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Sequential Growth of Molecular Complexity via Alternating Ground State and Photochemical Reactions

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A new strategy of increasing molecular complexity by post photochemical oxidation followed by secondary intramolecular photochemical reaction is developed. It is based on the mild oxidation of photochemical generated alcohol by primary intramolecular cycloaddition of aromatic *o*-aminoaldehydes and a secondary intramolecular cycloaddition of aromatic *o*-aminoketone. Both cycloadditions are triggered via excited-state intramolecular proton transfer (ESIPT). Additionally, an efficient continuous reaction of photocatalyzed 2−nitrobenzyl alcohol intramolecular reduction and aryl nitroso Diels-Alder (NDA) reaction was discovered.

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List of Abbreviations and Acronyms

Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
cat.	catalyst(or catalytic amount)
DCM	dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMP	Dess–Martin periodinane
eq.	equivalent
ESIPT	excited-state intramolecular proton transfer
Et	ethyl
EtOAc	ethyl acetate
EWG	electron withdrawing group
FMO	frontier molecular orbital
HPLC	High-Resolution Liquid Chromatography
HOMO	Highest occupied molecular orbital
hv	light
ISC	Intersystem crossing
IC	Internal Conversion

LUMO	Lowest Occupied Molecular Orbital
LED	Light-emitting Diode
Me	Methyl
NMR	Nuclear Magnetic Resonance
NDA	Nitroso Diels-Alder
Ph	Phenyl
PCC	pyridinium chlorochromate
i-Pr	iso-propyl
sat.	saturated
SOMO	singly-occupied molecular orbitals
THF	tetrahydrofuran
TIPSCl	triisopropylsilyl chloride
TMSCl	trimethylsilyl chloride
TBAF	tetra-n-butylammonium fluoride
VR	Vibrational Relaxation

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Chapter 1: Literature Review

1.1 Features of Photochemistry

Photochemical reactions are defined as chemical reactions caused by absorption of ultraviolet, visible, or infrared radiation within a part of the substrate, that is, its chromophore.[1] The substrate is excited from a ground state to an excited state with a higher energy level, which changes the electronic configuration and the reactivity. So compared to general methods, photochemical reactions can easily produce thermodynamically forbidden products such as some stereo structures and small rings. Additionally, photochemical reactions have several features as follows[2-6]:

1. The reaction can be controlled by a definite wavelength because the different chromophores have a specific range of wavelength absorption.
2. The reaction can be triggered directly by irradiation or catalyzed by other substrates, such as organometallic catalysts.
3. A protection group is not necessary for photochemical reaction.
4. Energy input can be controlled by wavelength and the power of the lamp.
5. The light is traceless and renewable.
6. Most photoreactions can be safely stopped by turning off the light source.

Different than these advantages, photochemical reactions also have some drawbacks based on the limitation of the available technology:

1. Strong irradiation is hazardous to human bodies as well as reactor materials. The maintenance of these reactors is expensive.

2. Long time irradiation with powerful right source may cause temperature increase; therefore, cooling equipment is necessary.

3. Artificial light sources must be replaced frequently due to the limited lifetime, which increases the costs.

4. To get the best yields, different photochemical reactions entail different hazardous organic solvents, which are toxic.

5. Over irradiation may degrade unstable products, also lowering yields.

6. Some photochemical reactions suffer poor quantum efficiencies due to dominant photophysical deactivation pathways.

1.2 Photoinduced Reactions

Photochemical substrates can only absorb a photon in a certain range of the wavelength, causing an excitation of molecules from the ground state (S_0) to the excited state (S_n). As the photoprecursor gets excited, the excited state energy can trigger chemical reactions, such as: cycloadditions, rearrangements, cyclizations or electron transfer.

1.2.1 Photochemical Electron Transfer

In the ground state, the highest occupied molecular orbital (HOMO) of the donor is occupied by a paired of electrons. During irradiation, the donor or acceptor is excited and one electron is promoted from the HOMO to the lowest unoccupied molecular orbital

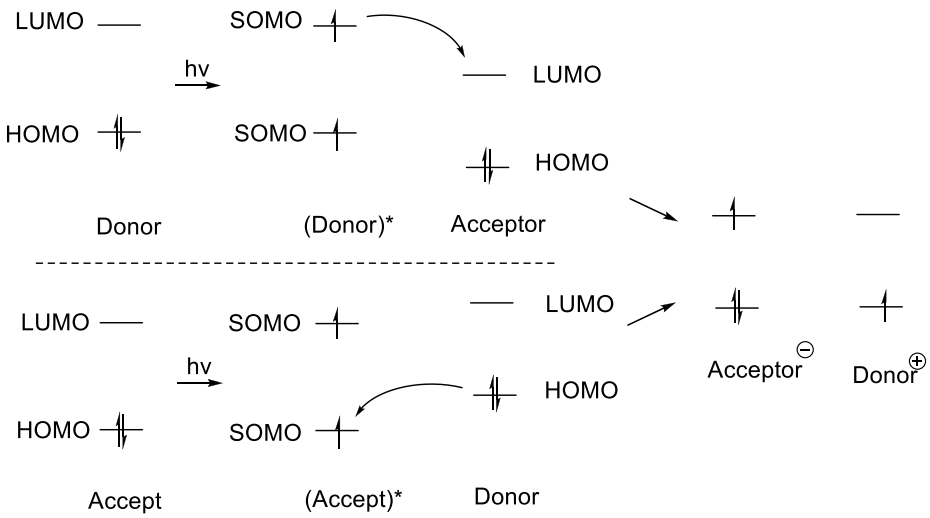


Figure 1.1 Frontier orbital theory(FMO) of photochemical electron transfer

LUMO. Both HOMO and LUMO become singly-occupied molecular orbitals (SOMO). Therefore, electron transfer can exothermically occur when the electron of the excited donor jumps from higher SOMO into the empty LUMO orbital of acceptor or the electron of HOMO is transferred into the half occupied SOMO orbital of the excited acceptor[7] (Figure 1.1).

The Rehm-Weller equation can be used to define the free enthalpy (∆G) of the process.[8]

$$\Delta G = E(D^+/D) - E(A/A^-) - \Delta G_{00} - \frac{e^2}{\varepsilon d}$$

$E(D^+/D)$ is the reduction potential that describes the process: $D_P^+ + e \rightarrow D$;

$E(A/A^-)$ is the reduction potential of the process: $A_P + e \rightarrow A_P^-$;

ΔG_{00} is the energy of the $S_0 \rightarrow S_1$ transition of the fluorophore;

$\frac{e^2}{\varepsilon d}$ is the coulombic attraction. ε is the dielectric constant of the solvent, and d is the distance between charges.

1.2.2 Rearrangements

Photoinduced rearrangement is an old topic of interest. There have been reports of various compounds undergoing photoinduced rearrangements. An important rearrangement called the "Curtius rearrangement" was first discovered by Theodor Curtius in 1885 (Figure 1.2). The rearrangement was reported under heating and descripted as a two-step reaction, releasing nitrogen gas by forming nitrene, followed by the formation of isocyanate with R-group migration.[9] However, the following theoretical

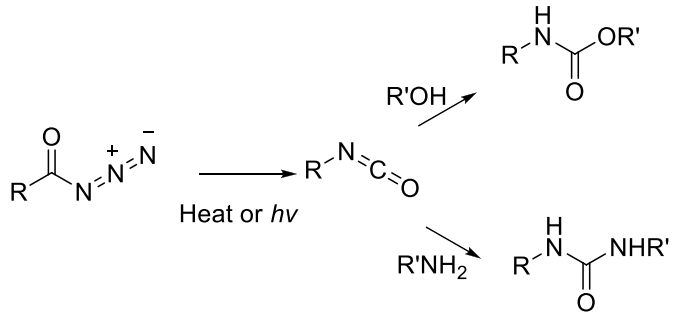


Figure 1.2 Curtius rearrangement of acyl azide

study of Arvi Rauk and Paul F. Alewood in 1976 indicated that the two steps reaction happened at the same time by failed to observe the nitrene trapping products[10]. The rearrangement cannot only be triggered by heating, but also, it was reported to obtain phenyl isocyanate as the main product as well as phenyl cyanate as byproduct through the irradiation of benzoyl azide.[11]

1.2.3 Cyclization

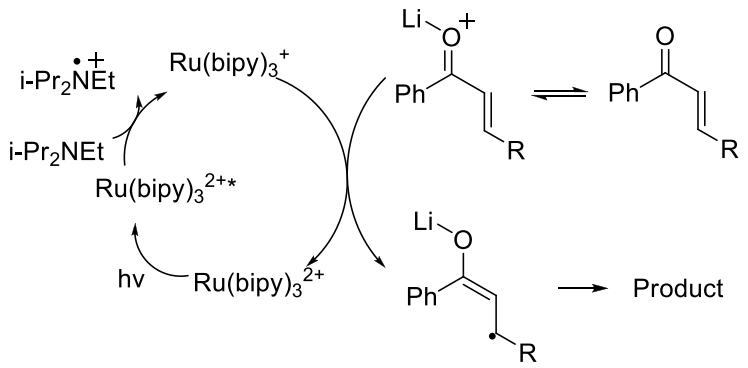


Figure 1.3 Purposed mechanism of Ru catalyzed cycloaddition

Photoinduced cyclization is widely used in organic synthesis and new methods have been discovered frequently in recent years. The molecules, triggered to excited states followed by intramolecular cyclization, will form specific isomers, which cannot be obtained by a general synthesis method.

$Ru(bipy)_3^{2+}$ was reported as a popular reagent to serve as the photocatalyst for intramolecular [2+2], [3+2] and [4+2] cycloaddition involving radical anion and cation intermediates, which has been well studied. In 2008, Yoon and coworkers reported a

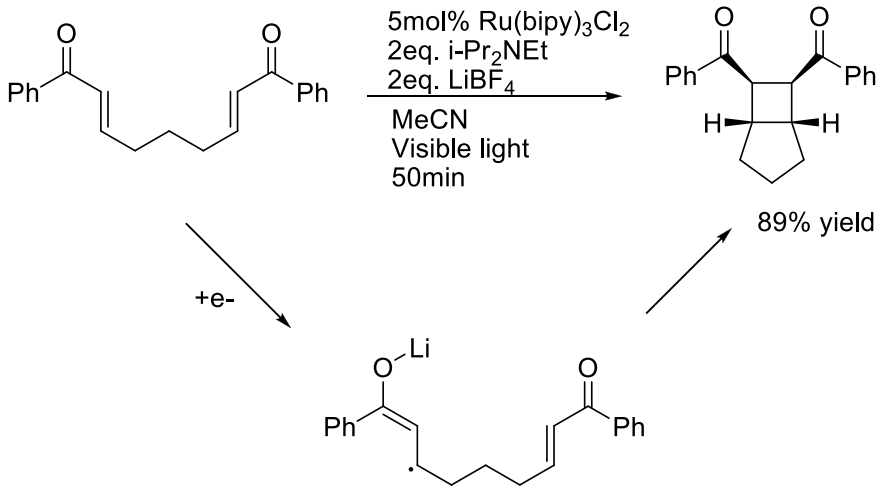


Figure 1.4 Ru catalyzed [2+2] photoinduced intramolecular cycloaddition

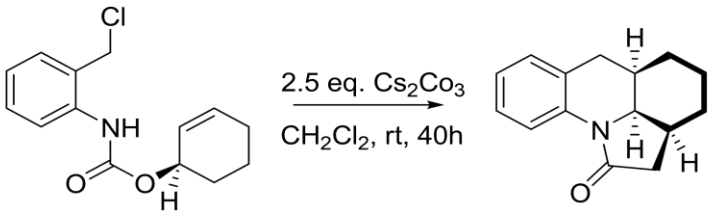
ruthenium catalyzed [2+2] enone cycloadditions by visible light.[12] Irradiation of $Ru(bipy)_3^{2+}$ with visble light(λ_{max}=452nm) produced a photo excited state ($Ru(bipy)_3^{2+*}$) which had a long lifetime (about 600 ns) and effective photoredox catalyst (Figure 1.3). Then it underwent reductive quenching by oxidation of *i*-Pr_2NEt and the generated $Ru(bipy)_3^{+}$ complex was a strong reductive reagent that could transfer an electron to the lithium activated enone. The activated bis(enones) could give a [2+2] intramolecular cycloaddition product with high yield and diastereoselectivity. For example, in Figure 1.4, cis-dione was obtained with 89% yield.

Chapter 2: Photogenerated Azaxylylene Intramolecular Cycloaddition

2.1 Introduction

2.1.1 Ground State and Excited State Cycloaddition

Azaxylylenes were first reported by Gerald Smolinsky in 1961, but their synthetic utilities as short life excited states were not fully reported. In 1999, Henning Steinhagen and E.J Corey described a convenient method to generate *o*-azaxylylenes.[13] The reaction was first triggered by base-induced elimination of hydrogen chloride of amide derivatives **1**, which generates *o*-azaxylylenes. The *o*-azaxylylenes were then trapped by alkene and gave [4+2] intermolecular and intramolecular Diels-Alder cycloaddition products (Figure



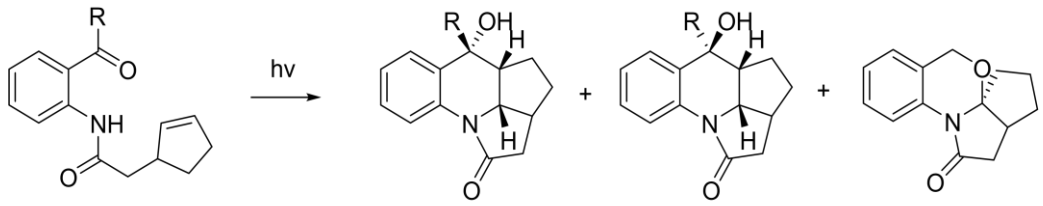
1 **2** 76%

Figure 2.1 Ground state azaxylylenes cycloaddition reaction

2.1).[14] For the intramolecular version to synthesize hydroquinolines, the reactions happened in DCM with 2.5 equivalent of Cs_2CO_3 or NaOH for 40 hours and finally gave the syn cycloaddition product with 76% of yield. Even if it was carried out in a mild

condition, the reaction commonly took more than one day, followed by the cycloaddition to form **2**.

In contrast, our group has discovered the intramolecular cycloaddition with unsaturated pendants functionalities by photo generated *o*-azaxylyenes. The reactions were efficiently carried out by 365 nm irradiation in a mild condition and the products were mostly very clean.



3 **4** **5**

Figure 2.2 Excited state azaxylylenes cycloaddition reaction

Specifically, in 2011, Olga Mukhina reported similar [4+2] cycloaddition reactions which were accelerated at elevated temperatures (Figure 2.2).[15] The acetophenone derivatives photoprecursor (R=Me) was heated to reflux and irradiated within 3 hours. The irradiation showed remarkable diastereoselectivity which also gave 3:1 ratio of **3** and **4** and a minor aminal photoproduct **5** was obtained which might be generated from the intramolecular radical disproportionation with subsequent addition of benzylic alcohol to the formed *N*-acyl enamine. Additionally, reactions with aldehyde photoprecursors (R=H) could happen in a mild or low temperature.

Compared with the two reported methods of generating azaxylylenes discussed above, photo cycloaddition reactions with photogenerated azaxylyenes have three

advantages: mostly undergoing under a mild condition with high efficiency; having excellent stereoselectivity; directly producing photoproduct without any other reagents.

2.1.2 Excited States Process

Before discussing the mechanism of photocycloaddition reaction of photogenerated azaxylylenes, it is important to know the principal pathways which could happen in photochemical events. An excellent approach to understand excited state processes is through the Jablonski diagram which was proposed by Alexander Jablonski in the 1930s (Figure 2.3). While absorbing a photon, the molecule is excited from ground state (S_0) to an electronic excited state (S_n). After internal conversion(IC) and vibrational relaxation (VR), most excited state molecules will be back to S_1 singlet excited state. From the S_1 singlet excited state, the excited molecule may reverse to the ground state (S_0) by emitting a lower energy photon, known as fluorescence and the second pathway

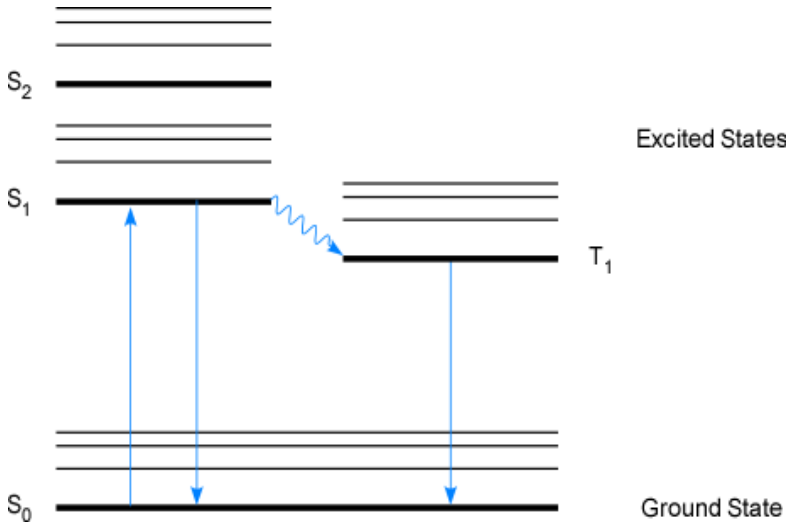
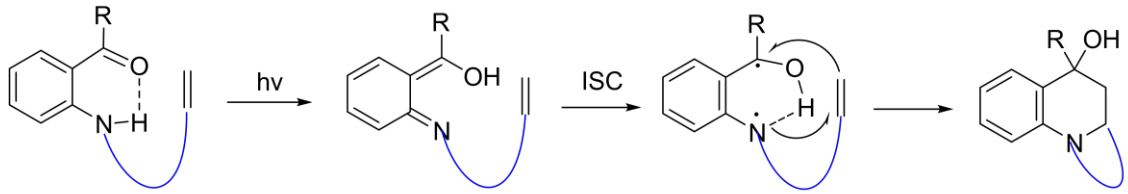


Figure 2.3 Jablonski diagram[17]

can transfer it to a triplet excited state (T_1) by intersystem crossing (ISC). The relaxation of triplet excited state will cause phosphorescence.[16]

2.1.3 Intramolecular Cycloaddition of Photogenerated Azaxylylenes

In the ground state, in aromatic *o*-aminoaldehydes and aromatic *o*-aminoketones **6** (R=H, Me), due to the hydrogen bond, the oxygen of the carbonyl group is toward the nitrogen of amide. Therefore, when they are irradiated (λ=365nm), the ground state molecules are excited to the singlet excited state **7** (S_n) by excited-state proton transfer (ESIPT) and converted to the triplet excited state **8** by ISC.[18] Additionally, in triplet excited state **8**, the hydrogen bond between oxygen and nitrogen still exists and it causes a high energy barrier of the rotation of carbonyl bond.



6 **7** **8** **9**

Figure 2.4 Excited state azaxylylenes cycloaddition reaction

Then the photogenerated azaxylylenes are trapped by unsaturated pendants unsaturated group such alkene, phenyl and *N, O, S*-heterocycles and therefore form [4+2] and [4+4] photocyclization products **9**.[15,19,20]

The photocycloaddition reactions with tethered furan were very reactive, which gave both [4+2] and [4+4] cycloproducts. However, the [4+2] products were not very stable and might decompose by over irradiation, and therefore, monitoring the irradiation

process was necessary. In addition, the [4+2] cycloproducts could not survive by the oxidation of PCC, but some of them could be oxidized by milder oxidizing reagent such as DMP from alcohols to ketones.

In contrast, the irradiation of thiophene derivatives and *N*-tethered pyrroles generate [4+2] cycloproducts.

2.1.4 Stereochemistry Studies

Diastereoselectivity was observed in the cycloproducts. For the syn/anti configuration of the hydroxy group to the heteroatom-containingbridge, [4+2] cycloproducts were anti diastereomer and the [4+4] cycloproducts were syn diastereomer.

The accurate mechanism of these diastereomers distributions was still unclear. This was because of the rotatable carbonyl bond of triplet excited state, which gave two reasonable mechanisms. Our assumption was the polarity of solvent also influenced the stereostructure of photoproducts.[15] For example, when triplet excited state formed by the irradiation of **10**, triplet azaxylylenes were formed. Due to the existence of hydrogen bond, the rotation of carbonyl bond was constrained and the reaction preferred to go through **12→13→14** (Figure 2.5). However, polar solvents such as DMSO could speed up the rotation of carbonyl group by forming a hydrogen bond between solvent and the alcohol to give **15**. It could also go through the pathway **12→15→16** and gave the same product. Until now, we did not know to what extent, the solvent effect could control the preference of the isomers, and no evidence could show which pathway(s) the photo reaction exactly goes through.

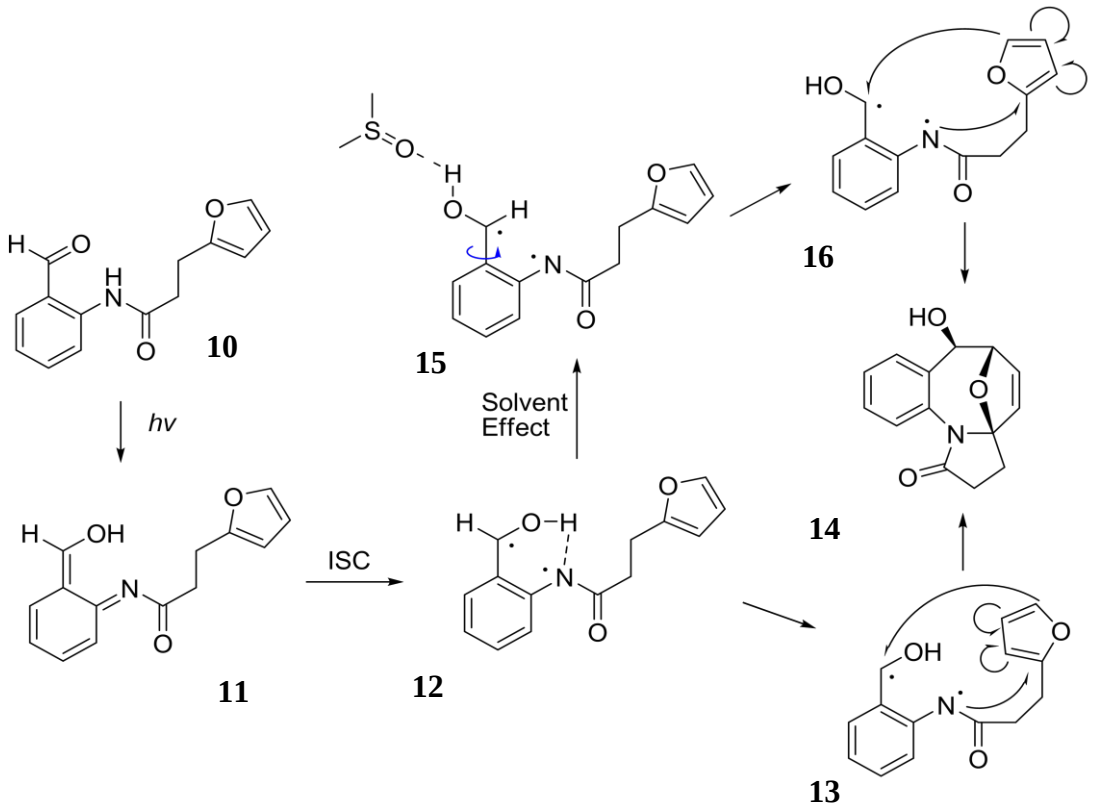


Figure 2.5. Two proposed mechanisms to form [4+4] product.

However, the irradiation of amidotetralone-based photoprecursors could give a reasonable pathway (Figure 2.6). Due to the non-rotatable carbonyl group, exo-alcohol could not be formed, and therefore only the pathway **18→19→20** could be achieved.[15]

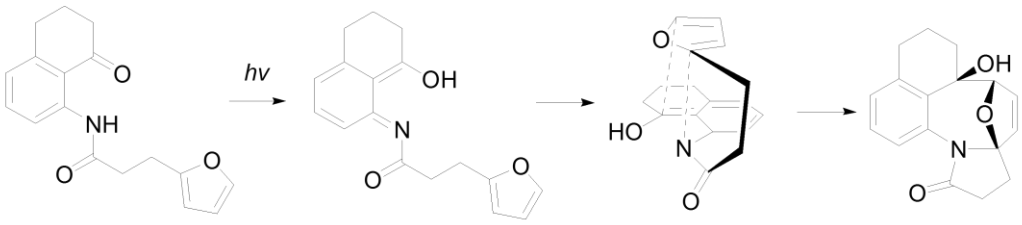
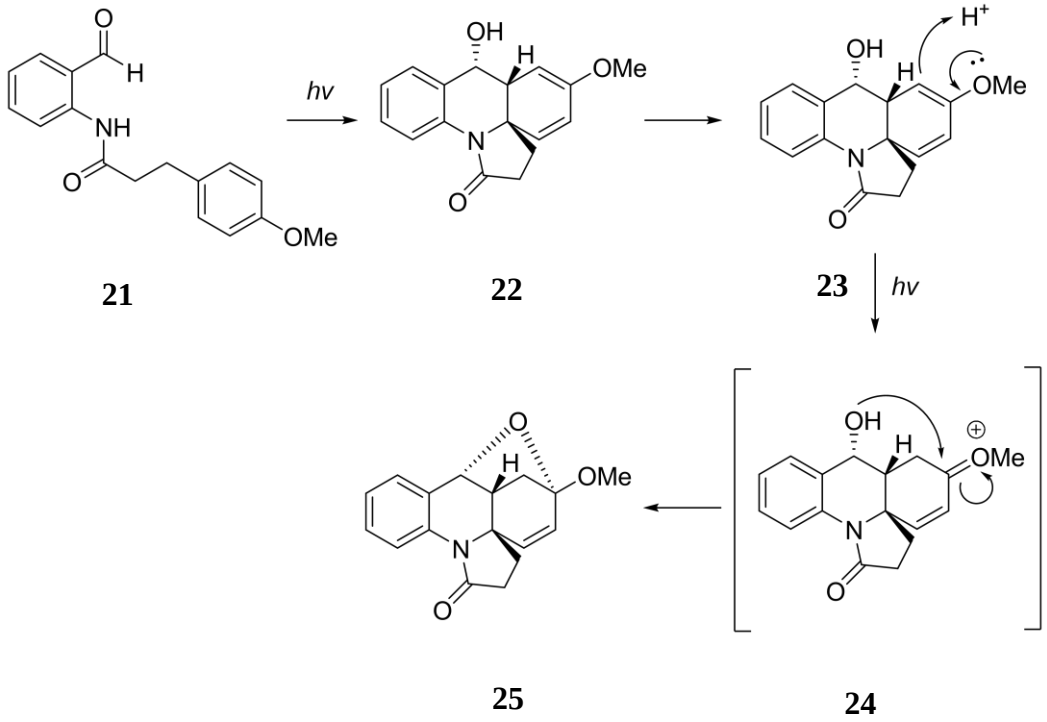


Figure 2.6 [4+4] photoproduct formation of amidotetralone-based photoprecursors

Intramolecular cycloaddition reactions of arenes were also reported by our group in 2016.[21] Compared with photocycloaddition reactions with furan, the arenes were less reactive and only [4+2] photo products, for example **22** in Figure 2.6, could be obtained. For aldehyde-based photoprecursors, the irradiation would form syn-diastereomers of the relative position of alcohol and cyclohexadiene. In contrast, for the amidotetralone-based photoprecursors, the irradiation would give anti-diastereomers.



21 **22** **23** **24** **25**

Figure 2.7 Rearrangement of methoxyl substituted arenes photoprecursor

In most cases, as an electron donor, the unsubstituted arenes or electron withdrawing group, such as NO_2 and CN substituted arenes, were less reactive to trigger these reactions to form cyclohexadiene-fused heterocyclic products. Therefore, to increase the reactivity, we generally studied the photoprecursors in which arenes had methoxy substituent, such as **21**. However, in several cases, it would cause rearrangement

to form ketal during the irradiation or post-modification process. The proposed mechanism was going through the intermediate **24** (Figure 2.7).[21]

2.2 Diversity-oriented and Complex Increase Strategy

One of the advantages of photocatalyzed azaxylylenes cycloaddition is that the reaction sequence rapidly can increase the complexity in a few simple steps. Additionally, the complexity of photoproducts also can be enhanced by using different post-photochemical modification steps which is congruent with diversity-oriented synthesis.

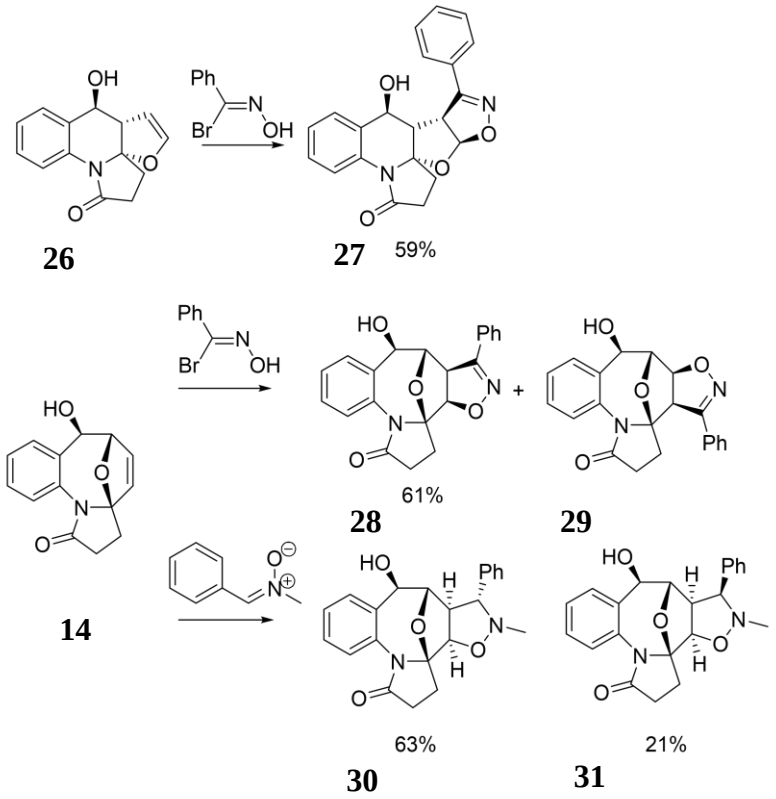


Figure 2.8 Reactions with 1,3-dipoles

2.2.1 Reaction with 1,3-dipoles

The residual alkene of photoproducts, which come from furan, thiophene tethered photoprorecursors, is still very reactive and it could cause cycloaddition with dipoles or dienes. In 2015, Weston J. reported the syn-**14** and anti-**26** can react with benzonitrile oxide or bromonitrile oxide from the exo-face (Figure 2.8). The [4+4] photoproduct **14** underwent an exo-preferred cycloaddition and generate two regioisomers **28** and **29** with the ratio 3:1. However, the [4+2] photoproduct **26** went through a charge-controlled pathway and only **27** was observed with the 59% yield.[22]

2.2.2 Hetero Diels-Alder reactions

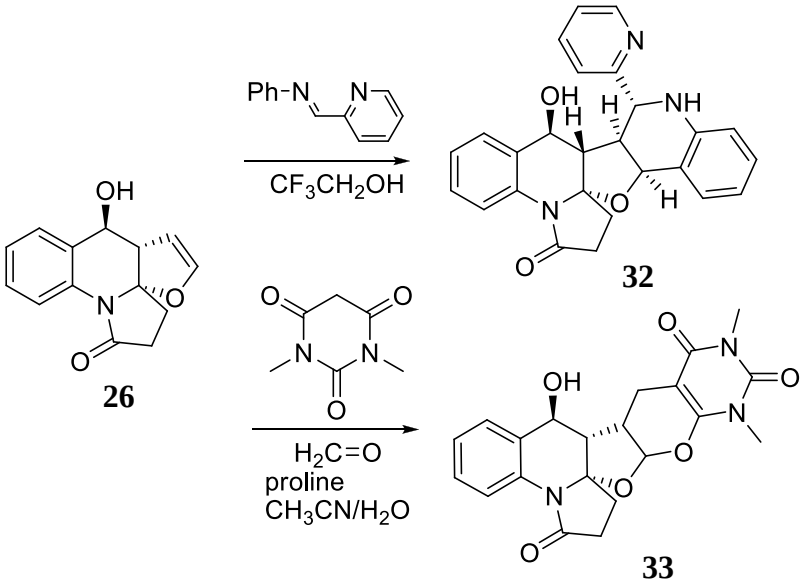


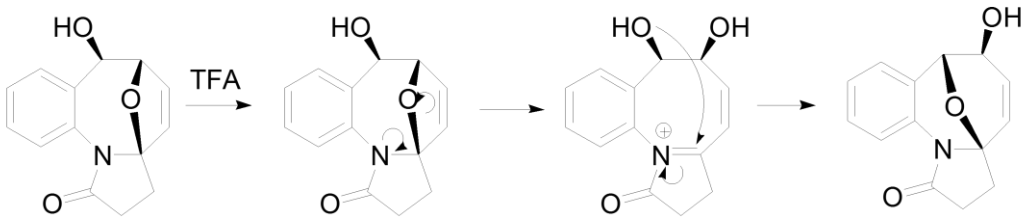
Figure 2.9 Povarov and the oxa-Diels-Alder reactions of [4+2] photoproduct

Different from the [4+4] photoproduct **14**, furan-, thiophene- and pyrrole-based [4+2] photoproducts **26** could cause the Povarov and the oxa-Diels-Alder reactions. These photoproducts could both react with 2-azadienes in 2,2,2-trifluoroethanol to form

32 and Meldrum's acid with the presence of oxymethylene and proline to form **33**. The reactions could only happen at the less hindered exo-face. [22]

2.2.3 Rearrangement

The residual alkene of the [4+4] photoproduct **14** has less reactivity. However, it promotes the rearrangement of photogenerated alcohol by the ring-opening and reclosing mechanism (Figure 2.10). Based on the stability of different [4+4] photoproducts, the reaction condition of these reactions varies. It can be triggered by the presence of acid such as TFA, heated in DMSO, oxidized by strong oxidizing agent such as PCC, or catalyzed by silica.[22, 23]



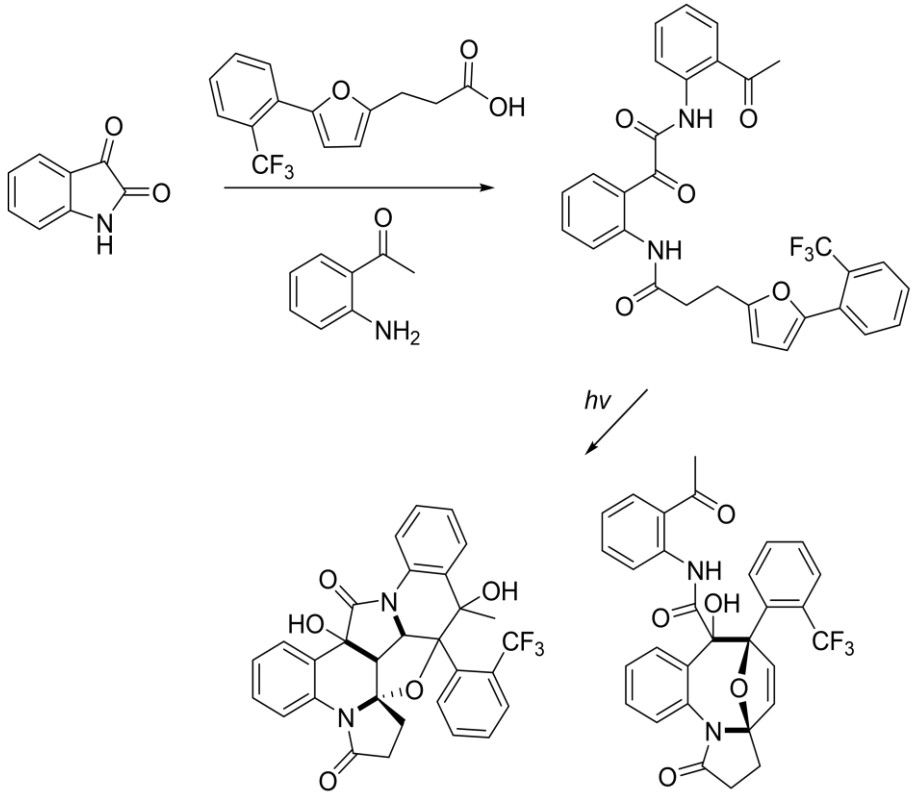
14 **34**

Figure 2.10 Rearrangement of [4+4] photoproduct

2.2.4 Photoinduced "Double click" Cycloaddition

In 2016, William C. designed a photoinduced "double click" cycloaddition for accessing accessing complex *N*, *O*-polyheterocycles by ESIPT of *o*-acylanilides.[24] The photoprecursors were synthesized by acylating isatin and furanpropanoic acids followed by the reaction with aromatic *o*-aminoketones, amino tetralone or acetophenone(Figure 2.11). The photoprecursors were exposed to 365nm irradiation and both [4+2] and [4+4]

photoproducts were obtained. The remaining alkenes of dihydrofuran in [4+2] photoproducts, which was still a reactive photoactive core, produced secondary photoproducts “double click” cycloaddition **35**. However, the residual double bond in [4+4] photoproduct **36** was less reactive and no further cycloaddition reaction occurred.



35 **36**

Figure 2.11 “Double click” cycloaddition

2.3 Discussion

Even though several strategies of post-photochemical modification have been applied by our group, a secondary intramolecular photocycloaddition based on the photoproduct of primary photocycloaddition was never studied. I studied a new strategy that broadened the diversity of post photochemical modification (Figure 2.12): by oxidizing the photoreaction generated secondary alcohol, a designed aromatic *o*-aminoketone photoprecursor was obtained and it could be irradiated to give secondary

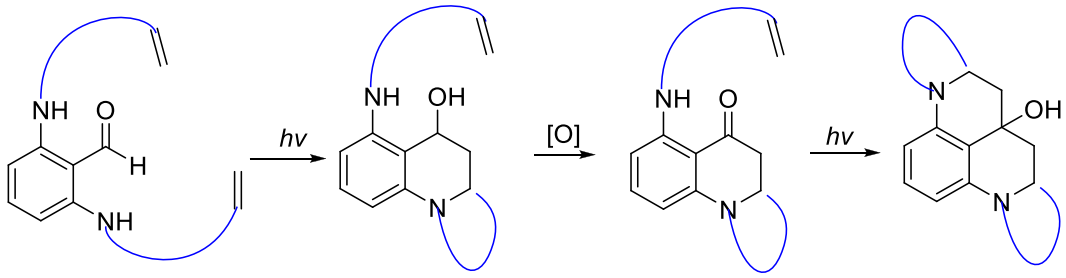
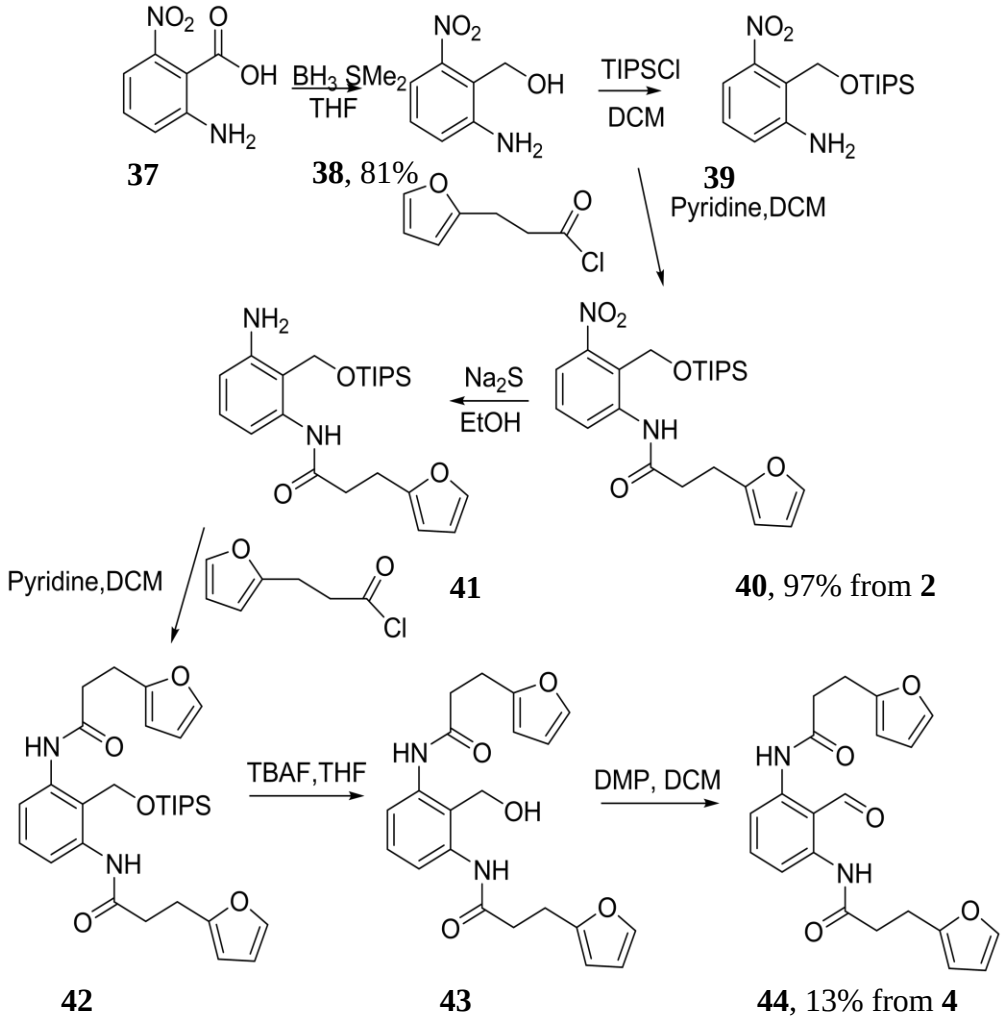


Figure 2.12 A secondary irradiation based on the primary irradiation product photoproducts.

2.3.1 Primary Photoprecursor Synthesis Pathway

N, *N*'-(2-formyl-1,3-phenylene) bis(3-(furan-2-yl) propanamide) was synthesized from 2-amino-6-nitrobenzoic acid **37** (Figure 2.13).

37 was reduced from carboxylic acid to alcohol **38** by borane dimethyl sulfate by refluxing in THF with 81% yield. Four equivalents of $LiAlH_4$ was used to reduce both carboxylic acid and nitro groups of **37** at the same time at room temperature. However, by monitoring the reaction mixture, the reaction was slow and nitro group is not reduced.



37 **38**, 81% **39** **40**, 97% from **2**

41

42 **43** **44**, 13% from **4**

Figure 2.13 Synthesis process of primary photoprecursor

This might be because the presence of amine. Additionally, the reaction with $LiAlH_4$ only gave 28% yield and the unreacted acid **37** was difficult to recycle because it would go to aqueous phase by quenching with water and NaOH solution.

The alcohol of **38** was protected by reacting with TIPSCl and imidazole, and then the amine was coupled with 3-(furan-2-yl) propanoyl chloride which was prepared from 3-(furan-2-yl) propanoic acid to get **40**. These two steps gave an excellent yield.

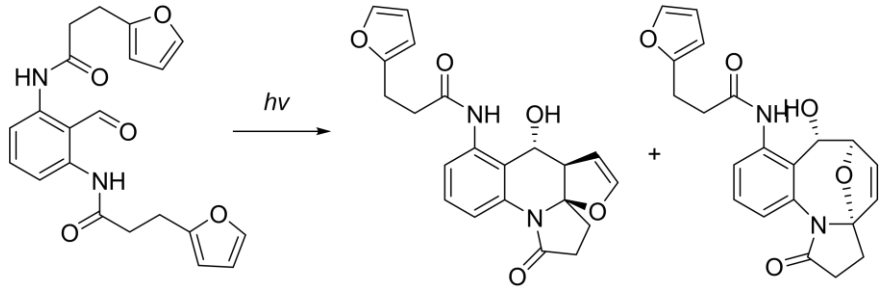
The nitro group of **40** was reduced to amine of **41** by Na_2S under the reflux condition and further purification was not necessary. $SnCl_2$ was also used to reduce the nitro group. However, the product was difficult to separate from reaction sediment during work up, which lowered the yield.

After that, the product was coupled with another 3-(furan-2-yl) propanoyl chloride. Notably, different from the other coupling reaction from **39** to **40**, the ratio of **41** to acid chloride of the coupling reaction to synthesize **42** needs to be strictly controlled to 1:1. Overloading of acid chloride would cause that both amine hydrogens of **41** were replaced.

The silyl ether was removed by TBAF to obtain **43** and it was oxidized to aldehyde by PCC or DMP in DCM to get **44**.

2.3.2 Photocatalyzed Intramolecular Cycloaddition

The photoprecursor was irradiated under 365nm LEDs in DCM and gave both intramolecular anti-[4+2] **45** and syn-[4+4] **46** cycloaddition products with the ratio 2: 1 (Figure 2.14 Methanol and DMSO also be used as solvent, but there was no great



44 **45**, 31% **46,** 18%

Figure 2.14 Primary irradiation

difference compared to DCM. [4+2] photoproduct **45** was treated with DMP and the alcohol was oxidized to ketone(Figure 2.15) Then it was irradiated under 365nm LEDs

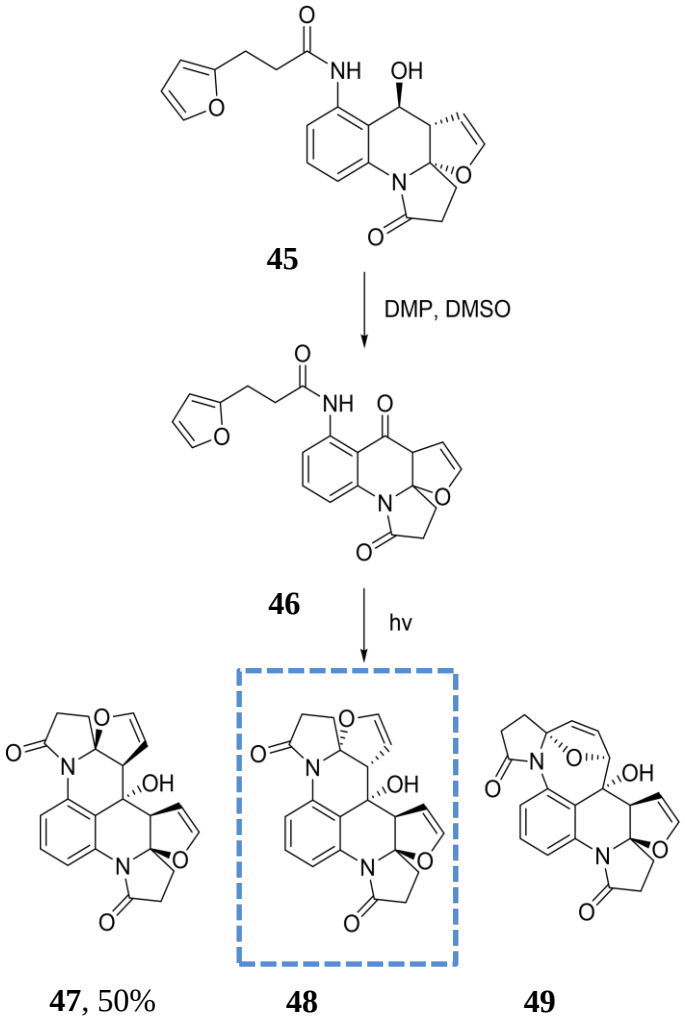


Figure 2.15 Oxidation of primary [4+2] photoproduct and secondary irradiation

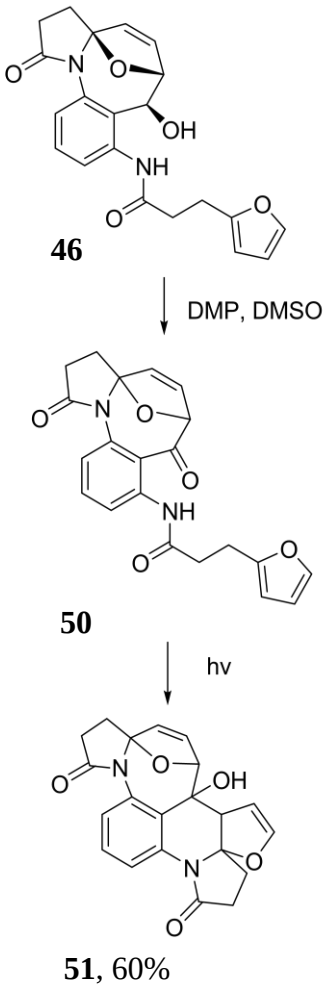


Figure 2.16 Oxidation of primary [4+4] photoproduct and secondary irradiation

and **47** was the major secondary photoproduct. Only trace amount of **48** and **49** were obtained. Because **47** and **48** are diastereomers, **48** cannot be isolated by LC columns and the structure of **48** was our hypothesis. However, the major photoproduct **47** can be

isolated by crystallization. The structures of **47** and **49** were predicted based on the calculation.

The primary [4+4] photoproduct **46** was also oxidized by DMP to get **50** (Figure 2.16). It was irradiated under 365nm LEDs and only [4+2] cycloaddition products were obtained. However, the photoproducts also could not be isolated by LC column, so the structure cannot be identified. By comparing the NMR spectrum of **49** and mixture **51**, **49** is possible to be one of the product of **51**.

Chapter 3: Hetero Diels-Alder Cycloaddition with Nitroso Compounds

3.1 Introduction

3.1.1 Photogenerated Nitroso Compound

In 1992, Hideo Tomioka, Naoki Ichikawa and Kazunori Komatsu reported that the irradiation (λ>350nm) of (2-nitrophenyl) diazomethane **52** generated 2-nitrosobenzaldehyde **54** by intramolecular oxygen migration of (2-nitrophenyl) carbene **53**. However, over-irradiation would decompose the nitrosobenzaldehyde to give a

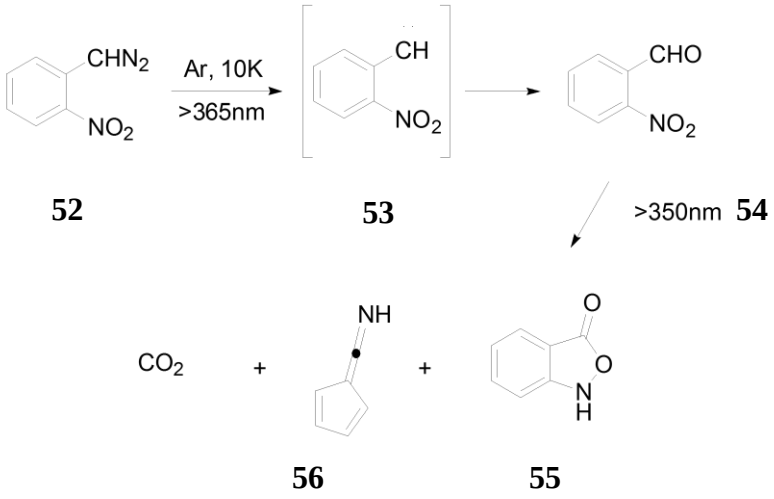


Figure 3.1 Photogenerated 2-nitrosobenzaldehyde from (2-nitrophenyl) diazomethane

mixture of 2,1-benzisoxazol-3(1H)-one **55** and carbonylcyclopentadiene imine **56** along with CO_2. [25]

Another method to generate nitroso compounds by irradiation was through 2-nitrobenzyloxycarbonyl compounds **57** (Figure 3.2). The removal of the carbonyl group was triggered by irradiation at wavelengths greater than 320nm. The excited nitro group got a hydrogen from the α-methylene carbon followed by rearrangement of *o*-nitrosobenzaldehyde **61**, and deprotected alcohol and carbon dioxide were generated at the same time.[26]

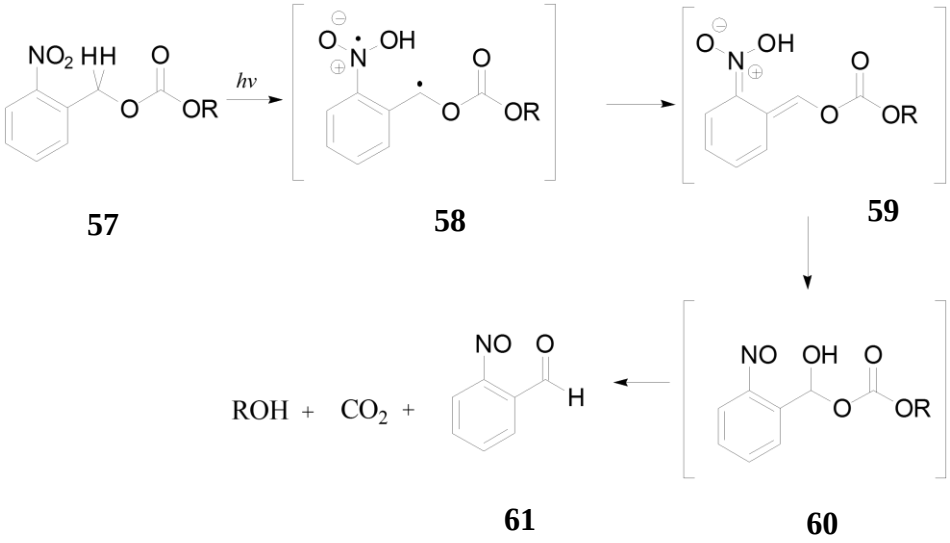


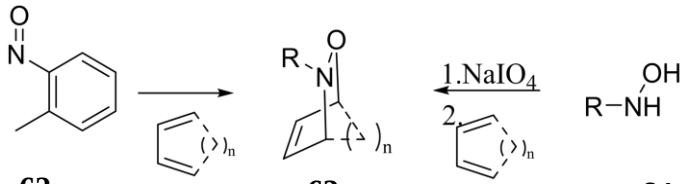
Figure 3.2 Photogenerated 2-nitrosobenzaldehyde 2-nitrobenzyloxycarbonyl compounds

3.1.2 Nitroso Diels-Alder Reaction

The Nitroso compounds have been studied decades ago due to the potential capacity in asymmetric synthesis. [27] Nitroso Diels-Alder (NDA) reaction is an essential reaction which has high regioselectivity and enantioselectivity by using various substituted dienes and catalysts.[28] C-nitroso compounds which are used in NDA reactions are arylnitroso, acylnitroso, cyanonitroso, vinylnitroso and α-chloronitroso. In particular,

NDA reaction of acylnitroso compounds is playing an important role due to the high reactivity. However, acylnitroso compounds are unstable and most of them cannot be isolated.

In 2010, J.C Monbaliu, A. Cukalovic and J. Marchand-Brynaert reported microflow studies of cycloadditions of nitroso dieniphiles with cyclodienes (Figure 3.3).[29] The temperature was set to the range from 0 to 95°C and flow rate was set from 0.2 to 1mL/min. The NDA reaction of 2-nitrosotoluene **62** with cyclohexadiene gave



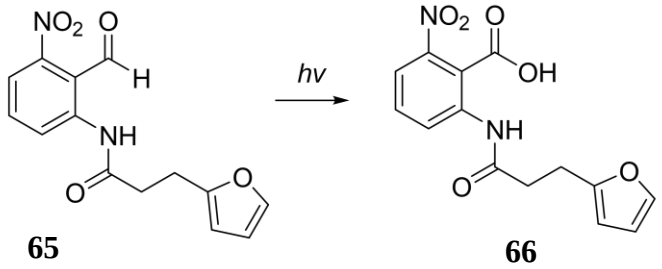
62 **63** **64**

Figure 3.3 NDA reactions from arylnitroso and acylnitroso compounds

92% of cycloproduct; however, no reaction was observed by using cyclopentadiene. In contrast, acylonitroso compounds **64** (R=Ac, Boc, Bz), synthesized from the oxidation of hydroxamic acids by periodate, gave a range of 70 to 92% yield.

3.2 Discussion

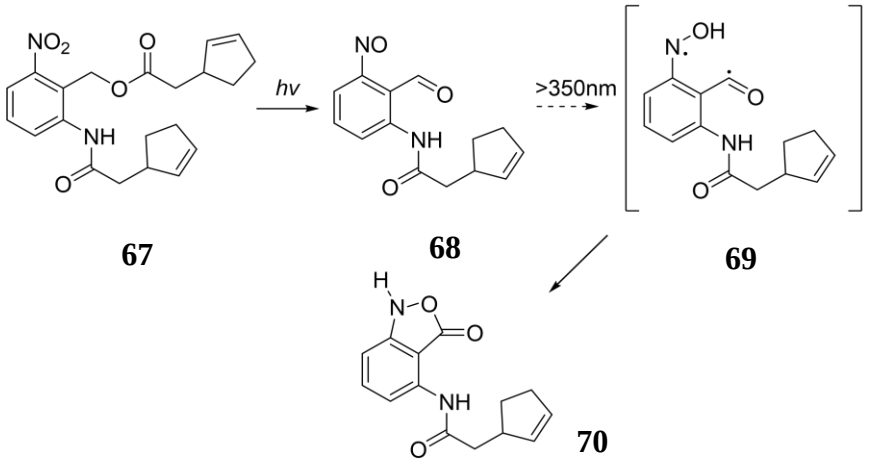
The irradiation of *o*-nitrobenzaldehyde photoprecursor failed to produce cycloaddition product. Instead, by NMR scale experiment, the aldehyde disappeared quickly by a short time irradiation. We assumed that during the irradiation, the nitro group oxidized the aldehyde to acid and itself became the nitroso group (Figure 3.4).



65 **66**

Figure 3.4 Irradiation of *o*-nitrobenzaldhyde photoprecursor

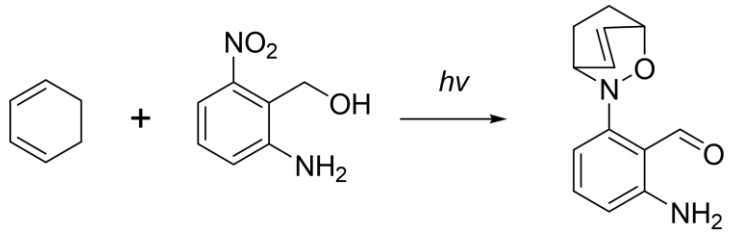
Obviously, the oxidation of aldehyde by the nitro group was much faster than the cycloaddition with furan. To protect the aldehyde, we tried to generate the aldehyde by the oxidation of alcohol or ester by the nitro group during the irradiation. So, we tried to irradiate **65** in DCM, which assumed to generate aldehyde by the oxidation of nitro group and release cyclopentene acetic acid as well (Figure 3.5). The small scale irradiation was monitored by NMR, which shows a quick generation of aldehyde **68**. However, after a longer time irradiation, benzisoxazole **70** was generated by the cycloaddition of the aldehyde and nitroso group. This was consistent with Hideo Tomioka's report.[25]



67 **68** **69** **70**

Figure 3.5 Irradiation of 2-nitrobenzyl acetate photoprecursor

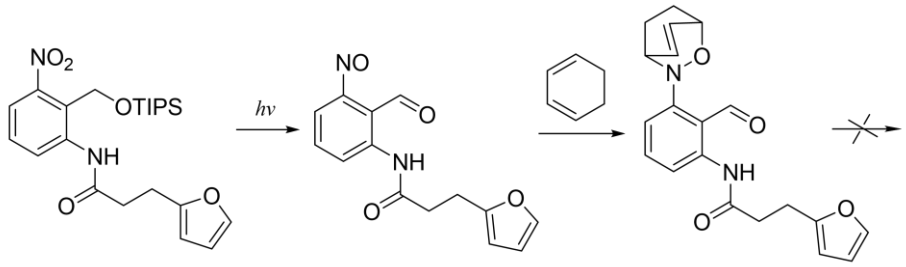
The photogenerated nitroso group prevented the cycloaddition with cyclopentene, so the only solution was to trap the nitroso group immediately when it was generated. NDA reaction is one plausible way to achieve this.



71 **72** **73**, 18%

Figure 3.6 Irradiation of *o*-nitrophenyl methanol with cyclohexadinene

Following the above assumption, a mixture of (2-amino-6-nitrophenyl) methanol **72** and two equivalents of cyclohexadiene **71** in chloroform was irradiated under 365nm LEDs (Figure 3.6). The irradiation was monitored by NMR spectra and it showed the aldehyde was formed during the irradiation. Additionally, a hetero Diels-Alder [4+2] cycloaddition product **73** was detected with no byproduct.



74 **75** **76**, 52%

Figure 3.7 Irradiation of 2-nitrobenzyloxy silane phoroprecursor

Then **74** was irradiated and the hetero Diels-Alder cycloaddition product **76** was observed. Unfortunately, intramolecular cycloaddition with tethered furan did not occur.

This might be because the nitrogen in the heterocyclic ring was quenching the formation of azaxylylene by lone pair electrons.

Chapter 4: Summary

The central focus in my research was to explore new strategy of post-photochemical modification. As the most reactive furan based photoprecursor, it reacted vary fast with a nice yield. Nonetheless, the reaction produced many products, due to the fact that a furan based photoprecursor could have [4+2] and [4+4] cycloadditions at the same time. This limitation can be overcome by using other alkenes such as thiophene tethered photoprecursors, which can only trigger [4+2] cycloaddition.

Additionally, NDA reaction of photocatalyzed 2-nitro benzyl alcohol was discovered. Even if we have proved that the NDA cycloaddition product could have photogenerated azaxylylenes cycloaddition, it gave us some points about how the ortho-*N* substituted compounds influence the cycloaddition.

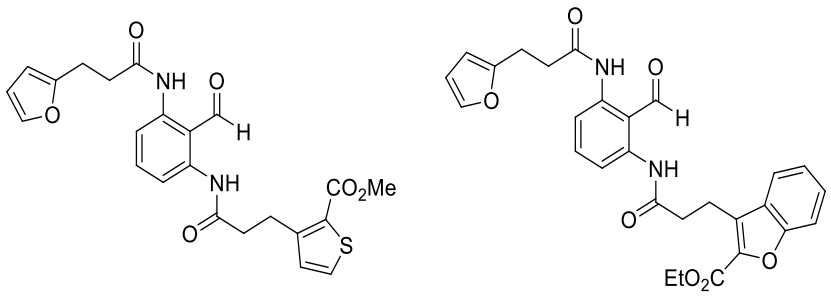


Figure 4.1 Photoprecursors synthesis in progress

Since secondary irradiation discussed in this thesis, a further research with different alkenes is necessary. A synthesis study of thiophene and benzofuran based photoprecursors was still in progress (Figure 4.1).

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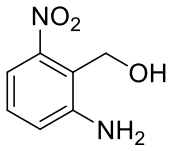
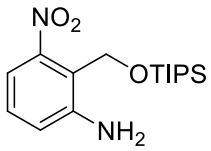
Appendix: Experimental

(2-amino-6-nitrophenyl) methanol



1g of 2-amino-6-nitrobenzoic acid was dissolved in 50mL of distilled THF, then 5.5mL, 2eq. of borane dimethyl sulfide (2M in toluene) was slowly added. The mixture was heated to reflux for 2.5 hours. Small portion was quenched by MeOH, all solvent was evaporated and the residue was checked by NMR. Upon completed, 10mL of MeOH was added drop wise at 0 °C. When complete, the mixture was stirred for 15min and evaporated all the solvent completely. The residue was purified by column and obtained 0.75g pure product with yield: 81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.18 (m, 2H), 6.95 (dd, J = 7.6, 1.6 Hz, 1H), 4.70 (s, 2H).

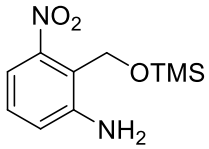
3-nitro-2-((triisopropylsilyloxy)methyl) aniline



0.75g, 4.46mmol, 1eq. of (2-amino-6-nitrophenyl) methanol was dissolved in 30mL of DCM, then 1.48mL, 1.5eq. triisopropylsilyl chloride (TIPSCl) and 0.62g, 2eq. of imidazole were added. It was stirred at room temperature overnight. The reaction process was checked by NMR. Upon complete, it was washed by 20mL of water. The water layer was extracted by 3×10mL of DCM, then all solvent was evaporated. Obtained 1.76g crude product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, J = 8.0 Hz, 1H), 7.11 (dd, J = 8.0, 1.2 Hz, 1H), 6.88 (dd, J = 8.0, 1.3 Hz, 1H), 5.00 (s, 2H), 1.22 – 1.11 (m, 3H), 1.07 (s, 18H).

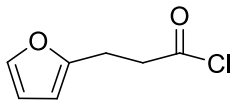
3-nitro-2-((trimethylsilyloxy)methyl)aniline



To a stirred solution of 0.84g, 5mmol, 1eq. of (2-amino-6-nitrophenyl) methanol in 25mL DCM, 0.64mL, 1 eq trimethylsilyl chloride (TMSCl) and 1.4mL, 2eq of TFA was added. The reaction mixture was stirred at room temperature for 2 day. When complete, the reaction was quenched with 10mL of sat. NH_4Cl. The organic layer was separated and aqueous phase was extracted with DCM. The organic fractions were combined and dried over Mg_2SO_4, filtered and the solvent was removed by vacuum. 0.76g, 3.2mmol of product was obtained.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (t, J = 8.0 Hz, 1H), 7.10 (dd, J = 8.0, 1.2 Hz, 1H), 6.88 (dd, J = 8.0, 1.2 Hz, 1H), 4.83 (s, 2H), 0.15 (s, 9H).

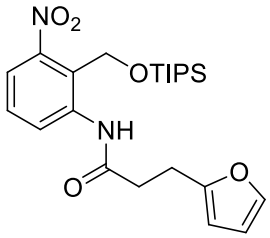
3-(furan-2-yl) propanoyl chloride



Under nitrogen protection, 0.8g, 5.7mmol, 1eq. of 3-(furan-2-yl) propanoic acid and 1.2mL, 2.5 eq. of thionyl chloride were treated in 25mL of anhydrous DCM, then one drop of DMF was added. The mixture was heated to reflux for 3 hours. Checked NMR after 3 hours reaction. If complete, the solvent was evaporated under vacuum for one hour. The product was not need to purified and directly used for next step.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, J = 1.9, 0.8 Hz, 1H), 6.32 (dd, J = 3.3, 1.9 Hz, 1H), 6.12 – 6.05 (m, 1H), 3.27 (t, J = 7.6, 7.0 Hz, 2H), 3.06 (t, J = 7.2 Hz, 2H).

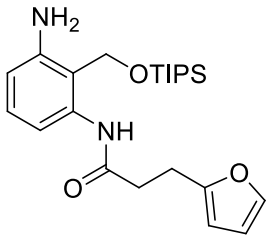
3-(furan-2-yl)-N-(3-nitro-2-((triisopropylsilyloxy)methyl) phenyl) propanamide



Under nitrogen atmosphere, 4.46mmol, 1eq. of crude 3-nitro-2-((triisopropylsilyloxy)methyl) aniline and 0.71mL, 2eq. of anhydrous pyridine was dissolved in 20mL of anhydrous DCM. Then 3-(furan-2-yl) propanoyl chloride in 20mL anhydrous DCM was added to it drop wise at 0°C. Upon finished adding, it was stirring for 10min and then the mixture was allowed to warm to room temperature. The reaction was kept for overnight. Reaction process was checked by NMR. Upon complete, it was diluted over 50mL of water, and extracted with 3×15mL DCM. The organic layer was washed with 10mL sat. $NaHCO_3$ aq. and brine. The organic layer was then dried over anhydrous Na_2SO_4. The residue was purified by column and obtained 1.93g, 4.33mmol of pure product with yield 97% synthesized from (2-amino-6-nitrophenyl) methanol.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 7.52 (dd, J = 8.1, 1.3 Hz, 1H), 7.44 (t, J = 8.1 Hz, 1H), 7.34 (dd, J = 1.9, 0.9 Hz, 1H), 6.31 (dd, J = 3.2, 1.9 Hz, 1H), 6.08 (dt, J = 3.1, 0.9 Hz, 1H), 5.02 (s, 2H), 3.19 – 3.06 (m, 2H), 2.74 (t, J = 7.4 Hz, 2H), 1.24 – 1.14 (m, 3H), 1.06 (d, J = 7.3 Hz, 18H).

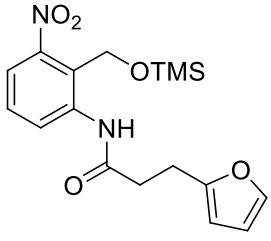
N-(3-amino-2-((triisopropylsilyloxy)methyl) phenyl)-3-(furan-2-yl) propanamide



0.84g, 2.5eq. of sodium sulfide was added into 25mL of ethanol in a 100mL round bottom flask. Then, 1.93g, 4.33mmol of 3-(furan-2-yl)-*N*-(3-nitro-2-((triisopropylsilyloxy)methyl) phenyl) propanamide was dissolved in 30mL of ethanol, and it was added into the flask. The mixture was refluxed for 1 hour and 45 minutes. Checked process by NMR. When it was finished, the mixture was concentrated. The residue was then dissolved in 20mL of EtOAc and 20mL of water was added. The organic phase was separated and the aqueous phase was extracted with 3×20mL EtOAc. Combined organic phases were washed with 10mL of brine and dried over Na_2SO_4. Evaporated all the solvent to obtain crude product 1.86g. It was not necessary to purify.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.34 (d, J = 4.1 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 6.36 – 6.23 (m, 1H), 6.11 – 6.05 (m, 1H), 4.75 (s, 2H), 3.10 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 1.19 (m, J = 13.4, 7.0, 6.6 Hz, 3H), 1.07 (d, 18H).

3-(furan-2-yl)-N-(3-nitro-2-((trimethylsilyloxy)methyl)phenyl)propanamide

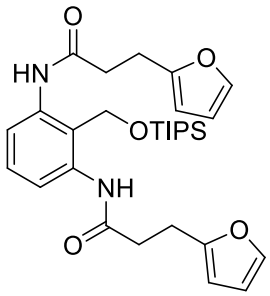


A solution of acyl chloride 3.6 mmol in dry 20mL DCM(25mL)was slowly added to a stirred solution of (about 3.2mmol) 3-nitro-2-((trimethylsilyloxy)methyl)aniline and (0.88mL 2eq) dry pyridine in 20mL DCM at 0 °C. After stirring

for 10 min the mixture was allowed to warm to room temperature, at which it was maintained overnight. It was then diluted over water (100mL) extracted with EtOAc(3×50mL) The organic layer was dried over anhydrous Na_2SO_4. Evaporated all the solvent and obtained 1.28g of crude product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.48 (d, J = 8.2 Hz, 1H), 7.51 (dd, J = 8.1, 1.3 Hz, 1H), 7.44 (t, J = 8.2 Hz, 1H), 7.35 (dd, J = 1.9, 0.8 Hz, 1H), 6.32 (dd, J = 3.2, 1.9 Hz, 1H), 6.10 (dd, J = 3.1, 0.9 Hz, 1H), 4.88 (s, 2H), 3.12 (t, J = 7.3 Hz, 2H), 2.75 (t, J = 7.4 Hz, 2H), 0.18 (s, 9H).

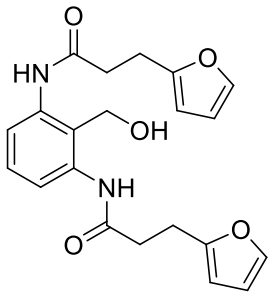
N, N'-(2-((triisopropylsilyloxy)methyl)-1,3-phenylene) bis(3-(furan-2-yl) propanamide)



Under nitrogen atmosphere, 4.46mmol, 1eq. of crude *N*-(3-amino-2-((triisopropylsilyloxy)methyl) phenyl)-3-(furan-2-yl) propanamide and 0.71mL, 2eq. of anhydrous pyridine was dissolved in 20mL of anhydrous DCM. Then 3-(furan-2-yl) propanoyl chloride in 20mL anhydrous DCM was added to it drop wise at 0°C. Upon finished adding, it was stirring for 10min and then the mixture was allowed to warm to room temperature. The reaction was kept for overnight. Reaction process was checked by NMR. Upon complete, it was diluted over 50mL of water, and extracted with 3×15mL DCM. The organic layer was washed with 10mL sat. $NaHCO_3$ aq. and brine. The organic layer was then dried over anhydrous Na_2SO_4. Evaporated all the solvent and obtain 2.50g crude product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (dd, J = 5.5, 1.8 Hz, 2H), 8.18 (s, 2H), 7.72 (tt, J = 7.6, 1.8 Hz, 1H), 7.51 (d, J = 8.1 Hz, 2H), 6.32 (m, J = 3.0 Hz, 2H), 6.09 (m, J = 3.2, 1.9 Hz, 2H), 4.72 (s, 2H), 3.10 (t, J = 7.4 Hz, 4H), 2.71 (t, J = 7.5 Hz, 4H), 1.29 – 1.09 (m, 3H), 1.08 (d, J = 0.9 Hz, 18H).

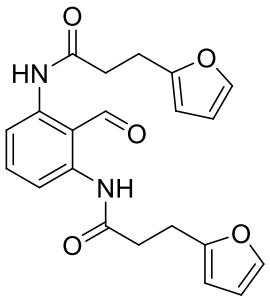
N, N'-(2-(hydroxymethyl)-1,3-phenylene) bis(3-(furan-2-yl) propanamide)



2.50g of crude *N, N'*-(2-((triisopropylsilyloxy)methyl)-1,3-phenylene) bis(3-(furan-2-yl) propanamide) was dissolved in 30mL of THF in 50mL round bottom flask. To this flask, 1.49g of TBAF·$3H_2O$ was slowly added at 0°C. The reaction mixture was stirred at room temperature for overnight. Checked process by NMR. Upon complete, evaporated THF by vacuum and redissolved in 20mL of EtOAc. It was dried over anhydrous Na_2SO_4 and then evaporated EtOAc completely.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 8.26 Hz, 2H), 7.31 (s, 2H), 7.18 (t, J = 8.1 Hz, 1H), 6.29 (d, J = 2.8 Hz, 2H), 6.11 (d, J = 3.1 Hz, 2H), 4.55 (s, 2H), 3.08 (t, J = 7.7 Hz, 4H), 2.80 (t, J = 7.7 Hz, 4H).

N, N'-(2-formyl-1,3-phenylene) bis(3-(furan-2-yl)propanamide)

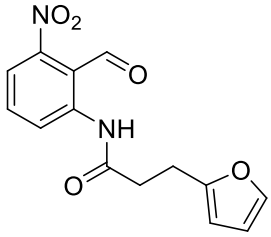


In a 100mL round bottom flask, 4.33mmol of crude *N, N'*-(2-(hydroxymethyl)-1,3-phenylene) bis(3-(furan-2-yl) propanamide) was dissolved in 40mL of DCM and then 2.2g, 1.2eq. of DMP was added. It was stirred at room temperature for 1 day. Check the reaction process by NMR. When completed, 10mL 20wt% of $Na_2S_2O_3$ aq. and 20mL of sat. $NaHCO_3$ aq. were added. The solution was stirred for 30min. Then the organic layer was separated, and the aqueous layer was washed by 3×20mL DCM. Combined all the organic phases and dried over anhydrous Na_2SO_4. It was filtered and evaporated all the solvent completely. The crude product was purified by column and obtained 0.21g, 0.55mol pure product with 12.7% of yield over 4 steps from *N*-(3-amino-2-((triisopropylsilyloxy)methyl)phenyl)-3-(furan-2-yl) propanamide.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 9.42 (s, 2H), 7.73 (s, 2H), 7.55 (t, J = 8.2 Hz, 1H), 7.36 (dd, J = 1.9, 0.9 Hz, 2H), 6.33 (dd, J = 3.2, 1.9 Hz, 2H), 6.15 – 6.08 (m, 2H), 3.11 (t, J = 7.2 Hz, 4H), 2.81 (t, J = 7.3 Hz, 4H).

N-(2-formyl-3-nitrophenyl)-3-(furan-2-yl)propanamide

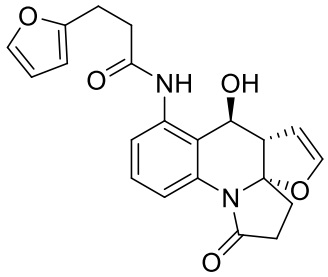
3.2mol of 3-(furan-2-yl)-*N*-(3-nitro-2-((trimethylsilyloxy)methyl)phenyl)propanamide was dissolved in 35mL of DCM in a 100mL round bottom flask. Then 1.04g, 4.8mmol, 1.5eq. of PCC was added slowly. It was stirred at room temperature for overnight. The



residue was washed thought celite and washed by EtOAc. The organic fraction was evaporated and the product was purified by column. 0.53g of product was obtained with the yield 58%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.18 (s, 1H), 9.04 (ddd, J = 8.4, 1.4, 0.7 Hz, 1H), 7.79 – 7.58 (m, 2H), 7.35 (dd, J = 1.9, 0.9 Hz, 1H), 6.30 (dd, J = 3.2, 1.9 Hz, 1H), 6.10 (dd, J = 3.2, 0.9 Hz, 1H), 3.12 (dd, J = 8.0, 7.0 Hz, 2H), 2.86 (dd, J = 8.1, 6.8 Hz, 2H).

3-(furan-2-yl)-N-[(6S,10S,11S)-11-hydroxy-3-oxo-7-oxa-2-azatetracyclo[10.4.0.0^{2,6}.0^{6,10}]hexadeca-1(16),8,12,14-tetraen-13-yl]propanamide

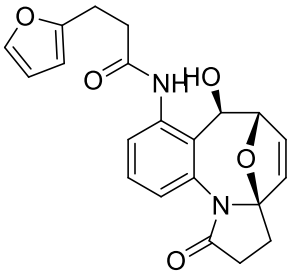


0.55mmol of *N*, *N'*-(2-formyl-1,3-phenylene)bis(3-(furan-2-yl)propanamide) was dissolved in 180mL of DCM, after 10min degas process, it was irradiated under 365nm lamp(20W) for 6 min. The reaction was finished proved by checking NMR. Evaporated all the solvent and purified by column and obtained 64mg, 0.17mmol [4+2] cycloaddition product with the yield: 31%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 1H), 7.40 (dd, J = 1.9, 0.9 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 2.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.37 (dd, J = 3.2, 1.8 Hz, 1H), 6.22 (t, J = 2.8 Hz, 1H), 6.20 – 6.14 (m, 1H), 4.60 (d, J = 2.2 Hz, 1H), 4.50 (dd, J = 3.0, 2.3 Hz, 1H), 3.79 (q, J = 2.4 Hz, 1H), 3.17 (dt, J = 14.9, 7.4 Hz, 1H),

3.09 (dt, J = 14.9, 7.4 Hz, 1H), 2.85 (ddd, J = 16.4, 10.4, 8.3 Hz, 1H), 2.79 (t, J = 7.1 Hz, 2H), 2.57 (td, J = 8.6, 1.2 Hz, 2H), 2.55 – 2.45 (m, 2H).

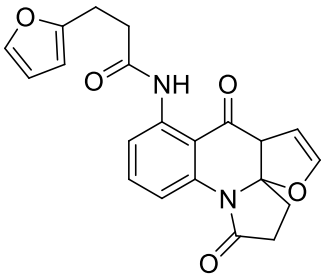
3-(furan-2-yl)-N-[(1R,12R,13S)-12-hydroxy-4-oxo-16-oxa-5-azatetracyclo[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6,8,10,14-tetraen-10-yl]propanamide



Same procedure shown above. After purified by column, it gave 36mg, 0.1mmol [4+4] cycloaddition product with the yield: 18%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.44 – 7.37 (m, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.28 – 7.25 (m, 1H), 6.34 (dd, J = 3.3, 1.9 Hz, 1H), 6.27 (dd, J = 5.8, 1.9 Hz, 1H), 6.13 (d, J = 3.1 Hz, 1H), 5.69 (dd, J = 5.8, 1.2 Hz, 1H), 5.02 (dt, J = 3.1, 1.6 Hz, 1H), 4.58 (s, 1H), 3.12 (t, J = 7.2 Hz, 2H), 2.86 – 2.73 (m, 3H), 2.69 – 2.39 (m, 3H).

N-{3,11-dioxo-7-oxa-2-azatetracyclo[10.4.0.0^{2,6}.0^{6,10}]hexadeca-1(16),8,12,14-tetraen-13-yl}-3-(furan-2-yl)propanamide

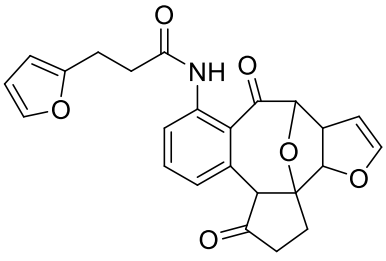


64mg of 3-(furan-2-yl)-*N*-[(1R,12R,13S)-12-hydroxy-4-oxo-16-oxa-5-azatetracyclo[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6,8,10,14-tetraen-10-yl]propanamide was dissolved in 2mL of DMSO, and then 80mg of DMP was added. The reaction mixture was

stirred at room temperature overnight. Reaction was monitored by NMR. DMSO was evaporated by high vac. The residual was dissolved in 10mL of DCM. 10mL of $NaHCO_3$ aq. and 5mL 20wt% of $Na_2S_2O_3$ aq. were added. It was stirred for half an hour. The organic layer was separated and the aqueous layer was washed with 3×10mL DCM. Combined all organic solvent and dried over anhydrous Na_2SO_4. Evaporated all the solvent completely and obtained 78mg of crude product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.42 (s, 1H), 8.52 (dd, J = 8.6, 1.0 Hz, 1H), 7.94 (dd, J = 8.2, 1.0 Hz, 1H), 7.62 (t, J = 8.4 Hz, 1H), 7.33 (dd, J = 1.9, 0.9 Hz, 1H), 6.47 (t, J = 2.6 Hz, 1H), 6.29 (dd, J = 3.2, 1.9 Hz, 1H), 6.08 (dq, J = 3.0, 0.9 Hz, 1H), 5.05 (t, J = 3.0 Hz, 1H), 3.89 (dd, J = 3.1, 2.3 Hz, 1H), 3.14 – 3.07 (m, 2H), 2.92 (ddd, J = 17.2, 10.9, 8.8 Hz, 1H), 2.81 (td, J = 7.4, 2.2 Hz, 2H), 2.67 – 2.53 (m, 2H), 2.25 (ddd, J = 13.5, 10.9, 9.3 Hz, 1H).

3-(furan-2-yl)-N-[(1R,12R,13S)-12-hydroxy-4-oxo-16-oxa-5-azatetracyclo[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6,8,10,14-tetraen-10-yl]propanamide

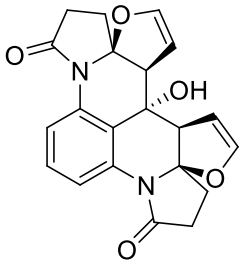


36mg of 3-(furan-2-yl)-*N*-[(1R,12R,13S)-12-hydroxy-4-oxo-16-oxa-5-azatetracyclo[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6,8,10,14-tetraen-10-yl]propanamide was dissolved in 2mL of DMSO, and then 55mg of DMP was added. The reaction mixture was stirred at room temperature for overnight. Checking NMR to confirm the reaction was complete. DMSO was evaporated by high vac. The residual was

dissolved in 10mL of DCM. 10mL of $NaHCO_3$ aq. and 5mL 20wt% of $Na_2S_2O_3$ aq. were added. It was stirred for half an hour. The organic layer was separated and the aqueous layer was washed with 3×10mL DCM. Combined all organic solvent and dried over anhydrous Na_2SO_4. Evaporated all the solvent completely and obtained 32mg of crude product.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.14 (dd, J = 8.4, 1.2 Hz, 1H), 7.50 (t, J = 8.2 Hz, 1H), 7.35 (dd, J = 1.9, 0.9 Hz, 1H), 7.22 (dd, J = 8.1, 1.2 Hz, 1H), 6.48 (dd, J = 5.8, 2.0 Hz, 1H), 6.30 (dd, J = 3.2, 1.9 Hz, 1H), 6.08 (dd, J = 3.2, 0.9 Hz, 1H), 5.95 (dd, J = 5.8, 1.1 Hz, 1H), 5.00 (dd, J = 2.0, 1.1 Hz, 1H), 3.10 – 3.04 (m, 2H), 2.93 (dt, J = 17.0, 9.7 Hz, 1H), 2.78 – 2.65 (m, 4H), 2.50 (ddd, J = 13.9, 9.4, 1.3 Hz, 1H).

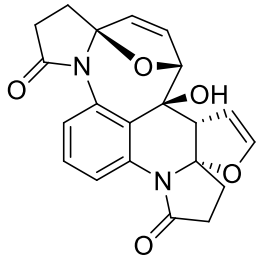
1-hydroxy-5,21-dioxa-10,16 diazaheptacyclo[13.9.1.0^{2,6}.0^{6,10}.0^{11,25}.0^{16,20}.0^{20,24}]pentacosa-3,11,13,15(25),22-pentaene-9,17-dione



32mg of *N*-{3,11-dioxo-7-oxa-2-azatetracyclo[10.4.0.0^{2,6}.0^{6,10}]hexadeca-1(16),8,12,14-tetraen-13-yl}-3-(furan-2-yl)propanamide was dissolved in 50mL of DCM. After 5min degas process by nitrogen, it was irradiated under 365nm LEDs (20W) for 15min. The irradiation was monitored by NMR. Upon complete, all DCM was evaporated and the products were purified by column.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2H), 7.41 – 7.36 (t, 1H), 6.28 (t, J = 2.4 Hz, 2H), 5.17 (t, J = 2.7 Hz, 2H), 3.65 (t, J = 2.4 Hz, 2H), 2.78 (m, 2H), 2.52 (t, J = 10.6 Hz, 2H), 2.32 (q, J = 11.1 Hz, 2H), 2.18 (m, 2H).

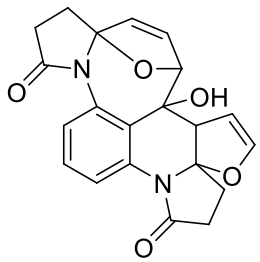
(1S,2R,5S,19S,23S)-1-hydroxy-20,25-dioxa-9,15-diazaheptacyclo[12.9.1.1^{2,5}.0^{5,9}.0^{10,24}.0^{15,19}.0^{19,23}]pentacosa-3,10(24),11,13,21-pentaene-8,16-dione



Same procedure shown above. Trace amounts of this compound was separated by LC column.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, J = 7.9, 1.4 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.1, 1.4 Hz, 1H), 6.49 (dd, J = 6.0, 1.9 Hz, 1H), 6.38 (t, J = 2.9 Hz, 1H), 5.87 (dd, J = 6.0, 1.3 Hz, 1H), 4.81 (t, J = 1.6 Hz, 1H), 4.77 (dd, J = 3.2, 2.3 Hz, 1H), 3.66 (t, J = 2.5 Hz, 1H), 2.93 – 2.82 (m, 1H), 2.66 – 2.27 (m, 7H).

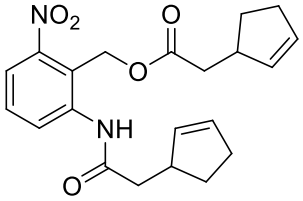
1-hydroxy-20,25-dioxa-9,15-diazaheptacyclo[12.9.1.1^{2,5}.0^{5,9}.0^{10,24}.0^{15,19}.0^{19,23}]pentacosa-3,10(24),11,13,21-pentaene-8,16-dione



20mg of 3-(furan-2-yl)-*N*-[(1R,12R,13S)-12-hydroxy-4-oxo-16-oxa-5-azatetracyclo[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6,8,10,14-tetraen-10-

yl]propanamide was dissolved in 18mL of DCM, after 5min degas process by nitrogen, it was irradiated under 365nm LEDs(20W) for 6 min. When complete, all solvent war evaporated, the residue was separated by LC column. However, the mixture could not be separated by column.

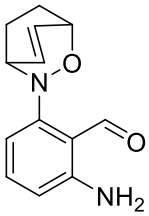
2-(2-(cyclopent-2-enyl)acetamido)-6-nitrobenzyl 2-(cyclopent-2-enyl)acetate



This compound was the byproduct of the coupling reaction of 3-nitro-2-((trimethylsilyloxy)methyl)aniline and 2-(cyclopent-2-enyl)acetyl chloride.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.26 (d, J = 8.3 Hz, 1H), 7.72 (dd, J = 8.1, 1.2 Hz, 1H), 7.55 (t, J = 8.2 Hz, 1H), 5.89 – 5.82 (m, 1H), 5.82 – 5.73 (m, 2H), 5.59 (dq, J = 5.9, 2.1 Hz, 1H), 5.42 (s, 2H), 3.34 – 3.22 (m, 1H), 3.13 – 2.97 (m, 1H), 2.66 – 2.15 (m, 7H), 2.13 – 2.01 (m, 1H), 1.71 – 1.56 (m, 1H), 1.43 (ddt, J = 12.8, 8.8, 6.3 Hz, 1H).

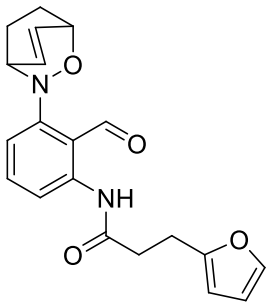
2-amino-6-(2-oxa-3-azabicyclo[2.2.2]oct-7-en-3-yl)benzaldehyde



0.08g, 0.48mmol of (2-amino-6-nitrophenyl)methanol was added into 160mL of cholorform, (2eq, 91uL) of cyclohexadiene was added. After 10min degas by nitrogen, it was irradiated under 365nm lamp for 30min. When it was complete, all the solvent was evaporated and the crude product was purified by column. 0.08g of product were obtained with the yield 18%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.37 (d, J = 0.6 Hz, 1H), 7.16 (t, J = 8.1 Hz, 1H), 6.70 (ddd, J = 8.0, 5.9, 1.7 Hz, 1H), 6.45 (dd, J = 7.9, 1.0 Hz, 1H), 6.33 (dt, J = 8.2, 0.9 Hz, 1H), 6.24 (s, 2H), 6.12 (ddd, J = 8.0, 5.9, 1.5 Hz, 1H), 4.75 (td, J = 4.2, 2.1 Hz, 1H), 4.09 – 3.99 (m, 1H), 2.39 (ddt, J = 12.5, 9.3, 3.3 Hz, 1H), 2.29 (ddt, J = 13.2, 9.6, 3.6 Hz, 1H), 1.54 (dt, J = 12.0, 3.1 Hz, 1H), 1.48 – 1.39 (m, 1H).

_N_-(3-(2-oxa-3-azabicyclo[2.2.2]oct-7-en-3-yl)-2-formylphenyl)-3-(furan-2-yl)propanamide



0.6mmol *N*-(2-formyl-3-nitrophenyl)-3-(furan-2-yl)propanamide Was dissolved in 200mL of MeOH, 0.11mL, 2eq of cyclohexadiene was added in a square bottom. After 10min degas by nitrogen, it was irradiated for 40min. The reaction was finished. Evaporated all the solvent completely and purified by column. 0.11g, 0.31mmol of product was obtained with 52% of yield.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 11.48 (s, 1H), 10.39 (d, J = 0.7 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.3 Hz, 1H), 7.36 (dd, J = 1.9, 0.9 Hz, 1H), 6.95 (dd, J = 8.2, 1.1 Hz, 1H), 6.79 – 6.68 (m, 1H), 6.32 (dd, J = 3.2, 1.8 Hz, 1H), 6.15 – 6.02 (m, 2H), 4.77 (d, J = 5.4 Hz, 1H), 3.98 (s, 1H), 3.08 (t, J = 7.6 Hz, 2H), 2.80 (dd, J = 8.1, 7.0 Hz, 2H), 2.39 (dtd, J = 12.9, 6.7, 3.4 Hz, 1H), 2.32 – 2.18 (m, 1H), 1.63 – 1.55 (m, 1H), 1.51 – 1.40 (m, 1H).