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[3+2] Annulation of Cyclopropylanilines with Alkynes under Photocatalysis

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[3+2] Annulation of Cyclopropylanilines with Alkynes under Photocatalysis

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Abstract

Over the past decade, pharmaceutical industries have prioritized their focus on discovering new innovative drugs, yet the syntheses are often either inefficient or the approach of environmental sustainability presents a great deal of concern. Moreover, the methodology developments for amine syntheses have continued to flourish due to their important role and wide use in pharmaceutics. Yet their syntheses often lack sustainability and efficiency. Synthetic chemists have continued to explore potential innovative avenues for conducting chemical reactions more effectively and efficiently. One of the most abundant, renewable natural resources is solar energy and to harvest, use, and store it directly is an ongoing development. To reduce our dependency on fossil energy sources, methods of direct and proficient conversion of solar energy to chemical energy become critically important. Recently, visible light photoredox catalysis has become a highly prominent tool in the development of many successful organic transformations. This work describes an innovative approach of using visible light photocatalysis to develop efficient one-step syntheses for the construction of structurally diverse carbocycles substituted with amines from simple starting materials under mild conditions.

Under photocatalysis, amines can function as both the sacrificial electron donor and substrate. Incorporating the oxidation of the amine and a subsequent irreversible reaction will allow the amine to posses its dual roles. To accomplish this, cyclopropylanilines were used and subjected to ring opening to form reactive β-carbon radical iminium ions via nitrogen radical cations upon oxidation of the cyclopropylanilines. As a result, an intermolecular [3+2] annulation of cyclopropylanilines with alkynes was developed to afford highly useful synthetic intermediates and motifs such as fused indolines, which are found in various bio-active alkaloids and pharmaceuticals. This method exhibited significant group tolerance particularly with

heterocycles. Moreover, the [3+2] annulation enabled rapid assembly of diverse cyclic allylic amine derivatives. Expansion of the [3+2] annulation to include substituted cyclopropylanilines and other types of π-bonds, such as enynes and diynes to afford structurally diverse carbo- and heterocycles were studied. Lastly, a protocol for an oxidative cleavage of *N*-aryl group was successfully accomplished upon screening various oxidants and installing various removable aryl or heteroaryl group.

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Lastly, I thank the Chemistry & Biochemistry department for their financial support.

Dedication

I dedicate this dissertation to my wonderful and loving parents, Hanh and Hai Nguyen.

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Chapter 1. Introduction: Photoredox Catalysis

1.1. Background/ Basic Concept of Photochemistry

Photochemistry can be defined as the reactions of molecules induced by energy in the form of light. Upon activation, the molecule attains an electronically excited state which causes the distribution of electrons to differ significantly from the electronic ground state. Since a molecule's chemical nature is determined by the state of its electrons, very different chemical and physical properties arise between the electronic excited and ground states leading to two different chemical species. Organic reactions affected by light have been in pursuit since the early twentieth century.[1, 2] One of the earliest pioneers, Giacomo Ciamician, began studying the behavior of organic compounds toward light more than 100 years ago. The "founding father of photochemistry" envisioned the potential of utilizing solar energy as an alternative for chemical industry to one day replace high energy synthetic methods with clean photochemical reactions. In his lecture titled "The Photochemistry of the Future," he strongly suggested natural sunlight to be superior to all known sources of energy and predicted solar home heating, photoelectric batteries, increased agricultural utilization of light, and industrial and synthetic applications of solar fuel.[2] His ambitious idea of discovering new and more sustainable synthesis using sunlight has impacted the growth and development of successful chemical transformation in photochemistry.

The earlier works of photochemistry primarily focused on direct excitation of molecules, by short wavelength (λ) ultraviolet irradiation (λ = 250-300 nm). However, the short wavelength, blocked by the protected ozone layer, in solar irradiation inhibits the conversion of molecules. The insufficient UV wavelengths of the solar spectrum prevent direct use of sunlight as the source of UV light, and alternative light source such as UV lamps are required. These

lamps require intensive input of energy to generate high-energy UV radiation, leading to increase cost of light source and ecological footprint. Moreover, specialized and expensive photoreactors are needed to transmit UV light. Particularly in industry scales, the scale factor is solely dependent upon the size of the photoreactor and large UV photoreactors are costly. Alternatively, renewable and abundant, ambient sunlight as an ideal reagent would be beneficial due to its environmental friendly characteristics. The majority of the solar spectrum is made up of visible light with its highest intensity found in the blue, green, and red region (λ = 400-650 nm). In principle, promoting visible light in photochemical reactions is fitting for the development of clean, cost-efficient synthetic methods for the chemical industry. The photochemical transformations can be conducted in a facile manner, in addition to possessing high atom economy. Nevertheless, synthetic methods directly engaged in the use of visible light (λ = 400-800 nm) are less developed. Most organic compounds cannot absorb visible light efficiently. To address this issue, the presence of visible light absorbing chromophores/photocatalysts is required. These photocatalysts are employed to further enhance the photochemical reactivity upon undergoing electron or energy transfer pathway to photosensitize organic molecules. Notably, inorganic and material chemists have investigated the redox properties of these photocatalysts for their applications in water splitting[3, 4] and reduction of carbon dioxide to methane.[5]

The most commonly used versatile visible light photocatalysts are transition metal polypyridyl complexes, particularly ruthenium Ru(II)[6-8] and iridium Ir(III).[9, 10] $Ru(bpy)_3^{2+}$, the most commonly used Ru(II) source, has been studied in many applications in both solar-energy conversion and complex synthesis due to its unique photophysical and chemical properties.[11-14] The metal polypyridyl complex ($Ru(bpy)_3^{2+}$) shows excellent chemical stability and tolerance for

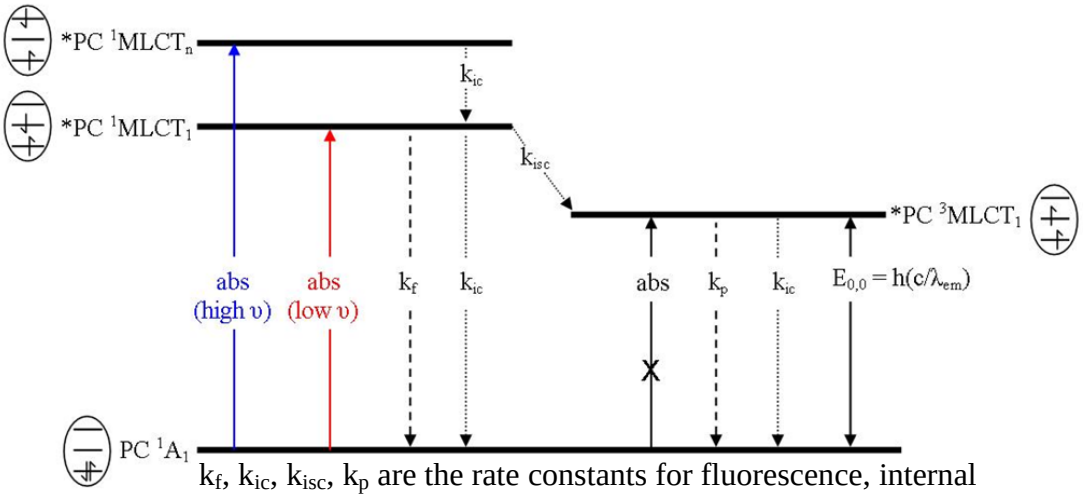
high temperature conditions and strongly basic or acidic conditions.[15] Its strong, broad absorption band at ~450 nm (visible range) corresponds to a metal-to-ligand charge transfer (MLCT) transition to produce a redox active photoexcited state. This complex is known to exhibit high quantum efficiency in generating a relatively long-lived photoexcited state. Much attention centers on the ability of the MLCT state to function as either an electron donor or an electron acceptor in intermolecular redox reactions involving quenchers.[11, 16] These photoexcited states of both Ru(II) or Ir(III) polypyridyl complexes are capable of initiating outer-sphere one-electron transfer processes with organic molecules, including amines. Reactions based on this odd-electron or open-shell chemistry demonstrate potential for forming C-C bonds. In principle, synthetic methods can be conducted more selectively using visible light due to its lower energy than UV. Photoreactions utilize the natural resources of direct sunlight or inexpensive visible light sources such as compact fluorescent or LED lights. The seminal works by MacMillan,[17, 18] Yoon,[19-21] Stephenson,[22, 23] and others[14, 24] have shown great potential for the future of visible light photocatalysis in organic synthesis.

1.2. Photophysical Properties of Photocatalyst

A desired photocatalyst requires the ability to absorb light and utilize the energy for chemical reactions, though remain unchanged from the reaction sequence. The energy produced from the absorption must be sufficient to allow the substrate molecule to undergo the reaction. However, the reaction should induce no modifications to the photocatalyst as it recovers to its original state. The photocatalyst, itself, should be stable in the absence of the substrate. Therefore, it is imperative that the photophysics of the photocatalyst without the substrate should be first addressed and discussed. Both ruthenium- and iridium-based polypyridyl complexes undergo the similar discussed processes of generating the excited state photocatalyst. The

photophysical process is popularly illustrated by the Jablonski diagram shown in Figure 1.1.[6]

All photochemical reactions are initiated by the absorption of a photon to excite the ground state photocatalyst, PC $^1A_1$, to any of the higher energy excited states *PC $^1MLCT_n$. The needed photon energy, hυ, must be large enough to give the excitation energy for the first excited state. The excitation process may involve an allowed transition in which the electron being transferred does not undergo a spin flip when going from the lower energy to higher energy orbital. This leads to an excited singlet state where the electron spins are opposite in two singly occupied orbitals. Usually, the relaxation to the lowest spin-allowed excited state, *PC $^1MLCT_1$, from the higher excited singlet states is quite fast. Thus, the maximum energy available for the photochemical transformation is that of *PC $^1MLCT_1$. The reverse deexcitation pathway from singlet excited states to the ground states with electron spins paired in a single orbital is a spin allowed process, which is termed fluorescence (k_f). This spin-allowed light emission from an excited singlet state is short-lived. Moreover, the *PC $^1MLCT_1$ state undergoes rapid intersystem crossing (k_{isc}), a transition of one electronic state to another one with a different spin



k_f, k_{ic}, k_{isc}, k_p are the rate constants for fluorescence, internal conversion, intersystem crossing, and phosphorescence, respectively and λ_{em} is the maximum emission wavelength of the photocatalyst.

Figure 1.1. Jablonski diagram for photocatalyst.

multiplicity. Intersystem crossing to its triplet state is realized followed by internal conversion to provide a long-lived first triplet excited state, *PC $^3MLCT_1$, where the electron spins are parallel in the two orbitals. Consequently, the triplet excited state, *PC $^3MLCT_1$, exhibits a sufficiently longer lifetime to undergo bimolecular quenching reactions via electron or energy transfer processes in competition with the minor deactivation pathways of fluorescence and internal conversion from *PC $^3MLCT_1$. Unimolecular deexcitation process of a triplet excited state can occur to provide a ground state with two electrons of opposite spins in the lower level orbital, which is considered a forbidden process due to the violation of the Pauli principle. The long-lived emission from the triplet state to the singlet ground state that is spin forbidden is termed phosphorescence (k_p).

The excited state species of the photoredox catalysts have been thoroughly examined with emphasis on their importance in triggering photochemical transformations that are of interest for preparative organic chemistry.[12] Using $Ru(bpz)_3$ as a representive Ru polypyridyl complex, initial absorption of visible light leads to efficient excitation to give the lowest singlet excited state, shown in Figure 1.2. The generated singlet state ($^1MLCT_1$) undergoes intersystem crossing to yield the long-lived luminescent triplet excited state $[Ru(bpz)_3]^{2+*}$ ($^3MLCT_1$), which

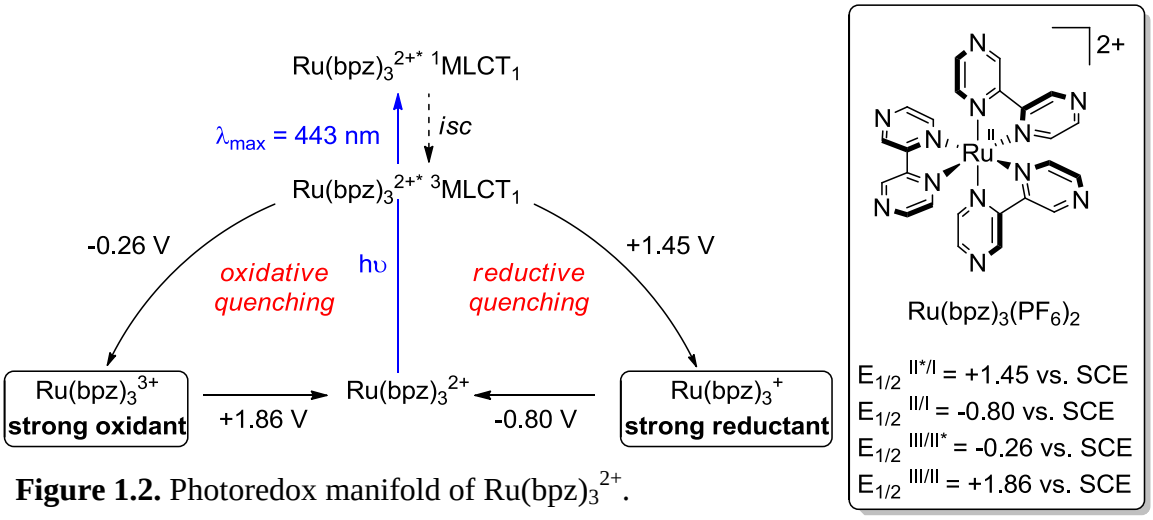


Figure 1.2. Photoredox manifold of $Ru(bpz)_3^{2+}$.

has a half-life time of 740 ns.[25] This high energy species can react either as a single electron oxidant or reductant, depending on the presence of other chemical species. Single electron reduction (reductive quenching) of $[Ru(bpz)_3]^{2+*}$ generates the strongly reducing species $[Ru(bpz)_3]^{+}$ (-0.80 V vs. SCE in CH_3CN), whereas single-electron oxidation (oxidative quenching) produces the strongly oxidizing species $[Ru(bpz)_3]^{3+}$ (+1.86 V vs. SCE in CH_3CN). The reduction potential measures the potential associated with the electrochemical half-reaction written in the direction from the oxidized to the reduced species. For example, the half-reaction $Li^+ + e^- \rightarrow Li$ is described by the reduction potential E_{red} $[Li^+/Li]$ = -3.39 V vs. SCE).

Both Ru(II) and Ir(III) polypyridyl complexes are the most commonly used photoredox catalysts largely due to their photochemical stability and tunable redox properties.[10, 26] Modifying both the ligands and metal centers enables the catalysts' redox properties to be tuned for optimization of a desired reaction. Generally, the MLCT transition state is viewed as the ground state oxidation of the metal center and the ground state reduction of the ligands, thus creating a charge separation that stores photoenergy. Ligand modification can have effects on the ground state redox properties of catalyst. Figure 1.3 illustrates the effects of ligand's electron richness on the ruthenium center's redox properties. Electron rich ligands facilitate the metal-centered oxidation and increase the difficulty of ligand-centered reduction. For example, $Ru(bpy)_3$ has a ground state oxidation of +1.29 V $[Ru^{3+}/Ru^{2+}]$ and ground state reduction of -1.33 V $[Ru^{2+}/Ru^{1+}]$.[27] Addition of σ-donating methyl substituents to the bipyridine ligands, resulting in $Ru(dmb)_3$, shifts its reduction potentials to -1.45 V $[Ru(dmb)_3^{2+}/ Ru(dmb)_3^{1+}]$ and +1.09 V $[Ru(dmb)_3^{3+}/ Ru(dmb)_3^{2+}]$, respectively.[28] The more negative reduction potential indicates that the chemical species is more easily oxidized, while allowing reduction to become more difficult, and therefore is a strong reducing species. Conversely, electron poor ligands

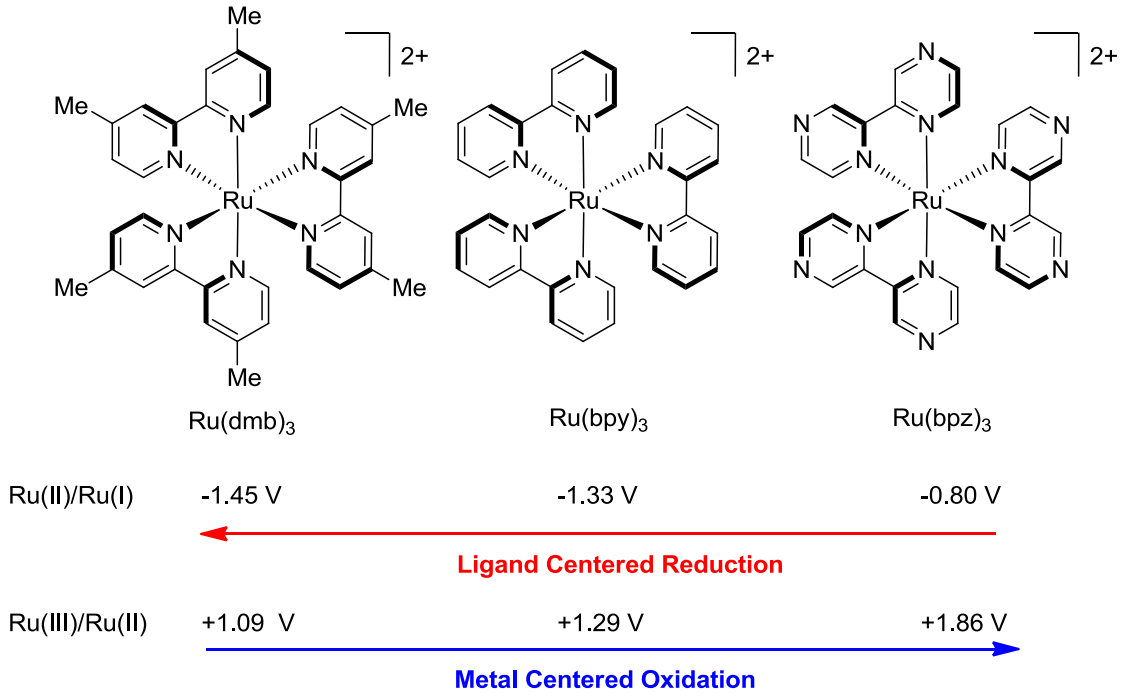


Figure 1.3. Ligand effects on redox properties.

facilitate the ligand-centered reduction and increase the difficulty of metal-centered oxidation. For instance, replacing 2,2'-bipyridine with stronger π-accepting ligand, 2,2'-bipyrazine, to form $Ru(bpz)_3$ makes the reduction [$Ru(bpz)_3^{2+}$/ $Ru(bpz)_3^{1+}$ = -0.80 V] facile while increasing the difficulty of the oxidation [$Ru(bpz)_3^{3+}$/ $Ru(bpz)_3^{2+}$ = +1.86 V].[29] Therefore, ligand substitution can alter the metal complexes' redox potentials significantly. A Ru(II) complex with a more difficult ligand-centered reduction results in a Ru(I) ground state as a strong reductant, while a more difficult metal centered oxidation results in a Ru(III) ground state as a strong oxidant. Moreover, electron rich ligands deliver a more strongly reducing complex, while electron poor ligands deliver a more strongly oxidizing complex.

Ground state redox potentials are usually measured using cyclic voltammetry (CV), which cannot be accomplished for excited states. Instead, the excited state redox potential of a catalyst is approximated using its ground state potentials and zero-zero excitation energy ($E_{0,0}$).[30]

The energy difference between *PC ^{3}MLCT$_1$ and PC ^{1}A$_1$ is the $E_{0,0}$, which is also the maximum emission of the catalyst (Figure 1.1). Although other variables such as temperature, solvent, and concentration can affect the excited-state redox potential, the ability of the excited state to be a powerful oxidant and/or reductant is largely dependent on the ground state redox potentials and $E_{0,0}$ (Eq. 1 & 2).

Oxidative quenching: $E_{red}[PC^{1+}/ *PC] = E_{red}[PC^{1+}/PC] - E_{0,0}$ (Eq. 1)

Reductive quenching: $E_{red}[*PC/ PC^{1-}] = E_{red}[PC/ PC^{1-}] + E_{0,0}$ (Eq. 2)

$E_{0,0}$ is also related to the size of the Stokes shift, which is the difference in wavelength between the absorption and emission spectra. Large Stokes shift, commonly observed in ruthenium complexes, results in a lower $E_{0,0}$ value which leads to the excited states being less potent oxidants and reductants than the ground state. In contrast, iridium complexes often exhibit small Stokes shift. When it comes to designing reactions, the excited state redox potential plays a significant role in determining its abililty to be oxidatively or reductively quenched in order to access the ground state. For instance, Ru(bpy)$_2$(CN)$_2$ is a strong single electron reductant [Ru^{2+}/ Ru^{1+} = -1.68 V] through the reductive quenching cycle, but a low $E_{0,0}$ renders the excited state a weaker oxidant [$*Ru^{2+}$/ Ru^{1+} = +0.37 V].[31] The excited Ru(bpy)$_2$(CN)$_2$ is not a strong enough oxidant to oxidize the most commonly used reductive quenchers such as tertiary amines (E_{red} = +0.50 to +0.96 V).[32] In contrast, *fac*-Ir(ppy)$_3$ is also a strong reductant [Ir(IV)/ Ir(III)* = -1.73 V] and a strong oxidant [Ir(IV)/ Ir(III) = +0.77 V] via the oxidative quenching cycle.[10] Tertiary amines are suitable for reducing the ground state of Ir(IV) to (III). The versatility of how photocatalysts such as Ru(II) and Ir(III) polypyridyl complexes participate in photoredox processes enable a variety of organic transformations with the proper choice of catalyst (metal-ligand combinations) and presence of other chemical species such as organic or inorganic

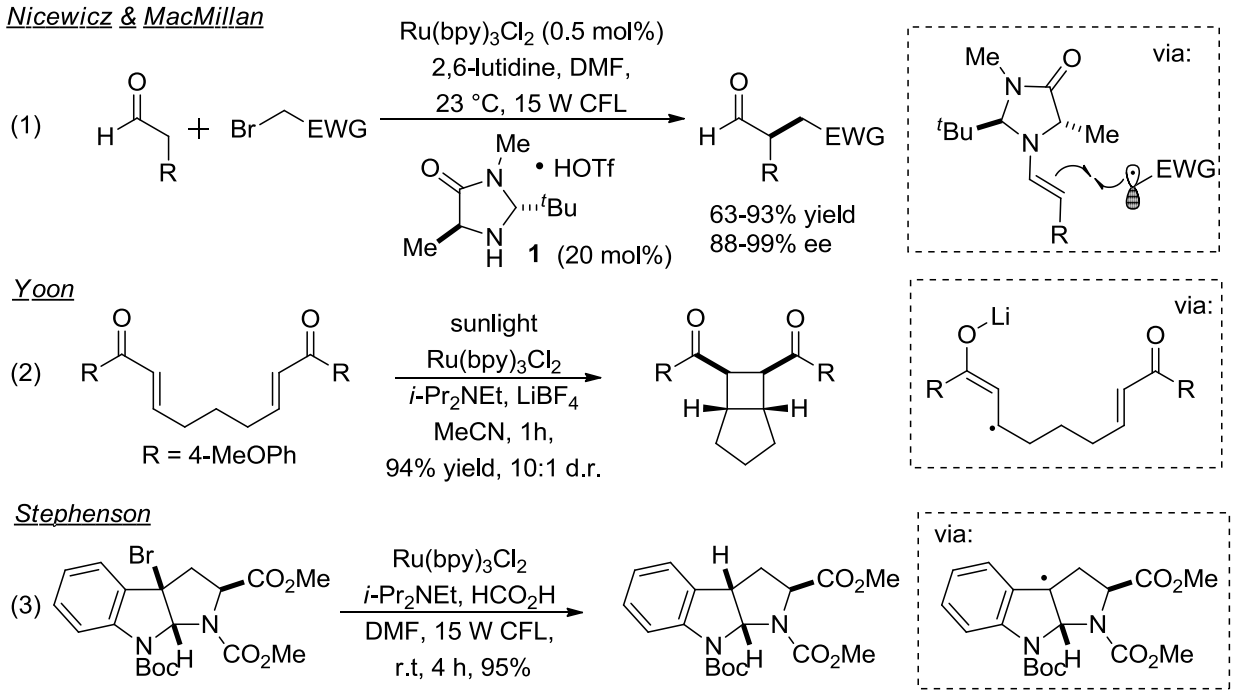
quenchers.

1.3. Synthetic Applications of Visible Light Photocatalysis

The applications of photoredox properties of $Ru(bpy)_3^{2+}$ in organic synthesis were developed in the twentieth century by the pioneering efforts of research groups Kellogg,[33] Pac,[34] Deronzier,[35] Fukuzumi,[36] Okada and Oda,[37] Willner,[38] and Tomioka.[39] Their early attempts showcased reduction of carbon-halogen (C-X) bonds, olefins, carbonyls, nitroalkenes, and diazonium salts with $Ru(bpy)_3Cl_2$. Although the limited number of examples remained unsuitable for important transformations in organic synthesis, these pioneer studies scratched the surface of the enormous potential of $Ru(bpy)_3^{2+}$'s ability to accomplish organic transformations and inspired organic chemists to pursue photocatalysis as one of the mainstream synthetic methods. The inspiration rapidly expanded the concept and development in the field of visible light photoredox catalysis in 2008 and 2009 by seminal works of Nicewicz, MacMillan, Yoon, and Stephenson on applications of $Ru(bpy)_3Cl_2$ modes of reactivity. Nicewicz and MacMillan showcased the application of dual catalysis by merging photoredox catalysis and organocatalysis to accomplish direct asymmetric α-alkylation of aldehydes (Scheme 1.1, Eq. 1).[18] They envisioned the photogenerated strong reductant $Ru(bpy)_3^{+}$, produced from the photoredox pathway, to reductively cleave the C-Br bond, thus furnishing an electron-deficient radical that adds to the enamine, upon merging of the organocatalytic cycle. High yields and high enantiocontrol were achieved with a variety of alkyl aldehydes and bromides.

Yoon and coworkers reported that $Ru(bpy)_3Cl_2$ served as a photocatalyst for [2+2] enone cycloadditions under visible light conditions (Scheme 1.1, Eq. 2).[40] They proposed the photogenerated $Ru(bpy)_3^{+}$ would reduce the lithium-activated enone, subsequently generating the radical anion to initiate the [2+2] intramolecular cycloaddition. A variety of aryl enones were

tolerable to furnish the cyclobutane products in high yields and excellent diastereoselectivity. In 2009, the Stephenson group demonstrated a tin-free reductive dehalogenation reaction using the combination of $Ru(bpy)_3Cl_2$, Hunig's base, and formic acid/ Hantzsch ester as the hydrogen atom source (Scheme 1.1, Eq. 3).[23] Their work harnessed visible light energy to chemoselectively remove halogens from complex functionalized intermediates in the presence of other functional groups such as hydroxyls, olefins, and alkynes. The proposed mechanism details the excited state $Ru(bpy)_3^{2+}$* to be reductively quenched by the Hunig's base to form the strong reductant $Ru(bpy)_3^{+}$, which reduces the C-Br bond via a single-electron transfer to generate the alkyl radical. Subsequent hydrogen abstraction by the alkyl radical furnishes the dehalogenated product.



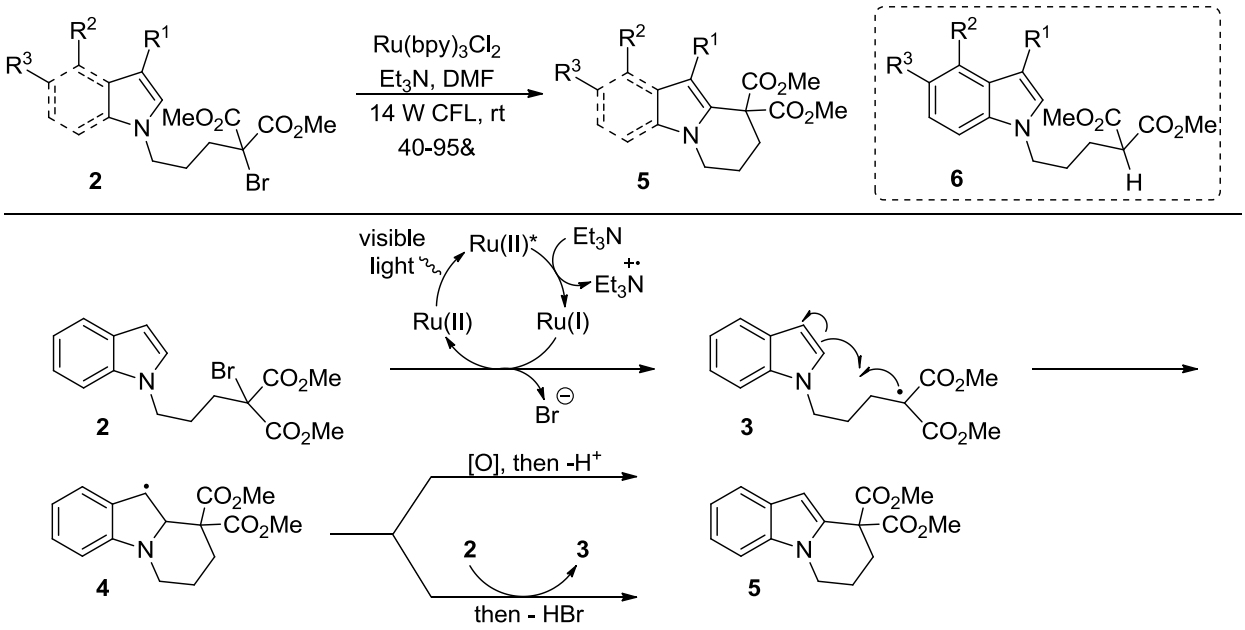
Scheme 1.1. Application of $Ru(bpy)_3Cl_2$ modes of reactivity.

The versatility and applicability of $Ru(bpy)_3^{2+}$ in the selected examples shown above have drawn much attention to the synthetic community due to its unique photophysical properties, enabling the use of abundant, inexpensive sources of visible light. Useful organic

transformations initiated by one-electron redox processes were highlighted by the reactivity of $Ru(bpy)_3^{2+}$ and related complexes. Its relevance in organic synthesis has impacted the future of preparative organic chemistry with the growing number of publications. Moreover, the early contributions of MacMillan, Yoon, and Stephenson have catapulted the application of visible light photoredox catalysis by demonstrating the versatility of ruthenium and iridium complexes that participates in a reductive, oxidative, or energy transfer quenching cycle. The ability to easily tune the complex to achieve desired redox potentials by ligand modification or changing the metal centre is another major advantage in improving available reactivity of photocatalysts. The following sections will illustrate recent literature reports of synthetic applications of using the three quenching cycles.

1.3.1. Reductive Quenching Cycle

The Stephenson group successfully demonstrated a reductive dehalogenation of organic halides possessing activated C-X (X = halogen) bonds via a reactive alkyl radical produced by $Ru(bpy)_3Cl_2$ (Scheme 1.1, Eq. 3). Thereafter, the group modified conditions to develop a

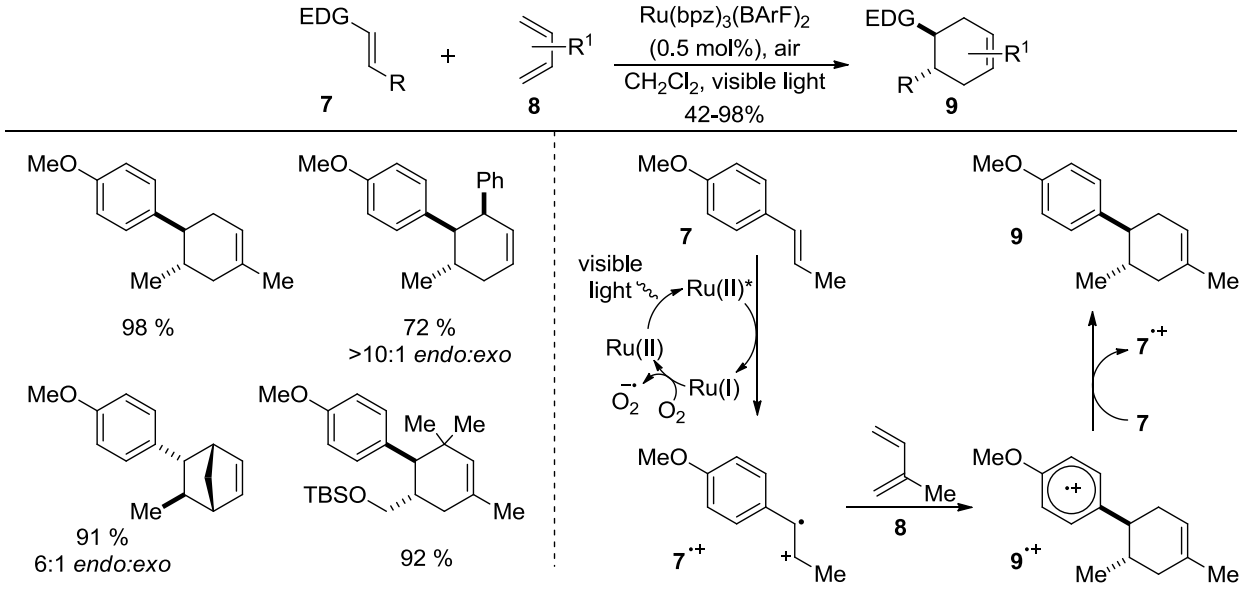


Scheme 1.2. Intramolecular radical functionalization of indoles and pyrroles.

reductive dehalogenation of reducing a range of bromomalonates **2** to intramolecularly add to indoles or pyrroles (Scheme 1.2).[41] This environmentally benign chemical transformation is an alternative approach to previously reported methods of Mn(III)-based oxidative process of malonyl radicals by Kerr and Snider.[42] Triethylamine (Et_3N) was used as a reductive quencher to minimize the competing formation of dehalogenated products. Other amine bases (DABCO, Me_3N, and $(HOCH_2CH_2)_3N$) were also screened, but their strong hydrogen donor abilities favored the formation of reduced indole **6**. They proposed the generated photoexcited state Ru(II)* would be reductively quenched by Et_3N to give the corresponding amine radical cation and electron-rich Ru(I) complex. Single electron transfer of the reduced Ru (I) species to **2** affords alkyl radical **3** by selective homolysis of C-Br bond, thus regenerating the ground state catalyst. Intramolecular radical cyclization of **3** provides benzylic radical **4**, which subsequently undergoes oxidation by either the excited state Ru(II)* or **2** and then elimination to give aromatized product **5**. A range of substituted indoles and pyyroles were realized by this efficient intramolecular functionalization reaction initiated by visible light photoredox catalysis.

Recently, Yoon and co-workers disclosed an efficient radical cation Diels-Alder cycloaddition of electron-rich dienophiles promoted by $Ru(bpz)_3^{2+}$ (Scheme 1.3).[19] Ligand modification of $Ru(bpy)_3^{2+}$ provided a tris(bipyrazyl) analogue that can sufficiently oxdize **7** (+1.1 V), without a co-oxidant, due to the excited state oxidation potential of $Ru(bpz)_3^{2+}$ (Ru(II)*/Ru(I) = +1.45 V). The counteranions (PF_6 vs. BArF) were also examined and the BArF anion proved to be the most effective because of its ability to solubilize the Ru complex in less polar solvents. Reduced catalyst loading to 0.5 mol % provided the Diels-Alder cycloaddition adducts in good to high yields (42-98%). The mechanistic detail outlines the oxidation of **7** to the corresponding radical cation $\mathbf{7}^{\bullet+}$ by the photoexcited state of $Ru(bpz)_3^{2+}$*. The resulting

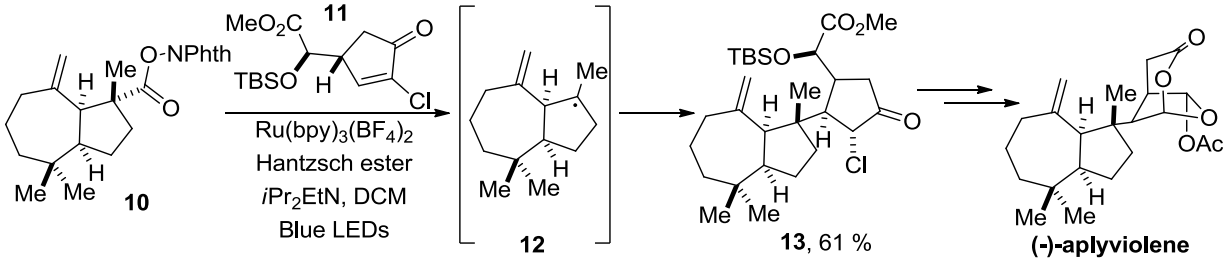
radical cation can undergo a [4+2] cycloaddition to give the radical cation Diels-Alder adduct $\mathbf{9}^{\bullet+}$. Subsequent abstraction of an electron from **7** in a chain-propagation step furnishes the final product **9**, while oxygen turns over the catalyst to regenerate photoactive ground state $Ru(bpz)_3^{2+}$. Compared to traditional Diels-Alder reactions, Yoon's radical cation Diels-Alder process exhibits an umpolung reactivity that reverses both intrinsic dienophile electronic character and the overall regiochemical preference. Moreover, their convenient strategy promotes electronically mismatched Diels-Alder cycloadditions with electron-rich coupling partners, which is usually a challenging task that requires more forcing conditions and longer reaction times. Notably, their method also showcased ligand modification of Ru complexes that enables tuning of electrochemical properties to accomplish the cycloaddition reactions.



Scheme 1.3. Radical cation Diels-Alder cycloaddition.

The use of the reductive quenching cycle was illustrated in an improved second-generation total synthesis of (-)-aplyviolene by Overman,[43] in 2012. The key transformation features a stereoselective coupling of a tertiary carbon radical and carbon electrophile to provide new quaternary carbon stereocenters with high selectivity (Scheme 1.4). The authors initially

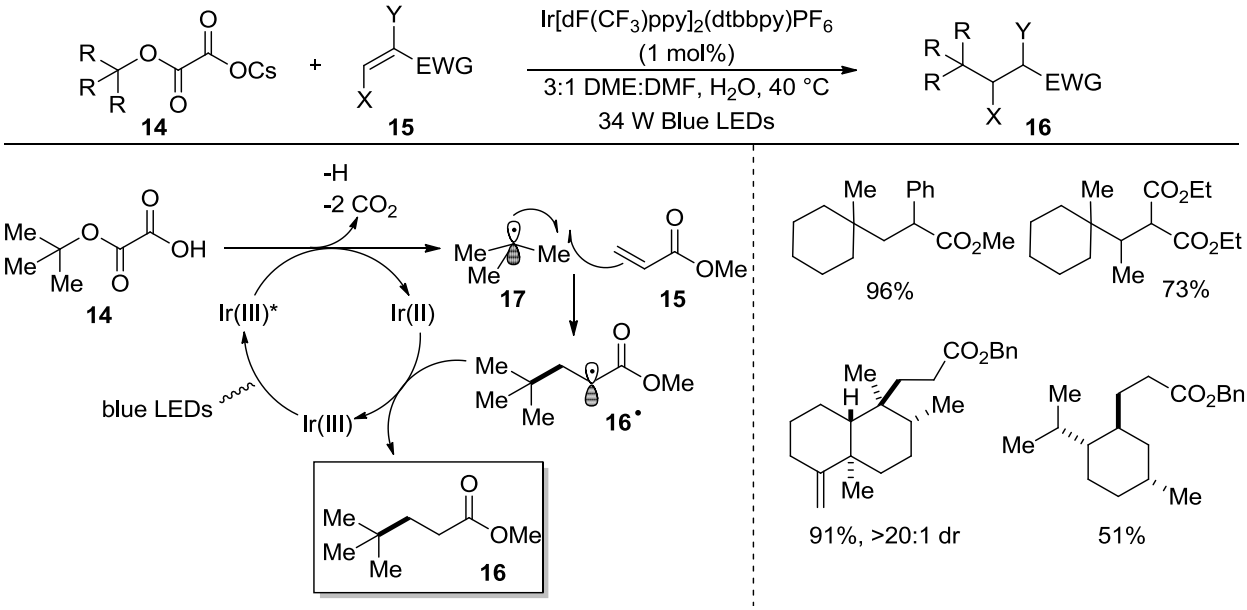
noted the method of photodecarboxylation using (*N*-acyloxy)phthalimides developed by Okada[37] and realized the use of (*N*-acyloxy)phthalimides as radical precursors in conjugate addition reactions. Their optimizing conditions included $Ru(bpy)_3(BF_4)_2$ (1 mol%), Hantzsch ester (1.5 equiv.), *N*,*N*-diisopropylethylamine (2.25 equiv.), and CH_2Cl_2 with blue LEDs. A decarboxylative reduction of (*N*-acyloxy)phthalimides **10**, mediated by $Ru(bpy)_3^{2+}$, produces tertiary radical **12** that adds in a 1,4-fashion to α-chlorocyclopentenone **11** and affords the



Scheme 1.4. Tertiary radical conjugate addition for synthesis of (-)-aplyviolene.

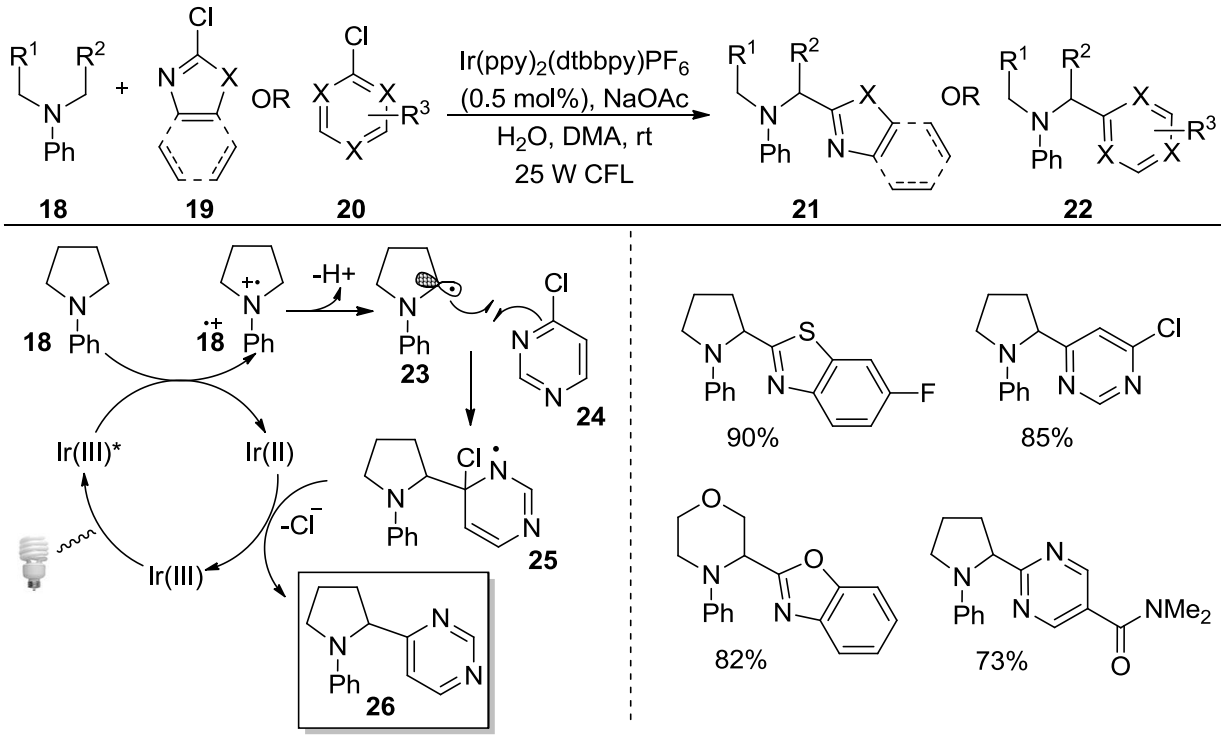
desired intermediate **13** in 61% yield. Overman later expanded the method and introduced *N*-phthalimidoyl oxalate derivatives of tertiary alcohols for the reductive coupling of tertiary radicals and α,β-unsaturated systems.[44] Most recently, a similar approach was reported by Overman and MacMillan using oxalate salts of tertiary alcohols for the redox-neutral formation of quaternary carbon centers through photocatalytic coupling with electron-deficient alkenes in the presence of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (Scheme 1.5).[45] The proposed pathway begins with irradiation of Ir(III) complex to generate long-lived (τ = 2.3 μs) excited state Ir(III)* [Ir(III)*/ Ir(II) = +1.21 V] that further oxidizes the conjugate base of **14** (E_{red} = +1.28 V) via single-electron transfer. Subsequent loss of two molecules of CO_2 affords alkyl radical **17**, which rapidly undergoes nucleophilic addition to an electron-deficient alkene, such as α,β-unsaturated system **15**. Finally the resulting adduct radical **16•** (E_{red} = -0.59 to -0.73 V) is further reduced by strong reducing agent Ir(II) [Ir(III)/ Ir(II) = -1.37 V], followed by protonation to yield the 1,4-addition product **16** while simultaneously, regenerating the ground-state Ir(III) complex, thus

completing the catalytic cycle. Upon optimization, the cesium salts of the starting acids were employed because of their bench stable and nonhygroscopic properties. A 3:1 mixture of DME/DMF was the optimal solvent in addition to 10 equivalents of water that solubilize the oxalate salt and also provide a proton source after radical coupling and reduction. The scope of the reaction included a variety of tertiary and secondary cesium oxalates coupling with a diverse array of electron-deficient alkenes to afford 1,4-addition products in high yields (70-98%). Moreover, the authors developed a redox-netural process of activating alcohols for radical generation under visible light photoredox conditions.



Scheme 1.5. Cesium oxalates radical formation for coupling tertiary/secondary alcohols with Michael acceptors.

Another successful example of utilizing the strong oxidizing Ir(III)* excited state is an amine α-heteroarylation developed by MacMillan and co-workers.[46] Due to the high number of heterocycles and heteroaromatics present in pharmaceuticals, the ability to access relevant transformations for further functionalization/derivatization, such as coupling heterocyclic moieties with other molecular fragments, is essential in medicinal synthesis. In particular, the



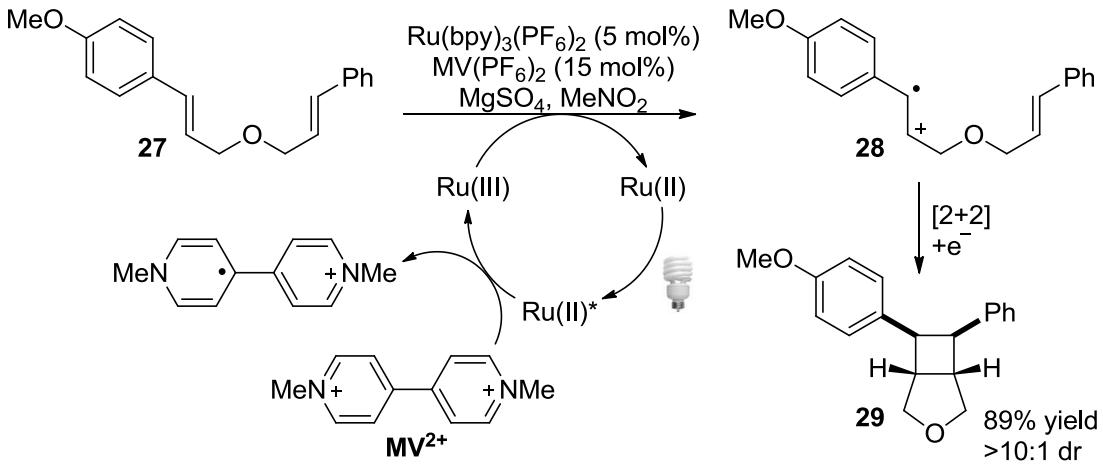
Scheme 1.6. Photoredox amine α-heteroarylation.

authors' previous report of a photoredox-based α-C-H arylation of amines with electron-deficient benzonitriles[47] has sparked their interest in development of amine α-heteroarylation via a different pathway of homolytic aromatic substitution. α-Heteroarylations of tertiary amines successfully tolerated a wide range of electrophilic five- and six-membered heteroarenes (Scheme 1.6). They postulated the strongly oxidizing photocatalyst Ir(III)* oxidized the amine **18** to the amine radical cation $\mathbf{18}^{\bullet+}$, simultaneously forming a reduced Ir(II) complex. Deprotonation of radical cation $\mathbf{18}^{\bullet+}$ at the α-C-H position gives the neutral α-amino radical species **23**, which may add to an electrophilic heteroarene **24** *via* homolytic aromatic substitution. The newly formed radical σ-complex **25** is further reduced by Ir(II), followed by loss of an anion group (Cl^-) to furnish the α-heteroaryl amine product **26** while concurrently, regenerating the ground state Ir(III) photocatalyst. In contrast, this pathway is different than the radical anion-neutral radical coupling mechanism suggested in their findings of α-amine

arylation with benzonitriles.[47] Notably, the redox-neutral process is accredited to the anionic leaving group, incorporated in the arene coupling partner, which forms only byproduct HCl with no stoichiometric oxidants or reductants required.

1.3.2. Oxidative Quenching Cycle

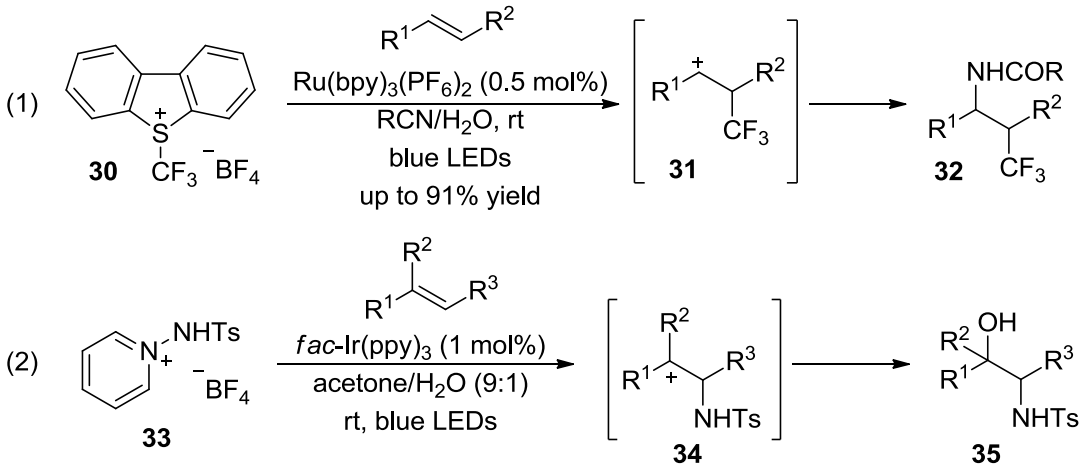
The ability of photoredox catalysts to initiate organic transformations has been employed by utilizing the reductive quenching cycle; however, competing side reactions (i.e. hydrogen atom abstraction and enamine coupling)[48] from reactive intermediates in the intermolecular processes hinder the completion of the desired transformation. Alternatively, the oxidative quenching pathway has been explored to suppress this issue and to develop highly useful synthetic methods. In 2012, the Yoon group employed an oxidative quenching cycle to engage electron-rich bis(styrenes) in [2+2] cycloadditions via visible light photocatalysis (54-92% yield).[21] Methyl viologen (MV^{2+}) was selected to oxidatively quench $Ru(bpy)_3^{2+*}$ to generate the strongly oxidizing $Ru(bpy)_3^{3+}$ species. Subsequent oxidation of the electron-rich styrene **27** provides its radical cation **28** along with regenerating the ground state photocatalyst $Ru(bpy)_3^{2+}$. The radical cation then undergoes a [2+2] cycloaddition followed by reduction to furnish the *cis*-substituted cyclobutane adduct **29** in excellent yield. A limitation of the scope is the requirement



Scheme 1.7. Photooxidative [2+2] cycloaddition of electron-rich bis(styrenes).

of at least one of the styrenes to bear an electron-donating substituent (typically a methoxy group) at the *para* or *ortho* position. Notably, the efficiency of the $Ru(bpy)_3^{2+}/MV^{2+}$ system to promote the radical cation mediated cycloaddition was highlighted on a gram scale, completed in 2.5 h while providing identical yields to the smaller-scale experiments.

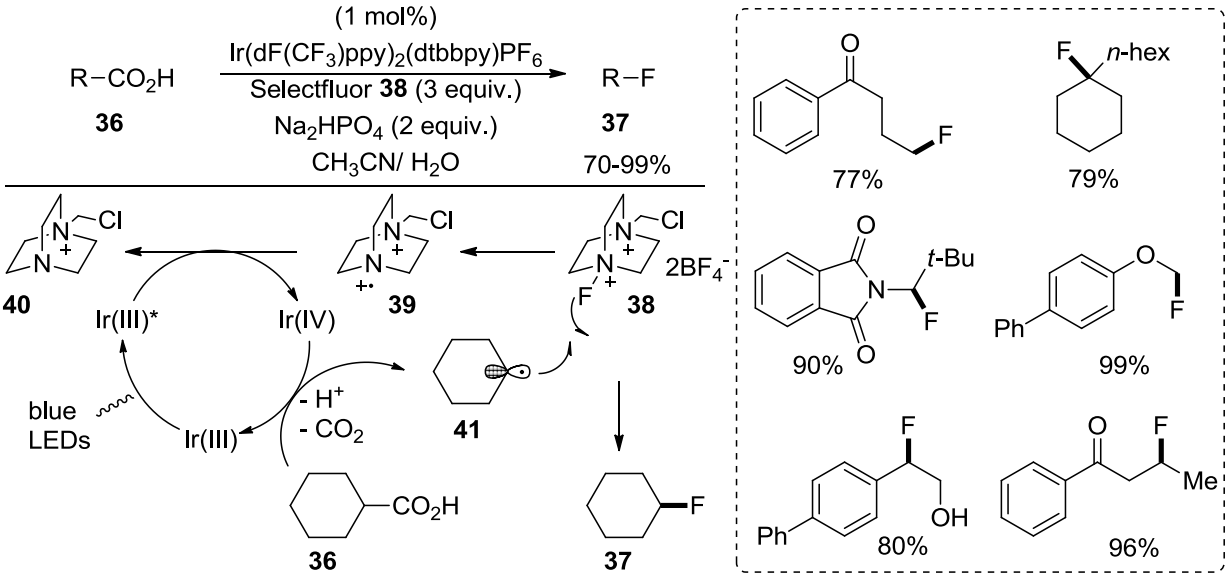
Previously, the Akita group used the atom transfer radical addition (ATRA) method to develop a photoredox-catalyzed trifluoromethylative difunctionalization of olefins using electrophilic CF_3 reagents such as Umemoto's reagent (sulfonium salt) and Togni's reagent (hypervalent iodine species).[49] Their success inspired them to expand the method to aminative difunctionalization of olefins. An application of utilizing the oxidative quenching cycle was disclosed by the group for the intermolecular aminotrifluoromethylation of alkenes catalyzed by $Ru(bpy)_3(PF_6)_2$ (Scheme 1.8, Eq.1).[50] This photocatalytic method enabled rapid access to CF_3-containing derivatives, which are structurally important in bioactive compounds. Driven by visible light, highly efficient and regioselective functionalization of C=C bonds were accomplished to yield a range of β-trifluoromethylamines. The substrate scope included terminal alkenes, specifically styrene derivatives, and internal alkenes. They propose that the photoexcited $Ru(bpy)_3^{2+}$* is oxidatively quenched by Umemoto's reagent **30**, thus generating the



Scheme 1.8. Vicinal difunctionalization of olefins.

trifluoromethyl radical ($^{\bullet}CF_3$). Interception of the β-trifluoromethylated carbocation **31** and hydrolysis via Ritter—type amination affords the aminotrifluoromethylated adduct **32**. Recently, the authors employed a similar strategy for the intermolecular aminohydroxylation of olefins shown in Scheme 1.8, Eq. 2.[51] This route is an alternative to the Os-catalyzed system developed by Sharpless that uses toxic Os species.[52] Synthesis of vicinal aminoalcohol derivatives **35** was realized by the regiospecific aminohydroxylation using a photocatalytic system. The key reagent, *N*-protected 1-aminopyridinium salt **33**, serves both as an electron acceptor and an amidyl radical precursor in the presence of the strong photoexcited state reductant *fac*-Ir(ppy)$_3$.

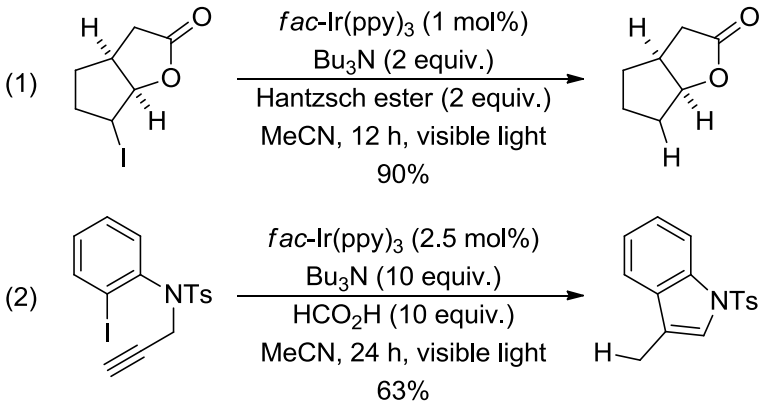
Most recently, the MacMillan group extended their development of engaging photoredox catalysis in organic transformations, particularly sp^3 carbon-fluorine bond formation, by unveiling a direct conversion of aliphatic carboxylic acids to the corresponding alkyl fluorides.[53] Although important advances have been made in the development of sp^3 C-F formation, it remains challenging to develop methods possessing attractive features of high regioselectivity, operation simplicity, bond strength independence, and accessibility to inexpensive starting



Scheme 1.9. Decarboxylative fluorination of sp^3 aliphatic carboxylic acids.

material. Their previous findings of a photon-induced decarboxylation strategy[54] was a blueprint to their investigated decarboxylative fluorination of sp^3 carboxylic acids, in which $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ was chosen as the optimal photocatalyst with blue LEDs as the light source. Selecfluor was selected as the electrophilic source of fluorine. A proposed pathway detailed an oxidative quenching of photoexcited Ir(III)* [Ir(IV)/ Ir(III)* = -0.89V) by N-F bond of Selectfluor **38** (+ 0.33 V) via SET process to provide the strongly oxidizing Ir(IV) agent (Scheme 1.9). Subsequent oxidation of the aliphatic carboxylic acid **36**, then decarboxylation generates the sp^3-alkyl radical **41**, while concomitantly reducing Ir(IV) to Ir(III) thus completing the catalytic cycle. The formed radical **41** can abstract a fluorine atom from Selectfluor **38** to afford the desired fluoroalkane **37**, while producing the corresponding Selectfluor radical cation **39**. The radical cation **39** can then serve as an appropriate electron acceptor to generate the strong oxidant Ir(IV) from Ir(III)* in subsequent photoredox cycles. The redox-neutral decarboxylative fluorination protocol successfully tolerated a wide range of substituted carboxylic acids, including primary, secondary, and tertiary alkyl carboxylic acid to furnish alkyl fluorides in excellent yields (70-99%).

Lastly, another example of utilizing the oxidative quenching cycle was presented by the Stephenson group in a *fac*-$Ir(ppy)_3$ catalyzed radical reductive dehalogenations of unactivated alkyl, alkenyl, and aryl iodides (Scheme 1.10).[55] Unlike their previous reports of reductive dehalogenation of



Scheme 1.10. Radical reductive deiodination.

carbon-bromide bonds via the reductive quenching cycle, this method is driven by the strong reducing power of photoexcited state *fac*-$Ir(ppy)_3$ (Ir(IV)/Ir(III)* = -1.73 V). Harnessing Ir(III)'s capability of cleaving carbon-iodide bonds in alkyl, alkenyl, and aryl iodides is favorable due to their high negative reduction potentials that are measured between -1.59 V and -2.24 V. The resulting carbon-centred radical may undergo intramolecular cyclization and/ or hydrogen atom abstraction from tributylamine in combination with Hantzsch ester or formate. The reductive protocol exhibited excellent functional group compatibility and easy scale-up to provide good to excellent yields under mild conditions.

The recent contributions by the pioneering groups have demonstrated the broad utility of transition metal photoredox catalysis in organic synthesis by highlighting the various new modes of reactivity. The discussed synthetic applications of visible light photoredox catalysis emphasize the unique dual nature of ruthenium and iridium complexes by employing either a reductive or oxidative quenching cycle. More importantly, the unique photophysical properties of photocatalysts and its ability to modulate permit challenging organic transformations to be accomplished. The relevance of photoredox catalysis in organic synthesis continues to grow and show great promises.

1.3.3. Energy Transfer Reactions

The excited state species of the photoredox catalysts have been investigated and discussed thus far to trigger photochemical transformations by electron transfer pathways. Alternatively, another pathway for quenching the photoexcited states is an energy transfer process, typically a triplet-triplet energy transfer (TTET) (Figure 1.4).[16] The energy transfer process occurs only when the emission spectrum of triplet excited state photocatalyst (PC*) and the absorption spectrum of acceptor (also referred as the substrate) overlaps, and the photons

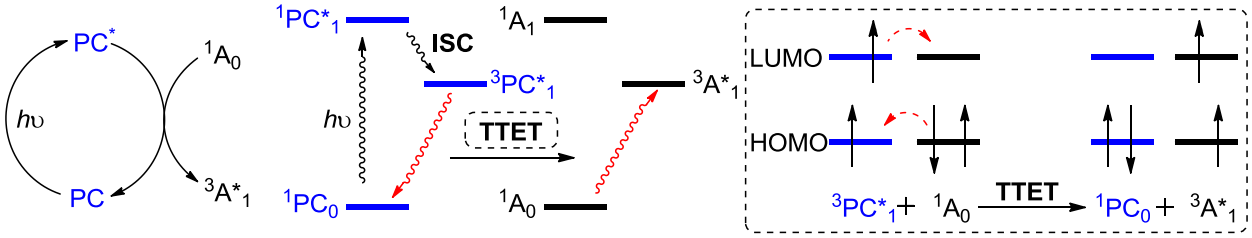
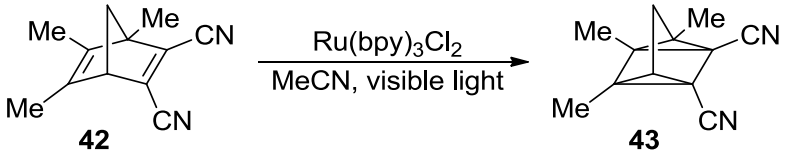


Figure 1.4. Triplet-triplet energy transfer from PC* to acceptor.

emitted by PC* are absorbed by the acceptor. Upon irradiation of photocatalyst (PC), followed by intersystem crossing (ISC), the long-lived lowest-energy triplet state ($^3PC^*_1$) may engage in energy transfer. Quenching of the triplet excited state PC* by an appropriate substrate results in promotion of its ground singlet state ($^1A_0$) to its lowest-energy triplet state ($^3A^*_1$), with concurrent conversion of the triplet excited state PC* to the singlet ground state.

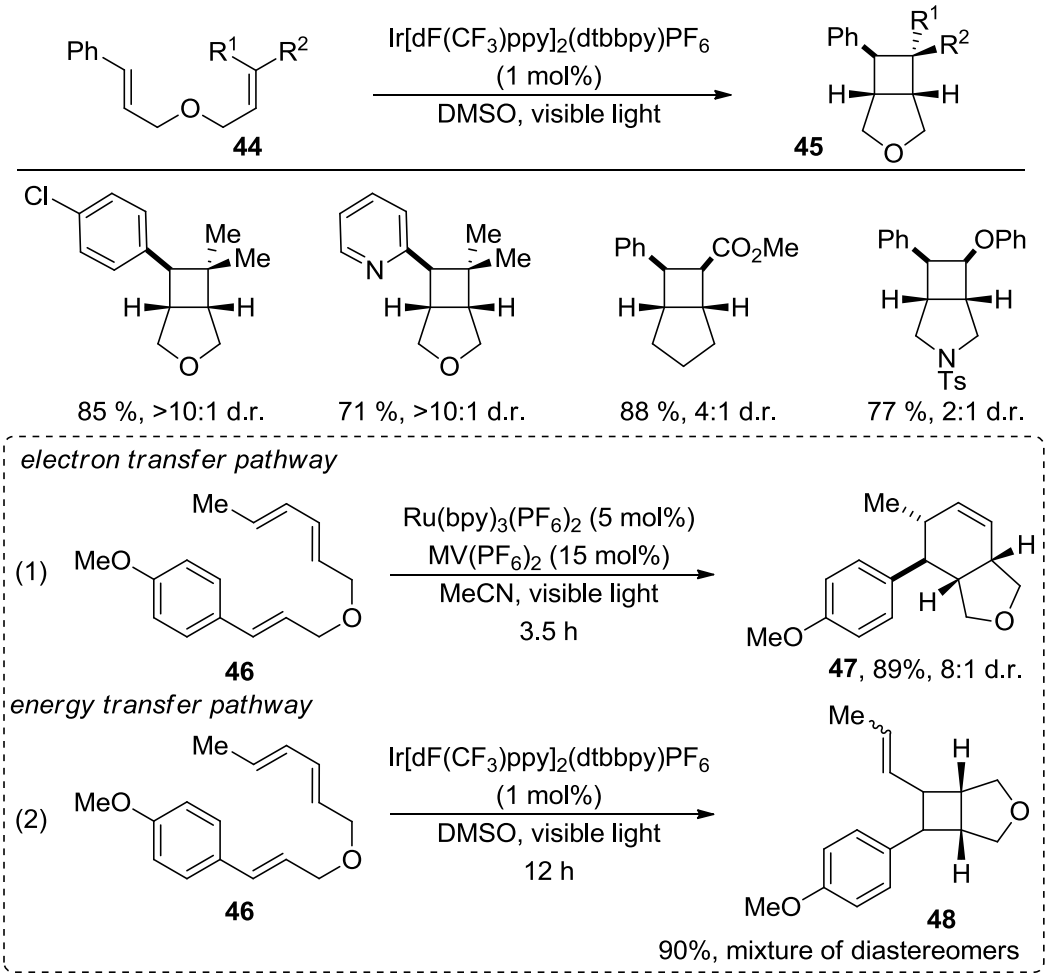
The triplet-triplet energy transfer process, related to quenching the luminescence of $Ru(bpy)_3^{2+}$ by organic compounds, such as anthracene, *trans*-styryl pyridine, and *trans*-stillbene, has been well documented.[56] However, synthetic applications involving triplet sensitization of organic substrates with visible light photocatalysts, to accomplish organic transformations, remain less explored. An early example by Kutal reported the $Ru(bpy)_3^{2+}$-induced valence photoisomerization of substituted norbornadiene **42** to quadricyclene **43 (**Scheme 1.11).[57] Direct photoexcitation promotes norbornadiene to its triplet state by the triplet-triplet energy transfer from triplet excited state $Ru(bpy)_3^{2+}$*, which then isomerizes to the corresponding quadricyclane. An electron-transfer pathway is not likely to occur due to the insufficient oxidation and reduction potentials of substrate **42** to quench $Ru(bpy)_3^{2+}$*. Another similar triplet-triplet energy transfer



Scheme 1.11. Photoisomerization of substituted norbornadiene to quadricyclene.

process was demonstrated by Castellano in the dimerization of anthracene sensitized by $Ru(dmb)_3^{2+}$ (dmb = 4,4'-dimethyl-2,2'-bipyridine).[58]

Recent reports by Yoon and co-workers described a [2+2] cycloaddition of styrenes catalyzed by $Ru(bpy)_3^{2+}$ via an electron transfer pathway. However, an electron-rich substitutent was required for one of the styrene in order to undergo single-electron oxidation to generate the key radical cation intermediate. To circumvent this limitation, the authors attempted to explore an energy transfer pathway for the [2+2] styrene photocycloaddition (Scheme 1.12).[59] Their control studies selected $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as the energy transfer catalyst and DMSO as the optimal solvent. They envisioned the Ir(III) complex to promote the [2+2] cycloaddition of

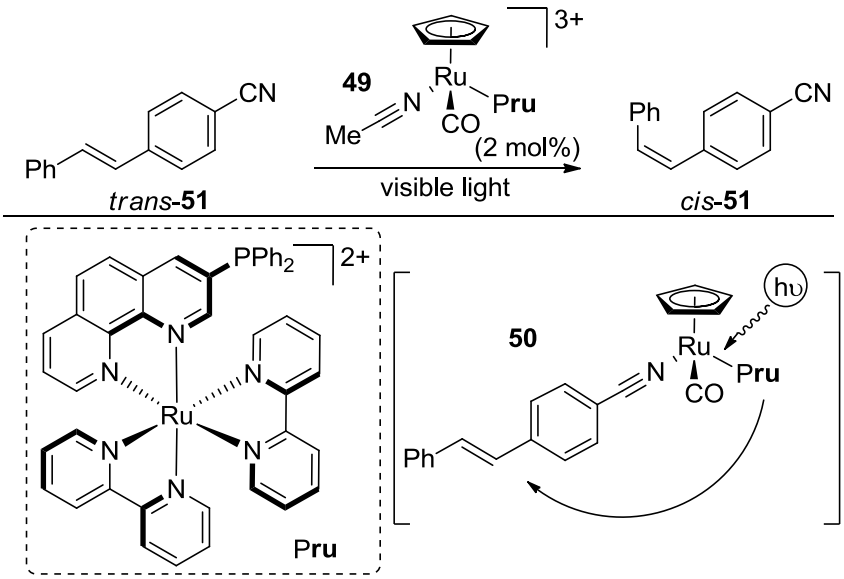


Scheme 1.12. [2+2] styrene cycloaddition via energy transfer pathway.

the electron neutral styrene to furnish the cyclobutane adducts. The styrene's high oxidation potential (+ 1.42 V) does not permit single-electron oxidation to the corresponding radical cation by the Ir(III) complex due to the insufficient redox potential of the photocatalyst [Ir(III)*/Ir(II) = +1.21 V]. Therefore, it is highly unlikely that the reaction proceeds via electron-transfer pathway. On the other hand, the excited state triplet energy of the Ir(III) complex, 61 kcal/mol, corresponds to the excited state triplet energies of styrenes, ~ 60 kcal/mol, thus enabling Ir(III) to promote sensitizing triplet-state reactions of styrene via an energy transfer pathway. The authors also probed the impact of the two different pathways on the product formation by conducting two parallel reactions that involve the same electron-rich styrene **46**, but under two different sets of conditions. The [4+2] product **47** was generated through a radical cation intermediate via an electron-transfer pathway (Scheme 1.12, Eq. 1). Conversely, the Ir(III) complex promoted cyclization of the electron-rich styrene **46** to yield the diastereomeric [2+2] cycloadduct **48** via an energy transfer pathway (Scheme 1.12, Eq. 2). In exploring the reaction scope, a wide range of substituted styrenes possessing both electron-rich and electron-deficient characters, in addition to heterostyrenes, were susceptible to the photocycloaddition. Enones, enoates, enol ethers, haloalkenes, and allenes were suitable coupling partners along with tolerable functional groups such as unprotected alcohols, halogens, and sulfonamides. However, aliphatic, non-conjugated alkenes were unable to undergo photocycloaddition, due to their higher triplet state energies.

In 2001, Osawa and co-workers reported a photocatalytic *trans*-to-*cis* isomerization of cyanostilbene[60] promoted by a bimetallic ruthenium (III) complex **49**, composed of "light-harvesting" ligand, identified as P**ru**. The unique ligand P**ru** is composed of a *tert*-phosphane ligand bearing a photosensitizing $Ru(bpy)_2(phen)$ fragment as a substituent. They envisioned photo-energy to be absorbed at the photoactive ruthenium complex ("sensitizer unit") in the

phosphane ligand and transmitted to the non-photoactive ruthenium metal center through a Ru-P bond. The authors prepared the bimetallic complex [CpRu(CH_3CN)(CO)(P**ru**)](PF_6)$_3$ (Cp= cyclopentadiene) to investigate the efficient visible-light activity at the CpRu center. The *trans*-to-*cis* isomerization of 4-cyanostilbene was catalyzed by the CpRu—P**ru** system in 85% yield. They postulated the formation of intermediate complex **50** in which the acetonitrile on the metal is substituted by 4-cyanostilbene. Through bridging the two ruthenium centers via the Ru—P**ru** bond, Osawa proposed the isomerization is mediated by triplet-triplet energy transfer from the P**ru** ligand to the cyanostilbene. Moreover, high concentration of acetonitrile lead to a dramatic decrease in the *trans*-to-*cis* isomerization, likely due to blocking the coordination of 4-cyanostilbene to the CpRu center. They concluded the approach of intramolecular sensitization via intermediate **50** is much more effective than that of intermolecular sensitization.



Scheme 1.13. *Trans*-to-*cis* isomerization of cyanostilbene via energy transfer.

1.4. Amine Radical Cations*

*Portion of this chapter has been published in Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. *Beilstein J. Org. Chem*. **2013**, *9*, 1977-2001.

Amine radical cations have emerged as useful reactive intermediates in amine synthesis due to its ability to access several modes of reactivity.[61] These odd-electron species can be

generated by the one-electron oxidation process of the corresponding amines. This method of accessing amine radical cations has been realized by using electrochemistry,[62] chemical oxidants,[63] metal-catalyzed oxidation,[64] UV light-mediated photochemistry,[65] and most recently visible light photocatalysis.[66, 67] Typically, due to amines inability to absorb visible light efficiently, photocatalysts such as ruthenium and iridium polypyridyl complexes or organic dyes are incorporated to initialize the single electron-transfer process. The initiation results from the generated photoexcited state which can be reductively or oxidatively quenched by an electron donor or acceptor, respectively. Amines are stable substrates, and are routinely used as reductive quenchers, to quench the photoexcited state while subsequently being oxidized to amine radical cations.

Introduced in the late 1970s, examples of amines being used as sacrificial electron donors were reported in water splitting[4, 68] and carbon dioxide reduction.[69] The innovative approach of using amine radical cations, generated via oxidation of amines under visible light photoredox conditions, has not been brought to the forefront until recently. Recent research efforts of the synthetic utility of amine radical cations have highlighted amines' ability to function as both the sacrificial electron donor and the substrate as well as participate in cascade reactions to undergo

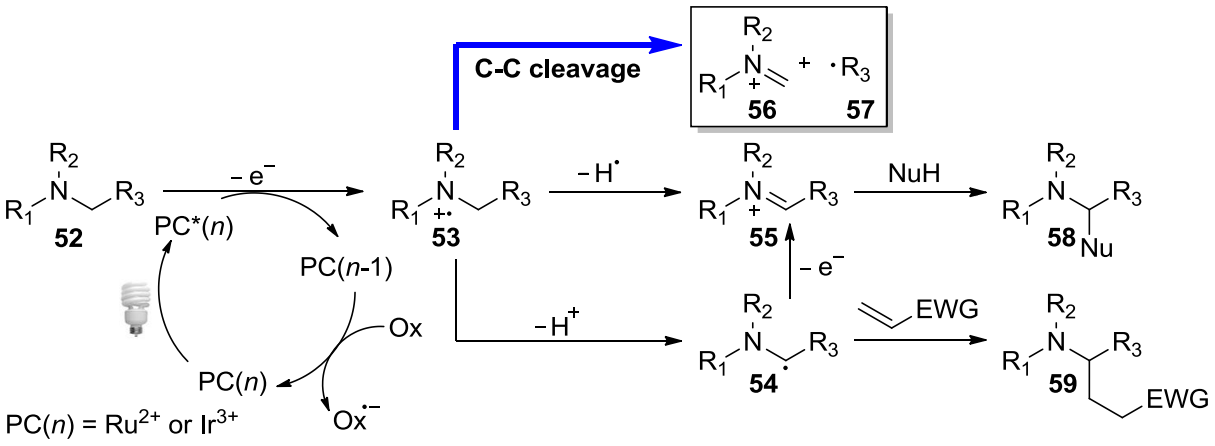


Figure 1.5. Amine radical cations' mode of reactivity.

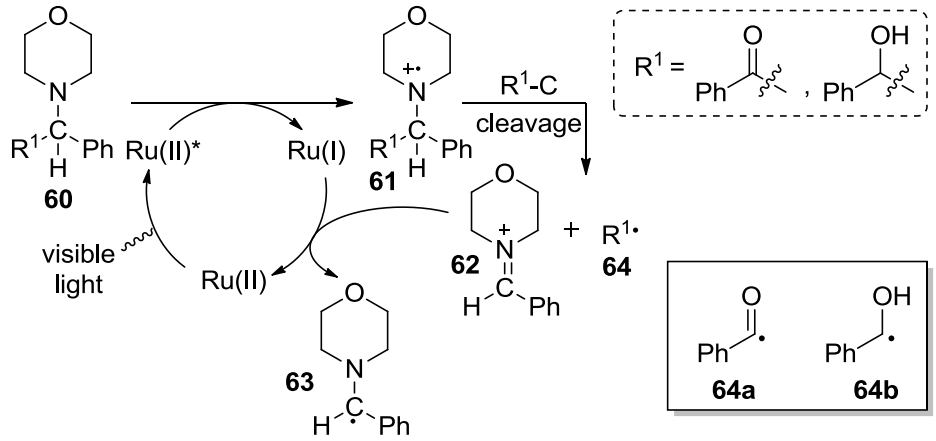
multiple bond formations in one synthetic operation.

Reductive quenching of the photoexcited state photocatalyst PC*(n) by amine **52** is controlled by the reduction potentials of the photoexcited state and the amine (Figure 1.5). The amine's reduction potential should be less positive than that of the photoexcited state (PC*). Upon oxidation, the fate of amine radical cations can vary depending on the reaction conditions. However, the pathways remain limited. Typically, electron-transfer reactions involving amine radical cations favor polar solvent, although the optimal solvent should be determined experimentally. Once formed, amine radical cation **53** has shown to possess four modes of reactivity. The first mode is the back electron transfer reaction of amine radical cation **53** to PC(n−1). This competing pathway of **53** accepting an electron from to the reduced photocatalyst is a major side reaction. Two alternatives[70] can be suggested in addressing this competing side reaction: modify the ligand of the PC to increase the difficulty of back electron transfer or design fast, irreversible cascade reactions of **53**. The second mode involves the loss of a proton from amine radical cation **53** to form a nucleophilic α-amino radical **54**. The newly formed radical can add to an electron-deficient pi bond, such as an alkene substituted with an electron-withdrawing group (EWG), to form a C-C bond and provide an α-amino substituted product **59** or undergo another one-electron oxidation to produce an iminium ion **55**. The rate for deprotonating **53** has been experimentally measured by several groups, though a broad range was reported.[71] The strong reducing nature of α-amino radical **54** suggests that the one-electron oxidation is facile. The third mode involves the loss of a hydrogen radical from **53** to produce the iminium ion **55**. In the presence of a good hydrogen atom acceptor, hydrogen atom abstraction has been accomplished in several reported reductions[23, 36, 55, 72] mediated by visible light. The electrophilic iminium ion **55** can be intercepted by a variety of nucleophiles to furnish

α-amino substituted products like **58**. The last mode is cleavage of a C-C bond α to the amine of radical cation **53**, thus generating iminium ion **56** and neutral free radical **57**. Notably, the synthetic utility of amine radical cations, as key intermediates to trigger cascade reactions, has been well documented in recent seminal works. Of all the active modes of amine radical cations, the C-C bond cleavage α to the nitrogen atom has been less exploited, and reports involving the cleavage remain limited. Select applications highlighting the fate of photogenerated amine radical cations that undergo C-C and N-N bonds are discussed in the following sections.

1.4.1. Cleavage of C-C and N-N bonds

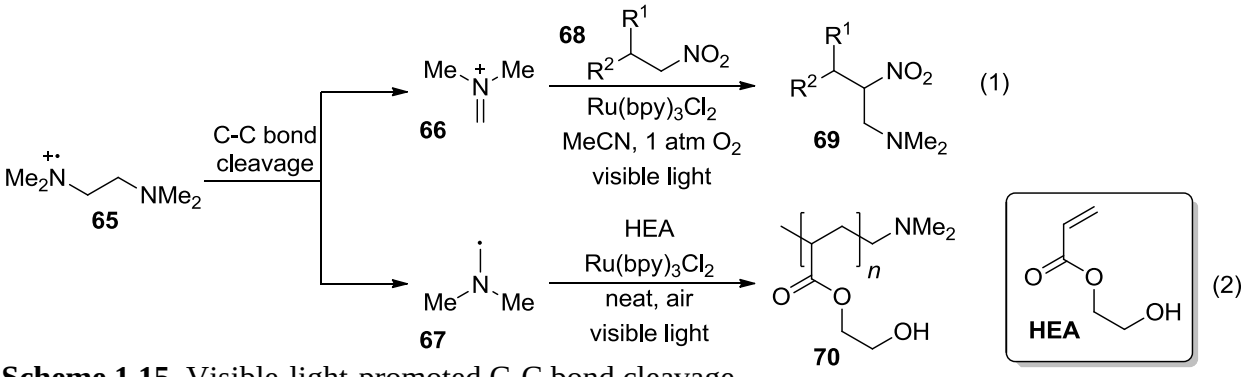
An early report by the Whitten group in 1986 showcased the fate of the amine radical cation by the cleavage of C-C bond via irradiation of substituted tertiary amines with a ruthenium complex under visible light (Scheme 1.14).[73] As a result, the generated carbon radicals (**64a** and **64b**) were identified by trapping the radials using electron spin resonance (ESR) spectroscopy in the presence of a spin trap. Detection of benzaldehyde by HPLC and vapor-phase chromatography (VPC) provided the evidence for the radical formation.



Scheme 1.14. Photoinduced C-C bond cleavage of tertiary amines.

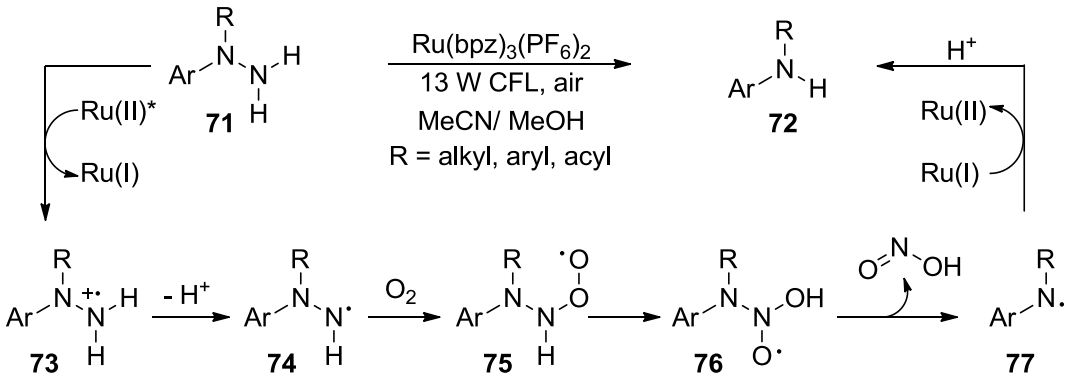
In 2012, Li and Wang described the cleavage of 1,2-diamines and exploited the utility of the cleaved products (Scheme 1.15).[74] Upon exposure to visible light, nitroalkanes **68** and tetramethylethylenediamine (TMEDA) were catalyzed by $Ru(bpy)_3Cl_2$ under a balloon of oxygen to provide the aza-Henry

products **69**, reasonably by intercepting the iminium ion **66** that is formed by cleaving amine radical cation **65** of TMEDA (Eq. 1). Formation of the amine radical cation is accomplished by the reductive quenching of Ru(II)* by TMEDA. Additionally, the amino radical pathway was detected by free-radical photopolymerization of 2-hydroxyethylacrylate (HEA) in presence of TMEDA and photocatalyst (Eq. 2). The incorporated dimethylamino group, generated by cleaving TMEDA, most likely induced the polymerization.



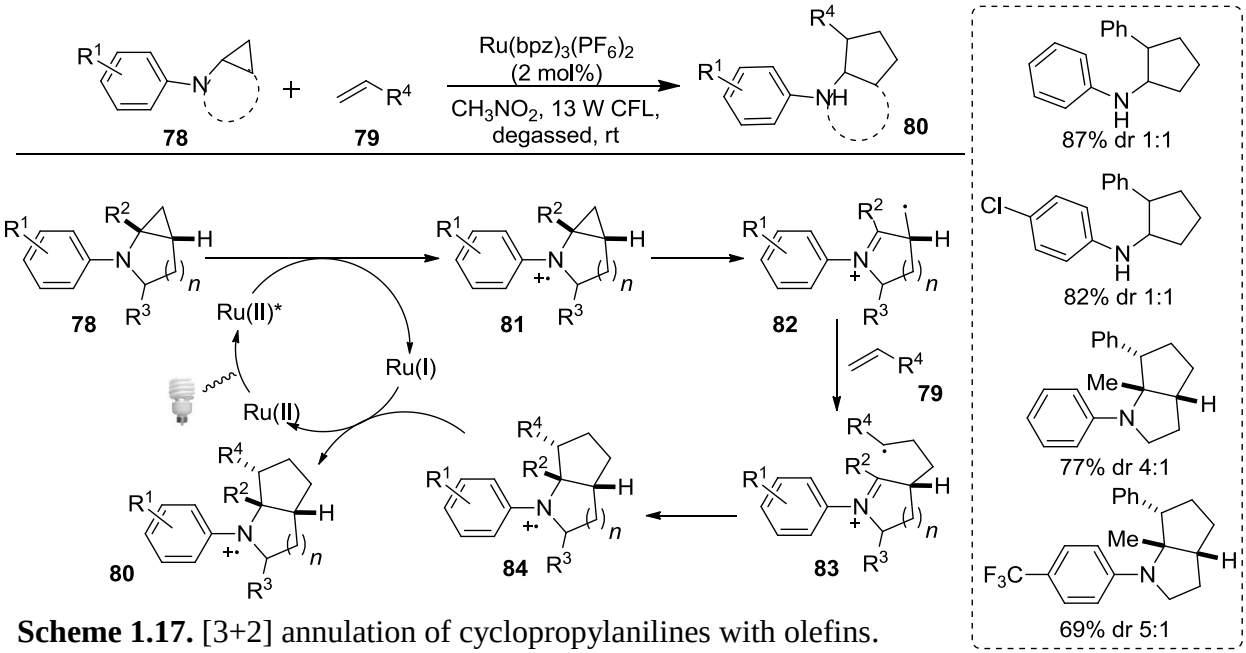
Scheme 1.15. Visible-light-promoted C-C bond cleavage.

Our group realized a photoinduced cleavage of N-N bonds of aromatic hydrazines and hydrazides by visible light (Scheme 1.16).[75] The catalytic system, which included $Ru(bpz)_3(PF_6)_2$, 13 W CFL, and air, was generally effective for *N*,*N*-disubstituted hydrazines and hydrazides. An aryl group as one of the two substituents on the nitrogen atom was required. Electron-rich hydrazines were reported to be more reactive than hydrazides, as we postulated the photoexcited state of Ru(II) complex to be reductively quenched by these electron-rich donors. We proposed the initiation of cleavage corresponded to the oxidation of hydrazines/ hydrazides **71** to the amine radical cation **73** by the photoexcited state catalyst. Upon deprotonation, the formed neutral radical **74** reacted with oxygen to afford radical **75**. Radical **75** was converted to an oxygen-based radical **76**, which subsequently underwent a cleavage reaction to give secondary amine radical **77**. Lastly, reduction followed by protonation of amine radical **77** produced secondary amine **72**.



Scheme 1.16. Photoinduced cleavage of N-N bonds of aromatic hydrazines/hydrazides.

In 2012, our group applied amine radical cations of *N*-cyclopropylanilines to cleave a C-C bond, resulting in a [3+2] annulation with olefins catalyzed by $Ru(bpz)_3^{2+}$.[76] The cleavage (α to the nitrogen atom) provided a distonic radical cation bearing a β-carbon radical and an iminium ion, which was then intercepted by olefins to yield the [3+2] annulation adducts (Scheme 1.17). Cyclopropanes were introduced to serve as a three-carbon synthon, upon ring-opening due to ring strain. Mechanistically, we envisioned reductive quenching of the photoexcited state Ru(II)* by *N*-cyclopropylaniline **78**, concomitantly being oxidized to the amine radical cation **81** and producing the reduced Ru(I). The newly formed amine radical cation **81** then underwent a C-C bond cleavage to generate β-carbon radical iminium ion **82**, which subsequently adds intermolecularly to the olefin **79** in a Giese-type fashion yielding a more stable radical **83**. Intramolecular addition of the stabilized radical to the iminium ion, followed by reduction via Ru(I) furnished the cyclopentane adduct **80**, thus completing the catalytic cycle. The optimal catalytic system detailed a degassed solution of $Ru(bpz)_3(PF_6)_2$ (2 mol %) in nitromethane at room temperature, irradiated with a 13 W CFL. The concept of using amines as both the sacrificial donor and the substrate was introduced, although the scope was limited to secondary or tertiary amines substituted with an aryl group. A required aryl group helps lower the reduction potential of the amine to allow the initial oxidation by photoexcited



Scheme 1.17. [3+2] annulation of cyclopropylanilines with olefins.

$Ru(bpz)_3$ to occur readily. Mono- and bicyclic cyclopropylanilines were susceptible to the annulation to afford cyclopentanes and fused bicyclic systems in moderate to excellent yields. However, modest diastereoselectivity was achieved with the bicyclic systems, unlike the monocyclic systems that underwent the annulation with little diastereoselectivity. The described [3+2] annulation catalyzed by visible light photoredox catalysis was 100% atom economy and overall redox-neutral.

Amine radical cations have displayed its utility in amine synthesis as reactive, synthetic intermediates. As a result, the accessibility to several modes of their reactivity triggers multiple downstream pathways of generating diverse synthetic intermediates such as electrophilic iminium ions and nucleophilic radicals. Trapping of these intermediates has accomplished various organic transformations to derivatize amines, which is beneficial in amine synthesis. Notably, synthetic methods detailing the use of amine radical cations in applications of C-C and N-N bond cleavage were induced by visible light photoredox catalysis, showcasing the new method for accessing synthetic intermediates. In particular, our findings of the [3+2]

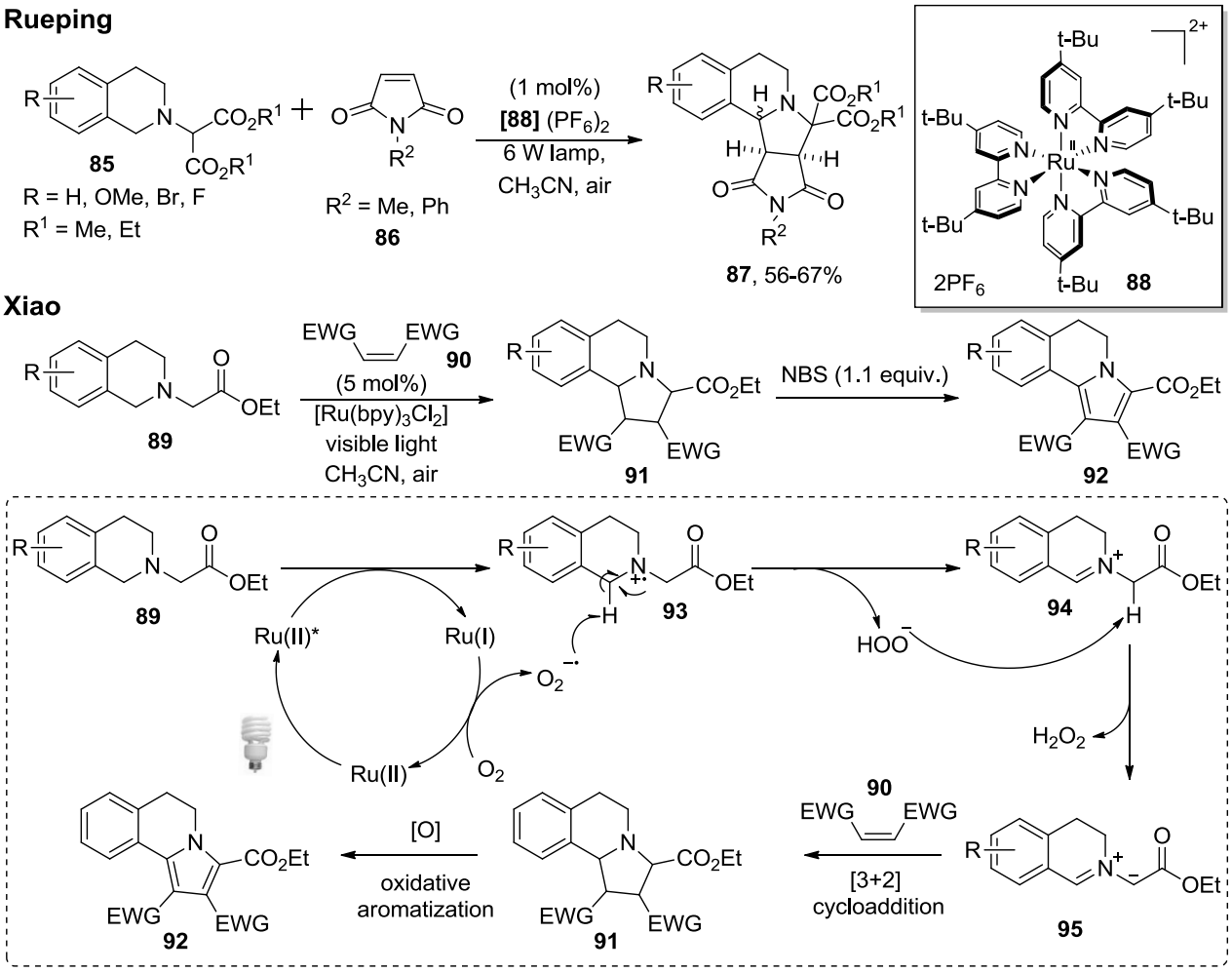
cycloaddition with olefins, which involved cyclopropyl C-C bond cleavage initiated by the photogenerated amine radical cation, have provided new insights to cycloaddition reactions. The combining of photoredox processes with cycloaddition reactions has further enhanced the benefits and values for this class of reactions. Researchers have recently recognized this powerful tool and have investigated numerous cycloadditions mediated by visible-light.

1.5. Visible-light Mediated [3+2] Cycloadditions

Developing efficient and innovative approaches of constructing five-membered rings remains of great interest to synthetic chemists. Five-membered rings, such as cyclopentanes and the heterocycles analogues, continue to serve as an important class of building blocks in organic synthesis. A common method of accessing them is [3+2] cycloadditions. This powerful class of reactions is an essential tool for constructing structurally complex compounds possessing five-membered rings via the simultaneous formation of two new σ-bonds and up to four stereocenters. Formation of new C-C and/or C-heteroatom bonds, rings, and stereocenters all in one application highlights the efficiency of this process. Recently, a new variant of the [3+2] cycloaddition mediated by visible light has demonstrated great utility for the production of complex five-membered ring systems. Reported examples have highlighted the reductive quenching of the photoexcited catalysts as the favorable pathway.

Cycloaddition of azomethine ylide formation

In 2011, Xiao[77] and Rueping[78] independently described a method of forming fused pyrrolidines and pyrrole via a [3+2] dipolar cycloaddition of tetrahydroisoquinolines and a range of dipolarphiles (Scheme 1.18). The authors recognized that the photooxidation of derived tetrahydroisoquinolines, substituted with a methylene group adjacent to the N-atom, would form the highly reactive iminium ions which can be readily converted to the corresponding stabilized



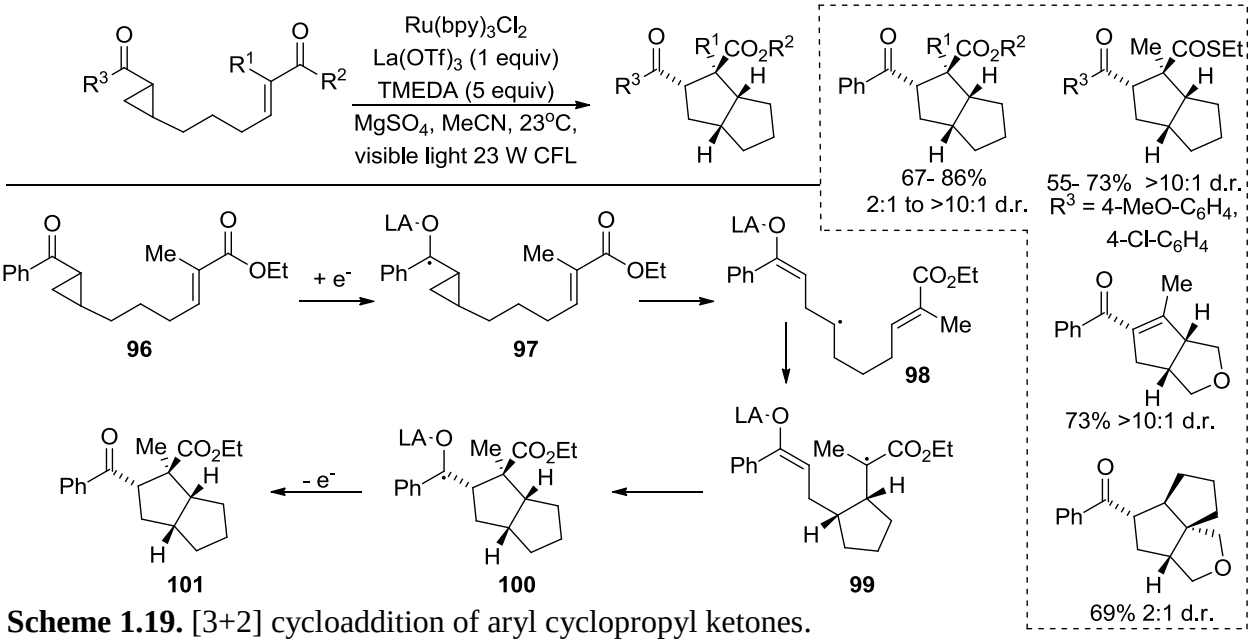
Scheme 1.18. [3+2] dipolar cycloaddition of azomethine ylide formation.

azomethine ylide via loss of a proton. This important class of ylides has been reported to participate in the [3+2] dipolar cycloaddition. The azomethine ylides, generated *in situ*, was then intercepted by a range of dipolarophiles to produce fused pyrrolidines **87** and **91**. Additionally, Xiao recognized further oxidation of the pyrrolidine ring to furnish aromatized fused pyrrole **92** upon treatment with NBS. Separately, Xiao and Rueping successfully produced highly functionalized heterocycles in good to excellent yields. The authors proposed a plausible mechanism of the [3+2] dipolar cycloaddition, illustrated in Scheme 1.18. Upon irradiation by visible light, the photoexcited state of Ru^{2+} would oxidize tetrahydroisoquinoline **89** to amine radical cation **93**. The turnover of the catalyst, by oxidation with molecular oxygen, provided

superoxide radical, which abstracted a hydrogen atom to generate the highly reactive iminium ion **94**. Deprotonation by a molecule of hydroperoxide anion would convert iminium ion **94** to azomethine ylide **95** with the release of hydrogen peroxide. A subsequent [3+2] dipolar cycloaddition with a dipolarophile **90** would yield fused pyrrolidine **91**. In Xiao's work, further oxidation aromatized the pyrrolidine moiety, furnishing pyrrole **92**.

Cycloaddition of aryl cyclopropyl ketones

Yoon and co-workers disclosed cycloadditions of cyclopropyl ketones mediated by visible light photoredox conditions, based upon the formation of a distonic radical anion via ring opening of cyclopropyl ketones (Scheme 1.19).[20] The [3+2] cycloaddition of simple aryl cyclopropyl ketones efficiently underwent the desired transformations based on a mechanism analogous to the one Yoon proposed for [2+2] cycloadditions involving the generation of radical anions. They envisioned the photoreduced $Ru(bpy)_3^{1+}$ would initiate the ring opening of cyclopropyl ketones and catalyze the two C-C bond formation. It was proposed that the one-electron reduction of aryl cyclopropyl ketone **96** produced radical anion **97**, which subsequently

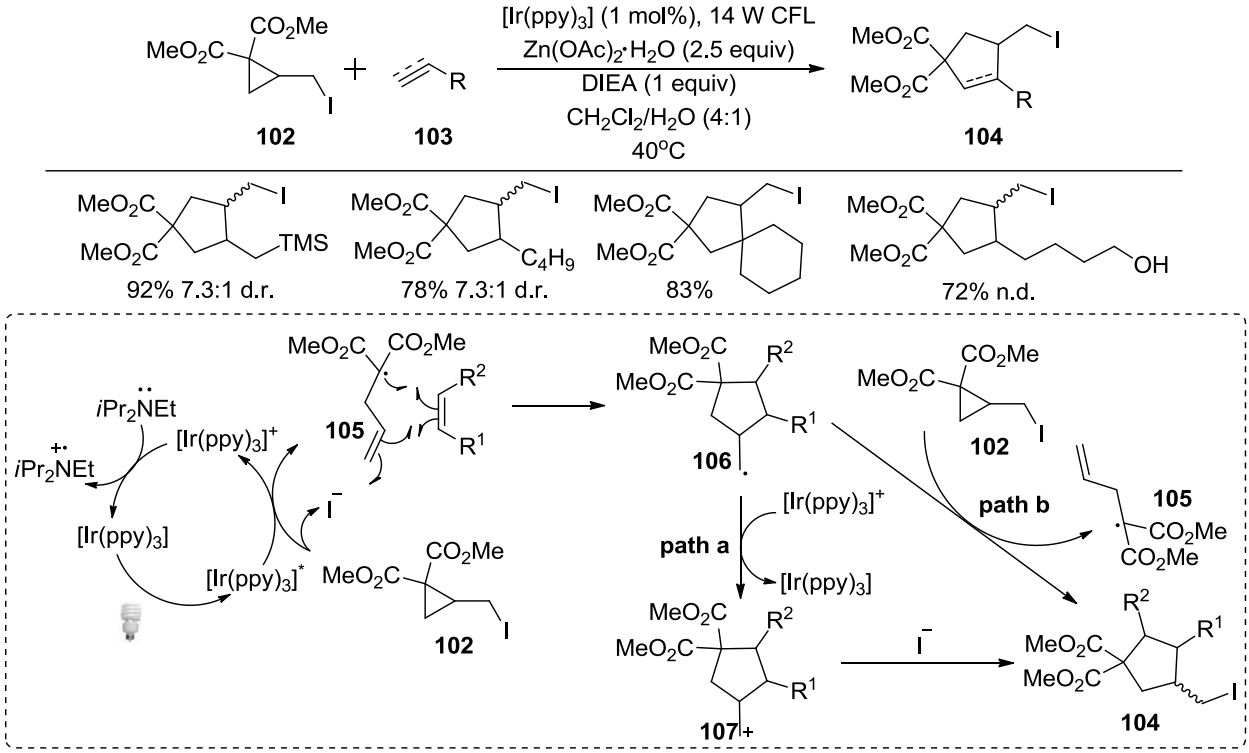


Scheme 1.19. [3+2] cycloaddition of aryl cyclopropyl ketones.

underwent ring opening to furnish distonic radical anion **98**. Upon two radical cyclization and loss of an electron, the intramolecular [3+2] cycloadduct **101** was provided. In addition to $Ru(bpy)_3Cl_2$, a strong Lewis acid $La(OTf)_3$, stoichiometric reductant TMEDA, and $MgSO_4$ played essential roles to afford the cycloadduct in acceptable yields (55-86%). Various esters, ketones, and thioesters (in particular α-substituted) were well tolerated to provide excellent diastereoselectivity of the quaternary carbon stereocenters generated in the product. In regards to the scope, the authors observed that a ketone bearing an aryl group was required.

Cycloaddition of 2-(Iodomethyl)cyclopropane-1,1-dicarboxylate with Alkenes/Alkynes

Atom-transfer radical additions or cyclizations (ATRA/ ATRC) have become a successful tool in constructing highly functionalized cyclic frameworks by forming two new C-C bonds. However, stoichiometric hazardous radical initiators are usually employed. Alternatively, using strong reducing photoexcited $Ir(ppy)_3$ presents a convenient method for



Scheme 1.20. Yao's intermolecular visible-light ATRC [3+2] cycloaddition.

forming carbon radicals from alkyl, alkenyl, or aryl halides. Recently, Yao[79] reported a nonreductive, intermolecular visible-light photoredox [3+2] ATRC reaction of unactivated alkyl iodides as radical precursors. Initially optimizing the reaction with dimethyl-2-(iodomethyl) cyclopropane-1,1-dicarboxylate **102** and electron-rich terminal alkene **103**, the ideal conditions required [$Ir(ppy)_3$] as the photocatalyst using a 14 W CFL and *N*,*N*-diisopropylethylamine (DIEA) as the sacrificial electron donor to produce product cycloadduct **104**. Polar solvents (e.g. CH_2Cl_2/H_2O (4:1)) displayed a significant effect in promoting the reaction to excellent yields. To their delight, the aide of a Lewis acid, which is thought to coordinate to the carbonyl groups of the dicarboxylate, enhanced the reactivity towards less electron-rich alkenes. $Zn(OAc)_2•2H_2O$ revealed to be the best Lewis acid among those screened. The reaction conditions were applied to other substrates, proceeding smoothly to give the desired cyclopentane/cyclopentene derivatives. Terminal alkynes and terminal alkenes with various functional groups were tolerated to afford the desired products in moderate to excellent yields (23-92%). A radical chain reaction mechanism was proposed, depicted in Scheme 1.20. An on/off light-switching experiment was employed as a mechanistic study to facilitate and support their plausible mechanism. Upon irradiation, photoexcited Ir complex would be oxidized by malonic ester **102**. As the halogen atom in **102** accepted the electron, it would leave as a halide anion while generating homoallylic radical **105**. Sequentially the [3+2] cyclization would occur with an olefin to furnish cyclopentyl carbinyl radical **106**. From here, two pathways may occur for conversion to the desired product **104**. Along pathway a, radical intermediate **106** could be oxidized by the Ir^+ complex to give the cyclopentyl carbinyl cation **107**, which then could be intercepted by the iodide anion to afford cycloadduct **104**. Along pathway b, abstraction of the iodine from **102** by **106** would give cycloadduct **104**, thus regenerating radical **105**. In studying

the radical propagation step, Yao's observations support a radical/polar crossover pathway (pathway a); however pathway b cannot be excluded.

Visible light photoredox catalysis has shown to be a prominent tool to promote cycloaddition reactions. This new attractive approach of merging the photoredox cycle with cycloaddition reactions has accomplished unique cycloaddition reactions, including the construction of highly functionalized and complex carbo- and heterocycles. Notably, the development of photoredox catalyzed [3+2] cycloadditions has valued the use of radical ring-opening of cyclopropanes. Examples described by Yoon, Yao, and our group employed this strategy by recognizing the ability of cyclopropanes to serve as reactive three-carbon synthons. Thus, cyclopropanes are advantageous building blocks for the construction of complex systems due to its ring-opening strategies.

1.6. Types of Activated Cyclopropane: Ring-opening Strategies

Cyclopropane derivatives are widely used as versatile substrates in organic synthesis due to its excellent reactivity and accessibility.[80, 81] They are commonly recognized in natural products of biological interest and applied as useful synthetic intermediates to prospective biologically active compounds.[82] More recently, the ring opening strategies of cyclopropanes have drawn much attention to synthetic applications.[83, 84] Because cyclopropanes are relatively stable, they are not susceptible to bond cleavage unless activated; thus, polarizing one of the C-C bonds is desired. The activation of the strained three-carbon carbocycle (115 kJ/mol)[85] is highly influenced by the nature of its substituents, generally electron-donating or –accepting functional groups. As a result, different substituents would be able to access different reaction pathways of the ring system. More importantly, the modified substituents are able to tune the reactivity and selectivity of activated cyclopropanes to achieve excellent regio- and stereoselectivities. The

modes of activation for cyclopropanes, by nucleophiles or electrophiles, have accomplished various organic transformations that include ring opening or ring expansion reactions, cyclodimerizations and cycloadditions. Among the activated cyclopropanes are three main classes of substituted cyclopropanes with an acceptor, a donor, or a donor-acceptor (Figure 1.6).

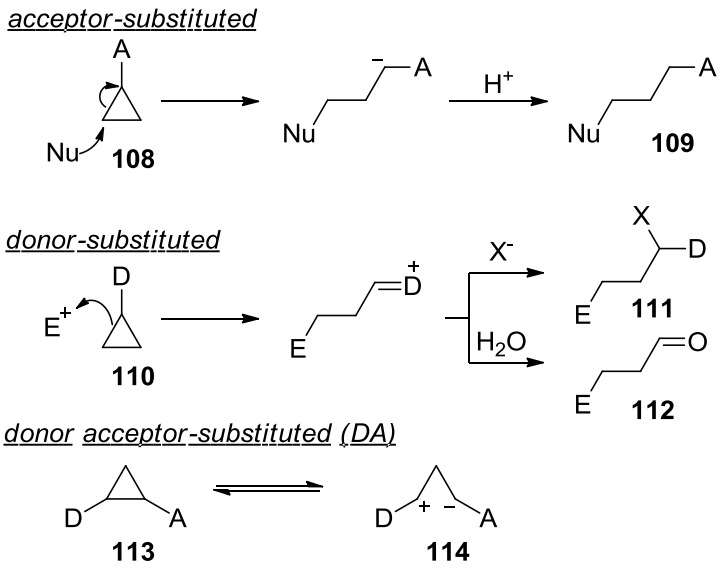


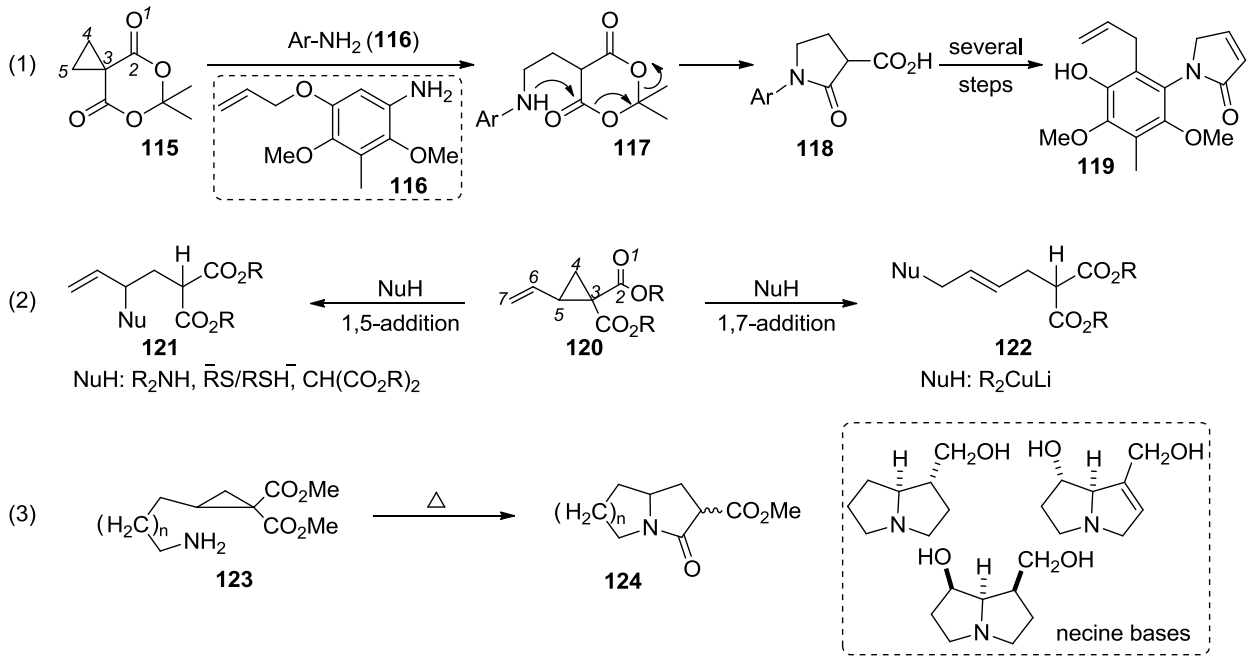
Figure 1.6. Types of substituted cyclopropanes.

Acceptor-substituted cyclopropane **108** functions as a homologous Michael system that can undergo nucleophilic attack, as opposed to a donor-substituted cyclopropane **110**, a homologous enolate equivalent, that acquires an electrophile to further provide either **111** or **112**. Prominently, donor-acceptor substituted (DA) cyclopropane **113** is commonly employed in a variety of synthetic applications due to its high versatility after ring cleavage. The readily cleaved process results in zwitterionic intermediate **114** in which the negative charge is stabilized by the acceptor while the positive charge is stabilized by the donor. The 1,3-zwitterionic relationship can further undergo different transformations such as cycloaddition and rearrangement.[80, 83, 86]

1.6.1. Acceptor-substituted Cyclopropanes

Early approaches of utilizing electrophilic cyclopropanes in organic synthesis were investigated to study the ring-opening processes.[87] Inter- and intramolecular nucleophilic ring-openings of the activated cyclopropanes were disclosed, thus showing new methods and

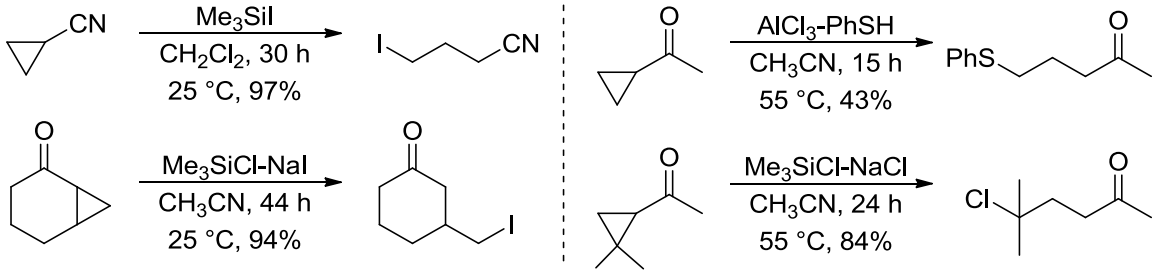
strategies to access synthetic intermediates. The early work of Danishefsky reported the ring-opening strategies to formulate a homologous (or 1,5) version of the Michael reaction.[87] In general, nucleophilic ring-openings involve two geminal substituents on the cyclopropanes, typically electron-withdrawing groups such as esters, carbonyls, nitriles, or other groups that can stabilize carbanions. Cleavage of the doubly activated cyclopropane is rationalized by the overlapping of the cleaved C-C bond and both carbonyl activating groups. For instance, intermolecular ring opening of diester activated cyclopropane (spiroacylal) **115** was realized with aromatic amine **116**, subsequently followed by intramolecular acylation to yield 1-arylpyrrolinone **118**, which can be readily converted to Δ^3-pyrrolone **119** (Scheme 1.21, Eq. 1). When activated cyclopropanes are extended with olefins, a new mode of the ring opening emerges. Although the 1,5-addition pathway is predominantly favored, influences of certain nucleophiles can promote another possible mode of cleavage, referred as the 1,7-addition (Eq. 2). Danishefsky discovered this minor competing pathway in vinylcyclopropanes doubly activated



Scheme 1.21. Inter- and intramolecular nucleophilic addition to electrophillic cyclopropane.

with ester groups such as **120**.[88] Danishefsky was also interested in the concept of achieving ring openings of doubly activated cyclopropanes via an intramolecular nucleophilic addition. The approach of an intramolecular ring opening successfully demonstrated the conversion of amino diester **123** to lactam ester **124** (Eq. 3). The author envisioned the method to provide new synthetic routes to the stereospecifc synthesis of necine bases, in addition to synthesis of bicyclic ring systems.

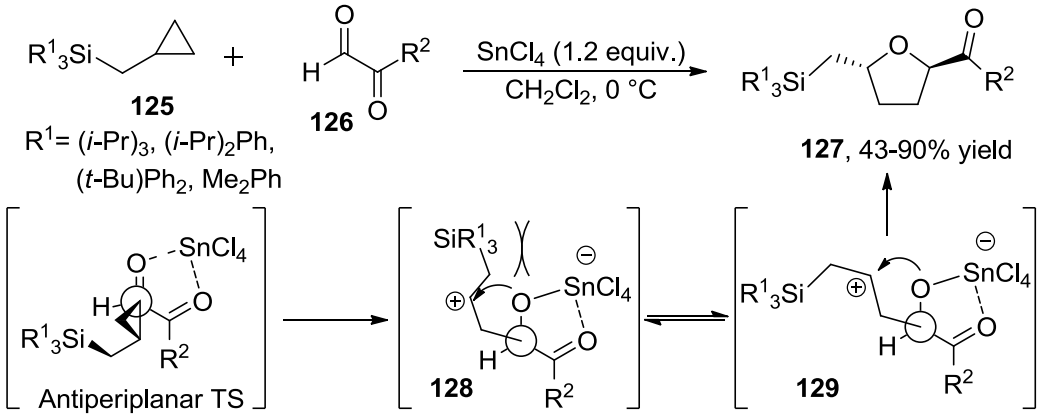
The nucleophilic ring-opening reactions discussed above have been confined to doubly activated cyclopropanes, bearing two geminal electron-withdrawing groups. Thus, accomplishing the same ring opening strategy with monoactivated cyclopropanes, under mild reaction conditions, would improve the scope of this strategy. Dieter developed a method of introducing reagents such as Me_3SiCl-NaBr, $AlCl_3$-PhSH, and Me_3SiI, in combination with an appropriate nucleophile, to successfully cleave the conjugated cyclopropanes (Scheme 1.22).[89] Importantly, the authors recognized the parallel between the soft β-carbon of cyclopropyl carbonyl compound and the α,β-unsaturated carbonyl compound to further explore the scope of the homologous Michael addition process. Applying the hard and soft acids/bases principle, the most effective in promoting ring-opening of monoactivated cyclopropanes involved the combination of a hard acid with a soft nucleophile; however, the scope was limited to halide and sulfur nucleophiles.



Scheme 1.22. Ring-opening of monoactivated electrophilic cyclopropanes.

1.6.2. Donor-substituted Cyclopropanes

The electron donor substituted cyclopropanes are frequently employed in electrophilic ring-opening reactions, primarily due to facile and regio-cleavage of the C-C bond. They are regarded as homoenolate equivalents in which the activated donor substituted cyclopropane is attacked by an electrophile. With respect to electrophilic ring-opening, cyclopropanes bearing hydroxy, silyloxy, silylmethyl, and aryl groups as donor substituents have been well-documented; however, alkylthio, arylthio, and amino substitutents have been less studied. In the late 1970s, trimethylsilylmethyl was introduced as donor substitutents to assist in ring opening of cyclopropanes, resulting in the production of substituted olefins.[90] Due to its unique properties, silicon groups are commonly employed to aid in the stabilization of the β-carbocation through either hyperconjugation via the β-effect or formation of a siliranium cation via internal neighboring group participation. In 2005, Akiyama and co-workers demonstrated a [3+2] cycloaddition reaction of cyclopropylmethylsilanes **125** and α-keto aldehyes **126** for the *trans*- and *cis*-selective preparation of 2-silylmethyltetrahydrofurans (Scheme 1.23).[91] Lewis-acid



Scheme 1.23. [3+2] cycloaddition with trimethylsilylmethyl cyclopropane.

$SnCl_4$ was found to be the optimal promoter to form the *trans*-tetrahydrofuran derivatives **127**, at 0 °C. However, conducting the reaction at -78 °C revealed the preferred *cis*-tetrahydrofuran derivatives. To rationalize the stereochemical outcome, the authors proposed

cyclopropylmethylsilane to attack the electrophillic $SnCl_4$–activated aldehyde in an anti-periplanar transition state, thus giving the β-silyl carbocation. Upon ring closure, the *cis* adduct can be formed kinetically via transition state **128**; however when warmed up to 0 °C, the intermediate can undergo isomerization through thermodynamic transition state **129** to further obtain the *trans* adduct. Various silanes and α-keto aldehydes, including heteroaromatic glyoxals and butyl glyoxylate were suitable substrates to afford the tetrahydrofuran derivatives in 43-90% yield. Independently, the Dobbs group was intrigued by the facile access of the 2,5-disubstituted THF motif as they are widely found in nature and in polyether-containing compounds and antibiotics. The authors confirmed the temperature controlled outcome of the identical [3+2] cycloaddition reaction by further defining the scope as well as the relative stereochemistry of the adducts by NOE measurements and X-ray crystallography.[92] Notably, the novel scaffolds demonstrated potential usage in heterocycle synthesis by subsequent transformation of the 2,5-disubstituted THF adducts.[93]

In addition to silylmethylcyclopropane as effective donor-substituted cyclopropanes, frequent reports of ring-opening strategies have been documented with hydroxy-substituted cyclopropanes, cyclopropanols. Among the most commonly used heteroatom-substituted cyclopropanes, cyclopropanol and its derivatives are characterized as useful intermediates in organic synthesis due to their ability to participate in synthetically useful transformations involving regiocontrolled ring opening of the strained carbocycle.[94] The regioselective ring cleavage involves the hydroxyl group to direct the ring opening that result in the electron-deficient center to reside on the donor oxygen atom (as in

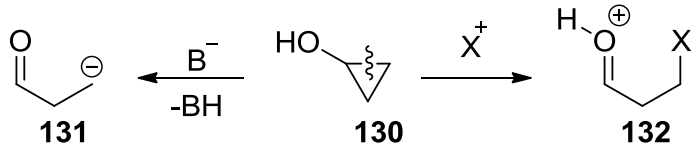
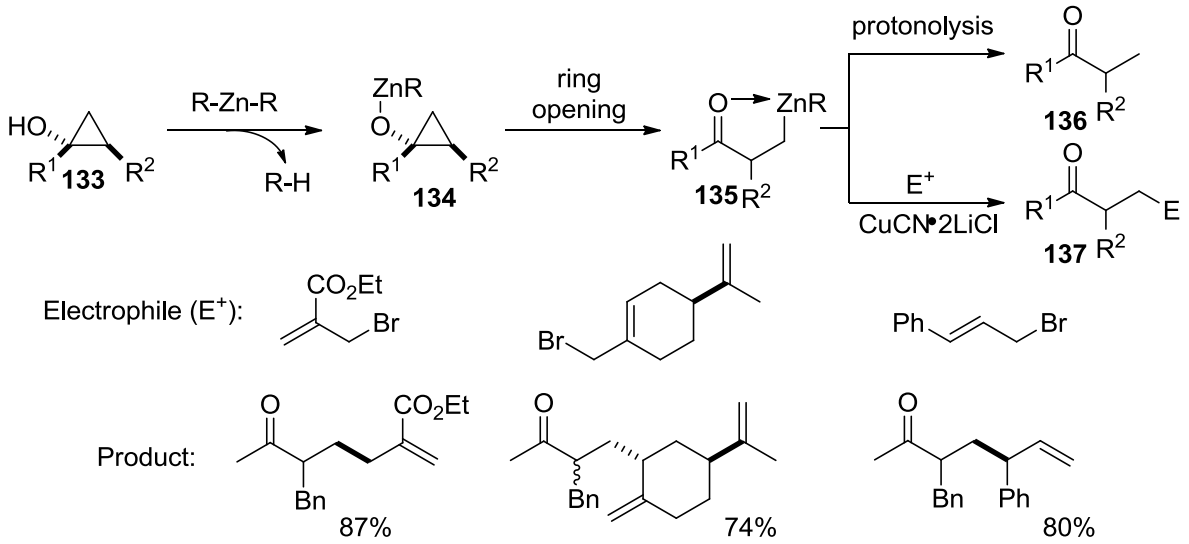


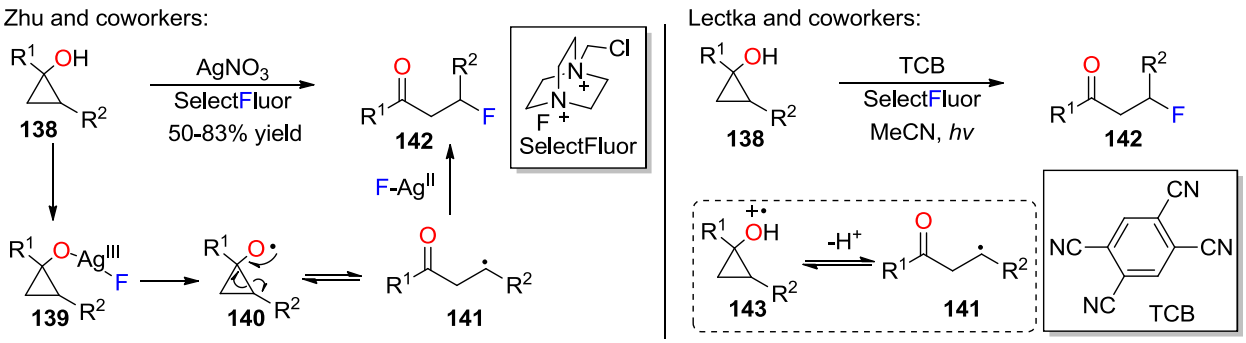
Figure 1.7. Ring cleavage of cyclopropanol.

132), while the carbanion resides at the β-position of the carbonyl group (as in **131**). Prominently, the resulted ring cleavage functions as a homoenolate anion equivalent to serve as a valuable tool for the synthesis of functionalized acyclic carbonyl-containing organic molecules.



Scheme 1.24. Zinc homoenolates via ring-opening of cyclopropanols.

Recently, Cha and co-workers prepared functionalized zinc homoenolates, from the ring opening of cyclopropanols promoted by dialkylzinc reagents, for the synthesis of α-methyl substituted ketones (Scheme 1.24).[95] They envisioned the zinc alkoxide **134** to undergo regioselective ring opening to furnish the zinc homoenolate **135**, accompanied by a proton transfer pathway to yield **136**. The authors continued their studies of metal homoenolates by developing a S_N2' alkylation of cyclopropanols via mixed zinc/copper keto homoenolates to access C-C bond formation.[96] To a THF solution of the racemic cyclopropanol **133** and $ZnEt_2$ was added CuCN•2LiCl and an allylating reagent (E^+). The in situ trapping of zinc homoenolate **135** was accomplished by the allylic reagent to give the alkylating adducts **137**. The use of various allylating reagents, including nonracemic allylating reagents, and functionalized cyclopropanols were compatible to result in regioselective preference of S_N2' over S_N2.

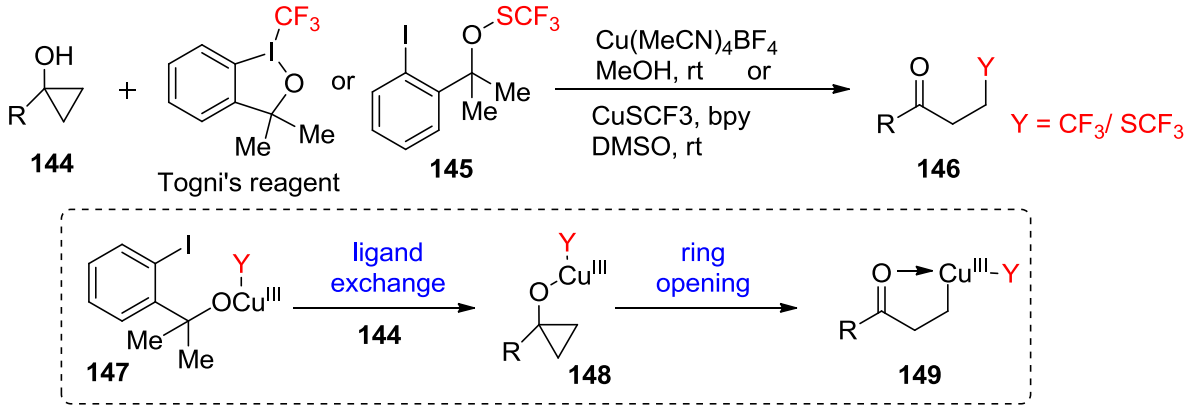


Scheme 1.25. Ring-opening/ β-fluorination of cyclopropanols.

The β-keto radicals, which are analogous to the homoenolates and also generated via ring-opening of cyclopropanols, have been routinely used to synthesize functionalized acyclic carbonyl compounds via C-C bond formation. Notably, with the introduction of fluorine atoms found in organic molecules, developing an efficient fluorination method would be beneficial in pharmaceuticals, agrochemicals, and material sciences. Thus, a regioselective synthesis of β-fluorinated ketones from tertiary cycloalkanols via a silver-catalyzed ring opening strategy was described by Zhu and co-workers[97] (Scheme 1.25). The conversion of cyclopropanols to β-fluorinated ketones was accomplished using silver salt $AgNO_3$, and fluorinating agent, SelectFluor. The authors proposed a mechanistic pathway that involves the formation of F-Ag^{III} species **139** leading to oxo-radical cyclopropane **140**. The β-keto radical **141**, formed upon ring opening, reacts with the F-Ag^{II} species to give the desired β-fluoroketone **142**. Recently, a photocatalyzed protocol of the same transformation was reported using photosensitizer 1,2,4,5-tetracyanobenzene (TCB) and SelectFluor (Scheme 1.25).[98] It was suggested that the photoexcited TCB* oxidizes the cyclopropanol to the radical cation **143** via electron transfer, which is followed by subsequent ring opening/fluorination to furnish the β-fluorinated ketones **142**.

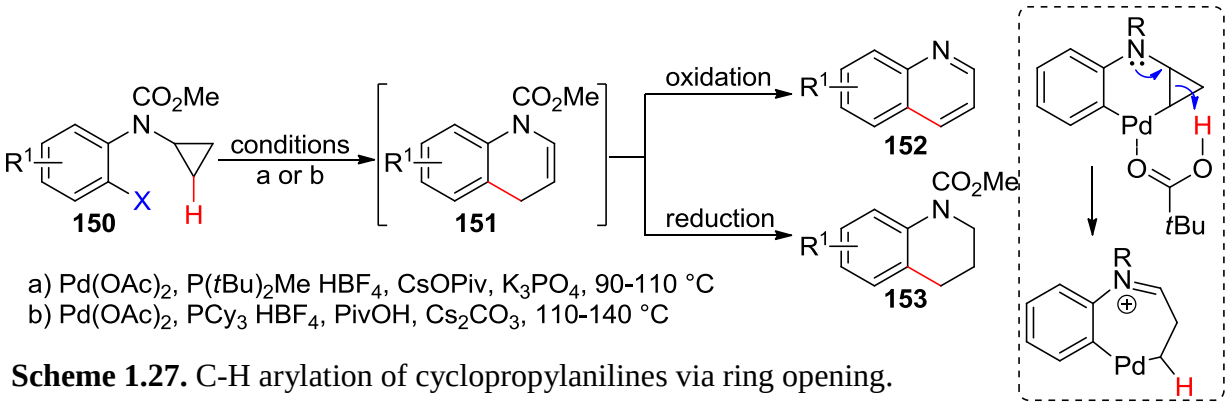
Continuing the development of new efficient fluorination strategies, recent efforts of the Dai group showcased the first copper-catalyzed ring-opening electrophilic trifluoromethylation

and trifluoromethylthiolation of cyclopropanols (Scheme 1.26).[99] The transformations tolerated a wide range of functional groups for the synthesis of β-CF_3 and β-SCF_3 substituted ketones via the Togni reagent and a benziodoxole derivative **145**, respectively. The role of copper was proposed to undergo oxidation with the Togni reagent/ derivative **145** followed by ligand exchange of the Cu(III) intermediate **147** with cyclopropanol **144** to yield intermediate **148**. Cyclopropyl C-C bond cleavage rendered homoenolate **149**, which enabled the C_{sp3}-CF_3/ C_{sp3}-SCF_3 bond formation. Notably, their methodology was applied in the preparation of a clinical drug for type 2 diabetes mellitus.



Scheme 1.26. Ring-opening/ β-trifluoromethylation of cyclopropanols.

As discussed above, cyclopropanols have been overwhelmingly exploited to accomplish a variety of synthetic transformation via electrophilic ring-opening of the cyclopropyl group. However, reports with aminocyclopropanes still remain limited. Over the past decade, the development of methods for C-H bond functionalization has significantly impacted synthetic strategies in organic synthesis, particularly sp^3 C-H bonds. Seminal work by Fagnou described a palladium(0)-catalyzed intramolecular arylation of cyclopropylanilines for the synthesis of qunioline and tetrahydroquinoline derivatives (Scheme 1.27).[100] Substituted phenyl cyclopropyl carbamates **150** were subjected to the catalytic system (Pd source, base, and pivalate additive), to provide the dihydroquinolines **151**. Subsequent one-pot oxidation by 2,3-dichloro-5,6-



Scheme 1.27. C-H arylation of cyclopropylanilines via ring opening.

dicyanobenzoquinone (DDQ) or reduction by Pd/C furnished the quinolines **152** or tetrahydroquinolines **153**, respectively. Mechanistic experiments supported the rationale of the sp^3 C-H functionalization to occur prior to the ring opening.

Electrophilic ring-opening reactions with donor substituted cyclopropanes have exhibited much value in the advances of new synthetic strategies applied in organic transformations. Moreover, the generated homoenolate equivalent serves as the key synthetic intermediate for new bond formations, thus illustrating its potential growth in the development of new opportunities for valuable applications.

1.6.3. Donor-Acceptor (DA)- substituted Cyclopropanes

The increased reactivity of donor-acceptor (DA) cyclopropanes **113** results from the vicinal relationship between both donor and acceptor groups, which work in a synergistic manner to activate the C-C bond for cleavage.[80, 101] The activated vicinal DA cyclopropanes serve as synthetically useful 1,3-dipolar synthons **114**, via the push-pull effect, to promote a variety of reactions

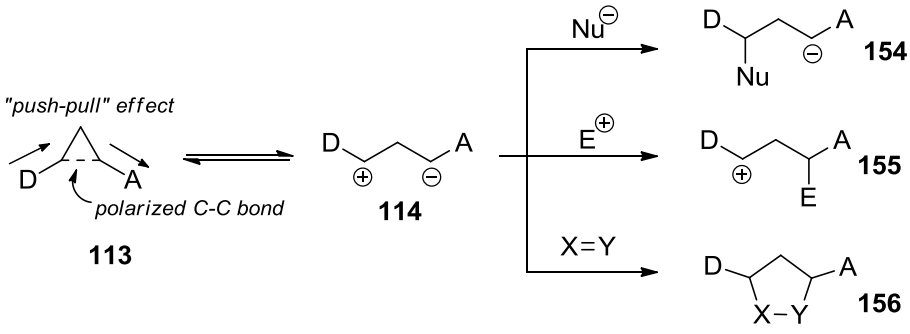
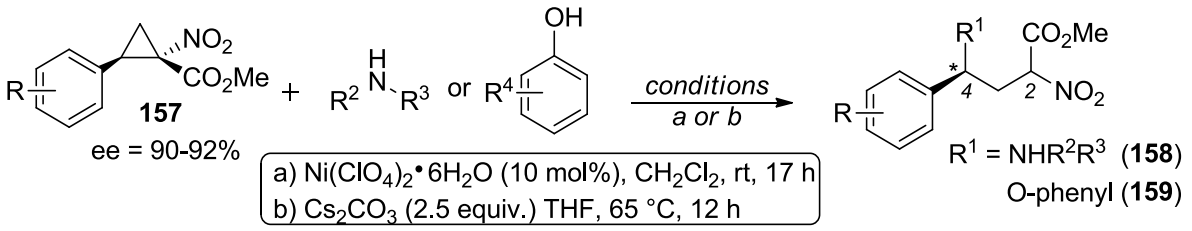


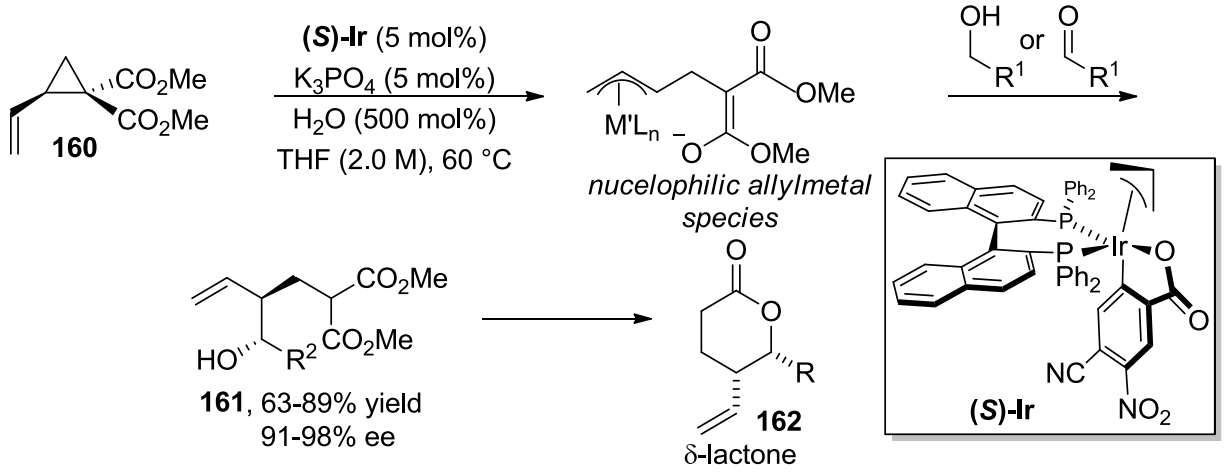
Figure 1.8. Reactions of activated vicinal DA cyclopropanes.



Scheme 1.28. Ring-opening reactions of DA cyclopropanes with nucleophiles.

with nucleophiles, electrophiles, or dipolarphiles (Figure 1.8). The dual activation of vicinal substituents further enhances the synthetic applications of cyclopropanes by combining both homo-Michael and homo-enolate equivalents into one synthon. In addition, the acquired umplung reactivity is advantageous to achieve transformations that are challenging by previous routes. One of the approaches to ring opening reactions of DA cyclopropanes is nucleophilic addition by heteroatom nucleophiles or electron rich arenes, usually mediated by a Lewis acid. The carbanion **154** bearing the acceptor group can then be protonated to provide 1,3-bifunctionalized acyclic derivatives, which are found in biologically active small molecules . A ring opening strategy by Charette reported a nucleophilic addition of primary or secondary amine nucleophiles to enantiomerically enriched DA cyclopropanes (methyl 1-nitrocyclopropanecarboxylates **157**) catalyzed by $Ni(ClO_4)_2$ as a Lewis acid (Scheme 1.28).[102] The amino-functionalized products **158** were achieved in good yields (63-94%) with complete retention of enantiomeric excess at C-4. The doubly activated cyclopropanes were employed again in a similar ring opening strategy using a variety of phenol derivatives as nucleophiles to provide the 1,3-bifunctional adducts **159** (53-84%), in the presence of Cs_2CO_3 as the base.[103] This method enabled quick access to 3-aryl-3-phenoxypropane motifs, which are found in numerous monoamine reuptake inhibitors, such as Strattera.

Another approach to ring opening of DA cyclopropanes proceeds through reactions with electrophiles to yield 1,3-substituted acyclic systems, analogous to the transformed adducts

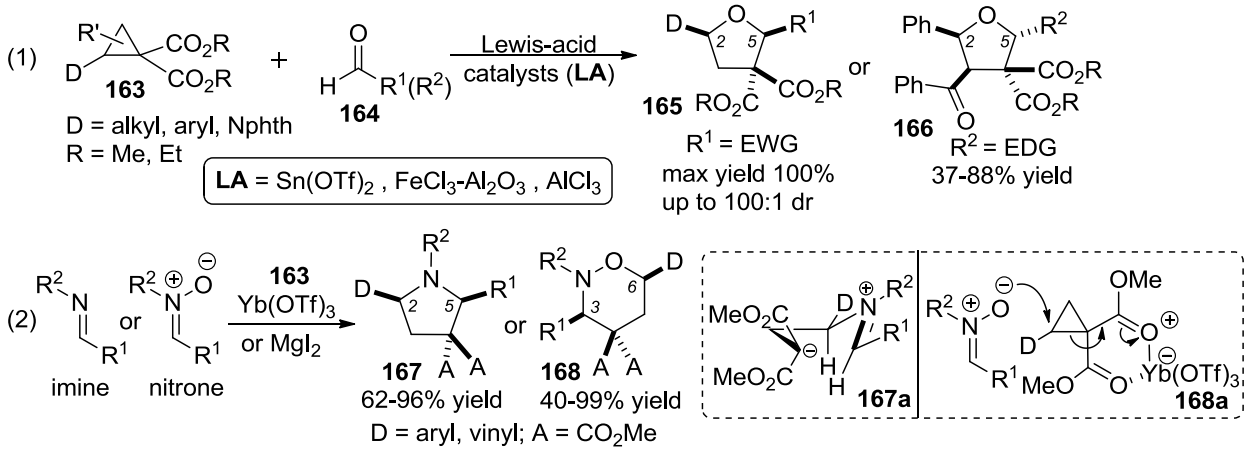


Scheme 1.29. Ring-opening reactions of DA cyclopropanes with electrophiles.

mentioned with nucleophiles. Recent developments introduced transition metals to promote the ring cleavage, while employing acceptor-substituted vinylcyclopropanes as suitable substrates to undergo the transformation. The key nucleophilic π-allyl-metal species formed thus enables an inverse of polarity and reactivity of DA cyclopropanes by the observed electrophilic trapping at the donor site. In contrast to the normal polarity, the nucleophilic reactivity at the donor site arises as a result of the umpolung reactivity. In 2011, the Krische group investigated a DA cyclopropane-mediated carbonyl allylation catalyzed by a cyclometalated iridium complex (Scheme 1.29).[104] The enantioselective C-C coupling process tolerated alcohols or aldehyde oxidation levels as effective carbonyl electrophiles to provide the desired enantiomerically enriched products **161**. Moreover, further conversion to disubstituted δ-lactones **162** was successfully realized.

In addition to the nucleophilic and electrophilic approaches to ring opening of activated DA cyclopropanes, cycloadditions with various dipolarophiles have been commonly exploited as a pathway to ring-opening cyclization. Cycloadditions has become a prominent tool for the construction of highly functionalized and complex polycyclic structures, produced in one single step. The bond breaking and bond forming event (stepwise or concerted) provides the ability to

control the stereochemical outcome of the reaction. Moreover, high regioselectivity is attained by the preferential addition of the partially charged centers in the dipolarophiles with the 1,3-dipole cyclopropane. Both inter- and intramolecular cycloadditions of DA cyclopropanes have been widely investigated and have continued to showcase its applicability in organic synthesis and natural products. For instance, numerous reports by Johnson,[105] Waser,[106] Yang,[107] and others described aldehyde compounds undergoing [3+2] cycloadditions with DA cyclopropanes **163** for the formation of tetrahydrofuran (THF) derivatives (Scheme 1.30, Eq. 1). Alkyl- and aryl-substituents were susceptible donor groups on the cyclopropane while the acceptor groups were limited to geminal ester substituents. Successfully catalyzed by various Lewis-acids, cycloadditions with neutral or electron-deficient aldehydes resulted in high stereoselectivity for the preferred 2,5-*cis*-configured tetrahydrofuran adducts **165**. Likewise, amino-substituted tetrahydrofuran derivatives were synthesized by replacing the donor group with an amine substituent (i.e. Nphth) on cyclopropane **163**. Notably, the stereochemical outcome of the cycloaddition was highly influenced by the choice of aldehyde as 2,5-*trans* products **166** were observed with electron-rich aryl aldehydes.



Scheme 1.30. Ring-opening cycloaddition of DA cyclopropanes with aldehydes, imines, and nitrones.

Analogous to the carbonyl systems are imines and nitrones which have been reported to participate in the cycloadditions with DA cyclopropanes to provide tetrahydropyrroles/ pyrrolidines and 1,2-oxazines, respectively (Scheme 1.30, Eq. 2). The Kerr group investigated the preparation of 2,5-*cis*-pyrrolidines **167** from a [3+2] cycloaddition of aldimines and 1,1-cyclopropanediesters **163** catalyzed by a mild Lewis-acid, $Yb(OTf)_3$.[108] The diastereoselectivity was rationalized by model **167a**, similar to Johnson's, illustrating a Mannich-type ring closure in which the diaxial interaction between substituent (R^1) of the imine and ester of the cyclopropane was minimized. Under the same Lewis acidic conditions or promoted by magnesium iodide (MgI_2), the authors revealed a [3+3] cycloaddition of nitrones with 1,1-cyclopropanediester to yield tetrahydro-1,2-oxazines **168**, as the cis isomer exclusively.[109] Upon generating the nitrone *in situ*, via an aldehyde and hydroxylamine, the oxygen anion produced is proposed to open the cyclopropane ring in a nucleophilic fashion (see **168a**). Further mechanistic evidences supported a stepwise pathway rather than a concerted pathway. While much intermolecular ring opening cyclizations of DA cyclopropanes have been well-documented, examples involving an intramolecular transformation have become more frequent.[110] Likewise, the required acid needed to activate the ring cleavage has lead to the ongoing development of various catalytic procedures. Major advantages of the intramolecular route include increased and controllable reactivity to achieve high selectivities, as well as rapid formation of complex polycycles and natural products.

The modes of activation for cyclopropanes have allowed development of various ring-opening strategies to further showcase its broad utility in organic transformations. The susceptibility to C-C bond cleavage has permitted substituted cyclopropanes to serve as valuable substrates in synthetic applications. Among the activated cyclopropanes, cyclopropanols have

been most frequently investigated as donor-substituted cyclopropanes. However, ring-opening strategies with aminocyclopropanes remain less explored. Successful cycloadditions with DA cyclopropanes have sparked the interest of investigating cycloadditions with aminocyclopropanes as an effective ring-opening strategy for donor-substituted cyclopropanes. To the best of our knowledge, no reports of aminocyclopropane undergoing cycloaddition, mediated by visible light photocatalysis, has been documented prior to our group's discovery of the [3+2] annulation of cyclopropylanilines.

1.7. Conclusion

Visible light photoredox catalysis has emerged as a prominent tool for the development of efficient photochemical reactions. The adopted photochemical method has showcased a variety of promising organic transformations contributed by a number of researchers. The use of transition metal polypyridyl complexes, including ruthenium and iridium, highlighted the catalytic activation of organic substrates to engage in either single-electron transfer or energy transfer pathway. Moreover, the advantage of tuning and modulating the photophysical properties of the photocatalysts has lead to newly discovered reactions in addition to accomplishing challenging novel transformations and reaction efficiencies. The emphasis of these photocatalysts operating as either strong reductants or oxidants has broadened their utility in organic synthesis, as demonstrated in recent synthetic applications which included the chemistry of amine radical cations. Induced by photoredox catalysis, the synthetic utility of amine radical cations as reactive intermediates was highlighted by their accessibility to several modes of reactivity. As a result, the finding of a ring-opening strategy of cyclopropylaniline was disclosed, which prompted the development of visible light mediated [3+2] annulation reactions.

The effective and versatile method of merging visible light photocatalysis with

cycloaddition reactions has accomplished the construction of complex carbocyclic and heterocyclic substances, prepared in an atom economical fashion. Furthermore, complex products can be formed under mild reaction conditions due to the benefits of incorporating the photoredox cycle. The continuous efforts by organic chemist have uncovered the use of visible light to promote cycloadditions, which has greatly impacted the synthetic community. Overall, visible light photoredox catalysis exhibits a promising future in the discovery of applicable synthetic chemistry. The ongoing progress in this field continues to make significant advances by developing new and valuable transformations along with addressing challenges and limitations. Bringing to the forefront are the diverse applications of visible light mediated reactions that establish new potential avenues for further exploitation.

Chapter 2. Intermolecular [3+2] Annulation of Cyclopropylanilines with Alkynes

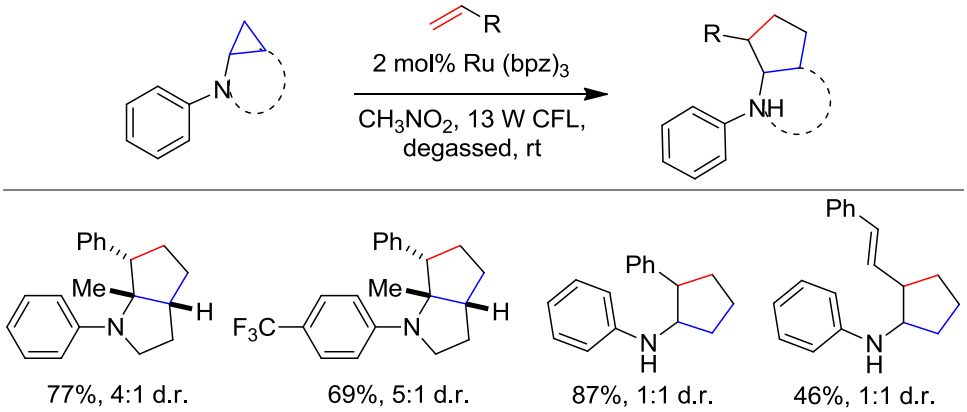
2.1. Introduction

Cycloaddition or annulation reactions are among the most important classes of versatile reactions utilized in organic synthesis, particularly in natural products and biologically active substances.[111] These types of reactions are most commonly effective for the production of structurally diverse and complex carbocycles and heterocycles of various sizes, such as small molecules, emphasizing their prominence in diversity-oriented synthesis (DOS).[112] When considering what constitutes a cycloaddition reaction, one can consider the concerted or the stepwise reaction, proceding in either an intramolecular or intermolecular-like fashion. In addition to their excellent atom economy, cycloaddition enables the construction of complex multiple bonds and stereocenters in one single step with predictable stereochemistry. These appealing features highlight cycloadditions as preferred reactions in organic synthesis. Therefore, developing novel approaches to promote cycloaddition reactions has acquired the attention of synthetic chemist.

Recently, visible light photocatalysis has been illustrated to promote cycloaddition reactions as a strong synthetic strategy.[16, 113, 114] The activation is initiated by electron transfer or energy transfer via visible light in the presence of a photocatalyst. This new attractive method of merging the photoredox cycle with cycloaddition reactions has accomplished unique organic transformations, while significantly expanding the scope and utility of cycloaddition reactions. Within the past eight years, newly reported cycloaddition methods mediated by visible light have been realized by several research groups.[20, 21, 40, 59, 76-79, 115] Their use of reductive quenching cycle, oxidative quenching cycle, or energy transfer pathway sufficiently demonstrated the impact of visible-light promoted cycloadditions by forming multiple bonds and stereocenters in

one single step. Our group was particularly intrigued in the development of visible-light mediated [3+2] cycloadditions. The application of photoredox processes in atom economical reactions, for the construction of 5-membered rings, sparked our interest to further explore the potential of [3+2] annulation reactions. Although several reports have showcased this cycloaddition/ annulation strategy,[20, 77-79] much research effort to expand the scope of visible light photoredox catalysis to provide reactive intermediates for [3+2] annulation reactions and their application to synthesis is in continual progress.

Our group's initial investigation of an oxidation-triggered cycloaddition synthetic strategy resulted in the findings of a [3+2] annulation of mono- and bicyclic cyclopropylanilines with terminal olefins, such as styrene.[76] Mediated by photoredox catalysis, the annulation provided saturated heterocycles in synthetically useful yields and modest to poor diastereoselectivity, as shown in Scheme 2.1. The afforded fused saturated heterocycles, from the annulation with bicyclic cyclopropylanilines, displayed synthetic relevance as a motif of interest commonly present in natural products and pharmaceuticals. Interestingly in the presence of two olefins, such as a conjugated diene (i.e. 1-phenyl-1,3-butadiene), annulation was observed with the preferred terminal double bond in complete chemoselectivity. Furthermore, diastereoselectivity was better achieved in annulation with the bicyclic cyclopropylanilines



Scheme 2.1. [3+2] annulation of cyclopropylanilines with olefins.

versus the moncyclic cyclopropylanilines. Driven to better comprehend the lack of diastereoselectivity, we directed our focus towards investigating the annulation of monocyclic cyclopropylanilines with alkynes to furnish unsaturated cyclopentenes.

2.2. Results and Discussion: [3+2] Annulation with Alkynes*

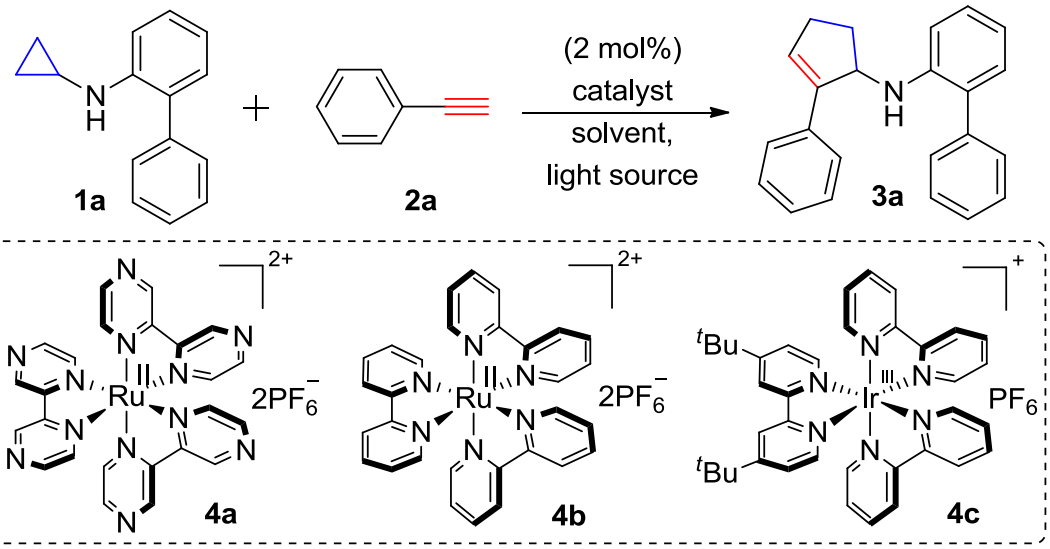
*Portion of this chapter has been published in Nguyen, T. H.; Maity, S.; Zheng, N. *Beilstein J. Org. Chem*. **2014**, *10*, 975-980.

The visible-light mediated [3+2] annulation with olefins presented a facile method of synthesizing various amino-containing compounds from simple starting material. To address the poor diastereoselectivity observed in the monocyclic system, it was envisioned that a similar intermolecular [3+2] annulation could be accomplished with alkynes, instead of alkenes, to provide aminocyclopentenes.[116] These desired aminocyclopentenes can be useful synthetic building blocks for various amine derivatives such as aminocyclopentitols. This class of amine compounds has been shown to exhibit properties as a potent inhibitor for glycosidases, which are important targets for developing treatments of numerous diseases such as diabetes, cancer, and viral infections.[117] Importantly, the synthetic strategy of utilizing the [3+2] annulation approach provides rapid access to cyclic allylic amines, which can further serve as templates to other unique derivatives.

2.2.1. Reaction Optimization of Cyclopropylaniline with Phenylacetylene

Biphenylcyclopropylamine **1a** and phenylacetylene **2a** were chosen as the standard substrates to optimize the catalyst system for the [3 + 2] annulation with alkynes (Table 1). The data was collected using gas chromatography (GC) with dodecane as the internal standard. Similar to the annulation with alkenes, several reactivity patterns were observed. CH_3NO_2 was far superior to DMF and CH_3CN as the solvent (Table 1, entries 1–3). CH_3NO_2 that was dried

Table 1. Optimization of [3+2] annulation with phenylacetylene.



Entry[a]	Catalyst	Light	Solvent	GC yield (%)[b]
1	$Ru(bpz)_3(PF_6)_2$ (**4a**)	18 W LED	CH_3NO_2	82 (80)[c]
2	$Ru(bpz)_3(PF_6)_2$ (**4a**)	18 W LED	DMF	20
3	$Ru(bpz)_3(PF_6)_2$ (**4a**)	18 W LED	CH_3CN	36
4	$Ru(bpy)_3(PF_6)_2$ (**4b**)	18 W LED	CH_3NO_2	55
5	$Ir(ppy)_2(dtbbpy)PF_6$ (**4c**)	18 W LED	CH_3NO_2	47
6[d]	$Ru(bpz)_3(PF_6)_2$ (**4a**)	18 W LED	CH_3NO_2	41
7	$Ru(bpz)_3(PF_6)_2$ (**4a**)	13 W CFL	CH_3NO_2	68
8[e]	$Ru(bpz)_3(PF_6)_2$ (**4a**)	Blue LEDs	CH_3NO_2	46[f]
9	$Ru(bpz)_3(PF_6)_2$ (**4a**)	(18 W LED) X 2	CH_3NO_2	50
10	No catalyst	18 W LED	CH_3NO_2	6
11	$Ru(bpz)_3(PF_6)_2$ (**4a**)	No light	CH_3NO_2	3

[a]Conditions: **1a** (0.2 mmol), **2a** (1 mmol), solvent (2 mL), degassed, and irradiated at rt for 8 h. [b]Dodecane was used as an internal standard. [c]Isolate yield by silica gel chromatography. [d]The reaction was conducted in the presence of air. [e]Reaction time of 45 h. [f]NMR yield.

over 4 Å molecular sieves was sufficient, since distilled CH_3NO_2 gave comparable yields.

$Ru(bpz)_3(PF_6)_2$ was observed to be the most effective photocatalyst when compared to $Ru(bpy)_3(PF_6)_2$ and $Ir(ppy)_2(dtbbpy)PF_6$ (Table 1, entries 4 & 5). Among the reduction potential

of the photoexcited state of the three photocatalysts: Ru(II)*/(I) vs NHE: $Ru(bpz)_3$, 1.45 V; $Ru(bpy)_3$, 0.77 V; Ir(III)*/(II) vs NHE: $Ir(ppy)_2(dtbbpy)$ 0.66 V, $Ru(bpz)_3^{2+}$ possessed the highest reduction potential, thus characterized as the strongest oxidant. Exposure to air was detrimental to the annulation reaction, further highlighting the importance of the required degassed conditions (Table 1, entry 6). Previous finding of an unstable endoperoxide product was reported via an aerobic opening of cyclopropylaniline.[76] Moreover, we observed the annulation with alkynes was slower than with alkenes, previously reported by our group. To compensate for lower reactivity of alkynes, we investigated commercially available light sources that were stronger than 13 W compact fluorescent lamps (CFLs). 13 W CFLs were used as the light source to mediate the annulation with alkenes;[76] however with alkynes, longer reaction time was required for completion and diminished yields were observed (Table 1, entry 7). The same reaction pattern was observed with blue LEDs as an alternative light source (Table 1, entry 8). White 18 W LEDs were found to be more effective for the annulation with alkynes, resulting in a higher yield. The reaction was then screened using two 18 W LEDs, conducted in a water bath to control the temperature as exposure to two LEDs generated heat; however no improvement in the yields (Table 1, entry 9). Control studies indicated that both the photocatalyst and light were required, though some background reaction was observed (Table 1, entries 10 & 11). The preliminary results sparked our curiosity of exploring another catalytic system because the photocatalyst often plays a significant role in determining the outcome of the annulation reaction. Experiments were conducted using biphenylcyclopropylamine **1a** and phenylacetylene as substrates with photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ and a variety of solvents under degassed conditions (Table 2). Surprisingly, the reaction condition using the Ir(III) complex in trifluoroethanol (CF_3CH_2OH) resulted in an isolated yield of 77% (Table 2, entry 1). Various

alcohol solvents were screened, including CH_3OH which provided comparable yields. Other solvents that were previously explored in the annulation with alkenes, such as CH_3NO_2, DMF, and CH_3CN, were also screened. None of them gave a higher yield than trifluoroethanol (Table 2, entries 5-7). The unexpected result with CF_3CH_2OH as an optimal solvent with the Ir complex prompted us to examine $Ru(bpz)_3(PF_6)_2$ in CF_3CH_2OH (Table 2, entry 4); however, a diminished NMR yield was observed. Although the catalytic system involving Ir(III) complex in CF_3CH_2OH appeared to be optimal, these conditions were best suitable for only cyclopropylanilne **1a** in particular. $Ru(bpz)_3(PF_6)_2$ was found to be more effective than the Ir complex for most of the substrates other than **1a**. Therefore, the optimal conditions for the intermolecular [3+2] annulation detailed the use of 2 mol % $Ru(bpz)_3(PF_6)_2$ in CH_3NO_2 under degassed conditions at room temperature, irradiated with one 18 W LED.

Table 2. Optimization of Ir(III) catalytic system.

Entry[a]	**Catalyst**	**Solvent**	**Time (h)**	**NMR Yield**[b]
1	$Ir(ppy)_2(dtbbpy)PF_6$	CF_3CH_2OH	20	90% (77%)[c]
2	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3OH	20.5	81% (75%)[c]
3	$Ir(ppy)_2(dtbbpy)PF_6$	iPrOH	20	50%
4	$Ru(bpz)_3(PF_6)_2$	CF_3CH_2OH	18.5	65%
5	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3NO_2	18.5	69%
6	$Ir(ppy)_2(dtbbpy)PF_6$	DMF	19.5	50%
7	$Ir(ppy)_2(dtbbpy)PF_6$	CH_3CN	19.5	70%

[a]Conditions: **1a** (0.2 mmol), **2a** (1 mmol), catalyst (2 mol%), solvent (2 mL), degassed, and irradiated with 18 W LED at rt. [b]Dibromomethane was used as an internal standard. [c]Isolate yield by silica gel chromatography.

Further screening of additives was investigated in pursuit to improve the yields. With concerns of water possibly having an effect on the reaction, 4Å molecular sieves and anhydrous $MgSO_4$ were incorporated, though providing a decrease in yields of 48% and 38%, respectively (Table 3,

Table 3. Screening of additives.

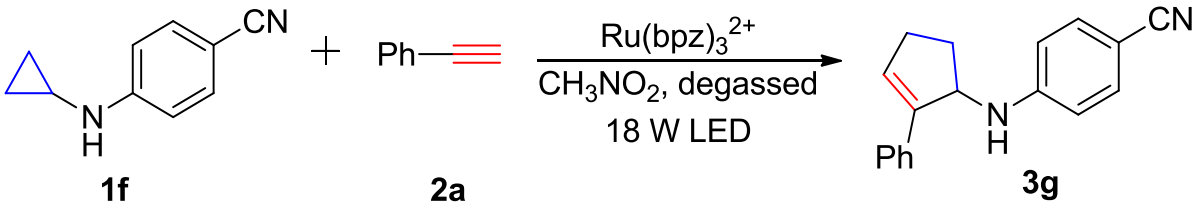
Entry[a]	Additives	Light	Time (h)	Isolated Yield[b] (NMR Yield)[c]
1	4Å molecular sieves	18 W LED	6.5	48%
2	$MgSO_4$	18 W LED	6.5	38%
3	$MgSO_4$	13 W CFL	40.5	(46%)[c]
4	$MgSO_4$	Blue LEDs	40.5	(63%)[c]

[a]Conditions: **1a** (0.2 mmol), **2a** (1 mmol), $Ru(bpz)_3(PF_6)_2$ **4a** (2 mol%), CH_3NO_2 (2 mL), 80 mg of additive, degassed, and irradiated at rt. [b]Isolated yield by silica gel chromatography. [c]Dibromomethane was used as an internal standard.

entries 1 & 2). Screening alternative light sources, such as 13 W CFL and blue LEDs, confirmed the 18 W LED to be optimal (Table 3, entries 3 & 4). With no improvement, other additives, which include acid and graphene oxide (GO), were explored as they have been reported to enhance yields of various reactions by photoredox catalysis. It was envisioned that the role of the acid, with regards to its participation in the proposed mechanism (Scheme 2.2), was to ensure protonation of the photogenerated iminium ions. Although the use of GO as a "carbocatalyst" in organic transformations has been reported, the potential application of GO in synthetic photochemistry has not been deeply explored.[118] A [3+2] annulation of phenylacetylene with 4-cyano-*N*-cyclopropylaniline **1f** to yield **3g** was conducted in three separate experiments with the optimized conditions discussed previously as the control (Table 4, entry 1), followed by introduction of additives: one equivalence of pivalic acid and 50% by weight of GO, respectively (Table 4, entry 2 and 3). NMR analysis was performed using dibromomethane as an internal standard to provide the following data in Table 4. The results with the acid and GO afforded the cycloadduct in comparable yields though no significant improvment on the annulation. The reaction time was screened at 19 h, although 6 h was sufficient for completion (Table 4, entry 4). The reported similar yields indicated that the cycloadduct was stable with no signs of

decomposition or formation of undesired by-products while consuming longer exposure to light. Conclusively, the unsuccessful results of introducing additives lead to their omission in the reaction due to their inability to further exhibit progression in the development of the annulation. Thus, the lack of improvement has driven the annulation reactions to be conducted under the optimized condition in the absence of additives.

Table 4. Screening of alternative additives and reaction time.



1f **2a** **3g**

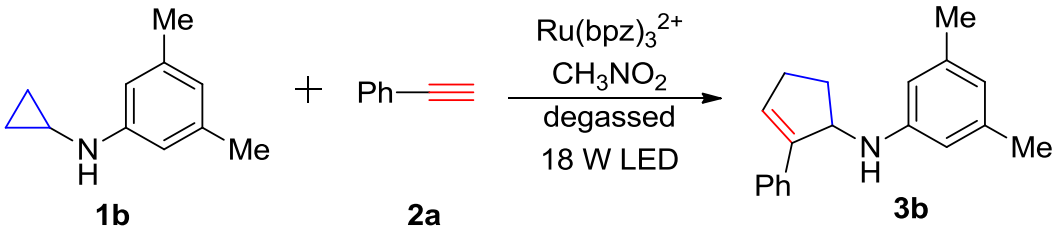
Entry[a]	Additives	Time (h)	NMR Yield (%)[b]
1	None	19	50 (49%)[c]
2	Pivalic acid[d]	19	56
3	Graphene oxide[e]	19	53
4	None	6	46[c]

[a]Conditions: **1f** (0.2 mmol), **2a** (1 mmol), $Ru(bpz)_3(PF_6)_2$ **4a** (2 mol%), CH_3NO_2 (2 mL), degassed, and irradiated at rt. [b]Dibromomethane was used as an internal standard. [c]Isolated yield by silica gel chromatography. [d]One equivalent of pivalic acid. [e]50% by weight of GO.

With the established optimized conditions, interest in the range of scalability was moderately explored. The limited scalability of batch reactors in photochemical synthesis continues to be a challenging issue for synthetic chemists. Moreover, conducting large scale processes in batch protocols usually require longer reaction times, which result in poor yields and/or production of side-products. Our initial efforts involved the annulation of 3,5-Dimethyl-*N*-cyclopropylaniline (**1b**) with phenylacetylene (Table 5). The attention was focused on the scaling up of the annulation from the standard 0.2 mmol to 0.5 mmol. By simply increasing the standard scale by a factor of 2.5, a significant decrease in yield (42%) was noted in comparison

to the standard with 62% yield (Table 5, entries 1 & 2). Due to the doubling of the reaction scale, attempts of doubling the catalyst loading to 4 mol% unfortunately furnished comparable yields (Table 5, entry 3). Therefore, moving forward, the [3+2] annulations were performed only on a 0.2 mmol reaction scale.

Table 5. Screening of reaction scalability.



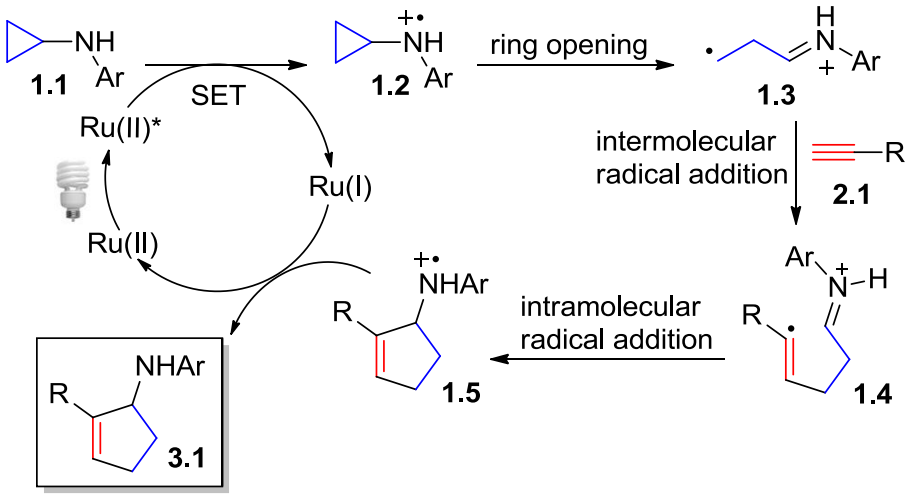
Entry[a]	Reaction Scale (1b)	Catalyst Loading	Time (h)	Isolated Yield (%)[b]
1	0.2 mmol	2 mol%	8	62
2	0.5 mmol	2 mol%	13	42
3	0.5 mmol	4 mol%	13	45

[a]Conditions: **1b** (0.2 or 0.5 mmol), **2a** (5 equiv.), $Ru(bpz)_3(PF_6)_2$ **4a** (2 or 4 mol%), CH_3NO_2 (2 or 5 mL, 0.1 M), degassed, and irradiated at rt. [b]Isolated yield by silica gel chromatography.

2.2.2. Proposed Catalytic Cycle

Mechanistically, the annulation with alkynes can be anticipated to proceed through a pathway similar to the one proposed for the annulation with alkenes (Scheme 2.2). The key transformation involves the ring opening of a cyclopropyl ring, hence serving as a three-carbon building block. To accomplish this, it was envisioned that an activated donor-substituted cyclopropane was required, thus an amino cyclopropyl ring was incorporated. Amines have been used as a sacraficial electron donor to reduce the excited state of photocatalysts, while subsequently being oxidized to amine radical cations. Our group and others have taken advantage of this facile redox process and developed a number of synthetic methods that harness

Scheme 2.2. Proposed catalytic cycle.

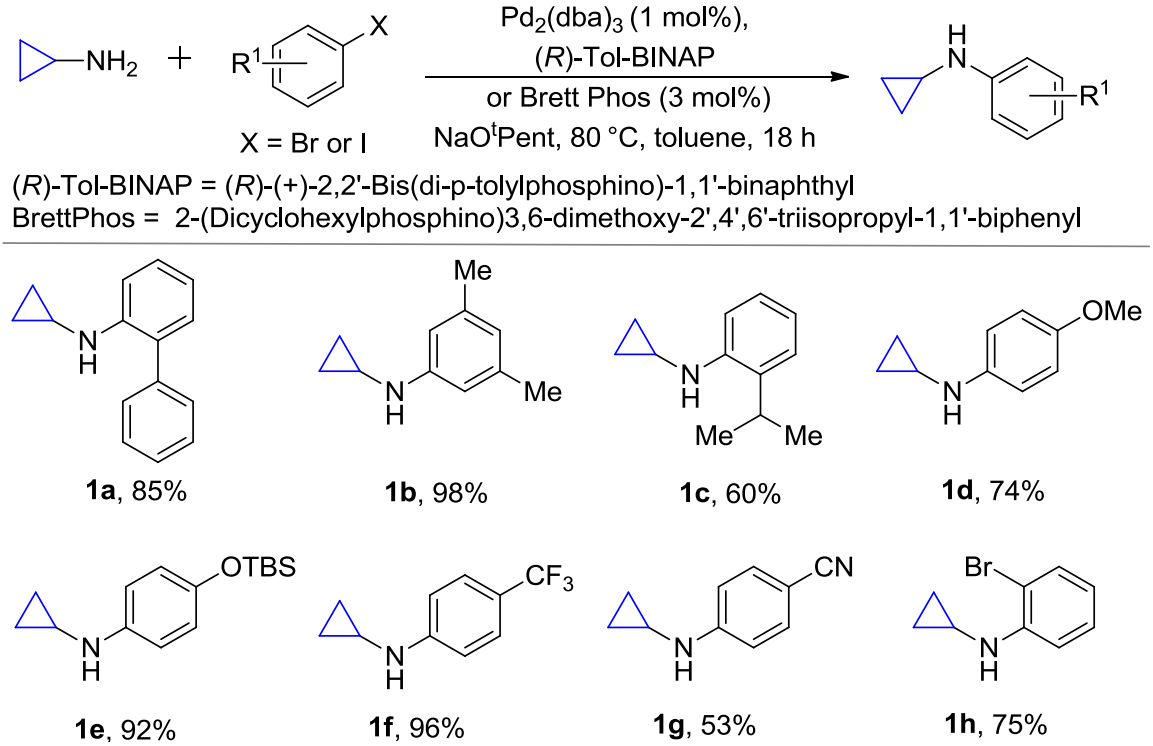


the synthetic potential of amine radical cations.[16, 66, 119] Upon exposure to visible light, the generated photoexcited $Ru(bpz)_3^{2+}$* oxidizes cyclopropylaniline **1.1** to the corresponding amine radical cation **1.2** via single electron transfer (SET). As a result, this triggers the cyclopropyl ring opening to generate distonic radical cation **1.3**. The primary carbon radical of iminium ion **1.3** adds to the terminal carbon of electron deficient alkyne **2.1** to afford vinyl radical **1.4**. Intramolecular addition of the vinyl radical to the iminium ion of distonic radical cation **1.4** closes the five membered ring and furnishes amine radical cation **1.5**. Finally, $Ru(bpz)_3^{1+}$ reduces amine radical cation **1.5** to the desired annulation product **3.1** while regenerating $Ru(bpz)_3^{2+}$. The proposed mechanism accounts for lower reactivity of alkynes towards intermolecular addition of nucleophilic carbon-centered radicals as well as their regiochemistry in the annulations.[120] Addition of radicals to alkynes generally occurs at the less hindered carbon, i.e., the terminal carbon.

2.2.3. Substrate Scope/ Synthesis of Fused Indoline

With the optimized conditions in hand, the next objective was to investigate the substrate scope of the [3+2] annulation. To determine the scope of the annulations process, a range of cyclopropylanilines with various electronic and steric characteristics were prepared. The

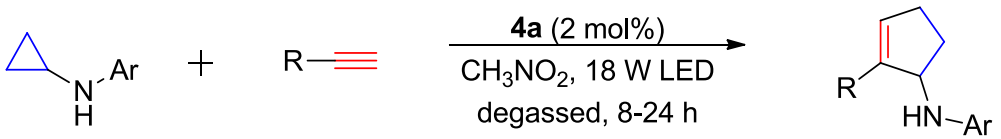
preparation of various monocyclic cyclopropylanilines, shown in Scheme 2.3, was accomplished by the Buchwald-Hartwig cross coupling reaction of aryl halides with cyclopropylamines.[121] A range of aryl bromide and iodides, including electron-donating and electron-withdrawing substituents, were well tolerated and the corresponding products were obtained in good to excellent yields (60-98%).

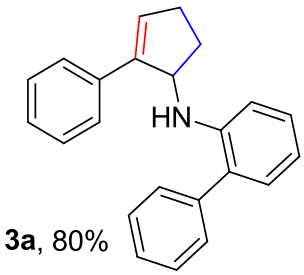


Scheme 2.3. Preparation of monocyclic cyclopropylanilines.

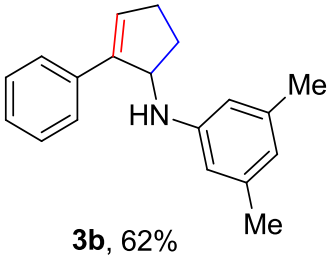
Intermolecular [3+2] annulation reactions of monocyclic cyclopropylanilines with electron-deficient terminal alkynes were successfully accomplished to furnish unsaturated cyclopentenes in moderate yields. The results of the scope studies are summarized in Scheme 2.4. Both electron-donating (OMe, **3d**, and OTBS, **3e**) and electron-withdrawing (CF3, **3f**, **3k**, **3o**, and CN, **3g**, **3j**) substituents were suitable substrates, and the annulation products were generally obtained in modest to good yields. The annulation process also tolerated steric hindrance. Hindered cyclopropylanilines, such as those possessing an *ortho*-isopropyl group,

Scheme 2.4. Substrate scope of [3+2] annulation with alkynes.

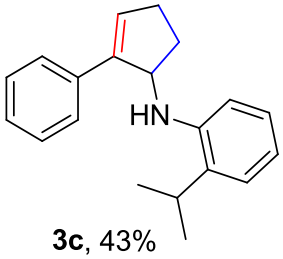




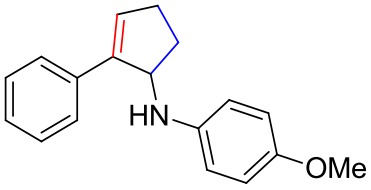
3a, 80%



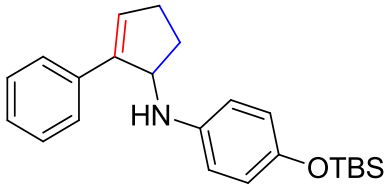
3b, 62%



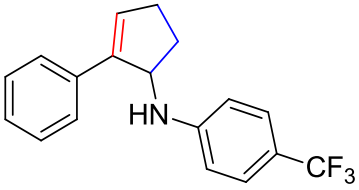
3c, 43%



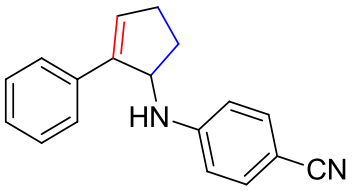
3d, 45%



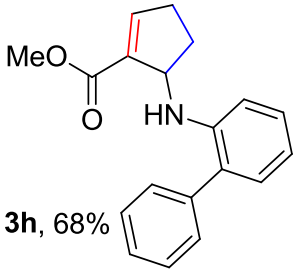
3e, 66%



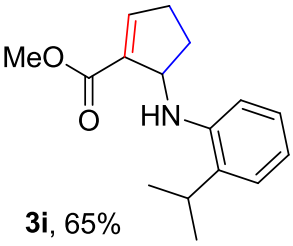
3f, 59%



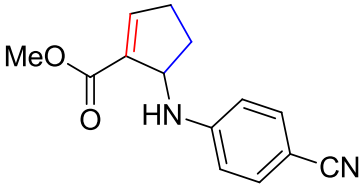
3g, 49%



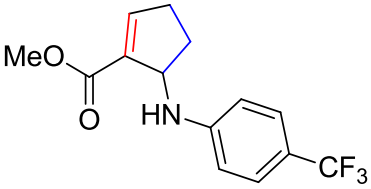
3h, 68%



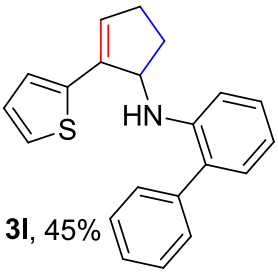
3i, 65%



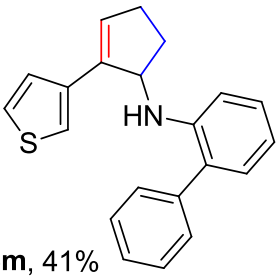
3j, 72%



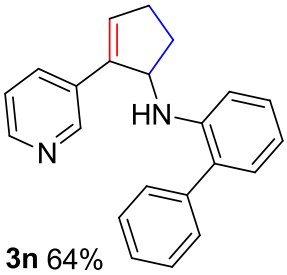
3k, 70%



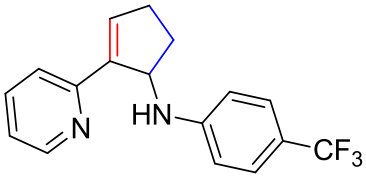
3l, 45%



3m, 41%



3n 64%

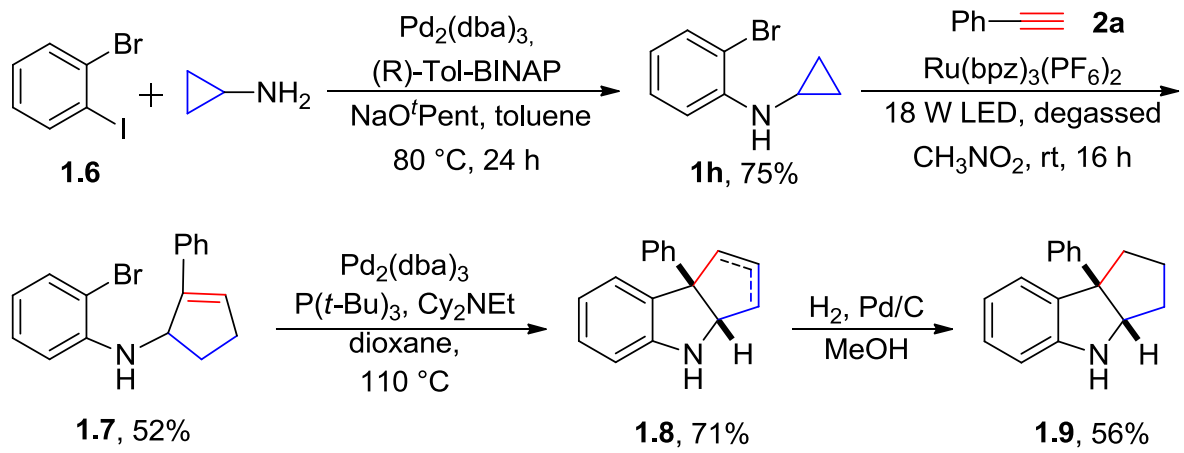


3o, 42%

were satisfactorily converted to the annulation products (**3c** and **3i**). With respect to the other annulation partner, terminal alkynes substituted with an electron-withdrawing group were typically required for the annulation process. Alkylsubstituted terminal alkynes (i.e. 1-hexyne) and internal alkynes (i.e. diphenylacetylene and dimethyl acetylenedicarboxylate) were not reactive under the optimized conditions. This reactivity trend towards alkynes is consistent with that exhibited in intermolecular addition of nucleophilic carbon-based radicals to alkynes.[120] In addition to phenylacetylene, acetylenic methyl ester was a viable annulation partner, leading to annulation products **3h**-**3k** in good yields. Heterocycles are commonly present in organic electronic materials[122] and their abundance in pharmaceuticals[123] emphasizes their promising values in medicinal chemistry. Thus, the ability to incorporate them is usually considered a benchmark for developing new synthetic methods. This method has certainly demonstrated this standard as two pairs of heterocycle-containing alkynes underwent the [3 + 2] annulation with cyclopropylanilines uneventfully (**3l-3o**). The alkyne moiety at the C2 or C3 position of thiophene or pyridine showed comparable reactivity towards the annulation.

Structural motifs of closely related indolines have been reported in a large number of various biologically active alkaloids and pharmaceuticals.[114, 124] Like indoles, indoline motifs make up an important substructure of nitrogen-containing heterocycles that are prevalent in natural products. An important subgroup of indoline motifs is fused indolines. Eminent strategies of synthesizing fused indolines have been developed, which include functionalization of oxindoles,[125] aromatic C-H aminations,[126] C-H activation of *N*-cyclohexyl-substituted carbamate,[127] and derivatization of indole precursors.[128] Another approach to provide fast entry to fused indoline motifs is the [3+2] annulation of monocyclic cyclopropylanilines with alkynes (Scheme 2.5). Starting from commercially available 1-bromo-2-iodobenzene **1.6** and

cyclopropylamine, 2-bromo-*N*-cyclopropylaniline **1h** was prepared in 75% yield via the Buchwald-Hartwig amination.[129] Under the optimized catalyst system, the [3+2] annulation of 2-bromo-*N*-cyclopropylamine **1h** and phenylacetylene **2a** was completed to afford cyclic allylic amine **1.7** in 52% yield. The fused indoline motif was formed by a cyclization via an intramolecular Heck reaction under Fu's conditions[130] to yield a mixture of two olefinic regioisomers **1.8**, which were converted to saturated fused indoline **1.9** under standard catalytic hydrogenation conditions in a combined yield of 40% from **1.7**.



Scheme 2.5. Synthesis of fused indoline **1.9**.

In summary, the expansion of the [3 + 2] annulation of cyclopropylanilines to include alkynes was successfully accomplished, yielding a variety of cyclic allylic amines in fair to good yields. The annulation process with alkynes exposed some existing limitations in the annulation with alkenes. The immediate benefits of using alkynes include eliminating the diastereoselectivity issue observed in the annulations of monocyclic cyclopropylanilines with alkenes and introducing an alkene functionality into the annulated adducts. Furthermore, the rapid access to cyclic allylic amines is an attractive feature since the synthesis of these structures is non-trivial in general. Serving as highly useful synthetic intermediates, the utility of the

annulation products was demonstrated by a four-step synthesis of fused indolines in which the [3 + 2] annulation with alkynes was used to set up the backbone of indolines. The next focused task was to continue the studies of the [3+2] annulation by further expanding the scope to include substituted anilines and other types of π-bonds.

2.2.4. Experimental Section

General Experimental Procedures

All reactions were carried out under a nitrogen atmosphere. Nitromethane (CH_3NO_2), acetonitrile (CH_3CN), and dimethylformamide (DMF) were 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 ^1H NMR, ^{13}C NMR, IR spectroscopy, high-resolution mass spectroscopy (HRMS), and melting point. 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) at room temperature. Relative configurations of new compounds were established by HMQC experiments. 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 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 Stuart SMP10 Melting Point Apparatus and were uncorrected.

General Procedure 1: Preparation of *N*-cyclopropylanilines

To an oven-dried test tube equipped with a stir bar were added 0.01 mmol of $Pd_2(dba)_3$ and

0.03 mmol of ligand ((*R*)-Tol-BINAP or BrettPhos). Glove box was used to add 1.5 mmol of NaO^{t}Pent and the tube was sealed with a Teflon screw cap. 1 mmol of aromatic halide, 1.6 mmol of cyclopropylamine, and 2 mL of toluene were then added to the reaction mixture and heated at 80 °C for 18 h. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether, filtered over a short pad of silica gel, and concentrated in vacuum. Purification by flash chromatography on silica gel afforded *N*-cyclopropylaniline.

***N*-Cyclopropyl-2-biphenylamine (1a).** Following GP1 with 2-bromobiphenyl (860 µL, 5 mmol, 1 equiv.) and (*R*)-Tol-BINAP (102 mg, 0.15 mmol, 3 mol% equiv.), product was isolated after flash chromatography on silica gel (1:20 EtOAc/hexane) as a colorless oil (889 mg, 85%).[76]

3,5-Dimethyl-*N*-cyclopropylaniline (1b). Following GP1 with 5-bromo-*m*-xylene (680 µL, 5 mmol, 1 equiv.) and BrettPhos (80.5 mg, 0.15 mmol, 3 mol% equiv.), product was isolated after flash chromatography on silica gel (1:20 EtOAc/hexane) as a pale-yellowish oil (774 mg, 96%); IR υ_{max} (cm^{-1}) 3387, 3087, 2961, 1604, 1477, 1364, 1336, 824; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.44 (dddd, *J* = 10.2, 2.9, 1.5, 0.7 Hz, 3H), 4.32 (s, 1H), 2.42 (tt, *J* = 6.4, 3.5 Hz, 1H), 2.30 – 2.20 (m, 6H), 0.76 – 0.63 (m, 2H), 0.52 (dddd, *J* = 4.9, 3.9, 3.3, 2.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.66, 138.68, 119.62, 110.95, 25.17, 21.43, 7.34. GC/MS *m/z* $[M+H]^+$, calc'd for $C_{11}H_{15}N$ 162; found 162.12.

2-Isopropyl-*N*-cyclopropylaniline (1c). Following GP1 with 1-bromo-2-isopropylbenzene (150 µL, 1 mmol, 1 equiv.) and (*R*)-Tol-BINAP (20.4 mg, 0.03 mmol, 3 mol% equiv.), product was isolated after flash chromatography on silica gel (100:1 EtOAc/hexane) as a colorless oil (106 mg, 60%); IR υ_{max} (cm^{-1}) 3420, 3007, 2961, 2870, 1603, 1503, 1451, 1365, 1302, 1039, 746; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 – 7.07 (m, 3H), 6.84 – 6.74 (m, 1H), 4.21 (s, 1H), 2.80 (p, *J* = 6.8 Hz, 1H), 2.45 (tt, *J* = 6.4, 3.6 Hz, 1H), 1.29 – 1.23 (m, 6H), 0.82 – 0.73 (m, 2H), 0.61

– 0.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.40, 131.90, 126.62, 124.76, 117.73, 111.80, 27.11, 25.51, 22.52, 22.36, 7.74; GC/MS *m/z* $[M+H]^+$, calc'd for $C_{12}H_{17}N$ 176; found 176.14.

4-Methoxy-*N*-cyclopropylaniline (1d). Following GP1 with 4-bromoanisole (628 µL, 5 mmol, 1 equiv.) and BrettPhos (80.5 mg, 0.15 mmol, 3 mol% equiv.), product was isolated after flash chromatography on silica gel (1:5 EtOAc/hexane) as a pale-yellowish oil (602 mg, 74%); IR υ_{max} (cm^{-1}) 3378, 3002, 2947, 2832, 1607, 1512, 1365, 1237, 1035, 821; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.87 – 6.70 (m, 4H), 3.95 (d, *J* = 14.8 Hz, 1H), 3.76 (s, 3H), 2.39 (tt, *J* = 6.5, 3.6 Hz, 1H), 0.75 – 0.65 (m, 2H), 0.55 – 0.46 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.34, 142.89, 114.80, 114.19, 55.85, 25.94, 7.30; GC/MS *m/z* $[M+H]^+$, calc'd for $C_{10}H_{13}NO$ 164; found 164.10.

4-*tert*-butyldimethylsilyl ether-*N*-cyclopropylaniline (1e). Following GP1 with (4-bromophenoxy)-tert-butyldimethylsilane (490 µL, 2 mmol, 1 equiv.) and BrettPhos (32.2 mg, 0.06 mmol, 3 mol% equiv.), product was isolated after flash chromatography on silica gel (1:5 EtOAc/hexane) as a colorless oil (486 mg, 92%); IR υ_{max} (cm^{-1}) 3377, 2945, 2858, 1509, 1465, 1364, 1249, 916, 832; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.71 – 6.49 (m, 4H), 3.86 (s, 1H), 2.29 (tt, *J* = 6.6, 3.1 Hz, 1H), 0.94 – 0.83 (m, 9H), 0.63 – 0.52 (m, 2H), 0.44 – 0.33 (m, 2H), 0.11 – 0.02 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.67, 143.11, 120.53, 114.02, 25.90, 25.79, 18.20, 7.27, -4.45; GC/MS *m/z* $[M+H]^+$, calc'd for $C_{15}H_{25}NOSi$ 264; found 264.17.

4-Trifluoromethyl-*N*-cyclopropylaniline (1f). An oven-dried schlenk tube was charged with CuI (9.5 mg, 0.05 mmol), K_2CO_3 (276 mg, 2 mmol), proline (23 mg, 0.2 mmol), cyclopropylamine (140 µL, 2 mmol), 4-iodobenzotrifluoride (150 µL, 1 mmol), DMSO (2 mL) and a stir bar. After purging with argon for a few seconds, the tube was sealed with a Teflon screw cap. The mixture was heated at 70 ^{o}C for 12 h. The reaction mixture was then cooled to

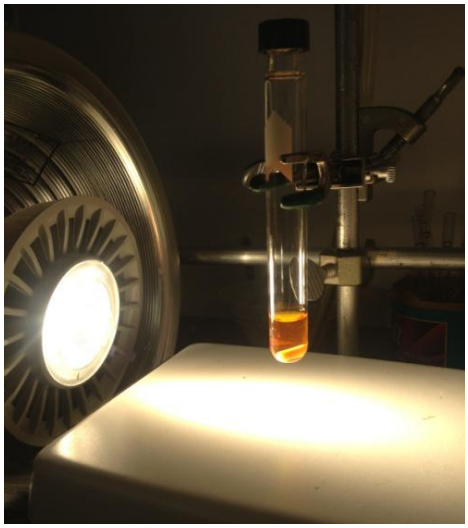
room temperature, quenched with brine and diluted with diethyl ether. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification of the residual mass by silica gel flash chromatography (5% EtOAc/hexane) afforded product (193 mg, 96%) as a yellowish oil.[76]

4-Cyano-*N*-cyclopropylaniline (1g). Following GP1 with 4-bromobenzonitrile (1.82 g, 10 mmol, 1 equiv.) and (*R*)-Tol-BINAP (204 mg, 0.3 mmol, 3 mol% equiv.), product was isolated after flash chromatography on silica gel (1:3 EtOAc/hexane) as a pale-yellowish solid (836 mg, 53%); IR υ_{max} (cm^{-1}) 3364, 2991, 2210, 1603, 1519, 1338, 1166, 825; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.39 (m, 2H), 6.79 – 6.70 (m, 2H), 4.61 (s, 1H), 2.47 (ttd, *J* = 6.6, 3.6, 0.6 Hz, 1H), 0.88 – 0.74 (m, 2H), 0.63 – 0.50 (m, 2H); ^{13}C NMR (101 MHz, CDCl3) δ 151.96, 133.53, 120.53, 112.78, 99.20, 24.60, 7.63; GC/MS *m/z* $[M+H]^+$, calc'd for $C_{10}H_{10}N_2$ 159; found 159.09.

2-Bromo-*N*-cyclopropylaniline (1h). Following GP1 with 1-bromo-2-iodobenzene (128 µL, 1 mmol, 1 equiv.) and (*R*)-Tol-BINAP (20.4 mg, 0.03 mmol, 3 mol% equiv.), product was isolated after flash chromatography on silica gel (1:150 EtOAc/hexane) as a colorless oil (160 mg, 75%).[100]

General Procedure 2: [3+2] Annulation

An oven-dried test tube (16 × 125 mm) equipped with a stir bar was charged with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$[131] (2 mol %), cyclopropylaniline (0.2 mmol), alkyne (1.0 mmol), and dry CH_3NO_2 (2 mL). The test tube was sealed with a Teflon screw cap. The reaction mixture was degassed by Freeze–Pump–Thaw cycles and then irradiated at room temperature with one white LED (18 watts) positioned 8 cm from the test tube. After the reaction was complete as



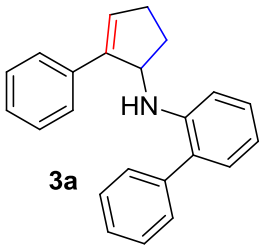
monitored by TLC, the mixture was diluted with diethyl ether and filtered through a short pad of silica gel. The filtrate was concentrated in vacuum and purified by silica gel flash chromatography to afford the desired allylic amine.

Catalyst Optimization (Table 1)

Following the above procedure (**GP2**), *N*-cyclopropyl-2-biphenylamine **1a** (42 mg, 0.2 mmol), phenylacetylene **2a** (116 µL, 1.0 mmol), $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ **4a** (3.8 mg, 2 mol%), and solvent (2 mL) were mixed and irradiated with a LED light for 8 h. The reaction mixture was then diluted with Et_2O (2 mL) and *n*-dodecane (45 µL) was added as the internal standard. An aliquot (0.5 mL) was filtered through a syringe filter, diluted to 1 mL, and analyzed by GC.

Characterization (Scheme 2.4)

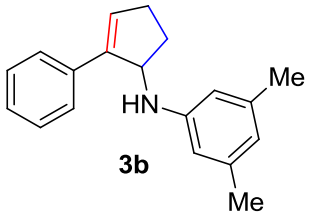
***N*-(2-phenylcyclopent-2-enyl)biphenyl-2-amine (3a)**. Following **GP2** with *N*-cyclopropyl-2-biphenylamine **1a** (41.8 mg, 0.2 mmol) and phenylacetylene **2a** (116 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (15:1 hexane/EtOAc) as a white yellowish solid, m.p. 113-115 °C, (48 mg, 77%). IR υ_{max} (cm^{-1}) 3300, 2939, 1559, 11505, 1488, 1436, 1312, 1071, 755, 695; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.32 (m, 2H), 7.24 – 7.19 (m, 3H), 7.19 – 7.14 (m, 2H), 7.11 (q, *J* = 1.0 Hz, 4H), 7.00 (dt, *J* = 7.4, 1.5 Hz, 1H), 6.83 – 6.76 (m, 1H), 6.70 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.18 (td, *J* = 2.5, 1.1 Hz, 1H), 4.83 (d, *J* = 7.2 Hz, 1H), 4.00 (s, 1H), 2.54 – 2.38 (m, 2H), 2.36 – 2.25 (m, 1H), 1.90 (ddt, *J* = 12.8, 8.3, 3.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.50, 142.88, 139.28, 134.79, 130.51, 129.94, 129.16, 128.73, 128.72,



3a

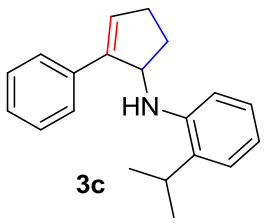
128.42, 127.73, 127.33, 126.95, 126.41, 116.70, 110.87, 59.55, 31.88, 31.08; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{23}H_{21}N$ 312.1742; found 312.1708.

3,5-dimethyl-*N*-(2-phenylcyclopent-2-enyl)aniline (3b). Following **GP2** with 3,5-dimethyl-*N*-cyclopropylaniline **1b** (34.2 mg, 0.2 mmol) and phenylacetylene **2a** (116 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (5:1 hexane/EtOAc) as a pale yellowish oil, (32.5 mg, 62%). IR υ_{max} (cm^{-1}) 3401, 2918, 1599, 1496, 1337, 1183, 820, 757, 691; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 (ddd, *J* = 6.4, 3.8, 1.6 Hz, 2H), 7.30 – 7.21 (m, 2H), 7.21 – 7.14 (m, 1H), 6.43 – 6.30 (m, 2H), 6.27 – 6.21 (m, 2H), 4.88 – 4.77 (m, 1H), 3.68 (s, 1H), 2.60 (dddd, *J* = 15.3, 7.4, 6.0, 3.6 Hz, 1H), 2.45 (ddt, *J* = 17.6, 8.9, 3.1 Hz, 1H), 2.35 – 2.25 (m, 1H), 2.23 – 2.18 (m, 6H), 1.99 (ddt, *J* = 13.4, 8.3, 2.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.66, 142.82, 138.99, 134.64, 129.97, 128.53, 127.31, 126.20, 119.05, 110.91, 58.91, 31.74, 30.99, 21.58; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{19}H_{21}N$ 264.1737; found 264.1708.



3b

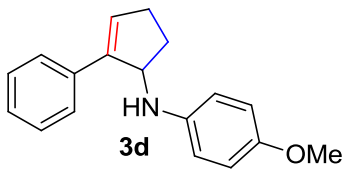
2-isopropyl-*N*-(2-phenylcyclopent-2-enyl)aniline (3c). Following **GP2** with 2-isopropyl-*N*-cyclopropylaniline **1c** (35 mg, 0.2 mmol) and phenylacetylene **2a** (116 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (25:1 hexane/EtOAc) as a yellow/orange oil, (24.1 mg, 43%). IR υ_{max} (cm^{-1}) 3440, 2960, 1602, 1503, 1448, 1304, 1038, 745, 692; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 – 7.42 (m, 2H), 7.29 – 7.20 (m, 2H), 7.20 – 7.07 (m, 3H), 6.83 – 6.66 (m, 2H), 6.38 (ddd, *J* = 3.2, 2.4, 1.0 Hz, 1H), 4.86 (d, *J* = 7.1 Hz, 1H), 3.75 (s, 1H), 2.67 – 2.55 (m, 2H), 2.33 (ddt, *J* = 13.1, 8.9, 7.1 Hz, 1H), 1.99 (ddt, *J* = 13.4, 8.2, 2.8 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.26, 142.94,



3c

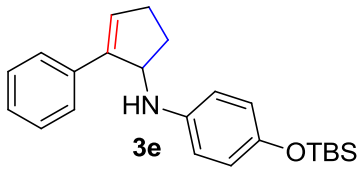
134.63, 132.23, 130.07, 128.52, 127.39, 126.76, 126.25, 125.06, 116.95, 110.81, 59.28, 31.82, 31.12, 27.08, 22.28, 22.19; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{20}H_{23}N$ 278.1891; found 278.1864.

4-methoxy-*N*-(2-phenylcyclopent-2-enyl)aniline (3d). Following **GP2** with **4**-methoxy-*N*-cyclopropylaniline **1d** (32.6 mg, 0.2 mmol) and phenylacetylene **2a** (116 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (10:1 hexane/EtOAc) as a reddish-brown oil, (23.9 mg, 45%). IR υ_{max} (cm^{-1}) 3394, 2929, 1510, 1231, 1178, 1038, 818, 753, 693; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.39 (m, 2H), 7.29 – 7.19 (m, 2H), 7.19 – 7.11 (m, 1H), 6.78 – 6.69 (m, 2H), 6.60 – 6.49 (m, 2H), 6.30 (ddd, *J* = 3.3, 2.3, 1.0 Hz, 1H), 4.81 – 4.70 (m, 1H), 3.68 (d, *J* = 0.7 Hz, 3H), 3.50 (s, 1H), 2.63 – 2.51 (m, 1H), 2.42 (ddt, *J* = 17.5, 9.1, 3.0 Hz, 1H), 2.25 (ddt, *J* = 13.1, 9.0, 7.1 Hz, 1H), 2.02 – 1.88 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.89, 142.97, 142.00, 134.74, 129.87, 128.56, 127.33, 126.22, 115.02, 114.27, 59.94, 55.89, 31.60, 31.01; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{18}H_{19}NO$ 266.1532; found 266.1500.



3d

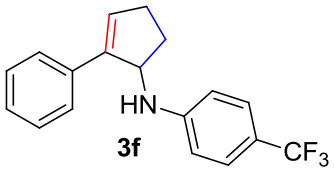
4-(tert-butyldimethylsilyloxy)-*N*-(2-phenylcyclopent-2-enyl)aniline (3e). Following **GP2** with 4-*tert*-butyldimethylsilyl ether-*N*-cyclopropylaniline **1e** (52.7 mg, 0.2 mmol) and phenylacetylene **2a** (116 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (10:1 hexane/EtOAc) as a reddish-brown oil, (48.1 mg, 66%). IR υ_{max} (cm^{-1}) 3400, 2929, 2856, 1508, 1250, 922, 839, 779, 756, 693; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.40 (m, 2H), 7.29 – 7.19 (m, 2H), 7.20 – 7.11 (m, 1H), 6.68 – 6.60 (m, 2H), 6.51 – 6.41 (m, 2H), 6.30 (td, *J* = 2.7, 1.0 Hz, 1H), 4.72 (dt, *J* = 7.1, 2.6 Hz, 1H), 3.41 (s, 1H), 2.66 – 2.49 (m, 1H), 2.47 – 2.35 (m, 1H), 2.24 (ddt, *J* = 13.2, 9.0, 7.1 Hz, 1H), 2.00 – 1.89 (m, 1H), 0.91 (s, 9H), 0.10 (s, 6H); ^{13}C



3e

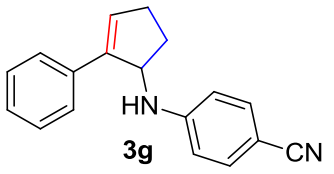
NMR (101 MHz, $CDCl_3$) δ 147.82, 143.69, 142.89, 135.40, 130.46, 129.17, 127.93, 126.86, 121.28, 114.83, 60.60, 32.23, 31.61, 26.44, 18.84, -3.78; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{23}H_{31}NOSi$ 366.2247; found 366.2208.

***N*-(2-phenylcyclopent-2-enyl)-4-(trifluoromethyl)aniline (3f)**. Following **GP2** with 4-trifluoromethyl-*N*-cyclopropylaniline **1f** (40.2 mg, 0.2 mmol) and phenylacetylene **2a** (116 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (20:1 hexane/EtOAc) as a yellow solid, m.p. 97-100 °C, (37.8 mg, 59%). IR υ_{max} (cm^{-1}) 3403, 3057, 2994, 2851, 1616, 1530, 1326, 1112, 1064, 824, 755; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.33 (m, 4H), 7.30 – 7.23 (m, 2H), 7.22 – 7.16 (m, 1H), 6.64 – 6.53 (m, 2H), 6.37 (t, *J* = 2.7 Hz, 1H), 4.85 (d, *J* = 7.2 Hz, 1H), 4.03 (s, 1H), 2.69 – 2.53 (m, 1H), 2.47 (ddt, *J* = 17.6, 8.8, 3.1 Hz, 1H), 2.33 (ddt, *J* = 12.9, 8.8, 7.1 Hz, 1H), 1.93 (ddt, *J* = 13.7, 8.2, 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.26, 142.48, 134.57, 130.93, 128.98, 127.90, 127.0 (q, *J* = 3.7 Hz), 126.42, 125.16 (q, *J* = 270.7 Hz), 118.8 (q, *J* = 32.4 Hz), 112.41, 59.03, 31.74, 31.34; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{18}H_{16}F_3N$ 304.1299; found 304.1268.



3f

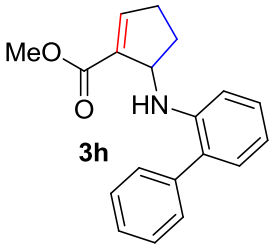
4-(2-phenylcyclopent-2-enylamino)benzonitrile (3g). Following **GP2** with 4-cyano-*N*-cyclopropylaniline **1g** (31.6 mg, 0.2 mmol) and phenylacetylene **2a** (116 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (5:1 hexane/ EtOAc) as a white-yellow solid, m.p. 108-109 °C, (25.5 mg, 49%). IR υ_{max} (cm^{-1}) 3348, 2983, 2212, 1606, 1519, 1338, 1172, 824, 769; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.35 (dq, *J* = 8.2, 1.8, 1.1 Hz, 4H), 7.23 (tt, *J* = 6.7, 1.3 Hz, 2H), 7.21 – 7.14 (m, 1H), 6.50 (dd, *J* = 9.2, 2.2 Hz, 2H), 6.42 – 6.31 (m, 1H), 4.83 (dt, *J* = 7.3, 2.5 Hz, 1H), 4.20 (s, 1H), 2.67 – 2.52 (m, 1H), 2.46 (ddt, *J* = 17.7, 8.7, 3.1 Hz,



3g

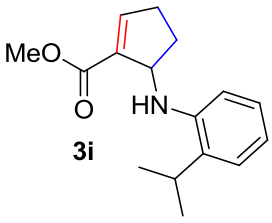
1H), 2.31 (ddt, *J* = 13.1, 8.7, 7.1 Hz, 1H), 1.89 (ddt, *J* = 13.7, 8.2, 3.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.54, 141.82, 134.02, 133.78, 130.93, 128.70, 127.70, 126.04, 120.49, 112.54, 98.61, 58.58, 31.37, 31.01; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{18}H_{16}N_2$ 261.1383; found 261.1347.

methyl 5-(biphenyl-2-ylamino)cyclopent-1-enecarboxylate (3h). Following **GP2** with *N*-cyclopropyl-2-biphenylamine **1a** (41.8 mg, 0.2 mmol) and methyl propiolate (95 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (10:1 hexane/EtOAc) as a yellow oil, (42.1 mg, 68%). IR υ_{max} (cm^{-1}) 3418, 2949, 1718, 1507, 1456, 1289, 1097, 748, 703; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.30 (m, 4H), 7.24 (dddd, *J* = 10.0, 5.0, 2.4, 1.2 Hz, 1H), 7.21 – 7.14 (m, 1H), 7.08 – 6.98 (m, 1H), 6.87 (td, *J* = 2.6, 1.2 Hz, 1H), 6.77 – 6.66 (m, 2H), 4.61 (d, *J* = 7.5 Hz, 1H), 4.09 (s, 1H), 3.69 – 3.57 (m, 3H), 2.58 – 2.42 (m, 1H), 2.42 – 2.21 (m, 2H), 1.89 (dddd, *J* = 13.3, 6.9, 3.0, 1.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.83, 148.12, 144.65, 139.56, 136.59, 130.38, 129.33, 128.81, 128.59, 128.17, 127.12, 117.15, 111.52, 58.77, 51.50, 32.07, 31.21; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{19}H_{19}O_2$ 294.1499; found 294.1449.



3h

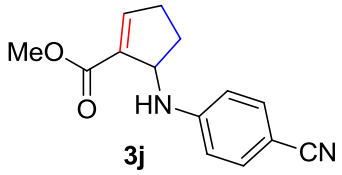
methyl 5-(2-isopropylphenylamino)cyclopent-1-enecarboxylate (3i). Following **GP2** with 2-isopropyl-*N*-cyclopropylaniline **1c** (35 mg, 0.2 mmol) and methyl propiolate (95 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (10:1 hexane/EtOAc) as an orange-brown oil, (33.6 mg, 65%). IR υ_{max} (cm^{-1}) 3142, 2961, 1717, 1602, 1504, 1448, 1361, 1291, 1100, 744; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 – 7.14 (m, 2H), 7.14 – 7.08 (m, 1H), 6.86 – 6.70 (m, 2H), 4.78 – 4.66 (m, 1H), 4.15 (s, 1H), 3.77 (s, 3H), 2.87 (hept, *J* = 6.8



3i

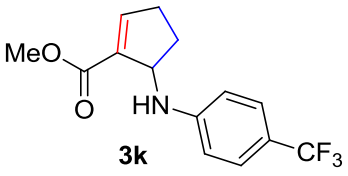
Hz, 1H), 2.76 – 2.62 (m, 1H), 2.62 – 2.47 (m, 1H), 2.41 (dddd, *J* = 13.4, 9.1, 7.4, 6.5 Hz, 1H), 2.11 – 1.98 (m, 1H), 1.26 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.19, 148.32, 144.53, 136.61, 133.12, 126.57, 124.97, 117.66, 111.63, 58.76, 51.62, 32.04, 31.36, 27.12, 22.52, 22.16; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{16}H_{21}O_2$ 260.1643; found 260.1606.

methyl 5-(4-cyanophenylamino)cyclopent-1-enecarboxylate (3j). Following **GP2** with 4-cyano-*N*-cyclopropylaniline **1g** (31.6 mg, 0.2 mmol) and methyl propiolate (95 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (2:1 hexane/EtOAc) as a white-yellow solid, m.p. 80-83 °C, (34.9 mg, 72%). IR υ_{max} (cm^{-1}) 3356, 2949, 2211, 1714, 1606, 1523, 1296, 1173, 1098, 825; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.38 (m, 2H), 7.06 (td, *J* = 2.6, 1.0 Hz, 1H), 6.69 – 6.60 (m, 2H), 4.93 (s, 1H), 4.74 (dtd, *J* = 7.6, 2.6, 1.3 Hz, 1H), 3.73 (d, *J* = 0.7 Hz, 3H), 2.77 – 2.63 (m, 1H), 2.61 – 2.48 (m, 1H), 2.38 (dddd, *J* = 13.6, 9.1, 7.6, 6.5 Hz, 1H), 2.02 – 1.90 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.61, 150.60, 148.49, 135.86, 133.63, 120.44, 112.94, 98.97, 57.80, 51.76, 31.59, 31.23; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{14}H_{14}N_2O_2$ 243.1117; found 243.1089.



3j

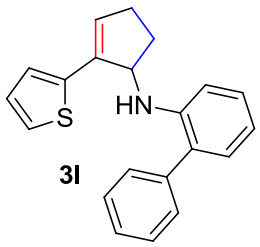
methyl 5-(4-(trifluoromethyl)phenylamino)cyclopent-1-enecarboxylate (3k). Following **GP2** with 4-trifluoromethyl-*N*-cyclopropylaniline **1f** (40.2 mg, 0.2 mmol) and methyl propiolate (95 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (10:1 hexane/EtOAc) as a pale-yellow solid, m.p. 103-105 °C, (41.8 mg, 70%). IR υ_{max} (cm^{-1}) 3386, 2954, 1710, 1616, 1533, 1328, 1298, 1105, 1063, 826; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.36 (m, 2H), 7.05 (td, *J* = 2.4, 1.1 Hz, 1H), 6.69 – 6.60 (m, 2H), 4.77 – 4.70 (m, 1H), 4.26 (s, 1H), 3.74 (d, *J* = 0.8 Hz, 3H), 2.75 – 2.60 (m, 1H), 2.59 – 2.45 (m, 1H), 2.45 – 2.31 (m,



3k

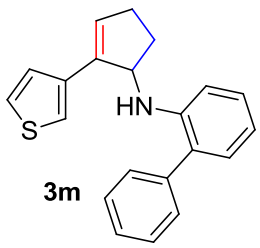
1H), 2.02 – 1.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.12, 150.33, 148.63, 136.51, 126.85 (q, *J* = 3.9 Hz), 125.31 (q, *J* = 269.4 Hz), 119.28 (q, *J* = 32.5 Hz), 112.96, 58.40, 52.04, 31.93, 31.57; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{14}H_{14}F_3NO_2$ 286.1044; found 286.1010.

***N*-(2-(thiophen-2-yl)cyclopent-2-enyl)biphenyl-2-amine (3l)**. Following **GP2** with *N*-cyclopropyl-2-biphenylamine **1a** (41.8 mg, 0.2 mmol) and 2-ethynylthiophene (95 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (100:1 hexane/EtOAc) as a yellow solid, m.p. 104-106 °C, (30 mg, 45%). IR υ_{max} (cm^{-1}) 3418, 3055, 2926, 1506, 1488, 1436, 1310, 771, 747, 703; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.36 – 7.27 (m, 6H), 7.19 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.13 (dt, *J* = 7.5, 1.7 Hz, 1H), 7.06 (dd, *J* = 3.8, 1.4 Hz, 1H), 6.97 (ddd, *J* = 5.1, 3.5, 1.4 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.82 (tt, *J* = 7.4, 1.4 Hz, 1H), 6.15 (hept, *J* = 1.2 Hz, 1H), 4.94 – 4.82 (m, 1H), 4.16 (s, 1H), 2.66 – 2.32 (m, 3H), 2.04 – 1.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.66, 139.61, 139.14, 137.51, 130.85, 129.64, 129.56, 129.10, 129.00, 128.25, 127.55, 127.37, 124.64 (two carbons overlap, see HMQC), 117.21, 111.40, 61.22, 32.19, 31.27; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{21}H_{19}NS$ 318.1313; found 318.1272.



3l

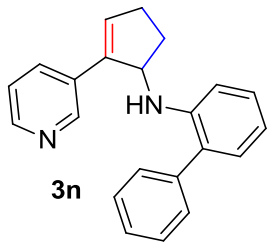
***N*-(2-(thiophen-3-yl)cyclopent-2-enyl)biphenyl-2-amine (3m)**. Following **GP2** with *N*-cyclopropyl-2-biphenylamine **1a** (41.8 mg, 0.2 mmol) and 3-ethynylthiophene (98 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (100:1 hexane/EtOAc) as a white-yellow solid, m.p. 104-106 °C, (27.2 mg, 41%). IR υ_{max} (cm^{-1}) 3418, 3055, 2926, 1506, 1488, 1436, 1310, 771, 747, 703; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.08 (m, 9H), 7.03 (dq, *J* = 7.3, 1.9 Hz, 1H), 6.84 – 6.65 (m, 2H), 6.04 (tt, *J* = 2.5, 1.1 Hz, 1H), 4.80 – 4.73 (m, 1H), 3.99 (s, 1H), 2.53 – 2.19 (m, 3H), 1.93 – 1.76 (m, 1H); ^{13}C NMR (101 MHz,



3m

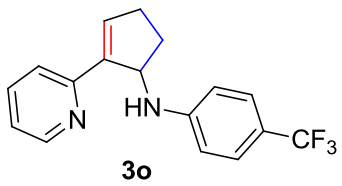
$CDCl_3$) δ 144.52, 139.33, 138.37, 136.60, 130.54, 129.21, 129.14, 128.77, 128.72, 127.82, 127.02, 126.24, 125.48, 121.12, 116.76, 110.95, 60.49, 31.84, 30.84; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{21}H_{19}NS$ 318.1305; found 318.1272.

***N*-(2-(pyridin-3-yl)cyclopent-2-enyl)biphenyl-2-amine (3n)**. Following **GP2** with *N*-cyclopropyl-2-biphenylamine **1a** (41.8 mg, 0.2 mmol) and 3-ethynylpyridine (103 mg, 1.0 mmol), product was isolated after column chromatography on silica gel (25:1 hexane/EtOAc) as a yellow-brown solid, m.p. 113-117 °C, (41.7 mg, 64%). IR υ_{max} (cm^{-1}) 3416, 3030, 2928, 2848, 1580, 1507, 1436, 1309, 748, 704; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 8.50 (d, *J* = 4.8 Hz, 1H), 7.71 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.35 – 7.21 (m, 7H), 7.11 (dd, *J* = 7.4, 1.7 Hz, 1H), 6.95 – 6.76 (m, 2H), 6.39 (dt, *J* = 2.6, 1.5 Hz, 1H), 4.98 (d, *J* = 6.2 Hz, 1H), 3.94 (s, 1H), 2.72 – 2.38 (m, 3H), 2.10 – 1.91 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.23, 147.83, 144.09, 140.05, 139.16, 133.39, 131.77, 130.54, 130.52, 129.14, 128.73, 127.99, 127.08, 123.21, 117.10, 111.03, 59.33, 31.61, 31.20, 31.13; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{22}H_{20}N_2$ 313.1705; found 313.1660.



3n

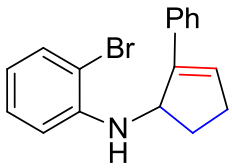
N-(2-(pyridin-2-yl)cyclopent-2-enyl)-4-(trifluoromethyl)aniline (3o). Following **GP2** with 4-trifluoromethyl-*N*-cyclopropylaniline **1f** (40.2 mg, 0.2 mmol) and 2-ethynylpyridine (101 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (5:1 hexane/EtOAc) as a yellow-brown solid, m.p. 115-118 °C, (25.9 mg, 42%). IR υ_{max} (cm^{-1}) 3279, 2934, 1614, 1534, 1326, 1112, 1063, 822, 775; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.52 (td, *J* = 7.7, 1.9 Hz, 1H), 7.39 – 7.28 (m, 2H), 7.28 – 7.22 (m, 1H), 7.05 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 6.84 – 6.74 (m, 1H), 6.65 – 6.53 (m, 2H), 4.88 (d, *J* = 7.2 Hz, 1H), 4.38 (s,



3o

1H), 2.72 – 2.55 (m, 1H), 2.55 – 2.44 (m, 1H), 2.35 (ddt, *J* = 13.2, 9.0, 7.1 Hz, 1H), 2.02 – 1.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.62, 150.51, 149.83, 142.96, 136.93, 136.07, 126.9 (q, *J* = 3.8 Hz), 125.3 (q, *J* = 270.5 Hz), 122.50, 121.27, 118.9 (q, *J* = 32.5 Hz), 112.77, 58.98, 31.90, 31.46; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{17}H_{15}F_3N_2$ 305.1253; found 305.1221.

2-bromo-*N*-(2-phenylcyclopent-2-enyl)aniline (1.7). Following **GP2** with 2-Bromo-*N*-cyclopropylaniline **1h** (42.4 mg, 0.2 mmol) and phenylacetylene **2a** (116 µL, 1.0 mmol), product was isolated after column chromatography on silica gel (100:1 hexane/EtOAc) as a white/pale yellow solid, m.p. 78-80 °C, (32.7 mg, 52%). IR υ_{max} (cm^{-1}) 3402, 3059, 2929, 2846, 1592, 1495, 1317, 1019, 741, 691; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.38 (m, 2H), 7.33 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.22 (tt, *J* = 6.8, 0.9 Hz, 2H), 7.19 – 7.11 (m, 2H), 6.73 (ddd, *J* = 8.1, 1.5, 0.6 Hz, 1H), 6.50 (ddd, *J* = 7.8, 7.3, 1.5 Hz, 1H), 6.36 (ddd, *J* = 3.2, 2.4, 1.0 Hz, 1H), 4.80 (d, *J* = 7.0 Hz, 1H), 4.36 (s, 1H), 2.70 – 2.54 (m, 1H), 2.50 – 2.38 (m, 1H), 2.28 (ddt, *J* = 13.1, 8.9, 7.1 Hz, 1H), 1.92 (tdd, *J* = 10.7, 5.4, 2.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.48, 142.36, 134.48, 132.60, 130.57, 128.57, 128.49, 127.47, 126.13, 117.54, 111.88, 110.03, 59.45, 31.74, 31.02; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{17}H_{16}BrN$ 314.0539, 316.0520; found 314.0500, 316.0479.



1.7

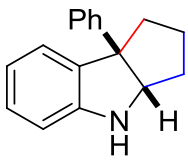
Procedure for synthesis of fused indoline 1.9 (Scheme 2.5)

To an oven-dried test tube equipped with a stir were added **1.7** (0.2 mmol) and $Pd_2(dba)_3$ (1.5 mol%). Inside the glovebox were then added Cy_2NMe (1.1 eq), P(t-Bu)$_3$ (3.0 mol%), and dioxane. The reaction was sealed and removed from the glovebox. The reaction vessel was heated at 110 °C for 16.5 h. After completion, the reaction was quenched with diethyl ether and filtered through a short pad of silica gel. The solution was concentrated in vacuum and purified by silica gel flash chromatography (10:1 Hexane/EtOAc) to afford mixture of two olefinic

products **1.8** (33 mg, 71% yield). *Note: Cy_2NMe and dioxane were degassed by Freeze-Pump-Thaw cycles before taken into glovebox.*

For the catalytic hydrogenation: To a clean dried 3-neck round bottom flask equipped with a stir bar was added **1.8** (0.1 mmol). After stirring in anhydrous MeOH (0.4 mL) for 5 min. Pd(C) (10 mol%) was added carefully under N_2 atmosphere. A balloon filled with H_2 was equipped to the flask and stirred for 22 h at room temperature. After completion, celite was added to the reaction and stirred for additional 5 min. prior to filtering through a pad of celite and washing with MeOH. The solution was concentrated in vacuum and purified by silica gel flash chromatography (10:1 Hexane EtOAc) to afford fused indoline **1.9**.

(3a*S*,8b*R*)-8b-phenyl-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indole (1.9): red-brown solid,



1.9

m.p. 61-64 °C, (13.1 mg, 56%). Silica gel column chromatography (10:1 hexane/EtOAc). IR υ_{max} (cm^{-1}) 3392, 3050, 2949, 16030, 1483, 740, 699, 432; ^1H NMR (300 MHz, Chloroform-*d*) δ 7.42 – 7.28 (m, 4H), 7.26 – 7.15 (m, 1H), 7.04 (td, *J* = 7.6, 1.3 Hz, 1H), 6.92 (ddd, *J* = 7.4, 1.3, 0.6 Hz, 1H), 6.77 – 6.60 (m, 2H), 4.38 – 4.28 (m, 1H), 2.49 – 2.30 (m, 2H), 2.03 (ddt, *J* = 13.0, 11.8, 6.4 Hz, 1H), 1.94 – 1.74 (m, 2H), 1.74 – 1.57 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.83, 148.36, 135.95, 128.32, 127.61, 126.31, 125.94, 124.60, 118.64, 108.79, 71.95, 62.49, 40.77, 38.09, 25.45; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{17}H_{17}N$ 314.0539, 236.1426; found 236.1395.

2.3. Intermolecular [3+2] Annulation of Cyclopropylanilines with Alkynes, Enynes, and Diynes*

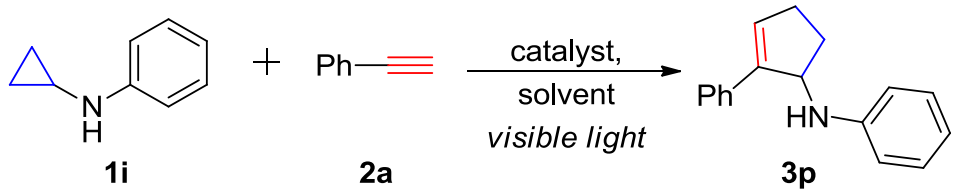
*Portion of this chapter has been published in Nguyen, T. H.; Morris, S. A.; Zheng, N. *Adv. Synth. Catal.* **2014,** *356* (13), 2831-2837.

Photocatalyzed cycloaddition or annulation reactions are ideal reactions for constructing small molecule libraries due to the specific interaction of photoexcited catalysts and small molecules,[8, 10] which facilitates high chemoselectivity for the photochemical transformations and exhibits tolerance for various functional groups. The application of visible light photocatalysis in cycloaddition or annulation reactions has demonstrated great potential in DOS, as the success of a library of small molecules was developed in the [3+2] annulations of cyclopropylanilines with alkynes.[116] However, the preliminary results displayed constraints with respect to both reacting partners, cyclopropylanilines and alkynes. An aryl group on the cycloropylamine moiety was required, while only terminal alkynes were reactive. In order to address both limitations, a full-scale study of the [3+2] annulation was thoroughly investigated.

2.3.1. Reaction Optimization

Previous findings of the optimized conditions for the [3+2] annulation of cyclopropylanilines with alkynes using ruthenium polypyridyl complexes only provided the desired annulation products in modest yields. Determined to improve the yields, more conditions were examined, as shown in Table 6. Using cyclopropylaniline **1i** and phenylacetylene **2a** as the chosen standard substrates, the annulation was investigated in a continuous flow format (Table 6, entry 2). Notably in comparison to the batch format (Table 6, entry 1), the reaction time was shortened from 8 h to 3 h as expected, though the yield did not improve. The use of cyclometalated iridium complexes was also examined to catalyze the

Table 6. Additional reaction optimization of **3p**.



1i **2a** **3p**

Entry[a]	Catalyst	Solvent	Light	GC Yield (%)[b]
1	$Ru(bpz)_3(PF_6)_2$	CH_3NO_2	18 W LED	69 (68)[c]
2	$Ru(bpz)_3(PF_6)_2$	CH_3NO_2	flow[d]	60
3	$Ir(ppy)_2(dtb\text{-}bpy)(PF_6)$	CF_3CH_2OH	18 W LED	60
4	$Ir[dF(CF_3)ppy]_2(dtb\text{-}bpy)(PF_6)$	CF_3CH_2OH	18 W LED	36
5[e,f]	$Ru(bpz)_3(PF_6)_2$	CH_3NO_2	18 W LED	7

[a]Conditions: **1i** (0.2 mmol), **2a** (5 equiv.), catalyst (2 mol%), solvent (2 mL), degassed, and irradiated at rt for 8 h. [b]Using dodecane as an internal standard. [c]Isolated yield. [d]Reaction time of 3 h. [e]19 h reaction. [f]Using 1 equiv. of TEMPO.

annulation. These complexes are another important class of photocatalysts that have been used in a number of synthetic applications in photochemistry.[9] Two iridium complexes were explored, though neither furnished a better yield than $Ru(bpz)_3(PF_6)_2$ (Table 6, entries 3 & 4). Lastly, the reaction was conducted in the presence of TEMPO (Table 6, entry 5). It was previously proposed that the distonic radical cation **1.3** in Scheme 2.2 was one of the key intermediates in the [3+2] annulation of cyclopropylanilines with alkenes and alkynes. The distonic radical cation is formed presumably from the ring opening of cyclopropylaniline that is induced by one-electron photooxidation of the parent amine to the amine radical cation via the excited state of $Ru(bpz)_3(PF_6)_2$. In principle, the use of TEMPO was designed to intercept the radical moiety of the distonic radical cation and quench the annulation. Indeed, the annulation product was isolated in a negligible yield, thus supporting the involvement of distonic ion **1.3**. Since no improvement in the yield was achieved using the flow or the Ir catalyst, the previous optimized conditions (Table 6, entry 1) were set as the standard conditions for the scope studies.

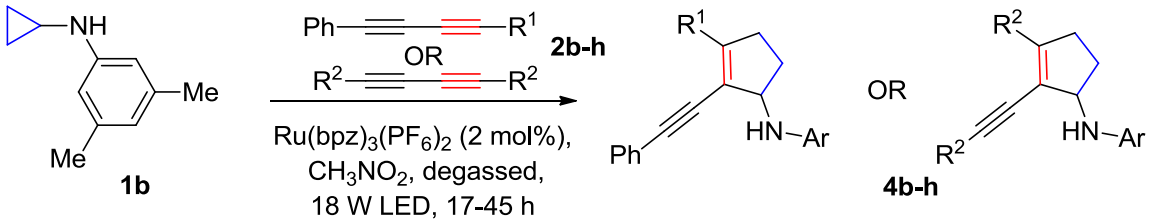
2.3.2. [3+2] Annulation with Diynes and Enynes

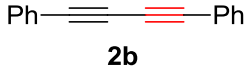
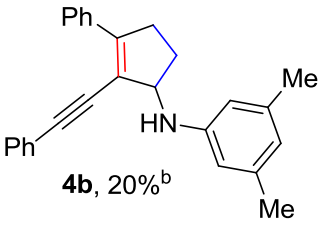
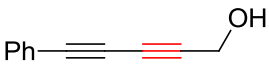
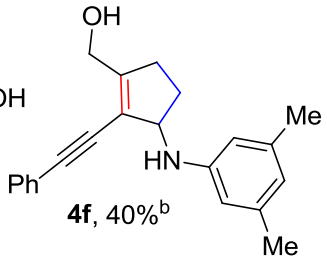
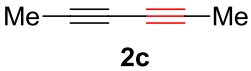
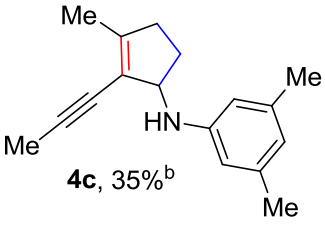
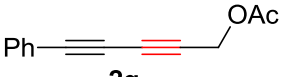
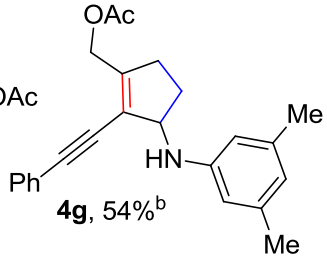
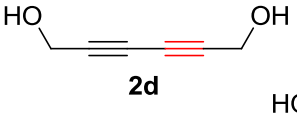
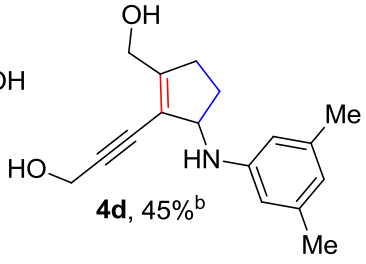
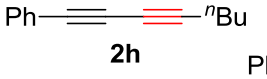
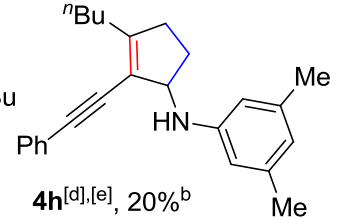
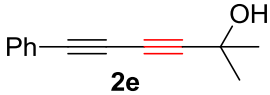
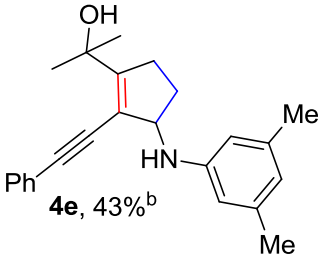
The use of 1,3-conjugated diynes and enynes in the [3+2] annulation offers great potential to further enhance the value of the annulation in diversity-oriented synthesis (DOS). The expected annulation products would possess a 1,3-conjugated enyne moiety from 1,3-conjugated diynes or a 1,3-conjugated diene moiety from 1,3-conjugated enynes. The conjugated adducts can further participate in cycloaddition reactions such as the Diels-Alder reaction to construct complex fused carbocycles or heterocycles, and thus enable cycloaddition cascades to access these complex structures, rapidly. However, [3+2] annulation with 1,3-conjugated diynes and enynes presented more challenges than with simple alkynes. Preliminary results showcased that the annulation was sensitive to substitution on alkynes, including their electronic characters. For instance, *n*-hexyne and diphenyl acetylene were unreactive. Initially, it was uncertain whether addition of one more π bond would enhance the original π bond's reactivity enough to take part in the annulation. Moreover, addressing the predicted regiochemistry in 1,3-conjugated diynes and enynes could be challenging. Lastly, the issue of chemoselectivity for unsymmetrical diynes and enynes, since two different π bonds are present, may arise as addition can occur to either or both π bonds.

2.3.2.1. Scope Studies with Symmetrical and Asymmetrical Diynes

To our surprise, under the optimized conditions, symmetrical and asymmetrical 1,3-conjugated diynes successfully underwent the intermolecular [3+2] annulation with monocyclic cylopropylaniline **1b** to afford the conjugated cyclopentene adducts **4b-h** (Table 7). Symmetrical diynes bearing phenyl **2b**, methyl **2c**, and hydroxymethyl **2d** groups proceeded in fair yields (20-45%). Asymmetrical diynes also produced the annulation products in similar

Table 7. Scope studies with symmetrical and asymmetrical diynes.

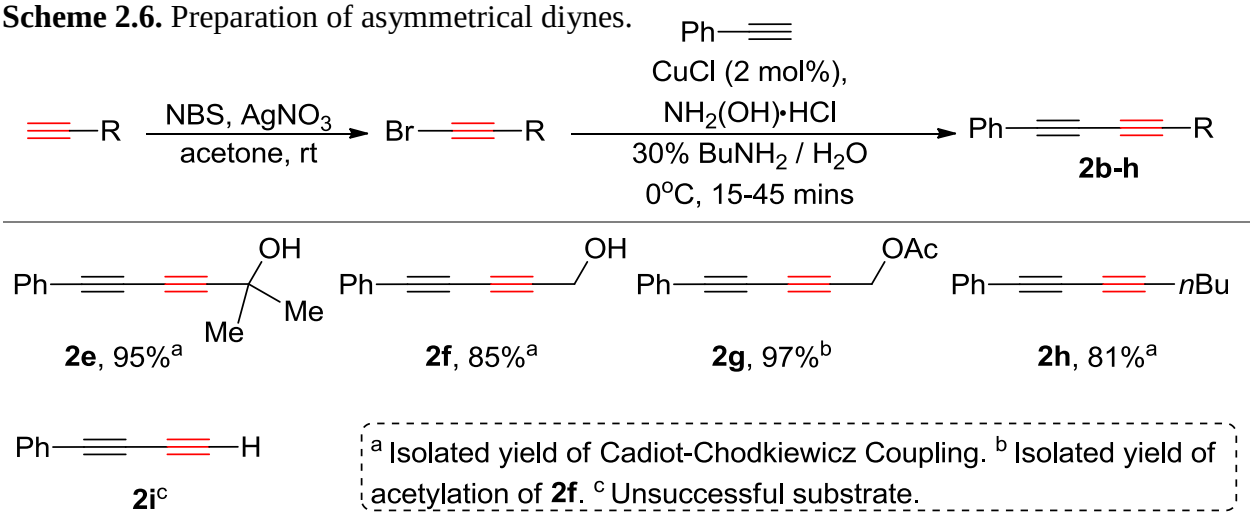


Diyne **2**	Product[a]	Diyne **2**	Product[a]
 **2b**	 **4b**, 20%[b]	 **2f**	 **4f**, 40%[b]
 **2c**	 **4c**, 35%[b]	 **2g**	 **4g**, 54%[b]
 **2d**	 **4d**, 45%[b]	 **2h**	 **4h**[d],[e], 20%[b]
 **2e**	 **4e**, 43%[b]		

Conditions: a solution of **1b** (0.2 mmol), $Ru(bpz)_3(PF_6)_2$ (2 mol%), and **2b-h** (5 equiv.) in 2 mL of CH_3NO_2 was degassed via freeze-pump-thaw cycles and irradiated using an 18 W white LED. [a]Ratio >20:1, determined using GC. [b]Isolated yields. [c]Ratio 12:1, determined using GC. [d]Unidentified minor isomer.

yields (20-54%). These diynes **2e–h** all bore a phenyl group on one end, while a variety of moieties, such as *n*-Bu, hydroxymethyl, and acetoxymethyl groups, were tolerated on the other end. It is worth noting that a quaternary center adjacent to the reactive carbon center of diyne **2e** was well tolerated. Although the annulation products were reported in modest yields, complete regiocontrol was observed universally in all but one example (Table 7, entry 7, **4h**), where 12:1 regioselectivity was observed.

Scheme 2.6. Preparation of asymmetrical diynes.



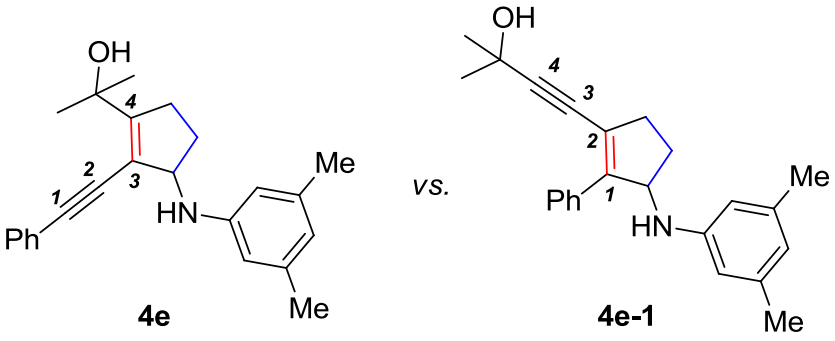
In regards to the preparation of the diynes, symmetric diynes **2b**-**2d** were commercially available, while asymmetric diynes **2e**-**2h** were prepared according to literature procedures in two short steps. Upon bromination of the commercially available terminal alkynes, subsequent Cadiot-Chodkiewicz cross coupling with phenylacetylene afforded diynes **2e**, **2f**, and **2h** in high yields (Scheme 2.6). Hydroxymethyl diyne **2f** was subjected to acetic annhydride to furnish acetoxymethyl diyne **2g**. The initial approach was to synthesize 1-phenyl-1,3-butadiyne **2i** for subjection to annulation, anticipating addition to occur at the terminal alkyne. However, instability of diyne **2i** due to polymerization led to the selection of its precursor, diyne **2e**.

2.3.2.2. Determining Regioselectivity and Rationale

The complete regiocontrol observed in the [3+2] annulation with symmetric and

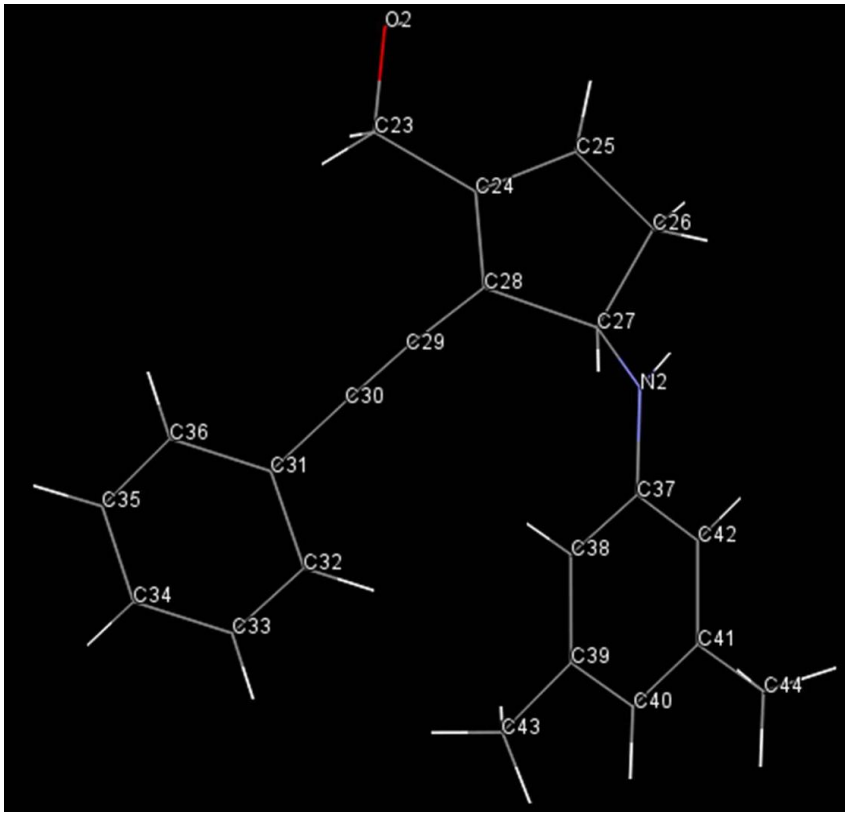
asymmetric diynes demonstrates great potential in diversity-oriented synthesis (DOS); however, addressing the issue of chemoselectivity in regards to which π bond underwent the annulation is more challenging (Figure 2.1). Unfortunately, the routinely use of 1D NMR analysis was not sufficient to confidently assign the annulation product. Several approaches to determine the regiochemistry included: 1) growing crystals of the annulation product and perform X-ray crystallography; 2) conducting 2D NMR experiments such as HMBC and NOESY; and 3) fragmentation reaction of the tertiary alcohol in adduct **4e-1** using Carreira's method[132] to provide a terminal alkyne moiety which can be analyzed via 1D NMR. Initial efforts of employing the last approach entailed the use of **4e-1** in the presence of 18-crown-6 and K_2CO_3 in refluxing toluene, though no fragmentation of the tertiary alcohol was observed. Carrerira reported the fragmentation of functionalized alkynes such as 2-methyl-3-butyn-2-ol, an identical moiety depicted in the regioisomer **4e-1**. If the fragmentation was to occur, it can be supported that **4e-1** could be a possible regioisomer as it employs the same functionalized alkyne moiety. Although the fragmentation was unsuccessful, the result was inconclusive to completely omitt **4e-1** as a possible regioismer. The attention was then shifted towards confirming the assigned structure via X-ray crystallography. Multiple attempts of growing crystals of adduct **4e**, unfortunately, resulted in poor quality crystals. Despite the poor sample quality with a high R-factor value of 17% (a non-ideal refinement), the predicted structure was resolved as shown in Figure 2.2 with the assistance of Prof. Wu at UCSB.

Figure 2.1. Possible regioisomers of **4e**.



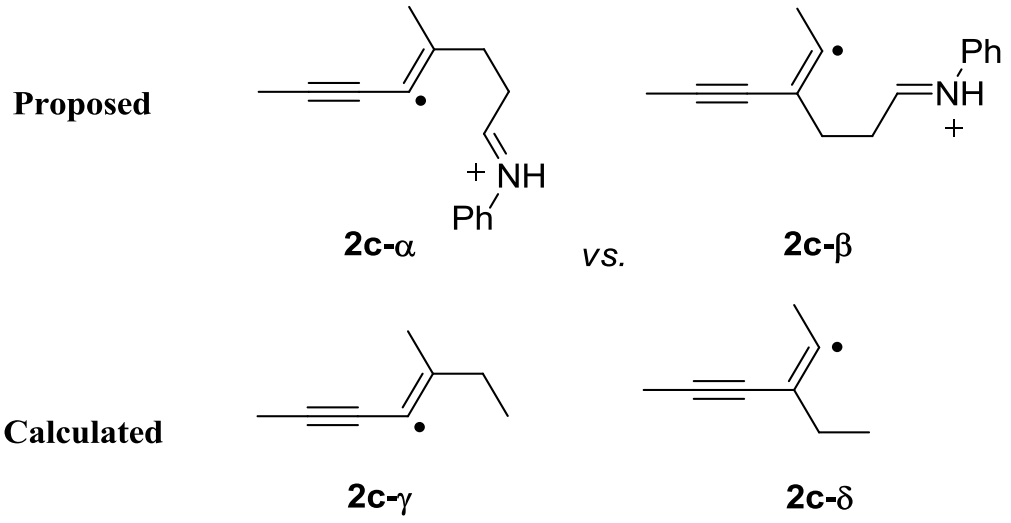
Therefore, it can be concluded that the annulation occurred at alkyne C3-C4 rather than alkyne C1-C2. Additional 2D NMR analysis was collected for adduct **4f** to support the assignment of the annulation product (See Experimental Section 2.3.5.).

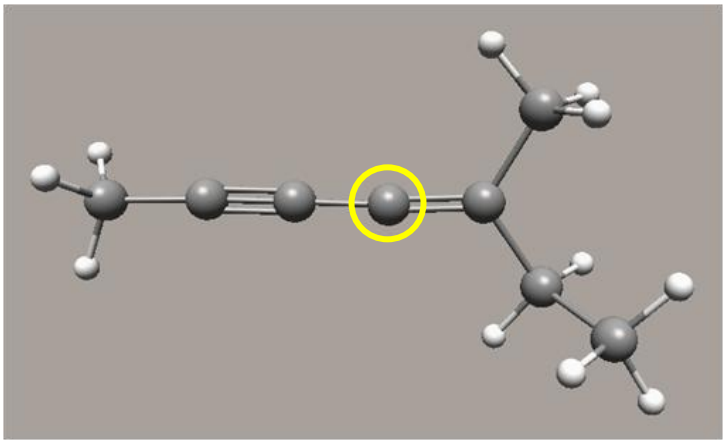
Figure 2.2. X-ray crystallography of adduct **4e**.



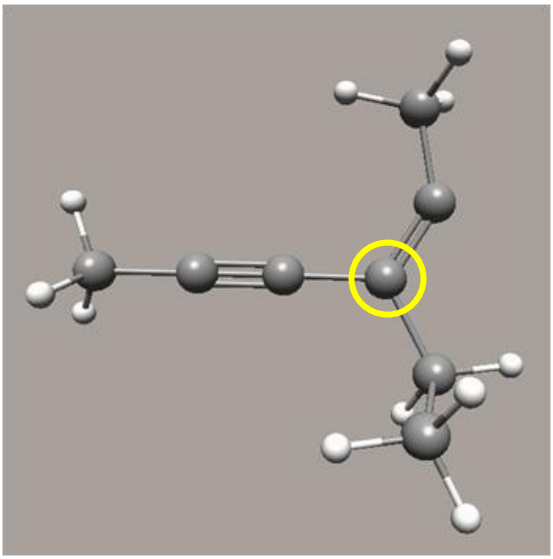
With the structure assignment completed, the rationalization of the observed excellent regioselectivity was to be discussed. The suggested rationale was based on the stability of radicals generated after the first C-C bond formation, shown in Figure 2.3. To support this argument, DFT calculations on two regioisomeric radicals (**2c-γ** and **2c-δ**) that model the proposed regioisomeric radicals (**2c-α**and **2c-β**) were performed. At the B3LYP/6-31++g-dp level, enyne **2c-γ** (5-methylhepta-2-yne-4-ene) with the radical at the C-4 position was found to be more stable than enyne **2c-δ (**4-ethylhexa-2-yne-4-ene) with radical at C-5 by 44 kJ/mol. Images of the optimized lowest energy isomers of each radical structure are illustrated in Figure 2.3. In radical structure **2c-γ**, the double bond and triple bond are aligned with one another, presumably to enable a conjugating effect among the pi bonds. In radical structure **2c-δ**, with two isomers nearly isoenergetic at the calculated level, this feature is absent. A similar

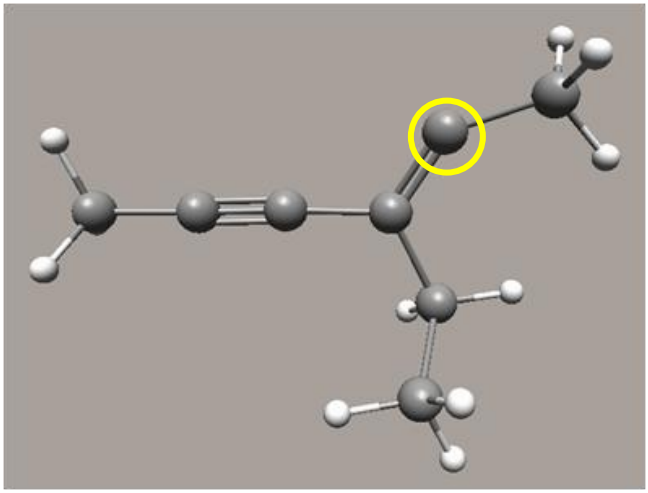
Figure 2.3. DFT calculations for the observed selectivity of diyne **2c**.





Calculated **2c-γ** with radical at C-4.

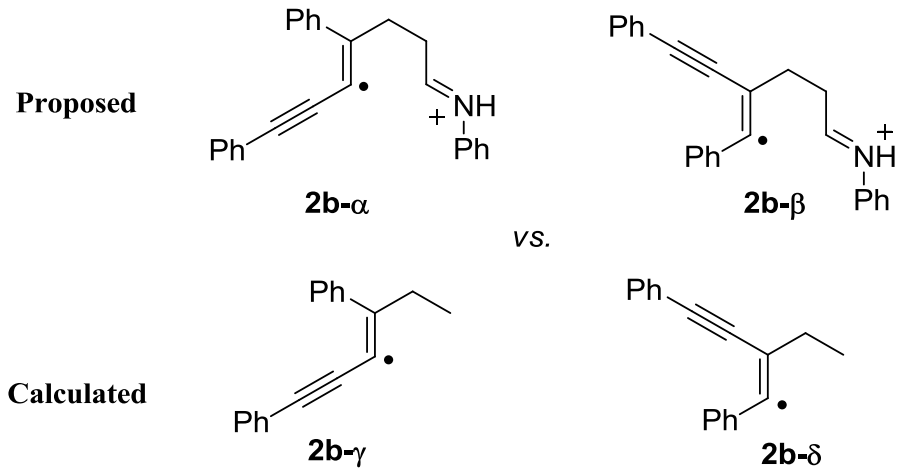


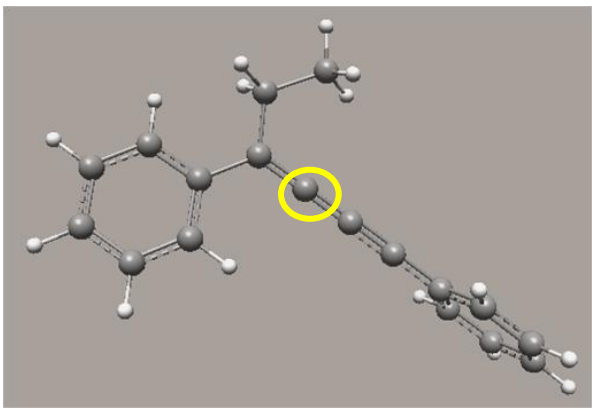


Calculated **2c-δ** with radical at C-5 (2 isomers isoenergetic at this level)

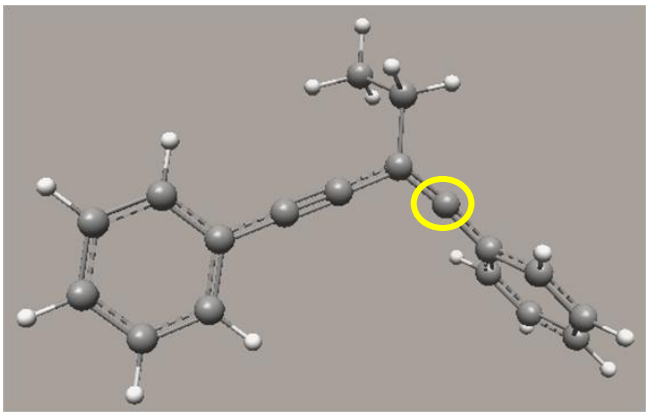
stability trend of the two regioisomeric radicals was also observed in diyne **2b** (Figure 2.4). Diyne **2b-γ (**hex-3-en-1-yne-1,4-diyldibenzene) with the radical at the C-3 position was calculated to be more stable than **2b-δ** at the B3LYP/6-31g* level by 41.92 kJ/mol. While the radical seems to delocalize over the pi systems in both isomers and both seem to have some allene character, the more stable of the two has a greater degree of linearity due to the position of the ethyl group. Upon formation of the initial C-C bond, the ethyl group forces the affected carbon into the traditional trigonal planar geometry.

Figure 2.4. DFT calculations for the observed selectivity of diyne **2b**.





Calculated **2b-γ** with radical at C-3.



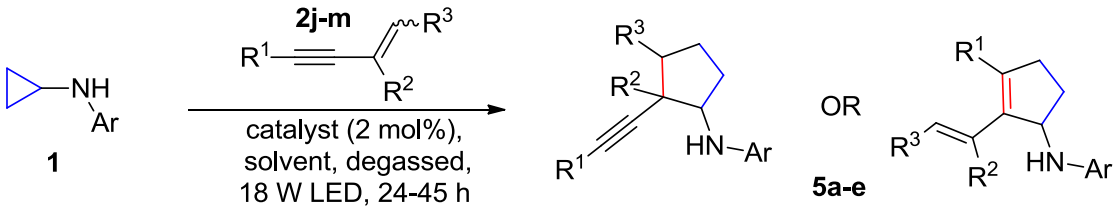
Calculated **2b-δ** with radical at C-4.

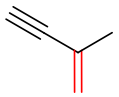
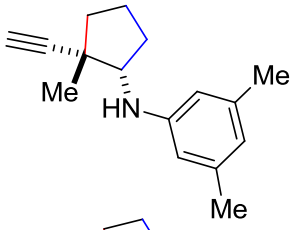
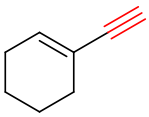
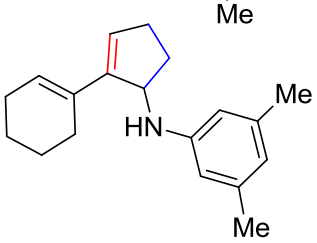
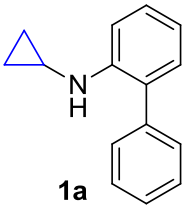
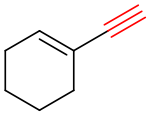
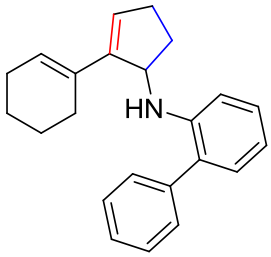
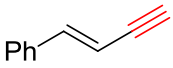
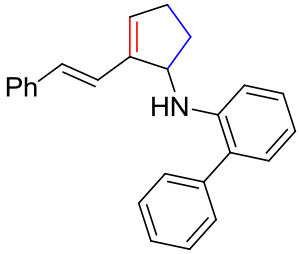
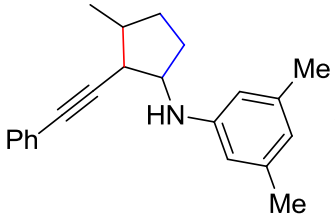
2.3.2.3. Scope Studies with Enynes

As anticipated, annulation reactions with enynes were more complicated than with diynes due to the issue of chemoselectivity, in addition to regioselectivity. In the presence of both an

active alkyne and alkene moiety, a competition in the annulation proposes a problem. Generally, alkenes are more reactive than alkynes, as observed in an earlier report of annulation with alkynes.[116] However, because of steric effects, this reactivity trend can be reversed if the alkene is more substituted than the alkyne. Moreover, if the alkene moiety is more reactive than the alkyne moiety, the issue of diastereoselectivity also needs to be addressed. Indeed, 1,3-conjugated enynes **2j**-**2m** participated in the annulation to produce a mixture of isomeric products (Table 8). Commercially available enyne, 2-methyl-1-buten-3-yne (**2j**), possessing both a terminal alkyne and a terminal alkene, successfully underwent the [3+2] annulation predominately with the alkene moiety to provide the annulation products in 50% combined yields, with the minor isomer being identified as the annulation with the alkyne. The chemoselectivity, favoring the alkene moiety, was 10 to 1. Commercially available enyne, 1-ethynylcyclohexene (**2k**), bearing a terminal alkyne and a trisubstituted alkene, was subjected to the annulation with cyclopropylaniline **1b** and **1a**, respectively, to afford the corresponding conjugated 1,3-dienes **5b** and **5c** in moderate yields, 43-53%, (Table 8, entries 2 & 3). In both cases, the annulation favored the terminal alkyne of enyne **2k**. It is worth noting that for these two enynes (**2j** and **2k**), the catalyst system composed of $Ir(ppy)_2(dtb\text{-}bpy)(PF_6)$ in a 1:1 mixture of CH_3NO_2 and CF_3CH_2OH proved to be more effective than the standard catalyst system of $Ru(bpz)_3(PF_6)_2$ in CH_3NO_2. Synthetically prepared enyne **2l**, bearing a terminal alkyne and a 1,2-disubstituted alkene, underwent the annulation to furnish annulated adduct **5d** in 59% combined yields, with the 1,3-diene as the major isomer (Table 8, entry 4). Lastly, enyne **2m** was prepared and treated with cyclopropylaniline **1b** under the standard conditions. Possessing both an internal alkyne and a 1,2-disubstituted alkene, it was anticipated that the annulation would occur with the olefin due to its greater reactivity than alkynes. The major products **5e,**

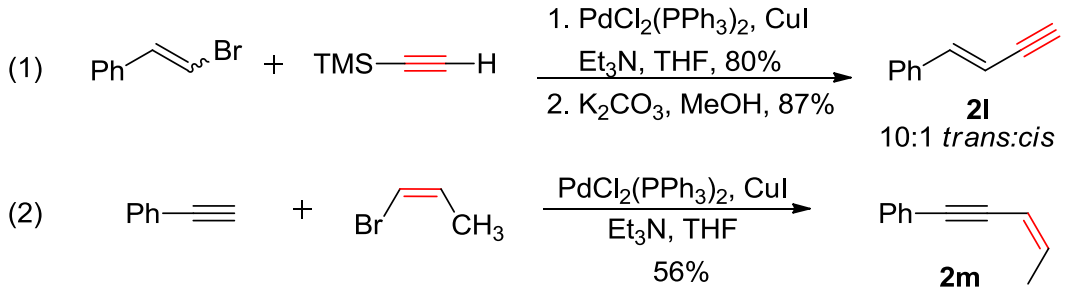
Table 8. Scope studies with enynes.



Entry	Substrate	Enyne **2**	Product[b]		Yield (%)[c],[d]
1	**1b**	 **2j**		**5a**[e]	50 (10:1)
2	**1b**	 **2k**		**5b**	43 (11:2[f]:1[f])
3	 **1a**	 **2k**		**5c**	53 (8:1[f]:1[f])
4[g]	**1a**	 **2l**[i]		**5d**	59 (4:1[h]:1[f])
5[g]	**1b**	 **2m**		**5e**	66 (2:1:2:2)[j]

[a] A solution of cyclopropylaniline (0.2 mmol), $Ir(ppy)_2(dtb\text{-}bpy)(PF_6)$ (2 mol%), and enyne (5 equiv.) in 2 mL CH_3NO_2:CF_3CH_2OH (1:1), was degassed via freeze-pump-thaw cycles then irradiated using an 18 W white LED. [b] Major isomer shown. [c] Isolated yields. [d] Isomer ratios (determined by GC-MS). [e] 7:3 dr. [f] Unidentified minor isomers. [g] Using $Ru(bpz)_3(PF_6)_2$. [h] Identified as the *cis*-alkene of **5d**. [i] Ratio 10:1 *trans:cis.* [j] All identified as diastereomers of **5e**.

composed of four diastereomers, were obtained in 66% combined yields with poor diastereoselectivity as expected. The synthetic preparation of enynes **2l** and **2m** are described in Scheme 2.7. Enyne **2l** was prepared in two short steps involving a Sonogashira Cross-Coupling of β-bromostyrene and trimethylsilylacetylene, followed by deprotection of the trimethylsilyl (TMS) group with K_2CO_3 in methanol. Likewise, enyne **2m** was prepared in a similar fashion, excluding the deprotection step, using phenylacetylene and *cis*-1-bromo-1-propene.



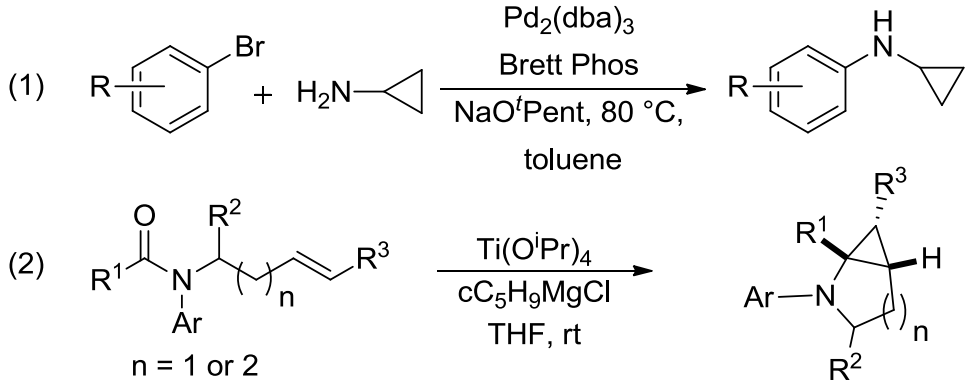
Scheme 2.7. Preparation of enynes **2l** and **2m**.

2.3.3. [3+2] Annulation of Substituted Cyclopropylanilines

Since expanding the [3+2] annulation scope to include various types of π-bonds as annulation partners was successfully investigated, the next focus was to continue the expansion by studying the scope of cyclopropylanilines. To maximize the potential of the [3+2] annulation, it was imperative to examine substituents on the nitrogen atom and the cyclopropyl ring. Particularly for the latter, if succeeded, it would allow decoration on the cyclopentene ring of the annulation products.

2.3.3.1 Preparation of Substituted Cyclopropylanilines

Limited use of cyclopropylanilines has been seen in organic synthesis. This is due to the minimal access of making many structurally diverse cyclopropylanilines. Our group has relied on two known methods for constructing *N*-arylcyclopropylamines: 1) Buchwald-Hartwig cross coupling reaction of aryl bromides and cyclopropylamines or Cu-catalyzed amination[133] to

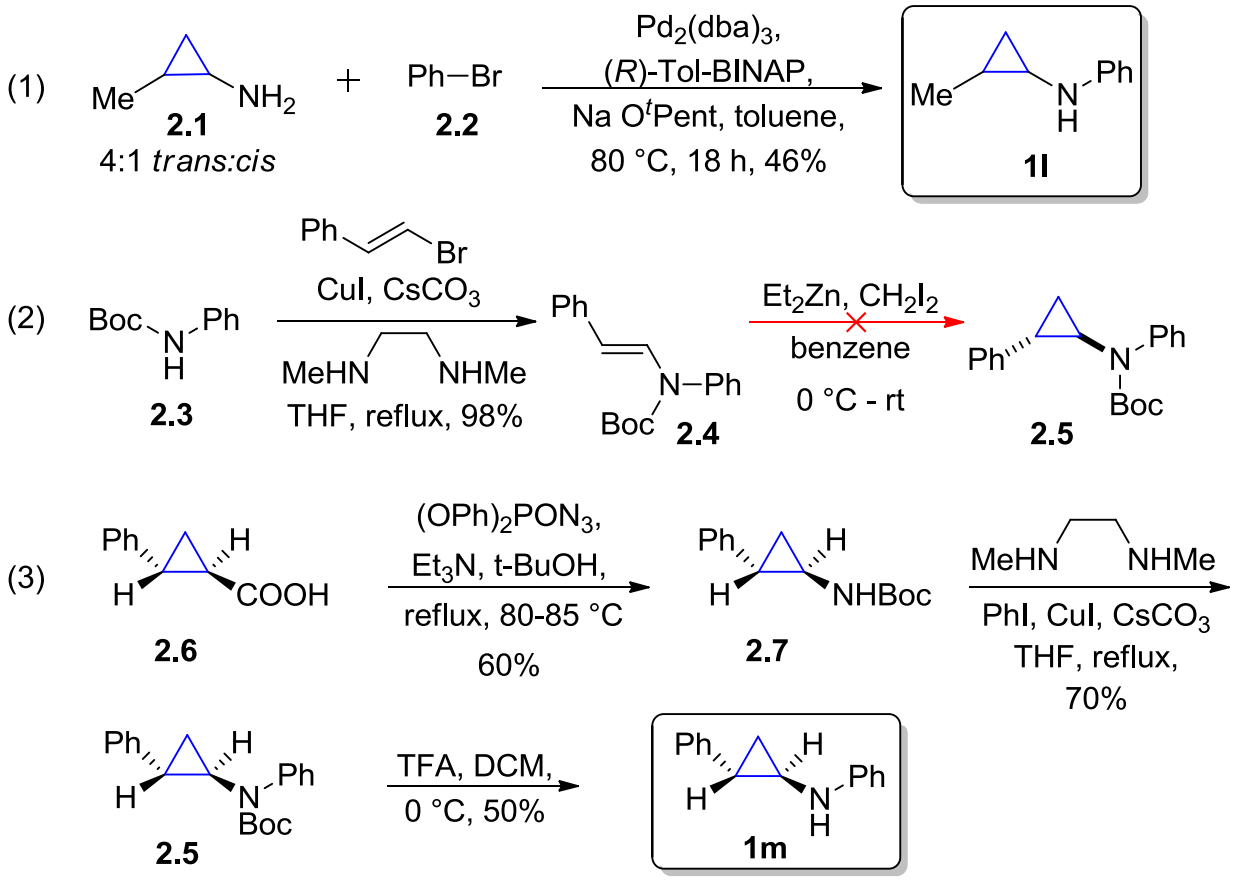


Scheme 2.8. Preparation of *N*-arylcyclopropylamines.

synthesize monocyclic *N*-arylcyclopropylamines;[121] 2) Kulinkovich-de Meijere reaction of amides to prepare bicyclic *N*-arylcyclopropylamines[134] (Scheme 2.8). Both methods, however, experience limitations. For the Buchwald-Hartwig amination reaction, commercially available cyclopropylamines are limited, which includes restriction of substituents on the cyclopropyl ring. Methods of introducing substituents to the nitrogen atom and cyclopropyl ring of cyclopropylamines would be essential to decorate the cyclopentene ring of the annulation products. For the Kulinkovic-de Meijere reaction, the precursor amides are often lengthy to synthesize. Also, both methods lack the ability to achieve enantiomeric pure cyclopropylanilines. Therefore, the synthetic routes to prepare *N*-(2-methylcyclopropyl)aniline **1l** and N-(*trans*-2-phenylcyclopropyl)aniline **1m** were eagerly pursued. Cyclopropylaniline **1l** was simply prepared from a Buchwald-Hartwig amination of bromobenzene and 2-methylcyclopropylamine, which was commercially available as a 4:1 *trans*:*cis* mixture (Scheme 2.9, eq. 1). The amination, commonly a high yielding reaction, unfortunately, afforded **1l** in a moderate yield of 46%. For the synthetic route to enantiomeric pure cyclopropylaniline **1m**, it was initially envisioned a Cu-mediated amination of Boc-protected aniline **2.3** with β-bromostyrene would furnish enamine **2.4** (Scheme 2.9, eq. 2). Subsequent cyclopropanation of the enamine with diethylzinc would afford the carbamate **2.5**. Although the formation of

enamine **2.4** was high yielding, the cyclopropanation step was unsuccessful. Discouraged by the results, an alternative synthetic route was pursued. N-(*trans*-2-phenylcyclopropyl)aniline **1m** was prepared from commercially available optically active

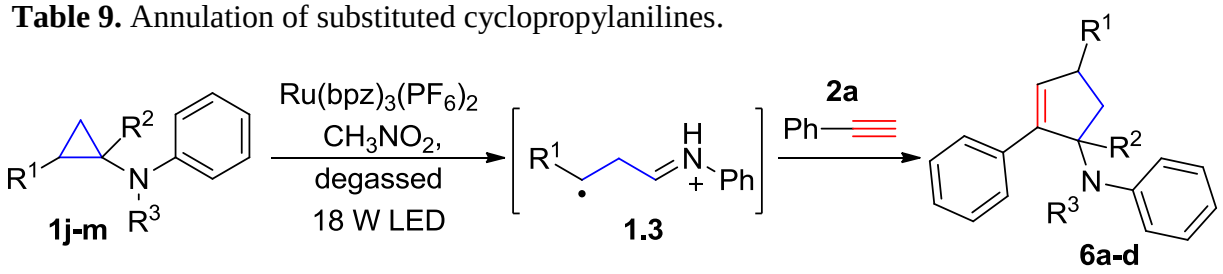
Scheme 2.9. Synthetic routes of cyclopropylanilines **1l** and **1m**.

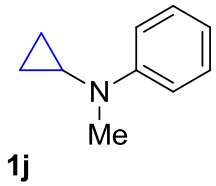
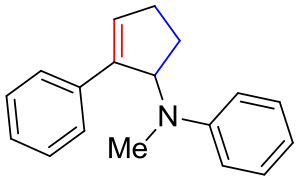
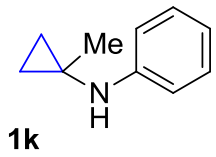
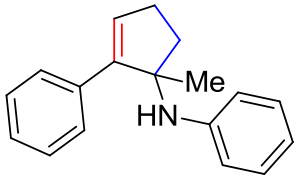
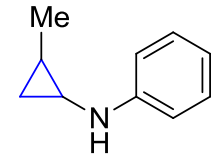
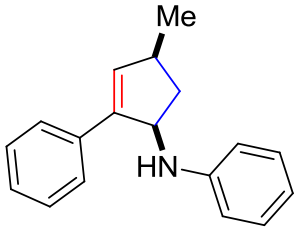
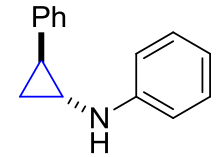
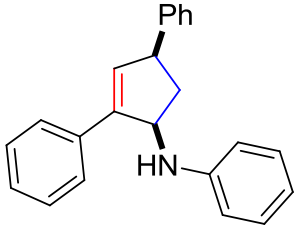


trans-2-phenyl-1-cyclopropanecarboxylic acid **2.6** (Scheme 2.9, eq. 3). A Curtius-type rearrangement via Shioiri's method[135] was then applied using diphenylphosphorylazide, triethylamine, and *t*-butanol to furnish carbamate **2.7**. Cu-mediated amination with iodobenzene was conducted to give newly formed carbamate **2.5**, which then was subjected to deprotection of the Boc group using trifluoroacetic acid in dry dichloromethane to afford the desired enantio-enriched cyclopropylaniline **1m**.

2.3.3.2 Scope Studies of Substituted Cyclopropylanilines with Phenylacetylene

Table 9. Annulation of substituted cyclopropylanilines.



Entry	Substrate	Time (h)	Product		Yield (%)[b]
1	 **1j**	16		**6a**	0[c]
2	 **1k**	15		**6b**	33
3	 **1l**	18		**6c**[d]	46[e]
4	 **1m**	36		**6d**[d]	30[f]

[a]A solution of **1j-m** (0.2 mmol), $Ru(bpz)_3(PF_6)_2$ (2 mol%), and **2a** (5 equiv.) in 2 mL of CH_3NO_2 was degassed via freeze-pump-thaw cycles. The resulting solution was irradiated using an 18 W white LED. [b]Isolated yields. [c]Determined using GC-MS. [d]Major isomer shown. [e]Ratio 2:1 *cis*:*trans*, determined by GC-MS. [f]Ratio 4:1 cis:trans, determined by GC-MS.

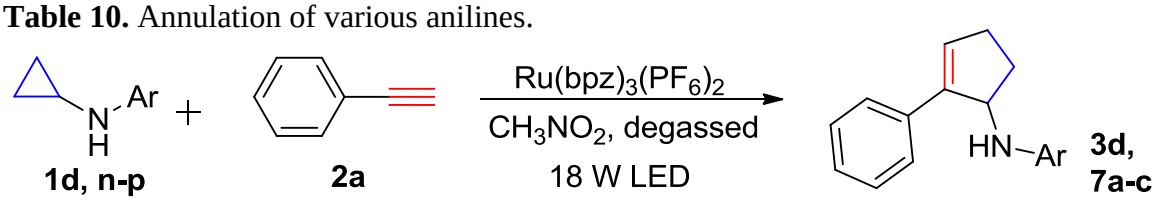
Using phenylacetylene **2a** as the model alkyne, the annulation of *N*-cyclopropyl-*N*-methylaniline **1j** to form **6a** was investigated, but no reaction was observed (Table 9, entry 1). This is in accordance with the result reported by Tanko and coworkers in which the ring opening of the

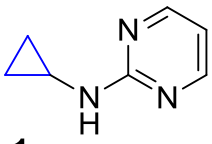
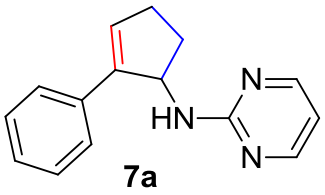
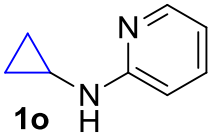
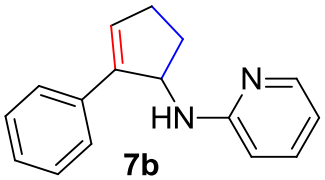
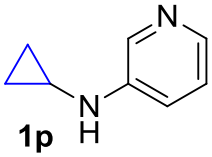
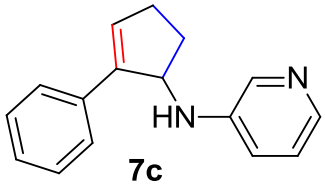
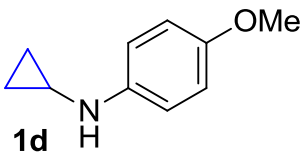
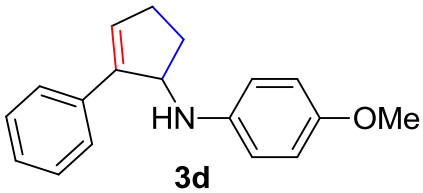
amine radical cation derived from **1j** was found to be very sluggish.[136] On the other hand, substitution on the cyclopropyl ring was generally tolerated. *N*-(1-methylcyclopropyl) aniline **1k** provided the annulation product **6b** bearing a quaternary carbon center in 33% yield when subjected to the standard conditions (Table 9, entry 2). The [3+2] annulation was also effective using 2-substituted cyclopropyl rings, as demonstrated with methyl **1l** and phenyl **1m** substituents (Table 9, entries 3 & 4). In both examples, the ring opening was completely regioselective, presumably cleaving the C-C bond between substituent R^1 and the amino group to generate the more substituted stable carbon radical **1.3**. Modest diastereoselectivity of 2:1 *cis*:*trans* was observed in the [3+2] annulation with 2-methyl substituted cyclopropylaniline **1l**, while a higher diastereoselectivty of 4:1 *cis*:*trans* was observed with 2-phenyl substituted cyclopropylaniline **1m**. The provided major products, cis isomer, were isolated in fair yields of 30-40%.

2.3.4. Cleavage of N-Aryl Group

The requirement of an aniline moiety has been a limitation to the [3+2] annulation, as it lowers the generality of the reaction. To circumvent this limitation, it was highly desired to install a removable aryl or heteroaryl group that was also capable of mediating the annulation. Some of these potential candidates include pyrimidine **1n**,[137] pyridines **1o**, **lp**[138] and para-methoxyphenyl (PMP) **1q**[139] groups. With this in mind, *N*-arylcyclopropylamines **1n–q** were synthesized bearing these groups and subjected to the standard conditions to react with phenylacetylene **2a**. The results are summarized in Table 10. No reaction was observed with 2-pyrimidyl-substituted cyclopropylamine **1n** (Table 10, entry 1). Surprisingly, 2-pyridyl-substituted cyclopropylamine **1o** afforded the annulation product **7b** in a low yield (13%), which was not synthetically useful (Table 10, entry 2). In comparison, a much higher yield of 48% was obtained with 3-pyridyl-

Table 10. Annulation of various anilines.



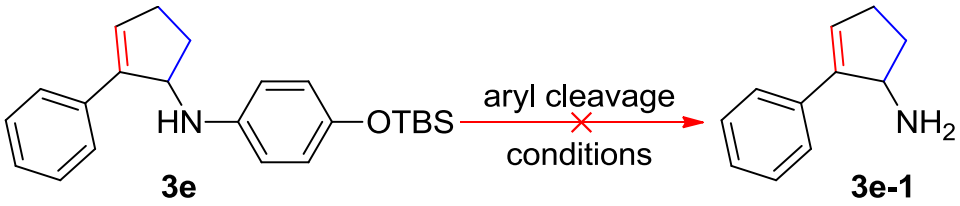
Entry[a]	Substrate	Time (h)	Product	Yield (%)[b]
1	 **1n**	48	 **7a**	0[c]
2	 **1o**	16	 **7b**	13
3	 **1p**	21	 **7c**	48
4	 **1d**	18	 **3d**	47

[a]A solution of **1d, n-p** (0.2 mmol), $Ru(bpz)_3(PF_6)_2$ (2 mol%), and **2a** (5 equiv.) in 2 mL CH_3NO_2 was degassed via freeze-pump-thaw cycles. The resulting solution was irradiated using an 18 W white LED. [b]Isolated yields. [c]Determined using GC-MS.

substituted cyclopropylamine **1p** (Table 10, entry 3). Unfortunately, the 3-pyridyl group was not cleavable. A similar yield (47%) was achieved with PMP-substituted cyclopropylamine **1q** (entry 4). In addition to the cleavable aryl groups mentioned above, *para-tert*-butyldimethylsilyloxy (OTBS) phenyl can be viewed as a cleavable group as oxidation of phenol, upon subsequent deprotection of TBS group, can transpire for cleavage. Previously introduced in Scheme 2.4, *para*-(OTBS) substituted cyclopropylamine **1e** underwent the

annulation to successfully afford cyclopentene **3e** in 66% yield. Thus, the initial approach for cleavage of the aryl group with annulated adduct **3e** was investigated. Efforts of exploring this aryl cleavage step are summarized in Table 11. The first attempt inquired a two step procedure of converting the *para*-OTBS-phenyl moiety of **3e** to phenol via cleavage of the silyl group in the presence of tetrabutylammonium fluoride (TBAF), then subsequent oxidative cleavage with a hypervalent iodide reagent, [bis(trifluroacetoxy)iodo]benzene (Table 11, entry 1). However, no desired cleavage product **3e-1** was detected. A similar observation was made when an alternative oxidant CAN/$Fe(bpy)_3(PF_6)_2$[140] was explored (Table 11, entry 2). The concern of isolating the cleaved product as a free allylic amine was questioned as its stability was unknown. Thus, it was envisioned for adduct **3e** to be treated with a Boc protection step first, followed by oxidative cleavage to provide a Boc-protected **3e-1** (Table 11, entry 3). Unfortunately, Boc-protecting the secondary allylic amine was ineffective. Since the attempts of aryl cleavage with adduct **3e** were unsuccessful, the attention was shifted towards studying the cleavage of the PMP group using **1d**.

Table 11. Aryl cleavage conditions for **3e**.



3e **3e-1**

Entry	Conditions
1	1. TBAF, 0 °C, THF; 2. $PhI(OCOCF_3)_2$, CH_3CN/H_2O
2	CAN, $Fe(bpy)_3(PF_6)_2$, CH_3CN/H_2O
3	1. NaHMDS, Boc_2O, THF; 2. oxidation

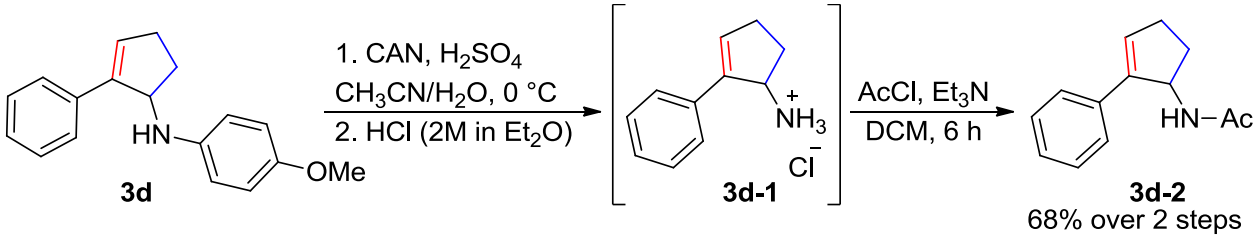
The PMP group is generally cleaved under oxidative conditions, and a number of oxidants are suitable for the cleavage.[139] Annulated product **3d** was subjected to various

oxidants, including ceric ammonium nitrate (CAN), periodic acid (H_5IO_6), trichloroisocyanuric acid (TCCA), and CAN/Fe $(bpy)_3(PF_6)_2$ (Table 12, entries 1-4). The effort of removing the methyl group with EtSNa to then subsequently cleave the para-hydroxy group with a hypervalent iodide was introduced (Table 12, entry 5), though no trace of the converted phenol was observed. Condition of acylating the adduct **3d**, followed by CAN oxidation was examined, however, oxidative cleavage of the PMP group from the newly formed carbamate was difficult (Table 12, entry 6). Thus, among the conditions examined, CAN in sulfuric acid provided the most promising results. Upon subjection to the oxidative conditions with CAN, the cleavage product was initially isolated as the HCl salt **3d-1** and then immediately acylated in the presence of Et_3N and acetyl chloride to give the corresponding acetamide **3d-2** in 68% isolated yield over 2 steps (Scheme 2.10). The successful removal of the PMP group circumvents the previous limitation of our chemistry and allows for more structural diversification of the [3+2] annulation products.

Table 12. Cleavage of PMP group under oxidative conditions.

Entry	Conditions
1	CAN, H_2SO_4, MeCN/ H_2O, 0 °C
2	H_5IO_6, 1 M H_2SO_4, MeCN/ H_2O
3	TCCA, H_2SO_4, MeCN/ H_2O
4	CAN, $Fe(bpy)_3(PF_6)_2$, CH_3CN/H_2O
5	1. EtSNa, DMF, 100 °C; 2. $PhI(OAc)_2$
6	1. *n*-BuLi/ $ClCO_2Et$; 2. CAN, MeCN/ H_2O

Scheme 2.10. Deprotection of *para*-methoxyphenyl (PMP) group.



In summary, the significant expansion on studies of the [3+2] annulation of cyclopropylanilines with alkynes was thoroughly examined and illustrated. These studies were

highlighted on multiple fronts including catalyst optimization, mechanistic studies, expansion of the substrate scope for both cycloproylanilines and alkynes, and identification of a removable *N*-aryl group for cyclopropylamines. Using simple building blocks, the [3+2] annulation enables rapid assembly of diverse cyclic allylic amine derivatives. Most of these amines possess embedded functional groups that allow for further structural diversification. Moreover, it can be anticipated that this method can find usage particularly in diversity-oriented synthesis (DOS).

2.3.5. Experimental Section

General Procedure 1 (GP1): Preparation of *N*-cyclopropylanilines (See Section 2.2.4.)

***N*-Cyclopropylaniline (1i)**. Following procedure GP1 with bromobenzene (527 μL, 5 mmol, 1 equiv.) and BrettPhos (80.5 mg, 0.15 mmol, 3 mol%), product was isolated after column chromatography on silica gel (3:100 EtOAc/hexane) as a colorless oil (611 mg, 92%). Spectral data correspond to those described in the literature.[141]

Preparation and characterization of compounds **3,5-Dimethyl-*N*-cyclopropylaniline (1b)** and ***N*-Cyclopropyl-2-biphenylamine (1a)** correspond to those described in the literature.[116] (See Section 2.2.4.)

***N*-cyclopropyl-*N*-methylaniline (1j).** Following a literature procedure,[142] to a suspension of cyclopropyl boronic acid (353 mg, 4.11 mmol, 2 equiv.), *N*-methylaniline (220 mg, 2.05 mmol, 1 equiv.), and Na_2CO_3 (435 mg, 4.11 mmol, 2 equiv.) in dichloroethane was added $Cu(OAc)_2$ (373 mg, 2.05 mmol, 1 equiv.) and bipyridine (321 mg, 2.05 mmol, 1 equiv.). The mixture was warmed to 70 °C and stirred for 4 h. The resulting mixture was cooled to room temperature and a 25% aqueous NH_4OH solution was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over Na2SO4, filtered, and concentrated under vacuum. Purification of the residual

mass by silica gel column chromatography (1:100 EtOAc/hexane) afforded the product as a colorless oil (101 mg, 33%). Spectral data correspond to those described in the literature.[143]

Preparation and characterization of compound ***N*-(1-methylcyclopropyl)aniline (1k)** correspond to those described in the literature.[144]

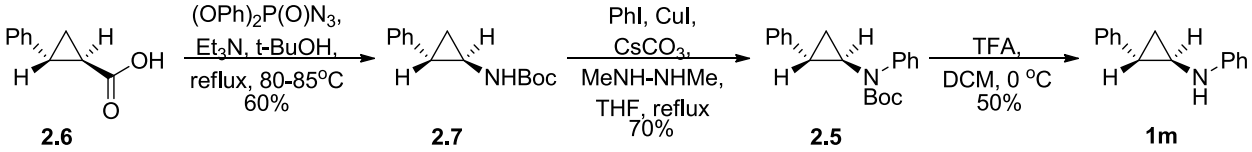
***N*-(2-methylcyclopropyl)aniline (1l).** Following procedure **GP1** with 2-methylcyclopropylamine (71.1 mg, 1 mmol, 4:1 mixture purchased from Sigma-Aldrich, 1.6 equiv.), bromobenzene (67 μL, 0.625 mmol, 1 equiv.) and BrettPhos (10.1 mg, 0.0188 mmol, 3 mol% equiv.), product was isolated after column chromatography on silica gel (3:100 EtOAc/hexane) as a colorless oil (68 mg, 46%). Spectral data correspond to those described in the literature.[144]

Preparation and characterization of compound ***N*-Cyclopropylpyrimidin-2-amine (1n)** correspond to those described in the literature.[145]

***N*-cyclopropylpyridin-2-amine (1o).** Following procedure **GP1** with 2-bromopyridine (0.2 mL, 2 mmol, 1 equiv.) and BrettPhos (32 mg, 0.06 mmol, 3 mol%), product was isolated after column chromatography on silica gel (1:1 EtOAc/hexane) as a yellow solid, m.p. 68-70 °C, (165 mg, 61%). IR υ_{max} (cm^{-1}) 3425, 3242, 1646, 1615, 1581, 1446, 1290, 1152, 776; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (ddd, *J* = 5.0, 1.8, 0.9 Hz, 1H), 7.48 (ddd, *J* = 8.7, 7.2, 1.9 Hz, 1H), 6.73 (dt, *J* = 8.4, 1.0 Hz, 1H), 6.61 (ddt, *J* = 7.2, 5.0, 1.1 Hz, 1H), 5.23 (s, 1H), 2.49 (ttd, *J* = 6.7, 3.6, 1.4 Hz, 1H), 0.82 – 0.69 (m, 2H), 0.58 – 0.47 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.03, 148.42, 137.78, 113.61, 106.31, 24.19, 7.78; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_8H_{10}N_2$ 135.0917; found 135.0912.

***N*-cyclopropylpyridin-3-amine (1p).**[76] Following procedure **GP1** with 3-bromopyridine (0.2 mL, 2 mmol, 1 equiv.) and BrettPhos (32 mg, 0.06 mmol, 3 mol%), product was isolated after column chromatography on silica gel (1:1 EtOAc/hexane) as a yellow oil (228 mg, 85%).

Preparation and characterization of compound **4-Methoxy-*N*-cyclopropylaniline (1d)** correspond to those described in the literature.[116] (See Section 2.2.4.)



***N*-((1*R*,2*S*)-2-phenylcyclopropyl)aniline (1m)** (Scheme 2.9). *trans*-2-Phenyl-1-cyclopropanecarboxylic acid **2.6** (250 mg, 1.54 mmol, 1 equiv.), diphenylphosphoryl azide (0.36 mL, 1.69 mmol, 1.1 equiv.), Et_3N (0.26 mL, 1.85 mmol, 1.2 equiv.) and *tert*-butyl alcohol (1.5 mL, 15.41 mmol, 10 equiv.) was stirred in toluene (5 mL) at 80-85 °C for 24 h. The mixture was cooled to room temperature, H_2O was added, and extracted with ethyl acetate three times. The combined organic layers were washed with 1 N HCl, H_2O, saturated $NaHCO_3$, and brine then dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the residual mass by silica gel column chromatography (1:5 EtOAc/hexane) afforded the product, *trans*-*N*-Boc-2 phenylcyclopropylamine **2.7**, as a yellow solid (216 mg, 60%).

CuI (19.1 mg, 0.1 mmol, 0.2 equiv.), Cs_2CO_3 (327 mg, 1.0 mmol, 2 equiv.), and *trans*-*N*-Boc-2 phenylcyclopropylamine **2.7** (117 mg, 0.5 mmol, 1 equiv.) were added to a test tube equipped with a stir bar. After purging with N_2 for a few seconds, the tube was sealed with Teflon screw cap. *N*,*N*'-dimethylethylenediamine (22 µL, 0.2 mmol, 0.4 equiv.) and iodobenzene (62 µL, 0.55 mmol, 2 equiv.) was added under N_2 followed by the addition of dry THF (2 mL). The resulting mixture was then heated to reflux for 24 h. After completion, the mixture was cooled to room temperature, diluted with ethyl acetate, and filtered over a short pad of silica. Purification of the

residual mass by silica gel column chromatography (1:5 EtOAc/hexane) afforded the product **2.5** as a colorless oil (108 mg, 70%). IR υ_{max} (cm^{-1}) 3034, 2979, 2934, 1712, 1601, 1494, 1346, 1163, 1056, 776, 700; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.29 (m, 3H), 7.29 – 7.23 (m, 3H), 7.22 – 7.16 (m, 2H), 7.11 – 7.07 (m, 2H), 3.17 (ddd, *J* = 7.5, 4.3, 3.3 Hz, 1H), 2.08 (ddd, *J* = 9.8, 6.6, 3.3 Hz, 1H), 1.45 (d, *J* = 0.5 Hz, 9H), 1.32 (dt, *J* = 7.0, 6.4 Hz, 1H), 1.17 – 1.08 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.53, 142.30, 140.81, 128.54, 128.45, 126.48, 126.34, 126.18, 125.56, 80.77, 40.32, 28.56, 27.59, 18.55; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{20}H_{23}NO_2$ 310.1802; found 310.1805.

To a solution of the carbamate **2.5 (**1.07 mmol, 1 equiv.) in dry CH_2Cl_2 (2 mL) cooled to 0 °C was added trifluoroacetic acid (4.28 mmol, 4 equiv.). The reaction was stirred for 5 h at 0 °C. Upon completion of the reaction, monitored by TLC, was added water. The aqueous layer was basified and then extracted with CH_2Cl_2 three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuum. Purification of the residual mass by silica gel column chromatography (1:10 EtOAc/hexane) afforded the product *N*-((1*R*,2*S*)-2-phenylcyclopropyl)aniline **1m** as a clear-yellow oil (112 mg, 50%); IR υ_{max} (cm^{-1}) 3398, 1628, 1507, 1314, 1269, 1179, 1034, 872, 762, 700; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.21 (m, 2H), 7.18 – 7.07 (m, 3H), 7.05 (dq, *J* = 8.2, 1.5 Hz, 2H), 6.73 – 6.57 (m, 3H), 4.20 (s, 1H), 2.55 (tdd, *J* = 6.4, 3.3, 0.9 Hz, 1H), 1.97 – 1.86 (m, 1H), 1.25 – 1.11 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.35, 141.65, 129.56, 128.77, 126.17, 126.05, 118.30, 113.49, 36.70, 26.45, 17.80; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{15}H_{15}N$ 210.1277; found 210.1273.

Synthesis of diynes and enynes

Preparation and characterization of diynes **2e**, **2f**, **2g**, **2h** correspond to those described in the literature.[146] Diyne **2b** (1,4-Diphenylbutadiyne) was purchased from Sigma-Aldrich. Diyne **2c**

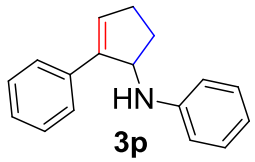
(2,4-Hexadiyne) was purchased from Alfa Aesar. Diyne **2d** (2,4-Hexadiyne-1,6-diol) was purchased from TCI America. Enyne **2j** (2-Methyl-1-buten-3-yne) was purchased from Acros. Enyne **2k** (1-Ethynylcyclohexene) was purchased from Sigma-Aldrich.

For the preparation of enyne **2l** (Scheme 2.7): $Pd(PPh_3)_2Cl_2$ (140 mg, 0.2 mmol, 2 mol%) and CuI (76 mg, 0.4 mmol, 4 mol%) were massed and transferred to a dry round bottom flask equipped with a stir bar. The flask was then vacuumed and purged with N_2 (3-5 cycles). Under N_2, β-bromostyrene (mixture of *trans* and *cis*) (1.30 mL, 10 mmol, 1 equiv.), TMS-acetylene (2.2 mL, 15 mmol, 1.5 equiv.) and Et_3N (2.8 mL, 20 mmol, 2 equiv.) were added, followed by dry THF (40 mL). The reaction was stirred overnight. Upon completion, the reaction was diluted with Et_2O and filtered through a short pad of silica. The crude product (801 mg, 4 mmol, 1 equiv.) was then deprotected in MeOH (40 mL) with K_2CO_3 (553 mg, 4 mmol, 1 equiv.). The product was then purified by silica gel flash chromatography to afford the desired product (436 mg, 85% yield). Spectral data correspond to those described in the literature.[147]

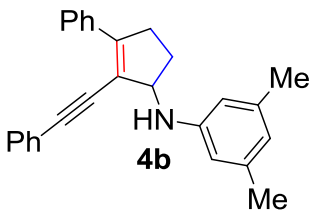
For the preparation of enyne **2m** (Scheme 2.7): To a solution of *cis*-1-bromo-1-propene (1.04 mL, 12.2 mmol, 1 equiv.), $Pd(PPh_3)_2Cl_2$ (257 mg, 0.37 mmol, 3 mol%) and CuI (46.5 mg, 0.24 mmol, 2 mol%) in Et_2NH (6 mL), cooled in an ice bath, was added phenylacetylene (1.3 mL, 12.2 mmol, 1 equiv.). The reaction was warmed to room temperature and solid Et_2NH•HCl formed gradually. After 1 h the reaction mixture color turned brownish-black. Water was added then extracted with Et_2O three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuum. The product was then purified by silica gel flash chromatography to afford the desired product (1.0 g, 58% yield). Spectral data correspond to those described in the literature.[148]

General Procedure 2 (GP2): [3 + 2] annulation of cyclopropylanilines with alkyne, enyne, and diyne: an oven-dried test tube (16 × 125 mm) equipped with a stir bar was charged with catalyst (2 mol %), cyclopropylaniline (0.2 mmol), alkyne, enyne, or diyne (1.0 mmol), and dry solvent (2 mL). The test tube was sealed with a Teflon screw cap. The reaction mixture was degassed by Freeze–Pump–Thaw cycles and then irradiated at room temperature with one white LED (18 watts) positioned 8 cm from the test tube. After the reaction was complete as monitored by TLC, the mixture was diluted with diethyl ether and filtered through a short pad of silica gel. The filtrate was concentrated in vacuum and purified by silica gel flash chromatography to afford the desired product.

***N*-(2-phenylcyclopent-2-enyl)aniline (3p).** Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). White solid, m.p. 66-68 °C, (27 mg, 57%); Silica gel column chromatography (30:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3411, 2848, 1639, 1605, 1505, 1429, 1318, 1256, 1097, 993, 752, 693; ^1H NMR (400 MHz, Chloroform-d) δ 7.47 – 7.36 (m, 2H), 7.29 – 7.19 (m, 2H), 7.19 – 7.06 (m, 3H), 6.65 (tq, J = 7.4, 1.1 Hz, 1H), 6.57 (dq, J = 7.7, 1.1 Hz, 2H), 6.35 (td, J = 2.5, 1.2 Hz, 1H), 4.87 – 4.77 (m, 1H), 3.71 (s, 1H), 2.66 – 2.53 (m, 1H), 2.45 (ddt, J = 17.6, 9.0, 3.1 Hz, 1H), 2.36 – 2.23 (m, 1H), 1.98 (dddd, J = 13.3, 7.3, 3.9, 2.2 Hz, 1H); ^{13}C NMR (101 MHz, CDCl3) δ 147.78, 142.91, 134.78, 130.27, 129.49, 128.74, 127.55, 126.38, 117.19, 113.22, 59.20, 31.78, 31.20; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{17}H_{17}N$ 236.1434; found 236.1436.

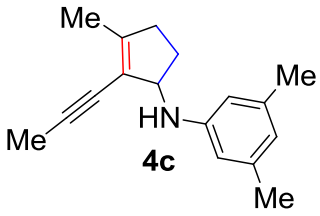


3,5-dimethyl-*N*-(2-phenyl-3-(phenylethynyl)cyclopent-2-enyl)aniline (4b). Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Light yellow oil, (15 mg, 20%); Silica gel column chromatography (100:1 hexane/EtOAc to elute excess diyne then 20:1 hexane/EtOAc);



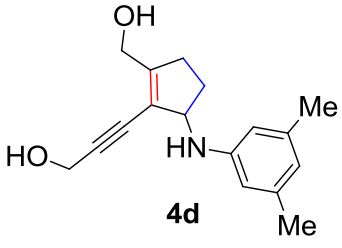
IR υ_{max} (cm^{-1}) 3397, 3034, 2925, 2854, 1600, 1487, 1335, 1187, 821, 757, 690; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 – 7.92 (m, 2H), 7.45 – 7.39 (m, 2H), 7.37 – 7.32 (m, 3H), 7.32 – 7.28 (m, 3H), 6.41 (d, *J* = 3.7 Hz, 3H), 4.82 – 4.73 (m, 1H), 4.04 (s, 1H), 3.02 (dddd, *J* = 17.0, 8.8, 4.7, 2.0 Hz, 1H), 2.89 (dddd, *J* = 16.8, 8.2, 6.3, 1.5 Hz, 1H), 2.54 (dtd, *J* = 12.9, 8.4, 7.9, 4.8 Hz, 1H), 2.26 (s, 6H), 1.97 – 1.85 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.40, 147.84, 139.23, 136.10, 131.84, 128.75, 128.60, 128.56, 128.53, 127.63, 123.71, 120.75, 119.73, 111.76, 96.85, 87.16, 63.99, 33.79, 31.86, 21.90; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{27}H_{25}N$ 364.2060; found 364.2063.

3,5-dimethyl-*N*-(2-methyl-3-(prop-1-ynyl)cyclopent-2-enyl)aniline (4c). Following **GP2** with



$[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL) . Light yellow solid, m.p. 68-72 °C, (17 mg, 35%); Silica gel column chromatography (15:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3396, 2917, 2849, 1601, 1508, 1473, 1437, 1335, 1184, 820, 689; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.36 (d, *J* = 1.1 Hz, 1H), 6.29 (d, *J* = 1.5 Hz, 2H), 4.43 – 4.36 (m, 1H), 3.85 (s, 1H), 2.52 – 2.40 (m, 1H), 2.38 – 2.28 (m, 2H), 2.24 (s, 6H), 1.98 (s, 3H), 1.91 – 1.83 (s, 3H), 1.79 – 1.67 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.12, 148.38, 139.09, 120.70, 119.46, 111.59, 90.73, 75.24, 62.65, 36.05, 31.88, 21.86, 16.40, 4.89; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{17}H_{21}N$ 240.1747; found 240.1745.

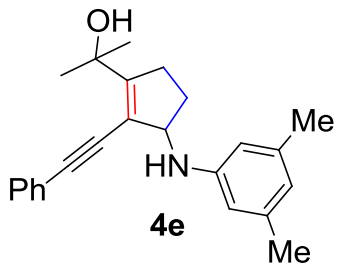
3-(3-(3,5-dimethylphenylamino)-2-(hydroxymethyl)cyclopent-1-enyl)prop-2-yn-1-ol (4d).



Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Light brown solid, m.p. 100-103 °C, (25 mg, 45%); Silica gel column chromatography (1:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3361, 2922, 2856, 2216, 1601, 1336, 1184, 1017, 829,

691; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.39 (qd, *J* = 1.6, 1.1 Hz, 1H), 6.32 (dt, *J* = 1.7, 0.9 Hz, 2H), 4.57 (ddd, *J* = 7.8, 5.0, 2.5 Hz, 1H), 4.38 (s, 2H), 4.32 (s, 2H), 2.67 – 2.56 (m, 1H), 2.53 – 2.46 (m, 1H), 2.40 (dddd, *J* = 13.4, 8.8, 7.1, 4.1 Hz, 1H), 2.26 – 2.20 (s, 6H), 1.83 – 1.68 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.68, 147.82, 139.16, 121.33, 120.25, 112.24, 94.36, 80.39, 62.95, 60.83, 51.67, 32.08, 31.55, 21.81; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{17}H_{21}NO_2$ 272.1645; found 272.1641.

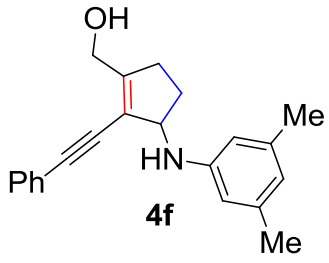
2-(3-(3,5-dimethylphenylamino)-2-(phenylethynyl)cyclopent-1-enyl)propan-2-ol (4e).



4e

Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Orange brown oil, (31 mg, 43%); Silica gel column chromatography (5:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3426, 2973, 2929, 2857, 1604, 1492, 1335, 1186, 954, 825, 760, 692; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, 5H), 6.45 – 6.30 (m, 3H), 4.60 (ddt, *J* = 7.3, 5.3, 1.9 Hz, 1H), 3.06 (s, 1H), 2.67 – 2.61 (m, 1H), 2.55 – 2.47 (m, 1H), 2.38 (dddd, *J* = 13.0, 8.5, 7.4, 4.6 Hz, 1H), 2.22 (s, 6H), 1.74 (dddd, *J* = 12.9, 8.9, 6.1, 5.4 Hz, 1H), 1.50 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.94, 148.25, 139.19, 131.58, 128.73, 128.60, 123.12, 119.74, 118.33, 111.71, 97.92, 84.94, 72.77, 63.48, 32.67, 31.94, 29.52, 29.27, 21.87; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{24}H_{27}NO$ 346.2165; found 346.2166.

(3-(3,5-dimethylphenylamino)-2-(phenylethynyl)cyclopent-1-enyl)methanol (4f).

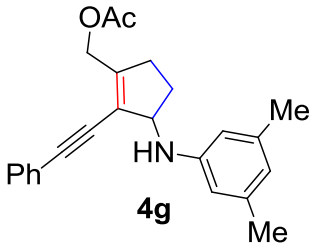


4f

Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Orange-brown oil, (25 mg, 40%); Silica gel column chromatography (2:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3354, 2925, 1600, 1489, 1336, 1186, 1032, 822, 755, 690; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.13 (m, 5H), 6.39 – 6.29 (m, 1H), 6.27 (dd, *J* = 1.7, 0.9 Hz, 2H),

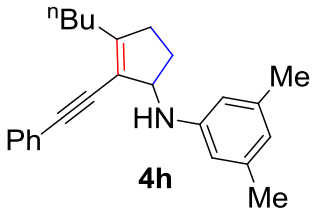
4.62 – 4.49 (m, 1H), 4.45 – 4.35 (m, 2H), 2.67 – 2.53 (m, 1H), 2.53 – 2.32 (m, 2H), 2.16 (s, 6H), 1.79 – 1.63 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.27, 148.14, 139.17, 131.78, 128.65, 128.57, 123.21, 122.18, 119.82, 111.75, 96.37, 83.95, 62.73, 61.34, 32.14, 32.08, 21.86; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{22}H_{23}NO$ 318.1852; found 318.1854.

(3-(3,5-dimethylphenylamino)-2-(phenylethynyl)cyclopent-1-enyl)methyl acetate (4g).



Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Orange-brown oil, (39 mg, 54%); Silica gel column chromatography (10:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3386, 3023, 2928, 2849, 1740, 1600, 1232, 1030, 822, 756, 690; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.14 (m, 6H), 6.34 – 6.23 (m, 3H), 4.84 (d, *J* = 1.6 Hz, 2H), 4.56 (dd, *J* = 7.6, 4.5 Hz, 1H), 3.80 (s, 1H), 2.59 – 2.31 (m, 4H), 2.18 – 2.13 (s, 6H), 2.02 (d, *J* = 0.7 Hz, 3H), 1.78 – 1.66 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.18, 148.08, 147.01, 139.20, 131.90, 128.72, 128.56, 124.92, 123.17, 119.85, 111.73, 96.83, 83.54, 62.59, 62.21, 32.35, 32.02, 21.87, 21.18; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{24}H_{25}NO_2$ 360.1958; found 360.1955.

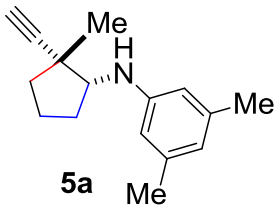
***N*-(3-butyl-2-(phenylethynyl)cyclopent-2-enyl)-3,5-dimethylaniline (4h).**



Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Light yellow oil, (14 mg, 20%); Silica gel column chromatography (100% hexane to elute excess diyne then 100:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 2958, 2931, 2858, 1601, 1335, 1190, 824, 755, 693; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.31 (m, 2H), 7.29 – 7.25 (m, 3H), 6.42 – 6.31 (m, 3H), 4.56 (d, *J* = 5.3 Hz, 1H), 3.92 (s, 1H), 2.60 – 2.47 (m, 1H), 2.45 – 2.34 (m, 4H), 2.26 – 2.22 (s, 6H), 1.78 (ddt, *J* = 12.0, 9.1, 4.1 Hz, 1H), 1.54 – 1.45 (m, 2H), 1.43 – 1.32 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.57, 148.29, 139.03, 131.61, 128.40, 128.05, 123.85,

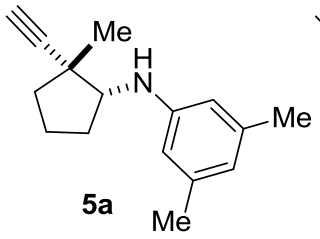
120.37, 119.44, 111.57, 94.51, 85.31, 62.40, 33.83, 31.97, 30.51, 29.95, 22.76, 21.76, 14.17; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{25}H_{29}N$ 344.2373; found 344.2372.

***N*-((1R,2R)-2-ethynyl-2-methylcyclopentyl)-3,5-dimethylaniline (5a).**

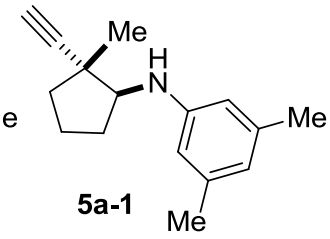


5a

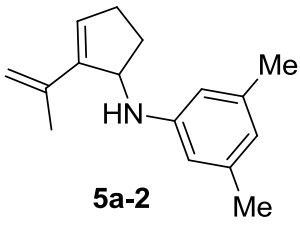
Following **GP2** with $Ir(ppy)_2(dtb\text{-}bpy)(PF_6)$ (2 mol %) and dry 1:1 CF_3CH_2OH: CH_3NO_2 (2 mL). Light yellow oil, (23 mg, 50%); Silica gel column chromatography (100% hexane to elute excess enyne then 20:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3405, 3293, 2966, 2868, 1602, 1517, 1337, 1190, 822, 690, 633; ^1H NMR (400 MHz, Chloroform-*d*) δ 6.50 – 6.31 (m, 3H), 3.95 (t, *J* = 7.6 Hz, 1H), 3.50 (s, 1H), 2.36 – 2.27 (m, 2H), 2.24 (q, *J* = 0.6 Hz, 6H), 2.18 (s, 1H), 2.12 – 1.99 (m, 1H), 1.83 – 1.67 (m, 3H), 1.49 – 1.35 (m, 1H), 1.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.26, 139.14, 119.54, 111.59, 92.51, 68.78, 63.45, 40.69, 40.45, 32.82, 21.84, 21.80, 21.28; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{16}H_{21}N$ 228.1747; found 228.1745.



5a



5a-1

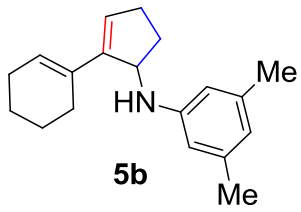


5a-2

^1H NMR (400 MHz, Chloroform-*d*, mixture of three isomers: two diastereomers and one regioisomer) δ 6.39 (dt, *J* = 1.3, 0.7 Hz, 2H), 6.35 (dddq, *J* = 5.9, 3.0, 1.5, 0.8 Hz, 3H), 6.30 – 6.27 (m, 2H), 6.25 (dt, *J* = 1.4, 0.7 Hz, 2H), 5.97 (t, *J* = 2.6 Hz, 1H), 5.01 (dt, *J* = 1.7, 1.0 Hz, 1H), 4.96 (s, 1H), 4.58 (dt, *J* = 7.4, 2.0 Hz, 1H), 3.95 (t, *J* = 7.6 Hz, 1H), 3.41 (dd, *J* = 9.1, 7.3 Hz, 1H), 2.57 (dt, *J* = 16.8, 7.7 Hz, 1H), 2.44 – 2.34 (m, 2H), 2.34 – 2.28 (m, 2H), 2.28 – 2.26 (m, 2H), 2.25 (q, *J* = 0.6 Hz, 6H), 2.23 (q, *J* = 0.6 Hz, 11H), 2.20 – 2.13 (m, 3H), 2.10 – 1.97 (m, 4H), 1.95 (dd, *J* = 1.4, 0.7 Hz, 4H), 1.89 (d, *J* = 17.2 Hz, 1H), 1.82 – 1.66 (m, 5H), 1.66 – 1.59 (m, 2H), 1.59 – 1.50 (m, 3H), 1.46 – 1.36 (m, 2H), 1.33 (s, 3H), 1.28 – 1.23

(m, 5H), 1.22 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of three isomers: two diastereomers and one regioisomer) δ 148.36, 148.13, 148.12, 144.92, 139.10, 139.01, 137.83, 131.63, 119.39, 119.19, 119.12, 113.82, 111.44, 111.39, 111.00, 92.38, 88.17, 71.83, 68.65, 63.31, 62.84, 58.81, 43.10, 40.56, 40.31, 39.25, 32.69, 32.03, 31.21, 31.02, 29.94, 25.86, 21.78, 21.72, 21.72, 21.66, 21.27, 21.15, 20.32

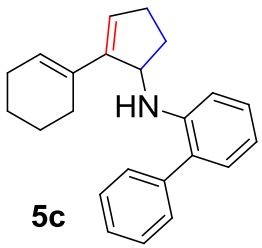
***N*-(2-cyclohexenylcyclopent-2-enyl)-3,5-dimethylaniline (5b).**



5b

Following **GP2** with $Ir(ppy)_2(dtb\text{-}bpy)(PF_6)$ (2 mol %) and dry 1:1 CF_3CH_2OH: CH_3NO_2 (2 mL). Light yellow oil, (24 mg, 43%); Silica gel column chromatography (100% hexane to elute excess enyne then 20:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3406, 3051, 2924, 2855, 1601, 1335, 1305, 1191, 1097, 819, 690; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.41 – 6.32 (m, 1H), 6.32 – 6.25 (m, 2H), 5.83 (dt, *J* = 6.7, 3.5 Hz, 2H), 4.56 (d, *J* = 6.8 Hz, 1H), 3.66 (s, 1H), 2.54 (dt, *J* = 16.5, 8.0 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.27 – 2.24 (s, 6H), 2.15 – 2.05 (m, 3H), 1.97 (ddt, *J* = 13.0, 7.9, 2.0 Hz, 1H), 1.69 (dq, *J* = 10.0, 6.5, 5.7 Hz, 3H), 1.64 – 1.52 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.29, 145.26, 139.22, 131.59, 127.66, 126.08, 119.09, 111.08, 58.50, 31.90, 31.06, 26.58, 26.03, 23.08, 22.66, 21.91; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{19}H_{25}N$ 268.2060; found 268.2064.

***N*-(2-cyclohexenylcyclopent-2-enyl)biphenyl-2-amine (5c).**

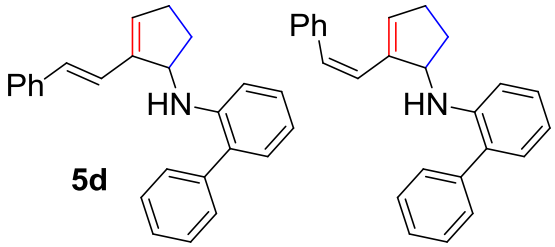


5c

Following **GP2** with $Ir(ppy)_2(dtb\text{-}bpy)(PF_6)$ (2 mol %) and dry 1:1 CF_3CH_2OH: CH_3NO_2 (2 mL). Light yellow oil, (35 mg, 53%); Silica gel column chromatography (100% hexane to elute excess enyne then 20:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3426, 2925, 2851, 1649, 1509, 1492, 1438, 1192, 746, 705; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.27 (m, 5H), 7.08 (ddt, *J* =

7.4, 1.7, 0.5 Hz, 1H), 6.81 – 6.70 (m, 2H), 5.79 – 5.70 (m, 2H), 4.57 (d, *J* = 7.2 Hz, 1H), 4.07 (s, 1H), 2.44 (q, *J* = 8.4, 7.7 Hz, 1H), 2.39 – 2.28 (m, 1H), 2.26 – 2.14 (m, 2H), 1.94 (ddt, *J* = 13.1, 8.2, 2.5 Hz, 1H), 1.68 – 1.60 (m, 2H), 1.56 (dt, *J* = 9.8, 3.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.16, 144.90, 139.94, 131.52, 130.69, 129.66, 129.00, 127.76, 127.70, 127.30, 126.15, 116.65, 111.02, 100.30, 59.24, 32.08, 31.17, 26.61, 26.05, 23.11, 22.69; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{23}H_{25}N$ 316.2060; found 316.2058.

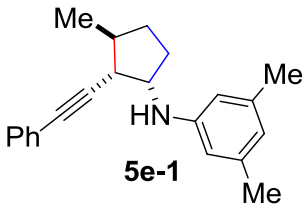
(*E*)-*N*-(2-styrylcyclopent-2-enyl)biphenyl-2-amine (5d).



Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %), enyne (1 mmol, 10:1 *trans*:*cis*) and dry CH_3NO_2 (2 mL).Yellow paste, (40 mg, 59%); Silica gel column chromatography (100% hexane to elute excess enyne then 25:1 hexane/EtOAc) as an inseparable mixture of two diastereoisomers; IR υ_{max} (cm^{-1}) 3428, 1646, 1508, 1491, 1439, 1318, 966, 752, 707, 696; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of diastereomers) δ 7.41 – 7.38 (m, 1.3H), 7.38 (d, *J* = 1.5 Hz, 0.7H), 7.36 (t, *J* = 1.6 Hz, 2H), 7.34 (t, *J* = 1.6 Hz, 1.2H), 7.33 (t, *J* = 1.6 Hz, 1H), 7.32 – 7.30 (m, 1.7H), 7.30 – 7.28 (m, 1H), 7.28 – 7.25 (m, 2H), 7.24 – 7.22 (m, 2H), 7.21 (t, *J* = 0.4 Hz, 0H), 7.20 – 7.17 (m, 1.3H), 7.17 – 7.13 (m, 0.6H), 7.11 (dt, *J* = 7.4, 1.7 Hz, 1H), 7.06 (dt, *J* = 7.5, 1.6 Hz, 0.3H), 6.88 – 6.83 (m, 1.4H), 6.83 – 6.77 (m, 1.6H), 6.71 (td, *J* = 7.4, 1.2 Hz, 0.3H), 6.60 (d, *J* = 16.3 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 0.3H), 6.48 – 6.41 (m, 0.3H), 6.04 (d, 0.3H), 5.97 (d, *J* = 3.0 Hz, 1H), 5.82 – 5.76 (m, 0.3H), 4.77 (d, *J* = 7.8 Hz, 1H), 4.44 (s, 0.3H), 4.09 (s, 1H), 2.51 (dt, *J* = 16.6, 7.7 Hz, 1H), 2.45 – 2.39 (m, 1H), 2.39 – 2.28 (m, 2H), 2.28 – 2.21 (m, 0.3H), 2.03 – 1.92 (m, 1H), 1.78 – 1.66 (m, 0.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.72, 144.63, 142.61, 140.90, 139.73, 139.56, 138.01, 137.67, 135.19, 133.75,

131.46, 130.68, 130.37, 129.92, 129.53, 129.46, 128.96, 128.95, 128.85, 128.78, 128.63, 128.60, 128.14, 127.93, 127.68, 127.58, 127.23, 127.19, 127.02, 126.49, 124.84, 123.58, 116.77, 116.70, 111.14, 111.07, 60.85, 58.45, 32.04, 31.75, 31.08, 30.94; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{25}H_{23}N$ 338.1903; found 338.1916.

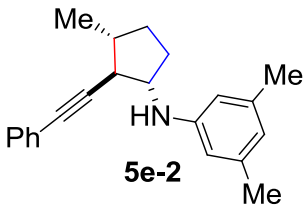
3,5-dimethyl-*N*-((1S,2S,3S)-3-methyl-2-(phenylethynyl)cyclopentyl)aniline (5e-1).



5e-1

Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Light-yellow oil, (40 mg, 66% combined yields); Silica gel column chromatography (100% hexane to elute excess enyne then 2:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3425, 2965, 2924, 2869, 1646, 1608, 1339, 1194, 824, 759, 693; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.32 (m, 2H), 7.31 – 7.27 (m, 3H), 6.40 – 6.33 (m, 1H), 6.33 – 6.26 (m, 2H), 4.21 (s, 1H), 3.92 (q, *J* = 6.2 Hz, 1H), 2.71 (dd, *J* = 8.9, 6.9 Hz, 1H), 2.35 – 2.25 (m, 1H), 2.24 (d, *J* = 0.8 Hz, 6H), 2.22 – 2.13 (m, 1H), 2.03 (dtd, *J* = 16.4, 7.9, 3.7 Hz, 1H), 1.73 (dtd, *J* = 13.6, 8.5, 5.3 Hz, 1H), 1.30 – 1.23 (m, 1H), 1.19 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.20, 139.00, 131.88, 128.41, 128.02, 123.71, 119.46, 111.64, 100.19, 89.27, 56.35, 44.53, 40.66, 32.92, 32.14, 21.75, 20.06; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{22}H_{25}N$ 304.2060; found 304.2063.

3,5-dimethyl-*N*-((1S,2R,3R)-3-methyl-2-(phenylethynyl)cyclopentyl)aniline (5e-2).

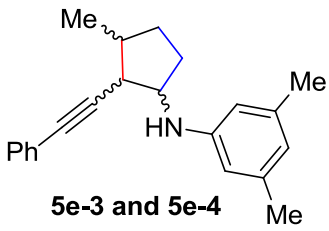


5e-2

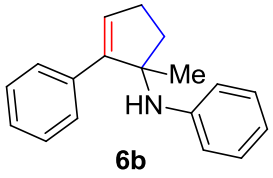
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.39 (m, 2H), 7.34 – 7.28 (m, 3H), 6.36 (tt, *J* = 1.6, 0.7 Hz, 1H), 6.33 – 6.28 (m, 2H), 4.13 (s, 1H), 3.96 (q, *J* = 7.8 Hz, 1H), 3.26 (t, *J* = 5.9 Hz, 1H), 2.23 (q, *J* = 0.6 Hz, 6H), 2.21 – 2.12 (m, 2H), 1.89 – 1.76 (m, 1H), 1.70 – 1.56 (m, 2H), 1.19 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.08, 139.04, 131.90, 128.47, 128.01, 123.92, 119.67, 111.96, 87.06, 86.91, 57.50, 42.11, 36.70, 30.84, 30.00, 21.74, 17.62.

3,5-dimethyl-*N*-(3-methyl-2-(phenylethynyl)cyclopentyl)aniline (5e-3 and 5e-4).

^{1}H NMR (400 MHz, Chloroform-*d*, mixture of two diastereomers) δ 7.46 – 7.40 (m, 2H), 7.40 – 7.35 (m, 2H), 7.33 – 7.26 (m, 4H), 6.40 – 6.36 (m, 3H), 6.35 (dt, *J* = 1.5, 0.7 Hz, 2H), 3.98 (dt, *J* = 7.9, 4.4 Hz, 1H), 3.88 (td, *J* = 8.1, 5.9 Hz, 1H), 3.74 (s, 2H), 2.94 – 2.88 (m, 1H), 2.49 – 2.37 (m, 1H), 2.31 – 2.26 (m, 2H), 2.25 (q, *J* = 0.6 Hz, 6H), 2.23 (q, *J* = 0.6 Hz, 6H), 2.16 – 2.05 (m, 1H), 1.93 (dddd, *J* = 23.7, 11.7, 7.4, 3.6 Hz, 2H), 1.60 – 1.49 (m, 5H), 1.49 – 1.36 (m, 2H), 1.18 (dd, *J* = 6.7, 4.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of two diastereomers) δ 144.59, 139.16, 139.06, 131.85, 131.81, 128.41, 128.34, 127.83, 127.82, 124.17, 123.95, 119.79, 111.68, 90.21, 84.48, 65.51, 63.41, 61.69, 61.44, 61.42, 59.45, 58.56, 47.58, 43.66, 41.40, 36.37, 32.98, 32.87, 32.26, 31.71, 21.77, 21.74, 19.43, 16.95.



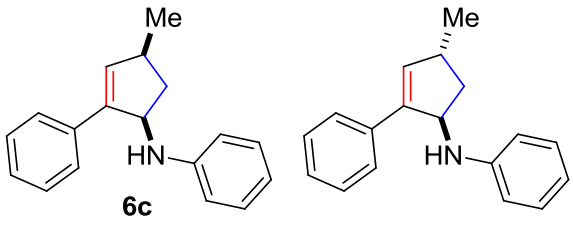
5e-3 and 5e-4



6b

***N*-(1-methyl-2-phenylcyclopent-2-enyl)aniline (6b).** Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Clear oil, (16 mg, 33%); Silica gel column chromatography (98:2 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3411, 3052, 2962, 2927, 2844, 1605, 1501, 1322, 1194, 762, 693; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.47 (m, 2H), 7.20 – 7.13 (m, 3H), 7.07 – 6.98 (m, 2H), 6.68 – 6.55 (m, 3H), 6.00 (t, *J* = 2.6 Hz, 1H), 3.84 (s, 1H), 2.58 – 2.31 (m, 3H), 1.88 – 1.75 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.42, 146.83, 136.11, 129.46, 129.20, 129.05, 128.31, 127.35, 117.47, 115.30, 67.43, 35.84, 29.31, 29.26; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{18}H_{19}N$ 250.1590; found 250.1591.

***N*-((1R,4S)-4-methyl-2-phenylcyclopent-2-enyl)aniline (6c).**



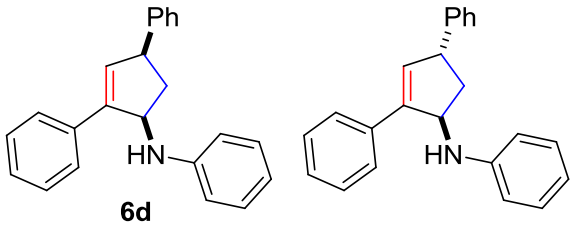
6c

69:31 *cis:trans*

Following **GP2** with $[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Clear oil, (23

mg, 46%); Silica gel column chromatography (99:1 hexane/EtOAc) as an inseparable mixture of two diastereoisomers; IR υ_{max} (cm^{-1}) 3411, 3052, 2955, 2927, 2869, 1600, 1501, 1311, 765, 748; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of diastereomers) δ 7.57 – 7.48 (m, 3H), 7.36 – 7.30 (m, 3H), 7.29 – 7.20 (m, 4.4H), 6.74 (tq, *J* = 7.3, 1.0 Hz, 1.4H), 6.69 – 6.62 (m, 3H), 6.34 (d, *J* = 2.1 Hz, 0.4H), 6.33 (dd, *J* = 2.7, 1.3 Hz, 1H), 4.96 – 4.91 (m, 0.4H), 4.91 – 4.86 (m, 1H), 3.83 (s, 1H), 3.11 (qt, *J* = 7.1, 2.1 Hz, 0.4H), 2.99 – 2.87 (m, 1H), 2.75 (ddd, *J* = 13.2, 8.4, 7.5 Hz, 1H), 2.32 (ddd, *J* = 13.2, 7.3, 1.6 Hz, 0.4H), 1.82 (dt, *J* = 12.9, 7.1 Hz, 0.4H), 1.59 (dt, *J* = 13.2, 4.1 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diastereomers) δ 147.72, 141.86, 136.45, 135.91, 134.80, 134.65, 129.54, 129.49, 128.76, 128.70, 127.64, 127.58, 126.60, 126.35, 121.20, 118.00, 117.24, 117.17, 113.27, 113.14, 59.47, 59.15, 40.87, 40.51, 38.80, 38.62, 22.60, 20.95 ; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{18}H_{19}N$ 250.1590; found 250.1589.

***N*-((1R,4S)-2,4-diphenylcyclopent-2-enyl)aniline (6d).** Following **GP2** with



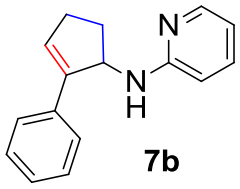
6d

79:21 *cis*:*trans*

$[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Clear-yellow oil, (19 mg, 30%); Silica gel column chromatography (50:1 hexane/EtOAc) as an inseparable mixture of two diastereoisomers; IR υ_{max} (cm^{-1}) 3411, 3054, 2930, 2102, 1643, 1605, 1505, 1315, 752, 696; ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of diastereomers) δ 7.52 – 7.44 (m, 3H), 7.30 – 7.19 (m, 9H), 7.19 – 7.08 (m, 5H), 7.02 – 6.97 (m, 0.8H), 6.86 (td, *J* = 7.3, 1.1 Hz, 0.4H), 6.64 (dtt, *J* = 12.3, 7.4, 1.1 Hz, 1H), 6.60 – 6.52 (m, 3H), 6.41 (d, *J* = 2.2 Hz, 0.3H), 6.31 (dd, *J* = 2.6, 1.5 Hz, 1H), 4.99 – 4.95 (m, 0.3H), 4.93 (ddt, *J* = 7.3, 4.2, 1.5 Hz, 1H), 4.17 (tt, *J* = 7.7, 2.1 Hz, 0.3H), 4.05 – 3.96 (m, 1H), 3.80 (s, 1H), 3.03 (ddd, *J* = 13.6, 9.1, 7.6 Hz, 1H), 2.54 (ddd, *J* =

13.3, 7.7, 1.6 Hz, 0.3H), 2.11 (ddd, *J* = 13.2, 7.6, 6.8 Hz, 0.3H), 1.86 (ddd, *J* = 13.6, 5.3, 4.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diastereomers) δ 147.69, 147.59, 145.45, 145.25, 143.95, 143.65, 143.29, 134.45, 134.23, 133.65, 132.78, 129.56, 129.54, 129.50, 128.88, 128.80, 128.77, 128.04, 127.96, 127.59, 127.45, 126.85, 126.65, 126.56, 121.18, 117.98, 117.40, 113.26, 59.45, 59.24, 49.95, 49.73, 42.71, 41.96; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{23}H_{21}N$ 312.1747; found 312.1746.

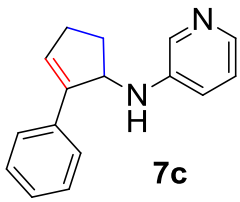
***N*-(2-phenylcyclopent-2-enyl)pyridin-2-amine (7b).** Following **GP2** with



7b

$[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). Orange solid, m.p. 102-105 °C, (6.2 mg, 13%); Silica gel column chromatography (2:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3428, 2100, 1646, 1594, 1487, 1328, 1152, 983, 762; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (ddt, *J* = 5.1, 1.7, 0.8 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.41 (dddd, *J* = 8.4, 7.1, 1.9, 0.7 Hz, 1H), 7.29 (dddd, *J* = 7.5, 6.8, 1.6, 0.9 Hz, 2H), 7.24 – 7.19 (m, 1H), 6.57 (ddt, *J* = 6.9, 5.1, 0.8 Hz, 1H), 6.44 – 6.34 (m, 2H), 5.29 (d, *J* = 6.1 Hz, 1H), 4.57 (s, 1H), 2.64 (dddt, *J* = 13.1, 10.9, 5.7, 3.0 Hz, 1H), 2.57 – 2.40 (m, 2H), 2.03 – 1.90 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.32, 148.39, 143.04, 137.53, 134.81, 130.41, 128.70, 127.55, 126.40, 112.82, 107.65, 57.52, 32.50, 31.03; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{16}H_{16}N_2$ 237.1386; found 237.1381.

***N*-(2-phenylcyclopent-2-enyl)pyridin-3-amine (7c).** Following **GP2** with



7c

$[Ru(bpz)_3](PF_6)_2 \cdot 2H_2O$ (2 mol %) and dry CH_3NO_2 (2 mL). White-ivory solid, m.p. 142-145 °C, (22 mg, 48%); Silica gel column chromatography (1:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3382, 2099, 1650, 1587, 1480, 1418, 1308, 797, 762, 710; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 – 7.76 (m, 2H), 7.44 – 7.30 (m, 2H), 7.22 (tt, *J* = 6.8, 1.3 Hz, 2H), 7.19 – 7.11 (m, 1H), 7.06 – 6.94 (m, 1H), 6.82 (ddd, *J* = 8.3,

2.9, 1.4 Hz, 1H), 6.33 (td, *J* = 2.7, 1.0 Hz, 1H), 4.78 (d, *J* = 7.1 Hz, 1H), 3.73 (d, *J* = 7.4 Hz, 1H), 2.65 – 2.49 (m, 1H), 2.44 (ddt, *J* = 17.7, 8.9, 3.2 Hz, 1H), 2.29 (ddt, *J* = 13.2, 8.9, 7.1 Hz, 1H), 1.96 – 1.85 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.69, 142.53, 138.70, 136.40, 134.51, 130.65, 128.80, 127.72, 126.30, 123.93, 118.97, 58.99, 31.50, 31.17; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{16}H_{16}N_2$ 237.1386; found 237.1385.

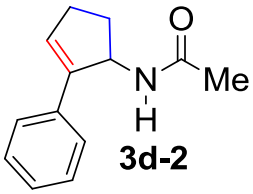
Preparation and characterization of compound **4-methoxy-*N*-(2-phenylcyclopent-2-enyl)aniline (3d)** correspond to those described in the literature.[116] (See Section 2.2.4.)

General Procedure 3 (GP3): Deprotection of the PMP Group (Scheme 2.10): To a pre-cooled solution of *para*-methoxyphenyl amine (51 mg, 0.2 mmol) in 3:1 CH_3CN:H_2O (2 mL) was slowly added concentrated H_2SO_4 (22 μL, 0.385 mmol) at 0 °C. Ceric ammonium nitrate (220 mg, 0.4 mmol) was then added in one portion, and the mixture was stirred for one hour at 0 °C. The resulting mixture was then diluted with water (2 mL) and separated. The aqueous phase was then washed with Et_2O (3 x 5 mL). The combined organic phase was then extracted with 0.1 N HCl (1 x 15 mL), and the obtained aqueous phase was added to the previous aqueous mixture, which was immediately basified to pH 14 using 5 N KOH. The basic aqueous layer was then extracted with Et_2O (2 x 30 mL). The combined organic layer was then acidified to pH 1 using hydrogen chloride (2 M in Et_2O). The resulting solution was then dried over $MgSO_4$ and concentrated to give the HCl salt as a dark brown oil. The crude HCl salt was used in the next step without further purification.

To a solution of the HCl salt (35 mg, 0.18 mmol) in dry CH_2Cl_2 (5 mL) was added Et_3N (56 μL, 0.4 mmol) dropwise at room temperature. Acetyl chloride (16 μL, 0.22 mmol) was slowly added and the reaction was stirred for 6 hours at room temperature. The reaction was quenched with water (10 mL) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x

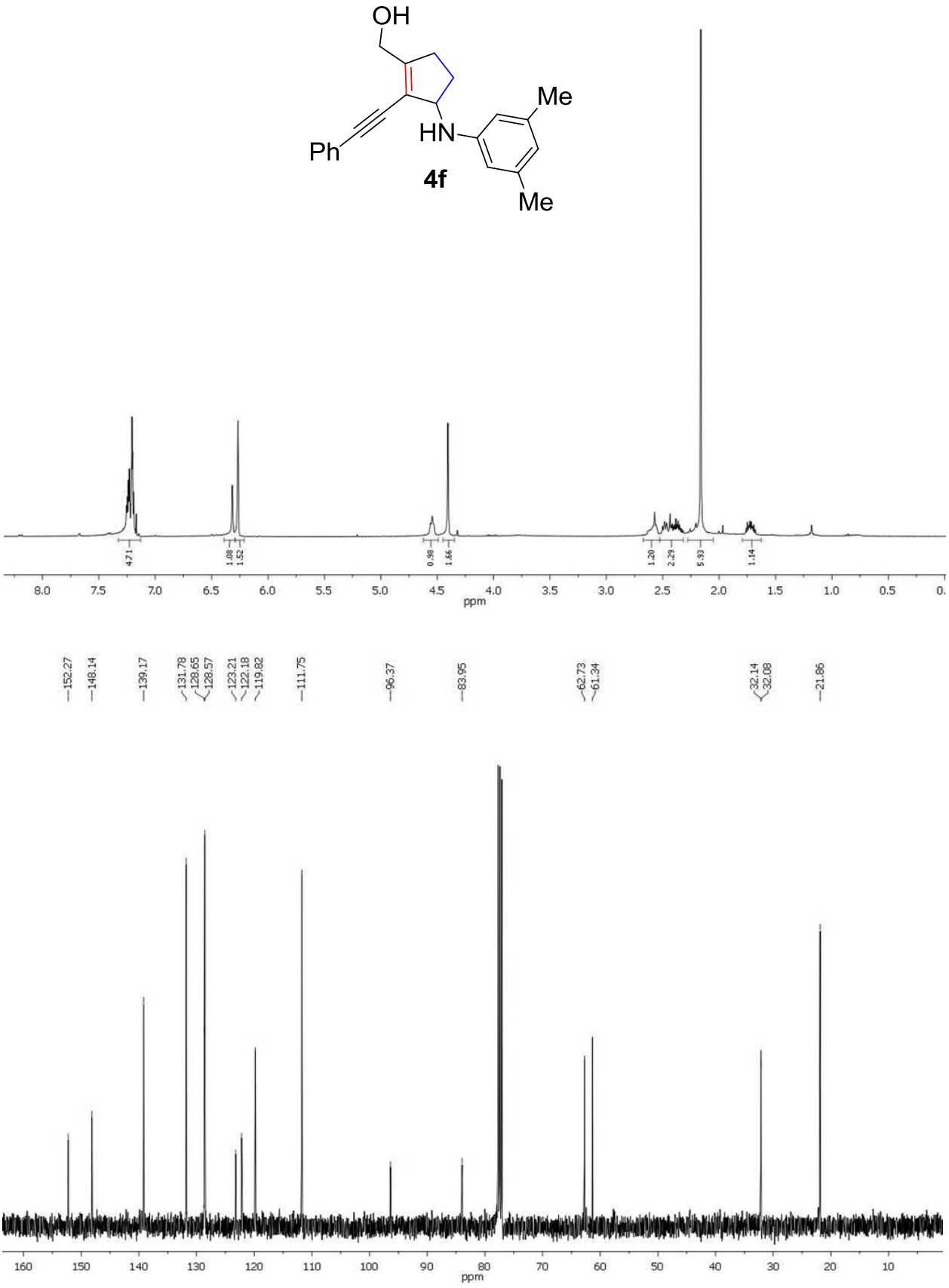
10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give the crude product. Purification using silica gel chromatography (1:1 hexanes:EtOAc) provided the desired acylated product (26.5 mg, 68% over 2 steps).

N-(2-phenylcyclopent-2-enyl)acetamide (3d-2). Following **GP3** the product was isolated as a



3d-2

red-brown oil, (26.5 mg, 68% over two steps); Silica gel column chromatography (1:1 hexane/EtOAc); IR υ_{max} (cm^{-1}) 3421, 2934, 2855, 1774, 1646, 1556, 1449, 1377, 1204, 759, 696; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.31 – 7.23 (m, 2H), 7.20 – 7.12 (m, 2H), 7.10 – 7.04 (m, 1H), 6.18 (t, *J* = 2.5 Hz, 1H), 5.40 – 5.20 (m, 2H), 2.44 – 2.26 (m, 3H), 1.74 (s, 3H), 1.70 – 1.59 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.91, 142.57, 134.29, 130.62, 128.83, 127.73, 126.23, 55.16, 32.78, 30.88, 23.67; HRMS (ESI) *m/z* $[M+H]^+$, calc'd for $C_{13}H_{15}NO$ 202.1226; found 202.1232.


OH
Me
HN
Ph
4f
Me
4.71
1.08
1.52
0.98
1.66
1.20
2.29
5.93
1.14
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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148.14
139.17
131.78
128.65
128.57
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122.18
119.82
111.75
96.37
83.95
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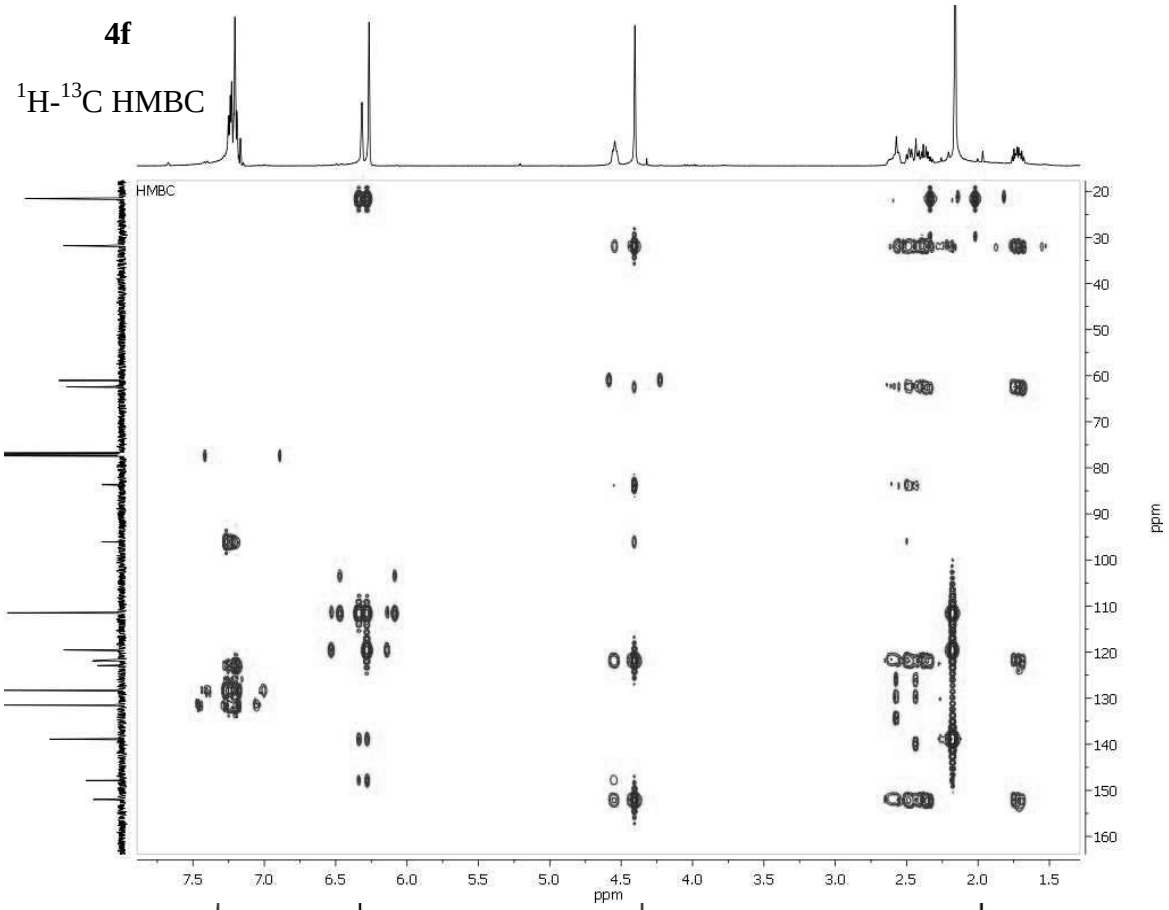
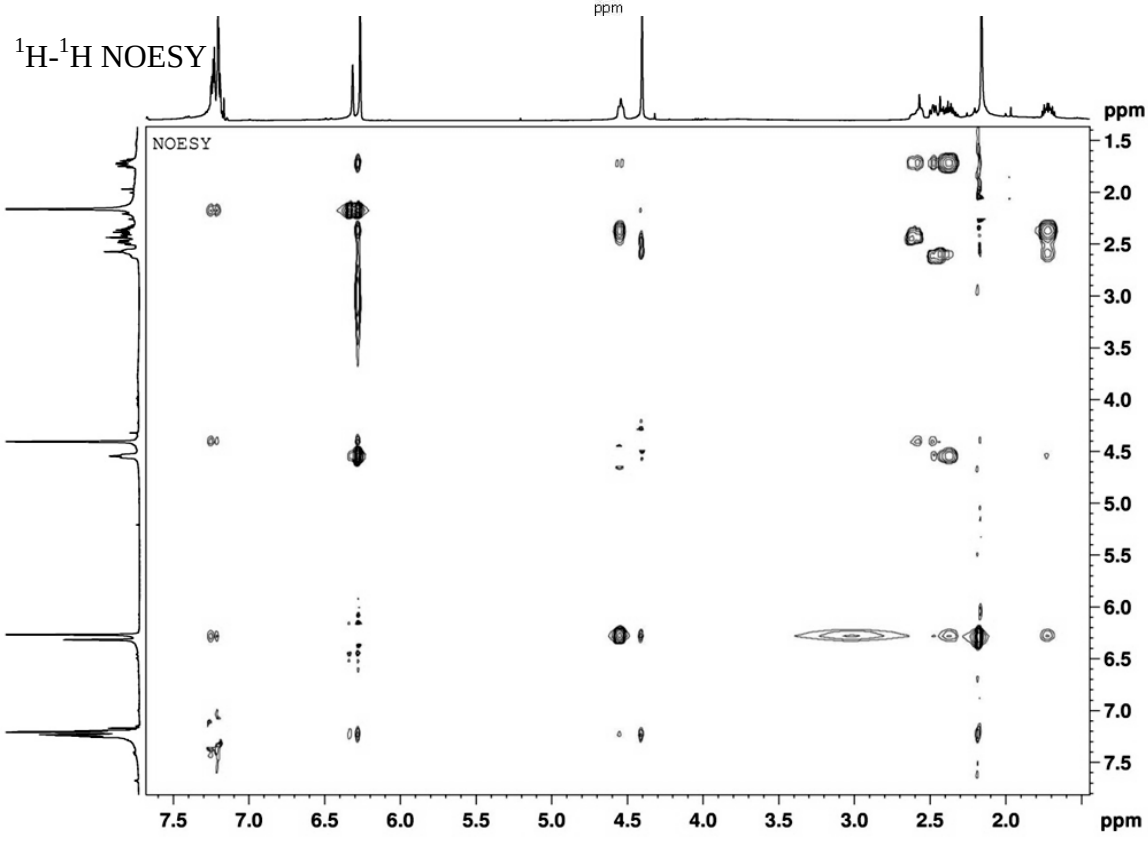
61.34
32.14
32.08
21.86
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

4f

^{1}H-^{13}C HMBC



^{1}H-^{1}H NOESY



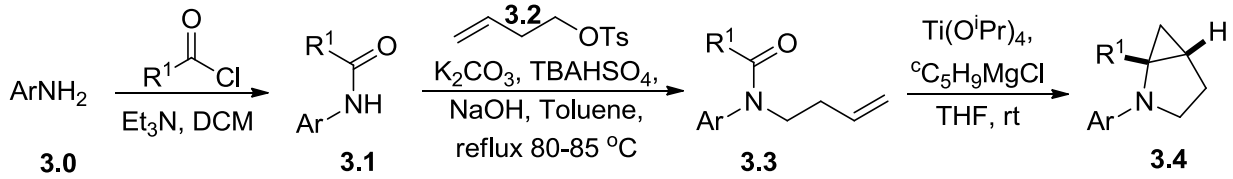
2.4. [3+2] Annulation of Bicyclic Cyclopropylanilines

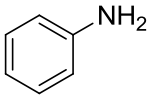
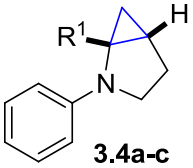
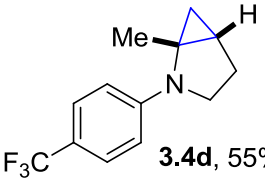
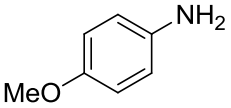
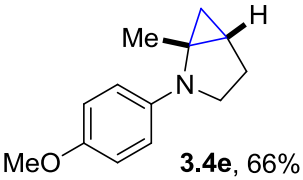
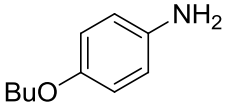
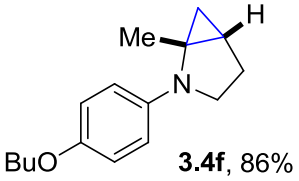
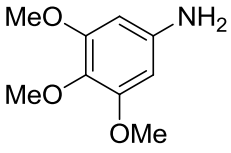
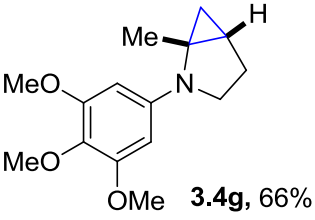
Preliminary results have showcased the participation of bicyclic cyclopropylanilines in the [3+2] annulation with alkenes to successfully afford fused saturated heterocycles.[76] Due to the high volume of these motifs found in natural products and pharmaceuticals, it was of interest to synthesize these heterocyclic analogues for further studies of their biological activity potentials. Initially intrigued with the success of the monocyclic cyclopropylanilines with alkynes,[116] in addition to the preliminary results of annulation with the bicyclic cyclopropylanilines, the attention of subjecting bicyclic cyclopropylanilines and alkynes to the optimized standard conditions was eagerly explored. Moreover, the issue of diastereoselectivity would be omitted, which is a contrast to the earlier work of annulation with alkene systems. Unlike the preparation of monocyclic cyclopropylanilines accomplished in one simple step, the synthetic route to bicyclic cyclopropylanilines required three steps. The construction of the bicyclic framework **3.4** involved a titanium-mediated cyclopropanation of the corresponding carboxylic amide precursor **3.3** via an intramolecular Kulinkovich-de Meijere reaction (Table 13). The sequence of synthesizing the *N*-alkenyl amides **3.3** began with acylation of the appropriate aniline substrate with the desired acyl chloride to afford the aryl amide **3.1**, followed by alkylation of the aryl amide with but-3-enyl toluene-4-sulfonate **3.2** (via tosylation of 3-buten-1-ol). A variety of bicyclic cycloproylanilines were synthesized including an array of alkyl groups (R^1= Me, Et, and *i*Pr) substituted on the quaternary carbon (α to the amine) and both electron donating (OMe and OBu) and electron withdrawing (CF_3) aryl substitutents, which were well tolerated.

2.4.1. Annulation with Phenylacetylene

The prepared [3.1.0] bicyclic cyclopropylanilines **3.4** were then subjected to the

Table 13. Preparation of bicyclic cyclopropylanilines.

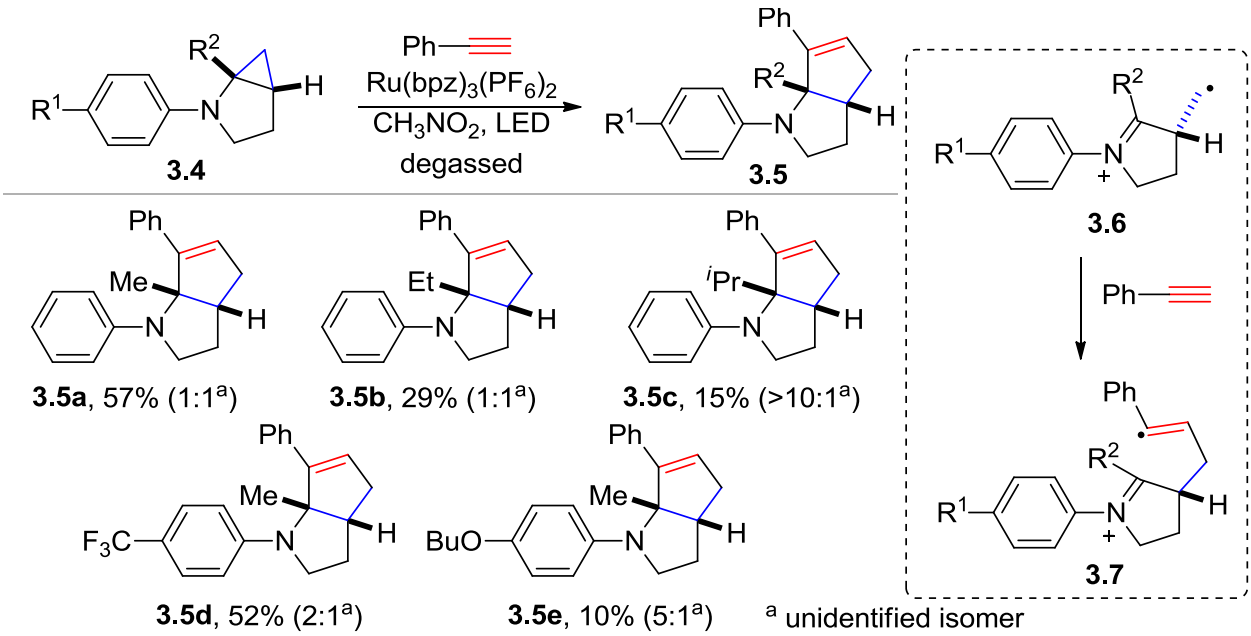


Aniline **3.0**	Yield of **3.1**	Yield of **3.3**	Yield of **3.4**
	R^1 = Me, 88% R^1 = Et, 85% R^1 = *i*Pr, 79%	R^1 = Me, 83% R^1 = Et, 78% R^1 = *i*Pr, 76%	 **3.4a-c** R^1 = Me, 80% R^1 = Et, 67% R^1 = *i*Pr, 64%
----	----	46%	 **3.4d**, 55%
	97%	87%	 **3.4e**, 66%
	86%	90%	 **3.4f**, 86%
	96%	69%	 **3.4g,** 66%

optimized conditions for cycloaddition with phenylacetylene, as the standard substrate, to provide 5,5-fused bicyclic heterocycles **3.5** (Scheme 2.11). Surprisingly, the annulation proceeded in low to moderate yields in comparison to previous reports of the annulation with styrene. As previously reported, cycloaddition of the bicyclic cyclopropylanilines with styrene provided two diastereomers in good diastereoselectivity. In the case of cycloaddition with phenylacetylene, it was anticipated that one major cycloadduct would be formed, as an alkene

moiety is introduced in the desired product. However, two major isomers were isolated, unexpectedly, in moderate to poor selectivity. The methyl substituted bicyclic cyclopropylaniline **3.4a** underwent the cycloaddition to provide a 1:1 mixture of two isomers **3.5a** in a combined 57% yield, with the major product as shown. As the methyl group of **3.5a** was replaced with more sterically hindered substituents (i.e. ethyl and isopropyl), a dramatic decrease of yields in the annulation was observed (29% and 15%, respectively), but a significant increase in selectivity was obtained in particularly the later (>10:1). This is in accordance with results reported by our group in regards to a cycloaddition of *tert*-butyl substituted bicyclic cyclopropylaniline with styrene, 28% yield, >25:1 d.r. Electron-withdrawing (CF_3) aryl substituted cycloadduct **3.5d** was tolerated in moderate yield, though the annulation yielding the electron-donating (OBu) cycloadduct **3.5e** was not synthetically useful.

Scheme 2.11. [3+2] annulation of bicyclic cyclopropylanilines with phenylacetylene.



Of the two inseparable isomers isolated after chromatography, for each substrate, one was identified as the predicted cycloadduct, as drawn in Scheme 2.11, and confirmed with further characterization using ^{1}H NMR and ^{13}C NMR, while the other isomer was undetermined. The

task of identifying the unknown isomer was quite challenging, considering the limited possibilities of alternative adducts based on the proposed mechanism. Efforts to solving the unidentified isomer began with subjecting the 1:1 mixture of unsaturated fused heterocycle **3.5a** and the unidentified isomer **3.5a-1** to catalytic hydrogenation conditions. Gas chromatography/ mass spectroscopy (GC/MS) was used to confirm the identical mass and relative ratio of the fused heterocycles in the initial mixture. It was envisioned that the alkene moiety would undergo hydrogenation to give the saturated fused heterocycle **3.8**, which has been previously reported by our group. Interestingly, upon hydrogenation of the inseparable mixture, GC/MS detected two peaks with a relative 1:1 ratio. One peak (mass of 278) corresponded to the saturated fused heterocycle **3.8**, while the other peak corresponded to a mass (276) identical to unknown isomer

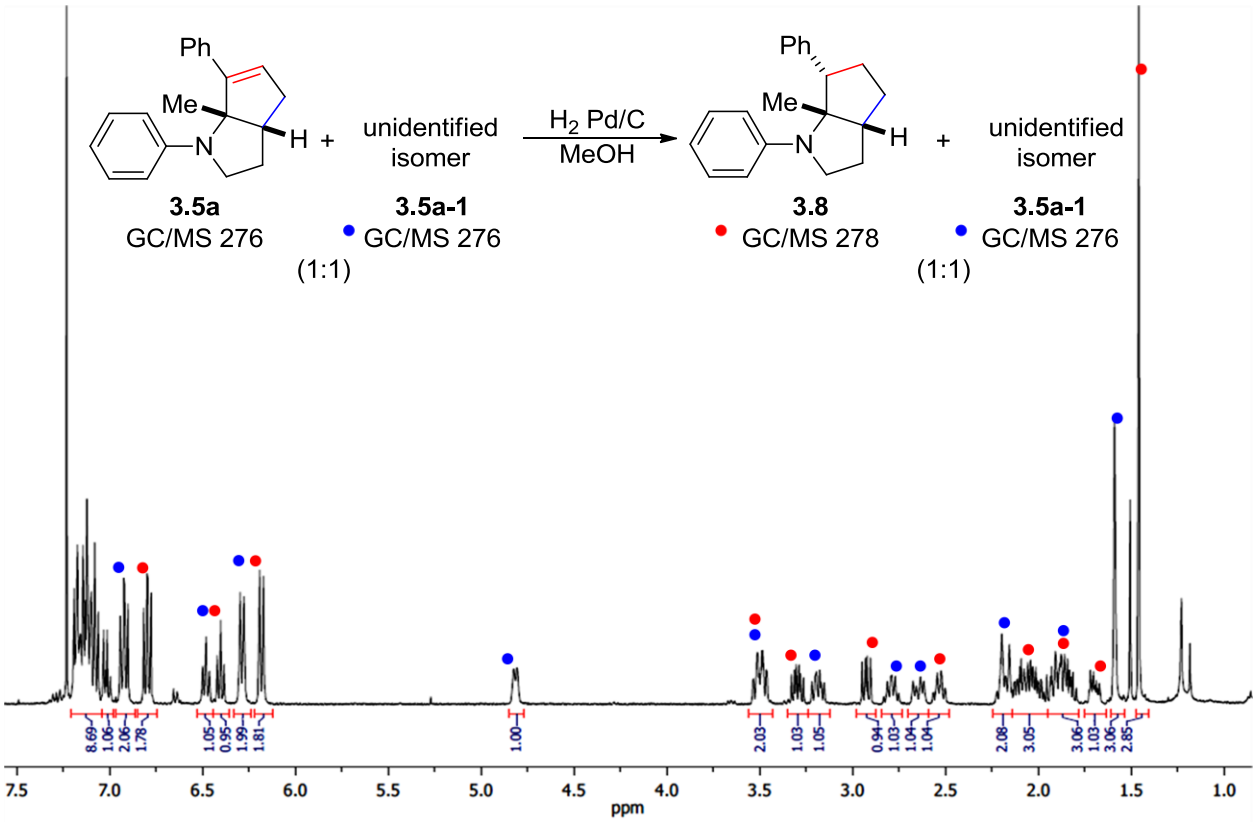


Figure 2.5. ^{1}H NMR analysis of hydrogenation of mixture **3.5a** and **3.5a-1**.

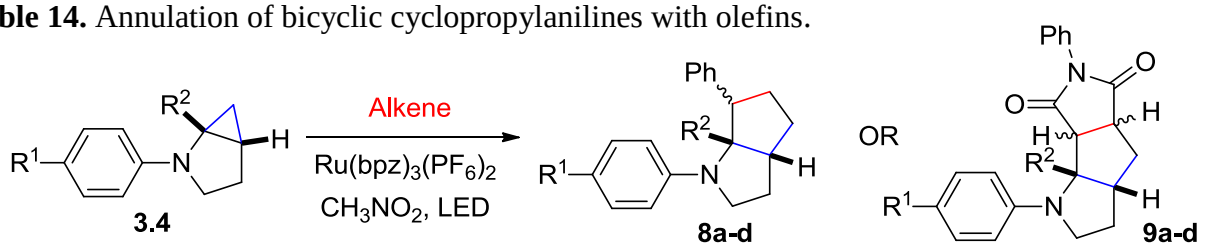
3.5a-1 from the starting mixture. ^{1}H NMR identified the saturated fused heterocycle **3.8**, labeled as the red dot in Figure 2.5, thus confirming cycloadduct **3.5a** as one of the isomers from the annulation. Moreover, the unidentified isomer **3.5a-1**, labeled as the blue dot, was unreactive under the hydrogenation conditions. The results were very puzzling, as one isomer was hydrogenated while the other remained untouched. Although the predicted annulation product **3.5a** was assigned and confirmed, efforts of identifying the unknown isomer were unsuccessful.

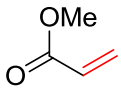
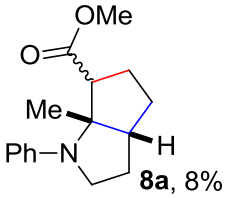
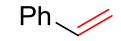
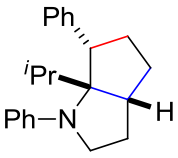
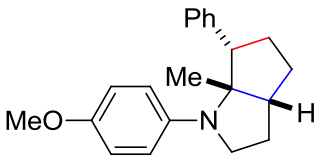
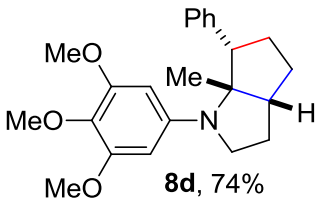
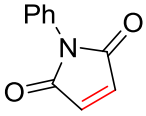
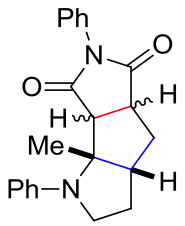
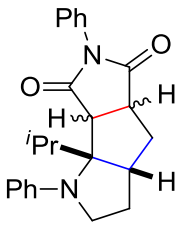
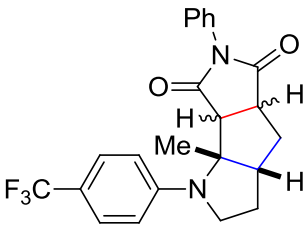
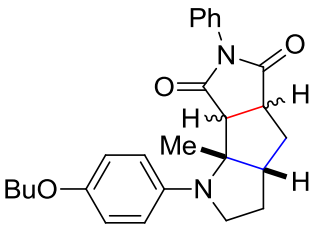
2.4.2. Annulation with Olefins

Discouraged by the unexpected results in the cycloaddition of bicyclic cyclopropylanilines with alkynes, the attention was shifted towards studying the cycloaddition of the bicyclic system with alkenes (Table 14). With the reported success of the cycloaddition with styrene as the standard substrate, advances in expanding the scope with various alkenes were investigated. The objective was centered on generating a substrate scope comprised of various fused heterocycles that could be further submitted for evaluation of potential biological activity. Eli-Lilly provides an Open Innovation Drug Discovery program that uses a confidential, automatic algorithm to select structures for biological screening.[149] Upon submission of the substrates, if a compound generates promising results, collaboration with Eli-Lilly in a partnership for further studies would be highly desired. The cycloadditions with olefins were conducted under the optimized conditions, similar with alkynes, in the presence of one 18 W LED light source. In exploring various alkenes, methyl acrylate and acrylonitrile were not suitable annulation partners, as no reaction and trace amount of product were observed via GC/MS, respectively. Conversely, alkene source phenyl maleimide underwent the [3+2] annulation to give fused saturated tricyclic heterocycles in moderate yields and good diastereoselectivity. The cycloadducts were obtained as a separable mixture of two

diastereoisomers using preparative thin layer chromatography (prep TLC). A similar reactivity trend of steric effects, mentioned previously, was observed when replacing methyl (**9a**) with isopropyl (**9b**) in the cycloaddition with phenyl maleimide. Moreover, the electronic characters of both electron-donating and electron-withdrawing aryl groups were well tolerated. *Para*-methoxy-phenyl and 3,4,5-trimethoxy-phenyl of cycloadducts **8c** and **8d** were introduced to serve as cleavable groups to further increase the generality of the annulation. Subjected under oxidative conditions with oxidant cerium ammonium nitrate (CAN), both removable groups were incapable of cleavage. Instead, the cycloadducts were recovered with no decomposition.

Table 14. Annulation of bicyclic cyclopropylanilines with olefins.

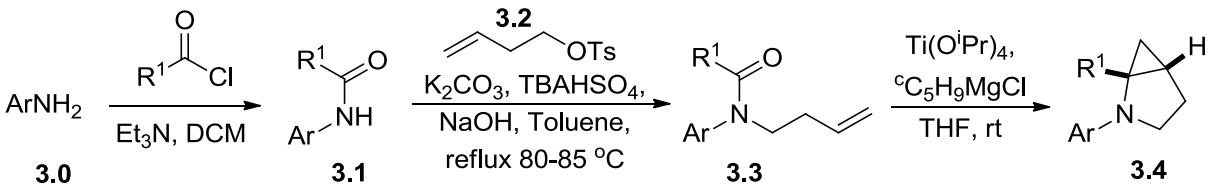


Alkene	Product
	 **8a**, 8%
	 **8b**, 25% d.r. >25:1  **8c**, 48%, d.r. 5:1  **8d**, 74%
	 **9a**, 55% d.r. 2:1  **9b**, 20% d.r. >25:1  **9c**, 43%  **9d**, 30%

2.4.3. Experimental Section

Synthesis of bicyclic cyclopropylanilines (Table 13). For the preparation and characterization of compounds **3.4a** and **3.4f**: see (a) Madelaine, C.; Six, Y.; Buriez, O. *Angew. Chem. Int. Ed*. **2007**, *46*, 8046 – 8049. For preparation and characterization of compound **3.4d** and **4b**: see Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N. *Angew. Chem., Int. Ed.* **2012,** *51*, 222-226.

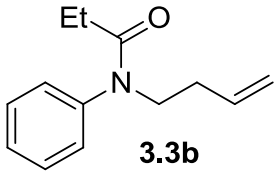
The following sequence was applied for the preparation of bicyclic cyclopropylanilines **3.4b, 3.4c, 3.4e,** and **3.4g**:



A solution of acid chloride in dichloromethane was added dropwise at 0 °C to a solution of aniline **3.0** and triethylamine. The resulting mixture was stirred overnight at room temperature. Upon completion, the solvent was removed under vacuum and the crude was purified by silica gel chromatography to afford the anilide **3.1**. Potassium carbonate (1.02 equiv.), tetrabutylammonium hydrogensulfate (0.05 equiv.), ground sodium hydroxide (4 equiv.), and anilide **3.1** (7.4 mmol, 1 equiv.) were massed and transfer to a round bottom flask equipped with a stir bar. Toluene (30 mL) was added and the mixture was stirred at 20 °C for 1 h, then at 80 °C for 15 min. But-3-enyl-*p*-toluenesulfonate **3.2** (1.5 equiv.) was added and stirring was continued at 80 °C for 6 h. After cooling to room temperature, 1N aqueous HCl solution (30 mL) was added. The organic layer was separated, and the aqueous extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried with sodium sulfate, filtered and concentrated. Purification of the crude by column chromatography afforded the *N*-alkenyl amide **3.3**. To a magnetically stirred solution of *N*-alkenyl amide (6.98 mmol, 1 equiv.) in THF (35 mL) was

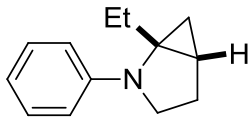
added titanium(IV) *iso*-propoxide (1.7 equiv.), followed by addition of cyclopentylmagnesium chloride (2.0 M in Et_2O, 4.4 equiv.) dropwise at room temperature over 5 mins. After 1 h, water (2 mL) was added at 0 °C and stirring was continued until the color dissipated. Et_2O (35 mL) was then added. The organic layer was separated, and the aqueous phase was extracted with Et_2O (30 mL x 2). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. Purification of the crude mass by column chromatography on silica/ alumina gel provided the bicyclic cyclopropylaniline **3.4**.

***N*-(but-3-enyl)-*N*-phenylpropionamide (3.3b)**. Following the above sequence with *N*-phenylpropanamide **3.1b** (500 mg, 3.35 mmol), but-3-enyl-*p*-toluenesulfonate **3.2** (1.14 g or 0.95 mL; 1.5 equiv), K_2CO_3 (472.3 mg, 1.02 equiv), NaOH (536 mg, 4 equiv), and $n$$Bu_4NHSO_4$ (57.7 mg, 0.05 equiv or 5 mol%) in 13.4 mL toluene, product was isolated after column chromatography on silica gel (85:15 hexanes/EtOAc) as a yellow liquid, 78%; IR υ_{max} (cm^{-1}) 3511, 3075, 2979, 2934, 1656, 1494, 1400, 1267, 916, 703; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.48 – 7.27 (m, 3H), 7.19 – 7.08 (m, 2H), 5.74 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.10 – 4.92 (m, 2H), 3.82 – 3.68 (m, 2H), 2.33 – 2.17 (m, 2H), 2.00 (q, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.66, 142.66, 135.46, 129.72, 128.51, 127.91, 116.63, 48.40, 32.31, 27.92, 9.72; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{13}H_{17}NO$ found 204.



3.3b

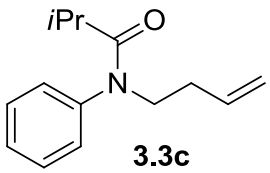
(1*R*,5*S*)-1-ethyl-2-phenyl-2-azabicyclo[3.1.0]hexane (3.4b). Following the above sequence with *N*-(but-3-enyl)-*N*-phenylpropionamide **3.3b** (190 mg, 0.93 mmol), $Ti(O^iPr)_4$ (1.7 equiv, 470 uL), and Grignard reagent (4.4 equiv, 2 mL) in 0.35 mL THF, product was isolated after column chromatography on silica gel (98:2 hexanes/EtOAc) as a clear liquid, (117 mg, 67%); ^{1}H NMR (400 MHz, Chloroform-*d*)



3.4b

δ 7.41 – 7.30 (m, 2H), 7.01 – 6.93 (m, 2H), 6.88 (tt, *J* = 7.3, 1.1 Hz, 1H), 4.08 (td, *J* = 9.7, 3.8 Hz, 1H), 3.07 (ddd, *J* = 9.9, 8.6, 7.8 Hz, 1H), 2.51 – 2.31 (m, 2H), 2.11 – 1.98 (m, 1H), 1.52 – 1.38 (m, 2H), 1.10 – 0.97 (m, 4H), 0.83 (t, *J* = 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.05, 128.85, 117.79, 116.66, 54.04, 48.64, 26.97, 25.27, 22.57, 18.93, 10.93; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{13}H_{17}N$ found 188.

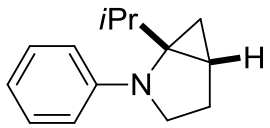
***N*-(but-3-enyl)-2-methyl-*N*-phenylpropionamide (3.3c)**. Following the above sequence with



3.3c

2-methyl-*N*-phenylpropanamide **3.1c** (547 mg, 3.35 mmol), but-3-enyl-*p*-toluenesulfonate **3.2** (1.14 g or 0.95 mL; 1.5 equiv), K_2CO_3 (472.3 mg, 1.02 equiv), NaOH (536 mg, 4 equiv), and nBu$_4$NHSO$_4$ (57.7 mg, 0.05 equiv or 5 mol%) in 13.4 mL toluene, product was isolated after column chromatography on silica gel (85:15 hexanes:EtOAc) as a white solid (41–44 °C m.p.), 76%; IR υ_{max} (cm^{-1}) 3514, 3068, 2973, 1653, 1594, 1403, 1257, 1136, 917; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.40 (dddd, *J* = 14.3, 8.6, 5.2, 3.6 Hz, 3H), 7.21 – 7.12 (m, 2H), 5.76 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.12 – 4.93 (m, 2H), 3.80 – 3.70 (m, 2H), 2.40 (p, *J* = 6.7 Hz, 1H), 2.32 – 2.21 (m, 2H), 1.00 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.06, 142.64, 135.38, 129.57, 128.35, 127.76, 116.46, 48.30, 32.16, 31.26, 19.65; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{13}H_{17}N$ found 218.

(1*R*,5*S*)-1-isopropyl-2-phenyl-2-azabicyclo[3.1.0]hexane (3.4c). Following the above sequence

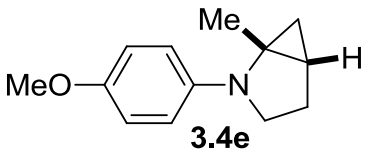


3.4c

with *N*-(but-3-enyl)-2-methyl-*N*-phenylpropionamide **3.3c** (1.18 g, 5.43 mmol), Ti(O^{i}Pr)$_4$ (1.7 equiv, 2.7 mL), Grignard reagent (4.4 equiv, 11.7 mL) in 20 mL THF, product was isolated after column chromatography on silica gel (100% hexanes) as a clear liquid, (700 mg, 64%); IR υ_{max} (cm^{-1}) 3065, 3034, 2957, 1599, 1498, 1361, 1312, 1035, 750, 695; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.19 – 7.08 (m, 2H), 6.76 – 6.60 (m, 3H), 3.86 (tdd, *J* = 9.7, 4.3, 1.4 Hz, 1H), 2.90 (dddd, *J* = 10.2, 8.8, 7.3, 1.4

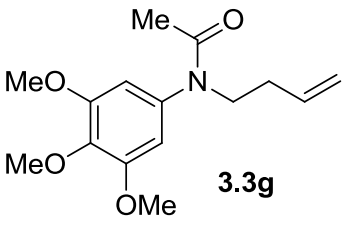
Hz, 1H), 2.41 (hept, *J* = 6.8 Hz, 1H), 2.21 – 2.05 (m, 1H), 1.86 (dddt, *J* = 12.9, 8.9, 4.4, 1.2 Hz, 1H), 1.35 – 1.24 (m, 1H), 1.05 (ddt, *J* = 9.1, 5.3, 1.0 Hz, 1H), 0.91 (dd, *J* = 6.5, 1.7 Hz, 3H), 0.64 (dd, *J* = 7.1, 1.5 Hz, 3H), 0.48 (td, *J* = 5.3, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.94, 128.86, 117.44, 116.37, 53.95, 52.92, 27.24, 26.28, 20.65, 18.73, 18.66, 17.87; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{13}H_{17}N$ found 202.

(1*R*,5*S*)-2-(4-methoxyphenyl)-1-methyl-2-azabicyclo[3.1.0]hexane (3.4e). Following the above sequence with *N*-3-buten-1-yl-*N*-(4-methoxyphenyl)-acetamide **3.3e** (1.53 g, 6.98 mmol), $Ti(O^iPr)_4$ (1.7 equiv, 3.5 mL), Grignard reagent (4.4 equiv, 15.3 mL) in 35 mL THF, product was isolated after column chromatography on alumina gel (15:1 hexanes: EtOAc) as a clear liquid, (933 mg, 66%); IR υ_{max} (cm^{-1}) 2954, 2929, 1506, 1463, 1452, 1444, 1370, 1235, 1179, 816; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.99 – 6.88 (m, 2H), 6.88 – 6.79 (m, 2H), 3.84 (td, *J* = 9.5, 1.9 Hz, 1H), 3.77 (s, *J* = 0.4 Hz, 3H), 2.66 (td, *J* = 9.9, 8.2 Hz, 1H), 2.35 – 2.19 (m, 1H), 1.98 – 1.85 (m, 1H), 1.49 (s, 3H), 1.34 – 1.23 (m, 1H), 0.80 (t, *J* = 5.1 Hz, 1H), 0.75 – 0.66 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.27, 144.39, 119.54, 114.50, 55.83, 53.70, 43.34, 26.42, 24.09, 20.15, 15.27; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{13}H_{17}NO$ found 204.



3.4e

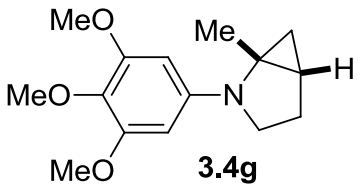
***N*-(but-3-enyl)-*N*-(3,4,5-trimethoxyphenyl)acetamide (3.3g)**. Following the above sequence with *N*-(3,4,5-trimethoxyphenyl)-acetamide **3.1g** (1.0 g, 4.44 mmol), but-3-enyl-*p*-toluenesulfonate **3.2** (1.25 mL, 1.5 equiv), K_2CO_3 (626 mg, 1.02 equiv), NaOH (710 mg, 4 equiv), and $n$$Bu_4NHSO_4$ (75.4 mg, 0.05 equiv or 5 mol%) in 25 mL toluene, product was isolated after column chromatography on silica gel (1:3 hexanes/EtOAc) as a yellow solid, (854 mg, 69%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.38 (s, 2H), 5.78 (ddt, *J* = 17.0,



3.3g

10.2, 6.7 Hz, 1H), 5.13 – 4.99 (m, 2H), 3.87 (d, *J* = 0.4 Hz, 3H), 3.85 (s, 6H), 3.79 – 3.70 (m, 2H), 2.37 – 2.24 (m, 2H), 1.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.56, 153.89, 138.85, 137.81, 135.77, 116.85, 105.72, 61.19, 56.46, 48.35, 32.61, 22.89; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{15}H_{21}NO_4$ found 280.

(1R,5S)-1-methyl-2-(3,4,5-trimethoxyphenyl)-2-azabicyclo[3.1.0]hexane (3.4g). Following

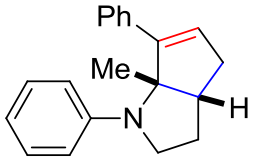


3.4g

the above sequence with *N*-(but-3-enyl)-*N*-(3,4,5-trimethoxyphenyl)acetamide **3.3g** (803 mg, 2.87 mmol), Ti(O^{i}Pr)$_4$ (1.7 equiv, 1.45 mL), Grignard reagent (4.4 equiv, 6.3 mL) in 15 mL THF, product was isolated after column chromatography on alumina gel (10:1 hexanes/EtOAc then 2:1 hexanes/EtOAc) as a clear liquid, (502 mg, 66%); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.15 (s, 2H), 3.90 (td, *J* = 9.6, 2.6 Hz, 1H), 3.85 (s, 6H), 3.79 (s, 3H), 2.81 (ddd, *J* = 9.8, 9.0, 8.4 Hz, 1H), 2.29 (dtd, *J* = 12.8, 9.3, 5.8 Hz, 1H), 1.93 (ddd, *J* = 13.0, 8.4, 2.6 Hz, 1H), 1.53 (s, 3H), 1.34 (dq, *J* = 7.9, 5.4 Hz, 1H), 0.83 – 0.74 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.56, 146.88, 131.22, 95.50, 61.25, 56.20, 53.84, 43.36, 26.52, 24.86, 20.29, 17.38; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{15}H_{21}NO_3$ found 264.

General Procedure 4 (GP4): [3 + 2] annulation of bicyclic cyclopropylanilines with phenylacetylene and olefins: an oven-dried test tube (16 × 125 mm) equipped with a stir bar was charged with $Ru(bpz)_3(PF_6)_2$ (2 mol %), bicyclic cyclopropylaniline (0.2 mmol), phenylacetylene or olefin (1.0 mmol), and dry CH_3NO_2 (2 mL). The test tube was sealed with a Teflon screw cap. The reaction mixture was degassed by Freeze–Pump–Thaw cycles and then irradiated at room temperature with one white LED (18 watts) positioned 8 cm from the test tube. After the reaction was complete as monitored by TLC, the mixture was diluted with diethyl ether and filtered through a short pad of silica gel. The filtrate was concentrated in

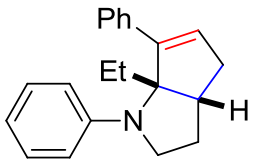
vacuum and purified by silica/ alumina gel flash chromatography to afford the desired product.



3.5a

(3a*R*,6a*S*)-6a-methyl-1,6-diphenyl-1,2,3,3a,4,6a-hexahydrocyclopenta[b]pyrrole (3.5a). Following **GP4**, the product was isolated as a yellow oil, 57%; Silica gel column chromatography (20:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 3020, 2922, 2843, 1597, 1500, 1325, 1155, 744, 690, 513; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 – 7.10 (m, 5H), 7.00 – 6.91 (m, 2H), 6.51 (t, *J* = 7.2 Hz, 1H), 6.35 – 6.25 (m, 2H), 4.84 (d, *J* = 7.3 Hz, 1H), 3.54 (ddd, *J* = 9.6, 7.6, 2.0 Hz, 1H), 3.21 (td, *J* = 9.9, 6.6 Hz, 1H), 2.82 (p, *J* = 7.7 Hz, 1H), 2.67 (dd, *J* = 16.2, 7.2 Hz, 1H), 2.27 – 2.14 (m, 2H), 1.91 (dtd, *J* = 12.2, 10.2, 7.6 Hz, 1H), 1.62 (q, *J* = 1.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.16, 138.40, 138.23, 135.45, 129.47, 128.53, 128.05, 126.62, 115.88, 112.99, 75.18, 49.34, 41.38, 40.30, 32.30, 15.58; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{20}H_{21}N$ found 276.

(3a*R*,6a*S*)-6a-ethyl-1,6-diphenyl-1,2,3,3a,4,6a-hexahydrocyclopenta[b]pyrrole (3.5 b).

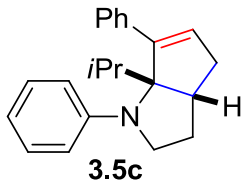


3.5b

Following **GP4**, the product was isolated as a 1:1 mixture of isomers, yellow oil, 29%; Silica gel column chromatography (20:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 3034, 2960,2845,1597, 1500, 1354, 1332, 744, 690, 514; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 – 7.01 (m, 9H), 6.91 – 6.82 (m, 2H), 6.81 – 6.73 (m, 1H), 6.47 – 6.39 (m, 2H), 6.25 – 6.19 (m, 2H), 6.19 – 6.14 (m, 2H), 5.40 (dd, *J* = 2.9, 2.0 Hz, 1H), 4.75 (d, *J* = 7.3 Hz, 1H), 3.46 (ddd, *J* = 9.5, 7.8, 1.9 Hz, 1H), 3.38 (ddd, *J* = 9.5, 7.2, 2.6 Hz, 1H), 3.24 (ddd, *J* = 9.9, 8.8, 6.0 Hz, 1H), 3.12 (ddd, *J* = 10.7, 9.2, 6.6 Hz, 1H), 2.82 – 2.69 (m, 2H), 2.65 – 2.54 (m, 1H), 2.50 (ddd, *J* = 16.7, 7.1, 1.9 Hz, 1H), 2.21 – 2.03 (m, 4H), 1.92 (dq, *J* = 14.8, 7.2 Hz, 2H), 1.81 (ddt, *J* = 19.4, 9.4, 2.6 Hz, 2H), 1.77 – 1.64 (m, 1H), 0.96 – 0.84 (m, 3H), 0.61 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.58, 149.09, 147.25,

140.88, 139.40, 138.28, 137.93, 132.33, 129.48, 129.44, 128.50, 128.06, 128.02, 127.96, 127.78, 126.96, 126.62, 116.57, 115.81, 115.38, 112.88, 82.84, 75.18, 50.88, 49.27, 48.45, 40.19, 38.01, 35.35, 32.24, 30.77, 27.08, 22.65, 13.05, 8.75; GC/MS (CI) *m/z* $[M+H]^+$ for $C_{21}H_{23}N$ found 290.

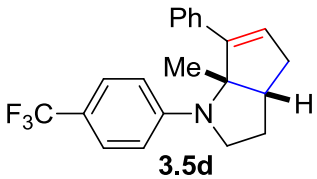
(3a*R*,6a*S*)-6a-isopropyl-1,6-diphenyl-1,2,3,3a,4,6a-hexahydrocyclopenta[b]pyrrole (3.5c).



3.5c

Following **GP4**, the product was isolated as a **r**ed-brown oil, 15%; Silica gel column chromatography (20:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 3032, 2954, 2868, 1597, 1500, 1355, 1309, 1035, 993, 744, 690; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 (dddd, *J* = 7.9, 7.0, 3.4, 1.7 Hz, 5H), 7.04 – 6.98 (m, 3H), 6.86 – 6.79 (m, 1H), 6.74 – 6.67 (m, 3H), 6.56 – 6.42 (m, 2H), 6.39 (ddt, *J* = 8.3, 7.3, 1.0 Hz, 1H), 6.20 – 6.07 (m, 3H), 5.54 – 5.44 (m, 1H), 3.34 (ddd, *J* = 8.9, 6.8, 3.4 Hz, 1H), 3.10 (td, *J* = 9.3, 5.9 Hz, 2H), 2.84 – 2.72 (m, 2H), 2.48 – 2.35 (m, 2H), 2.17 – 2.02 (m, 4H), 1.74 – 1.62 (m, 3H), 0.98 (d, *J* = 6.8 Hz, 4H), 0.59 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.41, 139.89, 129.70, 129.44, 129.34, 128.49, 128.09, 128.01, 127.98, 126.86, 116.76, 115.97, 86.86, 50.98, 43.99, 37.92, 32.21, 29.63, 18.30, 16.93; GC/MS (CI) *m/z* $[M+H]^+$ for $C_{22}H_{25}N$ found 304.

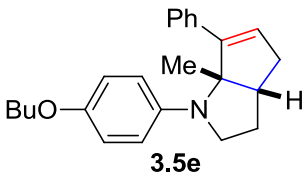
(3a*R*,6a*S*)-6a-methyl-6-phenyl-1-(4-(trifluoromethyl)phenyl)-1,2,3,3a,4,6a-hexahydrocyclopenta[b]pyrrole (3.5d). Following **GP4**, the product was isolated as a 2:1 mixture of isomers, yellow oil, 52%; Silica gel column chromatography (20:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 2927, 2846, 1612, 1525, 1317, 1101, 1066, 815, 700; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.60 – 7.44 (m, 1H), 7.28 – 7.21 (m, 2H), 7.19 (td, *J* = 5.1, 1.9 Hz, 5H), 7.14 (s, 1H), 7.09 (dd, *J* = 7.3, 2.5 Hz, 3H), 6.27 (dd, *J* = 16.5, 8.7 Hz, 3H), 5.50 (t, *J* = 2.0 Hz, 0H), 4.90 (dq, *J* = 7.3, 1.9 Hz, 1H), 3.57 (ddd, *J* = 10.1, 8.0, 2.4 Hz, 1H), 3.51 – 3.38 (m, 1H), 3.27 (td, *J* =



3.5d

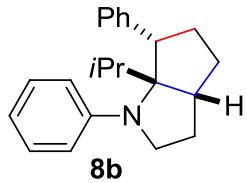
9.9, 6.8 Hz, 1H), 2.95 – 2.80 (m, 1H), 2.74 (dt, *J* = 7.0, 1.6 Hz, 0H), 2.68 (ddt, *J* = 6.0, 4.3, 2.2 Hz, 1H), 2.65 – 2.59 (m, 0H), 2.34 – 2.14 (m, 3H), 1.96 (dddd, *J* = 14.6, 10.2, 7.3, 4.3 Hz, 2H), 1.63 (q, *J* = 1.2 Hz, 3H), 1.52 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.87, 149.91, 148.95, 138.77, 137.82, 137.77, 136.24, 132.33, 129.35, 129.24, 128.51, 128.27, 128.23, 127.50, 127.42, 126.91, 125.76 (q, *J* = 3.0 Hz), 125.18 (q, *J* = 4.0 Hz), 117.19 (q, *J* = 117.19 Hz), 114.45, 112.13, 112.11, 79.03, 74.64, 53.67, 50.33, 49.03, 41.34, 40.33, 34.17, 32.08, 29.64, 22.49, 22.46, 15.49, 15.46; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{21}H_{20}F_3N$ found 344.

(3a*R*,6a*S*)-1-(4-butoxyphenyl)-6a-methyl-6-phenyl-1,2,3,3a,4,6a-hexahydrocyclopenta[b]pyrrole (3.5e). Following **GP4**, the product was isolated as a 5:1 mixture of isomers, brown oil, 10%; Silica gel column chromatography (50:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 2956, 2927, 1508, 1240, 1070, 813, 758, 698, 524; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.19 (s, 7H), 6.53 – 6.44 (m, 2H), 6.35 – 6.27 (m, 2H), 5.50 (t, *J* = 2.5 Hz, 1H), 3.80 (t, *J* = 6.5 Hz, 3H), 3.41 – 3.22 (m, 2H), 2.67 – 2.54 (m, 2H), 2.30 – 2.09 (m, 3H), 1.94 – 1.77 (m, 1H), 1.71 – 1.59 (m, 4H), 1.45 (s, 4H), 0.97 – 0.86 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.48, 129.11, 127.94, 127.38, 126.88, 118.55, 115.20, 114.37, 113.96, 79.12, 68.26, 52.87, 50.70, 35.09, 32.60, 31.71, 30.85, 23.57, 19.47, 14.11; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{24}H_{29}NO$ found 348.



3.5e

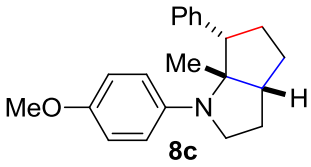
(3a*R*,6*S*,6a*S*)-6a-isopropyl-1,6-diphenyloctahydrocyclopenta[b]pyrrole (8b). Following **GP4**, the product was isolated as a yellow oil, 25%; Silica gel column chromatography (100:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 2953, 2870, 1595, 1500, 1355, 1336, 1309, 1141, 744, 694; ^{1}H NMR (300 MHz, Chloroform-*d*) δ 6.94 – 6.87 (m, 2H), 6.83 – 6.69 (m, 3H), 6.53 – 6.42 (m, 2H), 6.08 (tt, *J* = 7.2, 1.0 Hz, 1H), 5.93 – 5.85 (m, 2H), 3.32 (ddd, *J* = 9.0, 8.0, 2.6 Hz, 1H), 3.11 – 2.90 (m, 2H), 2.70 – 2.54 (m,



8b

2H), 1.94 – 1.80 (m, 2H), 1.80 – 1.59 (m, 2H), 1.55 – 1.35 (m, 2H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.30 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.66, 144.43, 129.98, 127.86, 127.60, 126.04, 115.09, 114.10, 81.05, 53.75, 51.94, 46.59, 36.57, 32.78, 31.12, 29.73, 19.72, 18.53; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{22}H_{27}N$ found 306.

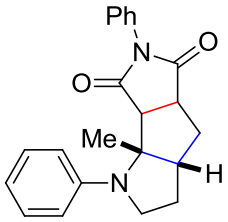
(3a*R*,6S,6a*S*)-1-(4-methoxyphenyl)-6a-methyl-6-phenyloctahydrocyclopenta[b]pyrrole (8c).



8c

Following **GP4**, the product was isolated as a brown oil, 48%; Alumina gel column chromatography (30:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 3043, 2946, 2870, 1620, 1452, 1244; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 – 7.19 (m, 3H), 7.19 – 7.13 (m, 2H), 6.49 – 6.40 (m, 2H), 6.19 – 6.09 (m, 2H), 3.65 (s, 3H), 3.50 – 3.43 (m, 1H), 3.29 (ddt, *J* = 10.4, 9.1, 5.1 Hz, 1H), 2.90 (dd, *J* = 11.0, 7.2 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.13 – 2.04 (m, 3H), 1.99 – 1.92 (m, 1H), 1.92 – 1.81 (m, 2H), 1.73 (ddt, *J* = 12.8, 6.2, 2.2 Hz, 1H), 1.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.01, 143.62, 141.10, 129.68, 128.05, 126.17, 116.37, 113.39, 74.18, 58.24, 55.87, 55.65, 51.19, 36.18, 29.28, 28.97, 27.19; GC/MS (CI) *m*/*z* $[M+H]^+$ for $C_{21}H_{25}NO$ found 308.

Data for **5a**: Following **GP4**, the product was isolated as a yellow oil, 55%; Silica gel column chromatography (10:1 hexanes/EtOAc then 5:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 2929, 1697, 1597, 1490, 1454, 1379, 1265, 1186, 742, 688; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 (dddd, *J* = 7.8, 7.1, 1.6, 0.9 Hz, 2H), 7.17 – 7.11 (m, 1H), 7.10 – 7.04 (m, 2H), 7.00 – 6.96 (m, 3H), 6.91 (dddd, *J* = 7.8, 6.1, 1.6, 0.9 Hz, 1H), 3.27 – 3.20 (m, 1H), 3.04 – 2.98 (m, 1H), 2.96 – 2.88 (m, 2H), 2.71 – 2.65 (m, 1H), 1.75 (dddd, *J* = 13.3, 10.5, 7.2, 2.5 Hz, 1H), 1.63 (d, *J* = 12.2 Hz, 1H), 1.51 (ddt, *J* = 9.1, 6.9, 2.3 Hz, 1H), 1.40 (ddt, *J* = 12.1, 5.0, 1.4 Hz, 1H), 1.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.90, 178.01, 150.77, 133.41, 130.51, 130.07, 129.92, 128.20, 127.71, 126.43, 68.54,

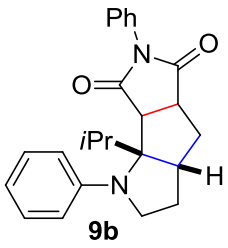


9a

51.77, 50.42, 49.84, 46.26, 39.99, 32.21, 25.09; GC/MS (CI) *m/z* $[M+H]^+$ for $C_{22}H_{22}N_2O_2$ found 347.

Data for **5a-1**: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 – 7.45 (m, 2H), 7.45 – 7.36 (m, 1H), 7.32 – 7.22 (m, 6H), 7.11 – 7.02 (m, 1H), 3.65 (dd, *J* = 10.3, 7.6 Hz, 1H), 3.42 (ddd, *J* = 13.5, 7.2, 5.3 Hz, 1H), 3.32 – 3.20 (m, 2H), 3.02 (dtd, *J* = 7.6, 5.2, 2.5 Hz, 1H), 2.21 (d, *J* = 11.7 Hz, 1H), 2.16 – 2.03 (m, 1H), 2.03 – 1.93 (m, 1H), 1.77 (ddd, *J* = 11.8, 4.9, 1.7 Hz, 1H), 1.42 (s, 3H).

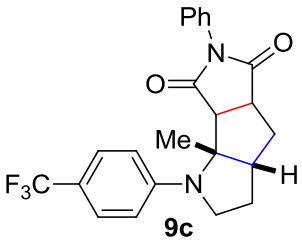
Data for **5b**: Following **GP4**, the product was isolated as a yellow oil, 28%; Silica gel column



9b

chromatography (3:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 2920, 1701, 1487, 1377, 1186, 1143, 763, 742, 727, 704; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.40 (m, 2H), 7.39 – 7.32 (m, 1H), 7.29 – 7.22 (m, 6H), 7.00 (p, *J* = 4.6 Hz, 1H), 3.78 (d, *J* = 7.8 Hz, 1H), 3.46 – 3.31 (m, 1H), 3.14 (d, *J* = 7.7 Hz, 1H), 2.98 – 2.84 (m, 2H), 2.79 (p, *J* = 6.7 Hz, 1H), 1.98 (d, *J* = 16.1 Hz, 1H), 1.74 (dd, *J* = 4.1, 1.7 Hz, 2H), 1.69 – 1.59 (m, 1H), 0.80 (d, *J* = 6.5 Hz, 3H), 0.63 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.29, 150.90, 132.14, 129.23, 129.03, 128.59, 126.28, 124.22, 123.11, 74.18, 51.69, 51.44, 48.82, 36.40, 35.33, 30.73, 29.60, 19.87, 19.73; GC/MS (CI) *m/z* $[M+H]^+$ for $C_{24}H_{26}N_2O_2$ found 375.

Data for **5c**: Following **GP4**, the product was isolated as a yellow oil, 43%; Silica gel column

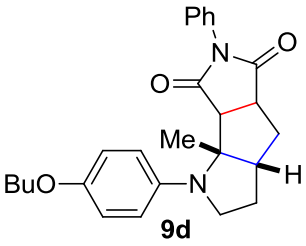


9c

chromatography (2:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 1707, 1610, 1496, 1456, 1371, 1321, 1161, 1103, 1068, 848, 732, 690; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.42 (m, 4H), 7.41 – 7.36 (m, 1H), 7.35 – 7.30 (m, 2H), 7.24 – 7.18 (m, 2H), 3.64 (dd, *J* = 10.2, 7.6 Hz, 1H), 3.49 – 3.38 (m, 1H), 3.27 (d, *J* = 10.2 Hz, 1H), 3.18 (dt, *J* = 12.7, 6.4 Hz, 1H), 3.00 (dddt, *J* = 8.5, 7.2, 4.8, 2.0 Hz, 1H), 2.29 – 2.20 (m, 1H), 2.18 – 2.07 (m, 1H), 2.01 – 1.91 (m, 1H), 1.77

(ddd, *J* = 12.0, 4.8, 1.6 Hz, 1H), 1.50 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.63, 176.03, 152.54, 132.15, 129.43, 128.82, 126.59, 126.20, 125.39 (q, J = 3.6 Hz), 124.89, 115.62, 67.66, 56.58, 50.60, 46.77, 44.77, 34.77, 27.07, 26.61; GC/MS (CI) *m/z* $[M+H]^+$ for $C_{23}H_{21}F_3N_2O_2$ found 415.

Data for **5d**: Following **GP4**, the product was isolated as a yellow-brown oil, 30%; Alumina gel



9d

column chromatography (3:1 hexanes/EtOAc); IR υ_{max} (cm^{-1}) 2926, 2850, 1764, 1703, 1508, 1373, 1172, 1136, 1016, 831, 742, 686; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.44 (m, 2H), 7.42 – 7.36 (m, 1H), 7.32 – 7.28 (m, 2H), 7.15 – 7.10 (m, 2H), 6.77 – 6.72 (m, 2H), 3.90 (t, *J* = 6.5 Hz, 2H), 3.61 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.34 – 3.18 (m, 3H), 2.98 (dtd, *J* = 7.8, 5.0, 2.9 Hz, 1H), 2.18 – 2.10 (m, 1H), 2.03 (dtd, *J* = 15.6, 7.8, 5.0 Hz, 1H), 1.94 (ddtd, *J* = 12.8, 8.0, 4.9, 3.9, 2.6 Hz, 1H), 1.73 (dddd, *J* = 8.9, 7.8, 6.9, 5.9 Hz, 3H), 1.51 – 1.42 (m, 2H), 1.32 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.11, 175.97, 156.15, 143.00, 132.48, 129.41, 129.01, 128.67, 126.64, 114.11, 67.96, 67.29, 56.84, 50.00, 47.27, 46.92, 35.75, 31.62, 27.21, 27.16, 19.48, 14.09; GC/MS (CI) *m/z* $[M+H]^+$ for $C_{26}H_{30}N_2O_3$ found 419.

2.5. Conclusion

The [3+2] annulation of cyclopropylanilines with alkynes via visible light photocatalysis has been demonstrated as an effective atom-economical pathway for the construction of structurally diverse carbocycles substituted with amines from simple building blocks under mild conditions. More importantly, the transformations were accomplished via the synthetic utility of amine radical cations, induced by photoredox catalysis, which resulted in a ring-opening strategy of cyclopropylanilines. The annulation products from alkynes were showcased as highly useful synthetic intermediates in a four-step synthesis of fused indolines. Continued studies on further

expanding the scope of the [3+2] cycloaddition to include substituted anilines and other types of π-bonds (i.e. enynes and diynes) were accomplished. A rapid access to fused saturated/unsaturated heterocycles with bicyclic cyclopropylanilines was described and prepared in submission for further analysis of their biological potential. Furthermore, the newly developed [3+2] cycloaddition, promoted by visible light photocatalysis, has emerged as an innovative method for synthesizing various cyclic allylic amine derivatives, thus contributing to the advances of newly developed transformations. This successful environmentally sustainable chemical process highlights the growing potential avenues of introducing visible light mediated reactions to accomplish organic transformations in synthetic chemistry.

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Appendices

Appendix 1: [4+2] Cycloaddition of Cyclobutylanilines in Continuous Flow*

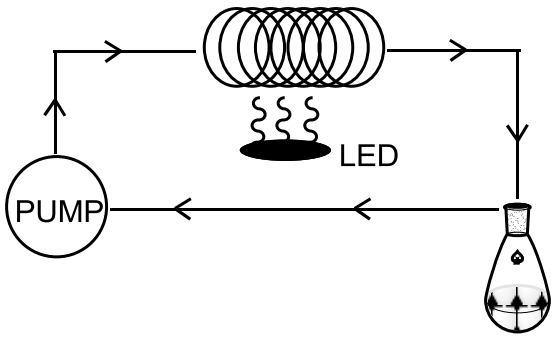
*Portion of this chapter has been published in Nguyen, T. H.; Wang, J.; Zheng, N. *Science China Chem*. **2015**, *59*, 180-183.

The merging of visible light photocatalysis and cycloaddition reactions has exhibited considerable potential as an effective, synthetic method to construct complex carbocycles and heterocycles. More importantly, a [3+2] cycloaddition of cyclopropylanilines mediated by visible light has been established to serve as a new synthetic strategy for assembling amine-substituted five-membered rings. Utilizing the unique photophysical properties of ruthenium complexes, ring-opening strategy of a donor-substituted cyclopropane was disclosed. The promoted cleavage was proposed by a photooxidation of the parent amine to the corresponding amine radical cation. Thus, initiating the ring-opening of the cyclopropyl ring furnished a three-carbon synthon, which further underwent the annulation. Likewise, the same synthetic application can be envisioned for cyclobutylanilines in a [4+2] cycloaddition, as the oxidation potential of both cyclopropylaniline and cyclobutylanilines were found to be similar. As a result, the ring-opening of a cyclobutyl ring would afford a four-carbon synthon, which subsequently follows an annulation sequence to provide a rapid entry to complex 6-membered carbocycles. Recently, our group developed a [4+2] annulation of cyclobutylanilines with alkynes under visible-light photocatalysis, furnishing an array of amine-substituted six-membered carbocycles in moderate to excellent yields.[1] However, long reaction time (12 to 24 h) was typically required for reaction completion. In addition, the scale-up strategy was problematic, which is a known disadvantage associated with batch photochemistry. Thus, seeking an alternative method or technique to drive reactions' efficiency and address the above issues was highly pursued.

Synthetic chemists have continued to explore potential innovative avenues for conducting chemical reactions more effectively and efficiently. Recently, increasing attention has emerged in the advances of new technology, as alternative approaches for synthetic applications.[2] In particular, continuous flow has productively showcased their applicability in photochemical transformations of both laboratory and industrial scales.[3] Reactions conducted in continuous flow can be advantageous to circumvent some limitations and drawbacks reported in traditional batch reactions. Because of the use of photons, photochemistry suffers some inherent limitations associated with how efficiently photons are transmitted through solutions.[4] The benefits of using continuous flow as a preferred technology include shorter reaction time, decrease of undesired by-products, and higher yields. This is attributed to the flow reactor's high surface-to-volume ratio, precise control of irradiation time, and maximum penetration of light, which improves the reaction's exposure to direct uniform irradiation of the solution.[5] Most importantly, the limited scalability with batch reactions in photochemical synthesis can be addressed and assured with continuous flow, thus providing a resolution to the batch's small scale restriction and improving the reactions' efficiency to benefit production scale processes.

Herein, the application of continuous flow in the [4+2] annulation of cyclobutylanilines with alkenes, alkynes, and diynes mediated by photoredox catalysis was investigated for improvement in the annulation's efficiency. Although annulation with alkynes was recently developed, annulation of cyclobutylanilines with alkenes and diynes has not yet been reported. Comparing against the previously reported annulation with alkynes in batch,

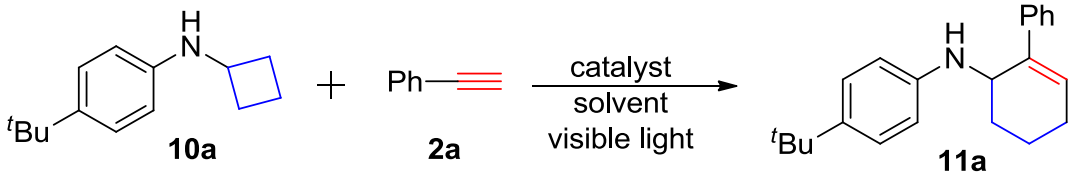
Figure 2.6. The continuous flow setup.



similar and improved yields with significantly shorter reaction time were observed in continuous flow. Moreover, using the continuous flow technique in a gram-scale annulation was successfully demonstrated. A schematic drawing of the continuous flow setup is depicted in Figure 2.6 with more details described in the experimental section.

Results and Discussion: [4+2] annulation of monocyclobutylaniline with alkynes

Table 15. Optimization of [4+2] annulation in continuous flow.

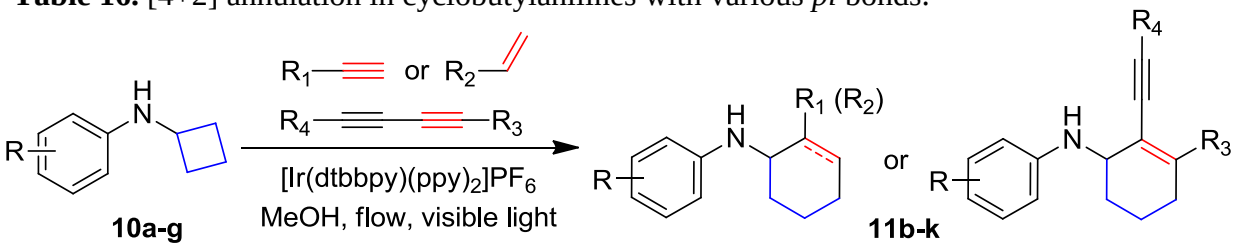


Entry[a]	Catalyst	Solvent	GC Yield (%)[b]
1	$Ir(ppy)_2(dtbbpy)PF_6$ (**4c**)	MeOH	99%
2	$Ru(bpy)_3(PF_6)_2$ (**4b**)	MeOH	81%
3[c]	$Ru(bpz)_3(PF_6)_2$ (**4a**)	MeOH + MeCN	51%
4[c]	$Ir(ppy)_3$ (**4d**)	MeOH + MeCN	43%
5	$Ir[dFCF_3ppy]_2(bpy)PF_6$ (**4e**)	MeOH	54%
6[d]	None	MeOH	<1%
7[e]	$Ir(ppy)_2(dtbbpy)PF_6$ (**4c**)	MeOH	<1%
8[f]	$Ir(ppy)_2(dtbbpy)PF_6$ (**4c**)	MeOH	65%

[a]Reaction conditions: **10a** (0.2 mmol, 0.1 mol/L in degassed solvent), **2a** (0.6 mmol), **4a-d** (2 mol%) in flow with Royal blue LED; [b]Used dodecane as an internal standard; [c]Co-solvent of MeOH and MeCN (1:1) used due to the solubility issue of the catalyst; [d]Reaction conducted in the absent of catalyst; [e]Reaction conducted in dark; [f]Reaction conducted in the presence of air.

Cyclobutylaniline **10a** and phenylacetylene **2a** were chosen as the standard substrates to optimize the catalyst system for the [4+2] annulation in flow (Table 15). Similar to the annulation in batch,[1] the use of Ir $(ppy)_2(dtbbpy)PF_6$ (**4c**) as the catalyst in methanol showed to be superior (entry 1) among other catalysts that were screened in flow (entries 2–5). The desired

Table 16. [4+2] annulation in cyclobutylanilines with various *pi* bonds.



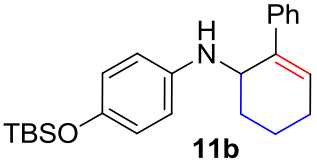
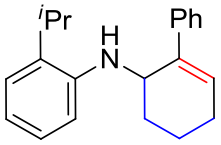
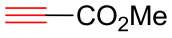
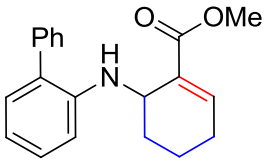
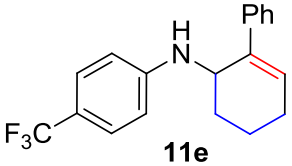
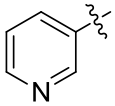
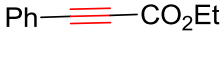
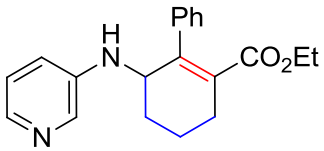
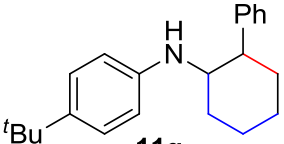
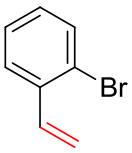
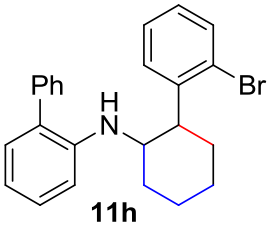
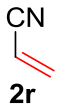
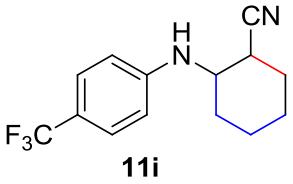
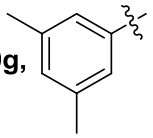
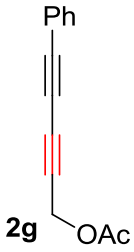
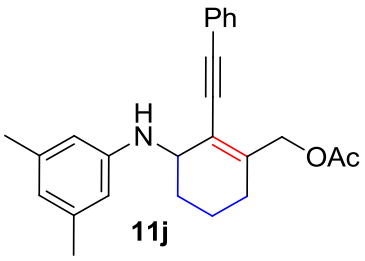
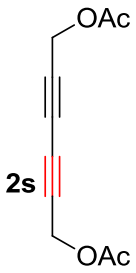
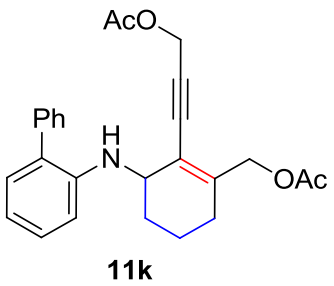
Entry[a]	Substrate	Olefin	Product	t [h]	Yield(%)[b]
1	**10b,** R = 4-OTBS	**2a**	 **11b**	22	32
2	**10c,** R = 2-^{i}Pr	**2a**	 **11c**	12	70
3	**10d,** R = 2-phenyl	 **2n**	 **11d**	9	73
4	**10e,** R = 4-CF_3	**2a**	 **11e**	12	79
5	**10f,** 	 **2o**	 **11f**	12	55
6[c]	**10a**	 **2p**	 **11g**	6	90
7[d, f]	**10d**	 **2q**	 **11h**	8	53

Table 16 continued.

Entry[a]	Substrate	Olefin	Product	t [h]	Yield(%)[b]
8[e]	**10e**	 **2r**	 **11i**	8	69
9	 **10g,**	 **2g**	 **11j**	14	60
10	**10d**	 **2s**	 **11k**	12	85

[a] Reaction condition: substrate (0.2 mmol, 0.1 M in degased MeOH), **2a-s** (1 mmol), **4c** (2 mol%), flow LED. [b] Isolated yields. [c] d.r. = 3:2, [d] d.r. = 2:1 and [e] d.r. = 1:1 as determined by ^{1}H NMR spectroscopy of crude products. [f]DMSO used as solvent.

product **11a** was obtained in 99% GC yield (93% isolated yield) after 6 h irradiation. The results were comparable with the previous reports in batch, except the reaction time was decreased by a half. Control studies demonstrated that both light and catalyst were required for the annulation (entries 6 & 7), as no formation of product was observed in the absence of both components. When the reaction was conducted in the presence of air (oxygen in air), the yield of **11a** was diminished to 65%. The results from optimizing the reaction were fully consistent with those obtained in batch.

Under the optimized conditions, the scope of the annulation of cyclobutylanilines with variable electronic and steric characters was examined in continuous flow and summarized in

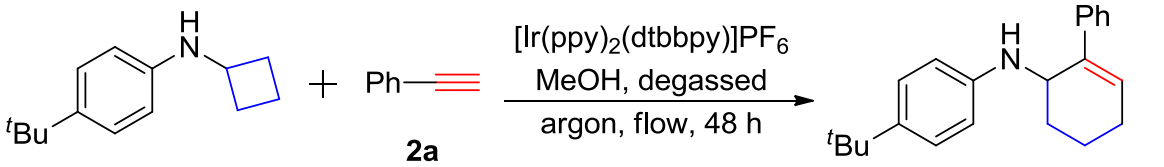
Table 16. Substrate **10b** with an electron-donating substituent (OTBS) afforded the desired product in an improved 32% yield, compared to an 8% yield after 24 h in batch (Table 16, entry 1). Conversely, substrate **10e** with an electron-withdrawing substituent (CF_3), which performed better in batch (79% yield after 24 h), provided comparable yields of **11e** with shortening of the reaction time by half (Table 16, entry 4). Observed in both batch and continuous flow, steric effects had no interference with the annulation. Using flow, shorter reaction time was observed with *ortho*-isopropyl substituted **10c** (entry 2) and also an improved yield for tolerated *ortho*-phenyl substituted **10d** (entry 3). *N*-(3-pyridyl)-cyclobutylamine **10f**, which had not been studied in the annulation with alkyne **2o** in batch, underwent the annulation in flow uneventfully, providing pyridine-containing product **11f** in a modest yield (entry 5). Using flow, [4+2] annulation of cyclobutylanilines with alkenes (**2p-2r**) were subjected to the optimized conditions with completion in 6 to 8 h. Modest to excellent yields were achieved, but with poor diastereoselectivity. This was no surprise as the same selectivity issue was observed in the [3+2] annulation of cyclopropylanilines with alkenes.[6] Unlike reactive alkenes, diynes generally exhibit poor reactivity, as reported in the [3+2] annulation.[7] Unsymmetric diyne **2g** and symmetric diyne **2s** underwent the [4+2] annulation in a reasonable amount of time (12 to 14 h) with the assistance of flow. Cycloadducts **11j** and **11k**, possessing a 1,3-conjugated enyne moiety, were afforded in good to excellent yields (60-85%) with complete regioselectivity. This observation of complete regiocontrol is in accordance with the result reported in the [3+2] annulation. Moreover, this commonality suggests that both types of annulation may proceed through similar reaction pathways involving the proposed distonic iminum ions. To further confirm the structure of **11k,** the two acetate groups were cleaved to provide the diols (**11l**, see below Experimental Section) and subsequent 2D NMR experiments were performed to assign

the structure.

Gram-scale Reaction

Lastly, a gram scale reaction of a selected [4+2] cycloaddition was showcased in continuous flow. Using the standard substrates acquired in the optimization studies, a slight modification of the conditions was considered. Cyclobutylaniline **10a** (1 g, 4.8 mmol), phenylacetylene **2a** (1.46 g, 14.4 mmol), and [Ir(dtbbpy)(ppy)$_2$](PF$_6$) (21 mg, 0.024 mmol, 0.5 mol%) were mixed with MeOH (30 mL). The resulting solution was sparged with argon for 30 min and then flowed through the photoreactor (Scheme 2.12). In continuous flow, much lower catalyst loading (0.5 mol % vs. 2 mol %) was realized; however, a longer reaction time (48 h vs. 6 h) was acquired for completion. Although the annulation was accomplished on a gram scale using flow, the isolated yield of product **11a** was slightly diminished (73% vs. 93%).

Scheme 2.12. Gram-scale reaction in continuous flow.



10a, 1.0 g

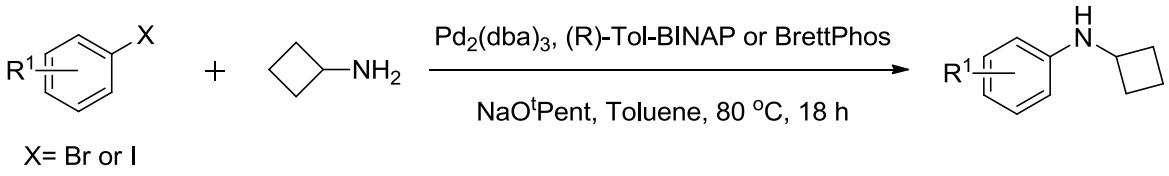
11a, 1.06g, 73% yield

In summary, application of the [4+2] annulation of cyclobutylanilines with various π bonds in continuous flow was successfully developed, to further demonstrate the reactions' improved efficiency and the shorter reaction times achieved. Previously accomplished substrates of the [4+2] annulation with alkynes in batch were subjected to flow conditions. In addition, the scope was extended to include alkenes and diynes that have not been reported. Comparable and improved yields with significant decrease of reaction times were obtained. Notably, the annulation reaction was conducted on a gram scale using a much lower catalyst loading with the assistance of the continuous flow technique.

Experimental Section

All reactions were carried out under argon atmosphere, unless stated otherwise. Anhydrous methanol (CH3OH, 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. Phenylacetylene **2a**, Ethyl phenylpropiolate **2o**, Styrene **2p**, and Acrylonitrile **2r** were purchased from Sigma-Aldrich. Methyl propiolate **2n** and 2-Bromostyrene **2q** were purchased from Matrix Scientific. Diynes **2g**[8] and **2s**[9] were prepared as described in the literature.

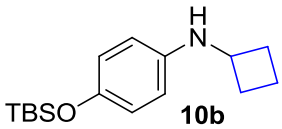
General Procedure 5 (GP5): Preparation of *N*-cyclobutylanilines



(R)-Tol-BINAP = (R)-(+)-2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl
BrettPhos = 2-(Dicyclohexylphosphino)3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl

To an oven-dried test tube equipped with a stir bar were added 0.01 mmol of $Pd_2(dba)_3$ and 0.03 mmol of ligand ((*R*)-Tol-BINAP or BrettPhos). Glove box was used to add 1.5 mmol of NaO^tPent and the tube was sealed with a Teflon screw cap. 1 mmol of aromatic halide, 1.6 mmol of cyclobutylamine, and 2 mL of toluene were then added to the reaction mixture and heated at 80 °C for 18 h. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether, filtered over a short pad of silica gel, and concentrated in vacuum. Purification by flash chromatography on silica gel afforded *N*-cyclobutylaniline.

4-*tert*-Butyldimethylsilyl ether-*N*-cyclobutylaniline (10b). Following **GP5** with (4-bromophenoxy)-*tert*-butyldimethylsilane (1.23 mL, 5 mmol, 1 equiv) and BrettPhos (80.5 mg, 0.15 mmol, 3 mol % equiv), product was isolated after flash chromatography on silica gel (5:1

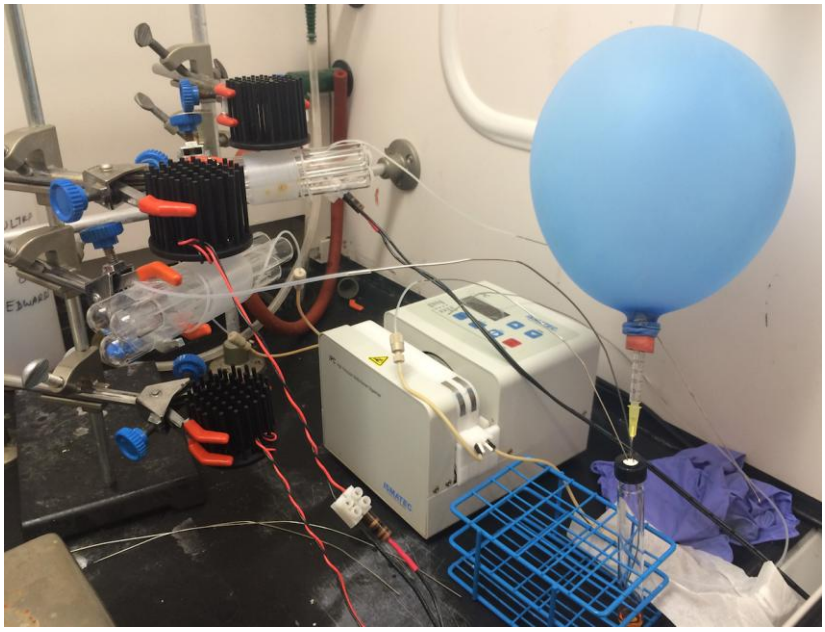


10b

hexane/ EtOAc) as a colorless oil (1.22 g, 88%); IR υmax (cm-1) 3403, 3062, 2956, 2931, 2889, 2857, 1509, 1471, 1463, 1247, 1163, 922, 908, 839; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.70 – 6.60 (m, 2H), 6.48 – 6.39 (m, 2H), 3.86 – 3.75 (m, 1H), 2.43 – 2.29 (m, 2H), 1.90 – 1.67 (m, 4H), 0.94 (d, *J* = 0.6 Hz, 9H), 0.13 (d, *J* = 0.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.73, 141.74, 120.84, 114.48, 80.56, 50.11, 31.49, 25.97, 18.39, 15.43, -4.26; HRMS (ESI) *m/z* [M+H]+, calc'd for $C_{16}H_{27}NOSi$ 278.1935; found 278.1927.

Preparation and characterization of cyclobutylanilines **10a**, **10b**, **10c**, **10d**, **10e**, **10f**, **10g** correspond to those described in the literature.[1]

The continuous flow setup



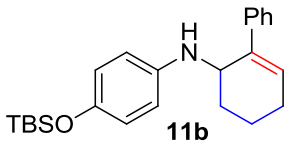
The continuous flow setup was adopted from Professor Stephenson and coworkers' method.[10] Seven prearanged Luxeon Rebel high power LEDs (royal blue color, λmax = 447.5 nm) were used as the light source. PFA Tubing (IDEX Health and Science, Part # 1514L) was wrapped around three borosilicate glass test tubes, supported on both ends by small pieces of cardboards. A total volume of 1.34 mL was placed inside the test tubes. The tubing was then connected to the peristaltic pump tubing (IDEX Health and Science, Part # SC0717) with a conical adapter (IDEX Health and Science, Part # P-797). The distance between

the light and the tubing was 3 cm (Figure 2.6).

General Procedure 6 (GP6): [4+2] annulation in continuous flow. An oven-dried test tube equipped with a stir bar was charged with Ir(dtbbpy)(ppy)$_2$PF$_6$ (2 mol%), cyclobutylaniline derivative (0.2 mmol), alkyne, olefin, or diyne derivative (1 mmol), and dry MeOH (2 mL). The test tube was capped with a Teflon screw cap, degassed by Freeze-Pump-Thaw (3-5 cycles), and then backfilled with argon. The reaction mixture was next pumped through a flow photoreactor in a closed loop system at a flow rate of 75 µL min-1 under the protection of an argon balloon. After the reaction was complete, monitored by TLC, the solution was collected in a flask and concentrated in vacuum. Purification by silica gel flash chromatography afforded the corresponding annulation products.

Characterization of annulation products **11a**, **11c**, **11d**, and **11e** were described in the literature.[1]

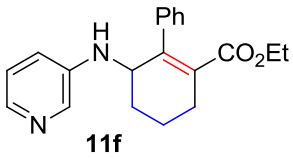
4-(tert-butyldimethylsilyloxy)-*N*-(2-phenylcyclohex-2-enyl)aniline (11b). Following **GP6** with cyclobutylaniline **10b** (55 mg, 0.2 mmol) and phenylacetylene **2a** (110 µL, 1 mmol), cycloadduct **11b** (24 mg, 32%) was obtained after silica gel column chromatography (30:1 hexane/ EtOAc) as colorless



11b

oil; IR υmax (cm^{-1}) 3417, 3022, 2950, 2930, 2903, 1507, 1471, 1250, 1229, 1112, 838; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 – 7.39 (m, 2H), 7.33 – 7.26 (m, 2H), 7.26 – 7.20 (m, 1H), 6.76 – 6.63 (m, 2H), 6.59 – 6.47 (m, 2H), 6.39 – 6.27 (m, 1H), 4.40 (d, *J* = 2.5 Hz, 1H), 3.49 (s, 1H), 2.40 – 2.08 (m, 3H), 1.78 – 1.61 (m, 3H), 1.00 (s, *J* = 0.7 Hz, 9H), 0.19 (s, *J* = 0.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.29, 141.97, 140.58, 137.67, 128.70, 128.57, 127.14, 125.74, 120.84, 114.31, 49.32, 27.86, 26.23, 25.98, 18.38, 17.25, -4.24; HRMS (ESI) *m/z* [M+H]$^+$, calc'd for $C_{24}H_{33}NOSi$ 380.2404; found 380.2414.

Ethyl 2-phenyl-3-(pyridin-3-ylamino)cyclohex-1-enecarboxylate (3f). Following **GP6** with

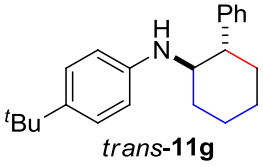


11f

cyclobutylaniline **10f** (30 mg, 0.2 mmol) and Ethyl phenylpropiolate **2o** (165 µL, 1 mmol), cycloadduct **11f** (35 mg, 55%) was obtained after silica gel column chromatography (20:1 hexane/ EtOAc then 1:2 hexane/ EtOAc) as a green gray solid, m.p. 151-153 °C; IR υmax (cm^{-1}) 3261, 2941, 1689, 1585, 1417, 1269, 1236, 1049, 790, 756, 696; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.83 (m, 2H), 7.24 – 7.20 (m, 3H), 7.20 – 7.15 (m, 2H), 7.01 – 6.92 (m, 1H), 6.74 (ddd, *J* = 8.3, 3.0, 1.4 Hz, 1H), 4.35 – 4.25 (m, 1H), 3.90 – 3.83 (m, 2H), 3.73 (d, *J* = 8.0 Hz, 1H), 2.67 – 2.54 (m, 1H), 2.36 – 2.22 (m, 1H), 2.13 – 1.99 (m, 1H), 1.83 – 1.64 (m, 3H), 0.82 (td, *J* = 7.2, 0.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.14, 143.08, 142.16, 140.56, 139.02, 136.56, 133.28, 128.39, 127.87, 127.65, 123.82, 118.96, 60.76, 51.75, 27.71, 27.11, 17.27, 13.72; HRMS (ESI/APCL) *m/z* [M+H]+, calc'd for $C_{20}H_{22}N_2O_2$ 323.1754; found 323.175.

Following **GP6** with cyclobutylaniline **10a** (41 mg, 0.2 mmol) and styrene **2p** (115 µL, 1 mmol), annulation product **11g** (55 mg, 90 %) was obtained after silica gel column chromatography (30:1 hexane/ EtOAc) as a 3:2 mixture of two diastereoisomers.

4-tert-butyl-*N*-((1*R*,2*S*)-2-phenylcyclohexyl)aniline. Data for *trans*-**11g**: red-brown oil; IR

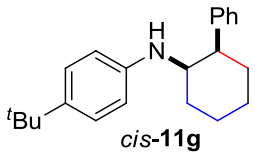


trans-**11g**

υmax (cm-1) 2926, 2854, 1614, 1516, 1448, 1259, 1193, 817, 754, 698, 545; ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.36 – 7.24 (m, 4H), 7.24 – 7.17 (m, 1H), 7.16 – 7.06 (m, 2H), 6.48 – 6.40 (m, 2H), 3.48 (td, *J* = 10.7, 3.8 Hz, 1H), 3.35 (s, 1H), 2.55 (ddd, *J* = 11.8, 10.4, 3.7 Hz, 1H), 2.44 (dtd, *J* = 10.6, 3.7, 2.0 Hz, 1H), 1.99 (dddd, *J* = 13.2, 6.2, 3.6, 2.3 Hz, 1H), 1.92 – 1.81 (m, 2H), 1.71 – 1.37 (m, 4H), 1.29 – 1.23 (m, 9H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 145.77, 145.30, 140.00, 128.97,

127.99, 126.84, 126.36, 113.05, 56.76, 51.76, 36.46, 34.32, 34.16, 31.83, 27.07, 25.83; HRMS (ESI/APCL) *m/z* [M+H]+, calc'd for $C_{22}H_{29}N$ 308.2373; found 308.2381.

4-tert-butyl-*N*-((1*R*,2*R*)-2-phenylcyclohexyl)aniline. Data for *cis*-**11g**: colorless oil; IR υmax

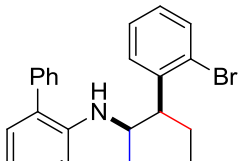


cis-**11g**

(cm-1) 2920, 2854, 1614, 1517, 1323, 1192, 817, 748, 696, 542; ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.38 – 7.22 (m, 4H), 7.16 (ddt, *J* = 6.6, 5.9, 2.6 Hz, 1H), 7.09 – 7.01 (m, 2H), 6.40 – 6.32 (m, 2H), 3.79 (q, *J* = 3.2 Hz, 1H), 3.63 (s, 1H), 3.00 (dt, *J* = 12.5, 3.8 Hz, 1H), 2.16 – 2.02 (m, 1H), 1.96 – 1.80 (m, 3H), 1.60 – 1.50 (m, 4H), 1.20 (s, 9H); ^{13}C NMR (101 MHz, CD2Cl2) δ 146.02, 144.89, 139.97, 128.68, 128.02, 126.63, 126.30, 113.22, 54.19, 46.76, 34.13, 31.80, 30.71, 26.60, 26.03, 20.75; HRMS (ESI/APCL) *m/z* [M+H]+, calc'd for $C_{22}H_{29}N$ 308.2373; found 308.2382.

Following **GP6** with cyclobutylaniline **10d** (45 mg, 0.2 mmol) and 2-Bromostyrene **2q** (125 µL, 1 mmol) in DMSO (2 mL), cycloadduct **11h** (43 mg, 53%) was obtained after silica gel column chromatography (100 % hexane then 100:1 hexane/ EtOAc) as a mixture of two diastereoisomers.

***N*-((1*R*,2*R*)-2-(2-bromophenyl)cyclohexyl)biphenyl-2-amine**. Data for *cis*-**11h**: colorless oil,

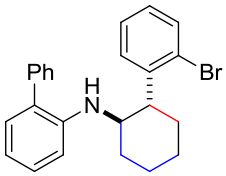


cis-**11h**

IR υmax (cm^{-1}) 2926, 2854, 1577, 1508, 1467, 1435, 1317, 1022, 1008, 736, 702; ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.55 – 7.47 (m, 3H), 7.46 – 7.39 (m, 1H), 7.34 – 7.28 (m, 2H), 7.13 – 7.06 (m, 1H), 7.05 – 6.97 (m, 2H), 6.94 (ddd, *J* = 7.5, 1.7, 0.4 Hz, 1H), 6.79 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.57 (td, *J* = 7.4, 1.1 Hz, 1H), 6.36 – 6.28 (m, 1H), 4.09 (d, *J* = 7.8 Hz, 1H), 3.98 (dq, *J* = 6.7, 3.1 Hz, 1H), 3.31 (ddd, *J* = 11.3, 5.5, 3.2 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.82 – 1.72 (m, 1H), 1.67 – 1.57 (m, 1H), 1.54 (dd, *J* = 8.4, 3.3 Hz, 2H), 1.46 – 1.35 (m, 1H), 1.34 – 1.19 (m, 2H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 144.98, 143.02, 140.10, 133.27, 130.17, 130.06, 129.35, 129.32, 129.04,

128.27, 128.18, 127.82, 127.62, 125.11, 116.53, 110.79, 51.08, 46.51, 30.42, 26.69, 26.03, 20.68; HRMS (ESI/APCL) m/z [M+H]+, calc'd for$C_{24}H_{24}BrN$ 406.1165; found 406.1160.

***N*-((1*R*,2*S*)-2-(2-bromophenyl)cyclohexyl)biphenyl-2-amine**. Data for *trans*-**11h**: colorless

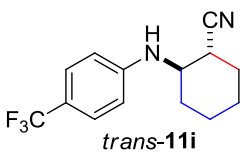


trans-**11h**

oil; IR υmax (cm^{-1}) 2927, 2852, 1577, 1508, 1435, 1317, 1022, 744, 734, 702; ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.56 – 7.50 (m, 1H), 7.27 (dddd, *J* = 4.9, 3.0, 1.9, 0.8 Hz, 5H), 7.16 – 7.09 (m, 1H), 7.09 – 7.03 (m, 1H), 6.90 (ddd, *J* = 7.4, 1.7, 0.4 Hz, 1H), 6.88 – 6.80 (m, 2H), 6.68 – 6.56 (m, 2H), 3.71 (d, *J* = 7.0 Hz, 1H), 3.46 (d, *J* = 32.3 Hz, 1H), 3.04 (td, *J* = 11.2, 3.6 Hz, 1H), 2.37 (dddd, *J* = 12.0, 5.1, 3.5, 1.6 Hz, 1H), 1.95 – 1.85 (m, 1H), 1.85 – 1.71 (m, 2H), 1.53 – 1.31 (m, 3H), 1.19 – 1.07 (m, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 144.74, 143.88, 139.72, 133.20, 130.68, 129.49, 129.41, 129.01, 128.40, 128.31, 128.07, 127.79, 127.43, 125.85, 116.59, 110.42, 57.17, 49.45, 34.90, 34.15, 26.81, 25.70; HRMS (ESI/APCL) *m/z* [M+H]+, calc'd for $C_{24}H_{24}BrN$ 406.1165; found 406.1159.

Following **GP6** with cyclobutylaniline **10e** (43 mg, 0.2 mmol) and acrylonitrile **2r** (65 μL, 1 mmol), cycloadduct **11i** (37 mg, 69%) was obtained after silica gel column chromatography (5:1 hexane/ EtOAc) as a mixture of two diastereoisomers.

(1*R*,2*R*)-2-(4-(trifluoromethyl)phenylamino)cyclohexanecarbonitrile. Data for *trans*-**11i**:

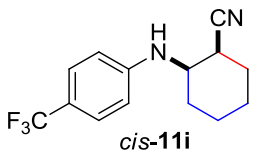


trans-**11i**

white solid, m.p. 117-119 °C; IR υmax (cm^{-1}) 3338, 2951, 2247, 1614, 1541, 1315, 1095, 1062, 831, 503; ^{1}H NMR (400 MHz, Methylene Chloride-d_2) δ 7.44 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 4.31 (d, *J* = 8.8 Hz, 1H), 3.52 (ddt, *J* = 12.5, 8.5, 4.0 Hz, 1H), 3.36 (p, *J* = 3.3 Hz, 1H), 2.08 (dp, *J* = 12.4, 2.9 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.95 – 1.86 (m, 1H), 1.77 – 1.69 (m, 1H), 1.68 – 1.60 (m, 2H), 1.60 – 1.53 (m, 1H), 1.44 (qt, *J* = 12.7, 3.8 Hz, 1H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 149.21,

127.29 (q, *J* = 3.7 Hz), 126.28 (q, *J* = 268.6 Hz), 120.06, 119.70 (q, *J* = 32.6 Hz), 113.00, 52.07, 34.01, 29.95, 28.02, 25.17, 22.04; HRMS (ESI/APCL) *m/z* $[M+H]^+$, calc'd for $C_{14}H_{15}F_3N_2$ 269.1260; found 269.1247.

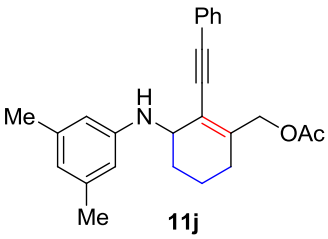
(1*S*,2*R*)-2-(4-(trifluoromethyl)phenylamino)cyclohexanecarbonitrile. Data for *cis*-**11i**:



cis-**11i**

yellow solid, m.p. 97-100 °C; IR υmax (cm^{-1}) 3358, 2954, 2241, 1614, 1533, 1317, 1093, 1062, 827, 590; ^1H NMR (300 MHz, Methylene Chloride-d_2) δ 7.40 (dd, *J* = 13.6, 8.5 Hz, 2H), 6.71 (dd, *J* = 8.8, 2.6 Hz, 2H), 4.13 – 3.99 (m, 1H), 3.62 (qd, *J* = 9.1, 3.9 Hz, 1H), 2.56 (ddd, *J* = 10.0, 9.1, 3.9 Hz, 1H), 2.24 – 2.04 (m, 1H), 1.76 (dddd, *J* = 14.0, 10.8, 6.3, 3.2 Hz, 2H), 1.56 – 1.42 (m, 1H), 1.41 – 1.33 (m, 1H), 1.32 – 1.19 (m, 2H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 149.78, 127.18 (q, *J* = 3.8 Hz), 126.12 (q, *J* = 268.8 Hz), 121.66, 119.65 (q, *J* = 32.6 Hz), 114.53, 113.04, 53.48, 35.58, 32.41, 29.23, 24.35, 24.07; HRMS (ESI/APCL) *m/z* $[M+H]^+$, calc'd for $C_{14}H_{15}F_3N_2$ 269.1260; found 269.1257.

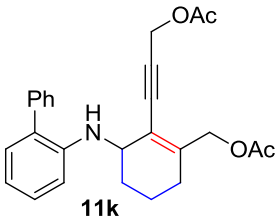
(3-(phenylamino)-2-(phenylethynyl)cyclohex-1-enyl)methyl acetate. Following **GP6** with cyclobutylaniline **10g** (35 mg, 0.2 mmol) and diyne **2g** (198 mg, 1 mmol), cycloadduct **11j** (45 mg, 60%) was obtained after silica gel column chromatography (30:1 hexane/ EtOAc) as yellow brown oil;



11j

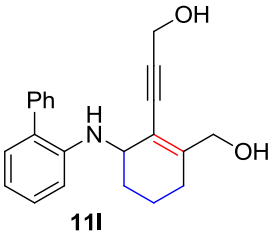
IR υmax (cm^{-1}) 3360, 2939, 2864, 1724, 1597, 1369, 1242, 1182, 1024, 756, 690; ^1H NMR (400 MHz, Methylene Chloride-d_2) δ 7.39 – 7.15 (m, 5H), 6.44 – 6.25 (m, 3H), 5.01 – 4.85 (m, 2H), 4.27 – 4.07 (m, 1H), 2.28 – 2.19 (m, 7H), 2.12 – 2.04 (m, 3H), 1.90 – 1.64 (m, 5H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 171.23, 148.38, 143.05, 139.31, 131.89, 128.79, 128.71, 123.67, 121.90, 119.73, 111.72, 94.60, 87.52, 66.56, 51.93, 29.01, 27.61, 21.78, 21.22, 18.71; HRMS (ESI/APCL) *m/z* $[M+H]^+$, calc'd for $C_{25}H_{27}NO_2$ 374.2115; found 374.2130.

3-(2-(acetoxymethyl)-6-(biphenyl-2-ylamino)cyclohex-1-enyl)prop-2-ynyl acetate.



11k

Following **GP6** with cyclobutylaniline **10d** (45 mg, 0.2 mmol) and diyne **2s** (120 mg, 1 mmol), cycloadduct **11k** (71 mg, 85%) was obtained after silica gel column chromatography (30:1 hexane/ EtOAc to elute excess diyne, then 10:1 hexane/ EtOAc) as brown oil; IR υmax (cm^{-1}) 2933, 2864, 1739, 1735, 1508, 1436, 1217, 1024, 908, 731, 704; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.52 – 7.43 (m, 4H), 7.43 – 7.36 (m, 1H), 7.32 – 7.27 (m, 1H), 7.15 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 4.85 – 4.72 (m, 2H), 4.70 (s, 2H), 4.06 (d, *J* = 5.0 Hz, 1H), 2.18 – 2.10 (m, 2H), 2.09 (d, *J* = 0.6 Hz, 3H), 2.08 (d, *J* = 0.7 Hz, 3H), 1.88 (ddt, *J* = 16.3, 7.6, 4.0 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.66 – 1.50 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.96, 170.32, 144.30, 144.04, 139.65, 130.71, 129.56, 129.03, 128.72, 128.05, 127.30, 120.05, 117.15, 111.13, 88.31, 83.79, 66.10, 52.87, 51.64, 28.26, 27.00, 20.97, 20.88, 18.16; HRMS (ESI/APCL) *m/z* $[M+H]^+$, calc'd for $C_{26}H_{27}NO_4$ 418.2040; found 418.2035.



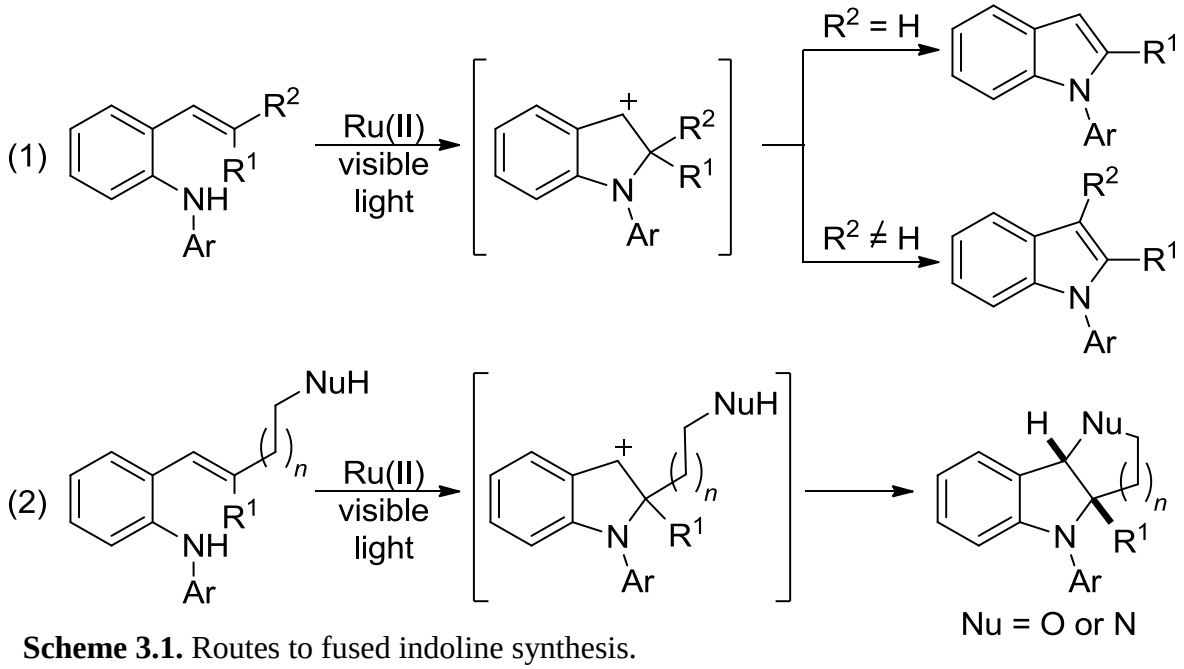
11l

The diol was formed by cleavage of the two acetate groups of **11k**. It was used to further confirm **11k**'s structure. Yellow oil; IR υmax (cm-1) 3313, 2926, 2858, 1577, 1508, 1309, 1166, 1012, 742, 702; ^{1}H NMR (400 MHz, Methylene Chloride-*d*2) δ 7.50 – 7.38 (m, 3H), 7.38 – 7.29 (m, 1H), 7.24 – 7.15 (m, 1H), 7.09 – 6.98 (m, 1H), 6.80 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.72 (td, *J* = 7.4, 1.1 Hz, 1H), 4.22 (s, 4H), 4.09 – 4.01 (m, 1H), 2.20 – 2.11 (m, 2H), 1.80 – 1.68 (m, 3H), 1.66 – 1.49 (m, 4H); ^{13}C NMR (101 MHz, CD2Cl2) δ 148.64, 145.12, 140.13, 130.99, 129.90, 129.47, 129.06, 128.46, 127.72, 118.43, 117.37, 111.68, 92.56, 83.49, 65.19, 52.17, 51.83, 28.97, 27.47, 18.92; HRMS (ESI/APCL) *m/z* [M+H]+, calc'd for $C_{22}H_{23}NO_2$ 334.1802; found 334.1809.

Appendix 2: Fused *N*-Arylindolines: Preparation of Styryl Anilines*

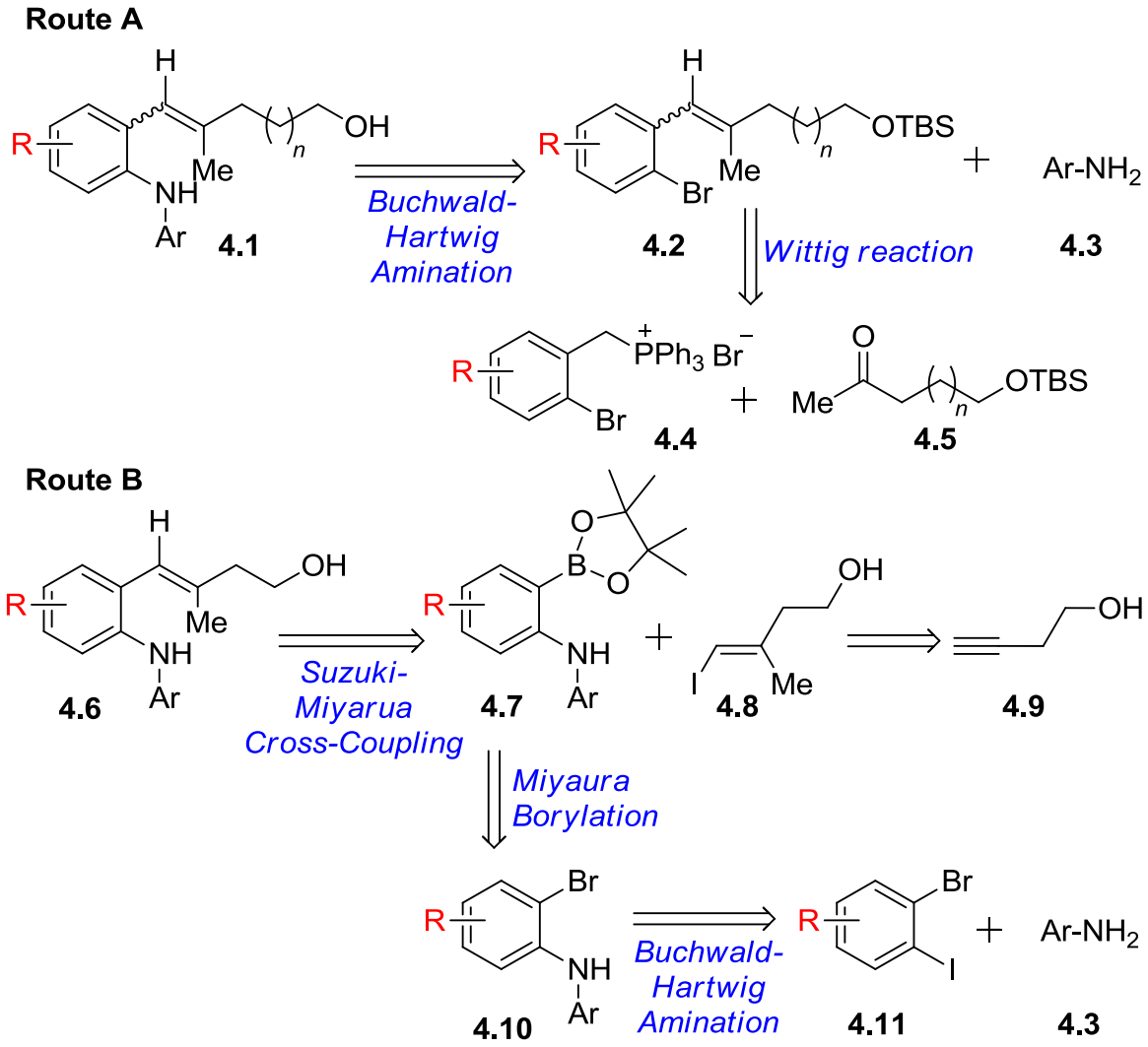
*Portion of this chapter has been published in Morris, S. A.; Nguyen, T. H.; Zheng, N. *Adv. Synth. Catal*. **2015**, *357*, 2311 –2316.

As previously discussed in section 2.2.3, the structural motifs of fused indolines are prevalently found in bioactive alkaloids and pharmaceuticals. As an important substructure of nitrogen-containing heterocycles, their frequent occurrence in natural products has drawn chemists' attention towards developing innovative and efficient approaches to their synthesis. An application of the developed [3+2] annulation of cyclopropylanilines with alkynes described a route of accessing fused indolines in four short synthetic steps.[11] Recently, our group disclosed a diastereocontrol method of synthesizing fused *N*-arylindolines in one step from styrylanilines using visible light photoredox catalysis.[12] The work was an expansion of a previous application of preparing mono- and disubstituted indoles (at the C-2 and C-3 positions) through an intermediate benzylic carbocation via a photogenerated amine radical cation (Scheme 3.1, eq. 1).[13] The same oxidative C-N bond formation cascade triggered by visible light was envisioned



Scheme 3.1. Routes to fused indoline synthesis.

for the synthesis of fused indolines, followed by subsequent interception of the benzylic carbocation with tethered nucleophiles (Scheme 3.1, eq. 2). Appropriate nucleophiles included oxygen and nitrogen atoms. In order to conduct the cascade, developing synthetic routes for accessing the starting materials, styrylanilines bearing a trisubstituted alkene and a *para*-alkoxyphenylaniline substituent, were highly desired. Two synthetic methods were disclosed with the first hinging on the use of a Wittig reaction of ketone **4.5** and the ylide generated from phosphonium salt **4.4** to furnish the trisubstituted alkene, subsequently followed by a Buchwald-Hartwig amination to install the *para*-alkoxyphenylaniline group (Scheme 3.2, Route A).

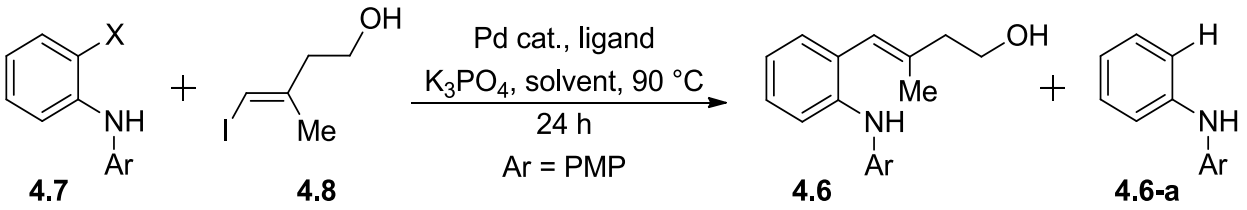


Scheme 3.2. Synthetic routes to styrylanilines.

However, this lengthy synthesis of styrylanilines, in which lacks convergence, lead to the development of an alternative and more convergent route (Scheme 3.2, Route B). Route B describes a rapid access to styrylanilines centered on a Suzuki-Miyaura Cross-Coupling of boronate ester **4.7** and vinyl iodide **4.8**. Moreover, the use of synthetic Route B eliminates the need of protecting the hydroxyl group, as disclosed in Route A with OTBS groups. The preparation of boronate ester **4.7** was accomplished in two short steps involving a Miyaura borylation of *N*-arylaniline **4.10** as a result of a Buchwald-Hartwig amination of commercially available arylhalide **4.11** and aniline **4.3**. Separately, vinyl iodide **4.8** was realized in one step via a zirconium-catalyzed carboalumination of 3-butyn-1-ol **4.9**. My contribution to this project focused on screening the Suzuki-Miyaura Cross-Coupling reaction in addition to the preparation of four styrylanilines utilizing Route B.

Boronate ester **4.7** and vinyl iodide **4.8** were used as standard substrates to screen the Suzuki-Miyaura Cross-Coupling reaction. Considerable efforts were applied in finding suitable conditions for the reaction, as competitive protodeboronation of the boronate esters became a leading issue. Protodeboronation of boronate esters is a known side reaction in the Suzuki-Miyaura Cross-Coupling.[14] With a number of approaches reported to remedy this issue,[15] I planned to solve the problematic protodeboronation by choosing appropriate boronate esters and/or catalyst systems. Initially, potassium trifluoroborate salt **4.7b** was employed, as potassium trifluoroborate salts are considered as superior organoboron reagents in Suzuki-Miyaura Cross-Coupling due to their slow release of the corresponding boronic acid. However, significant protodeboronation was observed in the presence of $Pd(OAc)_2$ with Buchwald ligands in a 10:1 mixture of toluene to H_2O (Table 17, entries 1-3). Likewise, changing the Pd source to $Pd(PPh_3)_4$ or $PdCl_2(dppf)$•DCM offered no improvement to the yield of styrylaniline **4.6** (entries

Table 17. Screening of the Suzuki-Miyarua Cross-Coupling reaction.



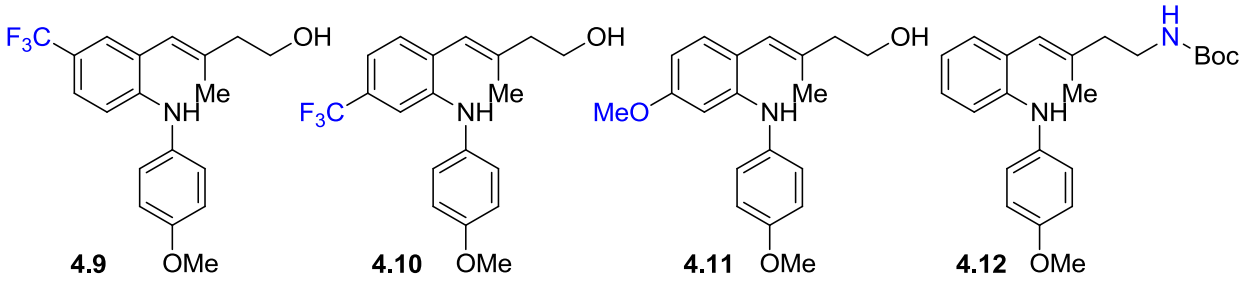
4.7 **4.8** **4.6** **4.6-a**

Entry[a]	X	Pd Source	Ligand	Solvent	Yield of **4.6**[b]	Yield of **4.6-a**[b,c]
1	BF_3K **4.7b**	$Pd(OAc)_2$	RuPhos	Toluene/ H_2O (10:1)	5%	118%
2	BF_3K **4.7b**	$Pd(OAc)_2$	SPhos	Toluene/ H_2O (10:1)	4%	125%
3	BF_3K **4.7b**	$Pd(OAc)_2$	XPhos	Toluene/ H_2O (10:1)	5%	130%
4	BF_3K **4.7b**	$Pd(PPh_3)_4$	None	Toluene/ H_2O (10:1)	8%	76%
5	BF_3K **4.7b**	$PdCl_2$(dppf) •DCM	None	Toluene/ H_2O (10:1)	0%	81%
6	BPin **4.7a**	$Pd(OAc)_2$	RuPhos	Toluene/ H_2O (10:1)	55%	87%
7	Bpin **4.7a**	$Pd(OAc)_2$	SPhos	Toluene/ H_2O (10:1)	30%	124%
8	BPin **4.7a**	$Pd(OAc)_2$	XPhos	Toluene/ H_2O (10:1)	16%	135%
9	BPin **4.7a**	$Pd(PPh_3)_4$	None	Toluene/ H_2O (10:1)	9%	115%
10	BPin **4.7a**	$PdCl_2$(dppf) •DCM	None	Toluene/ H_2O (10:1)	10%	122%
11	BPin **4.7a**	$Pd(OAc)_2$	RuPhos	THF/ H_2O (10:1)	83%	13%
12	BPin **4.7a**	$Pd(OAc)_2$	RuPhos	EtOH/ H_2O (1:1)	90%	47%
13	BPin **4.7a**	$Pd(OAc)_2$	RuPhos	Toluene/EtOH/H_2O (2:1:1)	91%	13%
14	BPin **4.7a**	$Pd(OAc)_2$	RuPhos	Benzene/EtOH/ H_2O (2:1:1)	87%	12%
15	BPin **4.7a**	$Pd(OAc)_2$	RuPhos	THF/ EtOH/ H_2O (2:1:1)	95% (88%)[d]	11%

[a]conditions: boronate ester or trifluoroborate salt **4.7** (1.5 equiv.), Pd source (2 mol%), ligand (4 mol%), and ground K_3PO_4 (3 equiv.). The reaction was sealed and then subjected to three cycles of evacuation/refill with N_2. Alcohol **4.8** (1 equiv., 0.22 mmol) and solvent (1 mL, degassed) were then added. [b] Used dodecane as an internal standard. [c] Since 1.5 equiv of **4.7** was used, the maximum yield would be 150%. [d] Isolated yield.

4 & 5). Alternatively, boronate ester **4.7a** served as a suitable boron reagent providing the desired **4.6** in 55% GC yield with a slight decrease in protodeboronation (entry 6). Screening of other Buchwald ligands suggested RuPhos to be the optimal ligand (entries 7 & 8). It became apparent that $Pd(PPh_3)_4$ and $PdCl_2$(dppf)•DCM were inferior to Pd source $Pd(OAc)_2$ (entries 9 & 10). Other solvent mixtures were then investigated to find the optimal solvent system. When toluene was replaced with THF and EtOH (with a ratio decrease of EtOH from 10 to 1), the yield dramatically increased to 83% and 90%, respectively (entries 11 & 12). The yield was further increased with minimal protodeboronation observed when a 2:1:1 mixture of THF/EtOH/H_2O was incorporated (entry 15). Replacement of THF with toluene or benzene in the three-solvent system gave slightly inferior results, confirming the THF/EtOH/H_2O mixture as the optimal solvent system (entries 13 & 14).

Figure 2.7. Targeted styrylanilines.

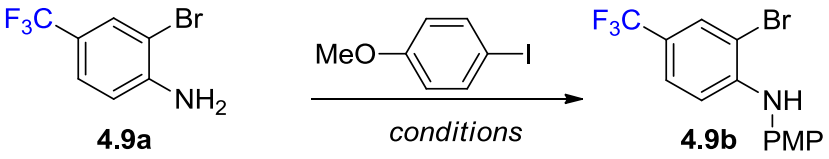


With the Suzuki-Miyaura screening established, Route B was acquired for the preparation of four targeted styrylanilines to contribute to the substrate scope. It was envisioned to decorate the *N*-arylaniline with electron-donating and electron-withdrawing groups in addition to installing tethered oxygen and nitrogen nucleophiles. To accomplish this, styrylanilines substituted with trifluoromethyl and methoxy groups *para* and *meta* to the *para*-methoxyphenyl

(PMP) moiety (**4.9**, **4.10**, and **4.11**) were prepared along with tethered amine nucleophile **4.12** (Figure 2.7). Initial efforts of synthesizing styrylaniline **4.9** began with introducing the PMP group to commercially available 2-bromo-4-(trifluoromethyl)aniline via an amination procedure with 4-iodoanisole. Unexpectedly, the amination step was problematic as several conditions

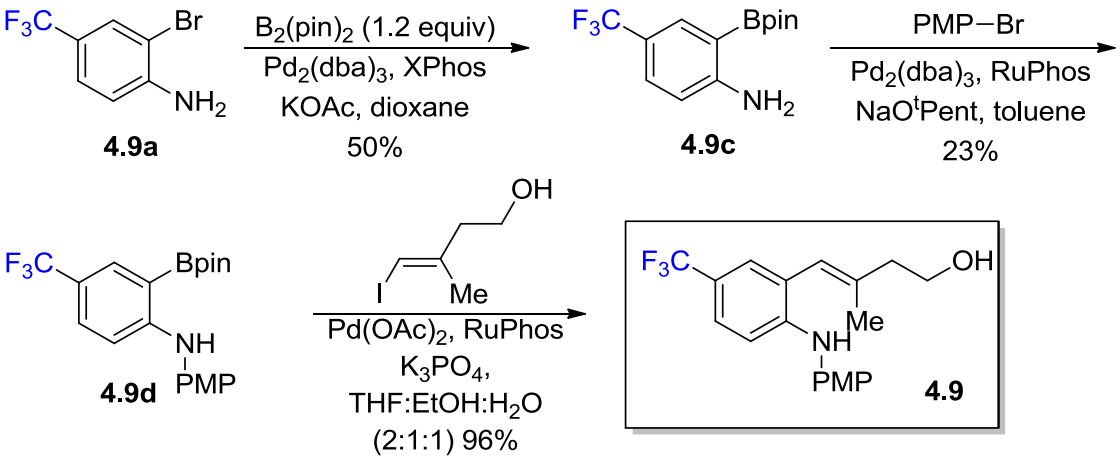
Scheme 3.3. Synthetic route of styrylaniline **4.9**.

(1)



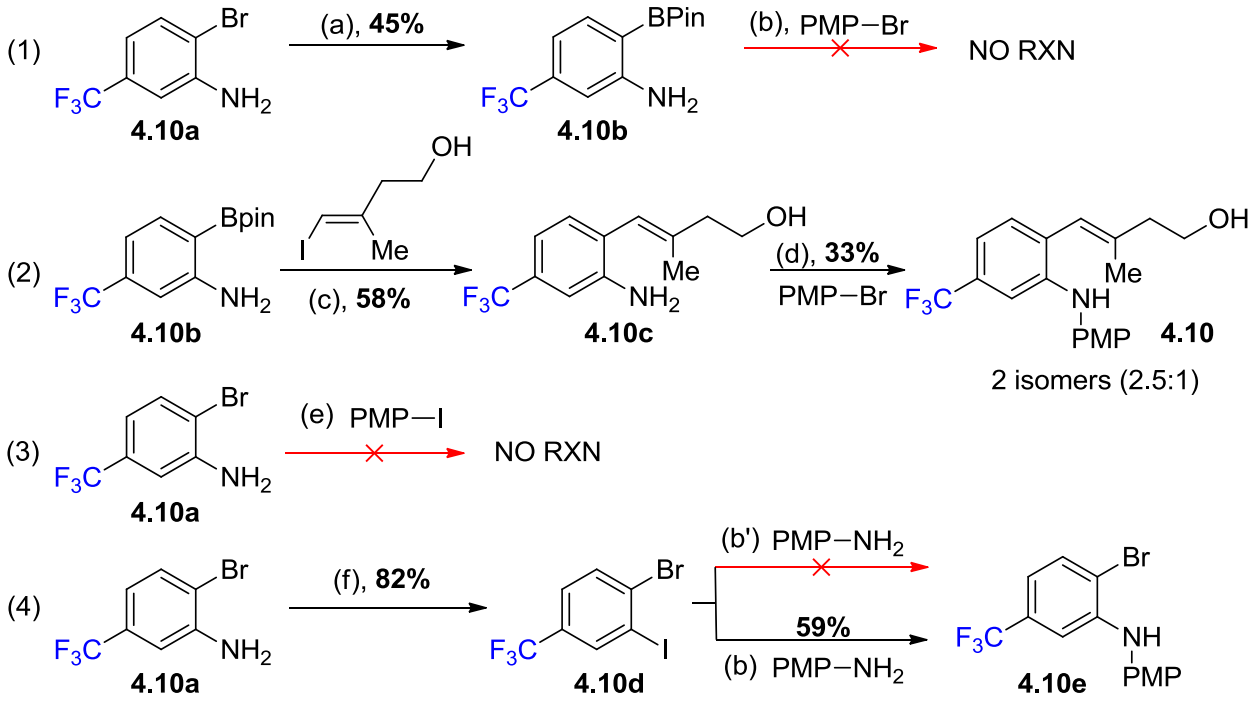
Entry	Ligand	Base	Catalyst	Solvent	Yield
1	DPEPhos	NaO^{t}Pent	$Pd(OAc)_2$	Toluene	NO RXN
2	XantPhos	NaO^{t}Pent	$Pd(OAc)_2$	Dioxane	NO RXN
3	XantPhos	Cs_2CO_3	$Pd(OAc)_2$	Dioxane	25%
4	Proline	K_2CO_3	CuI	DMSO	NO RXN

(2)



were screened, but provided no positive results (Scheme 3.3, eq. 1). The combination of electronic characters with the aniline moiety and the arylhalide, bearing the methoxy group, appeared to have an effect on the amination step. It was then strategized to install the boronate ester **4.9c** first, followed by an amination to provide the precursor to the Suzuki-Miyaura Cross-Coupling **4.9d** (Scheme 3.3, eq. 2). Although the amination step for this particular substrate was not synthetically useful, the Miyaura borylation and the Suzuki-Miyaura Cross-Coupling

Scheme 3.4. Efforts toward the preparation of styrylaniline **4.10**.

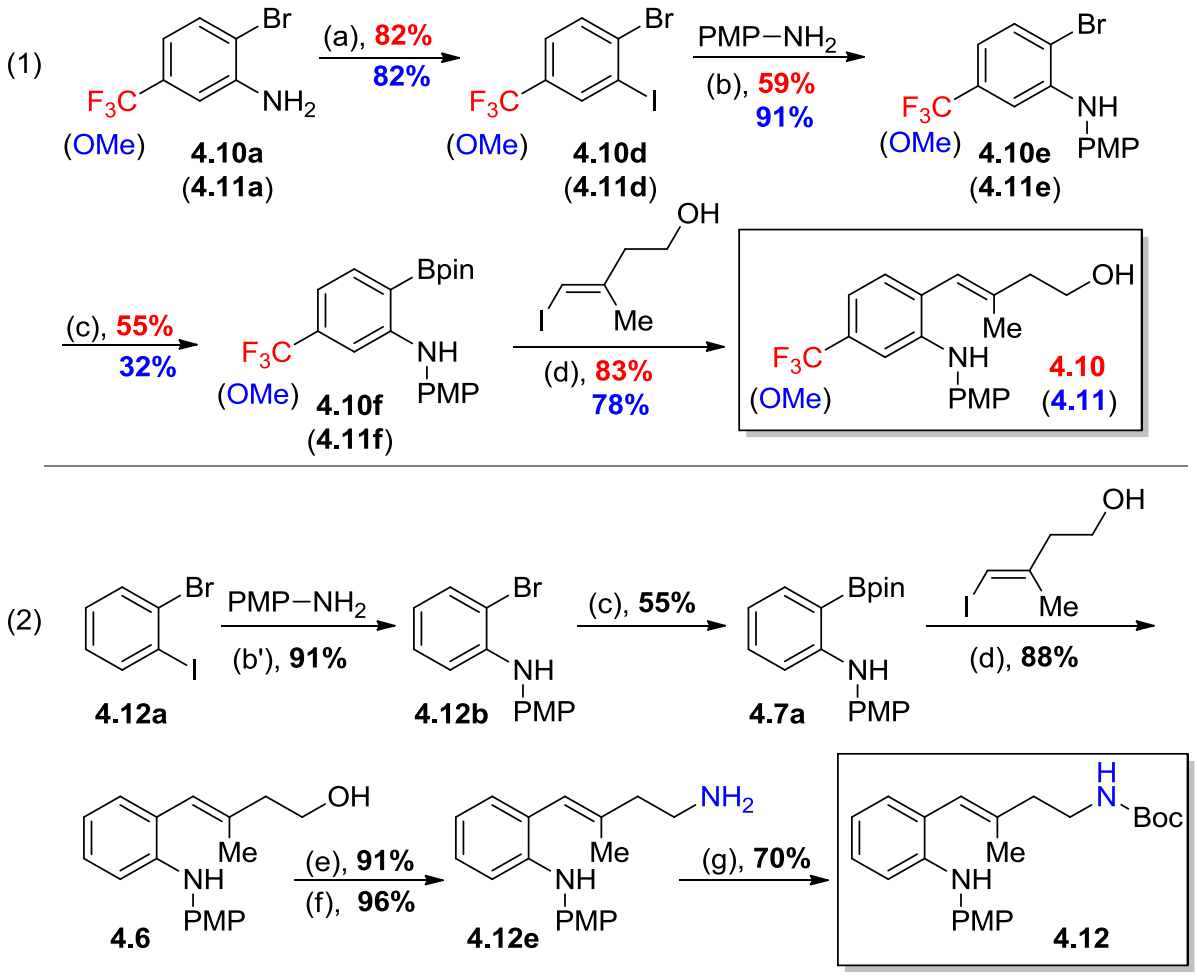


conditions: (a) HBpin (3 equiv), (dppf)$PdCl_2$.DCM, Et_3N, dioxane; (b) $Pd_2(dba)_3$, (*R*)-tol-BINAP [(b') DPEPhos], NaO^{t}Pent, toluene; (c) $Pd(OAc)_2$, RuPhos, K_3PO_4, THF:EtOH:H_2O (2:1:1); (d) $Pd_2(dba)_3$, DavePhos, LiN(TMS), THF; (e) CuI, Proline, K_2CO_3, DMSO; (f) $NaNO_2$, KI H_2O

reaction were accomplished in good to excellent yields (50% and 95%, respectively) to afford the desired styrylaniline **4.9**. For the preparation of styrylaniline **4.10**, substituted with a trifluoromethyl group meta to the PMP group, it was thought that the same sequence could be applied; however, amination of the prepared boronate ester **4.10b** was unsuccessful (Scheme 3.4, eq. 1). The boronate ester was then subjected to the Suzuki-Miyaura cross-coupling conditions, furnishing the trisubstituted alkene aniline **4.10c** in 58% yield (eq. 2). Unfortunately, the following amination step afforded styrylaniline **4.10** in a poor yield as a 2.5:1 mixture, detected by GC/MS. It is unclear how two possible isomers are produced, thus the lowered ratio isomer of the mixture is currently unidentified. The discouraging results lead to an attempt of acquiring Route B by introducing the amination step first. Direct amination of 4-iodoanisole with

commercially available 2-bromo-5-(trifluoromethyl)aniline **4.10a** detected no product formation (eq. 3), thus, the aniline was converted to iodobenzene derivative **4.10d** in the presence of sodium nitrite and potassium iodide. Buchwald-Hartwig amination of **4.10d** with *para*-methoxyaniline was carried out in a moderate yield of 59% using ligand (R)-tol-BINAP, as no reaction was observed with ligand DPEPhos (eq. 4). Subsequent subjection to Miyaura borylation and Suzuki conditions successfully gave the desired styrylaniline **4.10** (Scheme 3.5,

Scheme 3.5. Preparation of styrylanilines **4.10-4.12**.



conditions: (a) $NaNO_2$, KI, H_2O; (b) $Pd(OAc)_2$, (*R*)-tol-BINAP, [(b') DPEPhos], NaO^tPent, toluene; (c) $B_2(Pin)_2$, $Pd_2(dba)_3$, XPhos, KOAc, dioxane; (d) $Pd(OAc)_2$, RuPhos, K_3PO_4, THF:EtOH:H_2O (2:1:1); (e) phthalimide, PPh_3, DIAD, THF; (f) $N_2H_4H_2O$, EtOH, reflux; (g) Boc_2O, DMAP, DCM

eq. 1). Likewise, the same sequence was applied for the synthesis of styrylaniline **4.11**, substituted with a methoxy group instead of the trifluoromethyl group (eq. 1). All four synthetic steps were high yielding (78% -91%), except for the conversion of aryl bromide **4.11e** to boronate ester **4.11f** (32%). Lastly, styrylaniline **4.12** with a tethered amine nucleophile was easily generated from the corresponding alcohol substrate **4.12d** using a Gabriel synthesis followed by a Boc protection. Much like the previously disclosed syntheses, styrylaniline **4.12d** was prepared via Route B in moderate to excellent yields.

The styrylanilines were successfully synthesized and given to my colleague, Scott Morris, for the preparation of *N*-arylindolines subjected under visible light photoredox conditions. Moreover, synthetic route B was developed for accessing the starting materials, substituted with various electronic characters, permitting flexibility in regards to decorating the *N*-arylindolines and ultimately expanding the substrate scope. Finding the appropriate conditions suitable for the Suzuki-Miyarua cross-coupling reaction was a key component in contributing to the successful convergent synthesis of styrylanilines.

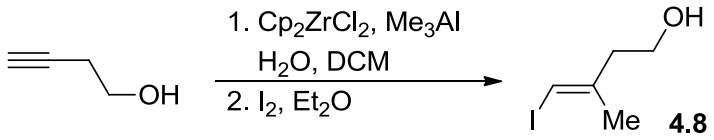
Experimental Section

General Procedure 7 (GP7): Preparation of *N*-Arylanilines using a Buchwald-Hartwig Amination

Preparation of *N*–arylanilines was accomplished using a literature procedure.[13] To an oven-dried Schlenk flask equipped with a stir bar was added 0.5–8 mol % $Pd(OAc)_2$ or $Pd_2(dba)_3$ and 1.5–12 mol % ligand. Glove box was used to add 1.5–2 equiv of NaO^tPent and the tube was sealed. 1 equiv of aromatic halide, 1.2–1.5 equiv of aniline, and anhydrous 1,4–dioxane or toluene (0.5–0.8 M) were then added to the reaction mixture and heated at 110 °C for 18 h. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether, filtered over a

short pad of silica gel, and concentrated in vacuum. Purification by flash chromatography on silica gel afforded the corresponding *N*-arylaniline.

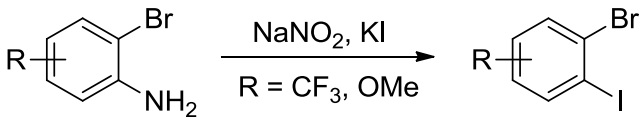
Preparation of (*E*)-4-iodo-3-methylbut-3-en-1-ol 4.8



4.8

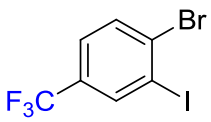
Preparation and characterization of (*E*)-4-iodo-3-methylbut-3-en-1-ol **4.8** from commercially available 3-butyn-1-ol in one step correspond to those described in literature.[16]

General Procedure 8 (GP8): Preparation of 1-bromo-2-iodoanilines



Preparation of 1-bromo-2-iodoanilines was performed using a literature procedure.[17] To a cooled solution (0 °C) of the aniline (1 equiv, 5 mmol) and aq. HCl (3.6 M, 13 mL) in a round bottom flask equipped with a stir bar was added slowly $NaNO_2$ (1.2 equiv, 6 mmol, 414 mg) in H_2O (10 mL, 0.6 M). Once the solid dissolved, a separate solution of KI (1.5 equiv, 7.5 mmol, 1.24 g) in H_2O (5 mL, 1.5 M) was added dropwise to the aniline-containing solution. The resulting solution was warmed to room temperature and stirred for 30 minutes prior to heating at 70 °C for 1 hour. The mixture was then cooled to room temperature and neutralized by slow addition of $Na_2S_2O_3$ (0.4 M). The neutralized solution was then extracted with DCM (3 x 20 mL), and the combined organic layers were washed with H_2O (3 x 20 mL). The organic layer was then dried over $MgSO_4$ and concentrated in vacuum to give crude product. Purification by flash chromatography on silica gel provided the desired product.

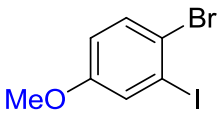
1-bromo-2-iodo-4-(trifluoromethyl)benzene. Following procedure **GP8** with commercially available 2-bromo-5-(trifluoromethyl)aniline (1.2 g, 0.72 mL), the desired product was obtained



4.10d

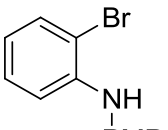
after flash chromatography on silica gel (100% hexanes) as a clear yellow oil (1.45 g, 83%). Characterization of the pure compound matched literature values.[17]

1-bromo-2-iodo-4-methoxybenzene. Following procedure **GP8** with commercially available 2-bromo-5-methoxyaniline (1.01g, 0.66 mL), the desired product was obtained after flash chromatography on silica gel (100% hexanes) as a clear yellow oil (1.28 g, 82%). Characterization of the pure compound matched literature values.[17]



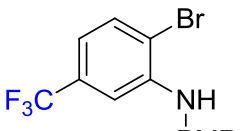
4.11d

2-bromo-*N*-(4-methoxyphenyl)aniline. Following procedure **GP7** with commercially available 1-bromo-2-iodobenzene **4.12a** (1 equiv, 7.79 mmol, 2.20 g), $Pd(OAc)_2$ (0.5 mol %, 0.039 mmol, 8.7 mg), DPEPhos (1.5 mol %, 0.117 mmol, 63 mg), *p*–anisidine (1.2 equiv, 9.35 mmol, 1.2 g) and NaO^{t}Pent (1.5 equiv, 11.7 mmol, 1.3 g) in 15 mL of toluene. Purification by flash chromatography on silica gel (99:1 hexanes:EtOAc) afforded the desired product as a white solid (2.17 g, 76%). Characterization of the pure compound matched described literature values.[18]



4.12b

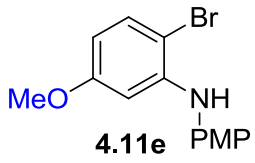
2-bromo-*N*-(4-methoxyphenyl)-5-(trifluoromethyl)aniline. Following procedure **GP7** with 1-bromo-2-iodo-4-(trifluoromethyl)benzene **4.10d** (1 equiv, 2 mmol, 702 mg), $Pd(OAc)_2$ (8 mol %, 0.16 mmol, 36 mg), (*R*)-T-BINAP (12 mol %, 0.24 mmol, 163 mg), *p*–anisidine (1.5 equiv, 3 mmol, 369 mg), and NaO^{t}Pent (2 equiv, 4 mmol, 440 mg) in 4 mL of toluene. Purification by flash chromatography on silica gel (90:10 hexane:EtOAc) afforded the desired product as a red–orange oil (406 mg, 59%). IR υmax (cm^{-1}) 3408, 2838, 1602, 1514, 1433, 1333, 1249, 1169, 1125, 1079. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dq, *J* = 8.3, 0.8 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.08 (dd, *J* =



4.10e

2.2, 0.7 Hz, 1H), 6.98 – 6.91 (m, 2H), 6.90 – 6.82 (m, 1H), 6.16 – 6.06 (m, 1H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.37, 144.16, 133.34, 132.89, 130.94 (q, *J* = 32.3 Hz), 125.74, 124.06 (q, *J* = 272.5 Hz), 115.60, 115.24, 113.46, 1, 109.92, 55.75; GC/MS (CI) *m*/*z* [M+H]+ for $C_{14}H_{11}BrNO_2$ found 308.

2-bromo-5-methoxy-N-(4-methoxyphenyl)aniline. Following procedure **GP7** with 1-bromo-2-iodo-4-methoxybenzene **4.11d** (1 equiv, 3.2 mmol, 1.0 g), $Pd(OAc)_2$ (8 mol %, 0.256 mmol, 57.5 mg), (*R*)-T-BINAP (12 mol %, 0.384 mmol, 261 mg), p–anisidine (1.5 equiv, 4.8 mmol, 591 mg), and NaO^{t}Pent (2 equiv, 6.4 mmol, 705 mg) in 4 mL of toluene. Purification by flash chromatography on silica gel (95:5 hexane:EtOAc) afford the desired product as a pale cloudy oil (900 mg, 91%). IR υmax (cm^{-1}) 3391, 3005, 2958, 2835, 1591, 1510, 1448, 1170, 832, 598. ^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 – 7.33 (m, 1H), 7.21 – 7.09 (m, 2H), 6.97 – 6.85 (m, 2H), 6.52 (t, J = 2.7 Hz, 1H), 6.27 (ddd, J = 8.8, 2.8, 1.2 Hz, 1H), 5.95 (s, 1H), 3.83 (d, J = 0.9 Hz, 3H), 3.70 (d, J = 0.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.11, 156.73, 144.30, 134.03, 133.12, 125.19, 114.97, 105.25, 101.69, 100.23, 55.75, 55.57; GC/MS (CI) m/z [M+H]+ for $C_{18}H_{20}N_2O$ found 281.



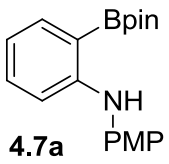
4.11e

General Procedure 9 (GP9): Preparation of *N*–aryl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilines from 2-bromo-*N*-arylanilines using a Miyaura Borylation

Preparation of *N*–aryl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilines was performed using a literature procedure.[19] To an oven-dried Schlenk flask equipped with a stir bar was added 1.2–2 equiv of Bis(pinacolato)diboron ($B_2(pin)_2$), 4 mol % $Pd_2(dba)_3$ and 8 mol % XPhos. Glove box was used to add 3 equiv of KOAc and the tube was sealed with a Teflon screw cap. 1 equiv of Aromatic halide and 1,4-dioxane (0.33–0.5 M) were then added to the reaction mixture

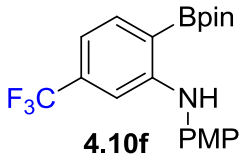
and heated at 110 °C for 24–48 h. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether, and filtered over a short pad of Celite. The Celite was washed with ethyl acetate and the combined filtrate was concentrated in vacuum and purified by flash chromatography on silica gel to afford the corresponding *N*–aryl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline.

***N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline**. Following procedure **GP9** with 2-bromo-*N*-(4-methoxyphenyl)aniline (1 equiv, 14.4 mmol, 4.0 g), $B_2(Pin)_2$ (2 equiv, 28.8 mmol, 7.3 g), $Pd_2(dba)_3$ (4 mol %, 0.57 mmol, 527 mg), XPhos (8 mol %, 1.15 mmol, 548 mg), and KOAc (3 equiv, 43.1 mmol, 4.23 g) in 30 mL of anhydrous 1,4–dioxane. The reaction was heated for 24 h. Purification by flash chromatography on silica gel (97:3 hexanes:EtOAc) afforded **4.7a** as a brown solid, m.p. 89–91 °C (2.6 g, 55%). IR υmax (cm^{-1}) 3388, 2983, 2834, 1602, 1514, 1462, 1372, 1143, 1038, 753. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.71 (ddd, *J* = 7.4, 1.8, 0.5 Hz, 1H), 7.24 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.21 – 7.16 (m, 2H), 6.97 (ddd, *J* = 8.4, 1.0, 0.5 Hz, 1H), 6.93 – 6.88 (m, 2H), 6.73 (td, *J* = 7.3, 1.0 Hz, 1H), 3.83 (s, 3H), 1.36 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.92, 151.20, 138.66, 137.52, 132.81, 118.24, 113.42, 99.33, 84.09, 61.26, 56.33, 25.24, 25.14; HRMS (ESI) *m*/*z* [M+H]+, calc'd for $C_{19}H_{24}BNO_3$ 326.1925; found 326.1926.



4.7a

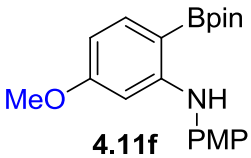
***N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)aniline**. Following procedure **GP9** with 2- bromo-*N*-(4-methoxyphenyl)-5-(trifluoromethyl)aniline (1 equiv, 1.01 mmol, 350 mg), $B_2(pin)_2$ (1.2 equiv, 1.21 mmol, 308 mg), $Pd_2(dba)_3$ (4 mol %, 0.04 mmol, 37 mg), XPhos (8 mol %, 0.08 mmol, 38 mg), and KOAc (3 equiv, 3.03 mmol, 298 mg) in 2 mL of anhydrous 1,4–dioxane. The reaction was heated for 24 h. Purification by flash



4.10f

chromatography on silica gel (90:10 hexanes:EtOAc) afforded **4.10f** as a yellow solid, m.p. 86–90 °C. (220 mg, 55%) IR υmax (cm^{-1}) 3390, 2986, 1576, 1511, 1435, 1333, 1248, 1167, 1126, 861. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.65 (s, 1H), 7.23 – 7.13 (m, 2H), 7.10 (d, *J* = 1.6 Hz, 1H), 6.99 – 6.87 (m, 3H), 3.85 (s, 3H), 1.38 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.71, 152.84, 137.97, 134.46 (q, *J* = 31.7 Hz), 134.14, 125.32, 124.34 (q, *J* = 272.8 Hz), 122.98, 115.03, 113.24, 108.05, 84.44, 55.78, 25.12; FTMS (ESI) *m*/*z* [M+H]+, calc'd for $C_{20}H_{23}BF_3NO_3$ 394.1799; found 394.1800.

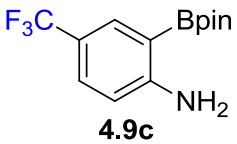
5-methoxy-*N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline.



4.11f

Following procedure **GP9** with 2-bromo- 5-methoxy-*N*-(4-methoxyphenyl)aniline (1 equiv, 2.54 mmol, 783 mg), $B_2(pin)_2$ (1.2 equiv, 3.05 mmol, 774 mg), $Pd_2(dba)_3$ (4 mol %, 0.1 mmol, 93 mg), XPhos (8 mol %, 0.2 mmol, 97 mg), and KOAc (3 equiv, 7.62 mmol, 748 mg) in 5 mL of anhydrous 1,4–dioxane. The reaction was heated for 24 h. Purification by flash chromatography on silica gel (85:15 hexanes:EtOAc) afforded **4.11f** as a yellow, m.p. 121–125 °C (292 mg, 32%). IR υmax (cm^{-1}) 3388, 2979, 2838, 1609, 1511, 1441, 1358, 1035, 861, 661. ^{1}H NMR (400 MHz, Methylene Chloride-*d*2) δ 7.55 (d, *J* = 8.3 Hz, 1H), 7.18 – 7.11 (m, 2H), 6.91 – 6.85 (m, 2H), 6.43 (d, *J* = 2.3 Hz, 1H), 6.26 (dd, *J* = 8.3, 2.3 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (101MHz, CD_2Cl_2) δ 164.23, 156.53, 154.60, 139.18, 135.37, 124.99, 115.04, 103.81, 97.59, 84.09, 56.01, 55.43, 25.23; FTMS (ESI) *m*/*z* [M+H]+, calc'd for $C_{20}H_{26}BNO_4$ 356.2031; found 356.2029.

2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4- (trifluoromethyl)aniline. Preparation of

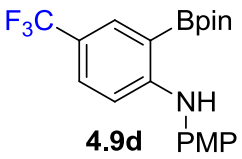


4.9c

4.9c was performed using a literature procedure.[20] To an oven-dried Schlenk flask equipped with a stir bar was added Bis(pinacolato)diboron (2

equiv, 2 mmol, 508 mg), $Pd_2(dba)_3$ (4 mol %, 0.04 mmol, 37 mg) and XPhos (8 mol %, 0.08 mmol, 38 mg). Glove box was used to add KOAc (3 equiv, 3 mmol, 294 mg) and the tube was sealed with a Teflon screw cap. Commercially available 2-bromo-4-(trifluoromethyl)aniline (1 equiv, 1 mmol, 240 mg) and 1,4-dioxane (2 mL) were then added to the reaction mixture and heated at 110 °C for 24 h. After completion, the reaction mixture wascooled to room temperature, diluted with diethyl ether, and filtered over a short pad of Celite. The Celite was then washed with ethyl acetate. The combined filtrate was concentrated in vacuum and purified by flash chromatography on silica gel (90:10 hexanes:EtOAc) to afford boronic ester **4.9c** (138 mg, 48%). Characterization of the pure compound matched described literature values.[20]

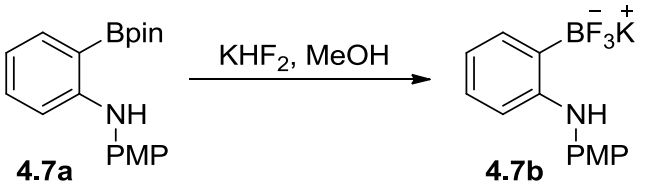
***N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-**



4.9d

(trifluoromethyl)aniline. Following procedure **GP7** with 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline **4.9c** (1.2 equiv, 0.48 mmol, 138 mg), $Pd_2(dba)_3$ (1 mol %, 0.004 mmol, 3.7 mg), RuPhos (3 mol %, 0.012 mmol, 5.6 mg), bromoanisole (1.0 equiv, 0.40 mmol, 75 mg) and NaO^tPent (1.5 equiv, 0.6 mmol, 66 mg) in 0.8 mL of anhydrous toluene. Purification by flash chromatography on silica gel (90:10 hexanes:EtOAc) afforded **4.9d** as a white solid (36 mg, 23%). IR υmax (cm^{-1}) 3387, 2983, 1618, 1512, 1368, 1316, 1268, 1142, 1109, 1077. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 – 7.92 (m, 1H), 7.78 (s, 1H), 7.43 – 7.37 (m, 1H), 7.21 – 7.15 (m, 2H), 6.97 – 6.91 (m, 2H), 6.90 –6.85 (m, 1H), 3.84 (s, 3H), 1.38 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.99, 155.24, 134.72, 133.81, 129.72, 129.18, 125.98, 125.21 (q, J = 270.6 Hz), 118.72 (q, J = 32.5 Hz), 114.94, 111.15, 84.44, 55.78, 25.12; FTMS (ESI) *m*/*z* [M+H]+, calc'd for $C_{20}H_{23}BF_3NO_3$ 394.1799; found 394.1801.

Preparation of potassium trifluoro(2-(4-methoxyphenylamino)phenyl)borate



4.7a **4.7b**

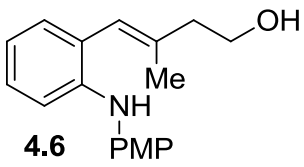
Preparation of potassium trifluoro(2-(4-methoxyphenylamino)phenyl)borate **4.7b** was performed using a literature procedure.[21] To a flask equipped with a stir bar was added *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4.7a** (1 equiv, 9.22 mmol, 3 g) and MeOH (25 mL, 0.37 M). Potassium hydrogen difluoride (5.6 equiv, 51.63 mmol, 4.03 g) in H_2O (11.25 mL, 4.5 M) was then added to the boronic ester solution and the contents were stirred for 15 minutes. The solution was then concentrated in vacuum and the resulting solid was dissolved in hot acetone. The mixture was then filtered and the filtrate was concentrated in vacuum. Recrystallization with hot acetone and diethyl ether yielded the desired trifluoroborate salt **4.7b** as a white solid (2.02 g, 73%). IR υmax (cm^{-1}) 1597, 1567, 1511, 1295, 1274, 1247, 1190, 1035, 935, 758. ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.29 – 7.21 (m, 1H), 7.02 – 6.94 (m, 2H), 6.90 (td, *J* = 4.8, 4.2, 2.7 Hz, 3H), 6.85 – 6.76 (m, 2H), 6.57 (td, *J* = 6.3, 5.1, 2.7 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 153.08, 146.89, 137.65, 132.94, 132.91, 125.98, 119.38, 117.80, 114.47, 112.24, 55.23.

General Procedure 10 (GP10): Suzuki-Miyaura Cross Coupling Reaction

To an oven-dried Schlenk flask equipped with a stir bar was added 1.1–1.5 equiv of the boronate ester **4.7a**, 2 mol % $Pd(OAc)_2$, 4 mol % RuPhos, and 3 equiv of ground K_3PO_4. The tube was then sealed with a Teflon screw cap and filled with nitrogen. Vinyl iodide **4.8** (1 equiv) and THF:EtOH:H_2O (2:1:1, degassed via Freeze-Pump-Thaw or sparged with N_2 for 30 minutes, 0.15–0.5 M) were then added to the reaction mixture and the contents were heated at 90 °C for 24 h. After completion, the reaction mixture was cooled to room temperature and the bottom

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 to afford the corresponding (*E*)-4-(2-(arylamino)phenyl)-3-methylbut-3-en-1-ol **4.6**.

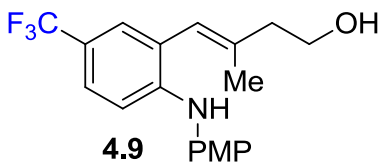
(*E*)-4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-en-1-ol. Following procedure **GP10**



4.6

with *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4.7a** (1.5 equiv, 0.33 mmol, 107 mg), (*E*)-4-iodo-3-methylbut-3-en-1-ol **4.8** (1 equiv, 0.22 mmol, 47 mg), $Pd(OAc)_2$ (2 mol %, 0.0044 mmol, 1 mg), RuPhos (4 mol %, 0.0088 mmol, 4.1 mg), and ground K_3PO_4 (3 equiv, 0.66 mmol, 140 mg) in 0.44 mL of THF:EtOH:H_2O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded **4.6** as a yellow oil (55 mg, 88%). IR υmax (cm^{-1}) 3389, 2943, 1599, 1518, 1452, 1293, 1240, 1041, 825, 751. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 – 7.08 (m, 2H), 7.08 – 7.02 (m, 3H), 6.90 – 6.80 (m, 3H), 6.26 – 6.20 (m, 1H), 5.56 (s, 1H), 3.83 (d, *J* = 6.3 Hz, 2H), 3.81 (s, 3H), 2.48 (td, *J* = 6.3, 1.1 Hz, 2H), 1.78 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.29, 142.88, 137.99, 136.17, 130.36, 127.74, 126.00, 123.75, 122.36, 119.12, 114.78, 114.42, 60.61, 55.78, 42.87, 17.66; HRMS (ESI) *m*/*z* [M+H]+, calc'd for $C_{18}H_{21}NO_2$ 284.1640; found 284.1641.

(*E*)-4-(2-(4-methoxyphenylamino)-5-(trifluoromethyl)phenyl)-3-methylbut-3-en-1-ol.

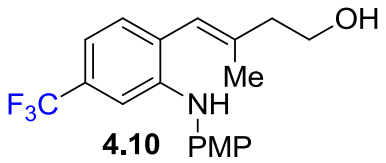


4.9

Following procedure **GP10** with *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)aniline **4.9d** (1.2 equiv, 0.41 mmol, 163 mg), (*E*)-4-iodo-3-methylbut-3-en-1-ol **4.8** (1 equiv, 0.34 mmol, 73 mg), $Pd(OAc)_2$ (2 mol %, 0.0069 mmol, 1.5 mg), RuPhos (4 mol %, 0.014 mmol, 6.4 mg), and ground K_3PO_4 (3 equiv, 1.04

mmol, 220 mg) in 2 mL of THF:EtOH:H_2O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded **4.9** as a brown oil (115 mg, 96%). IR υmax (cm^{-1}) 3373, 2940, 1612, 1516, 1330, 1111, 1075, 1038, 912, 826. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.28 (m, 2H), 7.17 – 7.06 (m, 2H), 6.98 (dd, *J* = 9.3, 0.8 Hz, 1H), 6.94 – 6.85 (m, 2H), 6.19 (s, 1H), 5.91 (s, 1H), 3.86 (t, *J* = 6.2 Hz, 2H), 3.82 (s, 3H), 2.50 (td, *J* = 6.3, 1.1 Hz, 2H), 1.77 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.51, 146.36, 140.12, 134.24, 127.23, 125.12 (q, *J* = 270.7 Hz), 124.96, 124.52, 124.46, 122.32, 119.95, 119.83 (q, *J* = 32.5 Hz), 119.63, 114.95, 111.92, 60.52, 55.76, 42.64, 17.64; FTMS (ESI) *m*/*z* [M+H]+, calc'd for $C_{19}H_{20}F_3NO_2$ 352.1519; found 352.1521.

(*E*)-4-(2-(4-methoxyphenylamino)-4-(trifluoromethyl)phenyl)-3-methylbut-3-en-1-ol.

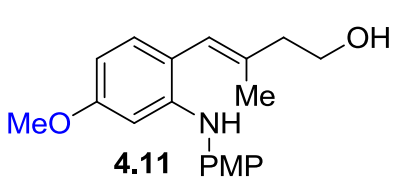


4.10

Following procedure **GP10** with *N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)aniline **4.10f** (1.2 equiv, 0.51 mmol, 200 mg), (*E*)-4-iodo-3-methylbut-3-en-1-ol **4.8** (1 equiv, 0.42 mmol, 89 mg), $Pd(OAc)_2$ (2 mol %, 0.008 mmol, 2 mg), RuPhos (4 mol %, 0.017 mmol, 8 mg), and ground K_3PO_4 (3 equiv, 1.27 mmol, 270 mg) in 2 mL of THF:EtOH:H_2O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded **4.10** as an orange–brown oil (122 mg, 83%). IR υmax (cm^{-1}) 3388, 2939, 2840, 1575, 1513, 1434, 1338, 1245, 1121, 830. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.22 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.17 (dt, *J* = 7.9, 0.9 Hz, 1H), 7.13 – 7.04 (m, 2H), 7.04 – 6.98 (m, 1H), 6.95 – 6.85 (m, 2H), 6.20 (d, *J* = 1.8 Hz, 1H), 5.77 (s, 1H), 3.85 (t, *J* = 6.3 Hz, 2H), 3.82 (s, 3H), 2.50 (td, *J* = 6.3, 1.1 Hz, 2H), 1.77 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.16, 143.72, 139.93, 134.71, 130.54, 129.92 (q, *J* = 31.9 Hz), 128.53, 124.53 (q, *J* =

272.2 Hz), 123.59, 122.53, 115.04, 115.00, 114.93, 109.59, 60.50, 55.76, 42.71, 17.69; FTMS (ESI) *m*/*z* [M+H]+, calc'd for $C_{19}H_{20}F_3NO_2$ 352.1519; found 352.1521.

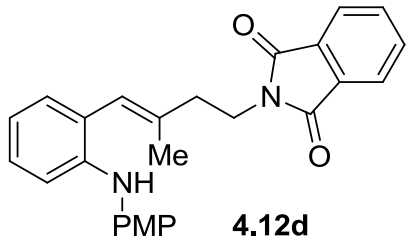
(*E*)-4-(4-methoxy-2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-en-1-ol. Following



4.11

procedure **GP10** with 5-methoxy-*N*-(4-methoxyphenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4.11f** (1.1 equiv, 0.51 mmol, 180 mg), (*E*)-4-iodo-3-methylbut-3-en-1-ol **4.8** (1 equiv, 0.46 mmol, 98 mg), $Pd(OAc)_2$ (2 mol %, 0.0092 mmol, 2.1 mg), RuPhos (4 mol %, 0.0184 mmol, 8.6 mg), and ground K_3PO_4 (3 equiv, 1.38 mmol, 293 mg) in 2 mL of THF:EtOH:H_2O (2:1:1). Purification by flash chromatography on silica gel (70:30 hexanes:EtOAc) afforded **4.11** as an orange–brown oil (112 mg, 78%). IR υmax (cm^{-1}) 3379, 2946, 2839, 1607, 1515, 1445, 1291, 1168, 1041, 828. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 7.05 (m, 2H), 7.02 (dt, *J* = 8.4, 0.7 Hz, 1H), 6.91 – 6.82 (m, 2H), 6.62 (d, *J* = 2.5 Hz, 1H), 6.39 (dd, *J* = 8.3, 2.6 Hz, 1H), 6.17 (s, 1H), 3.83 – 3.78 (m, 5H), 3.74 (d, *J* = 0.7 Hz, 3H), 2.51 – 2.41 (m, 2H), 1.79 – 1.74 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.55, 155.53, 144.19, 137.48, 135.66, 131.03, 123.27, 122.96, 118.53, 114.80, 104.06, 100.14, 60.61, 55.74, 55.33, 42.88, 17.63; FTMS (ESI) *m*/*z* [M+H]+, calc'd for $C_{19}H_{23}NO_3$ 314.1751; found 314.1752.

(*E*)-2-(4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-enyl)isoindoline-1,3-dione. The

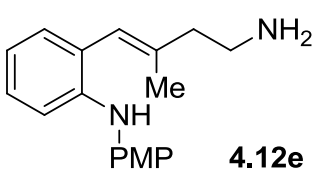


4.12d

preparation of **4.12d** was accomplished using a literature procedure.[22] To an oven–dried flask equipped with a stir bar was added triphenylphosphine (2.4 equiv, 2.19 mmol, 573 mg) and anhydrous THF (2.0 mL) under N_2 atmosphere. The contents were stirred at 0 °C for 10 minutes prior to the dropwise addition of DIAD (2 equiv, 1.82 mmol, 0.353 mL). After stirring for 1 hour at the same temperature, a separate solution

containing (*E*)-4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-en-1-ol **4.6** (1 equiv, 0.91 mmol, 258 mg) and phthalimide (1.5 equiv, 1.4 mmol, 201 mg) in THF (2 mL) was added dropwise over 10 minutes. After stirring at 0 °C for 1 hour, the ice bath was removed and the solution was stirred at room temperature for 7 hours. Once complete, the solution was concentrated in vacuum and purified by flash chromatography on silica gel (80:20 hexanes:EtOAc) to afford the corresponding (*E*)-styrylisoindoline-1,3-dione **4.12d** as a yellow oil (320 mg, 85%). IR υmax (cm^{-1}) 3386, 2942, 1769, 1709, 1511, 1447, 1395, 1240, 1031, 719. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.83 – 7.72 (m, 2H), 7.71 – 7.62 (m, 2H), 7.00 (dd, *J* = 20.3, 8.6 Hz, 6H), 6.90 – 6.67 (m, 3H), 6.09 (d, *J* = 2.2 Hz, 1H), 4.00 – 3.88 (m, 2H), 3.82 (s, 3H), 2.59 (t, *J* = 6.3 Hz, 2H), 1.90 – 1.77 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.70, 155.44, 143.14, 138.15, 135.85, 134.14, 132.08, 130.39, 127.68, 125.24, 124.02, 123.44, 123.11, 118.75, 114.67, 113.74, 55.77, 38.85, 36.81, 17.99; HRMS (ESI) *m*/*z* [M+H]+, calc'd for $C_{26}H_{24}N_2O_3$ 413.1860; found 413.1866.

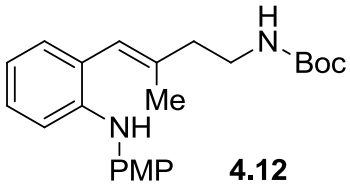
(*E*)-*tert*-butyl 4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-enylcarbamate.



4.12e

Preparation of **4.12** was achieved using a literature procedure.[22] To an oven–dried flask equipped with a stir bar were added (*E*)-2-(4-(2-(4-methoxyphenylamino)phenyl)-3-methylbut-3-enyl)isoindoline-1,3-dione (1 equiv, 0.78 mmol, 320 mg) and EtOH (14 mL). Hydrazine hydrate (1.4 equiv, 1.1 mmol, 54 μL) 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, 7.8 mmol, 0.7 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 (5 mL), and

basified to pH 13 using 10 M NaOH. The aqueous solution was then extracted with DCM (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum to give the intermediate styrylamine as a brown oil, which was taken to the next step without purification.



4.12

The resulting styrylamine (1 equiv, 0.53 mmol, 150 mg), DMAP (10 mol %, 0.053 mmol, 6.5 mg) and anhydrous DCM (0.60 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 di-*tert*-butyl dicarbonate (1.1 equiv, 0.58 mmol, 128 mg) in anhydrous DCM (0.5 mL) over 10 minutes. 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 **4.12** as a clear oil (137 mg, 46%over 2 steps). IR υmax (cm^{-1}) 3389, 2985, 1705, 1602, 1511, 1450, 1265, 1174, 1037, 755. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.02 (m, 5H), 6.90 – 6.84 (m, 2H), 6.84 – 6.77 (m, 1H), 6.20 (s, 1H), 5.53 (s, 1H), 4.60 (s, 1H), 3.81 (s, 3H), 3.36 (q, *J* = 6.6 Hz, 2H), 2.39 (t, *J* = 6.6 Hz, 2H), 1.78 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.21, 155.38, 143.02, 138.68, 136.07, 130.49, 127.73, 125.69, 123.20, 122.69, 118.99, 114.80, 114.24, 79.50, 55.79, 40.29, 39.01, 28.60, 17.88; FTMS (ESI) *m*/*z* [M+H]+, calc'd for $C_{23}H_{30}N_2O_3$ 383.2329; found 383.2328.

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