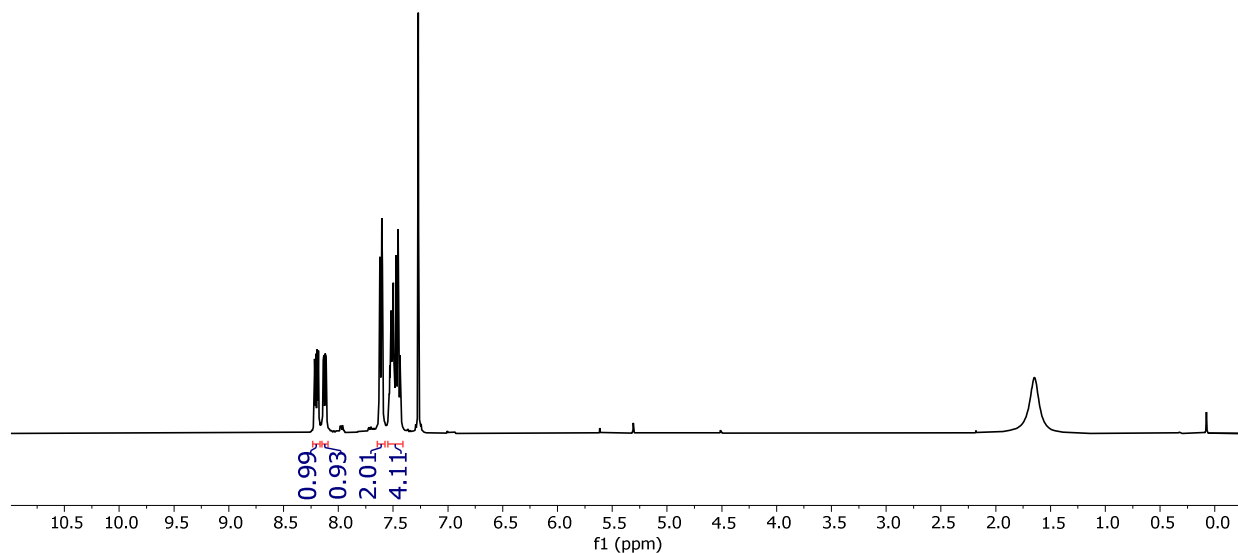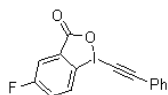
(7) Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. Visible-light-induced chemoselective deboronative alkynylation under biomolecule-compatible conditions. *Journal of the American Chemical Society* **2014**, *136* (6), 2280-2283.

(8) Gonzalez, D.; Brand, J.; Mondiere, R.; Waser, J. Ethynylbenziodoxolones (EBX) as Reagents for the Ethynylation of Stabilized Enolates. *Advanced Synthesis & Catalysis* **2013**, *355* (8), 1631-1639, Article. DOI: 10.1002/adsc.201300266.
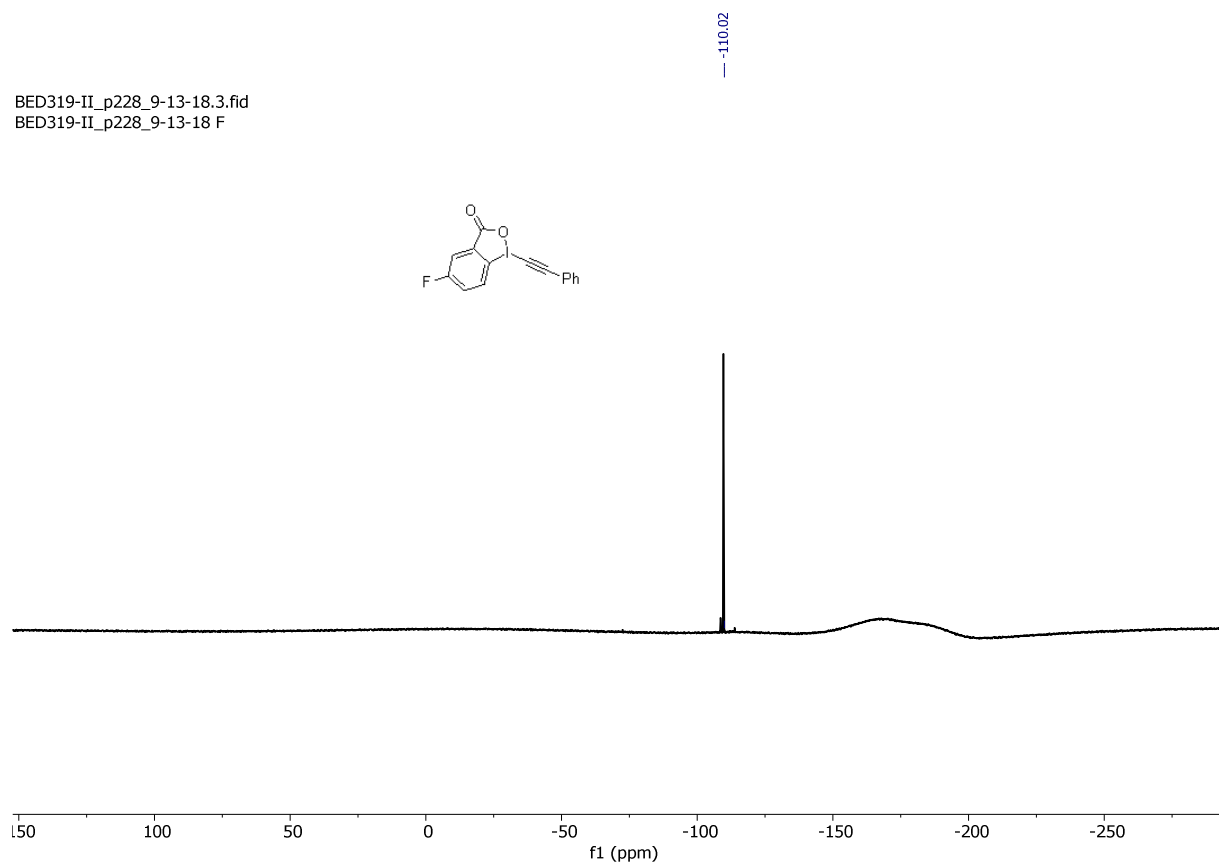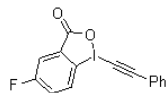
B.4. NMR Spectra for Chapter 3

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BED319-II_p228_9-13-18_5-Fluoro PhEBX filter paper H check

294

—110.02

0.97 0.92 2.81 2.77 3.00

BED320-II_p228_7-21-2022.2.fid
BED320-II_p228_7-21-2022_5-Methyl PhEBX_ C13

167.02
142.54
135.89
133.10
132.91
131.29
130.76
128.82
126.18
120.75
112.56
106.29
50.11
20.82

f1 (ppm)
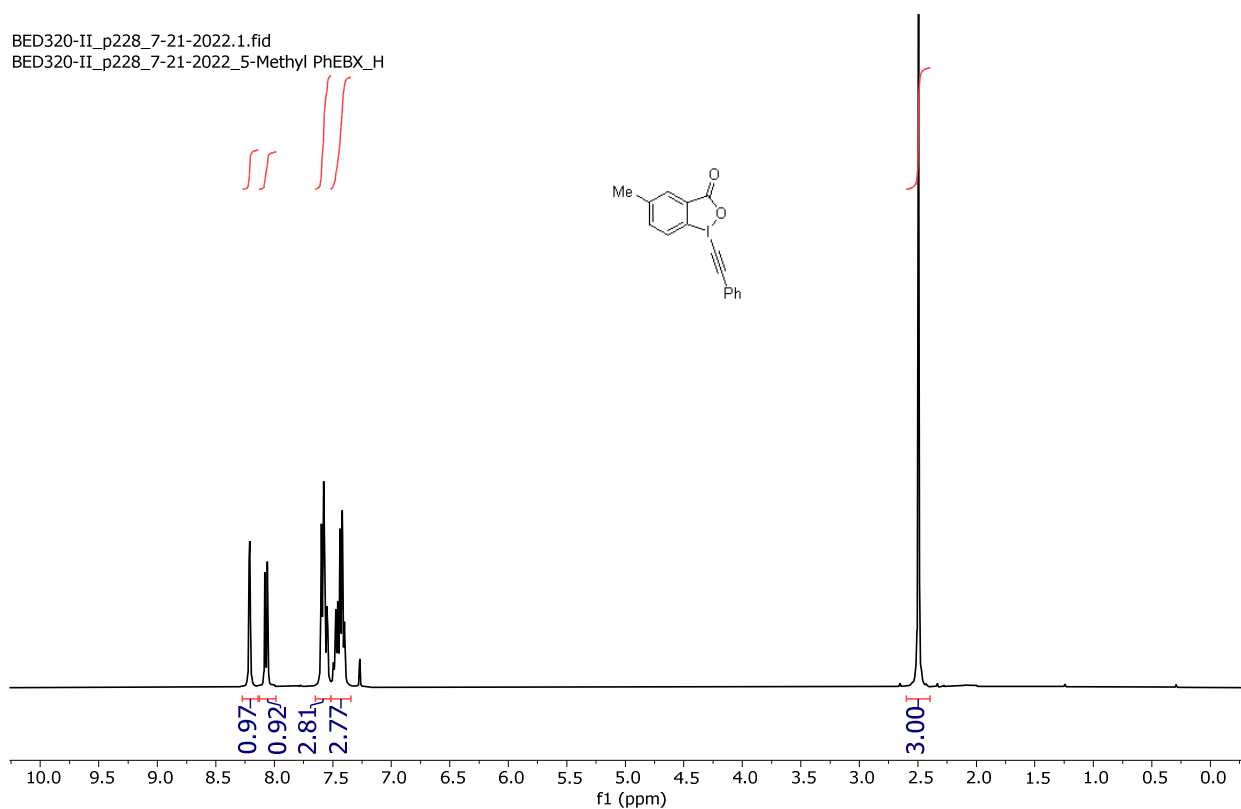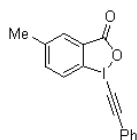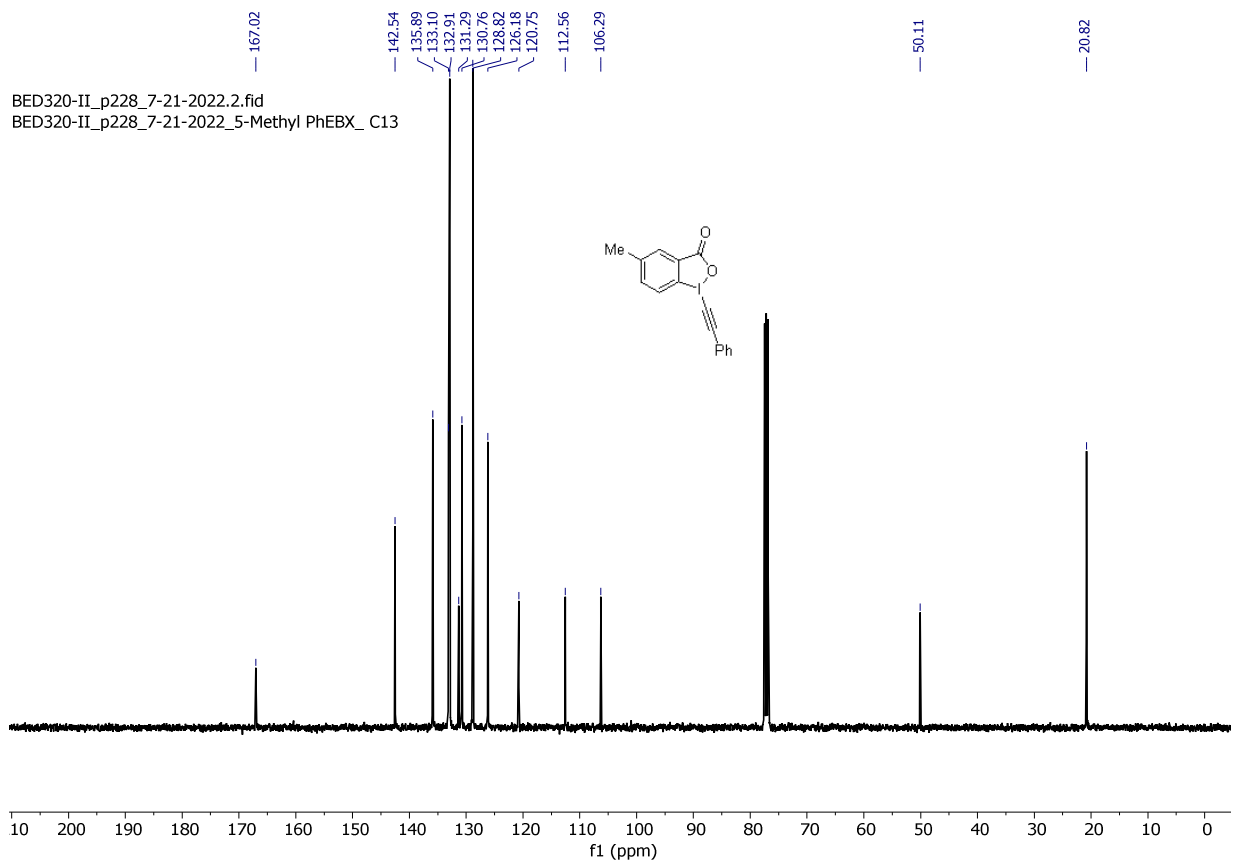
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1.00
1.04
1.03
1.00
1.06
4.12
2.05

f1 (ppm)

296

163.69
147.51
133.85
127.81
117.59
115.22
115.16
70.49
38.45
12.07
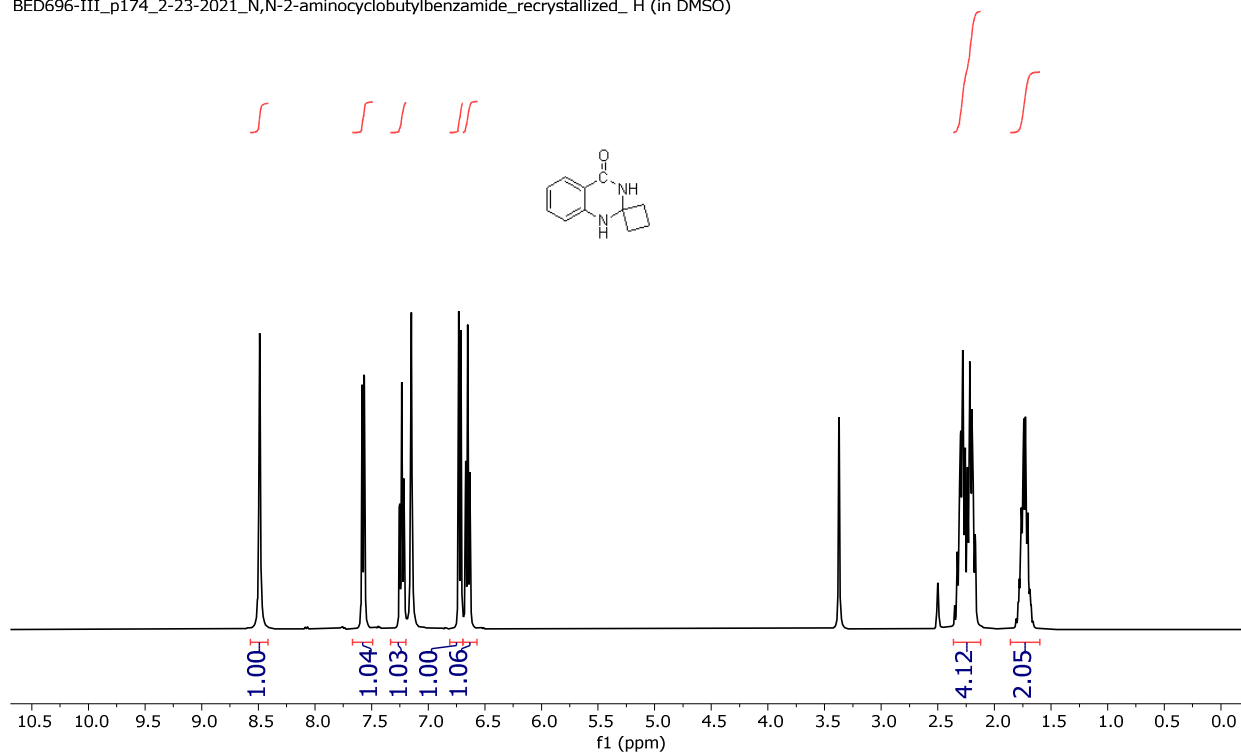
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50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

133.69
128.06
117.42
114.98
38.27
11.90
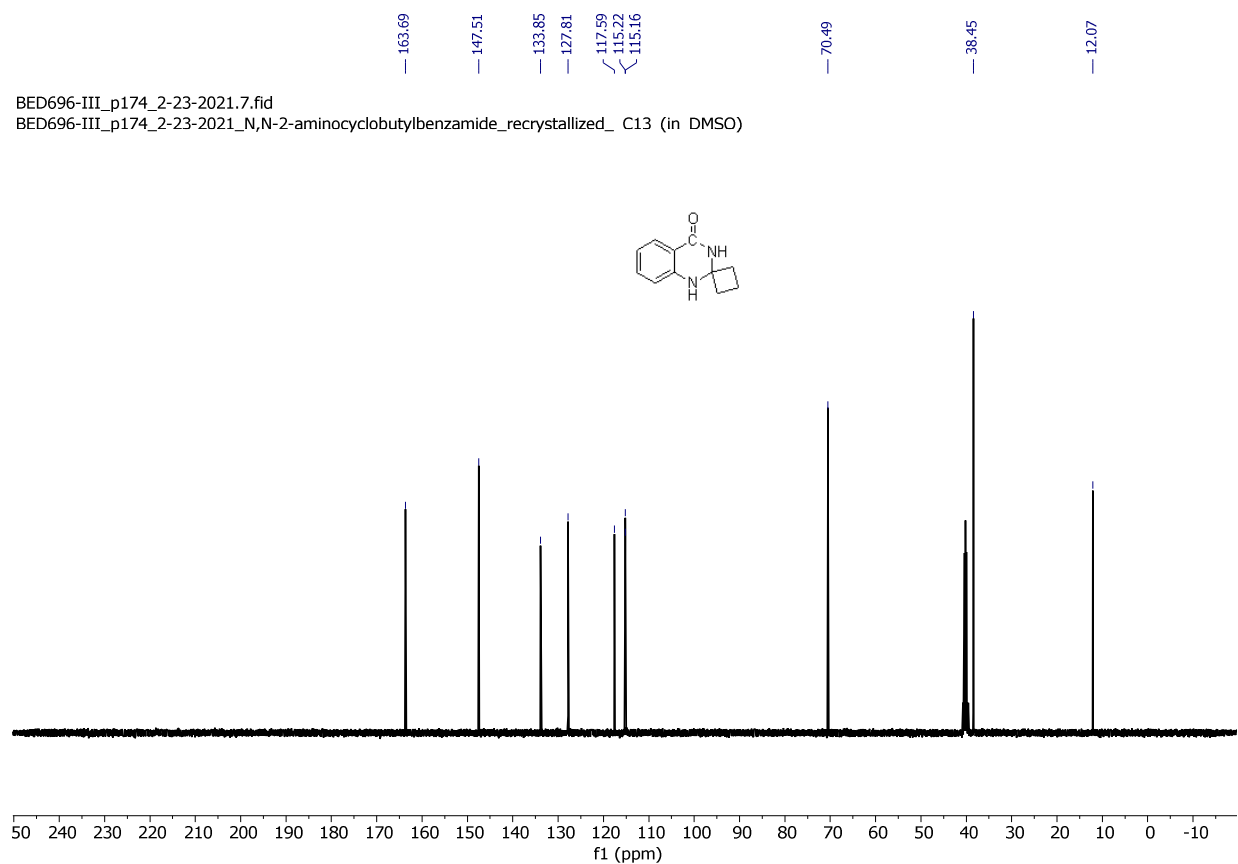
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50 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -
f1 (ppm)

297

BED 710
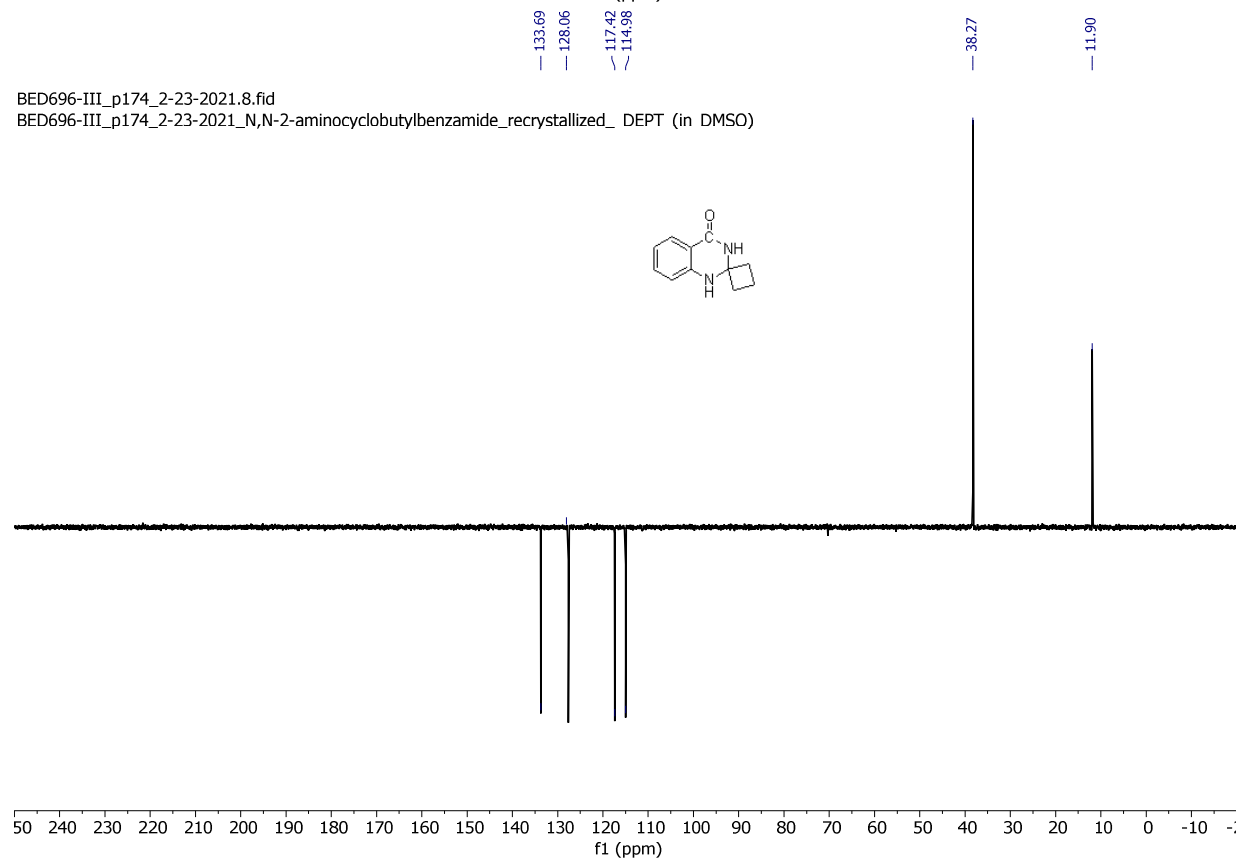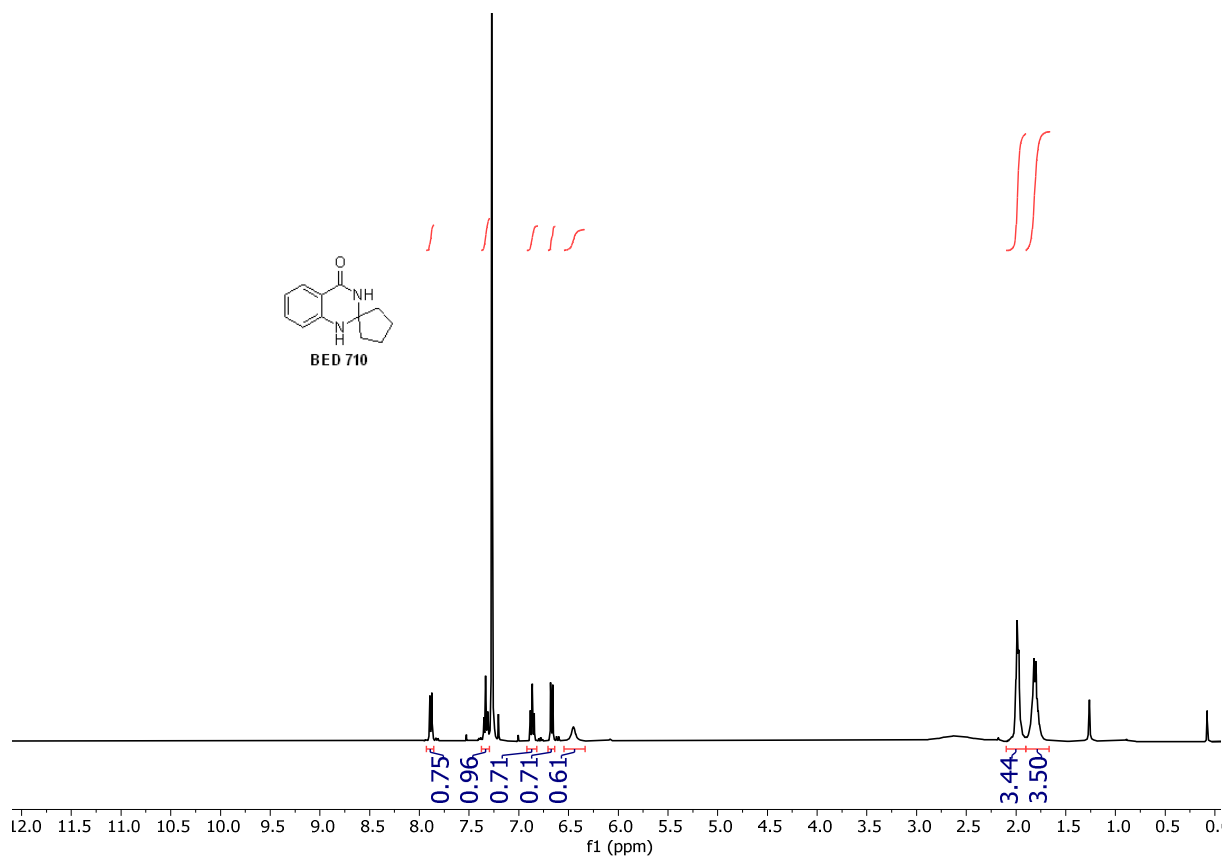
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BED141_F14-16_cyclobut-trimethylsilylethynylbenziodoxolone_MeOH_6-29-17 C13

146.96
138.15
124.34
116.45
116.11
54.71
39.03
28.65
21.60
14.22

f1 (ppm)

BED141_F14-16_cyclobut-trimethylsilylethynylbenziodoxolone_MeOH_6-29-17.5.fid
BED141_F14-16_cyclobut-trimethylsilylethynylbenziodoxolone_MeOH_6-29-17 dept

123.80
115.60
54.37
40.08
28.64
20.86
15.70

f1 (ppm)

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BED141_F14-16_cyclobut-trimethyls___odoxolone_MeOH__6-29-17 COSY

BED141_F14-16_cyclobut-trimethyls___odoxolone_MeOH_6-29-17.7.ser
BED141_F14-16_cyclobut-trimethyls___odoxolone_MeOH_6-29-17 HSQC

(3a)

+

(3b)

Arkansas Statewide Mass Spectrometry Facility

LC Chromatogram

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Sample id#: 1840
Instrument: Shimadzu QQQ
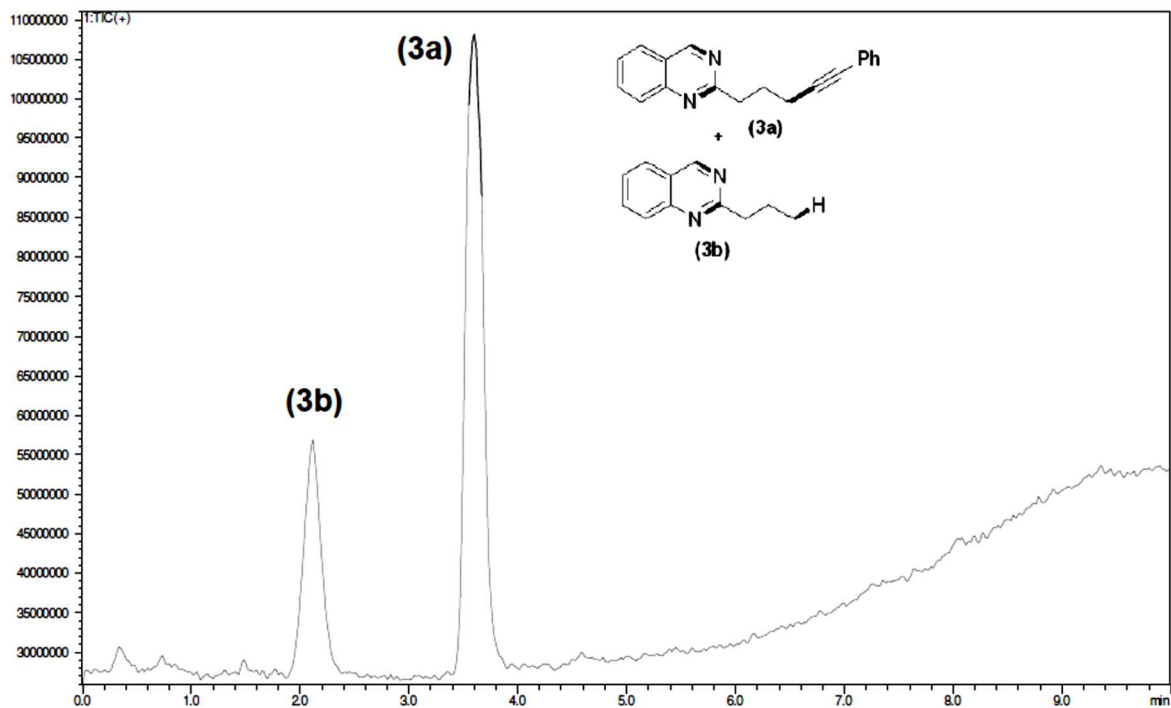
9/19/2018

Arkansas Statewide Mass Spectrometry Facility

ESI Mass Spectrum

Sample Name: BED324-spot 3
Sample id#: 1840
Instrument: Shimadzu QQQ

9/19/2018

2.12 min
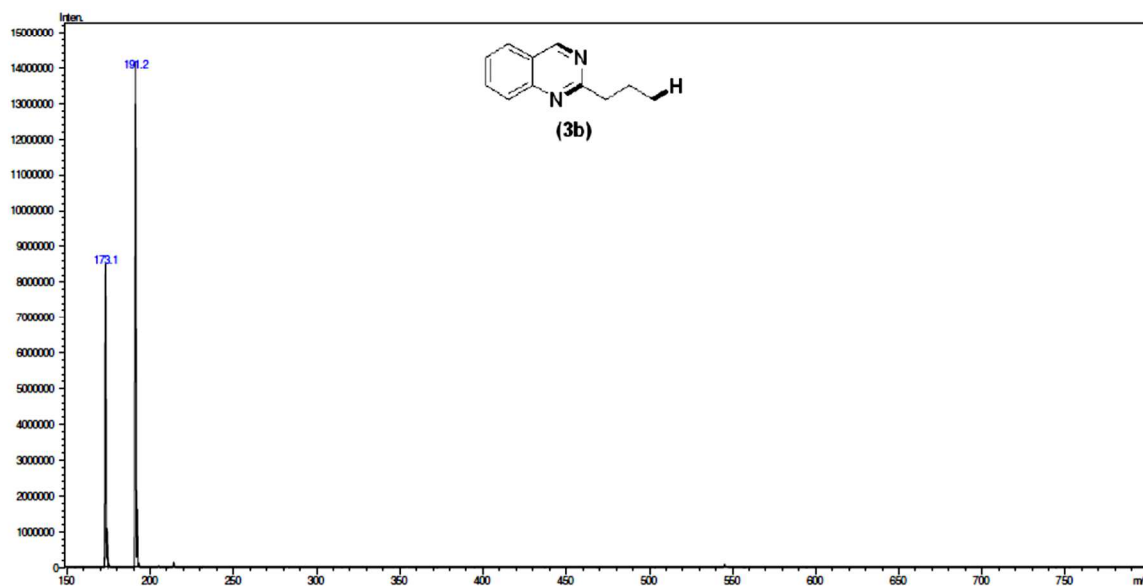
Arkansas Statewide Mass Spectrometry Facility

ESI Mass Spectrum

Sample Name: BED324-spot 3
Sample id#: 1840
Instrument: Shimadzu QQQ

9/19/2018

3.60 min
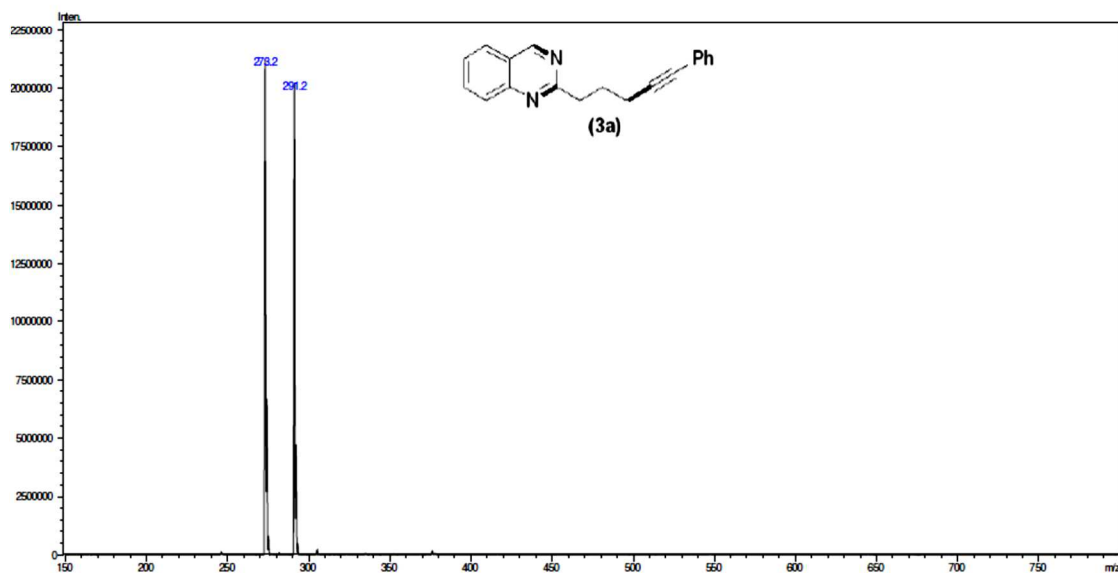
1.75
2.65

0.95
1.70
1.00
0.97
3.20
3.39

f1 (ppm)

212.54

131.02
128.36
128.05
123.44

91.12
83.59

49.05
43.59
36.42
28.02
27.48
24.11

f1 (ppm)
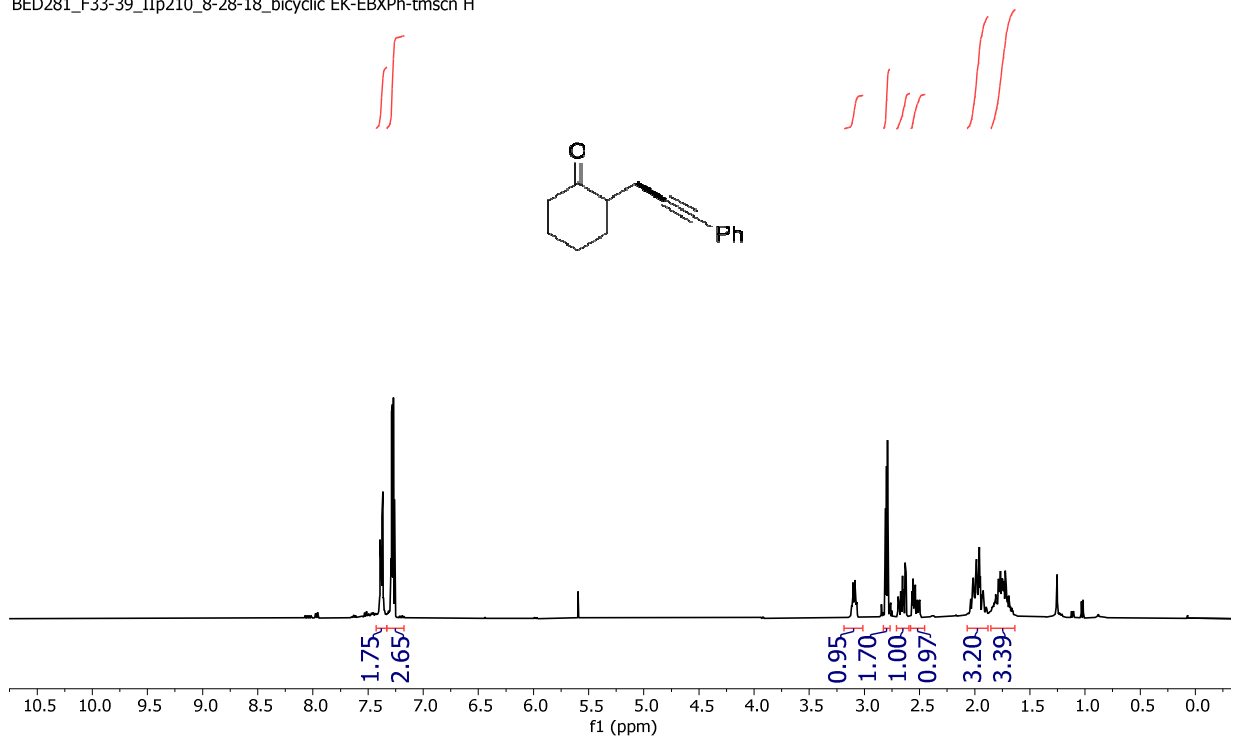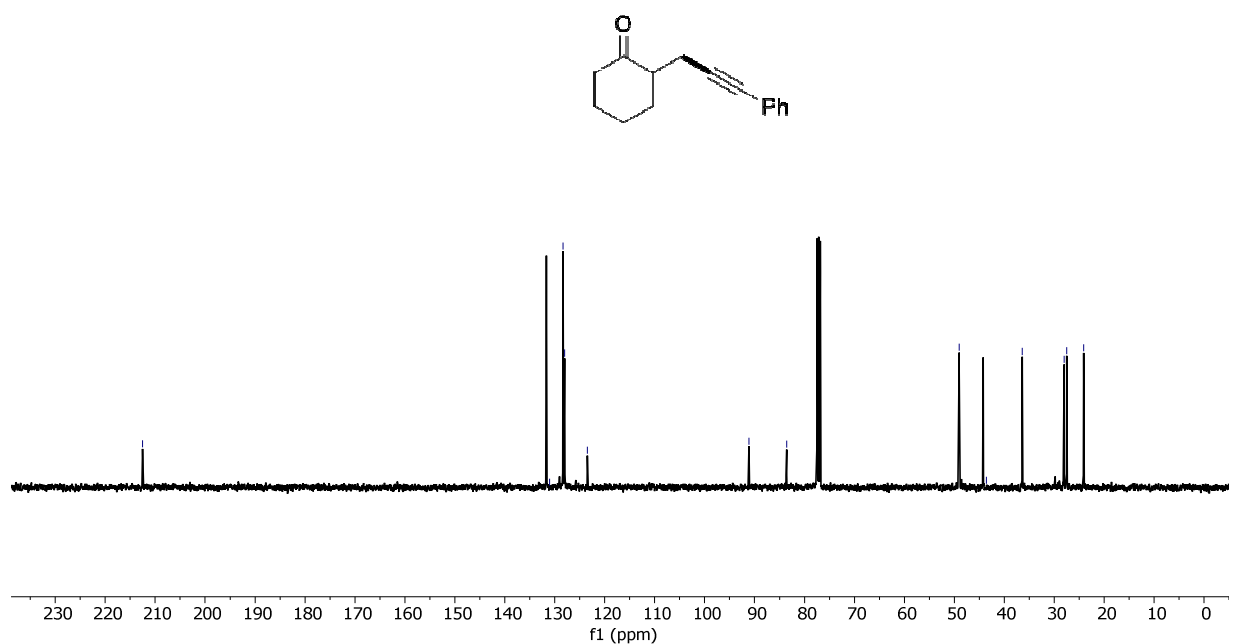
BED281-II_p210-7-28-18.13.fid
BED281-II_p210-8-28-18_dept 135

131.47
128.16
127.36

48.84
44.00
36.20
28.61
26.27
23.90

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED281-II_p210-7-28-18.14.ser
BED281-II_p210-8-28-18 F33-39 HSQC

f2 (ppm)

f1 (ppm)

304

0.82
1.14 2.20 3.40 2.78
2.00 2.04 2.07

3.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1
f1 (ppm)

170.63
164.57
142.05
135.30
133.37
131.94
128.54
128.53
128.33
128.04
126.98
126.71
123.97
120.79
89.05
82.21
34.97
26.52
19.44

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

305

141.71
134.94
133.03
131.60
128.19
127.99
127.70
126.61
126.36
34.65
26.18
18.32

f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

0.84
1.02
2.06
1.21
1.74
3.15
2.00
1.69
1.92
2.64

f1 (ppm)
3.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1

306

171.28
163.71
135.24
131.67
129.00
128.30
127.75
126.97
126.54
123.89
120.79
89.55
81.35
29.85
28.29
26.80
19.32

f1 (ppm)

BED716-III_p187_3-6-2021.5.fid
BED711-716-III_p187_3-6-2021_N-cyclopentyl-N-benzamide-PhEBX-Ir-DCE-18h_ spot 4_Dept135

134.88
131.47
128.55
127.55
126.96
125.69

29.36
28.10
27.06

19.12

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED763-III_p214_4-10-2021.2.fid
BED763-III_p214_4-10-2021_cyclopentylanilinobenzamide-maleimide-Ir-DMF_ spot 2_ H

0.95
1.05
1.13
1.05
1.06
2.11
2.28
2.37
3.00

3.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1
f1 (ppm)

164.22
157.00
134.68
127.93
126.77
126.61
125.14
120.39
35.50
29.94
22.73
14.77

f1 (ppm)

Appendix C

Experimental Data for Chapter 4—Visible Light-mediated Deconstruction/Refunctionalization of Unstrained Cycloalkanones Using Diamines as Activating Groups

General Considerations

Unless stated otherwise, all reactions were carried out under a nitrogen atmosphere. Acetonitrile (CH₃CN) was pre-dried over molecular sieves. Toluene and THF were collected under argon from a solvent purification system. 1,4–Dioxane was dried over activated molecular sieves (8–12 mesh) prior to use. Column chromatography was performed using silica gel (230-400 mesh) or neutral alumina gel flash grade 32-63u. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, high-resolution mass spectroscopy (HRMS), and melting point when applicable. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance DPX-300 and Bruker Avance DPX-400. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual proton or carbon signals in CDCl₃ (7.27 ppm, 77.23ppm), CD₂Cl₂ (5.32 ppm, 54.0 ppm), and DMSO-d6 (2.50 ppm, 39.51 ppm) at room temperature. 2D NMR experiments were performed on some of the new compounds to establish their structure including relative configuration. NMR yields of products were determined using ^{1}H NMR of crude products. IR spectra were recorded (thin film on NaCl plates) on a PerkinElmer Spectrum 100 series instrument. High Resolution Mass spectra were recorded on either a Bruker Ultraflex II TOF/TOF mass spectrometer or a Bruker Apex–Qe mass spectrometer with an ESI source (Fourier Transform Mass Spectrometry). Gas chromatography/mass spectroscopy (GC/MS) analyses were performed on an Agilent 6890N Network GC System/5973 inert Mass Selective Detector. Gas

chromatography analyses were performed using a Shimadzu GC-2010 Plus instrument. When applicable, melting points (m.p.) were recorded using a Stuart SMP10 Melting Point Apparatus and were uncorrected.

C.1. General Procedure GPC1: Synthesis of the Spiro-cycloalkane-dihydroquinazolinones:
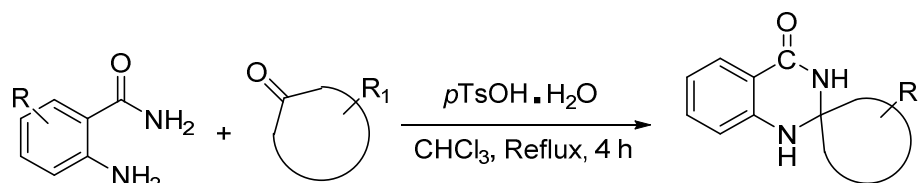
Scheme C.1.1. Syntheses of Spiro-cycloalkane-dihydroquinazolinones

Procedure: A round-bottom flask containing 2-aminobenzamide (2.0 g, 14.7 mmol), cyclic ketone (1.1 equiv) and catalytic amount of *p*-toluenesulfonic acid monohydrate (0.5 mol%) in chloroform (36 mL) was fitted to a water condenser and refluxed at 75 °C for 4 hours. Upon the completion of the reaction, as monitored by TLC, the mixture was concentrated to form solids, filtered over filter paper, and washed with water and ethyl acetate to give the crude solid product. The crude solid product was then recrystallized with methanol afforded the desired spiro-cycloalkane-dihydroquinazolinone product. Alternatively, the crude product can be purified by flash column chromatography using silica gel as stationary phase. Much improved yields of the products can be obtained by employing 20 mol% of *p*-toluenesulfonic acid monohydrate.[361]

Figure C.1.1 below show the structures of the dihydroquinazolinones and related compounds investigated in this work.
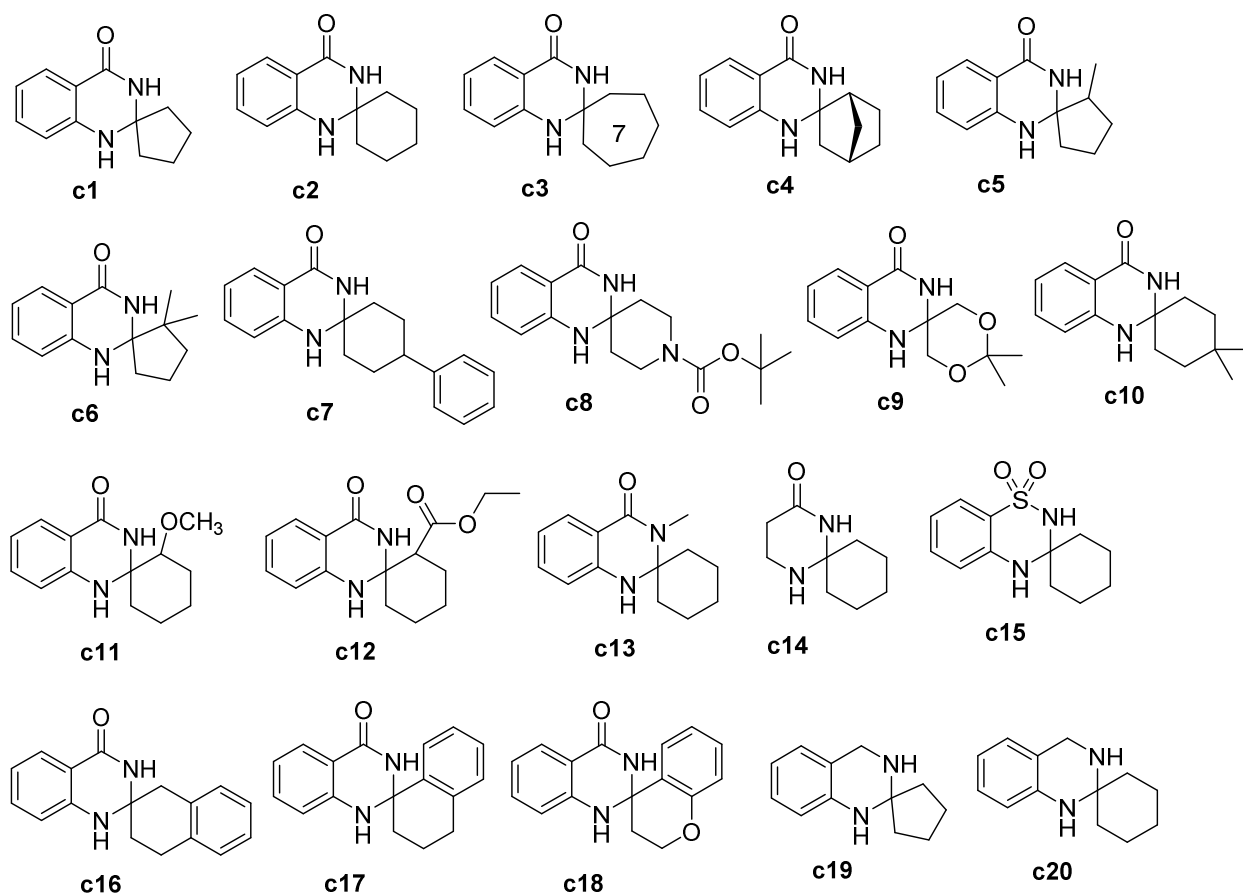
Figure C.1.1. Structures of the Dihydroquinazolinones Studied

Substrates **c1**, **c2**, **c3, c4, c8, c13** and **c17** are known compounds and the spectroscopic data from their syntheses matched with those reported in literature.[360, 364] The spectral data for c15 corresponded with that reported in literature.[365] Also, the spectroscopic data for compounds **c7**[366] and **c12**[367] correspond with those reported in literature. Compounds **c19**[368] and **c20**[369] were synthesized by following **GPC1** above, albeit without the use of acid, and the products was isolated by flash column chromatography as viscous pale yellow liquids which solidifies under air. Their spectral data matched with those reported. The syntheses of substrates **c16**[370] and **c18**[371] have been reported by other groups and our spectral data corresponds with those reported for the latter (the analytical data of the **c16** was absent in the reported work).
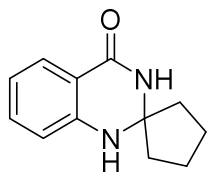
1'H-spiro[cyclopentane-1,2'-quinazolin]-4'(3'H)-one: White crystals (2.0 g, 67%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (dd, J = 1.6, 7.8 Hz, 1H), 7.33 (td, J = 1.6, 7.6, 7.7 Hz, 1H), 6.87 (m, 1H), 6.67 (d, J = 8.1 Hz, 1H), 6.45 (s, 1H), 1.99 (s, 3H), 1.81 (m, 3H).
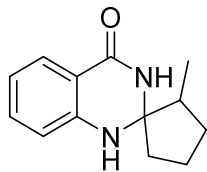
2-methyl-1'H-spiro[cyclopentane-1,2'-quinazolin]-4'(3'H)-one: Following **GPC1** with 2-aminobenzamide (2.0 g, 14.7 mmol) and 2-dimethylcyclopentan-1-one (1.9 mL, 17.6 mmol). Product is an off-white solid (2.0 g, 62%). ^{1}H NMR (400 MHz, DMSO) δ 7.88 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.19 (t, J = 7.6, 7.6 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.58 (dt, J = 6.0, 6.0, 14.9 Hz, 1H), 6.51 (s, 1H), 1.93 (dddd, J = 5.5, 9.1, 12.7, 17.6 Hz, 2H), 1.76 (m, 2H), 1.60 (m, 2H), 1.44 (dtd, J = 6.4, 9.7, 9.8, 12.3 Hz, 1H), 0.86 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 164.40, 164.35, 148.75, 148.43, 133.89, 133.88, 127.88, 127.80, 116.89, 116.75, 114.77, 114.72, 114.69, 114.52, 79.20, 78.92, 45.14, 44.93, 30.15, 29.92, 19.75, 19.73, 15.12, 14.55. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{13}$H$_{16}$N$_2$O 217.1335; found 217.1332
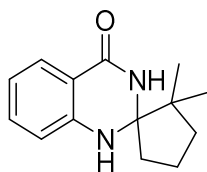
2,2-dimethyl-1'H-spiro[cyclopentane-1,2'-quinazolin]-4'(3'H)-one: Following **GPC1** with 2-aminobenzamide (681 mg, 14.7 mmol) and 2,2-dimethylcyclopentan-1-one (2.0 mL, 17.6 mmol) the product was obtained as a pale brown solid (1.4 g, 41%), and was used in the next step without purification by chromatography or recrystallization. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (dd, J = 1.6, 7.8 Hz, 1H), 7.29 (m, 1H), 6.78 (t, J = 7.5, 7.5 Hz, 1H), 6.61 (d, J = 8.1 Hz, 1H),

6.11 (s, 1H), 2.10 (dqd, J = 4.6, 9.4, 9.5, 9.5, 24.0 Hz, 2H), 1.71 (dqd, J = 4.9, 8.2, 8.2, 8.3, 18.2 Hz, 4H), 1.04 (d, J = 2.0 Hz, 6H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 165.25, 146.81, 134.37, 129.20, 119.04, 114.19, 81.06, 46.66, 38.89, 37.02, 23.73, 23.57, 18.90. ^{13}C DEPT135 NMR (101 MHz, CDCl$_3$) δ 136.88, 128.21, 118.28, 113.84, 38.54, 36.67, 23.38, 21.89, 17.01. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{14}$H$_{18}$N$_2$O 231.1492; found 231.1494
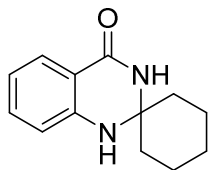
1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 – 7.81 (m, 1H), 7.31 (ddd, J = 1.7, 5.9, 7.7 Hz, 1H), 6.92 – 6.78 (m, 1H), 6.68 (t, J = 9.2, 9.2 Hz, 1H), 6.34 (s, 1H), 3.27 (s, 2H), 1.85 (h, J = 7.9, 7.9, 8.6, 8.6, 8.6 Hz, 4H), 1.73 – 1.54 (m, 4H), 1.54 – 1.36 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.2, 145.7, 134.1, 128.6, 122.2, 119.0, 115.0, 68.6, 38.0, 24.8, 22.1.
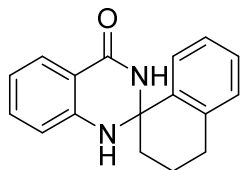
3,4-dihydro-1'H,2H-spiro[naphthalene-1,2'-quinazolin]-4'(3'H)-one: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 (dd, J = 1.6, 7.8 Hz, 1H), 7.45 (s, 1H), 7.33 (m, 1H), 7.30 (d, J = 5.4 Hz, 4H), 7.22 (ddt, J = 2.5, 2.5, 6.3, 8.8 Hz, 1H), 6.85 (t, J = 7.5, 7.5 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 2.58 (dq, J = 7.7, 7.7, 8.4, 16.1 Hz, 1H), 2.45 (dq, J = 3.0, 3.0, 3.0, 13.6 Hz, 2H), 1.91 (td, J = 2.8, 6.6, 8.4 Hz, 4H), 1.62 (dt, J = 8.9, 8.9, 13.1 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.96, 145.65, 138.32, 138.11, 134.48, 129.40, 129.37, 128.88, 128.79, 127.17, 119.02, 114.92, 114.73, 70.35, 37.44, 30.06, 29.56, 19.48.
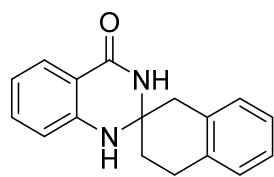
 3,4-dihydro-1H,1'H-spiro[naphthalene-2,2'-quinazolin]-4'(3'H)-one:

Following **GPC1** with 2-aminobenzamide (681 mg, 5.0 mmol) and β-tetralone (0.73 mL, 5.5 mmol). Product is an off-white or pale brown solid (433 mg, 33%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 (d, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5, 7.5 Hz, 1H), 7.20 (qd, J = 4.5, 8.8, 8.8, 9.2 Hz, 3H), 7.09 (d, J = 7.1 Hz, 1H), 6.86 (t, J = 7.4, 7.4 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.40 (s, 1H), 3.19 (m, 3H), 3.00 (tq, J = 8.6, 8.6, 10.8, 17.8, 17.8 Hz, 2H), 2.20 (t, J = 6.7, 6.7 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.63, 145.81, 134.58, 134.51, 134.15, 132.22, 130.43, 129.37, 128.82, 127.42, 127.00, 119.53, 115.33, 115.31, 68.40, 42.64, 34.21, 26.30. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{17}$H$_{16}$N$_2$O 265.1335; found 265.1331.
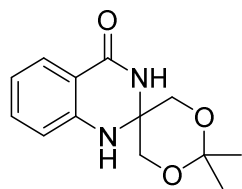
 2',2'-dimethyl-1H-spiro[quinazoline-2,5'-[1,3]dioxan]-4(3H)-one:

Following **GPC1** with 2-aminobenzamide (681 mg, 5 mmol) and 2,2-dimethyl-1,3-dioxan-5-one (0.66 mL, 5.5 mmol) the product was obtained as a white solid (465 mg, 37%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 (t, J = 7.6, 7.6 Hz, 1H), 7.34 (m, 1H), 6.85 (q, J = 7.4, 7.4, 7.6 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 3.91 (m, 4H), 1.50 (s x 2, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.83, 145.65, 134.84, 128.75, 119.48, 115.38, 114.51, 99.28, 77.69, 77.37, 77.06, 67.63, 63.88, 26.86, 20.42. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{17}$H$_{16}$N$_2$O 249.1234; found 249.1234.
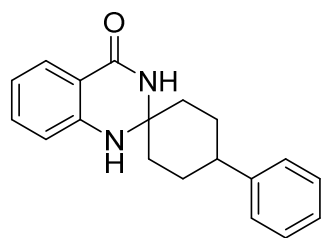
4-phenyl-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one: White solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 (dd, J = 1.6, 7.8 Hz, 1H), 7.45 (s, 1H), 7.33 (m, 1H), 7.30 (d, J = 5.4 Hz, 4H), 7.22 (ddt, J = 2.5, 2.5, 6.3, 8.8 Hz, 1H), 6.85 (t, J = 7.5, 7.5 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 2.58 (dq, J = 7.7, 7.7, 8.4, 16.1 Hz, 1H), 2.45 (dq, J = 3.0, 3.0, 3.0, 13.6 Hz, 2H), 1.91 (td, J = 2.8, 6.6, 8.4 Hz, 4H), 1.62 (dt, J = 8.9, 8.9, 13.1 Hz, 2H). ^{13}C NMR (400 MHz, CDCl$_3$) δ 146.39, 145.84, 134.74, 134.56, 128.92, 128.89, 127.22, 126.81, 119.36, 115.57, 115.14, 68.66, 43.81, 38.75, 29.50. ^{13}C DEPT135 NMR (101 MHz, CDCl$_3$) δ 134.81, 128.52, 126.87, 126.65, 125.65, 118.92, 114.72, 45.00, 38.47, 29.17. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{19}$H$_{20}$N$_2$O 293.1648; found 293.1642.
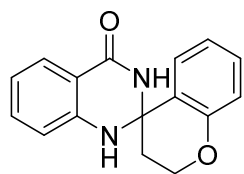
1'H-spiro[chromane-4,2'-quinazolin]-4'(3'H)-one: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (dd, J = 1.7, 7.8 Hz, 1H), 7.79 (dd, J = 1.8, 7.9 Hz, 1H), 7.35 (td, J = 1.7, 7.7, 7.7 Hz, 1H), 7.24 (d, J = 7.0 Hz, 1H), 6.98 (t, J = 7.6, 7.6 Hz, 1H), 6.87 (m, 2H), 6.68 (d, J = 8.1 Hz, 1H), 6.08 (s, 1H), 4.27 (t, J = 5.6, 5.6 Hz, 2H), 2.39 (q, J = 4.6, 4.7, 4.7 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.06, 155.43, 145.14, 134.77, 131.42, 128.91, 128.65, 123.96, 121.65, 119.73, 117.74, 115.49, 114.94, 66.46, 63.21, 36.63. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{17}$H$_{16}$N$_2$O 267.1128; found 267.1131.
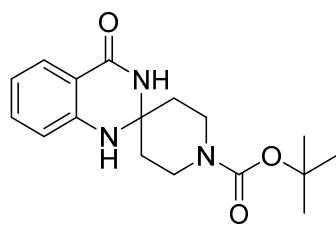
tert-butyl **4'-oxo-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinazoline]-1-carboxylate:** ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 (dd, J = 1.7, 7.8 Hz, 1H), 7.51 (s, 1H), 7.32 (t, J = 7.7, 7.7 Hz, 1H), 6.86 (t, J = 7.4, 7.4 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 3.57 (t, J = 5.7, 5.7 Hz, 4H), 2.00 (dt, J = 5.2, 5.2, 11.8 Hz, 2H), 1.84 (dt, J = 6.2, 6.2, 13.0 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.91, 154.89, 145.48, 134.55, 128.78, 119.81, 115.80, 115.68, 80.46, 80.45, 67.41, 47.94, 37.55, 28.79, 28.75. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{17}$H$_{23}$N$_3$O$_3$ 318.1812; found 318.1814.
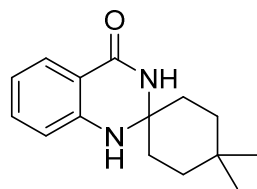
4,4-dimethyl-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one:

Following **GPC1** with 2-aminobenzamide (681 mg, 5 mmol) and 4,4-dimethylcyclohexan-1-one (0.66 mL, 5.5 mmol), the product was obtained as a white crystals (768 mg, 63%) and used without purification by flash column chromatography or recrystallization. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.88 (d, J = 7.5 Hz, 1H), 7.31 (m, 1H), 6.84 (q, J = 6.8, 6.8, 7.4 Hz, 1H), 6.69 (t, J = 6.9, 6.9 Hz, 1H), 6.48 (s, 1H), 3.43 (s, 1H), 1.88 (m, 4H), 1.42 (dtd, J = 6.2, 13.7, 13.8, 26.7 Hz, 4H), 0.99 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.58, 145.95, 134.38, 134.29, 128.78, 119.30, 119.24, 115.56, 115.30, 115.25, 68.86, 68.81, 35.04, 34.24, 29.69, 29.68. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{15}$H$_{20}$N$_2$O 245.1648; found 245.1647.
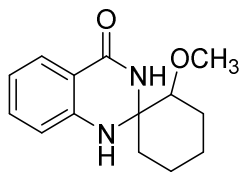
2-methoxy-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one: Following

GPC1 with 2-aminobenzamide (681 mg, 5 mmol) and 2-methoxycyclohexan-1-one (712 mg, 5.6

mmol), the product is a pale yellow solid (1.1 g, 60%) isolated by flash column chromatography

(Hexane:EtOAc = 1:1) as a mixture of diastereomers in the ratio 1: 2.8 : 4 : 12. ^{1}H NMR (400

MHz, CDCl$_3$) δ 7.89 (d, J = 7.7 Hz, 0H), 7.84 (d, J = 7.7 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 6.84

(d, J = 3.1 Hz, 1H), 6.80 (t, J = 7.6, 7.6 Hz, 1H), 6.67 (dd, J = 4.4, 8.2 Hz, 1H), 6.46 (s, 0H), 3.50

(m, 1H), 3.42 (d, J = 4.4 Hz, 0H), 3.37 (d, J = 4.1 Hz, 1H), 3.31 (d, J = 4.0 Hz, 3H), 1.90 (m, 2H),

1.80 (dt, J = 8.7, 8.7, 17.5 Hz, 1H), 1.63 (tt, J = 5.6, 5.6, 14.7, 14.7 Hz, 2H), 1.47 (m, 4H). ^{13}C

NMR (101 MHz, CDCl$_3$) δ 164.43, 164.12, 147.07, 145.43, 134.92, 134.46, 134.17, 128.70,

128.52, 119.30, 119.01, 115.66, 115.35, 115.23, 80.82, 79.40, 70.16, 69.58, 57.39, 57.20, 33.70,

33.43, 24.54, 23.87, 21.66, 21.11, 19.00, 18.89. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{14}$H$_{18}$N$_2$O$_2$

247.1441; found 247.1446.

Ethyl 4'-oxo-3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinazoline]-2-

carboxylate: Following **GPC1** with 2-aminobenzamide (681 mg, 5 mmol) and ethyl 2-

oxocyclohexane-1-carboxylate (941 mg, 5.5 mmol), the product is a white solid (1.1 g, 50%)

isolated by flash column chromatography (Hexane:EtOAc = 1:1) as a mixture of diastereomers.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85 (dd, J = 1.6, 7.7 Hz, 1H), 7.30 (m, 1H), 6.82 (q, J = 7.1, 7.1,

7.2 Hz, 1H), 6.65 (m, 2H), 4.07 (m, 2H), 3.93 (dq, J = 7.1, 7.1, 7.1, 10.7 Hz, 1H), 2.78 (dd, J = 4.4,

8.9 Hz, 1H), 2.30 (m, 1H), 1.91 (m, 3H), 1.66 (m, 3H), 1.47 (p, J = 6.5, 6.5, 7.0, 7.0 Hz, 1H), 1.22

(m, 1H), 1.17 (t, J = 7.1, 7.1 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 173.96, 173.26, 172.58,

164.32, 164.02, 146.00, 145.83, 145.47, 134.45, 134.32, 134.28, 128.75, 128.63, 128.49, 119.35, 119.28, 119.10, 115.81, 115.40, 115.20, 115.16, 115.10, 69.49, 69.48, 68.77, 61.32, 60.61, 51.90, 50.09, 38.17, 37.91, 36.40, 34.42, 29.02, 25.60, 25.42, 25.05, 24.78, 22.91, 22.53, 22.27, 21.74, 21.68, 14.59, 14.55, 14.41, 14.36. HRMS (ESI) m/z [M+H]$^+$, calc'd for $C_{16}H_{20}N_2O_3$ 289.1547; found 289.1552.
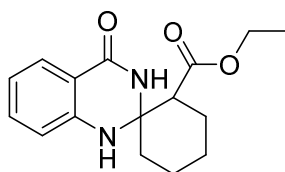
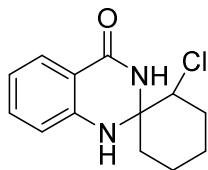**2-chloro-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one:** Following **GPC1** with 2-aminobenzamide (681 mg, 5 mmol) and 2-chlorocyclohexan-1-one (844 mg, 5.5 mmol), the product is a pale brown solid (1.1 g, 50%) isolated by flash column chromatography (Hexane:EtOAc = 1:1) as a mixture of diastereomers in the ratio 1 : 1.1. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, J = 7.7 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.32 (m, 2H), 7.16 (s, 1H), 6.85 (q, J = 7.0, 7.0, 7.0 Hz, 2H), 6.70 (t, J = 8.7, 8.7 Hz, 2H), 6.65 (s, 1H), 4.52 (d, J = 3.9 Hz, 1H), 4.27 (t, J = 4.6, 4.6 Hz, 1H), 2.04 (m, 8H), 1.78 (m, 6H), 1.54 (ddtt, J = 5.1, 5.1, 9.3, 9.3, 13.6, 21.8 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.21, 164.05, 145.39, 144.95, 134.87, 134.60, 128.76, 128.57, 119.75, 119.61, 115.55, 115.22, 115.03, 70.55, 70.03, 65.22, 64.05, 32.81, 31.05, 29.71, 21.31, 20.93, 19.20. HRMS (ESI) m/z [M+H]$^+$, calc'd for $C_{13}H_{15}ClN_2O$ 251.0946; found 251.0951.
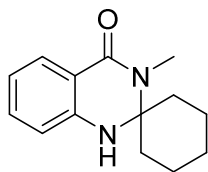
3'-methyl-1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one: Off-white solid (1.0 g, 91%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.92 (dd, J = 1.7, 7.9 Hz, 1H), 7.28 (m, 1H), 6.84 (q, J = 7.1, 7.1, 7.5 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 4.60 (s, 1H), 3.09 (m, 3H), 2.07 (s, 2H), 1.76 (m, 5H), 1.45 (tdd, J = 6.2, 11.3, 14.8, 14.8 Hz, 2H), 1.21 (dddd, J = 4.1, 9.0, 13.0, 16.9 Hz,

1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.14, 144.35, 144.34, 133.47, 129.02, 119.36, 117.26, 115.14, 72.32, 42.34, 33.28, 27.37, 26.88, 24.93, 22.68. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{14}$H$_{18}$N$_2$O 231.1492; found 231.1493.
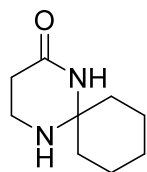
1,5-diazaspiro[5.5]undecan-2-one: A reported solventless approach for synthesizing a similar compound (1,4-diazaspiro[4.5]decan-2-one)[372] was adapted for the synthesis of this compound. A mixture of 3-aminopropanamide hydrochloride (624 mg, 5 mmol), cyclohexanone (1.5 mL, 14.5 mmol), and triethylamine (0.70 mL, 5 mmol) in chloroform (1 mL) was stirred overnight at room temperature. The solvent was then removed with a rotary evaporator and the product was isolated by flash column chromatography (DCM:MeOH = 4:1) as a pale brown solid (334 mg, 40%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.55 (s, 1H), 3.09 (t, J = 6.1, 6.1 Hz, 2H), 2.30 (t, J = 6.1, 6.1 Hz, 2H), 1.70 (m, 3H), 1.52 (qd, J = 4.3, 10.7, 10.7, 11.6 Hz, 4H), 1.37 (dp, J = 5.8, 5.8, 5.9, 5.9, 14.9 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.76, 70.28, 38.87, 37.04, 32.86, 25.50, 22.45. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_9$H$_{16}$N$_2$O 169.1335; found 169.1340.
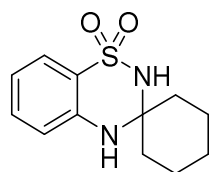
2H,4H-spiro[benzo[e][1,2,4]thiadiazine-3,1'-cyclohexane] 1,1-dioxide: ^{1}H NMR (400 MHz, DMSO) δ 7.40 (dd, J = 1.5, 8.0 Hz, 1H), 7.24 (ddd, J = 1.6, 7.0, 8.6 Hz, 1H), 6.93 (s, 1H), 6.76 (d, J = 8.4 Hz, 1H), 6.65 (t, J = 7.5, 7.5 Hz, 1H), 2.19 (d, J = 12.7 Hz, 2H), 1.52 (m, 7H), 1.22 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 143.58, 133.00, 124.51, 121.15, 116.80, 116.21, 71.41, 37.03, 25.52, 22.28.
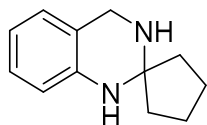
3',4'-dihydro-1'H-spiro[cyclopentane-1,2'-quinazoline]: Isolated by flash column chromatography with silica gel stationary phase (Hexanes:EtOAc = 1:1) as a yellow viscous liquid which solidifies under ambient temperature (1.2 g, 77%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.03 (td, J = 1.5, 7.7, 7.7 Hz, 1H), 6.94 (m, 1H), 6.68 (td, J = 1.2, 7.4, 7.4 Hz, 1H), 6.50 (m, 1H), 4.03 (s, 2H), 1.80 (m, 10H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 143.38, 127.46, 126.43, 120.86, 117.76, 115.28, 76.42, 43.72, 40.23, 40.05, 39.88, 39.83, 24.65, 24.07, 23.89, 23.59.
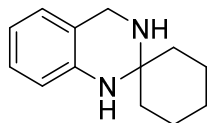
3',4'-dihydro-1'H-spiro[cyclohexane-1,2'-quinazoline]: Isolated by flash column chromatography with silica gel stationary phase (Hexanes:EtOAc = 1:1) as a yellow viscous liquid which solidifies under ambient temperature (1.3 g, 80%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.02 (m, 1H), 6.92 (d, J = 7.4 Hz, 1H), 6.66 (t, J = 7.4, 7.4 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 3.97 (s, 2H), 1.73 (m, 4H), 1.55 (m, 6H).

C.2. General Procedure GPC2: Photochemistry for Deconstructive Functionalization of Unstrained Cycloalkanones
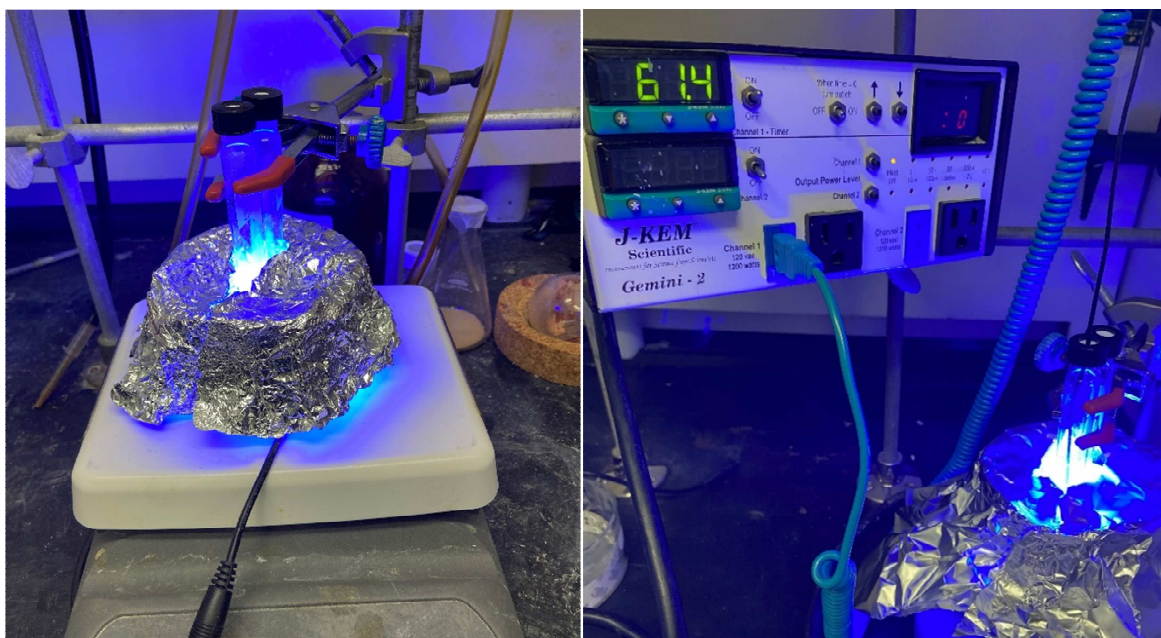
(a) Setup of Photochemistry reaction   (b) Measuring temperature at the end of reaction

Figure C.2.1. Setup of the Photochemistry for Deconstruction/Functionalization of Unstrained Cycloalkanone

Procedure: An oven-dried test tube equipped with a stir bar was charged with the spirodihydroquinazolinone (0.2 mmol), Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%), oven-dried K$_3$PO$_4$ (0.4 mmol, 2 equiv), and 2 mL *N,N-Dimethylformamide* (*DMF*). The test tube was capped with a Teflon screw cap and the mixture was degassed using several Freeze-Pump-Thaw (FPT) cycles. The reaction mixture was then backfilled with nitrogen and irradiated using blue light by placing the test tube in the center of a circle of four-row blue LEDs and wrapping the setup with aluminum foil (**Figure C2.1**a). The internal reaction temperature was measured at the end of the reaction and found to be in the range of 58 ℃ - 61 ℃ (**Figure C2.1**b). After completion of the reaction (~6 h), the reaction mixture was diluted with diethyl ether and filtered through a short pad of silica gel. The solvent was distilled off using a short-stem distillation apparatus to give the crude, and the products were then isolated by flash chromatography using silica gel as stationary phase

(Hexanes:EtOAc = 1:2). The reaction is sluggish (~6 times slower) when conducted at 50 ºC by not wrapping the setup with aluminum foil.
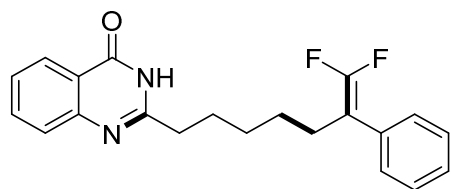
2-(7,7-difluoro-6-phenylhept-6-en-1-yl)quinazolin-4(3H)-one: White solid (65 mg, 92%) from reaction conducted at 60 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.90 (s, 1H), 8.26 (dd, J = 1.5, 7.9 Hz, 1H), 7.78 (ddd, J = 1.6, 7.0, 8.4 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.46 (ddd, J = 1.3, 6.9, 8.0 Hz, 1H), 7.36 – 7.21 (m, 5H), 2.90 – 2.64 (m, 2H), 2.43 (ddq, J = 2.4, 2.4, 2.4, 4.8, 7.2 Hz, 2H), 1.87 (dq, J = 7.2, 7.2, 7.2, 11.3 Hz, 2H), 1.47 (p, J = 3.1, 3.1, 3.2, 3.2 Hz, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.4, 156.8, 156.6, 153.7, 150.9, 149.6, 135.0, 133.8, 128.5, 128.4, 128.4, 128.3, 127.4, 126.6, 126.3, 120.6, 92.5, 92.4, 92.2, 35.9, 28.7, 27.6, 27.5, 27.5, 27.5, 27.3. ^{19}F NMR (376 MHz, CDCl$_3$) δ -92.1. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{21}$H$_{20}$F$_2$N$_2$O 355.1616; found 355.1612.
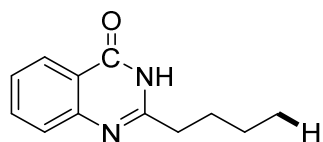
2-butylquinazolin-4(3H)-one: White solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.38 (s, 1H), 8.29 (dd, J = 1.5, 8.0 Hz, 1H), 7.88 – 7.63 (m, 2H), 7.48 (td, J = 1.3, 6.9, 7.5 Hz, 1H), 2.80 (t, J = 7.9, 7.9 Hz, 2H), 1.88 (dq, J = 7.6, 7.6, 7.7, 9.3 Hz, 2H), 1.50 (dt, J = 7.4, 7.4, 14.8 Hz, 2H), 1.01 (t, J = 7.3, 7.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.22, 157.15, 149.69, 135.17, 127.51, 126.77, 126.61, 120.89, 36.02, 30.05, 29.94, 22.73, 14.11. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{12}$H$_{14}$N$_2$O 203.1179; found 203.1178.
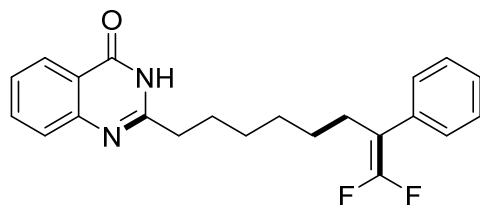
2-(8,8-difluoro-7-phenyloct-7-en-1-yl)quinazolin-4(3H)-one: Off-white solid (34 mg, 46%) from reaction conducted at 50 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.07 (s, 1H), 8.29 (dd, J = 1.5, 8.0 Hz, 1H), 7.79 (ddd, J = 1.5, 6.8, 8.5 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.37 – 7.21 (m, 5H), 2.88 – 2.69 (m, 2H), 2.40 (tq, J = 2.5, 2.5, 2.5, 4.7, 4.7 Hz, 2H), 1.88 (dq, J = 6.9, 6.9, 7.5, 15.3 Hz, 2H), 1.56 – 1.30 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.8, 157.5, 157.3, 156.8, 153.9, 151.0, 149.7, 135.2, 134.1, 134.1, 128.7, 128.6, 128.6, 128.5, 128.5, 127.5, 127.5, 127.5, 127.5, 126.7, 126.5, 120.8, 92.8, 92.7, 92.7, 92.5, 36.2, 36.1, 29.2, 29.0, 27.9, 27.9, 27.9, 27.9, 27.8, 27.8, 27.6. ^{19}F NMR (376 MHz, CDCl$_3$) δ -92.19. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{22}$H$_{22}$F$_2$N$_2$O 369.1773; found 369.1764.
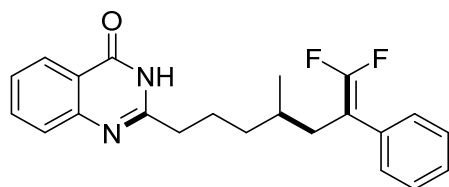
2-(7,7-difluoro-4-methyl-6-phenylhept-6-en-1-yl)quinazolin-4(3H)-one: White solid (quant). ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.35 (s, 1H), 8.29 (dd, J = 1.6, 8.1 Hz, 1H), 7.83 – 7.75 (m, 1H), 7.72 (d, J = 8.5 Hz, 1H), 7.48 (t, J = 7.6, 7.6 Hz, 1H), 7.32 (d, J = 3.5 Hz, 1H), 7.25 (ddd, J = 2.6, 7.4, 12.9 Hz, 2H), 2.81 – 2.72 (m, 2H), 2.46 (ddt, J = 3.1, 3.1, 6.1, 14.3 Hz, 1H), 2.26 (ddd, J = 2.7, 7.9, 14.3 Hz, 1H), 2.02 – 1.75 (m, 2H), 1.53 (tt, J = 5.3, 5.3, 10.4, 10.4 Hz, 2H), 1.32 (dtt, J = 5.6, 5.6, 9.8, 9.8, 19.6 Hz, 2H), 0.92 (d, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.0, 157.2, 157.2, 154.4, 154.3, 151.5, 149.8, 135.2, 134.2, 134.1, 134.1, 134.1, 128.8, 128.7, 128.6, 128.6, 127.6, 127.6, 126.7, 126.5, 120.8, 91.9, 91.8, 91.7, 91.6, 36.4, 36.3, 35.2, 35.2, 31.2, 31.2, 31.2, 25.3, 19.4. ^{19}F NMR (376 MHz, CDCl$_3$) δ -91.7, -91.8, -91.9, -92.1. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{22}$H$_{22}$F$_2$N$_2$O 369.1773; found 369.1772.
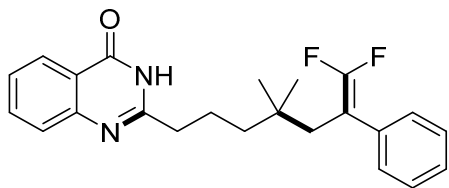
2-(7,7-difluoro-4,4-dimethyl-6-phenylhept-6-en-1-yl)quinazolin-4(3H)-one: White solid (quant). ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.10 (s, 1H), 8.30 (dd, J = 1.5, 8.0 Hz, 1H), 7.79 (ddd, J = 1.6, 6.9, 8.5 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.30 (d, J = 4.5 Hz, 4H), 7.26 – 7.18 (m, 1H), 2.63 (t, J = 7.8, 7.8 Hz, 2H), 2.39 (t, J = 2.4, 2.4 Hz, 2H), 1.81 (ddt, J = 6.4, 6.4, 11.7, 16.4 Hz, 2H), 1.36 – 1.23 (m, 3H), 0.81 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.8, 157.6, 157.2, 154.7, 154.7, 151.8, 149.8, 135.9, 135.9, 135.9, 135.8, 135.2, 128.9, 128.9, 128.8, 128.6, 128.4, 127.6, 127.4, 126.7, 126.5, 120.8, 91.3, 91.1, 91.0, 90.9, 42.3, 39.8, 39.8, 36.8, 35.7, 35.6, 35.6, 35.6, 27.5, 27.5, 22.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ -89.9, -90.0, -92.2, -92.3. HRMS (ESI) *m/z* [M+H]$^{+}$, calc'd for C$_{23}$H$_{24}$F$_2$N$_2$O 383.1929; found 383.1927.
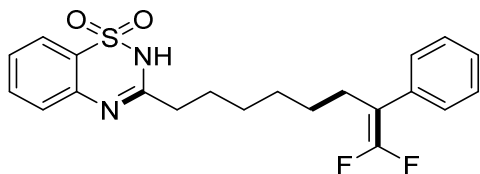
3-(8,8-difluoro-7-phenyloct-7-en-1-yl)-2H-benzo[e][1,2,4]thiadiazine 1,1-dioxide: Pale brown solid (52.1 mg, 64%) from the reaction at 60 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 10.17 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 7.7, 7.7 Hz, 1H), 7.35 (dd, J = 5.6, 12.5 Hz, 4H), 7.31 – 7.20 (m, 3H), 2.54 (t, J = 7.7, 7.7 Hz, 2H), 2.35 (t, J = 6.8, 6.8 Hz, 2H), 1.71 (p, J = 7.2, 7.2, 7.7, 7.7 Hz, 2H), 1.38 – 1.20 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 161.6, 161.4, 156.8, 153.9, 151.0, 135.5, 134.0, 133.6, 128.8, 128.6, 128.6, 128.5, 128.1, 127.8, 127.6, 127.0, 124.1, 121.2, 121.2, 118.0, 92.8, 92.6, 92.5, 36.6, 28.9, 27.9, 27.8, 27.8, 27.8, 26.8, 26.6. ^{19}F NMR (376 MHz, CDCl$_3$) δ -92.2, -92.2. HRMS (ESI) *m/z* [M+H]$^{+}$, calc'd for C$_{21}$H$_{22}$F$_2$N$_2$O$_2$S 405.1443; found 405.1441.
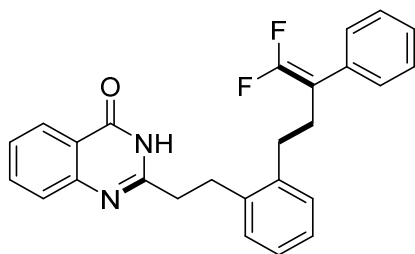
2-(2-(4,4-difluoro-3-phenylbut-3-en-1-yl)phenethyl)quinazolin-4(3H)-one: White solid (7.9 mg, 10%) after 36 h from the reaction conducted at 50 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.68 (s, 1H), 8.26 (d, J = 8.1 Hz, 1H), 7.88 – 7.71 (m, 2H), 7.49 (t, J = 7.4, 7.4 Hz, 1H), 7.34 (dd, J = 3.0, 6.0 Hz, 1H), 7.28 (s, 5H), 7.25 – 7.11 (m, 4H), 3.16 (dd, J = 5.7, 10.3 Hz, 2H), 3.00 (dd, J = 6.1, 10.0 Hz, 2H), 2.82 (dd, J = 5.5, 10.3 Hz, 2H), 2.76 – 2.66 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.3, 157.0, 156.2, 154.1, 154.1, 151.2, 139.4, 138.3, 135.3, 133.7, 133.7, 133.7, 133.6, 130.0, 129.8, 129.8, 128.8, 128.8, 128.5, 128.5, 128.5, 127.7, 127.5, 127.2, 127.1, 127.0, 126.6, 120.8, 92.4, 92.3, 92.2, 92.1, 37.5, 31.4, 31.4, 30.5, 30.1, 29.8. ^{19}F NMR (376 MHz, CDCl$_3$) δ -90.9, -91.0, -91.5, -91.5, -91.6, -91.7. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{26}$H$_{22}$F$_2$N$_2$O 417.1773; found 417.1767.
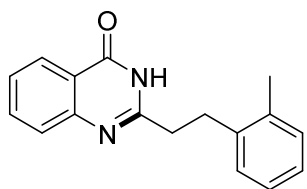
2-(2-methylphenethyl)quinazolin-4(3H)-one: White solid (2.4 mg, 5%) after 36 h from the reaction conducted at 50 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.21 (s, 1H), 8.29 (d, J = 7.9 Hz, 1H), 7.81 (p, J = 8.0, 8.0, 8.1, 8.1 Hz, 2H), 7.52 (t, J = 7.2, 7.2 Hz, 1H), 7.21 – 7.08 (m, 3H), 3.22 (dd, J = 5.9, 10.1 Hz, 2H), 3.06 (dd, J = 6.3, 9.5 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.8, 155.8, 149.5, 139.3, 136.2, 135.0, 130.6, 130.0, 129.2, 127.4, 126.8, 126.5, 126.4, 120.8, 36.7, 32.1, 19.5. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{17}$H$_{16}$N$_2$O 265.1335; found 265.1331.
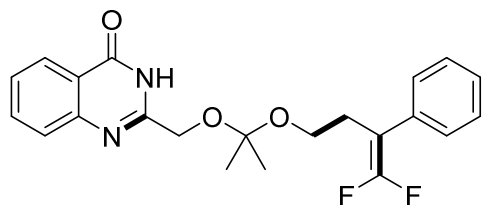
2-((((2-((4,4-difluoro-3-phenylbut-3-en-1-yl)oxy)propan-2-yl)oxy)methyl)quinazolin-4(3H)-one: White solid (46.2 mg, 58%) isolated after 22 h from reaction conducted at 50 ºC. NMR yield 84%. ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.72 (s, 1H), 8.30 – 8.24 (m, 1H), 7.82 – 7.75 (m, 1H), 7.67 (d, J = 8.2 Hz, 1H), 7.49 (t, J = 7.5, 7.5 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.18 (t, J = 7.6, 7.6 Hz, 2H), 7.10 – 7.03 (m, 1H), 4.47 (s, 1H), 3.47 (t, J = 6.8, 6.8 Hz, 2H), 2.72 – 2.62 (m, 2H), 1.43 (s, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 161.7, 157.1, 154.3, 154.2, 153.4, 151.4, 148.9, 134.9, 134.9, 133.1, 133.0, 133.0, 133.0, 128.8, 128.7, 128.5, 128.5, 128.1, 128.1, 128.0, 127.4, 127.4, 127.1, 126.7, 126.7, 121.6, 101.5, 101.5, 101.4, 89.7, 89.6, 89.5, 89.4, 60.2, 60.1, 59.2, 59.2, 59.2, 59.2, 31.0, 28.4, 28.4, 24.8, 24.8, 24.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ -70.2, -70.2, -90.0, -90.1, -90.2, -90.3, -90.6. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{22}$H$_{22}$F$_2$N$_2$O$_3$ 401.1671; found 177.0667, 282.2790.

2-(8,8-difluoro-3,7-diphenyloct-7-en-1-yl)quinazolin-4(3H)-one: Off-white solid (26.5 mg, 30%) isolated after 35 h from reaction conducted at 50 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.69 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.79 (t, J = 7.5, 7.5 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 7.4, 7.4 Hz, 1H), 7.22 (ddt, J = 7.3, 7.3, 14.4, 28.8 Hz, 9H), 2.74 – 2.51 (m, 3H), 2.36 (t, J = 7.2, 7.2 Hz, 2H), 2.20 (dddt, J = 5.8, 5.8, 9.6, 13.8, 29.4 Hz, 2H), 1.72 (dddt, J = 5.1, 5.1, 9.8, 13.9, 19.1 Hz, 2H), 1.29 (tp, J = 6.2, 6.2, 6.4, 6.4, 14.3, 14.3 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.1, 156.8, 156.5, 153.7, 150.8, 149.4, 144.5, 144.2, 134.9,

133.7, 133.7, 128.6, 128.6, 128.5, 128.3, 128.3, 128.3, 128.0, 127.8, 127.3, 127.2, 126.5, 126.4, 126.3, 120.6, 92.4, 92.2, 92.2, 92.0, 45.6, 36.0, 34.4, 34.3, 34.2, 33.9, 27.6, 27.5, 27.5, 25.5, 25.5, 25.5. ^{19}F NMR (376 MHz, CDCl$_3$) δ -92.0. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{28}$H$_{26}$F$_2$N$_2$O 445.2086; found 445.2088.
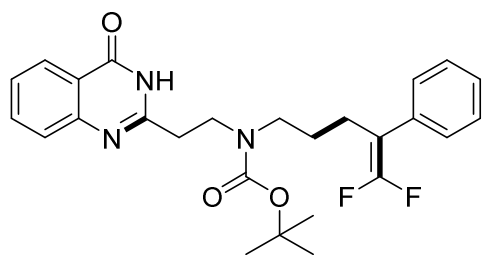
tert-butyl (5,5-difluoro-4-phenylpent-4-en-1-yl)(2-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)carbamate: Viscous colorless liquid (18.8 mg, 20%) isolated after 36 h from the reaction conducted at 50 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.76 (d, J = 192.9 Hz, 1H), 8.27 (dt, J = 2.6, 2.6, 7.9 Hz, 1H), 7.76 (t, J = 7.4, 7.4 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.46 (q, J = 6.4, 6.4, 7.4 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.30 – 7.20 (m, 4H), 3.64 (t, J = 6.8, 6.8 Hz, 2H), 3.44 – 3.15 (m, 2H), 2.98 (ddd, J = 5.5, 15.4, 19.6 Hz, 2H), 2.44 – 2.33 (m, 2H), 1.61 (q, J = 7.5, 7.5, 7.7 Hz, 2H), 1.37 (d, J = 5.3 Hz, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.7, 163.0, 156.7, 156.0, 154.8, 153.8, 151.0, 149.3, 135.1, 133.7, 129.2, 128.9, 128.6, 128.5, 127.9, 127.7, 127.4, 126.9, 126.7, 121.1, 92.3, 92.1, 92.0, 80.5, 47.8, 45.3, 35.3, 30.1, 28.6, 27.1, 25.4. ^{19}F NMR (376 MHz, CDCl3) δ -91.4. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{26}$H$_{29}$F$_2$N$_3$O$_3$ 470.2250; found 470.2256.
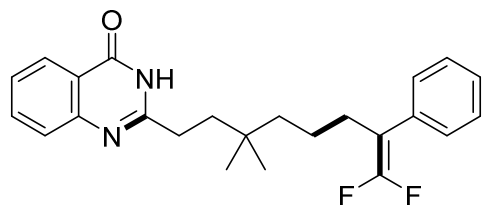
2-(8,8-difluoro-3,3-dimethyl-7-phenyloct-7-en-1-yl)quinazolin-4(3H)-one: Pale brown viscous liquid (26.9 mg, 34%) isolated after 37 h from the reaction at 50 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.16 (s, 1H), 8.23 (dt, J = 1.8, 1.8, 8.0 Hz, 1H),

7.83 – 7.67 (m, 2H), 7.51 – 7.41 (m, 1H), 7.35 – 7.24 (m, 4H), 7.22 (ddd, J = 1.8, 5.1, 8.1 Hz, 1H), 2.82 – 2.74 (m, 1H), 2.74 – 2.63 (m, 2H), 2.39 (ddd, J = 2.4, 4.9, 7.4 Hz, 2H), 1.83 – 1.75 (m, 1H), 1.75 – 1.66 (m, 2H), 1.48 – 1.35 (m, 2H), 1.35 – 1.24 (m, 2H), 1.00 (d, J = 2.1 Hz, 2H), 0.97 – 0.81 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.2, 164.8, 164.8, 158.5, 158.2, 156.9, 154.0, 151.1, 149.6, 135.2, 134.0, 134.0, 128.9, 128.8, 128.7, 128.6, 128.6, 128.6, 128.5, 127.5, 127.4, 126.7, 126.5, 120.8, 92.8, 92.6, 92.6, 92.4, 41.6, 39.9, 39.7, 34.8, 34.5, 33.4, 33.3, 33.2, 31.7, 31.6, 28.6, 27.0, 26.7, 22.4, 22.4, 22.4, 8.8. ^{19}F NMR (376 MHz, CDCl$_3$) δ -92.0. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{24}$H$_{26}$F$_2$N$_2$O 397.2086; found 397.2091.
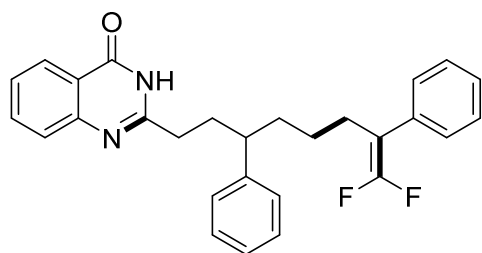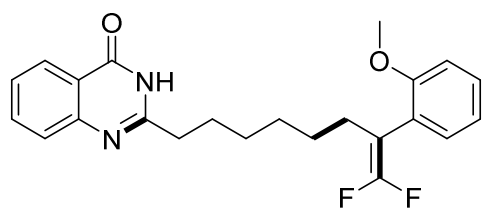

2-(8,8-difluoro-7-(2-methoxyphenyl)oct-7-en-1-yl)quinazolin-4(3H)-one: White solid (21.4 mg, 27%) isolated after 43 h from the reaction conducted at 50 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.98 (s, 1H), 8.28 (dq, J = 1.6, 1.9, 1.9, 8.0 Hz, 1H), 7.77 (ddt, J = 1.7, 1.7, 7.0, 8.5 Hz, 1H), 7.74 – 7.68 (m, 1H), 7.59 – 7.38 (m, 1H), 7.30 – 7.22 (m, 1H), 7.10 (dd, J = 3.9, 5.6 Hz, 1H), 6.94 – 6.85 (m, 2H), 3.93 – 3.72 (m, 3H), 2.78 (tt, J = 3.4, 3.4, 7.7, 7.7 Hz, 2H), 2.51 – 2.25 (m, 2H), 1.83 (s, 2H), 1.58 – 1.17 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.7, 157.7, 157.7, 157.3, 156.2, 153.3, 150.5, 149.7, 135.2, 131.4, 131.4, 131.4, 129.4, 127.5, 126.7, 126.6, 126.6, 123.1, 123.1, 123.0, 123.0, 120.8, 120.8, 120.7, 111.3, 89.8, 89.6, 89.5, 89.4, 55.8, 36.2, 29.3, 29.0, 28.0, 28.0, 27.9, 27.8, 27.7, 27.6, 27.6. ^{19}F NMR (376 MHz, CDCl3) δ -90.8, -90.9, -94.6, -94.7. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{23}$H$_{24}$F$_2$N$_2$O$_2$ 399.1879; found 399.1877.
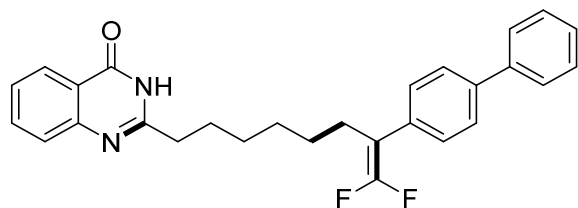
2-(7-([1,1'-biphenyl]-4-yl)-8,8-difluorooct-7-en-1-yl)quinazolin-4(3H)-one: Colorless liquid (39.3 mg, 44%) from the reaction conducted at 50 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.76 (d, J = 74.4 Hz, 1H), 8.28 (ddq, J = 1.8, 1.8, 2.0, 3.6, 7.9 Hz, 1H), 7.83 – 7.66 (m, 2H), 7.57 (dddd, J = 2.0, 4.4, 8.6, 10.8 Hz, 4H), 7.49 – 7.40 (m, 3H), 7.36 (dtd, J = 3.2, 4.8, 5.9, 8.6 Hz, 3H), 2.78 (t, J = 7.8, 7.8 Hz, 2H), 2.43 (tt, J = 3.9, 3.9, 4.7, 7.0 Hz, 2H), 1.98 – 1.80 (m, 2H), 1.56 – 1.36 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.3, 164.2, 157.0, 156.7, 153.8, 150.9, 149.3, 140.7, 140.1, 135.7, 135.0, 132.8, 129.1, 128.9, 128.8, 128.7, 128.7, 128.6, 128.3, 127.5, 127.2, 127.1, 127.1, 126.8, 126.7, 126.6, 126.3, 120.6, 92.3, 92.2, 92.1, 92.0, 35.9, 29.9, 29.8, 29.5, 29.0, 29.0, 28.8, 27.7, 27.7, 27.7, 27.6, 27.5, 27.5. ^{19}F NMR (376 MHz, CDCl$_3$) δ -91.5, -91.5. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{28}$H$_{26}$F$_2$N$_2$O 445.2086; found 445.2089.
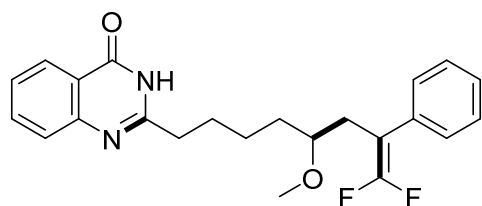
2-(8,8-difluoro-5-methoxy-7-phenyloct-7-en-1-yl)quinazolin-4(3H)-one: Colorless liquid (58.6 mg, 74%) isolated after 37 h from the reaction conducted at 50 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.17 (s, 1H), 8.36 – 8.20 (m, 1H), 7.77 (ddt, J = 1.7, 1.7, 7.0, 9.8 Hz, 1H), 7.70 (dd, J = 1.3, 8.4 Hz, 1H), 7.46 (ddt, J = 1.7, 1.7, 7.0, 8.1 Hz, 1H), 7.34 – 7.29 (m, 4H), 7.24 (ddt, J = 2.3, 2.3, 5.5, 8.6 Hz, 1H), 3.23 (d, J = 2.0 Hz, 3H), 3.14 (dq, J = 2.0, 2.3, 2.3, 6.3 Hz, 1H), 2.79 (td, J = 2.0, 7.8, 7.9 Hz, 2H), 2.64 (ddt, J = 2.4, 2.4, 6.6, 14.3 Hz, 1H), 2.48 (ddt, J = 2.3, 2.3, 6.4, 14.4 Hz, 1H), 1.93 – 1.79 (m, 2H), 1.61 – 1.39 (m, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.5, 162.8, 157.1, 156.9, 154.3, 151.4, 149.5, 134.9, 133.8, 129.0, 128.6,

128.4, 128.4, 128.4, 128.2, 128.0, 127.5, 127.4, 127.2, 126.5, 126.3, 120.6, 90.2, 90.1, 89.9, 79.0, 78.9, 78.9, 56.9, 35.9, 35.8, 33.4, 33.2, 32.4, 27.6, 24.7, 24.3. ^{19}F NMR (376 MHz, CDCl$_3$) δ -90.9. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{23}$H$_{24}$F$_2$N$_2$O$_2$ 399.1879; found 399.1883.
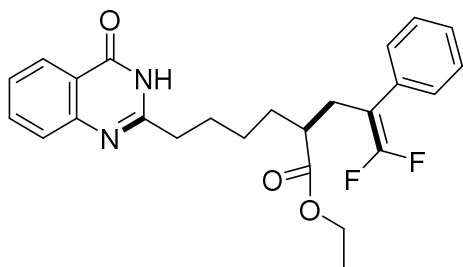
Ethyl 2-(3,3-difluoro-2-phenylallyl)-6-(4-oxo-3,4-dihydroquinazolin-2-yl)hexanoate: Colorless liquid (55.9 mg, 63%) isolated after 37 h from the reaction at 50 ℃. ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.09 (s, 1H), 8.28 (ddd, J = 0.6, 1.6, 8.0 Hz, 1H), 7.77 (ddd, J = 1.6, 7.0, 8.5 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.46 (ddd, J = 1.3, 7.0, 8.2 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.27 – 7.21 (m, 3H), 3.99 (q, J = 7.1, 7.1, 7.1 Hz, 2H), 2.84 – 2.67 (m, 3H), 2.56 (ddt, J = 2.4, 2.4, 6.5, 14.4 Hz, 1H), 2.38 (tdd, J = 4.9, 6.4, 8.7, 8.7 Hz, 1H), 1.85 (dddd, J = 2.1, 6.4, 8.9, 13.9 Hz, 2H), 1.78 – 1.66 (m, 1H), 1.56 (dddd, J = 4.9, 6.2, 9.5, 13.2 Hz, 1H), 1.41 (dtt, J = 6.3, 6.3, 9.9, 9.9, 16.6 Hz, 2H), 1.15 (t, J = 7.1, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 175.0, 164.5, 157.0, 156.7, 154.1, 151.2, 149.5, 135.0, 133.0, 132.9, 128.6, 128.6, 128.5, 128.5, 128.2, 127.7, 127.3, 126.5, 126.4, 120.6, 90.7, 90.6, 90.5, 90.4, 60.5, 43.9, 43.8, 43.8, 35.6, 31.4, 30.6, 27.4, 26.7, 14.2. ^{19}F NMR (376 MHz, CDCl$_3$) δ -90.6, -90.7, -90.8, -90.9. HRMS (ESI) m/z [M+H]$^+$, calc'd for C$_{25}$H$_{26}$F$_2$N$_2$O$_3$ 441.1984; found 441.1988.
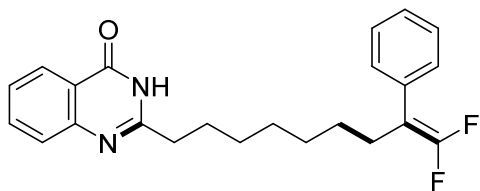
2-(9,9-difluoro-8-phenylnon-8-en-1-yl)quinazolin-4(3H)-one: White solid (44.5 mg, 59%) from the reaction at 50 ℃. ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.16 (s, 1H), 8.27 (dd, J = 1.6, 8.0 Hz, 1H), 7.77 (ddd, J = 1.6, 6.8, 8.4 Hz, 1H), 7.71 (d, J = 8.1

Hz, 1H), 7.44 (t, J = 7.4, 7.4 Hz, 1H), 7.37 – 7.21 (m, 5H), 2.79 (t, J = 7.8, 7.8 Hz, 2H), 2.37 (q, J = 5.1, 5.1, 7.2 Hz, 2H), 1.88 (q, J = 7.5, 7.5, 7.7 Hz, 2H), 1.44 (p, J = 7.0, 7.0, 7.4, 7.4 Hz, 2H), 1.39 – 1.15 (m, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.6, 157.2, 156.5, 153.7, 150.8, 149.6, 134.9, 133.9, 133.9, 128.5, 128.4, 128.3, 128.3, 127.3, 127.3, 126.5, 126.3, 120.6, 92.7, 92.5, 92.5, 92.3, 36.0, 29.8, 29.3, 29.0, 28.9, 27.8, 27.8, 27.8, 27.7, 27.6. ^{19}F NMR (376 MHz, CDCl$_3$) δ -92.2. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{23}$H$_{24}$F$_2$N$_2$O 383.1929; found 383.1929.
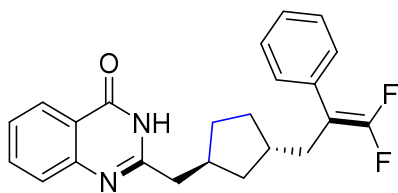
2-((((1S,3S)-3-(3,3-difluoro-2-phenylallyl)cyclopentyl)methyl)quinazolin-4(3H)-one: Pale brown viscous liquid (6.16 mg, 81%) isolated after 36 h from the reaction conducted at 50 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.98 (s, 1H), 8.18 (d, J = 7.7 Hz, 1H), 7.75 – 7.66 (m, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.39 (t, J = 7.4, 7.4 Hz, 1H), 7.19 (tq, J = 7.0, 7.2, 7.2, 14.3, 14.3 Hz, 5H), 2.73 (d, J = 7.5 Hz, 1H), 2.70 – 2.63 (m, 1H), 2.57 (dq, J = 7.7, 8.4, 8.4, 15.3 Hz, 1H), 2.46 – 2.21 (m, 3H), 2.03 – 1.56 (m, 4H), 1.47 (q, J = 7.2, 7.2, 7.4 Hz, 1H), 1.43 – 1.07 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.4, 156.9, 156.8, 156.5, 154.1, 154.0, 154.0, 153.9, 151.2, 151.1, 149.5, 134.9, 133.9, 133.9, 133.9, 133.9, 128.5, 128.5, 128.4, 128.4, 128.2, 127.6, 127.3, 126.5, 126.3, 120.6, 120.6, 92.4, 92.3, 92.2, 92.2, 92.2, 92.1, 92.0, 92.0, 42.0, 41.9, 39.6, 38.7, 38.2, 38.2, 38.2, 37.7, 37.5, 37.4, 36.9, 36.9, 36.9, 34.1, 34.0, 32.4, 32.1, 31.2, 31.0. ^{19}F NMR (376 MHz, CDCl$_3$) δ -92.1, -92.2, -92.3, -92.3, -92.4, -92.4, -92.5, -92.5. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{23}$H$_{22}$F$_2$N$_2$O 381.1773; found 381.1776.
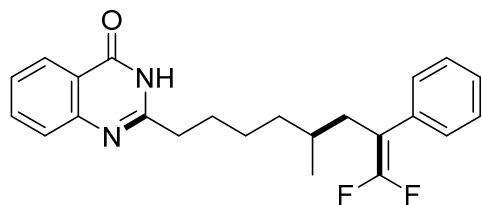
2-(8,8-difluoro-5-methyl-7-phenyloct-7-en-1-yl)quinazolin-4(3H)-one: White solid (quant) from reaction at 60 ºC. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.28 (s, 1H), 8.32 – 8.20 (m, 1H), 7.83 – 7.73 (m, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.50 – 7.40 (m, 1H), 7.35 – 7.27 (m, 3H), 7.26 – 7.18 (m, 2H), 2.73 (q, J = 8.9, 8.9, 9.7 Hz, 2H), 2.38 (ddt, J = 2.9, 2.9, 6.0, 13.9 Hz, 1H), 2.21 (dddd, J = 1.3, 2.6, 8.1, 14.2 Hz, 1H), 1.79 (dt, J = 7.7, 7.7, 11.6 Hz, 2H), 1.53 – 1.29 (m, 4H), 1.21 (dt, J = 9.1, 9.1, 12.4 Hz, 1H), 0.91 – 0.77 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.0, 156.7, 154.1, 135.0, 134.0, 128.5, 128.4, 127.3, 126.6, 126.4, 120.7, 36.1, 36.0, 35.0, 31.1, 27.8, 26.6, 19.2. ^{19}F NMR (376 MHz, CDCl$_3$) δ -91.7, -91.9, -92.0, -92.1. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{23}$H$_{24}$F$_2$N$_2$O 382.1857; found .
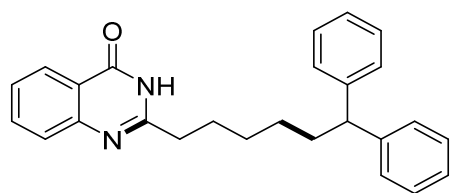
2-(6,6-diphenylhexyl)quinazolin-4(3H)-one: White solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.85 (s, 1H), 8.26 (dd, J = 1.5, 8.0 Hz, 1H), 7.77 (ddd, J = 1.6, 7.0, 8.4 Hz, 1H), 7.70 (dd, J = 1.2, 8.3 Hz, 1H), 7.45 (ddd, J = 1.3, 7.0, 8.1 Hz, 1H), 7.27 – 7.24 (m, 2H), 7.23 – 7.21 (m, 4H), 7.20 (d, J = 1.8 Hz, 1H), 7.17 – 7.12 (m, 2H), 3.88 (t, J = 7.8, 7.8 Hz, 1H), 2.92 – 2.66 (m, 2H), 2.12 – 2.02 (m, 2H), 1.93 – 1.80 (m, 2H), 1.57 – 1.45 (m, 2H), 1.42 – 1.29 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.4, 156.9, 149.6, 145.3, 134.9, 128.5, 127.9, 127.4, 126.5, 126.3, 126.2, 120.6, 51.4, 36.0, 35.6, 29.7, 29.3, 27.8, 27.5, 27.2. HRMS (ESI) *m/z* [M+H]$^+$, calc'd for C$_{26}$H$_{26}$N$_2$O 382.2045; found .

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(372) Miklos, F.; Fulop, F. "Dry" and "Wet" Green Synthesis of 2,2 '-Disubstituted Quinazolinones. *European Journal of Organic Chemistry* **2010**, *2010* (5), 959-965, Article. DOI: 10.1002/ejoc.200901052.

C.4. NMR Spectra for Chapter 4

BED 710
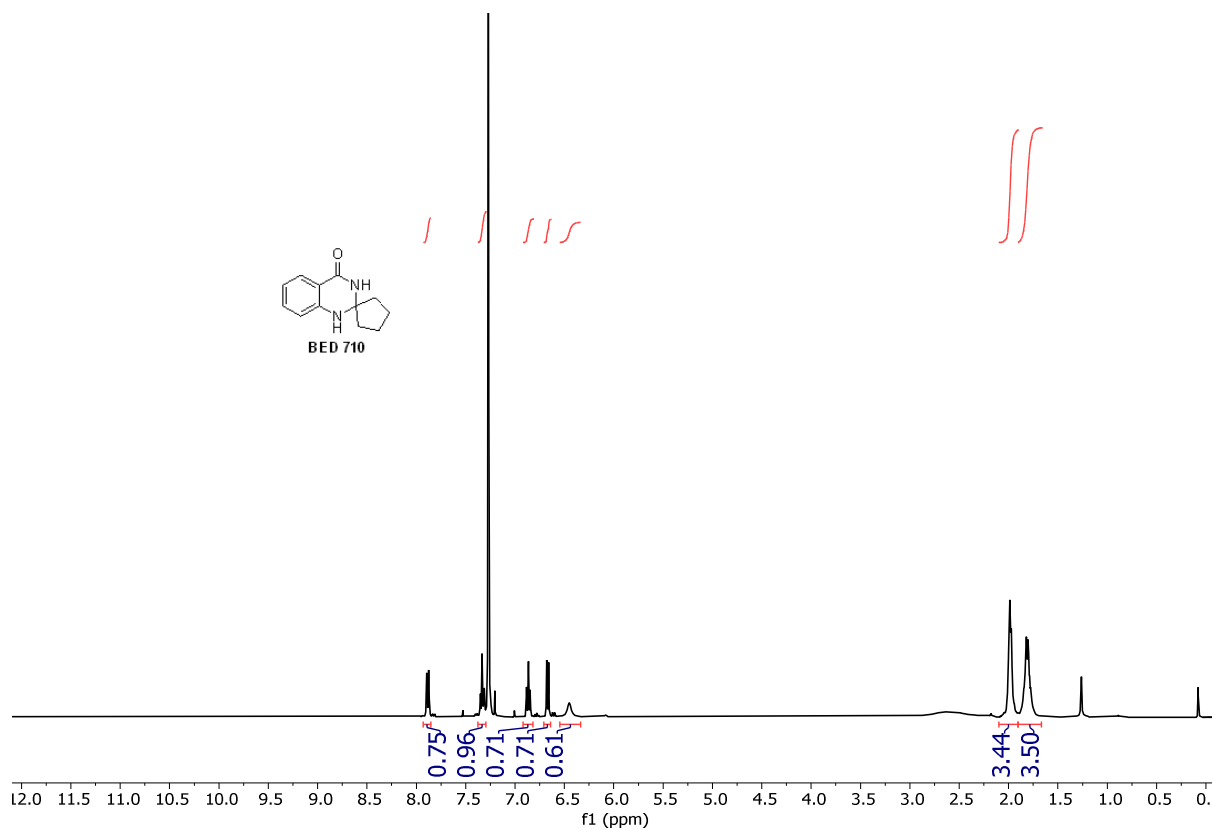
BED779-III_p222_4-29-2021.5.fid
BED779-III_p222_4-29-2021_2-methylcyclopentylanilinobenzamide_check b4 recrys in dmso_H

374

164.40
164.35
148.75
148.43
133.89
133.88
127.88
127.80
116.89
116.75
114.77
114.72
114.69
114.52
79.20
78.92
45.14
44.93
40.25
30.15
29.92
19.75
19.73
15.12
14.55

BED779-III_p222_4-29-2021.6.fid
BED779-III_p222_4-29-2021_2-methylcyclopentylanilinobenzamide_check b4 recrys in dmso_ C13

:00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

148.09
133.55
127.54
127.46
116.54
116.40
114.34
114.17
78.58
44.79
44.58
39.90
29.09
19.38
14.78
14.20

BED779-III_p222_4-29-2021.7.fid
BED779-III_p222_4-29-2021_2-methylcyclopentylanilinobenzamide_check b4 recrys in dmso_Dept135

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

375

BED 780

BED 780

377

—136.88
—128.21
—118.28
—113.84
38.54
36.67
23.38
21.89
17.01

BED 780

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED791-III_p231_6-17-2021.4.fid
BED791-III_p231_6-17-2021_cyclohexylanilinobenzylamine-2nd batch_ H

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

1.00
1.17
1.01
1.03
0.97
1.56
4.24
4.27
2.03

378

— 164.23

— 145.68

— 134.13
— 128.59

⌇ 122.16
∕ 119.03
∖ 114.98

— 68.60

— 37.99

— 24.82
— 22.10

f1 (ppm)

— 134.30

— 128.37

— 121.04

— 116.12

— 36.73

— 24.62
— 21.17

f1 (ppm)

379

BED 890

0.99
1.00
3.00
1.03
0.99
0.99
0.92

2.59
2.30

2.02

f1 (ppm)

164.41

145.60
134.36
134.29
133.93
132.00
130.21
129.16
128.61
127.21
126.79

119.31
115.12
115.09

68.18

42.43

33.99

26.09
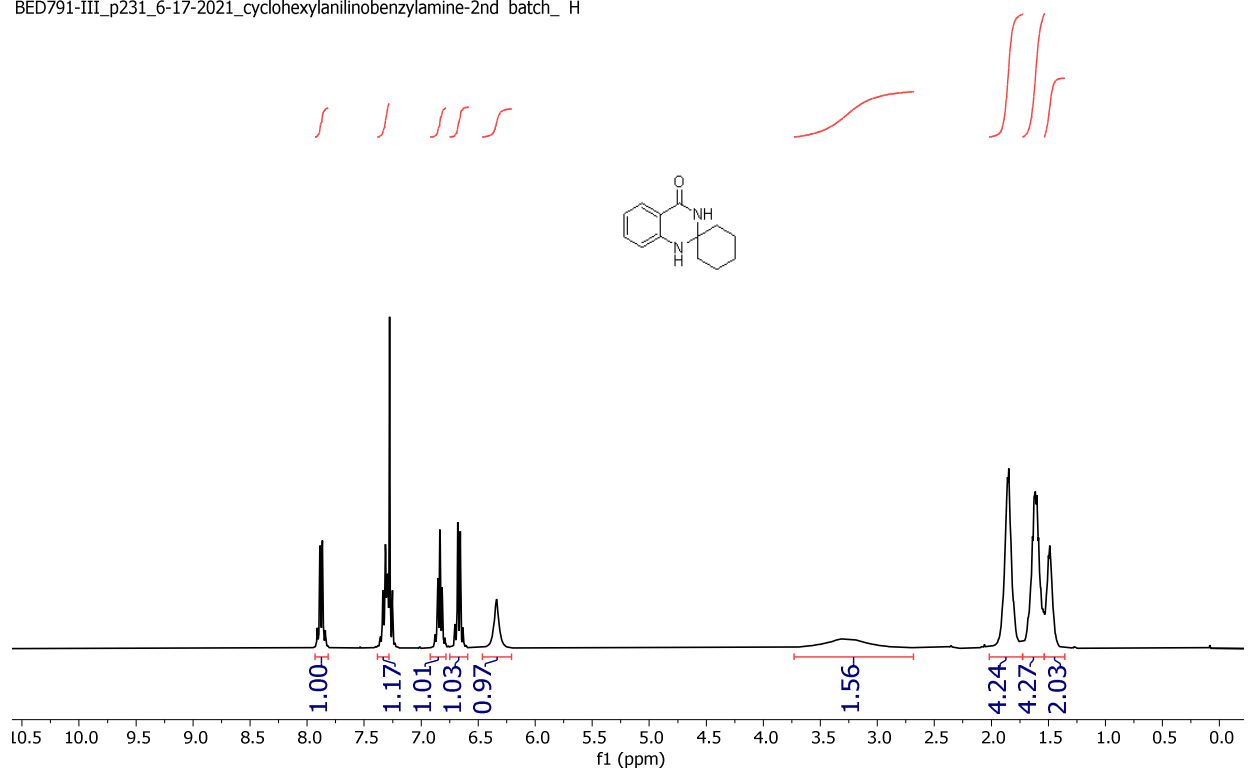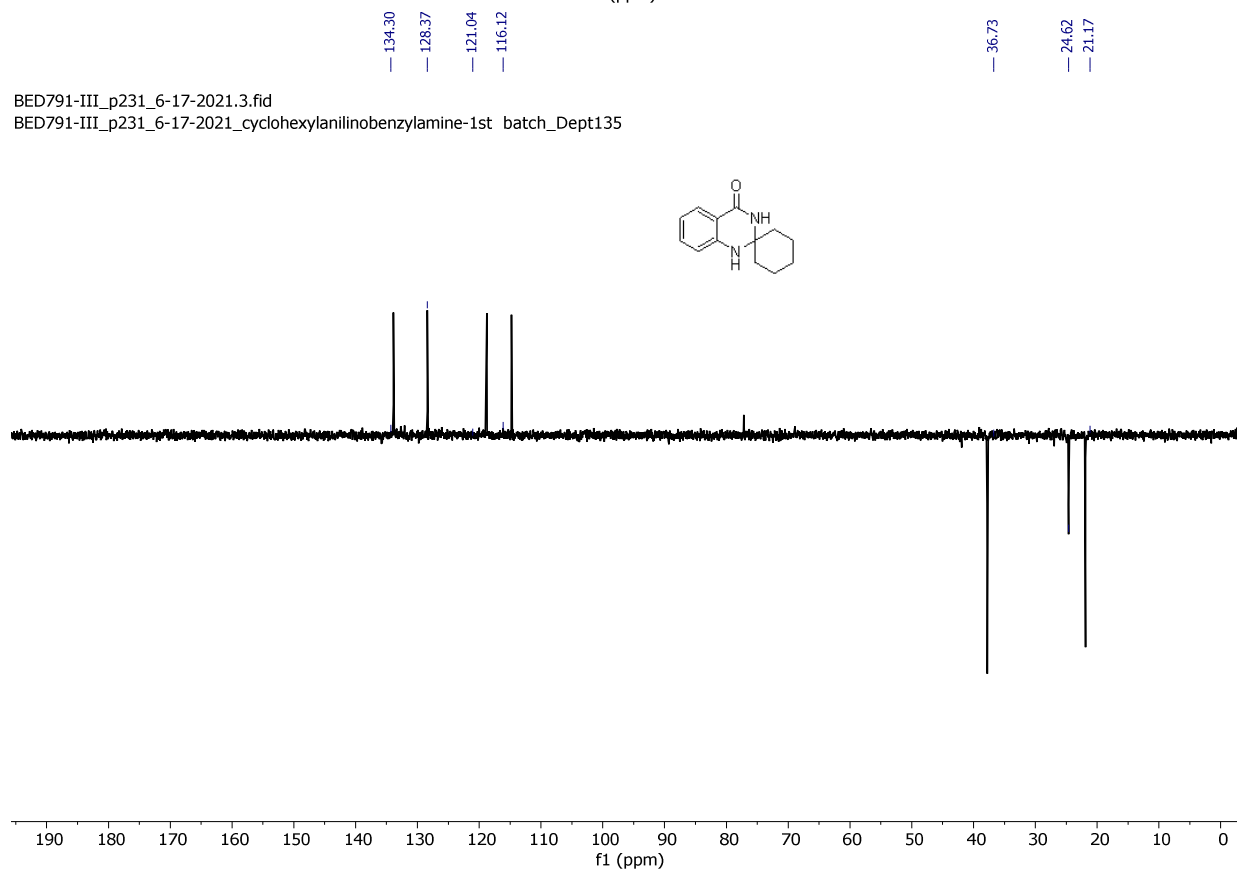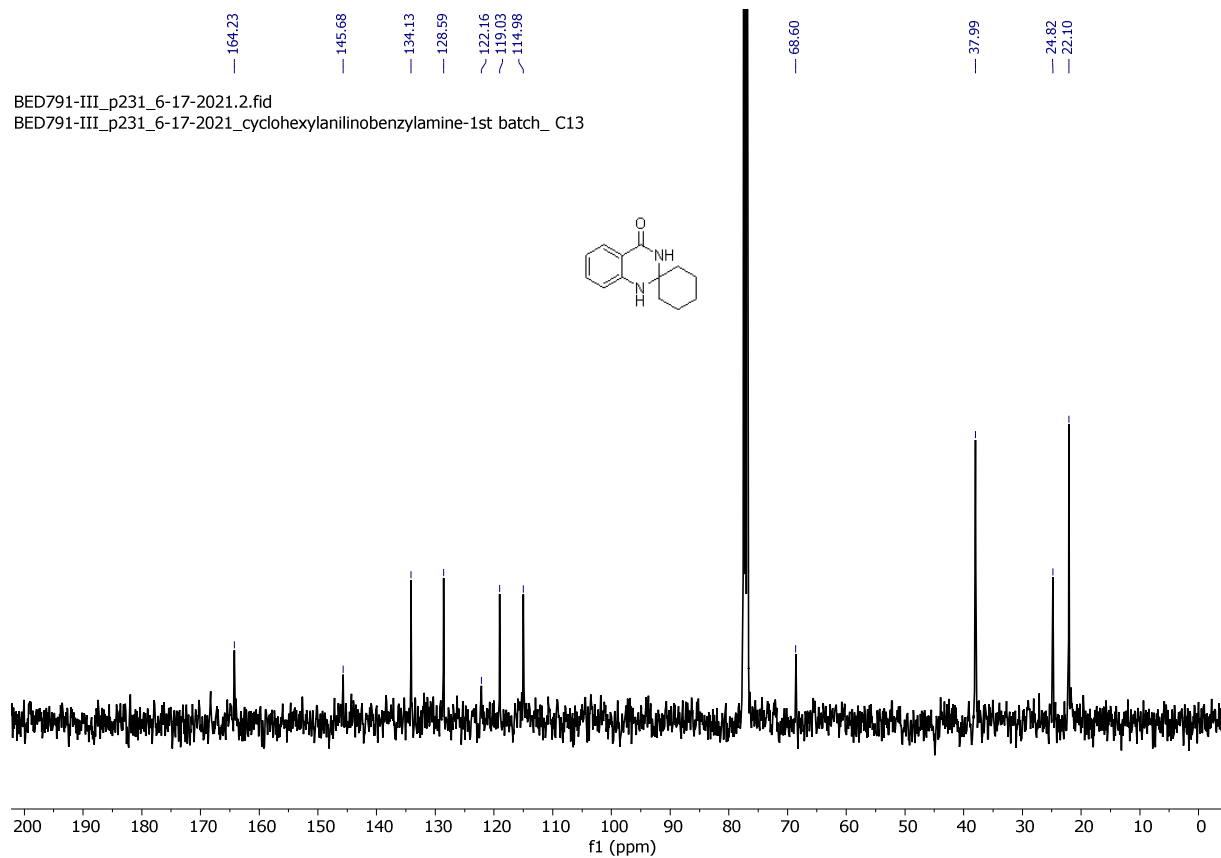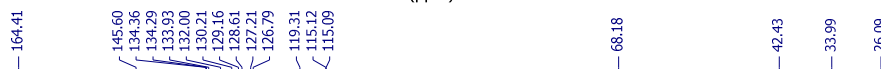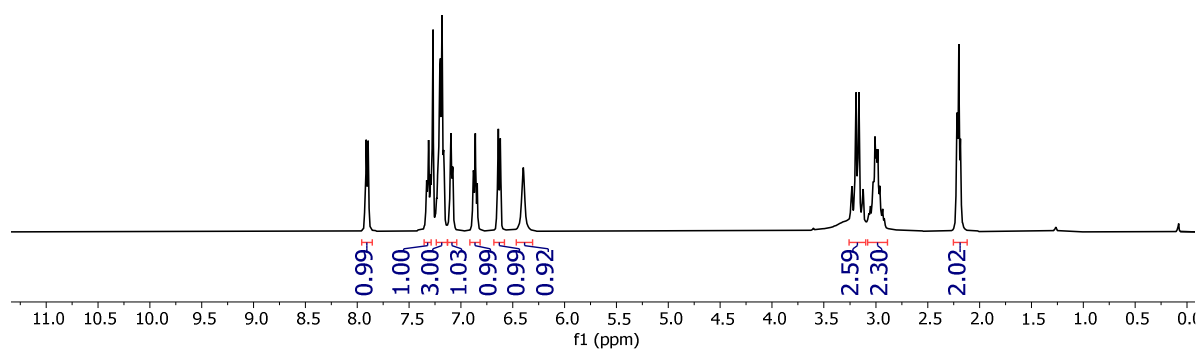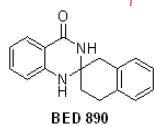
BED890-III_p285_9-11-2021.2.fid
BED890-III_p285_9-11-2021_2-aminobenzamide- beta tetralone condensation_ C13

f1 (ppm)

134.14
130.09
129.03
128.48
128.25
127.63
127.07
126.94
126.87
126.66
119.14
114.93

42.32
35.23
25.97

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

163.96

145.65
138.32
138.11
134.48
129.40
129.37
128.88
128.79
127.17
119.02
114.92
114.73

70.35

37.44
30.06
29.56
19.48

f1 (ppm)

134.14
129.05
129.02
128.54
128.44
126.83
118.67
114.58

36.59
28.53
19.13

f1 (ppm)

BED 896

BED 896

BED 896

134.48
128.17
119.14
115.86
67.29
26.51
20.49

BED 897

1.00
0.91
1.22
3.60
1.18
0.99
0.96
1.15
2.15
3.94
2.07

386

BED 897

BED 897

BED 905

1.00 1.01 1.01 0.85 1.03 2.08 1.03 0.95 2.08 2.06

163.84
155.21
144.92
134.55
131.20
128.69
128.42
123.74
121.43
119.51
117.52
115.27
114.72
66.24
62.99
36.41

BED 905

BED 905

134.44
131.08
128.56
128.30
121.31
119.39
117.40
115.15

62.86

36.27

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED 907

0.86
0.81
0.87
0.88
0.87

4.04

1.68
1.80
9.00

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

390

BED 907

134.81
128.43
120.04
113.53
60.42
37.20
28.40

BED 907

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED 909

0.93
1.08
0.96
0.95
0.84
1.29
3.86
3.98
6.00

12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

BED 919

BED 919

394

134.12
133.83
128.36
128.18
118.95
118.67
114.88
114.85
80.47
79.05
57.04
56.44
33.88
25.31
23.52
21.32
20.76
18.65

BED 919

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED 920

1.00
0.79
0.99
1.89
0.40
0.44
1.58
0.55
0.47
0.52
1.16
3.22
3.38
1.06
1.48
1.53

1.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

BED 924

BED 924

397

BED 924

134.46
134.19
128.33
128.14
119.32
119.18
115.12
114.59

64.79
63.62

32.37
30.62
29.27
20.87
20.49
18.76

240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -

f1 (ppm)

BED 925

1.00
1.23
1.02
1.05
0.91
3.11
2.09
5.36
2.10
1.05

11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

BED 925

BED 925

400

BED 936

BED 936

401

BED 936

BED 799

— 38.52
〜 36.70
— 32.51
— 25.16
— 22.11

f1 (ppm)

1.00
0.97
0.91
0.92
0.96

1.91

7.38
1.13

f1 (ppm)

143.58
133.00
124.51
121.15
116.80
116.21
71.41
37.03
25.52
22.28

BED 799

BED786-III_p227_5-7-2021.1.fid
BED786-III_p227_5-7-2021_cyclopentylanilinobenzylamine_ater column_ H

1.10
1.03
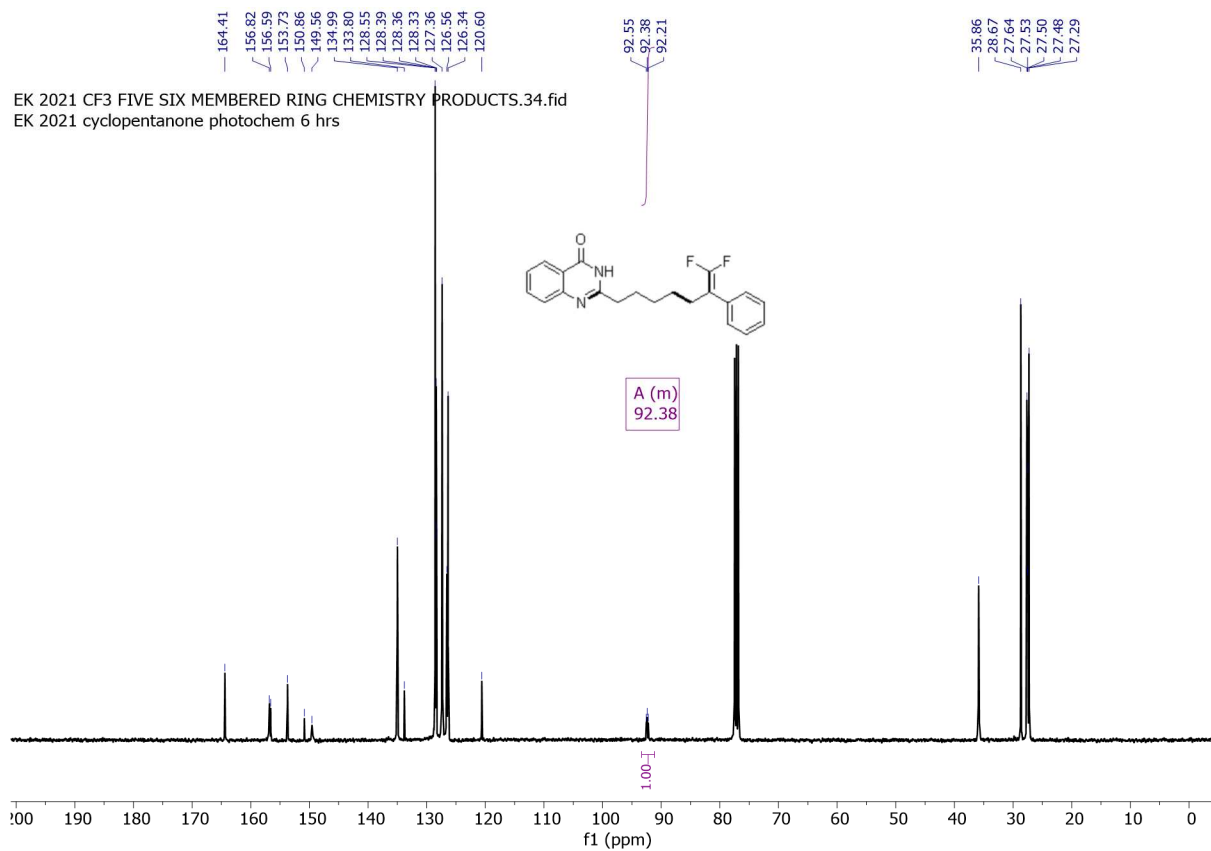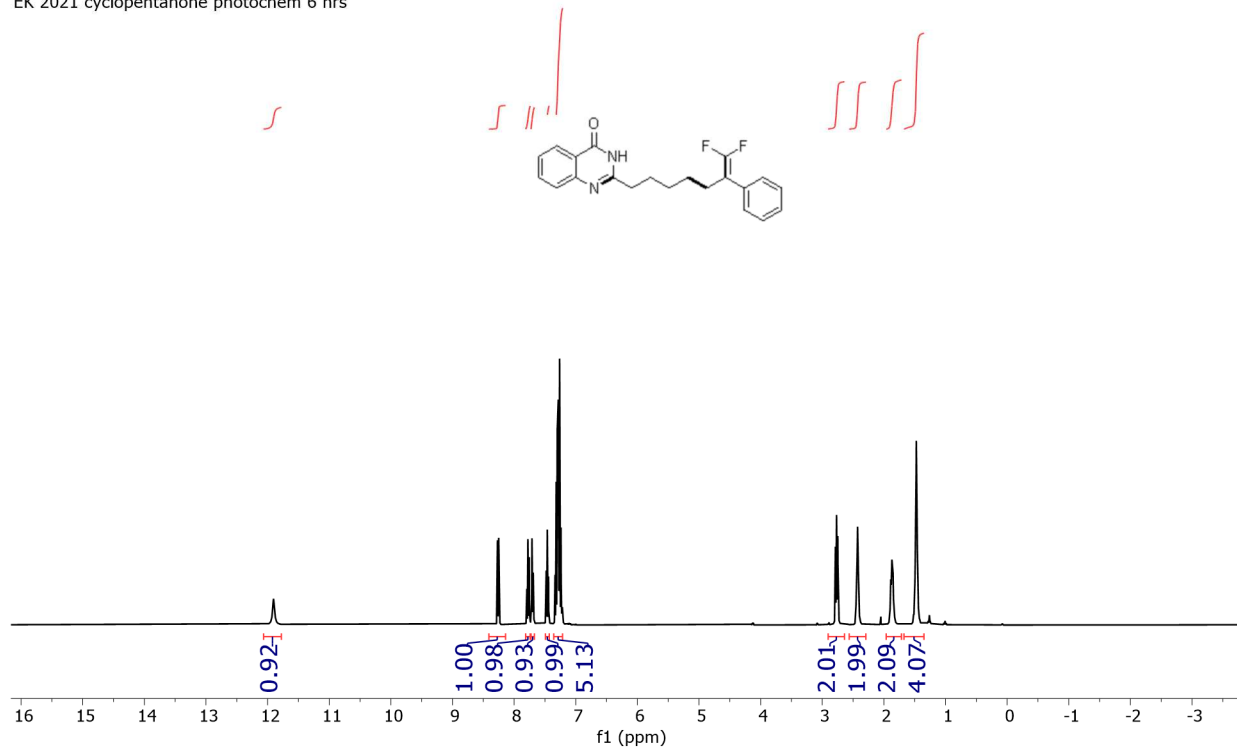1.09
1.00
2.48
10.16

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

143.38
127.46
126.43
120.86
117.76
115.28
76.42
43.72
40.23
40.05
39.88
39.83
24.65
24.07
23.89
23.59

BED786-III_p227_5-7-2021.2.fid
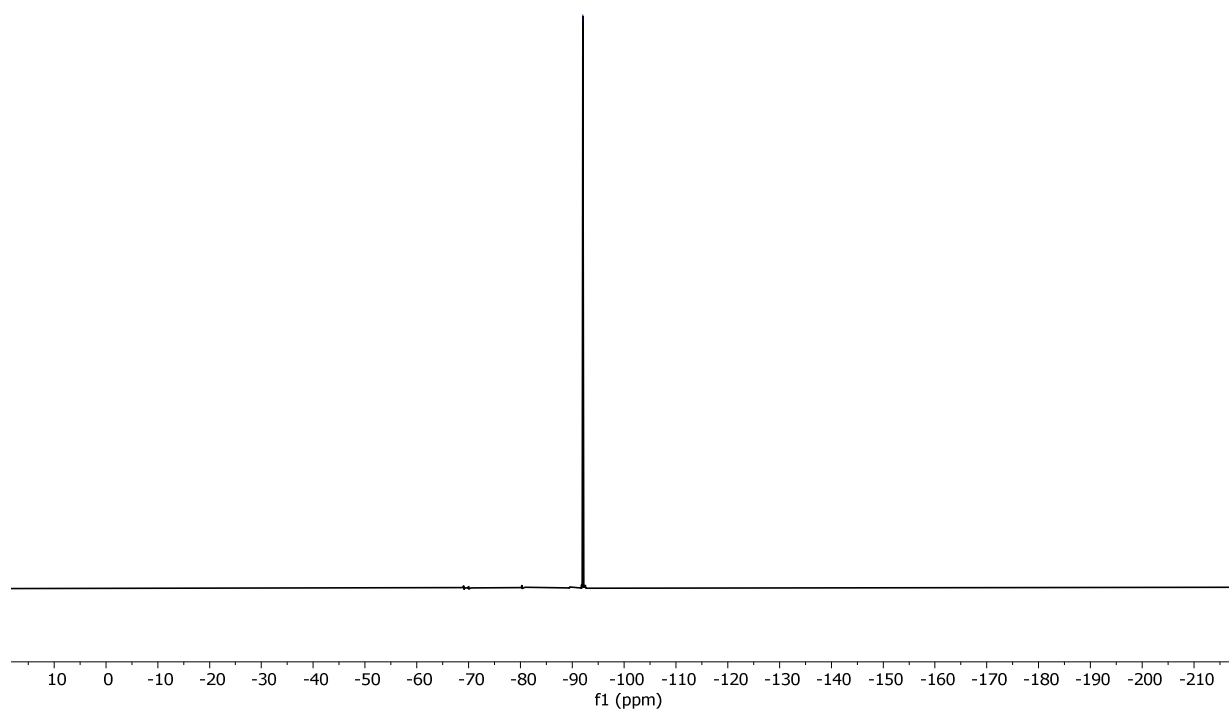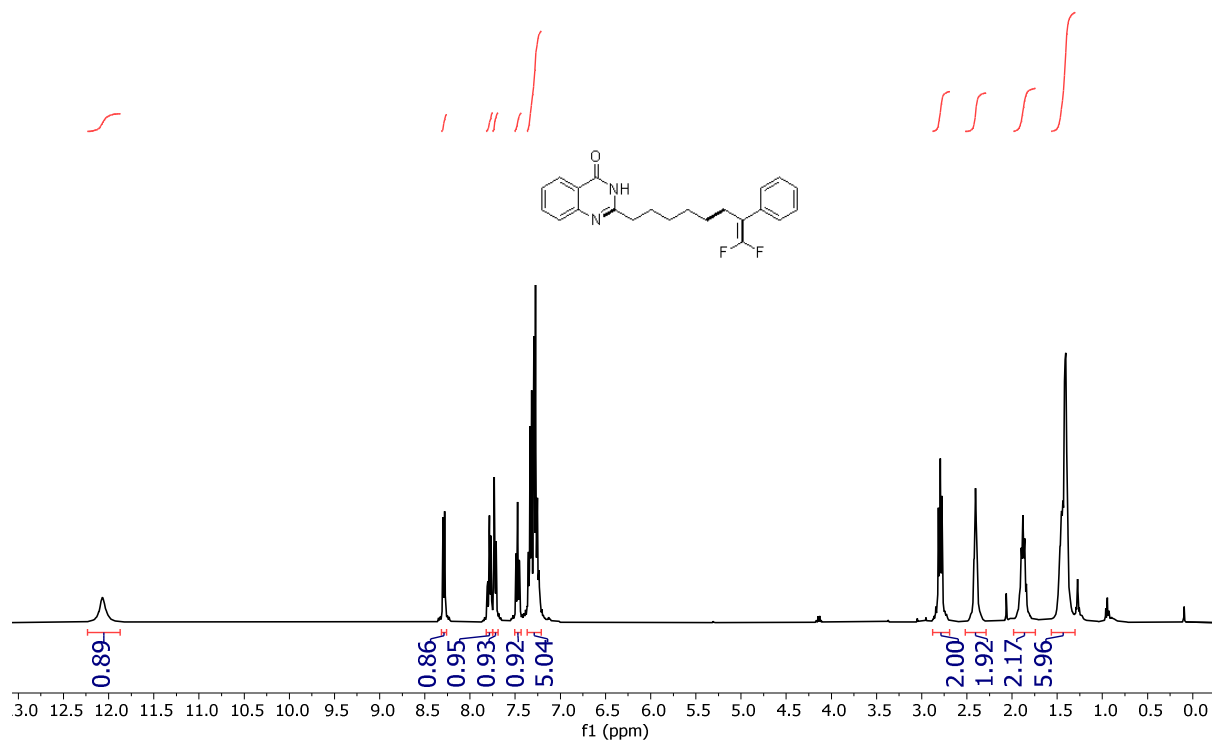BED786-III_p227_5-7-2021_cyclopentylanilinobenzylamine_after column_ C13

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

404

127.11
126.09
117.41
115.89
114.94
43.37
43.15
39.87
39.48
23.54

f1 (ppm)

BED787-III_p227_5-7-2021.1.fid
BED787-III_p227_5-7-2021_cyclohexyylanilinobenzylamine_after column-1st batch_ H

0.94
0.87
0.94
0.86
2.12
4.07
6.00

f1 (ppm)

407

134.80
128.34
128.18
128.15
128.12
127.16
126.37
126.14

35.63
28.47
27.43
27.27
27.09

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

92.06

10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

409

164.79
157.52
157.33
156.78
153.91
151.05
149.75
135.18
134.10
134.09
128.74
128.61
128.58
128.55
128.48
127.53
127.53
127.52
127.51
126.72
126.54
120.80
92.83
92.67
92.66
92.49
36.23
36.13
29.22
28.96
27.92
27.90
27.89
27.87
27.84
27.78
27.62

f1 (ppm)

BED778-III_p221_4-22-2021.5.ser
BED778-III_p221_4-22-2021_cyclohexylanilinobenzamide-CF3styrene-Ir-Na2SO4-K3PO4_spot_3_HSQC

— 92.19

413

134.84
129.01
128.41
128.32
128.29
128.25
127.22
126.38
126.17

36.01
35.97
34.89
30.90
30.85
24.94
19.04

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED781-III_p224_4-30-2021.6.ser
BED781-III_p224_4-30-2021_2-methylcyclopentylanilinobenzamide_CF3tyr-Ir-dmf-18h_spot 2_HSQC

12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)

f1 (ppm)

415

BED781-III_p224_4-30-2021.7.ser
BED781-III_p224_4-30-2021_2-methylcyclopentylanilinobenzamide_CF3tyr-Ir-dmf-18h_spot_2_COSY

-91.68
-91.80
-91.93
-92.05

BED 782

BED782-III_p224_4-30-2021.7.ser
BED782-III_p224_4-30-2021_2,2-dimethylcyclopentylanilinobenzamide_CF3tyr-Ir-dmf-18h_spot 2_HSQC

418

BED782-III_p224_4-30-2021.8.ser
BED782-III_p224_4-30-2021_2,2-dimethylcyclopentylanilinobenzamide_CF3tyr-Ir-dmf-18h_spot 2_COSY

-89.89
-90.00
-92.19
-92.30

133.25
128.44
128.25
128.22
128.18
127.73
127.47
127.25
126.67
123.80
117.63

36.30

28.57
27.49
27.46
26.45

BED822-III_p253_6-28-2021.12.ser
BED822-III_p253_6-28-2021_cyclohexylsulfonamide-CF3styr-Ir-K3PO4-spot 5_HSQC

f1 (ppm)

f2 (ppm)

-92.18
-92.24

0.76

1.00
2.07
1.09
1.18
4.88
3.97

1.83
1.86
1.86
1.99

f1 (ppm)

422

163.83
155.85
149.48
139.29
136.25
135.01
130.61
130.03
129.16
127.44
126.83
126.46
126.41
120.77

36.71
32.10
19.48

134.89
130.48
129.03
127.29
126.70
126.59
126.33
126.28

37.22
31.02
19.35

10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

425

f1 (ppm)

0.85
1.03
1.05
1.07
1.09
2.44
1.99
1.00
1.88
2.00
2.04
6.00

161.70
157.12
154.25
154.22
153.36
151.36
148.87
134.95
134.90
133.05
133.02
133.01
132.98
128.76
128.66
128.53
128.51
128.12
128.08
128.05
127.39
127.38
127.07
126.74
126.65
121.62
101.48
101.46
101.42
89.72
89.58
89.51
89.37
77.16 CDCl3
60.18
60.12
59.25
59.22
59.21
59.19
31.02
28.42
28.40
24.82
24.80
24.74

f1 (ppm)

426

BED901-III_p292_9-16-2021.4.fid
BED901-III_p292_9-16-2021_dimethyldimethoxypropanebenzamide-CF3styr-K3PO4-dmf-14h_ spot 2_Dept135

134.83
129.08
128.42
128.17
128.00
127.30
126.98
126.66
126.58
59.98
59.12
58.67
30.94
28.74
28.31
24.76
24.71

00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED902-III_p292_9-16-2021.2.fid
BED902-III_p292_9-16-2021_4-Phcyclohexylbenzamide-CF3styr-K3PO4-dmf-35h_spot 2_H

0.70   0.86 0.87 0.86 1.00 8.53   2.65 1.67 1.88 2.00 2.30

2.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

427

164.14
156.84
156.55
153.68
150.82
149.37
144.46
144.18
134.93
133.69
133.68
128.62
128.55
128.47
128.35
128.31
128.28
127.97
127.82
127.27
127.20
126.50
126.41
126.33
120.57
92.39
92.22
92.20
92.04
77.16 CDCl3
45.61
36.04
34.43
34.28
34.23
33.94
27.56
27.55
27.53
25.53
25.50
25.48

f1 (ppm)

134.74
128.42
128.35
128.27
128.14
128.11
128.08
127.77
127.62
127.07
127.00
126.30
126.21
126.13
77.16 CDCl3
45.41
35.84
35.39
34.22
34.18
34.04
27.34
25.32
25.27

f1 (ppm)

428

BED911-III_p296_10-6-2021.2.fid
BED911-III_p296_10-6-2021_N-bocpiperidinyl-2-aminobenzamide-CF3styr-K3PO4-dmf_isolated spot_ H

0.65

0.97
1.02
0.97
1.05
2.32
3.78

1.89
2.27
2.44
1.93

1.92
9.00

12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

163.68
163.02
156.71
155.98
154.77
153.84
150.98
149.35
135.10
133.66
129.24
128.87
128.55
128.52
127.93
127.74
127.38
126.92
126.70
121.08

92.30
92.13
91.96

80.47

47.84
45.30

35.26
30.06
28.64
27.06
25.43

BED911-III_p296_10-6-2021.7.fid
BED911-III_p296_10-6-2021_N-bocpiperidinyl-2-aminobenzamide-CF3styr-K3PO4-dmf_isolated spot_ C13

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

429

BED911-III_p296_10-6-2021.4.fid
BED911-III_p296_10-6-2021_N-bocpiperidinyl-2-aminobenzamide-CF3styr-K3PO4-dmf_isolated spot_Dept135
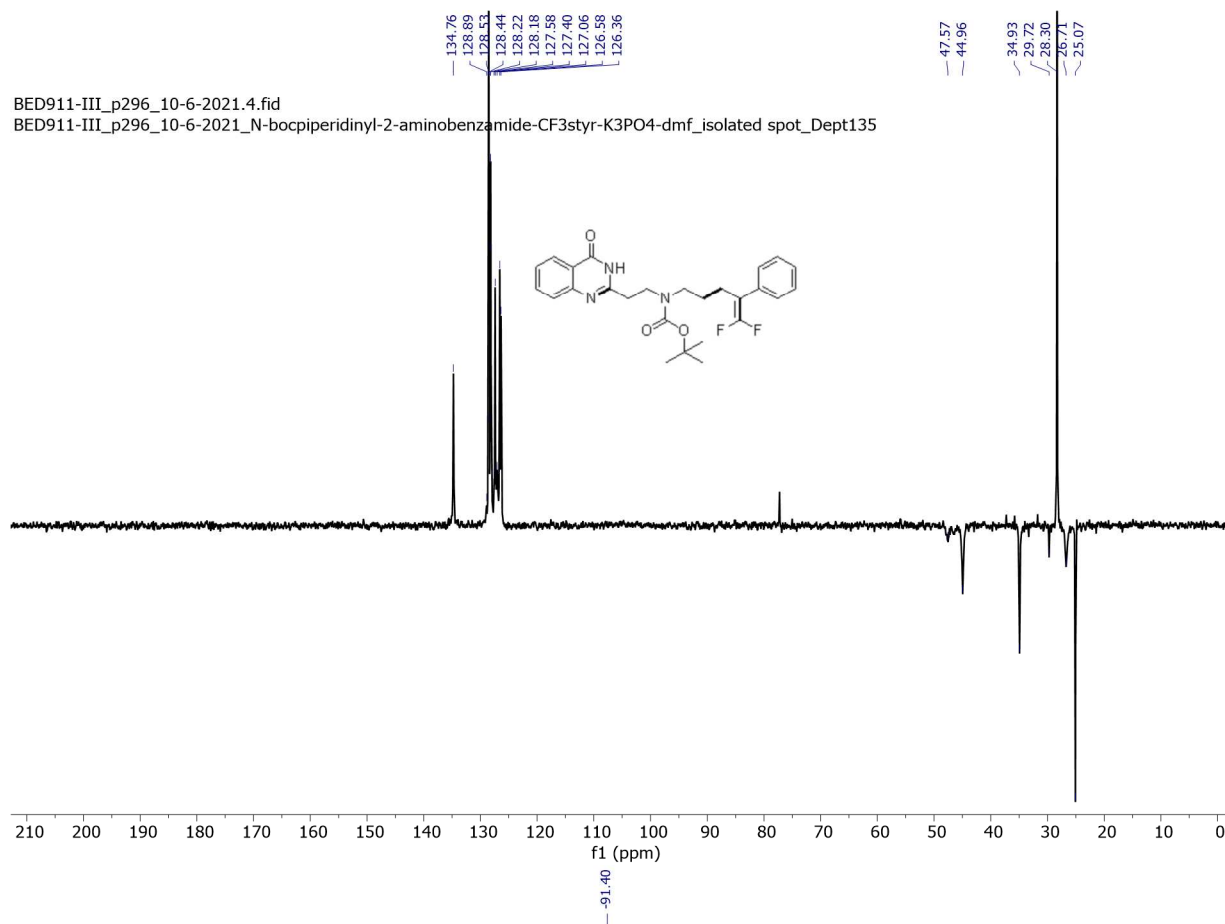
BED911-III_p296_10-6-2021.3.fid
BED911-III_p296_10-6-2021_N-bocpiperidinyl-2-aminobenzamide-CF3styr-K3PO4-dmf_isolated spot_ F19
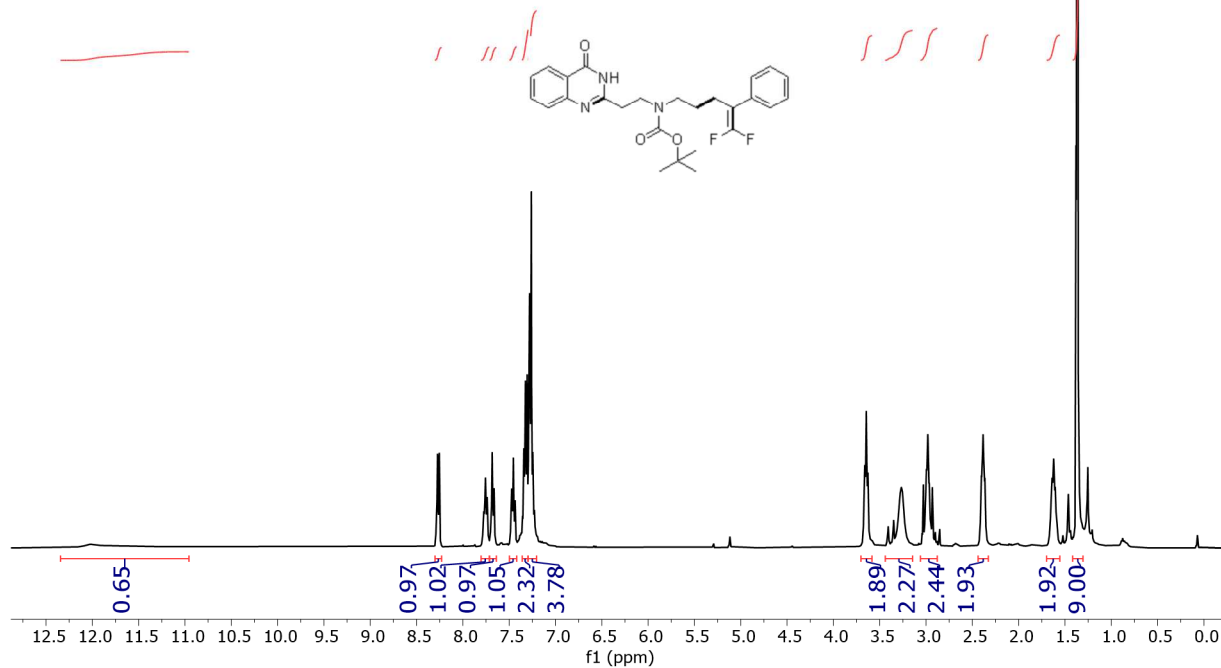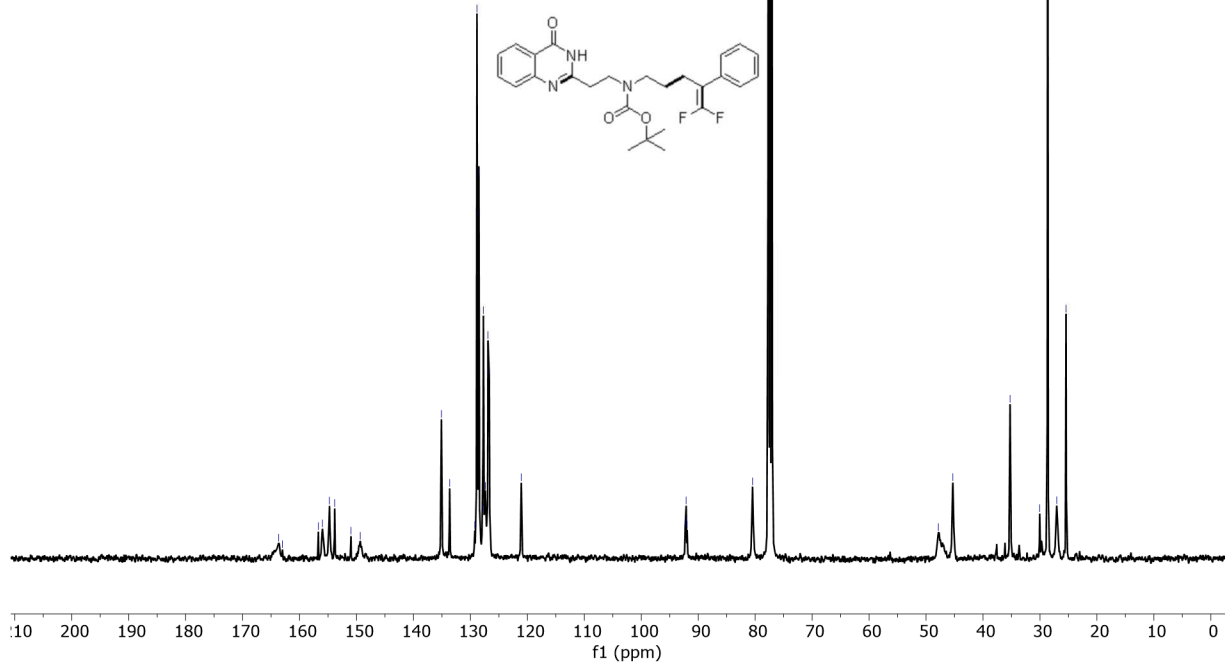

430
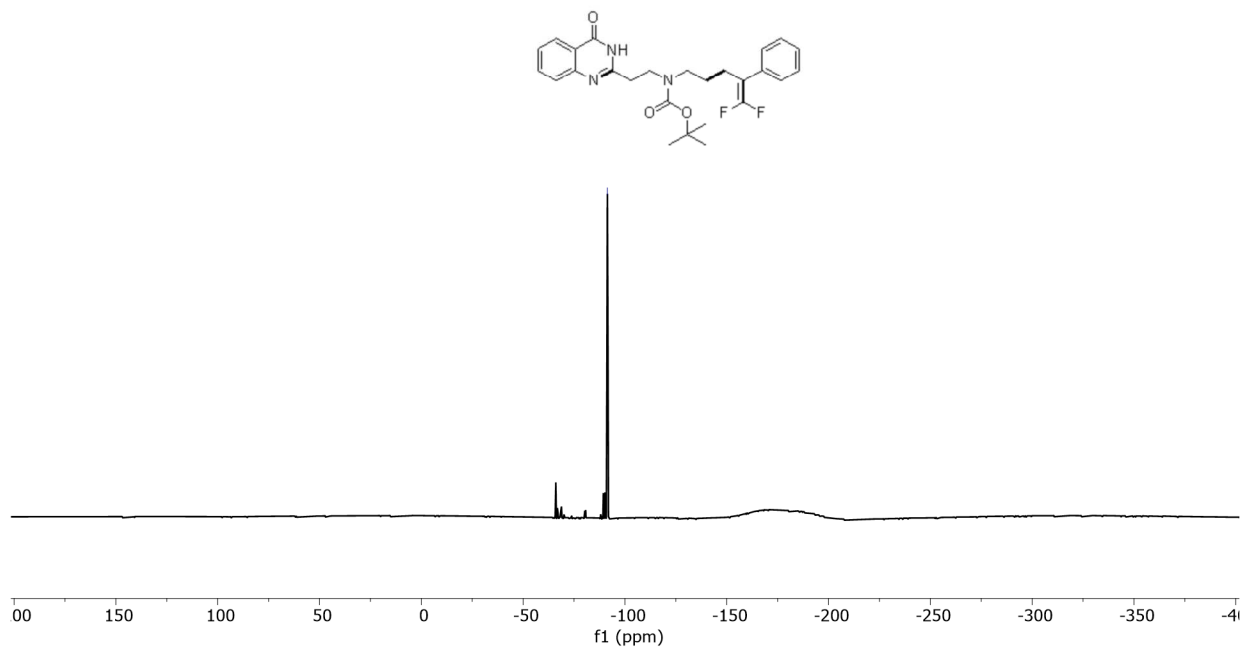
BED912-III_p297_10-6-2021.2.fid
BED912-III_p297_10-6-2021_4,4-dimethylcyclohexylaminobenzamide-CF3styr-K3PO4-dmf_isolated spot_ H
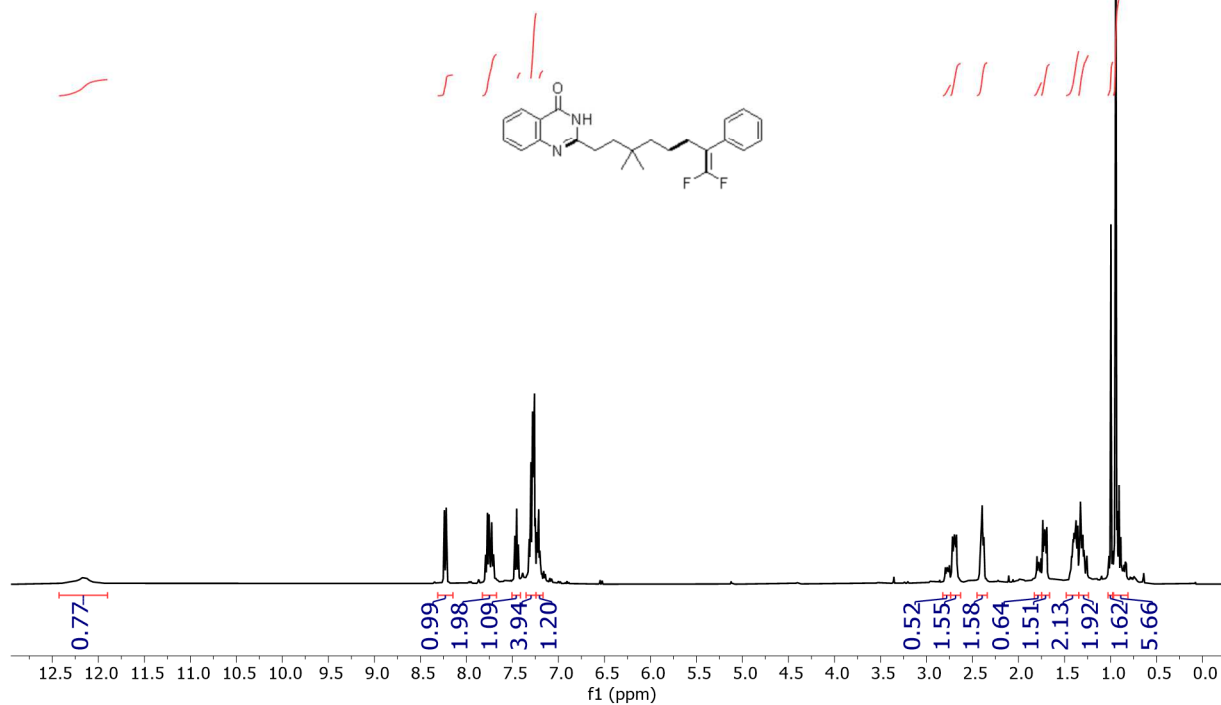
BED912-III_p297_10-6-2021.6.fid
BED912-III_p297_10-6-2021_4,4-dimethylcyclohexylaminobenzamide-CF3styr-K3PO4-dmf_isolated spot_ C13

431

134.84 128.39 128.29 128.26 128.23 127.19 127.06 126.40 126.15

42.16 39.59 39.31 34.63 31.24 28.71 26.68 26.38 22.06

8.45

BED912-III_p297_10-6-2021.4.fid
BED912-III_p297_10-6-2021_4,4-dimethylcyclohexylaminobenzamide-CF3styr-K3PO4-dmf_isolated spot_Dept135

f1 (ppm)

—91.99

BED912-III_p297_10-6-2021.3.fid
BED912-III_p297_10-6-2021_4,4-dimethylcyclohexylaminobenzamide-CF3styr-K3PO4-dmf_isolated spot_ F19

f1 (ppm)

432
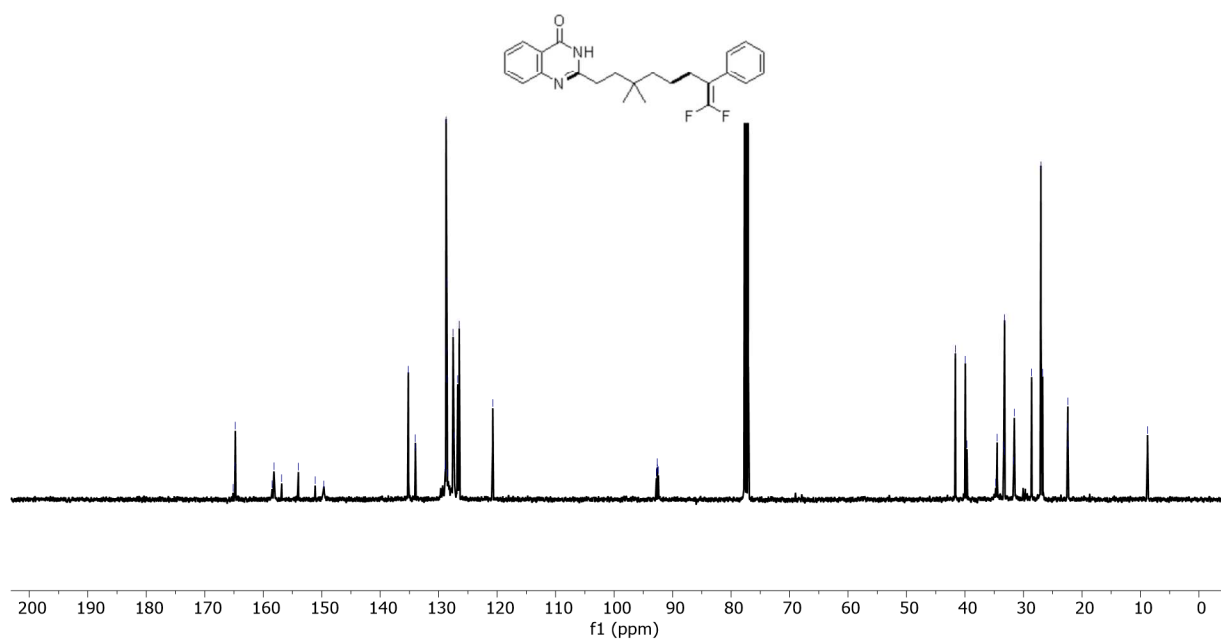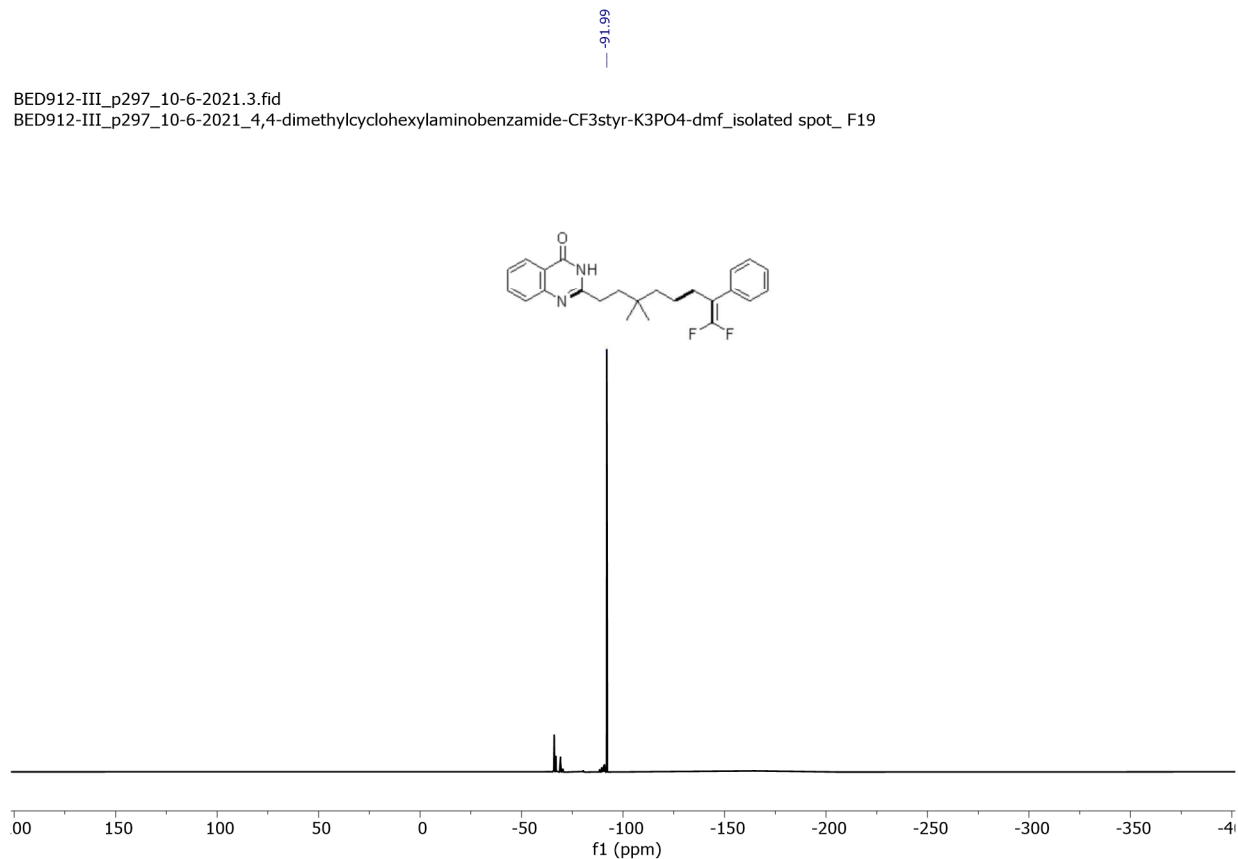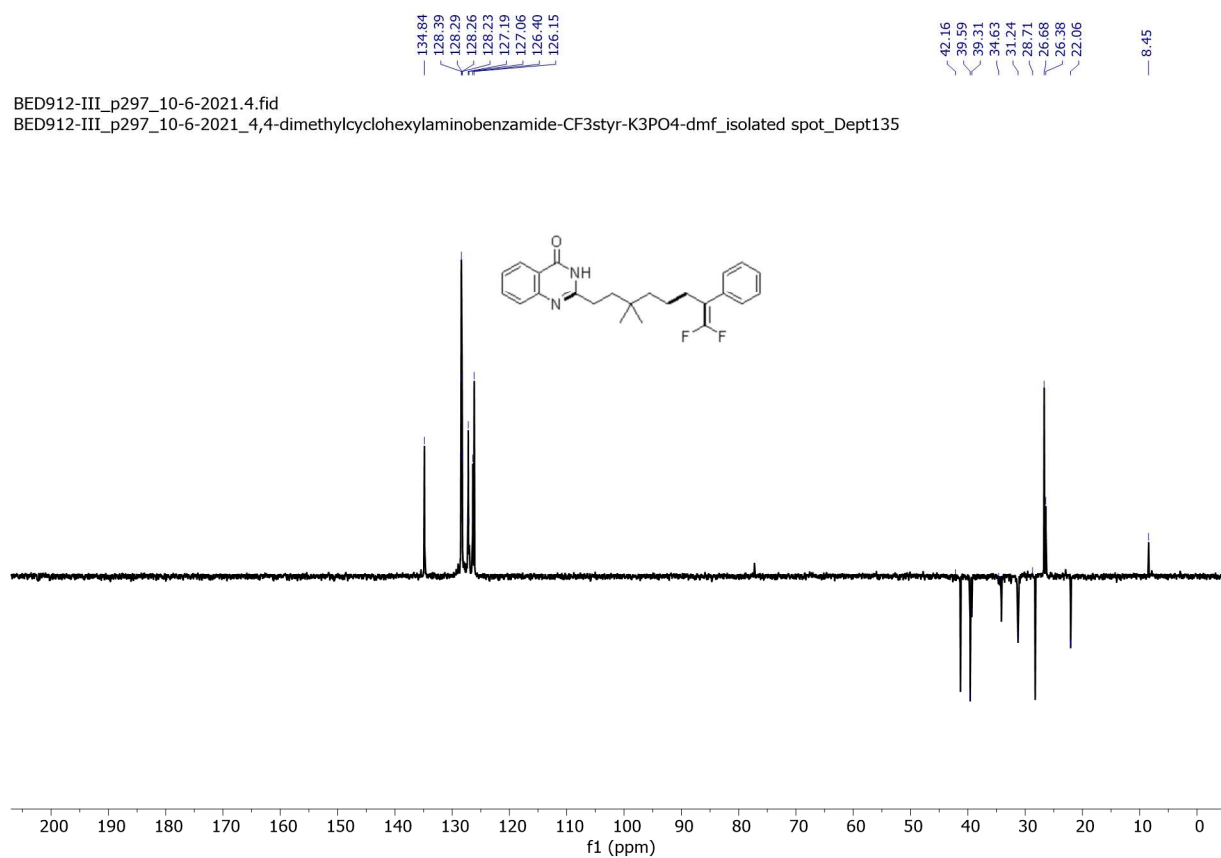
BED916-III_p299_10-11-2021.2.fid
BED916-III_p299_10-11-2021_cyclohexylbenzamide-2-MeO-CF3styr-K3PO4-dmf-43h_spot 2_ H
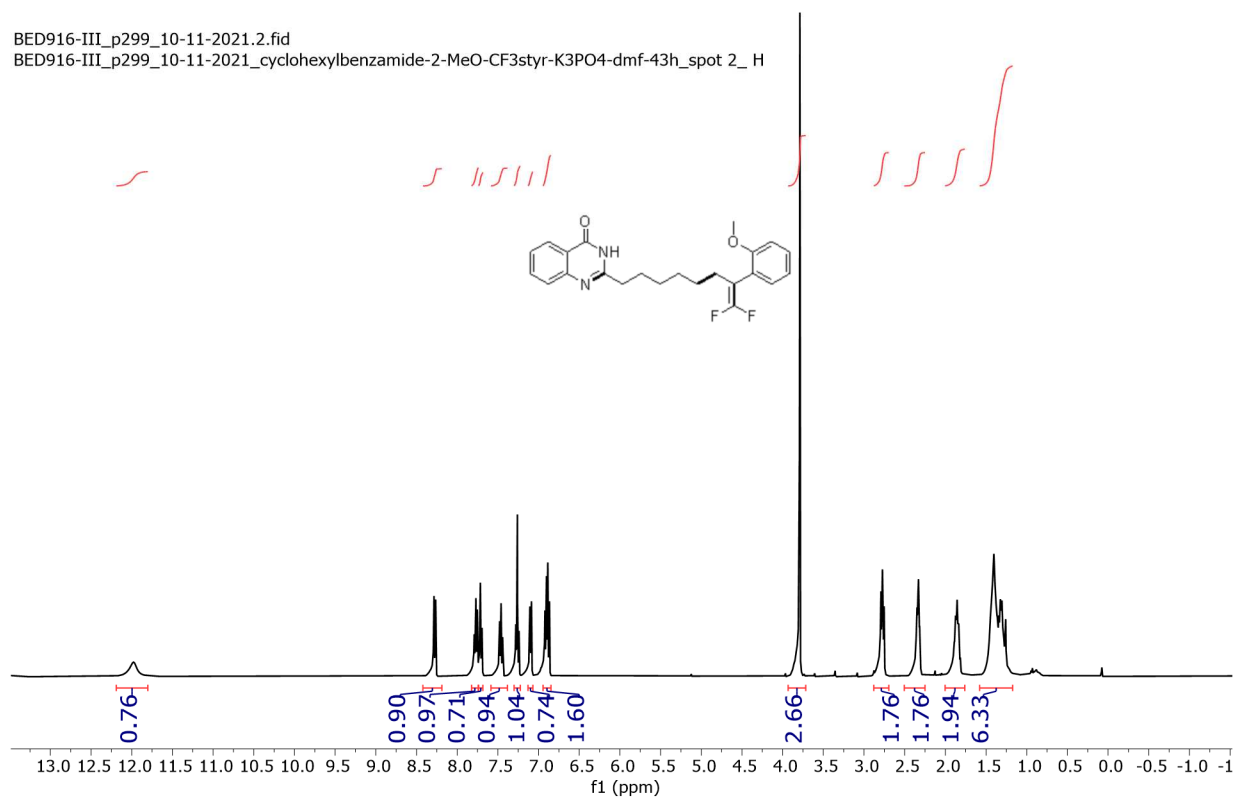
BED916-III_p299_10-11-2021.5.fid
BED916-III_p299_10-11-2021_cyclohexylbenzamide-2-MeO-CF3styr-K3PO4-dmf-43h_spot 2_ C13

433

134.74
130.96
128.92
127.07
126.30
126.14
120.29
110.87
55.37
35.77
28.88
28.54
27.58
27.49
27.40
27.31
27.21

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

90.80
90.92
94.60
94.72

-50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120
f1 (ppm)

434
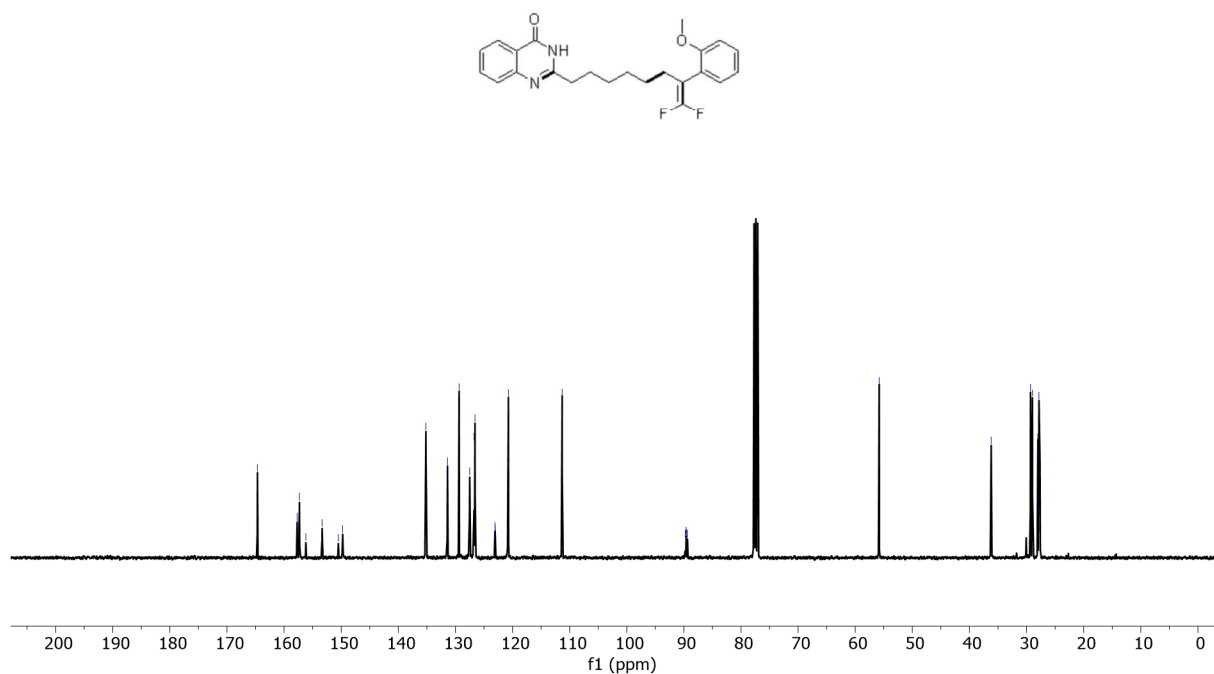
BED917-III_p299_10-11-2021.4.fid
BED917-III_p299_10-11-2021_cyclohexylbenzamide-4-PhenylCF3styr-K3PO4-dmf-43h_2nd fraction_ H
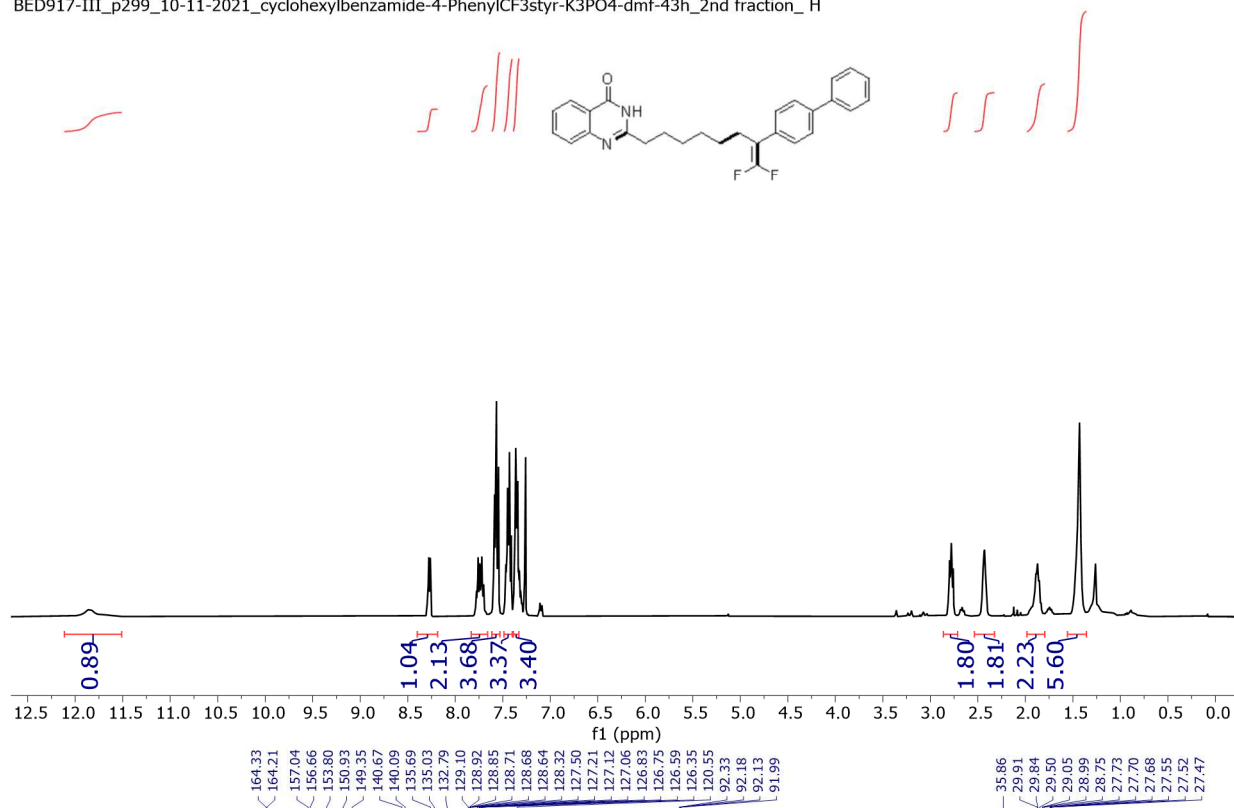
BED917-III_p299_10-11-2021.6.fid
BED917-III_p299_10-11-2021_cyclohexylbenzamide-4-PhenylCF3styr-K3PO4-dmf-43h_2nd fraction_ C13

435

134.83
128.89
128.71
128.64
128.50
128.47
128.44
128.11
127.30
127.00
126.92
126.85
126.63
126.54
126.38
126.14

35.66
28.78
28.55
27.33
26.86

BED917-III_p299_10-11-2021.7.fid
BED917-III_p299_10-11-2021_cyclohexylbenzamide-4-PhenylCF3styr-K3PO4-dmf-43h_2nd fraction_Dept135

BED917-III_p299_10-11-2021.5.fid
BED917-III_p299_10-11-2021_cyclohexylbenzamide-4-PhenylCF3styr-K3PO4-dmf-43h_2nd fraction_ F19

436

BED921-IV_p204_10-17-2021.2.fid
BED921-IV_p204_10-17-2021_2-MeOcyclohexylbenzamide-CF3styr-K3PO4-dmf-37h_spot 2_ H

0.74

0.99
1.02
0.98
1.08
4.08
1.35

3.00
0.99
1.93
1.17
0.99
1.98
3.93

f1 (ppm)

164.52
162.82
157.15
156.95
154.28
151.41
149.49
134.92
133.80
128.98
128.57
128.41
128.38
128.35
128.23
128.01
127.54
127.43
127.25
126.48
126.32
120.57

90.25
90.07
89.89

78.97
78.94
78.91

56.94

35.91
35.76
33.39
33.22
32.35
27.64
24.68
24.26
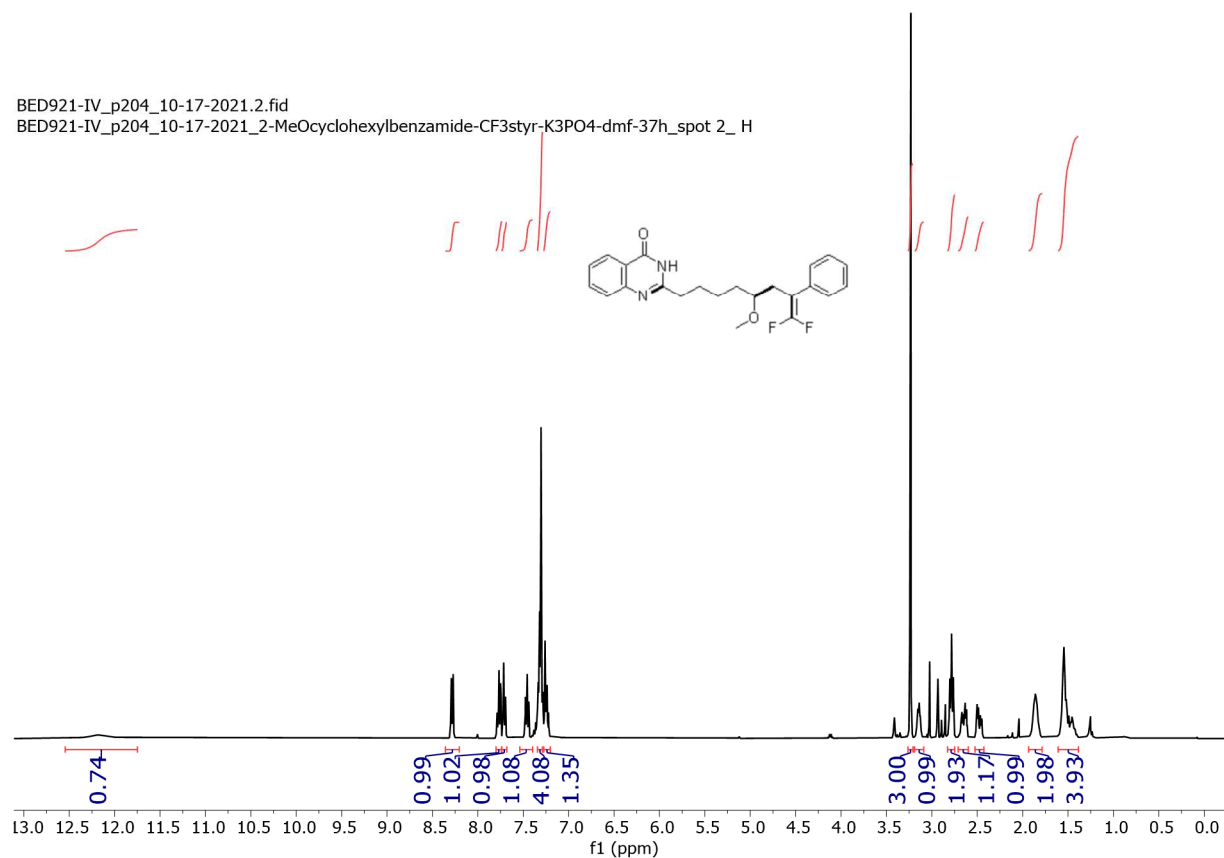
BED921-IV_p204_10-17-2021.4.fid
BED921-IV_p204_10-17-2021_2-MeOcyclohexylbenzamide-CF3styr-K3PO4-dmf-37h_spot 2_ C13

f1 (ppm)

437

BED921-IV_p204_10-17-2021.5.fid
BED921-IV_p204_10-17-2021_2-MeOcyclohexylbenzamide-CF3styr-K3PO4-dmf-37h_spot 2_Dept135

161.07

133.18
127.24
126.83
126.67
126.64
126.61
126.48
126.27
125.80
125.69
125.50
124.74
124.57

55.20

34.16
31.47
30.60
25.90
22.94

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

90.92

BED921-IV_p204_10-17-2021.3.fid
BED921-IV_p204_10-17-2021_2-MeOcyclohexylbenzamide-CF3styr-K3PO4-dmf-37h_spot 2_ F19

00 150 100 50 0 -50 -100 -150 -200 -250 -300 -350 -4(
f1 (ppm)

438

BED922-IV_p204_10-17-2021.2.fid
BED922-IV_p204_10-17-2021_2-carboxycyclohexylbenzamide-CF3styr-K3PO4-dmf-37h_spot 3_ H
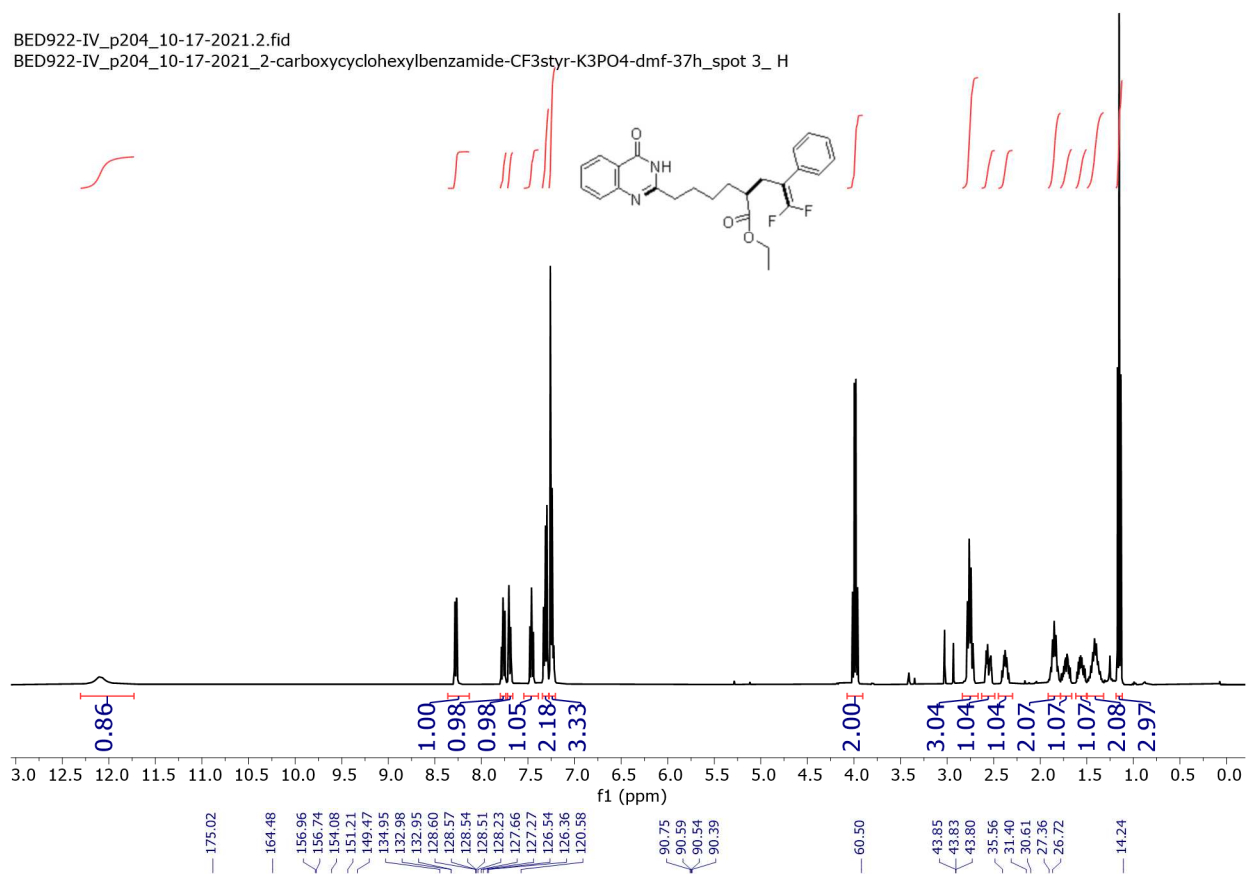
BED922-IV_p204_10-17-2021.4.fid
BED922-IV_p204_10-17-2021_2-carboxycyclohexylbenzamide-CF3styr-K3PO4-dmf-37h_spot 3_ C13

439

BED922-IV_p204_10-17-2021.5.fid
BED922-IV_p204_10-17-2021_2-carboxycyclohexylbenzamide-CF3styr-K3PO4-dmf-37h_spot 3_Dept135

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

BED922-IV_p204_10-17-2021.3.fid
BED922-IV_p204_10-17-2021_2-carboxycyclohexylbenzamide-CF3styr-K3PO4-dmf-37h_spot 3_ F19

100   50   0   -50   -100   -150   -200   -250   -300   -350
f1 (ppm)

440
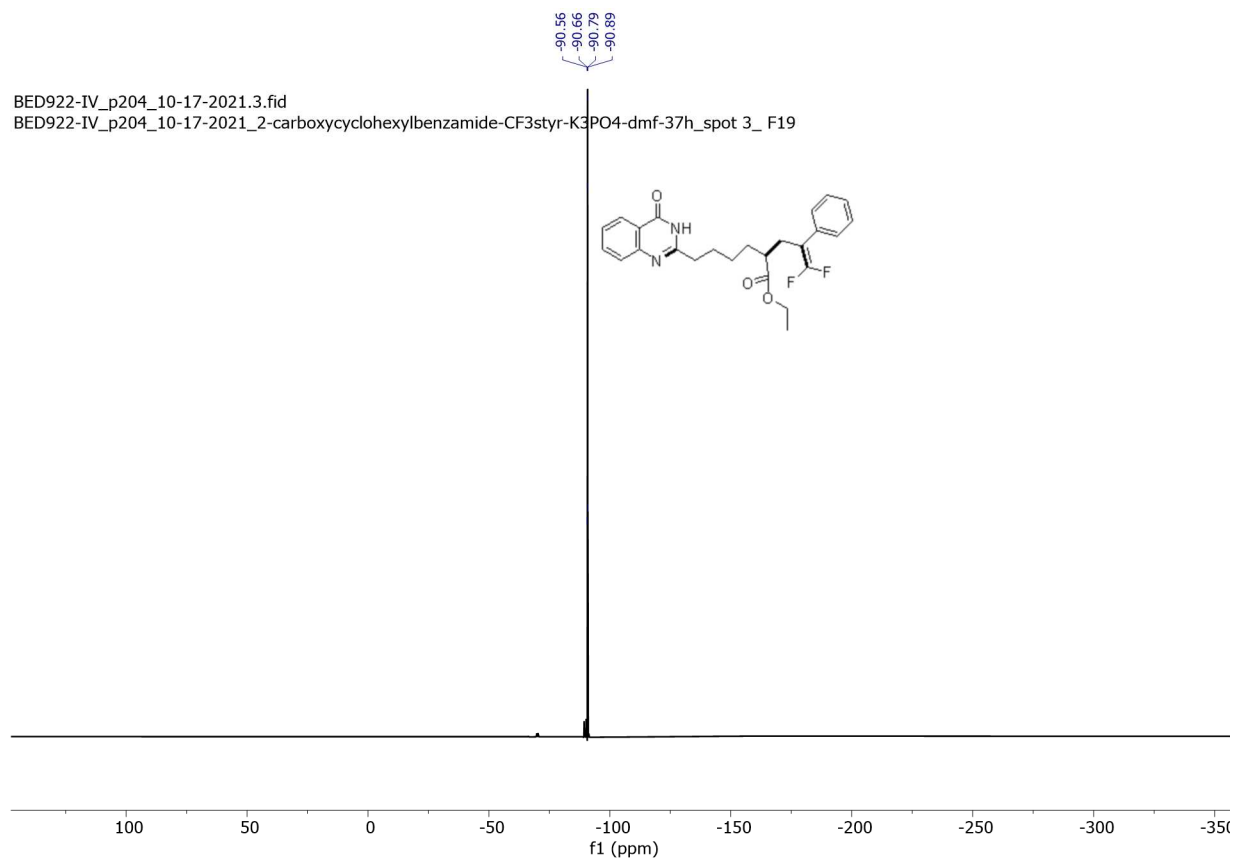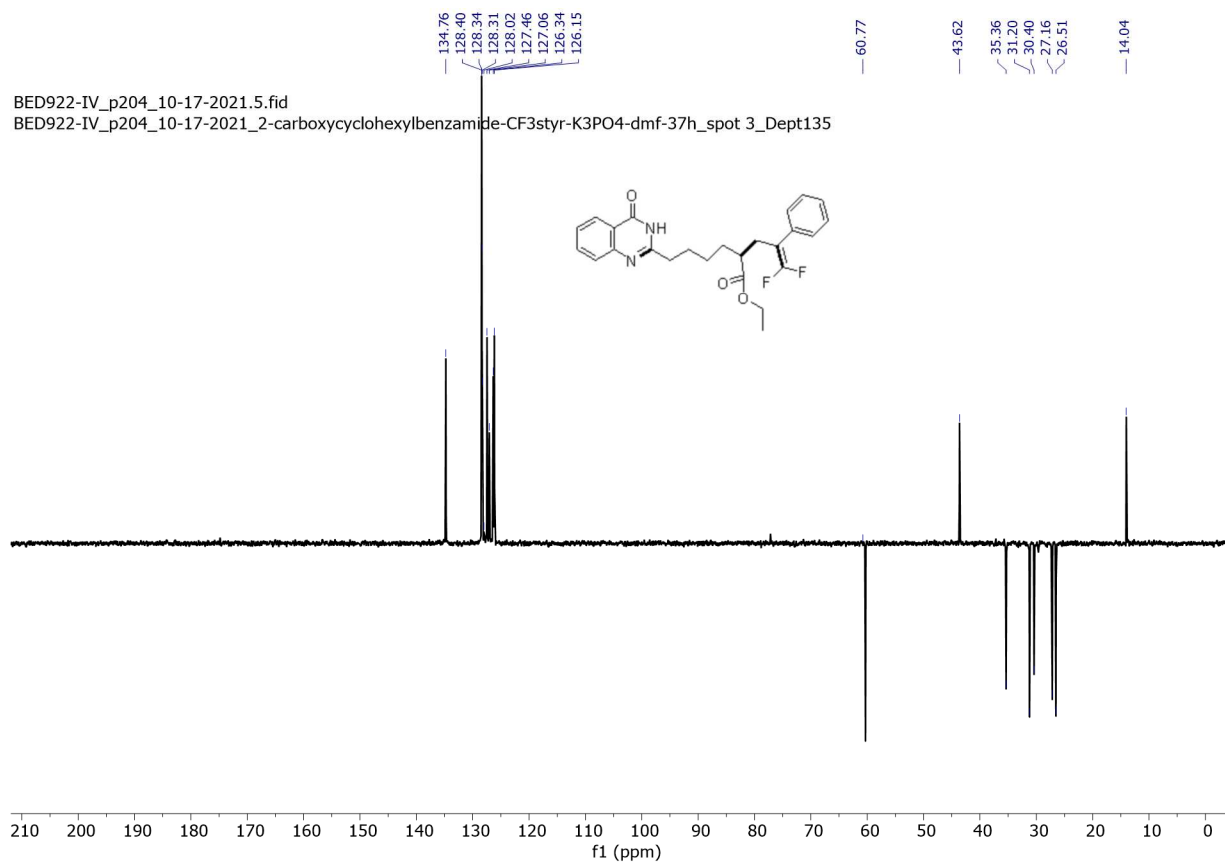
BED923-IV_p205_10-17-2021.2.fid
BED923-IV_p205_10-17-2021_cycloheptylbenzamide-CF3styr-K3PO4-dmf-37h_spot 2_ H

13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

0.85   1.00 0.99 0.99 1.01 5.16   1.98 1.98 2.04 2.16 6.20

164.58
157.16
156.53
153.67
150.81
149.56
134.94
133.94
133.92
128.50
128.38
128.34
128.31
127.30
127.27
126.46
126.31
120.57
92.67
92.51
92.49
92.33
35.96
29.83
29.26
29.03
28.94
27.81
27.79
27.76
27.70
27.60
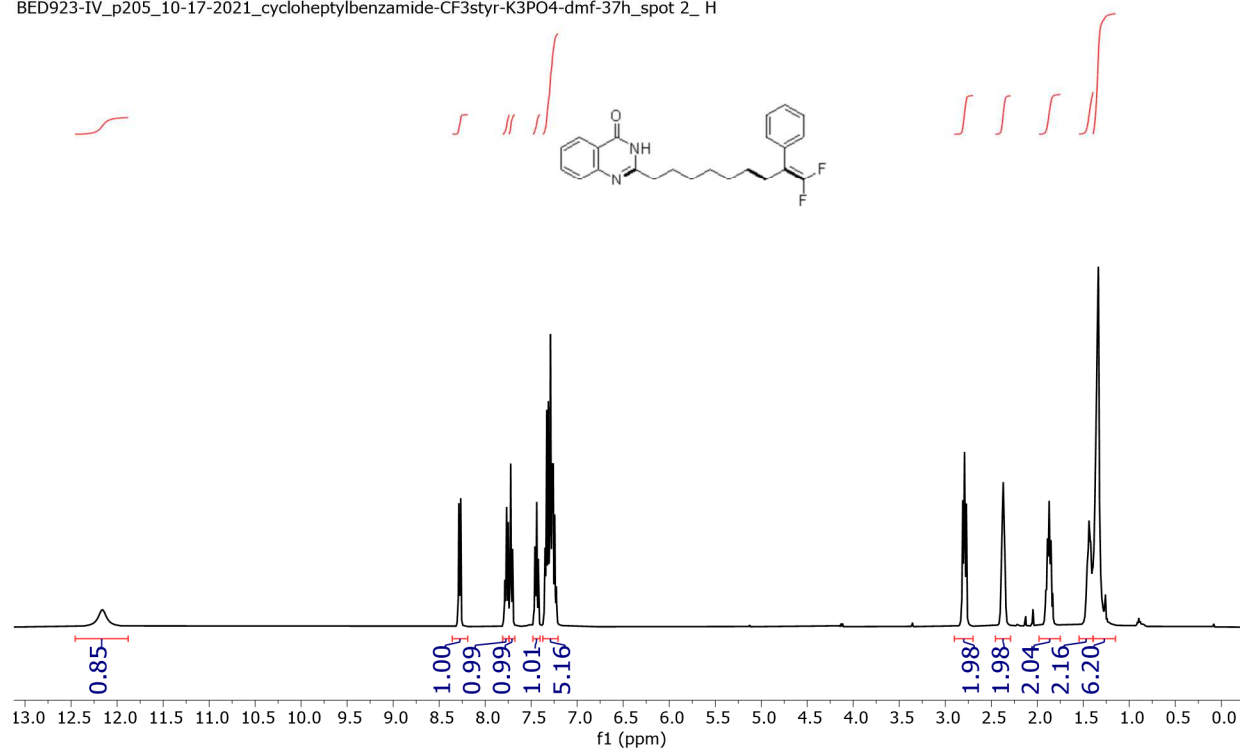
BED923-IV_p205_10-17-2021.4.fid
BED923-IV_p205_10-17-2021_cycloheptylbenzamide-CF3styr-K3PO4-dmf-37h_spot 2_ C13

10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

441
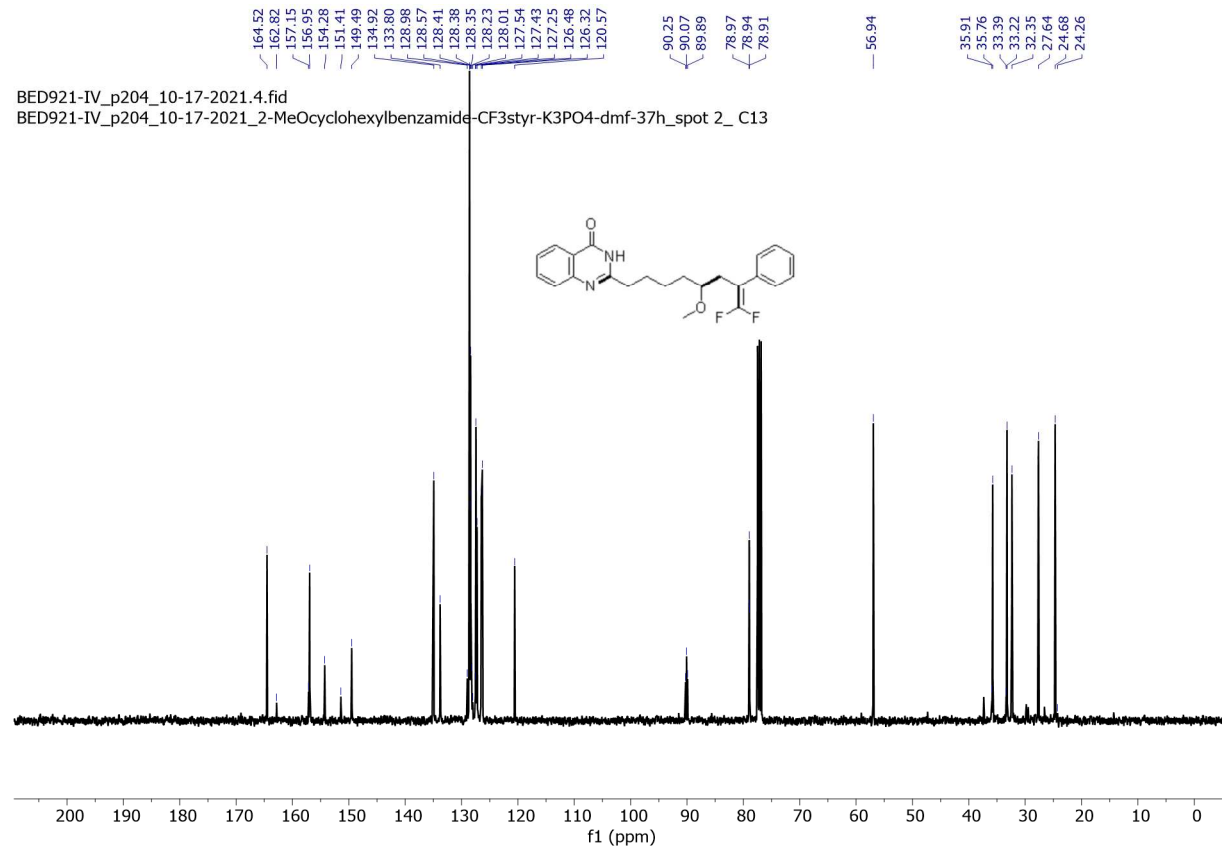
BED923-IV_p205_10-17-2021.5.fid
BED923-IV_p205_10-17-2021_cycloheptylbenzamide-CF3styr-K3PO4-dmf-37h_spot 2_Dept135

134.74
128.29
128.17
128.13
128.10
127.07
126.26
126.10

35.75
29.56
28.78
28.74
27.53
27.45
27.44
27.40

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

92.22
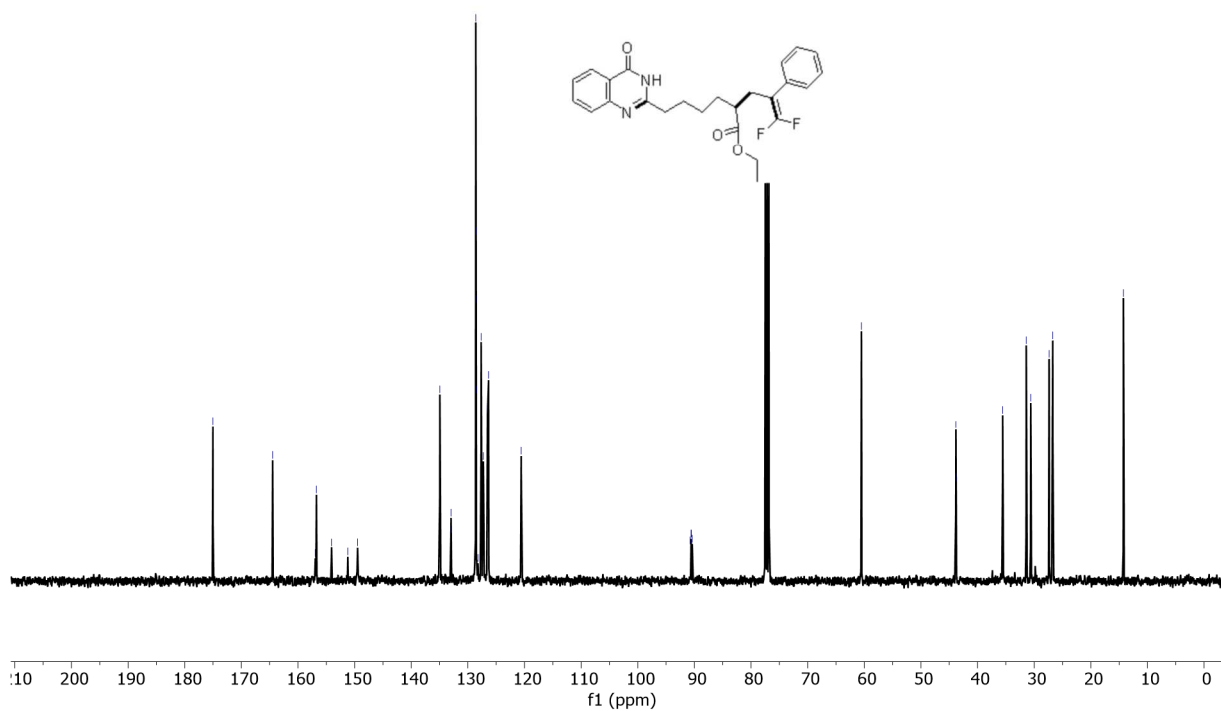
BED923-IV_p205_10-17-2021.3.fid
BED923-IV_p205_10-17-2021_cycloheptylbenzamide-CF3styr-K3PO4-dmf-37h_spot 2_ F19

140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240 -260 -280 -300 -320 -340 -360
f1 (ppm)

BED935-IV_p211_10-27-2021.2.fid
BED935-IV_p211_10-27-2021_camphoraminobenzamide-CF3styr-K3PO4-isolated spot_ H

3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

0.87 1.00 1.02 0.98 1.15 5.68 0.86 1.09 0.74 2.51 3.69 1.18 2.20
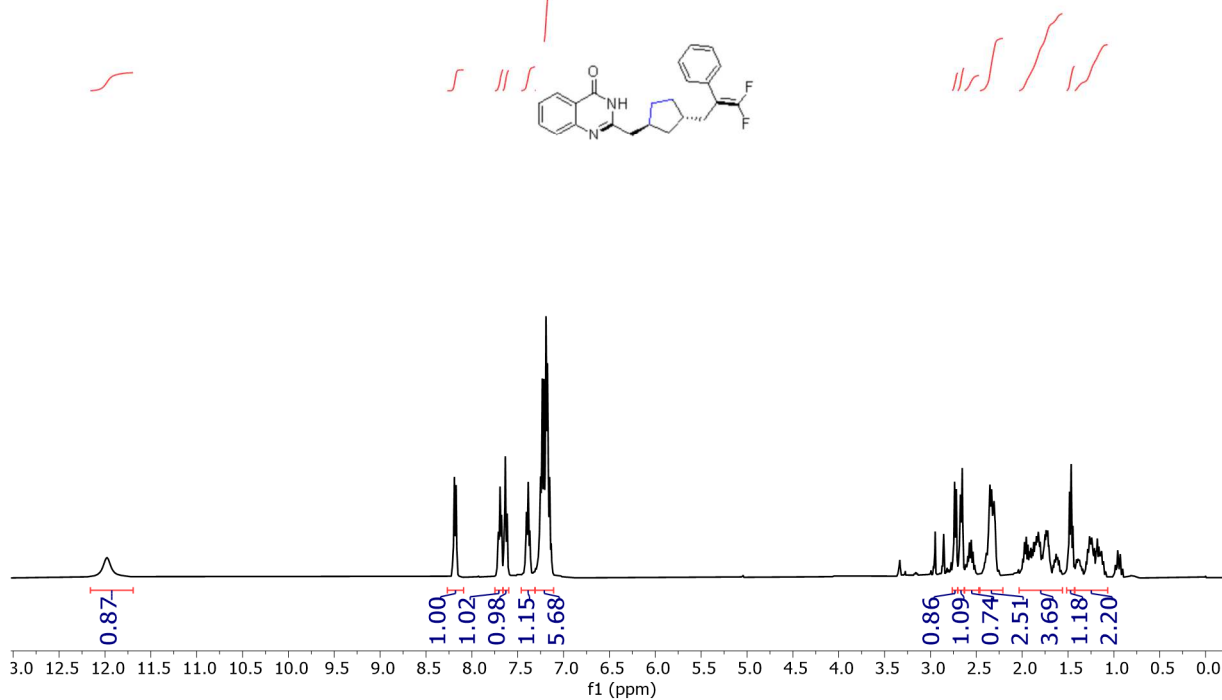
BED935-IV_p211_10-27-2021.5.fid
BED935-IV_p211_10-27-2021_camphoraminobenzamide-CF3styr-K3PO4-isolated spot_Dept135

134.74 128.29 128.24 127.36 127.14 127.10 126.30 126.12
41.78 41.73 39.43 38.47 38.01 37.53 37.28 36.67 33.86 33.84 32.23 31.92 31.03 30.75

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

443
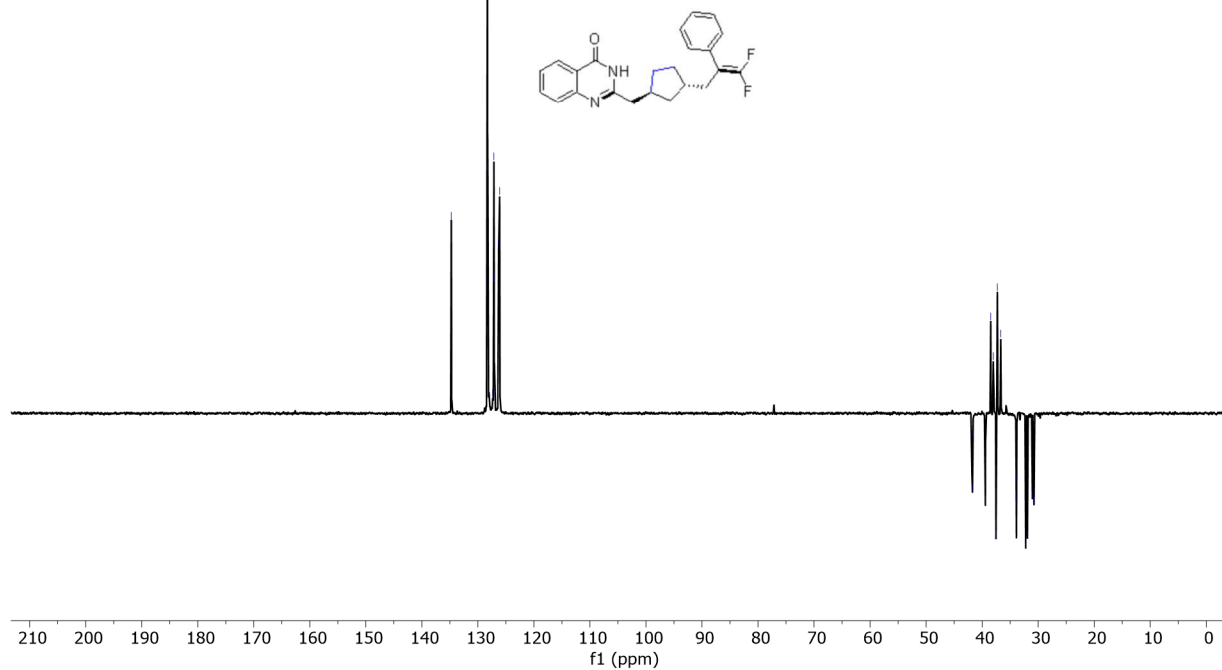
-92.14
-92.18
-92.26
-92.30
-92.38
-92.42
-92.50
-92.53

f1 (ppm)

EK 2021 FIVE MEMBERED RING CHEMISTRY p.5.fid
EK 2021 FIVE MEMBERED RING CHEMISTRY methylcyclohexanone cf3 styrene base 6hr hrs dmf

f1 (ppm)

444

163.96
156.69
154.12
135.01
134.00
128.54
128.44
127.33
126.60
126.40
120.66
36.13
35.97
35.04
31.05
27.77
26.59
19.24

EK 2021 FIVE MEMBERED RING CHEMISTRY p.6.fid
EK 2021 FIVE MEMBERED RING CHEMISTRY methylcyclohexanone cf3 styrene base 6hr hrs dmf

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

134.84
128.33
128.23
127.13
126.42
126.20
35.92
34.83
30.84
27.58
26.38
19.03

EK 2021 FIVE MEMBERED RING CHEMISTRY p.9.fid
EK 2021 FIVE MEMBERED RING CHEMISTRY methylcyclohexanone cf3 styrene base 6hr hrs dmf dpet rpt

10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

EK 2021 FIVE MEMBERED RING CHEMISTRY p.8.fid
EK 2021 FIVE MEMBERED RING CHEMISTRY methylcyclohexanone cf3 styrene base 6hr hrs dmf

-91.75
-91.87
-92.00
-92.12

EK 2021 FIVE MEMBERED RING CHEMISTRY dipenyl 2nd run.1.fid
EK 2021 FIVE MEMBERED RING CHEMISTRY dipenyl 2nd

164.38
156.90
149.62
145.26
134.91
128.51
127.95
127.38
126.48
126.35
126.17
120.63
51.40
36.01
35.62
29.66
29.32
27.83
27.47
27.21

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

134.71
128.31
127.74
127.17
126.27
126.14
125.97
51.19
35.81
35.41
29.11
27.62
27.27

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

447