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Reactivity of Photogenerated Amine Radical Cations

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Reactivity of Photogenerated Amine Radical Cations

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by

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Abstract

Recently photoredox catalysis has emerged as a powerful tool in organic synthesis led by Professor McMillan, Stephenson, Yoon. Upon absorption of visible light, photocatalyst can be excited to its singlet state followed by intersystem crossing to form a long lived excited triplet state. While amine serves as electron donor, single electron transfer (SET) can happen between excited triplet photocatalyst and nitrogen atom on amine to give a reduced photocatalyst and amine radical cation.

Cyclopropylamines or cyclobutylamines can be oxidized by excited photocatalyst to generate amine radical cations and due to the ring strain, subsequent C-C bond cleavages can lead to distonic radical cation with an iminium site and a carbon radical site. Prof. Zheng's group has utilized the distonic radical cation to undergo [3+2] and [4+2] annulations to furnish cyclopentyl or cyclohexylanilines. These reactions are initiated via radical addition to unsaturated bonds such as olefins and alkynes. When a different type of cyclobutylaniline, namely benzo-cyclobutylaniline, is employed as substrate, multisubstituted naphthalenes can be obtained as product as a result of fully aromatization via elimination of the aniline moity. Further exploration to take advantage of the binary reactivity of distonic radical cation revealed a difunctionalization protocol which use TMSCN as nucleophile to react with iminium ion and α-CF_3 styrenes as radical acceptors. This protocol also for the first time employed amines instead of anilines as substrates. One of the intrinsic limitations to use amine radical cation to induce α C-C bond cleavge is the tertiary amines which generally are not very active towards ring-opening process. To tackle this long standing issue we devised a two-electron ring-opening system which bypassed the formation of distonic radical cation. Electrophilic iodine was used directly to

induce C-C bond cleavage via a S_N2 type like pathway and the subsequent β-iodo iminium ion can be intercepted by various nucleophiles such as TMSCN, succinimide and indole.

Amine radical cations can also directly engage in C-N bond formation as an electrophilic species. Intramolecular addition of amine radical cation to tetrasubstituted styrenes followed by 1,2-carbocation shift yielded tetracyclic scaffolds that is commonly seen in akuammiline natural products.

Acknowledgments

I thank my parents for their great support and encouragement throughout this long journey of a doctoral program, I could not have done this without them.

I am grateful for my advisor Prof. Nan Zheng for all his advices and knowledge and, most importantly, for pushing me to become a better chemist.

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Chapter 1. Introduction

1.1. Photoredox Catalysis

Photochemistry in organic reaction can be dated back to as early as late 19th century when santonin, an active ingredient of Levant wormseed, was observed to turn yellow upon the exposure to sunlight.[1] This discovery has inspired the exploration of photon promoted organic reactions for the next few decades.[2] The introduction of metal complex chromophore such as Ruthenium complex to conduct catalysis was initially applied to inorganic chemistry for water splitting, reduction of CO_2, etc. Photoredox catalysis using Ruthenium complex in the context of organic synthesis has been sporadically until 2008, the groups of Macmillan, Yoon and Stephenson renewed the interest of visible light photoredox catalysis in among organic synthetic community.[3]

Ground state photocatalyst such as $Ru(bpz)_3^{2+}$ can absorb visible light to reach its singlet excited state $Ru(bpz)_3^{2+*}$ via metal-ligand charge transfer process. Subsequent intersystem crossing can generate the long live triplet excited $Ru(bpz)_3^{2+*}$ which generally is the active specie in photoredox catalysis.

Figure 1.1. Excitation Diagram of $Ru(bpz)_3^{2+}$.

The unique property of excited triplet state of $Ru(bpz)_3^{2+*}$ or any other photocatalysts is, it can function both as oxidant and reductant via single electron transfer (SET). This allows the in-situ generation of catalytic amount of oxidant or reductant to selectively engage with target substrates. Another important feature of metal based photocatalysts is the oxidation potential and reduction potential are tunable by different ligands. Electron rich ligands on the metal core can increase the reducing power of the photocatalyst and electron deficient ligands can increase the oxidation power.[2]

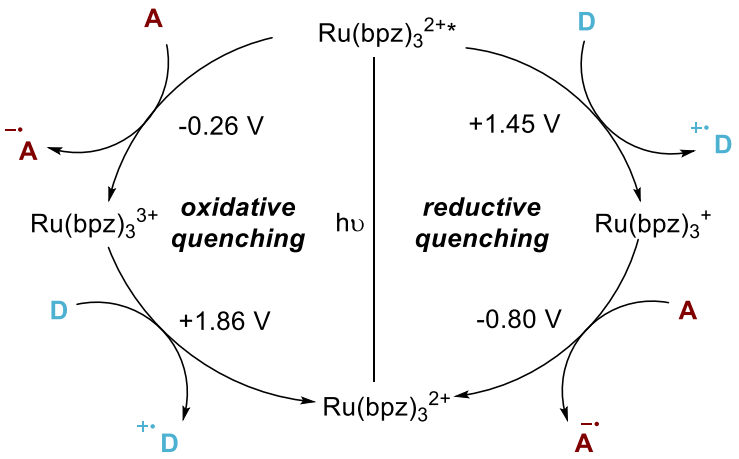
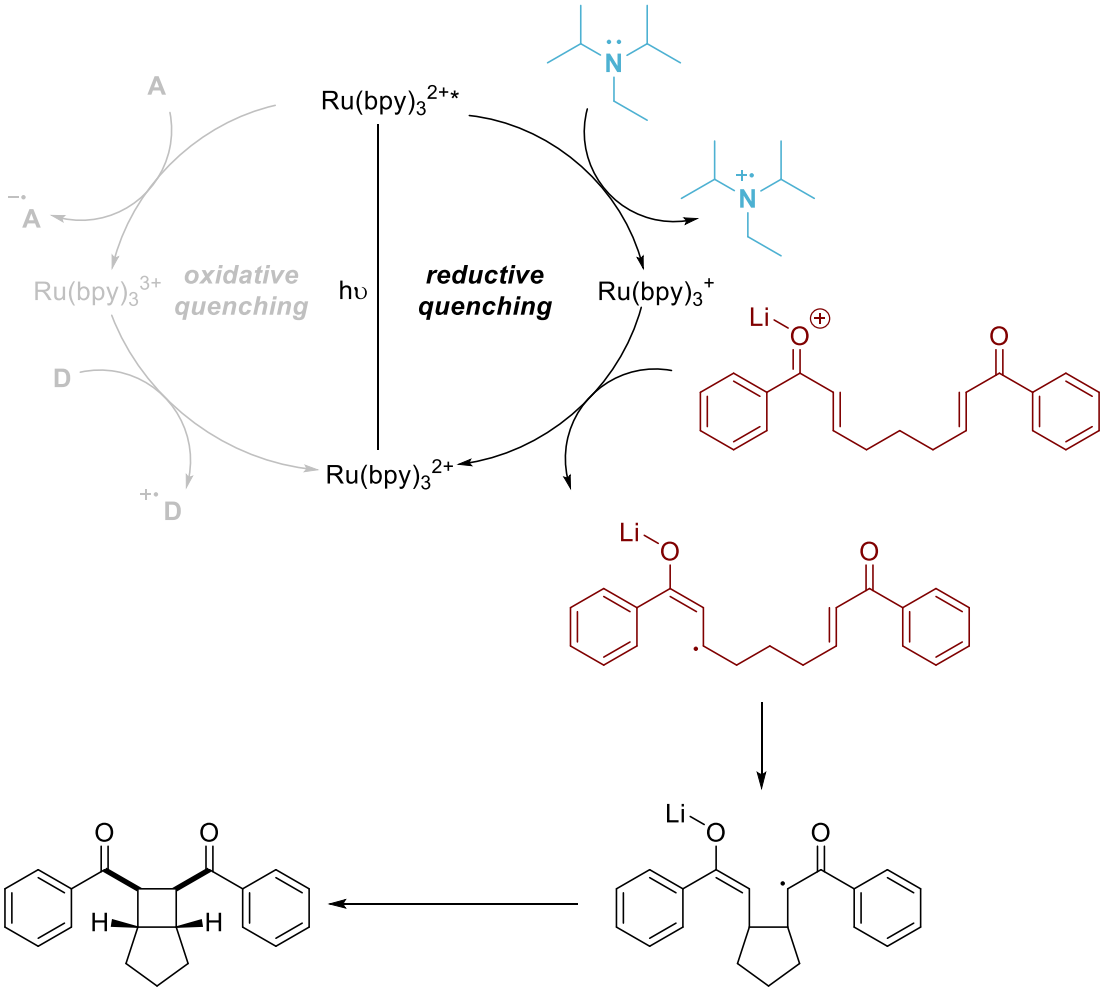


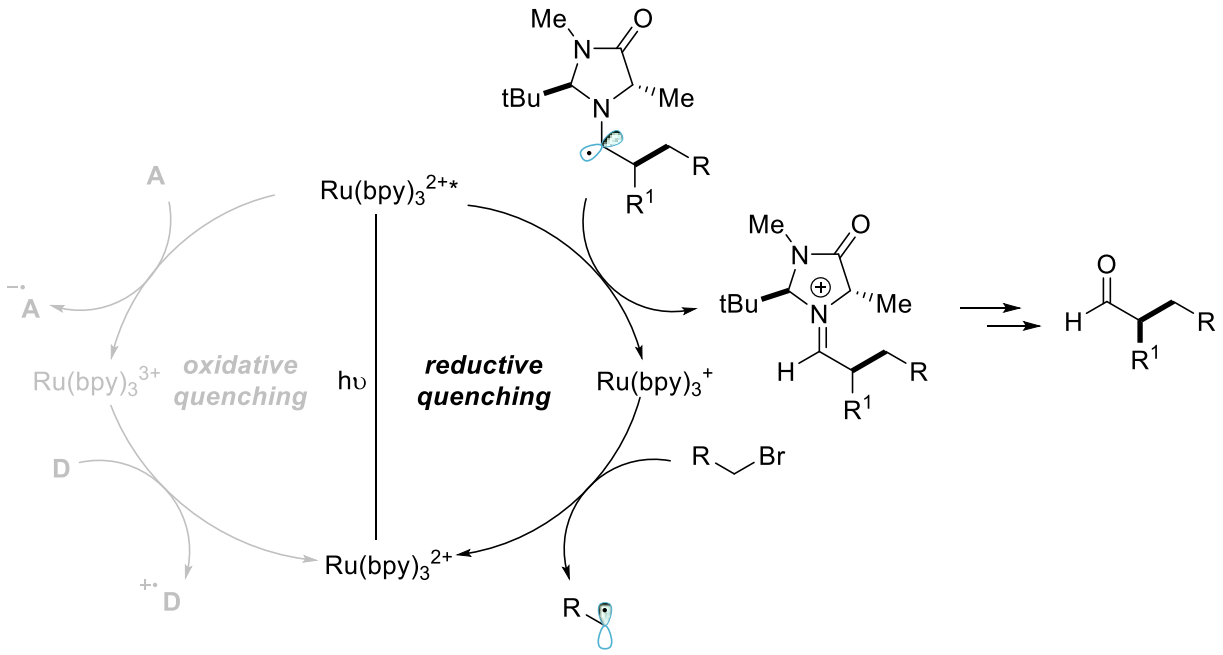
Figure 1.2. Catalytic Cycle of $Ru(bpz)_3^{2+}$

Upon the absorption of visible light and formation of triplet state excited $Ru(bpz)_3^{2+*}$ two potential quenching mechanism are plausible depicted in Figure 1.2. $Ru(bpz)_3^{2+*}$ can undergo SET with electron acceptor (A) to yield oxidized ground state $Ru(bpz)_3^{3+}$ and reduced electron acceptor $A^{-\cdot}$. Resulting $Ru(bpz)_3^{3+}$ can subsequently take an electron from donor (D) to regenerate ground state $Ru(bpz)_3^{2+}$ and finish the redox cycle. The quenching of excited $Ru(bpz)_3^{2+*}$ step is formally an oxidation process, thus this quenching is termed oxidative quenching. On the other hand, when triplet state excited $Ru(bpz)_3^{2+*}$ is quenched by electron donor, ground state $Ru(bpz)_3^{+}$ is generated along with oxidized donor $D^{+\cdot}$. $Ru(bpz)_3^{+}$ can then be oxidized by electron acceptor to yield $Ru(bpz)_3^{2+}$ and close the catalytic cycle. This other pathway is termed reductive quenching because the excited $Ru(bpz)_3^{2+*}$ is quenched via reduction of $Ru(bpz)_3^{2+*}$.[2]



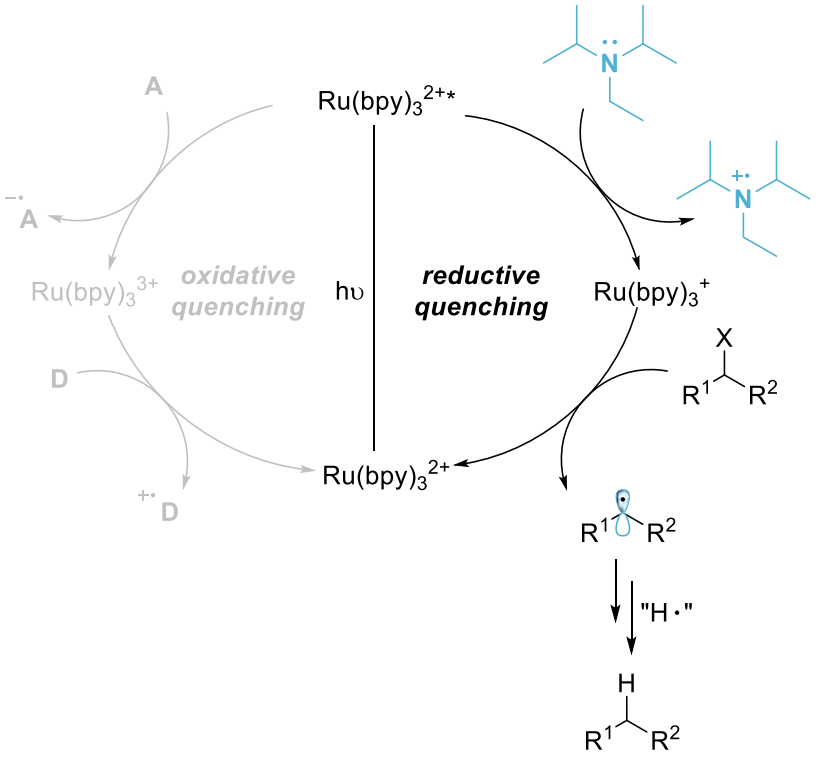
Scheme 1.1 $Ru(bpy)_3^{2+}$ catalyzed [2+2] cyclization by Prof. Yoon.

In 2008, Prof. Yoon and coworkers revealed a [2+2] cyclization catalyzed by $Ru(bpy)_3^{2+}$ under visible light.[3b] *i*Pr_2NEt was used as electron donor to quench the excited $Ru(bpz)_3^{2+*}$ to generate $Ru(bpz)_3^{+}$ which subsequently underwent single electron transfer to α,β unsaturated ketones to form allylic radical. The nascent radical underwent intramolecular radical addition to furnish [2+2] cyclization product (Scheme 1.1.).



Scheme 1.2 $Ru(bpy)_3^{2+}$ catalyzed α-alkylation of aldehyde by Prof. Macmillan.

In the same year, a $Ru(bpy)_3^{2+}$ catalyzed α-alkylation of aldehyde method was reported by Prof Macmillan and coworker.[3c] In the proposed mechanism, $Ru(bpz)_3^{2+*}$ underwent a reductive quenching which oxidized α-amino radical to iminium ion. The subsequent $Ru(bpz)_3^{+}$ reduced the alkyl bromide into radical and regenerated $Ru(bpy)_3^{2+}$ to close the catalytic cycle.

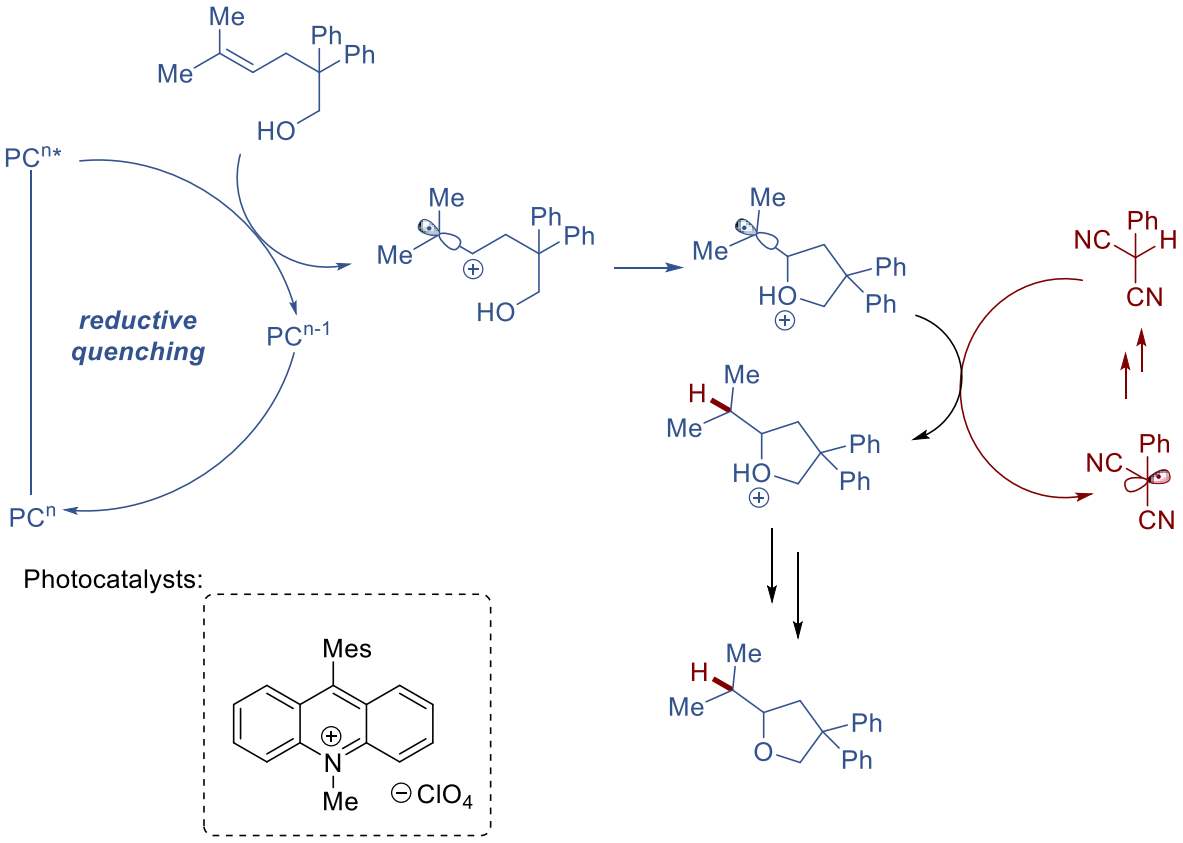


Scheme 1.3 $Ru(bpy)_3^{2+}$ catalyzed dehalogenation reaction by Prof. Stephenson.

In 2009, Prof. Stephenson and coworkers reported a reductive dehalogenation reaction under visible light condition via $Ru(bpy)_3^{2+}$ catalysis.[3d] Amine, *i*Pr_2NEt, was employed as a quencher for $Ru(bpz)_3^{2+*}$ as well as terminal reductant. Excited photocatalyst $Ru(bpz)_3^{2+*}$ was reductively quenched to give $Ru(bpz)_3^{+}$ followed by single electron transfer to halogen containing substrate to give carbon radical and eventually leaded to dehalogenated product.

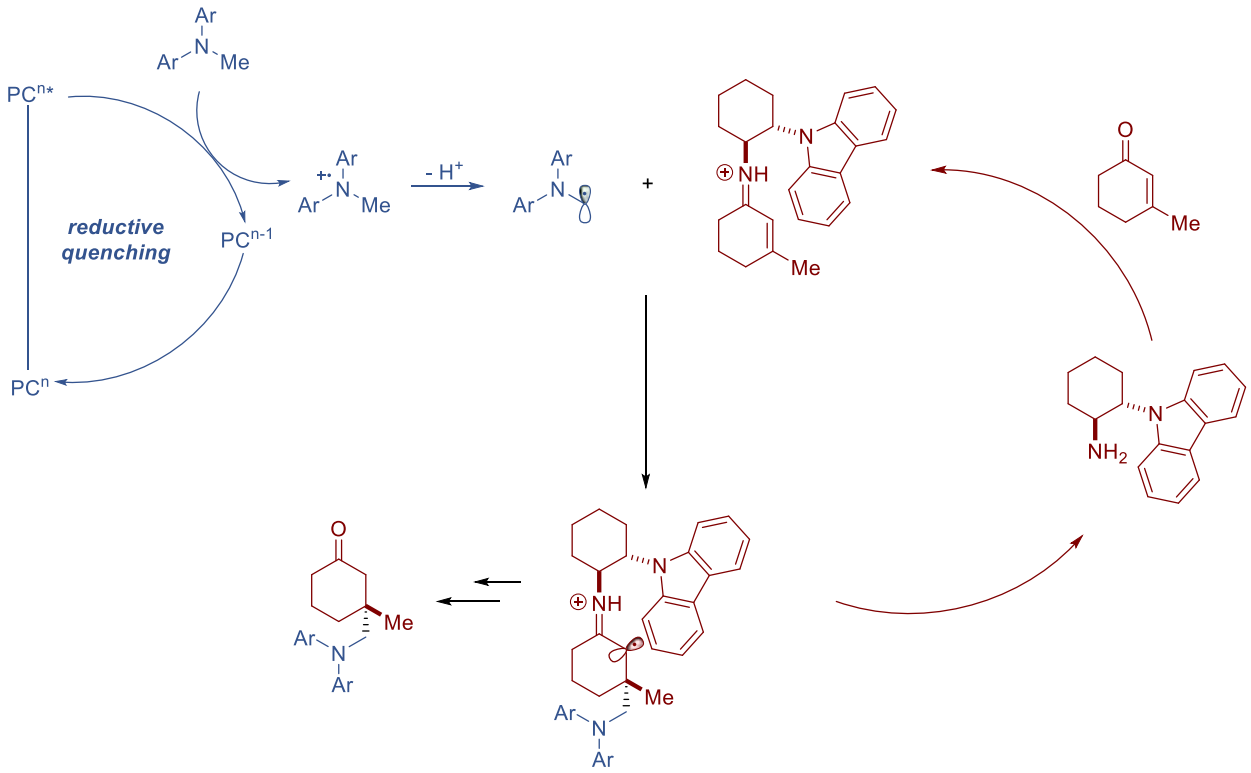
These three seminal works of photoredox catalysis revived the research of photochemistry in organic synthesis and inspired numerous works to take advantage of the unique yet powerful properties of photocatalysts in the next decade.

With the aid of the development of catalysis in other field such as organocatalysis, photoredox catalysis flourished in collaboration with other catalysis system under dual catalysis platform achieving unprecedented transformations under mild conditions.



Scheme 1.4 HAT and Photoredox Dual Catalysis by Prof. Nicewicz.

A dual catalysis protocol incorporating hydrogen atom transfer (HAT) and photoredox catalysis was reported by Prof. Nicewicz. A strongly oxidizing organic photocatalyst 9-mesityl-10-methylacridinium perchlorate was used to undergo single electron transfer with olefins.[4] Intramolecular nucleophilic addition of alcohol to radical cation followed by HAT and deprotonation furnished the anti-Markovnikov hydroetherification product.



Scheme 1.5 Organo and Photoredox Dual Catalysis by Prof. Melchiorre.

An organo and photoredox dual catalysis protocol was reported by Prof. Melchiorre and coworkers.[5] The amine organic catalyst function both as enantiocatalyst and electron pool. Upon the formation of iminium ion, radical Michael addition generated a quaternary center at the β position as well as an α-carbon radical. The radical was subsequently reduced by aniline electron pool intramolecularly to furnish the product.

1.2. Amine Radical Cation

Amine radical cations, arise from formally removing one electron of nitrogen atom's electron lone pair, can be generated using chemical oxidant, electrochemistry and photochemistry etc. Because of its abundance and inexpensive price, amine was largely used as stoichiometry or super stoichiometry reductant (electron donor).[6] In the 1970s, water splitting

and carbon dioxide reduction sparked the interest in amine radical cations which were the first intermediate in the amine degradation pathway. Recently, amines were found to be excellent quencher for excited photocatalysts. Upon the single electron oxidation of amines by excited photocatalyst, amine radical cations were generated. As the "photochemistry renaissance" progressed since 2008, the request for the ultimate fate of this popular reductant and its potential synthetic utility also intrigued among chemists.

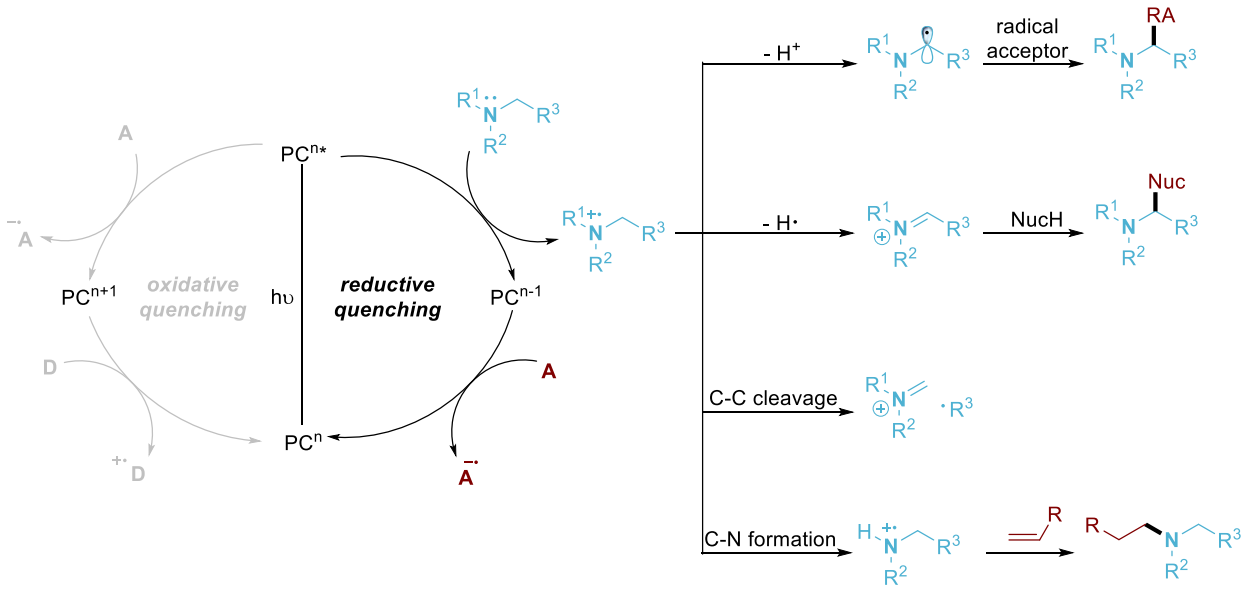
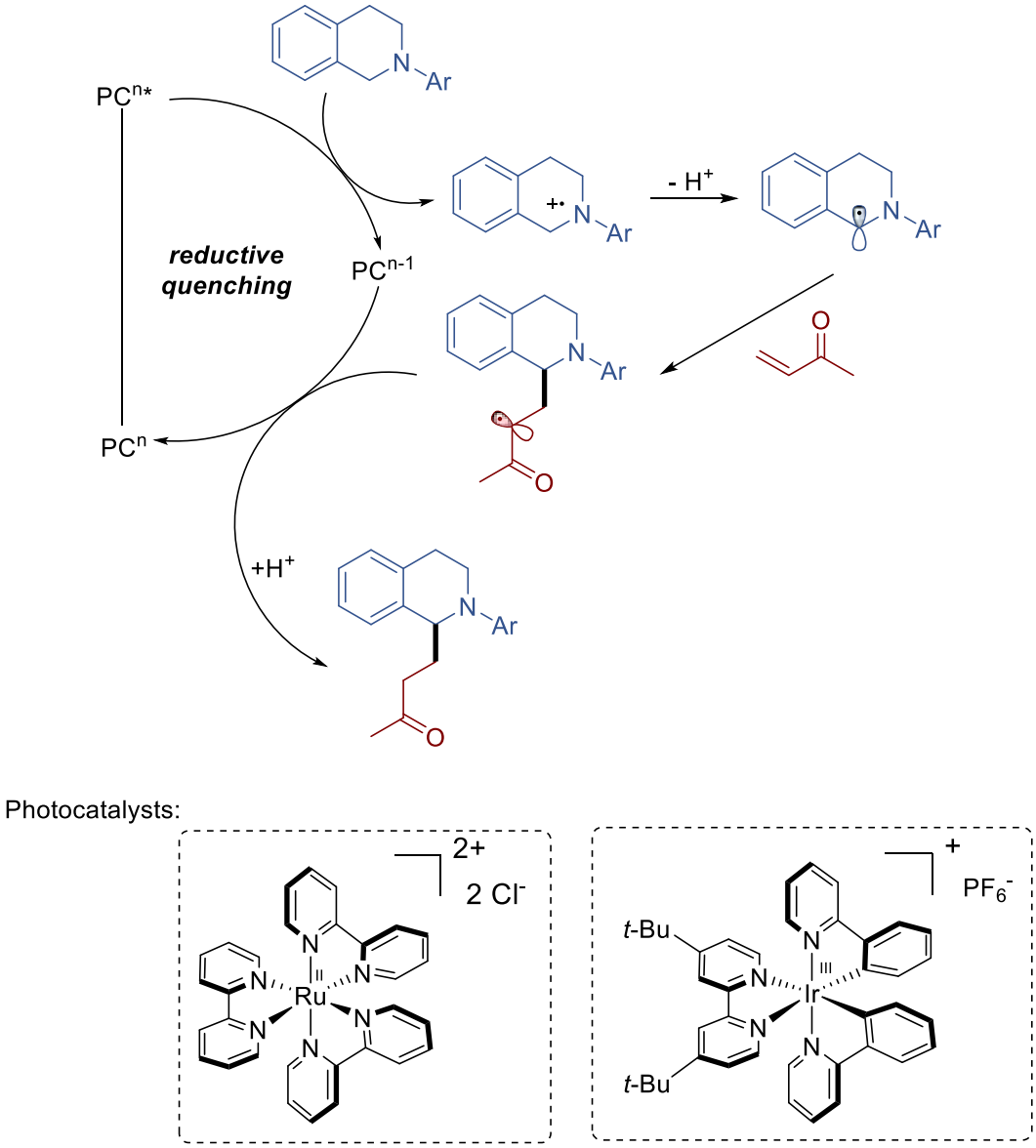


Figure 1.3 Degradation Pathways of Amine Radical Cation

Three degradation pathways were disclosed for amine radical cations. First pathway is the deprotonation of amine radical cation at α position to generate α-amino radical. This α-amino radical can readily engage in radical addition to unsaturated system or react with other radical acceptors. Second pathway involves losing a hydrogen atom which results the formation of iminium ion followed by nucleophilic addition with a nucleophile to give α-functionalized amines. Third pathway is less common which amine radical cations induced the α C-C bond cleavage to generate either a pair of radical and iminium ion or a distonic radical cation. The third pathway will be discussed in the next section, distonic radical cation, in detail. Under

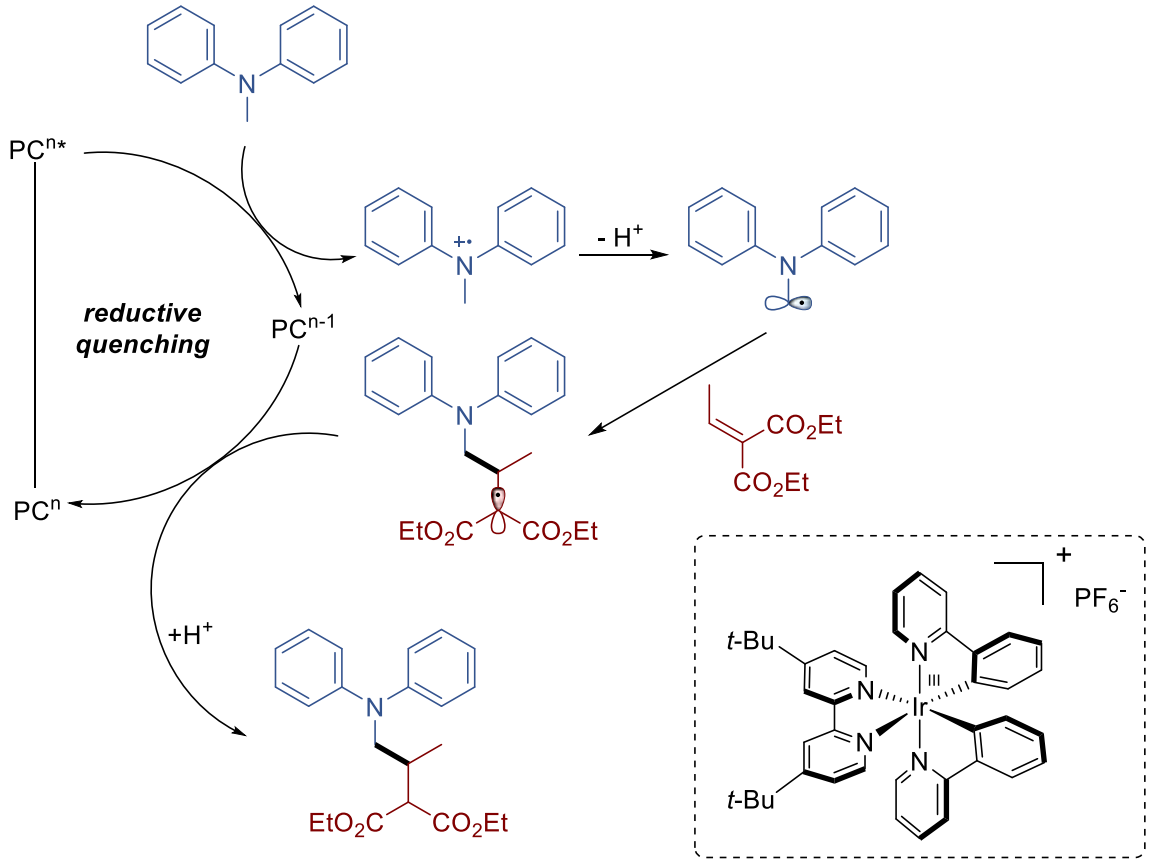
certain conditions, Nitrogen can also be the reaction center for amine radical cations which engages in direct C-N bond formation with olefins. [6]



Scheme 1.6 α-Amino Radical Addition via Photoredox Catalysis by Prof. Reiser.

In 2012, Prof. Reiser and coworkers disclosed a α-amino radical addition to Michael acceptors initiated via deprotonation of amine radical cation under photoredox catalysis. Tetrahydroisoquinoline can be oxidized by excited photocatalysts ($Ru(bpy)_3Cl_2$ and $[Ir(ppy)_2(dtbbpy)]PF_6$) to generate amine radical cation. Tetrahydroisoquinoline can undergo

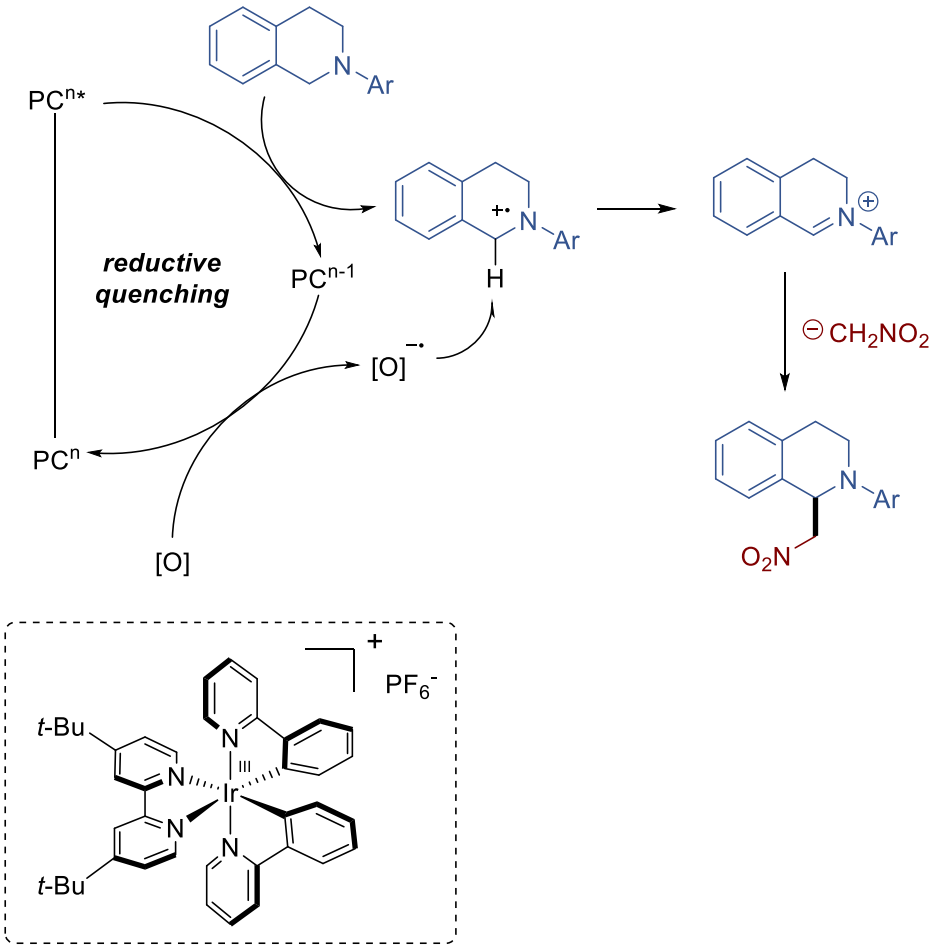
deprotonation to give a α-amino radical followed by radical addition to Michael acceptors. The resulting α-carbonyl radical can oxidize PC^{n-1} to furnish the product and at the same time close the catalytic cycle by regenerating the ground state photocatalyst.[7]



Scheme 1.7 α-Amino Radical Addition via Photoredox Catalysis by Prof. Nishibayashi.

In the same year, a protocol to generate α-amino radicals derived from amines other than tetrahydroisoquinoline motif was reported by Prof. Nishibayashi and coworkers. α-amino radicals can be produced from a more general amine scope such as aniline and noncyclic N-alkyl amines. Contrary to previous report that common Michael acceptors with one electron withdrawing group can react with the α-amino radicals, the noncyclic α-amino radicals generated from this protocol needed to couple with highly electron deficient Michael acceptors (two electron withdrawing groups attached) or otherwise the reaction yield diminished dramatically.[8]

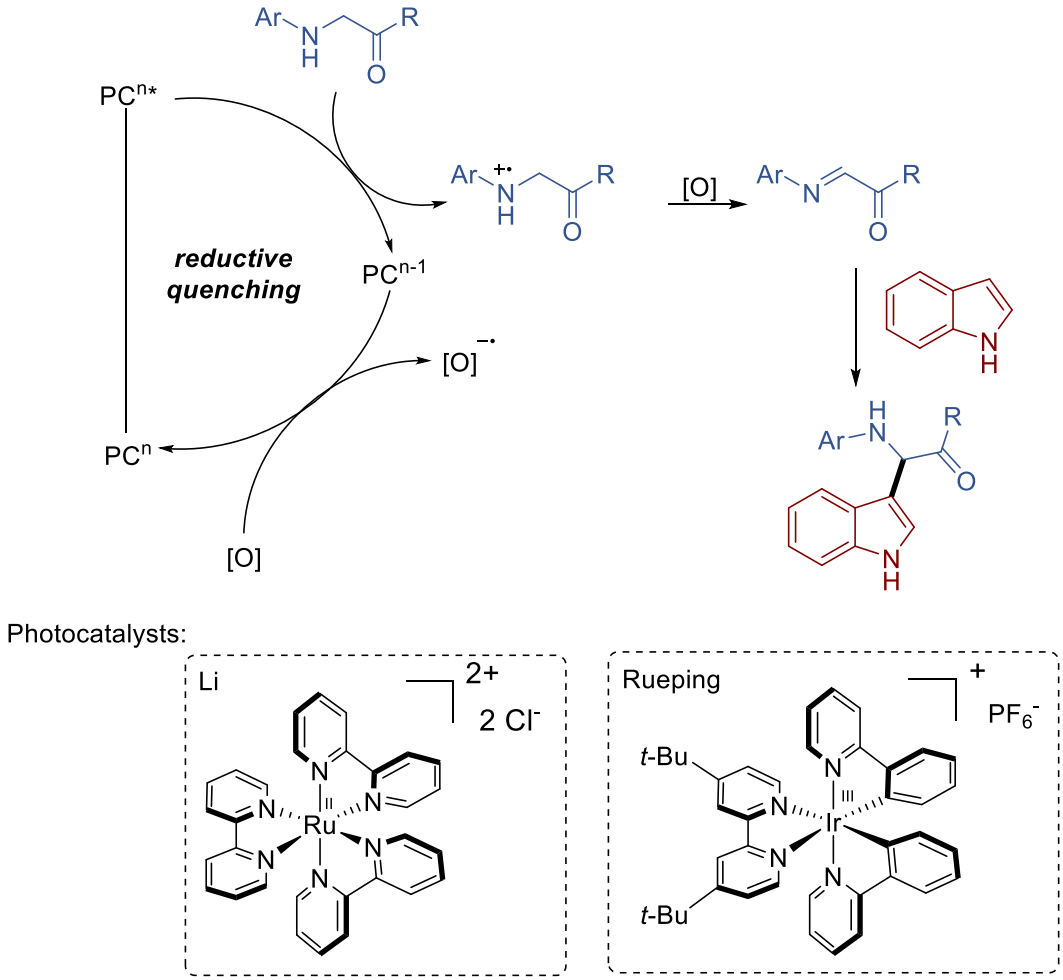
Compared with deprotonation pathway to give α-amino radicals, iminium ion formation by either hydrogen atom abstraction or further oxidation is a much more common pathway. Although the iminium ion formation is largely limited to substrates bearing tetrahydroisoquinoline motif, many nucleophiles were successfully developed in compatible with photoredox catalysis to furnish α-functionalized amine products.



Scheme 1.8 Aza-Henry Reaction via Photoredox Catalysis by Prof. Stephenson.

In 1980, Prof Giannotti and Whitten disclosed a study of iminium ion formation via amine oxidation catalyzed by $Ru(bpy)_3^{2+}$ under irradiation.[9] It is proposed that amine was first oxidized via SET to form amine radical cation followed by hydrogen atom abstraction to yield iminium ion. Three decades later, Prof. Stephenson and coworkers explored the synthetic utility

of this in-situ formed iminium ion in aza-Henry reaction.[10] Tetrahydroisoquinoline can be oxidized by excited $Ir(dtbbpy)(ppy)_2PF_6$ which lead to tetrahydroisoquinoline radical cation followed by hydrogen atom abstraction to give iminium ion intermediate. At this point, deprotonated nitromethane served as nucleophile to undergo aza-Henry reaction to furnish nitroamines. Nitromethane or molecular oxygen was proposed to be the terminal oxidant for this catalytic cycle accepting electrons from iridium catalyst.

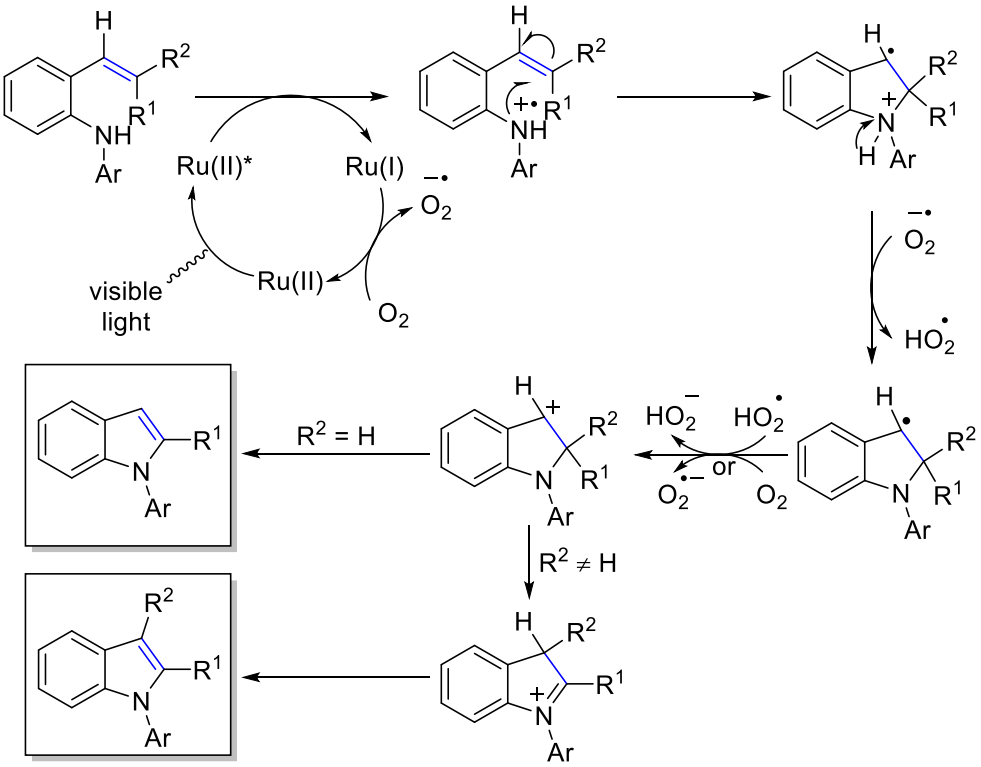


Scheme 1.9 α-arylation of aniline via Photoredox Catalysis by Prof. Li and Rueping.

While many protocols have developed for α-functionalization of tetrahydroisoquinoline presumably because of its stable corresponding iminium ion which enables wide range of nucleophiles to undergo nucleophilic attack, studies based on noncyclic amines were rarely

reported. In 2012, Prof. Li and Prof. Rueping have independently reported protocols to functionalize aniline at α position using either $Ru(bpy)_3Cl_2$ or $Ir(dtbbpy)(ppy)_2PF_6$. Notably, strong nucleophile indole was necessary to facilitate this process.[11]

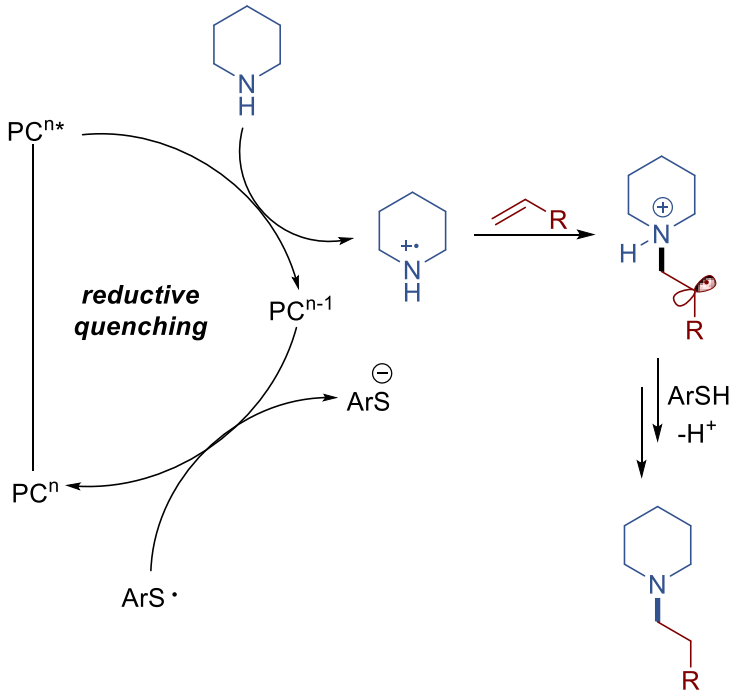
Besides deprotonation and losing a hydrogen atom, amine radical cations can also, although rarely, participated in direct C-N bond formation in an umpolung fashion because of the amine radical cation formation.[12]



Scheme 1.10 Photocatalytic Entry to N-Arylindoles by Prof. Zheng.

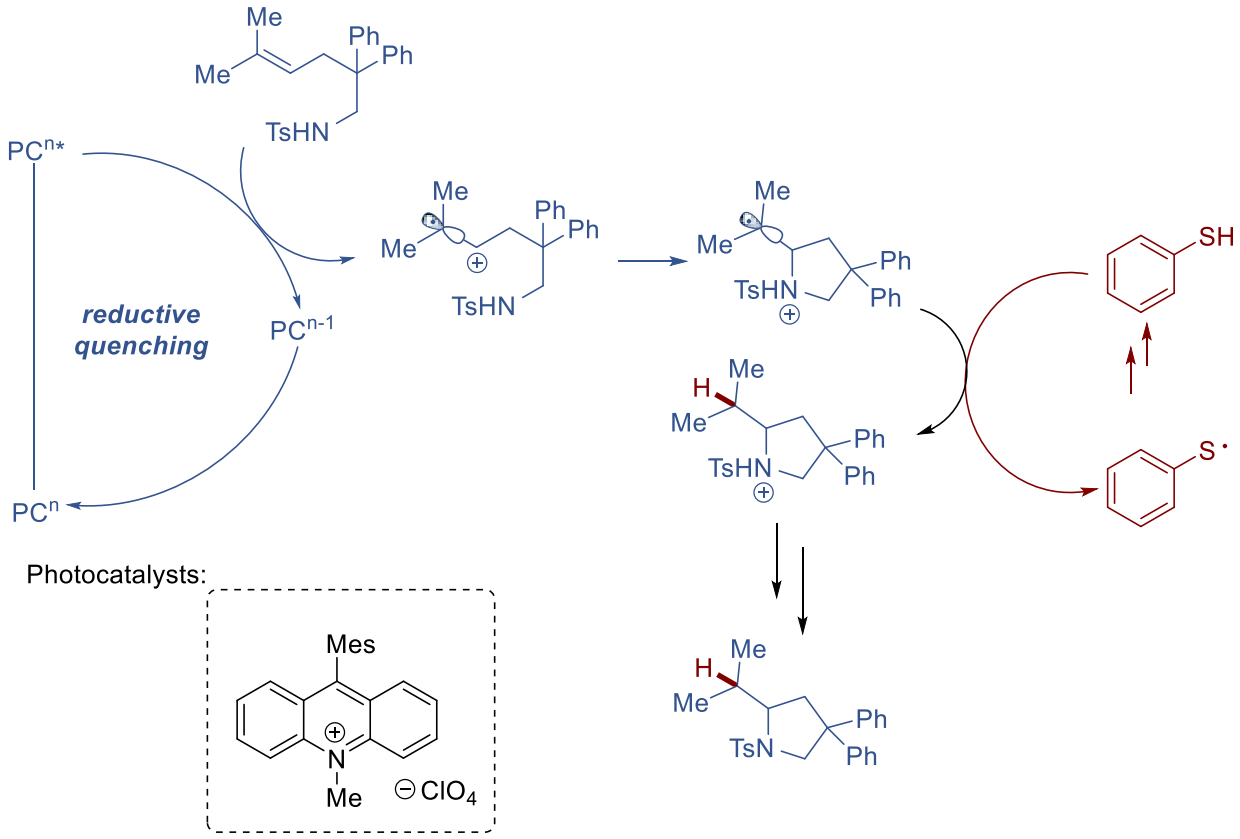
In 2012, a $Ru(bpz)_3^{2+}$ catalyzed N-Arylindoles formation was reported by Prof. Zheng and coworker.[13] Aniline was oxidized by $Ru(bpz)_3^{2+*}$ to reach amine radical cation. With no available α-hydrogen for deprotonation and hydrogen atom abstraction, the amine radical cation underwent intramolecular electrophilic attack to nearby alkene to form a distonic radical cation which was quickly deprotonated to benzylic radical followed by further oxidation to benzylic

cation. Depends on the substitution pattern on alkene, benzylic cation from mono-substituted alkene underwent direct deprotonation to complete aromatization furnishing mono-substituted N-Arylindoles while benzylic cation from di-substituted alkene underwent 1,2-carbocation shift prior deprotonation to give di-substituted N-Arylindoles.



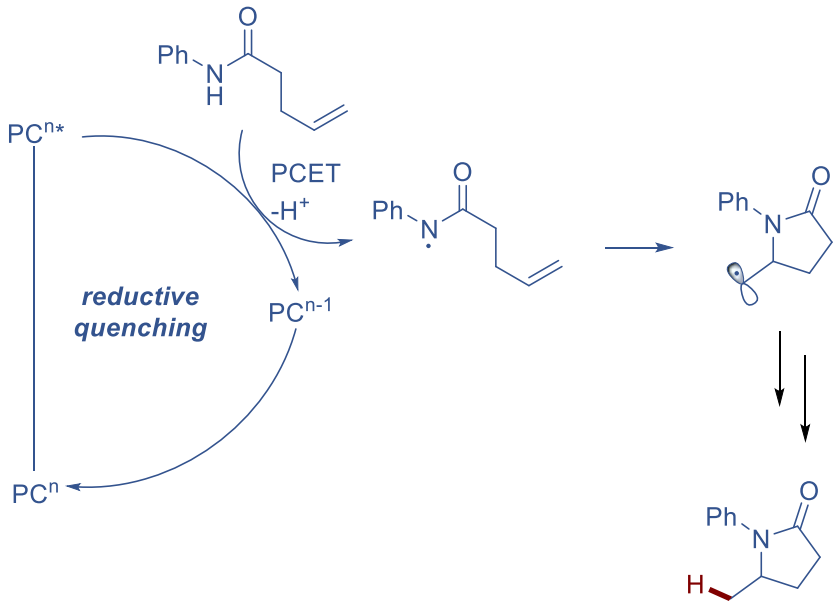
Scheme 1.11 Intermolecular Hydroaminations by Prof. Knowles.

In 2017, an intermolecular C-N bond formation protocol enabled by amine radical cation was reported by Prof. Knowles and coworkers.[14] Amine radical cation can be produced upon the single electron oxidation of amine by excited iridium-based photocatalyst. Fast intermolecular addition to olefin was promised by the secondary amine motif to compete against unproductive back electron transfer. Subsequent addition product, distonic amine radical cation, underwent hydrogen atom transfer from thiol and deprotonation to furnish the product.



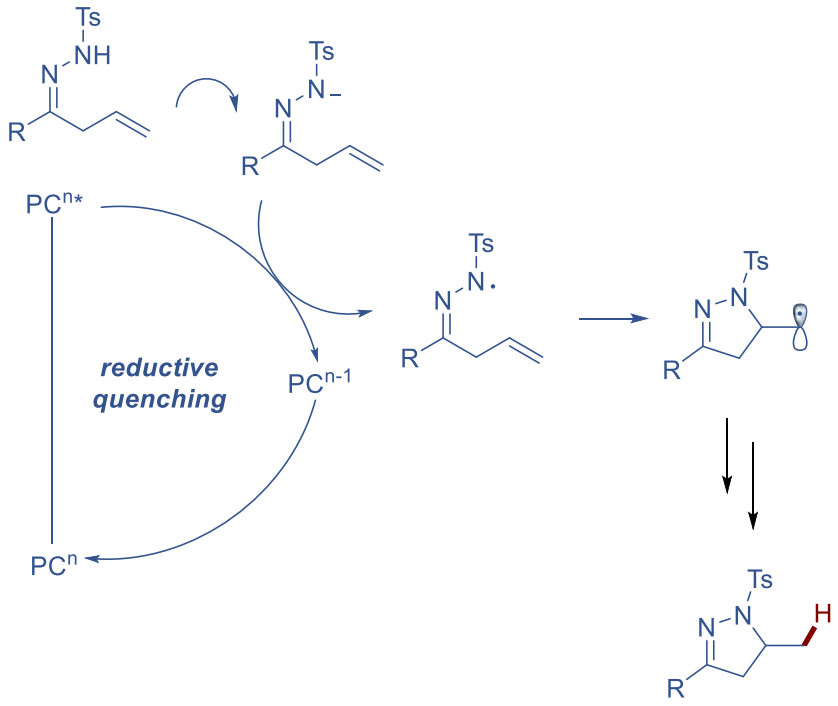
Scheme 1.12 Hydroamination of Alkene by Prof. Nicewicz.

Hydroamination of alkenes can also be achieved by direct single electron oxidation of alkenes instead of amines. Prof. Nicewicz and coworkers reported a photoredox catalysis hydroamination protocol which strongly oxidizing excited state photocatalyst underwent single electron transfer with alkene and corresponding radical cation was produced.[15] Subsequent HAT from thiophenol and deprotonation produced hydroamination product.



Scheme 1.13 Hydroamination of Alkene by Prof. Knowles.

Besides N-aryl amines and N-alkyl amines, amides were also an important family of nitrogen containing functionality. Due to the electron withdrawing group on nitrogen atom, it is very difficult to directly oxidize amide to radical cation. To overcome this unfavorable oxidation, PCET approach was introduced by Prof. Knowles to provide enough thermodynamic driving force to generate amide radical.[16] Upon the formation of amide radical, intramolecular radical addition to alkene followed by HAT yield the hydroamination product.



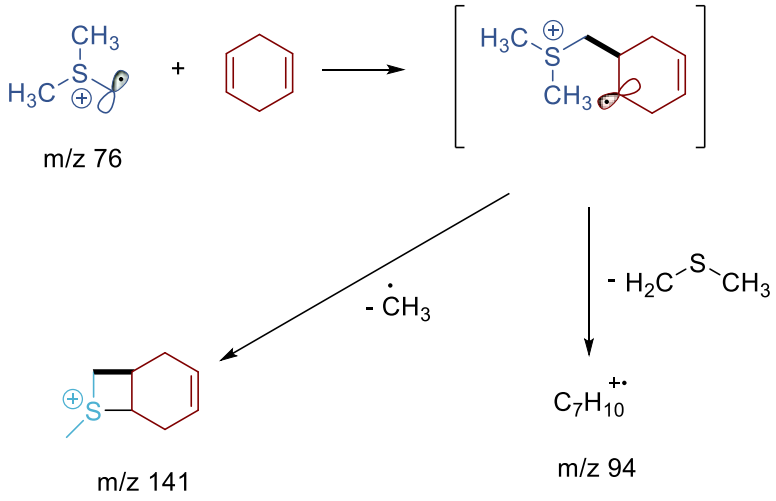
Scheme 1.14 Hydroamination of Alkene with Hydrozonyl Radical by Prof. Xiao and Chen.

Different from concerted PCET, stepwise deprotonation, which rendered a nitrogen anion and more oxidizable, and single electron transfer strategy was developed by Prof Xiao and Chen.[17] Hydrozone underwent sequential deprotonation and single electron transfer to give nitrogen-centered radical. Subsequent radical addition to alkene followed by HAT furnished the desire hydroamination product.

1.3 Distonic Radical Cations

As a potential degradation pathway for radical cations, distonic radical cations, molecules with spatially separated charge site and radical site, were most studied computationally and in mass spectrometry.[18] In 1993, Prof. Kenttämaa and coworkers reported a study on methylenedimethylsulfonium ion which showed a chemically inert sulfonium charge site and a reactive radical site.[19] Because of this “reactive radical with an inert charge site” property,

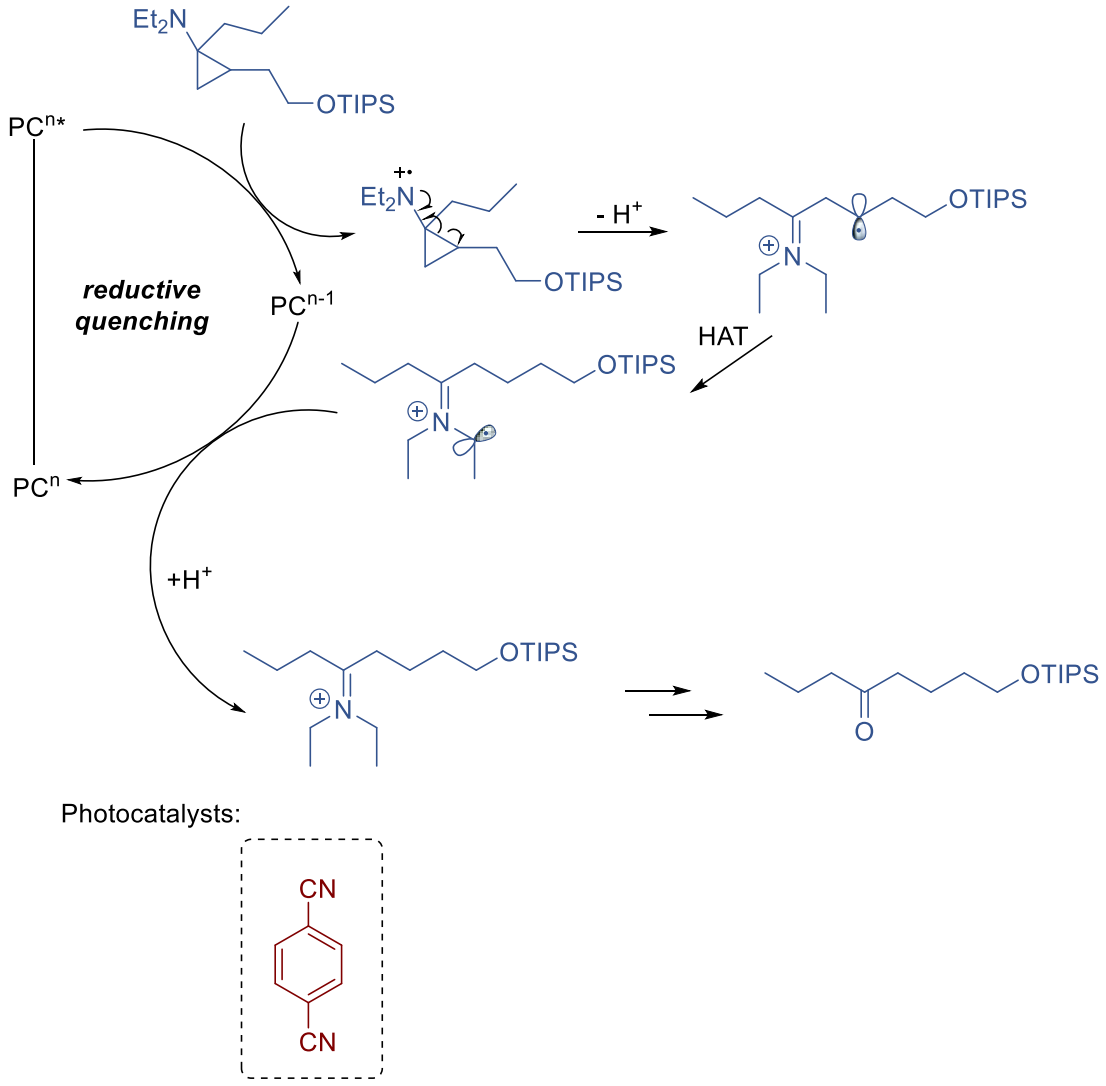
distonic radical cations (DRC) have been widely used in mass spectrometry for online analysis of free radical chemistry in gaseous phase.



Scheme 1.15 Distonic Radical Addition to Cyclic Alkenes by Prof. Kenttämaa.

In 1994, Prof. Kenttämaa and coworkers studied the reactivity of methylenedimethylsulfonium ion with various cyclic alkenes including cyclohexene, 1,3-cyclohexadiene and 1,4-cyclohexadiene.[20] Two mass (m/z 141, 94) were detected which can both be traced back to the same reaction intermediate corresponded to the radical addition of distonic radical cation to cyclic alkene.

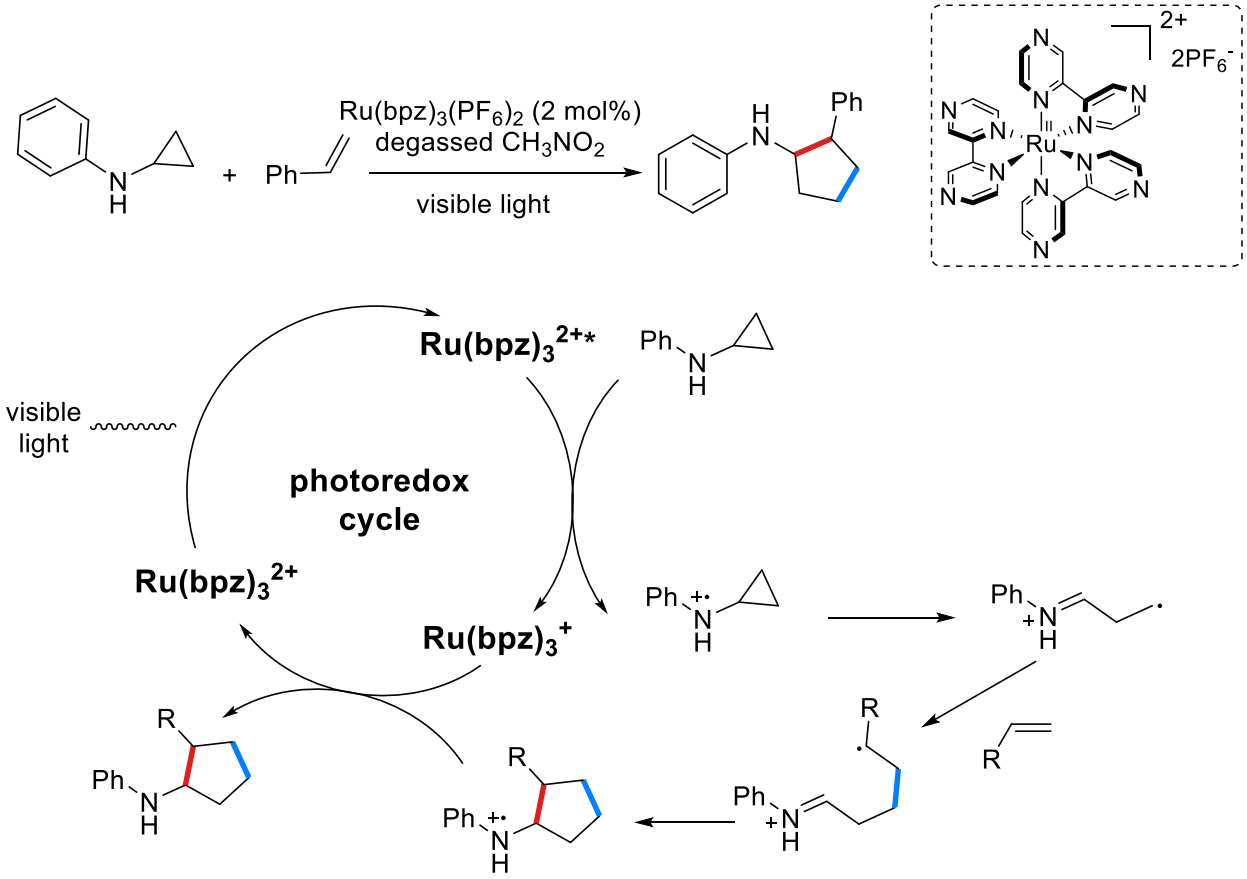
Although the reactivity of distonic radical cations has been studied in mass spectrometry, rarely has it been adapted in the context of organic synthesis.



Scheme 1.16 Ring Opening of Cyclopropylamines via Photooxidation by Prof. Cha.

1997, a seminal work by Prof. Cha revealed a ring opening process of cyclopropylamines by photoredox catalysis.[21] The amine radical cation was first generated via single electron oxidation of cyclopropylamine by excited organic photocatalyst 1,4-dicyanobenzene and then undergo ring opening to form distonic radical cation. The newly formed distonic radical cation, consistent with "reactive radical with inert charge site", underwent intramolecular hydrogen atom transfer (HAT) to generate α-iminium ion radical which was subsequently reduced and

protonated to yield an iminium ion. The iminium ion was eventually hydrolyzed to furnish ketone as product.

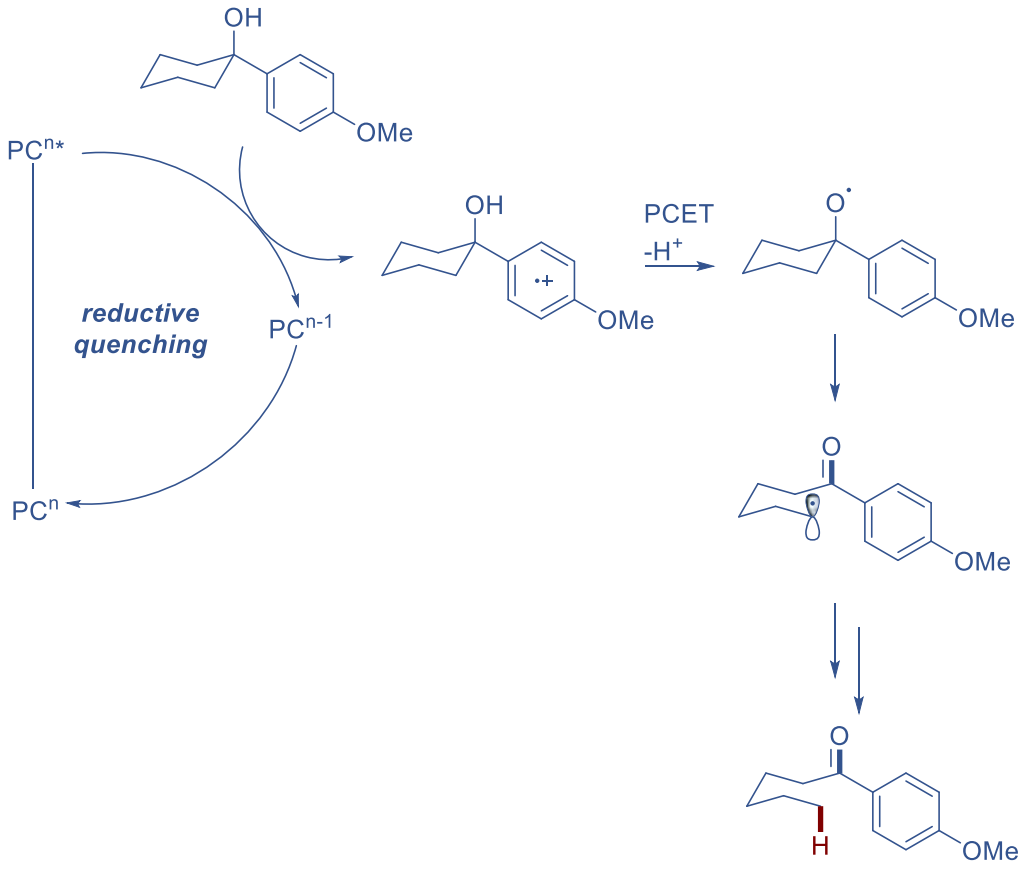


Scheme 1.17 [3+2] annulation via Photoredox Catalysis by Prof. Zheng.

In 2011, Prof. Zheng's group reported a [3+2] annulation protocol via photoredox catalysis under visible light condition.[22] In this report, cyclopropylaniline can be oxidized by of $Ru(bpz)_3^{2+*}$ to amine radical cation followed by rearrangement to yield distonic radical cation intermediate. Intermolecular radical addition to alkene and subsequent intramolecular addition to iminium ion generated a cyclopentylaniline radical cation specie. This cyclopentylaniline radical cation can then be reduced to cyclopentylaniline product along with the regeneration of ground state photocatalyst of $Ru(bpz)_3^{2+}$.

1.4 Ring Opening Under Photoredox Catalysis

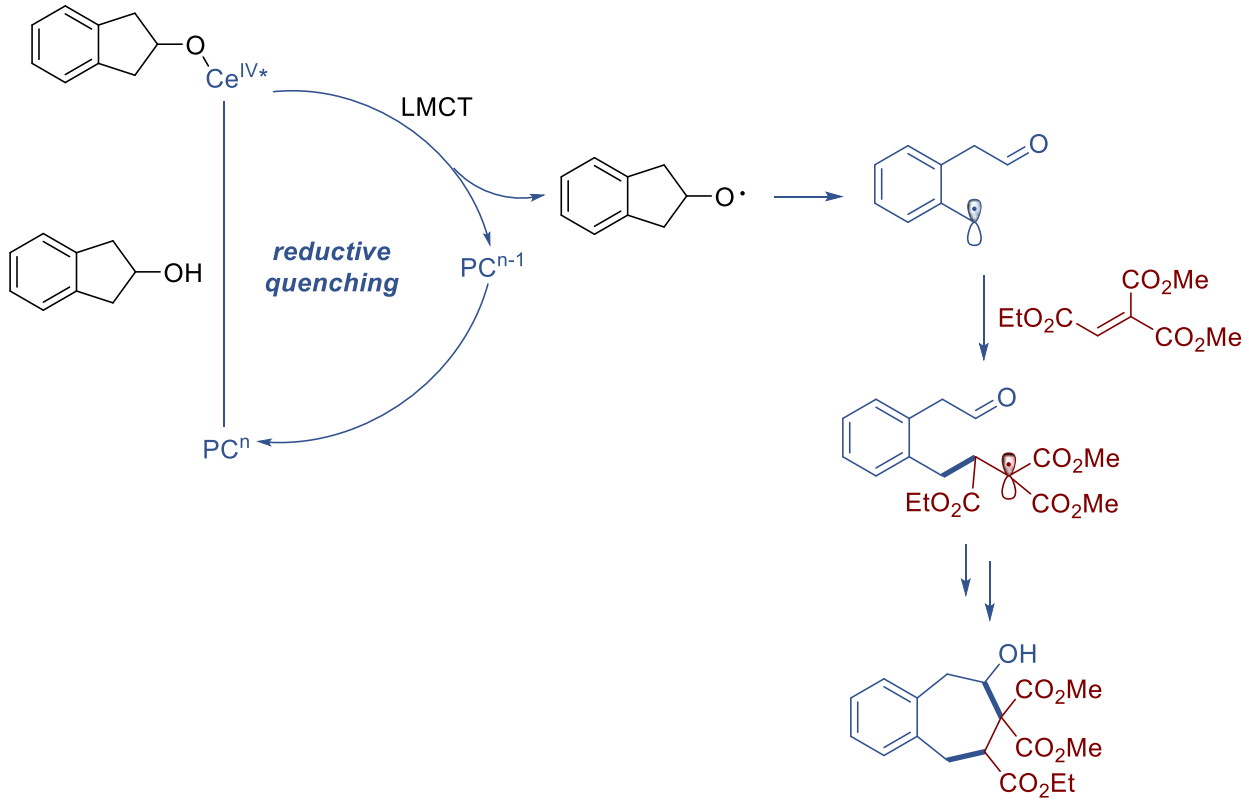
Closely related to radical cation promoted ring-opening process, strategies to use neutral radical to induce C-C bond cleavage were also highly sought after. Photoredox catalysis is an attractive platform to initiate the oxidation accompanied by deprotonation or removal of a charge site. The strategies developed can reach beyond strained cyclic compounds which greatly improved the utilities of these type of protocols.



Scheme 1.18 Catalytic Ring-Opening of Cyclic Alcohols by Prof. Knowles.

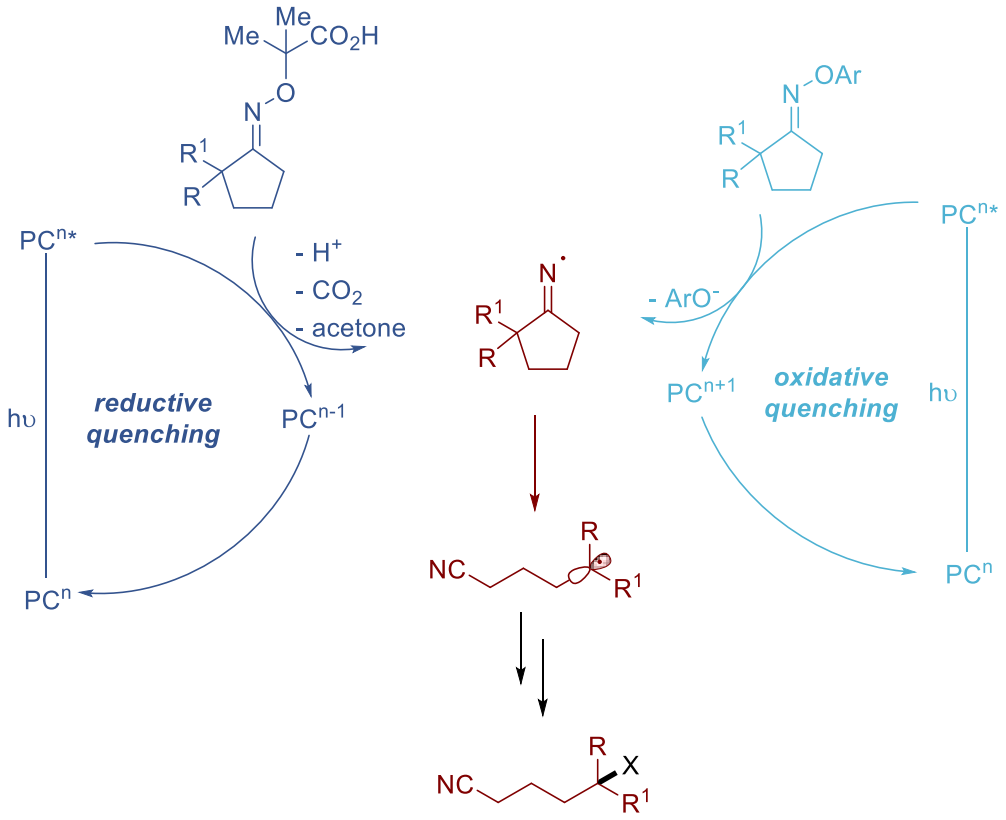
Ring-opening strategies promoted by adjacent heteroatoms such as nitrogen and oxygen under photoredox catalysis have also been achieved.[23] Prof. Knowles reported a study showing cyclic alcohols underwent C-C bond cleavage induced by oxygen radical to generate a ketone and a terminal carbon radical.[24] Subsequent hydrogen atom transfer gave the desire product.

Intramolecular proton coupled electron transfer (PCET) was crucial for the formation of oxygen-centered radical as alcohols were also difficult to be oxidized directly by photocatalysts.



Scheme 1.19 LMCT Ring-Opening of Cycloalkanols by Prof. Zuo.

A novel catalysis engaging ligand-metal charge transfer from alkoxide (alcohol) ligand to cerium metal was achieved by Prof. Zuo and coworkers.[25] Upon the absorption of visible light by alkoxide ligated cerium center, single electron flowed from the ligand to metal resulting oxidized alkoxide and reduced cerium metal center. Subsequent dissociation of the ligand with a formal oxygen-centered radical release a cycloalkanol radical which underwent ring-opening to form a ketone and terminal carbon radical. Subsequent radical addition to electron deficient alkenes followed by reduction and intramolecular cyclization furnished the seven-membered cycloalkanol product.



Scheme 1.20 Iminyl Radical Promoted Ring-Opening by Prof Zhou, Xiao and Leonori.

In 2017, inspired by the previous work of Zard and many others using non-photoredox catalysis, Prof Zhou, Xiao and Leonori independently reported ring-opening strategies utilizing iminyl radical intermediate, which is generated either from reductive or oxidative quenching of the excited state photocatalysts.[26] The nascent iminyl radical induced subsequent C-C bond cleavage which furnished a nitrile group and terminal carbon radical. Various radical acceptors then can intercept the radical to give remote functionalized nitrile products.

1.4 References

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Chapter 2. Synthesis of Multisubstituted Naphthalenes by [4 + 2] Annulation

2.1 Introduction

Substituted naphthalenes and their derivatives, such as naphthoquinones, are ubiquitous in many valuable molecules across a broad spectrum of usage.[1] Selected examples in this class of compounds include 9,10-anthraquinone-2,7-disulphonic acid (AQDS), an excellent energy storage material for flow batteries,[2] justicidin A, a potent antitumor natural product,[3] and rumexoside, isolated from the roots of a Turkish medicinal plant (Figure 1).[4] Synthesis of substituted naphthalenes remains challenging due to the limitation of functional group tolerance as well as regioselectivity.[5] Most of these syntheses fall into two categories: 1) they start from a simple naphthalene core and then often require stepwise and lengthy elaboration to install the requisite functional groups;[6] 2) they begin with a suitably functionalized arene and proceed through annulation or cyclization to install the other arene.[7] Between the two approaches, the later is generally considered to be more desirable because it is convergent and modular.

The embedded ring strain in benzocyclobutenes renders the usually inert C-C bonds cleavable under various conditions, thereby making them a versatile precursor in the synthesis of naphthalenes and dihydronaphthalenes.[8] Benzocyclobutenols, which bear a hydroxyl group on the cyclobutenyl ring, display similar versatility in the ring opening process.[9, 10] Photo-irradiation, base treatment, or heating generally favors cleavage of the distal C-C bond, revealing a quinodimethane intermediate that readily participates in the Diels-Alder reaction to provide dihydronaphthalenes.[11] On the other hand, cleavage of the proximal C-C bond can be realized by transition metal complexes such as Pd and Rh complexes to furnish aryl-palladium or -rhodium intermediates that can participate in a number of C-C bond formation reactions.[9a, 12] Although

amino-benzocyclobutenes can be conveniently synthesized by [2+2] cycloaddition of arynes with ketenes followed by reductive amination, they have been much less exploited than benzocyclobutenols in organic synthesis (scheme 1).[13] Two notable examples using amino-benzocyclobutenes as precursors to synthesize substituted arenes and dihydronaphthalenes include Shi's work on addition of vinylogous amides to arynes and Hsung's on syntheses of chelidonine and norchelidonine. In both works, a quinodimethane intermediate was proposed to be generated in situ via the ring opening and then was intercepted by a nucleophile or underwent the Diels-Alder reaction.[14]

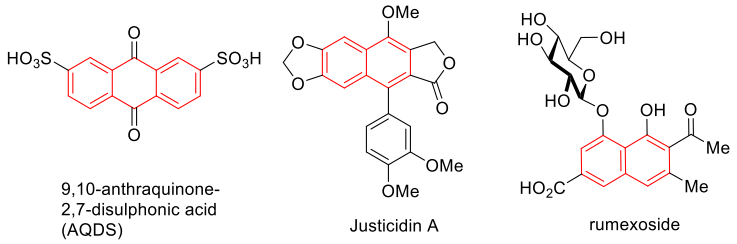


Figure 2.1 Selected examples of substituted naphthalenes.

Few studies on amino-benzocyclobutenes' utility as synthetic building blocks prompted us to examine their synthetic applications, particularly in the context of visible light photocatalysis. We envisioned that single electron photooxidation of amino-benzocyclobutenes would induce cleavage of the distal C-C bond to furnish a distonic radical cation.[15] This reactive species would then undergo two sequential C-C bond formations mediated by radicals to form a dihydronaphthalene. We expected that its reactivity would be distinct from that of a quinodimethane and thereby could furnish a completely different subclass of dihydronaphthalenes. Herein we report our studies on intermolecular annulations of amino-benzocyclobutenes with alkynes and diynes, which results in a three-component (benzynes, lithium enolates or silyl ketene acetals, and alkynes) synthesis of substituted naphthalenes.

Anilines play a dual role in this reaction: it first engages in the photooxidation to induce the ring opening and then serves as a leaving group to complete aromatization.

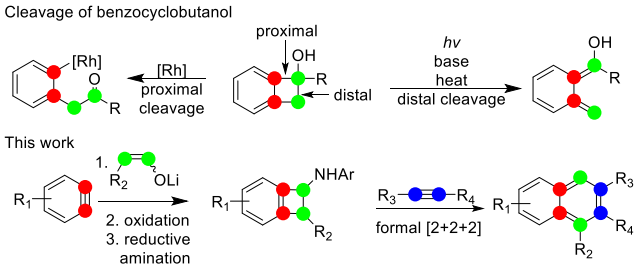


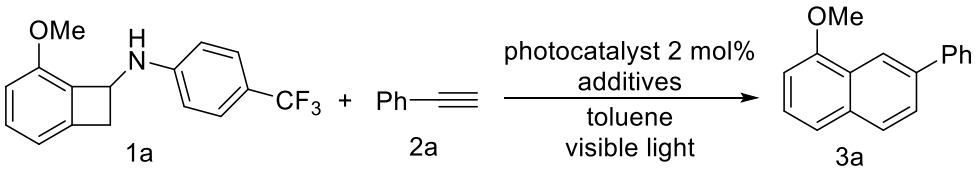
Figure 2.2 Selected examples of substituted naphthalenes.

2.2 Reaction Optimization of the [4+2] Annulation

Amino-benzocyclobutene **1a** and phenylacetylene were chosen as the representative substrates to optimize the reaction conditions (table 1). The substituent on the aniline moiety was found to greatly affect the reaction, and amino-benzocyclobutenes bearing electron-withdrawing groups performed much better than those bearing electron-donating ones (see SI). The -CF_3 group was selected as the standard substituent because of its chemical inertness under the photoredox conditions and the availability of commercially available cheap precursor, 4-(trifluoromethyl)-aniline. Among the solvents screened, toluene was found to be the best. Other aromatic solvents and polar solvents such as methanol and nitromethane all gave inferior results (see SI). For the photocatalyst, we focused on those soluble in toluene. $[Ir(ppy)_2(dtbbpy)][PF_6]$ was more effective than $[Ir\{dF(CF_3)ppy\}_2(dtbpy)][PF_6]$ (entries 1 and 2), whereas $Ru(bpy)_3(BArF)_2$ was surprisingly inactive (see SI). Addition of an inorganic base such as K_2HPO_4 increased the yield of **3a** from 37% to 48% (entry 3). However, use of more basic K_3PO_4 gave a slightly lower yield of **3a** (entry 4). Interestingly, use of a more soluble base such as Cs_2CO_3 or tetrabutylammonium hydroxide resulted in a much lower yield of **3a**, suggesting a

delicate balance of the base's strength and solubility in order to achieve the optimal yield (see SI). Increasing the concentration and switching from 18 W white LED to 6 W blue LED both helped the reaction, furnishing product **3a** in 62% yield (entries 5 and 6). Control experiments showed that both light and the photocatalyst were essential to the reaction (entries 7 and 8). These results suggested that the Diels-Alder reaction pathway unlikely operated in the reaction.[14a, 14c] It was worth of note that because incomplete elimination of the aniline was observed in the conditions examined, concentrated HCl was added during the workup to ensure completion of the elimination[16].

Table 2.1 Optimization of [4+2] annulation



Entry	Photocatalyst	Additives (1 equiv.)	Yield of 3a [%][b]
1	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)][PF_6]$		22
2	$[Ir(ppy\}_2(dtbpy)][PF_6]$		37
3	$[Ir(ppy\}_2(dtbpy)][PF_6]$	K_2HPO_4	48
4	$[Ir(ppy\}_2(dtbpy)][PF_6]$	K_3PO_4	36
5	$[Ir(ppy\}_2(dtbpy)][PF_6]$	K_2HPO_4	59[c]
6	$[Ir(ppy\}_2(dtbpy)][PF_6]$	K_2HPO_4	62[c, d]
7	$[Ir(ppy\}_2(dtbpy)][PF_6]$	K_2HPO_4	N.R.[c, e]
8		K_2HPO_4	N.R.[c, d]

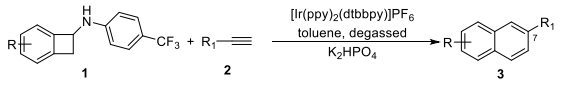
[a]Conditions: **1a** (0.1 mmol, 0.1 M in degassed toluene), **2a** (0.5 mmol), irradiation with 18 W white LED at room temperature for 36 h, concentrated HCl is added. 20 s later, the mixture is filtered through silica gel. [b]Yield determined by GC analysis using dodecane as an internal standard unless noted. [c]0.2 M of 1a in degassed toluene. [d]Irradiation with 6 W blue LED. [e]No light.

2.3 Substrates Scope of Amino-benzocyclobutenes and Alkynes.

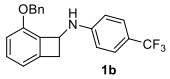
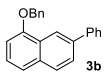
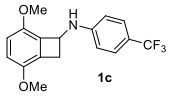
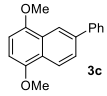
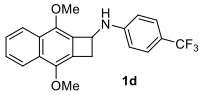
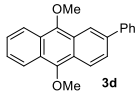
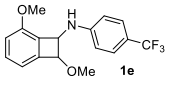
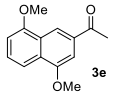
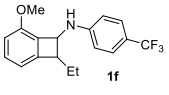
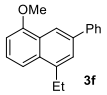
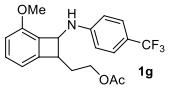
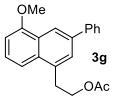
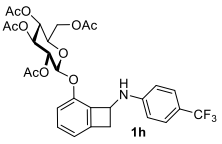
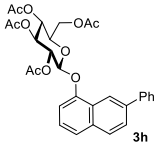
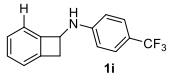
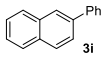
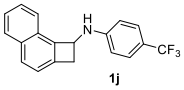
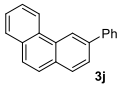
Using phenylacetylene (**2a**) as the alkyne partner, we examined the scope of amino-benzocyclobutenes (table 2). Replacement of the -OMe substituent with a more labile -OBn group had little effect on the product's yield (**3b**). Addition of another -OMe group para to the original one (**1c**) furnished 1,4-dimethoxy-7-phenylnaphthalene **3c**, a naphthoquinone precursor in 58% yield. Fusion of a benzene ring to amino-benzocyclobutene **1d** was easily accomplished by modifying the corresponding benzyne precursor, and the expected product 9,10-Dimethoxy-2-phenylanthracene **3d**, an anthraquinone precursor was prepared in 54% yield. Additional substituents were readily incorporated into amino-benzocyclobutenes by choosing silyl ketene acetals bearing the substituents for the [2+2] cycloaddition with the corresponding benzynes. These substituted amino-benzocyclobutenes (**1e**: -OMe; **1f**: -Et; **1g**: $-CH_2CH_2OAc$) underwent the annulation with 3-butyn-2-one or phenylacetylene uneventfully, providing C5-substituted naphthalenes (**3e**, **3f**, and **3g**) in 54-68% yields. Aromatic O-glycosides such as naphthalene saccharides are a common structural motif in bioactive natural products. The common approach for synthesis of this motif is to form the glycosidic bond between an aglycone (e.g., naphthol) and a saccharide.[17] This method permits an alternative assembly strategy in which the glycosidic bond is formed between a simpler aglycone (e.g., a phenol derivative) and the saccharide and the subsequent annulation completes the synthesis of the more complex aglycone. Amino-benzocyclobutene **1h** bearing a tetraacetyl glucose with a β configuration at the anomeric carbon underwent the annulation with phenylacetylene to afford **3h** with the β configuration intact. Lastly, the alkoxy substituent in amino-benzocyclobutenes helped stabilize the aryne intermediate and thus improved the efficiency of the [2+2] cycloaddition to form the

cyclobutenyl ring. However, it was not required for the annulation. Amino-benzocyclobutenes (**1i** and **1j**), both lack of the alkoxy substituent, proceeded in the annulation to furnish 2-phenylnaphthalene **3i** and 3-phenylphenanthrene **3j** respectively.

Table 2.2 Substrate Scope of Amino-benzocyclobutenes.



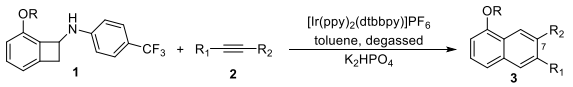
1 2 3

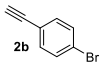
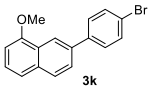
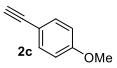
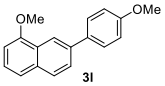
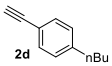
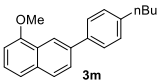
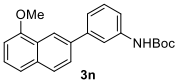
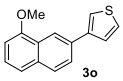
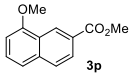
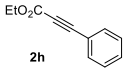
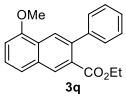
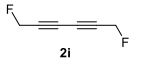
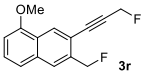
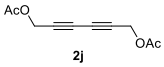
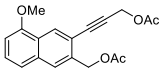
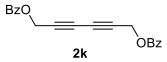
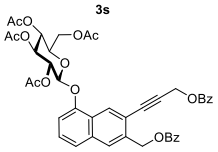
Entry[a]	Substrate	Product	Yield[%][b]
1	 1b	 3b	58
2	 1c	 3c	58
3	 1d	 3d	54
4	 1e	 3e	68
5	 1f	 3f	56
6	 1g	 3g	54
7	 1h	 3h	50
8	 1i	 3i	56
9	 1j	 3j	40

[a] Conditions: **1** (0.1 mmol, 0.2 M in degassed toluene), **2** (0.5 mmol), after irradiation with 6 W blue LED at room temperature for 60 h, concentrated HCl is added. 20 s later, the mixture is filtered through silica gel. [b] Isolated yields.

We next investigated the scope of alkynes (table 3). The substituents on the phenyl group of phenylacetylene were well tolerated. Several groups with various electronic characters at the para or meta position (**2b-e**) were compatible with the annulation reaction to provide naphthalenes **3k-n** in 51-64% yield. In addition to the aryl group at C7, other functional groups such as thiophene and methyl esters were easily incorporated into C7 of naphthalenes, as 3-ethynylthiophene **2f** and methyl propiolate **2g** both successfully underwent the annulation with **1a**, although in somewhat lower yields than phenylacetylene. Unsymmetrical internal alkyne **2h,** despite the increase in steric hindrance, participated in the annulation to furnish only one regioisomer **3q** in 58% yield albeit in longer reaction time. To our surprise, diynes **2i-k** worked really well in this method. Alkynyl naphthalenes **3r-s**, which are usually synthesized by cross coupling of terminal alkynes with prefunctionalized naphthalenes, were obtained in one step in 62-63% yield. Not surprisingly, the glycosidic bond survived in the annulation of **1h** with diyne **2k**, which allowed for rapid increase of the structural complexity of naphthalene saccharide **3t** in a respectable yield (61%).

Table 2.3 Substrate Scope of Alkynes.



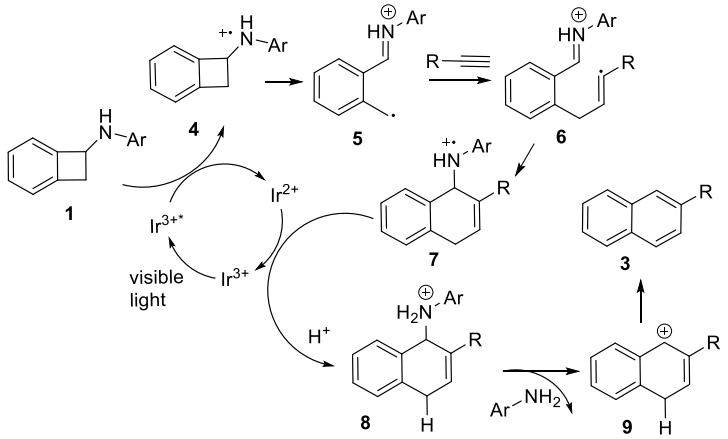
Entry[a]	alkynes	Product	Yield[%][b]
1			64
2			51
3			54
4			59
5			38
6			44
7			58[c]
8			62
9			63
10			61

[a] Conditions: **1** (0.1 mmol, 0.2 M in degassed toluene), **2** (0.5 mmol), after irradiation with 6 W blue LED at room temperature for 60 h, concentrated HCl is added. 20 s later, the mixture is filtered through silica gel. [b] Isolated yields. [c] 84 h

2.4 Mechanistic Study

We believed that the annulation probably proceeds in a mechanism similar to our previously reported [4+2] annulation of cyclobutylanilines with alkynes, as the reactivity trend and regiochemistry with respect to alkynes completely match with those observed for the latter

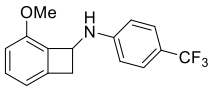
reaction.[15c] The photoexcited Ir(III) complex oxidizes amino-benzocyclobutene **1** to generate amino radical cation **4** followed by ring opening at the distal C–C bond to form distonic radical cation **5**, which subsequently adds to alkyne to furnish vinyl radical **6**. Ring closure is then achieved via intramolecular addition of the vinyl radical to the iminium ion to provide amino radical cation **7**, which is reduced by the Ir(II) complex to give 1,4-dihydronaphthalene **8** after protonation. Finally, elimination of the aniline group presumably by an E1-like pathway gives naphthalene **3** via benzylic carbocation **9** (scheme 2). The [4+2] annulation of amino-benzocyclobutenes with alkynes was considerably slower than that of cyclobutylanilines with alkynes. We attributed the slower annulation of amino-benzocyclobutenes to the stability and low reactivity of the incipient benzyl radicals. It has been reported that benzyl radicals add to alkenes much slower than alkyl radicals.[18] To support the proposed mechanism, the uneliminated 1,4-dihydronaphthalene intermediate from **2h** was successfully isolated. UV-Vis absorption spectra of amino-benzocyclobutene **1a** and $[Ir(ppy)_2(dtbbpy)]PF_6$ supported that the Ir complex was photoexcited by the blue LED. The oxidation half peak potential of **1a** was found to be 1.13 V vs. SCE, which is more positive than the reduction potential of the photoexcited Ir(III) complex (Ir^{3+*}/Ir^{2+} : 0.66 V vs. SCE).[19] Although thermodynamically unfavorable, such SET processes have been reported.[15c, 20] Stern-Volmer quenching studies also showed that amino-benzocyclobutene **1a** was able to quench the photoexcited Ir (III) complex. TEMPO completely inhibited the formation of the uneliminated dihydronaphthalene and naphthalene.



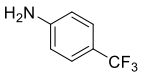
Scheme 2.1 Proposed Reaction Mechanism.

Cyclic Voltammetry Study

Cyclic voltammograms were recorded on a CH Instruments-Electrochemical Analyzer using a three-electrode cell at room temperature under an argon atmosphere. The reference electrode was a silver cryptand (Ag+/Ag-cryptand), which was separated from the solution by a bridge compartment filled with the same supporting electrolyte solution used in the cell. A platinum disc (2.0 mm diameter) was used as the working electrode and a platinum wire as the auxiliary electrode. Tetrabutylammonium hexafluorophosphate (0.1 M in CH3CN) was used as the supporting electrolyte. Voltammograms were taken in a solution of 1a and 11a in CH_3CN (c ~ 2.00-3mol.L-1).



1a



11a

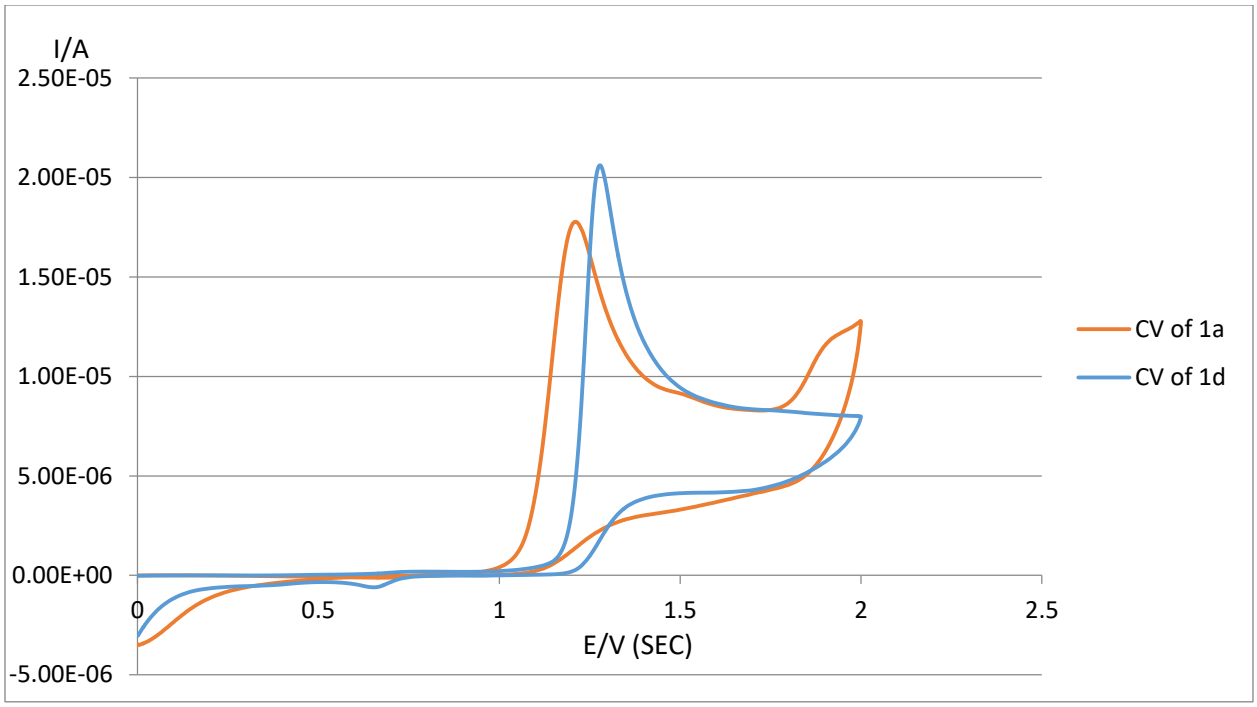


Chart 2.1 Cyclic Voltammograms of 1a and 3a.

Stern-Volmer Quenching study

Fluorescence quenching studies were conducted using a Photon Technology Fluorescence Spectrophotometer. In each experiment, a solution of 5.0 x 10^{-4} M $Ir(ppy)_2(dtbbpy)PF_6$ in toluene was mixed with a toluene solution of **1a** of various concentration in a screw-top 1.0 cm quartz cuvette. After degassing by sparging with argon for ten minutes, the resulting solution was irradiated at 375 nm, and fluorescence was measured at 558 nm. Plots were constructed according to the Stern-Volmer equation: $I_0/I = 1 + k_q\tau_0[Q]$.

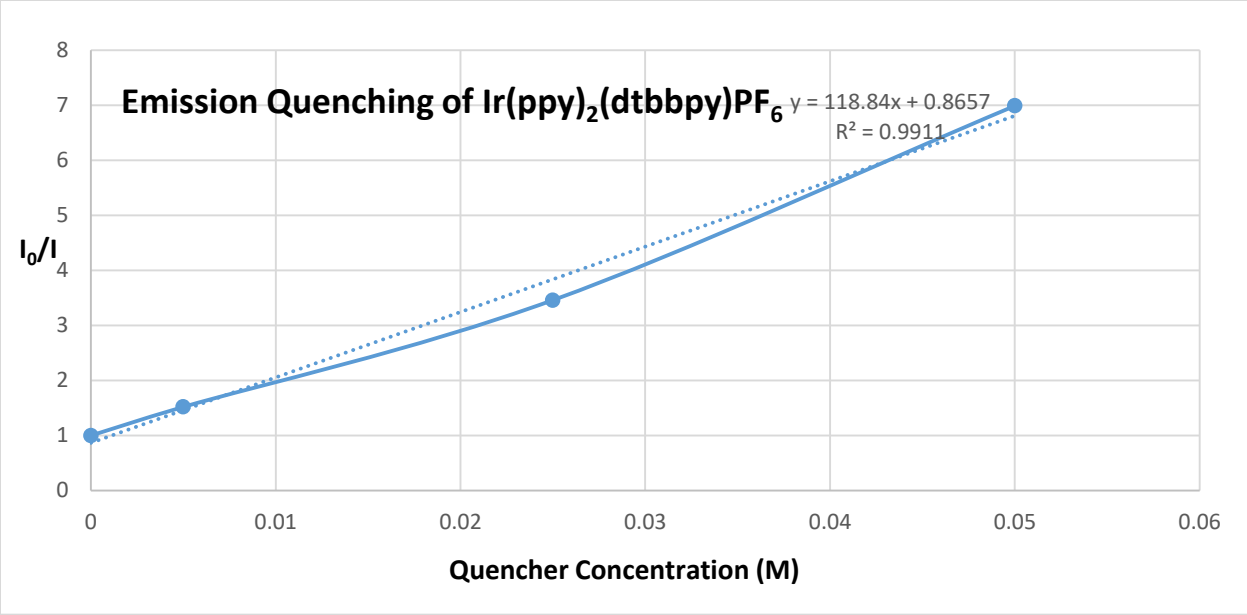


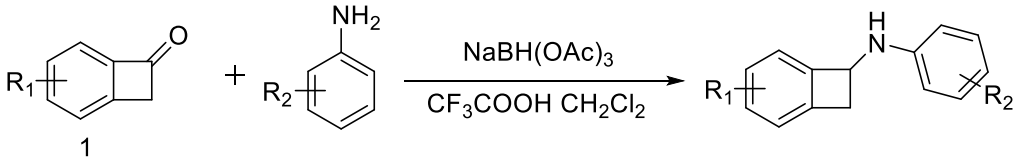
Chart 2.2 Fluorescence Quenching Studies.

2.5 Experimental Section

All reactions were carried out under argon atmosphere, unless stated otherwise. Anhydrous methanol (CH_3OH, AcroSeal) was purchased from Acros Organics and dimethylsulfoxide (DMSO) was pre-dried over molecular sieves. Toluene was collected under argon from a solvent purification system. Column chromatography was performed using silica gel (230-400 mesh). All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR spectroscopy, high-resolution mass spectroscopy (HRMS), and melting point if solid. 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 signals in $CDCl_3$ (7.26 ppm, 77.23 ppm) or CD_2Cl_2 (5.32 ppm, 54.00 ppm) at room temperature. IR spectra were recorded on a Shimadzu IRAffinity-1S instrument. High resolution mass spectra were recorded on a Bruker Ultraflex II TOF/TOF mass spectrometer. 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

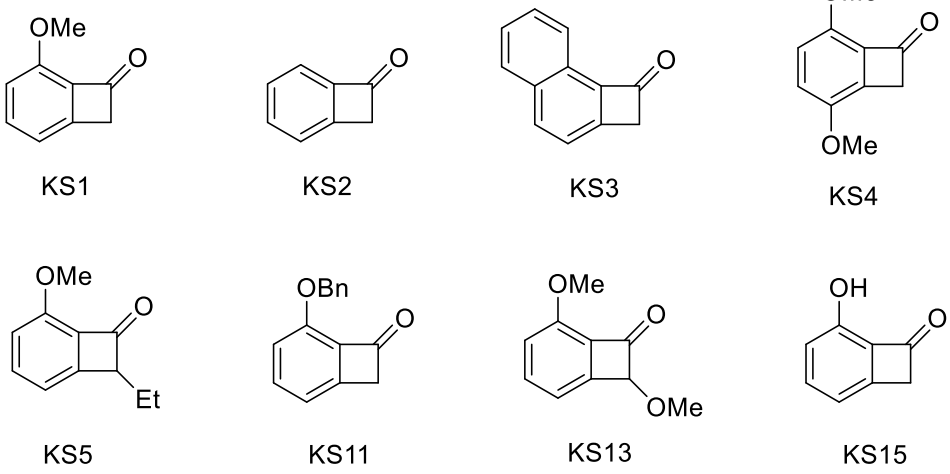
using a Shimadzu GC-2010 Plus instrument. Melting points (m.p.) were recorded using a Stuart SMP10 Melting Point Apparatus and were uncorrected.

General Procedure 1 (GP1): Preparation of benzocyclobuteneamines

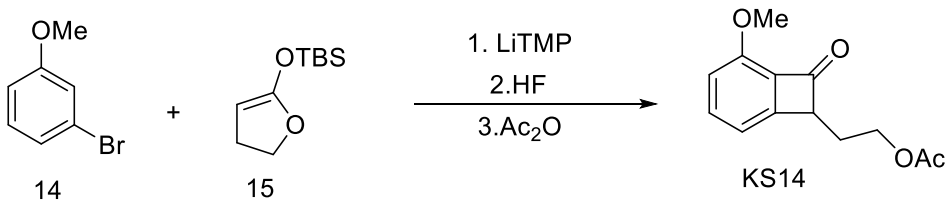


Benzocyclubutenone(1 equiv.) and anline (2 equiv.) were dissolved in CH_2Cl_2 (0.2M). Mixed with $NaBH(OAc)_3$ (2eq.) and CH_2Cl_2 (0.2M) is added. CF_3COOH (5 equiv. mL) is then added dropwise via syringe. Upon the completion of adding CF_3COOH, the reaction mixture was stirred under room temperature for 2h. Then the reaction was quenched with saturated $NaHCO_3$ solution (2mL/mmol). The reaction mixture was washed with $NaHCO_3$ three times (3ml/mmol), brine (5ml/mmol), and dry over Na_2SO_4. The crude was concentrated, and the residual was subjected to flash chromatography to give the pure product.

Ketones: KS1, KS4, KS5, KS11, KS15 are prepared followed by the Method reported by Guangbin Dong[1]. KS2, KS13 are prepared followed by literature reported by Keisuke Suzuki[2]. KS3 is prepared followed by literature reported by Zhixiang Yu[3].



Synthesis of KS14

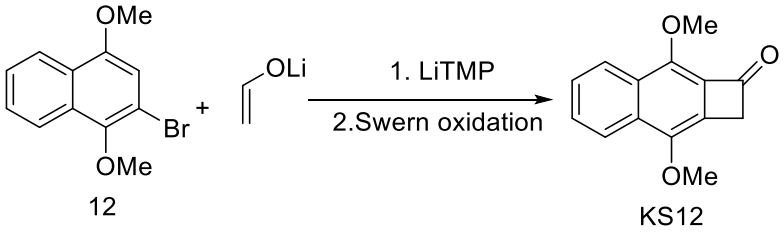


Ketone KS14 was synthesized followed by the Method reported by Guangbin Dong and Piero Melloni[1, 4].

To a 100 mL flamed-dried round bottom flask equipped with a stir bar and a nitrogen-filled balloon were added 2,2,6,6-tetramethylpiperidine (4 mL, 24 mmol, 1.2 equiv) and THF (30 mL). After cooling to 0 °C with an ice-water bath, *n*-BuLi (15 mL, 24 mmol, 1.6 M in hexane, 1.2 equiv) was added dropwise and the resulting mixture was stirred at 0 °C for 0.5 h. To a 250 mL round bottom flame-dried flask equipped with a stir bar and a nitrogen-filled balloon were added THF (30 mL), **14** (2.5mL, 20 mmol, 1 equiv.), and **15** (6.0g, 30 mmol, 1.5 equiv.), and the resulting mixture was cooled to −78 °C with an acetone-dry ice bath before the in situ generated LiTMP was added dropwise. The reaction progress was monitored by TLC. Aqueous NH_4Cl (30 mL) was added at −78 °C upon disappearance of the benzyne precursor 14. After warming up to rt, the reaction mixture was extracted with ethyl acetate (30 mL×3), washed with brine (30 mL), and concentrated under reduced pressure. Acetonitrile (75 mL) was added to the residual and the resulting solution was cooled to 0 °C with an ice-water bath followed by slow addition of hydrofluoric acid (7.0 mL, 27.6 M, 10 equiv.). Upon completion of the addition, the reaction mixture was heated to 40 °C overnight before water (100 mL) was added. The mixture was extracted with ethyl acetate (30 mL×3), washed with brine (30 mL), and dried with Na_2SO_4 and concentrated. The residual was mixed with acetic anhydride (14 mL) and then pyridine (0.3 mL)

was added. After 1 h, the reaction mixture was poured into a mixture of crushed ice and $NaHCO_3$, in order to decompose unreactive acetic anhydride. The mixture was extracted with ethyl acetate three times (20 mL x 3) and concentrated and then purified by flash chromatography (conditions) to give 1.94g KS14 (42% yield over 3 steps).

Synthesis of KS12

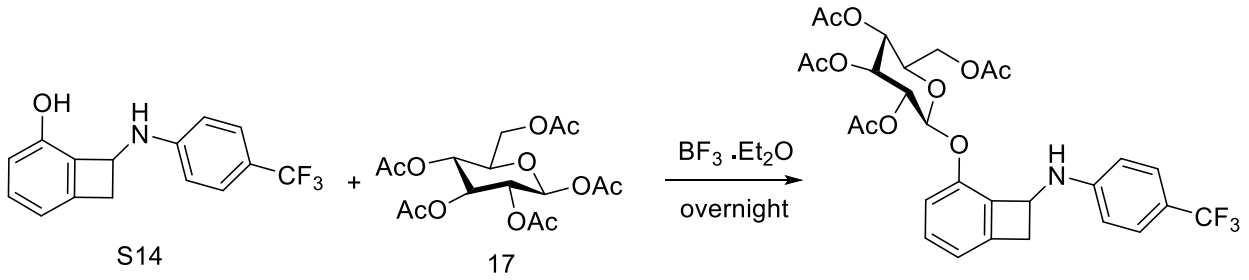


Following the method reported by Guangbin Dong[1]. To a 250 mL oven dried round bottom flask was added THF (60 mL). The flask was evacuated and backfilled with nitrogen five times. After cooling to 0 °C, n-BuLi (1.6 M in hexane, 11.25 mL, 18 mmol, 1.5 equiv) was added dropwise. Upon completion of the addition, the flask was warmed to room temperature and stirred for 16 h under nitrogen atmosphere. Separately, LiTMP was prepared by adding n-BuLi (1.6 M in hexane, 9 mL, 14.4 mmol, 1.2 equiv) dropwise to a solution of 2,2,6,6-tetramethylpiperidine (2.45 mL, 14.4 mmol, 1.2 equiv) in THF (36 mL) under nitrogen atmosphere at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 h. The 250 mL flask with the formed Li enolate of acetaldehyde was cooled to −78 °C with an acetone-dry ice bath. A solution of aryl bromide 12 (3.18 g, 12 mmol, 1.0 equiv) in THF (15 mL) was added followed by addition of the prepared LiTMP dropwise. After 1 h, aqueous NH_4Cl (30 mL) was added to quench the reaction at −78 °C. The mixture was then warmed to rt and H_2O (20 mL) was added. The mixture was extracted with ethyl acetate (30 mL×3), washed with brine, and dried over Na2SO4. The combined organic

extract was concentrated under reduced pressure, and the residual was used in the next step without further purification.

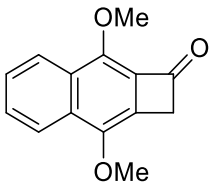
Oxalyl chloride (1.55 mL, 18 mmol, 1.5 equiv) and CH_2Cl_2 (23 mL) was added to a 100 mL oven dried round bottom flask. The flask was cooled to −78 °C and DMSO (2.6 mL, 36 mmol, 3 equiv.) in CH_2Cl_2 (15 mL) was added dropwise. After the reaction mixture was stirred at −78 °C for 20 min, the crude obtained from the previous step, dissolved in CH_2Cl_2 (15 mL), was added dropwisely and resulting mixture was stirred at −78 °C for another hour. Triethylamine (10 mL, 72 mmol, 6 equiv.) was added slowly. The reaction mixture was then warmed to room temperature and quenched with H_2O, and extracted with ethyl acetate (150 mL × 3). The combined organic extract was washed with brine (100 mL) and dried over Na_2SO_4. The organic extract was concentrated under reduced pressure and purified by column chromatography on silica gel to give 0.52g of KS12 (19% yield over 2 steps).

Synthesis of S16

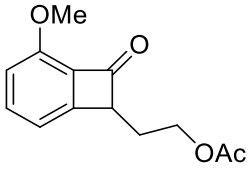


S14 (1mmol, 1eq), which is prepared by reductive amination procedure GP1 of corresponding benzocyclobutenone, is added into a test tube with 17 (2mmol, 2eq) and dissolved in DCM (5mL). the test tube is cool to 0 °C and BF_3 in Et_2O (0.67ml, 5eq) is added dropwise. The reaction mixture is stirred in room temperature for 12 h and quenched by $NaHCO_3$ at 0 °C.

Extraction with ethyl acetate three times and dry over Na2SO4 and concentrated and then purified by flash chromatography to give 0.3800g S15 (63% yield).

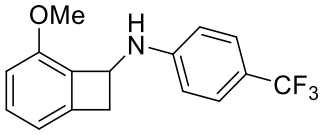


(K12). Following the procedure of synthesis of KS12, product was isolated after flash chromatography on silica gel (5:1 hexane/ EtOAc) as a pale green solid M.P. :158 °C - 160°C (1.22 g, 20%); IR υmax (cm-1) 3010, 2945, 2924, 2843, 1759, 1581, 1462, 1444, 1357, 1278, 1056, 914, 765, 655, 630; 1H NMR (400 MHz, Chloroform-d) δ 8.29 – 8.17 (m, 1H), 8.14 (dt, J = 8.6, 0.9 Hz, 1H), 7.59 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H), 7.45 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 4.33 (s, 3H), 4.26 (s, 2H), 4.07 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 186.96 , 144.59 , 142.78 , 131.69 , 128.94 , 126.77 , 126.50 , 125.87 , 124.93 , 122.37 , 117.45 , 61.04 , 57.65 , 51.75 .; 13C NMR DEPT135(101 MHz, Chloroform-d) δ 128.94 , 125.87 , 124.92 , 122.37 , 61.04 , 57.64 , 51.75 .;HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{14}H_{13}O_3$ 229.0859; found 229.0882.

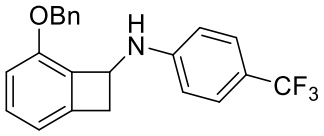


(KS14). Following the procedure of synthesis of KS14, product was isolated after flash chromatography on silica gel (7:1 hexane/ EtOAc) as a colorless oil (1.94 g, 42% 3 steps from 3-bromoanisole); IR υmax (cm-1) 2943, 1759, 1735, 1600, 1571, 1481, 1433, 1274, 1236, 1122, 1037, 790, 771; 1H NMR (300 MHz, Chloroform-d) δ 7.42 (dd, J = 8.4, 7.1 Hz, 1H), 7.11 – 6.95 (m, 1H), 6.80 (dt, J = 8.4, 0.6 Hz, 1H), 4.36 – 4.12 (m, 3H), 4.08 (s, 3H), 2.23 (ddt, J = 14.3, 6.8, 6.2 Hz, 1H), 2.15 – 1.98 (m, 4H).; 13C NMR (101 MHz, CDCl3) δ 187.40, 170.94, 154.71, 153.75, 137.82, 131.03, 116.37, 114.79, 62.28, 60.66, 59.77, 59.77, 29.23,

20.96.; 13C NMR DEPT135 (101 MHz, CDCl3) δ 137.82, 116.37, 114.79, 62.28, 60.66, 59.77, 29.23, 20.96.; HRMS (ESI) *m/z* [M+Na]+, calc'd for $C_{13}H_{14}O_4Na$ 257.0784; found 257.0788.

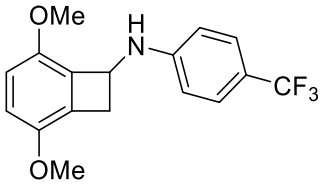


(1a). Following the above procedure GP1 with benzocyclobutenone KS1 and 4-(Trifluoromethyl)aniline, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as a white solid M.P. :86 °C - 88°C (3.86 g, 74%); IR υmax (cm-1) 3383, 3361, 3014, 2916, 1608, 1479, 1315, 1259, 1099, 1045, 825, 769, 507; 1H NMR (400 MHz, Methylene Chloride-d2) δ 7.50 (d, J = 8.7 Hz, 2H), 7.37 – 7.28 (m, 1H), 6.87 – 6.72 (m, 4H), 5.21 (ddd, J = 8.0, 4.2, 1.9 Hz, 1H), 4.90 (d, J = 8.0 Hz, 1H), 3.92 (s, 3H), 3.69 (ddd, J = 14.0, 4.3, 0.7 Hz, 1H), 2.95 (ddd, J = 14.0, 1.8, 0.8 Hz, 1H); 13C NMR (101 MHz, Methylene Chloride-d2) δ 154.92 , 150.35 , 145.81 , 131.65 , 129.37 , 127.16 (q, J = 4.1 Hz), 125.75 (q, J = 271.39 Hz), 119.56 (q, J = 32.7 Hz), 116.60 , 113.11 , 113.02 , 56.64 , 53.85 , 40.74 .; 13C NMR DEPT135(101 MHz, Benzene-d6) δ 131.90 , 127.39 (q, J = 3.7 Hz), 116.64 , 114.01 , 113.20 , 56.39 , 53.90 , 40.74 . 19F NMR (376 MHz, Benzene-d6) δ -60.85 . HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{16}H_{15}F_3NO$ 294.1100; found 294.1104.

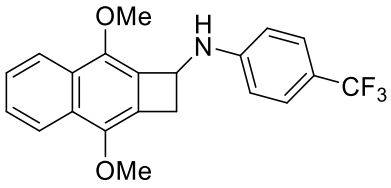


(1b). Following the above procedure GP1 with benzocyclobutenone KS11 and 4-(Trifluoromethyl)aniline, product was isolated after flash chromatography on silica gel (30:1 hexane/ EtOAc) as a white solid M.P. :122 °C - 124°C (0.76g, 52%); IR υmax (cm-1) 3377, 3037, 2964, 2929, 1612, 1323, 1313, 1251, 1161, 1097, 1060, 1028, 829, 771, 704, 474; 1H NMR (400 MHz, Benzene-d6) δ 7.31 (d, J = 8.6 Hz, 2H), 7.21 – 7.18 (m, 2H), 7.15 – 7.10 (m, 3H), 7.09 – 7.04 (m, 1H), 6.86 (d, J = 8.5 Hz, 1H), 6.64 (d, J = 7.2 Hz, 1H), 6.13 (d, J = 8.6

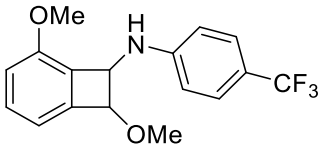
Hz, 2H), 5.06 – 4.77 (m, 2H), 4.57 (ddd, J = 8.8, 4.4, 2.0 Hz, 1H), 3.80 (d, J = 8.8 Hz, 1H), 3.14 (dd, J = 14.0, 4.4 Hz, 1H), 2.52 – 2.43 (m, 1H).; 13C NMR (101 MHz, Benzene-d6) δ 154.35 , 149.98 (d, J = 1.1 Hz), 145.62 , 138.05 , 131.78 , 129.73 , 129.11 , 128.43 , 127.50 , 127.23 (q, J = 3.8 Hz), 126.25 (q, J = 270.3 Hz), 120.08 (q, J = 32.5 Hz), 116.73 , 115.00 , 113.26 , 70.95 , 53.90 , 40.35 .; 13C NMR DEPT135 (101 MHz, Benzene-d6) δ 131.78 , 129.12 , 128.44 , 127.50 , 127.23 (q, J = 3.7 Hz), 116.73 , 115.00 , 113.26 , 70.94 , 53.89 , 40.35 .; 19F NMR (376 MHz, Benzene-d6) δ -60.84 . ;HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{22}H_{19}F_3NO$ 370.1413; found 370.1416.



(1c). Following the above procedure GP1 with benzocyclobutenone KS4 and 4-(Trifluoromethyl)aniline, product was isolated after flash chromatography on silica gel (5:1 hexane/ EtOAc) as a white solid M.P. :84 °C - 86°C (1.66 g, 72%); IR υmax (cm-1) 3336, 2941, 2927, 1614, 1490, 1255, 1097, 1037, 825, 584, 501; 1H NMR (400 MHz, Benzene-d6) δ 7.34 (d, J = 8.7 Hz, 2H), 6.74 (dd, J = 9.0, 0.6 Hz, 1H), 6.67 – 6.61 (m, 1H), 6.13 (dd, J = 8.6, 0.9 Hz, 2H), 4.61 (ddd, J = 8.2, 4.3, 1.9 Hz, 1H), 4.00 (d, J = 8.1 Hz, 1H), 3.46 (s, 3H), 3.44 (s, 3H), 3.23 (ddd, J = 13.4, 4.3, 0.7 Hz, 1H), 2.56 (ddd, J = 13.6, 2.0, 0.8 Hz, 1H).; 13C NMR (101 MHz, Benzene-d6) δ 150.04 (d, J = 1.1 Hz), 149.63 , 149.45 , 130.60 , 128.36 , 127.21 (q, J = 3.8 Hz), 126.27 (q, J = 270.2 Hz), 119.94 (q, J = 32.4 Hz), 116.91 , 115.00 , 113.03 , 56.41 , 56.40 , 53.54 , 40.04 .; 13C NMR DEPT135 (101 MHz, Benzene-d6) δ 127.21 (q, J = 3.8 Hz), 116.90 , 114.99 , 113.02 , 56.41 , 56.39 , 53.53 , 40.04 .; 19F NMR (376 MHz, Benzene-d6) δ -60.84 . ;HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{17}H_{17}F_3NO_2$ 324.1206; found 324.1207.

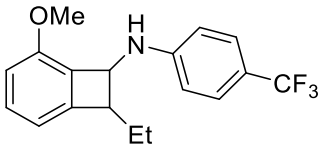


(1d). Following the above procedure GP1 with benzocyclobutenone KS12 and 4-(Trifluoromethyl)aniline, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as a white solid M.P. :152 °C - 154°C (0.1002 g, 34%); IR υmax (cm-1) 3367, 2924, 2848, 1614, 1525, 1332, 1099, 829, 763; 1H NMR (400 MHz, Benzene-d6) δ 8.54 – 8.45 (m, 2H), 7.39 (ddd, J = 9.9, 5.3, 1.6 Hz, 4H), 6.15 (d, J = 8.5 Hz, 2H), 4.62 (ddd, J = 9.2, 5.0, 2.5 Hz, 1H), 3.90 (d, J = 9.3 Hz, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 3.27 (dd, J = 13.9, 5.0 Hz, 1H), 2.59 (dd, J = 13.9, 2.5 Hz, 1H).; 13C NMR (101 MHz, Benzene-d6) δ 149.70 (d, J = 1.1 Hz), 144.45 , 143.73 , 128.28 , 127.77 , 127.33 (q, J = 3.8 Hz), 126.37 , 126.22 (q, J = 270.3 Hz), 125.81 , 123.24 , 122.76 , 121.94 , 120.30 (q, J = 32.6 Hz), 118.56 , 113.22 , 57.61 , 57.35 , 54.06 , 40.53 .; 13C NMR DEPT135 (101 MHz, Benzene-d6) δ 127.34 (q, J = 3.7 Hz), 126.37 , 125.81 , 123.24 , 122.77 , 113.22 , 57.61 , 57.35 , 54.05 , 40.53 .; 19F NMR (376 MHz, Benzene-d6) δ -60.87 . ;HRMS (ESI) *m/z* [M+ Na]+, calc'd for $C_{21}H_{18}F_3NO_2Na$ 396.1182; found 396.1183.

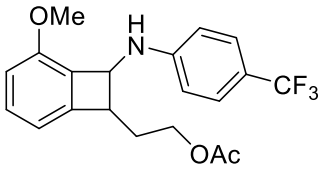


(1e). Following the above procedure GP1 with benzocyclobutenone KS13 and 4-(Trifluoromethyl)aniline, product was isolated after flash chromatography on silica gel (15:1 hexane/ EtOAc) as a white solid M.P. :103 °C - 107°C (1.75 g, 68%); IR υmax (cm-1) 3346, 2937, 2883, 1610, 1541, 1319, 1093, 1055, 823, 783, 503; 1H NMR (400 MHz, Benzene-d6) δ 7.35 (dd, J = 8.6, 0.9 Hz, 2H), 7.10 (ddd, J = 8.4, 7.3, 0.6 Hz, 1H), 6.79 (d, J = 7.2 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 6.32 (d, J = 9.0 Hz, 2H), 4.93 (dd, J = 9.9, 3.8 Hz, 1H), 4.70 (d, J = 3.8

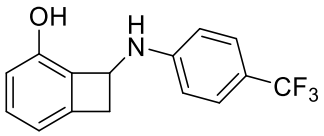
Hz, 1H), 4.50 (d, J = 9.9 Hz, 1H), 3.41 (s, 3H), 3.07 (s, 3H).; 13C NMR (101 MHz, Benzene-d6) δ 155.37 , 149.97 (d, J = 1.1 Hz), 147.29 , 131.10 , 129.96 , 126.47 (q, J = 3.8 Hz), 125.58 (q, J = 270.2 Hz), 118.94 (q, J = 32.4 Hz), 115.63 , 115.01 , 112.54 , 81.59 , 58.18 , 57.06 , 55.65 .; 13C NMR DEPT135 (101 MHz, Benzene-d6) δ 131.10 , 126.47 (q, J = 3.8 Hz), 115.63 , 115.01 , 112.54 , 81.59 , 58.18 , 57.06 , 55.65 .; 19F NMR (376 MHz, Benzene-d6) δ -60.78 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{17}H_{17}F_3NO_2$ 324.1206; found 234.1207.



(1f). Following the above procedure GP1 with benzocyclobutenone KS5 and 4-(Trifluoromethyl)aniline, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as a white solid M.P. :64 °C - 66°C (1.03 g, 38%); IR υmax (cm-1) 3402, 2968, 2933, 1614, 1527, 1479, 1317, 1261, 1103, 1064, 827, 773; 1H NMR (400 MHz, Benzene-d6) δ 7.32 (d, J = 8.3 Hz, 2H), 7.15 – 7.11 (m, 1H), 6.81 – 6.61 (m, 2H), 6.12 (d, J = 8.0 Hz, 2H), 4.80 (dd, J = 9.0, 4.3 Hz, 1H), 3.95 (d, J = 9.0 Hz, 1H), 3.46 (s, 3H), 3.37 – 3.26 (m, 1H), 1.41 – 1.16 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H).; 13C NMR (101 MHz, Benzene-d6) δ 155.84 , 150.91 , 150.27 (d, J = 1.1 Hz), 131.61 , 128.02, 127.27 (q, J = 3.8 Hz) , 126.28 (q, J = 271.15 Hz), 119.59 (q, J = 32.5 Hz), 116.01 , 114.20 , 112.57 , 56.23 , 56.13 , 52.61 , 23.00 , 12.77 . ; 13C NMR DEPT135 (101 MHz, Benzene-d6) δ 131.61 , 127.27 (q, J = 3.8 Hz), 116.01 , 114.21 , 112.57 , 56.24 , 56.12 , 52.61 , 23.01 , 12.77 .; 19F NMR (376 MHz, Benzene-d6) δ -60.52 . ;HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{18}H_{19}F_3NO$ 322.1413; found 322.1415.

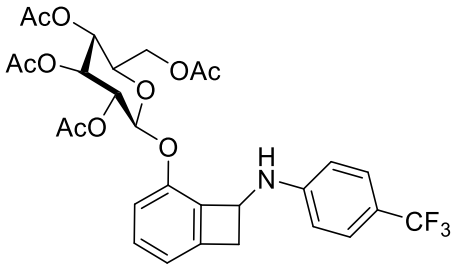


(1g). Following the above procedure GP1 with benzocyclobutenone KS14 and 4-(Trifluoromethyl)aniline, product was isolated after flash chromatography on silica gel (7:1 hexane/ EtOAc) as a white solid M.P. :104 °C - 107°C (0.8002 g, 26%); IR υmax (cm-1) 3373, 2941, 1724, 1612, 1533, 1319, 1244, 1097, 1062, 827, 783; 1H NMR (400 MHz, Benzene-d6) δ 7.35 – 7.26 (m, 2H), 7.11 – 7.07 (m, 1H), 6.74 – 6.65 (m, 2H), 6.12 (d, J = 8.4 Hz, 2H), 4.78 (dd, J = 8.6, 4.3 Hz, 1H), 4.17 (ddd, J = 11.0, 7.5, 6.8 Hz, 1H), 4.04 (ddd, J = 10.9, 7.2, 5.6 Hz, 1H), 4.00 – 3.94 (m, 1H), 3.51 – 3.43 (m, 1H), 3.42 (s, 3H), 1.67 (s, 3H), 1.65 – 1.57 (m, 1H), 1.54 – 1.42 (m, 1H).; 13C NMR (101 MHz, Benzene-d6) δ 170.56 , 155.73 , 149.96 (d, J = 1.1 Hz), 149.49 , 131.86 , 127.91 , 127.35 (q, J = 3.8 Hz), 126.21 (q, J = 269.5 Hz), 119.85 (q, J = 32.6 Hz), 116.33 , 114.22 , 112.53 , 63.26 , 56.17 , 56.01 , 47.61 , 28.88 , 20.87 .; 13C NMR DEPT135 (101 MHz, Benzene-d6) δ 131.15 , 126.64 (q, J = 3.9 Hz), 115.63 , 113.51 , 111.82 , 62.55 , 55.46 , 55.29 , 46.89 , 28.17 , 20.16 .; 19F NMR (376 MHz, Benzene-d6) δ -60.86 (d, J = 2.2 Hz).; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{20}H_{21}F_3NO_3$ 380.1468; found 380.1467.



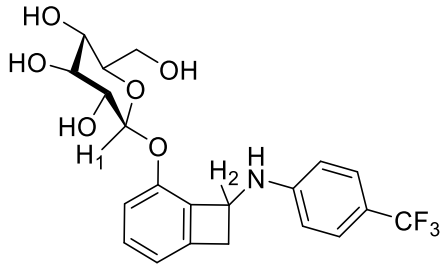
(S15). Following the above procedure GP1 with benzocyclobutenone KS15 and 4-(Trifluoromethyl)aniline, product was isolated after flash chromatography on silica gel (4:1 hexane/ EtOAc) as a white solid M.P. :109 °C - 110°C (2.2947 g, 96%); IR υmax (cm-1) 3302, 2922, 1616, 1456, 1317, 1153, 1097, 1064, 1006, 819, 773, 588; 1H NMR (400 MHz, Benzene-d6) δ 7.31 (d, J = 8.5 Hz, 2H), 7.10 – 7.01 (m, 1H), 6.58 (t, J = 7.7 Hz, 2H), 6.15 (d, J = 8.5 Hz, 2H), 6.02 (s, 1H), 4.63 – 4.33 (m, 1H), 3.88 (s, 1H), 3.11 (dd, J = 14.0, 4.3 Hz, 1H), 2.42

(ddd, J = 13.8, 2.0, 1.0 Hz, 1H).; 13C NMR (101 MHz, Benzene-d6) δ 150.79 , 149.91 (d, J = 1.1 Hz), 145.31 , 131.96 , 129.40 , 127.32 (q, J = 3.8 Hz), 126.07 (q, J = 270.4 Hz), 120.85 (q, J = 32.5 Hz), 116.68 , 115.19 , 113.79 , 52.96 , 40.07 .; 13C NMR DEPT135 (101 MHz, Benzene-d6) δ 131.26 , 126.61 (q, J = 3.7 Hz), 115.97 , 114.49 , 113.09 , 52.26 , 39.37 .; 19F NMR (376 MHz, Benzene-d6) δ -61.01 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{15}H_{13}F_3NO$ 280.0944; found 280.0948.



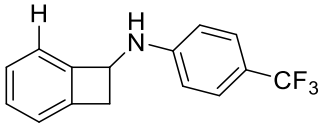
(1h). Following the above procedure for synthesis of S16, product was isolated after flash chromatography on silica gel (2.5:1 hexane/ EtOAc) as a white solid M.P. :68 °C - 71°C (0.38 g (β cis: trans 1:1 mixture), 63% from S15) β configuration is determined by H1 J coupling constant of S17; IR υmax (cm-1) 2939, 1747, 1735, 1319, 1211, 1033, 592; 1H NMR (400 MHz, Benzene-d6) δ 7.35 (dd, J = 8.5, 3.9 Hz, 2H), 7.06 (ddd, J = 9.2, 7.2, 2.4 Hz, 1H), 6.85 (dd, J = 12.0, 8.4 Hz, 1H), 6.71 – 6.59 (m, 1H), 6.32 (dd, J = 8.5, 4.6 Hz, 2H), 5.58 – 5.19 (m, 4H), 4.92 – 4.57 (m, 1H), 4.44 (d, J = 7.7 Hz, 0.5H), 4.20 (ddd, J = 12.4, 4.5, 1.0 Hz, 1H), 4.10 – 3.95 (m, 1.5H), 3.51 (dddd, J = 38.7, 9.9, 4.3, 2.7 Hz, 1H), 3.26 – 3.03 (m, 1H), 2.71 – 2.36 (m, 1H), 1.76 (s, 1.5H), 1.69 (s, 3H), 1.67 – 1.59 (m, 6H), 1.51 (s, 1.5H).; 13C NMR (101 MHz, Benzene-d6) δ 170.34 (d, J = 6.4 Hz), 170.28 (d, J = 4.2 Hz), 169.42 (d, J = 3.0 Hz), 169.31 (d, J = 5.2 Hz), 152.00 (d, J = 78.3 Hz), 150.03 (dd, J = 31.5, 1.1 Hz), 145.60 (d, J = 11.9 Hz), 131.92 (d, J = 1.0 Hz), 130.01 (d, J = 23.2 Hz), 127.49 (q, J = 3.7 Hz), 120.56 (dq, J = 48.6, 32.5 Hz), 118.70 (d, J = 9.0 Hz), 116.69 (d, J = 56.6 Hz), 113.41 (d, J = 45.6 Hz),

99.00 (d, J = 34.7 Hz), 73.43 (d, J = 10.7 Hz), 72.83 , 72.52 (d, J = 2.1 Hz), 68.71 (d, J = 12.6 Hz), 62.16 (d, J = 48.9 Hz), 53.84 (d, J = 12.5 Hz), 40.32 (d, J = 21.0 Hz), 20.60 , 20.51 , 20.49 , 20.49 , 20.47 , 20.37 , 20.27 .; 13C NMR DEPT135 (101 MHz, Benzene-d6) δ 131.93 , 127.50 (q, J = 3.8 Hz), 118.70 (d, J = 8.9 Hz), 116.70 (d, J = 56.7 Hz), 113.42 (d, J = 45.7 Hz), 98.99 (d, J = 35.1 Hz), 73.49 , 72.83 , 72.52 (d, J = 2.0 Hz), 68.71 (d, J = 12.7 Hz), 62.16 (d, J = 49.1 Hz), 53.84 (d, J = 12.5 Hz), 40.33 (d, J = 21.0 Hz), 20.61 , 20.51 , 20.49 , 20.47 , 20.38 , 20.27 .; 19F NMR (376 MHz, Benzene-d6) δ -60.94 , -61.03 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{29}H_{31}F_3NO_{10}$ 610.1895; found 610.1894.

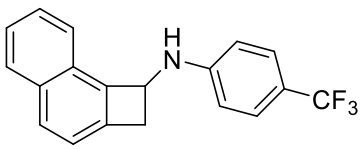


(S17). In order to better characterize compound S16, S17 was prepare from deprotection of S16 using NaOMe in quantitative yield. H_1 is determined by HSQC. Having J coupling constants of 7.7Hz and 7.4Hz of H_1 (2 H_1 from cis and trans) indicate that S17 is β configuration thus we conclude S16 should also be β configuration.; 1H NMR (400 MHz, Methanol-d4) δ 7.39 (dd, J = 8.9, 2.3 Hz, 2H), 7.24 (ddd, J = 8.5, 7.2, 3.9 Hz, 1H), 6.90 – 6.81 (m, 3H), 6.79 (dd, J = 7.1, 5.6 Hz, 1H), 5.37 (H_1, d, J = 7.7 Hz, 0.5H), 5.32 (H_2, d, J = 2.4 Hz, 0.5H), 5.25 (H_1+H_2, d, J = 7.4 Hz, 1H), 3.87 (td, J = 11.2, 10.5, 1.9 Hz, 1H), 3.71 – 3.50 (m, 2H), 3.46 – 3.23 (m, 4H), 2.94 – 2.67 (m, 1H).; 13C NMR (101 MHz, Methanol-d4) δ 151.94 (d, J = 44.1 Hz), 150.36 (d, J = 15.4 Hz), 144.90 (d, J = 3.7 Hz), 130.49 (d, J = 27.0 Hz), 128.62 (d, J = 25.4 Hz), 126.05 (dq, J = 7.7, 3.9 Hz), 125.21 (dq, J = 269.3, 1.6 Hz), 118.31 (qd, J = 32.2, 9.0 Hz), 116.72 (d, J = 34.8 Hz), 115.43 (d, J = 7.3 Hz), 112.33 (d, J = 15.4 Hz), 99.88 (d, J = 1.7 Hz), 76.66 (d, J = 23.2 Hz), 76.38 (d, J = 8.0 Hz), 73.64 (d, J = 11.8 Hz), 69.93 (d, J = 10.7 Hz),

61.23 (d, J = 12.9 Hz), 52.92 (d, J = 2.5 Hz), 39.34 (d, J = 30.3 Hz). (These should not be real d splitting rather 2 peaks coming from the same Carbon in cis and trans isomers which have similar chemical shift);

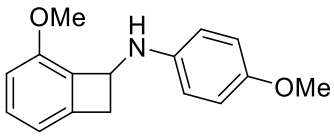


(1i). Following the above procedure GP1 with benzocyclobutenone KS2 and 4-(Trifluoromethyl)aniline, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as a white solid M.P. :78 °C - 83°C (0.45 g, 86%); IR υmax (cm-1) 3437, 3408, 3072, 2968, 2928, 1610, 1527, 1311, 1151, 1089, 1058, 823, 742, 509; 1H NMR (300 MHz, Benzene-d6) δ 7.36 (d, J = 8.5 Hz, 2H), 7.15 – 7.01 (m, 2H), 6.99 – 6.78 (m, 2H), 6.16 (d, J = 8.5 Hz, 2H), 4.56 (ddd, J = 7.4, 4.5, 2.1 Hz, 1H), 3.78 (d, J = 7.8 Hz, 1H), 3.21 (dd, J = 14.0, 4.4 Hz, 1H), 2.51 (dd, J = 14.0, 2.1 Hz, 1H); 13C NMR (101 MHz, Benzene-d6) δ 150.37 , 146.36 , 143.66 , 129.82 , 127.96 , 127.25 (q, J = 3.8 Hz), 126.31 (q, J = 270.2 Hz), 124.12 , 122.83 , 119.83 (q, J = 32.4 Hz), 113.00 , 54.08 , 40.37 . ; 13C NMR DEPT135 (100 MHz, Benzene-d6) δ 129.83 , 127.97 , 127.26 (q, J = 3.8 Hz), 124.13 , 122.84 , 113.00 , 54.08 , 40.37 . ;19F NMR (376 MHz, Benzene-d6) δ -60.80 . ;HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{15}H_{13}F_3N$ 264.0995; found 264.0999.

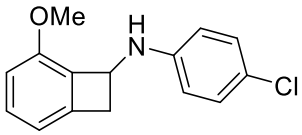


(1j). Following the above procedure GP1 with benzocyclobutenone KS3 and 4-(Trifluoromethyl)aniline, product was isolated after flash chromatography on silica gel (30:1 hexane/ EtOAc) as a pale yellow solid M.P. :78 °C - 81°C (0.47 g, 60%); IR υmax (cm-1) 3318, 3331, 3057, 2931, 1614, 1319, 1101, 1062, 812; 1H NMR (400 MHz, Benzene-d6)

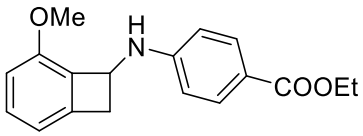
δ 7.74 – 7.68 (m, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.39 (dd, J = 8.7, 0.9 Hz, 2H), 7.33 – 7.20 (m, 2H), 7.17 – 7.15 (m, 1H), 7.08 (d, J = 8.2 Hz, 1H), 6.22 (d, J = 8.5 Hz, 2H), 4.81 (ddd, J = 8.9, 4.1, 1.7 Hz, 1H), 3.87 (d, J = 8.8 Hz, 1H), 3.31 (dd, J = 13.5, 4.0 Hz, 1H), 2.61 (dd, J = 13.5, 1.7 Hz, 1H).; 13C NMR (101 MHz, Benzene-d6) δ 150.44 (d, J = 1.1 Hz), 141.48 , 141.41 , 134.03 , 130.77 , 130.34 , 129.73 , 127.67 (q, J = 271.19 Hz), 127.53 , 127.32 (q, J = 3.8 Hz), 125.90 , 122.91 , 122.44 , 119.93 (q, J = 32.4 Hz), 113.05 , 53.49 , 40.72 ; 13C NMR DEPT135 (100 MHz, Benzene-d6) δ 130.78 , 130.34 , 127.53 , 127.33 (q, J = 3.8 Hz), 125.91 , 122.91 , 122.45 , 113.05 , 53.48 , 40.72 ; 19F NMR (376 MHz, Benzene-d6) δ -60.72 . ;HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{19}H_{15}F_3N$ 314.1151; found 314.1151.



(S6). Following the above procedure GP1 with benzocyclobutenone KS1 and p-anisidine, product was isolated after flash chromatography on silica gel (15:1 hexane/ EtOAc) as a pale yellow solid M.P. :65 °C - 68°C (0.89 g, 56%); IR υmax (cm-1) 3379, 3332, 2954, 2914, 2831, 1581, 1508, 1465, 1033, 872, 777; 1H NMR (400 MHz, Methylene Chloride-d2) δ 7.27 (ddd, J = 8.4, 7.2, 0.6 Hz, 1H), 6.86 – 6.81 (m, 2H), 6.80 – 6.75 (m, 2H), 6.72 – 6.64 (m, 2H), 5.13 (dd, J = 4.2, 2.0 Hz, 1H), 4.21 – 4.16 (m, 1H), 3.96 (s, 3H), 3.77 (s, 3H), 3.61 (ddd, J = 14.0, 4.2, 0.8 Hz, 1H), 3.06 – 2.73 (m, 1H).; 13C NMR (101 MHz, Methylene Chloride-d2) δ 155.03 , 153.13 , 146.06 , 141.79 , 131.18 , 130.08 , 116.43 , 115.34 , 115.21 , 113.53 , 56.88 , 56.12 , 55.44 , 40.73 ;HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{16}H_{18}NO_2$ 256.1332; found 256.1337.



(S7). Following the above procedure GP1 with benzocyclobutenone KS1 and 4-Chloroaniline, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as a pale yellow solid M.P. :100 °C - 101°C (0.1036g, 40%); IR υmax (cm-1) 3365, 3030, 2962, 2924, 1600, 1593, 1481, 1263, 1062, 808, 756, 491; 1H NMR (400 MHz, Benzene-d6) δ 7.13 (ddd, J = 8.4, 7.2, 0.6 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.75 (dd, J = 8.5, 0.7 Hz, 1H), 6.63 (dd, J = 7.2, 0.8 Hz, 1H), 6.19 – 6.05 (m, 2H), 4.64 (ddd, J = 9.1, 4.2, 1.9 Hz, 1H), 3.60 (d, J = 9.0 Hz, 1H), 3.49 (s, 3H), 3.28 – 3.04 (m, 1H), 2.57 – 2.48 (m, 1H).; 13C NMR (101 MHz, Benzene-d6) δ 155.34, 146.18, 145.77, 131.57, 129.75, 129.60, 123.25, 116.44, 115.08, 114.16, 56.40, 54.45, 40.56. ; 13C NMR DEPT135 (101 MHz, C6D6) δ 130.86, 129.05, 115.73, 114.37, 113.45, 55.69, 53.73, 39.85. ; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{15}H_{15}ClNO$ 260.0837; found 260.0841.

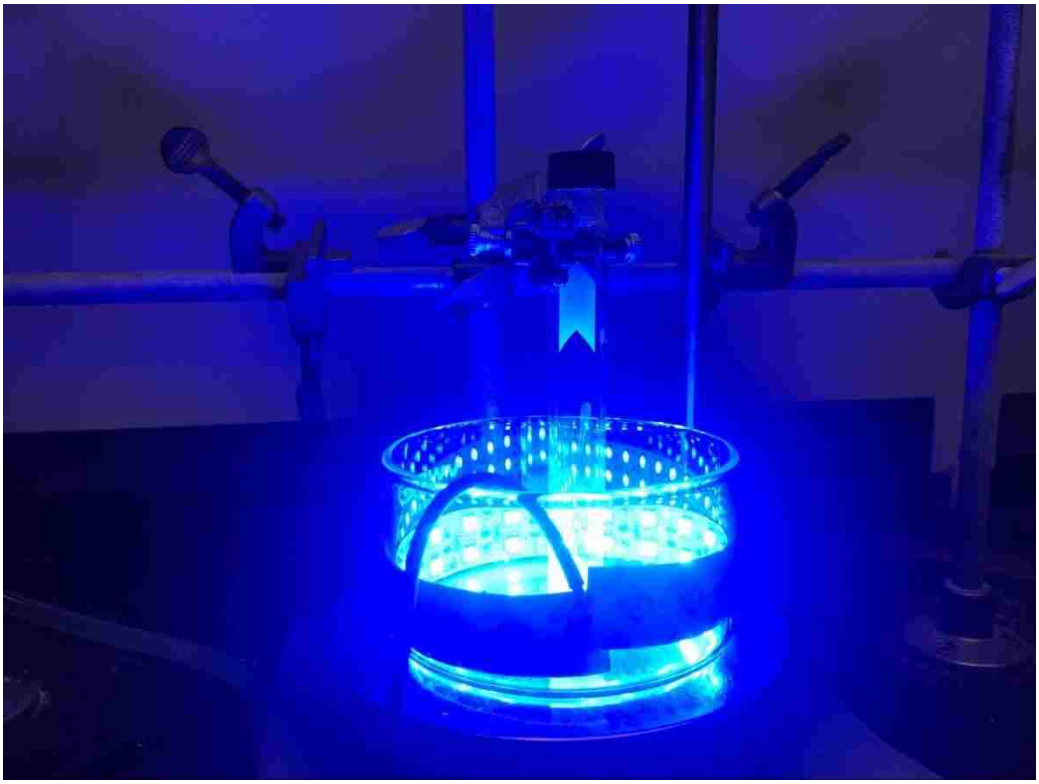


(S9). Following the above procedure GP1 with benzocyclobutenone KS1 and ethyl 4-aminobenzoate, product was isolated after flash chromatography on silica gel (10:1 hexane/ EtOAc) as a white solid M.P. :102 °C - 104°C (0.1512 g, 54%); IR υmax (cm-1) 3356, 2970, 2920, 1680, 1598, 1259, 1170, 1109, 767, 507, 474; H NMR (400 MHz, Benzene-d6) δ 8.28 – 7.96 (m, 2H), 7.12 (dd, J = 8.5, 7.2 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 7.1 Hz, 1H), 6.26 (d, J = 8.8 Hz, 2H), 4.70 (ddd, J = 8.6, 4.2, 1.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.07 (d, J = 8.4 Hz, 1H), 3.43 (s, 3H), 3.20 (dd, J = 14.0, 4.3 Hz, 1H), 2.57 – 2.31 (m, 1H), 1.08 (t, J = 7.1 Hz, 3H).; 13C NMR (101 MHz, Benzene-d6) δ 166.85, 155.25, 151.19, 145.71, 132.27, 131.65, 129.33, 120.69, 116.42, 113.97, 112.76, 60.55, 56.31, 53.76, 40.71, 14.87. ; 13C

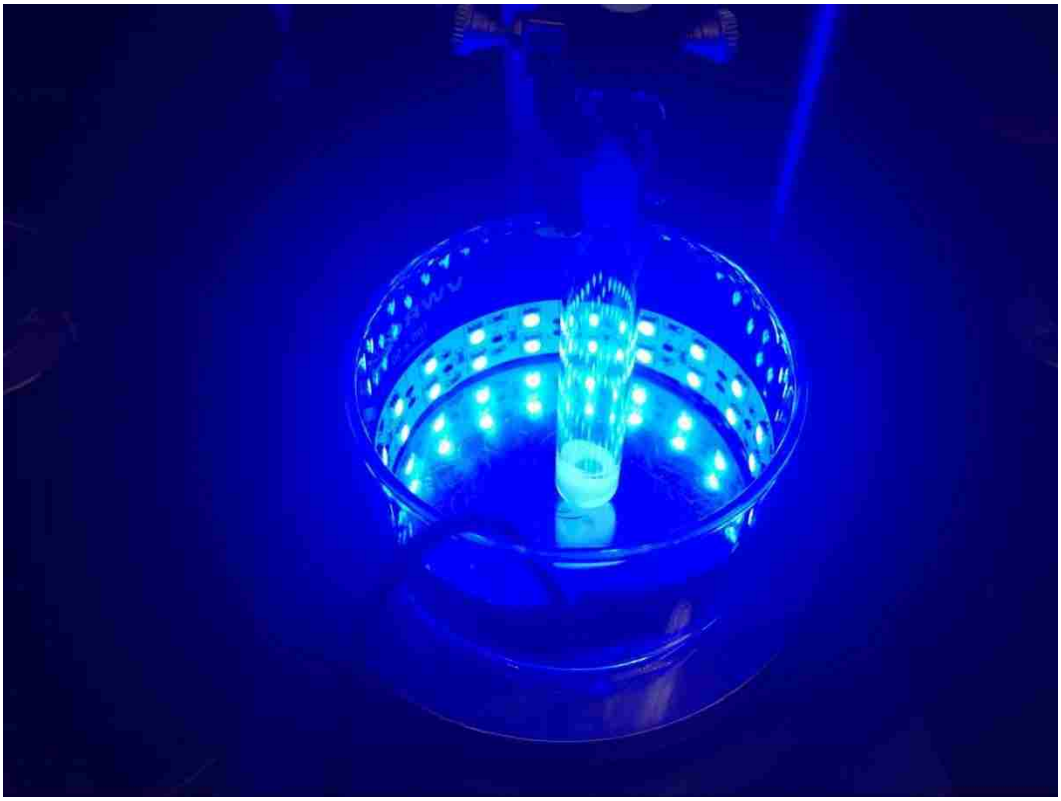
NMR DEPT135 (101 MHz, Benzene-d6) δ 131.56, 130.94, 115.71, 113.26, 112.06, 59.85, 55.60, 53.05, 40.00, 14.17.; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{18}H_{20}NO_3$ 298.1443; found 298.1442.

General Procedure 2 (GP2): [4+2] Annulation. An oven-dried test tube equipped with a stir bar was charged with Ir(dtbbpy)$(ppy)_2PF_6$ (2 mol%), benzocyclobuteneamine derivative (0.2 mmol), alkyne or diyne derivative (1 mmol), K_2HPO_4 (0.2mmol) and dry Toluene (1 mL). The test tube was capped with a Teflon screw cap and degassed by Freeze-Pump-Thaw (3 cycles) then backfilled with nitrogen. The reaction mixture was then sonicated for 1 minute. The test tube was then stirred under the irradiation of 6 W blue LED light (463 nm wavelength purchased from http://www.environmentallights.com/15032-blue-cc5050-60x2-kit.html) for 60-84 h. Upon the completion of the reaction, 3mL of ethyl ether was added into the test tube followed by adding 0.25ml concentrated hydrochloric acid and stir for 20 seconds. No fan was used and the internal temperature was found to be around 30 ° C. The reaction mixture was then filter through a short pad of silica gel and concentrated under reduced pressure. The crude was then purified by

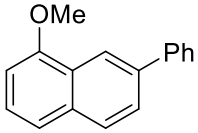
flash chromatography on silica gel to give pure product. Reaction setup as picture below.



Reaction setup (side view), photo credit :Qile Wang

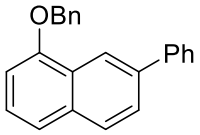


Reaction setup (top view), photo credit :Qile Wang

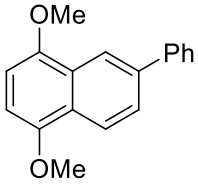


(3a) Following the above procedure with corresponding benzocyclobuteneamine 1a, alkyne 2a under irradiation of 60 h, product was isolated after flash chromatography on silica gel (50:1 hexane/ EtOAc) as a pale yellow oil (28.5mg, 61%); IR υmax (cm-1) 3055, 2935, 2837, 1571, 1492, 1460, 1269, 1232, 1101, 825, 756, 694; 1H NMR (300 MHz, Chloroform-d) δ 8.59 – 8.36 (m, 1H), 7.87 (dd, J = 8.5, 0.6 Hz, 1H), 7.80 – 7.65 (m, 3H), 7.56 – 7.29 (m, 5H), 6.84 (dd, J = 7.3, 1.2 Hz, 1H), 4.02 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 155.91 , 141.60 , 138.06 , 133.81 , 128.98 , 128.22 , 127.66 , 127.38 , 126.17 , 126.00 , 120.24 , 120.14 , 104.37 , 55.74 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 128.98 , 128.22 , 127.66 , 127.38 ,

126.18 , 120.24 , 120.14 , 104.36 , 55.74 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{17}H_{15}O$ 235.1117; found 235.1128.

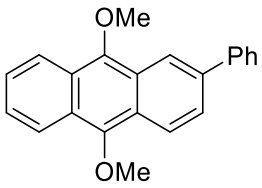


(3b). Following the above procedure with corresponding benzocyclobuteneamine 1b, alkyne 2a derivative under irradiation of 60 h, product was isolated after flash chromatography on silica gel (50:1 hexane/ EtOAc) as a white solid M.P. :98 °C - 101°C (35.9mg, 58%); IR υmax (cm-1) 3057, 3032, 2918, 2850, 1570, 1492, 1452, 1369, 1271, 1234, 1103, 732, 694; 1H NMR (400 MHz, Chloroform-d) δ 8.57 (d, J = 1.9 Hz, 1H), 7.88 (d, J = 1.4 Hz, 1H), 7.84 – 7.68 (m, 3H), 7.58 – 7.31 (m, 10H), 6.91 (d, J = 7.6 Hz, 1H), 5.29 (s, 2H).; 13C NMR (101 MHz, Chloroform-d) δ 154.94 , 141.67 , 138.22 , 137.33 , 133.90 , 129.00 , 128.82 , 128.27 , 128.11 , 127.74 , 127.54 , 127.40 , 126.32 , 126.18 , 126.14 , 120.43 , 120.36 , 105.89 , 70.37 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 129.00 , 128.82 , 128.27 , 128.11 , 127.74 , 127.55 , 127.40 , 126.32 , 126.14 , 120.43 , 120.36 , 105.88 , 70.37 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{23}H_{19}O$ 311.1430; found 311.1431.

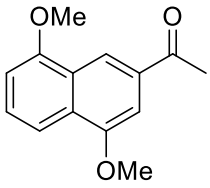


(3c) this compound has been reported by literature[5]. Following the above procedure with benzocyclobuteneamine 1c, alkyne 2a derivative under irradiation of 60 h, product was isolated after flash chromatography on silica gel (30:1 hexane/ EtOAc) (30.6mg, 58%); 1H NMR (400 MHz, Chloroform-d) δ 8.44 (dd, J = 2.0, 0.7 Hz, 1H), 8.27 (dd, J = 8.7, 0.7 Hz, 1H), 7.84 – 7.65 (m, 3H), 7.53 – 7.42 (m, 2H), 7.42 – 7.30 (m, 1H), 6.77 – 6.60 (m, 2H), 3.97 (s, 3H), 3.97 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 149.95 , 149.69 , 141.54 ,

138.66 , 128.96 , 127.68 , 127.44 , 126.79 , 125.61 , 125.53 , 122.66 , 120.06 , 103.83 , 103.51 , 55.97 , 55.96 .

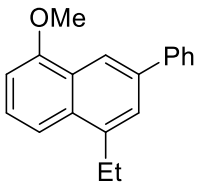


(3d) Following the above procedure with benzocyclobuteneamine 1d, alkyne 2a under irradiation of 60 h, product was isolated after flash chromatography on silica gel (50:1 hexane/ EtOAc) as a white solid M.P. :145 °C - 147°C (33.9mg, 54%); IR υmax (cm-1) 3061, 2937, 2839, 1674, 1618, 1444, 1361, 1348, 1064, 968, 769, 708, 692; 1H NMR (300 MHz, Chloroform-d) δ 8.54 – 8.48 (m, 1H), 8.39 (d, J = 9.0 Hz, 1H), 8.36 – 8.27 (m, 2H), 7.88 – 7.70 (m, 3H), 7.61 – 7.47 (m, 4H), 7.45 – 7.36 (m, 1H), 4.50 – 3.76 (m, 6H).; 13C NMR (101 MHz, Chloroform-d) δ 148.97 , 148.65 , 141.33 , 138.06 , 129.12 , 127.74 , 127.65 , 125.69 , 125.57 , 125.50 , 125.30 , 125.22 , 124.20 , 123.57 , 122.84 , 122.78 , 120.28 , 63.51 , 63.50 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 129.13 , 127.74 , 127.65 , 125.70 , 125.58 , 123.57 , 122.84 , 122.78 , 120.28 , 63.51 , 63.50 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{22}H_{19}O_2$ 315.1380; found 315.1391.

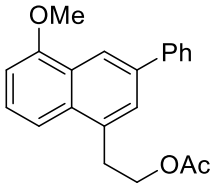


(3e) Following the above procedure with corresponding benzocyclobuteneamine 1e, alkyne 3-butyn-2-one under irradiation of 60 h, product was isolated after flash chromatography on silica gel (30:1 hexane/ EtOAc) as a pale yellow oil (31.2mg, 68%); IR υmax (cm-1) 2956, 2933, 1672, 1502, 1462, 1382, 1278, 1080, 1064, 802; 1H NMR (400 MHz, Chloroform-d) δ 8.48 (dd, J = 1.4, 0.8 Hz, 1H), 7.82 (dd, J = 8.5, 0.9 Hz, 1H), 7.49 (dd, J = 8.5, 7.7 Hz, 1H), 7.41 (d, J = 1.5 Hz, 1H), 6.89 (dd, J = 7.8, 1.0 Hz, 1H), 4.03 (s, 3H),

4.02 (s, 3H), 2.72 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 198.59 , 156.47 , 155.77 , 134.33 , 129.36 , 128.51 , 125.66 , 118.12 , 114.51 , 105.58 , 101.63 , 55.97 , 55.86 , 26.69 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 128.30 , 117.92 , 114.31 , 105.37 , 101.42 , 55.76 , 55.65 , 26.49 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{14}H_{15}O_3$ 231.1016; found 231.1035.

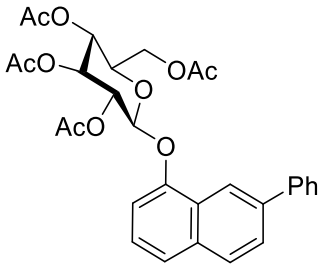


(3f). Following the above procedure with corresponding benzocyclobuteneamine 1f, alkyne 2a under irradiation of 60 h, product was isolated after flash chromatography on silica gel (50:1 hexane/ EtOAc) as a white solid M.P. :56 °C - 60°C (29.3mg, 56%); IR υmax (cm-1) 3057, 2966, 2933, 1583, 1496, 1460, 1255, 1060, 877, 758, 694; 1H NMR (400 MHz, Chloroform-d) δ 8.42 (dd, J = 2.0, 0.9 Hz, 1H), 7.81 – 7.74 (m, 2H), 7.68 – 7.63 (m, 2H), 7.52 – 7.46 (m, 2H), 7.43 (dd, J = 8.6, 7.6 Hz, 1H), 7.40 – 7.34 (m, 1H), 6.88 – 6.84 (m, 1H), 4.02 (s, 3H), 3.16 (q, J = 7.5 Hz, 2H), 1.43 (t, J = 7.5 Hz, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 156.45 , 141.87 , 140.71 , 137.70 , 132.24 , 128.92 , 127.66 , 127.28 , 126.43 , 125.90 , 125.33 , 118.42 , 116.19 , 104.08 , 55.77 , 26.70 , 15.38 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 128.92 , 127.66 , 127.28 , 125.90 , 125.33 , 118.42 , 116.19 , 104.08 , 55.77 , 26.70 , 15.38 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{19}H_{19}O$ 263.1430; found 263.1429.



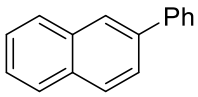
(3g) Following the above procedure with corresponding benzocyclobuteneamine 1g, alkyne 2a under irradiation of 60 h, product was isolated after flash chromatography on silica gel (30:1 hexane/ EtOAc) as a pale yellow oil (34.5mg, 54%); IR υmax (cm-1) 2960, 1710, 1423, 1359, 1220, 528, 443; 1H NMR (400 MHz, Chloroform-d) δ 8.55 –

8.41 (m, 1H), 7.77 – 7.71 (m, 2H), 7.69 – 7.64 (m, 2H), 7.52 – 7.41 (m, 3H), 7.37 (td, J = 7.3, 1.2 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 4.45 (t, J = 7.3 Hz, 2H), 4.01 (s, 3H), 3.44 (t, J = 7.4 Hz, 2H), 2.05 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 171.29 , 156.42 , 141.42 , 137.54 , 134.10 , 132.46 , 128.98 , 127.59 , 127.43 , 127.37 , 126.50 , 126.42 , 119.48 , 115.95 , 104.28 , 64.71 , 55.79 , 33.00 , 21.25 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 128.82 , 127.42 , 127.26 , 127.20 , 126.26 , 119.31 , 115.78 , 104.11 , 64.54 , 55.62 , 32.83 , 21.08 .; HRMS (ESI) *m/z* [M+Na]+, calc'd for $C_{21}H_{20}O_3Na$ 343.1305; found 343.1307.

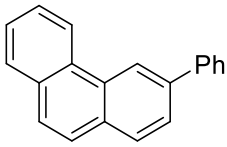


(3h) Following the above procedure with benzocyclobuteneamine 1h, alkyne 2a under irradiation of 60 h, product was isolated after flash chromatography on silica gel (2:1 hexane/ EtOAc) as a white solid M.P. :60 °C - 63°C (55.0mg, 50%); IR υmax (cm-1) 3059, 2958, 1743, 1367, 1121, 1056, 1033, 906, 831, 761, 696, 597; 1H NMR (400 MHz, Chloroform-d) δ 8.35 (d, J = 2.2 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.82 – 7.70 (m, 3H), 7.57 (d, J = 8.2 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.10 (dd, J = 7.6, 0.9 Hz, 1H), 5.52 (dd, J = 9.4, 7.8 Hz, 1H), 5.35 (t, J = 9.4 Hz, 1H), 5.24 (dd, J = 10.5, 8.7 Hz, 2H), 4.32 (dd, J = 12.3, 5.2 Hz, 1H), 4.21 (dd, J = 12.3, 2.5 Hz, 1H), 3.92 (ddd, J = 10.0, 5.3, 2.5 Hz, 1H), 2.05 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.91 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 170.73 , 170.35 , 169.62 , 169.59 , 153.25 , 140.80 , 138.55 , 133.76 , 129.03 , 128.32 , 127.64 , 127.36 , 126.27 , 126.20 , 125.73 , 123.06 , 119.55 , 110.19 , 100.01 , 72.78 , 72.23 , 71.35 , 68.57 , 62.10 , 20.82 , 20.79 , 20.78 , 20.77 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 129.03 , 128.31 , 127.63 , 127.36 , 126.20 , 125.73 , 123.06 , 119.55 , 110.19 , 100.00 , 72.77 , 72.22 , 71.34 ,

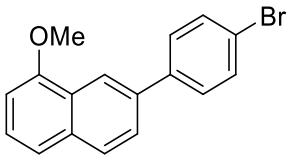
68.56 , 62.09 , 20.82 , 20.79 , 20.77 .; HRMS (ESI) *m/z* [M+Na]+, calc'd for $C_{30}H_{30}O_{10}Na$ 573.1731; found 573.1729.



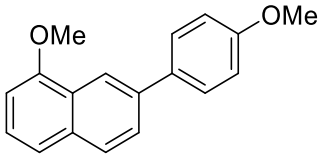
(3i) this compound has been reported by literature[6]. Following the above procedure with benzocyclobuteneamine 1i, alkyne 2a under irradiation of 60 h, product was isolated after flash chromatography on silica gel (50:1 hexane/ EtOAc) (22.8mg, 56%); 1H NMR (400 MHz, Chloroform-d) δ 8.13 – 8.02 (m, 1H), 7.96 – 7.84 (m, 3H), 7.79 – 7.71 (m, 3H), 7.58 – 7.47 (m, 4H), 7.44 – 7.34 (m, 1H).; 13C NMR (101 MHz, Chloroform-d) δ 141.32 , 138.75 , 133.87 , 132.81 , 129.06 , 128.61 , 128.40 , 127.84 , 127.63 , 127.55 , 126.48 , 126.13 , 126.00 , 125.80 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 128.98 , 128.22 , 127.66 , 127.38 , 126.18 , 120.24 , 120.14 , 104.36 , 55.74 .;



(3j) this compound has been reported by literature[7]. Following the above procedure with benzocyclobuteneamine 1j, alkyne 2a under irradiation of 60 h, product was isolated after flash chromatography on silica gel (50:1 hexane/ EtOAc) (20.3mg, 40%); 1H NMR (400 MHz, Chloroform-d) δ 8.88 (d, J = 1.7 Hz, 1H), 8.79 – 8.71 (m, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.92 – 7.88 (m, 1H), 7.84 (dd, J = 8.2, 1.8 Hz, 1H), 7.80 – 7.71 (m, 4H), 7.63 (dddd, J = 23.4, 8.1, 6.9, 1.4 Hz, 2H), 7.51 (dd, J = 8.4, 6.9 Hz, 2H), 7.43 – 7.36 (m, 1H).; 13C NMR (101 MHz, Chloroform-d) δ 141.56 , 139.42 , 132.32 , 131.19 , 130.54 , 130.41 , 129.03 , 128.93 , 128.69 , 127.62 , 127.41 , 127.03 , 126.71 , 126.62 , 126.57 , 126.03 , 122.68 , 121.15 .;

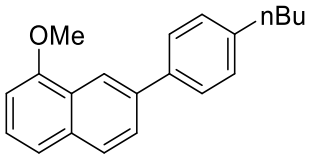


(3k) Following the above procedure with benzocyclobuteneamine 1a, alkyne 2b under irradiation of 60 h, product was isolated after flash chromatography on silica gel (100:1 hexane/ EtOAc) as a pale yellow oil (40.0mg, 64%); IR υmax (cm-1) 3053, 2954, 2935, 2839, 1575, 1489, 1456, 1377, 1271, 1234, 1101, 1068, 993, 812, 740, 721; 1H NMR (400 MHz, Chloroform-d) δ 8.61 – 8.32 (m, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.69 (dd, J = 8.5, 2.0 Hz, 1H), 7.63 – 7.56 (m, 4H), 7.47 – 7.36 (m, 2H), 6.84 (dd, J = 7.3, 1.3 Hz, 1H), 4.02 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 155.83 , 140.46 , 136.72 , 133.89 , 132.04 , 129.17 , 128.41 , 126.45 , 125.91 , 125.69 , 121.63 , 120.15 , 120.13 , 104.49 , 55.72 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 132.05 , 129.17 , 128.41 , 126.45 , 125.70 , 120.15 , 120.13 , 104.49 , 55.72 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{17}H_{14}BrO$ 313.0223; found 313.0262.

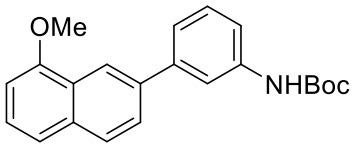


(3l) Following the above procedure with benzocyclobuteneamine 1a, alkyne 2c under irradiation of 60 h, product was isolated after flash chromatography on silica gel (100:1 hexane/ EtOAc) as a white solid M.P. :82 °C - 84°C (26.9mg, 51%); IR υmax (cm-1) 3008, 2956, 2935, 2835, 1600, 1500, 1452, 1274, 1232, 819, 810; 1H NMR (400 MHz, Chloroform-d) δ 8.54 – 8.37 (m, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.76 – 7.63 (m, 3H), 7.44 (dt, J = 8.2, 1.0 Hz, 1H), 7.37 (dd, J = 8.3, 7.5 Hz, 1H), 7.07 – 6.96 (m, 2H), 6.83 (dd, J = 7.6, 1.0 Hz, 1H), 4.02 (s, 3H), 3.86 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 159.32 , 155.78 , 137.67 , 134.12 , 133.48 , 128.63 , 128.16 , 126.05 , 125.98 , 125.86 , 120.14 , 119.43 , 114.43 , 104.32 , 55.71 , 55.56 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 128.63 , 128.16 , 125.98 ,

125.86 , 120.15 , 119.43 , 114.43 , 104.32 , 55.71 , 55.56 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{18}H_{17}O_2$ 265.1223; found 265.1227.

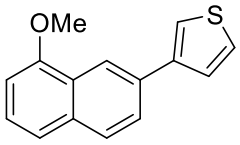


(3m) Following the above procedure with benzocyclobuteneamine 1a, alkyne 2d under irradiation of 60 h, product was isolated after flash chromatography on silica gel (100:1 hexane/ EtOAc) as a pale yellow oil (31.0mg, 54%); IR υmax (cm-1) 3053, 2953, 2927, 2854, 1577, 1458, 1269, 1234, 1101, 819, 740, 719, 563; 1H NMR (400 MHz, Chloroform-d) δ 8.56 – 8.45 (m, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.76 (dd, J = 8.5, 1.9 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.44 (dt, J = 8.3, 1.0 Hz, 1H), 7.37 (dd, J = 8.3, 7.4 Hz, 1H), 7.31 – 7.27 (m, 2H), 6.83 (dd, J = 7.6, 1.1 Hz, 1H), 4.02 (s, 3H), 2.71 – 2.63 (m, 2H), 1.73 – 1.61 (m, 2H), 1.40 (dq, J = 14.6, 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 155.87 , 142.21 , 138.90 , 138.05 , 133.68 , 129.08 , 128.14 , 127.47 , 126.15 , 126.04 , 125.98 , 120.15 , 119.89 , 104.31 , 55.74 , 35.54 , 33.90 , 22.64 , 14.22 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 129.08 , 128.14 , 127.47 , 126.15 , 125.98 , 120.15 , 119.89 , 104.30 , 55.73 , 35.54 , 33.91 , 22.64 , 14.22 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{21}H_{23}O$ 291.1743; found 291.1769.

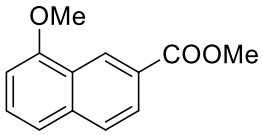


(3n) Following the above procedure with benzocyclobuteneamine 1a, alkyne 2e under irradiation of 60 h, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as a pale yellow oil (41.0mg, 59%); IR υmax (cm-1) 3332, 3053, 2976, 1703, 1537, 1365, 1232, 1153, 825, 790; 1H NMR (400 MHz, Chloroform-d) δ 8.60 – 8.42 (m, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.73 (dd, J = 8.5, 1.9 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.47 – 7.32 (m, 5H), 6.82 (dd, J = 7.5, 1.1 Hz, 1H), 6.65 (s, 1H), 4.00 (s, 3H), 1.55 (s, 9H).; 13C NMR (101

MHz, Chloroform-d) δ 155.87 , 153.01 , 142.46 , 139.01 , 137.68 , 133.87 , 129.58 , 128.17 , 126.20 , 126.16 , 125.90 , 122.42 , 120.26 , 120.11 , 117.71 , 117.58 , 104.32 , 80.75 , 55.66 , 28.57 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 129.59 , 128.17 , 126.20 , 126.17 , 122.42 , 120.26 , 120.11 , 117.72 , 117.58 , 104.32 , 55.67 , 28.57 .; HRMS (ESI) *m/z* [M+Na]+, calc'd for $C_{22}H_{23}NO_3Na$ 372.1570; found 372.1570.

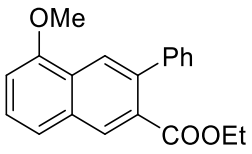


(3o) Following the above procedure with benzocyclobuteneamine 1a, alkyne 2f under irradiation of 60 h, product was isolated after flash chromatography on silica gel (50:1 hexane/ EtOAc) as a white solid M.P. :90 °C - 93°C (18.2mg, 38%); IR υmax (cm-1) 3101, 2939, 1575, 1456, 1392, 1359, 1240, 1105, 825, 781, 742, 617; 1H NMR (400 MHz, Chloroform-d) δ 8.54 – 8.47 (m, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.75 (dd, J = 8.5, 1.9 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.44 – 7.39 (m, 2H), 7.36 (dd, J = 8.2, 7.4 Hz, 1H), 6.82 (dd, J = 7.4, 1.1 Hz, 1H), 4.02 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 155.76 , 142.80 , 133.74 , 132.74 , 128.24 , 126.79 , 126.37 , 126.03 , 125.99 , 125.63 , 120.66 , 120.20 , 119.24 , 104.43 , 55.72 .; 13C NMR (101 MHz, Chloroform-d) δ 128.25 , 126.79 , 126.38 , 126.03 , 125.63 , 120.67 , 120.20 , 119.24 , 104.43 , 55.72 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{15}H_{13}OS$ 241.0682; found 241.0698.

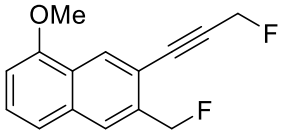


(3p) this compound has been reported by literature[8]. Following the above procedure with benzocyclobuteneamine 1a, alkyne 2g under irradiation of 60 h, product was isolated after flash chromatography on silica gel (15:1 hexane/ EtOAc) (19.0mg, 44%); 1H NMR (400 MHz, Chloroform-d) δ 9.08 – 8.61 (m, 1H), 8.05 (dd, J = 8.7, 1.8 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 6.83 (dd, J = 7.3, 1.1 Hz, 1H),

4.01 (s, 3H), 3.96 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 167.60 , 156.63 , 136.76 , 128.81 , 127.86 , 126.79 , 126.07 , 125.62 , 124.95 , 120.06 , 104.65 , 55.78 , 52.35 .

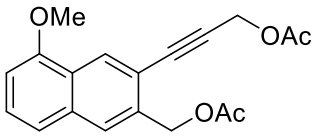


(3q) Following the above procedure with benzocyclobuteneamine 1a, alkyne 2h under irradiation of 84 h, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as a pale yellow oil (35.4mg, 58%); IR υmax (cm-1) 3057, 2980, 1710, 1460, 1269, 1201, 1109, 792, 763, 700; 1H NMR (400 MHz, Chloroform-d) δ 8.32 (s, 1H), 8.23 (s, 1H), 7.50 (dt, J = 8.4, 1.0 Hz, 1H), 7.47 – 7.30 (m, 6H), 6.89 (dd, J = 7.6, 1.0 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 1.02 (t, J = 7.1 Hz, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 169.08 , 155.58 , 142.19 , 138.31 , 132.84 , 130.49 , 130.23 , 128.88 , 128.13 , 127.10 , 127.02 , 126.66 , 124.30 , 120.85 , 106.01 , 61.24 , 55.80 , 13.93 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 130.50 , 128.88 , 128.14 , 127.10 , 127.02 , 124.30 , 120.85 , 106.01 , 61.24 , 55.80 , 13.93 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{20}H_{19}O_3$ 307.1329; found 307.1334.

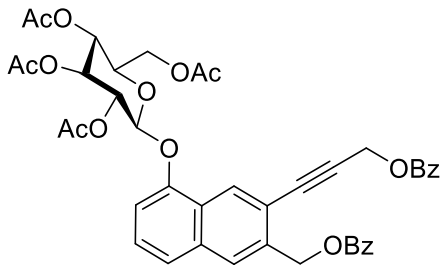


(3r) Following the above procedure with benzocyclobuteneamine 1a, diyne 2i under irradiation of 60 h, product was isolated after flash chromatography on silica gel (50:1 hexane/ EtOAc) as a white solid M.P. :78 °C - 81°C (30.5mg, 62%); IR υmax (cm-1) 3018, 2939, 2845, 2223, 1571, 1460, 1361, 1271, 1091, 964, 885, 744, 727; 1H NMR (400 MHz, Methylene Chloride-d2) δ 8.49 (s, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.56 – 7.45 (m, 2H), 6.92 (dd, J = 7.4, 1.4 Hz, 1H), 5.71 (d, J = 47.4 Hz, 2H), 5.31 (d, J = 47.4 Hz, 2H), 4.04 (s, 3H).; 13C NMR (101 MHz, Methylene Chloride-d2) δ 155.71 , 135.26 (dd, J = 16.3, 2.3 Hz), 134.63 (d, J = 0.8 Hz), 128.61 , 128.30 (d, J = 3.7 Hz), 127.05 (dd, J = 9.0, 0.6 Hz), 125.48 – 125.23 (m), 120.57 (d,

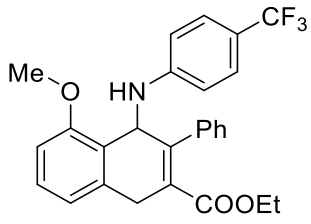
J = 1.1 Hz), 117.16 (t, J = 4.1 Hz), 105.64 (d, J = 1.1 Hz), 87.27 (dd, J = 12.0, 1.2 Hz), 87.16 (d, J = 21.5 Hz), 83.58 (d, J = 167.3 Hz), 71.81 (d, J = 164.7 Hz), 56.19 .; 13C NMR DEPT135 (101 MHz, Methylene Chloride-d2) δ 128.62 , 128.30 (d, J = 3.7 Hz), 127.05 (d, J = 9.1 Hz), 120.57 , 105.64 , 83.59 (d, J = 167.2 Hz), 71.82 (d, J = 164.7 Hz), 56.19 .; 19F NMR (376 MHz, Methylene Chloride-d2) δ -212.93 (t, J = 47.5 Hz), -214.02 (t, J = 47.7 Hz).; GC-MS (CI), 227, 247(M+1)，275(M+29)



(3s) Following the above procedure with benzocyclobuteneamine 1a, diyne 2j under irradiation of 60 h, product was isolated after flash chromatography on silica gel (50:1 hexane/ EtOAc) as a white solid M.P. :65 °C - 66°C (41.0mg, 63%); IR υmax (cm-1) 3014, 2941, 1732, 1573, 1369, 1232, 1217, 1203, 1047, 1024, 893, 790, 740, 601; 1H NMR (400 MHz, Chloroform-d) δ 8.41 (s, 1H), 7.74 (s, 1H), 7.46 – 7.31 (m, 2H), 6.79 (dd, J = 7.2, 1.4 Hz, 1H), 5.47 – 5.26 (m, 2H), 4.93 (s, 2H), 3.96 (s, 3H), 2.14 (s, 3H), 2.13 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 170.95 , 170.46 , 155.26 , 134.56 , 134.07 , 127.85 , 127.79 , 127.20 , 124.84 , 120.16 , 118.23 , 104.87 , 87.13 , 84.49 , 64.93 , 55.73 , 53.00 , 21.13 , 20.97 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 127.84 , 127.78 , 127.20 , 120.16 , 104.87 , 64.93 , 55.73 , 53.00 , 21.13 , 20.97.; HRMS (ESI) *m/z* [M+Na]+, calc'd for $C_{19}H_{18}O_5Na$ 349.1046; found 349.1050.



(3t) Following the above procedure with benzocyclobuteneamine 1h, diyne 2k under irradiation of 60 h, concentrate the crude product and separated again with flash chromatography on silica gel (1.0% MeOH in CH_2Cl_2) as a white solid M.P. :64 °C - 65°C (92.0mg, 61%); IR υmax (cm-1) 2949, 1747, 1720, 1367, 1265, 1211, 1093, 1064, 1033, 1026, 709; 1H NMR (400 MHz, Chloroform-d) δ 8.27 (s, 1H), 8.04 (ddd, J = 13.5, 8.3, 1.4 Hz, 4H), 7.88 (s, 1H), 7.53 (dddd, J = 11.9, 9.4, 5.2, 1.4 Hz, 3H), 7.43 – 7.32 (m, 5H), 7.14 (dd, J = 7.6, 1.0 Hz, 1H), 5.63 (s, 2H), 5.45 (dd, J = 9.3, 7.7 Hz, 1H), 5.32 (t, J = 9.2 Hz, 1H), 5.23 (d, J = 9.7 Hz, 1H), 5.20 – 5.12 (m, 3H), 4.29 (dd, J = 12.3, 5.2 Hz, 1H), 4.20 (dd, J = 12.3, 2.5 Hz, 1H), 3.89 (ddd, J = 9.9, 5.2, 2.5 Hz, 1H), 2.09 (s, 3H), 2.05 (s, 6H), 2.04 (s, 3H).; 13C NMR (101 MHz, Chloroform-d) δ 170.72 , 170.40 , 169.62 , 169.57 , 166.44 , 165.98 , 152.53 , 135.13 , 134.06 , 133.36 , 133.20 , 130.18 , 129.99 , 129.90 , 129.66 , 128.56 , 128.55 , 127.67 , 127.39 , 127.27 , 125.44 , 123.55 , 119.54 , 111.83 , 100.09 , 87.92 , 84.42 , 72.81 , 72.31 , 71.34 , 68.50 , 65.32 , 62.07 , 53.46 , 20.85 , 20.82 , 20.78 .; 13C NMR DEPT135 (101 MHz, Chloroform-d) δ 133.37 , 133.20 , 129.99 , 129.90 , 128.56 , 127.67 , 127.39 , 127.27 , 123.55 , 111.83 , 100.09 , 72.81 , 72.31 , 71.34 , 68.49 , 65.32 , 62.07 , 53.46 , 20.85 , 20.84 , 20.79 .; HRMS (ESI) *m/z* [M+Na]+, calc'd for $C_{42}H_{38}O_{14}Na$ 789.2154; found 789.2150.



(Intermediate-1) Following the above procedure without HCl in work up step, with corresponding benzocyclobuteneamine, alkyne or diyne derivative under irradiation

of 60 h, product was isolated after flash chromatography on silica gel (8:1 hexane/ EtOAc) as a pale yellow solid M.P. :112 °C - 115°C (19.0mg, 21%); IR υmax (cm-1) 3346, 1678, 1612, 1541, 1327, 1315, 1105, 1091, 819, 783, 705; 1H NMR (400 MHz, Benzene-d6) δ 7.21 – 7.15 (m, 2H), 7.15 – 7.10 (m, 2H), 7.07 – 6.91 (m, 4H), 6.70 (dd, J = 7.7, 1.2 Hz, 1H), 6.34 (d, J = 8.2 Hz, 1H), 6.12 (d, J = 8.4 Hz, 2H), 5.60 (dt, J = 9.1, 2.9 Hz, 1H), 4.06 – 3.72 (m, 4H), 3.65 (d, J = 9.1 Hz, 1H), 3.04 (s, 3H), 0.61 (t, J = 7.1 Hz, 3H).; 13C NMR (101 MHz, Benzene-d6) δ 168.71 , 157.92 , 150.90 (d, J = 1.1 Hz), 144.72 , 141.52 , 136.20 , 128.91 , 128.82 , 128.64 , 128.50 , 127.79 , 126.62 (q, J = 3.8 Hz), 126.28 (q, J = 270.1 Hz), 124.68 , 120.85 , 119.06 (q, J = 32.3 Hz), 113.12 , 108.93 , 60.73 , 55.14 , 52.86 , 32.03 , 13.93 .; 13C NMR DEPT135 (101 MHz, Benzene-d6) δ 128.21 , 127.93 , 127.79 , 127.08 , 125.91 (q, J = 3.8 Hz), 120.14 , 112.41 , 108.22 , 60.02 , 54.43 , 52.14 , 31.32 , 13.22 .; 19F NMR (376 MHz, Benzene-d6) δ -60.75 .; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{27}H_{25}F_3NO_3$ 468.1781; found 468.1776.

2.6 Summary

We report a visible-light-mediated synthesis of substituted naphthalenes via the [4+2] annulation of amino-benzocyclobutenes with alkynes. Upon one-electron photooxidation, amino-benzocylobutenes undergo ring opening to reveal presumably the distonic radical cation, which then participate in two sequential C-C bond formations en route to naphthalenes. Amino-benzocylobutenes tolerate substitution at C-2, C-5, and C-7 positions including a usually labile glycosidic bond at C-2. Terminal alkynes, internal alkynes and diynes are all shown to be a viable annulation partner, affording structurally diverse naphthalenes. The aniline moiety plays a critical role in the annulation, as it not only functions as a photo-oxidizable group to induce the

ring opening but also acts as a leaving group to complete aromatization. Because a different type of the ring-opening intermediate (e.g., the distonic radical cation) is involved, amino-benzocylobutenes display distinct chemistries from benzocyclobutenols in the annulation reaction.

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Chapter 3. Stabilized Iminium ion Strategy Enabled Difunctionalization of N-alkyl Cyclobutyl and Cyclopropyl Amines via Photoredox Catalysis

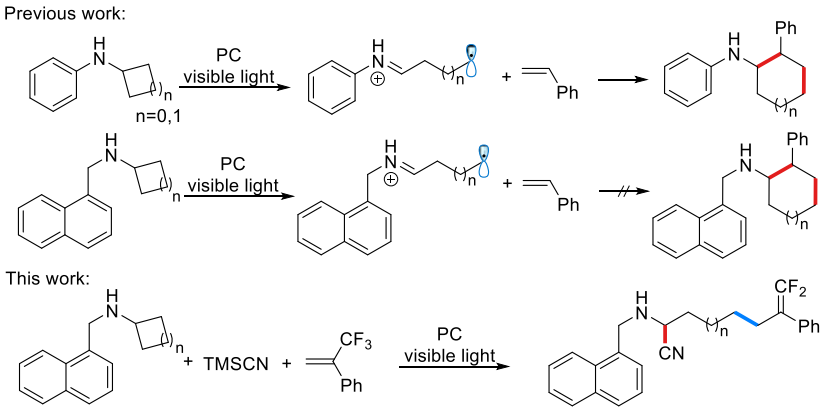
3.1 Introduction

Distonic radical cations (DRC) are a class of chemical species that carry separate cation and radical sites in one molecule.[1] Traditionally, DRC have been generated through homolysis of charged molecules or via rearrangement of radical cations.[2] Because the reactivity of DRC often entailed a reactive radical site with an inert charge site, they have become an important tool for organic chemists to understand radical chemistry via online analysis of the charged species through mass spectrometry.[3] This approach is highly informative on neutral radical reactivity such as reaction rate and product distribution if the radical site on DRC and neutral molecule behave in a similar fashion.

Ring-opening of cyclopropylamines to form distonic radical cation is one of the most studied systems due to its biological implication in enzyme inhibition.[4] Although many studies on this topic have been reported, the synthetic application of the downstream amine distonic radical cation are scarce. Seminal work by Cha and others disclosed intramolecular [3+2] annulations of cyclopropylamines and alkenes in the presence of quantitative oxidant.[5] We also recently reported intermolecular [3+2] and [4+2] annulations involving distonic radical cation under photoredox catalysis.[6] Notably, under our intermolecular annulation protocol, the amine scope was limited to aromatic amines such as anilines (Scheme 1a and 1b).

By comparing the DRC structures of *N*-aryl amine and *N*-alkyl amine, we hypothesized that the two types of amines would exhibit similar behavior at the radical site unless the charged site does affect the reactivity of the radical site, despite being spatially separated from it.[3c, 3e, 7] Inspired by previous mass spectrometry studies on oxonium DRC which documented a nucleophilic attack of

oxonium ion prior to the reaction on radical site, We hypothesized that a similar strategy could also be applied to iminium DRC to increase the reactivity on radical site.[2] To investigate this theory, we turned our attention to a difunctionalization protocol utilizing *N*-alkyl amines in which TMSCN could quench the charged site (iminium ion) of the generated distonic radical cation to unveil a neutral radical for subsequent radical addition to olefins (Scheme 1c).



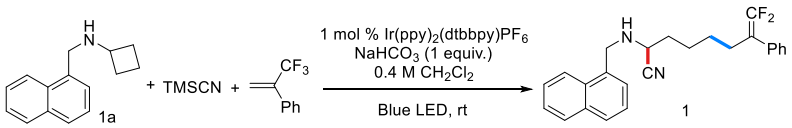
Scheme 3.1 Stablized Iminium Ion Strategy for N-Alkyl Amines.

3.2 Reaction Optimization

To commence our study, N-alkyl cyclobutylamine 1a was selected as model substrate and the attached naphthyl group served as chromophore. TMSCN was employed as a nucleophile to quench the iminium ion upon the generation of DRC and CF3 styrene was selected as a radical acceptor for nucleophilic radical. Under our optimal condition, $Ir(ppy)_2(dtbbpy)PF_6$ (1 mol%) was identified as the best photocatalyst, $NaHCO_3$ (1 equiv.) as a mild base and dichloromethane (0.4 M) as solvent (Entry 1). Other photocatalysts were also examined. $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was also a suitable photocatalyst gave only marginal decrease in yield however when $Ru(bpy)_3(PF_6)_2$ was used, no product was detected(Entry 2 and 3). Other solvents such as ethyl ether and acetonitrile gave inferior results too (Entry 4 and 5). It is worth

noting that base was not required in this protocol. Little yield difference was observed in the absence of base for substrate 1a but $NaHCO_3$ was found to be beneficial in some cases especially for anilines in subsequent substrate scope study.

Table 3.1 Reaction condition screening



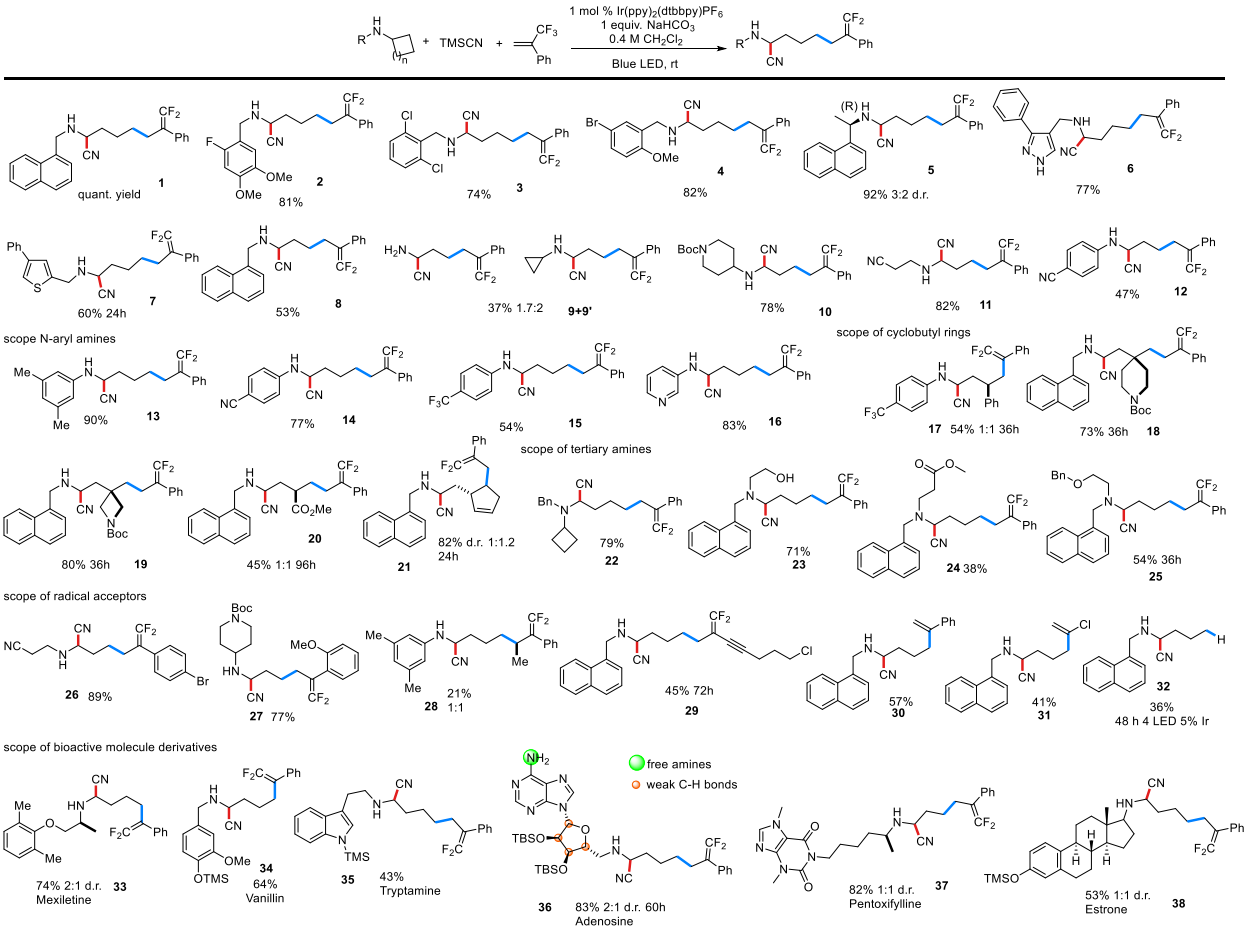
Entry	Variation from above conditions	Yield
1	none	quanti.
2	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	93%
3	$Ru(bpy)_3(PF_6)_2$	No Reaction
4	Et_2O	60%
5	MeCN	83%

3.3 Substrate Scope of Difunctionalization.

With the optimized conditions in hand, we proceeded to test the scope of cyclobutylamines. Functional groups such as aromatic halides, ethers, and hetero aromatics were all tolerated in the difunctionalization with yields of 60% to quantitative (1–7). Besides cyclobutylamines, cyclopropylamines were also suitable substrates and furnished 1,3-difunctionalization products. Primary amine (9+9'), Boc-protected amine (10) and cyano group (11) were all tolerated with good yields (37%-82%). Next, we examined if *N*-aryl cycloalkyl amines would be suitable substrates since they behaved differently in our previous [3+2] and [4+2] annulation system. Gladly, both cyclopropylaniline and cyclobutylanilines yielded the corresponding product uneventfully (12-17, 47%-90%).Scope of cyclobutyl ring was explored next, with spirocyclic (18, 19), phenyl-substituted (17), ester-substituted (20) and bicyclic

structures all undergoing the desired transformation in good yields (54%- 82%). It is worth noting that the reaction rate was more sensitive to the inductive effect of substituent on cyclobutyl ring than on the side chain. For example, substrate with ester substitution (γ to N) on cyclobutyl ring (20) took 96 h to react completely, while reaction with alkyl amine (11) bearing a CN-substituted side chain (β to N) was completed in 12 h. Tertiary *N*-aryl amines were not suitable substrates for this methodology, which is consistent with our previous observation of a slow ring opening of these amines. However, tertiary *N*-alkyl amines (22-25) successfully underwent the difunctionalization with decent efficiency (38%-79%). It is interesting that substrate 22 did not undergo a second ring opening and this is likely due to the inductive effect from α-CN group which made the oxidation of amine more difficult. The scope of radical acceptors were also examined. CF_3-styrenes bearing substituents such as bromide (26) or methoxy (27) groups, and also trisubstituted styrene (28) were well tolerated (21% -89%). The radical acceptor scope was not limited to CF_3-styrene scaffold, as enyne (29), allyl sulfones (30, 31), and H-donor (32) were all amenable to this system (36%-57%). To demonstrate the utilities of this protocol, several bioactive molecule derivatives were subjected to difunctionalization including adenosine, pentoxyfylline and estrone. It was pleasing that these complex molecules yielded the desired products with uncompromised efficiency (43%-83%), especially adenosine which has a free amine, heteroaromatic group and multiple weak C-H bonds.

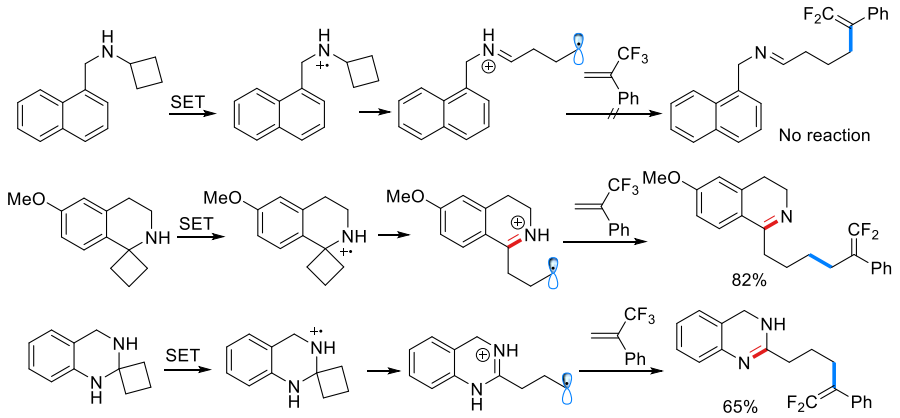
Table 3.2 Substrate Scope of Difunctionalization.



3.4 Mechanistic Study

We next questioned what the role TMSCN played in the difunctionalization and whether the charged iminium ion site of DRC affected the reactivity of terminal carbon radical. The control study showed that the presence of TMSCN was critical for radical addition to alkene. Without TMSCN, even with 20% Ir photocatalyst, no conversion of cyclobutylamine was observed indicating that radical addition to alkene was slow in the absence of TMSCN at room temperature. We hypothesized that the electrophilic iminium ion site interacts intramolecularly

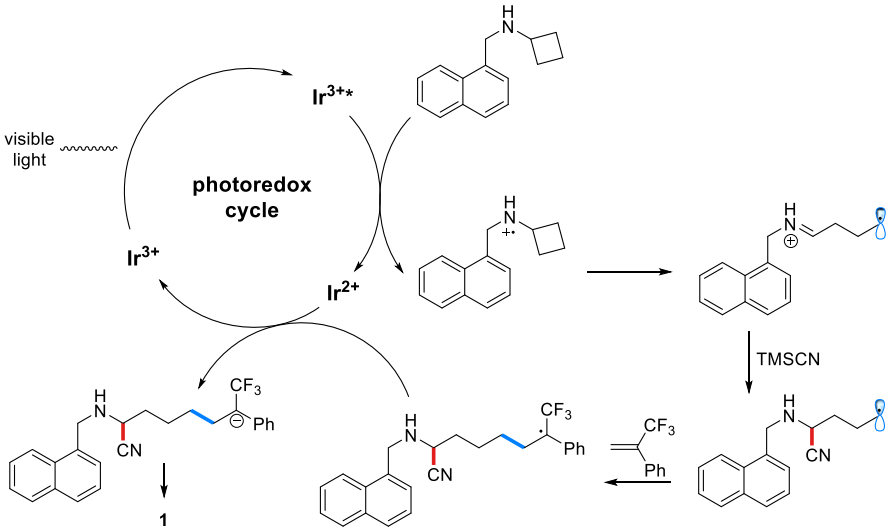
with nucleophilic carbon radical to reduce the reactivity of the radical, and thus the addition of TMSCN, serves to quench the iminium ion via Strecker reaction to resume the reactivity of a neutral radical. If this hypothesis is valid, then reducing the electrophilicity of the iminium ion by attaching a π-electron donating atom (group) should weaken the interaction between the electrophilic charged site and nucleophilic radical site, thus increasing the reactivity of the radical site. To test this hypothesis, two spirocyclic cyclobutylamines with electron donating atom (group) were synthesized. Upon the ring opening of the cyclobutyl ring, amine distonic radical cations with stabilized iminium ions would be formed. Under the optimized reaction condition, these DRCs were able to undergo radical addition to CF_3 styrene without TMSCN in 82% and 65% yields.



Scheme 3.2 Stablized Iminium Ion Promoted Radical Addition.

Based on the studies above, the reaction mechanism was depicted as follows. The excited Ir complex photocatalyst, generated via absorption of visible light, can undergo single electron transfer to oxidize the cyclobutylamine 1a to the radical cation. The radical cation can induce nearby C-C bond cleavage to form distonic radical cation. TMSCN will quench the distonic radical cation via Strecker reaction to give α-amino cyanide with a neutral radical. Radical

addition to olefin followed by one electron reduction and elimination of fluoride anion furnish the product 1.



Scheme 3.3 Proposed Reaction Mechanism.

3.5 Summary

In conclusion, cation site interacting with nucleophilic radical site in distonic radical cation was studied and its synthetic significance was demonstrated via 1,3 and 1,4-difunctionalization of N-alkyl cyclobutyl and cyclopropyl amines. TMSCN played a critical role to quench the iminium ion thus increased the reactivity of the radical site which enabled the radical addition to radical acceptors. Various functional groups were compatible under this protocol highlighted by 6 bioactive molecule derivative examples including adenosine derivative which bears a free amine, heteraromatic and multiple weak C-H bonds.

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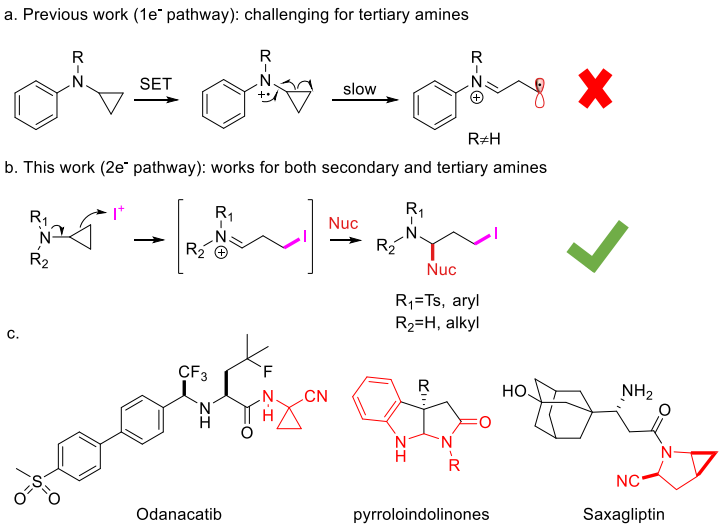
Chapter 4. Difunctionalization of cyclopropyl amines with NIS or in-situ formed ICN

4.1 Introduction

Cyclopropylamine and its derivatives are a versatile building block for nitrogen-containing compounds due to the heightened reactivity enabled by the cyclopropyl group's ring strain.[1] Various strategies have been developed to unleash the strain energy that is harvested to break up strong C-C bonds and reveal reactive intermediates for further functionalization. Notable examples include Lewis acid-catalyzed ring opening of donor-acceptor cyclopropylamines, transition metal-catalyzed C-C bond activation, and formation of amine radical cations via single electron transfer (SET).[1d, 2] We previously developed a [3+2] annulation reaction of cyclopropylanilines with pi bonds via the amine radical cations generated by photoredox catalysis.[3] Although the scope of the pi bonds was quite broad, the constraint on the cyclopropylamines was noticeable. Only cyclopropylanilines were viable for the annulation, and within this class of substrates, more limitations were observed. Tertiary monocyclic cyclopropylanilines were recalcitrant to the annulation reaction(Scheme 1a).[4] Tanko proposed a steric model to rationalize the difficulty in the ring opening process initialized by the amine radical cation of *N*-cyclopropyl-*N*-methylaniline.[5]

Although introduction of more restriction to the tertiary cyclopropylanilines by tethering it to another ring made it suitable again for the annulation reaction, we were enamored of a more general strategy with a broader scope to address this issue. Because of its unique bonding to accommodate the 60° bond angle, the cyclopropyl group exhibits a pronounced pi character and thus can act as a pi donor. On the other hand, since it is a rather weak pi acceptor, the resonance effect of the amine substituent on the cyclopropyl groups' nucleophilicity is modest. Additionally, the inductive effect by the nitrogen atom to reduce the nucleophilicity can not be

neglected. Even with these complications, we were intrigued by the potential of using cyclopropylamines as a pi donor in a 2e, S_N2-like pathway to avoid the involvement of amine radical cations, which seemed to be at the root of the inactivity of tertiary cyclopropylamines (Scheme 1b).



Scheme 4.1 1,3-Difunctionalization of cyclopropylamine.

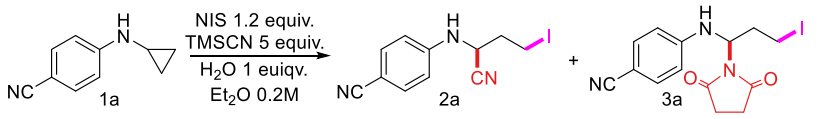
The choice of suitable electrophiles for ring opening of cyclopropylamines via the 2e pathway is scarce. Proton is the dominant option.[6] Alternatively, electrophilic halogen sources have been used to mediate the ring opening. To the best of our knowledge, there has been only one report by Harrity to use NIS and NBS to open a bicyclic cyclopropylamine.[7] We questioned whether we could identify suitable electrophilic halogen sources to open less constrained cyclopropylamines in conjunction with use of a nucleophile to intercept the in situ generated imine or iminium ion moiety. As a result, 1,3-difunctionalized products across a saturated backbone bearing alpha-amino nitrile or *N*,*N*'-aminal motifs, which are commonly found in natural products such as odanacatib, pyrroloindolinones and saxagliptin, could be produced (Scheme 1c). Herein, we report our studies of difunctionalizing cyclopropylamines by NIS or in situ formed ICN.

4.2 Reaction Optimization

4-cyanocyclopropyl aniline (**1a**) was selected as the model substrate to commence the studies. Unlike electron-neutral or -rich cyclopropylanilines that were prone to decomposition upon exposure to air, it was benchtop stable and easily prepared in one step from aryl bromide and cyclopropylamine. When *N*-Iodosuccinimide (NIS) was used as an electrophilic iodine source with TMSCN as a nucleophile in ether, the reaction proceeded smoothly to give the difunctionalization product **2a** exclusively in 95% yield (entry 1). Surprisingly, the yield of product **2a** was found to be inconsistent, and occasionally, product **3a** was isolated as a byproduct. This byproduct was presumably generated via the addition of succinimide derived from NIS to the in situ generated imine. Addition of 1 equivalent of water, presumably activating TMSCN to form HCN, proved to be the key to address the reproducibility issue (entry 2).[8] Otherwise the dryness of solvents and/or reagents was shown to affect both the yield and chemoselectivity. Attempts to use nucleophilic iodide sources such as combination of NaI and $PhI(OAc)_2$ or I_2 to replace NIS all led to inferior results (see SI).[9] Other solvents such as DMF or MeCN only gave a trace amount of product (see SI). Intrigued by the formation of byproduct **3a**, we conducted the reaction in the absence of TMSCN using DCM as solvent and obtained **3a** in 50% yield (entry 4). This product possesses a useful *N*,*N*'-aminal functionality that is common in pyrroloindolinone-based natural products. Addition of two extra equivalents of succinimide doubled the yield of **3a**, and water was not needed for the reliable production of **3a** (entry 5). Notably, unlike our previously reported [3+2] annulation of cyclopropylanilines in which radical intermediates were involved and thus exclusion of oxygen was required, this protocol was operated under air regardless of the identity of nucleophile (entry 1 and 5). The reactions were conducted with ambient light from the lab setting, and rigorous exclusion of light didn't affect

the reaction (see SI). These two sets of data indicated that a SET process might not operate in the reaction.

Table 4.1 Reaction condition screening



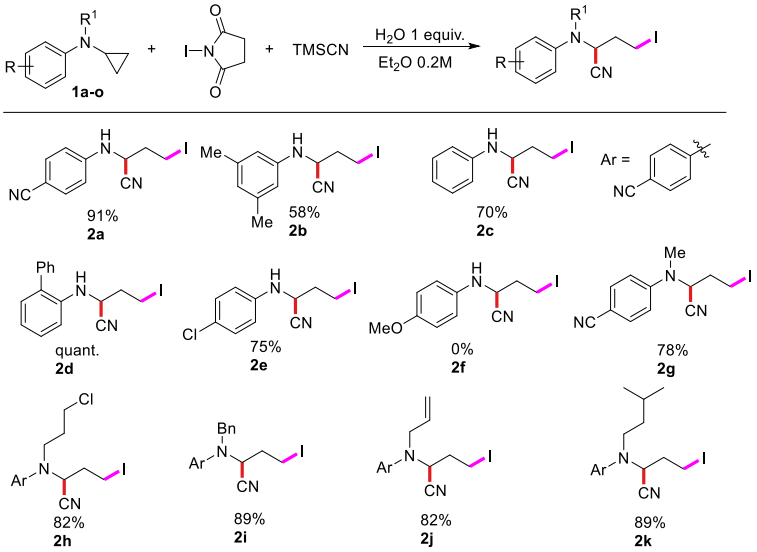
Entry	Variation from above conditions	Yield (%)
1	none	95% (2a:3a > 20:1)
2	no water	26~90% (3:1 > 2a:3a > 17:1)
3	NaI 4 equiv. + $PhI(OAc)_2$ 4 equiv. instead of NIS	38% (2a:3a > 20:1)
4	no TMSCN, no water, DCM as solvent	50% (only 3a)
5	Entry 4 + succinimide 2 equiv.	quant. (only 3a)

4.3 Substrate Scope of Difunctionalization.

We then explored the substrate scope of cyclopropylanilines using the combination of NIS and TMSCN with 1 equiv. of water to produce gamma-iodo alpha-amino nitriles. Substituents on the benzene ring were generally well tolerated except strongly electron-donating ones such as a para-methoxy group. In the latter example, the cyclopropylaniline decomposed without formation of any desired product. Cyclopropylanilines substituted with a nitrile (**2a**) or a chloride group (**2e**) at the para position furnished the products in higher yields (91% and 75%) than the unsubstituted aniline (**2c**, 70%). Ortho (**2d**) and meta (**2e**) substituents were also compatible with the conditions, and the corresponding products were obtained in good to excellent yields (58% and quant.). More impressively, monocyclic tertiary cyclopropylanilines, the class of problematic substrates that failed to undergo our previously reported [3+2]

annulation reaction, were viable substrates. Substituting the N-H atom with methyl (**2g**), 3-chloropropyl (**2h**), benzyl (**2i**), allyl (**2j**) or isopentyl (**2k**) all successfully led to the targeted products in 78% to 92% yields. Notably, some of these groups including 3-chloropropyl, benzyl, and allyl that could react with radical intermediates were completely compatible. This data lent credence to our hypothesis that this reaction likely proceeded through the S_N2-like, 2e process instead of the 1e process involving the amine radical cation.

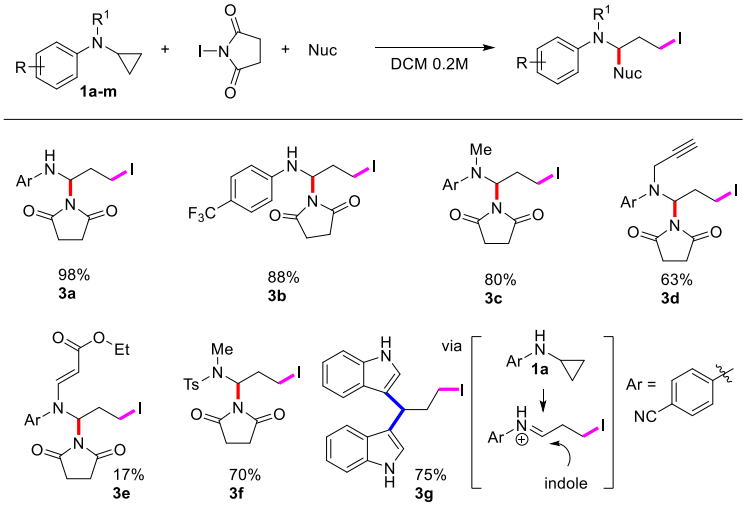
Table 4.2 Substrate Scope of NIS with TMSCN.



Next, we investigated alternative nucleophiles to TMSCN for the difunctionalization of monocyclic secondary and tertiary cyclopropylamines. DCM was identified as a better solvent than ether for these nucleophiles, and water was not added. With 2 equiv. of succinimide, secondary cyclopropylanilines para-substituted with CN (**3a**) or CF_3 (**3b**) were converted to gamma-iodo *N*,*N*'-aminals in excellent yields. Similarly, *N*-methyl (**3c**) or -propargyl (**3d**) substituted tertiary cyclopropylanilines furnished the products in good yields. However, the cyclopropylaniline bearing a vinylogous carbamate afforded product **3e** in poor yield.

Substituting the *N*-aryl group with a Ts group had impact on the efficiency of the reaction (longer reaction time, 24 h), yet product **3f** was isolated in 70% yield. In addition to succinimide, indole was found to be a viable nucleophile. Interestingly, double addition of indole to cyclopropylamine **1a** occurred to produce bisindole **3g** in 75% yield. Likely, the first equivalent of indole was added to the in situ formed imine or iminium ion, and the second equivalent displaced the aniline group.

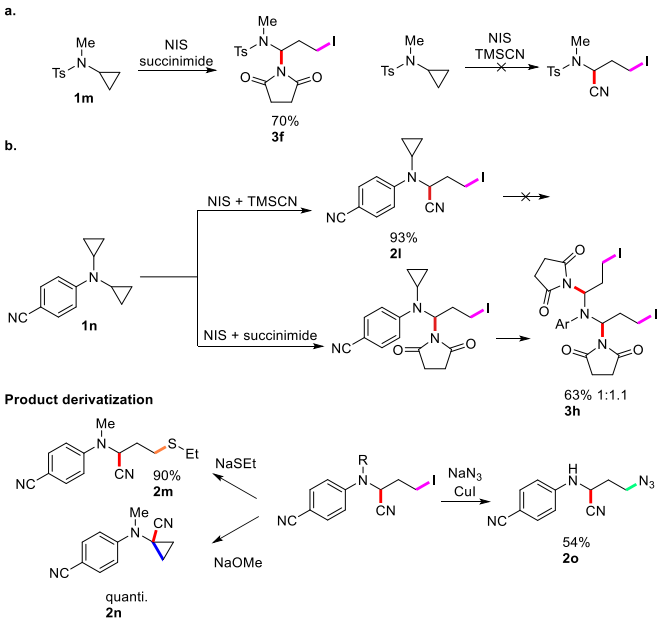
Table 4 .3 Substrate Scope of NIS and Other Nucleophiles.



When examining different nucleophiles, we noticed that Ts-substituted cyclopropylamine exhibited different reactivity depending on the nucleophile used. It reacted with the combination of NIS and succinimide to give **3f** but failed to react with that of NIS and TMSCN (Scheme 2a). This divergent reactivity was surprising to us, because based on our model for the reaction, only NIS was responsible for the ring opening and the nature of nucleophile should not affect the reaction. We suspected that ICN, a weaker electrophile than NIS and formed upon mixture of NIS and TMSCN, might not be electrophilic enough to promote the ring opening (see SI).

Indeed, when ICN was directly used to react with **1m**, no reaction was observed but substrate **1a** reacted with ICN to afford the desired product **2a** in 50% yield (see SI). To highlight the reactivity difference between the combination of NIS with TMSCN and that of NIS with succinimide, we prepared bicyclopropylaniline **1n** and subjected it to the two combinations (Scheme 2b). Only one of the two cyclopropyl rings opened using NIS and TMSCN to afford product **2l** in 93% yield whereas both rings opened using NIS and succinimide to furnish product **3h** in 63% yield as a 1.1:1 mixture of two diastereomers We reasoned that the α-cyano group inductively reduced the nucleophilicity of the remaining cyclopropylaniline and thus rendered ICN ineffective for the second ring opening.

Because alpha-amino nitriles' synthetic utility is well precedented in the literature and *N*,*N*-aminals are a highly useful functional group, we turned to focus on derivatization of the other functionality in the difunctionalization products, the gamma-iodo group. Nucleophilic substitution by NaSEt yielded product thioether **2m** in 90% yield. A copper-catalyzed displacement by NaN_3 produced alkyl azide **2o** in 54% yield. Lastly, treatment of gamma-iodo alpha-amino nitrile with NaOEt reformed the cyclopropyl ring (**2n**) via an intramolecular S_N2 reaction in a quantitative yield (Scheme 2).

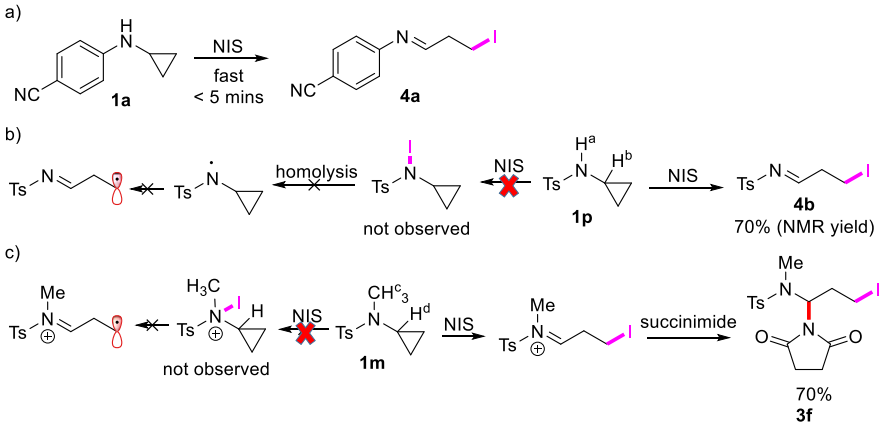


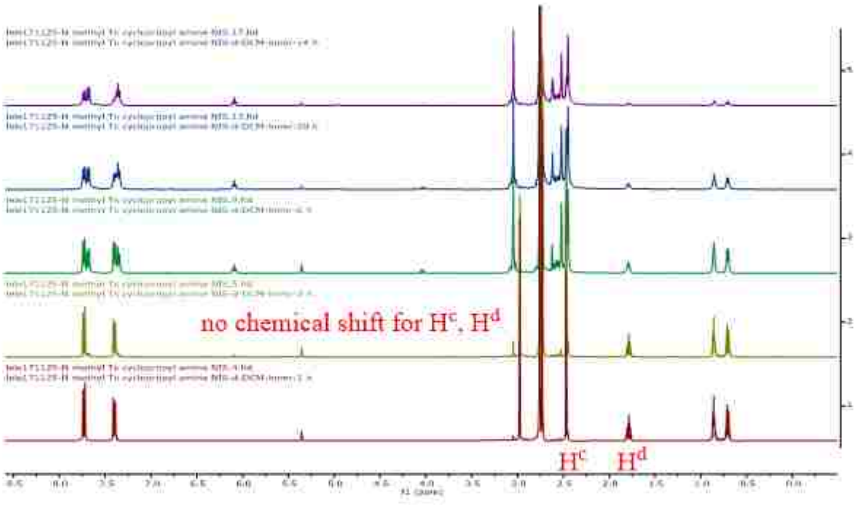
Scheme 4.2 In-situ formation of ICN and product derivatization.

4.4 Mechanistic Study

To probe the reaction pathway, we performed in situ NMR monitoring experiments that focused on ruling out the 1e pathway involving the amine radical or radical cation. Specifically, we searched for evidences to contradict the formation of a N-I bond, which could undergo homolysis to produce the radical or radical cation intermediate.[10] When 4-cyanocyclopropylaniline 1a was employed as the substrate, the ring-opening was very fast, and upon the addition of NIS at room temperature, the substrate was completely converted to the imine 4a within the first HNMR scan (<5 mins, Scheme 3a). Then, the imine 4a gradually reacted with the generated succinimide to yield gamma-iodo *N,N'*-aminal 3a. To slow down the ring opening process, we turned to Ts-substituted cyclopropylamines because Ts as a strong electron withdrawing group reduces the nucleophilicity of cyclopropylamines. Indeed, upon mixture of NIS with secondary Ts-substituted cyclopropylamine 1p, a slow ring-opening was

observed, and it took 6 h to consume the cyclopropylamine (scheme 3b). We ruled out the formation of N-I bond based on two NMR observations. There was no change in the chemical shifts of the cyclopropylamine nor disappearance of the N-H peak. Moreover, the 1:1 integral ratio of N-H^{a}: α-C-H^{b} was maintained throughout the reaction (see SI). Similar observations (no chemical shift for H^{c}, H^{d}) were also made with methylated tertiary cyclopropylsulfonamide (1m) that underwent a slow ring-opening without the formation of the N-I bond (Scheme 3c). In addition to the NMR experiments, control studies showed that the reaction occurred in dark at ambient temperature with the same efficiency (see SI). Since homolysis of N-I bonds generally requires light or heat, the result in dark suggested that the reaction didn't involve the homolysis of N-I bonds.[11] Another control study showed that phenyl cyclopropane was unreactive under standard condition, which emphasized the amnio group's importance in the reaction (see SI). All these results were consistent with our hypothesis that the reaction proceeded through the 2e, S_N2 like mechanism in which cyclopropylamines attacked electrophilic iodine species.





Scheme 4.3 Mechanistic Studies.

4.5 Experimental Section

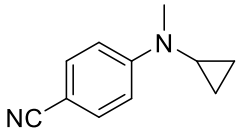
General Considerations

Unless stated otherwise, all reactions were carried out under a nitrogen atmosphere. THF was collected under argon from a solvent purification system. Acetonitrile and nitromethane were pre–dried over molecular sieves. Column chromatography was performed using silica gel (230–400 mesh). All new compounds were (at minimum) characterized using 2 of the following: ^{1}H NMR, ^{13}C NMR, IR spectroscopy, high–resolution mass spectroscopy (HRMS) or gas chromatography/mass spectroscopy (GC/MS), 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 $CDCl_3$ (7.27 ppm, 77.23 ppm), CD_2Cl_2 (5.32 ppm, 54.0 ppm), and benzene–d_6 (7.16 ppm, 128.39 ppm) at room temperature. IR spectra were recorded (thin film on NaCl plates) on a PerkinElmer Spectrum 100 series instrument. High Resolution Mass spectra were recorded on 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.

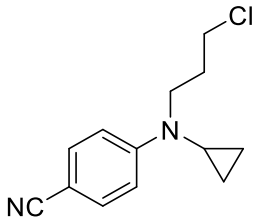
General procedure for preparation of tertiary amines: parent secondary amine 1 (2 mmol 1 equiv.) was mixed with NaH (2.4 mmol, 1.2 equiv.) in DMF (5 mL) and stirred for 10 mins under room temperature. After 10 mins, alkyl halide was added (MeI, 2.4 mmol, 1.2 equiv.). The resulting mixture was left overnight and quenched with brine and extracted with diethyl ether. The organic layer was concentrated under vacuum and isolated by flash chromatography to give corresponding tertiary amine 7 in 78% yield.

Compound(cyclopropylanilines) 1a-1f have been reported before and are synthesized according to our previous method(S. Maity, M. Zhu, R. S. Shinabery, N. Zheng, *Angew. Chem. Int. Ed.* **2012**, *51*, 222-226.).



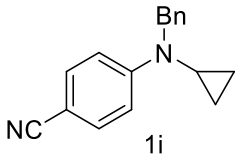
1g

Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 2953, 2922, 2852, 1457, 1377, 1362; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 3.05 (s, 3H), 2.56 (tt, *J* = 6.6, 3.8 Hz, 1H), 1.04 – 0.78 (m, 2H), 0.74 – 0.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.24, 133.09, 120.61, 112.99, 98.58, 38.23, 32.91, 9.30. ^{13}C DEPT135 NMR (100 MHz, $CDCl_3$) δ 133.10, 112.99, 38.23, 32.91, 9.30. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{11}H_{13}N_2$ 173.1073; found 173.1068.



1h

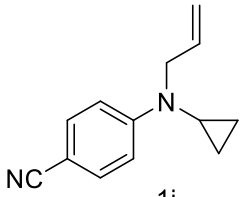
Following the above procedure, 1-Chloro-3-iodopropane (4.8 mmol, 1.2 equiv.), NaH (6.8 mmol, 1.7 equiv.) were used. product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid (1.02 mmol, 26%); IR υmax (cm-1) 2211, 1600, 1511, 1368, 1175, 819; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 – 7.37 (m, 2H), 7.13 – 6.89 (m, 2H), 3.91 – 3.47 (m, 4H), 2.56 (tt, *J* = 6.6, 3.9 Hz, 1H), 2.15 – 1.96 (m, 2H), 1.12 – 0.89 (m, 2H), 0.78 – 0.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.93, 133.26, 120.40, 113.55, 99.04, 47.43, 42.58, 31.81, 29.56, 9.43. ^{13}C DEPT135 NMR (100 MHz, $CDCl_3$) δ 133.27, 113.54, 47.43, 42.59, 31.82, 29.55, 9.43. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{13}H_{16}ClN_2$ 235.0997; found 235.0997.



1i

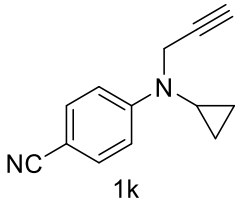
Following the above procedure, benzyl bromide (2 mmol, 1 equiv.) is used as alkyl halide, KOH(2 mmol, 1 equiv.) is used in DMSO (6 mL), product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid (50% yield); IR υmax (cm-1) 3028, 2212, 1512, 1363, 1174, 543; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.42 (m, 2H), 7.38 – 7.29 (m, 2H), 7.30 – 7.23 (m, 1H), 7.12 (dq, *J* = 7.1, 0.9 Hz, 2H), 6.99 – 6.83 (m, 2H), 4.71 (s, 2H), 2.75 (tt, *J* = 6.6, 3.8 Hz, 1H), 1.05 – 0.89 (m, 2H), 0.82 – 0.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.63, 138.25, 133.16, 128.78, 127.11, 125.93, 120.45, 113.58, 99.15, 55.41, 32.93, 9.06. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.17, 128.78, 127.11, 125.93,

113.58, 55.41, 32.93, 9.06. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{17}H_{17}N_2$ 249.1386; found 249.1388.



1j

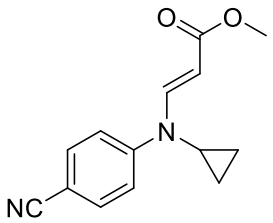
Following the above procedure, product was isolated in one pot from the same reaction of 8 after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid (1.3 mmol, 33%); IR υmax (cm-1) 2212, 1600, 1512, 1362, 1173, 817; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.42 (m, 2H), 7.00 – 6.85 (m, 2H), 5.85 (ddt, *J* = 17.1, 10.4, 4.4 Hz, 1H), 5.14 (dq, *J* = 10.4, 1.7 Hz, 1H), 5.04 (dq, *J* = 17.1, 1.8 Hz, 1H), 4.07 (dt, *J* = 4.1, 1.9 Hz, 2H), 2.64 (tt, *J* = 6.6, 3.8 Hz, 1H), 0.99 – 0.83 (m, 2H), 0.78 – 0.61 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.47, 133.62, 133.08, 120.55, 115.94, 113.42, 98.82, 53.89, 32.40, 8.80. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.62, 133.08, 115.94, 113.42, 53.89, 32.40, 8.80. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{13}H_{15}N_2$ 199.1230; found 199.1233.



1k

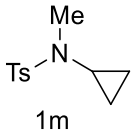
Following the above procedure, propargyl bromide is used (2.4 mmol, 2 equiv.) product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid (26%); IR υmax (cm-1) 2215, 1602, 1513, 1362, 1177, 822, 542; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.42 (m, 2H), 7.13 – 6.99 (m, 2H), 4.17 (d, *J* = 2.4 Hz, 2H), 2.67 (tt, *J* = 6.6, 3.8 Hz, 1H), 2.21 (t, *J* = 2.4 Hz, 1H), 1.06 – 0.91 (m, 2H), 0.81 – 0.68 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.74, 133.14, 120.20, 114.32, 100.37, 79.20, 72.06, 40.76, 32.26, 9.21.

^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.15, 114.32, 79.21, 72.06, 40.76, 32.26, 9.22. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{13}H_{13}N_2$ 197.1073; found 197.1080.



1l

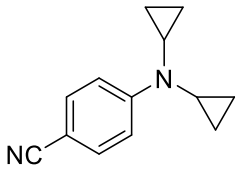
Following the above procedure, methyl propiolate (2.4 mmol, 1.2 equiv.) is used in stead of alkyl halide. Product was isolated after flash chromatography on silica gel (5:1 hexane/ EtOAc) as white solid M.P. :96 °C - 99°C (46%); IR υmax (cm-1) 2946, 1696, 1623, 1586, 1507, 1243, 1161, 819; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (d, *J* = 13.4 Hz, 1H), 7.63 (d, *J* = 8.9 Hz, 2H), 7.35 – 7.19 (m, 2H), 5.58 (d, *J* = 13.4 Hz, 1H), 3.76 (s, 3H), 2.79 (tt, *J* = 6.7, 3.9 Hz, 1H), 1.33 – 1.07 (m, 2H), 0.82 – 0.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.80, 148.84, 146.80, 133.22, 119.48, 118.78, 106.23, 95.53, 51.16, 29.02, 10.01. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 146.80, 133.22, 119.47, 95.52, 51.17, 29.01, 10.01. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{14}H_{15}N_2O_2$ 243.1128; found 243.1132.



1m

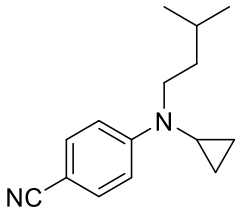
Following the above procedure, product was isolated after flash chromatography on silica gel (10:1 hexane/ EtOAc) as white solid M.P. :73 °C - 76°C (70% yield); IR υmax (cm-1) 1335, 1151, 1090, 816, 691, 542; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 8.1 Hz, 2H), 7.44 – 7.32 (m, 2H), 2.76 (d, *J* = 0.8 Hz, 3H), 2.46 (s, 3H), 1.81 (tt, *J* = 6.9, 3.6 Hz, 1H), 0.92 – 0.82 (m, 2H), 0.78 – 0.63 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.50, 132.94, 129.52, 128.04, 37.52, 32.13, 21.54, 7.52. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 129.52, 128.04,

37.53, 32.13, 21.55, 7.53. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{11}H_{16}NO_2S$ 226.0896; found 226.0889.



1n

15 is prepared through reductive amination of 1. 1 (2 mmol, 1 equiv.) is mixed with 1-Ethoxy-1-[(trimethylsilyl)oxy]cyclopropane (CAS: 27374-25-0, 4 mmol, 2 equiv.) and $NaBH_3CN$ (3 mmol, 1.5 equiv.) in acetic acid (2 mL). the mixture was stir at 85 ^oC for 3 hr. Product was isolated after flash chromatography on silica gel (50:1 hexane/ EtOAc) as white solid M.P. :90 °C - 95°C (71% yield); IR υmax (cm-1) 3008, 2212, 1601, 1352, 1029, 817, 520; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.55 – 7.37 (m, 2H), 7.13 – 6.81 (m, 2H), 2.52 (tt, *J* = 6.7, 3.8 Hz, 2H), 1.13 – 0.87 (m, 4H), 0.84 – 0.60 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.91, 132.65, 120.74, 113.84, 98.40, 30.48, 9.42. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 132.65, 113.84, 30.48, 9.42. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{13}H_{15}N_2$ 199.1230; found 199.1236.

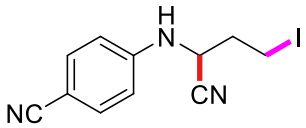


1o

Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid (95% yield); IR υmax (cm-1) 2955, 2212, 1601, 1512, 1365, 1174, 818, 545, 536; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.42 (m, 2H), 7.00 – 6.84 (m, 2H), 3.51 – 3.35 (m, 2H), 2.53 (tt, *J* = 6.6, 3.9 Hz, 1H), 1.73 – 1.53 (m, 1H), 1.52 – 1.36 (m, 2H), 1.02 – 0.87 (m, 8H), 0.72 – 0.54 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$)

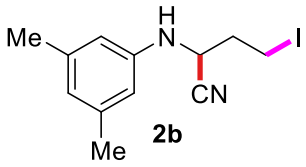
δ 152.27, 133.16, 120.65, 113.34, 98.25, 48.71, 35.54, 31.56, 26.34, 22.56, 9.23. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.16, 113.34, 48.71, 35.54, 31.56, 26.34, 22.57, 9.23. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{15}H_{21}N_2$ 229.1699; found 229.1695.

General procedure for difunctionalization with TMSCN: cyclopropylamine 1 (0.2 mmol 1 equiv.), TMSCN (1 mmol, 5 equiv.), H_2O (0.2 mmol 1 equiv.), Et_2O (1 mL) were added to a test tube followed by the addition of NIS (0.4 mmol, 2 equiv.). The resulting mixture was stirred for 1 hr under room temperature. After 1 hr, the mixture was filtered through a short pad of silica gel and concentrated under vacuum and isolated by flash chromatography to give product 2a in 91% yield.



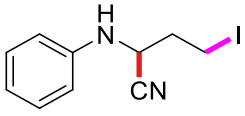
2a

Following the above procedure, product was isolated after flash chromatography on silica gel (10:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 3675, 2216, 1604, 1520, 1175, 825, 543; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 – 7.44 (m, 2H), 6.94 – 6.61 (m, 2H), 4.57 (q, *J* = 15.9, 11.9 Hz, 2H), 3.60 – 3.23 (m, 2H), 2.57 – 2.33 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.04, 134.02, 119.44, 117.66, 113.88, 102.60, 45.90, 36.17, -1.48. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 134.02, 113.88, 45.90, 36.16, -1.46. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{11}H_{11}IN_3$ 311.9992; found 311.9988.



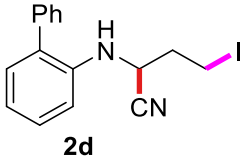
2b

Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 1600, 1457, 1190, 824, 689; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.59 (dt, *J* = 1.7, 0.9 Hz, 1H), 6.42 (d, *J* = 1.5 Hz, 2H), 4.49 (dt, *J* = 10.3, 7.3 Hz, 1H), 3.60 (s, 1H), 3.48 – 3.32 (m, 2H), 2.50 – 2.38 (m, 2H), 2.31 (d, *J* = 0.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.47, 139.40, 122.66, 118.83, 112.59, 46.94, 36.90, 21.47, -0.90. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 122.66, 112.58, 46.93, 36.89, 21.48, -0.88. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{12}H_{16}IN_2$ 315.0353; found 315.0354.



2c

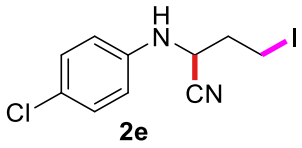
Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 1601, 1507, 1496, 1258, 1181, 750, 691; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.22 (m, 2H), 7.01 – 6.91 (m, 1H), 6.82 – 6.75 (m, 2H), 4.51 (dt, *J* = 10.2, 7.3 Hz, 1H), 3.81 (d, *J* = 10.2 Hz, 1H), 3.49 – 3.33 (m, 2H), 2.51 – 2.31 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.51, 129.66, 120.66, 118.81, 114.66, 46.90, 36.66, -0.70. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 129.67, 120.66, 114.65, 46.89, 36.65, -0.67. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{10}H_{12}IN_2$ 287.0040; found 287.0046.



2d

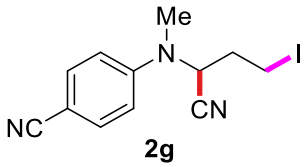
Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 1507, 1490, 1436, 1179, 749, 703; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.49 (m, 2H), 7.47 – 7.36 (m, 4H),

7.23 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.08 – 6.91 (m, 2H), 4.53 (dt, *J* = 10.0, 7.3 Hz, 1H), 3.97 (d, *J* = 9.9 Hz, 1H), 3.31 (t, *J* = 6.6 Hz, 2H), 2.37 – 2.24 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.52, 138.38, 130.86, 129.86, 129.39, 129.21, 129.00, 127.85, 120.41, 118.71, 112.89, 46.99, 36.51, -0.75. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 130.86, 129.39, 129.21, 129.00, 127.85, 120.41, 112.88, 46.98, 36.51, -0.73. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{16}H_{16}IN_2$ 363.0353; found 363.0361.



2e

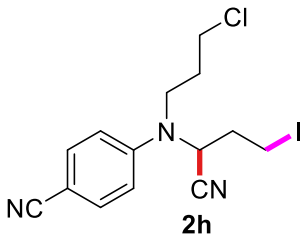
Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 1599, 1490, 1313, 1288, 1090, 815; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.18 (m, 2H), 6.78 – 6.65 (m, 2H), 4.47 (dt, *J* = 10.2, 7.3 Hz, 1H), 3.81 (d, *J* = 10.2 Hz, 1H), 3.46 – 3.29 (m, 2H), 2.42 (dtd, *J* = 7.7, 6.2, 3.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.06, 129.57, 125.61, 118.45, 115.87, 47.07, 36.50, -0.99. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 129.57, 115.87, 47.06, 36.49, -0.97. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{10}H_{11}ClIN_2$ 320.9650; found 320.9647.



2g

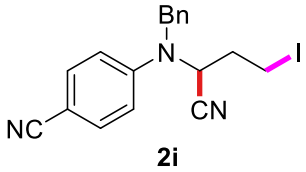
Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 2218, 1602, 1312, 1181, 934, 818, 542; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 – 7.53 (m, 2H), 7.03 – 6.93 (m, 2H), 4.99 (t, *J* = 7.6 Hz, 1H), 3.38 – 3.19 (m, 2H), 3.02 (d, *J* = 1.2 Hz, 3H), 2.43 (dt, *J* = 7.9, 6.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.24, 133.79, 119.32, 116.31, 114.85, 102.62, 52.57,

34.53, 34.16, -0.97. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.79, 114.84, 52.56, 34.53, 34.16, -0.95. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{12}H_{13}IN_3$ 326.0149; found 326.0145.



2h

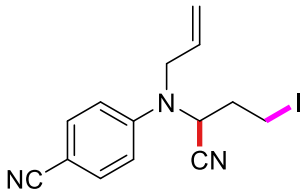
Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 2217, 1683, 1602, 1513, 1180, 820, 543; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.50 (m, 2H), 7.17 – 6.89 (m, 2H), 4.87 (t, *J* = 7.6 Hz, 1H), 3.75 – 3.54 (m, 4H), 3.30 (t, *J* = 6.3 Hz, 2H), 2.45 (dt, *J* = 7.4, 6.2 Hz, 2H), 2.27 – 1.98 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.37, 133.89, 119.15, 116.84, 116.10, 103.26, 53.20, 45.97, 42.13, 34.65, 29.68, -0.62. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.90, 116.09, 53.19, 45.96, 42.14, 34.64, 29.67, -0.59. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{14}H_{16}ClIN_2$ 388.0072; found 388.0077.



2i

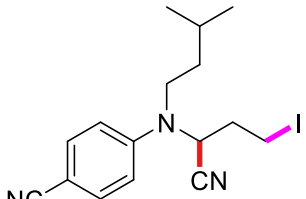
Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 2218, 1602, 1221, 1177, 818, 735, 697, 542; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.51 (m, 2H), 7.42 – 7.24 (m, 5H), 7.03 – 6.94 (m, 2H), 5.05 (t, *J* = 7.6 Hz, 1H), 4.80 – 4.56 (m, 2H), 3.45 – 3.13 (m, 2H), 2.49 – 2.30 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.24, 136.15, 133.78, 129.13, 127.96,

126.47, 119.22, 116.72, 115.63, 102.98, 53.58, 52.90, 34.88, -0.49. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.78, 129.14, 127.96, 126.46, 115.61, 53.57, 52.89, 34.87. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{18}H_{17}IN_3$ 402.0462; found 402.0459.



2j

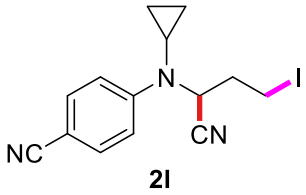
Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 2216, 1602, 1513, 1178, 817, 542; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.37 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.89 (ddt, *J* = 17.4, 10.1, 4.9 Hz, 1H), 5.40 – 5.18 (m, 2H), 4.96 (t, *J* = 7.6 Hz, 1H), 4.19 – 3.91 (m, 2H), 3.30 (tt, *J* = 10.6, 4.9 Hz, 2H), 2.42 (ddd, *J* = 13.3, 7.8, 5.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.89, 133.72, 132.42, 119.32, 118.41, 116.76, 114.94, 102.49, 51.90, 34.83, -0.64. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.72, 132.41, 118.41, 114.93, 51.97, 51.89, 34.82, -0.61. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{14}H_{15}IN_3$ 352.0305; found 352.0302.



2k

Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 2956, 2218, 1709, 1603, 1516, 1220, 1180, 819, 542, 528; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.50 (m, 2H), 7.04 – 6.78 (m, 2H), 4.88 (t, *J* = 7.6 Hz, 1H), 3.53 – 3.34 (m, 2H), 3.30 (t, *J* = 6.3 Hz, 2H), 2.42 (dtd, *J* = 7.7, 6.3, 2.5 Hz, 2H), 1.77 – 1.56 (m, 2H), 1.55 – 1.41 (m, 1H), 0.99 (dd, *J* = 6.4,

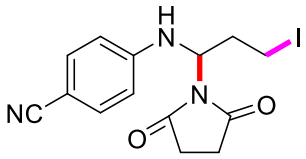
3.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.54, 133.79, 119.40, 116.98, 114.94, 102.06, 52.22, 47.75, 36.20, 34.81, 26.40, 22.42, -0.69. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.80, 114.92, 52.21, 47.74, 36.20, 34.80, 26.40, 22.43, -0.66. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{16}H_{21}IN_3$ 382.0775; found 382.0772.



2l

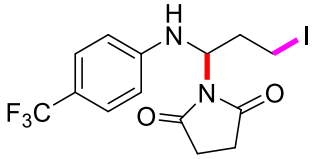
Following the above procedure, product was isolated after flash chromatography on silica gel (20:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 2218, 1602, 1507, 1177, 824, 543; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.46 (m, 2H), 7.23 – 7.05 (m, 2H), 4.85 (t, *J* = 7.7 Hz, 1H), 3.28 (tt, *J* = 6.3, 3.3 Hz, 2H), 2.66 (tt, *J* = 6.6, 3.8 Hz, 1H), 2.60 – 2.45 (m, 2H), 1.02 (dddd, *J* = 12.1, 9.7, 6.8, 4.1 Hz, 2H), 0.94 – 0.84 (m, 1H), 0.76 – 0.66 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.43, 133.34, 119.28, 117.47, 103.53, 54.66, 34.75, 30.49, 10.04, 8.86, -0.38. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.34, 117.40, 54.65, 34.74, 30.48, 10.04, 8.87, -0.35. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{14}H_{15}IN_3$ 352.0305; found 352.0299.

General procedure for difunctionalization with succinimide: cyclopropylamine 1 (0.2 mmol 1 equiv.), succinimide (0.4 mmol, 2 equiv.), DCM (1 mL) were added to a test tube followed by the addition of NIS (0.4 mmol, 2 equiv.). The resulting mixture was stirred for 1 hr under room temperature. After 1 hr, the mixture was filtered through a short pad of silica gel and concentrated under vacuum and isolated by flash chromatography to give product 3a in quant. yield.



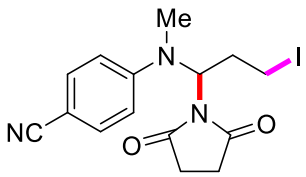
3a

Following the above procedure, product was isolated after flash chromatography on silica gel (5:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 3378, 2220, 1687, 1607, 1295, 1176, 823; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.42 (m, 2H), 6.85 – 6.64 (m, 2H), 5.82 (ddd, *J* = 11.4, 8.1, 6.1 Hz, 1H), 5.23 (d, *J* = 11.4 Hz, 1H), 3.39 – 3.08 (m, 2H), 2.81 – 2.67 (m, 5H), 2.56 – 2.37 (m, 1H), 2.06 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.06, 148.22, 133.99, 119.57, 113.99, 102.06, 61.68, 36.15, 27.95, -1.17. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.99, 113.99, 61.67, 36.14, 27.95, -1.15.



3b

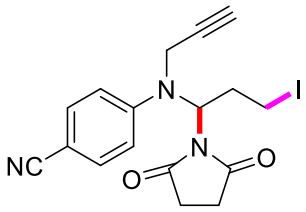
Following the above procedure, product was isolated after flash chromatography on silica gel (5:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 1700, 1601, 1322, 1169, 1125, 1066, 742, 635; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.82 (ddd, *J* = 11.5, 8.2, 5.9 Hz, 1H), 5.15 (d, *J* = 11.6 Hz, 1H), 3.37 – 3.15 (m, 2H), 2.76 – 2.60 (m, 5H), 2.54 – 2.33 (m, 1H ^{13}C NMR (101 MHz, Chloroform-*d*) δ 177.23 , 147.43, 126.91, 124.55, 121.47, 113.67 , 62.18 , 36.35 , 27.94 , -0.80 . ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 126.90, 113.67, 62.17, 36.34, 27.94, -0.78.



3c

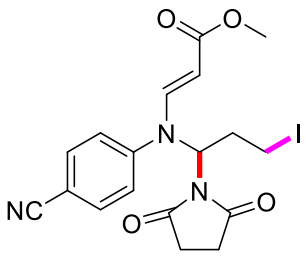
Following the above procedure, product was isolated after flash chromatography on silica gel (5:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 2210, 1700, 1603,

1521, 1293, 1175, 816, 547; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.40 (m, 2H), 7.13 – 6.91 (m, 2H), 6.11 (t, *J* = 7.2 Hz, 1H), 3.21 – 3.02 (m, 5H), 2.91 (ddt, *J* = 14.0, 8.0, 6.4 Hz, 1H), 2.72 (s, 4H), 2.68 – 2.57 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.43, 151.08, 133.57, 119.89, 113.32, 100.73, 66.52, 34.01, 33.26, 28.12, -0.86. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.57, 113.31, 66.51, 34.01, 33.26, 28.12, -0.85.



3d

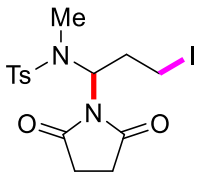
Following the above procedure, product was isolated after flash chromatography on silica gel (5:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 2215, 1684, 1602, 1517, 1170, 817, 635, 544; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.48 (m, 2H), 7.19 – 7.07 (m, 2H), 6.12 (t, *J* = 7.2 Hz, 1H), 4.69 (dd, *J* = 19.0, 2.5 Hz, 1H), 4.15 (dd, *J* = 19.0, 2.4 Hz, 1H), 3.31 – 3.13 (m, 2H), 3.00 (dtd, *J* = 15.0, 6.9, 5.9 Hz, 1H), 2.74 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.47, 149.50, 133.63, 119.68, 113.76, 101.63, 79.74, 72.86, 66.48, 35.94, 34.04, 28.07, -0.35. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 133.63, 113.75, 79.74, 72.86, 66.47, 35.94, 34.04, 28.07, -0.32.



3e

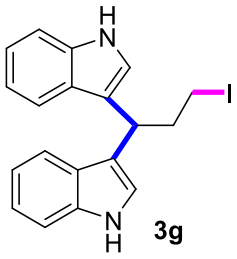
Following the above procedure, product was isolated after flash chromatography on silica gel (3:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 2215, 1700, 1606, 1248, 1153, 668; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 13.6 Hz, 1H), 7.81 – 7.70 (m, 2H), 7.49 – 7.39 (m, 2H), 5.79 (t, *J* = 7.6 Hz, 1H), 4.75 (d, *J* = 13.6 Hz, 1H), 3.68 (s, 3H), 3.25 –

3.11 (m, 2H), 3.02 – 2.88 (m, 1H), 2.83 – 2.68 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.53, 168.37, 146.91, 145.92, 133.99, 128.08, 117.92, 111.53, 94.07, 70.12, 51.10, 33.44, 27.95, -0.88. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 146.91, 133.99, 128.07, 94.07, 70.12, 51.11, 33.44, 27.95, -0.85.



3f

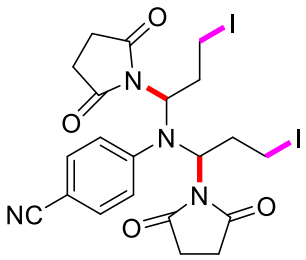
Following the above procedure, product was isolated after flash chromatography on silica gel (5:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 1704, 1339, 1217, 1151, 905, 650, 546; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 – 7.68 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.08 (t, *J* = 7.4 Hz, 1H), 3.07 (s, 3H), 3.04 – 2.92 (m, 2H), 2.66 – 2.48 (m, 6H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.41, 143.82, 136.01, 129.64, 127.39, 64.00, 33.85, 31.66, 27.95, 21.56. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 129.64, 127.38, 64.00, 33.85, 31.67, 27.95, 21.56. FTMS (ESI) *m/z* $[M+Na]^+$, calc'd for $C_{15}H_{19}IN_2O_4SNa$ 473.0002; found 472.9997.



3g

Following the above procedure, product was isolated after flash chromatography on silica gel (5:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 3406, 1456, 1418, 1339, 1219, 1092, 1009, 739; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 – 7.66 (m, 4H), 7.37 – 7.32 (m, 2H), 7.25 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 2H), 7.15 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 2H), 6.94 (d, *J* = 2.4 Hz, 2H), 4.73 (t, *J* = 7.3 Hz, 1H), 3.24 (t, *J* = 6.8 Hz, 2H), 2.75 (q, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.65, 126.80, 122.06, 121.91, 119.70, 119.34, 118.34, 111.35,

38.95, 34.97, 6.78. ^{13}C DEPT135 NMR (101 MHz, $CDCl_3$) δ 122.06, 121.91, 119.70, 119.34, 111.35, 38.94, 34.97, 6.81.



3h

Following the above procedure, product was isolated after flash chromatography on silica gel (5:1 hexane/ EtOAc) as liquid; IR υmax (cm-1) 1772, 1688, 1507, 1291, 1172, 817, 635; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.56 (m, 2H), 7.56 – 7.43 (m, 1H), 7.36 – 7.14 (m, 1H), 5.57 (dd, *J* = 9.0, 5.6 Hz, 1H), 5.50 (dd, *J* = 8.9, 5.8 Hz, 1H), 3.15 – 2.90 (m, 4H), 2.88 – 2.78 (m, 1H), 2.75 – 2.48 (m, 10H), 2.33 (dtd, *J* = 14.4, 7.1, 5.5 Hz, 1H). ^{13}C NMR (major product) (101 MHz, $CDCl_3$) δ 177.44, 145.69, 132.85, 129.90, 118.33, 109.68, 68.33, 34.91, 28.04, -0.38. ^{13}C DEPT135 NMR (major product) (101 MHz, $CDCl_3$) δ 132.85, 129.89, 68.32, 33.93, 28.04, -0.36.

4.6 Summary

In conclusion, we have developed two sets of reaction conditions, NIS/succinimide and NIS/TMSCN, for difunctionalization of monocyclic cyclopropylamines. Both conditions center on the ring opening via a 2e S_N2-like pathway in which cyclopropylamines act as a pi nucleophile to attack an electrophilic iodine source. This ring opening process effects a simultaneous installment of an iodide group at the gamma carbon and an imine at the alpha carbon. The latter group can be intercepted in situ by nucleophiles such as cyanide, succinimide, or indole to furnish multiple pairs of functional groups disposed in a 1,3-manner. The versatility

of the 1,3-oxidation pattern can be further enhanced by substituting the iodide group with nucleophiles such as NaSEt and NaN_3. In situ NMR studies revealed that the N-I bond was not formed during the reaction. Mechanistic studies supported that mixing NIS with TMSCN produced ICN in situ, which was a weaker and more selective electrophilic iodine source for opening cyclopropylamines than NIS. The 2e reactivity manifold both differs and complements to the 1e reactivity manifold, as is highlighted by the data that monocyclic tertiary cyclopropylamines only worked under the former manifold. Future efforts will seek to capitalize on the 2e reactivity manifold enabled by electrophilic iodine sources.

4.7 Reference:

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Chapter 5. A Photocatalyzed Cascade Approach Towards the Tetracyclic Core of Akuammiline Alkaloids

5.1 Introduction

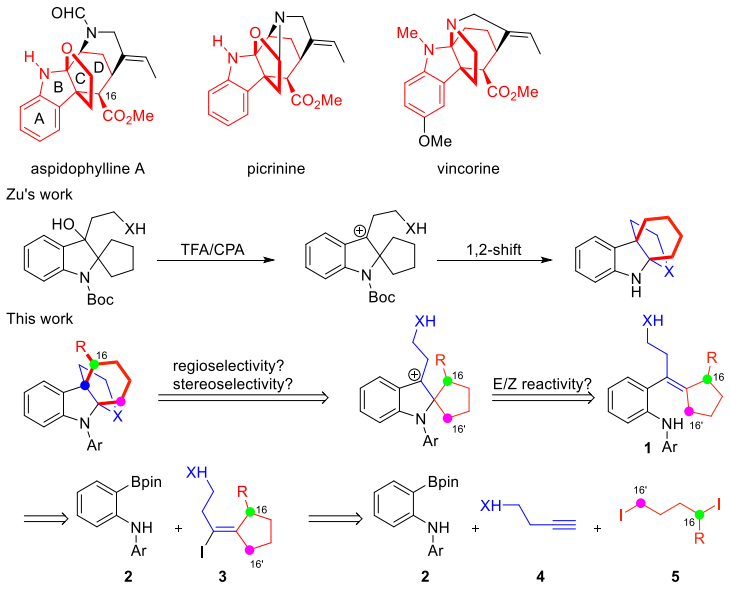
The akuammiline alkaloids that feature a complex tetracyclic core structure have been shown a broad range of biological activity, such as the reversal of drug resistance in drug-resistant KB cells by aspidophylline A, anti-inflammatory activity through inhibition of the 5-lipoxygenase enzyme by picrinine.[1] A family of synthetic tricyclic indolines also bearing the tetracyclic core, which was discovered by Wang through SAR studies on the aryl ring D and the protecting group of the indoline nitrogen atom, was shown to selectively potentiates the activity of β-lactam antibiotics.[2] However, SAR studies on other positions such as C-16 were not reported presumably because of the limitation of the synthetic method. Substitution at this position is critical because it is prevalent in the akuammiline alkaloids.[1a] For example, aspidophylline A, picrinine, vincorine and others all have an ester group at C-16.[3] The synthesis of these natural products reported by Zhu, Ma, Garg, MacMillan, and Qin introduced the ester group by a Diels-Alder reaction of α, β unsaturated esters or use of the acidic proton α to the ester group for azidation or oxidative coupling.[3a-h] However, these methods were not suitable for incorporating other substituents at C-16 because of the requirement of activation by a carbonyl group.

We planned to overcome the constraint of the C-16 substituent by developing a photocascade approach that was adapted from our previous work on an indole synthesis via 1, 2-shift initiated by a photogenerated amine radical cation.[4] We envisioned that by tethering a nucleophile (X of **1**, Scheme **1**) to the alkene, 1,2-shift followed by interception of the resulting

iminium ion by X would establish the tetracyclic core. The precursor for the photocascade, tetrasubstituted alkene **1**, could be assembled from three fragments with similar complexity, aniline boronic ester **2**, homopropargyl alcohol or amine **4**, and 1, 4-diiodobutane **5** in a highly convergent manner. The C-16 substituent, which could be readily installed to the last fragment, was expected to be compatible with a carbocation-initiated 1,2-shift and thus could overcome the constraint of the ester group. Moreover, our approach enabled us to quickly introduce different substituents to the aryl ring and modify the nucleophile such as a protected amino group or an alcohol. Such a convergent synthesis would be important for SAR studies as each module could be easily modified from simple fragments.

Zu recently applied a similar 1,2-shift to construct the tetracyclic core enantioselectively and also completed a total synthesis of calophyline and a formal synthesis of minfiensine.[5] The carbocation was produced by ionization of a tertiary benzylic alcohol under strong acidic conditions (TFA) or CPA (chiral phosphoric acid). The use of a symmetric cyclopentyl ring greatly simplified the 1,2-shift as only one diastereomer was possibly formed. The Driver group developed a series of Rh_2(II)-carboxylate-catalyzed syntheses of indoles from vinyl- or aryl azides. They proposed that a benzylic-carbocation-induced 1,2-shift follows a rhodium-nitrene-mediated electrocyclization and systematically studied the migratorial aptitude of beta-substituents in the shift.[6] However, they have not extended the 1,2-shift to synthesize indolines. Our approach towards the synthesis of C-16 substituted akuammiline alkaloid cores was centered on the 1,2-shift mediated by a benzylic carbocation with a spirocyclic cyclopentane at the beta carbon, which was produced by electrophilic addition of the amine radical cation to the tethered tetrasubstituted alkene. At the outset of our study, we had to address three challenges about the shift that have not been addressed before. First, since introduction of the C-16 substituent to the

cyclopentyl ring leads to desymmetrization of the alkene and E/Z isomers, would both isomers proceed to furnish the product with the same stereochemistry? Secondly, how would the C-16 substituent affect the regioselectivity between C-16 and C-16' in the shift? Lastly, what would be the stereoinduction in the 1,2-shift?



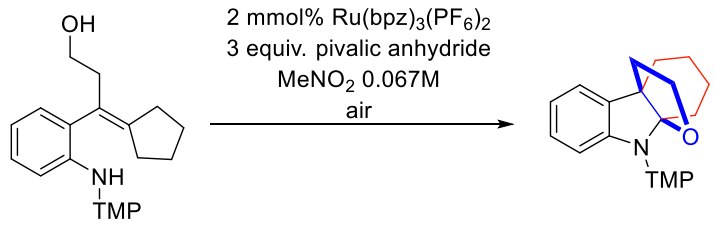
Scheme 5.1 Synthesis of Akuammiline Alkaloid Core Utilizing 1, 2-Shift.

5.2 Reaction Optimization

We commenced the study with unsubstituted substrate **1a** that was devoid of the three discussed challenges. Adapted from the photocatalyst system ($Ru(bpz)_3(PF_6)_2$ with acetic acid) developed for the synthesis of fused *N*-arylindolines, we discovered that pivalic anhydride was markedly better than acetic acid (the screening studies are detailed in SI). We suspected that pivalic anhydride might play two beneficial roles in the reaction. It could absorb water, one of the possible byproducts, which might hydrolyze the iminium ion generated by the 1,2-shift. Furthermore, the concomitant formation of pivalic acid provided the acidity that facilitated the

reaction. Using the modified catalyst system, we were able to obtain the tetracyclic core **2a** in 78% yield as a single isomer.

Table 5.1 Optimization of cyclization



deviation from standard condition	yield[a]
none	73%
3 equiv. pivalic acid	68%
1 equiv. pivalic acid	64%
1 equiv. acetic acid	56%

a: yields are determined by GC analysis with dodecane as internal standard

5.3 Scope of Photocascade Cyclization.

We next applied the revised catalyst system composed of $Ru(bpz)_3(PF_6)_2$ and pivalic anhydride to examine the scope of the substituents on the aryl rings as well as the tethered nucleophile(Figure **1)**. Although the *p*-methoxyphenyl (PMP)-aniline group (e.g., **1a**) was required for the cascade reaction, the methoxy group could be placed on the other aryl ring (e.g., **1b**), and the desired product **2b** was obtained in a comparable yield. The flexibility of placing the methoxy group on either the aryl ring is notable since the akuammiline alkaloid family is often substituted at C4 with this group. We also examined 3,4,5-trimethoxyphenyl (TMP) as an

alternative protecting group for the aniline moiety because it is easier to be deprotected by ceric ammonium nitrate (CAN). Since the product **2c** was furnished in a similar yield, the TMP group became the de facto protecting group. It was also successfully removed in the product **2c** using CAN (see SI). An increase of the tether's length by one carbon somewhat affected the reaction, and the product **2f** was afforded in a modest yield. In addition to the hydroxy group, an amine protected by -Boc or -CO_2Me was shown to be a viable nucleophile, and the products **2d** and **2e** were produced in modest to good yields.[7]

We then shifted our attention to the scope of the substituents on the cyclopentyl ring(Figure **2)**. Substrates bearing an exo alkene (**1g**) or an endo alkene (**1h**) were chosen to study the 1,2-shift initially because it was easier to analyze their 1,2-shift products. Only the regioselectivity issue was expected for **1g** and **1h** while the facial selectivity issue was not applicable. Moreover, the alkene moiety gave another handle for further functionalization of the cyclohexyl ring. Unfortunately, we were able to synthesize only the *Z* isomer of both substrates (**1g**, **1h**), which was converted to the respective product as a single regioisomer (**2g** and **2h**) in modest yields. The shift occurred via exclusive migration of the alkenyl group.

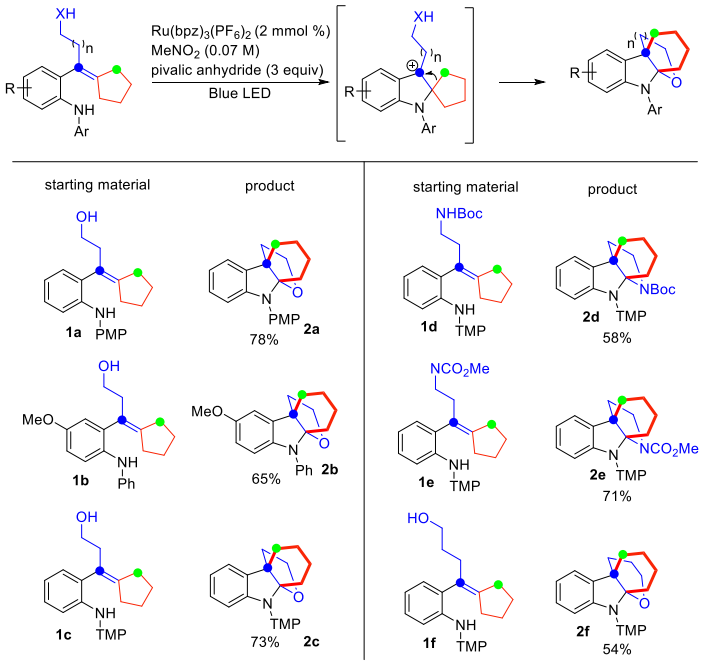


Table 5.2 Scope of Photocascade Cyclization.

We progressed to investigate the last class of the substrates for this study that bears a stereocenter at C-16(Figure **2)**. In addition to the aforementioned three challenges facing these substrates, we were surprised to discover that the substrates contain a chiral axis, the carbon-carbon single bond connecting the aryl group to the alkene moiety. Without the stereocenter at C-16, the axial chirality in the substrates was not distinguished by NMR because they are enantiomers. However, incorporation of the C-16 stereocenter into the substrates led to diastereomers. The existence of the diastereomers was evident by NMR spectra, as there were two sets of distinct peaks for either *E*- or *Z*-olefinic isomer (**1i-j** and **1k-l**). The diastereomeric ratio, which varied from 1.2:1 to 5:1, was affected by the C-16 substituent and, to a lesser extent, the olefinic geometry.

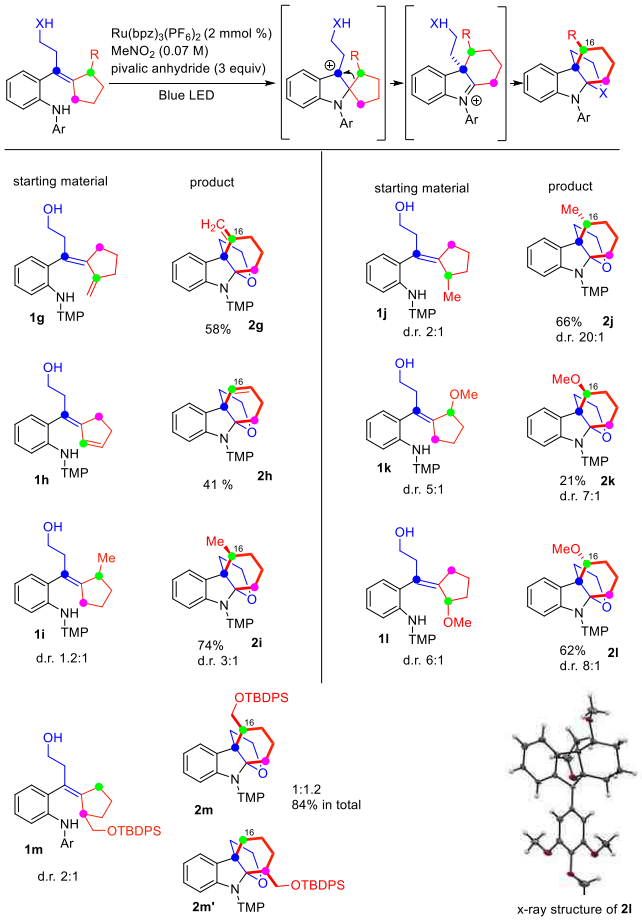


Table 5.3 Scope of Unsymmetrical Photocascade Cyclization.

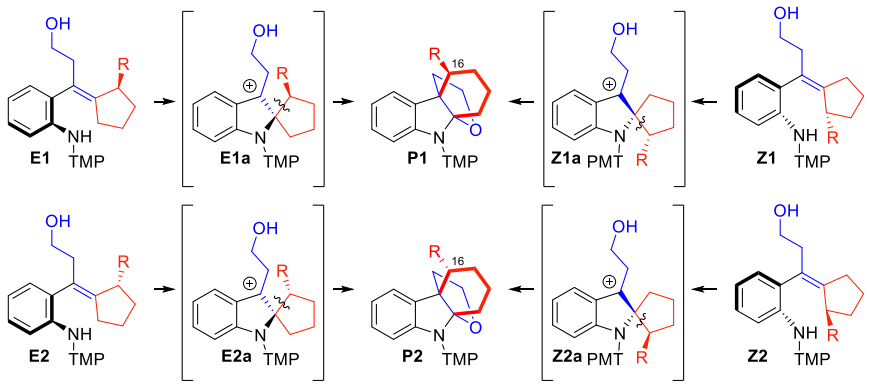
Substrates **1i-l** all underwent the 1,2-shift exclusively on the more substituted carbon to yield a single regioisomer **2i-l**. The exhibited regioselectivity was consistent with the substituents' migratory aptitude in a carbocation-mediated 1,2-shift.[8] However, the diastereoselectivity of the products **2i-l** varied depending on the diastereomeric ratio of the substrates. Furthermore, change of the olefinic geometry of the substrates resulted in a different epimer at C-16 as the major product. *E*-styryl aniline **1i**, which contained a 1.2:1 mixture of two diastereomers, furnished the product **2i** with a slightly improved d.r. (3:1) in a combined yield of 73%. On the other hand, *Z*-styryl aniline **1j** comprising a 2:1 mixture of two diastereomers afforded the product **2j** in a combined yield of 66% with a significantly improved d.r. (20:1) favoring the other diastereomer. This result was exciting as it indicated different major products

could be obtained by alternating the olefinic geometry of precursor. The same correlation between the olefinic geometry of the substrate (**1k** and **1l**) and the C-16 stereochemistry of the major product (**2k** and **2l**) was observed with the methoxy substrates. However, the *E*-isomer (**1k**) gave the product **2k** in a much lower yield (21%) due to significant decomposition. The assignment of **2l**'s stereochemistry was further secured by X-ray analysis of its single crystal in addition to 2D NMR spectra that were used to assign the stereochemistry of all the compounds including **2l**. Lastly, we examined the substrate bearing a CH_2OTBDPS group at C-16 since many members of the akuammiline alkaloid family have a CH_2OH group at C-16. While the *E*-substrate (not shown) gave an unidentified product, the *Z*-substrate (**1m**) (2:1 d.r.) afforded the desired products (**2m** and **2m'**) in a combined yield of 84%. Interestingly, excellent diatereoselectivity yet poor regioselectivity was observed. A 1:1 mixture of two regioisomers was obtained, and each regioisomer contained only one epimer at C-16 (**2m**) or C13 (**2m'**) although the stereochemistry of both products could not be verified by 2D NMR spectra. Non-selective migration of similar examples (CH_2-EWG vs. CH_3) has been reported in a Baeyer Villiger oxidation.[9]

5.4 Mechanistic Study

We proposed a concerted cationic 1,2-shift (the Wagner-Meerwein rearrangement) for the observed stereoselectivity (Scheme **2)**.[10] In this model, the suprafacial 1,2-shift would result in retention of the configuration at the migrating center. Since the substrate has three stereogenic centers (chirality axis, *E*/*Z*, and C-16), there are eight possible modes of stereoconversions that give a total of four stereoisomers including a pair of diastereomers and their corresponding enantiomers. A complete list of the eight modes of stereoconversions is shown in Scheme S10 of

SI. For example, the E1 and E2 substrates, which possess the same axial chirality and the *E* olefinic geometry but differ at the configuration of C-16, are converted to two diastereomeric products that retain the configuration of C-16. The same two products can be also obtained from another pair of substrates (Z1 and Z2) that have opposite axial chirality and the Z olefinic geometry comparing against E1 and E2 respectively. Unfortunately, we had to use a mixture of two inseparable diastereomeric substrates whose relative configuration could not be established. The lack of stereochemical information in the substrates compromised our analysis of the stereoconversions. Nevertheless, our observation that the *E* and *Z* substrates gave a different diastereomer as the major product supported the concerted 1,2-shift rather than a stepwise mechanism in which a discrete carbocation is formed upon completion of the 1,2-shift. The later pathway is detailed in Scheme S11 of SI.



Scheme 5.2 Proposed model for stereoselectivity of 1, 2-shift.

5.5 Experimental Section

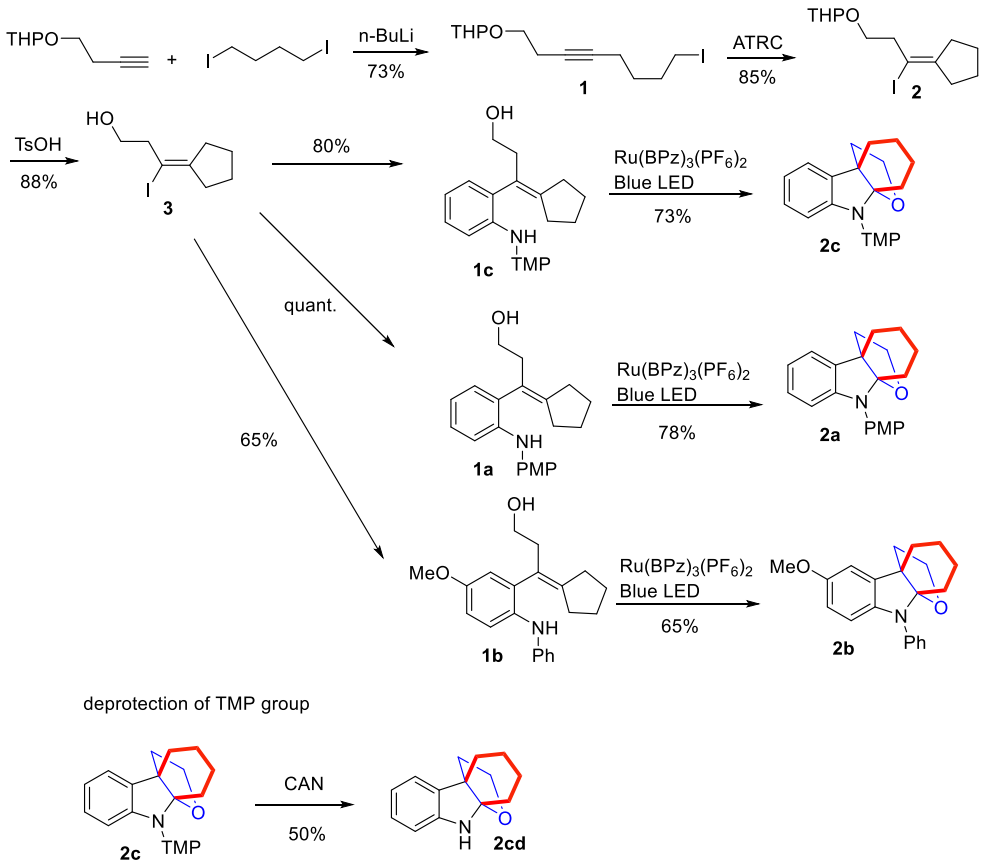
General Procedure for photocatalyzed cyclization:

To a test tube equipped with a stir bar was added 3–cyclopentylidene–3–(2–(3,4,5–trimethoxyphenylamino)phenyl)propan–1–ol **1c** (1 equiv, 0.2 mmol, 76.7 mg), $Ru(bpz)_3(PF_6)_2$ (2

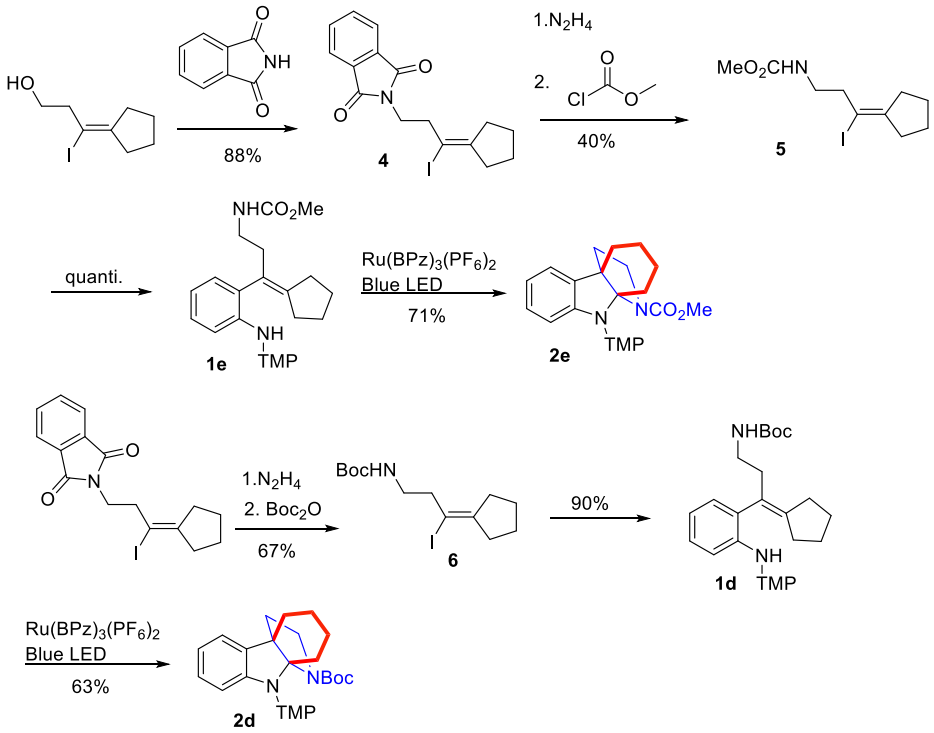
mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube (3 cm away from light source, see set up picture below) was irradiated by a 6W blue LED (463 nm wavelength purchased from http://www.environmentallights.com/15032-blue-cc5050-60x2-kit.html) and stirred (600 r.p.m) for 18 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral alumina gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel.

Reaction setup, photo credit :Qile Wang

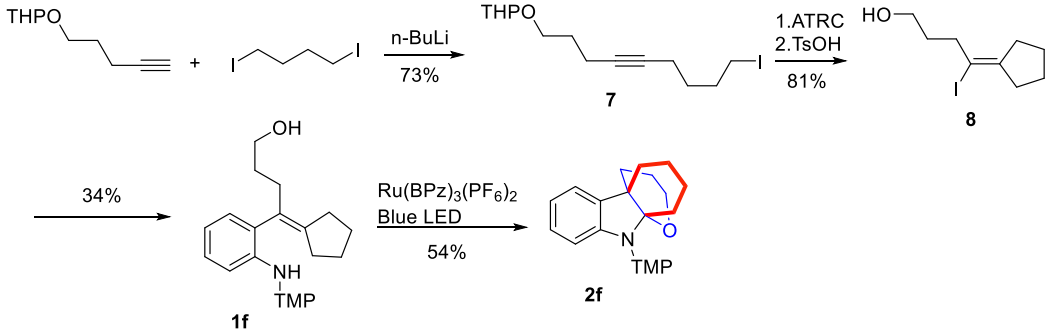
Summary of synthesis routes



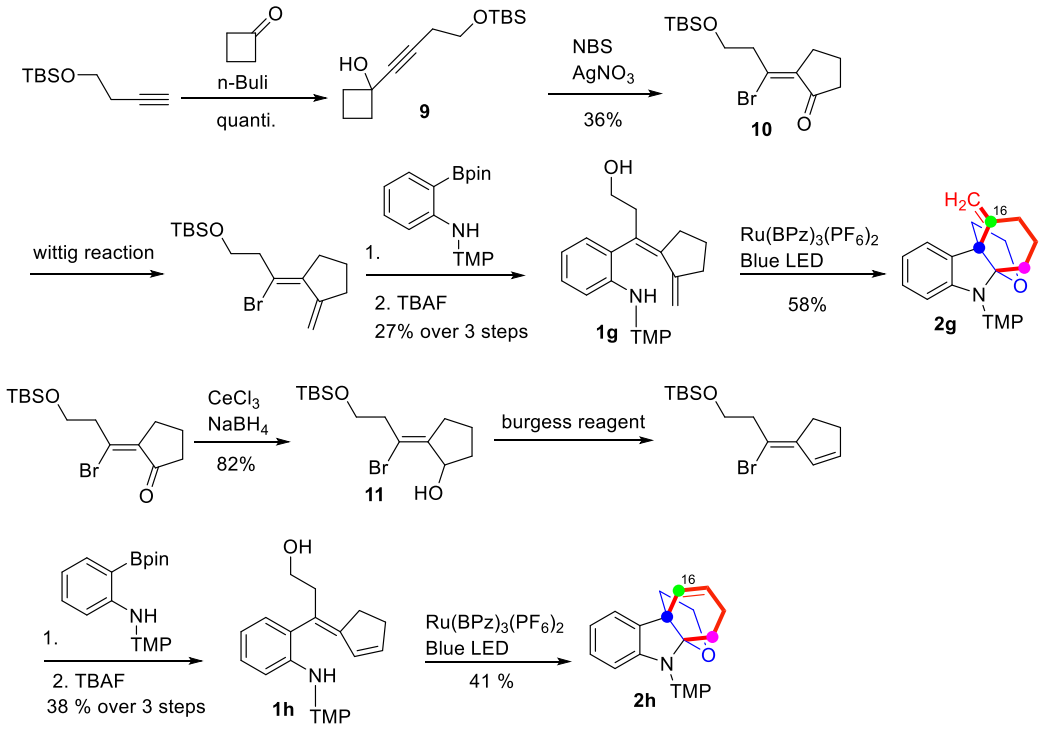
Scheme S2 (Series A)



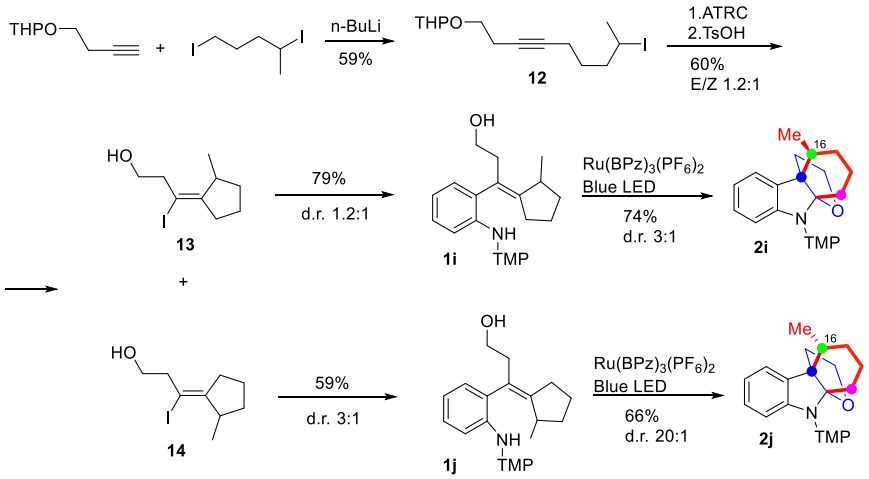
Scheme S3 (Series B)



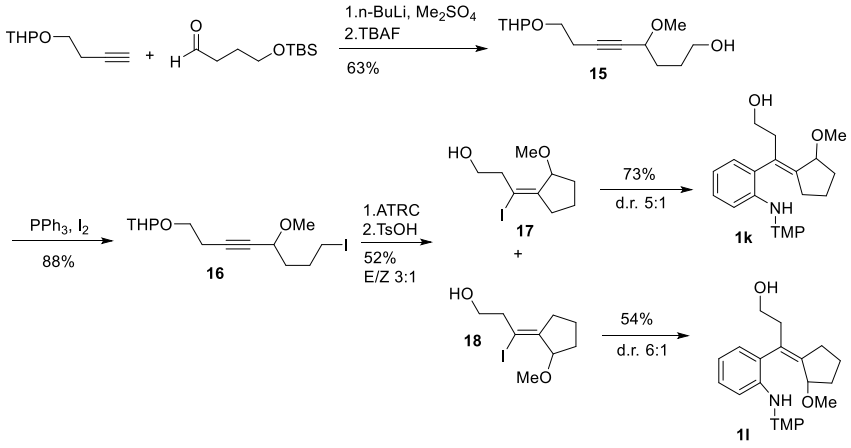
Scheme S4 (Series C)

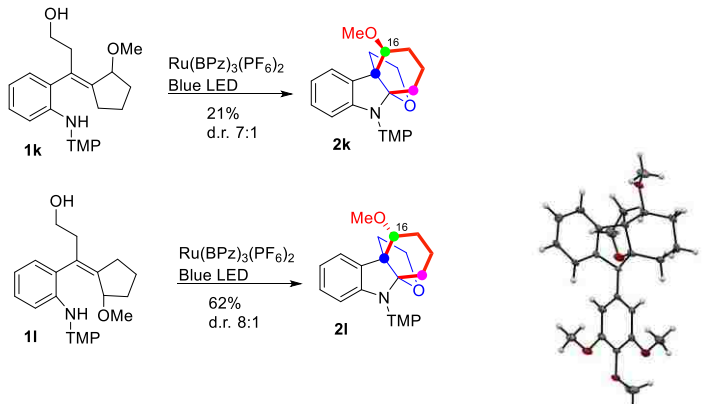


Scheme S5 (Series D)

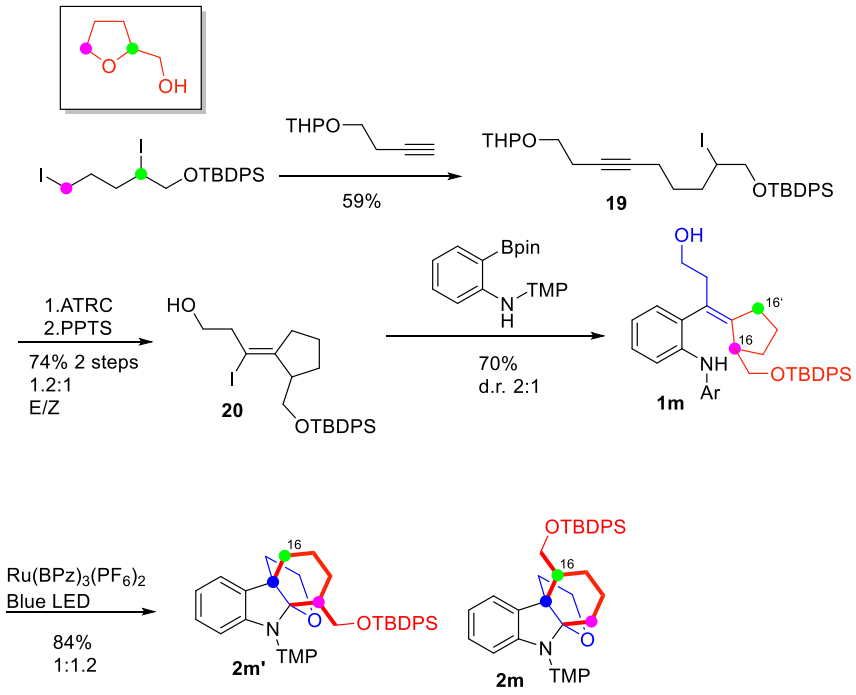


Scheme S6 (Series E)



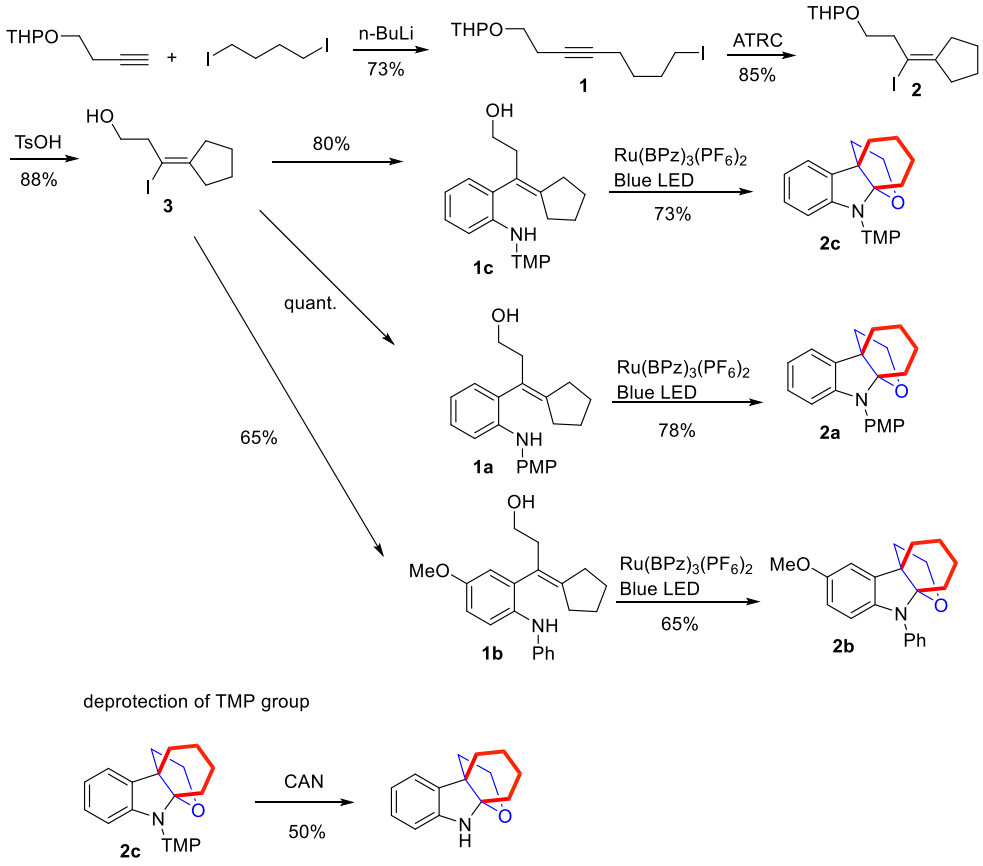


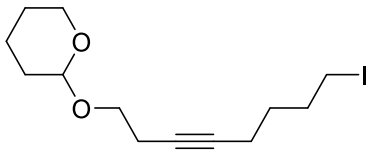
Scheme S7 (Series F)



Scheme S8 (Series G)

Synthesis route of series **A**

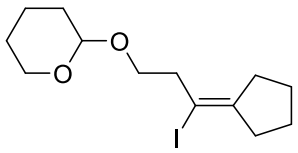




1

Preparation of 2–(8–iodooct–3–ynyloxy)tetrahydro–2*H*–pyran **1** was accomplished using a literature procedure.[1] To an oven–dried heavy wall pressure vessel equipped with a stir bar was added 2–(but–3–ynyloxy)tetrahydro–2*H*–pyran (1 equiv, 13 mmol, 2.0 g) in anhydrous THF (0.25 M, 52 mL). A septum was added and the flask was flushed with nitrogen for 5 minutes. The contents were then cooled to –78 °C and *n*–BuLi (1.6 M in hexanes, 1.1 equiv, 14.3 mmol, 8.9 mL) was then added dropwise over a 10 minute period under N_2 atmosphere. The resulting solution was stirred for 30 minutes at this temperature prior to the

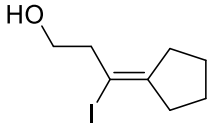
addition of 1,4–diiodobutane (1.5 equiv, 19.5 mmol, 2.6 mL). The mixture was then stirred for 30 minutes at –78 °C prior to warming to room temperature. The septum was then replaced with a screw cap and stirred at 60 °C for 14 hours. Once complete, the contents were cooled to room temperature and poured into 50 mL of saturated aq. NH_4Cl. The resulting mixture was extracted with Et_2O (3 x 40 mL). The combined organic layer was then dried over $MgSO_4$, concentrated in vacuum, and purified by flash chromatography on silica gel (97:3 hexanes:EtOAc) to afford 2–(8–iodooct–3–ynyloxy)tetrahydro–2*H*–pyran **a1** as a clear oil (3.2 g, 73%). IR υ_{max} (cm^{-1}) 2938, 2868, 1452, 1439, 1352, 1285, 1200, 1159, 1121, 1030. ^{1}H NMR (400 MHz, Chloroform–*d*) δ 4.70 – 4.57 (m, 1H), 3.94 – 3.83 (m, 1H), 3.83 – 3.72 (m, 1H), 3.57 – 3.44 (m, 2H), 3.20 (td, *J* = 7.0, 0.6 Hz, 2H), 2.45 (ttd, *J* = 7.2, 2.4, 0.7 Hz, 2H), 2.23 – 2.12 (m, 2H), 1.98 – 1.87 (m, 2H), 1.87 – 1.76 (m, 1H), 1.76 – 1.65 (m, 1H), 1.64 – 1.45 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 98.67, 80.20, 77.56, 66.08, 62.15, 32.35, 30.54, 29.53, 25.40, 20.16, 19.40, 17.68, 6.33; FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{13}H_{22}IO_2$ 338.0386/340.0366; found 338.0384/340.0364.



2

Preparation of 2–(3–cyclopentylidene–3–iodopropoxy)tetrahydro–2*H*–pyran **2** was accomplished using a literature procedure.[2] To a clean, dry test tube equipped with a stir bar was added 2–(8–iodooct–3–ynyloxy)tetrahydro–2*H*–pyran **1** (1 equiv, 0.8 mmol, 269 mg), hexabutylditin (10 mol%, 0.08 mmol, 40 μL), and anhydrous benzene (degassed *via* Freeze–Pump–Thaw; 0.67 M, 1.2 mL). The mixture was then irradiated using a 275W GE sunlamp at a 5 cm distance for 24 hours. Once complete, the solvent was evaporated in vacuum and the crude product was purified by flash chromatography on silica gel (97:3 hexanes:EtOAc) to afford 2–(3–cyclopentylidene–3–iodopropoxy)tetrahydro–2*H*–pyran **2** as a yellow liquid (228

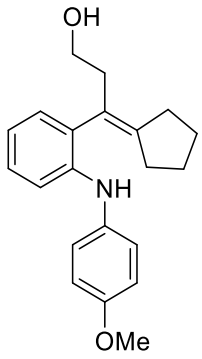
mg, 85%). IR υ_{max} (cm^{-1}) 2938, 2866, 1652, 1452, 1427, 1352, 1200, 1119, 1030, 986 968, 870. ^{1}H NMR (400 MHz, Chloroform–*d*) δ 4.62 (dd, *J* = 4.2, 2.8 Hz, 1H), 3.94 – 3.76 (m, 2H), 3.58 – 3.44 (m, 2H), 2.84 – 2.68 (m, 2H), 2.45 – 2.33 (m, 2H), 2.28 (ddq, *J* = 7.2, 5.9, 1.4 Hz, 2H), 1.89 – 1.74 (m, 3H), 1.74 – 1.63 (m, 3H), 1.62 – 1.49 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.24, 98.66, 90.82, 66.02, 62.11, 42.34, 41.34, 31.82, 30.63, 28.30, 25.81, 25.45, 19.42; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{13}H_{22}IO_2$ found 338/340.



3

Preparation of 3–cyclopentylidene–3–iodopropan–1–ol **3** was accomplished using a literature procedure.[3] To a clean, dry 25–mL round bottom flask was added 2–(3–cyclopentylidene–3–iodopropoxy)tetrahydro–2*H*–pyran **2** (1 equiv, 2.23 mmol, 752 mg) and *para*–toluenesulfonic acid monohydrate (PTSA•H_2O; 10 mol%, 0.224 mmol, 42.5 mg) in anhydrous MeOH (0.34 M, 6.6 mL). The contents were then stirred for 4 hours at room temperature. Upon completion, the solution was transferred to a separatory funnel and diluted with DCM (13 mL). The resulting mixture was washed with saturated aq. $NaHCO_3$ (3 x 5 mL). The aqueous layer was then extracted with DCM (3 x 5 mL). The organic layers were then combined and dried over $MgSO_4$. Subsequent concentration in vacuum and purification by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford 3–cyclopentylidene–3–iodopropan–1–ol **3** as a clear oil (495 mg, 88%). IR υ_{max} (cm^{-1}) 3308, 2947, 2864, 1647, 1423, 1304, 1233, 1188, 1036, 953, 860. ^{1}H NMR (300 MHz, Chloroform–*d*) δ 3.77 (dt, *J* = 8.8, 6.1 Hz, 2H), 2.71 (dd, *J* = 7.1, 5.1 Hz, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 2.31 (td, *J* = 7.5, 7.0, 1.9 Hz, 2H), 1.84 (p, *J* = 6.8 Hz, 2H), 1.71 (dd, *J* = 7.5, 5.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.49,

91.01, 61.54, 44.48, 41.47, 32.13, 28.24, 25.68; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_8H_{14}IO$ found 254/256.

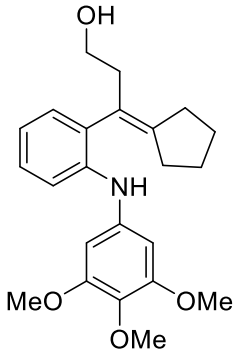


1a

Preparation of 3–cyclopentylidene–3–(2–(4–methoxyphenylamino)phenyl)propan–1–ol **a5** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added *N*–(4–methoxyphenyl)–2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)aniline (1.5 equiv, 3 mmol, 976 mg), $Pd(OAc)_2$ (2 mol%, 0.04 mmol, 9 mg), RuPhos (4 mol%, 0.08 mmol, 37 mg), K_3PO_4 (3 equiv, 6 mmol, 1.3 g) , 3–Cyclopentylidene–3–iodopropan–1–ol **3** (1 equiv, 2 mmol, 504.2 mg) and THF:EtOH:H_2O (2:1:1 0.2M in total), the reaction mixture was sonicated until all the K_3PO_4 are dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over $MgSO_4$ and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford 3–cyclopentylidene–3–(2–(4–methoxyphenylamino)phenyl)propan–1–ol **1a** as a brown oil (646 mg, quanti.) IR υ_{max} (cm^{-1}) 3343, 2949, 2866, 1597, 1574, 1508, 1449, 1292, 1233, 1179, 1034, 816, 746. ^{1}H NMR (400 MHz, Chloroform–*d*) δ 7.13 – 7.06 (m, 3H), 7.03 (ddt, *J* = 8.2, 1.1, 0.6 Hz, 1H), 6.98 (ddq, *J* = 7.5, 1.6, 0.5 Hz, 1H), 6.91 – 6.85 (m, 2H),

6.85 – 6.76 (m, 1H), 3.81 (dd, *J* = 1.3, 0.8 Hz, 3H), 3.70 (dt, *J* = 10.9, 5.6 Hz, 1H), 3.59 (ddd, *J* = 10.4, 8.0, 5.2 Hz, 1H), 2.81 – 2.65 (m, 1H), 2.49 (td, *J* = 14.8, 12.0, 5.7 Hz, 3H), 2.13 – 2.01 (m, 2H), 1.81 – 1.70 (m, 2H), 1.68 – 1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.51, 145.85, 142.72, 136.08, 130.56, 129.22, 127.46, 124.98, 123.12, 119.39, 114.79, 113.92, 60.96, 55.72, 38.40, 32.15, 30.71, 26.79, 26.77; ^{13}C NMR DEPT 135(75 MHz, Chloroform-*d*) δ 129.22 , 127.46 , 123.12 , 119.38 , 114.78 , 113.91 , 60.96 , 55.73 , 38.41 , 32.15 , 30.71 , 26.80 , 26.77 .

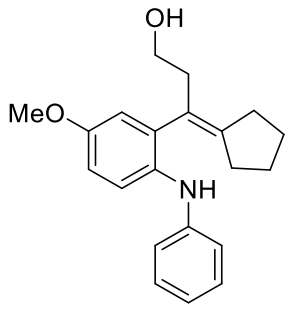
FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{21}H_{26}NO_2$ 324.1958; found 324.1953.



1c

Preparation of 3–cyclopentylidene–3–(2–(4–methoxyphenylamino)phenyl)propan–1–ol **a4** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 1.7 mmol, 656 mg), $Pd(OAc)_2$ (2 mol%, 0.023 mmol, 5.1 mg), RuPhos (4 mol%, 0.046 mmol, 21.1 mg), K_3PO_4 (3 equiv, 3.39 mmol, 720 mg) , 3–Cyclopentylidene–3–iodopropan–1–ol **3** (1 equiv, 1.1 mmol, 277 mg) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 are dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was

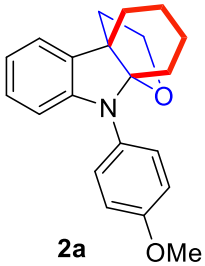
cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over $MgSO_4$ and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (65:35 hexanes:EtOAc) to afford 3–cyclopentylidene–3–(2–(3,4,5–trimethoxyphenylamino)phenyl)propan–1–ol **1c** as a brown solid, m.p. 115–119 °C (346 mg, 80%). IR υ_{max} (cm^{-1}) 3335, 2938, 1593, 1504, 1474, 1447, 1402, 1288, 1229, 1123, 1038, 1005, 748. ^{1}H NMR (400 MHz, Chloroform–*d*) δ 7.28 – 7.24 (m, 1H), 7.15 (ddd, *J* = 8.1, 7.2, 1.7 Hz, 1H), 7.06 – 6.96 (m, 1H), 6.87 (td, *J* = 7.4, 1.2 Hz, 1H), 6.33 (s, 2H), 6.03 (s, 1H), 3.82 (d, *J* = 0.6 Hz, 9H), 3.73 – 3.52 (m, 2H), 2.71 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.49 (dq, *J* = 13.2, 6.7, 6.2 Hz, 3H), 2.05 (ddt, *J* = 8.5, 7.2, 1.4 Hz, 2H), 1.81 – 1.69 (m, 2H), 1.66 – 1.55 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.65, 145.74, 141.07, 139.35, 132.67, 131.47, 129.28, 127.15, 124.51, 120.00, 115.34, 96.72, 60.92, 60.61, 55.97, 38.03, 31.88, 30.48, 26.51, 26.47; ^{13}C NMR DEPT 135 (101 MHz, Chloroform-*d*) δ 129.28 , 127.14 , 120.00 , 115.33 , 96.69 , 60.92 , 60.60 , 55.96 , 38.02 , 31.87 , 30.48 , 26.51 , 26.47 ; FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{23}H_{30}NO_4$ 384.2169; found 384.2172.



1b

Preparation of 3–cyclopentylidene–3–(2–(4–methoxyphenylamino)phenyl)propan–1–ol **1b** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added corresponding aniline (1.5 equiv, 3 mmol, 976 mg), $Pd(OAc)_2$ (2 mol%, 0.04 mmol, 9 mg), RuPhos (4 mol%,

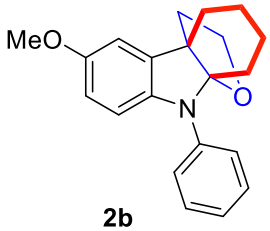
0.08 mmol, 37 mg), K_3PO_4 (3 equiv, 6 mmol, 1.3 g) , 3–Cyclopentylidene–3–iodopropan–1–ol **3** (1 equiv, 2 mmol, 504.2 mg) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 are dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over $MgSO_4$ and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford **1b** as pale green oil (420 mg, 65%). IR υ_{max} (cm^{-1}) 2952, 1598, 1507, 1495, 1205, 1035, 743, 692. 1H NMR (400 MHz, Chloroform-d) δ 7.31 – 7.18 (m, 3H), 7.01 – 6.95 (m, 2H), 6.89 – 6.81 (m, 1H), 6.77 (dd, J = 8.8, 3.0 Hz, 1H), 6.64 (d, J = 3.0 Hz, 1H), 5.86 (s, 1H), 3.81 (s, 3H), 3.70 – 3.62 (m, 1H), 3.55 (s, 1H), 2.68 (q, J = 8.7, 6.5 Hz, 1H), 2.45 (q, J = 8.4, 5.4 Hz, 3H), 2.03 (q, J = 7.6 Hz, 2H), 1.79 – 1.54 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.41, 145.50, 144.73, 134.96, 133.79, 129.27, 124.89, 119.85, 119.78, 116.58, 114.88, 112.43, 60.68, 55.55, 38.03, 32.07, 30.53, 26.56, 26.54. ^{13}C NMR DEPT 135 (101 MHz, $CDCl_3$) δ 129.27, 119.85, 119.78, 116.58, 114.87, 112.42, 60.68, 55.55, 38.03, 32.07, 30.53, 26.56, 26.54. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{23}H_{30}NO_4$ 324.1958; found 324.1961.



2a

Preparation of fused **2a** was accomplished using following procedure. To a test tube equipped with a stir bar was added 3–cyclopentylidene–3–(2–(4–methoxyphenylamino)phenyl)propan–1–ol **1a** (1 equiv, 0.2 mmol, 64.9 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), acetic anhydride (3 equiv, 0.6 mmol, 62mg) and CH_3NO_2 (0.067 M,

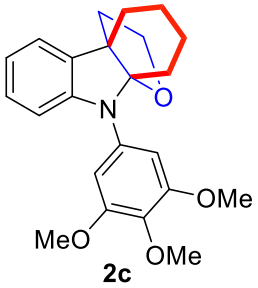
3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 18 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (95:5 hexanes:EtOAc) to afford the pure fused *N*–arylindoline **2a** as a white solid, m.p. 105–108 °C (50 mg, 78%). IR υ_{max} (cm^{-1}) 2940, 2860, 1593, 1506. 1481, 1454, 1443, 1373, 1288, 1236, 1167, 1030, 833, 808, 746, 757. ^{1}H NMR (400 MHz, Methylene Chloride–d_2) δ 7.36 – 7.31 (m, 2H), 7.11 (ddd, *J* = 7.3, 1.3, 0.6 Hz, 1H), 6.99 (ddd, *J* = 7.9, 7.4, 1.3 Hz, 1H), 6.95 – 6.90 (m, 2H), 6.71 (td, *J* = 7.4, 1.0 Hz, 1H), 6.42 (ddd, *J* = 7.9, 1.0, 0.5 Hz, 1H), 3.94 (ddd, *J* = 8.4, 6.1, 3.6 Hz, 1H), 3.82 (s, 3H), 3.66 – 3.55 (m, 1H), 2.27 – 2.16 (m, 2H), 1.98 – 1.87 (m, 2H), 1.86 – 1.75 (m, 1H), 1.61 – 1.43 (m, 3H), 1.37 – 1.22 (m, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 157.90, 149.89, 134.99, 133.59, 128.38, 128.11, 123.26, 118.63, 114.76, 107.06, 105.47, 65.97, 55.92, 54.40, 39.53, 33.40, 29.15, 19.49, 19.16; ^{13}C NMR (101 MHz, CD_2Cl2) δ 127.82, 127.54, 122.70, 118.07, 114.19, 106.50, 65.40, 55.35, 38.96, 32.83, 28.59, 18.93, 18.59. GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{21}H_{24}NO_2$ found 322. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{21}H_{24}NO_2$ 322.1802; found 322.1806.



2b

Preparation of fused **2b** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1b** (1 equiv, 0.2 mmol, 64.9 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for

18 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (95:5 hexanes:EtOAc) to afford the pure fused *N*–arylindoline **2b** as colorless oil(41 mg, 65%). IR υ_{max} (cm^{-1}) 2943, 2867, 1595, 1498, 1490, 1369, 1268, 1026. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.47 (m, 2H), 7.43 – 7.34 (m, 2H), 7.21 – 7.11 (m, 1H), 6.79 (dd, *J* = 2.0, 1.1 Hz, 1H), 6.67 – 6.60 (m, 2H), 4.02 (ddd, *J* = 8.6, 6.7, 3.0 Hz, 1H), 3.80 (s, 3H), 3.71 (ddd, *J* = 9.6, 8.5, 6.7 Hz, 1H), 2.29 – 2.17 (m, 2H), 2.08 (dt, *J* = 14.0, 4.6 Hz, 1H), 1.93 (dd, *J* = 6.9, 4.8 Hz, 2H), 1.72 – 1.60 (m, 1H), 1.58 – 1.44 (m, 2H), 1.43 – 1.26 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.26, 142.44, 140.99, 135.91, 128.98, 124.94, 124.25, 111.85, 110.25, 107.35, 105.43, 65.51, 55.98, 54.39, 39.36, 32.76, 28.51, 18.66, 18.49. ^{13}C NMR DEPT 135 (101 MHz, $CDCl_3$) δ 128.98, 124.93, 124.25, 111.85, 110.25, 107.35, 65.51, 55.98, 39.35, 32.76, 28.51, 18.66, 18.49. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{21}H_{24}NO_2$ 322.1802; found 322.1803.



2c

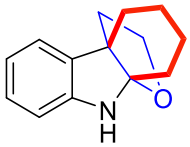
Preparation of fused *N*–arylindoline **2c** was accomplished using following procedure. To a test tube equipped with a stir bar was added 3–cyclopentylidene–3–(2–(3,4,5–trimethoxyphenylamino)phenyl)propan–1–ol **1c** (1 equiv, 0.2 mmol, 76.7 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 18 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral alumina gel. The filtrate was then concentrated in vacuum and purified by flash chromatography

on silica gel (85:15 hexanes:EtOAc) to afford the pure fused *N*–arylindoline **2c** as a yellow oil (55.6 mg, 73%).

1 mmol scale synthesis : To a round bottle flask equipped with a stir bar was added 3–cyclopentylidene–3–(2–(3,4,5–trimethoxyphenylamino)phenyl)propan–1–ol **1c** (1 equiv, 1 mmol, 383 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.02 mmol, 18 mg), pivalic anhydride (3 equiv, 3 mmol, 580 mg) and CH_3NO_2 (0.067 M, 15 mL). The flask was then sealed with a rubber septum containing and pierced with a 16–gauge needle. The falsk was irradiated by a 6W blue LED and stirred for 36 hours. The reaction mixture was then washed with saturated Na_2CO_3 solution and extracted with diethyl ether and then concentrated in vacuum and purified by flash chromatography on silica gel (85:15 hexanes:EtOAc) to afford the pure fused *N*–arylindoline **2c** as a yellow oil (175 mg, 46%).

IR υ_{max} (cm^{-1}) 2934, 2864, 1582, 1504, 1460, 1287, 1229, 1123, 1018, 741, 712, 656, 501. ^1H NMR (400 MHz, Benzene–d_6) δ 7.09 (ddt, *J* = 8.8, 6.2, 1.3 Hz, 1H), 7.00 (ddd, *J* = 7.4, 1.7, 0.9 Hz, 1H), 6.97 – 6.92 (m, 2H), 6.89 – 6.77 (m, 2H), 3.88 (tt, *J* = 3.1, 1.2 Hz, 3H), 3.81 – 3.74 (m, 1H), 3.64 – 3.53 (m, 1H), 3.42 (t, *J* = 0.9 Hz, 6H), 2.28 – 2.17 (m, 1H), 1.99 – 1.80 (m, 2H), 1.79 – 1.58 (m, 3H), 1.37 – 1.23 (m, 4H); ^{13}C NMR (101 MHz, C_6D_6) δ 154.90, 149.52, 137.44, 136.90, 135.01, 128.77, 123.56, 119.39, 108.04, 105.78, 104.27, 65.94, 60.96, 56.19, 54.71, 39.85, 33.37, 29.24, 19.50, 19.00; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{23}H_{28}NO_4$ found 382. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{23}H_{28}NO_4$ 382.2013; found 382.2016.

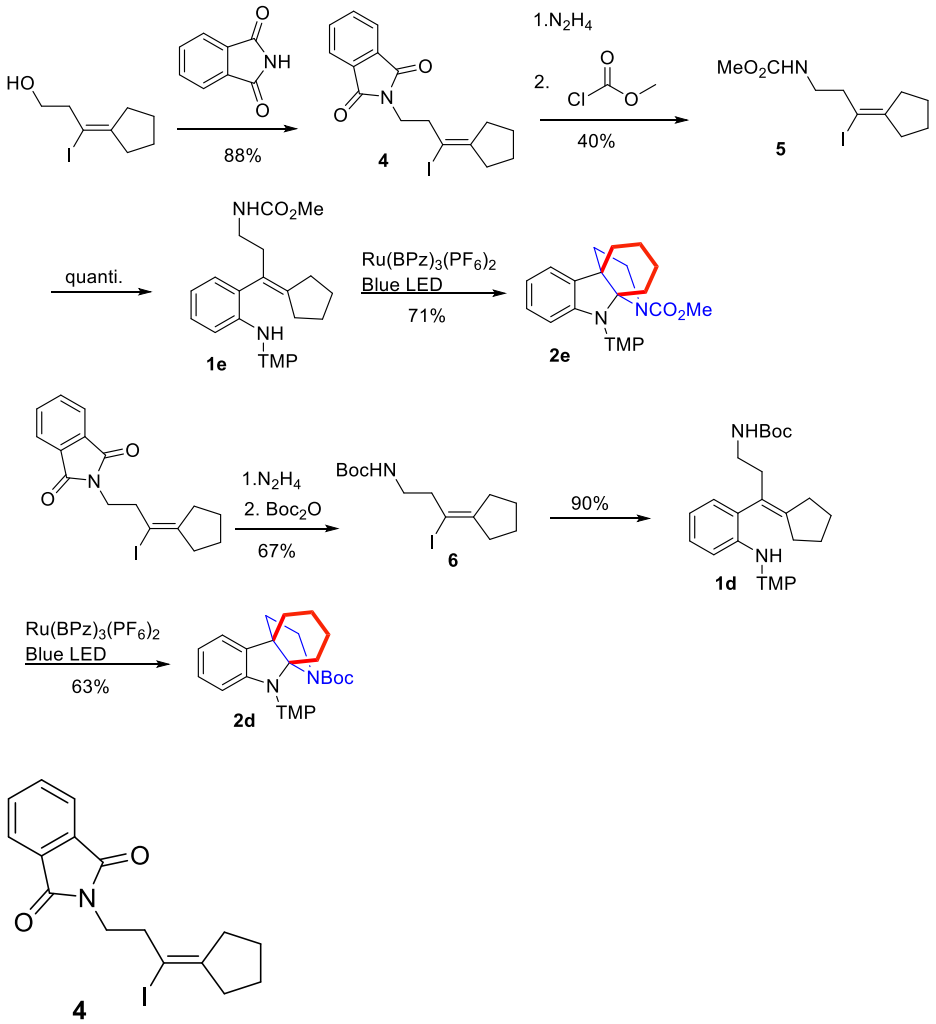
Oxidative Cleavage of 3,4,5–trimethoxyphenyl Group using Ceric Ammonium Nitrate



2cd

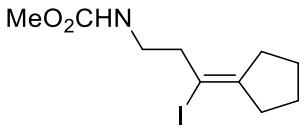
Formation of (9CI)–1,2,3,4–tetrahydro–9a,4a–(epoxyethano)–*H*–carbazole **2cd** was achieved using a literature procedure.[4] To a flask equipped with a stir bar was added fused *N*–arylindoline **2c** (1 equiv, 0.1 mmol, 38 mg) and a mixture of MeCN/H_2O (2.7:1, 0.12 M, 0.82 mL total). The mixture was cooled to 0 °C and H_2SO_4 (2.02 equiv, 0.202 mmol, 10.6 μL) was added along with immediate addition of ceric ammonium nitrate (2.15 equiv, 0.215 mmol, 118 mg) in one portion. The mixture was stirred at 0 °C for 10 minutes prior to dilution with H_2O (3 mL). The solution was separated and the aqueous layer was washed with diethyl ether (3 x 10 mL). The organic layer was saved and stored for a later time in the workup. The combined aqueous layer was quickly basified to pH 14 using 5 M KOH. The resulting solution was extracted with diethyl ether (3 x 25 mL) and combined. The saved organic layer from the initial wash was then extracted with 0.1 M HCl (3 x 15 mL). The combined aqueous phase was quickly basified to pH 14 using 5 M KOH. The resulting solution was extracted with diethyl ether (3 x 25 mL) and added to the previous organic extract from the basified extract. The organic layer was then dried of $MgSO_4$, concentrated in vacuum, and purified by flash chromatography on silica gel (85:15 hexanes:EtOAc) to afford (9CI)–1,2,3,4–tetrahydro–9a,4a–(epoxyethano)–*H*–carbazole **2cd** as a white solid, m.p. 82–85 °C (10 mg, 45%). This compound was documented by Zu et al.[5] IR υ_{max} (cm^{-1}) 3285, 2922, 2857, 1611, 1466, 1258, 1200, 1063, 1016, 976, 858, 743, 588. ^{1}H NMR (400 MHz, Benzene–d_6) δ 7.06 (td, *J* = 7.6, 1.3 Hz, 1H), 6.91 (ddd, *J* = 7.3, 1.4, 0.6 Hz, 1H), 6.80 (td, *J* = 7.4, 1.0 Hz, 1H), 6.42 (ddd, *J* = 7.8, 1.1, 0.6 Hz, 1H), 3.73 (ddt, *J* = 6.9, 5.1, 3.4 Hz, 2H), 3.57 (ddd, *J* = 9.1, 8.2, 7.0 Hz, 1H), 1.89 – 1.82 (m, 2H), 1.78 (dt, *J* = 13.8, 4.8 Hz, 1H), 1.70 – 1.61 (m, 2H), 1.50 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.46 – 1.39 (m, 1H), 1.38 – 1.23 (m, 2H), 1.20 – 1.13 (m, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{14}H_{18}NO$ found 216.

Synthesis route of series **B**



4 is prepared following the known procedure from **3**. In a test tube 3a(4mmol), THF(6.3ml), Ph_3P(1.1 equiv.), phthalimide (1.1 equiv.) was added and cool to 0^{o}C. DIAD(1.1 equiv.) was added. The reaction is stirred at RT until all the 3a is gone. And the crude was filtered and concentrated and purified by flash chromatography on silica gel (5:1 hexanes:EtOAc) to afford **4** as white solid, m.p. 106–107 °C (1.219g, 80%) IR υ_{max} (cm^{-1}) 2950, 2873, 1766, 1698, 1396, 1105, 996, 870, 781, 720, 713. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.92 – 3.83 (m, 2H), 2.93 – 2.86 (m, 2H), 2.37 – 2.23 (m, 4H), 1.80 – 1.71 (m, 2H), 1.70 – 1.59 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.15, 152.30,

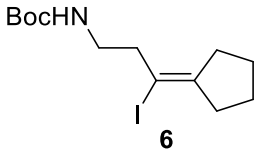
133.94, 132.08, 123.23, 89.45, 41.28, 40.69, 37.25, 31.67, 28.27, 25.67. ^{13}C NMR DEPT 135 (101 MHz, $CDCl_3$) δ 133.94, 123.23, 41.28, 40.70, 37.25, 31.68, 28.28, 25.68. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{16}H_{17}INO_2$ 382.0298; found 382.0303.



5

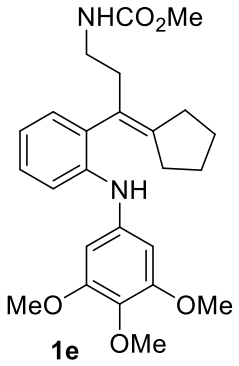
5 is prepared following the known procedure from **4**. To an oven–dried flask equipped with a stir bar were added **b1** (1 equiv, 3.4 mmol, 1.3g) and EtOH (60 mL). Hydrazine hydrate (1.4 equiv, 4.8 mmol, 0.15 mL) was then added and the reaction was refluxed for 24 hours. Once complete, the solution was cooled to room temperature and the mixture was filtered. The remaining white solid was washed with EtOH (3 x 10 mL) and concentrated HCl (10 equiv, 30 mmol, 3 mL) was added to the filtrate. The acidic solution was then stirred and heated at 60 °C for 30 minutes. The resulting solution was concentrated in vacuum, cooled to 0 °C, diluted with H_2O (15 mL), and basified to pH 13 using 10 M NaOH. The aqueous solution was then extracted with DCM (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give the intermediate free amine as a brown oil, which was taken to the next step without purification. The resulting free amine (1 equiv, 3.4 mmol), Et_3N(2.5 equiv., 8.5 mmol, 1.2mL) DMAP (2 mol %, 0.068 mmol, 8.0 mg) and anhydrous DCM (15 mL) was added to an oven-dried flask equipped with a stir bar. The resulting solution was stirred at 0 °C prior to the dropwise addition of acetyl chloride (1.1 equiv, 3.74 mmol, 0.29 mL). The mixture was then warmed to room temperature and stirred for 15 hours. Once complete, the solution was concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford acetyl-

protected **5** as pale yellow solid, m.p. 40–43 °C (410 mg, 40% over 2 steps). IR υ_{max} (cm^{-1}) 3349, 2952, 1696, 1536, 1295, 1194, 1013, 789, 630. ^{1}H NMR (400 MHz, Chloroform-d) δ 4.81 (s, 1H), 3.68 (s, 3H), 3.47 – 3.20 (m, 2H), 2.67 (t, J = 6.5 Hz, 2H), 2.40 – 2.25 (m, 4H), 1.93 – 1.79 (m, 2H), 1.71 (q, J = 6.9 Hz, 2H).; ^{13}C NMR (101 MHz, C6D6) δ 156.49, 151.35, 91.90, 51.32, 41.74, 41.16, 40.30, 31.52, 28.03, 25.44.; ^{13}C NMR DEPT 135(101 MHz, C_6D6) δ 127.97, 51.32, 41.74, 41.16, 40.30, 31.52, 28.03, 25.44. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{10}H_{17}INO_2$ 310.0298; found 310.0304.



6

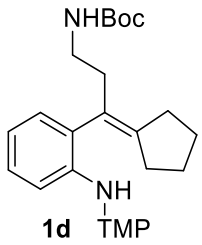
6 is prepared using the same crude free amine intermediate as **5**. The resulting free amine (1 equiv, 2.4 mmol), DMAP (10 mol %, 0.24 mmol, 29.3 mg) and anhydrous DCM (2.7 mL) was added to an oven-dried flask equipped with a stir bar. The resulting solution was stirred at 0 °C prior to the dropwise addition of Boc_2O (1.1 equiv, 2.64 mmol, 2.3 mL) in DCM(2.3 mL). The mixture was then warmed to room temperature and stirred for 15 hours. Once complete, the solution was concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford Boc-protected **b5** as pale yellow solid, m.p. 58–60 °C (700 mg, 67% over 2 steps). IR υ_{max} (cm^{-1}) 3316, 2940, 1680, 1530, 1363, 1289, 1253, 1164, 1139, 964, 796. ^{1}H NMR (400 MHz, Benzene-d_6) δ 4.26 (s, 1H), 3.17 (q, *J* = 6.5 Hz, 2H), 2.51 – 2.39 (m, 2H), 2.16 (t, *J* = 7.3 Hz, 2H), 2.07 (t, *J* = 7.3 Hz, 2H), 1.52 – 1.38 (m, 12H), 1.35 – 1.26 (m, 2H).; ^{13}C NMR (101 MHz, C_6D6) δ 155.39, 151.19, 92.39, 78.20, 41.78, 41.12, 39.82, 31.54, 28.15, 28.06, 25.46.; ^{13}C NMR DEPT 135(101 MHz, C_6D6) δ 127.97, 41.78, 41.12, 39.81, 31.54, 28.15, 28.06, 25.46.



1e

Preparation of **1e** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 1.5 mmol, 579 mg), $Pd(OAc)_2$ (2 mol%, 0.02 mmol, 4.5 mg), RuPhos (4 mol%, 0.04 mmol, 18.6 mg), K_3PO_4 (3 equiv, 3 mmol, 636 mg) , **5** (1 equiv, 1 mmol, 309 mg) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over Na_2SO_4 and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford **1e** as pale yellow oil (440 mg, quanti). IR υ_{max} (cm^{-1}) 3360, 2936, 1708, 1593, 1477, 1252, 1127, 1006, 757. ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.46 (d, *J* = 8.1 Hz, 1H), 7.11 (ddd, *J* = 8.4, 7.3, 1.6 Hz, 1H), 7.00 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.86 (td, *J* = 7.4, 1.2 Hz, 1H), 6.54 (s, 2H), 6.24 (s, 1H), 4.51 (s, 1H), 3.84 (s, 3H), 3.41 (s, 6H), 3.38 (s, 3H), 3.16 (s, 1H), 3.09 – 2.97 (m, 1H), 2.59 – 2.33 (m, 2H), 2.33 – 2.03 (m, 4H), 1.53 – 1.34 (m, 4H).; ^{13}C NMR (101 MHz, C_6D_6) δ 156.87, 154.50, 145.28, 141.41, 139.39, 134.25, 131.59, 129.66, 127.43, 125.68, 120.06, 116.13, 97.76, 60.35, 55.47, 51.34, 39.75, 35.78, 32.01, 30.38, 29.75, 26.46, 26.43.; ^{13}C NMR DEPT135(101 MHz, C_6D_6) δ 129.66, 127.97, 127.45, 120.06, 116.13,

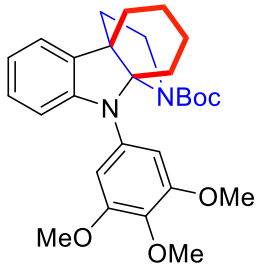
97.74, 60.35, 55.46, 51.34, 39.75, 35.79, 32.01, 30.38, 26.47, 26.43. FTMS (ESI) *m*/*z* $[M+Na]^+$, calc'd for $C_{25}H_{32}N_2NaO_5$ 463.2203; found 463.2209.



1d

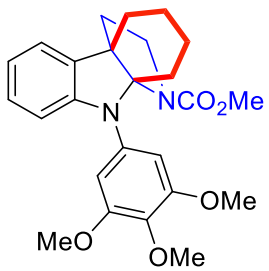
Preparation of **1d** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 2.7 mmol, 1.042 g), $Pd(OAc)_2$ (2 mol%, 0.036 mmol, 8.1 mg), RuPhos (4 mol%, 0.072 mmol, 33.6 mg), K_3PO_4 (3 equiv, 5.4 mmol, 1.1448 g) , **6** (1 equiv, 1.8 mmol, 631 mg) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over Na_2SO_4 and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford **1d** as white solid, m.p. 51–54 °C (780 mg, 90%). IR υ_{max} (cm^{-1}) 3314, 2936, 1700, 1593, 1503, 1475, 1230, 1167, 1123, 1006, 753. ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.50 (d, *J* = 8.2 Hz, 1H), 7.11 (ddd, *J* = 8.4, 7.3, 1.6 Hz, 1H), 7.02 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.86 (td, *J* = 7.4, 1.2 Hz, 1H), 6.58 (s, 3H), 4.36 – 4.16 (m, 1H), 3.85 (s, 3H), 3.43 (s, 6H), 3.26 – 3.10 (m, 1H), 2.97 – 2.76 (m, 1H), 2.48 – 2.06 (m, 6H), 1.53 (qt, *J* = 6.7, 3.4 Hz, 2H), 1.38 (s, 11H).; ^{13}C NMR (101 MHz, C_6D6) δ 155.85, 154.49, 144.85, 141.67, 139.69, 134.10, 131.83, 129.75, 127.35, 125.88, 119.98, 116.36, 97.63, 97.59, 78.26, 60.34, 55.52, 39.25, 36.46, 32.07, 30.44, 29.74, 28.14, 26.51, 26.48.; ^{13}C NMR DEPT

135(101 MHz, C_6D6) δ 129.75, 127.97, 127.35, 119.98, 116.37, 97.60, 60.34, 55.52, 39.25, 36.47, 32.08, 30.45, 28.14, 26.51, 26.48.



2d

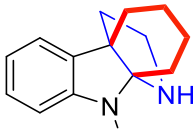
Preparation of fused *N*–arylindoline **2d** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1d** (1 equiv, 0.2 mmol, 96.4 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 18 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (85:15 hexanes:EtOAc) to afford the pure **2d** as a yellow oil (60 mg, 63%). IR υ_{max} (cm^{-1}) 2934, 1686, 1591, 1503, 1460, 1364, 1225, 1163, 1126. ^1H NMR (400 MHz, Benzene-d_6) δ 7.22 – 6.33 (m, 6H), 3.90 (s, 4H), 3.62 – 3.21 (m, 7H), 2.77 – 2.08 (m, 2H), 1.81 (d, J = 37.7 Hz, 2H), 1.47 – 1.18 (m, 14H). FTMS (ESI) m/z $[M+H]^+$, calc'd for $C_{28}H_{37}N_2O_5$ 481.2697; found 481.2693.



2e

Preparation of fused *N*–arylindoline **2e** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1e** (1 equiv, 0.2 mmol, 88 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 18 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (85:15 hexanes:EtOAc) to afford the pure **2e** as a yellow oil (62 mg, 71%). IR υ_{max} (cm^{-1}) 2936, 1700, 1585, 1503, 1444, 1364, 1328, 1215, 1122, 1006, 746. ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.10 – 6.37 (m, 6H), 3.87 (s, 3H), 3.54 – 3.10 (m, 11H), 2.71 – 1.94 (m, 2H), 1.85 – 1.22 (m, 8H). FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{25}H_{31}N_2O_5$ 439.2227; found 439.2225.

Both 2d and 2e shows broad signal for each peak which makes it difficult to interpret the structure based on NMR. We reason that such signal could be the result of hinder rotation of protecting group on Nitrogen and TMP. Thus, further deprotection of protecting group is carried to gain clear NMR spectroscopic data.

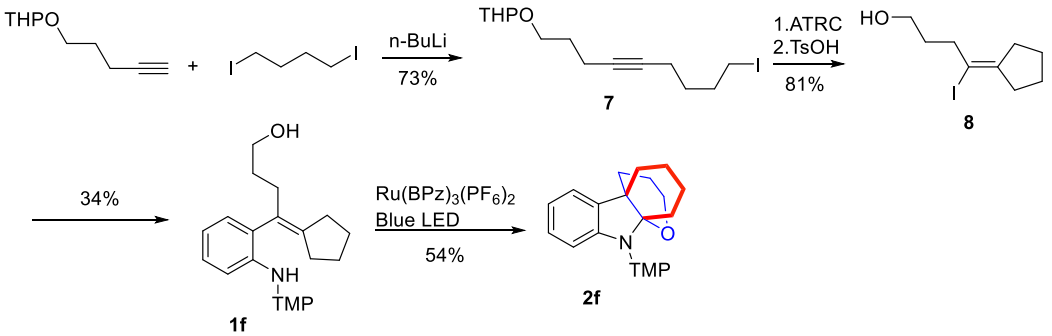


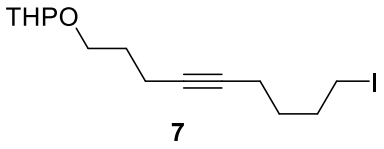
2dd

^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.12 (ddd, *J* = 7.3, 1.3, 0.6 Hz, 1H), 7.03 (td, *J* = 7.7, 1.4 Hz, 1H), 6.74 – 6.69 (m, 3H), 6.61 (dt, *J* = 7.8, 0.7 Hz, 1H), 3.84 (s, 6H), 3.82 (s, 3H), 3.10 (ddd, *J* = 10.2, 7.8, 3.8 Hz, 1H), 2.91 (ddd, *J* = 10.3, 8.4, 7.3 Hz, 1H), 2.11 (ddd, *J* = 12.2, 7.3, 3.8 Hz, 1H), 2.07 – 1.88 (m, 4H), 1.76 (ddd, *J* = 13.7, 10.6, 4.3 Hz, 1H), 1.65 – 1.52 (m, 2H), 1.45 (tt, *J* = 7.9, 5.9 Hz, 2H), 1.34 – 1.25 (m, 1H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 153.50, 148.44, 137.07, 135.45, 127.30, 122.73, 117.75, 107.49, 103.20, 92.54, 60.45,

56.03, 53.95, 43.84, 41.23, 32.19, 30.45, 19.52, 19.28.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 127.31, 122.74, 117.76, 107.50, 103.18, 60.45, 56.03, 43.84, 41.23, 32.19, 30.44, 19.52, 19.28.

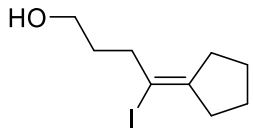
Synthesis route of series **C**





Preparation of **7** was accomplished using a literature procedure.[1] To an oven–dried heavy wall pressure vessel equipped with a stir bar was added alkyne (1 equiv., 20 mmol, 3.36 g) in anhydrous THF (0.25 M, 80 mL). A septum was added and the flask was flushed with nitrogen for 5 minutes. The contents were then cooled to –78 °C and *n*–BuLi (1.6 M in hexanes, 1.1 equiv., 22 mmol, 13.75 mL) was then added dropwise over a 10 minute period under N_2 atmosphere. The resulting solution was stirred for 30 minutes at this temperature prior to the addition of 1,4–diiodobutane (1.5 equiv., 30 mmol, 3.96 mL). The mixture was then stirred for 30 minutes at –78 °C prior to warming to room temperature. The septum was then replaced with a screw cap and stirred at 60 °C for 14 hours. Once complete, the contents were cooled to room temperature and poured into 50 mL of saturated aq. NH_4Cl. The resulting mixture was extracted with Et_2O (3 x 40 mL). The combined organic layer was then dried over $MgSO_4$, concentrated in

vacuum, and purified by flash chromatography on silica gel (97:3 hexanes:EtOAc) to afford **7** as a clear oil (4.2 g, 60%). IR υ_{max} (cm^{-1}) 2939, 2867, 1136, 1118, 1061, 1031, 1019, 988. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.56 (q, *J* = 3.7, 3.3 Hz, 1H), 3.89 – 3.71 (m, 2H), 3.44 (dtt, *J* = 15.7, 6.7, 2.7 Hz, 2H), 3.17 (tt, *J* = 7.0, 2.1 Hz, 2H), 2.18 (ddtd, *J* = 31.4, 9.3, 4.5, 2.2 Hz, 4H), 1.89 (dtdd, *J* = 9.7, 7.2, 4.9, 2.7 Hz, 2H), 1.82 – 1.62 (m, 4H), 1.58 – 1.43 (m, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 98.76, 80.24, 79.46, 66.04, 62.17, 32.48, 30.70, 30.70, 29.71, 29.25, 25.51, 19.54, 17.74, 15.64, 6.37.; ^{13}C NMR DEPT 135(101 MHz, $CDCl_3$) δ 98.62, 66.03, 62.17, 32.47, 30.69, 29.70, 29.24, 25.50, 19.53, 17.72, 15.63, 6.37. FTMS (ESI) *m*/*z* $[M+Na]^+$, calc'd for $C_{14}H_{23}INaO_2$ 373.0635; found 373.0637.

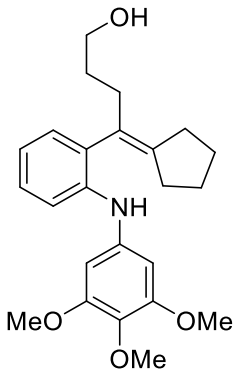


8

Preparation of 2–(3–cyclopentylidene–3–iodopropoxy)tetrahydro–2*H*–pyran **8** was accomplished using a literature procedure.[2] To a clean, dry test tube equipped with a stir bar was added **7** (1 equiv, 11.4 mmol, 4 g), hexabutylditin (10 mol%, 1.14 mmol, 0.57 mL), and anhydrous benzene (degassed *via* Freeze–Pump–Thaw; 0.67 M, 17 mL). The mixture was then irradiated using a 275W GE sunlamp at a 5 cm distance for 24 hours. Once complete, the solvent was evaporated in vacuum and the crude product was purified by flash chromatography on silica gel (97:3 hexanes:EtOAc). The resulting materials (9.7 mmol, 86%) are used in next step.

To a clean, dry 100–mL round bottom flask was added cyclized vinyl iodide from previous step(1 equiv, 9 mmol, 3.15 g) and *para*–toluenesulfonic acid monohydrate (PTSA•H_2O; 10 mol%, 0.9 mmol, 155 mg) in anhydrous MeOH (0.34 M, 27 mL). The contents were then stirred

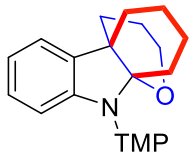
for 4 hours at room temperature. Upon completion, the solution was transferred to a separatory funnel and diluted with DCM (30 mL). The resulting mixture was washed with saturated aq. $NaHCO_3$ (3 x 5 mL). The aqueous layer was then extracted with DCM (3 x 10 mL). The organic layers were then combined and dried over Na_2SO_4. Subsequent concentration in vacuum and purification by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford **8** as a clear oil (2.2 g, 92%; 81% over 2 steps). IR υ_{max} (cm^{-1}) 2942, 2866, 1449, 1427, 1183, 1050, 996, 917. ^1H NMR (400 MHz, Benzene-d_6) δ 3.64 – 3.50 (m, 2H), 3.29 (d, *J* = 4.6 Hz, 1H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.37 – 2.28 (m, 2H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.90 – 1.74 (m, 2H), 1.65 (p, *J* = 6.8 Hz, 2H), 1.48 (p, *J* = 7.0 Hz, 2H).; ^{13}C NMR (101 MHz, C_6D6) δ 148.96, 96.40, 60.78, 41.27, 38.16, 32.28, 31.44, 28.22, 25.65.; ^{13}C NMR DEPT 135(101 MHz, C_6D6) δ 60.79, 41.27, 38.16, 32.28, 31.44, 28.22, 25.66.



1f

Preparation of **1f** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 4.5 mmol, 1.737 g), $Pd(OAc)_2$ (2 mol%, 0.06 mmol, 13.4 mg), RuPhos (4 mol%, 0.12 mmol, 55.9 mg), K_3PO_4 (3 equiv, 9 mmol, 1.908 g) , **8** (1 equiv, 3 mmol, 798 mg) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 dissolved. And the solution is degassed *via* Freeze–Pump–

Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over Na_2SO_4 and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (4:1 hexanes:EtOAc) to afford **c4** as pale yellow oil (400 mg, 34%). IR υ_{max} (cm^{-1}) 2937, 1592, 1507, 1446, 1228, 1123, 1004, 749. ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.53 (ddd, *J* = 8.2, 3.3, 1.2 Hz, 1H), 7.21 – 7.11 (m, 1H), 6.97 (tt, *J* = 7.3, 1.4 Hz, 1H), 6.52 (d, *J* = 1.0 Hz, 2H), 6.15 (d, *J* = 5.9 Hz, 1H), 3.89 (s, 3H), 3.54 (dd, *J* = 6.2, 3.0 Hz, 2H), 3.45 (s, 6H), 2.55 (t, *J* = 7.8 Hz, 2H), 2.40 (d, *J* = 7.2 Hz, 2H), 2.30 – 2.21 (m, 2H), 2.09 (q, *J* = 6.3 Hz, 1H), 1.77 – 1.60 (m, 4H), 1.55 (q, *J* = 6.6 Hz, 2H).; ^{13}C NMR (101 MHz, C_6D6) δ 154.36, 143.04, 141.17, 139.60, 134.02, 132.08, 129.80, 128.46, 127.27, 120.05, 115.99, 97.67, 62.47, 60.38, 55.45, 32.00, 31.66, 30.98, 30.14, 26.62, 26.58.; ^{13}C NMR DEPT 135(101 MHz, C_6D6) δ 129.80, 129.78, 127.27, 120.05, 120.03, 115.99, 115.95, 97.72, 97.65, 62.47, 60.38, 55.45, 32.00, 31.67, 30.98, 30.14, 26.62, 26.58. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{24}H_{32}NO_4$ 398.2326; found 398.2326.

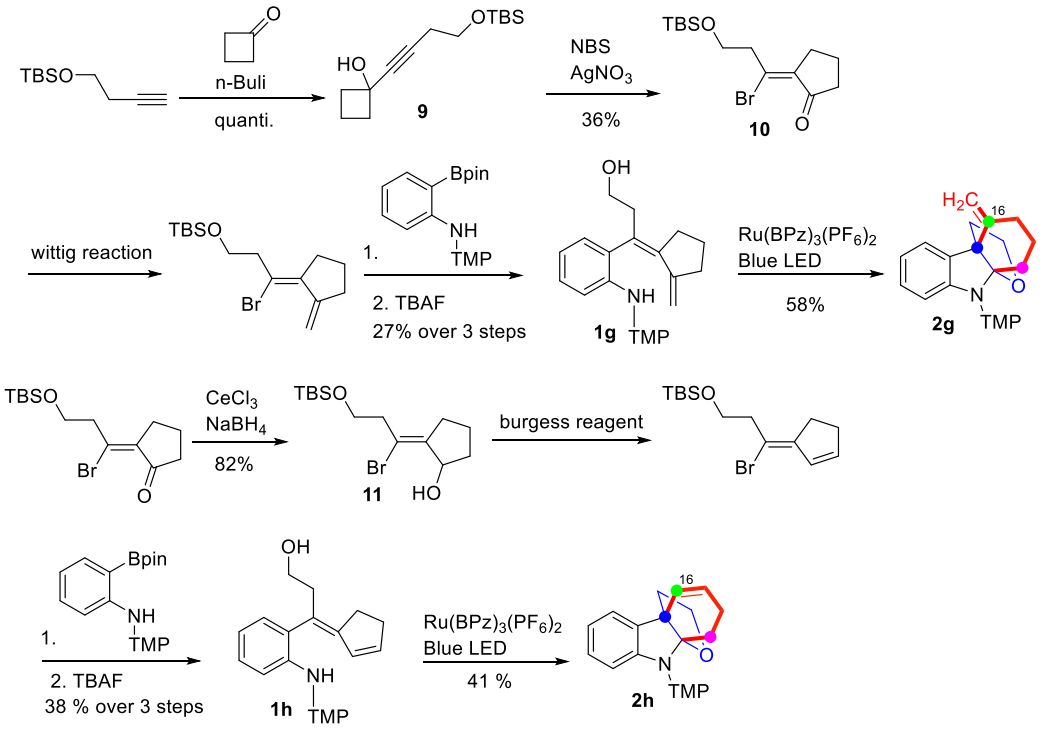


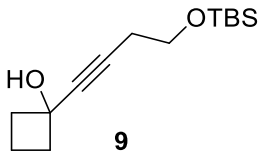
2f

Preparation of fused *N*–arylindoline **2f** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1f** (1 equiv, 0.2 mmol, 80 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a

16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 24 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (85:15 hexanes:EtOAc) to afford the pure **2f** as a yellow oil (42 mg, 54%). IR υ_{max} (cm^{-1}) 2936, 2857, 1585, 1503, 1478, 1460, 1228, 1125, 1012, 742. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.09 – 7.05 (m, 1H), 7.02 (td, *J* = 7.7, 1.3 Hz, 1H), 6.76 (td, *J* = 7.4, 1.0 Hz, 1H), 6.68 (d, *J* = 0.8 Hz, 2H), 6.53 (dd, *J* = 7.9, 1.0 Hz, 1H), 3.80 (s, 9H), 3.75 – 3.71 (m, 1H), 3.58 (ddd, *J* = 11.6, 9.2, 4.2 Hz, 1H), 2.02 – 1.98 (m, 2H), 1.95 – 1.78 (m, 2H), 1.66 – 1.40 (m, 8H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 153.39, 148.56, 136.28, 136.08, 135.90, 127.00, 120.97, 118.44, 108.34, 105.13, 98.75, 61.62, 60.43, 56.02, 46.05, 38.33, 27.12, 25.93, 22.83, 22.21, 20.99.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 127.00, 120.97, 118.44, 108.34, 105.12, 61.62, 60.43, 56.02, 38.34, 27.12, 25.93, 22.84, 22.22, 20.99. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{24}H_{30}NO_4$ 396.2169; found 396.2172.

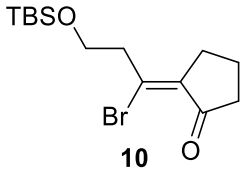
Synthesis route of series **D**





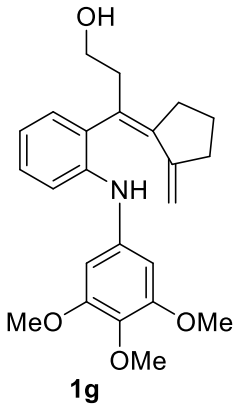
Preparation of **9** was accomplished using a literature procedure.[1] To an oven–dried flask equipped with a stir bar was added alkyne (1 equiv., 33 mmol, 6.07 g) in anhydrous THF (0.36 M, 90 mL). A septum was added and the flask was flushed with nitrogen for 5 minutes. The contents were then cooled to –78 °C and *n*–BuLi (1.6 M in hexanes, 1.1 equiv., 36.3 mmol, 22.68 mL) was then added dropwise over a 10 minute period under N_2 atmosphere. The resulting solution was stirred for 30 minutes at RT temperature prior to the addition of cyclobutanone (1 equiv., 33 mmol, 2.48 mL). The mixture was then stirred for 16 h at room temperature. Once complete, saturated aq. NH_4Cl was added to the flask. The resulting mixture was extracted with

Et_2O (3 x 40 mL). The combined organic layer was then dried over Na_2SO_4, concentrated in vacuum, and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford **9** as a clear oil (8.38 g, quanti.). IR υ_{max} (cm^{-1}) 2953, 2936, 2856, 1471, 1252, 1101, 834, 774. ^1H NMR (400 MHz, Chloroform-*d*) δ 3.74 (t, *J* = 7.1 Hz, 2H), 2.47 (t, *J* = 7.1 Hz, 2H), 2.42 – 2.35 (m, 2H), 2.33 – 2.14 (m, 3H), 1.88 – 1.71 (m, 2H), 0.93 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.83, 80.95, 68.08, 61.89, 38.63, 25.88, 23.16, 18.33, 12.80, -5.27.; ^{13}C NMR DEPT 135(101 MHz, $CDCl_3$) δ 61.90, 38.63, 25.89, 23.16, 12.80, -5.26. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{14}H_{27}O_2Si$ 255.1775; found 255.1778.



10

Preparation of **10** was accomplished using a modified literature procedure.[1] To an oven–dried flask equipped with a stir bar was added **9** (1 equiv., 33 mmol, 6.07 g), $AgNO_3$ (1 equiv., 1 mmol, 0.17 g), NBS (2 equiv., 2 mmol, 0.356 g) and DCE/H_2O (1:1, 6 mL). The resulting solution was stirred for 30 minutes at RT temperature prior to addition of cyclobutanone (1 equiv., 33 mmol, 2.48 mL). The mixture was then stirred for 48 h at room temperature. Once complete, the mixture was abstracted by DCM. The combined organic layer was then dried over Na_2SO_4, concentrated in vacuum, and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford **10** as a clear oil (0.12 g, 36%.). **10** undergoes fast decomposition upon concentration and thus is immediately used for next step.

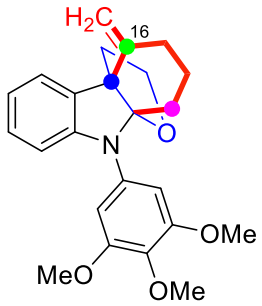


1g

Preparation of **1g** was accomplished using a literature procedure.[1] [1] To an oven–dried flask equipped with a stir bar was added Methyltriphenylphosphonium bromide (1.3 equiv., 1.95 mmol, 0.6962 g) and THF (4.5 mL). After cooling to 0°C, *n*–BuLi (1.6 M in hexanes, 1.2 equiv., 1.8 mmol, 1.12 mL) was added and stir at 0°C for 1 h. **10** (1.5 mmol) in dry THF (0.6 mL) was then slowly added to the flask and resulting mixture was stir for 18 h at RT. The mixture was filtered through a short pad of silica gel and concentrated. The crude was directly used in Suzuki-miyaura coupling without further purification.

To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 2.25 mmol, 0.8685 g), $Pd(OAc)_2$ (2 mol%, 0.03 mmol, 6.7 mg), RuPhos (4 mol%, 0.06 mmol, 28 mg), K_3PO_4 (3 equiv, 4.5 mmol, 0.954 g) , crude diene from previous step(1.5 mmol) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over Na_2SO_4 and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (20:1 hexanes:EtOAc) to afford give protected crude material.

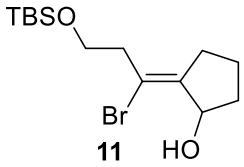
Resulting material from last step is dissolved in THF (1 mL) in a test tube and TBAF (2 equiv., 1 mmol, 1 mL) was added. The solution was stirred at room temperature for 4 h and concentrated in vacuum and purified by flash chromatography on silica gel (5:1 hexanes:EtOAc) to afford **1g** as pale yellow oil(160mg, 27% over 3 steps). IR υ_{max} (cm^{-1}) 2952, 1590, 1507, 1496, 1229, 1121, 1037, 1006, 747. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.29 – 7.12 (m, 2H), 7.05 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.97 (ddd, *J* = 7.5, 6.8, 1.6 Hz, 1H), 6.31 (s, 2H), 5.95 (s, 1H), 4.78 (q, *J* = 1.6 Hz, 1H), 4.33 (q, *J* = 1.7 Hz, 1H), 3.81 (s, 6H), 3.76 (s, 3H), 3.74 – 3.69 (m, 1H), 3.66 – 3.52 (m, 1H), 2.86 – 2.76 (m, 1H), 2.76 – 2.63 (m, 2H), 2.55 (dt, *J* = 14.1, 5.4 Hz, 1H), 2.47 (ddt, *J* = 9.0, 5.5, 1.9 Hz, 2H), 2.00 (s, 1H), 1.83 – 1.73 (m, 2H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 153.86, 148.06, 141.16, 139.69, 139.24, 133.17, 131.33, 129.29, 128.87, 127.60, 121.06, 116.09, 107.87, 97.43, 60.52, 60.04, 55.97, 55.96, 40.38, 36.68, 32.84, 23.56.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 128.87, 127.60, 121.06, 116.09, 107.86, 97.40, 60.52, 60.03, 55.95, 40.38, 36.69, 32.84, 23.56. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{24}H_{30}NO_4$ 396.2169; found 396.2171.



2g

Preparation of fused *N*–arylindoline **2g** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1g** (1 equiv, 0.2 mmol, 79 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 24 hours. The

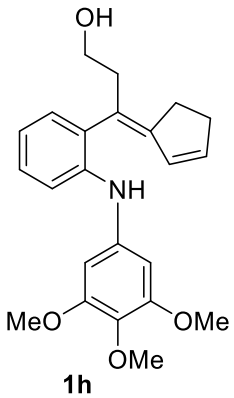
reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford the pure **2g** as a yellow oil (45 mg, 58%). IR υ_{max} (cm^{-1}) 2976, 1594, 1507, 1245, 1125. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 – 7.11 (m, 1H), 7.08 (ddd, *J* = 9.1, 6.6, 1.4 Hz, 1H), 6.79 – 6.74 (m, 3H), 6.72 (dt, *J* = 8.1, 0.7 Hz, 1H), 5.14 – 5.05 (m, 1H), 5.00 – 4.94 (m, 1H), 4.14 – 4.00 (m, 1H), 3.89 (s, 3H), 3.87 (s, 6H), 3.71 – 3.62 (m, 1H), 2.55 – 2.43 (m, 1H), 2.33 – 2.23 (m, 2H), 2.19 – 2.07 (m, 2H), 1.66 – 1.56 (m, 2H), 1.52 – 1.41 (m, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.45, 149.31, 148.98, 135.99, 135.39, 131.49, 128.18, 124.34, 118.43, 110.39, 106.86, 106.56, 102.60, 66.16, 61.12, 60.95, 56.19, 38.38, 29.42, 28.34, 19.05.; ^{13}C NMR DEPT 135(101 MHz, $CDCl_3$) δ 128.19, 124.34, 118.44, 106.86, 102.56, 66.17, 60.95, 56.18, 38.38, 29.42, 28.34, 19.04. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{24}H_{28}NO_4$ 394.2013; found 394.2014.



11

Preparation of **11** was accomplished using a modified literature procedure.[1] To an oven–dried flask equipped with a stir bar was added **10** (1 equiv., 7.5 mmol, 2.4975 g), CeCl3 (1.1 equiv., 8.25 mmol, 3.069 g) in MeOH (0.5 M, 15 mL). The flask is cooled to 0°C and NaBH4 (1.1 equiv., 8.25 mmol, 0.3121 g) was added and stirred for 10 mins before another portion of NaBH4 (0.55 equiv., 4.13 mmol, 0.1560 g) was added.The resulting solution was stirred for 12 h at room temperature. Once complete, the mixture was abstracted by DCM. The combined organic layer was then dried over Na_2SO_4, concentrated in vacuum, and purified by flash chromatography on silica gel (7:1 hexanes:EtOAc) to afford **11** as a clear oil (2.06 g, 82%). IR

υ_{max} (cm^{-1}) 2955, 2927, 2856, 1471, 1252, 1050, 833, 775, 668. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.68 (qd, *J* = 4.0, 2.6 Hz, 1H), 3.89 – 3.70 (m, 2H), 2.70 – 2.64 (m, 2H), 2.59 – 2.48 (m, 1H), 2.41 – 2.24 (m, 2H), 2.04 – 1.92 (m, 1H), 1.87 – 1.82 (m, 2H), 1.80 – 1.65 (m, 1H), 0.90 (s, 9H), 0.07 (d, *J* = 1.0 Hz, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.70, 118.46, 75.99, 60.74, 42.13, 34.81, 31.23, 25.86, 24.16, 18.25, -5.33, -5.36.; ^{13}C NMR (101 MHz, $CDCl_3$) δ 75.99, 60.74, 42.13, 34.81, 31.23, 25.86, 24.16, -5.32, -5.36.



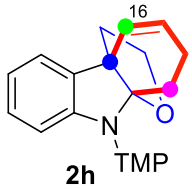
1h

Preparation of **1h** was accomplished using a literature procedure.[1] To an oven–dried flask equipped with a stir bar was added **11** (1 equiv., 4.8 mmol, 1.6 g), burgess reagent (2 equiv., 9.6 mmol, 2.2877 g) and benzene (50 mL). the reaction was stirred at 75°C for 2 h. The mixture was filtered through a short pad of silica gel and concentrated. The crude was directly used in Suzuki-miyaura coupling without further purification.

To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 7 mmol, 2.7 g), $Pd(OAc)_2$ (2 mol%, 0.094 mmol, 21.1 mg), RuPhos (4 mol%, 0.188 mmol, 88 mg), K_3PO_4 (3 equiv, 14.1 mmol, 2.9892 g) , crude diene from previous step(4.7 mmol) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at

90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over Na_2SO_4 and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (20:1 hexanes:EtOAc) to afford give protected crude material.

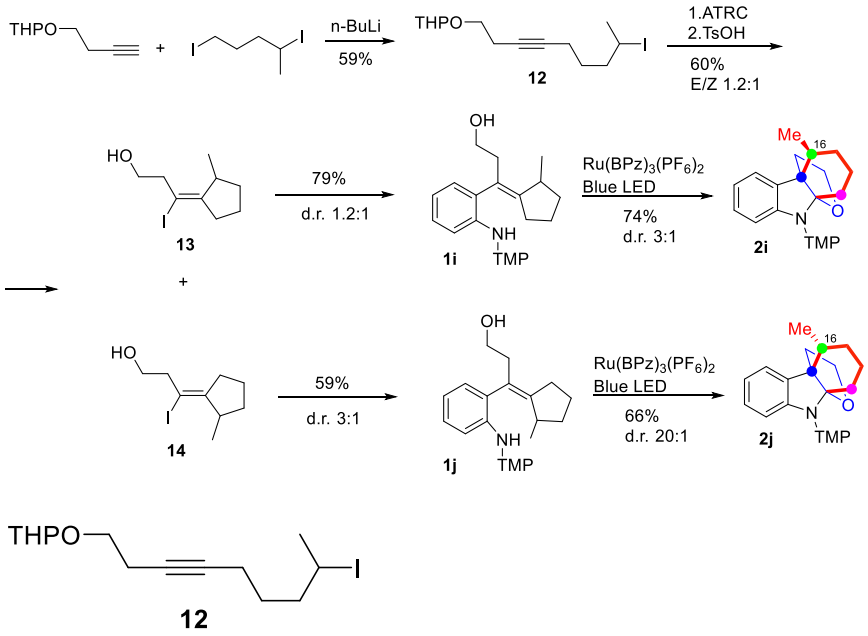
Resulting material from last step is dissolved in THF (4 mL) in a test tube and TBAF (2 equiv., 4 mmol, 4 mL) was added. The solution was stirred at room temperature for 4 h and concentrated in vacuum and purified by flash chromatography on silica gel (5:1 hexanes:EtOAc) to afford **1h** as pale yellow oil(556mg, 38% over 3 steps). IR υ_{max} (cm^{-1}) 2954, 2841, 1592, 1503, 1472, 1436, 1289, 1226, 1122, 1003, 744. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.15 (ddd, *J* = 8.3, 7.2, 1.7 Hz, 1H), 7.05 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.88 (td, *J* = 7.4, 1.3 Hz, 1H), 6.31 (s, 2H), 6.12 (dt, *J* = 5.4, 2.6 Hz, 1H), 5.95 (dt, *J* = 5.6, 2.1 Hz, 1H), 3.81 (s, 3H), 3.81 (s, 6H), 3.69 (dt, *J* = 11.2, 5.8 Hz, 1H), 3.58 (ddd, *J* = 10.6, 7.9, 5.4 Hz, 1H), 2.74 (td, *J* = 7.6, 7.0, 3.8 Hz, 3H), 2.61 (ddd, *J* = 9.3, 6.4, 3.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.75, 148.10, 141.69, 139.50, 139.27, 132.11, 130.90, 130.15, 127.49, 122.76, 120.20, 115.72, 97.38, 61.00, 60.76, 56.08, 38.16, 32.15, 29.25, 27.42.; ^{13}C NMR DEPT 135(101 MHz, $CDCl_3$) δ 139.50, 132.11, 130.15, 127.48, 120.20, 115.72, 97.37, 61.00, 60.76, 56.08, 38.16, 32.15, 27.42. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{23}H_{28}NO_4$ 382.2013; found 382.2013.



2h

Preparation of fused *N*–arylindoline **2h** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1h** (1 equiv, 0.2 mmol, 76.2 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 24 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of neutral silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford the pure **2h** as a yellow oil (31 mg, 41%). IR υ_{max} (cm^{-1}) 2936, 1594, 1584, 1507, 1484, 1286, 1236, 1127. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 (dd, *J* = 7.2, 1.3 Hz, 1H), 7.13 – 6.97 (m, 1H), 6.81 – 6.74 (m, 3H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.05 (dq, *J* = 9.8, 1.5 Hz, 1H), 5.81 (dt, *J* = 9.4, 4.1 Hz, 1H), 4.11 – 4.03 (m, 1H), 3.90 (d, *J* = 1.0 Hz, 3H), 3.87 (d, *J* = 1.0 Hz, 6H), 3.77 – 3.66 (m, 1H), 2.48 – 2.39 (m, 1H), 2.30 – 2.18 (m, 2H), 1.98 – 1.91 (m, 2H), 1.77 (dt, *J* = 13.0, 7.5 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.50, 148.03, 135.62, 132.83, 130.63, 127.98, 126.05, 123.14, 118.69, 107.17, 104.56, 103.17, 67.10, 66.40, 60.95, 56.17, 55.60, 40.38, 29.21, 22.40.; ^{13}C NMR DEPT 135(101 MHz, $CDCl_3$) δ 130.63, 127.98, 126.05, 123.14, 118.69, 107.17, 103.15, 66.40, 60.95, 56.16, 40.38, 29.21, 22.40. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{23}H_{26}NO_4$ 380.1856; found 380.1859.

Synthesis route of series **E**

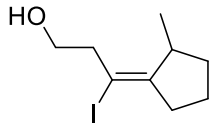


Preparation of **12** was accomplished using a literature procedure.[1] To an oven–dried heavy wall pressure vessel equipped with a stir bar was added 2–(but–3–ynyloxy)tetrahydro–2H–pyran (1 equiv., 5 mmol, 0.77 g) in anhydrous THF (0.33 M, 15 mL). A septum was added and the flask was flushed with nitrogen for 5 minutes. The contents were then cooled to –78 °C and *n*–BuLi (1.6 M in hexanes, 1.1 equiv., 5.5 mmol, 3.5 mL) was then added dropwise over a 10 minute period under N_2 atmosphere. The resulting solution was stirred for 30 minutes at this temperature prior to the addition of 1,4–diiodoalkane (1.5 equiv., 7.5 mmol, 2.4225 g). The mixture was then stirred for 30 minutes at –78 °C prior to warming to room temperature. The septum was then replaced with a screw cap and stirred at 60 °C for 14 hours. Once complete, the contents were cooled to room temperature and poured into 25 mL of saturated aq. NH_4Cl. The resulting mixture was extracted with Et_2O (3 x 40 mL). The combined organic layer was then dried over Na_2SO_4, concentrated in vacuum, and purified by flash chromatography on silica gel (15:1 hexanes:EtOAc) to afford **12** as a clear oil (1.08 g, 62%). IR υ_{max} (cm^{-1}) 2940, 2857, 1199, 1134,

1120, 1030, 970, 905, 868, 813. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.67 (dd, *J* = 4.2, 2.9 Hz, 1H), 4.21 (dqd, *J* = 8.9, 6.8, 4.5 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.81 (dt, *J* = 9.6, 7.2 Hz, 1H), 3.60 – 3.46 (m, 2H), 2.48 (tt, *J* = 7.2, 2.4 Hz, 2H), 2.25 – 2.16 (m, 2H), 1.95 (d, *J* = 6.8 Hz, 3H), 1.94 – 1.80 (m, 2H), 1.80 – 1.67 (m, 3H), 1.66 – 1.49 (m, 5H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 98.74, 80.38, 77.54, 66.16, 62.23, 41.81, 30.61, 29.69, 29.01, 28.97, 25.45, 20.22, 19.47, 17.93.; ^{13}C NMR (101 MHz, $CDCl_3$) δ 98.74, 66.16, 62.23, 41.81, 30.61, 29.70, 29.02, 28.97, 25.45, 20.22, 19.47, 17.93. FTMS (ESI) *m*/*z* $[M+Na]^+$, calc'd for $C_{14}H_{23}INaO_2$ 373.0635; found 373.0639.

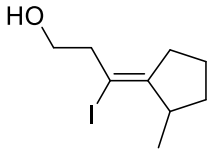
Preparation of **13, 14** was accomplished using a literature procedure.[2] To a clean, dry test tube equipped with a stir bar was added **12** (1 equiv, 4.28 mmol, 1.498 g), hexabutylditin (10 mol%, 0.43 mmol, 0.21 mL), and anhydrous benzene (degassed *via* Freeze–Pump–Thaw; 0.67 M, 6.4 mL). The mixture was then irradiated using a 275W GE sunlamp at a 5 cm distance for 24 hours. Once complete, the solvent was evaporated in vacuum and the crude product was purified by flash chromatography on silica gel (97:3 hexanes:EtOAc). The resulting materials (4 mmol, 93%) are used in next step.

To a clean, dry 100–mL round bottom flask was added cyclized vinyl iodide from previous step(1 equiv, 4 mmol, 1.4 g) and *para*–toluenesulfonic acid monohydrate (PTSA•H_2O; 10 mol%, 0.4 mmol, 68.9 mg) in anhydrous MeOH (0.34 M, 12 mL). The contents were then stirred for 4 hours at room temperature. Upon completion, the solution was concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford **13** and **14** (1.2:1) as a clear oil(2.57 mmol, 60% over 2 steps).



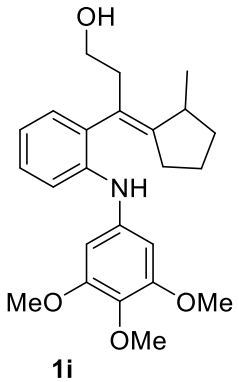
13

Clear oil. IR υ_{max} (cm^{-1}) 2952, 2867, 1371, 1306, 1183, 1152, 1035, 926, 901, 855, 831, 793. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 3.85 – 3.70 (m, 2H), 2.97 (pt, *J* = 7.2, 1.7 Hz, 1H), 2.85 – 2.63 (m, 2H), 2.52 – 2.38 (m, 1H), 2.27 (dddt, *J* = 17.5, 9.4, 7.9, 1.6 Hz, 1H), 1.98 – 1.87 (m, 1H), 1.82 (dddd, *J* = 17.0, 8.9, 4.0, 1.6 Hz, 1H), 1.76 – 1.67 (m, 3H), 1.07 (d, *J* = 7.2 Hz, 3H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 157.06, 93.74, 62.05, 43.85, 41.00, 37.87, 36.00, 22.50, 19.75.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 62.05, 43.85, 41.00, 37.87, 36.00, 22.51, 19.75.



14

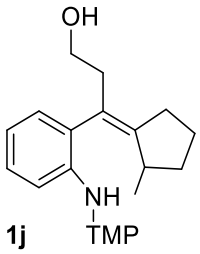
Clear oil. IR υ_{max} (cm^{-1}) 2955, 21231, 1171, 1149, 1035, 825. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 3.79 – 3.66 (m, 2H), 2.80 – 2.64 (m, 3H), 2.61 – 2.48 (m, 1H), 2.47 – 2.31 (m, 1H), 1.98 – 1.77 (m, 3H), 1.57 – 1.51 (m, 1H), 1.48 (t, *J* = 6.1 Hz, 1H), 1.09 (d, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 156.39, 90.40, 61.27, 45.56, 44.89, 33.27, 31.05, 24.96, 18.12.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 61.27, 45.57, 44.89, 33.27, 31.06, 24.96, 18.12.



1i

Preparation of **1i** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–

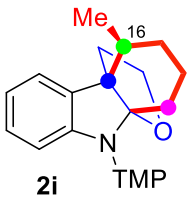
1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 1 mmol, 0.3879 g), $Pd(OAc)_2$ (2 mol%, 0.0134 mmol, 3.0 mg), RuPhos (4 mol%, 0.0268 mmol, 12.5 mg), K_3PO_4 (3 equiv, 2.01 mmol, 0.4261 g) , **13** (1 equiv, 0.67 mmol, 180 mg) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over Na_2SO_4 and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (3:1 hexanes:EtOAc) to afford **1i** as pale yellow oil (210 mg, 79%, d.r. 1.2:1). IR υ_{max} (cm^{-1}) 2954, 2867, 1700, 1608, 1503, 1449, 1407, 1123, 1006, 751. ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.56 – 7.39 (m, 1H), 7.18 – 7.08 (m, 1H), 7.00 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.91 – 6.64 (m, 2H), 6.48 (d, *J* = 5.6 Hz, 2H), 3.80 (dd, *J* = 6.3, 2.4 Hz, 3H), 3.55 – 3.43 (m, 2H), 3.42 – 3.22 (m, 6H), 2.95 – 2.67 (m, 2H), 2.41 – 1.85 (m, 4H), 1.70 (dddd, *J* = 11.8, 9.7, 5.5, 3.7 Hz, 1H), 1.57 – 1.26 (m, 3H), 1.11 (dd, *J* = 40.4, 7.1 Hz, 3H). ^{13}C NMR (101 MHz, C_6D6) δ 154.44, 154.35, 154.28, 150.12, 150.05, 149.92, 149.88, 142.15, 142.13, 141.84, 140.07, 139.97, 139.88, 133.59, 131.74, 131.67, 129.66, 128.75, 127.30, 127.27, 125.41, 125.18, 120.27, 120.10, 116.00, 115.52, 97.05, 96.58, 60.41, 60.04, 55.45, 55.42, 37.51, 37.43, 35.95, 35.85, 34.83, 34.49, 31.15, 30.92, 29.76, 23.63, 23.40, 20.94, 20.36.; ^{13}C NMR DEPT 135(101 MHz, C_6D6) δ 129.66, 128.75, 127.97, 127.30, 127.27, 120.28, 120.10, 116.00, 115.52, 97.02, 96.86, 96.54, 96.39, 60.41, 60.04, 55.44, 55.41, 37.51, 37.44, 35.95, 35.85, 34.83, 34.49, 31.16, 30.92, 23.63, 23.40, 20.94, 20.36. FTMS (ESI) *m*/*z* $[M+K]^+$, calc'd for $C_{24}H_{31}KNO_4$ 436.1885; found 436.1889.



1j

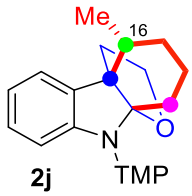
Preparation of **1j** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 1.29 mmol, 0.4979 g), $Pd(OAc)_2$ (2 mol%, 0.0172 mmol, 3.8 mg), RuPhos (4 mol%, 0.0344 mmol, 16.1 mg), K_3PO_4 (3 equiv, 2.58 mmol, 0.5470 g) , **14** (1 equiv, 0.86 mmol, 230 mg) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over Na_2SO_4 and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (3:1 hexanes:EtOAc) to afford **1j** as pale yellow oil (200 mg, 59%, d.r. 3:1). IR υ_{max} (cm^{-1}) 2952, 1591, 1503, 1449, 1286, 1228, 1123, 1003, 748. ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.48 (td, *J* = 8.5, 1.2 Hz, 1H), 7.14 – 7.10 (m, 1H), 7.03 (ddd, *J* = 22.1, 7.5, 1.7 Hz, 1H), 6.89 – 6.83 (m, 1H), 6.49 (d, *J* = 20.3 Hz, 2H), 3.83 (d, *J* = 1.6 Hz, 3H), 3.57 – 3.41 (m, 2H), 3.37 (d, *J* = 8.8 Hz, 6H), 2.81 – 2.50 (m, 2H), 2.49 – 2.10 (m, 3H), 1.71 – 1.59 (m, 2H), 1.26 (ddd, *J* = 11.1, 8.7, 4.7 Hz, 1H), 0.86 (dd, *J* = 12.3, 7.0 Hz, 3H). ^{13}C NMR (101 MHz, C_6D6) δ 154.41, 149.65, 142.01, 139.74, 130.74, 130.22, 127.33, 124.93, 119.55, 115.23, 97.54, 60.39, 55.45, 38.79, 37.48, 34.79, 30.04, 23.49, 19.63.; ^{13}C NMR DEPT 135(101 MHz, C_6D6) δ

130.23, 127.33, 119.55, 115.23, 97.51, 60.39, 59.87, 55.44, 38.79, 37.49, 34.79, 30.04, 23.49, 19.63. FTMS (ESI) *m/z* $[M+K]^+$, calc'd for $C_{24}H_{31}KNO_4$ 436.1885; found 436.1889.



2i

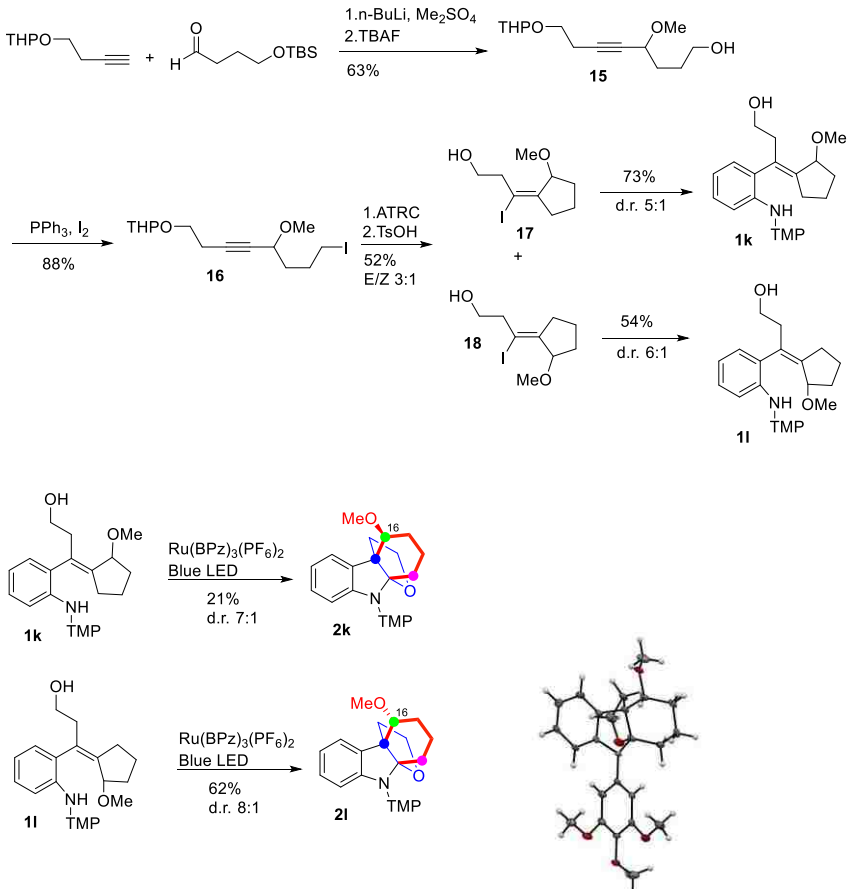
Preparation of fused *N*–arylindoline **2i** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1i** (1 equiv, 0.2 mmol, 80 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 24 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford the pure **2i** as a yellow oil (58 mg, 74%, d.r. 3:1). IR υ_{max} (cm^{-1}) 2936, 2864, 1585, 1503, 1484, 1465, 1461, 1228, 1125, 1009, 742. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.26 – 7.16 (m, 1H), 7.07 (td, *J* = 7.7, 1.3 Hz, 1H), 6.77 (s, 2H), 6.75 – 6.66 (m, 2H), 3.97 (ddd, *J* = 8.3, 7.2, 1.0 Hz, 1H), 3.85 (s, 6H), 3.82 (s, 3H), 3.49 (ddd, *J* = 11.6, 8.7, 4.7 Hz, 1H), 2.37 (ddd, *J* = 11.8, 4.7, 0.9 Hz, 1H), 2.14 (ddd, *J* = 14.6, 6.3, 1.9 Hz, 1H), 2.10 – 1.93 (m, 2H), 1.71 (ddd, *J* = 14.0, 12.7, 6.5 Hz, 1H), 1.57 – 1.29 (m, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.93 (tdd, *J* = 12.9, 10.0, 6.3 Hz, 1H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 153.46, 149.79, 136.04, 135.21, 129.39, 127.80, 126.30, 117.65, 106.15, 106.03, 102.54, 65.36, 60.46, 58.66, 56.02, 41.62, 36.86, 26.67, 25.72, 17.20, 17.12.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 127.80, 126.30, 117.65, 106.03, 102.53, 65.37, 60.46, 56.02, 41.62, 36.86, 26.67, 25.72, 17.20, 17.12. FTMS (ESI) *m/z* $[M+K]^+$, calc'd for $C_{24}H_{29}KNO_4$ 434.1728; found 434.1733.

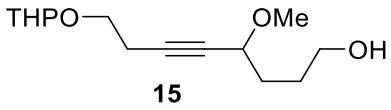


2j

Preparation of fused *N*–arylindoline **2j** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1j** (1 equiv, 0.2 mmol, 80 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 24 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford the pure **2j** as a yellow oil (47 mg, 66%, d.r. 20:1). IR υ_{max} (cm^{-1}) 2934, 2876, 1585, 1454, 1225, 1122, 1020, 964, 867, 742, 714. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.28 (ddd, *J* = 7.2, 1.2, 0.6 Hz, 1H), 7.07 (td, *J* = 7.7, 1.3 Hz, 1H), 6.79 (td, *J* = 7.4, 1.1 Hz, 1H), 6.69 (s, 2H), 6.58 – 6.53 (m, 1H), 4.02 (td, *J* = 8.3, 2.2 Hz, 1H), 3.84 (s, 6H), 3.83 (s, 3H), 3.65 (ddd, *J* = 10.1, 8.1, 6.8 Hz, 1H), 2.39 – 2.09 (m, 3H), 1.56 (dddd, *J* = 14.3, 11.9, 9.8, 6.0 Hz, 4H), 1.41 – 1.20 (m, 2H), 1.18 (d, *J* = 6.6 Hz, 3H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 153.54, 148.72, 135.98, 135.91, 135.09, 127.51, 123.36, 118.30, 107.89, 105.05, 104.72, 66.79, 60.43, 57.59, 56.01, 37.77, 30.02, 29.44, 29.17, 21.97, 17.00.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 127.51, 123.37, 118.30, 107.89, 104.71, 66.79, 60.43, 56.01, 37.78, 30.02, 29.43, 29.17, 21.98, 17.00. FTMS (ESI) *m/z* $[M+K]^+$, calc'd for $C_{24}H_{29}KNO_4$ 434.1728; found 434.1733.

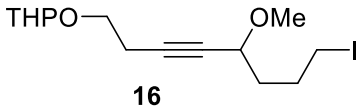
Synthesis route of series **F**





Preparation of **15** was accomplished using a literature procedure.[1] To an oven–dried heavy wall pressure vessel equipped with a stir bar was added 2–(but–3–ynyloxy)tetrahydro–2H–pyran (1 equiv., 5 mmol, 0.77 g) in anhydrous THF (0.33 M, 14 mL). A septum was added and the flask was flushed with nitrogen for 5 minutes. The contents were then cooled to –78 °C and *n*–BuLi (1.6 M in hexanes, 1 equiv., 5 mmol, 3.13 mL) was then added dropwise over a 10 minute period under N_2 atmosphere. The resulting solution was stirred for 30 minutes at this temperature prior

to the addition of aldehyde (1 equiv., 5 mmol, 1 g) in THF (1.5 mL). The mixture was then stirred for 1h at –78 °C prior to warming to room temperature and stirred 2 h at RT. Me_2SO_4 (1.3 equiv., 6.5 mmol, 0.61 mL) was then added to the solution and the mixture was stirred for 12 h. Once complete, 1M NaOH was added to quench the reaction and stirred for 30 mins. The resulting mixture was extracted with Et_2O (3 x 40 mL). The combined organic layer was then washed with brine and water and dried over Na_2SO_4, concentrated in vacuum. The crude was dissolved in THF (14mL) and TBAF (1M, 10 mL) was added. After 2 h, the solution is concentrated in vacuum and purified by flash chromatography on silica gel (3:1 hexanes:EtOAc) to afford **15** as a clear oil (0.806 g, 63%). IR υ_{max} (cm^{-1}) 2943, 1735, 1670, 1118, 1059, 1031,737. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.65 (dd, *J* = 4.3, 2.6 Hz, 1H), 3.99 (tt, *J* = 5.8, 2.0 Hz, 1H), 3.94 – 3.77 (m, 2H), 3.69 – 3.61 (m, 2H), 3.54 (tdd, *J* = 13.1, 6.6, 4.5 Hz, 2H), 3.40 (d, *J* = 2.1 Hz, 3H), 2.54 (td, *J* = 7.1, 2.0 Hz, 2H), 2.11 (d, *J* = 19.8 Hz, 1H), 1.78 (ddddd, *J* = 24.1, 14.4, 12.3, 9.1, 4.9 Hz, 6H), 1.64 – 1.47 (m, 4H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 98.76, 83.62, 79.40, 71.21, 71.20, 65.75, 62.50, 62.21, 62.20, 56.28, 32.48, 30.55, 28.60, 28.58, 25.41, 20.20, 19.37, 19.36.; ^{13}C NMR DEPT 135(101 MHz, $CDCl_3$) δ 98.76, 71.20, 65.74, 62.50, 62.20, 56.29, 32.48, 30.55, 28.59, 25.41, 20.20, 19.37. FTMS (ESI) *m*/*z* $[M+Na]^+$, calc'd for $C_{14}H_{24}NaO_4$ 279.1567; found 279.1570.



16

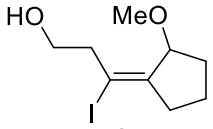
Preparation of **16** was accomplished using a literature procedure.[1] To an oven–dried flask equipped with a stir bar was added **15** (1 equiv., 7.3 mmol, 1.87 g), PPh_3 (1.3 equiv., 9.5 mmol, 2.49 g), imidazole (1.3 equiv., 9.5 mmol, 0.646 g) in anhydrous DCM (0.32 M, 23 mL). The

contents were then cooled to 0 °C and I_2 (1.3 equiv., 9.5 mmol, 2.4111 g) was then added in three portions over a 10 minutes period. Once complete, the mixture was filter through a short pad of silica gel and the solution is concentrated in vacuum and purified by flash chromatography on silica gel (20:1 hexanes:EtOAc) to afford **16** as a clear oil (2.35 g, 88%). IR υ_{max} (cm^{-1}) 2943, 1735, 1199, 1120, 1031, 868, 813. ^{1}H NMR (400 MHz, Benzene-d_6) δ 4.54 (t, *J* = 3.4 Hz, 1H), 3.84 – 3.71 (m, 3H), 3.45 – 3.30 (m, 2H), 3.23 (s, 3H), 2.74 (dd, *J* = 7.5, 6.7 Hz, 2H), 2.37 (tdd, *J* = 7.0, 1.9, 0.9 Hz, 2H), 1.87 – 1.76 (m, 2H), 1.76 – 1.70 (m, 1H), 1.69 – 1.61 (m, 2H), 1.59 – 1.51 (m, 2H), 1.41 – 1.17 (m, 3H).; ^{13}C NMR (101 MHz, C_6D6) δ 98.23, 98.22, 83.73, 79.59, 70.18, 65.53, 65.52, 61.26, 55.73, 36.66, 30.53, 29.48, 25.49, 20.21, 19.13, 5.98.; ^{13}C NMR DEPT 135(101 MHz, C_6D6) δ 127.97, 98.22, 70.17, 65.53, 61.26, 55.73, 36.66, 30.53, 29.48, 25.49, 20.21, 19.13, 5.99. FTMS (ESI) *m*/*z* $[M+Na]^+$, calc'd for $C_{14}H_{23}NaIO_3$ 389.0584; found 389.0587.

Preparation of **17, 18** was accomplished using a literature procedure.[2] To a clean, dry test tube equipped with a stir bar was added **16** (1 equiv, 7.1 mmol, 2.6 g), hexabutylditin (10 mol%, 0.71 mmol, 0.35 mL), and anhydrous benzene (degassed *via* Freeze–Pump–Thaw; 0.67 M, 10.6 mL). The mixture was then irradiated using a 275W GE sunlamp at a 5 cm distance for 48 hours. Once complete, the solvent was evaporated in vacuum and the crude product was purified by flash chromatography on silica gel (10:1 hexanes:EtOAc). The resulting materials (4.9 mmol, 65%) are used in next step.

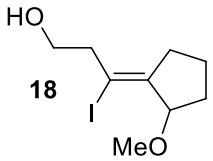
To a clean, dry 100–mL round bottom flask was added cyclized vinyl iodide from previous step(1 equiv, 4.9 mmol, 1.8 g) and *para*–toluenesulfonic acid monohydrate (PTSA•H_2O; 10 mol%, 0.49 mmol, 84.4 mg) in anhydrous MeOH (0.34 M, 15 mL). The contents were then

stirred for 4 hours at room temperature. Upon completion, the solution was concentrated in vacuum and purified by flash chromatography on silica gel (3:1 hexanes:EtOAc) to afford **17** and **18** (3:1) as a clear oil(3.69 mmol, 52% over 2 steps).



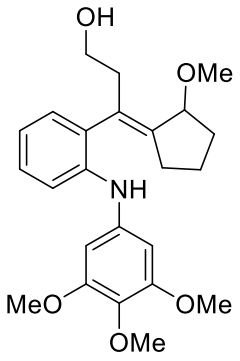
17

Clear oil. IR υ_{max} (cm^{-1}) 2956, 2819, 1646, 1424, 1339, 1178, 1074, 1047, 961. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 4.29 – 4.21 (m, 1H), 3.69 (ddd, *J* = 8.2, 6.2, 3.7 Hz, 2H), 3.33 (d, *J* = 1.0 Hz, 3H), 3.04 – 2.86 (m, 2H), 2.74 – 2.64 (m, 1H), 2.58 – 2.43 (m, 1H), 2.36 – 2.22 (m, 1H), 2.17 – 2.03 (m, 1H), 1.97 – 1.74 (m, 2H), 1.73 – 1.59 (m, 1H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 151.61, 102.64, 79.84, 59.86, 55.49, 45.05, 40.27, 32.84, 22.20.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 79.83, 59.86, 55.49, 45.05, 40.27, 32.84, 22.20. FTMS (ESI) *m*/*z* $[M+Na]^+$, calc'd for $C_9H_{15}NaIO_2$ 305.0009; found 305.0012.



18

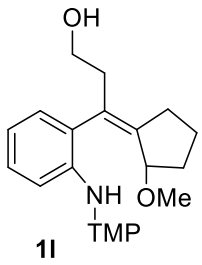
Clear oil. IR υ_{max} (cm^{-1}) 2958, 2924, 1653, 1436, 1340, 1068, 1047, 1015, 963, 928. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 4.11 – 4.02 (m, 1H), 3.76 (t, *J* = 6.2 Hz, 2H), 3.39 (s, 3H), 2.86 – 2.75 (m, 1H), 2.74 – 2.64 (m, 1H), 2.62 – 2.51 (m, 1H), 2.50 – 2.43 (m, 1H), 2.37 (dtdd, *J* = 16.8, 8.1, 1.3, 0.6 Hz, 1H), 2.00 – 1.80 (m, 3H), 1.74 – 1.59 (m, 1H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 150.86, 97.66, 88.34, 61.09, 56.52, 45.44, 31.03, 30.54, 24.43.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 88.34, 61.08, 56.53, 45.44, 31.03, 30.54, 24.44. FTMS (ESI) *m*/*z* $[M+Na]^+$, calc'd for $C_9H_{15}NaIO_2$ 305.0009; found 305.0012.



1k

Preparation of **1k** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 1.5 mmol, 0.579 g), $Pd(OAc)_2$ (2 mol%, 0.02 mmol, 4.5 mg), RuPhos (4 mol%, 0.04 mmol, 18.6 mg), K_3PO_4 (3 equiv, 3 mmol, 0.636 g) , **17** (1 equiv, 1 mmol, 282 mg) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over Na_2SO_4 and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (3:1 hexanes:EtOAc) to afford **1k** as pale yellow oil (300 mg, 73%, d.r. 5:1). IR υ_{max} (cm^{-1}) 2947, 2834, 1593, 1503, 1228, 1123, 1007. ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.63 – 7.43 (m, 2H), 7.21 – 7.09 (m, 2H), 7.01 (d, *J* = 1.7 Hz, 1H), 6.89 (td, *J* = 7.4, 1.1 Hz, 1H), 6.64 (s, 2H), 4.41 (d, *J* = 8.7 Hz, 1H), 3.94 (tt, *J* = 3.7, 1.3 Hz, 1H), 3.82 (s, 3H), 3.73 (ddd, *J* = 10.4, 5.7, 1.7 Hz, 1H), 3.52 (dddd, *J* = 12.7, 10.6, 8.8, 3.7 Hz, 1H), 3.37 (s, 6H), 2.88 (s, 3H), 2.76 (td, *J* = 12.9, 5.7 Hz, 1H), 2.50 (dtt, *J* = 16.2, 7.2, 1.9 Hz, 1H), 2.17 – 2.00 (m, 2H), 1.51 – 1.39 (m, 3H), 1.20 (ddt, *J* = 8.9, 4.8, 2.4 Hz, 1H).; ^{13}C NMR (101 MHz, C_6D6) δ 154.46, 144.25, 142.72, 139.78, 131.91, 130.26, 128.38, 127.81, 119.61, 115.22, 97.11, 81.04, 74.25, 60.32, 57.96, 55.37,

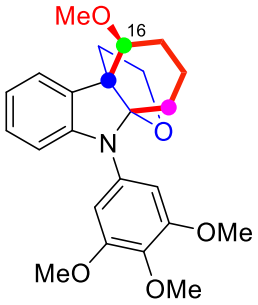
54.99, 38.15, 31.48, 30.96, 23.14.; ^{13}C NMR DEPT 135(101 MHz, C_6D6) δ 128.38, 127.82, 119.61, 115.22, 97.09, 81.04, 60.32, 57.95, 55.37, 54.99, 38.15, 31.48, 30.96, 23.14. FTMS (ESI) *m*/*z* $[M+H]^+$, calc'd for $C_{24}H_{32}NO_5$ 414.2285; found 414.2276.



1l

Preparation of **1l** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 1.5 mmol, 0.579 g), $Pd(OAc)_2$ (2 mol%, 0.02 mmol, 4.5 mg), RuPhos (4 mol%, 0.04 mmol, 18.6 mg), K_3PO_4 (3 equiv, 3 mmol, 0.636 g) , **18** (1 equiv, 1 mmol, 282 mg) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over Na_2SO_4 and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (3:1 hexanes:EtOAc) to afford **1l** as pale yellow oil (300 mg, 54%, d.r. 6:1). IR υ_{max} (cm^{-1}) 3464, 3330, 2941, 1593, 1507, 1127, 1008, 762. ^{1}H NMR (400 MHz, Benzene-d_6) δ 7.55 – 7.32 (m, 1H), 7.13 – 7.04 (m, 1H), 6.97 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.90 (td, *J* = 7.4, 1.2 Hz, 1H), 6.38 (s, 2H), 3.86 (s, 3H), 3.73 – 3.52 (m, 2H), 3.31 (s, 6H), 2.83 (s, 3H), 2.76 (ddd, *J* = 13.7, 8.1, 5.6 Hz, 1H), 2.57 (t, *J* = 8.3 Hz, 2H), 2.34 (dt, *J* = 13.8, 5.2 Hz, 1H), 2.24 – 2.04 (m, 1H), 1.83

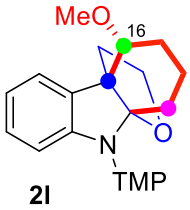
(ttd, *J* = 12.0, 9.2, 6.4 Hz, 1H), 1.70 (dd, *J* = 13.6, 6.5 Hz, 1H), 1.30 – 1.07 (m, 1H).; ^{13}C NMR (101 MHz, C_6D6) δ 154.65, 144.15, 143.13, 139.52, 134.18, 133.85, 133.53, 128.77, 121.16, 117.15, 97.37, 82.96, 60.35, 60.17, 55.47, 55.37, 39.68, 30.85, 28.65, 23.03.; ^{13}C NMR DEPT 135(101 MHz, C_6D6) δ 128.77, 127.97, 127.70, 121.17, 117.15, 97.36, 82.96, 60.35, 60.17, 55.47, 55.36, 39.69, 30.85, 28.65, 23.03. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{24}H_{32}NO_5$ 414.2285; found 414.2280.



2k

Preparation of fused *N*–arylindoline **2k** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1k** (1 equiv, 0.2 mmol, 82.6 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 18 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford **2k** as major product as a yellow oil (17 mg, 21%, d.r. 7:1). IR υ_{max} (cm^{-1}) 2951, 2868, 1594, 1507, 1127, 1105, 668. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.38 – 7.31 (m, 1H), 7.06 (ddd, *J* = 8.0, 7.4, 1.4 Hz, 1H), 6.75 (s, 2H), 6.73 – 6.56 (m, 2H), 4.04 (ddd, *J* = 8.7, 7.3, 1.4 Hz, 1H), 3.84 (s, 6H), 3.82 (s, 3H), 3.68 – 3.56 (m, 2H), 3.43 (d, *J* = 31.0 Hz, 3H), 2.37 (ddd, *J* = 12.0, 5.2, 1.5 Hz, 1H), 2.27 (ddd, *J* = 12.0, 11.2, 7.2 Hz, 1H), 2.06 –

1.99 (m, 1H), 1.91 (ddt, *J* = 13.3, 10.0, 4.1 Hz, 1H), 1.67 – 1.43 (m, 3H), 1.21 – 1.04 (m, 1H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 153.47, 149.23, 135.86, 129.93, 127.78, 126.80, 118.00, 106.66, 106.11, 102.62, 83.48, 65.49, 60.45, 58.92, 57.25, 56.03, 56.02, 41.60, 26.70, 21.74, 16.26.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 127.78, 126.80, 118.00, 106.11, 102.60, 83.48, 65.49, 60.45, 57.25, 56.03, 41.60, 26.70, 21.73, 16.25. FTMS (ESI) *m/z* $[M+Na]^+$, calc'd for $C_{24}H_{29}NNaO_5$ 434.1938; found 434.1936.

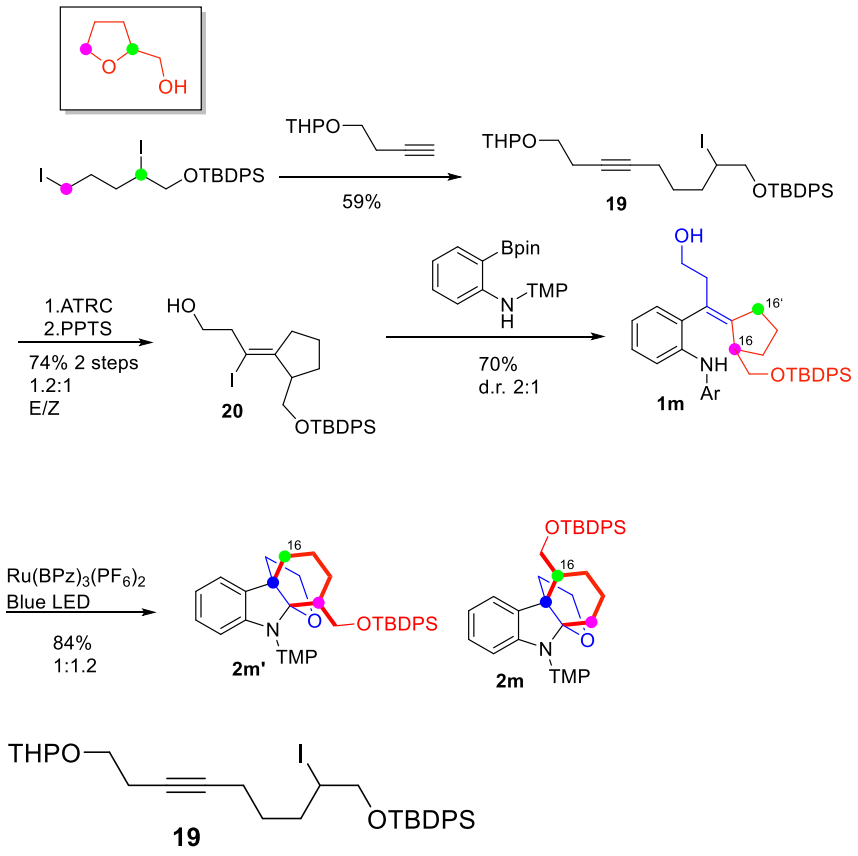


2l

Preparation of fused *N*–arylindoline **2l** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1l** (1 equiv, 0.2 mmol, 82.6 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 18 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford **2l** as major product as a yellow oil (50.5 mg, 62%, d.r. 8:1). IR υ_{max} (cm^{-1}) 2931, 2865, 1585, 1501, 1454, 1409, 1223, 1122, 1100, 1008, 1001, 758, 665. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.35 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.08 (td, *J* = 7.7, 1.4 Hz, 1H), 6.83 – 6.74 (m, 1H), 6.71 (s, 2H), 6.64 – 6.55 (m, 1H), 4.04 (td, *J* = 8.3, 2.0 Hz, 1H), 3.85 (s, 6H), 3.83 (d, *J* = 3.8 Hz, 3H), 3.67 (ddd, *J* = 10.5, 8.3, 6.1 Hz, 1H), 3.43 (d, *J* = 31.0 Hz, 3H), 3.33 (dd, *J* = 9.6, 4.4 Hz, 1H), 2.53 (ddd, *J* = 12.4, 10.5, 8.2 Hz, 1H), 2.23 (ddd, *J* = 12.4, 6.1, 1.9 Hz, 1H), 2.09 (tt, *J* = 11.1, 4.8 Hz, 1H), 1.93 – 1.77 (m, 1H), 1.73 – 1.59 (m, 2H), 1.49

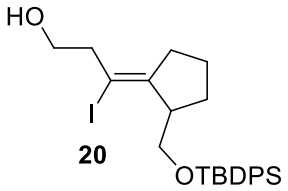
(ddt, *J* = 12.8, 9.3, 5.5 Hz, 1H), 1.41 – 1.27 (m, 1H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 153.54, 148.62, 135.86, 134.11, 127.79, 124.02, 118.64, 107.23, 105.65, 104.00, 83.66, 66.66, 60.44, 58.48, 57.17, 56.03, 56.02, 32.11, 28.89, 22.91, 18.35.; ^{13}C NMR DEPT 135 (101 MHz, CD_2Cl2) δ 127.79, 124.02, 118.64, 107.23, 103.98, 83.66, 66.66, 60.45, 57.17, 56.02, 32.10, 28.89, 22.91, 18.36. FTMS (ESI) *m/z* $[M+Na]^+$, calc'd for $C_{24}H_{29}NNaO_5$ 434.1938; found 434.1943.

Synthesis route of series **G**



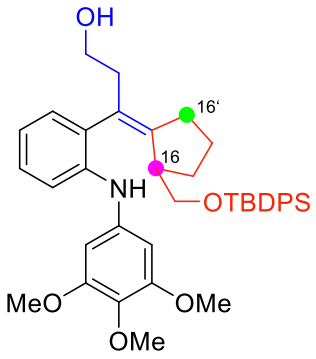
Preparation of **19** was accomplished using a literature procedure.[1] To an oven–dried heavy wall pressure vessel equipped with a stir bar was added 2–(but–3–ynyloxy)tetrahydro–2H–pyran (1 equiv., 18 mmol, 2.77 g) in anhydrous THF (0.33 M, 60 mL). A septum was added and the flask was flushed with nitrogen for 5 minutes. The contents were then cooled to –78 °C and *n*–BuLi

(1.6 M in hexanes, 1.1 equiv., 19.8 mmol, 12.4 mL) was then added dropwise over a 10 minute period under N_2 atmosphere. The resulting solution was stirred for 30 minutes at this temperature prior to the addition of 1,4–diiodoalkane (1.5 equiv., 27 mmol, 15.6 g). The mixture was then stirred for 30 minutes at –78 °C prior to warming to room temperature. The septum was then replaced with a screw cap and stirred at 60 °C for 14 hours. Once complete, the contents were cooled to room temperature and poured into 50 mL of saturated aq. NH_4Cl. The resulting mixture was extracted with Et_2O (3 x 40 mL). The combined organic layer was then dried over Na_2SO_4, concentrated in vacuum, and purified by flash chromatography on silica gel (15:1 hexanes:EtOAc) to afford **19** as a clear oil (6.4 g, 59%), 8.5 g (14.7 mmol) unreacted diiodoalkane are recovered. IR υ_{max} (cm^{-1}) 2930, 2856, 1427, 1111, 1068, 1032, 700, 689, 614. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.73 – 7.64 (m, 4H), 7.50 – 7.35 (m, 6H), 4.70 – 4.58 (m, 1H), 4.12 (tdd, *J* = 9.4, 4.2, 2.7 Hz, 1H), 3.96 – 3.86 (m, 2H), 3.86 – 3.72 (m, 2H), 3.55 – 3.47 (m, 2H), 2.47 (tt, *J* = 7.3, 2.4 Hz, 2H), 2.24 – 2.15 (m, 3H), 2.10 – 1.98 (m, 1H), 1.87 (dtdd, *J* = 13.3, 11.5, 9.0, 4.4 Hz, 2H), 1.73 (dddd, *J* = 11.6, 7.8, 4.4, 2.8 Hz, 2H), 1.66 – 1.47 (m, 4H), 1.11 (s, 9H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.63, 135.60, 133.27, 133.19, 129.83, 129.82, 127.76, 127.75, 98.75, 80.41, 69.18, 66.19, 62.23, 36.66, 35.16, 30.62, 28.60, 26.84, 25.46, 20.23, 19.49, 19.34, 18.09.; ^{13}C NMR DEPT 135(101 MHz, $CDCl_3$) δ 135.64, 135.60, 129.83, 127.76, 98.75, 69.18, 66.18, 62.24, 36.66, 35.16, 30.61, 28.60, 26.83, 25.46, 20.23, 19.49, 18.09. FTMS (ESI) *m*/*z* $[M+Na]^+$, calc'd for $C_{30}H_{41}INaO_3Si$ 627.1762; found 627.1763.



20

Preparation of **20** was accomplished using a literature procedure.[2] To a clean, dry test tube equipped with a stir bar was added **19** (1 equiv, 10 mmol, 2.6 g), hexabutylditin (10 mol%, 1 mmol, 0.5 mL), and anhydrous benzene (degassed *via* Freeze–Pump–Thaw; 0.67 M, 15 mL). The mixture was then irradiated using a 275W GE sunlamp at a 5 cm distance for 24 hours. Once complete, the solvent was evaporated in vacuum and the crude product was purified by flash chromatography on silica gel (10:1 hexanes:EtOAc). The resulting materials are used in next step. To a clean, dry 250–mL round bottom flask was added cyclized vinyl iodide from previous step (1 equiv.) and Pyridinium p-toluenesulfonate (4 mol%, 0.4 mmol, 100 mg) in anhydrous MeOH (0.12 M, 80 mL). The contents were then stirred for 12 hours at 60°C. Upon completion, the solution was concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford **20** as a clear oil(3.3 mmol, 74% (E/Z 1.2:1) over 2 steps). IR υ_{max} (cm^{-1}) 2955, 2936, 2856, 1428, 1111, 1085, 1037, 739, 701. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.85 – 7.66 (m, 4H), 7.49 – 7.38 (m, 6H), 3.85 (dd, *J* = 9.8, 4.2 Hz, 1H), 3.78 – 3.64 (m, 2H), 3.60 (dd, *J* = 9.8, 9.0 Hz, 1H), 2.96 – 2.85 (m, 1H), 2.75 – 2.66 (m, 2H), 2.51 – 2.39 (m, 2H), 2.19 (ddt, *J* = 8.5, 4.1, 1.9 Hz, 1H), 1.93 – 1.81 (m, 3H), 1.16 – 1.08 (m, 9H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 152.04, 135.70, 135.62, 133.81, 133.78, 129.57, 129.55, 127.66, 92.36, 63.17, 61.21, 45.17, 32.02, 28.15, 26.65, 24.99, 19.12.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 135.70, 135.67, 135.62, 135.58, 129.57, 129.55, 127.66, 127.61, 127.58, 63.16, 61.21, 53.42, 45.17, 32.02, 28.15, 26.65, 25.00. FTMS (ESI) *m*/*z* $[M+Na]^+$, calc'd for $C_{25}H_{33}INaO_2Si$ 543.1187; found 543.1187.

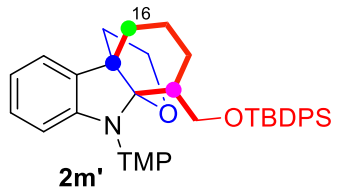


1m

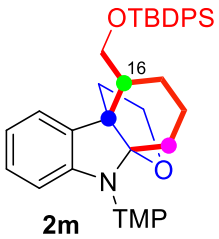
Preparation of **1m** was accomplished based on our previous reported method. To an oven–dried Schlenk flask equipped with a stir bar was added 3,4,5–trimethoxy–*N*–(2–(4,4,5,5–tetramethyl–1,3,2–dioxaborolan–2–yl)phenyl)aniline (1.5 equiv, 4.95 mmol, 1.91 g), $Pd(OAc)_2$ (2 mol%, 0.07 mmol, 14.8 mg), RuPhos (4 mol%, 0.13 mmol, 61.5 mg), K_3PO_4 (3 equiv, 9.9 mmol, 2.09 g) , **20** (1 equiv, 3.3 mmol, 1.7 g) and THF:EtOH:H_2O (2:1:1 0.2M in total). The reaction mixture was sonicated until all the K_3PO_4 dissolved. And the solution is degassed *via* Freeze–Pump–Thaw for three cycles. The reaction mixture is heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the water layer was carefully removed using a glass pipette. The remaining contents were dried over Na_2SO_4 and filtered over a short pad of silica gel. The filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (5:1 hexanes:EtOAc) to afford **f3Z** as pale yellow oil (1.4 g, 70%, d.r. 2:1). IR υ_{max} (cm^{-1}) 2942, 2858, 1593, 1507, 1448, 1428, 1233, 1126, 1106, 1005, 821, 741, 700, 689, 615. ^1H NMR (400 MHz, Benzene-d_6) δ 7.76 – 7.65 (m, 2H), 7.63 – 7.52 (m, 2H), 7.40 (ddd, *J* = 49.9, 8.2, 1.1 Hz, 1H), 7.28 – 7.12 (m, 6H), 7.13 – 6.64 (m, 4H), 6.38 (d, *J* = 119.0 Hz, 2H), 3.84 (d, *J* = 4.2 Hz, 3H), 3.67 (ddd, *J* = 44.4, 9.6, 4.5 Hz, 1H), 3.49 – 3.23 (m, 9H), 3.08 (dq, *J* = 10.3, 6.0, 5.5 Hz, 1H), 2.70 – 2.33 (m, 2H), 2.31 – 2.05 (m, 3H), 1.78 – 1.44 (m, 4H), 1.07 (s, 9H).; ^{13}C NMR (101 MHz, C_6D6) δ 154.46, 145.16, 141.82, 139.75, 135.60, 135.50, 134.21, 133.96,

130.34, 129.49, 129.37, 127.75, 127.17, 119.70, 115.61, 97.64, 64.59, 60.41, 59.72, 55.53, 45.98, 38.82, 30.70, 29.37, 26.80, 23.54, 19.21.; ^{13}C NMR DEPT 135(101 MHz, C_6D6) δ 135.60, 135.50, 129.98, 129.49, 129.37, 127.75, 127.68, 119.70, 115.61, 97.61, 60.41, 55.52, 45.98, 26.80. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{40}H_{50}NO_5Si$ 652.3453; found 652.3460.

Preparation of fused *N*–arylindoline **2m', 2m** was accomplished using following procedure. To a test tube equipped with a stir bar was added **1m** (1 equiv, 0.2 mmol, 130.2 mg), $Ru(bpz)_3(PF_6)_2$ (2 mol%, 0.004 mmol, 3.6 mg), pivalic anhydride (3 equiv, 0.6 mmol, 116mg) and CH_3NO_2 (0.067 M, 3 mL). The tube was then sealed with a screw cap containing a Teflon septum and pierced with a 16–gauge needle. The test tube was irradiated by a 6W blue LED and stirred for 18 hours. The reaction mixture was then diluted with diethyl ether and filtered through a pad of silica gel. The filtrate was then concentrated in vacuum and purified by flash chromatography on silica gel (10:1 hexanes:EtOAc) to afford **2m', 2m** as product (109 mg, 84%, 1:1.2).clear yellow oil. IR υ_{max} (cm^{-1}) 2934, 2857, 1585, 1503, 1472, 1460, 1428, 1227, 1126, 1105, 1066, 1018, 1007, 823, 739, 701, 612. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.65 (dt, *J* = 8.2, 1.6 Hz, 2H), 7.56 (dt, *J* = 8.1, 1.6 Hz, 2H), 7.49 – 7.34 (m, 6H), 7.12 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.07 – 6.99 (m, 1H), 6.79 – 6.72 (m, 1H), 6.70 (d, *J* = 1.7 Hz, 2H), 6.54 (ddd, *J* = 8.0, 1.8, 1.0 Hz, 1H), 3.91 (dddd, *J* = 8.9, 7.7, 2.6, 1.3 Hz, 1H), 3.82 (s, *J* = 1.5 Hz, 3H), 3.80 (s, *J* = 1.2 Hz, 6H), 3.69 – 3.61 (m, 1H), 3.56 (qd, *J* = 10.2, 1.6 Hz, 1H), 2.52 (dqd, *J* = 8.5, 4.6, 2.3 Hz, 1H), 2.18 – 2.03 (m, 2H), 1.92 (dddd, *J* = 17.4, 13.9, 10.5, 5.4 Hz, 2H), 1.70 (dtdd, *J* = 27.8, 18.9, 7.2, 3.5 Hz, 3H), 1.43 – 1.31 (m, 1H), 1.03 (s, *J* = 1.7 Hz, 9H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 153.58, 148.46, 136.41, 136.07, 135.49, 135.37, 134.25, 134.07, 133.98, 129.48,



127.62, 127.54, 127.54, 127.52, 122.22, 118.17, 106.66, 106.48, 104.25, 66.28, 63.77, 60.46, 55.96, 54.63, 41.88, 39.61, 32.72, 26.66, 21.80, 19.10, 17.07.; ^{13}C NMR DEPT 135(101 MHz, CD_2Cl2) δ 135.49, 135.37, 129.48, 127.62, 127.54, 127.52, 122.23, 118.17, 106.66, 104.23, 66.29, 63.77, 60.46, 55.96, 41.88, 39.60, 32.72, 26.66, 21.80, 17.07. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{40}H_{48}NO_5Si$ 650.3296; found 650.3301.



2m

clear yellow oil. IR υ_{max} (cm^{-1}) 2937, 2856, 1587, 1503, 1478, 1428, 1360, 1220, 1126, 1106, 1008, 822, 740, 701, 668, 610. ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.80 – 7.72 (m, 2H), 7.65 (dt, *J* = 6.8, 1.5 Hz, 2H), 7.53 – 7.32 (m, 6H), 7.06 (td, *J* = 7.7, 1.2 Hz, 1H), 6.93 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.69 (d, *J* = 6.5 Hz, 3H), 6.55 (dd, *J* = 7.8, 1.1 Hz, 1H), 4.11 (dd, *J* = 10.0, 3.3 Hz, 1H), 4.00 (td, *J* = 8.5, 1.7 Hz, 1H), 3.85 (s, 6H), 3.84 (s, 3H), 3.82 – 3.77 (m, 1H), 3.59 (ddd, *J* = 10.3, 8.0, 6.5 Hz, 1H), 2.38 (ddd, *J* = 12.4, 10.3, 8.6 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.15 (ddd, *J* = 12.5, 6.5, 1.7 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.69 (dt, *J* = 11.9, 4.2 Hz, 2H), 1.62 – 1.50 (m, 2H), 1.48 – 1.35 (m, 2H), 1.10 (s, 9H).; ^{13}C NMR (101 MHz, CD_2Cl2) δ 153.58, 148.74, 136.09, 135.82, 135.61, 135.58, 134.36, 133.76, 133.52, 129.63, 129.56, 127.69, 127.65, 127.59, 123.34, 118.45, 108.02, 105.70, 104.85, 67.38, 64.77, 60.44, 56.03, 55.41, 45.69, 30.27, 29.82, 26.63, 24.28, 21.80, 19.05.; ^{13}C NMR (101 MHz, CD_2Cl2) δ 135.61, 135.58, 129.63, 129.56, 127.69, 127.65, 127.60, 123.34, 118.45, 108.02, 104.84, 67.38, 64.77, 60.44, 56.03, 45.69, 30.27, 29.82, 26.63, 24.28, 21.80. FTMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{40}H_{48}NO_5Si$ 650.3296; found 650.3301.

5.6 Summary

We developed a highly convergent and modular approach for the synthesis of the akuammiline alkaloids' tetracyclic core. This approach featured a photocascade that was centered on a concerted cationic 1,2-shift. The application of the 1,2-shift in the complex molecular setting hinged on the successful address of some important stereoselectivity issues such as *E*/*Z* reactivity, regioselectivity, and stereoselectivity. An unexpected axial chirality was also discovered for the photocasade's precursor, which posed a significant challenge to us for establishing the stereoconversion models. The approach enabled us to start with three relatively simple fragments. The substituents on various parts of the tetracyclic core including C-16 as well as modification of the core were readily introduced to the fragments, which were then assembled in a highly convergent manner. This feature was essential to SAR studies of the akuammiline alkaloids.

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Conclusion

Chemistries centered around amine radical cations have been developed. Amine radical cations induced C-C bond cleavage to form amine distonic radical cations, which posesssed an iminium ion charge site and a terminal radical site. Distonic radical cations from benzocyclobutylamines underwent [4+2] annulation reactions with alkynes followed by elimination yielded multisubstituted napthalenes. Further understanding of the distonic radical cation reactivity has lead us to incorporate N-alkyl amines as substrate under photoredox catalysis. We hypothesized that the iminium ion charge site can interact with nucleophilic carbon radical in distonic radical cation thus reducing the reactivity of the radical site. Efforts to minimize the interaction between iminium ion and carbon radical by quenching the iminium ion and delocalizing the charge successfully activated the reactivity of the radical. Difunctionalization protocol employing TMSCN as nucleophilie, CF_3-styrene as radical acceptor was developed. Both N-aryl cycloalkyl amines and N-alkyl cycloalkyl amines were competent substrates. Through out the reaction scope studies, tertiary anilines were noticed to be challenging presumably due to slow ring-opening rate incurred by steric hindrance. To address this limitation, a two-electron approach bypassing the formation of amine radical cation was developed. Electrophilic iodine source such as NIS and in-situ generated ICN promoted the direct ring-opening of cyclopropylanilines via a Sn2 like mechanism which yielded a β-iodo iminium ion. Subsequent nucleophilic addition to iminium ion can furnish 1,3-difunctionalized product.

The electrophilic character of amine radical cations also provided a mean for umpolung C-N formation where amine radical cation underwent electrophilic addition to alkenes. Akuammiline alkaloids motifs which shared a tetracyclic core structure were synthesized

initiated by intramolecular addition of amine radical cation to tetrasubstituted alkenes followed by carbocation 1,2-shift.