Development of visible-light-mediated photoredox catalysis

Sarbjeet Kaur
University at Albany, State University of New York, sarbjeetkaur@albany.edu

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DEVELOPMENT OF VISIBLE-LIGHT-MEDIATED PHOTOREDOX CATALYSIS

by

Sarbjeet Kaur

A Dissertation
Submitted to the University at Albany, State University of New York
In Partial Fulfillment of
the Requirements for the Degree of
Doctor of Philosophy

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Department of Chemistry
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ABSTRACT

Chapter 1: Thiol-ene/Thiol-yne reactions can be initiated by visible-light irradiation in presence of organic photocatalyst (9-mesityl-10-methylacridinium tetrafluoroborate). Generation of key thyl radical intermediates occurs upon quenching of photoexcited catalyst with various thiols. This reaction was also successfully operated in aqueous medium. Two reaction pathways were found in different aqueous buffer system. Thiol-ene product is preferred in acidic reaction medium while disulfide formation is favored in basic reaction medium. Under the optimized conditions both thiol-ene/thiol-yne reaction between carbohydrates and peptides resulted in the formation of glycoconjugates in good yields. These efficient mild conditions can be potentially useful in bioconjugation.

Chapter 2: Visible-light-mediated oxidative cleavage of electron deficient indoles was carried out using Methylene Blue as catalyst. A variety of electron denoting and electron withdrawing groups were tolerated on indole backbone. This photocatalytic system was successfully applied to carry out Witkop-Winterfeldt reactions. The reaction mechanism was proposed and studied via density functional theory and Marcus theory calculations.

Chapter 3: Catalytic access to isolated alcohols was carried out by using N-heterocyclic carbenes as catalyst. This method relies on Sharpless Asymmetric Epoxidation to achieve the stereoselectivity. A variety of functional groups were tolerated under these mild conditions and various isolated alcohols were obtained in excellent yields.

Chapter 4: Synthesis of isoquinoline-5-sulfonamide compound was carried. Neuroimaging of rho/rho-kinase has been hindered by the lack of appropriate radiotracers. The development of ROCK PET imaging tracers labeled with $^{11}$C/$^{18}$F will be carried out which will enable proof-of-concept studies and dosing determination of ROCK inhibitors. (Collaboration Yale University)
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Dedicated to my beloved family
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>$[\alpha]$</td>
<td>Optical rotation</td>
</tr>
<tr>
<td>AIBN</td>
<td>Azobisisobutyronitrile</td>
</tr>
<tr>
<td>Boc</td>
<td><em>tert</em>-Butyloxycarbonyl</td>
</tr>
<tr>
<td>C</td>
<td>Celsius</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td>Natural stable isotope of Carbon</td>
</tr>
<tr>
<td>Calcd.</td>
<td>Calculated mass</td>
</tr>
<tr>
<td>CFL</td>
<td>Compact fluorescent lamp</td>
</tr>
<tr>
<td>cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>C-S</td>
<td>Carbon-sulfur</td>
</tr>
<tr>
<td>CuACC</td>
<td>Cu(l)-catalyzed azide-alkyne cycloaddition</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DFT</td>
<td>Density functional theory</td>
</tr>
<tr>
<td>DIBAL</td>
<td>Diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>N, N-Diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>DPAP</td>
<td>2,2-dimethoxy-2-phenylacetophenone</td>
</tr>
<tr>
<td>Dtbppy</td>
<td>4,4’-Di-tert-butyl-2,2’-dipyridyl</td>
</tr>
<tr>
<td>$E_{\text{red}}^{1/2}$</td>
<td>Half reduction potential</td>
</tr>
<tr>
<td>EDCI</td>
<td>$N$-(3-dimethylaminopropyl)-$N$’-ethylcarbodiimide</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl Acetate</td>
</tr>
<tr>
<td>equiv.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>g</td>
<td>Gram (s)</td>
</tr>
</tbody>
</table>
\(^1\text{H}\) Natural stable isotope of hydrogen

h Hour

HFIP Hexafluoroisopropanol

HOBt 1-hydroxybenzotriazole

HPLC High performance liquid chromatography

HRMS High-resolution mass spectrometry

IR Infrared

LED Light emitting diode

L-Hag L-Homoallylglycine

m-CPBA meta-Chloroperxybenzoic acid

mg Milligram (s)

MHz Mega hertz

MeCN Acetonitrile

MeOH Methanol

mL Millilitre (s)

min Minutes

mmol Millimole

MW Molecular weight

NaHCO\(_3\) Sodium bicarbonate

Na\(_2\)SO\(_4\) Sodium sulfate

NCL Native chemical ligation

NHC N-Heterocyclic carbene

nm Nano meter

NMR Nuclear Magnetic Resonance

PET Positron emission tomography

ppm Parts per million

RT Room temperature
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>SAR</td>
<td>Structure activity relationship</td>
</tr>
<tr>
<td>SPAAC</td>
<td>Strain promoted azide-alkyne cycloaddition</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TEC</td>
<td>Thiol-ene click chemistry</td>
</tr>
<tr>
<td>TES</td>
<td>Triethyilsilane</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THP</td>
<td>Tamm-Horsfall glycoprotein</td>
</tr>
<tr>
<td>TiO₂</td>
<td>Titanium dioxide</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TYC</td>
<td>Thiol-yne click chemistry</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>VA044</td>
<td>2,2’-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride</td>
</tr>
<tr>
<td>V</td>
<td>Volts</td>
</tr>
<tr>
<td>W</td>
<td>Watt</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shifts</td>
</tr>
<tr>
<td>μ</td>
<td>Micro</td>
</tr>
</tbody>
</table>
PREFACE

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Chapter 1: Metal-Free Photocatalytic Thiol-ene/Thiol-yne Reactions

1.1 Introduction

1.1.1 Photocatalysis

Many important processes including photosynthesis and ozone production in atmosphere are governed by light. In 1912, Ciamician realized that sunlight could be used as an economical, clean, and sustainable energy source for organic chemistry.\textsuperscript{1,2a} Over past few years the regeneration of radical chemistry has renewed the interest in field of photochemistry. One of the limitations to photochemical processes is inefficiency of common organic molecules to absorb light in range of visible wavelength. However, to overcome this barrier visible light absorbing photocatalyst can be employed which can use their electron/energy transfer process to sensitize organic molecules to accomplish required photochemical reaction.\textsuperscript{2b} Visible light photoredox catalysis is one of the most developing field of radical chemistry due to its ability to attain unique chemical reactivity under mild conditions which otherwise is considered challenging under typical organic reactions. It is an innovative method to develop reactive radical species which escapes the conventional pathway of using toxic and hazardous chemical reagents.\textsuperscript{2b}

1.1.2 Click Reactions:

In 2001 Sharpless\textsuperscript{3a,3b} introduced the concept of click reactions which focuses on making chemical compounds and materials from modular blocks. Click reactions generally exhibit certain properties such as stereospecificity, high yields, wide range of substrate scope, generate no or safe byproducts, require benign solvents or solvent less reaction conditions.\textsuperscript{4} The most common click reactions that deliver these standards includes cycloaddition reactions also known as Huisgen 1,3-dipolar cycloaddition\textsuperscript{5} and Diels-Alder reaction.\textsuperscript{6} The other reaction that falls under this category
are nucleophilic ring opening reactions of strained heterocyclic electrophiles which includes epoxides, aziridines and aziridinium ions.\textsuperscript{7} Thirdly, reactions of non-aldol carbonyl compounds which makes use of urea, oximes and hydrazones.\textsuperscript{8} Lastly, the reactions involving addition to carbon-carbon multiple bonds such as Michael additions and thiol-ene/thiol-yne reactions also fulfil these criteria.\textsuperscript{9}

The concept of using Cu(I)-catalyzed azide-alkyne cycloaddition (CuACC) for bioconjugation reactions has certain limitations. Cu(I) catalyst in CuACC has severe problems including cytotoxicity\textsuperscript{10}, denaturation of proteins.\textsuperscript{11} Purification techniques such as dialysis, microfiltration are necessary for removal of trace copper from peptide bioconjugates to carry out further biological testing of them.\textsuperscript{12} Later Bertozzi and Boons developed Strain promoted azide-alkyne cycloaddition (SPAAC) method to prevail the difficulty associated with metal catalyst in CuACC reactions.\textsuperscript{13} They used strained cyclooctynes to replace the alkynes in the Huisgen 1,3-dipolar cycloaddition and the strain in cyclooctynes readily react with an azide in absence of metal catalyst.\textsuperscript{14-16} Strain promoted azide-alkyne cycloaddition (SPAAC) is one of the important reactions to synthesize hybrid biomaterials but highly reactive strained cyclooctyne results in poor regioselectivity of products and this method uses expensive cyclooctynes which are difficult to synthesize.\textsuperscript{12} Another suitable method that is being used in synthesis of materials and organic compounds is thiol-Michael addition click chemistry.\textsuperscript{17} Many click reactions are being carried out between nucleophilic thiols and electrophilic epoxides, and Michael acceptors to afford desired product.\textsuperscript{18} These reactions proceed via non-radical pathway and can be initiated by use of mild base such as triethylamine. It is also seen that nucleophilic catalysts such as primary, secondary amines and phosphines can also help to carry out Michael addition of thiols.\textsuperscript{18}
Thiol-ene/Thiol-yne reactions are generally referred to as addition of thiol to an alkene/alkyne through formation of radical intermediate. Thiol-ene/Thiol-yne reactions has advantage over CuACC and SPAAC in bioconjugation chemistry as it does not make use of toxic metal catalyst such as Cu(I) and uses cost efficient thiols and alkenes/alkynes. One of the special features of light irradiated reactions as compared to thermal conventional reactions is that they can control the functionality spatially and temporally as they have capability to focus photons onto a specific area by varying times and wavelengths as required. Thiol-ene/Thiol-yne has cutting edge due to its mildness and efficiency for bioconjugation.

1.1.3 Thiol-ene/Thiol-yne Reactions

C-S bond formation holds utmost importance in synthesis of valuable chemical entities among numerous carbon heteroatom bond formation due to its extensive presence in nature and various biological systems. Many synthetic and biologically active natural products such as pencillin G, amoxicillin, actos, thiopineol, fluticasone propionate are organosulfur compounds. Various organosulfur compounds in particular amino acids, protein crosslinking agents, biotin, and ligands in bioinorganic complexes (101-105) as shown in (Figure 1.1) are key to carry out chemical and biological processes of many living organisms.

Many strategies are used for formation of carbon-sulfur (C-S) bond using substitution and addition reactions. Whereas thiol-ene click reaction is one of the most prominent method for formation of C-S bonds due to its numerous applications in pharmaceutical chemistry, polymer science and material synthesis. Following the Sharpless “click chemistry” concept TEC (thiol-ene click chemistry) has been acknowledged as robust tool for ligation. An outstanding significance of thiol-ene reactions is that it can be carried out under aerobic conditions with total atom economy and rapid kinetics, without the use of specialized and expensive UV equipment and potentially
toxic metal catalysts. Other advantage of thiol-ene reactions is that it can be initiated in wavelength range near to visible light not damaging delicate biomolecules such as peptides and carbohydrates. More importantly, thiol-ene reactions can be carried out in mild conditions at room temperature. Overall TEC chemistry is suitable for bioconjugation because of absence of cross reactivity with other functional groups present in biological environment.

**Figure 1.1:** Organosulfur compounds. Adapted with permission from https://pubs.acs.org/doi/full/10.1021/cr500235v?casa_token=E9UTdgdm5MEAAAAA:g5DHznby2TeXCC5Oy7k3bDYP3e8TOWfZtvgzYUpZujTGn5WDXLiP_0sBX4WSMY0fqLNS4T02O1NMCb8-UA

In 1905, Posner discovered the hydrothiolation of terminal alkenes while its free radical chain mechanism was found much later by Kharasch and co-workers.\textsuperscript{23,24} It is well known that in presence of light irradiation/radical initiator the thiols can be converted to thiyl radicals. The addition of thiyl radicals to alkene in Anti-Markovnikov’s fashion provides carbon centered thioalkyl radical. This thioalkyl radical thus abstracts the hydrogen radical from thiol and results in formation of thioether and new thiyl radical, which initiates propagation of the radical chain as shown in (**Scheme1.1**).
Scheme 1.1: Free radical chain mechanism.\textsuperscript{23,24}

As we have seen those previous studies of hydrothiolation reactions for addition of thiols to alkenes were carried by radical pathway. They were conducted in presence of radical initiators or specialized UV equipment. This method can be applied to limited systems as free radical addition results in low selectivity and employ harsh conditions.\textsuperscript{21b,25,26} Various metal mediated processes are carried out to achieve better regioselectivity and stereoselectivity for hydrothiolation reactions.\textsuperscript{27-29}

A study done from 1940s-1960s indicates that certain radical mediated “thiol-yne reactions” manifest features typically correlated with highly efficient thiol-ene chemistry.\textsuperscript{30-34} In conclusion, thiol-yne reactions offers a distinct opportunity to broaden the scope of chemistry related to thiol-ene reactions by providing access to vast range of new materials and properties. This area offers a chemical platform for smart material synthesis\textsuperscript{35}, polymers\textsuperscript{36}, dendimers\textsuperscript{37} and functionalized surfaces\textsuperscript{38,39}. Most importantly this method is implemented in synthesis of vinyl thioethers which are predecessor to various bioactive molecules\textsuperscript{40} and as well as are beneficial synthetic intermediates in total synthesis\textsuperscript{41}. Initially, the addition of thiols to alkynes was executed by free radical pathway\textsuperscript{42}. A major drawback of free-radical addition was low selectivity, harsh
conditions, and extensive formation of by-products, which decreased the usefulness of this method in organic synthesis\textsuperscript{42c}. Transition metal mediated processes enhanced the selectivity in favor of C-S bond formation\textsuperscript{43} but leaching of metal species\textsuperscript{44} and inevitable contamination with biologically active metal-containing impurities make this method unsuitable for bioconjugation.

1.1.4 Thiyl Radicals in Aqueous Medium

It is known that a broad range of synthetic scope across polymer science, bioconjugation, organocatalysis and heterocycle chemistry is displayed by highly reactive thiyl radical intermediates. Sulfur radicals have vital role in biological systems. In nature, the deoxygenation of ribonucleotide is carried out by cysteine mediated thiyl radicals. This transformation is employed by all living organisms in the synthesis of deoxyribonucleic acid (DNA).\textsuperscript{45} It is also known that cysteine residue in many proteins for instance thioredoxin, can act as sulfur radical precursor.\textsuperscript{45,46} Several enzymatic processes have been known to occur by involvement of those thiyl radicals. Sulfur radical chemistry has played a significant role in nature and biological systems and have captivated the recognition in organic synthesis.\textsuperscript{47,48}

A variety of sulfur radical reactions are known to be done in organic solvents. Previous studies have shown that sulfur radicals are adaptable in aqueous medium. Previous studies show that sulfur radicals will not be quenched in water, because of the bond dissociation energy of alkyl R-SH bond is 87 kcal/mol which is weaker than that of H-OH bond (BDE = 119.3 kcal/mol).\textsuperscript{48,49} Development of these radical reactions in aqueous media will be promising area for future studies. This advancement will expand the scope of sulfur radical reactions in area of glycopeptide chemistry because of solubility issues of protected peptides in organic solvents and hardships in purification of protected peptides.\textsuperscript{49}
1.1.5 Glycoconjugates

Glycoconjugate generally comprises of sophistication of molecules in which a carbohydrate moiety is linked to distinct molecule generally peptides or proteins. The physical, chemical, biological properties of glycoconjugates can vary adequately according to the presence of carbohydrate units in naturally occurring state or their mimetics. Many naturally occurring glycoproteins in various forms also known as glycoforms contain same peptide back-bone but differ in nature as well as site of glycosylation. To determine definite function through structure activity relationship (SAR) are often challenging due to number of characteristics displayed by each component within these microheterogeneous mixtures. Few studies have reported the comparison of single glycoforms successfully. The experimental research has shown that carbohydrates moieties can tune and detect particular tasks intrinsically as well as extrinsically by regulating the properties of protein to which they are bound. They can carry out this with exceptional control due to their remarkable structural diversity. Homogenous glycopeptides for biological studies are hard to obtain from biological sources due to challenging microheterogeneity in naturally produced glycopeptides. Therefore, it is important to the synthesize structurally defined glycopeptides for studying glycoproteins binding interactions and, cell-cell adhesion and receptor binding specificity.

Four distinct types of glycosylation are known and have been deeply studied: N-, O-, C-, S-glycosylation. The most relevant glycosyl-peptide linkages take place in glycoproteins are N-, O-linked structures. The replacement of anomeric oxygen, nitrogen atom by sulfur results in the S-linked glycopeptides which are known to be interesting synthetic targets due to their increased chemical stability. The first natural S-glycosidic linkage was discovered in 1971 by Lotte and Weiss. Following the discovery various methods have been developed for synthesis of S-linked
glycopeptides. Schmidt and co-workers in 2004 developed the synthetic method to synthesize S-linked glycopeptide analog obtained from Tamm-Horsfall glycoprotein (THP). THP is most abundant glycoprotein present in normal human urine. THP is known to play significant role in protecting kidneys from bacterial infection and in several pathological conditions.

Native O- and N-glycosidic of glycopeptides are vulnerable to hydrolytic cleavage by O- and N-glycosidases, whereas the synthetic C- and S- analogs show more endurance to the enzymatic degradation. Therefore, efforts are devoted towards synthesizing S-linked glycoconjugates and their applications in assembly of glycopeptides. It is easier to replace oxygen of O-linked glycoconjugate with sulfur atom to obtain isosteric mimicry. The S-linked glycopeptide modification is tolerated by most biological system. In addition, there is increase in stability of peptide-sugar linkage against chemical degradation.

The potential medicinal importance of glycoproteins and glycopeptides can be varied by modification of peptides and proteins with carbohydrate as it can alter the stability, structure and function of peptides or proteins. Various methods have been exploited to overcome this limitation and allowing applicability of the synthetic glycoproteins in some potentially useful therapeutic strategies. For example to enhance the binding to cognate receptors, a multivalent display of carbohydrate is exploited and such dendrimeric sugars can be further utilized in therapeutics as many key biological processes contain binding of sugar to the receptors.
1.2 Previous Work Done on Thiol-ene/ Thiol-yne Reactions

Yoon et al. developed radical thiol-ene reaction by using photoredox catalysis. The key thyl radical are generated from variety of thiols by photooxidation using Ru(bpz)$_3$(PF$_6$)$_2$ as catalyst. This method is limited by use excess of 4 equivalents of thiol.\textsuperscript{68} Later in 2014 Yoon addressed this limitation. They reported radical thiol-ene reaction initiated by photooxidation of sulfur-containing compounds in presence of transition metal catalyst Ru(bpz)$_3$(PF$_6$)$_2$ by using thiol as limiting reagent (Scheme 1.2).\textsuperscript{69} The success of this method lies in using $p$-toluidine as an additive which results in completion of reaction and leading to formation of desired product 8. Under these conditions variety of functional groups were tolerated. This reaction is also suitable for thiol-ene modification of cysteine containing biomolecules under aqueous conditions by assessing the conjugation of glutathione with different coupling partners of biological relevance.

\textbf{Scheme 1.2:} Transition metal mediated thiol-ene reaction.\textsuperscript{69}

In 2014, Stephenson demonstrated the thiol-ene reaction between thiol 9 and olefin 10 by using low catalyst loading of Ru(bpy)$_3$Cl$_2$ and substoichiometric quantities of redox additives bromotrichloromethane (Scheme 1.3).\textsuperscript{70} The scope comprises the coupling of alkyl, acyl, and benzyl thiols with alkenes. Solvent free amidation/hydrothiolation methodology was discovered during the process. Using this method pharmacologically relevant structural motifs were achieved successfully which further allows for the synthesis of structurally diversified thiomorpholinone derivatives.
Deming and Kramer demonstrated the method to synthesize glycopolymer-peptides that can undergo conformational changes. Thiol-ene coupling reaction between alkene terminated C-linked glycosides of D-galactose 12 to N-protected L-cysteine 13 can gain the hydrothiolation product 14 in high yield (94%). Radical thiol-ene reaction can be initiated by UVA lamp (λ\textsubscript{max} 365nm) in presence of catalytic amount of 2,2-dimethoxy-2-phenylacetophenone (DPAP) (Scheme 1.4).\(^7\)

The obtained hydrothiolation product is converted to α-amino acid N-carboxyanhydride (glyco-CNCA) monomers with Cl\textsubscript{2}CHOCH\textsubscript{3}. The living polymerization of glyco-C NCA monomer was accomplished by using (PMe\textsubscript{3})\textsubscript{4}CO as an initiator. This synthetic polymer sustains the α-helix to coil transition upon oxidation and remain water soluble in both states, suggesting potential utility of this approach for biomimetic studies.

Borbás et al. reported the free-radical hydrothiolation reaction between 2-acetoxy-D-glucal and variety of thiols to yield S-linked α-glucoconjugates and S-disaccharides with full regio- and stereoselectivity.\(^7\) This methodology can be applied to wide range of thiols including N-Acetyl-L-cysteine, captopril, tripeptide glutathione, glycosyl thiol and sugars with primary and secondary thiol functions in varying isolated yields (51%-88%). Solvent plays a major role in reaction
efficiency. Notably, the stereochemical outcome of thiol-ene reaction depends upon the glycan structure. The addition of ethanethiol 16 to hexose-derived 2-acetoxy glycals 15 advances with complete regio- and stereoselectivity providing 1,2-cis α-thioglucosides 17 (Scheme 1.5), explaining bulky C-6 group positioned on β-side of sugar ring which offers stereoselective formation of 1,2-cis C-2-radical intermediates upon addition of thiyl radical. The addition of ethanethiol to pentose-derived 2-acetoxy glycals resulted in loss of total selectivity whereas 2,3-unsaturated glycosides were found to be compatible with conditions.

Scheme 1.5: Free radical hydrothiolation reaction reported by Barbás et al.\textsuperscript{72}

Triola and co-workers accomplished the S-alkylated cysteines without racemization via radical initiated thiol-ene reaction.\textsuperscript{73} This was achieved in 3 steps, beginning with reduction of disulfide bond of N-Fmoc, O-tert butyl-protected cysteine with dithiothreitol (DTT), followed by azobisisobutyronitrile (AIBN) mediated thiol-ene coupling with hexadecene in dichloroethane (DCE) and lastly acid hydrolysis with trifluoroacetic acid (TFA) and triethylsilane (TES) afforded hexadecylated cysteine 19 in 42% isolated yield with 99% ee (Scheme 1.6).

Scheme 1.6: Formation of S-alkylated cysteines.\textsuperscript{73}

Molander et al. used dual nickel/photocatalytic cycle to develop cysteine arylation. The reaction is operated in DMF and uses aryl bromide as coupling partners and proceeds in presence of
ammonium bis(catechol) silicate as hydrogen atom transfer agent, \([\text{Ni(dtbbpy)}(\text{H}_2\text{O})_4]\text{Cl}_2\) (dtbbpy = 4,4’-di-tert-butyl-2,2’-dipyridyl) as cross-coupling catalyst, and \([\text{Ru(bpy)}_3(\text{PF}_6)_2]\) as photocatalyst (Scheme 1.7).

This reaction condition shows wide scope as glutathione exhibited coupling towards aryl bromides with various functional groups. These conditions were tolerated well by deprotected cysteine containing 9-mer peptide containing other reactive residues such as tryptamine, histidine, glutamine, tyrosine, with aryl bromides (20 equiv.). Carboxylate functionality and aromatic amino acids were shown not to interfere with the reaction, whereas the presence of arginine, proline, and lysine inhibited the reactivity.

Scheme 1.7: Dual catalytic system by Molander et al.\(^{74}\)

Greaney and co-workers replaced the transition metal catalyst with titanium dioxide (TiO\(_2\)) nanoparticles.\(^{75}\) The reaction was carried out between coupling partners primary alkyl and aryl thiols with primary and 1,1-disubstituted alkenes in presence of TiO\(_2\) (10 mol \%) irradiated by CFL light bulb (Scheme 1.8). In same year Fadeyi and co-workers demonstrated the use of Bi\(_2\)O\(_3\) as photocatalyst in combination with bromotrichloromethane as redox additive.\(^{76}\) A series of functional groups such as esters, alcohols, carboxylic acids, boronic pinacol esters were tolerated under these conditions.
Scheme 1.8: Thiol-ene reaction with titanium dioxide as catalyst.\textsuperscript{75}

In 2009, Dandoni et al. studied the hydrothiolation of allyl C-glycosides by SH-free cysteine derivative.\textsuperscript{77} They focused on coupling between peracetylated allyl-\(\alpha\)-C-galactoside 12 and N-Fmoc-cysteine 26 (2 equiv.) at room temperature by irradiation at \(\lambda_{\text{max}}\) 365 nm under argon in presence of 10\% DPAP as sensitizer to obtain galactosyl cysteine 27 in good yield (Scheme 1.9). This method development ensured efficient ligation method for site selective glycosylation of N- and C- protected cysteine derivative and for cysteine containing peptides such as glutathione. First site selective protein modification (hyperglycosylation) of bovine serum albumin (BSA) was reported in their studies.

Scheme 1.9: Hydrothiolation of allyl C-glycoside by SH free cysteine derivative.\textsuperscript{77}

Anseth et al. reported the synthetic route to on-resin peptide macrocyclization using type 1 photoinitiator, 2,2-dimethoxy-2-phenylacetophenone (DPAP) under irradiation of 365 nm light. A strained alkene was found to achieve cyclization within 20 min due to enhanced reaction kinetics.\textsuperscript{78} Later DeForest and Anseth used thiol-ene reaction for hydrogel conjugation with bioactive peptides. The introduction of photocleavable group in peptide chain promoted the photorelease of bioactive peptides into the surrounding medium. This success makes the method potentially useful in controlled drug release.\textsuperscript{79}
In 2010, Dondoni et al. developed a method for double glycosylation of cysteine-containing peptides (Scheme 1.10). They used nucleophilic substitution reaction under basic conditions with propargyl bromide to introduce alkyne functional group to cysteine molecule 28. Next, thiol-yne coupling between glucosyl thiol and alkylated cysteine 29 in MeOH in presence of 2,2-dimethoxy-2-phenylacetophenone (DPAP) under irradiation of 365 nm resulted in formation of bisthioether product 30 as mixture of diastereomers in yield of 53%. Under these conditions both unprotected sugars and peptides were tolerated and furnished bisthioether derivatives with \( >95\% \) transformation.  

Scheme 1.10: Double glycosylation of alkyne functional model cysteine substrate.  

Li and co-workers reported biorthogonal thiol-yne ligation method. Firstly, they incorporated alkynyl-pyrrolysine analogues into protein. Next, alkyne containing proteins were site-specifically dual-labelled with thiol containing fluorophores such as \( N, N'\)-bis(dansyl)cysteamine under 365 nm light irradiation in presence of radical initiator (Figure 1.2).  

Li and co-workers also reported the semiconductor-based photocatalysis. They made use of semiconductor based photocatalyst
ZnIn$_2$S$_4$ initiated by visible light to achieve the hydrothiolation of alkenes/alkynes with thiols in good yields. This method requires only stoichiometric amount of thiols and was tolerated well by variety of thiols and alkenes/alkynes.$^{82}$

**Figure 1.2**: Site specific thiol-ynе labeling of proteins carrying an alkyne handle.$^{81}$ Picture adapted with permission from [https://pubs.rsc.org/en/content/articlelanding/2013/OB/c3ob27116a](https://pubs.rsc.org/en/content/articlelanding/2013/OB/c3ob27116a)

Borbás and co-workers employed the thiol-ynе click chemistry in area of oligosaccharide mimics. They developed a method for synthesis of sialylated trisaccharide analogues. The reaction between 6-propargylated derivative and thiol in presence of photoinitiator DPAP afforded double thiosialytion minor adduct 33 in 11\% yield and $E/Z$ mixture of monosialylated vinyl sulfide 34 as major product in 82\% yield ([Scheme 1.11]).$^{83}$

**Scheme 1.11**: Thiol-ene click reaction for oligosaccharides.$^{83}$
In 2016, Ananikov et al. reported first metal free photoredox catalysis for formation of C-S bond by thiol-yne click chemistry.\textsuperscript{84} The thiol-yne reactions were initiated by 530 nm LED in presence of Eosin Y as photosensitizer resulting in wide range of vinyl sulfide adducts in unprecedented selectivities up to 60:1 (Scheme 1.12).

**Scheme 1.12:** Photocatalytic thiol-ene reaction by Ananikov et al.\textsuperscript{8}

Oshima et al. in 1998, described the radical reaction of benzenethiol \textsuperscript{38} to \(N\)-acetyldiallylamine \textsuperscript{39} in water at 60 °C in presence of 2,2’-azobis(2-methylpropanamidine) dihydrochloride leading to formation of \(N\)-acetylpyrrolidine derivative \textsuperscript{40} in 96% isolated yield. (Scheme 1.13)\textsuperscript{85}

**Scheme 1.13:** Sulfur radical addition in aqueous medium.\textsuperscript{85}

Besides the employment in small molecule synthesis, the Danishefsky-Wan desulfurization notably expands the scope of native chemical ligation (NCL) in peptide and protein synthesis. The cysteine in polypeptide \textsuperscript{41} can be converted to alanine \textsuperscript{42} in presence of water-soluble radical initiator Vazo44 (VA044, 2,2’-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride) (Scheme 1.14).\textsuperscript{86} The development of cysteine reduction protocol NCL strategy will no longer be confined
to cysteine site. Additionally, this metal free process can benefit the process for synthesis of glycopeptides and polypeptides.

Scheme 1.14: Danishefsky-Wan desulfurization.\textsuperscript{86}

In 2009, Davis and co-workers reported thiol-ene ligation strategy for protein modification that uses “tag-modify” approach for protein glycosylation.\textsuperscript{87} Thiol-ene coupling reaction of glycosyl thiol to L-homoallylglycine (L-Hag) resulted in formation of S-glycosyl amino acids in high yields. The hydrothiolation reaction carried out under photoinitiation of Vazo44 in aqueous medium resulted in convergent synthesis of S-linked glycoconjugates (Scheme 1.15). Use of excess thiol (3-10 equiv.) was key for complete conversion. This precise and site selective method accomplished S-linked virus-like particle Qβ (>95% yield).

Scheme 1.15: S-Linked glycoconjugate synthesis in aqueous medium.\textsuperscript{87}
1.3 Experimental Studies:

1.3.1 Development of Method for Formation of C-S Bond Using Thiol-ene/Thiol-yne Click Chemistry.

Intrigued by metal free opportunity, we report herein a strong oxidizing catalyst, 9-mesityl-10-methylacridinium tetrafluoroborate ($E_{1/2}^{\text{red}} = 2.06$ V vs SCE in MeCN) which acts as a visible light photoinitiator for thiol-ene/thiol-yne reactions. Our studies begin by examining thiol-ene reaction between benzyl mercaptan 46 and allyl alcohol 47 (Table 1.1). For initial studies a wide range of organic photocatalysts and reaction solvents were employed, we found that many organic catalysts successfully initiated the thiol-ene reactions under Blue LEDs irradiation in different solvent systems (Table 1.1 entries 1-14). While screening the reaction conditions, we observed that 9-mesityl-10-methylacridinium (A) in acetonitrile successfully provided the thiol-ene product in 90% isolated yield. This method requires only minimal excess of alkene (1.2 equiv.) for complete conversion of thiol to hydrothiolation product. Control experiments demonstrated that both catalyst and Blue LEDs irradiation are mandatory for reaction completion. (Table 1.1) shows studies for optimization of thiol-ene reaction using benzyl mercaptan with allyl alcohol. a
Reactions were conducted by irradiation of thiol (0.5 mmol), allyl alcohol (0.6 mmol), and photocatalyst A (1 mol %) in CH$_3$CN (1 mL) using two 12 W, 450 nm LED floodlamps for 6 h.  

**Table 1.1:** Optimization studies for thiol-ene reaction between benzyl mercaptan and allyl alcohol.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>CH$_2$Cl$_2$</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>THF</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>MeCN</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>DMF</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>1,4-Dioxane</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>PhMe</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>MeOH</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>B</td>
<td>MeCN</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>C</td>
<td>MeCN</td>
<td>69</td>
</tr>
<tr>
<td>10</td>
<td>Rhodamine 6G</td>
<td>MeCN</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>Riboflavin</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Eosin Y</td>
<td>MeCN</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>Rose Bengal</td>
<td>MeCN</td>
<td>33</td>
</tr>
<tr>
<td>14</td>
<td>Methylene blue</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>None</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>16$^c$</td>
<td>A</td>
<td>MeCN</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Reactions were conducted by irradiation of thiol (0.5 mmol), allyl alcohol (0.6 mmol), and photocatalyst A (1 mol %) in CH$_3$CN (1 mL) using two 12 W, 450 nm LED floodlamps for 6 h.  

$^b$Isolated yields.
1.3.2 Scope of Photocatalytic Thiol-ene Reaction.

Encouraged by these results we next evaluated the scope of thiols that can contribute to coupling process. Scheme 1.16 represents the scope of thiols that can be activated by using the optimized conditions. We were delighted to see that thiol-ene reaction between primary thiols such as benzyl mercaptan, para-methoxy benzyl mercaptan, methyl thioglycolate, cysteine derivative and allyl alcohol resulted in hydrothiolation adducts (52, 53, 54, and 55) in excellent isolated yields (82%-90%). Bulky thiols secondary thiols and tertiary thiols reacted efficiently with allyl alcohol to produce thiol-ene products (56-59) in high yields (77%-90%). Happily, aromatic thiols such as thiophenol were converted to corresponding thioether (60) in good yield (88%). The method was then evaluated on variety of alkenes. We were pleased to find that both styrene and aliphatic alkenes were tolerated well under these conditions to afford adducts (61-62) in good yields (90%-87%). We also found 1,1-disubstituted and 1,2-disubstituted alkenes were tolerated under the efficient conditions to give desired products (63-65) in good yields (80-83%). Various functional groups such as ester (66), formyl amide (67), alcohols (68), and silanes (69) were tolerated under this thiol-ene photocatalytic system. High anti-Markovnikov’s regioselectivity was examined in all the cases which is agreeable with the proposed radical pathway.
Scheme 1.16: Scope of photocatalytic thiol-ene reaction.
1.3.3 Thiol-ene Conjugations

Delighted by these results, we next evaluated the scope of this thiol-ene coupling process on formation of glycoconjugates from glycosyl thiols (Scheme 1.17a). We were pleased to see that thiol-ene reaction between various glycosyl thiols and an aspartic acid derivative resulted in formation of S-linked glycoconjugates (70-73) in excellent yields (73%-85%).

Under the optimized conditions glucosyl thiol can coupled with carbohydrate derivative to afford S-linked carbohydrate mimic (74) in yield of 91%. Next, we tried the efficient coupling of glucose thiol with nucleoside derivatives, and N-terminus functionalized dipeptide, resulting in S-linked glyconucleoside (75) and glycopeptide (76) in yields of 78% and 79% respectively. The reverse fashion of coupling between protected cysteine derivative and various alkenes resulted in corresponding conjugated adducts in good yields (Scheme 1.17b, 77-81, 75-90%). These examples signify the promising use of this synthetic method for bioconjugation.
Scheme 1.17: Photocatalytic thiol-ene conjugations.
1.3.4 Scope of Thiol-yne Reactions

Our next aim was to determine the applicability of this catalytic system on thiol-yne reaction (Scheme 1.17). Thiol-yne catalytic system preferably results in the first hydrothiolation between thiol (82) and alkyne (83) affording a vinyl sulfide adduct 84a, which further reacts with another molecule of thiol to result in formation of double hydrothiolation product 84b (Scheme 1.18a). Less sterically hindered thiols resulted in formation of double hydrothiolation products in good yields (85-88, 72%-95%). Even smaller stoichiometric amounts of thiol (82) resulted in the mixture of vinyl sulfide 84a and double hydrothiolation product 84b. We realized that it is challenging to control the reaction in first stage. Using more sterically hindered thiols, we realized that vinyl sulfides can be obtained as mixture of E:Z isomers (89-91, 70%-83%). However, in case of thiophenol we were able to control the reaction process in first and second stage by varying the time and amount of thiol and catalysts. The coupling of alkyne with stoichiometric amount of thiophenol under irradiation of light for 2 hours resulted in vinyl sulfide 92 in 63% yield. However, by changing the reaction time to 14 hours, catalyst amount to 3 mol% and using excess thiophenol (4 equiv.) resulted in double hydrothiolation product 93 in 96% isolated yield.
Scheme 1.18: Photocatalytic thiol-yne reactions. \(^a\)Reactions irradiated with two 12 W, 450 nm LED floodlamps for 14 h. \(^b\)Reactions irradiated with two 12 W, 450 nm LED flood lamps for 2 h.
1.3.5 Thiol-yne Conjugations

We next applied this photocatalytic system for thiol-yne conjugations (Scheme 1.19). We were delighted to see that glucosyl thiol was coupled with wide range of alkyne containing amino acids such as glycine, valine, cysteine, aspartic acid, tyrosine, and serine derived terminal alkyne resulting in S-linked glycoconjugates in excellent yields. (94-98, 61-73%). Both Boc protected amino groups and Fmoc protected amino groups were tolerated well under these efficient and mild conditions. Thiol-yne catalytic system was applied to coupling of glycosyl thiol with dipeptide to obtain S-linked dipeptide 99 in 65% yield.

Scheme 1.19: Photocatalytic thiol-yne conjugations.
1.3.6 Mechanism for Thiol-ene/Thiol-yne Recations

Photoexcitation of catalyst A results in strong oxidizing state (A*) which can further oxidize thiol to form thiol radical and one electron reduced acridinium 100. The intended oxidation of thiol over alkene depends upon their difference in reduction potentials. Next, the deprotonation of thiol radical cation results in formation of thiol radical which then couples with alkene in anti-Markovnikov’s selectivity to result in formation of C-S bond. The obtained alkyl radical can abstract hydrogen atom from another thiol to form thiol-ene adduct and further develops one more equivalent of thiol radical. Based on our experimental studies light irradiation is required for the reaction completion. Further, a molecule of oxygen results in oxidation of catalyst to regenerate the photocatalyst A. In thiol-yne photocatalytic system the thiol radical can react with alkyne to obtain vinyl radical which can further abstract a hydrogen atom from thiol to afford hydrothiolation product 101A. The resulting vinyl sulfide can then react with another thiol radical to furnish double hydrothiolation product 101B (Scheme 1.20).

Scheme 1.20: Proposed mechanism for thiol-ene/thiol-yne reaction.
1.3.7 Thiol-ene Reactions in Aqueous Medium

Having demonstrated the efficiency of thiol-ene and thiol-yne reactions in organic solvent reaction medium, we were interested in seeking an opportunity to apply our photocatalytic thiol-ene system in aqueous medium. To test the idea, we started our investigation by examining the thiol-ene reaction between glycosyl thiol (102) and allyl alcohol (103) in water in presence of organic photocatalyst (9-mesityl-10-methylacridinium tetrafluoroborate). We were delighted to see that thiol-ene adduct afforded in good yield under blue LEDs irradiation (72%, Scheme 1.21a). The reaction performance increased in CH₃CN: H₂O (1:1) mixture probably because of better solubility of protected glycosyl thiols in solvent (85%, Scheme 1.21b). Many glycoconjugate reactions are performed in aqueous buffers, we next planned to perform these reactions in buffers with common pH value, pH=6, pH=8 respectively (Scheme 1.21). The reaction resulted in formation of desired thiol-ene product 104 and an unexpected disulfide product 105 was isolated in 12% and 20% respectively (Scheme 1.21c, d). The result trend shows that byproduct formation was increased in more basic aqueous medium.
Scheme 1.21: Photocatalytic thiol-ene reactions in aqueous medium.
After seeing the unexpected formation of disulfide product, we tried organic solvent to check if base additive can change the thiol-ene reaction outcome. From our previous studies, it is known that thiol-ene adduct 107 can be obtained in good yield between benzyl mercaptan (106, 1 equiv.) and allyl alcohol (103, 1.2 equiv.) (Scheme 1.2). Next, triethylamine as an additive in different reaction. Surprisingly, we only got disulfide product 108. Disulfide formations in presence of base under photocatalytic system are consistent with previous work reported by Noel.92

![Scheme 1.2: Base promoted disulfide formation.](image)

We were interested in competing reaction pathway between thiol-ene and disulfide formation. We started by screening effect of pH value in aqueous medium. Davis and co-workers have reported glycoconjugate formation is favored in more acidic medium (pH = 4).93 We tried photocatalytic reaction in pH = 4 buffer (Table 1.2, entry 3). We saw that suppression of disulfide formation (5% of 105, Table 1.2, entry 3). Whereas more disulfide product was obtained in more basic medium (pH = 8 buffer, 36% of 105, Table 1.2, entry 4). The trend indicated that more acidic medium favors thiol-ene products, while the basic medium enhances the dimerization. Finally, we were able to suppress the formation of disulfide product at pH = 2.6 buffer, affording thiol-ene adduct 104 as only product with 72% yield (Table 1.2, entry 5). Control experiment indicates that light is necessary for this reaction, excluding the possibility of acid promoted reaction in such acidity medium.94
Intrigued by the success of thiol-ene photocatalytic system in aqueous medium, we wanted to evaluate the scope of this reaction in unprotected peptides. To our delight, the reaction between unprotected pentapeptide 109 with tethering an alkene on aspartic acid side chain with thioglycoside 102 resulted in formation of desired glycopeptide 110 in 50% isolated yield (Scheme 1.23).  

Scheme 1.23: Photocatalytic thiol-ene reaction of unprotected pentapeptide.

To expand the scope of alkene and thiol, we tried following reactions (Scheme 1.24). We have also tried the reaction with galactose thiol and allyl alcohol (Scheme 1.24a). To our delight, we saw the desired product 112 in 83% yield. We then tried to see the adaptability of reaction with dipeptide alkene 113 (Scheme 1.24b). The thiol-ene photocatalytic system resulted in corresponding adduct 115 in 65% yield.

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**Table 1.2:** Photocatalytic thiol-ene reaction in buffer.  

| entry | catalyst | solvent | yield (%)<sup>b</sup> 104 | yield (%)<sup>b</sup> 105  
|-------|----------|---------|--------------------------|--------------------------  
| 1     | A        | Buffer pH = 4 | 57 | 5  
| 2     | A        | Buffer pH = 6 | 56 | 12  
| 3     | A        | Buffer pH = 8 | 30 | 20  
| 4     | A        | Buffer pH = 10 | 20 | 30  
| 5     | A        | Buffer pH = 2.6 | 72 | 0  
| 6<sup>c</sup> | A | Buffer pH = 2.6 | 0 | 0  

<sup>a</sup>Reactions were conducted by irradiating thiol (0.137 mmol), alkene (0.165 mmol) and the photocatalyst (1 mol %) in solvent (0.274 mL) with two 12W, 450 nm LED floodlamps for 6 h.  
<sup>b</sup>Isolated yield.  
<sup>c</sup>Reaction conducted in dark.

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**Scheme 1.24:** Photocatalytic thiol-ene reaction of unprotected pentapeptide.
Scheme 1.24: Scope of reaction

1.3.8 Mechanism for Thiol-ene Reaction in Aqueous Medium

A proposed mechanism for thiol-ene product and disulfide product formation is outlined in Scheme 1.25. Upon photocatalytic single electron oxidation of thiol 116, key intermediates thiy radical are generated with one electron reduced acridinium. We proposed two pathways. First, in acidic medium release of thiy radical is slow which results in lower concentration of thiy radical. Thiol-ene adduct will be favored in first pathway, coupling with alkenes in anti-Markovnikov’s selectivity. Secondly, in basic medium the thiy radical will be released much faster, resulting in relatively high concentration of thiy radicals which favors dimerization, affording disulfide product. The oxidation of 100 by molecule of oxygen will result in regeneration of active catalyst A.
1.3.9: Conclusion
We were able to develop metal free visible-light-mediated thiol-ene and thiol-yne reactions for the formation of S-linked glycoconjugates. This method was further explored in aqueous medium and buffer systems to expand potential use of this method in bioconjugation.

1.4 Supporting Information
1.4.1 General Information
All commercially available chemicals were used without further purification unless otherwise noted. All reactions were carried out in well-ventilated fume hoods. Reactions were monitored by TLC on silica gel 60 F254. Flash column chromatography was performed using SiliaFlash P60 silica gel (40-63 μm). Visualization of developed TLC was performed by irradiation with UV light.
or treatment with a solution of ninhydrin or ceric ammonium molybdate stain followed by heating. Yields refer to purified compound unless otherwise noted. 

\(^1\)H NMR and \(^{13}\)C NMR spectra were recorded on a Bruker AM 400 MHz and 500 MHz spectrometers. Chemical shifts were reported as parts per million (ppm) relative to residual solvent CDCl\(_3\) (\(^1\)H, 7.26 ppm, \(^{13}\)C, 77.0 ppm). The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Infrared spectra were recorded on a PerkinElmer Spectrum Two IR spectrometer. Absorption bands are reported in wavenumbers (cm\(^{-1}\)) in the range of 4000-800 cm\(^{-1}\). High-resolution mass spectral analysis (HRMS) data were obtained using Agilent Technologies 6530 Accurate mass Q-TOF LC/MS. Technologies 6530 Accurate Mass Q-TOF LC/MS. Irradiation of photochemical reactions was carried out using two 12W 450nm Blue LEDs.

1.4.2 Experimental Procedures and \(^1\)H and \(^{13}\)C NMR

1.4.2.1 General Procedure for Thiol-ene Reaction:

To an oven-dried 1.5-dram vial equipped with a stirbar were added 0.5 mmol thiol, 0.6 mmol olefin, 0.005 mmol Mes-Acr-Me\(^+\)BF\(_4^-\), and 1 mL acetonitrile. The vial was sealed with a teflon cap and stirred at room temperature under irradiation with blue LEDs. Upon completion of the reaction, the solution was concentrated \textit{in vacuo}, and the residue was purified by flash column chromatograph to afford the thiol-ene adducts.

\[
\begin{align*}
\text{52} & \\
\end{align*}
\]

3-(benzylthio)propan-1-ol (52): To an oven-dried 1.5 dram vial equipped with a stirbar were added benzyl mercaptan (62 mg, 0.5 mmol), allyl alcohol (35 mg, 0.6 mmol), Mes-Acr-Me\(^+\)BF\(_4^-\) (2.4 mg, 0.005 mmol), and acetonitrile (1 mL). The vial was sealed with a teflon cap and stirred at
room temperature under irradiation with blue LEDs. Upon completion of the reaction (6 hours), the solution was concentrated in vacuo, and the residue was purified by flash column chromatography (hexanes/EtOAc = 4/1) to afford the colorless oil 82 mg (90%). For a synthetic method example of 1 mmol scale reaction: To an oven-dried 1.5-dram vial equipped with a stir bar were added benzyl mercaptan (124 mg, 1.0 mmol), allyl alcohol (70 mg, 1.2 mmol), Mes-Acr-Me+BF4- (4.8 mg, 0.01 mmol), and acetonitrile (2 mL). The vial was sealed with a teflon cap and stirred at room temperature under irradiation with blue LEDs. Upon completion of the reaction (10 hours), the solution was concentrated in vacuo, and the residue was purified by flash column chromatography (hexanes/EtOAc = 4/1) to afford the colorless oil 160 mg (88% yield).

1H NMR (400 MHz, CDCl3) δ 7.32 (d, J = 4.3 Hz, 4H), 7.29 – 7.19 (m, 1H), 3.71 (dd, J = 11.4, 5.2 Hz, 4H), 2.54 (t, J = 7.0 Hz, 2H), 1.81 (dt, J = 13.2, 6.6 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 138.3, 128.8, 128.5, 126.9, 61.6, 36.2, 31.5, 27.9.

3-((4-methoxybenzyl)thio)propan-1-ol (53): Colorless oil. 92 mg (0.43 mmol, 87% yield). 1H NMR (400 MHz, CDCl3) δ 7.21 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.69 – 3.63 (m, 4H), 2.50 (t, J = 7.1 Hz, 2H), 2.29 (s, 1H), 1.82 – 1.73 (m, 2H). 13C NMR (100 MHz, CDCl3) δ 158.4, 130.1, 129.7, 113.7, 61.4, 55.1, 35.4, 31.5, 27.7.
methyl 2-((3-hydroxypropyl)thio)acetate (54): Colorless oil. 67 mg (0.41 mmol, 82% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.75 – 3.69 (m, 5H), 3.23 (s, 2H), 2.74 (t, $J$ = 7.1 Hz, 2H), 2.05 (s, 1H), 1.83 (ddd, $J$ = 12.2, 7.1, 6.1 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.0, 61.1, 52.4, 33.4, 31.4, 29.2.

methyl N-(tert-butoxycarbonyl)-S-(3-hydroxypropyl)-L-cysteinate (55): Colorless oil. 126 mg (0.43 mmol, 86% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.43 (d, $J$ = 7.8 Hz, 1H), 4.47 (d, $J$ = 6.0 Hz, 1H), 3.71 (d, $J$ = 1.1 Hz, 3H), 3.66 (dd, $J$ = 6.8, 2.5 Hz, 2H), 2.97 – 2.81 (m, 2H), 2.67 – 2.46 (m, 3H), 1.83 – 1.67 (m, 2H), 1.39 (d, $J$ = 1.1 Hz, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.6, 155.1, 80.1, 60.7, 52.9, 52.5, 34.6, 31.7, 28.9, 28.2.

3-(cyclohexylthio)propan-1-ol (56): Colorless oil. 78 mg (0.45 mmol, 90% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.71 (t, $J$ = 6.1 Hz, 2H), 2.62 (dd, $J$ = 8.9, 5.3 Hz, 3H), 2.13 (s, 1H), 1.99 – 1.89 (m, 2H), 1.85 – 1.76 (m, 2H), 1.73 (dd, $J$ = 7.7, 5.4 Hz, 2H), 1.63 – 1.53 (m, 1H), 1.35 – 1.16 (m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 61.9, 43.4, 33.6, 32.2, 26.8, 26.0, 25.7. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3344, 2925, 2850, 1447, 1341, 1263, 1202, 1150, 1050, 998, 905, 885; HRMS (ESI): m/z Calcd for C$_9$H$_{18}$NaOS$^+$ (M+Na)$^+$: 197.0971; found: 197.0974.

3-((1-phenylethyl)thio)propan-1-ol (57): Colorless oil. 81 mg (0.42 mmol, 83% yield). $^1$H NMR
\[
\begin{align*}
(400 \text{ MHz}, \text{CDCl}_3) \delta & \ 7.40 - 7.31 (m, 4H), 7.27 - 7.18 (m, 1H), 3.97 (q, J = 7.0 Hz, 1H), 3.63 (t, J = 6.1 Hz, 2H), 2.42 (qt, J = 12.8, 7.1 Hz, 2H), 2.03 (s, 1H), 1.83 - 1.63 (m, 2H), 1.58 (d, J = 7.1 Hz, 3H). \quad ^{13}\text{C NMR} \ (100 \text{ MHz}, \text{CDCl}_3) \delta 143.8, 128.4, 127.1, 127.0, 61.5, 44.0, 31.6, 27.8, 22.4. \quad \text{IR (CH}_2\text{Cl}_2, \text{cm}^{-1}) 3351, 3027, 2925, 1601, 1491, 1451, 1373, 1264, 1222, 1053, 1026, 907; \quad \text{HRMS (ESI): m/z Calcd for C}_{11}\text{H}_{16}\text{NaOS}^+ (M+Na)^+: 219.0814; \text{ found: 219.0819.}
\end{align*}
\]

3-(tert-butythio)propan-1-ol (58): Colorless oil. 63 mg (0.43 mmol, 85% yield). \(^1\text{H NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta 3.71 (t, J = 6.1 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H), 2.03 (s, 1H), 1.87 - 1.75 (m, 2H), 1.30 (s, 9H). \quad ^{13}\text{C NMR} \ (100 \text{ MHz}, \text{CDCl}_3) \delta 62.0, 42.1, 32.3, 30.9, 25.0.

\[
\begin{align*}
\text{3-((3s,5s,7s)-adamantan-1-ythio)propan-1-ol (59): Colorless oil. 87 mg (0.39 mmol, 77\% yield). \quad ^1\text{H NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta & \ 3.70 (t, J = 6.1 Hz, 2H), 2.60 (t, J = 7.2 Hz, 2H), 2.10 (s, 1H), 2.00 (s, 3H), 1.86 - 1.74 (m, 8H), 1.72 - 1.59 (m, 6H). \quad ^{13}\text{C NMR} \ (100 \text{ MHz}, \text{CDCl}_3) \delta 62.0, 44.2, 43.5, 36.2, 32.6, 29.6, 22.4. \quad \text{IR (CH}_2\text{Cl}_2, \text{cm}^{-1}) 3361, 2902, 2848, 1448, 1342, 1300, 1264, 1101, 1042, 976, 907; \quad \text{HRMS (ESI): m/z Calcd for C}_{13}\text{H}_{22}\text{NaOS}^+ (M+Na)^+: 249.1284; \text{ found: 249.1294.}
\end{align*}
\]

3-(phenylthio)propan-1-ol (60): Colorless oil. 74 mg (0.44 mmol, 88% yield). \(^1\text{H NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \delta 7.39 - 7.25 (m, 4H), 7.22 - 7.13 (m, 1H), 3.77 (t, J = 6.1 Hz, 2H), 3.04 (t, J = 7.1
Hz, 2H), 1.89 (tt, $J = 7.0, 6.1$ Hz, 2H), 1.68 (d, $J = 0.9$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 136.2, 129.2, 128.9, 126.0, 61.3, 31.6, 30.2.

![benzyl(phenethyl)sulfane (61)](image)

**benzyl(phenethyl)sulfane (61):** Colorless oil. 86 mg (0.38 mmol, 76% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.19 (m, 10H), 3.79 (s, 2H), 3.01 – 2.87 (m, 2H), 2.75 (dd, $J = 9.2, 6.5$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 140.4, 138.3, 128.8, 128.4, 128.3, 126.9, 126.2, 36.3, 35.9, 32.7.

![benzyl(octyl)sulfane (62)](image)

**benzyl(octyl)sulfane (62):** Colorless oil. 102 mg (0.44 mmol, 87% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.33 (t, $J = 6.5$ Hz, 4H), 7.26 (dt, $J = 5.0, 3.4$ Hz, 1H), 3.73 (s, 2H), 2.43 (dd, $J = 7.4$ Hz, 2H), 1.69 – 1.50 (m, 2H), 1.47 – 1.19 (m, 10H), 0.92 (t, $J = 6.7$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.6, 128.74, 128.3, 126.7, 36.2, 31.7, 31.3, 29.2, 29.1, 28.8, 22.6, 14.0.

![4-(benzylthio)-3-methylbutan-1-ol (63)](image)

**4-(benzylthio)-3-methylbutan-1-ol (63):** Colorless oil. 87 mg (0.41 mmol, 83% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.31 (d, $J = 4.4$ Hz, 4H), 7.24 (dd, $J = 8.5, 4.2$ Hz, 1H), 3.70 (s, 2H), 3.67 – 3.55 (m, 2H), 2.43 (dd, $J = 12.7, 6.1$ Hz, 1H), 2.32 (dd, $J = 12.7, 7.0$ Hz, 1H), 1.93 (s, 1H), 1.80 (dq, $J = 13.2, 6.6$ Hz, 1H), 1.68 (td, $J = 13.1, 6.5$ Hz, 1H), 1.41 (td, $J = 13.7, 6.8$ Hz, 1H), 0.99 (d, $J = 6.7$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.4, 128.7, 128.3, 126.8, 60.5, 38.8, 38.7, 36.6, 29.6, 19.5.
benzyl(cyclohexyl)sulfane (64): Colorless oil. 85 mg (0.41 mmol, 83% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.34 \text{ (t, } J = 7.0 \text{ Hz, 4H), 7.31 – 7.13 \text{ (m, 1H), 3.77 (s, 2H), 2.67 – 2.45 \text{ (m, 1H), 2.09 – 1.91 \text{ (m, 2H), 1.77 (dd, } J = 8.1, 4.4 \text{ Hz, 2H), 1.62 \text{ (d, } J = 2.7 \text{ Hz, 1H), 1.44 – 1.22 \text{ (m, 5H).} \)\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 138.9, 128.7, 128.4, 126.7, 42.8, 34.5, 33.3, 25.9, 25.8.\)

benzyl(2,3-dihydro-1H-inden-2-yl)sulfane (65): Colorless oil. 96 mg (0.40 mmol, 80% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.46 – 7.35 \text{ (m, 4H), 7.30 \text{ (t, } J = 7.0 \text{ Hz, 1H), 7.26 – 7.16 \text{ (m, 4H), 3.86 (s, 2H), 3.54 (p, } J = 7.4 \text{ Hz, 1H), 3.30 (dd, } J = 15.9, 7.7 \text{ Hz, 2H), 2.99 (dd, } J = 15.9, 7.0 \text{ Hz, 2H).} \)\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 141.7, 138.5, 128.7, 128.5, 126.9, 126.5, 124.3, 42.4, 40.3, 36.1. \)HRMS (ESI): m/z Calcd for C\(_{16}\)H\(_{17}\)S\(^+\) (M+H\(^+\)): 241.1045; found: 241.1049.

1-(benzylthio)propan-2-yl acetate (66): Colorless oil. 96 mg (0.43 mmol, 86% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.31 \text{ (dd, } J = 14.0, 5.3 \text{ Hz, 4H), 7.25 (dt, } J = 8.8, 3.6 \text{ Hz, 1H), 5.03 (q, } J = 6.3 \text{ Hz, 1H), 3.75 (s, 2H), 2.60 (dd, } J = 13.8, 6.4 \text{ Hz, 1H), 2.49 (dd, } J = 13.8, 6.1 \text{ Hz, 1H), 2.05 (s, 3H), 1.28 (d, } J = 6.3 \text{ Hz, 3H).} \)\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 170.4, 138.0, 128.9, 128.5, 127.0, 69.5, 36.5, 36.4, 21.3, 19.3.\)
N-(2-(benzylthio)ethyl)formamide (67): Colorless oil. 80 mg (0.41 mmol, 82% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08 (s, 1H), 7.36 – 7.19 (m, 5H), 6.18 (s, 1H), 3.71 (s, 2H), 3.40 (q, $J$ = 6.2 Hz, 2H), 2.57 (t, $J$ = 6.4 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.1, 137.9, 128.8, 128.6, 127.2, 36.5, 35.8, 30.9. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3263, 2918, 2862, 1658, 1502, 1493, 1452, 1382, 1225, 1071, 1028; HRMS (ESI): m/z Calcd for C$_{10}$H$_{13}$NNaOS$^+$ (M+Na)$^+$: 218.0610; found: 218.0611.

1-(benzylthio)octan-3-ol (68): Colorless oil. 107 mg (0.42 mmol, 85% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32 (d, $J$ = 4.5 Hz, 4H), 7.30 – 7.13 (m, 1H), 3.73 (s, 2H), 3.69 (dd, $J$ = 7.6, 3.9 Hz, 1H), 2.65 – 2.42 (m, 2H), 1.82 – 1.56 (m, 3H), 1.41 (s, 3H), 1.38 – 1.20 (m, 5H), 0.90 (t, $J$ = 6.6 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.3, 128.8, 128.5, 126.9, 71.0, 37.4, 36.3, 36.2, 31.8, 27.9, 25.2, 22.6, 14.0. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3389, 2927, 2856, 1601, 1494, 1453, 1377, 1238, 1124, 1070, 1029, 915; HRMS (ESI): m/z Calcd for C$_{15}$H$_{24}$NaOS$^+$ (M+Na)$^+$: 275.1440; found: 275.1447.

(3-(benzylthio)propyl)trimethylsilane (69): Colorless oil. 95 mg (0.40 mmol, 80% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 (dd, $J$ = 9.7, 2.9 Hz, 4H), 7.31 – 7.14 (m, 1H), 3.73 (s, 2H), 2.46 (t, $J$ = 7.4 Hz, 2H), 1.77 – 1.44 (m, 2H), 0.71 – 0.41 (m, 2H), 0.01 (d, $J$ = 0.5 Hz, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.7, 128.7, 128.5, 126.8, 36.2, 35.0, 23.93, 16.3.
1.4.2.2 General Procedure for Thiol-ene Conjugations

To an oven dried vial equipped with stirbar were added thiol (0.2 mmol), followed by olefin (0.24 mmol), Catalyst A (0.002 mmol), and acetonitrile (1 mL). The vial was sealed with Teflon cap and stirred at room temperature under irradiation with Blue LEDs. Upon completion of reaction, the solvent was evaporated, and the residue was purified with flash column chromatography to yield thiol-ene adduct.

1-benzyl4-(3-(((2S,3R,5R,6R)-3,4,5-triaceoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)thio)propyl) (tert-butoxycarbonyl)-L-aspartate (70):
White solid. 272 mg (0.38 mmol, 75% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34 (d, $J$ = 7.3 Hz, 5H), 5.52 (d, $J$ = 8.4 Hz, 1H), 5.26 – 5.12 (m, 3H), 5.10 – 4.99 (m, 2H), 4.61 (d, $J$ = 7.7 Hz, 1H), 4.48 (d, $J$ = 10.0 Hz, 1H), 4.23 (dd, $J$ = 12.4, 4.9 Hz, 1H), 4.17 – 4.06 (m, 3H), 3.75 – 3.67 (m, 1H), 2.99 (dd, $J$ = 16.9, 4.3 Hz, 1H), 2.82 (dd, $J$ = 16.9, 4.8 Hz, 1H), 2.69 (dtd, $J$ = 20.3, 13.4, 7.2 Hz, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.89 (dd, $J$ = 13.2, 6.5 Hz, 2H), 1.42 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.9, 170.6, 170.5, 170.1, 169.3, 155.3, 135.2, 128.5, 128.4, 128.1, 85.0, 80.1, 75.9, 73.7, 69.7, 68.3, 67.4, 63.2, 62.0, 50.1, 36.7, 28.7, 28.2, 26.4, 20.6, 20.6, 20.5. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3378, 2975, 1741, 1499, 1455, 1366, 1215, 1162, 1036, 914; HRMS (ESI): m/z Calcd for C$_{33}$H$_{45}$NNaO$_{15}$S$^+$ (M+Na)$^+$: 750.2402; found: 750.2411.
1-benzyl4-(3-(((2S,3R,5S,6R)-3,4,5-triacetoxy-6-(acetoxyethyl)tetrahydro-2H-pyran-2-yl)thio)propyl) (tert-butoxycarbonyl)-L-aspartate (71):

Colorless oil. 265 mg (0.36 mmol, 73% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.33 (d, $J = 7.1$ Hz, 5H), 5.51 (d, $J = 8.4$ Hz, 1H), 5.41 (d, $J = 3.2$ Hz, 1H), 5.27 – 5.10 (m, 3H), 5.03 (dd, $J = 10.0$, 3.2 Hz, 1H), 4.66 – 4.54 (m, 1H), 4.46 (d, $J = 9.9$ Hz, 1H), 4.22 – 4.02 (m, 4H), 3.92 (t, $J = 6.6$ Hz, 1H), 2.86 – 2.60 (m, 3H), 2.13 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.8, 170.6, 170.2, 170.1, 169.9, 169.5, 155.2, 135.1, 128.4, 128.3, 128.1, 84.1, 80.0, 74.3, 71.7, 67.3, 67.1, 66.9, 63.2, 61.3, 50.0, 36.6, 28.7, 28.1, 26.6, 20.7, 20.6, 20.5, 20.5. IR (CH$_2$Cl$_2$, cm$^{-1}$) 2983, 1748, 1499, 1422, 1367, 1264, 1222, 1160, 1054, 896; HRMS (ESI): m/z Calcd for C$_{33}$H$_{45}$NNaO$_{15}$S$^+$ (M+Na)$^+$: 750.2402; found: 750.2407.

1-benzyl4-(3-(((2S,3R,5R)-3,4,5-triacetoxytetrahydro-2H-pyran-2-yl)thio)propyl) (tert-butoxycarbonyl)-L-aspartate (72):
White solid. 252 mg (0.38 mmol, 77% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 (s, 5H), 5.52 (d, $J = 8.0$ Hz, 1H), 5.30 – 5.10 (m, 3H), 5.03 – 4.87 (m, 2H), 4.70 – 4.56 (m, 1H), 4.51 (d, $J = 8.6$ Hz, 1H), 4.20 (dd, $J = 11.6$, 5.0 Hz, 1H), 4.10 (t, $J = 5.9$ Hz, 2H), 3.49 – 3.28 (m, 1H), 3.00 (dd, $J = 17.1$, 3.9 Hz, 1H), 2.82 (dd, $J = 16.9$, 4.7 Hz, 1H), 2.78 – 2.54 (m, 2H), 2.09 – 1.99 (m, 9H), 1.91 – 1.81 (m, 2H), 1.42 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.9, 170.7, 169.9, 169.7, 169.4, 155.3, 135.2, 128.5, 128.3, 128.1, 83.6, 80.1, 72.1, 69.6, 68.5, 67.3, 65.5, 63.3, 50.0, 36.7, 28.6, 28.2, 26.4, 20.7, 20.7, 20.6. IR (CH$_2$Cl$_2$, cm$^{-1}$) 2978, 1741, 1498, 1455, 1367, 1264, 1217, 1162, 954, 937, 908, 876; HRMS (ESI): m/z Calcd for C$_{30}$H$_{41}$NNaO$_{13}$S$^+$ (M + Na)$^+$: 678.2191; found: 678.2194.

**1-benzyl4-(3-(((2R,3S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)thio)propyl) (tert-butoxycarbonyl)-L-aspartate (73):**

Colorless oil. 85% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37 – 7.21 (m, 5H), 5.49 (d, $J = 8.3$ Hz, 1H), 5.36 – 5.02 (m, 6H), 4.57 (s, 1H), 4.39 – 4.21 (m, 2H), 4.07 (t, $J = 10.5$ Hz, 3H), 2.94 (d, $J = 16.9$ Hz, 1H), 2.79 (dd, $J = 16.8$, 4.6 Hz, 1H), 2.72 – 2.50 (m, 2H), 2.12 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.95 (s, 3H), 1.90 – 1.84 (m, 2H), 1.39 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.7, 170.5, 170.3, 169.7, 169.5, 169.4, 155.2, 135.1, 128.4, 128.2, 128.0, 82.6, 79.9, 77.3, 77.0, 76.7, 70.9, 69.2, 69.0, 67.2, 66.1, 63.0, 62.3, 49.9, 36.6, 28.3, 28.1, 27.8, 20.7, 20.5, 20.4. IR (CH$_2$Cl$_2$, cm$^{-1}$) 2980, 1743, 1499, 1367, 1263, 1221, 1103, 1048, 975, 898, 732, 701; HRMS (ESI): m/z Calcd for C$_{33}$H$_{45}$NNaO$_{13}$S$^+$ (M + Na)$^+$: 750.2402; found: 750.2409.
(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-((2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-
 tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4′,5′-d]pyran-5-yl)ethyl)thio)tetrahydro-
2H-pyran-3,4,5-triyl triacetate (74):

The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/8) to give
28 (113 mg, 91% yield) as colorless oil; 1H NMR (400 MHz, CDCl₃) δ 5.43 (d, J = 4 Hz, 1H),
5.17-5.12 (m, 1H), 5.03-4.92 (m, 2H), 4.53-4.51 (m, 2H), 4.25-4.23 (m, 1H), 4.17-4.05 (m, 3H),
3.85 (d, J = 6.8 Hz, 1H), 3.65 (d, J = 6.8 Hz, 1H), 2.75 (t, J = 6.8 Hz, 2H), 2.02-1.94 (m, 13H),
1.84-1.73 (m, 1H), 1.50 (s, 3H), 1.38 (m, 3H), 1.27 (s, 6H). 13C NMR (125 MHz, CDCl₃) δ 170.4,
169.9, 170.0, 169.2, 169.1, 108.8, 108.3, 96.3, 84.1, 75.5, 73.7, 72.5, 70.7, 70.3, 70.0, 68.2, 65.3,
62.0, 30.3, 27.1, 25.9, 25.8, 24.8, 24.2, 20.5, 20.5, 20.4. IR (CH₂Cl₂, cm⁻¹) 2987, 1748, 1433, 1372,
1213, 1175, 1141, 1064, 1036, 999; HRMS (ESI) m/z: [M+H]+ Calcd for C₂₇H₄₁O₁₄S⁺ 621.2212;
found: 621.2207.
(2R,3R,4S,6S)-2-(acetoxymethyl)-6-((3-((3aR,4R,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)propyl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (75):

Colorless oil. 78% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 (d, $J = 8.0$ Hz, 1H), 5.69 (d, $J = 8.0$ Hz, 1H), 5.60 (s, 1H), 5.17 (t, $J = 9.3$ Hz, 1H), 5.03 (t, $J = 9.7$ Hz, 1H), 4.98 – 4.86 (m, 3H), 4.48 (d, $J = 10.0$ Hz, 1H), 4.28 (s, 1H), 4.19 (dd, $J = 12.3$, 4.5 Hz, 1H), 4.08 (d, $J = 12.3$ Hz, 1H), 3.94 (s, 2H), 3.86 (d, $J = 11.8$ Hz, 1H), 3.77 (s, 1H), 3.71 – 3.64 (m, 1H), 3.09 (s, 1H), 2.75 – 2.65 (m, 1H), 2.65 – 2.56 (m, 1H), 2.03 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.95 (s, 3H), 1.92 – 1.85 (m, 2H), 1.53 (s, 3H), 1.32 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.6, 170.0, 169.3, 169.2, 162.4, 150.8, 140.3, 114.1, 101.7, 96.0, 86.9, 84.1, 83.3, 80.4, 75.7, 73.8, 69.8, 68.2, 62.5, 62.0, 40.1, 27.6, 27.5, 21.5, 20.6, 20.6, 20.5, 20.4, 20.4. IR (CH$_2$Cl$_2$, cm$^{-1}$) 2987, 1752, 1709, 1663, 1456, 1371, 1264, 1221, 1039, 914, 809, 734, 703; HRMS (ESI): m/z Calcd for C$_{29}$H$_{40}$N$_2$NaO$_{15}$S$^+$ (M+Na)$^+$: 711.2042; found: 711.2047.

(2R,3R,5R,6S)-2-(acetoxymethyl)-6-(((4S,7S)-4,7-dimethyl-3,6,9-trioxo-2,10-dioxo-5,8-diazatridecan-13-yl)thio)tetrahydro-2H-pyran-3,4,5-triy1 triacetate (76):

Colorless oil. 79% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.85 (d, $J = 7.2$ Hz, 1H), 5.53 (d, $J = 7.5$ Hz, 1H), 5.16 (t, $J = 9.3$ Hz, 1H), 5.04 – 4.91 (m, 2H), 4.47 (dd, $J = 19.2$, 8.4 Hz, 2H), 4.32 – 4.12 (m, 2H), 4.07 (d, $J = 10.7$ Hz, 3H), 3.67 (d, $J = 1.1$ Hz, 4H), 2.75 – 2.57 (m, 2H), 2.01 (d, $J = 0.9$ Hz, 3H), 1.99 (s, 3H), 1.95 (d, $J = 0.8$ Hz, 3H), 1.93 (d, $J = 0.9$ Hz, 3H), 1.85 (s, 2H), 1.32 (t, $J = 7.2$ Hz, 3H).
6.9 Hz, 6H). $^{13}$C NMR (150 MHz, CDCl$_3$) δ 171.9, 170.5, 169.9, 169.3, 169.2, 155.7, 83.3, 75.6, 73.6, 69.5, 68.1, 63.1, 61.9, 52.3, 50.1, 47.8, 29.0, 26.2, 20.5, 20.5, 20.4, 18.6, 17.4. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3341, 2954, 1745, 1670, 1537, 1453, 1370, 1219, 1156, 1037, 914, 735; HRMS (ESI): m/z Calcd for C$_{25}$H$_{38}$N$_2$NaO$_{14}$S$^+$ (M+Na)$^+$: 645.1936; found: 645.194.

1.4.2.3 General Procedure for Reverse Coupling

![Diagram of the reaction](image)

To an oven dried vial equipped with stirbar were added thiol (0.2 mmol), followed by olefin (0.24 mmol), Catalyst A (0.002 mmol), and acetonitrile (1 mL). The vial was sealed with teflon cap and stirred at room temperature under irradiation with Blue LEDs. Upon completion of reaction, the solvent was evaporated, and the residue was purified with flash column chromatography to yield thiol-ene adduct.

(2R,3R,5R,6S)-2-(acetoxyethyl)-6-((R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)thio)propoxy)tetrahydro-2H-pyrano-3,4,5-triyli triacetate (77):

Colorless oil. 284 mg (0.46 mmol, 91% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.43 (t, J = 9.8 Hz, 1H), 5.34 (d, J = 7.2 Hz, 1H), 5.08 – 4.99 (m, 2H), 4.85 (dd, J = 10.2, 3.7 Hz, 1H), 4.52 (s, 1H), 4.24 (dd, J = 12.3, 4.4 Hz, 1H), 4.08 (dd, J = 12.3, 1.8 Hz, 1H), 3.99 (dd, J = 10.2, 2.2 Hz, 1H), 3.83 – 3.71 (m, 4H), 3.48 (dt, J = 9.9, 6.1 Hz, 1H), 2.94 (qd, J = 13.8, 5.1 Hz, 2H), 2.62 (t, J = 6.9 Hz, 2H), 2.03 (dd, J = 24.4, 10.8 Hz, 12H), 1.92 – 1.81 (m, 2H), 1.43 (s, 9H). $^{13}$C NMR (100 MHz,
CDCl$_3$ δ 171.4, 170.6, 170.1, 170.1, 169.5, 95.7, 80.1, 70.7, 70.1, 68.4, 67.2, 66.4, 61.8, 53.1 52.5, 34.3, 28.9, 28.8 28.2, 20.7, 20.6, 20.6, 20.6. IR (CH$_2$Cl$_2$, cm$^{-1}$) 2984, 1746, 1713, 1501, 1436, 1367, 1264, 1222, 1165, 1033, 896; HRMS (ESI): m/z Calcd for C$_{26}$H$_{41}$NNaO$_{14}$S$^+$ (M+Na)$^+$: 646.2140; found: 646.2142.

methyl N-(tert-butoxycarbonyl)-S-(2-((3aR,5R,5aS,8aS,8bR)-2,2,7,7-
tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)ethyl)-L-cysteinate

(78):

The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/5) to give 78 (87 mg, 89% yield) as colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.46 (d, $J$ = 4 Hz, 1H), 5.36 (d, $J$ = 8 Hz, 1H), 4.55 (d, $J$ = 8 Hz, 1H), 4.48 (br, 1H), 4.25 (d, $J$ = 4 Hz, 1H), 4.08 (d, $J$ = 8 Hz, 1H), 3.90-3.85 (m, 1H), 3.72 (s, 3H), 2.93 (d, $J$ = 4 Hz, 2H), 2.67-2.63 (m, 1H), 2.60-2.55 (m, 1H), 1.99-1.90 (m, 1H), 1.69-1.66 (m, 1H), 1.51 (s, 3H), 1.41 (s, 12H), 1.29 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.5, 155.0, 109.0, 108.4, 96.3, 79.9, 72.7, 70.8, 70.4, 65.6, 53.1, 52.3, 34.3, 29.9, 28.8, 28.2, 25.9, 25.9, 24.9, 24.3. IR (CH$_2$Cl$_2$, cm$^{-1}$) 2981, 1715, 1499, 1369, 1166, 1212, 1000; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{22}$H$_{37}$NNaO$_{5}$S$^+$ 514.2081; found: 514.2088.
1-benzyl 4-((R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)thio)propyl)

(tert-butoxycarbonyl)-L-aspartate (79):

Colorless oil. 85% yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 (d, $J = 7.1$ Hz, 5H), 5.53 (d, $J = 8.1$ Hz, 1H), 5.36 (d, $J = 6.3$ Hz, 1H), 5.16 (q, $J = 12.3$ Hz, 2H), 4.65 – 4.56 (m, 1H), 4.52 (s, 1H), 4.09 (t, $J = 6.2$ Hz, 2H), 3.81 (s, 3H), 3.15 (d, $J = 4.2$ Hz, 1H), 2.90 (m, 3H), 2.53 (t, $J = 7.1$ Hz, 2H), 1.89 – 1.73 (m, 2H), 1.43 (s, 9H), 1.41 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.4, 171.1, 170.8, 170.7, 155.3, 155.0, 135.2, 128.5, 128.3, 128.1, 80.1, 80.0, 77.3, 77.0, 76.7, 67.3, 63.2, 53.2, 52.5, 52.4, 50.0, 41.2, 36.7, 34.4, 28.8, 28.3, 28.2, 28.1. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3373, 2978, 1711, 1499, 1455, 1392, 1366, 1264, 1169, 1051, 1023, 910, 860; HRMS (ESI): m/z Calcd for C$_{28}$H$_{42}$N$_2$O$_{10}$S$^+$(M+Na)$^+$: 621.2452; found: 621.2462.

methyl (tert-butoxycarbonyl)-S-(3-(3aR,4R,6R,6aR)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)propyl)-L-cysteinate (80):

Colorless oil. 86% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.41 (d, $J = 8.0$ Hz, 1H), 5.71 (d, $J = 8.0$ Hz, 1H), 5.60 (s, 1H), 5.48 (d, $J = 7.4$ Hz, 1H), 5.00 – 4.86 (m, 2H), 4.47 (s, 1H), 4.29 (s, 1H), 4.11 (s, 1H), 3.96 (t, $J = 6.6$ Hz, 2H), 3.88 (d, $J = 11.7$ Hz, 1H), 3.79 – 3.68 (m, 4H), 3.19 (s, 1H), 2.93 (d, $J = 3.6$ Hz, 2H), 2.52 (t, $J = 6.9$ Hz, 2H), 1.93 – 1.81 (m, 2H), 1.55 (s, 3H), 1.40 (s, 9H), 1.33 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.5, 162.5, 155.1, 150.8, 140.3, 114.1, 101.7, 96.1, 86.9, 84.1,
80.4, 80.0, 77.3, 77.0, 76.7, 62.5, 53.1, 52.4, 40.0, 34.3, 30.0, 28.2, 27.1, 27.0, 25.2. IR (CH₂Cl₂, cm⁻¹) 3356, 2979, 1745, 1705, 1658, 1500, 1456, 1366, 1211, 1160, 1105, 1069, 896, 678, 734; HRMS (ESI): m/z Calcd for C₂₄H₃₇N₃NaO₁₀S⁺ (M+Na)⁺: 582.2092; found: 582.2100.

methyl N-(tert-butoxycarbonyl)-S-(((S)-1-(((S)-1-methoxy-1-oxopropan-2-yl)amino)-1-oxopropan-2-yl)carbamoyl)oxy)propyl)-L-cysteinate (81):

Colorless oil. 75% yield. ¹H NMR (400 MHz, CDCl₃) δ 6.78 (s, 1H), 5.52 (s, 1H), 5.41 (d, J = 7.0 Hz, 1H), 4.60 – 4.43 (m, 2H), 4.23 (s, 1H), 4.12 (s, 2H), 3.73 (2, 3H), 3.71 (s, 3H), 2.91 (d, J = 5.1 Hz, 2H), 2.57 (t, J = 6.5 Hz, 2H), 1.92 – 1.75 (m, 2H), 1.42 (s, 9H), 1.37 (t, J = 6.8 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃) δ 173.1, 171.9, 171.5, 155.9, 155.1, 80.1, 63.3, 53.1, 52.5, 52.4, 50.2, 47.9, 34.3, 28.8, 28.2, 18.6, 18.0. IR (CH₂Cl₂, cm⁻¹) 3320, 2978, 1713, 1521, 1453, 1365, 1214, 1163, 1052, 778; HRMS (ESI): m/z Calcd for C₂₀H₂₅N₃NaO₉(M+Na): 516.1986, found: 516.1978.
1.4.2.4 General Procedure for Preparation of Starting Material (A):

\[
\text{NH}_{2}
\]

To a stirred solution of N-protected amino acid (1 equiv.) in DMF (0.4 M) at -10 °C was added anhydrous K$_2$CO$_3$ (1 equiv.). The resulting solution was stirred for 30 min. Propargyl bromide (80% solution in toluene, 1 equiv.) was added dropwise. The mixture was stirred at -10 °C for 1 h before warmed to room temperature. The solvent was evaporated. Then ethyl acetate (50 mL) was added followed by saturated citric acid solution (50 mL). The aqueous layer was separated and extracted with ethyl acetate (2 X 25 mL). The combined organic layers were washed with saturated solution of sodium chloride (50 mL), dried over Na$_2$SO$_4$, filtered, and concentrated by rotary evaporation. The residue was subjected to flash column chromatography to give desired product.

\[
\begin{array}{c}
\text{MeO} \\
\text{NH}_{2}
\end{array}
\]

4-methyl 1-(prop-2-yn-1-yl) (tert-butoxycarbonyl)-L-aspartate (S1):

The compound was prepared according to general procedure 1.4.2.4. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/1) to give S1 (465 mg, 80% yield) as colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) δ 5.47 (d, $J = 7.6$ Hz, 1H), 4.74 (s, 2H), 4.62-4.60 (m, 1H), 3.69 (s, 3H), 3.05-3.00 (m, 1H), 2.86-2.81 (m, 1H), 2.48 (s, 1H), 1.44 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.1, 170.3, 155.2, 80.1, 75.4, 53.0, 52.0, 49.9, 36.5, 28.2. IR (CH$_2$Cl$_2$ cm$^{-1}$) 3381, 2979, 1717, 1501, 1441, 1367, 1166, 1164, 1048; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{13}$H$_{19}$NNaO$_6^+$ 308.1105; found: 308.1094.
prop-2-yn-1-yl \(N\)-(tert-butoxycarbonyl)-\(S\)-(tert-butyl)-\(L\)-cysteinate (S2):

The compound was prepared according to general procedure 1.4.2.4. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/2) to give S2 (593 mg, 85% yield) as light yellow oil;

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.30 (d, \(J = 8\) Hz, 1H), 4.74 (s, 2H), 4.59 (br, 1H), 2.98 (s, 2H), 2.49 (s, 1H), 1.44 (s, 9H), 1.31 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.1, 154.9, 79.8, 75.6, 53.2, 52.8, 42.4, 30.7, 30.4, 28.1. IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3292, 2972, 1751, 1710, 1499, 1459, 1366, 1309, 1051, 1023, 941; HRMS (ESI) m/z: [M+H]\(^+\) Calcd for C\(_{15}\)H\(_{26}\)NO\(_4\)S\(^+\) 316.1577; found: 316.157.

prop-2-yn-1-yl \((tert\text{-}butoxycarbonyl)\)-(\(L\)-valylalaninate) (S3):

To a stirred solution of \(S_a\) (4.095 mmol) in DCM (40 mL) was added \(S_b\) (4.095 mmol) followed by \(N\), \(N\)-Diisopropylethylamine (10.23 mmol), HOBt (0.409 mmol), EDCI (4.504 mmol). The reaction mixture was stirred at room temperature for 4 h. Then ethyl acetate (50 mL) was added followed by water (50 mL). The aqueous layer was separated and extracted with ethyl acetate (2 X 50 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated by rotary evaporation. The residue was subjected to flash column chromatography (5% methanol in
DCM) to give S3 (1.2 g, 82% yield) as white solid; mp 80 -85 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.40 (br, 1H), 5.07-5.05 (m, 1H), 4.78-4.59 (m, 3H), 3.92 (d, \(J = 7.2\) Hz, 1H), 2.49 (s, 1H), 2.13-2.12 (m, 1H), 1.44 (s, 12H), 0.97 (d, \(J = 6.7\) Hz, 3H), 0.92 (d, \(J = 6.7\) Hz, 3H). \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 171.9, 171.4, 155.9, 79.8, 75.3, 59.6, 52.7, 47.8, 31.0, 28.3, 19.1, 17.8. IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3299, 2975, 1752, 1653, 1519, 1453, 1366, 1246, 1160, 1017, 991; HRMS (ESI) m/z: \([\text{M+Na}]^+\) Calcd for C\(_{16}\)H\(_{26}\)N\(_2\)O\(_5\)Na 349.1734; found: 349.1724.

![NHFmoc](image)

**prop-2-yn-1-yl N-(((9H-fluoren-9-yl)methoxy)carbonyl)-O-(tert-butyl)-L-serinate (S4):**

The compound was prepared according to general procedure 1.4.2.4. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/1) to give S4 (712 mg, 87% yield) as light yellow solid; melting point 80 °C;

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.79 (d, \(J = 6\) Hz, 2H), 7.66 (t, \(J = 6.4\) Hz, 2H), 7.43 (t, \(J = 6\) Hz, 2H), 7.35 (t, \(J = 6\) Hz, 2H), 5.76 (d, \(J = 7.2\) Hz, 1H), 4.80-4.78 (m, 2H), 4.60-4.58 (m, 1H), 4.49-4.46 (m, 1H), 4.42-4.39 (m, 1H), 4.29 (t, \(J = 6\) Hz, 1H), 3.91 (dd, \(J = 2.4, 2.4\) Hz, 1H), 3.65 (dd, \(J = 2.4, 2.4\) Hz, 1H), 2.53-2.52 (m, 1H), 1.21 (s, 9H). \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 169.9, 155.9, 143.8, 143.6, 141.1, 127.5, 126.9, 125.0, 124.9, 119.8, 76.7, 75.1, 73.3, 67.0, 61.8, 54.5, 52.5, 47.0, 27.1. IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3065, 2945, 1757, 1723, 1508, 1449, 1393, 1334, 1076, 1022; HRMS (ESI) m/z: \([\text{M+Na}]^+\) Calcd for C\(_{25}\)H\(_{27}\)N\(_2\)O\(_5\)Na 444.1781; found: 444.1768.
prop-2-yn-1-yl (S)-2-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(tert-butoxy)phenyl)propanoate (S5):

The compound was prepared according to general procedure 1.4.2.4. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/2) to give S5 (463 mg, 85% yield) as light yellow oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.80 (d, $J = 6$ Hz, 2H), 7.61 (t, $J = 6$ Hz, 2H), 7.43 (t, $J = 6$ Hz, 2H), 7.34 (t, $J = 6$ Hz, 2H), 7.07 (d, $J = 8$ Hz, 2H), 6.95 (d, $J = 8$ Hz, 2H), 5.44 (d, $J = 6.4$ Hz, 1H), 4.79-4.73 (m, 3H), 4.48-4.45 (m, 1H), 4.41-4.37 (m, 1H), 4.24 (t, $J = 6$ Hz, 1H), 3.18-3.08 (m, 2H), 2.54 (s, 1H), 1.36 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.9, 155.6, 154.6, 143.9, 143.7, 141.3, 130.2, 129.9, 127.7, 127.1, 125.2, 125.1, 124.2, 120.0, 78.4, 76.9, 75.7, 67.0, 54.8, 52.7, 47.2, 37.4, 28.8. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3065, 2945, 1757, 1723, 1508, 1449, 1393, 1334, 1076, 1022; HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{32}$NO$_5$ $^+$ 498.2275; found: 498.2268.

1.4.2.5 General Procedures for Synthesis of 84b:

![Chemical structure]

To an oven dried vial equipped with a stir bar were added 83 (0.5706 mmol), followed by Catalyst A (0.0171 mmol), 82 (2.282 mmol), and acetonitrile (1.14 mL). The reaction mixture was stirred at ambient temperature under Blue LEDs for 14 h. The solvent was evaporated, and residue was purified by flash column chromatography to give the double hydrothiolation products.
3,4-bis(benzylthio)butan-1-ol (85):

The compound was prepared according to the general procedure 1.4.2.5. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/8) to give 85 (169 mg, 93% yield) as light yellow oil;

$^{1}H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.33-7.25 (m, 10H), 3.71-3.64 (m, 6H), 2.78-2.72 (m, 2H), 2.62-2.58 (m, 1H), 2.08-1.97 (m, 1H), 1.61-1.53 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.1, 138.0, 128.8, 128.7, 128.5, 128.4, 127.0, 126.9, 60.2, 41.7, 37.5, 35.8, 35.4. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3378, 3060, 3026, 2914, 1601, 1493, 1452, 1420, 1238, 1198, 1069, 1028; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{18}$H$_{22}$NaOS$_2$+ 341.1004; found: 341.1018.

3,4-bis((4-fluorobenzyl)thio)butan-1-ol (86):

The compound was prepared according to the general procedure 1.4.2.5. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/6) to give 86 (192 mg, 95% yield) as light yellow oil;
\[ \text{H NMR (400 MHz, CDCl}_3\text{) } \delta 7.26-7.23 \text{ (m, 4H), 7.01-6.97 (m, 4H), 3.69-3.65 (m, 6H), 2.78-2.69 \text{ (m, 2H), 2.60-2.55 (m, 1H), 2.05-1.98 (m, 1H), 1.69-1.63 (m, 2H).} \]

\[ \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{) } \delta 162.9, 160.4, 133.7, 133.7, 133.6, 130.2, 130.1, 115.3, 115.2, 115.1, 115.0, 60.0, 41.8, 37.4, 36.0, 35.9, 34.6. \text{IR (CH}_2\text{Cl}_2, \text{cm}^{-1}) 3368, 3039, 2920, 1891, 1599, 1505, 1423, 1293, 1219, 1155, 1088, 1038, 1015, 830; \text{HRMS (ESI) m/z: [M+H]}^+ \text{Calcd for C}_{18}\text{H}_{21}\text{F}_2\text{O}_2\text{S}_2^+ 355.0996; \text{found: 355.0989.} \]

3,4-bis((4-methoxybenzyl)thio)butan-1-ol (87):

The compound was prepared according to the general procedure 1.4.2.5. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/7) to give 87 (156 mg, 72% yield) as colorless oil;

\[ \text{H NMR (400 MHz, CDCl}_3\text{) } \delta 7.20-7.18 \text{ (m, 4H), 6.85-6.83 (m, 4H), 3.78 (s, 6H), 3.67-3.64 (m, 6H), 2.77-2.74 \text{ (m, 2H), 2.60-2.54 (m, 1H), 2.04-1.99 (m, 1H), 1.71 (s, 1H), 1.64-1.59 (m, 1H).} \]

\[ \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{) } \delta 158.6, 130.3, 130.0, 129.9, 113.9, 113.8, 60.5, 55.2, 41.9, 37.6, 36.2, 35.9, 34.9. \text{IR (CH}_2\text{Cl}_2, \text{cm}^{-1}) 3417, 3000, 2952, 2907, 2833, 1608, 1583, 1509, 1463, 1440, 1316, 1300, 1238, 1031, 829; \text{HRMS (ESI) m/z: [M+H]}^+ \text{Calcd for C}_{20}\text{H}_{27}\text{O}_3\text{S}_2^+ 379.1396; \text{found: 379.1395.} \]
3,4-bis(cyclohexylthio)butan-1-ol (88):

The compound was prepared according to the general procedure 1.4.2.5. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/8) to give 88 (152 mg, 88% yield) as colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.80-3.78 (m, 2H), 2.95-2.91 (m, 2H), 2.88-2.61 (m, 3H), 2.21 (s, 1H), 2.12-2.09 (m, 1H), 1.94-1.91 (m, 4H), 1.74-1.60 (m, 7H), 1.29-1.24 (m, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 60.4, 44.2, 43.3, 41.5, 37.1, 36.4, 34.1, 33.8, 33.6, 33.5, 26.0, 25.9, 25.8, 25.6, 25.6, 25.6. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3390, 2923, 2850, 1447, 1340, 1262, 1201, 1178, 1047, 998; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{16}$H$_{30}$NaOS$_2^+$ 325.1630; found: 325.1626.

1.4.2.6 Procedure for Synthesis of Vinyl Sulfide Product

$t$-BuS$_2$CH=CHCH$_2$OH (89):

To an oven dried vial equipped with a stir bar were added 3-butyn-1-ol (132.1 mg, 1.885 mmol), followed by Catalyst A (5.38 mg, 0.011 mmol), $t$-butylthiol (100 mg, 1.108 mmol), and acetonitrile (0.2 M). The reaction mixture was stirred at ambient temperature under Blue LEDs for
2 h. The solvent was evaporated and residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/8) to give desired product **89** (148 mg, 83% yield, E:Z 1:3.5) as colorless oil; $^1$H NMR (400 MHz, CDCl$_3$, 1:3.5 mixture of E/Z isomers) $\delta$ 6.26 (d, $J = 9.6$ Hz, 1H$_{major}$), 6.19 (d, $J = 14.8$ Hz, 1H$_{minor}$), 5.85-5.78 (m, 1H$_{minor}$), 5.71-5.65 (m, 1H$_{major}$), 3.68-3.63 (m, 2H), 2.44-2.36 (m, 2H), 1.68 (br, 1H), 1.34 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 131.5, 126.4, 124.1, 123.4, 61.8, 43.5, 36.6, 32.5, 30.8, 30.7. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3335, 2960, 2924, 2897, 1605, 1457, 1364, 1162, 1044, 949, 889, 855; HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_8$H$_{17}$OS$^+$ 161.0995; found: 161.0998.

![Diagram](attachment:Diagram.png)

**4-(((3s,5s,7s)- adamantan-1-yl)thio)but-3-en-1-ol (90):**

To an oven dried vial equipped with a stir bar were added 3-butyln-1-ol (70.79 mg, 1.010 mmol), followed by Catalyst A (2.88 mg, 0.005 mmol), 1-Adamantanethiol (100 mg, 0.594 mmol), and acetonitrile (0.2 M). The reaction mixture was stirred at ambient temperature under Blue LEDs for 2 h. The solvent was evaporated and residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/7) to give **90** (70% yield, E:Z 1:1.7) as light yellow oil; $^1$H NMR (400 MHz, CDCl$_3$, 1:1.7 mixture of E/Z isomers) $\delta$ 6.32 (d, $J = 9.6$ Hz, 1H$_{major}$), 6.23 (d, $J = 14.8$ Hz, 1H$_{minor}$), 5.82-5.74 (m, 1H$_{minor}$), 5.70-5.65 (m, 1H$_{major}$), 3.69-3.63 (m, 2H), 2.45-2.36 (m, 2H), 2.04 (s, 3H), 1.89-1.86 (m, 6H), 1.72-1.65 (m, 6H), 1.50 (br, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, 1:1.7 mixture of E/Z isomers) $\delta$ 130.9, 126.2, 122.1, 121.6, 61.9, 61.7, 45.7, 43.5, 43.4, 36.6, 36.1, 32.5, 29.7, 29.5. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3408, 2901, 2848, 1608, 1511, 1449, 1342, 1299, 1251, 1100, 976; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{14}$H$_{22}$NaOS$^+$ 261.1284; found: 261.1270.
(2R,3R,4S,5R,6S)-2-(acetoxyethyl)-6-((4-hydroxybut-1-en-1-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (91):

To an oven dried vial equipped with a stir bar were added 3-butyn-1-ol (32.7 mg, 0.466 mmol), followed by Catalyst A (1.33 mg, 0.002 mmol), glucose thiol (100 mg, 0.2744 mmol), and acetonitrile (0.2 M). The reaction mixture was stirred at ambient temperature under Blue LEDs for 2 h. The solvent was evaporated and residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 2/1) to give 91 (85 mg, 71% yield, E:Z 1:4) as colorless oil;

1H NMR (400 MHz, CDCl3, 1:4 mixture of E/Z isomers) δ 6.22 (d, J = 8.8 Hz, 1Hmajor), 6.13 (d, J = 15.2 Hz, 1Hminor), 5.85-5.81 (m, 1H), 5.19 (t, J = 9.2 Hz, 1H), 5.07 (d, J = 9.2 Hz, 2H), 4.51 (d, J = 10 Hz, 1Hmajor), 4.44 (d, J = 10 Hz, 1Hminor), 4.24-4.20 (m, 1H), 4.12-4.09 (m, 1H), 3.73-3.71 (m, 1H), 3.67-3.64 (m, 2H), 2.36-2.34 (m, 2H), 2.36-1.97 (m, 12H). 13C NMR (100 MHz, CDCl3, 1:4 mixture of E/Z isomers) δ 170.5, 170.0, 169.3, 169.2, 135.8, 131.1, 120.5, 119.1, 82.8, 76.0, 73.7, 69.9, 69.5, 68.0, 61.9, 61.4, 61.2, 36.6, 32.5, 20.6, 20.5, 20.4. IR (CH2Cl2, cm⁻¹) 3517, 2955, 1748, 1431, 1367, 1217, 1090, 1037, 957, 914; HRMS (ESI) m/z: [M+H]⁺ Calcd for C₁₈H₂₇O₁₀S⁺ 435.1319; found: 435.1315.

Methyl N-(tert-butoxycarbonyl)-S-(4-hydroxybut-1-en-1-yl)-L-cysteinate (91̅):
To an oven dried vial equipped with a stir bar were added 3-butyln-1-ol (50.63 mg, 0.722 mmol), followed by Catalyst A (2.06 mg, 0.004 mmol), methyl (tert-butoxycarbonyl)-L-cysteinate (100 mg, 0.424 mmol), and acetonitrile (0.2 M). The reaction mixture was stirred at ambient temperature under Blue LEDs for 2 h. The solvent was evaporated and residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/1) to give 91* (104 mg, 80% yield, E:Z 1.2:1) as light yellow oil;

$^1$H NMR (400 MHz, CDCl$_3$, 1.2:1 mixture of E/Z isomers) $\delta$ 5.94 (d, $J = 8.4$ Hz, 1H$_{\text{minor}}$), 5.93 (d, $J = 13.6$ Hz, 1H$_{\text{major}}$), 5.73-5.59 (m, 1H), 5.47-5.37 (m, 1H), 4.51 (br, 1H), 3.70-3.69 (m, 3H), 3.64-3.58 (m, 2H), 3.09-2.92 (m, 2H), 2.37-2.26 (m, 2H), 1.39 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$, 1.2:1 mixture of E/Z isomers) $\delta$ 171.3, 171.0, 155.0, 129.9, 128.0, 126.4, 124.4, 80.2, 80.1, 61.4, 53.6, 52.9, 52.5, 52.4, 36.4, 35.3, 32.4, 28.2. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3373, 2977, 1743, 1693, 1502, 1436, 1391, 1366, 1309, 1247, 1214, 1159, 1049, 1017, 946, 859; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{13}$H$_{23}$NNaO$_5$S$^+$ 328.1189; found: 328.1187.

4-[(phenylthiol)but-3-en-1-ol (92):

To an oven dried vial equipped with a stir bar were added 3-butyln-1-ol (108.14 mg, 1.542 mmol), followed by Catalyst A (4.40 mg, 0.009 mmol), benzenethiol (100 mg, 0.907 mmol), and acetonitrile (0.2 M). The reaction mixture was stirred at ambient temperature under Blue LEDs for 2 h. The solvent was evaporated and residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/4) to give 92 (103 mg, 63% yield, E:Z 1:2) as light yellow oil;
$^1$H NMR (400 MHz, CDCl$_3$, E isomers) $\delta$ 7.28-7.19 (m, 5H$_{\text{minor}}$), 6.28 (d, $J = 15$ Hz, 1H$_{\text{minor}}$), 5.95-5.88 (m, 1H$_{\text{minor}}$), 3.70 (t, $J = 8$ Hz, 2H$_{\text{minor}}$), 2.45-2.40 (m, 2H$_{\text{minor}}$). $^1$H NMR (400 MHz, CDCl$_3$, Z isomers) $\delta$ 7.36-7.30 (m, 5H$_{\text{major}}$), 6.36 (d, $J = 9.6$ Hz, 1H$_{\text{major}}$), 5.87-5.82 (m, 1H$_{\text{major}}$), 3.75 (t, $J = 6.4$ Hz, 2H$_{\text{major}}$), 2.56-2.51 (m, 2H$_{\text{major}}$). $^{13}$C NMR (100 MHz, CDCl$_3$, 1:2 mixture of E/Z isomers) $\delta$ 135.8, 135.6, 131.2, 128.4, 126.4, 126.4, 125.9, 124.6, 61.8, 61.6, 36.3, 32.6.

IR (CH$_2$Cl$_2$, cm$^{-1}$) 3370, 3058, 2922, 2851, 1722, 1583, 1479, 1439, 1180, 1089, 1024, 918; HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{10}$H$_{13}$OS$^+$ 181.0682; found: 181.0690.

3,4-bis(phenylthiol)butan-1-ol (93):

The compound was prepared according to the general procedure 1.5.6. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/8) to give 93 (159 mg, 96% yield) as light yellow oil;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.33 (m, 3H), 7.28-7.27 (m, 3H), 7.22-7.20 (m, 4H), 3.89-3.86 (m, 2H), 3.31-3.28 (m, 2H), 2.96-2.89 (m, 1H), 2.32-2.24 (m, 1H), 1.82-1.73 (m, 1H), 1.70 (br, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.3, 133.4, 132.4, 129.6, 128.9, 128.8, 127.2, 126.1, 125.4, 61.5, 60.1, 45.1, 39.4, 36.1, 35.2, 32.4. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3343, 3055, 2923, 1755, 1582, 1478, 1437, 1302, 1218, 1156, 1088, 1040, 1024, 912; HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{16}$H$_{19}$OS$_2$$^+$ 291.0872; found: 291.0877.
1.4.2.7 General Procedure for Synthesis of S-linked Glycoconjugates Using Thiol-yne Photocatalytic System

To an oven dried vial equipped with a stir bar were added glucose thiol (0.2744 mmol), followed by Catalyst A (0.0027 mmol), alkyne containing amino acid derivative (0.4665 mmol), and acetonitrile (1.37 mL). The reaction mixture was stirred at ambient temperature under Blue LEDs for 2 h. The solvent was evaporated, and residue was purified by flash column chromatography to give the desired products.

\[(2R,3R,4S,5R,6S)-2-(acetoxymethyl)-6-((3-((tert-butoxycarbonyl)glycyl)oxy)prop-1-en-1-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (94):

The compound was prepared according to the general procedure 1.4.2.7. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/1) to give 94 (101 mg, 64% yield, E:Z 1.2:1) as colorless oil;

\[1^1H NMR (400 MHz, CDCl_3, 1.2:1 mixture of E/Z isomers) \delta 6.40 (d, J = 16 Hz, 1H_{major}), 6.37 (d, J = 12 Hz, 1H_{minor}), 5.90-5.83 (m, 1H), 5.22-5.17 (m, 1H), 5.10-5.01 (m, 3H), 4.70-4.67 (m, 1H), 4.62-4.53 (m, 2H), 4.25-4.21 (m, 1H), 4.13-4.11 (m, 1H), 3.90-3.88 (m, 2H), 3.76-3.72 (m, 1H), 2.06-1.97 (m, 12H), 1.42 (s, 9H).\]

\[13^C NMR (100 MHz, CDCl_3, 1.2:1 mixture of E/Z isomers) \delta 170.4, 169.9, 169.2, 169.0, 155.6, 126.7, 125.3, 123.8, 83.1, 82.9, 79.9, 76.1, 73.7, 73.6, 69.9, 69.7,\]
68.0, 64.7, 61.9, 61.6, 42.3, 28.2. IR (CH$_2$Cl$_2$, cm$^{-1}$) 2980, 1751, 1367, 1263, 1225, 1511, 1162, 1052, 955; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{24}$H$_{35}$NNaO$_{13}$S$^+$ 600.1721; found: 600.1728.

(2R,3R,4S,5R,6S)-2-(acetoxyethyl)-6-((3-(((tert-butoxycarbonyl)-L-alanyl)oxy)prop-1-en-1-yl)thio)tetrahydro-2H-pyran-3,4,5-triyl triacetate (95):

The compound was prepared according to the general procedure 1.4.2.7. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/1) to give 95 (106 mg, 65% yield, $E$:Z 1:1) as colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$, 1:1 mixture of $E$/Z isomers) $\delta$ 6.39 (d, $J = 15.6$ Hz, 1H), 6.36 (d, $J = 10.3$ Hz, 1H), 5.90-5.82 (m, 1H), 5.21-5.17 (m, 1H), 5.09-4.99 (m, 3H), 4.66-4.64 (m, 1H), 4.60-4.53 (m, 2H), 4.27-4.20 (m, 2H), 4.11-4.08 (m, 1H), 3.74-3.71 (m, 1H), 2.05-1.96 (m, 12H), 1.40 (s, 9H), 1.36-1.33 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 1:1 mixture of $E$/Z isomers) $\delta$ 172.8, 170.4, 169.9, 169.2, 169.0, 154.9, 126.9, 126.8, 125.1, 123.9, 83.1, 82.9, 79.7, 76.1, 76.0, 73.7, 73.6, 69.9, 69.7, 68.0, 64.7, 61.9, 61.6, 49.1, 28.2, 20.4, 18.4. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3392, 2986, 1753, 1375, 1225, 1168, 1052; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{25}$H$_{37}$NNaO$_{13}$S$^+$ 614.1878; found: 614.1887.

The compound was prepared according to the general procedure 1.4.2.7. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/1) to give 96 (127 mg, 68% yield, E:Z 1.1:1) as colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$, 1.1:1 mixture of E/Z isomers) $\delta$ 6.42 (d, $J = 15.2$ Hz, 1H$_{major}$), 6.36 (d, $J = 9.6$ Hz, 1H$_{minor}$), 5.92-5.83 (m, 1H), 5.32-5.28 (m, 1H), 5.23-5.17 (m, 1H), 5.10-5.01 (m, 2H), 4.67-4.52 (m, 4H), 4.26-4.22 (m, 1H), 4.13-4.09 (m, 1H), 3.76-3.71 (m, 1H), 2.95-2.94 (m, 2H), 2.06-1.97 (m, 12H), 1.41 (s, 9H), 1.27 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$, 1.1:1 mixture of E/Z isomers) $\delta$ 170.5, 170.4, 170.0, 169.2, 169.0, 155.0, 126.9, 126.5, 125.5, 123.7, 120.5, 118.7, 118.3, 117.0, 116.1, 115.7, 83.3, 83.0, 79.9, 76.1, 76.0, 73.7, 73.6, 69.9, 69.7, 65.1, 61.9, 61.8, 53.1, 42.6, 42.5, 30.7, 30.6, 28.2, 20.6, 20.4. IR (CH$_2$Cl$_2$, cm$^{-1}$) 2988, 2945, 1737, 1501, 1446, 1366, 1214, 1162, 1040, 937, 913, 847; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{29}$H$_{45}$NNaO$_{13}$S$_2^+$ 702.2225; found: 702.2224.
4-methyl 1-(3-(((2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl)thio)allyl) (tert-butoxycarbonyl)-D-aspartate (96*):

The compound was prepared according to the general procedures 1.4.2.7. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/1) to give 96* (109 mg, 61% yield, E:Z 1:1) as colorless oil; $^1$H NMR (400 MHz, CDCl$_3$, 1:1 mixture of E/Z isomers) $\delta$ 6.39 (d, $J$ = 15.6 Hz, 1H), 6.35 (d, $J$ = 10 Hz, 1H), 5.87-5.81 (m, 1H), 5.45 (br, 1H), 5.22-5.16 (m, 1H), 5.08-5.00 (m, 2H), 4.68 (m, 4H), 4.24-4.21 (m, 1H), 4.12-4.05 (m, 1H), 3.74-3.71 (m, 1H), 3.65 (s, 3H), 2.98-2.93 (m, 1H), 2.82-2.77 (m, 1H), 2.05-1.96 (m, 12H), 1.41 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$, 1:1 mixture of E/Z isomers) $\delta$ 171.2, 170.5, 170.4, 169.9, 169.2, 169.0, 155.2, 126.7, 126.4, 125.3, 123.7, 83.2, 82.9, 80.0, 76.1, 76.0, 73.7, 73.6, 69.9, 67.9, 65.1, 62.0, 61.8, 60.2, 51.9, 51.8, 49.9, 36.5, 28.2, 20.6, 20.4. IR (CH$_2$Cl$_2$, cm$^{-1}$) 2923, 2853, 1752, 1368, 1227, 1043; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{27}$H$_{39}$NNaO$_{15}$S$^+$ 672.1933; found: 672.1944.

(2S,3R,4S,5R,6R)-2-(((3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4(tert-butoxy)phenyl)propanoyl)oxy)prop-1-en-1-yl)thio)-6-(acetoxymethyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (97):

The compound was prepared according to the general procedure 1.4.2.7. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/3) to give 97 (161 mg, 68% yield, E:Z 1:1.1) as colorless oil;
$^1$H NMR (400 MHz, CDCl$_3$, 1:1.1 mixture of E/Z isomers) $\delta$ 7.77 (d, $J = 8$ Hz, 2H), 7.58-7.56 (m, 2H), 7.31 (t, $J = 8$ Hz, 2H), 7.00 (d, $J = 8$ Hz, 2H), 6.91-6.89 (m, 2H), 6.42 (d, $J = 10.8$ Hz, 1H$_{\text{minor}}$), 6.39 (d, $J = 5.2$ Hz, 1H$_{\text{major}}$), 5.87-5.82 (m, 1H), 5.30 (d, $J = 7.6$ Hz, 1H), 5.25-5.20 (m, 1H), 5.12-5.08 (m, 2H), 4.69-4.54 (m, 4H), 4.45-4.32 (m, 2H), 4.28-4.19 (m, 2H), 4.14-4.11 (m, 1H), 3.76-3.74 (m, 1H), 3.12-3.01 (m, 2H), 2.08-1.99 (m, 12H), 1.32 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$, 1:1.1 mixture of E/Z isomers) $\delta$ 171.1, 171.0, 170.5, 170.0, 169.2, 169.1, 155.4, 154.5, 143.8, 143.7, 141.2, 130.3, 129.7, 127.6, 127.0, 126.5, 126.3, 125.7, 125.0, 124.1, 124.0, 119.9, 83.1, 82.9, 78.4, 78.3, 76.2, 76.0, 73.7, 73.6, 69.9, 69.7, 68.0, 66.9, 64.9, 61.8, 60.3, 54.8, 47.1, 37.5, 28.8, 20.6, 20.4, 14.1. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3054, 2947, 1744, 1608, 1505, 1447, 1390, 1332, 1213, 1035, 912, 895; HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{45}$H$_{51}$NNaO$_{14}$S$^+$ 884.2922; found: 884.2929.

\[98\]


The compound was prepared according to the general procedure 1.4.2.7. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/2) to give 98 (134 mg, 62% yield, E:Z 1:1.1) as colorless oil;

$^1$H NMR (400 MHz, CDCl$_3$, 1:1.1 mixture of E/Z isomers) $\delta$ 7.76 (d, $J = 7.6$ Hz, 2H), 7.62 (t, $J = 8$ Hz, 2H), 7.39 (t, $J = 8$ Hz, 2H), 7.31 (t, $J = 8$ Hz, 2H), 6.43 (d, $J = 15.2$ Hz, 1H$_{\text{minor}}$), 6.38 (d, $J$...
= 9.6 Hz, 1H\textsubscript{major}), 5.93-5.87 (m, 1H), 5.69 (d, J = 8 Hz, 1H), 5.21 (t, J = 9.2 Hz, 1H), 5.12-5.03 (m, 2H), 4.73 (d, J = 6 Hz, 1H), 4.66 (d, J = 6 Hz, 1H), 4.59-4.32 (m, 4H), 4.27-4.23 (m, 2H), 4.13-4.10 (m, 1H) 3.84 (d, J = 8 Hz, 1H), 3.73 (d, J = 8 Hz, 1H), 3.60 (d, J = 8 Hz, 1H), 2.07-1.99 (m, 12H), 1.15 (s, 9H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}, 1:1.1 mixture of E/Z isomers) \( \delta \) 170.4, 170.2, 170.1, 170.0, 169.2, 169.0, 156.0, 143.9, 143.7, 141.2, 127.6, 127.0, 125.1, 123.7, 119.9, 83.2, 83.0, 79.4, 79.0, 78.7, 78.3, 77.9, 77.6, 77.3, 77.0, 76.6, 76.1, 76.0, 73.7, 73.6, 73.5, 73.4, 69.9, 69.7, 68.0, 67.1, 64.9, 62.0, 61.8, 60.2, 54.6, 47.1, 27.2, 20.9, 20.6, 20.4, 14.1. IR (CH\textsubscript{2}Cl\textsubscript{2}, cm\textsuperscript{-1}) 3374, 2929, 1745, 1704, 1503, 1437, 1392, 1366, 1250, 1214, 1162, 1051; HRMS (ESI) m/z: [M+H]\textsuperscript{+} Calcd for C\textsubscript{39}H\textsubscript{48}NO\textsubscript{14}S\textsubscript{+} 786.2790; found: 786.2796.


The compound was prepared according to the general procedure 1.4.2.7. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 2/1) to give 99 (124 mg, 65% yield, E:Z 1.25:1) as light yellow oil;

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, 1.25:1 mixture of E/Z isomers) \( \delta \) 6.59-6.54 (m, 1H), 6.41 (d, J = 15.6 Hz, 1H\textsubscript{major}), 6.38 (d, J = 10.4 Hz, 1H\textsubscript{minor}), 5.92-5.85 (m, 1H), 5.23-5.02 (m, 4H), 4.67-4.54 (m, 4H), 4.26-4.21 (m, 1H), 4.14-4.06 (m, 1H), 3.93 (br, 1H), 3.75-3.73 (m, 1H), 2.06-1.98 (m, 12H), 1.41 (m, 12H), 1.23 (t, J = 6.8 Hz, 1H), 0.95 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H). \textsuperscript{13}C
NMR (100 MHz, CDCl$_3$, 1.25:1 mixture of E/Z isomers) $\delta$ 172.1, 171.1, 171.0, 170.4, 169.9, 169.3, 169.2, 169.0, 155.7, 127.1, 126.7, 125.1, 124.0, 83.0, 82.8, 79.7, 76.1, 76.0, 73.7, 73.6, 70.0, 69.6, 68.0, 64.8, 61.9, 61.7, 59.6, 47.9, 30.9, 29.5, 28.2, 20.5, 20.4, 19.1, 18.1, 18.0, 17.6. IR (CH$_2$Cl$_2$, cm$^{-1}$) 2975, 1749, 1661, 1520, 1367, 1223, 1163, 1041; HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{30}$H$_{47}$N$_2$O$_3$S $^+$ 691.2743; found: 691.2748.

**1.4.2.8 General Procedure for Synthesis of 104, 105:**

![Chemical structure](image)

To a dried vile, equipped with a stir bar were added **102** (0.137 mmol), Catalyst A (0.00137 mmol), **103** (0.1648 mmol), and buffer solution with different pH (0.5 M). The flask was closed, and reaction was allowed to stir under Blue LEDs for 15 hours. Upon completion of reaction, ethyl acetate was added (10 mL). The aqueous layer was separated and extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with saturated solution of sodium chloride (20 mL), dried over Na$_2$SO$_4$, filtered, and concentrated by rotary evaporation. The residue was subjected to flash column chromatography to give desired product **104** (Ethyl acetate/Hexanes = 1/1) and **105** (Ethyl acetate/Hexanes = 1/3).

(2R,3R,5R,6S)-2-(acetoxymethyl)-6-((3-hydroxypropyl)thio)tetrahydro-2H-pyran-3,4,5-triy1 triacetate (104):
The compound was prepared according to the general procedure 1.4.2.8 with a buffer solution of pH = 2.6. Under this condition only compound 104 was obtained as a white solid (41.5 mg, 72%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.22 (t, \(J = 9.5\) Hz, 1H), 5.07 (t, \(J = 9.5\) Hz, 1H), 5.04 (t, \(J = 9.3\) Hz, 1H), 4.48 (d, \(J = 10.1\) Hz, 1H), 4.23 (dd, \(J = 4.9\) Hz, \(J = 12.4\) Hz, 1H), 4.15 (dd, \(J = 2.3\) Hz, \(J = 12.4\) Hz, 1H), 3.73-3.69 (m, 3H), 2.87-2.73 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.88-1.78 (m, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.9, 170.4, 169.8, 169.6, 83.7, 76.2, 73.9, 69.9, 68.4, 62.2, 60.7, 32.2, 26.3, 20.9, 20.8, 20.7.

![Structure 104](image)

104 57%

The compound was prepared according to the general procedure 1.4.2.8 with a buffer solution of pH = 4. Mixture of 104 and 105 was observed which was further purified by flash column chromatography.

\((2R,3R,5R,6S)-2\)-(acetoxymethyl)-6-\((3\)-hydroxypropyl\)thio\)tetrahydro-2\(H\)-pyran-3,4,5-triy1 triacetate (104):

White solid (33 mg, 57%)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.22 (t, \(J = 9.5\) Hz, 1H), 5.07 (t, \(J = 9.5\) Hz, 1H), 5.04 (t, \(J = 9.3\) Hz, 1H), 4.48 (d, \(J = 10.1\) Hz, 1H), 4.23 (dd, \(J = 4.9\) Hz, \(J = 12.4\) Hz, 1H), 4.15 (dd, \(J = 2.3\) Hz, \(J = 12.4\) Hz, 1H), 3.73-3.69 (m, 3H), 2.87-2.73 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.88-1.78 (m, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.9, 170.4, 169.8, 169.6, 83.7, 76.2, 73.9, 69.9, 68.4, 62.2, 60.7, 32.2, 26.3, 20.9, 20.8, 20.7.
\((2S,3S,5S)-2\text{-}(\text{acetoxymethyl})-6\text{-}((2S,3R,5R,6R)-3,4,5\text{-}\text{triacetoxy}-6\text{-}
\text{acetoxymethyl})\text{tetrahydro-2H-pyran-2-yl})\text{disulfaneyl})\text{tetrahydro-2H-pyran-3,4,5\text{-}triyl}
\text{triacetate (105)}:

Colorless oil (15 mg, 5%)

\(^1\text{H} \text{NMR} \ (500 \text{ MHz, CDCl}_3) \delta \ 5.26\text{-}5.15 \ (\text{m, 2H}), \ 5.08 \ (t, \ J=10 \text{ Hz, 1H}), \ 4.64 \ (d, \ J=10 \text{ Hz, 1H}), \ 4.32 \ (d, \ J=10 \text{ Hz, 1H}), \ 4.32 \ (dd, \ J=4.4 \text{ Hz, 1H}), \ 4.20 \ (dd, \ J=2.2 \text{ Hz, 1H}), \ 3.77 \ (ddd, \ J=2.2 \text{ Hz, 1H}), \ 2.11 \ (s, 3H), \ 2.08 \ (s, 3H), \ 2.01 \ (s, 3H), \ 1.98 \ (s, 3H). \ \ ^\text{13}C \text{NMR} \ (125 \text{ MHz, CDCl}_3) \delta \ 170.7, \ 170.1, \ 169.3, \ 169.1, \ 87.2, \ 76.1, \ 73.8, \ 69.7, \ 67.9, \ 61.5, \ 20.8, \ 20.6, \ 20.5.

The compound was prepared according to the general procedure 1.4.2.8 with a buffer solution of pH = 6. Mixture of 104 and 105 was observed which was further purified by flash column chromatography.

\((2R,3R,5R,6S)-2\text{-}(\text{acetoxymethyl})-6\text{-}(3\text{-}\text{hydroxypropyl})\text{thio})\text{tetrahydro-2H-pyran-3,4,5\text{-}triyl}
\text{triacetate (104)}:

White solid (32 mg, 56%) \(^1\text{H} \text{NMR} \ (500 \text{ MHz, CDCl}_3) \delta \ 5.22 \ (t, \ J=9.5 \text{ Hz, 1H}), \ 5.07 \ (t, \ J=9.5 \text{ Hz, 1H}), \ 5.04 \ (t, \ J=9.3 \text{ Hz, 1H}), \ 4.48 \ (d, \ J=10.1 \text{ Hz, 1H}), \ 4.23 \ (dd, \ J=4.9 \text{ Hz, 1H}), \ 4.15 \ (dd, \ J=2.3 \text{ Hz, 1H}), \ 3.73-3.69 \ (\text{m, 3H}), \ 2.87-2.73 \ (\text{m, 2H}), \ 2.08 \ (s, 3H), \ 2.06 \ (s, 3H), \ 2.02 \ (s, 3H), \ 2.00 \ (s, 3H), \ \delta \ 1.88\text{-}1.78 \ (\text{m, 2H}).
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.9, 170.4, 169.8, 169.6, 83.7, 76.2, 73.9, 69.9, 68.4, 62.2, 60.7, 32.2, 26.3, 20.9, 20.8, 20.7.

\((2S,3S,5S)-2-(\text{acetoxymethyl})-6-((2S,3R,5R,6R)-3,4,5-\text{triacetoxy}-6-(\text{acetoxymethyl})\text{tetrahydro-2H-pyran-2-yl})\text{disulfanyl})\text{tetrahydro-2H-pyran-3,4,5-triyl triacetate} (105):\)

Colorless oil (12 mg, 12 %)

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.29 - 5.17 (m, 2H), 5.08 (t, \(J = 10\) Hz, 1H), 4.64 (d, \(J = 10\) Hz, 1H), 4.32 (d, \(J = 10\) Hz, 1H), 4.32 (dd, \(J = 4.4\) Hz, \(J = 12.5\) Hz, 1H), 4.20 (dd, \(J = 2.2\) Hz, \(J = 12.5\) Hz, 1H), 3.77 (ddd, \(J = 2.2\) Hz, \(J = 4.4\) Hz, \(J = 10\) Hz, 1H), 2.11 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.7, 170.1, 169.3, 169.1, 87.2, 76.1, 73.8, 69.7, 67.9, 61.5, 20.8, 20.6, 20.5

\[\begin{align*}
\text{104} & \text{ 30\%} \\
\text{105} & \text{ 20\%}
\end{align*}\]

The compound was prepared according to the general procedure \textbf{1.4.2.8} with a buffer solution of pH = 8. Mixture of \textbf{104} and \textbf{105} was observed which was further purified by flash column chromatography.

\((2R,3R,5R,6S)-2-(\text{acetoxymethyl})-6-((3-\text{hydroxypropyl})\text{thio})\text{tetrahydro-2H-pyran-3,4,5-triyl triacetate} (104):\)

White solid (18.5 mg, 30%)

\(^{1}\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.22 (t, \(J = 9.5\) Hz, 1H), 5.07 (t, \(J = 9.5\) Hz, 1H), 5.04 (t, \(J = 9.3\) Hz, 1H), 4.48 (d, \(J = 10.1\) Hz, 1H), 4.23 (dd, \(J = 4.9\) Hz, \(J = 12.4\) Hz, 1H), 4.15 (dd, \(J = 2.3\) Hz,
$J = 12.4 \text{ Hz}, 1 \text{H}$), 3.73-3.69 (m, 3H), 2.87-2.73 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.88-1.78 (m, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.9, 170.4, 169.8, 169.6, 83.7, 76.2, 73.9, 69.9, 68.4, 62.2, 60.7, 32.2, 26.3, 20.9, 20.8, 20.7.


Colorless oil (20 mg, 20%)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.26- 5.15 (m, 2H), 5.08 (t, $J = 10$ Hz, 1H), 4.64 (d, $J = 10$ Hz, 1H), 4.32 (d, $J = 10$ Hz, 1H), 4.32 (dd, $J = 4.4$ Hz, $J = 12.5$ Hz, 1H), 4.20 (dd, $J = 2.2$ Hz, $J = 12.5$ Hz, 1H), 3.77 (ddd, $J = 2.2$ Hz, $J = 4.4$ Hz, $J = 10$ Hz, 1H), 2.11(s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.7, 170.1, 169.3, 169.1, 87.2, 76.1, 73.8, 69.7, 67.9, 61.5, 20.8, 20.6, 20.5.

![Chemical Structure of 104 and 105](image_url)

The compound was prepared according to the general procedure 1.4.2.8 with a buffer solution of pH = 10. Mixture of 104 and 105 was observed which was further purified by flash column chromatography.

$(2R,3R,5R,6S)$-2-(acetoxymethyl)-6-((3-hydroxypropyl)thio)tetrahydro-$2H$-pyran-3,4,5-triyl triacetate (104):

White solid (12 mg, 20%)
\( ^1 \text{H NMR (500 MHz, CDCl}_3 \) \( \delta 5.22 (t, J = 9.5 \text{ Hz}, 1 \text{H}), 5.07 (t, J = 9.5 \text{ Hz}, 1 \text{H}), 5.04 (t, J = 9.3 \text{ Hz}, 1 \text{H}), 4.48 (d, J = 10.1 \text{ Hz}, 1 \text{H}), 4.23 (dd, J = 4.9 \text{ Hz}, J = 12.4 \text{ Hz}, 1 \text{H}), 4.15 (dd, J = 2.3 \text{ Hz}, J = 12.4 \text{ Hz}, 1 \text{H}), 3.73-3.69 (m, 3 \text{H}), 2.87-2.73 (m, 2 \text{H}), 2.08 (s, 3 \text{H}), 2.06 (s, 3 \text{H}), 2.02 (s, 3 \text{H}), 2.00 (s, 3 \text{H}), 1.88-1.78 (m, 2 \text{H}). \)
\( ^13 \text{C NMR (125 MHz, CDCl}_3 \) \( \delta 170.9, 170.4, 169.8, 169.6, 83.7, 76.2, 73.9, 69.9, 68.4, 62.2, 60.7, 32.2, 26.3, 20.9, 20.8, 20.7. \)


Colorless oil (36 mg, 36%) 
\( ^1 \text{H NMR (500 MHz, CDCl}_3 \) \( \delta 5.26-5.15 (m, 2 \text{H}), 5.08 (t, J = 10 \text{ Hz}, 1 \text{H}), 4.64 (d, J = 10 \text{ Hz}, 1 \text{H}), 4.32 (d, J = 10 \text{ Hz}, 1 \text{H}), 4.32 (dd, J = 4.4 \text{ Hz}, J = 12.5 \text{ Hz}, 1 \text{H}), 4.20 (dd, J = 2.2Hz, J = 12.5 \text{ Hz}, 1 \text{H}), 3.77 (ddd, J = 2.2 \text{ Hz}, J = 4.4 \text{ Hz}, J = 10 \text{ Hz}, 1 \text{H}), 2.11 (s, 3 \text{H}), 2.08 (s, 3 \text{H}), 2.01 (s, 3 \text{H}), 1.98 (s, 3 \text{H}). \)
\( ^13 \text{C NMR (125 MHz, CDCl}_3 \) \( \delta 170.7, 170.1, 169.3, 169.1, 87.2, 76.1, 73.8, 69.7, 67.9, 61.5, 20.8, 20.6, 20.5. \)

![108](image)

\( 1,2\)-dibenzyl disulfane (108): white solid.
\( ^1 \text{H NMR (500 MHz, CDCl}_3 \) \( \delta 7.41 (m, 4 \text{H}), 7.36 (m, 2 \text{H}), 7.32 (m, 4 \text{H}), 3.68 (s, 4 \text{H}). \)
\( ^13 \text{C NMR (125 MHz, CDCl}_3 \) \( \delta 137.4, 129.5, 128.5, 127.5, 43.3. \)
IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 3027, 3060, 3084, 2911, 1948, 1877, 1803, 1754, 1600, 1583, 1452, 1334, 1229, 1156, 913, 836; Calcd for C\(_4\)H\(_{15}\)S\(_2^+\) 247.061; found 247.075.
1.4.2.9 Procedure for Synthesis of 109:

300 mg Fmoc-Val-NovaSyn® TGT resin (0.38 mmol/g) was employed in SPPS. Peptide was synthesized under standard Fmoc protocols using DMF as the solvent, deblocking for 5 min in piperidine/DBU/DMF (2:2:96, v/v/v), coupling for 25 min using HATU as coupling reagent. The sequence is designed as Boc-Ala-Asp(OAll)-Pro-Gly-Val-OH by using Boc-Ala-OH, Fmoc-Asp(OAll)-OH, Fmoc-Pro-OH and Fmoc-Gly-OH. Upon completion of the synthesis the peptide resin was washed into a peptide synthesis vessel using CH₂Cl₂. Resin was treated with CH₂Cl₂/TFE/AcOH (8:1:1, v/v/v) solution 40 min (×3). The resin was then removed by filtration, the combined cleavage solution was concentrated under reduced pressure, and global deprotection was performed under the treatment of TFA/H₂O/TIPS (95:2.5:2.5, v/v/v) solution for 20 min, and the filtrate was concentrated under a nitrogen atmosphere. The residue was washed with cold diethyl ether to give a white solid, which was then dissolved in a mixture of acetonitrile and water containing 5% of acetic acid.

Purification of the crude product using preparative HPLC (15 to 60% acetonitrile in water over 20 min, flow rate: 4 mL/min, Higgins Analytical Proto 200 5 μm 250 × 10 nm C18 column) afforded as a white solid after lyophilization (51.9 mg). Analytical HPLC: tᵣ = 12.61 min (15 to 40% acetonitrile in water over 20 min, flow rate: 0.6 mL/min, Higgins Analytical Proto 200 5 μm 150 × 2.0 nm C18 column).
((S)-4-(allyloxy)-2-((S)-2-aminopropanamido)-4-oxobutanoyl)-L-prolylglycyl-L-valine (109):

1H NMR (500 MHz, Deuterium Oxide) δ 5.88 (ddt, J = 17.4, 10.5, 5.7 Hz, 1H), 5.28 (dd, J = 17.3, 1.5 Hz, 1H), 5.21 (dd, J = 10.5, 1.3 Hz, 1H), 4.97 (dd, J = 8.1, 5.9 Hz, 1H), 4.57 (d, J = 5.6 Hz, 2H), 4.37 (dd, J = 8.5, 4.9 Hz, 1H), 4.20 (d, J = 6.0 Hz, 1H), 4.00 (q, J = 7.1 Hz, 1H), 3.89 (d, J = 1.2 Hz, 2H), 3.76 – 3.65 (m, 2H), 2.95 (dd, J = 16.9, 5.9 Hz, 1H), 2.73 (dd, J = 16.9, 8.1 Hz, 1H), 2.27 – 2.18 (m, 1H), 2.16 – 2.08 (m, 1H), 2.04 – 1.86 (m, 3H), 1.44 (d, J = 7.1 Hz, 3H), 0.87 (dd, J = 10.7, 6.9 Hz, 6H). 13C NMR (126 MHz, D2O) δ 175.16, 174.42, 171.75, 171.18, 170.32, 169.93, 131.55, 118.72, 66.45, 60.89, 58.39, 48.84, 48.40, 47.93, 42.27, 35.05, 29.91, 29.30, 24.49, 18.28, 17.26, 16.42. LRMS (ESI) m/z calcd. for C22H35N5O8 [M + H]+ 498.2558, found 498.5881.

Figure 1.3: Starting material 109.
1.4.2.9 Procedure for Synthesis of 110:

To a dried vire, equipped with a stir bar were added 102 (0.137 mmol), Catalyst A (0.00137 mmol), 109 (0.1648 mmol), and mixture of CH$_3$CN:H$_2$O (1:1) (0.5 M). The flask was closed, and reaction was allowed to stir under Blue LEDs for 15 hours. Purification of the crude product using preparative HPLC (20 to 50% acetonitrile in water over 20 min, flow rate: 4 mL/min, Higgins Analytical Proto 200 5 μm 250 × 10 nm C18 column) afforded as a white solid after lyophilization (11.3 mg). Analytical HPLC: $t_R = 9.40$ min (30 to 90% acetonitrile in water, flow rate: 0.6 mL/min, Higgins Analytical Proto 200 5 μm 150 × 2.0 nm C18 column).

$^1$H NMR (500 MHz, Deuterium Oxide) δ 5.29 (t, $J = 9.3$ Hz, 1H), 5.04 (t, $J = 9.8$ Hz, 1H), 4.96 (m, 2H), 4.83 (d, $J = 10.1$ Hz, 1H), 4.38 (dd, $J = 8.4$, 4.9 Hz, 1H), 4.27 (dd, $J = 12.7$, 4.2 Hz, 1H), 4.16 (m, 4H), 4.04 – 3.96 (m, 2H), 3.90 (s, 2H), 3.71 (m, 2H), 2.97 – 2.88 (m, 1H), 2.81 – 2.65 (m, 3H), 2.23 (m, 1H), 2.14 – 2.09 (m, 1H), 2.05 (s, 6H), 2.02 (s, 3H), 2.01 (m, 1H), 1.99 (s, 3H), 1.93 (m, 4H), 1.44 (d, $J = 7.1$ Hz, 3H), 0.87 (dd, $J = 12.9$, 6.8 Hz, 6H).

$^{13}$C NMR (126 MHz, D$_2$O) δ 175.65, 174.34, 173.65, 173.12, 172.73, 172.67, 172.02, 171.05, 170.32, 169.89, 83.25, 74.93, 74.09, 70.24, 68.20, 64.20, 62.02, 60.90, 58.76, 48.87, 48.38, 47.95, 42.36, 35.12, 30.05, 29.32, 28.20, 26.97, 24.53, 20.18, 20.14, 20.03, 18.45, 17.34, 16.44

LRMS (ESI) m/z calcd. for C$_{36}$H$_{55}$N$_5$O$_{17}$ [M + H]$^+$ 862.3386, found 862.5591.

Figure 1.5: LRMS of glycosylated pentapeptide compound 110.
1.4.2.10 Procedure for Synthesis of 112 and 115

To a dried vial, equipped with a stir bar were added thiol (0.137 mmol), Catalyst A (0.00137 mmol), olefin (0.1648 mmol), and H$_2$O:CH$_3$CN (1:1). The flask was closed, and reaction was allowed to stir under Blue LEDs for 15 hours. Upon completion of reaction, the residue was subjected to flash column chromatography to give desired product.
(2R,3S,5R,6S)-2-(acetoxyethyl)-6-((3-hydroxypropyl)thio)tetrahydro-2H-pyran-3,4,5-triy triacetate (112):
The compound was prepared according to general procedure 1.4.2.10. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 1/1) to give product (48 mg, 83%) as colorless oil;

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.40 (s, 1 H), 5.22 (t, $J = 10$ Hz, 1H), 5.02 (d, $J = 10$ Hz, 1H), 4.46 (d, $J = 10$ Hz, 1H), 4.13–4.06 (m, 2H), 3.92 (d, $J = 6$ Hz, 1H), 3.71 (s, 2H), 2.87–2.75 (m, 2H), 2.13 (s, 3H), 2.03 (d, $J = 11$ Hz, 6H), 1.96 (s, 3H), 1.82 (d, $J = 6.5$ Hz, 2H). $^{13}$C NMR (125 Hz, CDCl$_3$) $\delta$ 170.4, 170.2, 170.0, 169.8, 84.0, 74.5, 71.8, 67.3, 67.0, 61.5, 60.6, 32.0, 26.3, 20.8, 20.6, 20.5. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3508, 2939, 1748, 1370, 1224, 1054, 1083, 918, 599; Calcd for C$_{17}$H$_{26}$NaO$_{10}$S$^+$ 445.1139; found 445.1177.

![Image of compound 112](image)

(2R,3R,5R,6S)-2-(acetoxyethyl)-6-(((4R,7R)-4,7-dimethyl-3,6,9-trioxo-2,10-dioxo-5,8-diazatridecan-13-yl)thio)tetrahydro-2H-pyran-3,4,5-triy triacetate (115): The compound was prepared according to general procedure 1.4.2.10. The residue was purified by flash column chromatography (Ethyl acetate/Hexanes = 2/1) to give product Colorless oil, 65% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.85 (d, $J = 7.2$ Hz, 1H), 5.53 (d, $J = 7.5$ Hz, 1H), 5.16 (t, $J = 9.3$ Hz, 1H), 5.04–4.91 (m, 2H), 4.47 (dd, $J = 19.2$, 8.4 Hz, 2H), 4.32–4.12 (m, 2H), 4.07 (d, $J = 10.7$ Hz, 3H), 3.67 (d, $J = 1.1$ Hz, 4H), 2.75–2.57 (m, 2H), 2.01 (d, $J = 0.9$ Hz, 3H), 1.99 (s, 3H), 1.95 (d, $J = 0.8$ Hz, 3H), 1.93 (d, $J = 0.9$ Hz, 3H), 1.85 (s, 2H), 1.32 (t, $J = 6.9$ Hz, 6H). $^{13}$C NMR (150
MHz, CDCl₃) δ 171.9, 170.5, 169.9, 169.3, 169.2, 155.7, 83.3, 75.6, 73.6, 69.5, 68.1, 63.1, 61.9, 52.3, 50.1, 47.8, 29.0, 26.2, 20.5, 20.4, 18.6, 17.4. IR (CH₂Cl₂, cm⁻¹) 3341, 2954, 1745, 1670, 1537, 1453, 1370, 1219, 1156, 1037, 914, 735; HRMS (ESI): m/z Calcd for C₂₅H₃₈N₂NaO₁₄S⁺ (M+Na)⁺: 645.1936; found: 645.1940.
1.6 References:

1) Ciamician, G. Science, 1912, 36, 385.


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Chapter 2: Oxidative Cleavage of N-Carbonylated Indoles with Methylene Blue

2.1 Introduction

Oxidative cleavage reaction of aromatic rings is a common occurrence in nature. The oxidative cleavage reaction of aromatic rings plays a significant role in maintaining the global carbon cycle. Particularly, the oxidative transformation of tryptophan to N-formylkynurenine, catalyzed by tryptophan 2,3-dioxygenase, is the major oxidative and metabolic pathway of tryptophan. 

Mehler and Knox’s research showed that a mediator in the oxidation of tryptophan is formylkynurenine in the liver. In the liver system, they found the enzyme formylase, which is capable of hydrolyzing compounds such as formylkynurenine with the help of structural analogs of formylkynurenine. Formylkynurenines were identified using a test based on the use of the enzyme formylase. After identification, formylkynurenines were separated from tryptophan ozonolysis products. When they removed the enzyme formylase, which is responsible for the oxidation of tryptophan from the liver system, there was an accumulation of formylkynurenine that was identical to that isolated from the systemic reaction.

Autoxidation and catalytic oxygenation have been shown to convert tetrahydro carbazole to hydroperoxide which then readily converts to lactam. In 1951 Witkop et al. reported chemically oxidative cleavage by catalytic oxidation and autoxidation of the C-2-3 double bond of indoles. When Witkop et al. subjected a fresh solution of C-2-3 in chloroform to the determination of the infrared spectrum to obtain the indole spectrum, there were no absorption bands near 6 µ. After the solution stood for one day, compound was seen with a band at 6 µ. After two days of standing and in contact with air, the solution showed an absorption spectrum of
lactams. After Witkop et al. experiments developed various synthetic methods in which different reagents were used including peracids, periodic acid, chromic acid, and ozone (Scheme 2.1).\textsuperscript{5a,5b}

\textbf{Scheme 2.1:} Oxidative cleavage with various oxidants.

In the early 1950s, Witkop showed that various indole oxidizing reagents can result in manifestation of quinolones. Oxidative cleavage of the C-2-3 double bonds of the indole moiety is involved in these oxidation reaction mechanisms and this is known as Witkop oxidation, which is then followed by Camps cyclization where a cannon ring is formed. Winterfeldt discovered the method for conversion of Witkop oxidation intermediate to the camps cyclization product by use of oxidants such as NaH/O\textsubscript{2} and K\textsubscript{Ot}-Bu/O\textsubscript{2}.\textsuperscript{6} Following this, Witkop-Winterfeldt oxidation has been applied synthesize natural products and pharmaceutical agents.\textsuperscript{7} These oxidizing agents are not suitable to oxidize N-Substituted indoles as they are likely to withstand oxidation under these conditions.\textsuperscript{7}
Investigation was carried out to study the singlet oxygen reaction with N-alkylated indoles to give carbonyl and amide fragments (Scheme 2.2). However, these transformations could not be comprehended on electron-deficient N-acetylindoles. The poor nucleophilicities of electron deficient N-acetylindoles results in the formation of ene-type allylic oxidation product.

Scheme 2.2: Alkylated indoles oxidative cleavage.
The development of new ways of activating small molecules is the basic goal of the field of catalysis. Photoredox catalysis of visible light is an approach that has recently received much attention. This type of catalysis relies on the ability of the organic dye and the metal complex to engage in a single-electron-transfer process with substrates after photoexcitation with visible light. In addition to inorganic semiconductors and organic dyes, the other most efficient and commonly used photocatalysts are coordinatively saturated pyrylide transition metal complexes such as [Ru(bpy)₃]²⁺.¹⁰ Photochemical transformation represent one powerful strategy that leads to the formation of a high degree of molecular complexity from simple building blocks with the help of just one step. All light-induced transformations rely on the inclusion of electronically excited states that occur after photon absorption. Synthetic designs based on photochemical transformations have great potential to provide cleaved polycyclic hydrocarbons with a high degree of efficiency that would have great value in synthesis.¹¹,¹²
2.2 Quinolones:

Quinolones are widely present in many bioactive natural products and pharmaceutical agents. Antibacterial quinolones are the most important class of non-infectious agents in medical practice. Both 1,8-naphthyridine and quinolone are often labeled as "fluoroquinolone" or "quinolone" antibacterial agents. Once drugs of this class were approved for use, they had a very low therapeutic value and were used above all for the treatment of urinary tract infections of Gram-negative pathogens. In the early 1980s, the therapeutic use of this class of drugs increased when it was discovered that substitution at the quinolone sixth position with fluorine and the sitting position with the basic amino heterocyclic group leads to an increase in antimicrobial activity. This has also led to an expansion of the spectrum of action of the drug. The fluoroquinolone class of drugs has the possibility of treating many infections caused by gram-negative pathogens. After that, pharmaceutical companies developed many more drugs based on quinolones.

It is hypothesized that many antibiotics in the environment may not reach the concentrations required for inhibition and will rather act as signs or signals that will alter gene expression in microbes. Antibiotics modulate the transcription of bacterial genes in a dose-dependent manner and each of the antibiotics elicits a different response that may have adaptive values for the bacterium. Synthetic quinolone antibiotics have a subinhibitory effect on gene expression in microbes. In P. aeruginosa, five percent of the gene is expressed differently when subinhibitory concentrations of ciprofloxacin are present in its environment. Those five percent of genes include genes that are responsible for the virulence of the bacterium. When bacteria are treated with quinolone antibiotics, most of the changes that occur are beyond expected. Such changes suggest that the effects associated with quinolone antibiotics are outside the mechanisms of action of antibiotics.
Alkyl 4-quinolones represent a class of metabolites produced by the *Burkholderia* and *Pseudomonas* genera. These quinolones consist of four quinolone nuclei that are substituted by different pendant groups most commonly at the C-2 position. Many alkyl quinolones have simple hydrocarbon side chains. However, there is a wide range of structurally different examples found in several genera of bacteria, including those with sulfur side chains, isoprenoid, and aromatic side chains. In addition to having antimicrobial properties, alkyl quinolones also have antioxidant, antialgal, antifungal, and antimalarial properties. Among various quinolones, 4-Quinolone-3-carboxylic acid derivatives are entitled structural frameworks in drug discovery. They are present in synthetic antibiotics drugs such as Ciprofloxacin, Levofloxacin, and Moxifloxacin. Ivacaftor, an amide derivative is FDA approved for treating cystic fibrosis. Moreover, these compounds show various biological activities such as antiviral, antitumor, anti-inflammation, antiparasitic activities and show activities towards Alzheimer’s disease (*Figure 2.1*).
2.3 Experimental Studies

We initiated our studies by screening different catalysts such as 9-Mesityl-10-methyl-acridinium perchlorate, Eosin Y, Rose Bengal, and Methylene Blue for oxidation of tryptamine derivative \(212\). We were glad to find that Methylene Blue acted as an efficient catalyst in MeOH under Blue LEDs irradiation resulting in oxidative cleavage product \(213\) in 20% isolated yield. After screening different solvents (Table 2.1, entries 5-11), we found that higher yields of products are favored more in polar solvents (Table 2.1, entries 9-11).
Reactions initiated with two 12 W, 450nm light-emitting diode (LED) flood lamps for 10 h.

**Isolated yield.**

Reaction conducted in dark.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Photocatalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9-Mesityl-10-methyl-acridinium perchlorate</td>
<td>MeOH</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Eosin Y</td>
<td>MeOH</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Rose Bengal</td>
<td>MeOH</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td><strong>Methylene Blue</strong></td>
<td>MeOH</td>
<td><strong>20</strong></td>
</tr>
<tr>
<td>5</td>
<td>Methylene Blue</td>
<td>CH(_2)Cl(_2)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Methylene Blue</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Methylene Blue</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Methylene Blue</td>
<td>MeNO(_2)</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Methylene Blue</td>
<td>ClCH(_2)CH(_2)OH</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>Methylene Blue</td>
<td>CCl(_3)CH(_2)OH</td>
<td>47</td>
</tr>
<tr>
<td>11</td>
<td><strong>Methylene Blue</strong></td>
<td>CF(_3)CH(_2)OH</td>
<td><strong>88</strong></td>
</tr>
<tr>
<td>12</td>
<td>Methylene Blue</td>
<td>HFIP</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>9-Mesityl-10-methyl-acridinium perchlorate</td>
<td>CF(_3)CH(_2)OH</td>
<td>24</td>
</tr>
<tr>
<td>14</td>
<td>Eosin Y</td>
<td>CF(_3)CH(_2)OH</td>
<td>35</td>
</tr>
<tr>
<td>15</td>
<td>Rose Bengal</td>
<td>CF(_3)CH(_2)OH</td>
<td>0</td>
</tr>
<tr>
<td>16(^c)</td>
<td>Methylene Blue</td>
<td>CF(_3)CH(_2)OH</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>_</td>
<td>CF(_3)CH(_2)OH</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Reactions initiated with two 12 W, 450nm light-emitting diode (LED) flood lamps for 10 h. \(^b\)Isolated yield.

\(^c\)Reaction conducted in dark.

**Table 2.1:** Optimization of reaction conditions.
Trifluoroethanol (TFE) acted as efficient solvent in affording oxidative cleavage adduct in 88% yield (Table 2.1, entry 11). As our reactions are favored in more protic solvents, we thought of trying hexafluoroisopropanol (HFIP) to carry out reaction. The HFIP solvent resulted in decomposition of the reactants (Table 2.1, entry 12). To validate that methylene blue afforded better results, we also checked the reactivity of 9-Mesityl-10-methyl-acridinium perchlorate, Eosin Y, Rose Bengal in trifluoroethanol (Table 2.1, entries 13-15). Control experiments indicated that both light irradiation and catalyst are necessary for this reaction (Table 2.1, entries 16, 17).

After successfully optimizing the reaction conditions, we wanted to apply this method to explore the scope in various substituted indoles. Under the optimized conditions both acetyl (Ac) and tert-butoxycarbonyl (Boc) protected indoles were well tolerated to afford oxidative cleaved product in yields of 68%-75% (Table 2.2, entry 1, a-c). Substituted indoles were oxidized to obtain the corresponding products in good yields (Table 2.2, entry 1, d-f). These mild conditions were tolerated well by the tryptophan derivative 216, tryptamine derivative 218 and molecule containing free hydroxyl group 220 resulting in oxidized product in excellent yields (Table 2.2, entry 2,3,4). We also tested the tolerance of electron withdrawing and electron denoting substituents at C-5 and C-6 positions under these conditions (Table 2.2, entries 5-7). Happily, under these conditions the cyclic structures resulted in the formation of corresponding adduct in 70% and 62% yield (Table 2.2, entries 8 and 9).
Table 2.2: Oxidative cleavage of indoles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| 1     | ![Indole structure](#) | ![Product structure](#) | 215a: 66  
215b: 84  
215c: 75  
215d: 85  
215e: 68  
215f: 78 |
| 2     | ![Indole structure](#) | ![Product structure](#) | 216 |
| 3     | ![Indole structure](#) | ![Product structure](#) | 218 |
| 4     | ![Indole structure](#) | ![Product structure](#) | 220 |
Encouraged by these results, our investigation was focused on implementing this method to facilitate the Witkop-Winterfeldt oxidation for synthesis of 4-Quinolone-3-carboxylic acid derivatives (Scheme 2.3). We were successful in achieving the Witkop-Winterfeldt reaction in which oxidative C-2-3 bond cleavage takes places followed by Camps cyclization. We were able to achieve this method by treatment of silica gel after the total consumption of indole substrates.
Using these efficient and mild conditions indole acetic acid derivatives with methyl, methoxy and bromo group at C-5 positions were converted corresponding adduct in good yields. (232-234, 54%-84%). Happily, the amide analogue 235 was obtained in 73% yield and fluoro-substituted aryl amide 236 was isolated in 85% yield. Using this method, we were able to convert indoleacetic acid 237 to quinolone 238 in yield of 80%. The quinolone 238 is predecessor for synthesizing the Ivacaftor.

Scheme 2.3: Witkop-Winterfeldt indole oxidation.

2.4 Mechanism

The proposed mechanism and mechanistic studies are shown in Figure 2.2. We could not exclude the participation of singlet oxygen during the reaction process.21 To test that, we performed Stern
Volmer quenching experiments (Figure 2.2b). The experiments show there is a redox reactivity between tryptamine 239 and the methylene blue (M.B.\(^+\)) catalyst. So, we propose that methylene blue catalyst via single electron transfer will oxidize indole first. The coupling of radical cation 240 with oxygen molecule will result in formation of peroxy radical intermediate 241. The peroxy radical 241 can accept electron from reduced methylene blue species to transform into 242 and

Figure 2.2: Proposed mechanism and studies. Adapted with permission from https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0036-1592006
regenerating photoactive catalyst (M.B.\(^+\)). Next, formation of 1,2-dioxetane followed by decomposition results in formation of oxidative cleavage product 243. Next, to support the mechanistic studies we carried out density functional theory (DFT) calculations and Marcus theory calculations. According to the proposed mechanism, species 240 is formed by single electron transfer (SET) from 239 to excited methylene blue catalyst (M.B.\(^+\)) as methylene blue (M.B.\(\cdot\)) needs only 8.2 kcal/mol of Gibbs free energy barrier. The resulting radical cation 240 has spin density confined to benzylic carbon (for detailed explanation see supporting information) which advances the addition of dioxygen to benzylic radical center. The addition of dioxygen to benzylic radical center afforded two transition states ‘syn’ isomer \(\text{TS1}_{\text{syn}}\) and ‘anti’ transition state \(\text{TS1}_{\text{anti}}\). The tendency to result in syn-dioxygen addition is because of syn isomer \(\text{TS1}_{\text{syn}}\) has 1.8 kcal/mol lower energy barrier than the ‘anti’ addition. The previous computational studies show that dioxygen addition to pi system favors the syn isomer transition state.\(^{22}\) The \(\text{TS1}_{\text{syn}}\) and \(\text{TS1}_{\text{anti}}\) are both computed as doublets, and are only 15.9 and 17.8 kcal/mol.

The evaluation of \(\text{TS1}_{\text{syn}}\) and \(\text{TS1}_{\text{anti}}\) resulted in doublets, whereas these two transition states have 15.9 kcal/mol and 17.8 kcal/mol, high energy in contrast to radical cation 240 and triplet dioxygen. As per the DFT calculations we could not exclude the possibility of reaction of radical cation 240 with singlet oxygen.\(^{23}\) But the energy barrier calculations for dioxygen addition shows that radical cation 240 is strongly reactive with ground state triplet oxygen to obtain in peroxy radical 241. The resulting peroxy radical 241 undergoes single electron reduction to form zwitterionic complex 242. Next step is highly exergonic resulting in collapse of 242 to 1,2-dioxetane and 243. The final step results in thermal decomposition of 243 to obtain final adduct 244, and the mechanism for this step has been previously studied in literature.\(^{24}\)
2.5 Conclusion

In conclusion, visible-light-mediated oxidative cleavage of electron deficient indoles was developed. Various functional groups were tolerated under these mild conditions. A variety of electron denoting and electron withdrawing groups were accommodated well on indole backbone. Witkop-Winterfeldt reaction were conducted under the optimized conditions successfully. Reaction mechanism for photocatalytic system was proposed and studied via density functional theory (DFT) and Marcus theory calculations.

2.6 Supporting Information and $^1$H NMR, $^{13}$C NMR Spectra

2.6.1 General Methods

All commercially available chemicals were used without further purification unless otherwise noted. Reactions were monitored by thin layer chromatography using TLC silica gel 60-F 254 plates. TLC plates were visualized by UV fluorescence (254 nm) or stained by Cerium Molybdate followed by heating. The reaction products were purified by column chromatography Siliaflash-P60 (40-63 µm) silica gel available from Silicycle. $^1$H NMR spectra were recorded on a BRUKER AV-400 (400 MHz) and $^{13}$C NMR spectra were recorded on a BRUKER AV-400 or AV-600 (100 MHz or 150 MHz). Data for $^1$H-NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet), coupling constant in Hz and integration. Data for $^{13}$C NMR are reported in terms of chemical shift (δ, ppm). IR spectra were recorded on a PerkinElmer Spectrum Two IR spectrometer and only major peaks were reported in cm$^{-1}$. High-resolution mass spectral analysis (HRMS) data were obtained using Agilent Technologies 6530 Accurate Mass Q-TOF LC/MS. Optical rotations were measured on a Perkin-Elmer 351 polarimeter at 589 nm with a 100 mm path length cell. Irradiation of photochemical reactions was carried out using two 12W PAR38 blue LED flood lamps from ABi LED lighting.
Yields refer to chromatographically and spectroscopically purified compounds. For Emission quenching experiments: Emission intensities for Stern Volmer studies were recorded on Horiba Fluorolog®-3 model FL1039A/40A spectrofluorometer and is equipped with 450 W steady state xenon illuminator and single-grating emission monochromator and a photomultiplier tube (room temperature R928P).

### 2.6.2 Experimental Procedures and $^1$H, $^{13}$C NMR Data

#### 2.6.2.1 Procedure for Preparation of 2,3-dimethyl-6-chloro-5-fluoro indole 1$_2^5$ (S$_2^3$):

4-Chloro-5-fluorophenylhydrazine hydrochloride S$_2^1$ (1 g, 6.23 mmol) in acetic acid (20 mL) was heated at 50 °C for 30 minutes. To the stirred suspension butan-2-one S$_2^2$ (900 mg, 12.5 mmol, 2.0 equiv.) was added, and the reaction mixture was refluxed for 3 hours. The reaction mixture was cooled to room temperature and acetic acid was removed under vacuum. The residue was dissolved in ethyl acetate (30 mL) and resulting solution was washed with water and brine, dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated, and residue was purified by flash column chromatography (hexanes: EtOAc, 10:1) to obtain the 2,3-dimethyl indole S$_2^3$ as yellowish solid (400 mg, 31%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.60 (s, 1H), 7.21 (d, $J = 4.0$ Hz, 1H), 7.17 (d, $J = 8.8$ Hz, 1H), 2.34 (s, 3H), 2.17 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 153.93, 151.58, 133.25, 131.29, 128.52, 128.44, 113.98, 113.76, 110.96, 107.55, 107.50, 104.15, 103.92, 11.57, 8.31; ESI LRMS: m/z calcd for C$_{10}$H$_9$ClFN [M+Na]$^+$ 220.0, found 220.1; IR (CH$_2$Cl$_2$, cm$^{-1}$) 1477, 1263, 1136, 733, 704.
2.6.2.2 Preparation of Ethyl 2-(5-methyl-1H-indol-3-yl)acetate\textsuperscript{26} (S\textsubscript{6}):

\[
\begin{align*}
\text{Me} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{S}\textsubscript{4} \\
\text{S}\textsubscript{5} & \quad \text{S}\textsubscript{6}
\end{align*}
\]

To the solution of 5-methylindole S\textsubscript{4} (300 mg, 2.29 mmol) in 5 mL of THF, was added 1.57 mL (2.52 mmol) of 1.6 M n-BuLi dropwise at 0 °C. After 2 h, to the stirred solution ZnCl\textsubscript{2} (341 mg, 2.52 mol) in 5 mL of THF was added. The mixture was stirred for another 2 h at room temperature. To the mixture addition of ethyl 2-bromoacetate S\textsubscript{5} (420 mg, 2.52 mmol) was done dropwise, and the solution was further stirred for 24 h. After the reaction completion, mixture was then acidified with 1 N HCl and poured into ethyl acetate (20 mL). The organic layer was washed with brine and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography (hexanes: EtOAc, 3:1) to afford ester S\textsubscript{6} (158 mg, 32%) as colorless oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.14 (s, 1H), 7.49 (s, 1H), 7.19 (d, \(J = 8.3\) Hz, 1H), 7.09 (dd, \(J = 8.3, 0.8\) Hz, 1H), 6.98 (d, \(J = 0.8\) Hz, 1H), 4.25 (q, \(J = 7.1\) Hz, 1H), 3.82 (s, 2H), 2.54 (s, 3H), 1.35 (t, \(J = 7.1\) Hz, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 172.55, 134.54, 128.71, 127.45, 123.67, 123.48, 118.44, 111.05, 107.59, 60.86, 31.47, 21.55, 14.25; ESI HRMS: m/z calcd for C\textsubscript{13}H\textsubscript{15}NO\textsubscript{2} [M+Na]\textsuperscript{+} 240.0995, found 240.1003; IR (CH\textsubscript{2}Cl\textsubscript{2}, cm\textsuperscript{-1}) 1728, 1156, 1029, 796, 588.

2.6.2.3 General Procedure for Preparation of Boc-Protected Indoles\textsuperscript{27}

\[
\begin{align*}
\text{R} & \quad \text{R}_1 \\
\text{R}_2 & \quad \text{R}_1 \\
\text{S}\textsubscript{7} & \quad \text{S}\textsubscript{8}
\end{align*}
\]

To 0.5 M solution of indole or substituted indole (1 equiv.) in THF was added Boc\textsubscript{2}O (1.5 equiv.) and DMAP (0.1 equiv.) at room temperature. The reaction mixture was stirred for 3 h at room
temperature. After the reaction completion, mixture was quenched with a saturated solution of 
NaHCO₃ (20 mL). The aqueous layer was extracted with ethyl acetate 3 times. The combined 
organic layer was washed with brine and dried over anhydrous Na₂SO₄, filtered, and concentrated 
by rotary evaporation. The residue was purified by flash column chromatography to afford desired 
products.

_Tert-butyl 5-fluoro-2,3-dimethyl-1H-indole-1-carboxylate (222a):_

![Image of 222a]

General procedure 2.6.2.3 was followed to synthesize compound 222a as white solid in 89% yield. 
¹H NMR (400 MHz, CDCl₃) δ 8.06 (dd, J = 9.0, 4.6 Hz, 1H), 7.05 (dd, J = 8.8, 2.5 Hz, 1H), 6.95 
(td, J = 9.1, 2.5 Hz, 1H), 2.53 (s, 3H), 2.15 (s, 3H), 1.70 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 
160.37, 158.00, 150.52, 134.52, 131.86, 131.85, 131.79, 131.69, 116.17, 116.08, 113.53, 113.49, 
110.59, 110.35, 103.39, 103.15, 83.43, 28.22, 13.97, 8.60; ESI LRMS: m/z calcd for C₁₅H₁₈FNO₂ 
[M+Na]⁺ 286.1, found 285.9; IR (CH₂Cl₂ , cm⁻¹) 1726, 1471, 1359, 1160, 1129, 733.

_Tert-butyl 6-chloro-2,3-dimethyl-1H-indole-1-carboxylate (222c):_

![Image of 222c]

General procedure 2.6.2.3 was followed to synthesize compound 222c as white solid in 87% yield. 
¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, J = 1.6 Hz, 1H), 7.30 (t, J = 8.3 Hz, 1H), 7.18 (dd, J = 8.3, 
1.6 Hz, 1H), 2.51 (s, 3H), 2.16 (s, 3H), 1.68 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 150.40, 135.92, 
133.43, 129.21, 129.05, 122.64, 118.31, 115.60, 113.46, 83.77, 28.20, 13.89, 8.59; ESI LRMS:
m/z calcd for C$_{15}$H$_{18}$ClNO$_2$ [M+Na]$^+$ 302.0, found 302.0; IR (CH$_2$Cl$_2$, cm$^{-1}$) 1732, 1353, 1145, 733.

_Tert_-butyl 6-chloro-5-fluoro-2,3-dimethyl-1H-indole-1-carboxylate (226):

![Chemical structure of compound 226](image)

General procedure 2.6.2.3 was followed to synthesize compound 226 in 85% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.17 (d, $J = 6.6$ Hz, 1H), 7.09 (d, $J = 9.0$ Hz, 1H), 2.50 (s, 3H), 2.12 (s, 3H), 1.68 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 155.56, 153.16, 150.18, 134.84, 131.59, 131.58, 130.14, 130.06, 116.97, 116.04, 115.84, 113.37, 113.33, 104.26, 104.03, 84.00, 28.18, 14.05, 8.62; ESI LRMS: m/z calcd for C$_{15}$H$_{17}$ClFNO$_2$ [M+Na]$^+$ 320.0, found 320.1; IR (CH$_2$Cl$_2$, cm$^{-1}$) 1736, 1461, 1356, 1132, 732.

_Tert_-butyl 3-(2-ethoxy-2-oxoethyl)-5-methyl-1H-indole-1-carboxylate (S$_2$7):

![Chemical structure of compound S$_2$7](image)

General procedure 2.6.2.3 was followed to synthesize compound S$_2$7 as yellowish oil in 83% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.03 (s, 1H), 7.55 (s, 1H), 7.34 (s, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 3.69 (s, 2H), 2.47 (s, 3H), 1.67 (s, 9H), 1.29 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.09, 149.59, 133.59, 132.00, 130.26, 125.83, 124.39, 118.94, 114.85, 112.94, 83.33, 60.94, 31.16, 28.16, 21.36, 14.17; ESI HRMS: m/z calcd for C$_{18}$H$_{23}$NO$_4$ [M+Na]$^+$ 340.1519, found 340.1519; IR (CH$_2$Cl$_2$, cm$^{-1}$) 1731, 1457, 1376, 1254, 1155, 1080, 1017.
**Tert-butyl 3-(2-ethoxy-2-oxoethyl)-5-methoxy-1H-indole-1-carboxylate (S28):**

![Chemical structure of S28](image)

General procedure 2.6.2.3 was followed to synthesize compound S28 as colorless oil in 88% yield.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (s, 1H), 7.55 (s, 1H), 7.00 (d, $J = 2.4$ Hz, 1H), 6.94 (dd, $J = 9.0$, 2.4 Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.86 (s, 3H), 3.67 (s, 2H), 1.65 (s, 9H), 1.27 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.95, 155.85, 149.49, 130.88, 130.10, 124.97, 115.94, 113.12, 112.97, 101.79, 83.36, 60.94, 55.63, 31.25, 28.14, 14.18; ESI HRMS: m/z calcd for C$_{18}$H$_{23}$NO$_5$ [M+Na]$^+$ 356.1468, found 365.1473; IR (CH$_2$Cl$_2$, cm$^{-1}$) 1730, 1479, 1449, 1383, 1155, 1079.

**Tert-butyl 3-(2-oxo-2-(phenylamino)ethyl)-1H-indole-1-carboxylate (S29):**

![Chemical structure of S29](image)

General procedure 2.6.2.3 was followed to synthesize compound S29 as white solid in 71% yield.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.19 (d, $J = 7.9$ Hz, 1H), 7.64 (s, 1H), 7.57 (d, $J = 8.0$ Hz, 2H), 7.43–4.33 (m, 3H), 7.27 (m, 3H), 7.08 (t, $J = 7.4$ Hz, 1H), 3.82 (s, 2H), 1.69 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.44, 149.46, 137.52, 135.62, 129.67, 128.85, 125.05, 125.02, 124.45, 123.07, 120.07, 118.95, 115.44, 113.42, 84.04, 34.27, 28.16; ESI HRMS: m/z calcd for C$_{21}$H$_{22}$O$_3$ [M+K]$^+$ 389.1262, found 389.1267; IR (CH$_2$Cl$_2$, cm$^{-1}$) 1732, 1682, 1600, 1532, 1452, 1376, 1087, 691.
2.6.2.4 General Procedure for Photo-Oxidative Cleavage of Indoles

To 0.1 M stirred solution of indole substrate (0.2 mmol, 1 equiv.) in trifluoroethanol (TFE) was added catalyst methylene blue (2 mol %). The resulting solution was irradiated under blue LEDs in the open air for 10 h. After completion, reaction mixture was quenched with water and was extracted with ethyl acetate (3 × 5 mL). The combined organic layer was washed with brine and dried with anhydrous Na₂SO₄, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography to obtain desired oxidative cleavage product.

*tert*-Butyl (2-[(tert-Butoxycarbonyl)amino]propanoyl)phenyl)(formyl)carbamate (213):

Following general procedure 2.6.2.4 compound 212 (72 mg) resulted in formation of 213 as a colorless oil; yield: 69 mg (88%). ¹H NMR (400 MHz, CDCl₃): δ = 9.32 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 5.06 (s, 1H), 3.45 (dd, J = 5.8, 5.5 Hz, 2H), 3.12 (t, J = 5.5 Hz, 2H), 1.48 (s, 9H), 1.42 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 199.88, 163.23, 155.84, 151.90, 134.52, 132.92, 132.85, 130.76, 129.53, 128.97, 84.54, 79.15, 40.49, 35.54, 28.34, 27.88. ESI-HRMS: m/z calcd for C₂₀H₂₈N₂O₆Na [M+Na]⁺: 415.1840; found: 415.1842. IR (CH₂Cl₂, cm⁻¹): 1743, 1698, 1503, 1368, 1295, 1242, 1154.

N-acetyl-N-(2-acetlyphenyl)acetamide (215a):
Following the general procedure 2.6.2.4 compound 214a (37 mg) resulted in formation of 215a as a yellowish oil; yield: 29 mg (68%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.84 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.61 (td, $J = 7.6$, 1.6 Hz, 1H), 7.57–7.50 (td, $J = 7.6$, 1.1 Hz, 1H), 7.19 (dd, $J = 7.7$, 1.1 Hz, 1H), 2.55 (s, 3H), 2.26 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 199.09, 173.05, 137.50, 135.94, 133.03, 130.66, 129.91, 129.13, 28.71, 26.74. ESI-HRMS: $m/z$ calcd for C$_{12}$H$_{13}$NO$_3$Na [M+Na]$^+$: 242.0788; found: 242.0791. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1701, 1368, 1274, 1243, 1019, 747, 598.

$N$-$(2$-Acetylphenyl)$-N$formylacetamide (215b):

Following the general procedure 2.6.2.4 compound 214b (35 mg) resulted in formation of 215b as a yellow oil; yield: 35 mg (84%). $^1$H NMR (400 MHz, CDCl$_3$) δ 9.41 (s, 1H), 7.87 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.64 (td, $J = 7.6$, 1.5 Hz, 1H), 7.57 (td, $J = 7.6$, 1.2 Hz, 1H), 7.20 (dd, $J = 7.6$, 0.9 Hz, 1H), 2.55 (s, 3H), 2.10 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 198.73, 172.51, 162.68, 135.81, 133.58, 133.15, 130.69, 130.07, 129.66, 28.61, 23.98. ESI-HRMS: $m/z$ calcd for C$_{11}$H$_{11}$NO$_3$Na [M+Na]$^+$: 228.0631; found: 228.0640. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1730, 1701, 1367, 1272, 1243, 1019, 747, 598.
**tert-butyl formyl(2-formylphenyl)carbamate (215c):**

Following the general procedure 2.6.2.4 compound 214c (43 mg) resulted in formation of 215c as a reddish oil; yield: 37 mg (75%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.97$ (s, 1H), 9.42 (s, 1H), 7.92 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.69 (td, $J = 7.6$, 1.6 Hz, 1H), 7.60 (td, $J = 7.6$, 0.9 Hz, 1H), 7.23 (d, $J = 7.6$ Hz, 1H), 1.47 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 189.57$, 163.00, 151.66, 134.75, 134.51, 132.93, 132.08, 130.33, 129.35, 84.96, 27.80. ESI-HRMS: $m/z$ calcd for C$_{13}$H$_{15}$NO$_4$Na $[M+Na]^+$: 272.0893; found: 272.0897. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1744, 1699, 1371, 1353, 1291, 1239, 1058, 846, 759, 617.

**tert-butyl(2-acetylphenyl)(formyl)carbamate (215d):**

Following the general procedure 2.6.2.4 compound 214d (46 mg) resulted in formation of 215d as a yellowish oil; yield: 44 mg (85%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.32$ (s, 1H), 7.85 (d, $J = 7.7$ Hz, 1H), 7.58 (t, $J = 8.0$ Hz, 1H), 7.50 (t, $J = 7.6$ Hz, 1H), 7.18 (d, $J = 9.6$ Hz, 1H), 2.54 (s, 3H), 1.48 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.12, 163.25, 151.90, 135.04, 132.98, 132.70,
130.66, 129.93, 128.89, 84.42, 28.53, 27.84. ESI-HRMS: \( m/z \) calcd for \( C_{14}H_{17}NO_4Na \) [M+Na]^+: 286.1050; found: 286.1052. IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)): 1742, 1692, 1356, 1295, 1251, 1153, 1052, 762.

**tert-butyl acetyl(2-formylphenyl)carbamate (215e):**

![Structure of 215e]

Following the general procedure 2.6.2.4 compound 214e (46 mg) resulted in formation of 215e as a white solid; yield: 36 mg (68%); melting point 80 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 9.99 \) (s, 1H), 7.88 (dd, \( J = 7.6, 1.3 \) Hz, 1H), 7.65 (td, \( J = 7.6, 1.3 \) Hz, 1H), 7.54 (t, \( J = 7.6 \) Hz, 1H), 7.17 (d, \( J = 7.6 \) Hz, 1H), 2.68 (s, 3H), 1.34 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 189.96, 173.42, 139.32, 134.45, 132.44, 132.00, 130.01, 128.56, 83.61, 27.69, 26.36. \) ESI-HRMS: \( m/z \) calcd for \( C_{14}H_{17}NO_4Na \) [M+Na]^+: 286.1050; found: 286.1050. IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)): 1743, 1701, 1371, 1255, 1155, 764, 731.

**tert-butyl acetyl(2-acetylphenyl)carbamate (215f):**

![Structure of 215f]

Following the general procedure 2.6.2.4 compound 214f (49 mg) resulted in formation of 215f as a colorless oil; yield 43 mg (78%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 7.80 \) (d, \( J = 7.8 \) Hz, 1H), 7.52
(t, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 2.61 (s, 3H), 2.51 (s, 3H), 1.34 (s, 9H). 13C NMR (100 MHz, CDCl3) δ 198.35, 173.54, 152.15, 137.32, 134.61, 132.59, 130.37, 129.79, 128.07, 83.00, 28.60, 27.71, 26.52; ESI-HRMS: m/z calcd for C15H19NO4Na [M+Na]+: 300.1206; found: 300.1208. IR (CH2Cl2, cm⁻¹): 1743, 1689, 1371, 1282, 1157, 731.

Methyl (S)-2-((tert-butoxycarbonyl)amino)-4-(2-(N-(tert-butoxycarbonyl)formamido)phenyl)-4-oxobutanoate (217):

![Chemical structure of compound 217]

Following the general procedure 2.6.2.4 compound 216 (83 mg) resulted in formation of 217 as a reddish oil; yield: 87 mg (86%); [α]D20 +97.8 (c 1.5, CHCl3). 1H NMR (400 MHz, CDCl3) δ 9.28 (s, 1H), 7.82 (s, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 5.44 (s, 1H), 4.60 (s, 1H), 3.70 (s, 3H), 3.56 (s, 1H), 3.41 (d, J = 17.7 Hz, 1H), 1.46 (s, 9H), 1.44 (s, 9H). 13C NMR (100 MHz, CDCl3) δ 198.12, 197.56, 171.77, 171.63, 163.12, 162.98, 155.48, 151.78, 151.70, 134.08, 133.40, 133.10, 132.96, 130.92, 130.81, 130.11, 129.58, 129.04, 129.00, 84.56, 84.44, 79.97, 79.89, 52.56, 52.46, 49.42, 42.51, 42.30, 28.24, 27.88, 27.76. ESI-HRMS: m/z calcd for C22H34N2O6SNa [M+Na]+: 473.1894; found: 473.1897. IR (CH2Cl2, cm⁻¹): 1744, 1708, 1497, 1368, 1295, 1155, 761.

tert-butyl (2-(3-((N-(tert-butoxycarbonyl))-4-methylphenyl)sulfonamido)propanoyl)phenyl)(formyl)carbamate (219):
Following the general procedure 2.6.2.4, compound 218 (130 mg) resulted in formation of 219 as a colorless oil; yield: 111 mg (81%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.32 (s, 1H), 7.90 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 2H), 7.59 (td, $J = 7.7, 1.2$ Hz, 1H), 7.51 (td, $J = 7.6, 1.2$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 1H), 4.13 (t, $J = 7.6$ Hz, 2H), 3.40 (t, $J = 7.6$ Hz, 2H), 2.43 (s, 3H), 1.47 (s, 9H), 1.35 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.03, 163.14, 151.91, 150.71, 144.30, 137.06, 134.31, 133.08, 132.87, 130.72, 129.58, 129.30, 128.97, 127.72, 84.48, 84.46, 43.01, 40.92, 27.83, 21.55. ESI-HRMS: $m/z$ calcd for C$_{27}$H$_{34}$N$_2$O$_8$SNa [M+Na]$^+$: 569.1928; found: 569.1937. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1697, 1355, 1289, 1154, 746, 567, 546.

tert-butyl formyl[2-(3-hydroxypropanoyl)phenyl]carbamate (221):

Following the general procedure 2.6.2.4, compound 220 (52 mg) resulted in formation of 221 as a yellowish oil; yield: 43 mg (74%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.31 (s, 1H), 7.83 (dd, $J = 7.7, 1.3$ Hz, 1H), 7.59 (td, $J = 7.7, 1.3$ Hz, 1H), 7.50 (td, $J = 7.6, 1.3$ Hz, 1H), 7.20 (dd, $J = 7.8, 0.9$ Hz, 1H), 3.98–3.84 (m, 2H), 3.12 (t, $J = 5.4$ Hz, 2H), 2.41 (s, 1H), 1.48 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 201.09, 163.34, 151.91, 134.79, 132.90, 132.82, 130.72, 129.48, 128.99, 84.70, 58.19,
42.70, 27.85. ESI-HRMS: \( m/z \) calcd for \( \text{C}_{15}\text{H}_{19}\text{NO}_3\text{Na} \) [M+Na]\(^+\): 316.1155; found: 316.1155. IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)): 1744, 1296, 1153, 731.

tert-butyl acetyl(2-acetyl-4-fluorophenyl)carbamate (223a):

Following the general procedure 2.6.2.4, compound 222a (52 mg) resulted in formation of 223a as a yellowish oil; yield: 42 mg (72%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) = 7.47 (dd, \( J = 8.7, 2.9 \) Hz, 1H), 7.21 (td, \( J = 8.8, 2.9 \) Hz, 1H), 7.10 (dd, \( J = 8.7, 5.1 \) Hz, 1H), 2.60 (s, 3H), 2.49 (s, 3H), 1.35 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 197.07, 197.05, 173.51, 162.59, 160.11, 152.01, 136.27, 136.21, 133.16, 133.13, 132.11, 132.03, 119.38, 119.16, 116.69, 116.46, 83.31, 28.46, 27.70, 26.43. ESI-HRMS: \( m/z \) calcd for \( \text{C}_{15}\text{H}_{18}\text{FNO}_4\text{Na} \) [M+Na]\(^+\): 318.1112; found: 318.1113. IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)): 1743, 1701, 1276, 1254, 1156, 1100, 732, 701.

tert-butyl acetyl(2-acetyl-4-chlorophenyl)carbamate (223b):

Following the general procedure 2.6.2.4, compound 222b (56 mg) resulted in formation of 223b as a yellowish oil; yield: 33 mg (52%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.75 (d, \( J = 2.3 \) Hz, 1H), 7.50 (dd, \( J = 8.4, 2.3 \) Hz, 1H), 7.07 (d, \( J = 8.4 \) Hz, 1H), 2.61 (s, 3H), 2.51 (s, 3H), 1.36 (s, 9H). \(^{13}\)C
NMR (100 MHz, CDCl$_3$) δ 197.07, 173.45, 151.83, 136.06, 135.75, 133.84, 132.40, 131.72, 129.72, 83.48, 28.51, 27.73, 26.43. ESI-HRMS: $m/z$ calcd for C$_{15}$H$_{18}$ClNO$_4$Na [M+Na]$^+$: 334.0817; found: 334.0818. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1744, 1697, 1371, 1281, 1245, 1156, 1102, 845.

*tert*-Butyl Acetyl(2-acetyl-5-chlorophenyl)carbamate (223c):

Following the general procedure 2.6.2.4, compound 222c (56 mg) resulted in formation of 223c as yellow solid; yield: 54 mg (86%); melting point 86 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.75 (d, $J = 8.4$ Hz, 1H), 7.41 (dd, $J = 8.4$, 2.1 Hz, 1H), 7.15 (d, $J = 2.1$ Hz, 1H), 2.62 (d, $J = 8.7$ Hz, 3H), 2.50 (s, 3H), 1.36 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 197.14, 173.39, 151.67, 138.62, 138.15, 133.01, 130.82, 130.77, 128.27, 83.56, 28.54, 27.72, 26.45. ESI-HRMS: $m/z$ calcd for C$_{15}$H$_{18}$ClNO$_4$Na [M+Na]$^+$: 334.0817; found: 334.0817. IR (CH$_2$Cl$_2$, cm$^{-1}$) 1745, 1692, 1371, 1276, 1247, 1156, 1105, 764.

*tert*-Butyl Acetyl(2-acetyl-4-methoxyphenyl)carbamate (223d):

Following the general procedure 2.6.2.4, compound 222d (49 mg) resulted in formation of 223d as a yellowish oil; yield: 39 mg (70%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29 (d, $J = 1.3$ Hz, 1H),
7.03 (d, \( J = 1.3 \) Hz, 2H), 3.86 (s, 3H), 2.60 (s, 3H), 2.49 (s, 3H), 1.36 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 198.19, 173.73, 158.68, 152.47, 135.59, 131.20, 129.86, 116.98, 115.74, 82.96, 55.58, 28.56, 27.75, 26.56. ESI-HRMS: \( m/z \) calcd for C\(_{16}\)H\(_{21}\)NO\(_5\)Na [M+Na]\(^+\): 330.1312; found: 330.1316. IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)): 1738, 1693, 1370, 1281, 1252, 1157, 1042.

*tert*-Butyl Formyl(2-formyl-4-methoxyphenyl)carbamate (225):

Following the general procedure 2.6.2.4, compound 224 (43 mg) resulted in formation of 225 as a yellowish oil; yield: 39 mg (79\%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.90 (s, 1H), 9.43 (s, 1H), 7.41 (d, \( J = 2.9 \) Hz, 1H), 7.19 (dd, \( J = 8.6, 2.9 \) Hz, 1H), 7.12 (d, \( J = 8.6 \) Hz, 1H), 3.89 (s, 3H), 1.47 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 189.12, 163.23, 159.95, 151.98, 132.90, 131.25, 127.76, 120.43, 116.20, 84.92, 55.74, 27.83. ESI-HRMS: \( m/z \) calcd for C\(_{14}\)H\(_{17}\)NO\(_5\)Na [M+Na]\(^+\): 302.0999; found: 302.1000. IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)): 1742, 1696, 1500, 1276, 1256, 1152, 748.

*tert*-butyl acetyl(2-acetyl-5-chloro-4-fluorophenyl)carbamate (227):

Following the general procedure 2.6.2.4, compound 226 (59 mg) resulted in formation of 227 as a colorless oil; yield: 48 mg (74\%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.57 (d, \( J = 9.0 \) Hz, 1H), 7.22 (d, \( J = 6.6 \) Hz, 1H), 2.61 (s, 3H), 2.49 (s, 3H), 1.38 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 196.02,
ESI-HRMS: m/z calcd for C\textsubscript{15}H\textsubscript{17}ClFNO\textsubscript{4}Na [M+Na]\textsuperscript{+}: 352.0722; found: 352.0724. IR (CH\textsubscript{2}Cl\textsubscript{2}, cm\textsuperscript{-1}): 1747, 1696, 1371, 1281, 1155, 1102, 732.

**tert-butyl 2,6-Dioxo-3,4,5,6-tetrahydrobenzo[b]azocine-1(2H)-carboxylate (229):**

Following the general procedure 2.6.2.4, compound 228 (51 mg) resulted in formation of 229 as a white solid; yield: 40 mg (70%); melting point 88 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.98 (dd, J = 7.8, 1.6 Hz, 1H), 7.58 (td, J = 7.8, 1.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 2.95 (t, J = 8.0 Hz, 2H), 2.47 (t, J = 7.3 Hz, 2H), 2.09 - 1.96 (m, 2H), 1.37 (s, 9 H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 199.38, 172.29, 150.48, 138.67, 136.45, 133.41, 130.73, 129.75, 128.86, 84.03, 40.73, 33.89, 27.69, 21.12. ESI-HRMS: m/z calcd for C\textsubscript{16}H\textsubscript{19}NO\textsubscript{4}Na [M+Na]\textsuperscript{+}: 312.1206; found: 312.1205. IR (CH\textsubscript{2}Cl\textsubscript{2}, cm\textsuperscript{-1}) 1772, 1730, 1676, 1243, 1145, 731.

**tert-butyl 2,7-Dioxo-2,3,4,5,6,7-hexahydro-1H-benzo[b]azonine-1-carboxylate (231):**

Following the general procedure 2.6.2.4, compound 230 (54 mg) resulted in formation of 231 as a white solid; yield: 38 mg (62%); melting point 135 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.51 (td, J = 7.6, 1.0 Hz, 1H), 7.47 (dd, J = 7.6, 1.0 Hz, 1H) 7.39 (td, J = 7.6, 1.0 Hz, 1H), 7.23 (d, J = 7.6
Hz, 1H), 3.26 (s, 1H), 2.76 (d, $J = 4.8$ Hz, 2H), 2.46 (s, 1H), 2.08 (s, 1H), 1.90 (d, $J = 5.7$ Hz, 3H), 1.46 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 205.32, 177.82, 151.85, 139.26, 136.88, 131.43, 129.07, 128.25, 128.02, 83.97, 41.50, 38.51, 27.84, 26.26, 24.55. ESI-HRMS: $m/z$ calcd for C$_{17}$H$_{21}$NO$_4$Na [M+Na]$^+$: 326.1363; found: 326.1361. IR (CH$_2$Cl$_2$, cm$^{-1}$) 1732, 1698, 1451, 1288, 1152, 1115.

2.6.2.5 General Procedure for Synthesis of 4-Quinoline-3-Carboxylic Acid Derivatives.

To 0.1 M stirred solution of indole-3-acetic acid derivative (0.2 mmol, 1 equiv.) in trifluoroethanol (TFE) was added catalyst methylene blue (2 mol %). The reaction mixture was stirred under irradiation with blue LEDs in the open air for 36 h. The mixture was filtered, and the filtrate was stirred overnight with 10 equiv. of silica gel. The solvent was removed by rotary evaporation. The residue was purified by flash column chromatography to obtain the desired 4-quinoline-3-carboxylic acid derivative.

1-(tert-butyl) 3-ethyl 6-methyl-4-oxoquinoline-1,3(4H)-dicarboxylate (232):

\[ \text{Me} \quad \text{O} \quad \text{OEt} \]
\[ \text{N} \quad \text{Boc} \]
\[ \text{232} \]

The quinolone 232 was prepared according to general procedure 2.6.2.5. white solid; yield: 50 mg (76%); melting point 190 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.11 (s, 1H), 8.38 (d, $J = 8.9$ Hz, 1H), 8.22 (s, 1H), 7.47 (dd, $J = 8.9$, 1.8 Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 2.45 (s, 3H), 1.69 (s, 9H), 1.40 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 174.94, 164.81, 149.21, 144.63, 136.06, 135.35, 134.02, 127.79, 126.80, 119.60, 113.08, 87.66, 61.19, 27.83, 20.81, 14.26. ESI-HRMS:
$m/z$ calcd for $C_{18}H_{21}NO_5Na [M+Na]^+: 354.1312$; found: 354.1304. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1611, 1277, 1234, 1136, 763.

1-(tert-butyl) 3-ethyl 6-methoxy-4-oxoquinoline-1,3(4H)-dicarboxylate (233):

![Chemical Structure](image)

The quinolone 232 was prepared according to general procedure 2.6.2.5. yellow solid; yield: 37 mg (54%); melting point 310 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.12 (s, 1 H), 8.45 (d, $J = 9.5$ Hz, 1H), 7.86 (d, $J = 3.1$ Hz, 1H), 7.25 (dd, $J = 9.5$, 3.1 Hz, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 3.91 (s, 3H), 1.70 (s, 9H), 1.42 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.54, 164.95, 157.45, 149.17, 144.22, 131.59, 129.47, 122.35, 121.49, 112.49, 107.04, 87.75, 61.22, 55.66, 27.82, 14.26. ESI-HRMS: $m/z$ calcd for $C_{18}H_{21}NO_6Na [M+Na]^+: 370.1261$; found: 370.1254. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1744, 1682, 1489, 1244, 1137, 1020, 734.

1-(tert-butyl) 3-ethyl 6-bromo-4-oxoquinoline-1,3(4H)-dicarboxylate (234):

![Chemical Structure](image)

The quinolone 234 was prepared according to general procedure 2.6.2.5 yellow solid; yield: 66 mg (84%); melting point 341 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.14 (s, 1 H), 8.55 (d, $J = 2.3$ Hz, 1H), 8.44 (d, $J = 9.3$ Hz, 1H), 7.75 (dd, $J = 9.3$, 2.4 Hz, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 1.70 (s, 9H), 1.41
(t, J = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.50, 164.35, 148.81, 145.01, 136.32, 135.75, 129.85, 129.39, 121.79, 120.15, 113.52, 88.40, 61.42, 27.81, 14.24. ESI-HRMS: $m/z$ calcd for C$_{17}$H$_{18}$BrNO$_5$Na [M+Na]$^+$: 418.0261; found: 418.0254. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1682, 1421, 1264, 1137, 733.

**tert-butyl 4-oxo-3-(phenylcarbamoyl)quinoline-1(4H)-carboxylate (235):**

![Image of compound 235]

The compound 235 was prepared according to general procedure 2.6.2.5. Yellowish oil; yield: 53 mg (73%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 11.88 (s, 1H), 9.52 (s, 1H), 8.61 (d, J = 8.8 Hz, 1H), 8.52 (d, J = 8.1 Hz, 1H), 7.77 (t, J = 8.7 Hz, 3H), 7.56 (t, J = 8.4 Hz, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.14 (t, J = 7.1 Hz, 1H), 1.74 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.08, 161.71, 144.95, 137.85, 133.49, 128.91, 126.82, 126.21, 124.13, 120.46, 119.86, 113.14, 88.37, 27.81. ESI-HRMS: $m/z$ calcd for C$_{21}$H$_{20}$N$_2$O$_4$Na [M+Na]$^+$: 387.1315; found: 387.1312. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1766, 1681, 1605, 1552, 1473, 1279, 1232, 1136, 663.

**tert-butyl 3-(((4-fluorophenyl)carbamoyl)-4-oxoquinoline-1(4H)-carboxylate (236):**

![Image of compound 236]
Compound 236 was prepared according to general procedure 2.6.2.5. yellowish solid; yield: 32 mg (85%); melting point 360 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.49 (s, 1H), 8.59 (d, $J = 8.8$ Hz, 1H), 8.49 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.74 (ddd, $J = 9.0$, 7.8, 3.2 Hz, 3H), 7.54 (t, $J = 7.5$ Hz, 1H), 7.05 (t, $J = 8.7$ Hz, 2H), 1.73 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.05, 161.67, 160.45, 158.04, 149.05, 144.91, 137.83, 134.39, 134.36, 133.52, 126.82, 126.78, 126.23, 122.03, 121.95, 119.86, 115.61, 115.39, 112.92, 88.43, 27.80. ESI-HRMS: $m/z$ calcd for C$_{21}$H$_{19}$FN$_2$O$_4$Na [M+Na]$^+$: 405.1221; found: 405.1220. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1760, 1662, 1621, 1525, 1481, 1280, 1199, 1121.

1-(tert-butyl) 3-methyl 4-oxoquinoline-1,3(4H)-dicarboxylate (238):

Quinolone 238 was prepared according to general procedure 2.6.2.5. white solid; yield: 48 mg (80%); melting point 154 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.15 (s, 1H), 8.48 (d, $J = 8.8$ Hz, 1H), 8.45 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.72–7.64 (m, 1H), 7.46 (t, $J = 11.5$ Hz, 1H), 3.95 (s, 3H), 1.70 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.79, 165.45, 149.13, 145.22, 137.43, 132.86, 127.94, 127.32, 126.05, 119.70, 112.97, 87.98, 52.38, 27.82. ESI-HRMS: $m/z$ calcd for C$_{16}$H$_{17}$NO$_5$Na [M+Na]$^+$: 326.0999; found: 326.0998. IR (CH$_2$Cl$_2$, cm$^{-1}$): 1646, 1611, 1470, 1278, 1262, 1137, 732.
2.6.2.6 Procedure for Stern Volmer Studies

Excitation of methylene blue solution took place at 440 nm and the emission intensity collection was done at 710 nm. For initial emission collection, a screw top quartz was charged with 0.1 mM solution of catalyst Methylene Blue (M.B) in trifluoroethanol (TFE) 2 mL. A series of samples were prepared using 0.1 mM Methylene Blue (M.B) in TFE along with quencher compound 212 in gradient concentration of 10 mM, 20 mM, 30 mM, 40 mM, 50 mM, and were tested to collect emissions (Figure 2.3).

![Graph](image)

Figure 2.3: Stern Volmer quenching experiments.
Note: Computational studies and DFT calculations (Section 2.6.3) were done in collaboration with Cheng Fang, Peng Liu* of Department of Chemistry, Computational Modeling & Simulations Program, University of Pittsburg, 219 Parkman Avenue, Pittsburgh, PA 15260, United States.

2.6.3 DFT Calculations

2.6.3.1 Computational Details

The DFT calculations were done with the Gaussian 09 software package. The optimization of geometries was done using B3LYP functional and the 6-31G(d) basis set in solution. The calculations were done using the SMD solvation model and 2,2,2-trifluoroethanol as solvent. M06-2X and 6-311++G(3df,2p) along with SMD solvation model in 2,2,2-trifluoroethanol was used to calculate single point energies and NPA charges. Thermal corrections were carried out at 298 K and computation was done at standard concentration (1 mol/L) for the reported Gibbs free energies.

2.6.3.2 Spin Density and Charge Distribution Analysis for Radical Cations Involved in Dioxygen Addition Process

In Scheme 2.4, we have seen that formation of radical cation 240 results from oxidation of tryptamine derivative by methylene blue via single electron transfer. Radical cation 240 prevents the dioxygen addition on carbon radical center. To determine the nature of radical cation 240, we carried out spin density and charge calculations. The results shows that spin density was concentrated at benzyl carbon and positive charge is located on C-2 position on indole (Figure 2.4). From the results we see that benzyl radical is stabilized by benzene ring and positive charge
in radical cation 240 is stabilized by indole nitrogen atom. Calculations were performed to calculate the spin density and charge distributions for TS1 and 241.

**Figure 2.4:** Spin density and atomic charge distribution of radical cation species and dioxygen addition transition state the computed NPA atomic charges are shown in red, and the computed spin densities are shown in yellow.
2.6.3.3 Single Electron Transfer Barrier Estimated by Marcus Theory

Marcus theory was used to determine the free energy barriers for single electron transfer (SET) from 28 to excited methylene blue (*M.B.+)(SET1) and from M.B. to 30 (SET2). The methods used in these calculations are previously reported by our recent work. The detailed information regarding the geometric parameters, thermodynamic parameters and single electron transfer barriers are shown in Table 2.3.

\[ \begin{align*}
\text{239} & \quad \text{M.B.}^+ & \quad \text{240} & \quad \text{M.B.}^* \\
\text{SET1} \\
\text{241} & \quad \text{M.B.}^* & \quad \text{242} & \quad \text{M.B.}^+ \\
\text{SET2}
\end{align*} \]

**Scheme 2.4:** Formation of radical cations.

The barriers were calculated by using following equations as shown in Scheme 2.5.

\[ \Delta G_{\text{SET}}^\ddagger = \Delta G_0^\ddagger \left( 1 + \frac{\Delta G^*}{4\Delta G_0^\ddagger} \right)^2 \]

\[ \lambda_0 = 95 \left( \frac{1}{2r_{D}^{-}} + \frac{1}{2r_{A}^{-}} - \frac{1}{r_{D}^{-} + r_{A}^{-}} \right) \]

**Scheme 2.5:** Equations used for calculation of energy barriers.
\( \Delta r G^o \) belongs to reaction energy for single electron transfer step that can be directly derived by DFT calculations. Comparison was carried out with reaction energy \( \Delta r G^{oe} \) and calculated using experimental standard reduction potentials of \( E^{o \ast}_{M.B. +/M.B.} = 0.97 \text{ V vs SCE} \), \( E^{o \ast}_{M.B. +/M.B.} = -0.47 \text{ V vs SCE} \), and computed absolute reduction potentials of \( E^{o}_{29/28} = -10.06 \text{ V vs SCE} \), \( E^{o}_{30/31} = 0.044 \text{ V vs SCE} \). As described in Table 2.6.3.1 it is seen that DFT derived reaction energies and corresponding SET barriers \( \Delta G^a \) and \( \Delta_r G_{SET}^\ddagger \), whereas similar to those calculated by \( \Delta r G^{oe} \) and \( \Delta_r G_{SET}^{+ \ast} \).

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**Table 2.3:** The computed single electron transfer barriers and parameters used for determination of energy barriers.
**Cartesian Coordinates for Optimized Structures**

*M.B.*

B3LYP SCF energy in solution: -1182.8019983 a.u.
B3LYP enthalpy in solution: -1182.468961 a.u.
B3LYP free energy in solution: -1182.537427 a.u.
M06-2X SCF energy in solution: -1182.70095109 a.u.
M06-2X enthalpy in solution: -1182.367913 a.u.
M06-2X free energy in solution: -1182.436379 a.u.

Cartesian coordinates

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B3LYP free energy in solution: -1182.714282 a.u.

M06-2X SCF energy in solution: -1182.89549203 a.u.

M06-2X enthalpy in solution: -1182.563215 a.u.

M06-2X free energy in solution: -1182.631953 a.u.

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B3LYP free energy in solution: -1182.578372 a.u.
M06-2X SCF energy in solution: -1182.74888125 a.u.
M06-2X enthalpy in solution: -1182.414081 a.u.
M06-2X free energy in solution: -1182.480414 a.u.

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M06-2X enthalpy in solution: -594.613400 a.u.
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B3LYP SCF energy in solution:  -745.23543540 a.u.
B3LYP enthalpy in solution:     -744.989352 a.u.
B3LYP free energy in solution:  -745.049236 a.u.
M06-2X SCF energy in solution:  -745.17143444 a.u.
M06-2X enthalpy in solution:    -744.925351 a.u.
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M06-2X free energy in solution: -745.150977 a.u.

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B3LYP free energy in solution: -745.041845 a.u.
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15) Davies, J. Journal of Industrial Microbiology & Biotechnology, 2006, 33, 496.


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Chapter 3: Catalytic Access to Isolated Alcohol by N-Heterocyclic Carbenes

3.1 Introduction

3.1.1 Organocatalysis

The term organocatalyst is a catenation of two words organic and catalyst.\textsuperscript{1} Organocatalysis is defined as low molecular weight organic molecule that, when used in substoichiometric amounts can act as a catalyst for a chemical reaction.\textsuperscript{1,2} The process can be either achiral or chiral and could be made of C, H, N, P, and S. The lack of metal in organocatalysis has an advantage over other methods as it considers both principles regarding green chemistry and focuses on the economic point of view.\textsuperscript{2} The figure 3.1 shows a few examples of organocatalyst.

![Figure 3.1: Examples of organocatalyst.](image)

The process of organocatalysis is considered a novel synthetic philosophy and is an alternative to the existing transitional metal catalysis. The organocatalysis could be categorized into different types and these are as follows\textsuperscript{2}: 

1. L-Proline
2. Thiourea (R = alkyl, tert-butyl)
3. Phosphoric acid derivatives
4. MacMillan’s catalyst
5. Urea based catalyst
• Firstly, the activation of the reaction based on the nucleophilic or electrophilic properties of the catalyst.\(^3\)

• In second case, the organic molecules will form a reactive intermediate. The chiral catalyst can be consumed under this reaction condition and undergoes regeneration which runs in parallel with the catalytic cycle.\(^4\)

• Thirdly, the phase transfer reaction takes place. Under this condition, the chiral catalyst reacts to create a host-guest complex which is known to be present with a substrate and shuttles between the different standard organic solvents and the second phase. This method leads to catalytic enantioselective Enola alkylation.\(^5\)

• Lastly, the molecular-cavity-accelerate asymmetric transformation takes place in which the catalyst will be selected from different substrates that are competing based on their size and the structure criteria.\(^6\)

The main advantages of the process are as follows. a) The organic reactions that occur under the process are not possible in other forms of catalysis. b) These reactions condition have potential applications in many large-scale productions seen in different industries. e) The organocatalysts work at mild reaction conditions.

**3.1.2 Stereoselective-Synthesis**

Studies have mentioned that the world around us has a non-superimposable mirror image, often referred to the Greek term chiral.\(^7\) This means that the chiral compound would have a diverse pharmacological effect. In 1890 research carried out by Emil Fischer shows that addition of sodium cyanide to the chiral carbohydrate aldehyde can result in an uneven distribution for two possible diastereomers.\(^7\) To Synthesize optically active compounds, it is important to understand the connectivity of the atoms that are found inside the molecule and the stereoisomerism of the
molecule. The space between the molecules will have a huge impact on the different interactions that are seen between the different chiral compounds.\(^8\) The solution for these issues was figured out by stereoselective synthesis which allows the formation of one stereoisomer in preference against the other. Different strategies have been used to access enantiomerically enriched compounds including the resolution of the racemic mixture, asymmetric synthesis, or the chiral-pool approach. The stereoselective or asymmetric synthesis can be distinguished into many subgroups.\(^9\)\(^{12}\) These are as follows: Substrate control is the creation of a new stereogenic center which can be controlled because of the inherent chirality of the substrate. Whereas reagent control refers to creating a stereogenic center that can be governed by the chiral reagent or the catalyst which does not bound to the substrate through a covalent bond. In auxiliary control, the formation of the stereogenic center can be controlled with the help of the stoichiometric amount of chiral auxiliary compound, also known as the diastereoselective process.\(^9\)\(^{12}\)

### 3.1.3 N-Heterocyclic Carbenes (NHC)

N-Heterocyclic Carbenes are known highly versatile field in chemistry. First research focused on this element was carried out in 19th century by Eijkman and it was seen the rice husks can prevent beriberi like symptoms in hens that were suffering from malnutrition.\(^13\) This led to focus on compound responsible for the said effect and further guided for isolation of the thiamine, and its structure determination. The first biochemical reactions that made use of thiamine was the decarboxylation of pyruvate, which resulted in formation of acetaldehyde. Later, the thiazolium salts when reacted with benzaldehyde led to formation of benzoin.\(^14\)\(^{15}\) The mutual biochemical and synthetic importance related to the C-C coupling reaction, benzoin condensation being catalyzed by thiamine and the analogues has converted it to become one of the workhorses in the mechanistic investigations. Based on this recognized importance of synthetic value of the reaction,
the researchers established the NHC organocatalysis, which offers a remarkable and diverse portfolio that consists of highly efficient synthetic methods.\textsuperscript{16} The popularity of NHC and their reaction has increased importance and role in the development of medicine, biochemistry, and synthetic chemistry. The organocatalysis has an advantage over metal catalysis as it is free of toxicity from the metals.\textsuperscript{17} N-Heterocyclic Carbenes have been used as organocatalysts and ligands in different reactions related to metal catalysis.\textsuperscript{18}

\textbf{3.1.4 Isolated Alcohols}

When we talk about Chiral alcohols, irrespective of it being primary, secondary, or tertiary, they are used as optically active intermediates that have been seen to be in greater demand. Though they are quite straightforward as molecules, but they do present a lot of challenges when they are synthesized to enantiopure alcohols.\textsuperscript{19} The challenges are considerably more prominent when the synthesis is attempted for secondary and tertiary chiral alcohols more than the primary alcohols. The popularity and consumption increase in the pharmaceutical industry has led to the growing attention for the production of chiral compounds and secondary alcohols for drug development.\textsuperscript{20} An example of this is fluoxetine, which is a major component used in treating mental disorders like depression.\textsuperscript{19} Also, \((R)\)-benzyl-4-hydroxy-2-pentynoate is effective for treating Alzheimer's disease.\textsuperscript{21,22} The latter compound is a synthesized from the intermediate secondary alcohol \((R)\)-4-\((\text{trimethylsilyl})\)-3-butyn-2-ol.\textsuperscript{21,22} Thus, these chiral alcohols play a critical role in drug development.

One of the biggest challenges or limitations of these synthesis is that these processes make use of toxic metals or expensive and complex ligands.\textsuperscript{19} Different methods have been developed but the biotechnological approaches are preferred as they are considered to be a better and green alternatives and allow for mild reaction conditions which are desirable for these enantioselective
chemical reactions. Over the years, various methods have been developed under the enzymatic synthesis like enantioselective water addition to the alkenes, enantioselective coupling of ketones with hydrogen cyanide, and stereoselective hydroxylation of the C-H bonds that are inactivated being some of the popular approaches. A study focused on the enzymatic approaches for synthesis of enantiopure alcohols was undertaken, where seven strategies using the enzymatic synthesis were explored. It is found that the enzymatic strategies are quite effective in achieving the enantiopure alcohols as required while eliminating some of the challenges as seen in stereoselective synthesis, like toxicity from catalysts.

Another method employed in the synthesis of secondary chiral alcohols is catalytic synthesis. The asymmetric catalytic addition of organometallic reagents like that of carbonyl compounds is considered one of the unique and adaptable methods used in the synthesis of chiral alcohol. Reagent often used in these reaction is Grignard, which compared to the zinc or aluminum organometallic reagents have wider access or availability, increased reactivity, better efficiency of atoms, and increased efficiency tunability. These are least expensive and commonly used reagents, but they have their limitations and challenges when the focus is on achieving enantioselective alkylation of the carbonyl compounds. One of the biggest challenges of using the Grignard is that they make it difficult for the chiral catalysts to outcompete the uncatalyzed reactions, which would lead to the creation of racemic alcohol components. When using Grignard reagent chemoselectivity can be major challenge as these reagents are known to be highly basic, and their use could lead to deprotonate enolizable aldehydes and also ketones, as shown in Scheme 3.1.
Scheme 3.1: Chemoselectivity challenges related to Grignard Reagents.\textsuperscript{31} Adapted with permission from \textit{ACS Catal.} 2016, 6, 1952. Copyright 2016 American Chemical Society.

The above said issues have led to the restricted development of effective methodologies. One of the most effective methodologies is the use of Titanium-promoted catalysts. Titanium is one of the most used transition metals because these metals are known for their nontoxicity\textsuperscript{33}, low cost, and availability.\textsuperscript{34} These complexes exhibit specific diverse chemical reactivity that is critical. The rich coordination between the complex's properties with that of the Grignard ligands helps to provide more control of the stereochemistry for the different chemical processes that are carried out.\textsuperscript{31}

The use of enantioselective titanium with Grignard was not considered possible until 2008. The developed methodology, which is shown in Scheme 3.2, is known as the Harada methodology.\textsuperscript{35} This methodology allows for the catalytic alkylation and arylation of the aldehydes. For this purpose, they used Grignard reagents along with Titanium tetraisopropoxide. In this process, it was seen that the increase of the chiral ligand from 2 to 4 mol \% can help in improving the enantioselectivity of the final product, but there was no significant improvement in the yield of these products. This same method was used for different aldehydes, aryl, and alkyl reagents based on Grignard, and it was seen different factors can influence the enantioselectivity level.\textsuperscript{31}
Scheme 3.2: Grignard Reagent with Titanium catalyst reaction.\textsuperscript{35}

Over the decade, the number of methodologies focused on the generation of chiral alcohols with high enantioselectivity by making use of Grignard reagents. Although these methodologies have allowed a diverse range of transformations, many challenges still need to be tackled. One of the challenges is that the current methods require the use of super stoichiometric amounts of Ti(OiPr)\textsubscript{4}, which makes the process economically inefficient and complicates the workup of the reaction.\textsuperscript{31} These methods have become ineffective for the industrial processes. Another major limitation is the toxicity produced as the byproduct of these reactions, and hence it has become highly necessary to find improved methods which can help in the synthesis of the chiral alcohols. It was also seen that stereoselective preparation of the propargylic alcohol substrate is quite challenging.\textsuperscript{36,37}

We explore stereoselective synthesis process by making use of the NHC ligands as catalysts. In our reaction design we can control the stereoselectivity of the products by initially introducing the epoxide ring by Sharpless Asymmetric Epoxidation method. This reaction design provides access to isolated alcohols along with modification of epoxyaldehydes to esters and maintains the trisubstituted alkene functionality in the products.
Figure 3.2: Natural products containing trisubstituted alkene and alcohol functionalities.

The functionality trisubstituted alkene moiety along with isolated alcohol exist in many natural products. The figure 3.2 shows Rhizoxin D and Terpestacin natural products containing these functionalities. Rhizoxin D is an antimitotic agent which is used in the treatment of human carcinomas. The Terpestacin is another example that is created from the isolation of the compound from the Arthrinum fungal strain. This compound was found to inhibit the creation of syncytia which are giant-multinucleated cells that arise from the expression on the cell surfaces. Achieving success in this methodology can provide easy and stereoselective access to functionalities required in developing the overall natural products.
Scheme 3.3: Synthesis of anti-β − Hydroxyester from Epoxyldehydes.

In 2004, Bode et al. used the thiazolium salt as catalyst to convert epoxyaldehydes to β-Hydroxyesters (Scheme 3.3). Following their work, we wanted to explore synthetic method that results in formation of isolated alcohols along with esterification of aldehydes.40

3.2 Experimental Studies

We started our studies by designing starting material epoxy aldehyde 322 Scheme 3.4. Mixture of 316 and 317 in toluene at 75 °C resulted in formation of aldehyde 318. The reduction of aldehyde 318 by Diisobutylaluminum hydride (DIBAL) resulted in formation of alcohol 319. Epoxidation of 319 by meta-Chloroperoxybenzoic acid (m-CPBA) obtained 320, which was oxidized to obtain aldehyde 321. Lastly the reaction between aldehyde 321 and Wittig reagent 322 resulted in formation of final epoxyaldehyde product 323. Table 3.1 represents the starting materials prepared according to Scheme 3.4.
Scheme 3.4: Preparation of starting material.

Table 3.1: List of epoxy aldehydes.
We started our investigation by treating epoxyaldehyde 323 with thiazolium salt 334 in presence of methanol, DIPEA as base and DCM as solvent to afford isolated alcohol 335 (Table 3.2). We were happy to see that the reaction resulted in formation of desired alcohol product 336 in 71% of isolated yield. Intrigued by the result, we wanted to try epoxy aldehydes. We were glad to see that the electron donating groups (EDG) such as methyl and phenyl, methoxy on aryl epoxy aldehydes 325, 326, 239 resulted in formation of corresponding adducts 337, 338, 341 in 71%, 71%, 59% yields respectively. Electron withdrawing group (EWG) such as bromo, chloro on aryl epoxy aldehyde 327, 328 afforded the desired alcohol product in 339, 340 in 61%, 64% yields respectively. We also saw that CF₃ containing fluorine functional group was tolerated well under the mild conditions resulting in formation of product 342 in 61% yield. Naphthalene epoxy aldehyde 331 under the optimized conditions happily gave the isolated alcohol product 343 in 62% yield. Sterically hindered groups such as tert- butyldimethylsilyl and cyclohexane were tolerated well under these conditions affording adducts 344, 345 in 63% and 80% of isolated yields.
Table 3.2: Scope of substrates.

3.2.1 Mechanism:

Catalyst in presence of base is deprotonated and results in formation of activated catalyst A which reacts with epoxyaldehyde 346 to form intermediate species 347. The epoxide-opening step can occur via concentrated elimination to form 349 from 348 or in stepwise manner via stabilized anion 348’. Keto-enol tautomerism takes place and methanol acts as nucleophile to form final product 352.
3.3 Supporting Information

3.3.1 General Methods

All commercially available chemicals were used without further purification unless otherwise noted. Reactions were monitored by TLC on silica gel 60 F254. Flash column chromatography was performed using SiliaFlash P60 silica gel (40-63 μm). TLC was visualized by irradiation with UV light or treatment with a solution ceric ammonium molybdate stain followed by heating. Yields refer to purified compound unless otherwise noted. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AM 400 MHz spectrometers. Chemical shifts were reported as parts per million (ppm) relative to residual solvent CDCl$_3$ ($^1$H, 7.26 ppm, $^{13}$C, 77.0 ppm). The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Infrared
spectra were recorded on a PerkinElmer Spectrum Two IR spectrometer. Absorption bands are reported in wavenumbers (cm⁻¹) in the range of 4000-800 cm⁻¹. High-resolution mass spectral analysis (HRMS) data were obtained using Agilent Technologies 6530 Accurate mass Q-TOF LC/MS.

3.3.2 Experimental Procedures and ¹H NMR, ¹³C NMR Spectra

3.3.2.1 General Procedure for Synthesis Aldehydes

To an oven dried round-bottomed flask flushed with nitrogen, equipped with a stirbar were added epoxy-aldehyde 321 (1 equiv.), (formylmethylene)triphenylphosphorane 322 (1.7 equiv.), acetonitrile. The flask was closed, and the reaction was allowed to stir at 45 °C for 4 hours. Upon completion of the reaction, the solution was concentrated, and the residue was purified by flash column chromatography.

(324) (E)-3-((2R,3R)-2-methyl-3-phenyloxiran-2-yl)acrylaldehyde (324): To an oven-dried round bottomed flask flushed with nitrogen, equipped with a stirbar were added epoxy-aldehyde (1equiv.), (formylmethylene)triphenylphosphorane (1.7 equiv.), acetonitrile. The flask was closed, and the reaction was allowed to stir at 45 °C for 4 hours. Upon completion of reaction, the solution was concentrated, and the residue was purified by flash column chromatograph to afford light yellow solid (85% yield).¹H NMR (400 MHz, CDCl₃) δ 9.60 (d, J = 8 Hz, 1H), 7.36-7.28 (m, 5H), 6.73 (d, J = 16 Hz, 1H), 6.35 (dd, J = 8, 16 Hz, 1H), 4.05 (s, 1H), 1.25 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 192.9, 157.5, 134.2, 132.1, 128.2, 128.2, 126.5, 66.1, 61.2, 14.2.
IR (CH$_2$Cl$_2$, cm$^{-1}$): 2980, 2821, 2735, 1683, 1633, 1450, 1383, 1117, 972. HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{12}$H$_{13}$O$_2^+$ 189.0910; Found 189.0910.

(E)-3-((2R,3R)-2-methyl-3-(p-tolyl)oxiran-2-yl)acrylaldehyde (325): Compound was prepared according to general procedure 3.3.2.1. pale white solid (74%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.61 (d, $J$ = 8 Hz, 1H), 7.19 (s, 4H), 6.74 (d, $J$ = 16 Hz, 1H), 6.36 (dd, $J$ = 8, 16 Hz, 1H), 4.03 (s, 1H), 2.35 (s, 3H), 1.27 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.8, 157.6, 138.0, 132.1, 131.1, 128.9, 126.4, 66.2, 61.2, 21.1, 14.2. IR (CH$_2$Cl$_2$, cm$^{-1}$): 2927, 2818, 2734, 1684, 1514, 1446, 1382, 1117, 972. HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{15}$O$_2^+$ 203.1067; Found 203.1065.

(E)-3-((2R,3R)-3-([1,1'-biphenyl]-4-yl)-2-methyloxiran-2-yl)acrylaldehyde (326): Compound was prepared according to general procedure 3.3.2.1. white solid (82%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.64 (d, $J$ = 8 Hz, 1H), 7.61 (t, $J$ = 8 Hz, 4H), 7.45 (t, $J$ = 8 Hz, 2H), 7.40-7.35 (m, 3H), 6.77 (d, $J$ = 16 Hz, 1H), 6.40 (dd, $J$ = 8, 16 Hz, 1H), 4.11 (s, 1H), 1.33 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.8, 157.3, 141.1, 140.4, 133.2, 132.2, 128.8, 127.5, 127.0, 66.0, 61.3, 14. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3356, 3054, 3030, 2966, 2929, 2819, 2734, 2229, 1919, 1814, 1683, 1634, 1599, 1582, 1563, 1519, 1487, 1447, 1411, 1383, 1306, 1251, 1187, 1156, 1117, 1067, 1040, 1007. HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{18}$H$_{17}$O$_2^+$ 265.1223; Found 265.1224.
(E)-3-((2R,3R)-3-(4-bromophenyl)-2-methoxiran-2-yl)acrylaldehyde (327): Compound was prepared according to the general procedure 3.3.2.1. Light yellow solid (80%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.57 (d, $J = 8$ Hz, 1H), 7.46 (m, 2H), 7.15 (d, $J = 7.2$ Hz, 2H), 6.69 (d, $J = 15.4$ Hz, 1H), 5.45 (m, 1H), 3.98 (s, 1H), 1.22 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.6, 156.7, 133.3, 133.3, 132.2, 132.2, 131.4, 128.2, 122.2, 65.5, 61.2, 14.2. IR (CH$_2$Cl$_2$, cm$^{-1}$): 2969, 2818, 2734, 1685, 1636, 1488, 1119, 1068, 1010, 973. HRMS (ESI) m/z: [M+H]$^+$Calcd for C$_{12}$H$_{12}$BrO$_2^+$ 267.0015; Found 267.0014

(E)-3-((2R,3R)-3-(4-chlorophenyl)-2-methoxiran-2-yl)acrylaldehyde (328): Compound was prepared according to general procedure 3.3.2.1. Light yellow oil (69%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.59 (d, $J = 8$ Hz, 1H), 7.33 (d, $J = 8$ Hz, 2H), 7.23 (d, $J = 8$ Hz, 2H), 6.71 (d, $J = 16$ Hz, 1H), 6.33 (dd, $J = 8$, 16 Hz, 1H), 4.00 (s, 1H), 1.23 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.6, 156.7, 134.0, 132.8, 132.3, 128.5, 127.9, 77.3, 77.0, 76.7, 65.5, 61.2, 14.2. IR (CH$_2$Cl$_2$, cm$^{-1}$): 2821, 1689, 1492, 1383, 1119, 1090, 1014. HRMS (ESI) m/z: [M+H]$^+$Calcd for C$_{12}$H$_{12}$ClO$_2^+$ 223.0520; Found 223.0520.

(E)-3-((2R,3R)-2-methyl-3-(4-(trifluoromethyl)phenyl)oxiran-2-yl)acrylaldehyde (330):
Compound was prepared according to general procedure 3.3.2.1. Light yellow solid (89%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.62 (d, $J = 8$ Hz, 1H), 7.64 (d, $J = 8$ Hz, 2H), 7.44 (d, $J = 8$ Hz, 2H), 6.37 (dd, $J = 8$, 8 Hz, 1H), 4.10 (s, 1H), 1.26 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.5, 132.5, 126.9, 125.3, 125.2, 65.3, 61.3, 14.2. IR (CH$_2$Cl$_2$, cm$^{-1}$): 2935, 1691, 1620, 1420, 1324, 1234, 1123, 1065, 1018. HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{13}$H$_{12}$F$_3$O$_2$ 257.0784; Found 257.0785.

![Image of compound 331](image)

$^{(E)}$-3-((2$R$3$R$)-2-methyl-3-(naphthalen-2-yl)oxiran-2-yl)acrylaldehyde (331): Compound was prepared according to general procedure 3.3.2.1. pale white solid (70%). $^1$H NMR (400 MHz, CDCl$_3$) 9.65 (s, 1H), 7.82 (d, $J = 28$ Hz, 4H), 6.78 (d, $J = 16$ Hz, 1H), 6.41 (J = 8 Hz, 1H), 4.22 (s, 1H), 1.30 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.8, 157.3, 133.1, 132.9, 132.3, 131.7, 128.1, 127.9, 127.7, 126.5, 126.3, 125.7, 124.0, 66.3, 61.5, 14.3. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3356, 3054, 3002, 2966, 2930, 2818, 2734, 1683, 1633, 1601, 1508, 1470, 1445, 1383, 1345, 1305, 1271, 1250, 1191, 1167, 1124, 1114, 1068, 1018. HRMS (ESI) m/z: [M+H]$^+$ Calcd for C$_{16}$H$_{15}$O$_2$ $^+$ 239.1067; Found 239.1068.

![Image of compound 332](image)

$^{(E)}$-3-((2$R$3$R$)-3-((tert-butyldimethylsilyl)oxy)ethyl)-2-methyloxiran-2-yl)acrylaldehyde (332): To an oven dried round-bottomed flask flushed with nitrogen, equipped with a stirbar were added epoxyaldehyde (1 equiv.), (formylmethylene)triphenylphosphorane (1.7 equiv.), acetonitrile. The flask was closed, and the reaction was allowed to stir at 45 °C for 6 hours. Upon completion of the reaction, the solution was concentrated, and the residue was purified by flash
column to afford colorless oil (76%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.52 (d, $J = 8$ Hz, 1H), 6.55 (d, $J = 16$ Hz, 1H), 6.25 (dd, $J = 8$, 16 Hz, 1H), 3.77 (s, 2H), 3.01 (t, $J = 4$ Hz, 1H), 1.87-1.80 (m, 2H), 1.45 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) 192.7, 158.4, 131.9, 63.8, 59.9, 58.3, 31.8, 25.8, 18.1, 15.1, -5.49. IR (CH$_2$Cl$_2$, cm$^{-1}$): 2955, 2929, 2857, 1692, 1636, 1471, 1385, 1361, 1253, 1093, 834, 811, 776. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for 293.1543; Found 293.1545.

$^{(E)}$-3-((2R,3R)-3-cyclohexyl-2-methyloxiran-2-yl)acrylaldehyde (333):

Compound was prepared according to general procedure 3.3.2.1. pale white oil (83 %). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.47 (s, 1H), 6.50 (m, 1H), 5.16 (m, 1H), 2.57 (d, $J = 8$ Hz, 1H), 1.89-1.19 (m, 3H), 1.17 (s, 3H), 1.15-1.02 (m, 8H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.91, 158.86, 131.62, 70.14, 58.4, 37.15, 30.37, 28.50, 25.96, 25.37, 25.24, 14.39.

3.3.2.2 General Procedure for Preparation of Alcohols

To a vial equipped with stirbar were added epoxy-alkene aldehyde (1 equiv.), N-heterocyclic carbene catalyst (NHC) (0.25 equiv.), DCM, methanol (3 equiv.), Hunig base (0.4 equiv.). The vial was closed with teflon cap and reaction was run at room temperature for 17 hours. Upon completion reaction was quenched with aqueous saturated NH$_4$Cl, then extracted three times with
ethyl acetate. The organic layer was then washed with brine and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

![Chemical structure of compound 336](image)

**methyl (5S,E)-5-hydroxy-4-methyl-5-phenylpent-2-enolate (336):** Compound was prepared according to general procedure 3.3.2.2. Yellow oil (71%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.34-7.25 (m, 5H), 5.85 (s, 1H), 5.14 (s, 1H), 3.68 (s, 3H), 3.11 (d, $J = 4$ Hz, 2H), 2.67 (br, 1H), 1.49 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.4, 141.9, 140.7, 128.2, 127.3, 126.2, 117.6, 78.6, 51.7, 33.0, 12.3. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3442, 3061, 3027, 2952, 2923, 2854, 1733, 1603, 1493, 1449, 1436, 1322, 1261, 1199, 1168, 1015. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{13}$H$_{16}$NaO$_3$ $^+$ 243.0992; Found 243.0990.

![Chemical structure of compound 337](image)

**methyl (5S,E)-5-hydroxy-4-methyl-5-(p-tolyl)pent-2-enolate (337):** Compound was prepared according to general procedure 3.3.2.2. Yellow oil (71%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.24 (d, $J = 8$ Hz, 2H), 7.13 (d, $J = 8$ Hz, 2H), 5.85 (t, $J = 8$ Hz, 1H), 5.11 (s, 1H), 3.69 (s, 3H), 3.12(d, $J = 8$ Hz, 2H), 2.48 (br, 1H), 2.33 (s, 3H), 1.49 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.4, 140.7, 138.9, 137.0, 128.9, 126.2, 117.3, 78.4, 51.8, 33.0, 21.0, 12.4. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3441, 2951, 2922, 1736, 1512, 1436, 1321, 1262, 1200, 1171, 1017. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{14}$H$_{18}$NaO$_3$ $^+$ 257.1148; Found 257.1147.
methyl (5S,E)-5-([1,1'-biphenyl]-4-yl)-5-hydroxy-4-methylpent-2-enoate (338):

Compound was prepared according to general procedure 3.3.2.2. Yellow solid (71%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.58 (m, 4H), 7.46 (m, 4H), 7.34 (m, 1H), 5.91 (t, $J = 7.16$ Hz, 1H), 5.22 (s, 1H), 3.71 (s, 3H), 3.16 (d, $J = 8$ Hz, 2H), 2.59 (br, 1H), 1.55 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.3, 141.0, 140.8, 140.6, 140.3, 128.6, 127.1, 126.9, 126.9, 126.7, 117.8, 78.4, 51.7, 33.1, 12.4. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3440, 3028, 2952, 2923, 2854, 1735, 1600, 1564, 1487, 1436, 1404, 1323, 1263, 1200, 1170, 1007. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{19}$H$_{20}$NaO$_3$ $^+$ 319.1305; Found 319.1303.

methyl (5S,E)-5-(4-bromophenyl)-5-hydroxy-4-methylpent-2-enoate (339):

Compound was prepared according to general procedure 3.3.2.2. Yellow oil (64%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.44 (d, $J = 8$ Hz, 2H), 7.23 (d, $J = 8$ Hz, 2H), 5.83 (t, $J = 8$ Hz, 1H), 5.11 (s, 1H), 3.69 (s, 3H), 3.11 (d, $J = 8$ Hz, 2H), 2.51 (br, 1H), 1.46 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.3, 140.7, 140.3, 131.3, 127.9, 121.2, 118.3, 78.1, 51.9, 32.9, 12.1. IR (CH$_2$Cl$_2$, cm$^{-1}$): 2924, 2853, 1735, 1690, 1448, 1167, 1010. HRMS (ESI) m/z: [M+Na]$^+$Calcd for C$_{13}$H$_{15}$BrNaO$_3$ $^+$ 321.0097; Found 321.0098.
methyl (5S,E)-5-(4-chlorophenyl)-5-hydroxy-4-methylpent-2-enoate (340):

Compound was prepared according to general procedure 3.3.2.2. Colorless oil (61%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.28 (s, 4H), 5.83 (s, 1H), 3.68 (s, 3H), 3.11 (s, 2H), 2.56 (br, 1H), 1.46 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.3, 140.4, 140.3, 133.0, 128.3, 127.6, 118.2, 78.0, 77.3, 76.9, 76.6, 51.8, 32.9, 12.1. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3426, 2952, 2922, 2855, 2097, 2097, 1905, 1733, 1721, 1595, 1577, 1487, 1435, 1402, 1366, 1322, 1291, 1261, 1199, 1167, 1107, 1088, 1012. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{13}$H$_{15}$ClNaO$_3$+ 277.0602; Found 277.0600.

methyl (5S,E)-5-hydroxy-5-(4-methoxyphenyl)-4-methylpent-2-enoate (341):

Compound was prepared according to general procedure 3.3.2.2. Pale white Oil (59%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.26 (d, $J$ = 8 Hz, 2H), 6.85 (d, $J$ = 8 Hz, 2H), 5.84 (t, $J$ = 6.8 Hz, 1H), 5.09 (s, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.12 (d, $J$ = 8 Hz, 2H), 2.33 (br, 1H), 1.48 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.4, 158.9, 140.7, 134.0, 127.5, 117.1, 113.6, 78.1, 55.1, 51.8, 33.0, 12.5. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3452, 2999, 2922, 2952, 1735, 1610, 1585, 1510, 1461, 1437, 1365, 1322, 1302, 1246, 1198, 1170, 1110, 1033. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{14}$H$_{18}$NaO$_4$+ 273.1097; Found 273.1097.
methyl (5S,E)-5-hydroxy-4-methyl-5-(4-(trifluoromethyl)phenyl)pent-2-enoate (342):
Compound was prepared according to general procedure 3.3.2.2. White solid (61%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.58 (d, $J = 8$ Hz, 2H), 7.49 (d, $J = 8$ Hz, 2H), 5.87 (t, $J = 8$ Hz, 1H), 5.23 (s, 1H), 3.70 (s, 3H), 3.13 (d, $J = 8$ Hz, 2H), 2.42 (br, 1H), 1.48 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.2, 145.6, 140.2, 129.7, 129.3, 126.4, 125.4, 125.16, 125.12, 125.0, 122.7, 119.0, 112.9, 78.3, 51.8, 32.9, 11.9. IR (CH$_2$Cl$_2$, cm$^{-1}$) 3438, 2924, 2854, 1735, 1618, 1437, 1413, 1325, 1199, 1162, 1122, 1066, 1016. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{14}$H$_{15}$F$_3$NaO$_3$ $^+$ 311.0866; Found 311.0866.

![methyl (5S,E)-5-hydroxy-4-methyl-5-(4-(trifluoromethyl)phenyl)pent-2-enoate (342)](image)

methyl (5S,E)-5-hydroxy-4-methyl-5-(naphthalen-2-yl)pent-2-enoate (343):
Compound was prepared according to general procedure 3.3.2.2. Light yellow solid (62%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.86-7.79 (m, 4H), 7.48-7.42 (m, 3H), 5.94 (t, $J = 8$ Hz, 1H), 5.32 (s, 1H), 3.71 (s, 3H), 3.15 (d, $J = 8$ Hz, 2H), 2.73 (br, 1H), 1.52 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.4, 140.6, 139.3, 133.2, 132.8, 127.9, 127.6, 126.0, 125.7, 124.9, 124.4, 118.0, 78.7, 77.3, 77.0, 76.7, 51.8, 33.1, 12.3. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3425, 3054, 2951, 2922, 2854, 1735, 1436, 1322, 1262, 1200, 1166, 1017. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{17}$H$_{18}$NaO$_3$ $^+$ 293.1148; Found 293.1145.

![methyl (5S,E)-5-hydroxy-4-methyl-5-(naphthalen-2-yl)pent-2-enoate (343)](image)
methyl(5R,E)-7-((tart-butylidimethylsilyl)oxy)-5-hydroxy-4-methylhept-2-enoate (344):

Compound was prepared according to general procedure 3.3.2.2. Yellow oil (63%). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.65 (s, 1H), 4.25 (s, 1H), 3.80 (d, $J = 24$ Hz, 2H), 3.67 (s, 3H), 3.27 (br, 1H), 3.08 (d, $J = 8$ Hz, 2H), 1.78-1.74 (m, 2H), 1.63 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.3, 140.6, 117.4, 116.8, 116.5, 77.2, 76.9, 76.6, 76.2, 61.9, 51.6, 36.8, 33.1, 25.7, 18.0, 12.4, -5.60, -5.63. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3444, 2953, 2928, 2856, 2884, 1742, 1471, 1463, 1436, 1388, 1361, 1320, 1255, 1200, 1165, 1095, 1005. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{15}$H$_{30}$NaO$_4$Si$^+$ 325.1806; Found 325.1800.

![Structure 345](image)

methyl (5R,E)-5-cyclohexyl-5-hydroxy-4-methylpent-2-enoate (345):

Compound was prepared according to general procedure 3.3.2.2. Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.50 (m, 1H), 3.69 (s, 1H), 3.66 (s, 1H), 3.06 (d, $J = 12$ Hz, 2H), 1.95 (m, 1H), 1.59-1.41 (m, 7H), 1.22-1.20 (m, 3H), 1.16-1.10 (m, 3H), 0.36 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.2, 140.1, 118.4, 82.2, 77.2, 76.9, 76.6, 51.6, 40.6, 32.9, 29.5, 28.8, 26.3, 26.0, 25.8, 11.5. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3452, 2923, 2851, 1740, 1436, 1320, 1261, 1202, 1165, 1080 1013. HRMS (ESI) m/z: [M+Na]$^+$ Calcd for C$_{13}$H$_{22}$NaO$_3$ + 249.1461; Found 249.1461.

3.4 References:


18. Cavallo, L.; Cazin, C. S. J. "N-Heterocyclic Carbenes in Transition Metal Catalysis and


33. Nontoxicity has allowed their use for medical purposes (prostheses).

34. Titanium is the ninth-most abundant element in the Earth’s crust (5.65 × 10^3 ppm, 0.63% by mass), see: Lide, D. R. *CRC Handbook of Chemistry and Physics*, 88th ed.; Taylor & Francis Group: Boca Raton, FL, 2008.


Chapter 4: Synthesis of Biologically Relevant Compounds

4.1 Introduction

4.1.1 ROCK and ROCK Inhibitors

Rho-associated protein kinase (ROCK) belongs to a family of protein kinase (group AGC) that is responsible for catalytic activities and requires a C-terminal outside the kinase domain.\(^1\) It has an Adenosine 5’-triphosphate (ATP) binding pocket which is encircled by two lobes (N and C-terminal lobes).\(^2\) ROCK 1 is expressed on non-nerve tissues, for instance, kidneys, spleen, testes, and lungs.\(^3\) ROCK 2 is mainly found in the heart and brain.\(^2\) The binding pockets have three parts namely furanose, adenine, and distal regions. The hydrophobic adenine region is located at the bottom of the pocket. The spherical shaped furanose region is binding site for furanose ring of ATP.\(^2\) The pyrophosphoric acid group of ATP can be adapted in distal region. The shape of distal region can also be discovered by a part of nucleotide-binding loop.\(^2\)

ROCK is linked to activate nuclear factor (NF)-kB\(^4\), which further advances the production of inflammatory cytokines and Tumor Necrosis factors (TNF). ROCK effectors of Rho GTPase are vital in cellular functioning, cell migration, contraction and actin organization, and neurite elongation and cytokinesis.\(^5\) ROCK also acts by phosphorylating downstream targets, it plays a part in autoimmunity signaling pathways.\(^2\) Rho associated protein kinase pathway is also linked to range of neurological diseases, cardiovascular diseases, and oncology. Moreover, ROCK is considered an essential target for therapeutic interventions. ROCK inhibitors prevent the secretion of Interleukin (IL) and TNF-\(\alpha\).\(^2\)

ROCK inhibitors can be divided into various derivatives for example urea, indazole, and amino pyrimidine derivatives. It has helped to treat different neurological diseases such as stroke, Alzheimer’s disease, and spinal cord injury (SCI).\(^2\) Various diseases identify ROCK as their
potential target; therefore, studies should focus on ROCK inhibitors following ROCK signaling pathways. ROCK inhibition has shown positive results in controlling several diseases such as cerebral infrared, hypertension. It is crucial to search for a new ROCK inhibitor that have better and improved therapeutic effects and can reduce the side effects of drug interactions.$^2$

<table>
<thead>
<tr>
<th>Medicinal area</th>
<th>Compound</th>
<th>Biological effects</th>
<th>Species</th>
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<tr>
<td>Hypertension</td>
<td>Fasudil</td>
<td>Regulates blood pressure</td>
<td>Human$^6$</td>
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<tr>
<td></td>
<td>SAR407899</td>
<td>Regulates blood pressure</td>
<td>Rat$^7$</td>
</tr>
<tr>
<td>Alzheimer’s disease (AD)</td>
<td>Y27632</td>
<td>Lower prevalence of AD</td>
<td>Mouse$^8$</td>
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<tr>
<td></td>
<td>Hydroxyfasudil</td>
<td>Improve memory and spatial learning</td>
<td>Rat$^9$</td>
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<tr>
<td></td>
<td>Fasudil</td>
<td>Protect against Aβ-induced hippocampal neurodegeneration</td>
<td>Rat$^{10}$</td>
</tr>
<tr>
<td>Oncology</td>
<td>Fasudil</td>
<td>Inhibition of tumor growth, progression, and metastasis</td>
<td>Rat, mouse$^{11}$</td>
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</table>

Table 4.1: Therapeutic roles of ROCK.$^2$

4.1.2 PET Imaging

Positron emission tomography (PET) is sensitive and accurately quantified technique for molecular imaging in vivo vital systems.$^{12}$ Short lived radioisotopes such as $^{11}$C, $^{18}$F, $^{13}$N are employed as radionuclides in Positron emission tomography.$^{12}$ PET imaging has been used as the diagnostic tool for the intensive investigation of cancer treatments. The investigation has shown success in targeting protein kinases and small molecule kinase inhibitor that has been identified as the prominent therapeutic class.$^{13}$ PET is vital in finding the increasing application for monitoring and therapy of receptor density studies based on kinase isotopes of clinically approved kinase
inhibitors. This PET Imaging approach improve drug identification and uses radiotracer design, biological tracer evaluation, and radiochemistry approaches to explore the preclinical studies of PET neuroimaging and novel radio-ligands.

**Scheme 4.1:** Method for synthesis of H-1152 and radiolabeled H-1152.12
Suzuki et al. developed the method to synthesize a PET probe \textbf{404} \([^{11}\text{C}]\text{H}-1152\) \([^{11}\text{C}]\) (Scheme 4.1)\textsuperscript{12}. They used rapid Pd\textsuperscript{0}-mediated C-[\(^{11}\text{C}\)] methylation in presence of \([^{11}\text{C}]\) methyl iodide \textbf{402}. In compound \textbf{401} the deprotection of trifluoroacetyl group was carried out in 1 min using basic conditions to obtain compound \textbf{404}.

\textbf{4.2 Experimental Procedure}

To synthesize isoquinoline-5-sulfonamide compound, we started with preparation of compound \textbf{409}. The first step is N-Cbz protection of L-alaninol \textbf{405}. Compound \textbf{406} under O-mesylation resulted in formation of \textbf{407}. Compound \textbf{407} was alkylated with 3-amino-1-propanol and was successively protected by Boc (tert-Butyloxycarbonyl) and TBS (tert-Butyldimethylsilyl) group affording compound \textbf{409}. Cbz group was removed by catalytic hydrogenolysis to give \textbf{410}. Then condensation of amine \textbf{410} with 4-haloisoquinoline-5-sulfonyl chloride \textbf{411} in DCM followed by deprotection of TBS group by using tetrabutylammonium fluoride (TBAF) resulted in formation of \textbf{413}. Intramolecular cyclization of \textbf{413} using Mitsunobu’s condition afforded \textbf{414} and then under optimized conditions \textbf{414} was converted to form \textbf{415}.
**Scheme 4.2:** Starting material preparation.

**4.3 Supporting Information**

All commercially available chemicals were used without further purification unless otherwise noted. All reactions were carried out in well ventilated fume hoods. Reactions were monitored by TLC on silica gel 60 F254. Flash column chromatography was performed using SiliaFlash P60 silica gel (40-63 µm). Visualization of developed TLC was performed by irradiation with UV light or treatment with a solution ceric ammonium molybdate stain followed by heating. Yields refer to purified compound unless otherwise noted.

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AM 500 MHz spectrometers. Chemical shifts were reported as parts per million (ppm) relative to residual solvent CDCl$_3$ ($^1$H, 7.26 ppm, $^{13}$C, 77.0 ppm). The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Infrared spectra were recorded on a PerkinElmer Spectrum.
Two IR spectrometer. Absorption bands are reported in wavenumbers (cm$^{-1}$) in the range of 4000-800 cm$^{-1}$. High-resolution mass spectral analysis (HRMS) data were obtained using Agilent Technologies 6530 Accurate mass Q-TOF LC/MS. Technologies 6530 Accurate Mass Q-TOF LC/MS.

**benzyl (S)-(1-hydroxypropan-2-yl)carbamate (406):**  $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.36-7.28 (m, 5H), 5.36 (br, 1H), 5.11-5.05 (m, 2H), 3.77 (br, 1H), 3.60-3.57 (m, 1H), 3.48-3.40 (m, 2H), 1.12 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 156.6, 136.4, 128.5, 128.1, 128.0, 66.7, 66.2, 48.9, 17.2. ESI-HRMS: $m/z$ calcd for C$_{11}$H$_{15}$NNaO$_3$ $^{+}$ [M+Na]$^{+}$: 232.0944; found: 232.0958. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3320, 3034, 2972, 1694, 1533, 1454, 1411, 1341, 1258, 1175, 1067, 1045,993, 776, 738, 697.

**ESI**

**benzyl (S)-(1-hydroxypropan-2-yl)carbamate (406):**  $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.36-7.28 (m, 5H), 5.36 (br, 1H), 5.11-5.05 (m, 2H), 3.77 (br, 1H), 3.60-3.57 (m, 1H), 3.48-3.40 (m, 2H), 1.12 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 156.6, 136.4, 128.5, 128.1, 128.0, 66.7, 66.2, 48.9, 17.2. ESI-HRMS: $m/z$ calcd for C$_{11}$H$_{15}$NNaO$_3$ $^{+}$ [M+Na]$^{+}$: 232.0944; found: 232.0958. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3320, 3034, 2972, 1694, 1533, 1454, 1411, 1341, 1258, 1175, 1067, 1045,993, 776, 738, 697.

**ESI**

**benzyl (S)-(1-hydroxypropan-2-yl)carbamate (406):**  $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.36-7.28 (m, 5H), 5.36 (br, 1H), 5.11-5.05 (m, 2H), 3.77 (br, 1H), 3.60-3.57 (m, 1H), 3.48-3.40 (m, 2H), 1.12 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 156.6, 136.4, 128.5, 128.1, 128.0, 66.7, 66.2, 48.9, 17.2. ESI-HRMS: $m/z$ calcd for C$_{11}$H$_{15}$NNaO$_3$ $^{+}$ [M+Na]$^{+}$: 232.0944; found: 232.0958. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3320, 3034, 2972, 1694, 1533, 1454, 1411, 1341, 1258, 1175, 1067, 1045,993, 776, 738, 697.

**ESI**

**benzyl (S)-(1-hydroxypropan-2-yl)carbamate (406):**  $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.36-7.28 (m, 5H), 5.36 (br, 1H), 5.11-5.05 (m, 2H), 3.77 (br, 1H), 3.60-3.57 (m, 1H), 3.48-3.40 (m, 2H), 1.12 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 156.6, 136.4, 128.5, 128.1, 128.0, 66.7, 66.2, 48.9, 17.2. ESI-HRMS: $m/z$ calcd for C$_{11}$H$_{15}$NNaO$_3$ $^{+}$ [M+Na]$^{+}$: 232.0944; found: 232.0958. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3320, 3034, 2972, 1694, 1533, 1454, 1411, 1341, 1258, 1175, 1067, 1045,993, 776, 738, 697.
** tert-butyl (S)-(2-(((benzyloxy)carbonyl)amino)propyl)(3-((tert-butyldimethylsilyl)oxy)propyl) carbamate (409):**  
$^1$H NMR (500 MHz, CDCl$_3$): δ 7.31 (s, 5H), 5.61 (br, 1H), 5.05 (s, 2H), 3.89 (s, 1H), 3.59 (s, 3H), 3.32 (d, $J = 6.4$ Hz, 1H), 3.31-3.13 (m, 1H), 2.94 (d, $J = 13.3$ Hz, 1H), 1.70 (s, 2H), 1.41 (s, 9H), 1.12 (d, $J = 6.3$ Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).  
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 157.0, 156.1, 136.7, 128.2, 127.6, 79.6, 66.0, 60.2, 51.4, 47.0, 44.7, 31.6, 28.2, 25.7, 25.5, 18.7, 18.1, -3.65, -5.49. ESI-HRMS: $m/z$ calcd for C$_{25}$H$_{44}$N$_2$NaO$_5$S$^+$ [M+Na]$^+$: 503.2912; found: 503.2919. IR (CH$_2$Cl$_2$, cm$^{-1}$): 3334, 2954, 2929, 2857, 2886, 1722, 1694, 1517, 1471, 1454, 1415, 1390, 1365, 1348, 1305, 1287, 1249, 1095, 1006, 969, 939, 835, 775, 735, 696.

4.4 References


MeO

O

NHBoc

S

O

OBn

NHBoc

79

242
N
Boc
O
OEt
O
Me
232
342