THE ADVANCEMENT OF NHC CATALYZED C–C BOND FORMATION: APPLICATION TOWARDS CHROMONE SYNTHESIS, C–GLYOSYLATION AND TOTAL SYNTHESIS

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SCHOOL OF PHYSICAL & MATHEMATICAL SCIENCES

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THE ADVANCEMENT OF NHC CATALYZED C–C BOND FORMATION: APPLICATION TOWARDS CHROMONE SYNTHESIS, C–GLYCOSYLATION AND TOTAL SYNTHESIS

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A thesis submitted to the Nanyang Technological University in partial fulfillment of the requirement for the degree of Doctor of Philosophy

2012
To My Beloved Parents, friends and Teachers
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Seenuvasan Vedachalam.
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SUMMARY

Part 1: NHC Catalyzed Hydroacylation: Chromone Synthesis

Chromone is one of the most common heterocyclic motifs found in various pharmaceutically active compounds. An immense effort has been made to develop an efficient intramolecular carbon–carbon bond formation between aldehyde and nitrile to derive 3-aminochromones in good to excellent yields using an NHC catalyst. Furthermore, the same concept was applied to an activated alkyne to obtain 3-alkyl chromones derivatives.

Part 2: NHC Catalyzed Stetter Reaction: C–Glycosylation

C–glycosides show diversified biological roles including remarkable physiological stability. Described herein is an organocatalytic approach for acylanion addition to the anomeric carbon of 2-nitroglucal using NHC catalyst. Control over the reaction conditions gave β-selective and nitro-eliminated C–glycosides which could be applied for the formal synthesis of Scleropentaside A.
Part 3: NHC Catalyzed Claisen Rearrangement: Oleuropein Synthesis

Oleuropein is an Irinoid based natural product which possesses various biological activities including antioxidant, anti-inflammatory, anti-atherogenic, anti-cancer, antimicrobial and antiviral properties. A new chemical approach for Oleuropein synthesis using NHC catalyzed Claisen rearrangement reaction was applied and the key intermediate step was achieved.

Part 4: Appendix: Sugar-Porphyrin Conjugates for Photodynamic Activity

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<td>δ</td>
<td>chemical shift</td>
<td>DMF</td>
<td>N, N-dimethylformamide</td>
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<tr>
<td>Δ</td>
<td>reflux or heat</td>
<td>DMP</td>
<td>Dess–Martin periodinane</td>
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<td>degree centigrade</td>
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<td>Aq</td>
<td>aqueous</td>
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<tr>
<td>brs</td>
<td>broad singlet</td>
<td>ether</td>
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<td>fourier transfer infrared</td>
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<td>doublet</td>
<td>h</td>
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<td>high performance liquid</td>
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<td>iPr</td>
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<td>DMAP</td>
<td>4-(N, N-dimethylamino)</td>
<td>J</td>
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<td>kg</td>
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<td>Abbreviation</td>
<td>Full Form</td>
<td>Meaning</td>
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<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
<td>Nu nucleophile</td>
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<td>LiHMDS</td>
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<tr>
<td>M</td>
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<td>PCC pyridinium chlorochromate</td>
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<td>M+</td>
<td>parent ion peak (mass spectrum)</td>
<td>PDC pyridinium dichromate</td>
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<tr>
<td>m</td>
<td>multiplet</td>
<td>Ph phenyl</td>
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<td>mCPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
<td>PMB p-methoxybenzyl</td>
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<tr>
<td>Me</td>
<td>methyl</td>
<td>ppm parts per million</td>
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<td>MeCN</td>
<td>acetonitrile</td>
<td>PPTS pyridinium p-toluenesulfonate</td>
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<td>methanol</td>
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<td>mg</td>
<td>milligram</td>
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<td>minute</td>
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<td>TBAF tetrabutylammonium fluoride</td>
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<td>TBS tert-butyldimethylsilyl</td>
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<tr>
<td>MVK</td>
<td>methyl vinyl ketone</td>
<td>TFA trifluoroacetic acid</td>
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<td>NBS</td>
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<td>NHC</td>
<td>N-heterocyclic carbene</td>
<td>TMS trimethylsilyl</td>
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<td>NMR</td>
<td>nuclear magnetic resonance</td>
<td>v volume</td>
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CHAPTER 1

Introduction: Recent Advancements in N-Heterocyclic Carbene (NHC) Catalyzed Reactions
### 1.1 Nucleophilic carbene in acylanion generation

The discovery of novel and efficient synthetic methods for carbon–carbon bond formation reactions, remains to be the biggest challenge towards the development of sustainable chemical transformations.\(^1\) Organocatalysis mediated by nucleophilic molecules offer promising strategies in this respect and have seized much attention over the last few years.\(^2\) Their advantages include not only atom economy and operational simplicity, but also the possibility for the development of nontraditional retro-synthetic bond disconnections. A standard example for such a strategy is the inversion of traditional reactivity of functional groups (Umpolung).\(^3\) For example, the electrophilicity of a carbonyl functionality can be reversed (Scheme 1.1) and such polarity reversal can accommodate secondary reactions of functional groups that are otherwise not possible.

### Scheme 1.1 General umpolung strategy for aldehyde functional group

A neutral divalent derivative of carbon has only six electrons in their valence shell which is called carbenes. Based on the spin multiplicity, carbenes are categorized into singlet and triplet carbenes. Singlet carbene consists of a filled and a vacant orbital, thereby showing ambiphilic character, whereas triplet carbene has two singly occupied orbitals which are generally regarded as diradicals (Figure 1.1). If the carbene carbon is directly bonded to donor atoms such as oxygen, nitrogen, sulfur etc which can donate its lone pair into formally vacant \(p\)-orbital of singlet carbene carbon called nucleophilic \(N\)-heterocyclic carbene (NHC).
Recently N-heterocyclic carbenes (NHCs) emerged as potential catalysts for umpolung concepts on both carbonyl and non-carbonyl systems, which lead to an array of diverse reactivities. Like many other important discoveries in organic chemistry, the idea of a NHC can also be investigated through proper disconnection approach, likely to find an understandable mechanistic pathway. This part includes the basic principles of nucleophilic NHC especially the recent reports about umpolung insights on both carbonyl and non-carbonyl system which deals in the recent reports.

![Figure 1.1. Orbital features of carbenes](image)

### 1.1.1 Benzoin Condensation:

![Scheme 1.2 Lapworth's proposed mechanism for benzoin condensation](image)

In 1832, Wohler and Liebig reported first umpolung derived benzoin condensation between two benzaldehyde molecules using cyanide as a catalyst. In 1903, Lapworth proposed a mechanism for this reaction in which a carbanion intermediate was formed by hydrogen cyanide addition to benzaldehyde followed by deprotonation of the aldehyde...
proton (Scheme 1.2).\textsuperscript{[5]} According to Seebach and co-workers, here, the electrophilic carbonyl carbon function has been converted into a nucleophile called “active aldehyde or umpolung.”\textsuperscript{[6]} This activated aldehyde further reacts with another molecule of electrophilic aldehyde to form an adduct which further undergoes proton-shift followed by cyanide anion elimination finally produces condensation product. In 1943, Ugai et al. recognized that thiazolium salts also could be used as catalysts in the benzoin condensation reaction.\textsuperscript{[7]} In 1958, Breslow proposed a mechanistic model for the thiazolium salt-catalyzed benzoin condensation based on Lapworth's mechanism (Scheme 1.3).\textsuperscript{[8]}

\begin{center}
\textbf{Scheme 1.3.} Catalytic cycle of the benzoin condensation as proposed by Breslow.
\end{center}

In this mechanism, the catalytically active species called thiazolin-2-ylidene II (a carbene species) was generated \textit{in situ} by deprotonation of the thiazolium salt I. Breslow assumed that the thiazolin-2-ylidene II performed the nucleophilic attack of the carbonyl function of an aldehyde III, thereby generating the thiazolium salt adduct IV. Deprotonation of aldehyde proton leads to the active aldehyde V in the form of the resonance-stabilized enaminol-type intermediate VI. This intermediate VI reacts with an electrophilic carbonyl group of a second aldehyde molecule to form thiazolium adduct
VII which further under goes proton-shift followed by elimination of thiazolin-2-ylidene II to obtain benzoin VIII. In addition to thiazolium salts, other types such as, imidazolium based carbene by Wanzlick (Figure 1.2., 1.1)\textsuperscript{9} and Arduengo (Figure 1.2., 1.3-1.7)\textsuperscript{10} and triazolium based carbenes by Teles and Ender (Figure 1.2., 1.8.)\textsuperscript{11} have also been explored.

![Figure 1.2. Types of N-heterocycle carbenes.](image)

1.1.1a. Intermolecular asymmetric benzoin condensation:

Scheme 1.4, summarizes notable attempts on asymmetric benzoin condensation reaction. In 1966, Sheehan and Hunneman reported the first asymmetric benzoin condensation utilizing the chiral thiazolium salt 1.11 as precatalyst to obtain 22% enantiomeric excesses in 50 % yield (Scheme 1.4).\textsuperscript{12} Later, they employed chiral thiazolium salt 1.12 improving the ee to 52 % but with a drop in yield to 6 %.\textsuperscript{13} Takagi et al. developed menthyl-substituted thiazolium 1.13 to obtain an enantiomeric excess of 35 %.\textsuperscript{14} On the basis of this reactivity, in 1993 López Calahorra and co-workers synthesized bis-thiazolium salt 1.14, affording benzoin with 27 % ee in 11 % yield.\textsuperscript{15} Tsuda’s group developed chiral thiazolium salt with long chain functionalized amino acid 1.15.\textsuperscript{16} In 1996, Ender’s group developed first triazolium based chiral catalysts 1.16 for asymmetric benzoin condensation reaction and obtained 75 % ee in 66 % yield.\textsuperscript{17} Year later, Leeper developed bicyclic based chiral thiazolium catalyst 1.17–1.19 and obtained lower enantioselectivity.\textsuperscript{18} Ranwal introduced similar type of bicyclic thiazolium salt 1.20 with improved enantioselectivity.\textsuperscript{19} At the same time, Leeper introduced various
bicyclic triazolium chiral catalysts 1.21–1.23 which afforded highest 80% yield.\textsuperscript{20} Four years later, Ender developed bulky \textit{tert}-butyl based chiral triazolium catalyst 1.24 which

**Scheme 1.4.** Chiral catalysts for benzoin condensation.

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had produced 90 % enantiomeric excess.\cite{21} In 2008, Ender developed modified version of Leeper catalyst 1.22 to 1.25 which gave 95 % ee.\cite{22} At the same time, You group introduced dimeric triazole carbene catalyst 1.26 producing 95 % ee in 95 % yield.\cite{23}

Zeitler and Connon developed modified version of Ender catalysts 1.27 and 1.28, by introducing hydrogen bond concept with the Breslow intermediate.\cite{24} Takahiro Soeta introduced very recently pyridine fused triazolium based carbene catalyst 1.29 which led to 99 % ee.\cite{25} In addition to these various carbene catalysts enantioselective methodologies, benzaldehyde lyase (BAL) enzyme also perform highly enantioselective reaction.\cite{26}

1.1.1b. Intermolecular cross benzoin condensation:

![Scheme 1.5. Direct crossed acyloin condensations.](image)

The most important challenges associated with the development of an efficient and selective crossed-benzoin condensation protocol are of considerable interest, since there are possibilities of eight different products (4 chiral \( \alpha \)-hydroxyketones and its enantiomers, Scheme 1.5). In 1948, Buck \textit{et al.} reported the first crossed benzoin condensation between two aromatic aldehyde partners using cyanide ion.\cite{27} Later, Stetter developed thiazolium salt-derived carbene 1.31 catalyzed crossed benzoin condensation between aromatic and aliphatic aldehydes which involved, the reaction of aromatic acylanion with aliphatic aldehyde producing \( \alpha \)-hydroxy ketone 1.32 (Scheme 1.6a).\cite{28} Very recently, Zeitler and Connon reported triazolium precatalyst 1.35 to obtain chemoselective and
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Scheme 1.6. Direct crossed acyloin condensations: (a) arylacylanion based reaction.
(b) aliphatic acylanion based reaction.
enantioselective intermolecular crossed benzoin condensation reactions between two
aldehydes in reverse way so that aliphatic aldehyde acts as a acylanion, thereby
furnishing 1.36 (Scheme 1.6b).[29]

1.1.1c. Intermolecular aza-benzoin condensation:

The crossed-benzoin condensation is not limited to aldehyde partners alone.
Aldimines are also potential electrophiles as briefed in Scheme 1.7. Murry et al. (Scheme 1.7a) first developed thiazolium 1.31 catalyzed addition of aldehyde 1.37 to N-acylimine equivalent 1.38, which is analogous to aza-benzoin condensation to afford 1.39.[30] Arylsulfonylamide 1.38 served as precursor for the N-acylimine and were generated by in-situ elimination of the sulfonyl group (Scheme 1.7b).

The proposed mechanism is similar to benzoin reaction with in situ generation of the Breslow intermediate attacking the N-acylimine acceptor. Mattson and Scheidt had applied similar strategy with the catalytic addition of acylsilane 1.40 to N-phosphinylated imine 1.41 for the synthesis of α-aminoketone 1.43 using readily available thiazolium salt 1.42 as a carbene precursor, through Brook rearrangement (Scheme 1.7c).[31] In this case, formations of benzoin products were completely avoided. Miller and co-workers
employed chiral peptidic thiazolium salts 1.44 to employ asymmetric variant of the azabenzoin reaction (Scheme 1.7b).[32] You and co-workers have recently shown that aromatic aldehydes can also be coupled to unactivated imines 1.45 (Scheme 1.7d).[33] Eycken developed imidazolium catalyzed C3-arylation of 3,5-dichloro-2-(1H)-pyrazinones (1.47) using 1.49 (Scheme 1.7e).[34]

![Scheme 1.7](image)

**Scheme 1.7.** Various aza-benzoin condensations reactions.

### 1.1.1d. Intramolecular benzoin condensation:

In addition to the previously described intermolecular condensation reaction, intramolecular crossed-benzoin reactions have also been developed and are reviewed in Scheme 1.8. In 1976, Cookson and Lane performed the cyclization of glutaric aldehydes 1.51 to the corresponding hydroxycyclopentanones 1.53 with thiazolium salts 1.52 as precatalysts (Scheme 1.8a).[35] Later, Suzuki et al. developed a diastereoselective intramolecular crossed aldehyde-ketone (1.54) benzoin reaction in an elegant synthesis of preanthraquinones 1.56 (Scheme 1.8b).[36] Ender group later developed a more general
method using substrates of the type 1.57 for the carbene-catalyzed crossed-intramolecular benzoin-condensation in both chiral and achiral version (Scheme 1.8c and 1.8d).\(^{[37-38]}\)

Furthermore, Suzuki et al. extended methodology to synthesize various five- and six-membered cyclic acyloins (Schemes 1.8c and 1.8d).\(^{[39]}\)

### 1.1.2. Stetter reaction:

![Scheme 1.9. Basic mechanism for cyanide catalyzed Stetter reaction.](image)

In the early 1970s, Stetter and co-workers succeeded in transferring the concept of the cyanide catalyzed benzoin condensation to Michael acceptors.\(^{[40]}\) Since then, the catalytic 1,4-addition of acylanion to an acceptor bearing an activated double bond is called Stetter reaction (Scheme 1.9). Later, Stetter investigated a new catalytic pathway for the synthesis of 1,4-bifunctional molecules of broad range using thiazolium salts.

CHAPTER 1: Introduction: Recent Advancement in N-Heterocyclic Carbene Catalyzed Reactions
(Scheme 1.10).\textsuperscript{[41]}

\begin{align*}
\text{Scheme 1.10. Basic mechanism for thiazolium catalyzed Stetter reaction.}
\end{align*}

1.1.2a. Intermolecular Stetter reaction:

Following Stetter's breakthrough, acylanion addition to conjugated activated system soon became one of the most important reactions in organic chemistry. It is often overlooked as a contemporary challenge because of the widespread occurrence of 1,4-carbonyl group in modern pharmaceuticals and biologically active compounds. Here summarized various acylation reactions in activated conjugated systems. In 1989, Ender group developed first asymmetric Stetter reaction using chiral thiazolium salts 1.62 as a precatalyst (Scheme 1. yield of 4 %. Scheidt group disclosed Stetter reaction between acylsilanes 1.66 and α,β- unsaturated conjugate acceptors 1.64 promoted by an thiazolium catalyst 1.67 (Scheme 1.12).\textsuperscript{[43]} This catalytic process open accesses to useful 1,4-

\begin{align*}
\text{Scheme 1.11. First attempt of asymmetric Stetter reaction.}
\end{align*}
Scheme 1.12. Sila-Stetter reaction.

dicarbonyl products and significantly increased the scope of the Stetter reaction by utilizing acylsilanes as tunable acyl anion progenitors. Remarkably mild carbenes have been employed as new and effective nucleophilic catalysts for 1,2-silyl (Brook) rearrangements followed by Stetter reaction.

Later, he extended decarboxylative Stetter reaction (Scheme 1.13) under neutral aqueous conditions.\textsuperscript{[44]} In this case, the combination of β-ketocarboxylate 1.70 and thiazolium salt 1.31 produced reactive carbonyl nucleophile by the elimination of CO\textsubscript{2}, that readily underwent conjugate addition to versatile α-substituted unsaturated 2-acyl imidazole 1.69. Mechanistic investigations indicate that loss of carbon dioxide is necessary for the reaction to proceed. The same group further investigated the first direct nucleophilic carbonyl addition to nitroalkene 1.73 using silyl-protected thiazolium carbinol 1.72 (Scheme 1.14).\textsuperscript{[45]} In the presence of a fluoride anion, silyl-protected thiazolium carbinols 1.72 undergoes carbonyl anion reactivity via a presumed 1,2-hydrogen shift. This new fluoride-activated acyl anion strategy was different from the typical combinations of heteroazolium salts and bases which allows for the use of reactive nitroalkenes as substrates. Additionally, newly formed stereocenters in this reaction can be controlled by a chiral thiourea 1.76 and 74 % enantiomeric excess was obtained for
**Scheme 1.13.** Decarboxlative Stetter reaction.

In 2008, Ender group developed an asymmetric intermolecular Stetter reaction catalyzed by a novel triazolium salt 1.77 leading to 1,4-diketones 1.68 in moderate yield (66%) and moderate enantioselectivity (67%) (Scheme 1.15).[^46] The enantioselectivity could be enhanced by further recrystallization to give 99% ee.

**Scheme 1.14.** Fluoride/thiourea promoted carbonyl anion additions to nitroalkene.

**Scheme 1.15.** Ender’s enantioselective intermolecular Stetter reaction.

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[^46]: Introduce a specific reference citation here.
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**Scheme 1.16.** Rovis group’s intermolecular enantioselective Stetter reaction.

**Scheme 1.17.** Enantioselective acetaldehyde addition reaction

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**CHAPTER 1: Introduction: Recent Advancement in N-Heterocyclic Carbene Catalyzed Reactions**
In 2008, Rovis group, designed a new NHC catalyst 1.80 and applied intermolecular Stetter reaction between nitroalkene 1.78 and pyridine-2-carboxaldehyde, obtained product 1.79 with high enantioselectivity through manipulation of stereo-electronic as well as steric-effects (Scheme 1.16a).\textsuperscript{[47]} Next, they investigated an enantioselective intermolecular Stetter reaction involving glyoxamides 1.81 and alkylidenemalonates 1.82 in good yield with high asymmetric induction in the presence of a phenylalanine-derived carbene catalyst 1.83 (Scheme 1.16b).\textsuperscript{[48]} In consecutive communication alkylidenemalonates 1.82 were replaced with alkylidene ketoamides 1.85 (Scheme 1.16c).\textsuperscript{[49]} Furthermore, they have developed a highly efficient and enantioselective intermolecular Stetter reaction of cinnamaldehyde and nitroalkene 1.78 (Scheme 1.16d).\textsuperscript{[50]} The substrate cinnamaldehyde usually perform the homoenoenate reactivity, but in the presence of bifunctional Brønsted acids such as catechol significantly enhance the Stetter reactivity and chemical yield. Very recently they have identified that a trans fluorination on the catalyst architecture 1.88 induced high levels of enantio-induction in the intermolecular Stetter reaction of aliphatic aldehyde 1.63 and trans-β-nitrostyrene (Scheme 1.16e).\textsuperscript{[51]} Yang’s group developed the NHC-catalyzed non-asymmetric acetaldehyde 1.90 addition to conjugated ketone 1.64 as a mimic method to the enzymatic generation of the acylanion in biological system (Scheme 1.17).\textsuperscript{[52]}

![Scheme 1.18](image)

**Scheme 1.18.** Glorius group’s intermolecular enantioselective Stetter reactions.
Glorious group developed an NHC catalyzed enantioselective amino acid synthesis 1.96 using Stetter reaction technique involving a highly stereoselective proton transfer as the key step (Scheme 1.18).\footnote{53} This reaction is attractive due to the combination of C–C bond formation and an asymmetric protonation between the Breslow intermediate of 1.93 and the Michael acceptor 1.94 using 1.95. Chi group's had disclosed an enantioselective Stetter reaction between enals 1.97 and modified chalcones 1.98 (Scheme 1.19).\footnote{54} The reaction was found to be Stetter reaction of NHC-bound enal acyl anions to the modified chalcones (highly electrophilic). In this case, they optimized the proper choice of catalyst 1.99 and reaction conditions to produce selective Stetter product 1.100 which is similar to Rovis product 1.87 in contrast to the previously reported homoenolate product.\footnote{55} Gravel group, used \( \beta,\gamma \)-unsaturated-\( \alpha \)-ketoesters 1.102 in the intermolecular Stetter reaction furnished 1,2,5-tricarbonyl compound 1.103 in excellent yield and enantioselectivity using catalyst 1.80 (Scheme 1.20).\footnote{56}

Scheme 1.19. Chi group’s intermolecular enantioselective Stetter reactions.

Scheme 1.20. Gravel group’s intermolecular enantioselective Stetter reactions.
1.1.2b. Intramolecular Stetter reaction:

Scheme 1.21. Intramolecular Stetter reaction for chromone synthesis

After the successful discovery of the Stetter reaction, its intramolecular variant opened up access to new classes of compounds. In 1995, Ciganek's reported the first intramolecular Stetter reaction to the synthesis chromone derivative 1.105 using thiazolium catalyst 1.31. Later, Ender, Rovis and Miller developed asymmetric version, which are reviewed in Scheme 1.21. In 1996, Ender's group developed first asymmetric intramolecular Stetter reaction in moderate yield and enantioselectivity using previously described triazole based chiral catalyst 1.16. Later,
Bach’s group applied the same chemistry to his menthal derived thiazolium catalyst $\text{1.107}$ which resulted in good yield and moderate enantioselectivity.$^{[63]}$ Furthermore, Miller and co-worker applied using peptide backbone thiazolium salt $\text{1.44}$, achieving low yield and but reasonably good enantioselectivity. Subsequently, Rovis and co-workers extended the scope of this protocol. The reaction performed at room temperature with a variety of substrates having 1,4-dicarbonyl compounds in good yield and the catalyst loading can be decreased to 3 mol % using indanol $\text{1.110}$ and phenylalanine derived $\text{1.109}$ catalyst without loss of reactivity or enantioselectivity. The substrate scope has been extended to a range of electron-rich and electron-poor aromatic aldehydes. In addition, the incorporation of various tethered Michael acceptors $\text{1.111-1.118}$ that include amides, esters, thioesters, ketones, aldehydes, and nitriles offered good yield and enantioselectivity.

Scheme 1.22. Intramolecular Stetter reaction for cyclopentane synthesis
Rovis group had applied the strategy to the construction of enantioselective five-membered rings using indanol 1.110 and phenylalanine derived 1.109 catalysts, which are reviewed in Scheme 1.22.\textsuperscript{[61,64]} In this regards, both aromatic and aliphatic systems gave good yield and enantioselectivity. Dearomatization of aromatic compounds found to be a useful method for generation of alicyclic synthetic building block. In addition stereoselective process afforded enantio-enriched compounds in rapid fashion. Rovis group further developed, phenol-derived substrate 1.129 and applied asymmetric intramolecular Stetter reactions in very good yields (1.131) and excellent enantio-diastereoselectivity using 1.130 (Scheme 1.23).\textsuperscript{[65]}

![Scheme 1.23](image)

Scheme 1.23. Intramolecular Stetter reaction and desymmetrization of cyclohexadienones

1.1.3. Hydroacylation, aroylation and alkylation Reaction

1.1.3a. Hydroacylation

\[ \text{(1) } \mathrm{R} = \mathrm{H} + \text{C=C} \xrightarrow{\text{Hydroacylation}} \mathrm{R} = \mathrm{C} = \mathrm{H} \]

\[ \text{(2) } \mathrm{R} = \mathrm{H} + \text{O=C} \xrightarrow{\text{Hydroacylation}} \mathrm{R} \xrightarrow{\text{Reduction}} \mathrm{O} = \mathrm{C} = \mathrm{H} \]

Scheme 1.24. General concept of hydroacylation.

The interaction of \( N \)-heterocyclic carbenes with aldehydes to deliver carbonyl anions called \textit{umpolung} which could precisely attack simple C=C or O=C or C≡C leading
to hydroacylation products (Scheme 1.24). In this case, there is no activating group to form product. Scheidt groups, reported the first hydroacylation on O=C which is related to Cannizzaro-type reducing equivalent could control to reduce active ketones \(1.132\) (Scheme 1.25).\(^{66}\) The resulting alcohol \(1.135\) which undergoes an acylation process with the acyl iminium species formed \textit{in situ} in the reaction mixture.

**Scheme 1.25.** Scheidt's first intermolecular hydroacylation of activated ketones.

\[\text{Scheme 1.26.} \text{ Hydroacylation of cyclopropene.}\]

\[\text{Scheme 1.27.} \text{ Hydroacylation of arynes.}\]
Glorius group developed first intermolecular NHC 1.138 catalyzed hydroacylation of aromatic aldehyde 1.136 and electron-neutral olefins such as cyclopropenes 1.137 exploiting their inherent ring strain (Scheme 23).[67] Synthetically valuable acyclcyclopropane 1.139 obtained in good yield and diastereoselectivity through concerted syn hydroacylation pathway. Later he extended this work in enantioselective manner using electron rich triazolium salt 1.140.[68] They also developed hydroacylation of highly reactive aryne intermediates (Scheme 1.27).[69] The reaction was applied to wide variety of aldehydes with the aryne generated in situ from 2-trimethylsilylaryl triflate 1.141 using 1.142.

Scheme 1.28. First intramolecular hydroacylation.

Scheme 1.29. Intramolecular hydroacylation on alkene.

Scheme 1.30. Glorius intramolecular hydroacylation on alkyne
She and co-workers developed the first intramolecular hydroacylation reaction of enol ethers \textbf{1.144} using readily available thiazolium salt \textbf{1.145} led to the formation of benzofuranone \textbf{1.146} in excellent yield through concerted or stepwise formation of an oxonium species (Scheme 1.28).\textsuperscript{[70]} After the findings of She group’s hydroacylation, to obtain benzofuranone, Glorius group reported, various hydroacylation reaction to generate chromones using \textbf{1.142}.\textsuperscript{[71]} NHC-organocatalyzed cyclization of 2-allyloxy benzaldehyde \textbf{1.147} to the corresponding chromanone \textbf{1.148}, \textit{via} the intramolecular hydroacylation of unactivated C=C double bonds in good yield (Scheme 1.29). Subsequently, this methodology was applied to the asymmetric fashion leading to the formation of a quarternary stereocenter in good enatioselective chromanone structure using triazolium based chiral catalyst \textbf{1.149}.\textsuperscript{[72]} In consecutive report, they applied the steric hindered NHC-organocatalyzed hydroacylation of unactivated alkynes \textbf{1.150}, which leads to the formation of \(\alpha,\beta\)-unsaturated chromanone \textbf{1.151} (Scheme 1.30).\textsuperscript{[73]}

\subsection*{1.1.3b. Aroylation}

![Scheme 1.31. Suzuki’s intermolecular hydroaroylation.](image)

Very recently, Suzuki’s group reported, N-heterocyclic carbene (NHC) catalyzed hydroaroylation of 4-nitrofluorobenzenes \textbf{1.152}, fluoro group were replaced by aroyl groups, which generated arylketones \textbf{1.154} using 1,3,4,5-tetramethylimidazol-2-ylidene.
1.153 (Scheme 1.31). In this case, Michael acceptor property of nitro group plays an important role as it forms resonance stabilized aroylcarbocation, which is easily attacked by acylanion nucleophile leading to hydroaroylation product.

### 1.1.3c. Alkylation

![Scheme 1.32](image.png)

**Scheme 1.32.** Scheidt’s intermolecular hydroacylation on O-quinone methides.

![Scheme 1.33](image.png)

**Scheme 1.33.** Deng and Glorius group's intermolecular alkylation.

Scheidt's group reported the combination of the nucleophilic carbonyl anion equivalent (obtained in situ generation from 1.72 reacting tetramethylammonium fluoride) and electrophilic O-quinone methide (obtained in situ generation from 1.155 reacting tetramethylammonium floride) should provide the desired α-aryl ketones 1.156 in a single operation (Scheme 1.32). The main important aspects of this approach are the simultaneous generation of two highly reactive intermediates which leads to indirect benzylation of acylanion. Later Deng and Glorius group applied acylanion addition to benzyl halide 1.157 and diphenylbromomethane 1.160 to obtain the corresponding products.
ketones using \textbf{1.158} and \textbf{1.142} respectively (Scheme 1.33). At the same time, Yadav's group applied the similar chemistry on $\alpha$-bromoketone \textbf{1.163}\textsuperscript{[78]} and Baylis–Hillman bromide \textbf{1.165},\textsuperscript{[79]} to obtain the corresponding ketones (\textbf{1.164} and \textbf{1.166} respectively) using benzimidazolium catalyst \textbf{1.162} (Scheme 1.34). In both cases, the reaction yield is found to be good and it is an elegant method for the synthesis of the 1,3 and 1,4-dicarbonyls.

\begin{scheme}
\begin{center}
\textbf{Scheme 1.34.} Yadav group's intermolecular alkylation.
\end{center}
\end{scheme}

\begin{scheme}
\begin{center}
\textbf{Scheme 1.35.} Scheidt group's hydroacylation on indole.
\end{center}
\end{scheme}
**Scheme 1.36.** You group's hydroacylation on indole.

![Scheme 1.36](image-url)

**Scheme 1.37.** She group's Intramolecular alkylation.

In 2007, Scheidt reported that the reaction of a stoichiometrically generated acyl anion 1.72 with a silyl-protected gramine 1.167 derivative led to the formation of α-(3-indolyl) ketone 1.168 (Scheme 1.35).\(^\text{[75]}\) Later, You's group extended this technique in catalytic and asymmetric version using 3-(1-arylsulfonylalkyl)indole 1.169 to obtain substituted α-(3-indolyl) ketone (Scheme 1.36).\(^\text{[80]}\)

She's group applied intramolecular nucleophilic alkylation to construct benzopyrone and benzofuranone using salicylaldehyde derived compounds 1.171 and 1.172 (Scheme 1.37).\(^\text{[81]}\) If the X group was phenyl 1.171 it formed carbocation which is stabilized by phenolic-oxygen and produced benzofuranone 1.174. If the X group was hydrogen 1.172 benzopyranone 1.175 was formed. In both cases, the reaction condition was similar but different products were obtained.

**1.2 Nucleophilic Carbene in Homoenolate generation and application**

**1.2.1. Annulation reactions**

Homoenolate is a reactive enolate that is produced from β carbon to a carbonyl group or its synthetic equivalent. This kind of homoenolate could be generated from α,β-unsaturated aldehydes using N-heterocyclic carbene (NHC) catalysis which produced new
class of reactions. [82-84] In this case d^3 synthon required electrophile and d^1 synthon requires nucleophile. In most of the cases, the reactions include the use of electrophiles, such as aldehydes, imines, enones, dienones etc. resulting in annulated as well as acyclic products. The pictorial representation of this mechanism is given below (Scheme 1.38).

**Scheme 1.38.** General mechanism for homoenolate reaction reported by Glorius and Bode.

In this case, the nucleophilic carbene II reacts with α,β-unsaturated aldehyde I to form Breslow intermediate which undergoes resonance to form nucleophilic d^3 synthon IV which is trapped by electrophile to form V. At the same time electrophilic d^1 synthon VI was obtained by tautomerization of V. The newly formed active carboxylate undergoes nucleophilic addition to obtain VII, with regeneration of NHC for further catalytic cycle. The intermediate IV acts as the key by utilizing various electrophiles for d^3 synthon and various nucleophiles for d^1 synthon.

The first report on homoenolate based reaction was reported by Glorius[85] and Bode[86] in same time. Based on the general mechanism in Scheme 1.38, Glorius and Bode reported the first stereoselective synthesis of di-substituted γ-butyrolactones via the direct annulations of enal 1.176 and aldehydes (1.93, 1.136) or ketone (1.178) using
imidazolium catalyst 1.177 (Scheme 1.39). In this synthetic study the resulting lactone was obtained in cis fashion through catalytically generated homoenolates and activated carboxylates.

![Scheme 1.39](image)

**Scheme 1.39.** First homoenolate lactone formation reaction by Glorius (left) and Bode (right).

After the successful report by Glorius and Bode, many groups extended this chemistry to explore further homoenolate reaction. Scheme 1.40 summarized the application of homoenolate annulations chemistry. Most of the cases employed cinnamaldehyde 1.176 as the starting material. In this scheme the first reaction is the homocoupling between two cinnamaldehyde molecules to obtain lactone 1.183 using imidazolium catalyst 1.177. Bode extended this chemistry for the formation of azalactone 1.185 by using sulfonimine 1.184. In particular, homoenolates would be excellent Michael donors for electron-deficient carbon–carbon double bonds. Nair group employed enone 1.186 as Michael acceptor for a homoenolate anticipating formation of acyl cyclopentanones but they obtained 3,4-trans-disubstituted-1-aryl cyclopentene 1.187. Mechanistically, the enolate resulting from the addition of homoenolate to the chalcone undergoes an intramolecular aldol reaction followed by decarboxylation to afford cyclopentene 1.187. Later Bode et al. employed this chemistry in an asymmetric variant
Scheme 1.40. Various types of NHC generated-homoenolate reactions.

of the cyclopentene (1.189) synthesis using chiral triazole carbene 1.99.\textsuperscript{[89]} He proposed oxy-cope type rearrangement mechanism to rationalize the enhanced enantioselectivity

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and preferential formation of cis-substituted cyclopentene 1.189.

Both Nair's and Bode's cyclopentannulation reactions of homoenolates were extremely sensitive to the nature of the NHC catalyst, base and solvent. As Bode explained, chiral triazolium (1.99) and imidazolium (1.190) NHCs furnish cyclopentane fused β- and γ-lactones (1.193 and 1.192) respectively using the reaction between cinnamaldehydes and α-hydroxy enones 1.191. Nair's group applied cinnamaldehyde homoenolate to β-nitrostyrenes 1.194 and obtained stereoselectively acyclic γ-nitrocarboxylates 1.196 using imidazolidinium catalyst 1.195. Scheidt’s group employed homoenolate intermediate based formal [3+2] cycloaddition with an 1-acyl-2-aryldiazene 1.197 to afford pyrazolidinones 1.199 as a single regioisomer and stereoisomer using 1.198. Bode also applied this similar annulations chemistry using imines such as 1.200 and 1.202 to obtain annulations products 1.201 and 1.204 respectively using 1.99 in good yields and enantioselectivities based on previously described mechanism. Nair applied this annulations chemistry on 1,2-dicarbonyl compound such as isatin 1.204 and cyclohexanedione 1.205 using imidazolium based catalyst 1.177 to produce annulated products 1.204 and 1.205 respectively. Besides this, Ying and Scheidt obtained β and γ aminoacids (1.208 & 1.210) using nitroso 1.206 and nitrone 1.209 compounds respectively. Apart from this annulations products, Nair and Rovis obtained annulations product 1.212 from α,β-unsaturated conjugated imine 1.202 or in situ generated imine by cinnamaldehyde and tosylamine.

1.2.2. Cooperative Lewis acid\NHC reactions

Scheme 1.40 explains various homoenolate reactions with the stereoselective products using chiral catalyst as a chiral pool. Next people started investigating about the
Scheme 1.41. Various types of homoenolate- transition metal cooperative reactions combination of transition metal Lewis acid and NHC called cooperative catalyst. Scheidt found that Mg and Ti are well tolerant towards NHCs and he developed a few transformations in Scheme 1.41. This reaction was already reported without Lewis acid, and only the stereochemical outcome of the reactions obtained significant efficiency. In first, Mg(Oi-Pr)$_2$ was found to produce good yield and enantioselectivity on [3 + 2] cycloaddition between cinnamaldehyde and hydrazones 1.213 for the formation of azalactone 1.215 using 1.214. Next utilizing Ti(Oi-Pr)$_4$ and an additive i-PrOH to generate cis-isomers 1.216, 1.218, 1.220 as major products with excellent enantioselectivity using 1.64, 1.217 and 1.176 as a annulations partners respectively. In all the cases Lewis acids initial coordination with both hydroxyl-enamine intermediate and coupling partner to the enal which further promotes standard cyclopentane formation reactivities of 1.214 and 1.219.
1.3 Nucleophilic Carbene in enolate generation

![Chemical structure](image)

Scheme 1.42. Reactive species generated from \(\alpha,\beta\)-unsaturated aldehyde.

1.3.1. Six-membered lactone formation

![Chemical structure](image)

Scheme 1.43. Bode and Chi group’s enolate based lactone formation.

![Chemical structure](image)

Scheme 1.44. Intramolecular enolate based lactone formation.

Bode’s group identified that the combination of \(\alpha,\beta\)-unsaturated aldehyde and NHC was found to generate acylanion, homoenolate, enolate and activated carboxylate based on the
catalyst and base (Scheme 1.42). This obtained enolate reacts with various Michael acceptors, for examples 1.221, 1.223 obtained 1.222 and 1.224 using Bode catalyst 1.99 respectively. Scheidt reported a highly diastereo- and enantioselective intramolecular Michael reaction catalyzed by NHC. The addition of the carbene catalyst to an α,β- unsaturated aldehyde 1.225 and subsequent β-protonation generated a reactive enol intermediate which further undergoes Michael reaction to obtained indane fused lactone 1.226 (Scheme 1.44). Studer used this enol intermediate undergo in situ oxidation to obtained Michael acceptor was attacked by external nucleophile 1.228 to obtained another reactive enol intermediate which under-goes subsequent intramolecular Michael reaction to obtained 1.229.

1.4 Nucleophilic carbene in esterifications reaction

The ester moiety represents one of the most important functional groups in chemistry, playing a paramount role in biology and serves as a key intermediate or protecting group in synthetic transformations. NHC also contribute prominent role for ester bond formation reactions such as trans-esterification and Red-ox esterification reactions for aldehydes.

1.4.1. Trans-esterification

![Scheme 1.45. NHC catalyzed trans-esterification.](image)

Nolan group describe the first versatile catalytic method leading to the synthesis of esters 1.233 using N-heterocyclic carbenes (Scheme 1) as nucleophilic catalysts in trans-
esterification reactions.\textsuperscript{[106]}

### 1.4.2. Conversion of aldehyde to ester

![Scheme 1.45](image1.png)

**Scheme 1.45.** Esterification through generation of activated carboxylate.

Bode group developed a new method for the generation of activated carboxylates from epoxyaldehydes \textsuperscript{1.234} or α,β-aziridinylaldehyde \textsuperscript{1.237} using nucleophilic thiazolium carbene and its subsequent esterification using external alcohol nucleophile obtained a new approach for organocatalytic esterification.\textsuperscript{[107]} Rovis have demonstrated a unique synthesis of an enantioselective α-chloroesters \textsuperscript{1.240} based on chiral protonation using \textsuperscript{1.130} from \textsuperscript{1.239} (Scheme 1.46).\textsuperscript{[108]}

![Scheme 1.46](image2.png)

**Scheme 1.46.** Enatioselective esterification through chiral protonation.

![Scheme 1.47](image3.png)

**Scheme 1.47.** Redox esterification.
Zeitler reported a stereoselective, NHC-mediated redox esterification of alkynealdehyde 1.241 under mild condition to obtain (E)-configured, \( \alpha,\beta \)-unsaturated carboxylic ester 1.242 (Scheme 1.47).\(^{[109]}\) This organocatalytic method proceed through the generation of activated carboxylate intermediate which is subsequently attacked by alcohol nucleophile furnish carboxylic esters. Bode group identified a crucial role of base to obtain activated carboxylate to generated ester product 1.243 from cinnamaldehyde (Scheme 1.48).\(^{[110]}\) Mild base such as DIPEA plays an important role for proton shift in order to suppress the homoenolate chemistry and enhance the generation of activated carboxylate.

Scheme 1.48. Generation of activated carboxylate intermediate.

Scheme 1.49. Generation of activated carboxylate through cyclopropane ring open.

Ring-opening reactivity is a very important area for small and strained molecules to obtain the acyclic compounds. NHC open the ring of predetermined stereoisomer's of cyclopropane aldehyde 1.244 to obtain stereoselective product 1.245 (Scheme 1.49).\(^{[111]}\) Direct conversion from alcohol 1.246 to ester 1.248 is an excellent functional group.
conversion method. NHC plays important role for this conversion especially allylic alcohols to esters with manganese (IV) oxide which is an oxidant to convert hydroxy carbinol intermediate to activated carboxylate ester (Scheme 1.50).\(^{112}\)

\[
\text{Ph-CH(OH)-CH=CH}_2 + \text{MnO}_2 \rightarrow \text{Ph-CH\{(\text{O}^\ominus)\text{MeO}\}}
\]

\[
\text{Scheme 1.50. oxidative esterification.}
\]

**1.4.3. Aerobic oxygen based esterification**

An unexpected NHC catalyzed esterification of cinnamaldehydes with reactive cinnamyl bromide in the presence of air or oxygen is a new technique for functional group conversion.\(^{113}\) Oxygen inserted in hydroxyenaminol intermediate which further attacked another molecule of cinnamaldehyde to form dimeric product which gave two molecules of cinnamic acid. This cinnamic acid further underwent alkylation with cinnamyl bromide.
to form ester compound 1.251 (Scheme 1.51). In this reaction, mild amount of water played a key role; it formed acid which initiated to generate activated carboxylate.

1.5. Nucleophilic Carbene in rearrangement reactions

1.5.1 3, 3'-sigmatropic unusual rearrangement

![Scheme 1.52. Unusual 3,3'-sigmatropic rearrangement.](image)

Lupton’s group investigated an unexpected NHC catalyzed rearranged reaction with ester 1.252 in the presence of imidazolium NHC catalyst 1.6 to obtain rearrangement lactone product 1.253 through 3,3-sigmatropic or 1,4-addition mechanistic pathways (Scheme 1.52). This is a new technique for intramolecular six-membered lactone formation.

1.5.2 3,3-sigmatropic Claisen rearrangement

Furthermore, Bode investigated the reaction of alkynealdehyde 1.254 reacts with enol 1.255 to form an ester based on Zeitler report which served as a key intermediate for 3,3'-sigmatropic Claisen rearrangement to obtain cyclic lactone 1.256 (Scheme 1.53). This lactone further underwent trans-esterification with external alcohol to form ring
CHAPTER 1: Introduction: Recent Advancement in N-Heterocyclic Carbene Catalyzed Reactions

opened product 1.257 with good yield and selectivity. The activated carboxylated intermediate can also be generated by oxidation of hydroxyenaminol intermediate generated from cinnamaldehyde using oxidant 1.295. Enamine 1.258 served as a nucleophile to attack the activated carboxylated to form a precursor for aza-Claisen rearrangement, which subsequently underwent 3,3-sigmatropic rearrangement to form aza-Claisen product 1.260 (Scheme 1.54).\textsuperscript{[116]}

Scheme 1.53. 3,3-sigmatropic Claisen rearrangement.

Scheme 1.54. 3,3-sigmatropic aza-Claisen rearrangement.
1.6 Nucleophilic Carbene in total synthesis

1.6.1 Natural products synthesis: Stetter reaction

The use of NHCs as organocatalysts for carbonyl and non-carbonyl umpolung reactions has received enormous interest in total synthesis of natural products or drug intermediates. In 1979 Trost found the first NHCs catalyzed in situ formation of an acyl anion equivalent for an intramolecular Stetter reaction, which was achieved from 1.261 with 2.3 equiv of 1.262 and 50 equiv of triethylamine in refluxing 2-propanol for 5 h to give tricyclic ketone 1.263 (Scheme 1.55). \(^{[117]}\) This tricyclic ketone further underwent consecutive reaction steps to obtain Hirsutic acid C. In 1992, Roth introduced intermolecular Stetter reaction between 1.264 and 4-flurobenzaldehyde using thiazolium catalyst 1.67 to obtain 1.265 in moderate yield which further underwent several steps to obtain the drug CI-981 (Scheme 1.56). \(^{[118]}\) In 1999, Tius employed intermolecular Stetter reaction between 1.266

![Scheme 1.55. Synthesis of Hirsutic Acid C through intramolecular Stetter reaction.](image1.png)

![Scheme 1.56 Synthesis of CI-981 through intermolecular Stetter reaction.](image2.png)
and 1.267 using 1.31 to obtained 1.268 which is further applied to the synthesis of Roseophilin (Scheme 1.57).[^119]

![Scheme 1.57 Synthesis of Roseophilin through intermolecular Stetter reaction.](image)

**Scheme 1.57** Synthesis of Roseophilin through intermolecular Stetter reaction.

In 2004, Grée, applied Stetter reaction in ionic liquid, using 4-flurobenzaldehyde and methyl acrylate with thiazolium salts 1.31 and Et₃N as catalysts (Scheme 1.58).[^120] In these conditions the 4-flurobenzene-4-oxocarboxylic ester 1.269 was isolated in good yield which could not be obtained in classical organic solvents. Furthermore, product 1.269 was employed as a key starting material for the total synthesis of haloperidol. In 2008, Rovis applied enantioselective intramolecular Stetter reaction on 1.270 to obtain 1.271 which is the core product of FD-838 (Scheme 1.59).[^121]

![Scheme 1.58 Synthesis of Haloperidol through intermolecular Stetter reaction in ionic liquid.](image)

**Scheme 1.58** Synthesis of Haloperidol through intermolecular Stetter reaction in ionic liquid.

![Scheme 1.59. Synthesis FD-838 through enantioselective intramolecular Stetter reaction](image)

**Scheme 1.59.** Synthesis FD-838 through enantioselective intramolecular Stetter reaction.

[^119]: "Introduction: Recent Advancement in N-Heterocyclic Carbene Catalyzed Reactions"

[^120]: "Introduction: Recent Advancement in N-Heterocyclic Carbene Catalyzed Reactions"

[^121]: "Introduction: Recent Advancement in N-Heterocyclic Carbene Catalyzed Reactions"
1.6.2 Natural products synthesis: Rearrangement

Scheme 1.60 Synthesis of bakkenolides; Intramolecular homoenoate desymmetrization.

Scheme 1.61 Synthesis of (−)-7-deoxyloganin through rearrangement reaction.

Recently non-carbonyl umpolung reactions have been employed in various reactions which are discussed previously. Scheidt employed the desymmetrization of a 1,3-diketone 1.272 to obtain hydridane core 1.273 using imidazolium based chiral catalyst 1.198, which further applied to the synthesis of bakkenolides I, J and S (Scheme 1.60). Very recently, Lupton applied the 3,3'-sigmatropic rearrangement reaction on 1.274 to obtain enatioselective adduct 1.275 which is further applied to the synthesis of (−)-7-deoxyloganin (Scheme 1.61).
Objective of thesis work:

Nucleophilic carbene (NHC), is a small molecule attracting so many chemists to pursue novel reactions and new type of reactivities. The success of NHC catalysis is attribute to the unique activation mode that always pursue new type of reactivity with notable mechanistic features. The literature review explains not only the first applications of NHC based organocatalytic reactions but also give the reader an impression of how powerful the concept involved is and how it can help to simplify the traditional synthesis of complex organic compounds, natural products and biological active compounds. In addition, it includes mostly the works which are related to the consecutive chapters.

This thesis works mainly includes three different topics including synthesis of chromones based on hydroacylation, $C$–glycosylation based on Stetter reaction and an attempt of total synthesis of Oleuropein based on in situ esterification followed by 3,3-sigmatropic Claisen rearrangement. Final chapter which is not likely related to NHC catalyzed reaction but explains photodynamic activities of porphyrin based $C$–glycoside conjugates which show the practical biological application of $C$–glycosides.
1.7 References


CHAPTER 1: Introduction: Recent Advancement in N-Heterocyclic Carbene Catalyzed Reactions


CHAPTER 1: *Introduction: Recent Advancement in N-Heterocyclic Carbene Catalyzed Reactions*
Introduction


CHAPTER 1: Introduction: Recent Advancement in N-Heterocyclic Carbene Catalyzed Reactions
Introduction


CHAPTER 1: Introduction: Recent Advancement in N-Heterocyclic Carbene Catalyzed Reactions
CHAPTER 2

N-Heterocyclic Carbene Catalyzed Intramolecular Hydroacylation of Nitrile: An Easy Access to 3-Aminochromones

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2.1. Introduction

Chromone is one of the most common heterocyclic motifs found in pharmaceutically active compounds.[1-7] One of the most important sub-families of chromone is 3-aminochromone, whose derivatives show interesting therapeutic effects.[8] From previous research efforts (Figure 2.1), a wide variety of functionalized 3-aminochromone derivatives have been identified to possess anti-inflammatory (T-614) (I),[9,10] antirheumatic (I),[11-15] leukemic B-cells apoptosis (II),[16] and antimutagenic (II) activities.[17] They were found to be effective in the selective inhibition of v-abl tyrosine protein kinase (III).[18] Prolifine (IV) is a 3-aminochromone based natural product containing fused pyridine and chromone structure.[19] On the other hand, Etamicastat (V)(BIA 5-453) is a novel peripherally selective dopamine β-hydroxylase (DBH) inhibitor and used for the treatment of hypertension and congestive heart failure.[20]

![Figure 2.1. 3-aminochromone scaffold](image)

It is evident from prior research that the synthesis of the 3-aminochromone scaffold often suffers lengthy steps, harsh reaction conditions, and absence of diversified substrate scope.[5,21-22] The potential utility of 3-amoimochromones has prompted organic chemists to look for alternatives to replace conventional chromone syntheses. In this context, the N-heterocyclic carbene (NHC) catalyzed carbon-carbon bond formation strategy is, in our opinion, a more attractive and innovative approach. These reactions involve an alternating
acceptor and donor reactivity pattern called umpolung, which develops a new carbon–carbon bond and shortens the conventional synthetic routes in organic synthesis. Thus we felt that this umpolung derived strategy would allow the synthesis of 3-aminochromones in an expeditious manner.

Our synthetic strategy was acquired from the observation of two NHC-catalyzed reactions (Scheme 1): the reaction between two aldehydes (benzoin condensation, Scheme 2.1a)\(^{[23]}\) and between an aldehyde and an imine (aza-benzoin condensation, Scheme 2.1b)\(^{[24]}\). In both cases, Breslow intermediate generated from the aromatic aldehyde effortlessly attack the carbonyl and imine bonds to form new carbon–carbon bond. Based on both reactions one can envision that this umpolung derived reactivity could be applied to the intramolecular carbon–carbon bond formation reaction between aldehyde and nitrile, which would significantly simplify traditional synthetic routes and allow an easy access to diversity-oriented 3-aminochromones (Scheme 2.1c).

\[\text{Scheme 2.1. Blueprint for NHC catalyzed C–C bond formation strategy}\]

2.2. Results and Discussion

Our initial efforts were focused on the systematic evaluation of various catalysts and reaction conditions to optimize the reaction. In order to gauge the performance of the reaction, a simple phenyl (2.1a) was used as a model substrate. The scope of this trans forma-
CHAPTER 2: N-Heterocyclic Carbene-Catalyzed Intramolecular Hydroacylation of Nitrile: An Easy Access to 3-Aminochromones

Table 2.1 Optimization of intramolecular aldehyde-nitrile cross coupling

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Catalyst (equiv)</th>
<th>Base (equiv)</th>
<th>Solvent (0.1 M)</th>
<th>Yield[b] (%)</th>
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<td>DBU (0.10)</td>
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<td>2</td>
<td>B (0.10)</td>
<td>DBU (0.10)</td>
<td>CH₂Cl₂</td>
<td>Trace</td>
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<td>C (0.10)</td>
<td>DBU (0.10)</td>
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</table>

[a] All the reactions were carried out using dry solvents at rt for 24 h. [b] Isolated yields.

- tion was examined using the NHC catalyst precursors (A–F) (Table 2.1, entries 1–6).

Among the tested catalysts, catalyst D was found to be efficient (Entry 4). Use of solvent other than dichloromethane gave diminished yields (Entries 9–12). DBU was found to be the best among the bases tested (Entries 13–15). Finally, the optimized reaction condition was found to be, 0.1 equiv of catalyst D and 0.1 equiv of DBU in dichloromethane at room temperature for 24 h. With this optimized condition, we ensued to scrutinize the scope and
CHAPTER 2: **N-Heterocyclic Carbene-Catalyzed Intramolecular Hydroacylation of Nitrile: An Easy Access to 3-Aminochromones**

**Table 2.2** Reaction scope for 3-aminochromone derivatives.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Cataysl D (10 mol %)</th>
<th>DBU (10 mol %)</th>
<th>CH(_2)Cl(_2)</th>
<th>R(_3)</th>
<th>R(_4)</th>
<th>R(_1)</th>
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</tr>
<tr>
<td>2.30b</td>
<td>[(\text{Ph}_2\text{N}^-\text{BF}_4)]^-</td>
<td>(\text{N}_2)</td>
<td>(\text{N}_2)</td>
<td>85%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{[a]}\)Isolated product yield. \(^{[b]}\)Isolated as acetamide derivative due to unstable nature of amine upon column purification.

generality of the method using a variety of substrates. Our results show that cross coupling could be adapted for various salicylaldehyde derivatives ranging from electron poor to electron rich aromatic rings (Table 2.2). The alkyl substituted aldehydes (2.2b–2.6b) and
employment of fused ring aromatic system exhibited prominently good yields. A variety of methoxy (2.7b–2.10b) and hydroxy substituents (2.11b) also provided excellent yields.

Notably, halo (2.12b–2.18b) and nitro (2.19b and 2.20b) substituents were observed to give excellent yields. Thus, the scope of the reaction is wide, allowing the facile generation of a variety of 3-aminochromones. The high yields of the halo-substituted derivatives prompted us to study the biologically viable fluro-derivatives (2.21b–2.28b). For the fluro-substituted substrate study, results were equally good. Further implementations included the incorporation of methyl, phenyl substituents at R₄ position and the desired products were also produced in good to excellent yields (2.26b–2.30b). The structure of 3-amino-chromone motif was further confirmed by the X-ray crystallography (2.7b, Page no. 88).

**Scheme 2.2. Plausible mechanism**

Based on the results, we propose the reaction mechanism as illustrated above (Scheme 2.2). Presumably, the reaction proceeds through the Breslow intermediate 1 (Step 1), which reacts intramolecularly with the nitrile to give imine 3 (Step 2 & 3) which subsequently tautomerizes to form 3-aminochromone 4 (Step 4). The second step of the mec-
Scheme 2.3. Amine functionalization. Reagent and condition: [a] Table 2.2 conditions followed and proceed to next step [b] 1. Bromoacetyl bromide, Et₃N, 0 °C, CH₂Cl₂, 30 minutes. 2. Piperidine or morpholine, rt, 24h [c] 1. Triphosgene, Et₃N, 0 °C to rt, CH₂Cl₂, 30 minutes. 2. Morpholine, rt, 2 h

Table 2.3 Amine functionalized 3-aminochromone derivatives.
Hydroacylation of Nitrile

-ohanism is crucial since an imine anion intermediate 2 (Step 2) was formed when the mesomeric carbanion 1' from Breslow intermediate 1, attacked the $sp$ carbon of the nitrile. Subsequent proton exchange and NHC elimination results in imine 3, which further tautomerizes to form 3-aminochromone.

3-aminochromones served as a synthetic potential of amine functionalization (Scheme 2.3). After the formation of 3-aminochromone derivatives, further functionalization has been carried out in one pot or from 3-aminochromone derivatives (Table 2.3). Firstly, formation of the amide bond with bromoacetylbromide was achieved using standard amidation technique. Furthermore, the $\alpha$-bromine group was replaced with secondary amines morpholine and piperidine to obtained library of compounds for biological studies. Delightfully, similar morpholine attached chromones are synthesized as carbamate amide using triphosgene.

**Table 2.4.** IC$_{50}$ values for 3-aminochromone derivatives on Raji leukemia cancer cell line.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound numbers</th>
<th>Compounds structure</th>
<th>IC$_{50}$ values$^{[a]}$ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.1c</td>
<td><img src="image" alt="Structure1" /></td>
<td>38.1 ±1.9</td>
</tr>
<tr>
<td>2</td>
<td>2.8c</td>
<td><img src="image" alt="Structure2" /></td>
<td>64.8 ± 2.8</td>
</tr>
<tr>
<td>3</td>
<td>2.15c</td>
<td><img src="image" alt="Structure3" /></td>
<td>87.8 ± 2.9</td>
</tr>
</tbody>
</table>

$^{[a]}$ Biological activities tested on Raji leukemia cancer cell line.
The biological data of active compounds are given above (Table 2.4). In tables 2.2 & 2.3, various 3-aminochromones and amine functionalized compounds were synthesized. The compounds, were tested on various cancer cells including MCF-7 (breast cancer), HCT-116 (colon cancer), Hela (cervical cancer), Jurkat (Thymus lymphocyte cells for acute T cell leukemia) and Raji (Bone lymphocyte cells for acute B cell leukemia). The results indicate that the compounds were active against the Raji cancer cell lines while inactive against the rest of the cancer cells. The compounds with the best IC\textsubscript{50} values are further illustrated in Table 2.4, \textit{i.e.} compounds 2.1c (38.1 ± 1.9 μM), 2.8c (64.8 ± 2.8 μM) and 2.23c (87.8 ± 2.9 μM).

2.3. Conclusion

In conclusion, we have developed a novel method for carbon–carbon bond formation between \(sp^2\) carbon (aldehyde) and \(sp\) carbon (nitrile). This method allows the usage of salicylaldehyde derivatives to assemble a variety of heterocycles at room temperature and good to excellent yields were obtained. The results herein disclose considerable extension of the substrate scope for the synthesis of a wide pool of 3-aminochromones in an expeditious, straightforward, and efficient manner. This methodology is likely to find immediate synthetic applications, given that it is the first example of a carbon-carbon bond formation between aldehyde and nitrile. In addition, we functionalized this molecules and studied the biological activities. Among the tested compounds, we found that compound 2.1c exhibited good activity towards Raji leukemia cells. Summarizing the above, in short, we have successfully developed a new methodology to construct heterocycles using the umpolung strategy \textit{via} NHC and tested their biological activities.
2.4. Experimental Section

General experimental procedures for O-alkylation and their spectral details.\textsuperscript{[25]}

In an oven dried round-bottom flask, under a nitrogen atmosphere, salicylaldehyde (200 mg, 1.63 mmol, 1 equiv) was dissolved in dry DMF (1 mL) and stirred with anhydrous K$_2$CO$_3$ (339 mg, 2.46 mmol, 1.5 equiv) for 15 mins at room temperature. After formation of yellow solid, bromoacetonitrile (230 mg, 133 µL, 1.96 mmol, 1.2 equiv) was added and stirring was continued for 18-24 hr. The progress of the reaction was monitored using TLC. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate (100 mL), washed with water (3x100 mL), brine (2x10 mL), and dried over Na$_2$SO$_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica (Yield 72–93 %).

2-(2-Formylphenoxy)acetonitrile (2.1a): \textsuperscript{[25]}

The title compound was prepared according to the general procedure. The product was obtained as pale yellow solid; (240 mg, 91 % yield); m.p. 82–84 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 10.40 (s, 1H), 7.86 (d, $J = 5.5$ Hz, 1H), 7.60 (d, $J = 4.9$ Hz, 1H), 7.17 (d, $J = 6.3$ Hz, 1H), 7.06 (d, $J = 5.7$ Hz, 1H), 4.92 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 188.6, 158.2, 136.0, 129.4, 125.6, 123.2, 114.5, 112.6, 53.8; FT–IR (KBr): $\nu_{\text{max}}$ 2954, 2350, 1678, 1598, 1284, 1234, 1033, 761 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_9$H$_8$NO$_2$: 162.0555, found: 162.0552.
2-(2-Formyl-6-methylenoxy)acetonitrile (2.2a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (221 mg, 86 % yield); m.p. 75–77 °C; \( ^{1}H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 10.19 (s, 1H), 7.69 (d, \( J = 7.6 \) Hz, 1H), 7.51 (d, \( J = 7.4 \) Hz, 1H), 7.28 (t, \( J = 7.6 \) Hz, 1H), 4.80 (s, 2H), 2.41 (s, 3H); \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 189.8, 156.5, 137.9, 132.7, 130.2, 129.0, 125.9, 115.2, 59.0, 15.9; FT–IR (KBr): \( \nu_{\text{max}} \) 2993, 2005, 1685, 1585, 1467, 1394, 1249, 1190, 1008, 786 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^{+}\): calcd. for C\(_{10}\)H\(_{10}\)NO\(_2\): 176.0712, found: 176.0704.

2-(2, 4-Di-tert-butyl-6-formylphenoxy)acetonitrile (2.3a):

The title compound was prepared according to the general procedure. The product was obtained as pale yellow low melting solid; (207 mg, 89 % yield); m.p. 43–45 °C; \( ^{1}H \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 10.11 (s, 1H), 7.67 (dd, \( J_{1} = 4.7 \) Hz, \( J_{2} = 2.4 \) Hz, 1H), 4.81 (s, 2H), 1.45 (s, 9H), 1.34 (s, 9H); \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)): \( \delta \) 190.5, 155.2, 148.0, 143.4, 131.4, 129.2, 128.4, 115.0, 59.6, 35.5, 34.7, 31.2, 31.0; FT–IR (KBr): \( \nu_{\text{max}} \) 2956, 2326, 1689, 1475, 1363, 1201, 1016 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^{+}\): calcd. for C\(_{17}\)H\(_{24}\)NO\(_2\): 274.1807, found: 274.1808.

2-(1-Formylnaphthalen-2-yloxy)acetonitrile (2.4a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (206 mg, 84 % yield); m.p. 164–166 °C; \( ^{1}H \) NMR (300 MHz, CDCl\(_3\)): \( \delta \) 10.86 (s, 1H), 9.22 (d, \( J = 8.7 \) Hz, 1H), 8.13 (d, \( J = 9.1 \) Hz, 1H), 7.83 (d, \( J = 8.0 \) Hz, 1H), 7.68–7.64 (m, 1H), 7.50 (t, \( J = 7.9 \) Hz, 1H), 7.29 (d, \( J = 9.1 \) Hz, 1H), 5.01 (s, 2H); \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 190.8, 160.0, 137.7, 131.3, 130.3, 129.8, 128.4, 125.9, 125.2, 118.7, 114.4, 112.8, 54.9; FT–IR (KBr): \( \nu_{\text{max}} \) 2887, 2260, 1670, 1512.
1438, 1342, 1155, 1082, 813 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{13}\)H\(_{10}\)NO\(_2\): 212.0712, found: 212.0705.

2-(2-Formyl-4-methylphenoxy)acetonitrile (2.5a):

\[
\text{O} \quad \begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\]

The title compound was prepared according to the general procedure. The product was obtained as white solid; (223 mg, 87% yield); m.p. 79–81 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.34 (s, 1H), 7.62 (s, 1H), 7.37 (dd, \(J_1 = 8.4\) Hz, \(J_2 = 1.4\) Hz, 1H), 6.95 (d, \(J = 8.5\) Hz, 1H), 4.87 (s, 2H), 2.30 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 188.8, 156.4, 136.5, 132.9, 129.4, 125.3, 114.7, 112.9, 54.0, 20.3; FT-IR (KBr): \(\nu_{\text{max}}\) 2875, 2135, 1681, 1496, 1440, 1294, 1041 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{10}\)H\(_{10}\)NO\(_2\): 176.0712, found: 176.0705.

2-(2-Allyl-6-formylphenoxy)acetonitrile (2.6a):

\[
\text{O} \quad \begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\]

The title compound was prepared according to the general procedure. The product was obtained as brown viscous liquid; (210 mg, 85% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 10.19 (s, 1H), 7.74 (d, \(J = 7.6\) Hz, 1H), 7.53 (d, \(J = 7.5\) Hz, 1H), 7.34 (t, \(J = 7.6\) Hz, 1H), 6.01–5.94 (m, 1H), 5.15 (dd, \(J_1 = 10.1\) Hz, \(J_2 = 1.2\) Hz, 1H), 5.08 (dd, \(J_1 = 17.0\) Hz, \(J_2 = 1.4\) Hz, 1H), 4.80 (d, \(J = 0.8\) Hz, 2H), 3.53 (d, \(J = 6.0\) Hz, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 189.7, 156.0, 137.3, 135.8, 134.6, 131.1, 129.1, 126.1, 117.1, 115.0, 59.6, 33.4; FT-IR (KBr): \(\nu_{\text{max}}\) 2864, 2752, 1687, 1585, 1186, 1018, 792 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{12}\)H\(_{12}\)NO\(_2\): 202.0868, found: 202.0867.

2-(2-Formyl-6-methoxyphenoxy)acetonitrile (2.7a):\(^{[25]}\)

\[
\text{O} \quad \begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\]

The title compound was prepared according to the general procedure. The product was obtained as white solid; (233 mg, 93% yield); m.p. 117–119 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.42 (s, 1H), 7.46 (dd, \(J_1 = 7.6\) Hz, \(J_2 = 1.6\) Hz, 1H),
7.27–7.19 (m, 2H), 4.98 (s, 1H), 3.94 (s, 3H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\) 188.9, 152.0, 147.9, 130.0, 125.9, 119.9, 118.1, 115.0, 57.9, 56.1; \(\text{FT}\text{–IR}\) (KBr): \(v_{\text{max}}\) 3003, 2361, 1685, 1583, 1483, 1265, 1064, 999 cm\(^{-1}\); \(\text{HRMS}\) (ESI) m/z \([\text{M+Na}]^+\): calcd. for C\(_{10}\)H\(_9\)NO\(_3\)Na: 214.0480, found: 214.0477.

2-(2-Formyl-5-methoxyphenoxy)acetonitrile (2.8a):\(^{[26]}\)

The title compound was prepared according to the general procedure. The product was obtained as white solid; (206 mg, 82 % yield); \(\text{m.p.}\) 103–105 °C; \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 10.23 (s, 1H), 7.85 (d, \(J = 8.6\) Hz, 1H), 6.68 (dd, \(J_1 = 8.7\) Hz, \(J_2 = 1.9\) Hz, 1H), 6.52 (d, \(J = 2.1\) Hz, 1H), 4.89 (s, 2H), 3.88 (s, 3H); \(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \(\delta\) 187.2, 166.0, 159.9, 131.6, 119.5, 114.3, 107.9, 99.5, 55.9, 53.7; \(\text{FT}\text{–IR}\) (KBr): \(v_{\text{max}}\) 2980, 2063, 1672, 1612, 1450, 1269, 1165, 1120, 858 cm\(^{-1}\); \(\text{HRMS}\) (ESI) m/z \([\text{M+H}]^+\): calcd. for C\(_{10}\)H\(_{10}\)NO\(_3\): 192.0661, found: 192.0657.

Selective TBS protection:

![Selective TBS protection](image)

5-(Tert-butyldimethylsilyloxy)-2-hydroxybenzaldehyde (2.9):

The title compound was prepared by reaction between 2,5-dihydroxy benzaldehyde (1 equiv) and tetrabutyldimethylsilylchloride (TBSCI, 1 equiv). 2,5-dihydroxy benzaldehyde (200 mg, 1.449 mmol, 1 equiv) and imidazole (148 mg, 2.174 mmol, and 1.5 equiv) was dissolved in dry CH\(_2\)Cl\(_2\) and kept in ice bath, TBSCI (217 mg, 1.449 mmol, 1 equiv) was added slowly in small portions over the period of 15 minutes and stir the reaction mixture for another 12 hrs. After completion of the reaction (as judged by thin-layer chromatography, 5% ethyl acetate/hexanes) the reaction mixture was diluted
with CH$_2$Cl$_2$ (100 mL), washed with water (3x100 mL), brine (2x10 mL), and dried over Na$_2$SO$_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (Ethyl acetate/hexane 1:10) to yield 2.9 (295 mg, 81 % yield) as a viscous oil; $^1$H NMR (400 MHz, CDCl$_3$): δ 10.62 (s, 1H), 9.80 (s, 1H), 7.04 (dd, $J_1 = 8.9$ Hz, $J_2 = 2.9$ Hz, 1H), 6.96 (d, $J = 2.9$ Hz, 1H), 6.86 (d, $J = 8.9$ Hz, 1H), 0.98 (s, 9H), 0.18 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 196.1, 156.2, 148.3, 129.9, 122.7, 120.4, 118.4, 25.6, 18.1, –4.498; FT–IR (KBr): $v_{\text{max}}$ 2954, 2856, 1666, 1483, 1271, 1149, 881 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{13}$H$_{21}$O$_3$Si: 253.1260, found: 253.1262.

2-(4-(Tert-butyldimethylsilyloxy)-2-formylphenoxy)acetonitrile (2.9a):

The title compound was prepared according to the general procedure from 2.9. The product was obtained as pale yellow solid; (196 mg, 85 % yield); m.p. 47–48 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 10.34 (s, 1H), 7.31 (d, $J = 3$Hz, 1H), 7.08 (dd, $J_1 = 8.9$ Hz, $J_2 = 3$Hz, 1H), 6.97 (d, $J = 8.9$ Hz, 1H), 4.85 (s, 2H), 0.97 (s, 9H), 0.19 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 188.3, 152.9, 151.6, 127.4, 126.6, 119.4, 114.8, 114.6, 54.8, 25.5, 18.1, –4.5; FT–IR (KBr): $v_{\text{max}}$ 2927, 2079, 1683, 1496, 1280, 1045, 852 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{15}$H$_{22}$NO$_3$Si: 292.1369, found: 292.1360.

2-(2-Formyl-4-methoxyphenoxy)acetonitrile (2.10a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (228 mg, 91 % yield); m.p. 74–76 °C; $^1$H NMR (400 MHz, CDCl$_3$): δ 10.36 (s, 1H), 7.34 (d, $J = 3.1$ Hz, 1H), 7.15 (dd, $J_1 = 9.0$ Hz, $J_2 = 3.2$ Hz, 1H), 7.03 (d, $J = 9.0$ Hz, 1H), 4.86 (s, 2H), 3.80 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 188.4, 155.5, 152.8, 126.5, 123.0, 115.3, 114.8, 111.8, 55.9, 55.1; FT–IR (KBr): $v_{\text{max}}$ 2972, 2393, 1680, 1496, 1313, 1211, 1045 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for

CHAPTER 2: N-Heterocyclic Carbene-Catalyzed Intramolecular Hydroacylation of Nitrile: An Easy Access to 3-Aminochromones
C_{10}H_{10}NO_{3}: 192.0661, found: 192.0656.

**TBS deprotection:**

2-(2-Formyl-4-hydroxyphenoxy)acetonitrile (2.11a):[26]

The title compound was prepared by deprotection of TBS from 9a. To a solution of the corresponding aldehyde (2.9a) (300 mg, 1.030 mmol, 1.0 equiv) in dry THF, Tetrabutyl ammonium Fluoride (350 mg, 1.340 mmol, 1.3 equiv) was added and allowed to stir for 12hrs at room temperature. After completion of the reaction (as judged by thin-layer chromatography, 30 % ethyl acetate/hexanes), the solvent was evaporated and the crude product was diluted with Ethyl acetate (200 mL), washed with water (3x200 ml), brine (2x10 mL), and dried over Na_{2}SO_{4}. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (Ethyl acetate/hexane 30:70) to yield 11a as a white solid; (162 mg, 86 % yield); m.p. 121−123 °C; \(^1\)H NMR (400 MHz, DMSO-\textit{d}_6): \(\delta\) 10.24 (s, 1H), 9.70 (s, 1H), 7.22 (dd, \(J_1 = 6.6\) Hz, \(J_2 = 3.1\) Hz, 1H), 7.14−7.11 (m, 2H), 5.22 (s, 2H); \(^1^3\)C NMR (100 MHz, DMSO-\textit{d}_6): \(\delta\) 189.1, 153.3, 152.2, 126.5, 123.6, 117.1, 116.9, 113.3, 55.8; FT-IR (KBr): \(v_{\text{max}}\) 3454 (−OH), 2993, 2459, 1685, 1496, 1406, 1205, 1041 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^{+}\): calcd. for C_{9}H_{8}NO_{3}: 178.0504, found: 178.0501.

2-(4-Chloro-2-formylphenoxy)acetonitrile (2.12a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (220 mg, 88 % yield); m.p. 95−98°C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.35 (s, 1H), 7.84 (d, \(J = 2.7\) Hz, 1H), 7.57 (dd, \(J_1 = 8.8\) Hz,
\[ J_2 = 2.7 \text{ Hz}, 1H \], 7.04 (d, \( J = 8.9 \text{ Hz}, 1H \)), 4.92 (s, 2H); \(^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \)

187.1, 156.6, 135.4, 129.2, 129.1, 126.6, 114.3, 114.0, 54.1; \(^{\text{FT-IR}}\) (KBr): \( \nu_{\text{max}} \) 2058, 1691, 1591, 1273, 1143, 881 cm\(^{-1}\); \(^{\text{HRMS}}\) (ESI) m/z [M+Na]\(^+\): calcd. for C\(_9\)H\(_6\)NO\(_2\)ClNa: 217.9985, found: 217.9989.

2-(2, 4-Dichloro-6-formylphenoxy)acetonitrile (2.13a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (209 mg, 87% yield); \( \text{m.p.} \) 95–97 °C; \(^{1}\text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta \)

10.27 (s, 1H), 7.76 (d, \( J = 2.3 \text{ Hz}, 1H \)), 7.66 (d, \( J = 2.4 \text{ Hz}, 1H \)), 4.94 (s, 2H); \(^{13}\text{C NMR} \) (125 MHz, CDCl\(_3\)): \( \delta \)

186.5, 153.0, 135.9, 132.6, 131.7, 129.4, 128.1, 114.0, 58.7; \(^{\text{FT-IR}}\) (KBr): \( \nu_{\text{max}} \) 3068, 2403, 1697, 1566, 1448, 1220, 1168, 1002, 748, 657 cm\(^{-1}\); \(^{\text{HRMS}}\) (ESI) m/z [M+H]\(^+\): calcd. for C\(_9\)H\(_6\)NO\(_2\)Cl\(_2\): 229.9776, found: 229.9781.

2-(4-Bromo-2-formylphenoxy)acetonitrile (2.14a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (196 mg, 82% yield); \( \text{m.p.} \) 103–105 °C; \(^{1}\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \)

10.32 (s, 1H), 7.95 (d, \( J = 2.3 \text{ Hz}, 1H \)), 7.70 (dd, \( J = 2.4 \text{ Hz}, 1H \)), 6.98 (d, \( J = 8.8 \text{ Hz}, 1H \)), 4.91 (s, 2H); \(^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \)

187.1, 157.1, 138.4, 132.0, 126.8, 116.3, 114.6, 114.1, 54.0; \(^{\text{FT-IR}}\) (KBr): \( \nu_{\text{max}} \) 2997, 2067, 1681, 1589, 1477, 1276, 1217, 827, 653 cm\(^{-1}\); \(^{\text{HRMS}}\) (ESI) m/z [M+H]\(^+\): calcd. for C\(_9\)H\(_7\)NO\(_2\)Br: 239.9660, found: 239.9659.

2-(2, 4-Dibromo-6-formylphenoxy)acetonitrile (2.15a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (194 mg, 85% yield); \( \text{m.p.} \) 132–134 °C;
\textbf{1H NMR} (400 MHz, CDCl$_3$): $\delta$ 10.27 (s, 1H), 7.98 (dd, $J_1 = 7.0$ Hz, $J_2 = 2.2$ Hz, 2H), 4.94 (s, 2H); \textbf{13C NMR} (100 MHz, CDCl$_3$): $\delta$ 186.5, 154.5, 141.6, 132.1, 132.0, 120.2, 118.7, 114.0, 58.8; \textbf{FT–IR} (KBr): $v_{\text{max}}$ 2870, 2432, 1689, 1573, 1442, 1219, 1149, 1001, 719 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+H]$^+$: calcd. for C$_9$H$_6$NO$_2$Br$_2$: 317.8765, found: 317.8772.

\textbf{2-(2-Formyl-4,6-diiodophenoxy)acetonitrile (2.16a)}:

The title compound was prepared according to the general procedure. The product was obtained as white solid; (174 mg, 79 \% yield); \textbf{m.p.} 89 – 91 °C; \textbf{1H NMR} (400 MHz, CDCl$_3$): $\delta$ 10.16 (s, 1H), 8.38 (d, $J = 2.1$ Hz, 1H), 8.15 (d, $J = 2.1$ Hz, 1H), 4.89 (s, 2H); \textbf{13C NMR} (100 MHz, CDCl$_3$): $\delta$ 186.8, 157.8, 152.9, 139.7, 131.7, 113.9, 93.7, 91.4, 59.1; \textbf{FT–IR} (KBr): $v_{\text{max}}$ 2926, 2304, 1687, 1517, 1271, 640 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+H]$^+$: calcd. for C$_9$H$_6$NO$_2$I$_2$: 413.8488, found: 413.8479.

\textbf{2-(2-Formyl-4-iodo-6-methoxyphenoxy)acetonitrile (2.17a)}:

The title compound was prepared according to the general procedure. The product was obtained as white solid; (178 mg, 78 \% yield); \textbf{m.p.} 120 – 122 °C; \textbf{1H NMR} (500 MHz, CDCl$_3$): $\delta$ 10.29 (s, 1H), 7.77 (d, $J = 1.8$ Hz, 1H), 7.44 (d, $J = 2.1$ Hz, 1H), 4.89 (s, 2H), 3.93 (s, 3H); \textbf{13C NMR} (125 MHz, CDCl$_3$): $\delta$ 187.3, 152.6, 147.8, 131.0, 128.9, 126.8, 114.7, 89.1, 57.8, 56.5; \textbf{FT–IR} (KBr): $v_{\text{max}}$ 3089, 1982, 1685, 1568, 1475, 1301, 1184, 678 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+H]$^+$: calcd. for C$_{10}$H$_9$NO$_3$I: 317.9627, found: 317.9628.

\textbf{2-(2-Bromo-4-chloro-6-formylphenoxy)acetonitrile (2.18a)}:

The title compound was prepared according to the general procedure. The product was obtained as white solid; (212 mg, 91 \% yield); \textbf{m.p.} 127 – 129 °C; \textbf{1H NMR} (400 MHz, CDCl$_3$): $\delta$ 10.27 (s, 1H), 7.84 (dd, $J_1$ =
6.8 Hz, $J_2 = 2.4$ Hz, 2H), 4.94 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 186.6, 154.1, 138.8, 133.0, 131.8, 129.0, 118.4, 113.9, 58.9; FT–IR (KBr): $\nu_{\text{max}}$ 3064, 2430, 1701, 1577, 1446, 1219, 898, 731, 653 cm$^{-1}$; HRMS (ESI) m/z [M+Na]$^+$: calcd. for C$_9$H$_5$NO$_2$NaClBr: 295.9090, found: 295.9094.

2-(2-Formyl-6-methoxy-4-nitrophenoxo)acetonitrile (2.19a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (213 mg, 89 % yield); m.p. 121–123 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.39 (s, 1H), 8.31 (d, $J = 2.5$ Hz, 1H), 8.01 (d, $J = 2.5$ Hz, 1H), 5.12 (s, 2H), 4.06 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 186.7, 152.5, 152.2, 144.9, 129.6, 115.4, 114.3, 112.0, 58.0, 57.0; FT–IR (KBr): $\nu_{\text{max}}$ 3088, 1984, 1693, 1533, 1352, 1222, 1002 cm$^{-1}$; HRMS (ESI) m/z [M+Na]$^+$: calcd. for C$_{10}$H$_8$N$_2$O$_5$Na: 259.0331, found: 259.0327.

2-(2-Formyl-4-nitrophenoxo)acetonitrile (2.20a):

The title compound was prepared according to the general procedure. The product was obtained as pale yellow solid; (204 mg, 83 % yield); m.p. 115–117 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.43 (s, 1H), 8.76 (d, $J = 2.8$ Hz, 1H), 8.52 (d, $J = 2.8$ Hz, 1H), 7.24 (d, $J = 4.6$ Hz, 1H), 5.06 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 186.1, 161.5, 143.3, 130.6, 125.6, 125.2, 113.3, 112.8, 54.0; FT–IR (KBr): $\nu_{\text{max}}$ 3097, 2264, 1687, 1517, 1274, 1028 cm$^{-1}$ HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_9$H$_7$N$_2$O$_4$: 207.0406, found: 207.0400.

2-(2-Fluoro-6-formylphenoxy)acetonitrile (2.21a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (215 mg, 84 % yield); m.p. 81–83 °C; $^1$H
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**NMR** (500 MHz, CDCl₃): δ 10.36 (s, 1H), 7.68 (dd, J₁ = 7.8 Hz, J₂ = 0.8 Hz, 1H), 7.44–7.40 (m, 1H), 7.30–7.26 (m, 1H), 5.01 (s, 2H); **¹³C NMR** (125 MHz, CDCl₃): δ 187.7 (d, J CF = 3.2 Hz), 154.7 (d, J CF = 248.1 Hz), 145.9 (d, J CF = 11 Hz), 130, 125.9 (d, J CF = 7.2 Hz), 124.7 (d, J CF = 3.1 Hz), 123.0 (d, J CF = 18.9 Hz), 114.3, 58.6; **IR** (KBr): v max 3012, 2447, 1685, 1477, 1284, 1022 cm⁻¹; **HRMS** (ESI) m/z [M+H]+: calcd. for C₉H₇NO₂F: 180.0461, found: 180.0466

**2-(5-Fluoro-2-formylphenoxy)acetonitrile (2.22a):**

The title compound was prepared according to the general procedure. The product was obtained as white solid; (225 mg, 88 % yield); m.p. 60–62 °C; **HNMR** (400 MHz, CDCl₃): δ 10.31 (s, 1H), 7.92 (dd, J₁ = 8.7 Hz, J₂ = 6.9 Hz, 1H), 6.89 (dt, J₁ = 8.7 Hz, J₂ = 2.3 Hz, 1H), 6.79 (dd, J₁ = 9.6 Hz, J₂ = 1.8 Hz, 1H), 4.93 (s, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ 187.1, 167.3 (d, J CF = 257.6 Hz), 159.8 (d, J CF = 10.5 Hz), 131.8 (d, J CF = 11.4 Hz), 122.4, 114.0, 110.7 (d, J CF = 21.9 Hz), 101.0 (d, J CF = 25.8 Hz), 54.0; **FT–IR** (KBr): v max 3080, 2436, 1689, 1598, 1271 cm⁻¹; **HRMS** (ESI) m/z [M+H]+: calcd. for C₉H₇NO₂F: 180.0461, found: 180.0457.

**2-(2, 4-Difluoro-6-formylphenoxy)acetonitrile (2.23a):**

The title compound was prepared according to the general procedure. The product was obtained as white solid; (189 mg, 76 % yield); m.p. 62–64 °C; **HNMR** (400 MHz, CDCl₃): δ 10.32 (d, J = 2.9 Hz, 1H), 7.86 (ddd, J₁ = 7.8 Hz, J₂ = 2.8 Hz, J₃ = 1.8 Hz, 1H), 7.22–7.16 (m, 1H), 4.96 (s, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ 186.2, 158.9 (dd, J CF = 249.2 Hz and 10.5 Hz), 156.4 (d, J CF = 11.2 Hz), 153.9 (d, J CF = 11.2 Hz), 131.1 (d, J CF = 7.4 Hz), 114.0, 111.2 (dd, J CF = 27.4 Hz and 22.5 Hz), 110.6 (dd, J CF = 23.4 Hz and 3.5 Hz), 58.9 (d, J CF = 6.4Hz); **FT–IR** (KBr): v max 3089, 2449, 1693, 1477,
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1334, 1205, 993 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_9\)H\(_6\)NO\(_2\)F\(_2\): 198.0367, found: 198.0370.

2-(2-Formyl-4-(trifluoromethoxy)phenoxy)acetonitrile (2.24a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (209 mg, 88 % yield); m.p. 41–44 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.39 (s, 1H), 7.76 (d, \(J = 2.8\) Hz, 1H), 7.49 (dd, \(J_1 = 9.0\) Hz, \(J_2 = 2.9\) Hz, 1H), 4.94 (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 187.0, 156.3, 144.6, 128.4, 126.5, 121.7, 119.0, 114.2, 113.9, 54.2; FT–IR (KBr): \(\nu_{\text{max}}\) 3003, 2077, 1681, 1494, 1261, 1043 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{10}\)H\(_7\)NO\(_3\)F\(_3\): 246.0378, found: 246.0379.

2-(4-Fluoro-2-formylphenoxy)acetonitrile (2.25a):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (222 mg, 87 % yield); m.p. 98–100 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.37 (d, \(J = 2.8\) Hz, 1H), 7.57 (dd, \(J_1 = 8.0\) Hz, \(J_2 = 3.1\) Hz, 1H), 7.35–7.25 (m, 1H), 7.08 (dd, \(J_1 = 9.0\) Hz, \(J_2 = 3.6\) Hz, 1H), 4.91 (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 187.4, 158.3 (d, \(J_{\text{CF}} = 243.8\) Hz), 154.5, 126.8, 122.5 (d, \(J_{\text{CF}} = 24\) Hz), 115.2 (d, \(J_{\text{CF}} = 23.9\) Hz), 114.9 (d, \(J_{\text{CF}} = 7.5\) Hz), 114.3, 54.6; FT–IR (KBr): \(\nu_{\text{max}}\) 3076, 2247, 1683, 1492, 1365, 1261, 1041 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_9\)H\(_7\)NO\(_2\)F: 180.0461, found: 180.0462.

2-(5-Fluoro-2-formylphenoxy)propanenitrile (2.26a):

The title compound was prepared according to the general procedure. Here in place of bromoacetonitrile, 2-bromopropiononitrile was used for O-alkylation. The product was obtained as white solid; (242 mg, 88 % yield); m.p. 93–95 °C;
\( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta \) 10.33 (s, 1H), 7.92 (dd, \( J_1 = 8.2 \) Hz, \( J_2 = 7.0 \) Hz, 1H), 6.91–6.83 (m, 1H), 6.84 (dd, \( J_1 = 9.9 \) Hz, \( J_2 = 2.1 \) Hz, 1H), 4.99 (q, \( J = 6.7 \) Hz, 1H), 1.90 (d, \( J = 6.7 \) Hz, 3H); \( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 187.0, 167.1 (d, \( J_{CF} = 256.6 \) Hz), 159.5 (d, \( J_{CF} = 10.5 \) Hz), 131.5 (d, \( J_{CF} = 10.6 \) Hz), 122.4, 116.9, 110.5 (d, \( J_{CF} = 21.6 \) Hz), 101.9 (d, \( J_{CF} = 26 \) Hz), 62.9, 19.5; \( \text{FT-IR} \) (KBr): \( \nu_{\text{max}} \) 3078, 2330, 1680, 1606, 1276, 993 cm\(^{-1}\); \( \text{HRMS (ESI)} \) m/z [M+H]\(^+\): calcd. for C\(_{10}\)H\(_9\)NO\(_2\)F: 194.0617, found: 194.0611.

2-(2-Fluoro-6-formylphenoxy)propanenitrile (2.27a):

The title compound was prepared according to the general procedure. Here in place of bromoacetonitrile, 2-bromopropiononitrile was used for O-alkylation. The product was obtained colourless viscous liquid; (229 mg, 83% yield); \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 10.37 (s, 1H), 7.68 (d, \( J = 7.8 \) Hz, 1H), 7.44–7.39 (m, 1H), 7.30–7.25 (m, 1H), 5.14 (q, \( J = 6.8 \) Hz, 1H), 1.87 (d, \( J = 6.8 \) Hz, 2H); \( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 187.8 (d, \( J_{CF} = 3.2 \) Hz), 155.1 (d, \( J_{CF} = 248.2 \) Hz), 145.7 (d, \( J_{CF} = 11.2 \) Hz), 130.9, 125.9 (d, \( J_{CF} = 7.3 \) Hz), 124.5 (d, \( J_{CF} = 3.2 \) Hz), 122.8 (d, \( J_{CF} = 19.2 \) Hz), 117.3, 67.9 (d, \( J_{CF} = 6.6 \) Hz), 19.9; \( \text{FT-IR} \) (KBr): \( \nu_{\text{max}} \) 2877, 2360, 1691, 1475, 1247, 1093 cm\(^{-1}\); \( \text{HRMS (ESI)} \) m/z [M+H]\(^+\): calcd. for C\(_{10}\)H\(_9\)NO\(_2\)F: 194.0617, found: 194.0616.

2-(4-Fluoro-2-formylphenoxy)propanenitrile (2.28a):

The title compound was prepared according to the general procedure. Here in place of bromoacetonitrile, 2-bromopropiononitrile was used for O-alkylation. The product was obtained as white solid; (242 mg, 88% yield); \text{m.p.} 97–99 \(^\circ\)C; \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 10.36 (d, \( J = 2.5 \) Hz, 1H), 7.55 (dd, \( J_1 = 8.0 \) Hz, \( J_2 = 2.4 \) Hz, 1H), 7.34–7.29 (m, 1H), 7.13 (dd, \( J_1 = 9.0 \) Hz, \( J_1 = 3.8 \) Hz, 1H), 4.97 (q, \( J = 6.8 \) Hz, 1H), 1.87 (d, \( J = 6.7\)Hz, 3H); \( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 187.5, 158.4 (d, \( J_{CF} = 243.8 \) Hz),
154.3 (d, $J_{CF} = 2.3$ Hz), 127.2 (d, $J_{CF} = 6.1$ Hz), 122.5 (d, $J_{CF} = 24$ Hz), 117.3, 116.4 (d, $J_{CF} = 7.4$ Hz), 115.2 (d, $J_{CF} = 23.6$ Hz), 63.9, 19.7; FT–IR (KBr): $\nu_{max}$ 2877, 2783, 1687, 1487, 1273, 1205, 1051, 732 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{10}$H$_9$NO$_2$: 194.0617, found: 194.0618.

2-(2-Formyl-6-methoxyphenoxy)propanenitrile (2.29a):

The title compound was prepared according to the general procedure. Here in place of bromoacetonitrile, 2-bromopropiononitrile was used for O-alkylation. The product was obtained as colourless viscous liquid; (245 mg, 91 % yield); $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 10.44 (s, 1H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 6.4$ Hz, 1H), 7.20 (t, $J = 7.4$ Hz, 1H), 5.22 (q, $J = 6.8$ Hz, 1H), 3.93 (s, 3H), 1.82 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.1, 152.2, 147.6, 130.2, 125.7, 119.7, 117.9, 66.6, 56.1, 19.9; FT–IR (KBr): $\nu_{max}$ 2856, 2376, 1693, 1585, 1479, 1269 cm$^{-1}$; HRMS (ESI) m/z [M+Na]$^+$: calcd. for C$_{11}$H$_{11}$NO$_3$Na: 228.0637, found: 228.0637.

2-(2-Formyl-6-methoxyphenoxy)-2-phenylacetonitrile (2.30a): The title compound was prepared according to the general procedure. Here in place of bromoacetonitrile, 2-bromo-2-phenylacetonitrile was used for O-alkylation. The product was obtained as white solid; (267 mg, 76 % yield); m.p. 125–127°C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.29 (s, 1H), 7.62 (d, $J = 5.1$ Hz, 2H), 7.47-7.44 (m, 4H), 7.2 (d, $J = 6.6$ Hz, 2H), 6.18 (s, 1H), 3.98 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.0, 152.3, 147.4, 132.5, 130.5, 129.2, 127.8, 125.9, 119.7, 118.0, 116.5, ; FT–IR (KBr): $\nu_{max}$ 2941, 1965, 1697, 1477, 1269, 1062 cm$^{-1}$; HRMS (ESI) m/z [M+Na]$^+$: calcd. For C$_{16}$H$_{13}$NO$_3$Na: 290.0793, found: 290.0793.
General procedure for carbon-carbon bond formation reaction between aldehydes and nitrile and theirs optimization table

Typical general procedure for the intramolecular aldehyde-nitrile cross coupling reaction, as exemplified for the formation of **2.1b**: Precatalyst D (11.55 mg, 0.062 mmol, 0.1 equiv) and 2.1a (100 mg, 0.621 mmol, 1 equiv) was suspended with anhydrous CH2Cl2 (6 mL) in a round bottom flask under argon at room temperature. Next, DBU (9.31 µL, 0.062 mmol, 0.1 equiv) was added via syringe to the reaction mixture and allowed to stir for 18–24 h. Upon 100% conversion of the reaction (as judged by thin-layer chromatography, 30% ethyl acetate/hexanes), the solvent was evaporated and the crude product was purified by flash chromatography on silica gel (Ethyl acetate/hexane 1:3).

**Spectral details of 3-aminochromone derivatives**

**3-Amino-4H-chromen-4-one (2.1b)**: [18]

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (83 mg, 83% yield); **m.p.** 106–108 °C; **1H NMR** (500 MHz, CDCl3): δ 8.26 (d, J = 8 Hz, 1H), 7.78 (s, 1H), 7.63–7.60 (m, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.35 (dd, J1 = 8 Hz, J2 = 7.1 Hz, 1H), 3.64 (brs, 2H, –NH2); **13C NMR** (100 MHz, CDCl3): δ 173.4, 156.0, 137.7, 132.7, 131.4, 125.6, 124.1, 122.0, 118.1; **FT–IR** (KBr): νmax 3392, 3304, 1641, 1469, 1288, 1211 cm⁻¹; **HRMS** (ESI) m/z [M+H]+: calcd. for C9H8NO2: 162.0555, found: 162.0557.
3-Amino-8-methyl-4H-chromen-4-one (2.2b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (81 mg, 81 % yield); m.p. 128–130 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.01 (s, 1H), 7.92 (d, $J = 8.1$ Hz, 1H), 7.55 (d, $J = 7.1$ Hz, 1H), 7.28 (t, $J = 7.4$ Hz, 1H), 4.54 (brs, 2H, $-NH_2$); 2.41 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 173.7, 154.6, 137.7, 133.4, 131.2, 127.5, 123.6, 123.2, 121.8, 15.5; FT–IR (KBr): $\nu_{\text{max}}$ 3415, 3315, 1622, 1571, 1481, 1276, 1211, 1076, 767 cm$^{-1}$; HRMS (ESI)m/z [M+H]$^+$: calcd. for C$_{10}$H$_{10}$NO$_2$: 176.0712, found: 176.0706.

3-Amino-6, 8-di-tert-butyl-4H-chromen-4-one (2.3b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (88 mg, 88 % yield); m.p. 120–122 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.13 (d, $J = 2.0$Hz, 1H), 7.84 (s, 1H), 7.64 (d, $J = 2.0$Hz, 1H), 3.44 (brs, 2H, $-NH_2$), 1.47 (s, 9H), 1.37 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 174.0, 153.3, 146.4, 138.4, 136.8, 130.8, 128.0, 122.2, 119.3, 35.2, 34.9, 31.3, 29.9; FT–IR (KBr): $\nu_{\text{max}}$ 3439, 3331, 2958, 1625, 1556, 1479, 1361, 1278, 1246, 1186 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{17}$H$_{24}$NO$_2$: 274.1807, found: 274.1813.

2-Amino-1H-benzo[f]chromen-1-one (2.4b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (83 mg, 83 % yield); m.p. 125–127 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.02 (d, $J = 8.5$Hz, 1H), 8.18 (d, $J = 9.1$Hz, 1H), 8.07–8.03 (m, 2H), 7.77–7.73 (m, 1H), 7.67–7.61 (m, 1H), 4.66 (brs, 2H, $-NH_2$); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.3, 157.1, 135.0, 134.5, 133.7, 130.7, 130.0, 129.0, 128.1,
127.0, 126.3, 117.9, 114.9; **FT−IR** (KBr): $v_{\text{max}}$ 3417, 3319, 1637, 1620, 1571, 1425, 1242, 1182, 815 cm$^{-1}$; **HRMS** (ESI) m/z [M+H]$^+$: calcd. for C$_{13}$H$_{10}$NO$_2$: 212.0712, found: 212.0713.

**3-Amino-6-methyl-4H-chromen-4-one (2.5b):**

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (85 mg, 85 % yield); **m.p.** 88–90 °C; ¹H NMR (500 MHz, CDCl$_3$): $\delta$ 8.04 (s, 1H), 7.77 (s, 1H), 7.43 (d, $J = 8.5$Hz, 1H), 7.33 (d, $J = 8.5$Hz, 1H), 3.64 (brs, 2H, $\sim$NH$_2$), 2.46 (s, 3H); ¹³C NMR (125 MHz, CDCl$_3$): $\delta$ 173.4, 154.4, 137.8, 134.2, 134.0, 131.2, 124.7, 121.7, 117.9, 20.9; **FT−IR** (KBr): $v_{\text{max}}$ 3381, 3294, 1651, 1485, 1276, 1215, 1170 cm$^{-1}$; **HRMS** (ESI) m/z [M+H]$^+$: calcd. for C$_{10}$H$_{10}$NO$_2$: 176.0712, found: 176.0715.

**N-(8-Allyl-4-oxo-4H-chromen-3-yl)acetamide (2.6b):**

The title compound was prepared according to the general procedure with slight modification. Upon 100 % conversion of the reaction (as judged by thin-layer chromatography, 30 % ethyl acetate/hexanes) according to the general procedure, Et$_3$N (89 µL, 0.646 mmol, 1.3 equiv) and acetyl chloride (48 µL, 0.646 mmol, 1.3 equiv) was added one by one under 0 °C condition. After 15 mints, reaction mixture was allowed to stir at room temperature and reaction progress was monitor by TLC. After completion of the reaction, the reaction mixture was concentrated and diluted with Ethyl acetate (100 mL), washed with water (3x100 ml), brine (2x10 mL), and dried over Na$_2$SO$_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (Ethyl acetate/hexane 1:3) to yield 20b (97 mg, 81 % yield) as a white solid; **m.p.** 153–155 °C; ¹H NMR (400 MHz, CDCl$_3$): $\delta$ 9.40 (s, 1H), 8.17 (s, 1H),
Hydroacylation of Nitrile

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8.10 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)), 7.52 (d, \( J = 7.1 \text{ Hz}, 1\text{H} \)), 7.32 (t, \( J = 7.6 \text{ Hz}, 1\text{H} \)), 6.03–5.93 (m, 1H), 5.12–5.07 (m, 2H), 3.62 (d, \( J = 6.3 \text{ Hz}, 2\text{H} \)), 2.23 (s, 3H); \(^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3): \delta 172.0, 168.8, 153.7, 144.9, 135.0, 134.0, 130.0, 124.6, 124.4, 123.9, 121.9, 117.0, 33.5, 24.0; \( \text{FT-IR} (\text{KBr}): v_{\text{max}} 3328, 1678, 1602, 1583, 1442, 1246, 1165 \text{ cm}^{-1} \); \( \text{HRMS} (\text{ESI}) m/z [\text{M+Na}]^+: \text{calcd. for } C_{14}H_{13}NO_3Na: 266.0793, \text{ found: } 266.0800. \)

3-Amino-8-methoxy-4H-chromen-4-one (2.7b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (92 mg, 92 % yield); \textbf{m.p.} 131–133 °C; \(^1\text{H NMR} (400 \text{ MHz, CDCl}_3): \delta 7.99 (s, 1H), 7.78 (t, \( J = 4.7 \text{ Hz}, 1\text{H} \)), 7.28 (d, \( J = 4.6 \text{ Hz}, 1\text{H} \)), 3.95 (s, 3H), 3.67 (brs, 2H, \(-NH_2\)); \(^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3): \delta 173.2, 148.8, 146.7, 137.5, 131.6, 123.8, 123.0, 116.6, 112.9, 56.3; \( \text{FT-IR} (\text{KBr}): v_{\text{max}} 3452, 3348, 1637, 1566, 1492, 1278, 1068 \text{ cm}^{-1} \); \( \text{HRMS} (\text{ESI}) m/z [\text{M+H}]^+: \text{calcd. for } C_{10}H_{10}NO_3: 192.0661, \text{ found: } 192.0656. \)

3-Amino-7-methoxy-4H-chromen-4-one (2.8b): \(^{[22]}\)

The title compound was prepared according to the general procedure. The product was obtained as pale yellow solid; (95 mg, 95 % yield); \textbf{m.p.} 159–162 °C; \(^1\text{H NMR} (500 \text{ MHz, DMSO-}d_6): \delta 7.98 (d, \( J = 8.9 \text{ Hz}, 1\text{H} \)), 7.89 (s, 1H), 7.02 (d, \( J = 3 \text{ Hz}, 1\text{H} \)), 6.99 (dd, \( J_1 = 8.9 \text{ Hz}, J_2 = 2.3 \text{ Hz}, 1\text{H} \)), 4.48 (brs, 2H, \(-NH_2\)), 3.87 (s, 1H); \(^{13}\text{C NMR} (100 \text{ MHz, DMSO-}d_6): \delta 172.1, 163.2, 157.5, 136.5, 132.5, 126.6, 115.9, 114.5, 100.4, 56.3; \( \text{FT-IR} (\text{KBr}): v_{\text{max}} 3425, 3280, 1627, 1377, 1282, 1176, 1012 \text{ cm}^{-1} \); \( \text{HRMS} (\text{ESI}) m/z [\text{M+H}]^+: \text{calcd. for } C_{10}H_{10}NO_3: 192.0661, \text{ found: } 192.0660. \)
3-Amino-6-(tert-butyldimethylsilyloxy)-4H-chromen-4-one (2.9b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (91 mg, 91 % yield); m.p. 84–86 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.95 (s, 1H), 7.50 (d, $J = 9.1$ Hz, 1H), 7.38 (d, $J = 2.9$ Hz, 1H), 7.23 (dd, $J_1 = 9.1$ Hz, $J_2 = 2.9$ Hz 1H), 4.49 (brs, 2H, –NH$_2$), 0.96 (s, 9H), 0.21 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 173.1, 152.1, 151.3, 137.9, 130.6, 126.8, 122.7, 119.3, 113.3, 25.6, 18.2, –4.4; FT–IR (KBr): $v_{\text{max}}$ 3444, 3340, 2927, 1612, 1550, 1479, 1269, 840 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{15}$H$_{22}$NO$_3$Si: 292.1369, found: 292.1369.

3-Amino-6-methoxy-4H-chromen-4-one (2.10b):[22]

The title compound was prepared according to the general procedure. The product was obtained as pale yellow solid; (89 mg, 89 % yield); m.p. 95–97 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.95 (s, 1H), 7.51 (d, $J = 9.2$ Hz, 1H), 7.41 (d, $J = 9.2$ Hz, $J_2 = 3.0$ Hz, 1H), 4.52 (brs, 2H, –NH$_2$), 3.83 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.1, 156.0, 150.7, 137.1, 132.4, 123.1, 122.3, 120.3, 104.2, 56.0; FT–IR (KBr): $v_{\text{max}}$ 3385, 3265, 1616, 1492, 1273, 1205, 1028, 812 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{10}$H$_{10}$NO$_3$: 192.0661, found: 192.0657.

3-Amino-6-hydroxy-4H-chromen-4-one (2.11b):

The title compound was prepared according to the general procedure. The product was obtained as white solid; (86 mg, 86 % yield); m.p. 218–220 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.81 (s, 1H), 7.91 (s, 1H), 7.42 (d, $J = 9.0$ Hz, 1H), 7.33 (d, $J = 2.3$ Hz, 1H), 7.15 (dd, $J_1 = 9.0$ Hz, $J_2 = 2.4$ Hz, 1H), 4.43 (brs, 2H, –NH$_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 172.2, 154.1, 149.8, 137.2, 132.0, 122.9, 122.6, 120.0, 107.2; FT–IR (KBr): $v_{\text{max}}$ 3327, 3278, 1633, 1579, 1477, 1328, 1197, 792 cm$^{-1}$;
**HRMS** (ESI) m/z [M+H]^+; calcd. for C_{9}H_{8}NO_{3}: 178.0504, found: 178.0504.

3-Amino-6-chloro-4H-chromen-4-one (2.12b):[^22]

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (95 mg, 95 % yield); m.p. 174–176 °C; \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.22 (d, \(J = 2.3\) Hz, 1H), 7.78 (s, 1H), 7.52 (dd, \(J_1 = 8.9\) Hz, \(J_2 = 2.7\) Hz, 1H), 3.67 (brs, 2H, −NH\(_2\)); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 172.3, 154.4, 137.7, 133.1, 131.6, 130.1, 124.9, 122.9, 120.0; FT−IR (KBr): \(v_{\text{max}}\) 3410, 3251, 1628, 1554, 1267, 1176, 815 cm\(^{-1}\); HRMS (ESI) m/z [M+H]^+: calcd. for C_{9}H_{7}NO_{2}: 196.0165, found: 196.0169.

3-Amino-6, 8-dichloro-4H-chromen-4-one (2.13b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (93 mg, 93 % yield); m.p. 179–181 °C; \(^1H\) NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 8.07 (s, 1H), 8.01 (d, \(J = 2.4\) Hz, 1H), 7.94 (d, \(J = 2.4\) Hz, 1H), 4.77 (brs, 2H, −NH\(_2\)); \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 170.9, 149.8, 137.2, 133.5, 132.5, 128.5, 124.0, 123.5, 123.4; FT−IR (KBr): \(v_{\text{max}}\) 3377, 3288, 1647, 1552, 1469, 1247, 1186, 688 cm\(^{-1}\); HRMS (ESI) m/z [M+H]^+: calcd. for C_{9}H_{6}NO_{2}Cl: 229.9776, found: 229.9776.

3-Amino-6-bromo-4H-chromen-4-one (2.14b):[^22]

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (86 mg, 86 % yield); m.p. 162–164 °C; \(^1H\) NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 8.12 (d, \(J = 2.3\)Hz, 1H), 7.97 (s, 1H), 7.80 (d, \(J = 8.7\) Hz, 1H), 7.54 (d, \(J = 9.2\) Hz, 1H), 4.64 (brs, 2H, −NH\(_2\)); \(^{13}C\) NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 171.3, 154.5, 137.4, 135.7, 133.3, 127.3, 123.3, 121.6, 116.8; FT−IR (KBr):
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\( v_{\text{max}} \) 3300, 3080, 1620, 1544, 1462, 1386, 1269, 1205, 112, 607 cm\(^{-1}\); \text{HRMS} (ESI) m/z [M+H]\(^+\): calcd. for C\(_9\)H\(_7\)NO\(_2\)Br: 239.9660, found: 239.9663.

**3-Amino-6, 8-dibromo-4H-chromen-4-one (2.15b):**

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (91 mg, 91 % yield); \text{m.p.} 182–184 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 8.24 (s, 1H), 8.14 (s, 1H), 8.08 (s, 1H), 4.77 (brs, 2H, −NH\(_2\)); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) 170.8, 151.1, 137.9, 137.4, 133.5, 127.2, 123.8, 116.6, 113.4; FT−IR (KBr): \( v_{\text{max}} \) 3379, 3288, 1639, 1581, 1463, 1249, 1184, 802 cm\(^{-1}\); \text{HRMS} (ESI) m/z [M+H]\(^+\): calcd. for C\(_9\)H\(_6\)NO\(_2\)Br: 317.8765, found: 317.8767.

**3-Amino-6, 8-diiodo-4H-chromen-4-one (2.16b):**

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (82 mg, 82 % yield); \text{m.p.} 169–171 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 8.44 (s, 1H), 8.30 (d, \( J = 1.8 \) Hz, 1H), 8.07 (s, 1H), 8.72 (brs, 2H, −NH\(_2\)); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 171.5, 154.2, 149.6, 137.6, 135.0, 131.7, 123.6, 88.0, 86.6; FT−IR (KBr): \( v_{\text{max}} \) 3318, 1656, 1423, 780 cm\(^{-1}\); \text{HRMS} (ESI) m/z [M+H]\(^+\): calcd. for C\(_9\)H\(_6\)NO\(_2\)I\(_2\): 413.8488, found: 413.8486.

**3-Amino-6-iodo-8-methoxy-4H-chromen-4-one (2.17b):**

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (89 mg, 89 % yield); \text{m.p.} 208–210 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 7.99 (s, 1H), 7.87 (d, \( J = 1.6 \) Hz, 1H), 7.48 (d, \( J = 1.4 \) Hz, 1H), 4.63 (brs, 2H, −NH\(_2\)), 3.92 (s, 1H); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)): \( \delta \) 170.8, 149.8, 145.8, 137.0, 133.4, 124.4, 124.0,

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121.5, 88.3, 57.0; **FT–IR** (KBr): \( v_{\text{max}} \) 3396, 3305, 1637, 1560, 1338, 1273, 1074, 692, 572 cm\(^{-1}\); **HRMS** (ESI) m/z [M+H]: calcd. for C\(_{10}\)H\(_9\)NO\(_3\): 317.9627, found: 317.9622.

### 3-Amino-8-bromo-6-chloro-4\(H\)-chromen-4-one (2.18b):

The title compound was prepared according to the general procedure. The product was obtained as pale yellow solid; (93 mg, 93 % yield); **m.p.** 192–194 °C; **\(^1\)H NMR** (400 MHz, DMSO-\(d_6\)): \( \delta \) 8.16 (d, \( J = 2.4 \) Hz, 1H), 8.08 (s, 1H), 8.01 (d, \( J = 2.4 \) Hz, 1H), 4.77 (brs, 2H, \( -\text{NH}_2 \)); **\(^{13}\)C NMR** (100 MHz, DMSO-\(d_6\)): \( \delta \) 171.0, 150.9, 137.4, 135.6, 133.5, 129.0, 124.1, 123.4, 113.3; **FT–IR** (KBr): \( v_{\text{max}} \) 3371, 3290, 1639, 1622, 1585, 1550, 1465, 1247, 767, 715, 680 cm\(^{-1}\); **HRMS** (ESI) m/z [M+H]: calcd. for C\(_9\)H\(_6\)NO\(_2\)ClBr: 273.9270, found: 273.9269.

### 3-Amino-8-methoxy-6-nitro-4\(H\)-chromen-4-one (2.19b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (90 mg, 90 % yield); **m.p.** 185–187 °C; **\(^1\)H NMR** (400 MHz, DMSO-\(d_6\)): \( \delta \) 8.34 (d, \( J = 2.3 \) Hz, 1H), 8.03 (s, 1H), 7.89 (d, \( J = 2.3 \) Hz, 1H), 4.84 (brs, 2H, \( -\text{NH}_2 \)), 4.01 (s, 3H); **\(^{13}\)C NMR** (100 MHz, DMSO-\(d_6\)): \( \delta \) 171.6, 150.2, 149.4, 143.6, 137.0, 134.0, 121.5, 112.5, 106.8, 57.4; **FT–IR** (KBr): \( v_{\text{max}} \) 3454, 3342, 1647, 1620, 1568,1529, 1338, 1251, 1087, 707 cm\(^{-1}\); **HRMS** (ESI) m/z [M+H]: calcd. for C\(_{10}\)H\(_9\)N\(_2\)O\(_5\): 237.0511, found: 237.0509.

### 3-Amino-6-nitro-4\(H\)-chromen-4-one (2.20b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (83 mg, 83 % yield); **m.p.** 169–171 °C; **\(^1\)H NMR** (400 MHz, DMSO-\(d_6\)): \( \delta \) 8.76 (d, \( J = 2.3 \) Hz, 1H), 8.40 (dd, \( J_1 = 9.2 \) Hz, \( J_2 = 2.3 \) Hz, 1H), 8.01 (s, 1H), 7.78 (d, \( J = 9.2 \) Hz, 1H), 4.81 (brs, 2H, \( -\text{NH}_2 \)); **\(^{13}\)C NMR**...
(100 MHz, DMSO-d6): δ 171.8, 158.4, 143.8, 137.3, 133.7, 127.0, 121.9, 121.3, 121.1;

**FT–IR** (KBr): \( v_{\text{max}} \) 3454, 3350, 1645, 1622, 1521, 1471, 1336, 1267, 1103, 837 cm\(^{-1}\);

**HRMS** (ESI) m/z [M+H]: calcd. for C\(_9\)H\(_7\)N\(_2\)O\(_4\): 207.0406, found: 207.0405.

3-Amino-8-fluoro-4H-chromen-4-one (2.21b):

![Chemical structure of 3-Amino-8-fluoro-4H-chromen-4-one](structure.png)

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (83 mg, 83% yield); **m.p.** 164–166 °C; ¹H NMR (500 MHz, CDCl\(_3\)): δ 8.01 (td, \( J_1 \) = 8.1 Hz, \( J_2 \) = 1.3 Hz, 1H), 7.81 (s, 1H), 7.41–7.36 (m, 1H), 7.30–7.25 (m, 1H), 3.69 (brs, 2H, –NH\(_2\)); ¹³C NMR (100 MHz, CDCl\(_3\)): δ 172.5, 151.3 (d, \( J_{\text{CF}} \) = 250.9 Hz), 145.1, 137.2, 131.9, 123.9, 123.6 (d, \( J_{\text{CF}} \) = 6.7 Hz), 120.8 (d, \( J_{\text{CF}} \) = 3.8 Hz), 118.2 (d, \( J_{\text{CF}} \) = 16.2 Hz); ¹⁹F NMR (375 MHz, CDCl\(_3\)) δ −134.2 (dd, \( J_{1(FH)} \) = 10.1 Hz, \( J_{2(FH)} \) = 4.3 Hz, 1F); **FT–IR** (KBr): \( v_{\text{max}} \) 3388, 3305, 1645, 1566, 1492, 1263, 1024 cm\(^{-1}\); **HRMS** (ESI) m/z [M+H]: calcd. for C\(_9\)H\(_7\)NO\(_2\)F: 180.0461, found: 180.0458.

3-Amino-7-fluoro-4H-chromen-4-one (2.22b):

![Chemical structure of 3-Amino-7-fluoro-4H-chromen-4-one](structure.png)

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (87 mg, 87% yield); **m.p.** 172–174 °C; ¹H NMR (400 MHz, CDCl\(_3\)): δ 8.25 (dd, \( J_1 \) = 9.5 Hz, \( J_2 \) = 6.3 Hz, 1H), 7.74 (s, 1H), 7.11–7.07 (m, 2H), 3.64 (brs, 2H, –NH\(_2\)); ¹³C NMR (100 MHz, CDCl\(_3\)): δ 172.6, 165.2 (d, \( J_{\text{CF}} \) = 252.6 Hz), 157.0 (d, \( J_{\text{CF}} \) = 13.3 Hz), 137.6 (d, \( J_{\text{CF}} \) = 2Hz), 131.4, 128.2 (d, \( J_{\text{CF}} \) = 11.1 Hz), 118.9, 113.3 (d, \( J_{\text{CF}} \) = 23.2 Hz), 104.4 (d, \( J_{\text{CF}} \) = 24.9 Hz); ¹⁹F NMR (375 MHz, CDCl\(_3\)) δ −104.0 (dd, \( J_{1(FH)} \) = 15.9 Hz, \( J_{2(FH)} \) = 8.7 Hz, 1F); **FT–IR** (KBr): \( v_{\text{max}} \) 3385, 3352, 1639, 1456, 1261, 1114 cm\(^{-1}\); **HRMS** (ESI) m/z [M+H]: calcd. for C\(_9\)H\(_7\)NO\(_2\)F: 180.0461, found: 180.0459.
3-Amino-6, 8-difluoro-4H-chromen-4-one (2.23b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (81 mg, 81 % yield); m.p. 149–151 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.05 (s, 1H), 7.84–7.78 (m, 1H), 7.57 (dd, $J_1 = 8.5$ Hz, $J_2 = 1.8$ Hz, 1H), 4.73 (brs, 2H, −NH$_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 171.0, 157.3 (dd, $J_{CF} = 242.3$ Hz and 10.5 Hz), 151.6 (dd, $J_{CF} = 252.8$ Hz and 12.4 Hz ), 141.6 (d, $J_{CF} = 11.4$ Hz), 137.1, 133.2, 123.6 (d, $J_{CF} = 8.6$ Hz), 108.7 (dd, $J_{CF} = 29.6$ Hz and 21 Hz), 105.1 (dd, $J_{CF} = 23.3$ Hz and 4.8 Hz); $^{19}$F NMR (375 MHz, CDCl$_3$) $\delta$ –113.1 (dt, $J_{1(FF)} = 7.2$ Hz, $J_{2(FH)} = 4.3$ Hz, 1F), –128.5 (dd, $J_{1(FF)} = 10.1$ Hz, $J_{2(FH)} = 2.9$ Hz, 1F); FT–IR (KBr): $\nu_{max}$ 3379, 3292, 1656, 1573, 1458, 1244, 1006 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_9$H$_6$NO$_2$F$_2$: 198.0367, found: 198.0363.

3-Amino-6-(trifluoromethoxy)-4H-chromen-4-one (2.24b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (88 mg, 88 % yield); m.p. 106–108 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.02 (s, 1H), 7.92 (s, 1H), 7.77–7.71 (m, 2H), 4.67 (brs, 2H, −NH$_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 171.7, 154.0, 144.6, 137.5, 133.1, 126.7, 122.4, 121.8, 116.4; $^{19}$F NMR (375 MHz, CDCl$_3$) $\delta$ –58.1 (s, 3F); FT–IR (KBr): $\nu_{max}$ 3412, 3392, 1633, 1554, 1415, 1219, 1134 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{10}$H$_7$NO$_3$F$_3$: 246.0378, found: 246.0378.

3-Amino-6-fluoro-4H-chromen-4-one (2.25b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (85 mg, 85 % yield); m.p. 184–188 °C; $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.00 (s, 1H), 7.72 (dd, $J_1 = 8.7$ Hz, $J_2 = 2.7$ Hz, 1H), 7.32 (dd, $J_1 = 8.5$ Hz, $J_2 = 1.8$ Hz, 1H), 7.30 (dd, $J_1 = 8.5$ Hz, $J_2 = 1.8$ Hz, 1H), 4.73 (brs, 2H, −NH$_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 171.0, 157.3 (dd, $J_{CF} = 242.3$ Hz and 10.5 Hz), 151.6 (dd, $J_{CF} = 252.8$ Hz and 12.4 Hz ), 141.6 (d, $J_{CF} = 11.4$ Hz), 137.1, 133.2, 123.6 (d, $J_{CF} = 8.6$ Hz), 108.7 (dd, $J_{CF} = 29.6$ Hz and 21 Hz), 105.1 (dd, $J_{CF} = 23.3$ Hz and 4.8 Hz); $^{19}$F NMR (375 MHz, CDCl$_3$) $\delta$ –113.1 (dt, $J_{1(FF)} = 7.2$ Hz, $J_{2(FH)} = 4.3$ Hz, 1F), –128.5 (dd, $J_{1(FF)} = 10.1$ Hz, $J_{2(FH)} = 2.9$ Hz, 1F); FT–IR (KBr): $\nu_{max}$ 3379, 3292, 1656, 1573, 1458, 1244, 1006 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_9$H$_6$NO$_2$F$_2$: 198.0367, found: 198.0363.
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3-Amino-7-fluoro-2-methyl-4H-chromen-4-one (2.26b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (90 mg, 90 % yield); m.p. 151−153 °C; 1H NMR (400 MHz, CDCl3): δ 8.18-8.14 (m, 1H), 7.04–7.00 (m, 2H), 3.48 (brs, 2H, −NH2), 2.36 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 171.9, 164.9 (d, JCF = 251.6 Hz), 156.1 (d, JCF = 13.3 Hz), 147.6, 128.0, 127.8 (d, JCF = 11.9 Hz), 118.3, 113.0 (d, JCF = 23 Hz), 104.0 (d, JCF = 24.8 Hz), 16.3; 19F NMR (375 MHz, CDCl3) δ −117.1 (dt, J1(FH) = 8.6 Hz, J2(FH) = 4.3 Hz, 1F); FT−IR (KBr): vmax 3398, 3387, 1618, 1556, 1487, 1267, 1161 cm−1; HRMS (ESI) m/z [M+H]+: calcd. for C9H7NO2F: 180.0461, found: 180.0460.

3-Amino-8-fluoro-2-methyl-4H-chromen-4-one (2.27b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (81 mg, 81 % yield); m.p. 132−134 °C; 1H NMR (400 MHz, CDCl3): δ 7.95 (d, J = 8.1 Hz, 1H), 7.36–7.31 (m, 1H), 7.29–7.21 (m, 1H), 3.53 (brs, 2H, −NH2), 2.45 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 171.7 (d, JCF = 2.8 Hz), 150.9 (d, JCF = 250.8 Hz), 147.3, 144.1, 144.0, 128.3, 123.4 (d, JCF = 6.4 Hz), 120.6 (d, JCF = 4.2 Hz), 117.7 (d, JCF = 16.6 Hz), 16.3; 19F NMR (375 MHz, CDCl3) δ −134.5 (dd, J1(FH) = 10.7 Hz, J2(FH) = 4.6 Hz, 1F), FT−IR (KBr): vmax 3410, 3329, 1649,
1583, 1271, 1217, 1055 cm⁻¹; **HRMS** (ESI) m/z [M+H]⁺: calcd. for C₁₀H₉NO₂F: 194.0617, found: 194.0618.

3-amino-6-fluoro-2-methyl-4H-chromen-4-one (2.28b):

The title compound was prepared according to the general procedure. The product was obtained as pale yellow solid; (80 mg, 80 % yield); **m.p.** 166–168 °C; **¹H NMR** (400 MHz, DMSO-d₆): δ 7.66 (dd, J₁ = 8.7 Hz, J₂ = 3.0 Hz, 1H), 7.54 (dt, J₁ = 8.1 Hz, J₂ = 3.0 Hz, 1H), 4.41 (brs, 2H, −NH₂), 2.39 (s, 1H); **¹³C NMR** (100 MHz, DMSO-d₆): δ 170.9 (d, J_CF = 2.5 Hz), 158.5 (d, J_CF = 240.9 Hz), 151.4, 147.0, 128.8, 121.9 (d, J_CF = 7.4 Hz), 121.3, 121.0 (d, J_CF = 7 Hz), 109.3 (d, J_CF = 23.2 Hz), 16.7; **¹⁹F NMR** (375 MHz, DMSO-d₆) δ −117.3 (dt, J₁(FH) = 9.2Hz, J₂(FH) = 4.6Hz, 1F); **FT-IR** (KBr): v_max 3410, 3327, 1602, 1473, 1261, 939 cm⁻¹; **HRMS** (ESI) m/z [M+H]⁺: calcd. for C₁₀H₉NO₂F: 194.0617, found: 194.0616.

3-Amino-8-methoxy-2-methyl-4H-chromen-4-one (2.29b):

The title compound was prepared according to the general procedure. The product was obtained as yellow solid; (83 mg, 83 % yield); **m.p.** 173–175 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.67 (d, J = 7.5 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 3.88 (s, 3H), 3.50 (brs, 2H, −NH₂), 2.37 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 172.3, 148.4, 147.4, 145.7, 128.0, 123.5, 122.4, 116.4, 112.5, 56.1, 16.4; **FT-IR** (KBr): v_max 3388, 3309, 1631, 1581, 1448, 1271, 1230, 1099 cm⁻¹; **HRMS** (ESI) m/z [M+H]⁺: calcd. for C₁₁H₁₂NO₃: 206.0817, found: 206.0818.

3-Amino-8-methoxy-2-phenyl-4H-chromen-4-one (2.30b):

The title compound was prepared according to the general procedure. The product was obtained as pale yellow solid; (85 mg, 85 % yield); **m.p.**
124–128 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 7.94 (d, \(J = 8.3\) Hz, 2H), 7.64–7.56 (m, 3H), 7.51–7.49 (m, 1H), 7.34 (d, \(J = 7.2\)Hz, 2H), 4.73 (brs, 2H, −NH\(_2\)), 3.95 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 173.4, 148.9, 146.1, 144.1, 132.8, 129.6, 129.0, 128.2, 127.6, 123.6, 121.9, 116.6, 113.0, 56.2; FT–IR (KBr): \(\nu_{\text{max}}\) 3441, 3309, 1625, 1564, 1496, 1273, 1066 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{16}\)H\(_{14}\)NO\(_3\): 268.0974, found: 268.0976.

**Amine functionalization experimental procedure and spectral details**

2-Morpholino-N-(4-oxo-4H-chromen-3-yl)acetamide (2.1c):

Bromoacetyl bromide (160 mg, 0.80 mmol) was added using syringe to a solution of 2.1b (100 mg, 0.62 mmol) in acetonitrile (5 mL) at 0 °C condition in N\(_2\) atmosphere. After 15 mints the reaction mixture was allowed to stir at room temperature for 12 hrs. After completion of the reaction, (as judged by thin-layer chromatography, 20 % ethyl acetate/hexanes), morpholine (108 mg, 1.24 mmol) was added to the reaction mixture and allow to stir for another 12 h. The reaction was quenched by water (20 mL) and the reaction mixture was diluted with ethyl acetate (100 mL), washed with water (3x100 ml), brine (2x10 mL), and dried over Na\(_2\)SO\(_4\). The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane 1:3) to yield 2.1c (54 mg, 91 % yield) as a white solid; m.p. 150–152 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.80 (s, −NH, 1H), 9.39 (s, 1H), 8.26 (d, \(J = 8.0\) Hz, 1H), 7.72–7.68 (m, 1H), 7.52 (d, \(J = 8.5\) Hz, 1H), 7.42 (t, \(J = 7.8\) Hz, 1H), 3.84 (t, \(J = 4.5\) Hz, 4H), 3.84 (t, \(J = 4.5\) Hz, 4H).
3.19 (s, 1H), 2.63 (t, J = 4.4 Hz, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.9, 168.7, 155.8, 145.1, 133.9, 125.7, 124.9, 124.0, 122.2, 118.5, 67.0, 62.2, 53.8; FT–IR (KBr): $\nu_{\text{max}}$ 3325, 2846, 1627, 1521, 1386, 1220, 1114 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{15}$H$_{17}$N$_2$O$_4$: 289.1188, found: 289.1185.

$N$-(6,8-dichloro-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (2.2c):

The title compound was prepared according to 2.1c. The product was obtained as pale yellow solid; (37 mg, 69 % yield); m.p. 170–172 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.77 (s, 1H), 9.47 (s, 1H), 8.12 (d, J = 2.3 Hz, 1H), 7.75 (d, J = 2.3 Hz, 1H), 3.84 (t, J = 4.4 Hz, 4H), 3.20 (s, 2H), 2.64 (t, J = 4.4 Hz, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.4, 168.9, 150.0, 145.1, 134.0, 130.5, 124.8, 124.3, 123.8, 123.7, 67.0, 62.1, 53.8; FT–IR (KBr): $\nu_{\text{max}}$ 3337, 1694, 1628, 1599, 1495, 1182, 866 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{15}$H$_{15}$N$_2$O$_4$Cl$_2$: 357.0345, found: 357.0342.

$N$-(6-chloro-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (2.3c):

The title compound was prepared according to 2.1c. The product was obtained as pale yellow solid; (32 mg, 65 % yield); m.p. 215–217 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.78 (s, 1H), 9.38 (s, 1H), 8.21 (d, J = 2.5 Hz, 1H), 7.63 (dd, $J_1$ = 9.0Hz, $J_2$ = 2.5 Hz, 1H), 7.48, (d, J = 9.0 Hz, 1H), 3.83 (t, J = 4.5 Hz, 4H), 3.18 (s, 2H), 2.62 (t, J = 4.5 Hz, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 170.9, 168.8, 154.1, 145.2, 134.2, 130.9, 125.0, 124.1, 123.1, 120.3, 67.0, 62.1, 53.8; FT–IR (KBr): $\nu_{\text{max}}$ 3285, 2855, 1685, 1631, 1606, 1531, 1111, 831 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{15}$H$_{16}$N$_2$O$_4$Cl: 323.0715, found: 323.0711.
N-(6-methoxy-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (2.4c):

The title compound was prepared according to 2.1c. The product was obtained as pale yellow solid; (37 mg, 67% yield); m.p. 170–172 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.83 (s, 1H), 9.36 (s, 1H), 7.57 (d, $J$ = 3.0 Hz, 1H), 7.45 (d, $J$ = 9.2 Hz, 1H), 7.29 (dd, $J_1$ = 9.2 Hz, $J_2$ = 3.0 Hz, 1H), 3.89 (s, 1H), 3.84 (t, $J$ = 4.6 Hz, 4H), 3.18 (s, 2H), 2.63 (t, $J$ = 4.6 Hz, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.6, 168.7, 156.7, 150.8, 144.9, 124.5, 123.1, 122.7, 119.9, 104.1, 67.1, 62.1, 55.9, 53.8; FT–IR (KBr): $v_{\text{max}}$ 3278, 2959, 2854, 1680, 1631, 1587, 1491, 1113, 868 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{16}$H$_{19}$N$_2$O$_5$: 319.9294, found: 319.1294.

N-(8-(cyanomethoxy)-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (2.5c):

The title compound was prepared according to 2.1c in one pot reaction after the formation of 3-aminochromone. The product was obtained as pale white solid; (40 mg, 66 %, 28 % yield over 5 steps); m.p. 159–161 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.78 (s, 1H), 9.41 (d, $J$ = 3.5 Hz, 1H), 7.95 (dd, $J_1$ = 6.8 Hz, $J_2$ = 2.8 Hz, 1H), 7.39–7.33 (m, 2H), 4.95 (s, 1H), 3.81 (t, $J$ = 4.6 Hz, 4H), 3.17 (s, 2H), 2.61 (t, $J$ = 4.5 Hz, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.2, 168.8, 146.7, 145.5, 144.6, 124.5, 124.3, 123.6, 119.9, 117.9, 114.2, 66.9, 62.0, 55.0, 53.7; FT–IR (KBr): $v_{\text{max}}$ 3298, 2989, 2843, 1686, 1631, 1582, 1454, 1109, 868 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{17}$H$_{18}$N$_3$O$_5$: 344.1246, found: 344.1244.

N-(7-methoxy-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (2.6c):

The title compound was prepared according to 2.1c. The product was obtained as pale yellow solid; (38 mg, 66 % yield); m.p. 145–147 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.76 (s, 1H), 9.26 (s, 1H), 8.10 (dd,
Hydroacylation of Nitrile

\[ J_1 = 8.9 \text{ Hz}, J_2 = 2.1 \text{ Hz}, 1\text{H} \], 6.96 (dd, \( J_1 = 9.2 \text{ Hz}, J_2 = 2.3 \text{ Hz}, 1\text{H} \), 6.84 (d, \( J = 2.3 \text{ Hz}, 1\text{H} \), 3.88 (d, \( J = 1.8 \text{ Hz}, 3\text{H} \), 3.81 (t, \( J = 3.7 \text{ Hz}, 4\text{H} \), 3.15 (s, 2H), 2.60 (s, 4H); \(^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta 171.1, 168.6, 164.2, 157.6, 144.4, 126.9, 123.6, 116.0, 115.0, 99.9, 66.9, 62.0, 55.7, 53.7 \); \( \text{FT−IR} \) (KBr): \( \nu_{\text{max}} \) 3273, 3132, 2972, 2853, 1672, 1631, 1524, 1440, 1115, 864 cm\(^{-1}\); \( \text{HRMS} \) (ESI) m/z [M+H]\(^+\): calcd. for C\(_{16}\)H\(_{19}\)N\(_2\)O\(_5\): 319.1294, found: 319.1294.

\( N\)-(6-fluoro-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (2.7c):

The title compound was prepared according to 2.1c. The product was obtained as pale yellow solid; (40 mg, 61% yield); m.p. 82–84 °C; \(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta 9.77 \) (s, 1H), 9.39 (s, 1H), 7.87 (dd, \( J_1 = 8.1 \text{ Hz}, J_2 = 3.0 \text{ Hz}, 1\text{H} \), 7.53 (dd, \( J_1 = 9.2 \text{ Hz}, J_2 = 4.2 \text{ Hz}, 1\text{H} \), 7.45–7.40 (m, 1H), 3.83 (t, \( J = 4.5 \text{ Hz}, 4\text{H} \), 3.18 (s, 2H), 2.63 (d, \( J = 4.3 \text{ Hz}, 4\text{H} \); \(^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta 168.8, 160.4, 152.1, 145.3, 123.6, 123.2, 122.6, 122.3, 120.8, 120.7, 110.1, 110.2, 67.0, 62.1, 53.8 \); \( \text{FT−IR} \) (KBr): \( \nu_{\text{max}} \) 3244, 3059, 2961, 2859, 2821, 1690, 1636, 1581, 1485, 1111, 833 cm\(^{-1}\); \( \text{HRMS} \) (ESI) m/z [M+H]\(^+\): calcd. for C\(_{15}\)H\(_{16}\)N\(_2\)O\(_4\)F: 307.1094, found: 307.1093.

\( N\)-(8-methoxy-4-oxo-4H-chromen-3-yl)-2-morpholinoacetamide (2.8c):

The title compound was prepared according to 2.1c. The product was obtained as pale yellow solid; (42 mg, 69% yield); m.p. 145–148 °C; \(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta 9.71 \) (s, 1H), 9.35 (s, 1H), 7.70 (d, \( J = 8.2 \text{ Hz}, 1\text{H} \), 7.24 (t, \( J = 8.0 \text{ Hz}, 1\text{H} \), 7.09 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \), 3.92 (s, 3H), 3.75 (t, \( J = 4.5 \text{ Hz}, 4\text{H} \), 3.10 (s, 2H), 2.55 (t, \( J = 4.3 \text{ Hz}, 4\text{H} \); \(^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta 171.7, 168.7, 148.9, 146.3, 144.8, 124.6, 124.1, 123.1, 116.1, 114.0, 67.0, 62.1, 56.3, 53.8 \); \( \text{FT−IR} \) (KBr): \( \nu_{\text{max}} \) 3307, 1689, 1573, 1392, 1060, 812 cm\(^{-1}\); \( \text{HRMS} \) (ESI) m/z [M+H]\(^+\):
calcd. for $\text{C}_{16}\text{H}_{19}\text{N}_{2}\text{O}_{5}: 319.1294$, found: 319.1296.

**N-(8-methoxy-4-oxo-4H-chromen-3-yl)-2-(piperidin-1-yl)acetamide (2.9c):**

The title compound was prepared according to **2.1c**. The product was obtained as pale yellow solid; (36 mg, 62 % yield); **m.p.** 130–132 °C; $^1\text{H} \text{NMR}$ (400 MHz, CDCl$_3$): $\delta$ 9.94 (s, 1H), 9.43 (s, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.32–7.25 (m, 1H), 7.15 (d, $J = 7.9$ Hz, 1H), 3.98 (s, 3H), 3.09 (s, 2H), 2.52 (s, 4H), 1.70 (p, $J = 5.4$ Hz, 4H), 1.47 (d, $J = 4.7$ Hz, 2H); $^{13}\text{C} \text{NMR}$ (100 MHz, CDCl$_3$): $\delta$ 171.8, 169.9, 148.9, 146.3, 144.8, 124.5, 123.3, 123.3, 116.5, 113.9, 62.5, 56.3, 55.0, 26.2, 23.6; **FT–IR** (KBr): $v_{\text{max}}$ 3298, 2930, 2860, 1686, 1629, 1578, 1491, 1084, 760 cm$^{-1}$; **HRMS** (ESI) m/z [M+H]$^+$: calcd. for $\text{C}_{16}\text{H}_{19}\text{N}_{2}\text{O}_{5}$: 319.1296, found: 319.1296.

**N-(6-chloro-4-oxo-4H-chromen-3-yl)-2-(piperidin-1-yl)acetamide (2.10c):**

The title compound was prepared according to **2.1c**. The product was obtained as pale yellow solid; (35 mg, 60 % yield); **m.p.** 171–173 °C; $^1\text{H} \text{NMR}$ (400 MHz, CDCl$_3$): $\delta$ 9.94 (s, 1H), 9.39 (s, 1H), 8.21 (d, $J = 2.5$ Hz, 1H), 7.62 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.5$ Hz, 1H), 7.47 (d, $J = 9.0$ Hz, 1H), 3.11 (s, 2H), 2.53 (t, $J = 4.7$ Hz, 4H), 1.71 (p, $J = 5.6$ Hz, 4H), 1.49 (d, $J = 5.1$ Hz, 2H); $^{13}\text{C} \text{NMR}$ (100 MHz, CDCl$_3$): $\delta$ 170.8, 170.0, 154.1, 145.1, 134.0, 130.7, 125.0, 124.3, 123.2, 120.2, 62.5, 55.0, 26.2, 23.6; **FT–IR** (KBr): $v_{\text{max}}$ 3289, 2936, 2853, 1686, 1641, 1607, 1529, 1124, 829 cm$^{-1}$; **HRMS** (ESI) m/z [M+H]$^+$: calcd. for $\text{C}_{16}\text{H}_{18}\text{N}_{2}\text{O}_{3}\text{Cl}$: 320.0914, found: 320.0926.

**N-(6-methoxy-4-oxo-4H-chromen-3-yl)-2-(piperidin-1-yl)acetamide (2.11c):**

The title compound was prepared according to **2.1c**. The product was obtained as pale yellow solid; (40 mg, 67 % yield); **m.p.** 169–171 °C; $^1\text{H} \text{NMR}$ (300 MHz, CDCl$_3$): $\delta$ 9.92 (s, 1H), 9.38 (s, 1H), 7.60 (d,
$J = 3.6$ Hz, 1H), 7.43 (d, $J = 9.0$ Hz, 1H), 7.28 (dd, $J_1 = 9.0$ Hz, $J_2 = 3.5$ Hz, 1H), 3.88 (s, 3H), 3.11 (s, 2H), 2.54 (t, $J = 5.8$ Hz, 4H), 1.71 (p, $J = 5.8$ Hz, 4H), 1.51 (d, $J = 4.5$ Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.6, 169.8, 156.6, 150.8, 144.9, 124.4, 123.6, 122.8, 119.9, 104.2, 62.5, 55.8, 55.0, 26.3, 23.7; FT−IR (KBr): $v_{\text{max}}$ 3279, 2932, 2851, 1678, 1611, 1585, 1493, 1099, 818 cm$^{-1}$; HRMS (ESI) m/z [M+H$^+$]: calcd. for C$_{17}$H$_{21}$N$_2$O$_4$: 317.1501, found: 317.1504.

$N$-(8-(cyanomethoxy)-4-oxo-4H-chromen-3-yl)-2-(piperidin-1-yl)acetamide (2.12c):

The title compound was prepared according to 2.1c in one pot reaction after the formation of 3-aminochromone. The product was obtained as pale yellow solid; (23 mg, 67%, 30% yield over 5 steps); m.p. 140–142 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.92 (d, $J = 6.9$ Hz, 1H), 9.41–9.39 (m, 1H), 7.95–7.91 (m, 1H), 7.35–7.31 (m, 1H), 4.95 (d, $J = 1.8$ Hz, 2H), 3.10–3.08 (m, 2H), 2.52 (s, 4H), 1.68 (dd, $J_1 = 10.3$ Hz, $J_2 = 5.6$ Hz, 4H), 1.46 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.2, 169.8, 146.6, 145.5, 144.4, 124.4, 124.3, 123.7, 119.9, 117.8, 114.3, 62.3, 55.0, 54.8, 26.1, 23.5; FT−IR (KBr): $v_{\text{max}}$ 3277, 2926, 2803, 1676, 1618, 1577, 1512, 1125, 752 cm$^{-1}$; HRMS (ESI) m/z [M+H$^+$]: calcd. for C$_{18}$H$_{20}$N$_3$O$_4$: 342.1454, found: 342.1454.

$N$-(6-fluoro-4-oxo-4H-chromen-3-yl)-2-(piperidin-1-yl)acetamide (2.13c):

The title compound was prepared according to 2.1c. The product was obtained as pale yellow solid; (38 mg, 61% yield); m.p. 141–143 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.92 (s, 1H) 9.40 (s, 1H), 7.86 (dd, $J_1 = 8.2$ Hz, $J_2 = 3.0$ Hz, 1H), 7.51 (dd, $J_1 = 9.2$ Hz, $J_2 = 4.2$ Hz, 1H), 7.43–7.38 (m, 1H), 3.10 (s, 2H), 2.53 (s, 4H), 1.70 (p, $J = 5.6$ Hz, 4H), 1.48 (d, $J = 5.1$ Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.2, 170.0, 160.4, 157.9, 152.1, 145.2, 123.8, 123.2, 123.2, 122.4, 122.2, 120.7, 120.6,
110.2, 62.5, 55.0, 26.2, 23.6; \textbf{FT−IR} (KBr): $v_{\text{max}}$ 3294, 2936, 2855, 1692, 1643, 1582, 1483, 1159, 827 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+H]$^+$: calcld. for C$_{16}$H$_{18}$N$_2$O$_3$: 305.1301, found: 305.1302.

\textbf{N-(1-oxo-1H-benzo[f]chromen-2-yl)-2-(piperidin-1-yl)acetamide (2.14c)}: The title compound was prepared according to 2.1c. The product was obtained as pale yellow solid; (43 mg, 65 % yield); \textbf{m.p.} 136–138 °C; \textbf{\textsuperscript{1}H} NMR (400 MHz, CDCl$_3$): $\delta$ 10.07 (s, 1H), 9.96 (t, $J = 7.8$ Hz, 1H), 9.38–9.36 (m, 1H), 7.96–7.94 (m, 1H), 7.72 (t, $J = 6.9$ Hz, 1H), 7.57–7.56 (m, 1H), 7.41–7.40 (m, 1H), 3.13 (d, $J = 2.8$ Hz, 2H), 2.54 (s, 4H), 1.75 (p, $J = 5.5$ Hz, 4H), 1.49 (s, 2H); \textbf{\textsuperscript{13}C} NMR (100 MHz, CDCl$_3$): $\delta$ 172.6, 169.9, 156.9, 142.4, 143.5, 130.4, 130.1, 129.2, 128.2, 126.9, 126.6, 126.1, 117.8, 115.4, 62.7, 55.0, 26.2, 23.7; \textbf{FT−IR} (KBr): $v_{\text{max}}$ 3277, 2932, 2787, 1686, 1633, 1595, 1508, 1010, 827 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+H]$^+$: calcld. for C$_{20}$H$_{21}$N$_2$O$_3$: 337.1552, found: 337.1552.

\textbf{N-(8-methoxy-2-methyl-4-oxo-4H-chromen-3-yl)morpholine-4-carboxamide (2.15c)}:

Triphosgene (142 mg, 0.48 mmol) was added using syringe to a solution of 2.29b (100 mg, 0.48 mmol) in acetonitrile (5 mL) at 0 °C condition in N$_2$ atmosphere. After 15 mints the reaction mixture was allowed to stir at room temperature for 2 hrs. After completion of the reaction, (as judged by thin-layer chromatography, 20 % ethyl acetate/hexanes), morpholine (85 mg, 0.97 mmol) was added to the reaction mixture and allow to stir for another 2 h. The reaction was quenched by water (20 mL) and the reaction
mixture was diluted with ethyl acetate (50 mL), washed with water (3x100 ml), brine (2x10 mL), and dried over Na₂SO₄. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane 1:3) to yield 2.15c as pale white solid; (110 mg, 71 % yield); m.p. 89–91 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, J = 8.1 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 6.84 (s, 1H), 3.97 (s, 3H), 3.72 (t, J = 4.6 Hz, 4H), 3.54 (t, J = 4.6 Hz, 4H), 2.48 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 174.4, 161.5, 155.6, 148.5, 146.1, 124.5, 123.3, 121.4, 116.4, 113.9, 66.5, 56.3, 44.4, 18.7; FT-IR (KBr): ν max 3279, 2933, 2786, 1685, 1632, 1597, 1502, 1167, 1012, 825 cm⁻¹; HRMS (ESI) m/z[M+H]⁺: calcd. for C₁₆H₁₉N₂O₅: 319.1294, found: 319.1286.

N-(7-methoxy-4-oxo-4H-chromen-3-yl)morpholine-4-carboxamide (2.16c):

The title compound was prepared according to 2.15c. The product was obtained as pale yellow solid; (111 mg, 70 % yield); m.p. 102–104 °C; ¹H NMR (400 MHz, CDCl₃): δ 9.07 (s, 1H), 8.13 (d, J = 9.0 Hz, 7.47 (s, 1H), 6.99 (dd, J₁ = 9.0 Hz, J₂ = 2.3 Hz, 1H), 6.87 (d, J = 2.2 Hz), 3.91 (s, 3H), 3.75 (t, J = 4.8 Hz, 4H), 3.52 (t, J = 4.8 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃): δ 171.5, 164.2, 157.6, 154.2, 142.7, 127.0, 124.9, 115.5, 115.0, 99.9, 66.4, 55.8, 44.1; FT-IR (KBr): ν max 3278, 2934, 2788, 1683, 1637, 1599, 1501, 1166, 1015, 828 cm⁻¹; HRMS (ESI) m/z [M+H]⁺: calcd. for C₁₅H₁₇N₂O₅: 305.1137, found: 305.1133.
Crystal structure of 3-amino-8-methoxy-4H-chromen-4-one (2.7b):

Table 2.5 Crystal data and structure refinement for compound 2.7b.

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<th>Value</th>
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<td>Space group</td>
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<td>Unit cell dimensions</td>
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<tr>
<td></td>
<td>b = 15.5384(5) Å, β = 83.205(2)°</td>
</tr>
<tr>
<td></td>
<td>c = 15.8986(6) Å, γ = 81.899(2)°</td>
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<tr>
<td>Volume</td>
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<td>Density (calculated)</td>
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CHAPTER 2: N-Heterocyclic Carbene-Catalyzed Intramolecular Hydroacylation of Nitrile: An Easy Access to 3-Aminochromones

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<th>Independent reflections</th>
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<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
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<td>Max. and min. transmission</td>
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<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
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<td>Data / restraints / parameters</td>
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<td>Goodness-of-fit on F²</td>
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<td>Final R indices [I&gt;2sigma(I)]</td>
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<tr>
<td>R indices (all data)</td>
<td>R₁ = 0.0832, wR₂ = 0.1612</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.386 and -0.349 e.Å⁻³</td>
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</table>

**Biological assay**

**Cell Lines Culture.**

HeLa human cervical carcinoma, MCF-7 human breast carcinoma, HCT-116 human colorectal carcinoma, Jurkat human T-cell acute lymphoblastic leukemia cells and Raji human B-cell acute lymphocyte leukemia cell were purchased from American Type Cell Collection, ATCC (Rockville, MP). Human cancer cell lines including MCF-7, HCT-116 and HeLa were maintained in Dulbecco’s Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin (PS). Jurkat and Raji were cultured in RPMI-1640 (Hyclone, Logan, UT) supplemented with 1% (v/v) PS and 10% (v/v) FBS. All cells were also cultured in humidified 95% O₂/5% CO₂ atmosphere incubator at 37 °C.

**Cell Viability Assays.**

All assays were performed in triplicate. HeLa, MCF-7 and HCT-116 cells were trypsinized and seeded at a density of 5.0 x 10³ per well into 96-well plate and incubated for 24 h. Jurkat & Raji cells were seeded at a density of 10.0 x 10³ per well into 96-well plate.
incubated for 24 h. Cells were treated with 3-aminochromone library which have been prepared as stock solution in DMSO to provide the concentration range of 1 to 1000 µM. After incubating for 24 h, inherent cells with DMEM (Dulbecco’s Modified Eagle Medium) were removed, washed with PBS (Phosphate Buffered Saline) followed by addition of 100 µL of DMEM and 15 µL of MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) while suspension cells were added directly with 15 µL of MTS. Cells were then further incubated until colour change was observed before checking the absorbance at 490 nm.

The absorbance value of control wells without drug was set to 100 % cell viability and from this graphs of absorbance versus cell density per well, cell viability were assessed through graphs of percentage cell viability versus log concentration of test compound added and the IC$_{50}$ values for the various cancer cell line were calculated according to the sigmoidal inhibition curve using software Graphpad prism 5. CellTiter96® Aqueous One Solution Cell Proliferation Assay (MTS) was purchased from Promega Corporation (WI, USA). Absorbance was calculated using the BIO-RAD Benchmark Plus microplate reader spectrophotometer at 490 nm.

2.5. References


CHAPTER 2: N-Heterocyclic Carbene-Catalyzed Intramolecular Hydroacylation of Nitrile: An Easy Access to 3-Aminochromones


CHAPTER 3

N–Heterocyclic Carbene Catalyzed Intramolecular Hydroacylation of Activated Alkynes: Synthesis of Chromones

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3.1. Introduction

Chromones are useful heterocyclic motifs found commonly in pharmaceutical compounds and they often exhibit fascinating therapeutic effects. Our interests in drug discovery motivated us to devise methodologies for the chromone synthesis. In our previous report, we developed an NHC-catalyzed intramolecular cross–coupling between the aldehyde and nitrile function, affording 3-aminochromones in high yields (Scheme 3.1, equiv 1).\(^1\) Comparing this chemistry to that of the Stetter reaction (Scheme 3.1, equiv 2),\(^2\) it attracted us to investigate the possibility of a newly designed carbon-carbon bond forming reaction (Scheme 3.1, equiv 3).

![Scheme 3.1 Blue print for NHC catalyzed C–C bond formation strategy.](image)

3.2. Results and Discussion

To test the feasibility of the above design (Scheme 3.1, equiv. 3), a number of NHC catalysts were screened and the results are summarized in Table 3.1. We began our investigation by using simple phenyl substrate 3.1b as a control variable in order to optimize the reaction conditions. The initial screening was conducted at room temperature for 24 hours with 20 mol\% of imidazolium, triazolium or thiazolium catalysts (A–H).
### Table 3.1 Optimization of reaction conditions.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;[a]&lt;/sup&gt;</th>
<th>Catalyst (equiv)</th>
<th>Base (equiv)</th>
<th>Solvent (0.1 M)</th>
<th>Yield (%)&lt;sup&gt;[b]&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>A (0.2)</td>
<td>DBU (0.2)</td>
<td>DCM</td>
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<td>2</td>
<td>B (0.2)</td>
<td>DBU (0.2)</td>
<td>DCM</td>
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<td>3</td>
<td>C (0.2)</td>
<td>DBU (0.2)</td>
<td>DCM</td>
<td>-</td>
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<tr>
<td><strong>4</strong></td>
<td><strong>D (0.2)</strong></td>
<td><strong>DBU (0.2)</strong></td>
<td>DCM</td>
<td><strong>64</strong></td>
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<tr>
<td>5</td>
<td>E (0.2)</td>
<td>DBU (0.2)</td>
<td>DCM</td>
<td>-</td>
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<tr>
<td>6</td>
<td>F (0.2)</td>
<td>DBU (0.2)</td>
<td>DCM</td>
<td>-</td>
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<tr>
<td>7</td>
<td>G (0.2)</td>
<td>DBU (0.2)</td>
<td>DCM</td>
<td>-</td>
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<td>8</td>
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<td>THF</td>
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<td>DBU (0.2)</td>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CN</td>
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<td><strong>13</strong></td>
<td><strong>D (0.2)</strong></td>
<td><strong>DBU (0.2)</strong></td>
<td>DMF</td>
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<td>14</td>
<td>D (0.2)</td>
<td>DIPEA (0.2)</td>
<td>DMF</td>
<td>78</td>
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<tr>
<td><strong>15</strong></td>
<td><strong>D (0.2)</strong></td>
<td><strong>Et&lt;sub&gt;3&lt;/sub&gt;N (0.2)</strong></td>
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<td><strong>83</strong></td>
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<tr>
<td>16</td>
<td>D (0.2)</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO (0.2)</td>
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<td>17</td>
<td>D (0.2)</td>
<td>KHMDS (0.2)</td>
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</table>

<sup>[a]</sup> Unless otherwise specified, all of the reactions were carried out with freshly distilled dry solvents at room temperature for 24 hrs.  
<sup>[b]</sup> Yield of isolated product.

utilizing 20 mol% of DBU as the base and dichloromethane (0.1 M) as the solvent (Table 3.1, entries 1–8). Thiazolium salt D (Entry 4) afforded the chromones in highest yield (64 %) among the catalyst precursors. Subsequently, the effects of various solvents on the reaction were examined using catalyst D as a control (Entries 9–13). The use of DMF
exhibited a promising yield of 77 % (Entry 13). Using catalyst D and DMF as the solvent, we varied the bases (Entries 14–17) and found that mild bases afforded higher yields than strong bases. Et$_3$N was observed to be the most suitable base (Entry 15). Thus, the optimized condition was established to be as follows: thiazolium salt D as the pre-catalyst, Et$_3$N as the base, DMF as the solvent and stirring at room temperature for 24 hours.

Table 3.2 Reaction scope for chromone derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.1b</td>
<td>3.1c</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>3.2b</td>
<td>3.2c</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>3.3b</td>
<td>3.3c</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>3.4b</td>
<td>3.4c</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>3.5b</td>
<td>3.5c</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>3.6b</td>
<td>3.6c</td>
<td>92</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: D, 20 mol%; Et$_3$N, DMF; 24 h, rt.
We found that the aforementioned optimized conditions are applicable for the vast majority of substrates tested in this chromone-forming Stetter-type hydroacylation reaction. The access to the starting materials, that is, activated alkyne derivatives was developed from corresponding salicylaldehyde derivatives which dramatically expanded the substrate scope (Table 3.2 and Table 3.3). In preliminary efforts, a range of substrates with varied alkyl substituent's on the phenyl group of the salicylaldehyde derivatives afforded good yields (Table 3.2, entries 1–5). While investigating the substrate scope, we extended the study to electron donating substituents and these delivered chromones in
good to excellent yields (80–92%, entries 6–9). Similar extension of the present methodology to electron withdrawing substituents, such as the halides also gave desired chromones in good yields (75–82%, entries 10–12). However, we were not able to synthesize nitro substituted reactants to investigate their reactivity, although current data suggests that variations made to the phenyl motif has minimal impact on this carbon-carbon bond forming reaction. Substituting the two α-hydrogens of the alkyne moiety with two methyl groups also has little impact on the product yield (Table 3.2, entry 13).

As highlighted in Table 3.3, we were pleased to find that the reaction was also suitable for the substrates possessing ketone as the electron withdrawing group such as acetyl, trimethylacetyl, benzoyl and phenylacetyl functionalities, which further broaden the synthetic utility and demonstrate the tolerance of the NHC catalyzed reaction (Table 3.3, entries 1–4). All in all, this new method allows the preparation of a range of chromone derivatives in a straightforward manner. The structure of 3-alkylchromone motif was confirmed by the X-ray crystallography (3.8c, Page no. 126 & 3.15c, Page no. 128).

Table 3.3 Reaction scope of carbonyl Michael acceptors.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>EWG</th>
<th>Product</th>
<th>Yield (%)^[a]</th>
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<td>CH₃CO-</td>
<td>3.14c</td>
<td>74</td>
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<tr>
<td>2</td>
<td>3.15b</td>
<td>t-BuCO-</td>
<td>3.15c</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>3.16b</td>
<td>PhCO-</td>
<td>3.16c</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>3.17b</td>
<td>PhCH₂CO-</td>
<td>3.17c</td>
<td>68</td>
</tr>
</tbody>
</table>

^[a]Yield of isolated product.
With our current synthetic methodology, the success of the reaction mainly relies on the electron withdrawing group of the propargyl moiety. We had attempted to use simple propargyl surrogate, 2-(prop-2-yn-1-yl)oxybenzaldehyde (3.1a)\(^3\) without electron-withdrawing group but it was observed that intermolecular benzoin product instead of the desired hydroacylation product was formed. However, Glorius \(et\ al.\) recently reported hydroacylation reaction using hindered carbene from the same surrogate (3.1a) and salicylaldehyde derived unactivated olefin which might involve Conia-ene-type reaction at higher temperature.\(^4\) In this reaction system, hydroacylation exocylic product undergoes subsequent isomerization forms the aromatized chromone at room temperature. Indeed, several control experiments were carried out with the intermolecular reaction between benzaldehyde and methyl phenylpropiolate or dimethylacetylene dicarboxylate (DMAD) under the optimized condition and the viability of this pathway could not be supported. Apparently, Nair\(^5,6\) and Ma\(^7,8\) demonstrated the intermolecular reaction between activated alkyne (DMAD) and aldehyde using a quantitative amount of imidazolium or thiazolium NHC catalyst to obtain highly functionalized furanone derivatives which highlighted the absence of Stetter type product in the reaction. Based on our system, we infer that both reactive species are in closely proximity to each other, allowing the formation of the Stetter type product instead of other products which results from hydroxy enamine harder oxygen or alkyne as the first reacting species. Significantly, this type of intramolecular hydroacylation reaction allowed us to develop new class of heterocycles at room temperature.

A reasonable mechanism may be formulated as shown in Scheme 3.2. We proposed that the carbene first performs a nucleophilic attack on the electrophilic carbonyl
Scheme 3.2 Plausible reaction mechanism.

carbon of the aldehyde. Subsequent proton transfer results in an acyl anion equivalent (Breslow intermediate) which acts as a nucleophilic carbon to attack the Michael acceptor (activated alkyne) thus forming a carbon-carbon bond. Subsequent proton exchange, followed by elimination of the catalyst, then results in the exo-cyclic kinetic product. This exocyclic hydroacylation product, undergoes isomerization to give the aromatized product, driven by the energetic of the system as previously discussed.

Figure 3.1 Conformational analysis of the exocyclic-Stetter type products (I & II) and stable aromatized product (III).

Our proposed strategy involves the intramolecular reaction of an aldehyde and an activated alkyne (e.g. acetylenic ester) based on our previous work and the DFT calculations, in which aromatized chromones are formed from the less favored exo-cyclic
double bond. The calculated energy profiles\textsuperscript{[10]} (Figure 3.1, DFT, B3LYP/6-31G* level, page no. 129) of the exocyclic Stetter product and the aromatized product show that the exocyclic double bond I is higher in energy (ΔE, 12.8 kcal/mol) than that of the aromatized III, thus providing a driving force for the isomerization to chromone III. Indeed, the exocyclic double bond could be conformation I, because the conformation II is with a higher energy (ΔE, 3.5 kcal/mol) than conformation I.

### 3.3. Conclusion

In conclusion, the present methodology demonstrates the unique reactivity of these catalytically generated nucleophilic precursors and their subsequent Stetter character with activated alkynes. This versatile mechanistic platform can be applied not only to chromone products, but can also be further extended for the use in other novel synthetic methodologies. The catalytic activity of the catalyst D is remarkable especially in view of its low cost and commercial availability. This method also adds to the expanding use of organocatalyst-based heterocyclic synthesis which has been investigated less than its metal-catalyzed counterparts.
3.4. Experimental Section

Starting materials synthesis

General procedure for $O$-alkylation of salicylaldehydes (3.1a-3.12a) and their spectral details (3.1a-3.13a)$^{[3]}$

In an oven dried round-bottom flask, under nitrogen atmosphere, salicylaldehyde (300 mg, 2.46 mmol, 1 equiv) was dissolved in dry DMF (5 mL) and stirred with anhydrous K$_2$CO$_3$ (509 mg, 3.69 mmol, 1.5 equiv) for 15 min. at room temperature. After the formation of yellow solid, propargyl bromide (80% w/w, 467 mg, 3.19 mmol, 1.3 equiv) was added and stirring was continued for 15–24 h. The progress of the reaction was monitored by using TLC. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate (50 mL), washed with water (3×50 mL), brine (2×10 mL), and dried over Na$_2$SO$_4$. The solvent was evaporated and the crude product was purified by flash chromatography on silica (Yield 65–97%).
2-(Prop-2-ynyloxy) benzaldehyde (3.1a)[3]:

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (373 mg, 95 % yield); m.p. 64–66 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.48 (s, 1H), 7.85 (d, \(J = 7.6\) Hz, 1H), 7.58–7.54 (m, 1H), 7.12–7.06 (m, 2H), 4.83 (d, \(J = 2.1\) Hz, 2H), 2.56 (t, \(J = 2.1\) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 189.5, 159.7, 135.7, 128.5, 125.5, 121.6, 113.2, 77.6, 76.5, 56.3; FT–IR (KBr): \(v_{\text{max}}\) 3269, 2870, 2115, 1685, 1595, 1483, 1288, 1222, 1008 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{10}\)H\(_9\)O\(_2\): 161.0603, found: 161.0604.

3-Methyl-2-(prop-2-ynyloxy) benzaldehyde (3.2a)[13]:

The title compound was prepared according to the general procedure. The product was obtained as pale yellow viscous liquid; (360 mg, 94 % yield); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.41 (s, 1H), 7.71–7.69 (m, 1H), 7.45 (d, \(J = 7.4\) Hz, 1H), 7.16 (t, \(J = 7.6\) Hz, 1H), 4.67 (d, \(J = 2.4\) Hz, 2H), 2.52 (t, \(J = 2.4\) Hz, 1H), 2.35 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 190.5, 158.8, 137.4, 132.3, 130.1, 126.4, 124.9, 77.8, 76.6, 62.0, 15.8; FT–IR (KBr): \(v_{\text{max}}\) 3215, 2250, 1678, 1450, 1273, 1072, 708 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{11}\)H\(_{11}\)O\(_2\): 175.0759, found: 175.0753.

2-(Prop-2-ynyloxy)-1-naphthaldehyde (3.3a)[3]:

The title compound was prepared according to the general procedure. The product was obtained as pale orange solid; (355 mg, 97 % yield); m.p. 113–115 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.89 (d, \(J = 0.9\) Hz, 1H), 9.26 (d, \(J = 8.7\) Hz, 1H), 8.06 (dd, \(J_1 = 9.4\) Hz, \(J_2 = 2.1\) Hz, 1H), 7.78 (d, \(J = 8.2\) Hz, 1H), 7.62 (t, \(J = 7.8\) Hz, 1H), 7.44 (t, \(J = 7.5\) Hz, 1H), 7.37 (dd, \(J_1 = 9.4\) Hz, \(J_2 = 2.5\) Hz, 1H), 4.94 (t, \(J = 2.3\) Hz, 2H), 2.56 (t, \(J = 2.5\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 192.0, 161.9, 137.3,
130.0, 129.2, 128.3, 125.3, 125.2, 119.2, 114.0, 77.7, 76.7, 57.4; \textbf{FT-IR} (KBr): $v_{\text{max}}$ 3251, 2891, 2117, 1658, 1514, 1267, 1147, 1055, 804 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+H]$^+$: calcd. for C$_{14}$H$_{11}$O$_2$: 211.0759, found: 211.0754.

\textbf{5-Methyl-2-(prop-2-ynyloxy)benzaldehyde (3.4a)$^{[14]}$:}

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (353 mg, 92 \% yield); \textbf{m.p.} 69–71 °C; \textbf{1H NMR} (300 MHz, CDCl$_3$): $\delta$ 10.44 (s, 1H), 7.64 (d, $J = 2.1$ Hz, 1H), 7.36 (dd, $J_1 = 8.5$ Hz, $J_2 = 2.2$ Hz, 1H), 7.00 (d, $J = 8.5$ Hz, 1H), 4.79 (d, $J = 2.4$ Hz, 2H), 2.54 (t, $J = 2.4$ Hz, 1H), 2.31 (s, 3H); \textbf{13C NMR} (75 MHz, CDCl$_3$): $\delta$ 189.7, 157.8, 136.3, 131.2, 128.5, 125.2, 113.3, 78.2, 76.3, 56.5, 20.3; \textbf{FT-IR} (KBr): $v_{\text{max}}$ 3278, 2877, 2119, 1674, 1490, 1284, 1014, 707 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+H]$^+$: calcd. for C$_{11}$H$_{11}$O$_2$: 175.0759, found: 175.0762.

\textbf{3, 5-Di-tert-butyl-2-(prop-2-ynyloxy)benzaldehyde (3.5a)$^{[3]}$:}

The title compound was prepared according to the general procedure. The product was obtained as pale yellow solid; (317 mg, 91 \% yield); \textbf{m.p.} 79–81 °C; \textbf{1H NMR} (400 MHz, CDCl$_3$): $\delta$ 10.37 (s, 1H), 7.71 (d, $J = 2.4$ Hz, 1H), 7.64 (d, $J = 2.4$ Hz, 1H), 4.63 (d, $J = 2.3$ Hz, 2H), 2.61 (t, $J = 2.3$ Hz, 1H), 1.45 (s, 9H), 1.32 (s, 9H); \textbf{13C NMR} (100 MHz, CDCl$_3$): $\delta$ 190.7, 158.4, 147.0, 143.2, 130.9, 129.5, 124.6, 78.1, 76.7, 65.0, 35.3, 34.7, 31.2, 31.0; \textbf{FT-IR} (KBr): $v_{\text{max}}$ 2958, 2243, 1714, 1469, 1367, 1253, 995 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+H]$^+$: calcd. for C$_{18}$H$_{25}$O$_2$: 273.1855, found: 273.1853.
4-Methoxy-2-(prop-2-ynyloxy)benzaldehyde (3.6a)\(^{[15]}\):

![Image of 4-Methoxy-2-(prop-2-ynyloxy)benzaldehyde](image)

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (356 mg, 95 % yield); m.p. 76–78 °C; \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.29 (s, 1H), 7.83 (dd, \(J_1 = 7.3\) Hz, \(J_2 = 1.8\) Hz, 1H), 6.60 (d, \(J = 2.3\) Hz, 1H), 6.58 (d, \(J = 1.8\) Hz, 1H), 4.79 (d, \(J = 2.3\) Hz, 2H), 3.87 (s, 3H), 2.58 (t, \(J = 2.5\) Hz, 1H); \(^1^3^C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 188.0, 165.8, 161.4, 130.6, 119.4, 106.7, 99.3, 77.5, 76.6, 56.3, 55.6; FT-IR (KBr): \(v_{\text{max}}\) 3230, 2125, 1668, 1604, 1315, 1203, 1111 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{11}\)H\(_{11}\)O\(_3\): 191.0708, found: 191.0706.

5-Methoxy-2-(prop-2-ynyloxy)benzaldehyde (3.7a)\(^{[15]}\):

![Image of 5-Methoxy-2-(prop-2-ynyloxy)benzaldehyde](image)

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (352 mg, 94 % yield); m.p. 84–86 °C; \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.43 (s, 1H), 7.33 (d, \(J = 3.2\) Hz, 1H), 7.13 (dd, \(J_1 = 9.1\) Hz, \(J_2 = 3.2\) Hz, 1H), 7.06 (d, \(J = 9.1\) Hz, 1H), 4.77 (d, \(J = 2.3\) Hz, 2H), 3.79 (s, 3H), 2.53 (t, \(J = 2.3\) Hz, 1H); \(^1^3^C\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 189.4, 154.5, 126.2, 126.0, 123.3, 115.7, 110.4, 78.0, 76.4, 57.4, 55.8; FT-IR (KBr): \(v_{\text{max}}\) 3223, 2864, 2125, 1678, 1496, 1276, 1041, 736 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{11}\)H\(_{11}\)O\(_3\): 191.0708, found: 191.0715.

3-Methoxy-2-(prop-2-ynyloxy)benzaldehyde (3.8a)\(^{[3]}\):

![Image of 3-Methoxy-2-(prop-2-ynyloxy)benzaldehyde](image)

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (359 mg, 96 % yield); m.p. 49–51 °C; \(^1H\) NMR (500 MHz, CDCl\(_3\)): \(\delta\) 10.56 (s, 1H), 7.51–7.49 (m, 2H), 7.23 (d, \(J = 3.6\) Hz, 2H), 4.95 (d, \(J = 2.1\) Hz, 2H), 3.96 (s, 3H), 2.60 (t, \(J = 2.1\) Hz, 1H);
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 190.6, 152.8, 149.4, 131.1, 124.9, 118.8, 117.7, 78.2, 76.7, 60.8, 56.0; FT-IR (KBr): $\nu_{\text{max}}$ 3271, 2937, 2117, 1664, 1583, 1479, 1273, 1066, 912, 785 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{11}$H$_{11}$O$_3$: 191.0708, found: 191.0710.

2, 3-Bis(prop-2-ynyloxy)benzaldehyde (3.9a)$^3$:

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (450 mg, 97 % yield); m.p. 91–93 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.48 (s, 1H), 7.53–7.50 (m, 1H), 7.31–7.28 (m, 1H), 7.22–7.12 (m, 1H), 4.89 (d, $J = 2.3$ Hz, 2H), 4.79 (d, $J = 2.7$Hz, 2H), 2.57 (t, $J = 2.5$ Hz, 1H), 2.49 (t, $J = 1.1$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 190.4, 150.7, 150.1, 131.4, 124.8, 120.2, 120.0, 78.2, 77.7, 77.4, 76.6, 61.2, 56.8; FT-IR (KBr): $\nu_{\text{max}}$ 3252, 3248, 2877, 2119, 1681, 1583, 1479, 1247, 1055, 891, 702 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{13}$H$_{11}$O$_3$: 215.0708, found: 215.0703.

3,5-Dichloro-2-(prop-2-ynyloxy)benzaldehyde (3.10a)$^{14}$:

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (334 mg, 93 % yield); m.p. 85–87 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.38 (s, 1H), 7.76 (d, $J = 2.6$ Hz, 1H), 7.64 (d, $J = 2.6$ Hz, 1H), 4.88 (d, $J = 2.4$ Hz, 2H), 2.55 (t, $J = 2.4$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 188.1, 154.4, 135.5, 132.8, 131.3, 129.7, 126.4, 78.5, 76.7, 61.8; FT-IR (KBr): $\nu_{\text{max}}$ 3253, 3064, 2115, 1689, 1579, 1448, 1213, 972, 655 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{10}$H$_7$O$_2$Cl$_2$: 228.9823, found: 228.9823.

5-Chloro-2-(prop-2-ynyloxy)benzaldehyde (3.11a)$^3$:

The title compound was prepared according to the general procedure. The
product was obtained as pale white solid; (339 mg, 91 % yield); **m.p.** 74–76 °C; **$^1$H NMR** (300 MHz, CDCl$_3$): $\delta$ 10.39 (s, 1H), 7.79 (d, $J = 2.7$ Hz, 1H), 7.50 (dd, $J_1 = 8.9$ Hz, $J_2 = 2.7$ Hz, 1H), 7.08 (d, $J = 8.9$ Hz, 1H), 4.82 (d, $J = 2.4$ Hz, 2H), 2.58 (t, $J = 2.4$ Hz, 1H); **$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 188.1, 158.1, 135.2, 128.0, 127.4, 126.3, 114.9, 77.3, 76.7, 56.7; **FT–IR** (KBr): $\nu_{\text{max}}$ 3240, 2879, 2117, 1678, 1595, 1483, 1273, 1004, 810, 692, 655 cm$^{-1}$; **HRMS** (ESI) m/z [M+H]$^+$: calcd. for C$_{10}$H$_8$O$_2$: 195.0213, found: 195.0213.

**4-Fluoro-2-(prop-2-ynyloxy)benzaldehyde (3.12a):**

![Image]

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (362 mg, 95 % yield); **m.p.** 70–72 °C; **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 10.35 (s, 1H), 7.87 (dd, $J_1 = 8.5$ Hz, $J_2 = 6.9$ Hz, 1H), 6.83 (dd, $J_1 = 10.6$ Hz, $J_2 = 2.1$ Hz, 1H), 6.77 (dt, $J_1 = 8.3$ Hz, $J_2 = 2.1$ Hz, 1H), 4.81 (d, $J = 2.4$ Hz, 2H), 2.61 (t, $J = 2.1$ Hz, 1H); **$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 187.9, 167.3 (d, $J_{CF} = 255.0$ Hz), 161.3 (d, $J_{CF} = 10.9$ Hz), 130.9 (d, $J_{CF} = 11.4$ Hz), 122.1, 109.1 (d, $J_{CF} = 22.2$ Hz), 101.2 (d, $J_{CF} = 26.0$ Hz), 77.3, 76.7, 56.6; **FT-IR** (KBr): $\nu_{\text{max}}$ 3228, 2127, 1678, 1496, 1377, 1276, 1161, 1014, 968 cm$^{-1}$; **HRMS** (ESI) m/z [M+H]$^+$: calcd. for C$_{10}$H$_8$O$_2$F: 179.0508, found: 179.0513.

**2-(2-Methylbut-3-yn-2-yloxy)benzaldehyde (3.13a):**

![Image]

To a solution of 2-methyl-3-butyn-2-ol (1 g, 11.9 mmol, 1 equiv) in anhydrous CH$_3$CN (10 mL) under argon and cooled in an ice-salt bath (~5 °C) was added DBU (2.25 mL, 15.0 mmol, 1.3 equiv). Trifluoroacetic anhydride (2.5 g,
11.9 mmol, 1 equiv) was added over a 25 min. period while keeping the temperature at less than 2 °C. The resulting solution (A) was allowed to stir at 0 °C for additional 30 min. In another round bottom flask, 2-hydroxybenzaldehyde (1.35 g, 10.2 mmol, 0.86 equiv) was dissolved in anhydrous CH$_3$CN (10 mL) and stirred for 5 min. at -5 °C in an ice-salt bath. DBU (2.25 mL, 15.0 mmol, 1.3 equiv) and CuCl$_2$•2H$_2$O (0.16 g, 1.2 mmol, 0.1 equiv) were added and stirred for another 10 min.

The solution of (A), maintained at 0 °C, was added to the 2-hydroxybenzaldehyde solution over a 40 min. period while keeping temperature at 0 °C. After stirring for 5 h at 0 °C, the mixture was concentrated at reduced pressure and the residue was partitioned between ethylacetate (100 mL) and water (3×50 mL). The organic fraction was washed with 1N HCl (50 mL), 1N NaHCO$_3$ (50 mL), and brine (30 mL). After drying (Na$_2$SO$_4$), the solvent was removed at reduced pressure to give 3,13a as viscous pale yellow oil which was further purified by column chromatography. (For checking the TLC, double or triple elution was carried out using hexanes as eluent) (719 mg, 54 % yield); $^1$H NMR (400 MHz, CDCl$_3$): δ 10.43 (s, 1H), 7.85 (d, $J = 7.8$ Hz, 1H), 7.54–7.49 (m, 2H), 7.14–7.11 (m, 1H), 2.61 (s, 1H), 1.72 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 190.2, 158.3, 134.8, 128.7, 128.0, 122.8, 120.7, 84.9, 75.4, 73.8, 29.5; FT-IR (KBr): $v_{\text{max}}$ 2353, 1714, 1697, 1651, 1539, 1482, 1219, 1010 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{12}$H$_{13}$O$_2$: 189.0916, found: 189.0921.
**General procedure for synthesis of activated alkyne and their spectral details (3.1b–3.17b)**

![Chemical reaction diagram]

**Protection of aldehyde functionality: Step 1.** In an oven dried round-bottom flask, salicylaldehyde tethered with the propargyl group (3.1a–3.13a) (300 mg, 1.87 mmol, 1 equiv) was dissolved in dry ethanol (10 mL) under nitrogen atmosphere. Triethyl orthoformate (0.60 mL, 3.20 mmol, 1.7 equiv) and PPTS (5 mg, 0.02 mmol, 0.01 equiv) was added and the resulting solution was refluxed for 1–3 hr. The progress of the reaction was monitored using TLC. Upon completion, reaction mixture was quenched with few drops of Et₃N and concentrated. The oil was diluted in ethyl acetate (50 mL), washed with 10% NaHCO₃ (2×20 mL), followed by brine (2×10 mL) and then dried over Na₂SO₄. The solvent was evaporated, dried under vacuum and the protected salicylaldehyde derivative was used for the next step.

**Introduction of electron withdrawing moiety at terminal alkyne & deprotection of acetal group: Step 2.**

In an oven dried round-bottom flask, under nitrogen atmosphere, the acetal protected salicylaldehyde derivative (3.1a–acetal protected from Step 1) (1.88 mmol, 1 equiv) was dissolved in freshly distilled dry THF (10 mL). The solution was stirred at –78 °C (dry ice-acetone bath) for 10 min., butyllithium (2 M in cyclohexane) (1.40 mL, 2.82 mmol, 1.5 equiv) was slowly added to the flask over 10 min. and stirred for another 30 min. at the same temperature. Ethyl chloroformate (0.30 mL, 3.20 mmol, 1.7 equiv)
was slowly added to the reaction mixture and stir another 30–60 min. The progress of the reaction was monitored using TLC. Upon completion, the reaction mixture was allowed to warm to ambient temperature and quenched with saturated NH₄Cl (20 mL). Then the reaction mixture was diluted with ethyl acetate (50 mL), washed with water (3×50 mL), followed by brine (2×10 mL), and then dried over Na₂SO₄. The solvent was evaporated and the crude product was dissolved in CHCl₃ (20 mL), then water (10 mL), 50% TFA (3 mL) was added and stirred biphasic mixture for 15 to 30 min. The progress of deprotection was monitored by using TLC. Upon completion, the reaction mixture was diluted with ethyl acetate (50 mL), washed with aq.NaHCO₃ (2×50 mL), water (3×50 mL), followed by brine (2×10 mL), and then dried over Na₂SO₄. The solvent was evaporated and the crude product was purified by flash column chromatography (Yield 35–79 %). In few cases unreacted starting material was recovered (20–40%).

**Ethyl 4-(2-formylphenoxy)but-2-ynoate (3.1b):**

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (304 mg, 70 % yield); m.p. 50–52 °C; ¹H NMR (300 MHz, CDCl₃): δ 10.45 (s, 1H), 7.85 (dd, J₁ = 7.7 Hz, J₂ = 1.8 Hz, 1H), 7.59–7.53 (m, 1H), 7.12–7.04 (m, 2H), 4.94 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 189.1, 159.2, 152.6, 135.7, 128.7, 125.4, 122.0, 112.7, 80.3, 79.3, 62.3, 55.8, 13.8; FT-IR (KBr): νmax 2978, 2870, 2550, 1722, 1678, 1259, 1082 cm⁻¹; HRMS (ESI) m/z [M+H]⁺: calcd. for C₁₃H₁₃O₄: 233.0814, found: 233.0818.
Ethyl 4-(2-formyl-6-methylphenoxy)but-2-ynoate (3.2b):

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (296 mg, 70 % yield); m.p. 48–50 °C; \( ^1H \) NMR (400 MHz, CDCl₃): \( \delta \) 10.33 (s, 1H), 7.68 (dd, \( J_1 = 7.8 \) Hz, \( J_2 = 1.4 \) Hz, 1H), 7.46–7.44 (m, 1H), 7.20–7.16 (m, 1H), 4.78 (s, 2H), 4.20 (q, \( J = 7.3 \) Hz, 2H), 2.36 (s, 3H), 1.27 (t, \( J = 7.3 \) Hz, 3H); \( ^{13}C \) NMR (100 MHz, CDCl₃): \( \delta \) 190.0, 158.3, 152.7, 137.7, 132.6, 129.7, 127.6, 125.3, 81.1, 79.8, 62.4, 61.8, 16.0, 14.0; FT-IR (KBr): \( \nu_{\text{max}} \) 2958, 2237, 1718, 1685, 1469, 1261, 1072, 781 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C₁₄H₁₅O₄: 247.0970, found: 247.0973.

Ethyl 4-(1-formylnaphthalen-2-yloxy)but-2-ynoate (3.3b):

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (273 mg, 68 % yield); m.p. 106–108 °C; \( ^1H \) NMR (400 MHz, CDCl₃): \( \delta \) 10.87 (s, 1H), 9.25 (d, \( J = 9.1 \) Hz, 1H), 8.07 (d, \( J = 9.6 \) Hz, 1H), 7.79 (d, \( J = 8.2 \) Hz, 1H), 7.65–7.62 (m, 1H), 7.47–7.43 (m, 1H), 7.31 (d, \( J = 9.1 \) Hz, 1H), 5.05 (s, 2H), 4.23 (q, \( J = 7.3 \) Hz, 2H), 1.29 (t, \( J = 7.3 \) Hz, 3H); \( ^{13}C \) NMR (100 MHz, CDCl₃): \( \delta \) 191.6, 161.4, 152.7, 137.5, 131.4, 130.1, 129.3, 128.3, 125.4, 125.2, 118.0, 113.4, 80.3, 79.6, 62.5, 56.9, 14.0; FT-IR (KBr): \( \nu_{\text{max}} \) 2972, 2249, 1703, 1668, 1514, 1242, 1056, 748 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C₁₇H₁₅O₄: 283.0970, found: 283.0976.
Ethyl 4-(2-formyl-4-methylphenoxy)but-2-ynoate (3.4b):

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (275 mg, 65 % yield); m.p. 66–68 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.42 (s, 1H), 7.65 (d, $J = 1.9$ Hz, 1H), 7.36 (dd, $J_1 = 8.5$ Hz, $J_2 = 2.3$ Hz, 1H), 6.95 (d, $J = 8.5$ Hz, 1H), 4.91 (s, 2H), 4.22 (q, $J = 7.2$ Hz, 2H), 2.31 (s, 3H), 1.29 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.3, 157.4, 152.6, 136.3, 131.6, 128.8, 125.1, 112.8, 80.6, 79.1, 62.3, 56.0, 20.2, 13.8; FT-IR (KBr): $v_{\text{max}}$ 2980, 2247, 1714, 1681, 1496, 1381, 1246, 1018 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{14}$H$_{15}$O$_4$: 247.0970, found: 247.0972.

Ethyl 4-(2,4-di-tert-butyl-6-formylphenoxy)but-2-ynoate (3.5b):

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (280 mg, 74 % yield); m.p. 52–54 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.29 (s, 1H), 7.68 (d, $J = 1.4$ Hz, 1H), 7.64 (d, $J = 1.4$ Hz, 1H), 4.76 (s, 2H), 4.25 (q, $J = 7.0$ Hz, 2H), 1.44 (s, 9H), 1.32–1.30 (m, 12H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 190.4, 157.6, 152.8, 147.4, 143.3, 131.1, 129.1, 125.7, 81.1, 79.4, 64.1, 62.3, 35.4, 34.7, 31.2, 31.0, 13.9; FT-IR (KBr): $v_{\text{max}}$ 2962, 2245, 1712, 1685, 1371, 1234, 1082, 750 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{21}$H$_{29}$O$_4$: 345.2066, found: 345.2067.

Ethyl 4-(2-formyl-5-methoxyphenoxy)but-2-ynoate (3.6b):

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (256 mg, 62 % yield); m.p. 113–115 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.28 (s, 1H), 7.84 (d, $J = 9.6$ Hz, 1H), 6.63 (d, $J = 8.7$ Hz, 1H), 6.53 (s, 1H), 4.92 (s, 2H), 4.25 (q, $J = 6.8$ Hz, 2H), 3.88 (s, 3H).
1.31 (t, J = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 187.9, 166.0, 161.1, 152.7, 131.0, 119.5, 107.1, 99.3, 80.3, 79.3, 62.5, 56.0, 55.8, 14.0; FT-IR (KBr): $v_{\text{max}}$ 3080, 2247, 1703, 1672, 1386, 1273, 1203, 1114, 825 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{14}$H$_{15}$O$_5$: 263.0919, found: 263.0919.

**Ethyl 4-(2-formyl-4-methoxyphenoxy)but-2-ynoate (3.7b):**

![Chemical Structure](image)

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (268 mg, 65% yield); m.p. 85–87 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.40 (s, 1H), 7.32 (d, $J_1 = 9.0$ Hz, $J_2 = 3.0$ Hz, 1H), 7.00 (d, $J = 9.0$ Hz, 1H), 4.88 (s, 2H), 4.21 (d, $J = 7.1$ Hz, 2H), 3.78 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.0, 154.7, 154.0, 152.6, 126.0, 123.1, 115.2, 110.7, 80.7, 79.3, 62.4, 56.9, 55.8, 13.9; FT–IR (KBr): $v_{\text{max}}$ 2993, 2245, 1703, 1678, 1494, 1290, 1039, 723 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{14}$H$_{15}$O$_5$: 263.0919, found: 263.0921.

**Ethyl 4-(2-formyl-6-methoxyphenoxy)but-2-ynoate (3.8b):**

![Chemical Structure](image)

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (277 mg, 57% yield); m.p. 73–75 °C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 10.46 (s, 1H), 7.45 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, 1H), 7.19 (t, $J = 7.8$ Hz, 1H), 7.15 (dd, $J_1 = 8.1$ Hz, $J_2 = 1.8$ Hz, 1H), 4.99 (s, 2H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.90 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.8, 152.7, 152.5, 149.0, 130.7, 125.2, 119.2, 117.8, 81.3, 79.8, 62.2, 60.4, 56.0, 13.9; FT–IR (KBr): $v_{\text{max}}$ 2941, 2237, 1728, 1693, 1583, 1485, 1242, 1062, 779 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{14}$H$_{15}$O$_5$: 263.0919, found: 263.0917.
Diethyl 4,4’-(3-formyl-1,2-phenylene)bis(oxy)dibut-2-ynoate (3.9b):

The title compound was prepared according to the general procedure. Both BuLi and chloroethylformate was used, double the equiv from the general procedure. The product was obtained as pale white solid; (291 mg, 58 % yield); \textbf{m.p.} 63–65 °C; \textbf{^1H NMR} (400 MHz, CDCl$_3$): $\delta$ 10.46 (s, 1H), 7.56 (dd, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, 1H), 7.29–7.21 (m, 2H), 5.00 (s, 2H), 4.92 (s, 2H), 4.27–4.18 (m, 4H), 1.33–1.27 (m, 6H); \textbf{^{13}C NMR} (100 MHz, CDCl$_3$): $\delta$ 189.3, 152.6, 150.3, 149.7, 131.1, 125.3, 121.1, 120.1, 81.0, 80.2, 80.0, 79.5, 62.4, 62.3, 60.9, 56.7, 13.9, 13.8; \textbf{FT-IR} (KBr): $\nu_{\text{max}}$ 2999, 2235, 1722, 1693, 1583, 1477, 1257, 1082, 750 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+H]$^+$: calcd. for C$_{19}$H$_{19}$O$_7$: 359.1131, found: 359.1131.

Ethyl 4-(2, 4-dichloro-6-formylphenoxy)but-2-ynoate (3.10b):

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (213 mg, 54 % yield); \textbf{m.p.} 94–96 °C; \textbf{^1H NMR} (400 MHz, CDCl$_3$): $\delta$ 10.36 (s, 1H), 7.78 (d, $J = 2.5$ Hz, 1H), 7.65 (d, $J = 2.5$ Hz, 1H), 5.00 (s, 2H), 4.21 (q, $J = 7.1$ Hz, 2H), 1.29 (t, $J = 7.1$ Hz, 3H); \textbf{^{13}C NMR} (100 MHz, CDCl$_3$): $\delta$ 187.2, 154.1, 152.3, 135.6, 132.4, 131.7, 129.6, 126.8, 81.0, 79.5, 62.4, 61.3, 13.8; \textbf{FT-IR} (KBr): $\nu_{\text{max}}$ 2972, 2343, 1726, 1689, 1452, 1255, 1047, 731, 677 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+H]$^+$: calcd. for C$_{13}$H$_{11}$O$_4$Cl$_2$: 301.0034, found: 301.0044.

Ethyl 4-(4-chloro-2-formylphenoxy)but-2-ynoate (3.11b):

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (226 mg, 55 % yield);
Hydroacylation of Alkyne

**CHAPTER 4: N-Heterocyclic Carbene-Catalyzed Intramolecular Hydroacylation of Activated Alkynes: Synthesis of Chromone**

**Ethyl 4-(5-fluoro-2-formylphenoxy)but-2-ynoate (3.12b):**

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (240 mg, 57 % yield);

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| m.p. | 62–64 °C; | **1H NMR** (400 MHz, CDCl₃): δ 10.37 (s, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.51 (dd, J₁ = 8.8 Hz, J₂ = 2.2 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 4.94 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); **13C NMR** (100 MHz, CDCl₃): δ 187.8, 157.7, 152.5, 135.3, 128.3, 127.9, 126.3, 114.5, 79.7, 79.7, 62.5, 56.2, 13.9; **FT-IR** (KBr): ν_max 3064, 2249, 1689, 1593, 1475, 1274, 1018, 686 cm⁻¹; **HRMS** (ESI) m/z [M+H]+: calcd. for C₁₃H₁₂O₄Cl: 267.0424, found: 267.0427.

**Ethyl 4-(2-formylphenoxy)-4-methylpent-2-ynoate (3.13b)**

The title compound was prepared according to the general procedure. The product was obtained as a yellow viscous oil; (207 mg, 50 % yield);

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| m.p. | 57–59 °C; | **1H NMR** (300 MHz, CDCl₃): δ 10.32 (s, 1H), 7.87 (dd, J₁ = 8.4 Hz, J₂ = 6.8 Hz, 1H), 6.82–6.74 (m, 2H), 4.93 (s, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); **13C NMR** (100 MHz, CDCl₃): δ 187.5, 167.3 (d, J_CF = 255.5 Hz), 160.9 (d, J_CF = 10.8 Hz), 152.5, 131.0 (d, J_CF = 11.4 Hz), 122.1 (d, J_CF = 2.6 Hz), 109.4 (d, J_CF = 21.9 Hz), 100.9 (d, J_CF = 26.0 Hz), 79.7, 79.5, 62.5, 56.1, 13.8; **19F NMR** (375 MHz, CDCl₃) δ (−98.77 to −98.84) (m, 1F); **FT-IR** (KBr): ν_max 3080, 1249, 1699, 1681, 1604, 1375, 1276, 1168, 1020, 968 cm⁻¹; **HRMS** (ESI) m/z [M+H]+: calcd. for C₁₃H₁₂O₄F: 251.0720, found: 251.0724.
128.3, 123.2, 120.3, 87.1, 78.3, 73.2, 62.2, 28.8, 13.9; **FT-IR** (KBr): $\nu_{\text{max}}$ 2972, 2252, 1712, 1597, 1463, 1261, 1138, 945, 752 cm$^{-1}$; **HRMS** (ESI) m/z [M+H]$^+$: calcd. for C$_{15}$H$_{17}$O$_{4}$: 261.1127, found: 261.1125.

### 2-(4-Oxopent-2-ynyloxy)benzaldehyde (3.14b)

The title compound was prepared according to the general procedure. Instead of ethyl chloroformate, acetyl chloride (1.5 equiv) was used. The product was obtained as pale white solid; (193 mg, 51 % yield); **m.p.** 82–83 °C; **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 10.45 (s, 1H), 7.86 (dd, $J_1$ = 7.7 Hz, $J_2$ = 1.7 Hz, 1H), 7.59–7.54 (m, 1H), 7.11 (t, $J$ = 7.5 Hz, 1H), 7.04 (d, $J$ = 8.4 Hz, 1H), 4.97 (s, 2H), 2.32 (s, 3H); **$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 189.2, 183.5, 159.3, 135.8, 128.8, 125.5, 122.1, 112.9, 86.6, 84.4, 56.1, 32.5; **FT-IR** (KBr): $\nu_{\text{max}}$ 2872, 2216, 1678, 1595, 1483, 1010, 844, 771 cm$^{-1}$; **HRMS** (ESI) m/z [M+H]$^+$: calcd. for C$_{12}$H$_{11}$O$_{3}$: 203.0708, found: 203.0708.

### 2-(5,5-Dimethyl-4-oxohex-2-ynyloxy)benzaldehyde (3.15b)

The title compound was prepared according to the general procedure. Instead of ethyl chloroformate, trimethylacetyl chloride (1.5 equiv) was used. The product was obtained as yellow viscous liquid; (251 mg, 55 % yield); This compound is unstable at room temperature while keeping for longer hours. **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 10.46 (s, 1H), 7.85 (d, $J$ = 6.7 Hz, 1H), 7.56 (s, 1H), 7.11–7.04 (m, 2H), 5.00 (s, 2H), 1.11 (s, 9H); **$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 189.2, 189.0, 159.3, 135.7, 128.8, 125.5, 122.1, 120.0, 113.0, 112.9, 56.1, 25.9, 25.6; **FT-IR** (KBr): $\nu_{\text{max}}$ 2970, 2212, 1683, 1598, 1458, 1288, 1012, 933, 761 cm$^{-1}$; **HRMS** (ESI) m/z [M+H]$^+$: calcd. for C$_{15}$H$_{17}$O$_{3}$: 245.1178, found: 245.1183.
2-(4-Oxo-4-phenylbut-2-ynyloxy)benzaldehyde (3.16b)

The title compound was prepared according to the general procedure. Instead of ethyl chloroformate, benzoyl chloride (1.5 equiv) was used. The product was obtained as a pale white solid; (242 mg, 49 % yield); m.p. 95–97 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.52 (s, 1H), 8.00 (d, $J = 7.8$ Hz, 2H), 7.90 (d, $J = 7.6$ Hz, 1H), 7.59 (t, $J = 7.6$ Hz, 2H), 7.42 (t, $J = 7.6$ Hz, 2H), 7.16–7.11 (m, 2H), 5.12 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.2, 176.9, 159.3, 136.0, 135.8, 134.5, 129.5, 128.9, 128.7, 125.6, 122.2, 113.1, 87.1, 85.3, 56.3; FT-IR (KBr): $v_{\text{max}}$ 2877, 2245, 2204, 1685, 1635, 1598, 1377, 1234, 1024, 759 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{17}$H$_{13}$O$_3$: 265.0865, found: 265.0867.

2-(4-Oxo-5-phenylpent-2-ynyloxy)benzaldehyde (3.17b)

The title compound was prepared according to the general procedure. Instead of ethyl chloroformate, Phenyl acetylchloride (1.5 equiv) was used. The product was obtained as pale white solid; (155 mg, 30 % yield); m.p. 73–75 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.37 (s, 1H), 7.82 (d, $J = 7.6$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 1H), 7.19 (d, $J = 3.7$ Hz, 3H), 7.09–7.02 (m, 3H), 6.86 (d, $J = 8.4$ Hz, 1H), 4.85 (s, 2H), 3.73 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.2, 184.0, 159.2, 135.7, 132.1, 129.7, 129.3, 128.8, 127.5, 125.5, 122.0, 112.8, 86.7, 85.9, 55.9, 51.9; FT-IR (KBr): $v_{\text{max}}$ 3053, 2931, 2872, 2214, 1685, 1597, 1631, 1220, 758 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{18}$H$_{15}$O$_3$: 279.1021, found: 279.1020.
General procedure for intramolecular hydroacylation on activated alkyne:

Typical general procedure for the intramolecular chromone-forming Stetter reaction, as exemplified for the formation of 3.1c: Precatalyst D (12 mg, 0.043 mmol, 0.2 equiv) and 3.1b (50 mg, 0.216 mmol, 1 equiv) was suspended with anhydrous DMF (1 mL) in an oven-dried round bottom flask under nitrogen atmosphere at room temperature. Et₃N (6 µL, 0.043 mmol, 0.2 equiv) was added via micro syringe to the reaction mixture and allowed to stir for 24 hr at room temperature. The progress of the reaction was monitored using TLC. Upon completion, the reaction mixture was diluted with ethyl acetate (20 mL), washed with water (3×20 mL), followed by brine (2×10 mL), and then dried over Na₂SO₄. The solvent was removed and the crude product was purified by column chromatography on silica gel (eluent: hexanes/ethyl acetate 5:1) to afford 41.5 mg (83%) of 3.1c.

Ethyl 2-(4-oxo-4H-chromen-3-yl)acetate (3.1c) [16]:

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (41.5 mg, 83 % yield); m.p. 79–81 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.21 (dd, J₁ = 8.0 Hz, J₂ = 1.6 Hz, 1H), 7.94 (s, 1H), 7.68–7.63 (m, 1H), 7.45–7.36 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.47 (s, 2H), 1.27 (t, J = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 176.9, 170.6, 156.5, 153.7, 133.6, 125.9, 125.1, 123.6, 118.4, 118.0, 61.0, 30.9, 14.1; FT-IR (KBr): v max 3078, 2978, 1739,
1610, 1477, 1344, 1205, 1028, 759 cm$^{-1}$; \textbf{HRMS (ESI)} m/z [M+H]$^+$: calcd. for C$_{13}$H$_{13}$O$_4$: 233.0814, found: 233.0815.

\textbf{Ethyl 2-(8-methyl-4-oxo-4H-chromen-3-yl)acetate (3.2c):}

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (43 mg, 86 % yield); \textbf{m.p.} 80–82 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.06 (d, $J = 7.8$ Hz, 1H), 7.90 (s, 1H), 7.50 (d, $J = 6.8$ Hz, 1H), 7.30 (d, $J = 7.8$ Hz, 1H), 4.19 (q, $J = 6.8$ Hz, 2H), 3.48 (s, 2H), 2.47 (s, 3H), 1.28 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 177.3, 170.7, 155.0, 153.6, 127.5, 124.6, 123.5, 123.4, 118.2, 61.1, 31.0, 15.5, 14.1; \textbf{FT-IR} (KBr): $v_{\text{max}}$ 2985, 1726, 1627, 1336, 1180, 773 cm$^{-1}$; \textbf{HRMS (ESI)} m/z [M+H]$^+$: calcd. for C$_{14}$H$_{15}$O$_4$: 247.0970, found: 247.0970.

\textbf{Ethyl 2-(1-oxo-1H-benzo[f]chromen-2-yl)acetate (3.3c):}

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (42 mg, 84 % yield); \textbf{m.p.} 115–117 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.03 (d, $J = 8.6$ Hz, 1H), 8.06 (d, $J = 9.0$ Hz, 1H), 8.00 (s, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.73 (dd, $J_1 = 8.3$ Hz, $J_2 = 7.2$ Hz, 1H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.48 (d, $J = 9.0$ Hz, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 3.54 (s, 2H), 1.29 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.5, 170.8, 157.8, 151.3, 135.5, 130.5 (2c, fused benzene quaternary carbons overlap each other conformed by comparing DEPT 135), 129.2, 128.1, 127.2, 126.6, 121.2, 117.5, 117.0, 61.1, 31.4, 14.2; \textbf{FT-IR} (KBr): $v_{\text{max}}$ 2974, 1724, 1653, 1444, 1188, 1165, 823 cm$^{-1}$; \textbf{HRMS (ESI)} m/z [M+H]$^+$: calcd. for C$_{17}$H$_{15}$O$_4$: 283.0970, found: 283.0975.
**Ethyl 2-(6-methyl-4-oxo-4H-chromen-3-yl)acetate (3.4c)**:

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (45 mg, 90% yield); **m.p.** 73–75 °C; **^1H NMR** (400 MHz, CDCl₃): δ 7.98 (s, 1H), 7.91 (s, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.46 (s, 2H), 2.43 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); **^13C NMR** (100 MHz, CDCl₃): δ 177.0, 170.7, 154.8, 153.7, 135.1, 134.9, 125.1, 123.3, 118.2, 117.8, 61.1, 31.0, 14.1; **FT-IR (KBr)**: νmax 2920, 1730, 1635, 1485, 1321, 1186, 1155, 871 cm⁻¹; **HRMS (ESI) m/z [M+H]^+**: calcd. for C₁₄H₁₅O₄: 247.0970, found: 247.0969.

**Ethyl 2-(6,8-di-tert-butyl-4-oxo-4H-chromen-3-yl)acetate (3.5c)**:

The title compound was prepared according to the general procedure. The product was obtained as pale white solid; (38 mg, 76% yield); **m.p.** 91–93 °C; **^1H NMR** (400 MHz, CDCl₃): δ 8.11 (d, J = 1.8 Hz, 1H), 8.01 (s, 1H), 7.69 (d, J = 1.8 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.48 (s, 2H), 1.48 (s, 9H), 1.36 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H); **^13C NMR** (100 MHz, CDCl₃): δ 177.7, 170.9, 153.6, 152.6, 147.5, 138.4, 128.7, 123.7, 119.8, 117.7, 61.1, 35.2, 34.9, 31.3, 31.0, 30.0, 14.2; **FT-IR (KBr)**: νmax 2954, 2355, 1734, 1639, 1471, 1255, 1037, 817, 667 cm⁻¹; **HRMS (ESI) m/z [M+H]^+**: calcd. for C₂₁H₂₉O₄: 345.2066, found: 345.2074.

**Ethyl 2-(7-methoxy-4-oxo-4H-chromen-3-yl)acetate (3.6c)**:

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (46 mg, 92% yield); **m.p.** 102–104 °C; **^1H NMR** (400 MHz, CDCl₃): δ 8.10 (d, J = 8.9 Hz, 1H), 7.86 (s, 1H), 6.95 (dd, J₁ = 8.9 Hz, J₂ = 1.8 Hz, 1H), 6.81 (s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.61 (s, 3H), 3.40 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); **HRMS (ESI) m/z [M+H]^+**: calcd. for C₁₄H₁₅O₄: 247.0970, found: 247.0969.
Hydroacylation of Alkyne

3.88 (s, 3H), 3.44 (s, 2H), 1.26 (t, \( J = 7.1 \) Hz, 3H); \( ^{13} \text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 176.3, 170.8, 164.0, 158.3, 153.3, 127.3, 118.3, 117.6, 114.5, 100.1, 61.1, 55.8, 30.9, 14.1; \( \text{FT-IR} \) (KBr): \( v_{\text{max}} \) 2987, 1735, 1598, 1431, 1180, 1026, 821 cm\(^{-1}\); \( \text{HRMS (ESI)} \) m/z [M+H]\(^+\): calcd. for C\(_{14}\)H\(_{15}\)O\(_5\): 263.0919, found: 263.0919.

**Ethyl 2-(6-methoxy-4-oxo-4H-chromen-3-yl)acetate (3.7c):**

![Structure](image1)

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (44 mg, 88 % yield); \( \text{m.p.} \) 94–96 °C; \( ^{1} \text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 7.93 (s, 1H), 7.57 (d, \( J = 3.2 \) Hz, 1H), 7.39 (d, \( J = 9.2 \) Hz, 1H), 7.26 (dd, \( J_1 = 9.4 \) Hz, \( J_2 = 3.0 \) Hz, 1H), 4.19 (q, \( J = 7.1 \) Hz, 1H), 3.88 (s, 3H), 3.48 (s, 2H), 1.28 (t, \( J = 7.1 \) Hz, 3H); \( ^{13} \text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 176.9, 170.8, 156.9, 153.6, 151.5, 124.3, 123.9, 119.6, 117.7, 104.9, 61.2, 55.9, 31.1, 14.2; \( \text{FT-IR} \) (KBr): \( v_{\text{max}} \) 2986, 1724, 1647, 1483, 1317, 1193, 1024, 827 cm\(^{-1}\); \( \text{HRMS (ESI)} \) m/z [M+H]\(^+\): calcd. for C\(_{14}\)H\(_{15}\)O\(_5\): 263.0919, found: 263.0917.

**Ethyl 2-(8-methoxy-4-oxo-4H-chromen-3-yl)acetate (3.8c):**

![Structure](image2)

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (42 mg, 85 % yield); \( \text{m.p.} \) 126–128 °C; \( ^{1} \text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 7.99 (s, 1H), 7.77 (dd, \( J_1 = 8.1 \) Hz, \( J_2 = 1.2 \) Hz, 1H), 7.31 (t, \( J = 8.0 \) Hz, 1H), 7.16 (dd, \( J_1 = 7.9 \) Hz, \( J_2 = 1.0 \) Hz, 1H), 4.17 (q, \( J = 7.1 \) Hz, 2H), 3.99 (s, 3H), 3.47 (s, 2H), 1.26 (t, \( J = 7.1 \) Hz, 3H); \( ^{13} \text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 176.9, 170.5, 153.5, 148.6, 146.9, 124.8, 124.6, 118.6, 116.8, 114.1, 61.1, 56.4, 31.0 14.1; \( \text{FT-IR} \) (KBr): \( v_{\text{max}} \) 2939, 1735, 1649, 1579, 1334, 1192, 1178, 1078, 776 cm\(^{-1}\); \( \text{HRMS (ESI)} \) m/z [M+H]\(^+\): calcd. for C\(_{14}\)H\(_{15}\)O\(_5\): 263.0919, found: 263.0919.
Ethyl 4-(3-(2-ethoxy-2-oxyethyl)-4-oxo-4\(H\)-chromen-8-yloxy)but-2-ynoate (3.9c):

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (40 mg, 80% yield); m.p. 112–114 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.99 (s, 1H), 7.87 (dd, \(J_1 = 7.9\) Hz, \(J_2 = 1.2\) Hz, 1H), 7.36–7.27 (m, 2H), 4.99 (s, 2H), 4.27–4.16 (m, 4H), 3.48 (s, 2H), 1.32–1.26 (m, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 176.6, 170.4, 153.4, 152.6, 147.3, 146.2, 125.0, 124.7, 118.8, 118.7, 116.8, 80.2, 79.6, 62.4, 61.1, 56.8, 30.9, 14.1, 13.9; FT-IR (KBr): \(v_{\text{max}}\) 2993, 2249, 1720, 1654, 1581, 1490, 1330, 1186, 985, 752 cm\(^{-1}\); HRMS (ESI) m/z [M+H]+: calcd. for C\(_{19}\)H\(_{19}\)O\(_7\): 359.1131, found: 359.1132.

Ethyl 2-(6,8-dichloro-4-oxo-4\(H\)-chromen-3-yl)acetate (3.10c):

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (39 mg, 78% yield); m.p. 104–106 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.07 (d, \(J = 2.4\) Hz, 1H), 8.01 (s, 1H), 7.70 (d, \(J = 2.4\) Hz, 1H), 4.18 (q, \(J = 7.1\) Hz, 2H), 3.47 (s, 2H), 1.27 (t, \(J = 7.1\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 175.2, 170.1, 153.8, 150.8, 133.8, 130.8, 125.3, 124.3, 124.0, 119.0, 61.3, 30.8, 14.1; FT-IR (KBr): \(v_{\text{max}}\) 3072, 1718, 1658, 1460, 1325, 1166, 844, 686 cm\(^{-1}\); HRMS (ESI) m/z [M+H]+: calcd. for C\(_{13}\)H\(_{11}\)O\(_4\)Cl\(_2\): 301.0034, found: 301.0035.

Ethyl 2-(6-chloro-4-oxo-4\(H\)-chromen-3-yl)acetate (3.11c):

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (38 mg, 76% yield); m.p. 87–89 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): 8.17 (d, \(J = 2.4\) Hz, 1H), 7.94 (s, 1H), 7.60...
Hydroacylation of Alkyne

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(dd, \( J_1 = 8.9 \text{ Hz}, J_2 = 2.4 \text{ Hz}, 1\text{H} \)), 7.41 (d, \( J = 2.4 \text{ Hz}, 1\text{H} \)), 4.17 (q, \( J = 7.2 \text{ Hz}, 2\text{H} \)), 3.47 (s, 2\text{H} \)), 1.27 (t, \( J = 7.2 \text{ Hz}, 3\text{H} \)); \(^{13}\text{C} \text{NMR} \ (100 \text{ MHz, CDCl}_3): \delta 175.8, 170.3, 154.8, 153.9, 133.8, 131.0, 125.2, 124.5, 119.8, 118.5, 61.2, 30.8, 14.1; \text{FT-IR} \ (\text{KBr}): \nu_{\text{max}} 2991, 1726, 1639, 1469, 1315, 1157, 1029, 773 \text{ cm}^{-1}; \text{HRMS (ESI)} \ m/z [\text{M+H}]^+: \text{calcd. for C}_{13}\text{H}_{12}\text{O}_4\text{Cl}: 267.0424, \text{found: 267.0426.}

**Ethyl 2-(7-fluoro-4-oxo-4\text{H}-chromen-3-yl)acetate (3.12c):**

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (40 mg, 80 \% yield); \text{m.p.} 101−103 °C; \(^1\text{H} \text{NMR} \ (400 \text{ MHz, CDCl}_3): 8.22 (dd, \( J_1 = 9.2 \text{ Hz}, J_1 = 6.2 \text{ Hz}, 1\text{H} \)), 7.91 (s, 1\text{H} \)), 7.13 (d, \( J = 6.3 \text{ Hz}, 2\text{H} \)), 4.18 (q, \( J = 7.0 \text{ Hz}, 2\text{H} \)), 3.45 (s, 2\text{H} \)), 1.27 (t, \( J = 7.0 \text{ Hz}, 3\text{H} \)); \(^{13}\text{C} \text{NMR} \ (100 \text{ MHz, CDCl}_3): \delta 176.1, 170.5, 165.6 (d, \( J_{\text{CF}} = 253.5 \text{ Hz} \)), 157.5 (d, \( J_{\text{CF}} = 13.5 \text{ Hz} \)), 153.9, 128.5 (d, \( J_{\text{CF}} = 10.6 \text{ Hz} \)), 120.5, 118.7, 114.0 (d, \( J_{\text{CF}} = 22.7 \text{ Hz} \)), 104.7 (d, \( J_{\text{CF}} = 25.1 \text{ Hz} \)), 61.2, 30.8, 14.1; \(^{19}\text{F} \text{NMR} \ (375 \text{ MHz, CDCl}_3) \delta (-102.61−102.67) \text{ (m, 1F)}; \text{FT-IR} \ (\text{KBr}): \nu_{\text{max}} 3080, 1735, 1656, 1442, 1255, 1085, 1166 \text{ cm}^{-1}; \text{HRMS (ESI)} \ m/z [\text{M+H}]^+: \text{calcd. for C}_{13}\text{H}_{12}\text{O}_4\text{F}: 251.0720, \text{found: 251.0721.}

**(E)-Ethyl 2-(2, 2-dimethyl-4-oxochroman-3-ylidene)acetate (3.13c):**

The title compound was prepared according to the general procedure. The product was obtained as yellow viscous oil; (39 mg, 78 \% yield); \(^1\text{H} \text{NMR} \ (400 \text{ MHz, CDCl}_3): \delta 7.90 (d, \( J = 7.8 \text{ Hz}, 1\text{H} \)), 7.48 (t, \( J = 7.7 \text{ Hz}, 1\text{H} \)), 7.01 (t, \( J = 7.5 \text{ Hz}, 1\text{H} \)), 6.91 (d, \( J = 8.3 \text{ Hz}, 1\text{H} \)), 6.19 (s, 1\text{H} \)), 4.31 (q, \( J = 7.1 \text{ Hz}, 2\text{H} \)), 1.62 (s, 6\text{H} \)), 1.32 (t, \( J = 7.1 \text{ Hz}, 3\text{H} \)); \(^{13}\text{C} \text{NMR} \ (100 \text{ MHz, CDCl}_3): \delta 181.7, 167.4, 159.6, 144.2, 136.6, 127.6, 125.3, 121.6, 120.7, 118.4, 80.7, 61.5, 26.4, 13.9; \text{FT-IR} \ (\text{KBr}): \nu_{\text{max}} 2353, 1732, 1681, 1600, 1463, 1340, 1031, 758 \text{ cm}^{-1}; \text{HRMS (ESI)} \ m/z [\text{M+H}]^+: \text{calcd. for}
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C_{15}H_{17}O_4: 261.1127, found: 261.1127.

3-(2-Oxopropyl)-4H-chromen-4-one (3.14c):

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (37 mg, 74% yield); m.p. 96–98 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.20 (d, \(J = 7.9\) Hz, 1H), 7.88 (s, 1H), 7.67 (t, \(J = 7.8\) Hz, 1H), 7.45 (d, \(J = 8.4\) Hz, 1H), 7.40 (t, \(J = 8.5\) Hz, 1H), 3.56 (s, 2H), 2.33 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) : \(\delta\) 205.0, 177.1, 156.6, 53.9, 133.7, 125.9, 125.1, 123.6, 118.7, 118.1, 39.3, 30.2; FT-IR (KBr): \(\nu_{\text{max}}\) 3074, 1714, 1641, 1469, 1355, 1157, 754 cm\(^{-1}\); HRMS (ESI) m/z \([\text{M+H}]^+\): calcd. for C_{12}H_{11}O_3: 203.0708, found: 203.0707.

3-(3,3-Dimethyl-2-oxobutyl)-4H-chromen-4-one (3.15c):

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (36 mg, 72% yield); m.p. 124–126 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) : \(\delta\) 8.18 (d, \(J = 8.0\) Hz, 1H), 7.85 (s, 1H), 7.65 (t, \(J = 7.8\) Hz, 1H), 7.44 (d, \(J = 8.5\) Hz, 1H), 7.38 (t, \(J = 7.5\) Hz, 1H), 3.64 (s, 2H), 1.27 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) : \(\delta\) 212.0, 177.2, 156.6, 154.1, 133.6, 125.9, 125.1, 123.7, 119.1, 118.1, 44.7, 32.9, 26.5; FT-IR (KBr): \(\nu_{\text{max}}\) 2974, 2335, 1710, 1639, 1610, 1463, 1178, 754 cm\(^{-1}\); HRMS (ESI) m/z \([\text{M+H}]^+\): calcd. for C_{15}H_{17}O_3: 245.1178, found: 245.1185.

3-(2-Oxo-2-phenylethyl)-4H-chromen-4-one (3.16c):

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (33 mg, 66% yield); m.p. 130–132 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) : \(\delta\) 8.22 (d, \(J = 8.0\) Hz, 1H), 8.09 (d, \(J =\)
7.9 Hz, 2H), 7.97 (s, 1H), 7.66 (t, \( J = 7.8 \) Hz, 1H), 7.58 (t, \( J = 7.8 \) Hz, 1H), 7.50–7.44 (m, 3H), 7.39 (t, \( J = 7.5 \) Hz, 1H), 4.15 (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta 196.6, 177.0, 156.5, 154.2, 136.5, 133.6, 133.4, 128.7, 128.5, 126.0, 125.1, 123.7, 118.8, 118.1, 34.3; \)

FT-IR (KBr): \( \nu_{\text{max}} 3068, 2366, 2333, 1683, 1643, 1465, 1336, 1213, 993, 754 \text{ cm}^{-1}; \)

HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{17}\)H\(_{13}\)O\(_3\): 265.0865, found: 265.0869.

3-(2-Oxo-3-phenylpropyl)-4H-chromen-4-one (3.17c):

The title compound was prepared according to the general procedure. The product was obtained as a pale white solid; (34 mg, 68% yield); m.p. 89–91 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta 8.22 \) (dd, \( J_1 = 8.0 \) Hz, \( J_2 = 1.5 \) Hz, 1H), 7.84 (s, 1H), 7.71–7.66 (m, 1H), 7.47–7.28 (m, 8H), 3.94 (s, 2H), 3.57 (s, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta 204.7, 177.3, 156.3, 154.0, 133.7, 133.7, 129.6, 128.8, 127.2, 125.9, 125.2, 123.7, 118.8, 118.2, 50.3, 37.9; \)

FT-IR (KBr): \( \nu_{\text{max}} 2931, 2895, 2353, 2318, 1681, 1635, 1614, 1506, 1338, 972, 761 \text{ cm}^{-1}; \)

HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{18}\)H\(_{15}\)O\(_3\): 279.1021, found: 279.1021.

Crystal structure of compound 3.8c
### Table 3.4. Crystal data and structure refinement for liu34s.

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<tr>
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<tr>
<td>Wavelength</td>
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<td>Crystal system</td>
<td>Triclinic</td>
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<td>Space group</td>
<td>P-1</td>
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                      | $\alpha = 110.3090(10)^\circ$. |
                      | $b = 12.2795(3)$  
                      | $\beta = 106.480(2)^\circ$. |
                      | $c = 13.8639(5)$  
                      | $\gamma = 99.7610(10)^\circ$. |
| Volume              | 1267.03(6) Å³ |
| Z                   | 4 |
| Density (calculated)| 1.375 Mg/m³ |
| Absorption coefficient | 0.105 mm⁻¹ |
| F(000)              | 552 |
| Crystal size        | 0.42 x 0.40 x 0.12 mm³ |
| Theta range for data collection | 1.69 to 28.00°. |
| Index ranges        | -11 ≤ h ≤ 11, -16 ≤ k ≤ 16, -18 ≤ l ≤ 18 |
| Reflections collected | 32721 |
| Independent reflections | 6029 [R(int) = 0.0254] |
| Completeness to theta = 28.00° | 98.2 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9875 and 0.9573 |
| Refinement method   | Full-matrix least-squares on F² |
| Data / restraints / parameters | 6029 / 0 / 347 |
| Goodness-of-fit on F² | 1.069 |
| Final R indices [I>2sigma(I)] | R₁ = 0.0353, wR₂ = 0.0926 |
| R indices (all data) | R₁ = 0.0444, wR₂ = 0.1058 |
| Largest diff. peak and hole | 0.389 and -0.229 e Å⁻³ |
Table 3.5. Crystal data and structure refinement for liu36s.

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### Energy calculation

**Table 3.6.** Energy calculation for conformation I.

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CHAPTER 4: N-Heterocyclic Carbene-Catalyzed Intramolecular Hydroacylation of Activated Alkynes: Synthesis of Chromone
Sum of electronic and thermal Free Energies = -803.314173

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Table 3.7. Energy calculation for conformation II.

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Table 3.8. Energy calculation for conformation III.

Zero-point correction= 0.228110 (Hartree/Particle)
Thermal correction to Energy= 0.243018
Thermal correction to Enthalpy= 0.243962
Thermal correction to Gibbs Free Energy= 0.184095
Sum of electronic and zero-point Energies= -803.290257
Sum of electronic and thermal Energies= -803.275349
Sum of electronic and thermal Enthalpies= -803.274405
Sum of electronic and thermal Free Energies= -803.334273

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<td>0.23193100</td>
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<td>1.14342400</td>
</tr>
<tr>
<td>H</td>
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<td>1.44349100</td>
</tr>
<tr>
<td>H</td>
<td>-4.75834400</td>
<td>0.61362000</td>
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<tr>
<td>C</td>
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<td>2.32314600</td>
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<td>H</td>
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<td>H</td>
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CHROMONE
3.5. Reference section


CHAPTER 4

N-Heterocyclic Carbene Catalyzed $C\text{–}Glycosylation$: A Concise Approach from Stetter Reaction and Formal Synthesis of Scleropentaside A

4.1. Introduction

Given the various physiological roles of carbohydrate templates throughout different biological systems, which include numerous features of normal cellular function and survival, it is not surprising that both monosaccharide and polysaccharide structures can fulfill diversified biological tasks.\textsuperscript{[1-10]} In addition, various types of C–glycosides show similar aspects of biological role as a potential drug candidates including remarkable physiological stability.\textsuperscript{[11-18]} In addition, few examples of C–glycoside based natural products are listed in Figure 4.1, which includes (+) Varitriol (I),\textsuperscript{[19]} (–)-aspergillide C (II),\textsuperscript{[20]} C–mannosyltryptophan (III)\textsuperscript{[21]} and carbonyl based glycosides Scleropentaside A–E \textsuperscript{[22]} (IV-VIII). Therefore, the search for new methodologies for the expedient synthesis of C–glycosides has become of great interest to researchers.

![Figure 4.1. Examples of C–glycosides based natural products](image_url)

The potential pharmaceutical significance of this class of compounds has prompted various groups to develop different methodologies for C–glycosylation, including Lewis acid-mediated\textsuperscript{[23-27]} metal-mediated\textsuperscript{[28-36]} radical-mediated\textsuperscript{[37-39]} and base-mediated glycosylation.\textsuperscript{[40]} Recently, our group has actively investigated efficient
and stereoselective C–glycosylation techniques, such as Lewis acid-mediated glycosylation,[41] palladium-catalyzed decarboxylative glycosylation,[42] enol-triflate coupling glycosylation,[43] glycosidation based on sulfur ylide cycloaddition reactions[44] and sequential rhodium-catalyzed aziridination/indium-mediated Barbier allylation.[45] In addition to these methodologies, we substantiated the importance of glycosides by demonstrating the high activities of certain porphyrin conjugated C–glycosides towards biological systems which was explained in last chapter.[46]

Scheme 4.1. Various glycosylation techniques in 2-nitroglycol.

The development of C–glycoside especially organocatalytic approach, is an emerging area due to environment friendly and stereoselective glycosylation. NHC catalyzed acylanion addition to anomeric carbon is a new approach which extend new
classes of $C$–glycoside. Some time ago, Schmidt, Vanker and other groups devised a base-mediated glycosylation technique starting from 2-nitroglycol (4.7a) derivatives (Scheme 4.1).\textsuperscript{40} In this phenomenon various glycosyl acceptors had been investigated and steroselective products were obtained such as aminoacid based $O$–glycosides (4.1),\textsuperscript{47} disaccharides (4.2),\textsuperscript{48} Purine based $N$–glycosides (4.3),\textsuperscript{49} $S$–glycosides (4.4),\textsuperscript{50} 1,3-dicarbonyl based $C$–glycosides (4.5),\textsuperscript{51} metal mediated $C$–glycosides (4.6),\textsuperscript{52} aromatic ring fused glycosides (4.7)\textsuperscript{53} and phosphate glycosides (4.8)\textsuperscript{54}. Since 2-nitroglycol is a versatile Michael-type glycosyl donor under basic conditions, we envisioned that NHC catalyzed acylanion addition to 2-nitroglucal would afford a new class of $C$–glycosides (4.9). To our delight, very recently similar type of furan-2-carbonyl $C$–glycosides based natural products has been isolated (Figure 4.1).\textsuperscript{22}

### 4.2. Result and discussion

Our initial study commenced with the reaction of pyridine-2-carboxaldehyde (1 equiv) and tri-$O$-benzyl-2-nitro-$D$-glucal (4.7a, 1.3 equiv) using various NHC catalysts (A–F, 0.1 equiv) and DBU (0.1 equiv) in dichloromethane (0.05 M) at room temperature (Table 1, entries, 1–6). We observed that only thiazolium salts B and E led to the formation of two kind of products, namely, the Stetter type $\beta$–selective $C$–glycoside 4.1b and the subsequent base-mediated nitro-eliminated $C$–glycoside 4.1c (Entries, 2 and 5).\textsuperscript{55} The reactions with other precatalysts including triazolium salts D and imidazolium salts A, C, F were unsuccessful. To our delight, precatalyst E led to the formation of $C$–glycoside products 4.1b and 4.1c in yields of 10 % and 59 % respectively (Entry 5) which prompted us to further investigate the condition used in this reaction. The scope of this optimized reaction was subsequently explored by varying the catalyst and base loadings.
Table 4.1. Optimization of NHC catalyzed C–glycosylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (equiv)</th>
<th>Base (equiv)</th>
<th>Solvent (0.05 M)</th>
<th>Yield (%) 4.1b[b]</th>
<th>Yield (%) 4.1c[c]</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>A (0.1)</td>
<td>DBU (0.1)</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>B (0.1)</td>
<td>DBU (0.1)</td>
<td>CH₂Cl₂</td>
<td>5</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>C (0.1)</td>
<td>DBU (0.1)</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>D (0.1)</td>
<td>DBU (0.1)</td>
<td>CH₂Cl₂</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>E (0.1)</td>
<td>DBU (0.1)</td>
<td>CH₂Cl₂</td>
<td>10</td>
<td>59</td>
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<tr>
<td>6</td>
<td>F (0.1)</td>
<td>DBU (0.1)</td>
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<td>-</td>
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<tr>
<td>7</td>
<td>E (0.1)</td>
<td>Et₃N (0.1)</td>
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<td>63</td>
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<tr>
<td>8</td>
<td>E (0.1)</td>
<td>DIPEA (0.1)</td>
<td>CH₂Cl₂</td>
<td>62</td>
<td>18</td>
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<tr>
<td>9</td>
<td>E (0.1)</td>
<td>Cs₂CO₃ (0.1)</td>
<td>CH₂Cl₂</td>
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<td>68</td>
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<td>10</td>
<td>E (0.1)</td>
<td>Cs₂CO₃ (2)</td>
<td>CH₂Cl₂</td>
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<td>87</td>
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<tr>
<td>11</td>
<td>E (0.1)</td>
<td>Cs₂CO₃ (2)</td>
<td>CH₃CN</td>
<td>-</td>
<td>65</td>
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<td>12</td>
<td>E (0.1)</td>
<td>Cs₂CO₃ (2)</td>
<td>THF</td>
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<td>13</td>
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<td>Cs₂CO₃ (2)</td>
<td>dioxane</td>
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<td>14</td>
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<td>17</td>
<td>E (0.15)</td>
<td>DIPEA (0.1)</td>
<td>toluene</td>
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<td>10</td>
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[a] Unless otherwise noted, all of the reactions were carried out using freshly distilled dry solvent at rt for 24 h. [b,c] Yield of isolated product.

as well as subjecting the reaction to different bases. By employing precatalyst E (0.1 equiv), the scope of this transformation was evaluated with various bases (0.1 equiv) (Et₃N, DIPEA, Cs₂CO₃) (Entries 7–9) at room temperature using dichloromethane as solvent. Compound 4.1b was formed as the major product in a yield of 62 % (Entry 8)
when DIPEA was used as the base (0.1 equiv) while glycoside 4.1c was formed in 68 % yield when Cs₂CO₃ was used as the base (Entry 9). Therefore, we expanded our optimization studies for each glycoside, 4.1b and 4.1c. Increasing loading of Cs₂CO₃ to 2 equiv under the same reaction conditions led to compound 4.1c with yield of 87 % (Entry 10). In order to confine the reactivity towards 4.1c, we fixed the conditions to 2 equiv (less than 2 equiv provides minor amount of 4.1b) of Cs₂CO₃ and 0.1 equiv of precatalyst E, and then screened various organic solvents (Entries 11–13), with the result that the reaction in dichloromethane produced the highest yield of 87 % (Entry 10). The C–glycoside 4.1b was somewhat sensitive to basic conditions due to elimination of the nitro group to form 4.1c. Indeed, the usage of 2 equiv of DIPEA produced 4.1c in a reasonable yield along with 10–20 % of 4.1b as a minor product, which was not found in the case of Cs₂CO₃. This prompted us to use DIPEA as a base to obtain Stetter type β–selective C–glycoside 4.1b. Earlier, it was found that 0.1 equiv DIPEA produced an optimal yield of 62 % (entry 8). To avoid the conversion of compound 4.1b to 4.1c, the catalyst loading was increased to 0.15 equiv to trap any unused DIPEA (0.1 equiv) and various solvents were screened in order to selectively obtain 4.1b (entries 14–17). Similarly, the best result for obtention of 4.1b was achieved when dichloromethane was used as the solvent, producing 77 % yield along with a small amount of compound 4.1c (5 % yield) (entry 14).

The optimized conditions for the formation of 4.1b involve, employment of 0.15 equiv of precatalyst E in the presence of 0.1 equiv of DIPEA in dichloromethane (0.05 M), and stirring at room temperature for 24 h (entry 14). On the other hand, the conditions for formation of the nitro-eliminated product 4.1c involve employment of 0.1 equiv of
Table 4.2. Scope of Stetter type $\beta$–selective $C$–glycosides.$^{[a]}$

\[
\text{R}^+\text{CGlycosylation} + \text{H}^-\text{R}_1 \xrightarrow{\text{NHC E (0.15 equiv)}} \text{R}^+\text{CGlycosylation}
\]

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
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<tr>
<td>4.1b, 77%</td>
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<tr>
<td>4.2b, 89%</td>
<td></td>
</tr>
<tr>
<td>4.3b, 82%</td>
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</tr>
<tr>
<td>4.4b, 75%</td>
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<tr>
<td>4.5b, 76%</td>
<td></td>
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<tr>
<td>4.6b, 84%</td>
<td></td>
</tr>
<tr>
<td>4.7b, 78%</td>
<td></td>
</tr>
<tr>
<td>4.8b, 82%</td>
<td></td>
</tr>
</tbody>
</table>

$^{[a]}$Unless otherwise noted all the reactions were carried out under standard optimized condition and isolated yields are recorded above.

Precatalyst E in the presence of 2 equiv of Cs₂CO₃ in dichloromethane (0.05 M), at room temperature for 24 h (entry 10). With these optimized reaction conditions in hand, we began to explore substrate scope (Table 4.2 and 4.3). At the outset of this study, a few examples of $N$–containing heterocyclic aldehydes and 3,4,6-tri-$O$-benzyl-2-nitro-$D$-glucal were subjected to the Stetter type $\beta$–selective $C$–glycosidation (Table 4.1), as we found that 2-formyl-$N$-containing heterocycles were competent substrates with good to moderate yields being obtained for 2-quinoline (4.2b, 89%), 6-methyl-2-pyridine (4.3b, 82%), 6-hydroxymethyl-2-pyridine (4.4b, 75%) and 8-formylquinoline (4.5b, 75%). The formation of compound 4.4b indicates that the reaction underwent specifically with the aldehyde functional group even in the presence of hydroxymethyl group, which proves that $C$–glycosylation is more facile than $O$–glycosylation. Concurrently, different sugars such as benzyl protected 2-nitro-$D$-galactal (4.6b, 84%), methyl protected 2-nitro-$D$-glucal
Table 4.3. Scope of nitro-eliminated C–glycosides.[a]

<table>
<thead>
<tr>
<th>Structure</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>4.1c</td>
<td>87%</td>
</tr>
<tr>
<td>4.2c</td>
<td>85%</td>
</tr>
<tr>
<td>4.3c</td>
<td>72%</td>
</tr>
<tr>
<td>4.4c</td>
<td>74%</td>
</tr>
<tr>
<td>4.5c</td>
<td>83%</td>
</tr>
<tr>
<td>4.6c[b]</td>
<td>74%</td>
</tr>
<tr>
<td>4.7c</td>
<td>78%</td>
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<td>4.8c</td>
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<td>82%</td>
</tr>
<tr>
<td>4.12c</td>
<td>78%</td>
</tr>
<tr>
<td>4.13c</td>
<td>84%</td>
</tr>
<tr>
<td>4.14c</td>
<td>67%</td>
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<td>68%</td>
</tr>
<tr>
<td>4.22c</td>
<td>69%</td>
</tr>
<tr>
<td>4.23c</td>
<td>87%</td>
</tr>
</tbody>
</table>

[a] All the reactions were carried out under standard optimized condition and isolated yields are recorded. [b] 2.5 equiv of tri-O-benzyl-2-nitro-D-galactal was used.

(4.7b, 78%) and 2-nitro-L-rhamnal (4.8b, 82%) also showed good yields. The base-mediated nitro-eliminated glycoside is a new class of C–glycoside, in contrast to Michael
addition type C–glycoside, which allows one to develop more diverse types of C–glycoside including of various heteroaromatic aldehydes, aromatic aldehydes and aliphatic aldehydes (Table 4.3). Pyridines with formyl groups at C–2, C–3 and C–4 (4.1c–4.3c) were screened and the results showed that good to moderate yields were obtained (87–72 %). 6-Methyl-2-pyridine (4.4c, 74 %) and 6-hydroxymethyl-2-pyridine (4.5c, 83 %) afforded the nitro-eliminated C–glycosides in good yield. By using 2.5 equiv of 2-nitroglucal (4.7a), a dimeric glucal type C–glycoside 4.6c was produced in which two sugars were linked by 2,6-pyridinedicarboxaldehyde which was formed in 74 % yield. Next, we investigated the possibility of preparing C–glycosides from commercially available quinoline sources with formyl groups at C–2, C–3 and C–8. The reaction proceeded smoothly with yields between 74–79 % (4.7c–4.9c). 2-Formylthiophene was also observed to give a moderate yield (64 %) of product 4.10c. Subsequently, the reaction scope was investigated on 2-nitro-tri-O-benzyl-D-galactal (4.11c), 2-nitrodihydropyran (4.12c), 2-nitro-di-O-benzyl-L-rhamnal (4.16c) and all were found to be viable substrates, with different aldehydes. Similarly, the reaction scope was screened towards different protecting groups on the 2-nitroglucal (4.13c–4.15c) and it was found that long chain alkyl substituent showed moderate yield of 67 % while the rest showed good yields (84–86%). This organocatalytic C–glycosylation protocol was further extended to aliphatic aldehydes such as butyraldehyde and acetaldehyde (4.17c and 4.18c), and the corresponding C–glycosides were obtained in moderate yields of 72 % and 74 % respectively. Various benzaldehyde derivatives were employed as glycosyl acceptors, and these produced moderate yields of product (52–69 %). However, 4-bromobenzaldehyde was able to achieve good yield (4.23c, 87 %).
Finally, this reaction pattern was applied to the disaccharide 4.18a and a moderate yield was obtained for 4.24c (Scheme 4.2, 69%) showing this glycosylation is tolerant of a wide range of substrates. All the products are well characterized and the structures of 4.2b and 4.8c was confirmed by X-ray crystallography (Figure 4.3, page 178 and 4.4, page 179). This methodology can be applied to the total synthesis of Scleropentaside A (Scheme 4.3). The nitro eliminated glycosides 4.25c is a key intermediate for Scleropentaside-A easy to generate by hydroboration and MnO₂ oxidation to obtained 4.27. The tribenzylprotected 4.27 is a key skeleton for Scleropentaside-A.

The possible catalytic cycle for this reaction is depicted in Scheme 4.4. Presumably, the reaction proceeds through the nucleophilic addition of carbene to aldehyde (I), forming the Breslow intermediate II. This, then attacks the more favored ⁵H₄ conformation (III) of (4.7a) to form IV, which then proton shift followed by NHC ejection to form C–glycoside (4.1b). Schmidt's group explained that 2-nitroglucal may favour the ⁵H₄ conformation as opposed to the ⁴H₅ conformation due to allylic strain. This would favour the acyl anion preferentially adding from the β-side of III.
4.3. Conclusion

In conclusion, we have developed a new method for an organocatalytic C–glycosidation, which is the first example of acylanion equivalent addition to anomic carbon of sugars. Furthermore this method was applied to formal synthesis of Scleropentaside A.

4.4. Experimental Section

General procedure for synthesis of 2-nitroglucal derivatives and their spectral details

Preparation of D-galactal (III):[56] A small portion (0.5 g) of D-(+)-galactose (5.0 g, 27.7 mmol, 1 equiv) was dissolved in Ac₂O (18.2 mL) at 0 °C. 70% Perchloric acid (0.5 mL)
was then added drop wise to initiate the reaction. The remaining galactose was added portionwise to the suspension and stirred for 3 hours at room temperature. After completion of the acetylation reaction, bromination at anomeric position was carried out using hydrogen bromide (17 mL) in acetic acid (33 % w/w) stirring at ambient temperature for 12 h. The completion of the reaction was monitor by using TLC (Ethyl acetate/hexanes 1:1). Then the reaction mixture was diluted with dichloromethane (200 mL), washed successively with ice water (3×100 mL), cold 5 % aqueous NaHCO₃ solution (2×50 mL), followed by brine (1×50 mL), and dried over anhydrous Na₂SO₄. The solvent was evaporated and the resulting yellow syrup was dissolved in aqueous solution of 50 % v/v acetic acid in water (37.5 mL). The solution was then cooled to −20 °C followed by the portionwise addition of zinc dust (9.0 g, 137.6 mmol, 5 equiv) under vigorous stirring. After the addition of zinc, the suspension was stirred at 0 °C and the completion of the reaction was monitored by TLC. Upon the completion of the reaction, the suspension was filtered through a Celite pad and washed with dichloromethane (150 mL) and ice water. The filtrate was separated and the dichloromethane layer was washed with water (2×100 mL), saturated NaHCO₃ solution (2×50 mL), brine (50 mL), and dried over anhydrous Na₂SO₄. Solvent was removed and crude product was purified by column chromatography on silica gel using ethyl acetate-hexane (1:4) as eluting solvent afforded the solid compound 3,4,6-tri-O-acetyl-D-galactal (4.45 g, 59 % Yield) which is further subjected to deacetylation to get compound III. To a solution of 3,4,6-tri-O-acetyl-D-galactal (3.0 g, 11.0 mmol, 1 equiv) in MeOH (20 mL), sodium methoxide (0.178 g, 3.3 mmol, 0.3 equiv) was added and the mixture was stirred overnight at room temperature. After the reaction has been finished (TLC monitored), the resulting mixture was
evaporated and subjected to column chromatography on silica gel with eluent system of CH₂Cl₂–MeOH (10:1) to give pure product III (1.53 g, 95 % Yield).

**Synthesis of 3,4,6-Tri-O-benzyl-d-galactal IV (4.2a):**⁵⁵⁷

To a solution of sodium hydride (3.3 g, 82.2 mmol, 60 % suspension in mineral oil, and 4 equiv) in 4:1 THF/DMF mixture (100 mL), d-galactal III (3 g, 20.5 mmol, 1 equiv) was added slowly at 0 °C. The reaction mixture was heated to 60 °C after the addition of benzyl bromide (9.7 mL, 82.2 mmol, 4 equiv) at the same temperature. The mixture was then stirred for 4 hours at this temperature until all the starting material was consumed (TLC monitored). The solution was then diluted with diethyl ether (100 mL) and washed with ice water (2×100 mL). The organic layer was subsequently washed with brine (2×10 mL) and dried over anhydrous Na₂SO₄. After removing the solvent under reduced pressure, pure compound 4.2a was obtained from purification by column chromatography on silica gel hexane–ethyl acetate (10:1) as white solid; (6.15 g, 72 % yield); **m.p.** 53–54 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.32–7.21 (m, 15H), 6.36 (d, J = 8.0 Hz, 1H), 4.88–4.83 (m, 2H), 4.66–4.58 (m, 3H), 4.51–4.40 (m, 2H), 4.20–4.16 (m, 2H), 3.95–3.93 (m, 1H), 3.77 (dd, J₁ = 12.0 Hz, J₂ = 8.0 Hz, 1H), 3.65 (dd, J₁ = 12.0 Hz, J₂ = 4.0 Hz, 1H); **FT–IR** (Neat): νₘₐₓ 2866, 1643, 1454, 1161, 1094, 1061 cm⁻¹; **HRMS** (ESI) m/z [M+H]⁺: calcd. for C₂₇H₂₉O₄: 417.2066, found: 417.2061.

**3,4,6-Tri-O-benzyl-d-glucal (4.1a):**⁵⁵⁷

The title compound was synthesized according to the general procedure for 4.2a. The product was obtained as pale white solid; (6.4 g, 75 % yield); **m.p.** 57–58 °C; **HRMS** (ESI) m/z [M+H]⁺: calcd. for C₂₇H₂₉O₄: 417.2066, found: 417.2061.
CHAPTER 4: N-Heterocyclic Carbene-Catalyzed C-Glycosylation: A Concise Approach from Stetter Reaction and Formal Synthesis of Scleropentaside A

3,4,6-Tri-O-Octyl-D-glucal (4.3a):

The title compound was synthesized according to the general procedure for 4.2a. Here octyl bromide replaced benzyl bromide. The product was obtained as colourless oil; (6.4 g, 65 % yield);

\[
[a]^{23}_D = +22.8 \quad (c = 1.4, \text{CHCl}_3); \quad ^1H \text{NMR} \ (400 \text{ MHz, CDCl}_3): \delta \ 6.34 \ (d, J = 6.0 \text{ Hz, 1H}), 4.76 \ (dd, J_1 = 6.1 \text{ Hz, } J_2 = 2.5 \text{ Hz, 1H}), 4.16–4.02 \ (m, 1H), 3.96–3.40 \ (m, 10H), 1.68–0.85 \ (m, 45H); \quad ^{13}C \text{NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 161.1, 144.3, 100.3, 76.9, 76.4, 74.7, 72.0, 71.7, 69.2, 68.7, 64.1, [31.8, 31.7, 30.2, 30.1, 29.6, 29.4, 29.3, 29.3, 29.2, 29.1, 28.5, 26.2, 26.1, 25.8, 22.6, 14.0 \ (21\text{C}'s). \quad \text{FT-IR} \ (\text{Neat}): \nu_{\text{max}} \ 3018, 2927, 2399, 1467, 1215, 1101, \ 769 \ \text{cm}^{-1}; \quad \text{HRMS} \ (\text{ESI}) \ m/z \ [M+H]^+: \text{calcd. for } C_{30}H_{59}O_4: 483.4413, \text{ found: 483.4409.}

3,4,6-Tri-O-methyl-D-glucal (4.4a):

The title compound was synthesized according to the general procedure with the slight change in benzyl protection. Here methyl iodide (5 equiv) replaced benzyl bromide. The product was obtained viscous liquid; (3.05 g, 79 % yield);

\[
{^1H \text{NMR}} \ (400 \text{ MHz, CDCl}_3): \delta \ 6.34 \ (d, J = 7.1 \text{ Hz, 1H}), 4.78 \ (dd, J_1 = 8.2 \text{ Hz, } J_2 = 3.7 \text{ Hz, 1H}), 3.95–3.83 \ (m, 2H), 3.63–3.36 \ (m, 12H).

3,4,6-Tri-O-m-nitrobenzyl-D-glucal (4.5a):

The title compound was synthesized according to the general procedure with the slight change in benzyl protection. Here m-nitrobenzylbromide replaced benzyl bromide. The product was obtained as pale yellow solid; (7.1 g, 63 % yield); \textbf{m.p.} 95–97 °C; \n
\[
[a]^{23}_D = -9.2 \quad (c = 1.0, \text{CHCl}_3); \quad ^1H \text{NMR} \ (400 \text{ MHz, CDCl}_3): \delta
\]
8.22‒8.10 (m, 6H), 7.67‒7.46 (m, 6H), 6.49 (d, $J = 6.1$ Hz, 1H), 5.00‒4.93 (m, 2H), 4.86‒4.62 (m, 5H), 4.34 (d, $J = 6.1$ Hz, 1H), 4.12 (d, $J = 8.1$ Hz, 1H), 4.00‒3.95 (m, 2H), 3.86 (dd, $J_1 = 10.8$ Hz, $J_2 = 2.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 148.3, 145.2, 140.3, 140.1, 133.2, 133.1, 133.0, 129.4 (2C), 129.3, 122.6 (2C), 122.6 (2C), 122.1 (2C), 122.0 (2C), 121.9 (2C), 99.2, 76.6, 74.9, 72.5, 72.3, 68.9. FT–IR (Neat): $v_{\text{max}}$ 3018, 2927, 1531, 1215, 1101, 758 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{27}$H$_{25}$N$_3$O$_{10}$Na: 574.1438, found: 574.1434.

1,5-Anhydro-2,6-dideoxy-3,4-bis-O-(phenylmethyl)-L-arabino-hex-1-enitol (4.6a):$^{[59]}$

The title compound was synthesized according to the general procedure using diacetyl rhamnal, deacetylation followed by benzyl protection (2.5 equiv.). The product was obtained as colourless oil; (5.2 g, 73 % yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38‒7.25 (m, 10H), 6.39 (d, $J = 6.0$ Hz, 1H), 4.93‒4.88 (m, 2H), 4.73 (d, $J = 11.3$ Hz, 1H), 4.71 (d, $J = 11.7$ Hz, 1H), 4.60 (d, $J = 11.7$ Hz, 1H), 4.25 (d, $J = 6.2$ Hz, 1H), 4.02‒3.97 (m, 1H), 3.52 (dd, $J_1 = 8.9$ Hz, $J_2 = 6.5$ Hz, 1H), 1.42 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 144.7, 138.3, 138.2, 128.3 (3C), 128.2 (2C), 127.9 (2C), 127.7 (2C), 127.5, 100.0, 79.4, 76.3, 74.0, 73.9, 70.4, 17.4; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{20}$H$_{23}$O$_3$: 311.1647, found: 311.1649.

(c) Synthesis of 3,4,6-Tri-O-benzyl-2-nitro-D-galactal (4.8a) (V):$^{[60]}$

Con. HNO$_3$ (0.8 mL, 19.2 mmol, 4 equiv) was added dropwise to Ac$_2$O (7 mL) at 10 °C under argon. During the addition, the external temperature was controlled at −10 °C to maintain the internal temperature at 20‒25 °C. The temperature was further decreased to −33 °C after the addition was completed. Compound (4.2a) (2 g, 4.8 mmol, 1 equiv) in acetic anhydride (4 mL) was added slowly
for a period of 10–15 mins and the mixture was allowed to be stirred for 30 min. The resulting mixture was then warmed to 0 °C by removing the cooling bath and then poured into ice water (20 mL). After adding 10 mL of brine, the aqueous layer was repeatedly extracted with diethyl ether (3×30 mL). The combined organic extract was subsequently dried with anhydrous Na₂SO₄ and evaporated. After removal of solvent, residue was dissolved in dichloromethane (10 mL), Et₃N (0.3 mL, 1.7 mmol, 0.4 equiv) was added dropwise and the mixture was stirred at 0 °C. The reaction mixture was next stirred for further 30 mints at ambient temperature. Completion of reaction was monitor by TLC. After completion the reaction mixture was further diluted with dichloromethane (100 mL) and subsequently washed with water, 1N of HCl, saturated NaHCO₃, brine and then dried with Na₂SO₄. After evaporation of solvent, the residue was purified by column chromatography on silica gel with eluent system of hexane-ethyl acetate (4:1) to give viscous oil; (1.6 g, 57 % yield); ¹H NMR (400 MHz, CDCl₃): δ 8.0 (s, 1H), 7.40‒7.27 (m, 15H), 4.91‒4.45 (m, 8H), 3.97‒3.91 (m, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 154.5, 138.0, 137.7, 136.9, 131.5, 128.7 (2C), 128.4 (2C), 128.3, 128.3 (2C), 127.9 (2C), 127.8 (3C), 127.7, 127.7 (2C), 78.1, 74.9, 73.5, 73.0, 72.1, 67.6, 67.5; HRMS (ESI) m/z [M+H]⁺: calcd. for C₂₇H₂₈NO₆: 462.1917, found: 462.1915.

3,4,6-Tri-O-benzyl-2-nitro-D-glucal (4.7a):[⁶¹,⁶²]

The title compound was synthesized according to the general procedure using tribenzylglucal (4.1a). The product was obtained as pale yellow solid; (1.12 g, 56 % yield); m.p. 53‒56 °C; ¹H NMR (300 MHz, CDCl₃): δ 8.20 (s, 1H), 7.35‒7.21 (m, 15H), 4.68‒4.44 (m, 8H), 3.87 (dd, J₁ = 3.1 Hz, J₂ = 2.4 Hz, 1H), 3.72 (dd, J₁ = 14.2 Hz, J₂ = 10.1 Hz, 1H), 3.60 (dd, J₁ = 14.2 Hz, J₂ = 7.1 Hz, 1H);
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 154.6, 137.5, 137.0, 128.8 (2C), 128.6 (4C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 128.1, 128.0 (2C), 127.9 (2C), 78.6, 73.6, 73.2, 71.9, 71.3, 67.9, 67.6; FT–IR (Neat): $v_{\text{max}}$ 3007, 2918, 2870, 1719, 1599, 1557, 1362, 1096 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{27}$H$_{28}$NO$_6$: 462.1917, found: 462.1916.

3,4,6-Tri-O-Octyl-2-nitro-D-glucal (4.9a):

The title compound was synthesized according to the general procedure. The product was obtained as viscous liquid; (1.3 g, 61% yield); $[\alpha]_{D}^{23}$ = −3.0 ($c = 0.1$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.20 (s, 1H), 4.70–4.66 (m, 1H), 4.50–4.49 (m, 1H), 3.80–3.40 (m, 9H), 1.29 (bs, 35H), 0.91–0.88 (m, 10H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.2, 130.8, 78.5, 71.9, 71.7, 70.6, 70.2, 68.2, 68.1, [31.8, 31.7, 29.9, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 26.1, 26.0, 25.9, 22.6, 22.6, 14.0] (21C). FT–IR (Neat): $v_{\text{max}}$ 2859, 2090, 1643, 1346, 1215, 1095, 756 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{30}$H$_{58}$NO$_6$: 528.4264, found: 528.4265.

3,4,6-Tri-O-methyl-2-nitro-D-glucal (4.10a):[61] The title compound was synthesized according to the general procedure using tri-methylglucal (4.4a). The product was obtained as colourless oil; (1.68 g, 68 % yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.20 (s, 1H), 4.75–4.70 (m, 1H), 4.46 (t, $J = 2.2$ Hz, 1H), 3.74 (dd, $J_1 = 2.4$ Hz, $J_2 = 1.8$ Hz, 1H), 3.66 (dd, $J_1 = 10.8$ Hz, $J_2 = 8.0$ Hz, 1H), 3.53–3.40 (m, 10H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.2, 130.5, 77.7, 72.8, 69.7, 68.9, 59.1, 57.8, 57.4.

5-Nitro-3,4-dihydro-2H-pyran (4.11a):[62,63]

The title compound was synthesized according to the general procedure using
DHP. The product was obtained as yellow liquid; (1.8 g, 60 % yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.19 (s, 1H), 4.11 (t, $J = 5.2$ Hz, 2H), 2.64 (t, $J = 6.4$ Hz, 2H), 2.01–1.95 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.7, 131.2, 67.4, 20.2, 20.1; FT–IR (Neat): $\nu_{\text{max}}$ 3414, 1628, 1618, 1491, 1341, 1281, 1230, 1186 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_5$H$_8$NO$_3$: 130.0504, found: 130.0504.

3,4,6-Tri-O-$m$-nitrobenzyl-2-nitro-D-glucal (4.12a):

The title compound was synthesized according to the general procedure using compound 4.5a. The product was obtained as viscous liquid; (1.34 g, 62 % yield); $[\alpha]^{23}_D = -21.0$ ($c = 0.4$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.29 (s, 1H), 8.18–8.08 (m, 6H); 7.66–7.45 (m, 6H); 4.94–4.77 (m, 6H), 4.68–4.57 (m, 2H), 4.18 (t, $J = 2.1$ Hz, 1H), 3.90–3.80 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.8, 148.3, 148.2, 139.5, 139.4, 138.8, 133.4, 133.3, 133.2, 130.2, 129.7, 129.5, 129.5, 129.5, 129.5, 123.1, 122.9, 122.8, 122.1, 121.9, 121.8, 77.6, 77.2, 72.0, 71.5, 70.6, 68.2, 67.8; FT–IR (Neat): $\nu_{\text{max}}$ 3442, 3018, 2399, 1637, 1533, 1350, 1215, 927, 758 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{27}$H$_{25}$N$_4$O$_{12}$: 597.1469, found: 597.1464.

1,5-anhydro-2,6-dideoxy-2-nitro-3,4-bis-O-(phenylmethyl)-L-arabino-hex-1-enitol (4.13a):$^{[53]}$

The title compound was synthesized according to the general procedure using 4.6a. The product was obtained as yellow liquid; (1.46 g, 64 % yield); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.25 (s, 1H), 7.42–7.28 (m, 10H), 4.82–4.68 (m, 4H), 4.56 (d, $J = 12.1$ Hz, 1H), 4.49 (d, $J = 12.0$ Hz, 1H), 3.71 (t, $J = 1.9$ Hz, 1H), 1.46 (d, $J = 7.2$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.5, 137.8, 137.0, 130.3, 128.6 (2C), 128.6 (2C), 128.5, 128.2 (2C), 128.1, 128.0, 127.7 (2C), 76.1, 74.4, 73.1, 71.7, 68.4, 16.1;

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HRMS (ESI) m/z [M+H]^+: calcd. for C\textsubscript{20}H\textsubscript{22}NO\textsubscript{5}: 356.1498, found: 356.1506.

**General Procedure for synthesis of aldehydes (4.14a–4.15a) and their spectral details**

(a) *Synthesis of 2,6-Pyridinedicarboxaldehyde (4.14a) and 6-(hydroxymethyl)picinaldehyde (4.15a):* 2,6-pyridinedimethanol (0.3 g, 2.1 mmol) was dissolved in chloroform (24 mL) and MnO\textsubscript{2} (1.9 g, 21.5 mmol) was added. The suspension was then stirred at reflux for 5 hours. The residue was then filtered and washed with chloroform and diethyl ether. The filtrate was then evaporated by using rotary evaporator and purified to afford both 4.14a & 4.15a with yield of 40 % & 20 % respectively.

**Pyridine-2,6-dicarbaldehyde (4.14a):[^64]**

The title compound was synthesized according to the general procedure. The product was obtained as pale white solid; (118 mg, 40 % yield); **m.p.** 122–123 °C; \(^1\text{H NMR}\) (400 MHz, CDCl\textsubscript{3}): \(\delta\) 10.17 (s, 2H), 8.18 (d, \(J = 7.4\) Hz, 2H), 8.10 (d, \(J = 7.4\) Hz, 1H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\textsubscript{3}): \(\delta\) 192.3 (2C), 152.9, 138.4 (2C), 125.3 (2C); **HRMS (ESI)** m/z [M+H]^+: calcd. for C\textsubscript{7}H\textsubscript{6}NO\textsubscript{2}: 136.0399, found: 136.0399.

**6-(Hydroxymethyl)picinaldehyde (4.15a):[^64]**

The title compound was synthesized according to the general procedure. The product was obtained as pale white solid; (59 mg, 20 % yield); **m.p.** 85–87 °C; \(^1\text{H NMR}\) (400 MHz, CDCl\textsubscript{3}): \(\delta\) 10.12 (s, 1H), 7.91 (d, \(J = 4.3\) Hz, 2H), 7.54 (t, \(J = 4.1\) Hz, 1H), 4.91 (s, 2H), 3.58–3.55 (m, 1H, –OH); **HRMS (ESI)** m/z [M+H]^+: calcd. for C\textsubscript{7}H\textsubscript{8}NO\textsubscript{2}: 138.0555, found: 138.0558.
Experimental procedure for disaccharide synthesis (4.18a):

1,5-Anhydro-2-deoxy-4-O-α-D-glucopyranosyl-D-arabino-hex-1-enitol (4.16a):[65]

The title compound was synthesized from deacetylation of corresponding hexaacyethyltrisaccharide[12] (3 g, 5.3 mmol) (maltose derived). The product was obtained as viscous oil; (1.58 g, 96 % yield); 1H NMR (400 MHz, MeOD-d₄): δ 6.38 (dd, J₁ = 6.0 Hz, J₂ = 1.5 Hz, 1H), 5.33 (d, J = 3.7 Hz, 1H), 4.71 (dd, J₁ = 6.0 Hz, J₂ = 2.3 Hz, 1H)), 4.41 (d, J = 6.6 Hz, 1H), 3.93‒3.61 (m, 8H), 3.46 (dd, J₁ = 9.7 Hz, J₂ = 3.7 Hz, 1H), 3.36‒3.27 (m, 1H); 13C NMR (100 MHz, MeOD-d₄): δ 143.5, 102.6, 99.8, 77.5, 76.6, 73.6, 73.2, 72.4, 70.2, 68.7, 61.3, 60.3; HRMS (ESI) m/z [M+H]+: calcd. for C₁₂H₂₁O₉: 309.1186, found: 309.1184.

1,5-Anhydro-2-deoxy-3,6-bis-O-(phenylmethyl)-4-O-[2,3,4,6-tetrakis-O-(phenylmethyl)-α-D-glucopyranosyl]-D-arabino-hex-1-enitol (4.17a):[66]

The title compound was synthesized according to the general procedure for benzyl protection using 8 equiv benzyl bromide. The product was obtained as viscous oil; (4.8 g, 59 % yield); 1H NMR (400 MHz, CDCl₃): δ 7.38‒7.16 (m, 30H), 6.53 (d, J = 6.2 Hz, 1H), 5.33 (d, J = 3.6 Hz, 1H) (may be merging of α-anomeric proton of glucosyl part), 4.99 (d, J = 10.8 Hz, 1H), 4.94 (dd, J₁ = 6.2 Hz, J₂ = 3.2 Hz, 1H), 4.85 (dd, J₁ = 10.7 Hz, J₂ = 7.2 Hz, 2H), 4.72–4.48 (m, 8H), 4.41–4.23 (m, 4H), 3.98‒3.52 (m, 8H); 13C NMR (100 MHz, CDCl₃): δ145.3, 138.9, 138.4, 138.2, 138.1, 138.0, 127.9, 128.4 (2C), 128.4 (2C), 128.4 (2C), 128.3 (2C), 128.3 (4C), 128.0 (2C), 127.9 (4C), 127.9 (2C), 127.8, 127.6 (4C), 127.6, 127.5, 127.4 (2C), 99.3, 96.2, 81.8, 79.7, 77.5, 76.3, 75.6, 75.0, 74.4, 73.4, 73.3, 72.8, 70.8, 70.3, 68.9, 68.3, 68.2; HRMS (ESI) m/z [M+Na]+: calcd. for C₅₄H₅₆O₉Na:
1,5-Anhydro-2-deoxy-2-nitro-3,6-bis-O-(phenylmethyl)-4-O-[2,3,4,6-tetrakis-O-(phenylmethyl)-α-D-glucopyranosyl]-D-arabino-hex-1-enitol (4.18a):[^54]

The title compound was synthesized according to the general procedure using 4.17a. The product was obtained as viscous oil; (1g, 48% yield); \(^{1}H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 8.34\) (s, 1H), 7.39–7.12 (m, 30H), 4.93 (d, \(J = 10.8\) Hz, 1H), 4.84–4.79 (m, 3H) (may be merging of \(\alpha\)-anomeric proton of glucosyl part), 4.74–4.60 (m, 6H) 4.52–4.4.40 (m, 5H), 4.10 (d, \(J = 1.7\) Hz, 1H), 3.85 (t, \(J = 9.2\) Hz, 1H), 3.75–3.60 (m, 6H); 3.52 (dd, \(J_1 = 9.6\) Hz, \(J_2 = 3.6\) Hz, 1H), \(^{13}C\) NMR (100 MHz, CDCl\(_3\)): \(\delta 154.6, 138.6, 138.0, 137.9, 137.7, 137.4, 137.2, 130.4, 128.6\) (2C), 128.4 (2C), 128.4 (4C), 128.4 (4C), 128.0 (2C), 128.0 (2C), 127.9 (2C), 127.9 (2C), 127.8 (2C), 127.8, 127.7 (2C), 127.6, 97.7, 81.5, 79.5, 79.1, 77.2, 76.8, 75.6, 75.2, 73.5, 73.5, 73.3, 72.8, 71.1, 70.4, 68.2, 67.6, 67.2; HRMS (ESI) m/z [M+Na]\(^+\): calcd. for C\(_{54}\)H\(_{55}\)NO\(_{11}\)Na: 916.3673, found: 916.3654.

**Experimental procedure and spectral detail of C-glycosides**

![Experimental procedure and spectral detail of C-glycosides](image)

Typical general experimental procedure for intermolecular Stetter reaction on 2-nitroglucal is illustrated for formation of 4.1b: Precatalyst E (6.7 mg, 0.025 mmol, 0.15 equiv), 3,4,6-Tri-O-benzyl-2-nitroglucal 4.7a (0.1 g, 0.217 mmol, 1.3 equiv), pyridine-2-carboxyaldehyde (16 \(\mu\)L, 0.167 mmol, 1 equiv) was dissolved in anhydrous dichloromethane (3 mL) in an oven-dried round bottom flask under nitrogen atmosphere
at room temperature. Then, DIPEA (2.9 μL, 0.0167 mmol, 0.1 equiv) was added to the reaction mixture using micro-syringe and stirred for 12–24 hrs at ambient temperature. After 12 hrs, the progress of reaction was monitored through TLC until all the starting material consumed completely. After completion of the reaction, the reaction mixture was quenched using (10 mL) of water and the reaction mixture was extracted using dichloromethane (3x20 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated. The crude product was purified through column chromatography on silica gel (ethyl acetate/hexane 1:4) to obtain β-selective C–glycosides.

**Pyridine-2-yl(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-β-D-glucopyranosyl)methanone (4.1b):**

The title compound was synthesized according to the general procedure. The product was obtained as viscous oil; (73.0 mg, 77% yield); \([\alpha]^{22}_{D} = +12.5 \ (c = 1.2, \ \text{CHCl}_3); \quad ^1\text{H NMR} \ (400 \text{ MHz, } \text{CDCl}_3): \ \delta 8.69 (d, J = 4.0 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.87 (dt, J$_1$ = 7.7 Hz, J$_2$ = 1.4 Hz, 1H), 7.52 (dd, J$_1$= 7.4 Hz, J$_2$ = 4.8 Hz, 1H), 7.37–7.22 (m, 15H), 5.90 (d, J = 10.1 Hz, 1H), 5.11 (t, J = 10.1 Hz, 1H), 4.86 (dd, J$_1$ = 10.7 Hz, J$_2$ = 2.7 Hz, 2H), 4.70–4.45 (m, 5H), 3.85–3.81 (m, 2H), 3.74 (d, J = 2.2 Hz, 2H); \quad ^{13}\text{C NMR} \ (100 \text{ MHz, } \text{CDCl}_3): \ \delta 192.9 (C=O), \text{ Ar–C}; 151.5 (Py–C$_1$), 149.2 (Py–C$_3$), 137.8 (Ph-Quaternary–C) , 137.6 (Ph-Quaternary–C), 137.1 (Ph-Quaternary–C), 137.0 (Py–C$_3$), 128.5 (Ph–2C), 128.5 (Ph–2C), 128.3 (Ph–2C), 128.1 (Ph–2C), 128.1 (Ph–C$_4$), 128.0 (Ph–C$_4$), 127.9 (Ph–C$_4$), 127.8 (Ph–2C), 127.7 (Ph–2C), 127.6 (Py–C$_4$), 123.3 (Py–C$_2$), Sug–C & Bn–CH$_2$; 85.8 (Sug–C), 82.6 (Sug–C), 80.4 (Sug–C), 77.8 (Sug–C), 75.6 (Bn–C), 75.2 (Bn–C), 74.7 (Sug–C),
73.4 (Bn‒C), 68.3 (Sug‒C); **FT‒IR** (Neat): \( \nu_{\text{max}} \) 2916, 2868, 1712, 1554, 1371, 1361, 1099 cm\(^{-1}\); **HRMS** (ESI) m/z [M+H]\(^+\): calcd. for C\(_{33}\)H\(_{33}\)N\(_2\)O\(_7\): 569.2288, found: 569.2287.

**Quinoline-2-yl(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-β-D-glucopyranosyl)methanone (4.2b):**

![Chemical structure of quinoline-2-yl(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-β-D-glucopyranosyl)methanone](image)

The title compound was synthesized according to the general procedure using quinoline-2-carboxaldehyde (0.167 mmol). The product was obtained as white solid; (92.0 mg, 89 % yield); m.p. 114–116 °C; \([\alpha]^{22}_D = +1.4\) (c = 1.1, CHCl\(_3\)); **\(^1\)H NMR** (400 MHz, CDCl\(_3\)): \( \delta \) 8.26 (d, \( J = 8.5 \) Hz, 1H), 8.16 (d, \( J = 8.5 \) Hz, 1H), 8.08 (d, \( J = 8.5 \) Hz, 1H), 7.85 (d, \( J = 8.0 \) Hz, 1H), 7.76 (dt, \( J_1 = 8.3 \) Hz, \( J_2 = 1.3 \) Hz, 1H), 7.67–7.63 (m, 1H), 7.34–7.17 (m, 15H), 6.13 (d, \( J = 10.1 \) Hz, 1H), 5.10 (t, \( J = 10.1 \) Hz, 1H), 4.84 (d, \( J = 10.7 \) Hz, 2H), 4.69–4.61 (m, 2H), 4.54–4.50 (m, 2H), 4.42 (d, \( J = 12.0 \) Hz, 1H), 3.90 (dt, \( J_1 = 9.8 \) Hz, \( J_2 = 3.1 \) Hz, 1H), 3.85–3.80 (m, 1H), 3.72 (d, \( J = 3.0 \) Hz, 2H); **\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)): \( \delta \) 193.1 (C=O), Ar–C; 151.0, 147.1, 137.8, 137.6, 137.2 (2C), 130.9, 130.3, 129.9, 129.2, 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.1 (3C), 127.9, 127.8 (2C), 127.7 (2C), 127.7, 127.6, 118.8, Sug‒C & Bn‒CH\(_2\); 86.2, 82.6, 80.5, 77.9, 75.7, 75.1, 74.7, 73.4, 68.4; **FT‒IR** (Neat): \( \nu_{\text{max}} \) 3018, 2870, 1714, 1558, 1423, 1361, 1099, 771 cm\(^{-1}\); **HRMS** (ESI) m/z [M+H]\(^+\): calcd. for C\(_{37}\)H\(_{35}\)N\(_2\)O\(_7\): 619.2444, found: 619.2441.

**6-methyl Pyridine-2-yl(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-β-D-glucopyranosyl)methanone (4.3b):**

![Chemical structure of 6-methyl Pyridine-2-yl(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-β-D-glucopyranosyl)methanone](image)

The title compound was synthesized according to the general procedure using 6-methylpyridine-2-carboxaldehyde (0.167 mmol). The product was obtained as viscous oil; (79.6 mg, 82 %...
yield); \([\alpha]_{D}^{22} = +6.9\) (c = 1.2, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.88\) (d, \(J = 7.6\) Hz, 1H), 7.74 (t, \(J = 7.7\) Hz, 1H), 7.37–7.23 (m, 16H), 5.94 (d, \(J = 10.1\) Hz, 1H), 5.06 (t, \(J = 10.1\) Hz, 1H), 4.86 (dd, \(J_1 = 10.8\) Hz, \(J_2 = 3.0\) Hz, 2H), 4.71–4.47 (m, 5H), 3.88–3.75 (m, 4H), 2.59 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 193.1\) (C=O), Ar–C; 158.3, 150.9, 137.8, 137.6, 137.1, 137.0 (2C), 128.5 (2C), 128.5 (2C), 128.3 (2C), 128.1 (2C), 127.9, 127.8 (2C), 127.7 (2C), 127.6, 120.3, Sug–C & Bn–CH\(_2\); 86.1, 82.6, 80.3, 77.9, 75.6, 75.1, 74.7, 73.3, 68.3, 24.3; FT–IR (Neat): \(v_{\text{max}}\) 3016, 2872, 2399, 1710, 1591, 1556, 1454, 1361, 1215, 1099 cm\(^{-1}\); HRMS (ESI) m/z [M+H]: calcd. for C\(_{34}\)H\(_{35}\)N\(_2\)O\(_7\): 583.2444, found: 583.2448.

6-Hydroxymethyl Pyridine-2-yl(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-\(\beta\)-D-glucopyranosyl) methanone (4.4b):

The title compound was synthesized according to the general procedure using 6-hydroxymethylpyridine-2-carboxyaldehyde (0.167 mmol). The product was obtained as pale yellow oil; (74.8 mg, 75 % yield); \([\alpha]_{D}^{23} = +2.0\) (c = 1.5, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.99\) (d, \(J = 7.6\) Hz, 1H), 7.88 (t, \(J = 7.7\) Hz, 1H), 7.50 (d, \(J = 7.7\) Hz, 1H), 7.45–7.20 (m, 15H), 5.78 (d, \(J = 10.1\) Hz, 1H), 5.04 (t, \(J = 10.0\) Hz, 1H), 4.84 (dd, \(J_1 = 10.8\) Hz, \(J_2 = 3.5\) Hz, 2H), 4.79 (d, \(J = 7.6\) Hz, 2H), 4.69–4.47 (m, 5H), 3.89–3.75 (m, 3H), 3.66 (dd, \(J_1 = 11.0\) Hz, \(J_2 = 5.1\) Hz, 1H) 3.40 (s, 1H, –OH); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 192.3\) (C=O), Ar–C; 159.4, 150.3, 137.7, 137.6, 137.4, 137.0, 128.5 (2C), 128.5 (2C), 128.3 (2C), 128.1 (3C), 128.0, 127.8 (4C), 127.7, 125.0, 121.9, Sug–C & Bn–CH\(_2\); 86.0, 82.7, 80.6, 77.8, 75.7, 75.6, 75.1, 73.3, 68.3, 64.2; FT–IR (Neat): \(v_{\text{max}}\) 3016, 2916, 2872, 2399, 1710, 1591, 1556, 1454, 1361, 1215, 1099 cm\(^{-1}\); HRMS (ESI) m/z [M+H]: calcd. for C\(_{34}\)H\(_{35}\)N\(_2\)O\(_8\):
Quinoline-8-yl(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-β-D-galactopyranosyl)methanone (4.5b):

The title compound was synthesized according to the general procedure using 8-quinolinecarboxaldehyde (0.167 mmol). The product was obtained as yellow liquid; (78.4 mg, 76 % yield); $\mathbf{[\alpha]}^{23}_D = \!\! ^{-}75.0$ (c = 0.8, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.96 (dd, $J_1$ = 4.1 Hz, $J_2$ = 1.7 Hz, 1H), 8.18 (dd, $J_1$ = 8.3 Hz, $J_2$ = 1.6 Hz, 1H), 8.13 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 1H), 8.02 (dd, $J_1$ = 8.1 Hz, $J_2$ = 1 Hz, 1H), 7.64 (t, $J$ = 7.7 Hz, 1H), 7.43–7.16 (m, 14H), 6.92 (d, $J$ = 6.4 Hz, 2H), 6.17 (d, $J$ = 10.1 Hz, 1H), 5.09 (t, $J$ = 10.0 Hz, 1H), 4.85 (dd, $J_1$ = 10.6 Hz, $J_2$ = 6.6 Hz, 2H), 4.70 (d, $J$ = 10.5 Hz, 1H), 4.59 (d, $J$ = 11.0 Hz, 1H), 4.47 (t, $J$ = 8.3 Hz, 1H), 4.16 (d, $J$ = 12.3 Hz, 1H), 4.04 (d, $J$ = 12.3 Hz, 1H), 3.79-3.71 (m, 2H), 3.49 (dd, $J_1$ = 11.3 Hz, $J_2$ = 3.8 Hz, 1H), 3.32 (d, $J$ = 11.2 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 197.6 (C=O), Ar–C; 150.4, 145.8, 137.6 (2C), 137.1, 136.3, 135.3, 132.9, 132.0, 128.5 (2C), 128.5 (2C), 128.3 (2C), 128.1 (3C), 127.9, 127.8, 127.7 (2C), 127.4, 127.4 (2C), 126.1, 121.5, Sug–C & Bn-CH$_2$; 85.8, 83.7, 80.9, 80.5, 77.7, 75.7, 75.1, 72.8, 67.8; FT–IR (Neat): $\nu_{\text{max}}$ 3030, 2870, 1683, 1556, 1373, 1215, 1101, 754 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{37}$H$_{35}$N$_2$O$_7$: 619.244, found: 619.244.

Pyridine-2-yl(3,4,6-tri-O-benzyl-2-deoxy-2-nitro-β-D-galactopyranosyl)methanone (4.6b):

The title compound was synthesized according to the general procedure using 2-nitrogalactal (1.3 equiv) instead of 2-nitroglucal. The product was obtained as pale yellow solid; (79.6 mg, 84 %
yield); m.p. 101–103 °C; [α]$_{D}^{23}$ = +24.9 (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.67–8.65 (m, 1H), 8.03 (d, $J$ = 7.8 Hz, 1H), 7.83 (dt, $J_1$ = 7.7 Hz, $J_2$ = 1.6 Hz, 1H), 7.49 (ddd, $J_1$ = 7.5 Hz, $J_2$ = 4.8 Hz, $J_3$ = 1.2 Hz, 1H), 7.41–7.25 (m, 15H), 5.86 (d, $J$ = 10.0 Hz, 1H), 5.44 (t, $J$ = 10.1 Hz, 1H), 4.95 (d, $J$ = 11.4 Hz, 2H), 4.72–4.57 (m, 3H), 4.48–4.39 (m, 2H), 4.33 (dd, $J_1$ = 10.4 Hz, $J_2$ = 2.7 Hz, 1H), 4.14 (d, $J$ = 2.2 Hz, 1H), 3.97 (t, $J$ = 6.4 Hz, 1H), 3.64–3.57 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 192.8 (C=O), Ar–C; 151.6, 149.1, 137.9, 137.6, 137.0, 136.7, 128.6 (2C), 128.4 (2C), 128.3 (2C), 128.2 (3C), 127.9 (2C), 127.9 (2C), 127.8, 127.8, 127.8, 123.3, Sug–C & Bn–CH$_2$; 83.4, 80.4, 78.7, 75.2, 74.8, 73.4, 72.4, 72.3, 68.2; FT–IR (Neat): $v_{\text{max}}$ 2914, 2872, 1710, 1554, 1454, 1375, 1215, 1114, 754 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{33}$H$_{33}$N$_2$O$_7$: 569.2288, found: 569.2285.

Pyridine-2-yl(3,4,6-tri-O-methyl-2-deoxy-2-nitro-β-D-glucopyranosyl)methanone (4.7b):

The title compound was synthesized according to the general procedure using methyl protected 2-nitroglucal$^6$ (1.3 equiv). The product was obtained as pale yellow liquid; (44.3 mg, 78 % yield); [α]$_{D}^{23}$ = +14.0 (c = 0.8, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.68 (d, $J$ = 4.3 Hz, 1H), 8.04 (d, $J$ = 7.8 Hz, 1H), 7.85 (dt, $J_1$ = 7.6 Hz, $J_2$ = 1.3 Hz, 1H), 7.51 (dd, $J_1$ = 6.9 Hz, $J_2$ = 5.1 Hz, 1H), 5.84 (d, $J$ = 10.1 Hz, 1H), 4.91 (t, $J$ = 10.1 Hz, 1H), 4.08 (t, $J$ = 9.4 Hz, 1H), 3.68–3.35 (m, 13H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 192.8 (C=O), Ar–C; 151.4, 149.2, 137.0, 127.9, 123.3, Sug–C & CH$_3$; 85.6, 84.3, 80.1, 79.4, 74.4, 70.6, 60.9, 60.7, 59.2; FT–IR (KBr): $v_{\text{max}}$ 3018, 2935, 2399, 1714, 1556, 1375, 1215, 1107, 756 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{15}$H$_{21}$N$_2$O$_7$: 341.1349, found: 341.1343.
Pyridine-2-yl(2,6-dideoxy-2-nitro-3,4-bis-O-(phenylmethyl)-β-L-mannopyranosyl) methanone (4.8b):

The title compound was synthesized according to the general procedure using 2-nitrorhamnal (1.3 equiv.) The product was obtained as viscous oil; (63.2 mg, 82% yield); [α]$^{23}$D = −11.8 (c = 0.8, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.71 (d, J = 4.5 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.87 (dt, J$_1$ = 7.7 Hz, J$_2$ = 1.5 Hz, 1H), 7.54–7.51 (m, 1H), 7.41–7.28 (m, 10H), 5.92 (d, J = 10.1 Hz, 1H), 5.07 (t, J = 10.1 Hz, 1H), 4.91 (d, J = 11.0 Hz, 1H), 4.85 (d, J = 10.5 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.68 (d, J = 10.5 Hz, 1H), 4.46 (t, J = 9.4 Hz, 1H), 3.82–3.75 (m, 1H); 3.38 (t, J = 9.1 Hz, 1H), 1.33 (d, J = 6.2 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 193.2 (C=O), Ar–C; 151.4, 149.2, 137.5, 137.1, 137.0, 128.5 (2C), 128.4 (2C), 128.1 (2C), 128.0, 127.9 (2C), 123.2, Sug–C & CH$_2$,CH$_3$; 86.3, 83.3, 82.3, 77.0, 75.7, 75.5, 74.2, 17.9; FT–IR (Neat): $\nu_{\text{max}}$ 3016, 2877, 2308, 1712, 1554, 1373, 1215, 1107 cm$^{-1}$. HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{26}$H$_{27}$N$_2$O$_6$: 463.1869, found: 463.1865.

Experimental procedure and spectral details of the nitro eliminated sugar derivatives

Typical experimental procedure for nitroeliminated C–glycosides is illustrated for formation of 4.1c: Precatalyst E (4.5 mg, 0.017 mmol, 0.1 equiv), Tri-O-benzyl-2-nitroglucal (4.7a) (0.1 g, 0.217 mmol, 1.3 equiv), 2-pyridine carboxaldehyde (16 μL,
0.167 mmol, 1 equiv) and Cs$_2$CO$_3$ (0.109 g, 0.334 mmol, 2 equiv) was dissolved in anhydrous dichloromethane (3 mL) in an oven-dried round bottom flask under nitrogen atmosphere at room temperature. After 12 hrs, the progress of reaction was monitored through TLC until all the aldehyde starting material consumed completely. After completion of the reaction, the reaction mixture was quenched using (10 mL) of water and the reaction mixture was extracted using dichloromethane (3x20 mL). The combined organic layer was dried over anhydrous Sodium sulfate and evaporated. The crude product was purified through column chromatography on silica gel (ethyl acetate/hexane 1:4) to obtain nitroeliminated C–glycosides.

**2,6-Anhydro-3-deoxy-1-C-(2-pyridyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.1c):**

The title compound was synthesized according to the general procedure. The product was obtained as viscous oil; (75.6 mg, 87 % yield); $[\alpha]^{23}_D = +30.8$ ($c = 1.3$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.69 (d, $J_1 = 4.7$ Hz, 1H), 7.93 (d, $J = 7.8$ Hz, 1H), 7.82 (dt, $J_1 = 7.7$ Hz, $J_2 = 1.6$ Hz, 1H), 7.47 (ddd, $J_1 = 7.5$ Hz, $J_2 = 4.8$ Hz, $J_3 = 1.1$ Hz, 1H), 7.39-7.29 (m, 15H), 6.40 (d, $J = 2.8$ Hz, 1H), 4.89 (d, $J = 11.2$ Hz, 1H), 4.76–4.61 (m, 5H), 4.51 (dd, $J_1 = 6.6$ Hz, $J_2 = 2.8$ Hz, 1H), 4.26 (td, $J_1 = 9.1$ Hz, $J_2 = 3.3$ Hz, 1H), 4.07 (dd, $J_1 = 9.1$ Hz, $J_2 = 6.8$ Hz, 1H), 3.97–3.92 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 187.3 (C=O), Ar–C & alkene; 154.2, 149.7, 148.6, 138.1, 138.0, 137.9, 136.9, 128.4 (2C), 128.4 (2C), 128.3 (3C), 127.9 (3C), 127.8 (4C), 127.6, 126.2, 124.6, 114.3, Sug & Bn-CH$_2$; 77.7, 76.7, 74.0, 73.7, 73.5, 71.2, 68.0; FT–IR (Neat): $\nu_{\text{max}}$ 3030, 3010, 2868, 1666, 1583, 1454, 1271, 1095, 1028, 748 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{33}$H$_{32}$NO$_5$: 522.2280, found:
2,6-Anhydro-3-deoxy-1-C-(3-pyridyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-
enose (4.2c):

The title compound was synthesized according to the general procedure using pyridine-3-carboxaldehyde (0.167 mmol). The product was obtained as yellow viscous oil; (73.9 mg, 85 % yield); \([\alpha]^{23}_D = +2.76 \ (c = 0.6, \text{CHCl}_3)\); \(^1\text{H} \text{NMR} \ (400 \text{ MHz, CDCl}_3)\): \(\delta 9.13 \ (d, \ J_1 = 4.7 \text{ Hz, 1H}), \ 8.75 \ (dd, \ J_1 = 7.7 \text{ Hz, } J_2 = 1.5 \text{ Hz, 1H}), \ 8.21 \ (td, \ J_1 = 7.7 \text{ Hz, } J_2 = 1.6 \text{ Hz, 1H}), \ 7.35–7.19 \ (m, 16\text{H}), \ 5.97 \ (d, \ J = 3.0 \text{ Hz, 1H}), \ 4.84 \ (d, \ J = 11.2 \text{ Hz, 1H}), \ 4.70 \ (d, \ J = 5.0 \text{ Hz, 1H}), \ 4.68 \ (d, \ J = 5.0 \text{ Hz, 1H}), \ 4.63–4.53 \ (m, 3\text{H}), \ 4.35 \ (dd, \ J_1 = 6.2 \text{ Hz, } J_2 = 3.0 \text{ Hz, 1H}), \ 4.29–4.25 \ (m, 1\text{H}); \ 1\text{H} \text{NMR} \ (400 \text{ MHz, CDCl}_3): \delta 187.8 \ (C=O), \text{Ar}–C; \ 152.8, \ 150.7, \ 150.6, \ 137.9, \ 137.7, \ 137.5, \ 131.9, \ 128.5 \ (2\text{C}), \ 128.4 \ (3\text{C}), \ 128.4 \ (2\text{C}), \ 127.9 \ (4\text{C}), \ 127.8 \ (2\text{C}), \ 127.7 \ (3\text{C}), \ 123.1, \ 109.4, \text{Sug} \ & \text{Bn}–\text{CH}_2; \ 77.7, \ 75.6, \ 73.9, \ 73.6, \ 73.5, \ 71.3, \ 67.9; \text{FT–IR} \ (\text{Neat}): \nu_{max} \ 3028, \ 2310, \ 1670, \ 1624, \ 1585, \ 1454, \ 1269, \ 1215, \ 1097, \ 1072, \ 754 \ cm^{-1}; \text{HRMS} \ (\text{ESI}) \ m/z \ [M+H]^+: \text{calcd. for C}_{33}\text{H}_{32}\text{NO}_{5}: 522.2280, \text{found: 522.2280.}

2,6-Anhydro-3-deoxy-1-C-(4-pyridyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-
enose (4.3c):

The title compound was synthesized according to the general procedure using pyridine-4-carboxaldehyde (0.167 mmol). The product was obtained as pale yellow solid; (62.6 mg, 72 % yield); \(\text{m.p.} \ 98–100 \ ^\circ\text{C}; \ [\alpha]^{23}_D = -85.6 \ (c = 0.3, \text{CHCl}_3)\); \(^1\text{H} \text{NMR} \ (400 \text{ MHz, CDCl}_3): \delta 8.67 \ (d,
J = 5.8 Hz, 2H), 7.67 (dd, J1 = 4.6 Hz, J2 = 1.4 Hz, 2H), 7.35-7.24 (m, 15H), 5.92 (d, J = 3.0 Hz, 1H), 4.84 (d, J = 11.2 Hz, 1H), 4.71-4.53 (m, 5H), 4.34 (dd, J1 = 6.2 Hz, J2 = 3.1 Hz, 1H), 4.28-4.24 (m, 1H), 4.00 (dd, J1 = 8.5 Hz, J2 = 4.8 Hz, 1H), 3.90 (dd, J1 = 10.8 Hz, J2 = 2.7 Hz, 1H); 13C NMR (100 MHz, CDCl3): δ 188.3 (C=O), Ar-C; 150.1 (2C), 150.1 (2C), 142.8, 137.8, 137.6, 128.5 (2C), 128.5 (2C), 128.0, 127.9 (2C), 127.8 (4C), 127.7 (2C), 122.8 (2C), 110.5, Sug & Bn–CH2; 77.7, 75.6, 73.9, 73.5, 73.4, 71.4, 67.8; FT–IR (Neat): \( \nu_{\text{max}} \) 3007, 2916, 2868, 1718, 1703, 1680, 1629, 1454, 1267, 1097 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{33}\)H\(_{32}\)NO\(_5\): 522.2280, found: 522.2280.

2,6-Anhydro-3-deoxy-1-C-(5-methyl-2-pyridyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.4c):

The title compound was synthesized according to the general procedure using 6-methylpyridine-2-carboxaldehyde (0.167 mmol).

The product was obtained as viscous oil; (66.1 mg, 74 % yield); \([\alpha]_{D}^{23} = +23.5 \) (c = 0.4, CHCl3); \(^1\)H NMR (400 MHz, CDCl3): δ 7.72–7.66 (m, 2H), 7.38–7.28 (m, 16H), 6.46 (d, J = 2.9 Hz, 1H), 4.89 (d, J = 11.1 Hz, 1H), 4.75–4.59 (m, 5H), 4.49 (dd, J1 = 6.7 Hz, J2 = 2.9 Hz, 1H), 4.25 (td, J1 = 9.2 Hz, J2 = 3.0 Hz, 1H), 4.08 (dd, J1 = 9.2 Hz, J2 = 6.7 Hz, 1H), 3.99–3.91 (m, 2H), 2.63 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 187.5 (C=O), Ar-C; 157.7, 153.7, 149.8, 138.1, 138.0, 137.9, 136.9, 128.4 (2C), 128.4 (2C), 128.3 (2C), 127.9 (2C), 127.8 (3C), 127.7 (3C), 127.6, 125.9, 121.7, 114.3, Sug & Bn–CH2; 77.7, 76.6, 74.0, 73.6, 73.5, 71.0, 67.9, 24.5; FT–IR (Neat): \( \nu_{\text{max}} \) 3028, 2920, 2866, 1666, 1633, 1587, 1454, 1228, 1095, 754 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{34}\)H\(_{34}\)NO\(_5\): 536.2437, found: 536.2437.
2,6-Anhydro-3-deoxy-1-C-(5-hydroxymethyl-2-pyridyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.5c):

The title compound was synthesized according to the general procedure using 6-hydroxymethylpyridine-2-carboxaldehyde (0.167 mmol). The product was obtained as viscous oil; (76.3 mg, 83 % yield); $[\alpha]^{23}_D = -24.8 \ (c = 0.5, \text{CHCl}_3)$; $^1H$ NMR (400 MHz, DMSO–d$_6$): $\delta$ 7.97 (t, $J$ = 7.7 Hz, 1H), 7.68 (t, $J$ = 7.7 Hz, 2H), 7.32–7.28 (m, 15H), 6.29 (d, $J$ = 2.8 Hz, 1H), 5.55 (t, $J$ = 5.4 Hz, 1H, −OH), 4.76 (d, $J$ = 11.3 Hz, 1H), 4.66–4.51 (m, 8H), 4.38–4.30 (m, 2H), 3.89–3.76 (m, 3H); $^{13}C$ NMR (100 MHz, CDCl$_3$): $\delta$ 187.4 (C=O), Ar–C; 158.5, 152.9, 150.1, 138.0, 138.0, 137.8, 137.4, 128.4 (2C), 128.3 (2C), 128.0 (2C), 127.9 (2C), 127.4 (2C), 127.6, 123.1, 112.8, Sug & Bn–CH$_2$; 77.8, 76.2, 73.9, 73.7, 73.4, 71.1, 67.9, 64.1; FT–IR (Neat): $v_{\text{max}}$ 3447, 3018, 2399, 1668, 1521, 1417, 1215, 1193, 756 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{34}$H$_{24}$NO$_6$: 552.2386, found: 552.2386.

Compound (4.6c):

The title compound was synthesized according to the general procedure using 2.6 equiv. of 2-nitroglucal and pyridine-2,6-dicarboxaldehyde. The product was obtained as pale yellow viscous oil; (119.0 mg, 74 % yield); $[\alpha]^{23}_D = +38.2 \ (c = 0.9, \text{CHCl}_3)$; $^1H$ NMR (400 MHz, CDCl$_3$): $\delta$ 8.07 (d, $J$ = 7.8 Hz, 2H), 7.91 (t, $J$ = 7.5 Hz, 1H), 7.36–7.24 (m, 30H), 6.53 (d, $J$ = 3.0 Hz, 2H), 4.86 (d, $J$ = 11.2 Hz, 2H), 4.71–4.57 (m, 10H), 4.43 (dd, $J_1 = 6.5$ Hz, $J_2 = 3.0$ Hz, 2H), 4.22 (td, $J_1 = 8.8$ Hz, $J_2 = 3.2$ Hz, 2H), 4.03 (dd, $J_1 = 9.0$ Hz, $J_2 = 6.6$ Hz, 2H), 3.95–3.86 (m, 4H); $^{13}C$ NMR (100 MHz, CDCl$_3$): $\delta$ 186.3 (2C, C=O), Ar–C; 153.0 (2C), 149.5 (2C), 138.0 (2C), 138.0 (2C), 137.8 (3C),
128.4 (4C), 128.4 (4C), 127.9 (4C), 127.8 (4C), 127.8 (4C), 127.6 (2C), 126.8 (2C), 114.7 (2C), Sug & Bn–CH₂; 77.7 (2C), 76.4 (2C), 73.9 (2C), 73.6 (2C), 73.5 (2C), 71.1 (2C), 67.9 (2C); FT-IR (Neat): $\nu_{\text{max}}$ 3030, 2866, 1668, 1633, 1454, 1284, 1217, 1095, 750 cm⁻¹; HRMS (ESI) m/z [M+H]⁺: calcd. for C₆₁H₅₈NO₁₀: 964.4061, found: 964.4056.

2,6-Anhydro-3-deoxy-1-C-(quinoline-2-yl)-4,5,7-tris-(phenylmethyl)-D-arabinohexit-2-enose (4.7c):

The title compound was synthesized according to the general procedure using quinoline-2-carboxaldehyde (0.167 mmol). The product was obtained as dark brown liquid; (74.3 mg, 78 % yield); $[\alpha]_{D}^{23} = +62.3$ (c = 0.7, CHCl₃); $^1$H NMR (400 MHz, CDCl₃): $\delta$ 8.28 (d, $J$ = 8.4 Hz, 1H), 8.18 (d, $J$ = 8.4 Hz, 1H), 7.98 (d, $J$ = 8.5 Hz, 1H), 7.90 (d, $J$ = 8.2 Hz, 1H), 7.83–7.79 (m, 1H), 7.70–7.66 (m, 1H), 7.39–7.26 (m, 15H), 6.65 (d, $J$ = 2.9 Hz, 1H), 4.92 (d, $J$ = 11.2 Hz, 1H), 4.78–4.62 (m, 5H), 4.55 (dd, $J_1$ = 6.8 Hz, $J_2$ = 2.9 Hz, 1H), 4.31 (td, $J_1$ = 9.2 Hz, $J_2$ = 3.3 Hz, 1H), 4.14 (dd, $J_1$ = 9.2 Hz, $J_2$ = 6.8 Hz, 1H), 4.16–4.00 (m, 2H); $^{13}$C NMR (100 MHz, CDCl₃): $\delta$ 187.5 (C=O), Ar-C; 154.0, 149.6, 146.6, 138.1, 138.1, 137.9, 136.9, 130.4, 130.2, 128.9, 128.4 (4C), 128.3 (2C), 128.0 (2C), 127.8 (7C), 127.6, 127.6, 120.7, 115.6, Sug & Bn–CH₂; 77.8, 76.8, 74.1, 73.7, 73.5, 71.1, 68.0; FT-IR (Neat): $\nu_{\text{max}}$ 3088, 2918, 2868, 1666, 1633, 1556, 1496, 1454, 1114, 1098 cm⁻¹; HRMS (ESI) m/z [M+H]⁺: calcd. for C₃₇H₃₄NO₅: 572.2437, found: 572.2429.
2,6-Anhydro-3-deoxy-1-C-(quinoline-3-yl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.8c):

The title compound was synthesized according to the general procedure using quinoline-3-carboxaldehyde (0.167 mmol). The product was obtained as white crystalline solid; (75.3 mg, 79 % yield); m.p. 114–116 °C; [α]$^23_D$ = -64.3 (c = 0.8, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 9.39 (d, $J$ = 2.1 Hz, 1H), 8.85 (d, $J$ = 1.9 Hz, 1H), 8.17 (d, $J$ = 8.4 Hz, 1H), 7.86–7.82 (m, 1H), 7.69 (d, $J$ = 7.4 Hz, 1H), 7.55 (t, $J$ = 7.4 Hz, 1H), 7.39–7.28 (m, 15H), 6.07 (d, $J$ = 3.0 Hz, 1H), 4.91 (d, $J$ = 11.2 Hz, 1H), 4.76 (dd, $J_1$ = 11.2 Hz, $J_2$ = 4.0 Hz, 2H), 4.68–4.62 (m, 3H), 4.42 (dd, $J_1$ = 6.2 Hz, $J_2$ = 3.0 Hz, 1H), 4.38–4.34 (m, 1H), 4.08 (dd, $J_1$ = 8.5 Hz, $J_2$ = 6.2 Hz, 1H), 3.97 (dd, $J_1$ = 10.8 Hz, $J_2$ = 4.9 Hz, 1H), 3.86 (dd, $J_1$ = 10.8 Hz, $J_2$ = 2.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 187.7 (C=O), 151.0, 150.2, 149.5, 139.5, 137.8, 137.6, 131.9, 129.5, 129.3, 128.6, 128.5 (2C), 128.5 (2C), 128.4 (2C), 127.9 (3C), 127.9 (2C), 127.7 (3C), 127.3, 126.6, 108.9, Sug & Bn–CH$_2$; 77.7, 75.6, 73.9, 73.6, 73.5, 71.3, 68.0; FT-IR (Neat): $v_{\text{max}}$ 3008, 2958, 1618, 1597, 1496, 1454, 1120, 1097, 1072 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{37}$H$_{34}$NO$_5$: 572.2437, found: 572.2429.

2,6-Anhydro-3-deoxy-1-C-(quinoline-8-yl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.9c):

The title compound was synthesized according to the general procedure using quinoline-8-carboxaldehyde (0.167 mmol). The product was obtained as brown viscous oil; (70.5 mg, 74 % yield); [α]$^23_D$ = -23.0 (c = 0.9, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.89 (dd, $J_1$ = 4.2 Hz, $J_2$ = 1.8 Hz, 1H), 8.16 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.7 Hz, 1H), 7.94 (dd, $J_1$ = 8.2 Hz, $J_2$ = 1.4 Hz, 1H), 7.77 (dd, $J_1$ = 7.0 Hz, $J_2$ = 1.4 Hz, 1H), 7.58 (dd, $J_1$ = 8.1 Hz, $J_2$ = 7.2 Hz, 1H), 7.39

The title compound was synthesized according to the general procedure using thiophene-2-carboxaldehyde (0.167 mmol). The product was obtained as pale white solid; (56.2 mg, 64 \% yield); m.p. 102–106 °C; [$\alpha$]$_D^{23}$ = $-2.7$ (c = 0.3, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.20 (dd, $J_1 = 3.9$ Hz, $J_2 = 1.1$ Hz, 1H), 7.67 (dd, $J_1 = 5.0$ Hz, $J_2 = 1.0$ Hz, 1H), 7.39–7.29 (m, 15H), 7.07 (dd, $J_1 = 4.9$ Hz, $J_2 = 4.0$ Hz, 1H), 6.16 (d, $J = 3.0$ Hz, 1H), 4.89 (d, $J = 11.3$ Hz, 1H), 4.77–4.60 (m, 5H), 4.39 (dd, $J_1 = 6.3$ Hz, $J_2 = 3.0$ Hz, 1H), 4.34–4.30 (m, 1H), 3.98 (dd, $J_1 = 8.8$ Hz, $J_2 = 6.4$ Hz, 1H), 4.34–4.30 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 179.6 (C=O), Ar–C; 150.9, 141.4, 138.0, 137.9, 135.9, 135.1, 128.6 (2C), 128.5 (2C), 128.5 (2C), 128.1, 128.0 (2C), 127.9 (4C), 127.9 (2C), 127.8 (2C), 107.0, Sug–C & Bn–CH$_2$; 77.9, 75.9, 74.0, 73.9, 73.6, 71.0, 68.4; FT–IR (Neat): $\nu_{\text{max}}$ 3018, 2306, 1635, 1532, 1458, 1256, 1194 cm$^{-1}$; HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{37}$H$_{34}$NO$_5$: 572.2437, found: 572.2435.
1506, 1423, 1215, 756 cm\(^{-1}\). **HRMS** (ESI) m/z [M+Na]\(^+\): calcd. for C\(_{32}\)H\(_{30}\)O\(_5\)SNa: 549.1712, found: 549.1710.

**Compound (4.11c):**

The title compound was synthesized according to the general procedure using 1.3 equiv. of 2-nitrogalactal. The product was obtained as pale yellow oil; (71.3 mg, 82 % yield); \([\alpha]_{23}^D = \text{–1.8 (c = 1.1, CHCl}_3\text{)}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.67 (ddd, \(J_1 = 4.8\) Hz, \(J_2 = 1.6\) Hz, \(J_3 = 0.9\) Hz, 1H), 7.87 (d, \(J = 7.8\) Hz, 1H), 7.78 (dt, \(J_1 = 7.6\) Hz, \(J_2 = 1.7\) Hz, 1H), 7.43 (ddd, \(J_1 = 7.6\) Hz, \(J_2 = 4.8\) Hz, \(J_3 = 4.6\) Hz, 1H), 7.32–7.28 (m, 15H), 6.38 (dd, \(J_1 = 2.4\) Hz, \(J_2 = 1.8\) Hz, 1H), 4.96 (d, \(J = 12\) Hz, 1H), 4.72–4.68 (m, 3H), 4.53–4.31 (m, 4H), 4.16–4.14 (m, 1H), 3.85 (d, \(J = 6.7\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 187.3 (C=O), Ar–C; 154.4, 149.2, 148.5, 138.3, 137.8, 137.8, 136.9, 128.5 (2C), 128.4 (2C), 128.3 (2C), 128.1 (2C), 128.0 (2C), 127.8 (2C), 127.7, 127.6 (2C), 126.0, 124.8, 115.9, Sug & Bn–CH\(_2\); 76.2, 74.1, 73.5, 72.9, 71.3, 69.3, 67.7; **FT–IR** (Neat): \(\nu_{\text{max}}\) 3028, 2868, 1666, 1583, 1454, 1099, 1066, 752 cm\(^{-1}\). **HRMS** (ESI) m/z [M+H]\(^+\): calcd. for C\(_{33}\)H\(_{32}\)NO\(_5\): 522.2280, found: 522.2283.

**O(3,4-Dihydro-2H-pyran-6-yl)(pyridin-2-yl)methanone (4.12c):**

The title compound was synthesized according to the general procedure using 2-nitro-DHP (0.167 mmol). The product was obtained as dark brown solid; (24.6 mg, 78 % yield); m.p. 72–73 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.63 (d, \(J = 4.8\) Hz, 1H), 7.81 (dd, \(J_1 = 4.9\) Hz, \(J_2 = 1.2\) Hz, 2H), 7.43–7.39 (m, 1H), 6.33 (t, \(J = 4.3\) Hz, 1H), 4.20 (t, \(J = 5.1\) Hz, 2H), 2.33–2.29 (m, 2H), 1.95–1.89 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 188.2 (C=O), Ar–C; 155.1, 150.4, 148.3, 136.9, 125.7, 124.3, 120.3,
DHP; 66.4, 21.4, 21.3; FT−IR (Neat): \( v_{\text{max}} \) 2933, 1660, 1581, 1433, 1276, 1058 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{11}\)H\(_{12}\)NO\(_2\): 190.0868, found: 190.0875.

2,6-Anhydro-3-deoxy-1-C-(2-pyridyl)-4,5,7-tris-O-(methyl)-D-arabino-hept-2-enose (4.13c):

The title compound was synthesized according to the general procedure using 3,4,6-tri-O-methyl-2-nitroglucal (1.3 equiv.) instead of 2-nitroglucal. The product was obtained as viscous oil; (43.1 mg, 84 % yield); \([\alpha]^{23}_D = +46.1 \ (c = 0.8, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 8.63 (d, \( J = 4.7 \) Hz, 1H), 7.85 (d, \( J = 7.7 \) Hz, 1H), 7.79 (dt, \( J_1 = 7.4 \) Hz, \( J_2 = 1.7 \) Hz, 1H), 7.41 (ddd, \( J_1 = 7.4 \) Hz, \( J_2 = 4.8 \) Hz, \( J_3 = 1.4 \) Hz, 1H), 6.32 (d, \( J = 3.0 \) Hz, 1H), 4.11 (dd, \( J_1 = 6.7 \) Hz, \( J_2 = 3.0 \) Hz, 1H), 4.07 (td, \( J_1 = 8.9 \) Hz, \( J_2 = 3.5 \) Hz, 1H), 3.78–3.72 (m, 2H), 3.59 (dd, \( J_1 = 9.0 \) Hz, \( J_2 = 6.7 \) Hz, 1H), 3.43 (s, 3H), 3.54 (s, 3H), 3.43 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 187.2 (C=O), Ar–C & alkene–C; 154.2, 149.5, 148.5, 136.9, 126.2, 124.5, 114.4, Sug & CH\(_3\); 78.0, 77.3, 75.0, 70.1, 59.5, 59.2, 56.6; FT−IR (Neat): \( v_{\text{max}} \) 3007, 2931, 1668, 1635, 1456, 1273, 1103, 750 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{16}\)H\(_{22}\)NO\(_5\): 308.1498, found: 308.1496.

2,6-Anhydro-3-deoxy-1-C-(2-pyridyl)-4,5,7-tris-O-(octyl)-D-arabino-hept-2-enose (4.14c):

The title compound was synthesized according to the general procedure using 3,4,6-tri-O-octyl-2-nitroglucal (1.3 equiv.) instead of 2-nitroglucal. The product was obtained as colourless oil; (65.6 mg, 67 % yield); \([\alpha]^{23}_D = +22.0 \ (c = 0.2, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 8.69 (d, \( J = 4.2 \) Hz, 1H), 7.90 (d, \( J = 7.8 \) Hz, 1H), 7.83 (dt, \( J_1 = 7.7 \) Hz, \( J_2 = 7.7 \) Hz, \( J_3 = 0.7 \) Hz, 1H).
\( J_2 = 1.7 \text{ Hz}, 1\text{H}) \), 7.45 (ddd, \( J_1 = 7.4 \text{ Hz}, J_2 = 4.8 \text{ Hz}, J_3 = 1.2 \text{ Hz}, 1\text{H}) \), 6.29 (d, \( J = 2.9 \text{ Hz}, 1\text{H}) \), 4.21 (dd, \( J_1 = 6.8 \text{ Hz}, J_2 = 2.8 \text{ Hz}, 1\text{H}) \), 4.10–3.46 (m, 10H), 1.29–0.88 (m, 45H); \(^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta 187.5 \) (C=O), Ar–C alkene; 154.4, 149.6, 148.7, 136.9, 126.2, 124.8, 115.2, Sug & alkyl; 78.0, 77.4, 74.0, 72.4, 71.9, 69.6, 68.7, 31.9, 30.3, 30.1, 29.8, 29.6, 29.5, 29.4, 26.3, 22.7, 14.2, (total 45C); \(^{1}\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta 8.65 \) (dd, \( J_1 = 4.6 \text{ Hz}, J_2 = 0.5 \text{ Hz}, 1\text{H}) \), 8.19–8.09 (m, 6H), 7.94 (d, \( J = 7.8 \text{ Hz}, 1\text{H}) \), 7.86 (dt, \( J_1 = 7.7 \text{ Hz}, J_2 = 1.6 \text{ Hz}, 1\text{H}) \), 7.71 (d, \( J = 7.6 \text{ Hz}, 1\text{H}) \), 7.64–7.45 (m, 6H), 6.48 (d, \( J = 2.7 \text{ Hz}, 1\text{H}) \), 4.99 (d, \( J = 12.3 \text{ Hz}, 1\text{H}) \), 4.90 (d, \( J = 12.3 \text{ Hz}, 1\text{H}) \), 4.82 (d, \( J = 12.5 \text{ Hz}, 2\text{H}) \), 4.72 (d, \( J = 12.5 \text{ Hz}, 2\text{H}) \), 4.59 (dd, \( J_1 = 7.0 \text{ Hz}, J_2 = 2.7 \text{ Hz}, 1\text{H}) \), 4.26 (td, \( J_1 = 9.5 \text{ Hz}, J_2 = 2.6 \text{ Hz}, 1\text{H}) \), 4.14–3.98 (m, 3H); \(^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta 186.8 \), Ar–C; 153.9, 149.9, 148.5, 148.2, 140.2, 140.1, 139.9 137.1, 133.4, 133.1 (3C), 129.4, 129.4, 129.3, 126.5, 124.6, 122.7, 122.6, 122.2, 122.1 (3C), 113.5, Sug & Bn-CH\(_3\); 77.6, 74.2, 72.8, 72.4, 69.7, 68.3; \(^{1}\text{FT–IR} \) (Neat): \( \nu_{\text{max}} \) 2868, 1668, 1525, 1271, 1093 cm\(^{-1}\). \(^{1}\text{HRMS} \) (ESI) m/z [M+Na]^+: calcd. for C\(_{36}\)H\(_{61}\)NO\(_5\)Na: 610.4447, found: 610.4442.

2,6-Anhydro-3-deoxy-1-C-(2-pyridyl)-4,5,7-tris-O-(m-nitrophenylmethyl)-D-arabino-hept-2-enose (4.15c):

The title compound was synthesized according to the general procedure using 3,4,6-tri-O-m-nitrobenzyl-2-nitroglucal (1.3 equiv) instead of 2-nitroglucal. The product was obtained as pale yellow solid; (94.2 mg, 86 % yield); m.p. 117–119 °C; \([\alpha]_{\text{D}}^{23} = +24.7 \) (c = 0.6, CHCl\(_3\) ); \(^{1}\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta 8.65 \) (dd, \( J_1 = 4.6 \text{ Hz}, J_2 = 0.5 \text{ Hz}, 1\text{H}) \), 8.19–8.09 (m, 6H), 7.94 (d, \( J = 7.8 \text{ Hz}, 1\text{H}) \), 7.86 (dt, \( J_1 = 7.7 \text{ Hz}, J_2 = 1.6 \text{ Hz}, 1\text{H}) \), 7.71 (d, \( J = 7.6 \text{ Hz}, 1\text{H}) \), 7.64–7.45 (m, 6H), 6.48 (d, \( J = 2.7 \text{ Hz}, 1\text{H}) \), 4.99 (d, \( J = 12.3 \text{ Hz}, 1\text{H}) \), 4.90 (d, \( J = 12.3 \text{ Hz}, 1\text{H}) \), 4.82 (d, \( J = 12.5 \text{ Hz}, 2\text{H}) \), 4.72 (d, \( J = 12.5 \text{ Hz}, 2\text{H}) \), 4.59 (dd, \( J_1 = 7.0 \text{ Hz}, J_2 = 2.7 \text{ Hz}, 1\text{H}) \), 4.26 (td, \( J_1 = 9.5 \text{ Hz}, J_2 = 2.6 \text{ Hz}, 1\text{H}) \), 4.14–3.98 (m, 3H); \(^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta 186.8 \), Ar–C; 153.9, 149.9, 148.5, 148.2, 140.2, 140.1, 139.9 137.1, 133.4, 133.1 (3C), 129.4, 129.4, 129.3, 126.5, 124.6, 122.7, 122.6, 122.2, 122.1 (3C), 113.5, Sug & Bn-CH\(_3\); 77.6, 74.2, 72.8, 72.4, 69.7, 68.3; \(^{1}\text{FT–IR} \) (Neat): \( \nu_{\text{max}} \) 2868, 1668, 1525, 1271, 1093 cm\(^{-1}\). \(^{1}\text{HRMS} \) (ESI) m/z [M+Na]^+: calcd. for C\(_{33}\)H\(_{28}\)N\(_4\)O\(_{11}\)Na: 679.1652, found: 679.1627.
Compound 4.16c:

The title compound was synthesized according to the general procedure using 2-nitrorhamnal (1.3 equiv) instead of 2-nitroglucal. The product was obtained as viscous oil; (57.5 mg, 83 % yield);

$[\alpha]^{23}_D = -31.9 (c = 0.7, \text{CHCl}_3)$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.68 (ddd, $J_1 = 4.7$ Hz, $J_2 = 1.4$ Hz, $J_2 = 1.0$ Hz, 1H), 7.91–7.88 (m, 1H), 7.84 (dt, $J_1 = 7.7$ Hz, $J_2 = 1.6$ Hz, 1H), 7.45 (ddd, $J_1 = 7.4$ Hz, $J_2 = 4.8$ Hz, $J_2 = 1.4$ Hz, 1H), 7.37–7.29 (m, 10H), 6.42 (d, $J = 2.8$ Hz, 1H), 4.92 (d, $J = 11.2$ Hz, 1H), 4.78–4.65 (m, 3H), 4.50 (dd, $J_1 = 7.0$ Hz, $J_2 = 2.8$ Hz, 1H), 4.21–4.14 (m, 1H), 3.61 (dd, $J_1 = 9.3$ Hz, $J_2 = 7.0$ Hz, 1H), 1.55 (d, $J = 6.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 187.5 (C=O), Ar-C; 154.3, 149.7, 148.5, 138.0, 137.9, 136.9, 128.4 (4C), 128.0 (2C), 127.9 (2C), 127.8 (2C), 126.2, 124.5, 115.6, Sug & Bn-CH$_2$; 78.7, 77.3, 74.8, 74.3, 71.3, 17.4; FT-IR (Neat): $v_{\text{max}}$ 3012, 2306, 1666, 1454, 1271, 1091, 750 cm$^{-1}$. HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{26}$H$_{26}$NO$_4$: 416.1862, found: 416.1857.

2,6-Anhydro-3-deoxy-1-C-(propyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2- enose (4.17c): The title compound was synthesized according to the general procedure. The product was obtained as viscous oil; (58.4 mg, 72 % yield); $[\alpha]^{23}_D = +20 (c = 0.2, \text{CHCl}_3)$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36–7.25 (m, 15H), 5.97 (d, $J = 3.0$ Hz, 1H), 4.85 (d, $J = 11.3$ Hz, 1H), 4.73–4.58 (m, 5H), 4.31 (dd, $J_1 = 6.1$ Hz, $J_2 = 3.1$ Hz, 1H), 4.19–4.16 (m, 1H), 3.94–3.81 (m, 3H), 2.65 (t, $J = 7.3$ Hz, 2H), 1.69–1.62 (m, 2H), 0.96 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 196.8 (C=O), Ar-C; 150.4, 138.0, 137.9, 137.8, 128.5 (2C), 128.4 (2C), 127.8 (2C), 127.8 (4C), 127.7, 127.6 (2C), 104.8, Sug, alkyl & Bn–CH$_2$;
77.4, 75.6, 73.8, 73.7, 73.4, 71.0, 68.1, 40.0, 17.0, 13.7; \textbf{FT–IR} (Neat): $\nu_{\text{max}}$ 2872, 1703, 1637, 1454, 1361, 1193, 1097 cm$^{-1}$; \textbf{HRMS} (ESI) m/z [M+Na]$^+$: calcd. for C$_{31}$H$_{34}$O$_5$Na: 509.2304, found: 509.2304.

**2,6-Anhydro-3-deoxy-1-C-(methyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.18c):**

The title compound was synthesized according to the general procedure using acetaldehyde (0.167 mmol). The product was obtained as viscous oil; (56.5 mg, 74 % yield); $[\alpha]_{23}^{23}$D = +8.9 (c = 0.4, CHCl$_3$); \textbf{1H NMR} (400 MHz, CDCl$_3$): $\delta$ 7.40–7.28 (m, 15H), 5.99 (d, $J = 3.0$ Hz, 1H), 4.85 (d, $J = 11.3$ Hz, 1H), 4.73–4.49 (m, 5H), 4.32 (dd, $J_1 = 6.2$ Hz, $J_2 = 3.1$ Hz, 1H), 4.22–4.18 (m, 1H), 3.94 (dd, $J_1 = 8.5$ Hz, $J_2 = 6.2$ Hz, 1H), 3.90–3.82 (m, 2H), 2.33 (s, 3H); \textbf{13C NMR} (100 MHz, CDCl$_3$): $\delta$ 194.4 (C=O), Ar–C; 150.4, 138.0, 137.9, 137.8, 128.5 (2C), 128.4 (2C), 127.9 (2C), 127.8, 127.8, 127.8 (2C), 127.7, 127.7 (2C), 105.6, Sug, alkyl & Bn; 77.5, 75.5, 73.8, 73.6, 73.4, 71.0, 68.0, 25.9; \textbf{FT–IR} (Neat): $\nu_{\text{max}}$ 3028, 2922, 1705, 1655, 1454, 1359, 1217, 1097, 752 cm$^{-1}$. \textbf{HRMS} (ESI) m/z [M+Na]$^+$: calcd. for C$_{29}$H$_{30}$O$_5$Na: 481.1991, found: 481.1989.

**2,6-Anhydro-3-deoxy-1-C-(phenyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.19c):**

The title compound was synthesized according to the general procedure using benzaldehyde (0.167 mmol). The product was obtained as viscous oil; (45.1 mg, 52 % yield); $[\alpha]_{23}^{23}$D = +9.6 (c = 0.6, CHCl$_3$); \textbf{1H NMR} (400 MHz, CDCl$_3$): $\delta$ 7.92 (d, $J = 7.1$ Hz, 2H), 7.58–7.54 (m, 1H), 7.39–7.27 (m, 17H), 5.88 (d, $J = 3.0$ Hz, 1H), 4.89 (d, $J = 11.2$ Hz, 1H), 4.75–4.58 (m,

5H), 4.39 (dd, $J_1 = 6.3$ Hz, $J_2 = 3.0$ Hz, 1H), 4.29–4.25 (m, 1H), 4.07 (dd, $J_1 = 8.7$ Hz, $J_2 = 6.4$ Hz, 1H), 3.96–3.85 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 189.7 (C=O), Ar–C; 156.6, 154.9, 151.1, 141.3, 138.0, 138.0, 137.8, 136.2, 132.7, 129.9 (2C), 128.5 (2C), 128.4 (2C), 128.1, 127.9, 127.8 (2C), 127.8 (2C), 127.6 (2C), 109.1, 77.7, 76.0, 73.9, 73.7, 73.4, 71.1, 68.0; FT–IR (Neat): $v_{\text{max}}$ 3030, 2866, 1668, 1454, 1265, 1097, 1028, 752 cm$^{-1}$; HRMS (ESI) m/z [M+Na]$^+$: calcd. for C$_{34}$H$_{32}$O$_5$Na: 543.2147, found: 543.2140.

2,6-Anhydro-3-deoxy-1-C-(4-trifluromethoxyphenyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enoate (4.20c):

The title compound was synthesized according to the general procedure using 4-trifluromethoxybenzaldehyde (0.167 mmol). The product was obtained as white solid; (64.5 mg, 64 % yield); m.p. 67–69 °C; $[\alpha]_{D}^{23} = -7.6$ (c = 0.8, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.02 (d, $J = 8.2$ Hz, 2H), 7.38–7.30 (m, 15H), 7.18 (d, $J = 8.2$ Hz, 2H), 5.92 (d, $J = 3.0$ Hz, 1H), 4.89 (d, $J = 11.3$ Hz, 1H), 4.75–4.57 (m, 5H), 4.38 (dd, $J_1 = 6.2$ Hz, $J_2 = 3.0$ Hz, 1H), 4.31–4.27 (m, 1H) 4.03 (dd, $J_1 = 8.5$ Hz, $J_2 = 6.3$ Hz, 1H), 3.94 (dd, $J_1 = 10.8$ Hz, $J_2 = 4.8$ Hz, 1H), 3.84 (dd, $J_1 = 10.8$ Hz, $J_2 = 2.6$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 187.9 (C=O), Ar–C; 154.2, 150.9, 137.9, 137.7, 134.2, 132.0 (2C), 128.5 (2C), 128.4 (2C), 127.9 (2C), 127.8 (2C), 127.7 (2C), 127.6 (2C), 121.9, 119.9 (2C), 108.8, Sug & Bn 77.6, 75.7, 73.9, 73.6, 73.4, 71.2, 67.9; $^{19}$F NMR (400 MHz, CDCl$_3$): $\delta$ –57.51 (s, 3F); FT–IR (Neat): $v_{\text{max}}$ 3030, 3014, 2916, 2868, 1670, 1506, 1454, 1257, 1097, 754 cm$^{-1}$; HRMS (ESI) m/z [M+Na]$^+$: calcd. for C$_{35}$H$_{31}$O$_6$NaF$_3$: 627.1970, found: 627.1976.
2,6-Anhydro-3-deoxy-1-C-(4-flurophenyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.21c):

The title compound was synthesized according to the general procedure using 4-flurobenzaldehyde (0.167 mmol). The product was obtained as white solid; (61.0 mg, 68 % yield); m.p. 73–76 °C; [α]$_{23}^D$ = +26.0 (c = 0.2, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.01 (dd, $J_1$ = 8.4 Hz, $J_2$ = 5.6 Hz, 2H), 7.36–7.24 (m, 15H), 7.05 (t, $J$ = 8.6 Hz, 2H), 5.91 (d, $J$ = 2.8 Hz, 1H), 4.89 (d, $J$ = 11.2 Hz, 1H), 4.75–4.57 (m, 5H), 4.39 (dd, $J_1$ = 6.0 Hz, $J_2$ = 2.8 Hz, 1H), 4.30–4.28 (m, 1H), 4.05 (dd, $J_1$ = 8.3 Hz, $J_2$ = 6.5 Hz, 1H), 3.95 (dd, $J_1$ = 10.8 Hz, $J_2$ = 4.6 Hz, 1H), 3.85 (dd, $J_1$ = 10.8 Hz, $J_2$ = 2.2 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 187.9, 151.1, 137.9 (d, $J_{CF}$= 3.2 Hz), 137.8, 132.7 (d, $J_{CF}$= 36.6 Hz) (2C), 132.3, 128.5 (2C), 128.4 (2C), 128.4 (2C), 128.4 (2C), 127.9 (2C), 127.9 (2C), 127.8 (2C), 127.8 (2C), 127.7 (2C), 127.6 (2C), 115.2 (d, $J_{CF}$= 21.8 Hz) (2C), 108.4, Sug & BnCH$_2$; 77.6, 75.7, 73.9, 73.7, 73.4, 71.2, 68.0; $^{19}$F NMR (400 MHz, CDCl$_3$): δ −105.2 (m, 1F) FT–IR (Neat): ν$_{max}$ 3032, 2873, 1672, 1635, 1587, 1454, 1271, 1089, 752 cm$^{-1}$; HRMS (ESI) m/z [M+Na]$^+$: calcd. for C$_{30}$H$_{31}$O$_5$NaF: 561.2053, found: 561.2056.

2,6-Anhydro-3-deoxy-1-C-(4-chlorphenyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.22c):

The title compound was synthesized according to the general procedure using 4-chlorobenzaldehyde (0.167 mmol). The product was obtained as white solid; (63.8 mg, 69 % yield); m.p. 81–83 °C; [α]$_{23}^D$ = −2.7 (c = 0.6, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.90 (d, $J_1$ = 8.5 Hz, 2H), 7.39–7.31 (m, 17H), 5.91(d, $J$ = 2.9 Hz, 1H), 4.89 (d, $J$ = 11.2 Hz, 1H), 4.75–4.57
(m, 5 H), 4.51 (dd, $J_1 = 6.2$ Hz, $J_2 = 3.0$ Hz, 1H), 4.30–4.26 (m, 1H), 4.03 (dd, $J_1 = 8.6$ Hz, $J_2 = 6.3$ Hz, 1H), 3.94 (dd, $J_1 = 10.9$ Hz, $J_2 = 4.7$ Hz, 1H), 3.85 (dd, $J_1 = 10.8$ Hz, $J_2 = 2.6$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 188.3 (C=O), Ar‒C; 150.9, 150.0, 139.2, 137.9, 137.7, 134.4, 131.4 (2C), 128.5 (2C), 128.4 (2C), 128.4 (2C), 127.9 (2C), 127.9, 127.8 (2C), 127.7, 127.6 (2C), 108.8, Sug & Bn; 77.6, 75.8, 73.9, 73.7, 73.4, 71.2, 67.9; FT–IR (Neat): $v_{\text{max}}$ 3032, 2918, 2891, 1672, 1635, 1587, 1454, 1271, 1089, 752 cm$^{-1}$; HRMS (ESI) m/z [M+Na]$^+$: calcd. for C$_{34}$H$_{31}$O$_5$ClNa: 577.1758, found: 577.1749.

2,6-Anhydro-3-deoxy-1-C-(4-bromophenyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.23c):

The title compound was synthesized according to the general procedure using 4-bromobenzaldehyde (0.167 mmol). The product was obtained as white solid; (86.8 mg, 87 % yield); m.p. 77–79 °C; $[^{23}]\alpha_D = -13.7$ (c = 0.7, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.82 (d, $J = 8.5$ Hz, 2H), 7.52 (d, $J = 8.5$ Hz, 2H), 7.39–7.31 (m, 15H), 5.91 (d, $J = 2.9$ Hz, 1H), 4.89 (d, $J = 11.3$ Hz, 1H), 4.75–4.57 (m, 5H), 4.39 (dd, $J_1 = 6.1$ Hz, $J_2 = 3.0$ Hz, 1H), 4.29–4.26 (m, 1H), 4.03 (dd, $J_1 = 8.6$ Hz, $J_2 = 6.3$ Hz, 1H), 3.94 (dd, $J_1 = 10.8$ Hz, $J_2 = 4.7$ Hz, 1H), 3.85 (dd, $J_1 = 10.8$ Hz, $J_2 = 2.6$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 191.3, 150.9, 137.9, 137.7, 134.8, 131.5 (2C), 131.4 (2C), 128.5 (3C), 128.4 (3C), 128.4 (2C), 127.9 (2C), 127.9 (2C), 127.8 (2C), 127.7, 127.6 (2C), 108.9, Sug & Bn; 77.6, 75.8, 73.9, 73.6, 73.4, 71.2, 67.9; FT–IR (Neat): $v_{\text{max}}$ 3030, 2914, 1670, 1622, 1583, 1454, 1267, 1068, 750 cm$^{-1}$; HRMS (ESI) m/z [M+Na]$^+$: calcd. for C$_{34}$H$_{31}$O$_5$BrNa: 621.1253, found: 621.1248.
**Compound 4.24c:**

The title compound was synthesized according to the general procedure using 4.18a (1.3 equiv). The product was obtained as viscous oil; (109.8 mg, 69% yield); \([\alpha]^{23}_D = +43.9\) (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.66 (d, \(J = 4.4\) Hz, 1H), 7.93 (d, \(J = 7.7\) Hz, 1H), 7.78 (t, \(J = 7.8\) Hz, 1H), 7.42 (t, \(J = 7.4\) Hz, 1H), 7.32–7.14 (m, 30H), 6.42 (d, \(J = 3.0\) Hz, 1H), 5.56 (d, \(J = 3.4\) Hz, 1H), 4.95 (d, \(J = 10.8\) Hz, 1H), 4.82 (dd, \(J = 10.7\) Hz, \(J = 5.2\) Hz, 2H), 4.69–4.32 (m, 12H), 3.99–3.87 (m, 4H) 3.73–3.46 (m, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 187.3, 154.0, 150.1, 148.7 (2C), 138.8, 138.4, 138.2, 138.1, 137.9, 137.8, 136.8 (2C), 128.4 (2C), 128.4 (2C), 128.3 (2C), 128.3 (2C), 128.2 (2C), 128.2 (2C), 127.9 (2C), 127.8 (4C), 127.8 (2C), 127.7, 127.7, 127.6 (3C), 127.5, 127.5 (2C), 126.2, 124.7, 113.0, Sug & Bn; 96.3, 81.8, 79.6, 77.5, 77.4, 77.2, 75.8, 75.6, 75.0, 73.4, 72.9, 70.8, 69.7, 69.3, 68.1, 67.7; FT–IR (Neat): \(\nu_{\text{max}}\) 3014, 2866, 1668, 1496, 1454, 1215, 1087, 1070, 752 cm\(^{-1}\); HRMS (ESI) m/z [M+H]\(^+\): calcd. for C\(_{60}\)H\(_{60}\)NO\(_{10}\): 954.4217, found: 954.4241.

**2,6-Anhydro-3-deoxy-1-C-(2-furyl)-4,5,7-tris-O-(phenylmethyl)-D-arabino-hept-2-enose (4.25c):**

The title compound was synthesized according to the general procedure using Furon-2-carboxaldehyde (0.167 mmol). The product was obtained as white solid; (85.1 mg, 85% yield); \([\alpha]^{23}_D = -30.2\) (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.59-7.58 (m, 2H), 7.27–7.18 (m, 15H), 6.37 (dd, \(J = 3.5\) Hz, \(J = 1.6\) Hz, 1H), 6.12 (d, \(J = 3\) Hz, 1H), 4.78 (d, \(J = 11.3\) Hz, 1H), 4.68–4.48 (m, 5H), 4.27 (dd, \(J = 6.2\) Hz, \(J = 3.0\) Hz, 1H), 4.22–4.18 (m, 1H), 3.82 (dd, \(J = 8.7\) Hz, \(J = 6.3\) Hz, 1H), 3.78 (d, \(J = 4.2\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\)
174.4, 150.6, 150.3, 147.6, 137.8, 137.8, 137.7, 128.5 (2C), 128.4 (2C), 128.4, 127.9 (2C), 127.9 (3C), 127.8 (3C), 128.8 (2C), 123.0, 112.3, 107.0, Sug & Bn; 77.5, 75.7, 73.9, 73.8, 73.4, 70.9, 68.5; HRMS (ESI) m/z [M+Na]^+: calcd. for C_{32}H_{31}O_{6}: 511.2121, found: 511.2107.

Formal synthesis of Scleropentaside A

Tri-O-benzyl protected Scleropentaside A (4.27):

The title of the compound was prepared from 4.25c using BH₃.SMe₂ (hydroboration-oxidation) and MnO₂ (allyl oxidation) according to standard procedure below. Hydroboration: To an ice-cooled solution of compound 4.25c (100 mg, 0.196 mmol) in anhydrous THF (5 ml), was added neat BH₃.SMe₂ (0.011 mL, 0.392 mmol) and stirring was continued at room temperature for 3 h. The reaction mixture was cooled to 0°C, treated with 3N NaOH (0.10 mL) followed by 30% H₂O₂ (0.15 mL) and stirred at room temperature for 6 h. Then THF was evaporated under reduced pressure, residual material was extracted with diethyl ether (25 mL) and washed with water (10 mL). The organic layer was dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by column chromatography and separated both diastereomers and used for further allylic oxidation step. The product was obtained as white solid (4.26); (87.1 mg, 83 % yield); one diastereomer's ¹H NMR (400 MHz, CDCl₃): δ 7.39–7.23 (m, 16H), 6.40 (d, J = 3.1 Hz, 1H), 6.34 (dd, J₁ = 3.1 Hz, J₂ = 1.8 Hz, 1H), 4.99-4.79 (m, 4H), 4.62–4.50 (m, 3H),
3.83–3.55 (m, 7H), 3.03 (d, J = 9.2 Hz, 1H), 2.42 (d, J = 2.7 Hz, 1H), \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) 154.4, 141.9, 138.5, 138.0, 137.9, 128.6 (2C), 128.4 (2C), 128.4 (2C), 127.9 (2C), 127.9 (2C), 127.8 (2C), 127.8 (2C), 127.7 (2C), 127.6, 110.3, 107.3, Sug & Bn; 86.6, 79.5, 79.0, 77.9, 75.3, 74.9, 73.3, 70.3, 68.9, 66.5;

\textbf{MnO}_2 \textit{selective allylic oxidation}: The obtained reduced diastereomers 4.26 (100 mg, 0.188 mmol) mixture was dissolved in dry dichloromethane and add MnO\(_2\) (10 equiv, 158 mg, 1.886 mmol) and stir for 2h until the complete conversion of allylic alcohol to ketone (by checking TLC). After complete conversion, the reaction mixture was subjected to celite filtration and concentrate the filtrate to obtained residual oil which upon column purification to obtained 4.27 as a white solid. (62.7 mg, 63 % yield); \([\alpha]^{23}_D = +3.0\) (c = 0.1, CHCl\(_3\)); \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 7.56–7.55 (m, 2H), 7.32–7.12 (m, 15H), 6.38 (dd, \(J_1 = 3.5\) Hz, \(J_2 = 1.5\) Hz, 1H), 4.95 (d, \(J = 11.2\) Hz, 1H), 4.81–4.78 (m, 2H), 4.51–4.43 (m, 3H), 4.07 (d, \(J = 9.5\) Hz, 1H), 3.98 (dt, \(J_1 = 8.8\) Hz, \(J_2 = 2.0\) Hz, 1H), 3.71 (d, \(J = 9.5\) Hz, 1H), 3.66–3.45 (m, 4H), 3.25 (d, \(J = 1.8\) Hz, 1H), \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) 185.8, 150.4, 147.8, 138.6, 137.9, 128.6 (3C), 128.4 (2C), 128.0 (2C), 127.0 (2C), 127.8, 127.8 (2C), 127.7, 127.7, 123.0, 112.4, Sug & Bn; 85.8, 80.5, 77.2, 75.4, 75.1, 73.4, 72.8, 69.3; \textbf{HRMS} (ESI) m/z [M+Na]^+: calcd. for C\(_{30}\)H\(_{34}\)O\(_7\)Na: 529.2202, found: 529.2201.

\textbf{Deuterium labeling studies}

Note: Due to the possibility of slight moisture, deuterium is not completely incorporated.
Crystal structure of compound 4.2b

Table 4.4. Crystal data and structure refinement for 4.2b.

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Reflections collected
Independent reflections
Completeness to theta = 33.87°
Absorption correction
Max. and min. transmission
Refinement method
Data / restraints / parameters
Goodness-of-fit on F^2
Final R indices [I>2sigma(I)]
R indices (all data)
Absolute structure parameter
Largest diff. peak and hole

Crystal structure of compound 4.8c

Table 4.5. Crystal data and structure refinement for 4.8c.

| Identification code | 4.8c |
### Chemical Information

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<td><strong>Unit cell dimensions</strong></td>
<td></td>
</tr>
<tr>
<td>a = 5.43620(10) Å</td>
<td>α = 90°</td>
</tr>
<tr>
<td>b = 30.4866(6) Å</td>
<td>β = 93.9740(10)°</td>
</tr>
<tr>
<td>c = 8.9076(2) Å</td>
<td>γ = 90°</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>1472.72(5) Å³</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Density (calculated)</strong></td>
<td>1.289 Mg/m³</td>
</tr>
<tr>
<td><strong>Absorption coefficient</strong></td>
<td>0.085 mm⁻¹</td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
<td>604</td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
<td>0.40 x 0.20 x 0.14 mm³</td>
</tr>
<tr>
<td><strong>Theta range for data collection</strong></td>
<td>2.29 to 32.80°</td>
</tr>
<tr>
<td><strong>Index ranges</strong></td>
<td>-5&lt;=h&lt;=8, -46&lt;=k&lt;=44, -13&lt;=l&lt;=13</td>
</tr>
<tr>
<td><strong>Reflections collected</strong></td>
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</tr>
<tr>
<td><strong>Independent reflections</strong></td>
<td>5529 [R(int) = 0.0375]</td>
</tr>
<tr>
<td><strong>Completeness to theta = 32.80°</strong></td>
<td>99.4 %</td>
</tr>
<tr>
<td><strong>Absorption correction</strong></td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td><strong>Max. and min. transmission</strong></td>
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</tr>
<tr>
<td><strong>Refinement method</strong></td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td><strong>Data / restraints / parameters</strong></td>
<td>5529 / 176 / 437</td>
</tr>
<tr>
<td><strong>Goodness-of-fit on F²</strong></td>
<td>1.066</td>
</tr>
<tr>
<td><strong>Final R indices [I&gt;2sigma(I)]</strong></td>
<td>R1 = 0.0445, wR2 = 0.1110</td>
</tr>
<tr>
<td><strong>R indices (all data)</strong></td>
<td>R1 = 0.0603, wR2 = 0.1273</td>
</tr>
<tr>
<td><strong>Largest diff. peak and hole</strong></td>
<td>0.353 and -0.251 e.Å⁻³</td>
</tr>
</tbody>
</table>
4.5. References


1998, 120, 1309.


C−Glycosylation


CHAPTER 4: *N*-Heterocyclic Carbene-Catalyzed C−Glycosylation: A Concise Approach from Stetter Reaction and Formal Synthesis of Scleropentaside A


CHAPTER 5

N-Heterocyclic Carbene Catalyzed Claisen Rearrangement: An Attempt of total Synthesis of Oleuropein

Unpublished results.
Introduction

Oleuropein is a Irinoid based natural product having a characteristic lactone ring.\textsuperscript{[1]} Similar natural products have also been identified, consolidating to over 250 members in this family.\textsuperscript{[2]} The Oleuropein analogues are biogenetically related to each other by an oxidative ring contraction and functional group modification.\textsuperscript{[3]} Oleuropein possesses a wide spectrum of biological activities including antioxidant,\textsuperscript{[4]} anti-inflammatory,\textsuperscript{[5]} anti-atherogenic,\textsuperscript{[6]} anti-cancer,\textsuperscript{[7]} antimicrobial,\textsuperscript{[8]} and antiviral properties.\textsuperscript{[9]} Oleuropein having a prime lactone ring like structure with 1,1'-glycosidic bond. In addition, it has exo-cyclic alkene bond and ester linkage with tyrosyl group (Figure 5.1).\textsuperscript{[2f]} With their compact organic structure and useful biological activities, this natural product synthesis stimulates considerable attention to us. Since there is no chemical synthesis for this active molecule, we are therefore interested to develop a general method which emphasizes the possibility of modified Oleuropein structure. This can lead to the acquirement of derivatives of Oleuropein analogue providing a key practical method for medicinal chemist.\textsuperscript{[10]} In addition few examples of Irinoid alkaloids\textsuperscript{[2]} as shown in Figure 5.2 could be obtained from general common key intermediates.

![Figure 5.1 Structure and functional features of Oleuropein](image)

Recently, many reports on the synthesis of Irinoid family based natural products have surfaced. Herein, we have selected to review few examples of the synthesis of
closely related natural products such as (E)-aglucone of Secologanin,\textsuperscript{[11]} monoterpeno elenolide,\textsuperscript{[11]} Dimethyl Secologanoside O-Methyl Ether\textsuperscript{[12]} and (−)-7-deoxyloganin\textsuperscript{[13]}.

Figure 5.2 Examples of Irinoid based natural products

In 1986, R.T. Brown reported\textsuperscript{[11]} the preparation of (E)-aglucone of secologanin (5.4) and the related monoterpeno elenolide (5.5) from substituted hydroxycyclopentene (5.2) in a short reaction sequence involving DIBAL-H reduction and NaIO\textsubscript{4} diol cleavage. The intermediate 5.3 obtained subsequently resulted in (E)-aglucone of secologanin (5.4) which further undergoes PCC oxidation to form monoterpeno elenolide (5.5) (Scheme 5.1). In 1989, Chang reported\textsuperscript{[12]} a total synthesis of Dimethyl Secologanoside O-Methyl Ether (5.9) from substituted cyclopentene (5.7) ozonolysis (5.8) followed by Lewis acid catalyzed glycosylation and alkene construction (Scheme 5.2). Very recently, Lupton
group reported the synthesis of (–)-7-deoxyloganin (5.11) using NHC-catalyzed rearrangement, (Scheme 5.3).\cite{13}

\[ 
\text{HO} \quad \text{1)} \text{BuH_2I, PhH} \quad \text{78°C} \\
\text{MeO}_2\text{C} \\
\text{5.2} \\
\text{2)} \text{HCl, NaIO}_4 \\
\]

\[ 
\text{HO} \quad \text{Et}_3\text{N} \quad \text{PCC} \\
\text{MeO}_2\text{C} \quad \text{CHO} \\
\text{5.3} \\
\text{5.4} \\
\text{5.5} \\
\]

**Scheme 5.1 Synthesis of (E)--aglucone of Secologanin and monoterpane elenolide**

\[ 
\text{MeOOC} \quad \text{MeOOC} \quad \text{MeOOC} \\
\text{PhSNa/THF} \quad \text{MeOOC} \quad \text{MeOOC} \\
\text{92%} \\
\text{5.6} \\
\text{5.7} \\
\text{1)} \text{O}_2/\text{CH}_2\text{Cl}_2 \quad \text{2)} \text{Zn/ACOH} \\
\]

\[ 
\text{MeOOC} \quad \text{MeOOC} \quad \text{MeOOC} \quad \text{MeOOC} \\
\text{1)} \text{MeOH/TsOH reflux, 52%} \quad \text{2)} \text{Toluene reflux, 18h, 41%} \\
\text{5.8} \\
\text{5.9} \\
\]

**Scheme 5.2 Synthesis of Dimethyl Secologanoside O-Methyl Ether**

\[ 
\text{MeO}_2\text{C} \\
\text{1.274} \\
\text{20 mol % 1.275} \\
\text{THF, -78°C} \\
\text{rt, 14h, 63% Yield} \\
\text{S-1.276} \\
\text{5.10} \\
\]

\[ 
\text{MeO}_2\text{C} \\
\text{1)} \text{NaBH}_4 \text{MeOH, 0°C, 10 min} \\
\text{2)} \text{Ac}_2\text{O, Py DMAP, CH}_2\text{Cl}_2 \quad 0°C, 15min \\
\text{41% Yield} \\
\text{5.11} \\
\]

**Scheme 5.3 Synthesis of (–)-7-deoxyloganin through rearrangement reaction**

From the introduction chapter (Chapter 1), NHC catalysis has undergone significant development recently and its application in complex molecule synthesis is one of the most promising areas. NHC catalysis provides efficient access to a variety of nucleophilic species such as acyl anion, homoenolate, enolate which are more attractive tactics for carbon-carbon bond-formation. In addition, generation of an activated carboxylate species is another attractive area for the delivery of ester and amide bonds. Zeitler introduced redox esterification on alkynyl aldehydes providing α,β-unsaturated ester.\cite{14} Later Bode, developed NHC-catalyzed Claisen rearrangement through one pot
esterification followed by 3,3'-sigmatropic rearrangement mechanism (Scheme 5.4).\[^{[15]}\]

Based on this key idea, we were able to design possible Oleuropein synthetic route.

![Scheme 5.4 Redox esterification and Claisen rearrangement](image)

## Results and Discussion

**Retrosynthesis:**

Based on the Bode mechanism for the construction of lactone ring though Claisen rearrangement, we predicted that this method is suitable for Oleuropein synthesis. The retrosynthetic approach for Oleuropein synthesis was illustrated in Scheme 5.5. From oleuropein, lactone ring (IV) is a core structure which would first be constructed and further functionalization could then be implemented such as alkene construction, glycosylation and esterification with tyrosyl group. Enantioselective lactone ring could be constructed from two aldehydes V and VI using NHC catalyst. After formation of the lactone ring IV further conversion to alkene was then carried out from the ring diastereotopic carbon. Then the lactone ring subsequently reduces to lactol which upon in
situ acetylation produce aglycon. This lactol further carry out glycosylation and after tyrosyl group introduction ends up Oleuropein.

![Chemical structures and reactions](image)

**Scheme 5.5 Retro synthesis of Oleuropein**

**Proposed synthesis:**

![Proposed synthetic route](image)

**Scheme 5.6 Proposed synthetic route for Oleuropein synthesis.**
In Scheme 5.6, the proposed synthetic route for Oleuropein synthesis through NHC catalyst technique as a key intermediate step was shown. Furthermore alkene construction was postulated either an aldon condensation or Wittig reaction. Then, the lactone ring would undergo mild reduction and convert to acetylated lactol which acts as a glycosyl donor. TBS protected alcohol would then be converted into acid which forms an ester bond with the tyrosyl group. Subsequently, tertbutyl ester group would then be changed to methyl ester group from conversional synthesis.

**Fragment synthesis:**

From Retrosynthetic analysis the fragments V, VI, II and III are the starting materials which can be prepared from homopropargyl alcohol, Meldrum acid, D-glucose and (3,4-dihydroxyphenyl)acetic acid respectively (Scheme 5.7-5.10). Alkynyl aldehyde 5.13 could be prepared from TBS protected homopropargyl alcohol 5.12\(^{[16]}\) using BuLi and DMF based conventional formylation (Scheme 5.9).\(^{[17]}\) t-butylformylacetate (5.16) was prepared through decarboxylative esterification of formyl Meldrum acid 5.15 (Scheme 5.10).\(^{[18]}\) For glycosylation, synthesis of glycosyl acceptor 5.19 was achieved from acetyl

![Scheme 5.7 Synthesis of propargyl fragment V (5.9).](image)

**Scheme 5.8 Synthesis of tert-butyl formyl fragment VI (5.10).**
CHAPTER 5: N-Heterocyclic Carbene Catalyzed Claisen Rearrangement: An Attempt of Total Synthesis of Oleuropein

Scheme 5.9 Synthesis of sugar fragment II (5.11).

Scheme 5.10 Synthesis of tyrosyl alcohol fragment III (5.12).

protected glucose 5.18 (Scheme 5.9).\textsuperscript{[19, 20]} Tyrosol group 5.21 was prepared from 3,4-dihydroxy phenylacetic acid (Scheme 5.10). The acid group of 3,4-dihydroxyphenylacetic acid was selectively acetylated and converted into ester and the phenolic group was then protected by TBS to give 5.20 which is subsequently reduced by LiAlH\textsubscript{4} to obtain alcohol 5.21.\textsuperscript{[21]}

**NHC-catalyzed key lactone synthesis:**

From Scheme 5.6, the proposed strategy for the synthesis of Oleuropein starting from 5.13 and 5.16 using NHC-catalyzed lactone synthesis is shown. Initial key step 5-lactone formation optimization was carried out using various catalysts (A–H) (Table 5.1). Our initial efforts were focused on the systematic evaluation of various precatalysts and reaction conditions to optimize the reaction. The scope of this optimization was examined using the NHC catalyst precursors (A–H) (Table 5.1, entries 1–8). Among the tested catalysts, catalyst G furnished the lactone product 5.22 in 52 % yield and 79 % enantioselectivity (Entry 11). Further screening of H was found to be efficient in yield and selectivity with DBU as a base in dry toluene (Entries 7 and 8) at room temperature.
Table 5.1 Optimization of key step for lactone formation.

<table>
<thead>
<tr>
<th>Entry[a]</th>
<th>Catalyst (equiv)</th>
<th>Base</th>
<th>Solvent (0.1 M)</th>
<th>Temperature °C</th>
<th>Yield<a href="%25">b</a></th>
<th>Eantiomeric excess (ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A (0.10)</td>
<td>DBU (0.10)</td>
<td>Toluene</td>
<td>20 °C</td>
<td>Trace</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>B (0.10)</td>
<td>DBU (0.10)</td>
<td>Toluene</td>
<td>20 °C</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>C (0.10)</td>
<td>DBU (0.10)</td>
<td>Toluene</td>
<td>20 °C</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>D (0.10)</td>
<td>DBU (0.10)</td>
<td>Toluene</td>
<td>20 °C</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>E (0.10)</td>
<td>DBU (0.10)</td>
<td>Toluene</td>
<td>20 °C</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>F (0.10)</td>
<td>DBU (0.10)</td>
<td>Toluene</td>
<td>20 °C</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>G (0.10)</td>
<td>DBU (0.10)</td>
<td>Toluene</td>
<td>20 °C</td>
<td>32</td>
<td>42</td>
</tr>
<tr>
<td>8</td>
<td>H (0.00)</td>
<td>DBU (0.10)</td>
<td>Toluene</td>
<td>20 °C</td>
<td>33</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>G (0.10)</td>
<td>DIPEA (0.10)</td>
<td>Toluene</td>
<td>20 °C</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>10</td>
<td>G (0.10)</td>
<td>No base</td>
<td>Toluene</td>
<td>20 °C</td>
<td>62</td>
<td>82</td>
</tr>
<tr>
<td>11</td>
<td>G (0.10)</td>
<td>No base</td>
<td>Toluene</td>
<td>40 °C</td>
<td>52</td>
<td>79</td>
</tr>
<tr>
<td>12</td>
<td>G (0.10)</td>
<td>No base</td>
<td>THF</td>
<td>20 °C</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>G (0.10)</td>
<td>No base</td>
<td>Hexane</td>
<td>20 °C</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>G (0.10)</td>
<td>No base</td>
<td>o-Xylene</td>
<td>20 °C</td>
<td>32</td>
<td>81</td>
</tr>
<tr>
<td>15</td>
<td>G (0.10)</td>
<td>No base</td>
<td>p-Xylene</td>
<td>20 °C</td>
<td>38</td>
<td>77</td>
</tr>
<tr>
<td>16</td>
<td>G (0.10)</td>
<td>No base</td>
<td>CF₃C₂H₅</td>
<td>20 °C</td>
<td>35</td>
<td>78</td>
</tr>
</tbody>
</table>

[a]Unless otherwise specified, all of the reactions were carried out with freshly distilled dry solvents at room temperature for 24 h. [b]Isolated yields.
chose catalyst G for further optimization reaction as it is easily prepared from commercially available sources.\textsuperscript{[22]} The base in this case participates in dual role for activating both the catalyst as well as generation of enol from 5.16. Unfortunately, diminished yields and selectivities were obtained for both DBU and DIPEA (Entries 7–9). The counter ion Cl\(^-\) is a very good and mild base which perform this dual role, hence, the reaction condition was tested without any base. This resulted in 62 % yield with 82 % enantiomeric excess (Entry 10). Next, the reaction carried out in 40 °C with different solvents and it was found the reaction is not feasible in THF and toluene based solvents such as o-xylene, p-xylene and trifluoro toluene. This toluene based solvents afforded moderate yields (32, 38 & 35 % respectively) and moderate selectivities (81, 77 & 78 %).
In Scheme 5.11, the possible mechanism and transition state for stereo selective-outcome can be explained. NHC reacts with alkynyl aldehyde 5.13 and forms activated carboxylate (V) which effortlessly attacked by enol form of t-butylformylacetate 5.16 to form hemiacetal adduct (VI) which undergoes 3, 3'-sigmatropic rearrangement followed by ring closure to obtain 5.22.

**Alkene construction:**

**Scheme 5.12** Alkene construction, (a) Horner-Wadsworth-Emmons, (b). Mukiyama aldol condensation.

Alkene construction is another key step due to the presence of acidic alkene proton and an additional ester functional group. Lactone ring 5.22, has a diastereotopic proton which is essential to construct trans alkene. The initial approach involves the investigation of a wittig reaction for the selective construction of trans alkene. In 2007, Wiemer reported trans methyl alkene from five member lactone through Horner-Wadsworth-Emmons (HWE) reaction by preparing phosphate diastereomeric mixture using LDA as a
base for α-protonation.\textsuperscript{[23]} However, a complex mixture was obtained when the same condition was applied to compound 5.22. The reactions were subsequently carried out at both −78 and −40 °C in dry THF (Scheme 5.12). However, in both cases, complex mixtures were obtained. Then, the strategy of Mukiyama aldol reaction condition using LDA as base to get OTMS protected lactone was implemented.\textsuperscript{[24]} Unfortunately, this reaction did not proceed to form TMS protected lactone. Even though this reaction was carried out in one pot protocol, no required product was obtained. In both cases, minor amount of starting material was recovered (Scheme 5.12).

Scheme 5.13 Alkene construction, aldol reactions; (a) LDA base and (b) LiHMDS base

Next, we turned our attention to aldol condensation reaction (Scheme 5.13). In this case, \textit{in situ} generated LDA was used to generate lactone enolate and then acetaldehyde was added to obtain the aldol product.\textsuperscript{[25]} In TLC, a complex mixture was acquired which is further subjected to mesylation and elimination to obtain unidentified products. The enolate generation is the main important step, so the reaction was then performed in LiHMDS and applied to aldol reaction.\textsuperscript{[26]} In this case, we were able to obtain diastereomeric mixture of aldol products which was isolated as mixture. This mixture was
subjected to mesylation and elimination to obtain the required alkene \(5.23\) (trans: cis-95:5). 

_Cis_ and _trans_ alkene could then be separated from column chromatography. The obtained alkene was subjected to lactone to lactol reduction.

**Lactone reduction:**

\[
\begin{align*}
\text{OTBS} & \quad \text{t-BuO}_2\text{C} \\
(\text{trans}) & \quad (\text{cis}) \\
5.23 & \quad 10\% \text{ yield} \\
5.24 & \quad 51\% \\
5.25 & \quad 75\% \text{ yield}
\end{align*}
\]

_Scheme 5.14. Reduction of lactone 5.23_

Reduction of lactone to lactol is also crucial step since there is the possibility of over reduction to primary alcohol. Based on Lupton group report on lactone to lactol using sodium borohydride in methanol, we investigated this condition on \(5.23\) (Scheme 5.14).\(^{[27]}\) The ring-opened product was obtained which was further isolated as acetyl protected compound \(5.24\) in 51 % yield with unidentified products. Next, we turned our attention to Rychnovsky method of one pot DIBAL-H reduction of lactone to lactol followed by acetylation.\(^{[28]}\) The result consisted of two major products \(5.26\) (ring opened primary alcohol) and \(5.25\) (ring opened \(\alpha,\beta\)-unsaturated aldehyde) which is unlikely to be the expected products. Then, controlled DIBAL-H reduction reaction was carried out to selectively achieve one product as the major product and good chemical yield, which supersedes sodium borohydride reduction involving undesired products (Table 5.2).

Initial reaction was carried out using 1.1 equiv of DIBAL-H at \(-78\ \degree\ C\) in dichloromethane to form the reduced product which upon subsequent acetylation, produced \(5.26\) and \(5.25\) in 55% & 10% yields respectively (Table 5.2, Entry 1). \(5.25\) is the
unavoidable side product which exists as open form of lactone. This is due to the exocyclic double bond which could conjugate with the aldehyde and form stable α,β-unsaturated aldehyde system. If DIBAL-H quantity was reduced to 0.5 equiv, 5.26 was still obtained in a 20% yield indicating that, after the lactone reduction to lactol, subsequent ring opening forms the α,β-unsaturated aldehyde (Entry 2). This α,β-unsaturated aldehyde immediately undergoes further reduction to produce primary alcohol.

Table 5.2 Optimization of lactone reduction using DIBAL-H and one pot acetylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>DIBAL-H 1 M in toluene (equiv)</th>
<th>time for reduction</th>
<th>temp. °C</th>
<th>solvent [0.1 M]</th>
<th>yield[bc] 5.26</th>
<th>yield[bc] 5.25</th>
<th>recovered starting material (5.23)[bc]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>2</td>
<td>-78</td>
<td>CH₂Cl₂</td>
<td>55</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>2</td>
<td>-78</td>
<td>CH₂Cl₂</td>
<td>20</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>2</td>
<td>-78</td>
<td>CH₂Cl₂</td>
<td>70</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>2</td>
<td>-78</td>
<td>CH₂Cl₂</td>
<td>75</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>2</td>
<td>-78</td>
<td>Toluene</td>
<td>52</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>1.1</td>
<td>2</td>
<td>-78</td>
<td>THF</td>
<td>51</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>2</td>
<td>-78</td>
<td>Toluene</td>
<td>72</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>2.0</td>
<td>2</td>
<td>-78</td>
<td>Toluene</td>
<td>71</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>2.0</td>
<td>4</td>
<td>-78</td>
<td>CH₂Cl₂</td>
<td>76</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>1.1</td>
<td>4</td>
<td>-78</td>
<td>CH₂Cl₂</td>
<td>56</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

[a]Unless otherwise specified, all of the reactions were carried out with freshly distilled dry solvents at -78°C. [b]Isolated yield. [c]After the mentioned reduction time the following reagents were added at the same temperature (-78°C) in the following order 2 equiv pyridine, 1.1 equiv DMAP in dichloromethane, 4 equiv of acetic anhydride and stirred for 12 h.

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instead of reducing another molecule of lactone 5.23. If the DIBAL-H quantity was increased to 1.5 and 2 equiv, 5.26 could be obtained in good yields of 70% & 75% respectively (Entries 3 and 4). Next, reaction was carried out in different solvents such as THF and toluene, and similar results were obtained as in dichloromethane (Entries 5–8). Furthermore, reaction time increased for 2 more hours produced similar results (Entries 9 and 10). Finally, we conclude that there are two different routes for obtaining the final Oleuropein (5.1) which is explained in Scheme 5.15 and 5.16.

In the initial approach in Scheme 5.15, after the reduction of 5.23 with DIBAL-H into primary alcohol which undergoes Swern oxidation, acetylation and the rest of the steps could be carried out based on the proposed synthetic route (Scheme 5.6). The possible major problem in this scheme is formation of lactol, in which a ring opened structure 5.25 and 5.26 as the main products from earlier DIBAL-H reduction. This approach mainly encourages that the lactone ring acting as a glycosyl donor.

Scheme 5.15 Modification of proposed synthesis

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In Scheme 5.16, an alternative approach was provided, starting from 5.26. The DIBAL-H reduction, followed by one pot acetylation protocol, could obtain the acetyl protected primary alcohol (5.26) which is the key starting material for further studies. The compound 5.26 could then be subjected to TBS deprotection followed by oxidation to obtain 5.27 which further undergoes EDC coupling with 5.21 to obtain 5.28. Next, tert-butyl ester could be converted into methyl ester based on standard functional modification to obtain 5.29. The acetyl group in compound 5.29 could then be deprotected and further undergoes Swern oxidation to obtain 5.30. This ring-opened intermediate which could make either glycosyl donor 5.31 or glycosyl acceptor 5.32 would eventually provide Oleuropein.

Scheme 5.16 Modification of proposed synthesis
Conclusion:

In conclusion, we have developed a new chemical approach for Oleuropein synthesis using NHC catalyzed Claisen rearrangement reaction. Although completion of the molecule was not achieved, two key steps including the lactone formation and the alkene construction were successfully investigated. Reduction was carried out using DIBAL-H and upon optimization, selective reduction to product 5.26 was obtained. Finally, based on the current result, we proposed two different routes to acquire aglycon of Oleuropein.

Experimental Sections

Synthesis of Propagyl fragment 5.13:

(But-3-yn-1-yl oxy)(tert-butyl)dimethylsilane (5.12):\(^{[16]}\)

To a solution of 3-butyn-1-ol (9.26 g, 132.1 mmol) and imidazole (21.59 g, 317.1 mmol) in tetrahydrofuran (200 mL) was added tert-butyl-dimethyl-silyl chloride (TBSCl) (23.90 g, 158.5 mmol). After stirring at ambient temperature for 3 h, the reaction mixture was filtered through a pad of silica and concentrated under reduced pressure. Gradient flash chromatography (Petroleum ether/Ethyl acetate, 100:0 \(\rightarrow\) 95:5) afforded the alkyne (23.62 g, 98 %) as a clear colorless oil: \(^1\text{H} \text{NMR} \) (400 MHz, CDCl\(_3\)) \(\delta\) 3.74 (t, \(J = 7.1\) Hz, 2 H), 2.40 (dt, \(J_1 = 7.1, J_2 = 2.6\) Hz, 2H), 1.95 (t, \(J = 2.6\) Hz, 1 H), 0.89 (s, 9 H), 0.07 (s, 6 H); \(^{13}\text{C} \text{NMR} \) (100 MHz, CDCl\(_3\)): \(\delta\) 81.5, 69.2, 61.7, 25.8, 22.8, 18.3; \(\text{HRMS} \) (ESI) m/z [M+H]\(^+\): calcd. for C\(_{10}\)H\(_{21}\)OSi: 185.1330, found: 185.1324.
5-((Tert-butyldimethylsilyloxy)pent-2-ynal (5.13);[17]

The alkyne (5 g, 27.0 mmol) was dissolved in dry THF (50 mL) and the solution was cooled to −40 °C under nitrogen. n-Butyl lithium (2 M in cyclohexane, 14.2 mL, 28.3 mmol) was added dropwise over 2 minutes maintaining the temperature between −35 and −40 °C. After completion of the addition, anhydrous DMF (4.16 mL, 54.0 mmol, 2 equiv) was added in one portion and the cold bath was removed. The reaction mixture was allowed to warm to room temperature and aged for 30 minutes. The THF solution was poured into a vigorously stirred biphasic solution prepared from a 10 % aqueous solution of KH₂PO₄ (150 mL, 100 mmol) and methyl tert-butyl ether (MTBE) (150 mL) cooled over ice to +5 °C. Layers were separated and the organic extract was washed with water (2x200 mL). Combined aqueous layers were back extracted with MTBE (150 mL). Combined organic layers were dried over MgSO₄, filtered and concentrated to give the crude acetylenic aldehyde as oil which was purified by column chromatography. ¹H NMR (400 MHz, CDCl₃) δ 9.1 (s, 1 H), 3.80 (t, J = 6.7 Hz, 2 H), 2.62 (dt, J₁ = 6.7, J₂ = 0.7 Hz, 2H), 0.89 (s, 1 H), 0.08 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃): δ 177.0, 96.2, 82.2, 60.5, 25.7, 23.7, 23.5, 18.2; HRMS (ESI) m/z [M+H]⁺: calcd. for C₁₁H₂₁O₂Si: 213.1388, found: 213.1331. Spectra consistent with known data.

Synthesis of fragment 5.16:
5-(methoxymethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (5.14):[18]

A mixture of Meldrum’s acid (15 g, 104.1 mmol) and 50 g. of CH(OMe)₃ was heated for 3 h at 85–95 °C. After complete conversion of starting material by checking the TLC, CH(OMe)₃ was removed and through rotavap. The light brown oil was diluted with 100 mL of 5 % CH₂Cl₂ in hexane and scratch the sides using spatula to obtained yellow solid which is filtered through Buchner to obtained 5.14. The product was obtained as yellow solid; (17.6 g, 91 % yield); ¹H NMR (400 MHz, CDCl₃): δ 8.17 (s, 1H), 4.29 (s, 3H), 1.74 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 175.0, 163.2, 158.6, 104.8, 96.8, 66.3, 27.3; HRMS (ESI) m/z [M+Na]^+: calcd. for C₈H₁₀O₅Na: 209.0401, found: 209.0411. Spectra consistent with known data.

2,2-dimethyl-4,6-dioxo-1,3-dioxane-5-carbaldehyde (5.15):[18]

The compound 5.14 (10 g, 53.7 mmol) which upon treatment with 2N HCl (30 mL) for 2 h obtained hydrolyzed product. The reaction mixture was diluted with ethyl acetate (200 mL) and separated through separating funnel. The aqueous layer again extracted with (2x50 mL) of ethyl acetate. The combined organic layer was dried over Na₂SO₄, filtered and concentrated to obtained light brown solid; (8.13 g, 88 % yield); ¹H NMR (400 MHz, CDCl₃): δ 8.56 (s, 1H), 1.77 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 177.0, 168.0, 160.6, 107.1, 95.4, 27.2; HRMS (ESI) m/z [M+H]^+: calcd. for C₇H₉O₅: 173.0450, found: 173.0457. Spectra consistent with known data.

t-Butyl formylacetate (5.16):[18]

A solution of formyl Meldrum’s acid (10 g, 58.1 mmol) and tert-butylalcohol (6.6 mL, 69.7 mmol) in dry benzene (100 mL) was refluxed for 90 min. The solvent was evaporated in vacuo at room temperature. Distillation of the residue in 35–60
°C in 11 torr obtained colourless oil which was immediately stored in −78°C fridge. (5.8 g, 70 % yield); $^1$H NMR (400 MHz, CDCl$_3$): mixture of Keto-enol tautomers δ 11.5 (d, $J$=12.5, 1H, –OH), 9.87 (t, $J$ = 2.4, 1H, –CHO), 7.46 (dd, $J_1$ = 7.6 Hz, $J_2$ = 1.6 Hz, 1H), 1.77 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 177.0, 168.0, 160.6, 107.1, 95.4, 27.2; HRMS (ESI) m/z [M+Na]$^+$: calcd. for C$_7$H$_{12}$O$_3$Na: 167.0684, found: 167.0681. Spectra consistent with known data.

Sugar fragment II (5.19):$^{[19]}$

Perchloric acid was added dropwise to a suspension of 0.5 g of glucose in acetic anhydride (36 mL) at 0 °C. Additional glucose (9.5 g, 55.5 mmol) was added portion wise then the solution was warmed to room temperature and stirred for additional 3 h. Quench and hydrolyzed the excess acetic anhydride by 2 N HCl (100 mL). The reaction mixture was extracted with ethylacetate (250 mL) and washed with water (3×100 mL), ammonium chloride (50 mL) and sodium chloride (50 mL). The organic layer was dried using Na$_2$SO$_4$, filtered and concentrated to obtained pentaacetyl glucose 5.6 as white solid which is used for further steps (17.3 g, 80 %).

Methyl amine in THF (1M) was added drop wise to a suspension of penta acetyl glucose 5.17 (3 g, 7.69 mmol), in dry THF (15 mL) to obtained tetraacetyl glucose 5.18 at 0 °C. Additionally the reaction
mixture was stirred for 3 h. Evaporate the solvent and the residue was purified by column chromatography obtained. 5.18 (100 mL) which is immediately used for next steps (2.32 g, 85 %).

\text**l-O-(Trimethylsilyl)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (5.19)**\textsuperscript{[20]}

![chemical structure of l-O-(Trimethylsilyl)-2,3,4,6-tetra-O-acetyl-β-D-glucopyranose (5.19)]

To a stirred solution of 5.18 (2 g, 5.7 mmol) in dichloromethane (15 mL) containing triethylamine (0.89 mL, 6.8 mmol) was added chlorotrimethylsilane (0.73 mL, 6.8 mmol) dropwise at room temperature. After being stirred for 2 h, the mixture was filtered through a pad of Celite and worked up to afford a residue that was crystallized to afford silyl derivative 5.19 in 85 % yield as a single anomer: mp 104–105 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 5.17 (t, J = 9.2 Hz, 1H), 5.04 (t, J = 9.6 Hz, 1H), 4.90 (dd, J\textsubscript{1} = 9.6 Hz, J\textsubscript{2} = 7.6 Hz, 1H), 4.73 (d, J = 7.6 Hz, 1H), 4.20–4.09 (m, 2H), 3.72–3.67 (m, 1H), 2.15 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 0.13 (s, 9H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 170.6, 170.3, 169.4, 169.3, 95.5, 73.2, 72.7, 71.8, 68.6, 62.2, 20.6 (3C), –0.02 (3C); HRMS (ESI) m/z [M+Na]\textsuperscript{+}: calcd. for C\textsubscript{17}H\textsubscript{28}O\textsubscript{10}SiNa: 443.1349, found: 443.1359. Spectra consistent with known data.

![chemical reaction](image)

\text**Methyl [3,4-Bis(tert-butyldimethylsilyloxy)phenyl]acetate 5.20**\textsuperscript{[21]}

At 0 °C acetyl chloride (6 mL) was added dropwise to the solution of (3,4-dihydroxyphenyl)acetic acid (6.51 g, 38.7 mmol) in MeOH (250 mL). After 1 h, the mixture was allowed to warm to room temperature. The progress
of the reaction was monitored by TLC which tells complete conversion after 2 h. The reaction mixture was concentrated to dryness, and the residue was redissolved in dry DMF (60 mL). From the reaction mixture, TBDMSCl (14 g, 92.8 mmol) and imidazole (3.8 g, 57 mmol) were added and the mixture was stirred for 2 h. After complete conversion by TLC the reaction mixture was diluted with diethyl ether (200 mL) and washed with water (3x100 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated to obtain a crude oil which upon column chromatography to form TBS protected ester (5.20). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.78–6.76 (m, 1H), 6.74 (s, 1H), 6.69 (dd, $J_1 = 8.2$ Hz, $J_2 = 2.1$ Hz, 1H), 3.67 (s, 3H), 3.49 (s, 3H), 0.98 (s, 18H), 0.19 (s, 12H), 0.13 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.1, 146.6, 145.9, 126.8, 122.0, 51.8, 40.4, 25.8; Spectra consistent with known data.

2-[3,4-Bis(tert-butyldimethylsilyloxy)phenyl]ethanol (5.21):$^{[21]}$

Methyl[3,4-bis(tert-butyldimethylsilyloxy)phenyl]acetate (5.20, 4.13 g, 10.03 mmol) in dry THF (25 mL) was added dropwise to a cooled (0°C) suspension of LiAlH$_4$ (400 mg, 10.5 mmol) in THF (25 mL) and stirred for 15 min. TLC analysis revealed complete disappearance of the starting material in this time period. The reaction was quenched by dropwise addition of methanol and diluted with diethyl ether and subsequently washed with water. The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure to obtain a residual oil which was purified through silica gel column chromatography. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.76 (d, $J = 7.8$ Hz, 1H), 6.69 (d, $J = 2.0$ Hz, 1H), 6.63 (dd, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz, 1H), 3.78 (q, $J = 4.2$ Hz, 1H), 2.73 (t, $J = 6.5$ Hz, 1H), 1.45 (s, 1H), 0.98 (s, 18H), 0.19 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 146.7, 145.4, 131.2, 121.8, 121.8, 121.0, 63.8, 38.4, 25.9, 18.4, −4.0,
Total Synthesis of Oleuropein

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\(-4.0; \text{HRMS (ESI) m/z [M+Na]}^+: \text{calcd. for C}_{20}\text{H}_{39}\text{O}_{3}\text{Si}_{2}: 383.2438, \text{found: 383.2425.}

Spectra consistent with known data.

\[(S)-\text{tert-butyl 4-}((\text{tert-butyldimethylsilyl})\text{oxy})\text{ethyl}-2\text{-oxo-3,4-dihydro-2H-pyran-5-carboxylate (5.22):}

\]

In an oven dried 10.0 mL round bottom flask, the reaction between 
\(((\text{tert-butyldimethylsilyl})\text{oxy})\text{pent-2-ynal (5.13) and tert-butyl formylacetate (5.16) was carried out using optimized Table 5.1 condition. tert-butyl formylacetate (5.16) (100 mg, 0.69 mmol, 1.0 equiv) and (R,S) triazolium precatalyst (G) (26.7 mg, 0.10 equiv) were added, followed by 4.0 mL toluene (0.1 M) and ((\text{tert-butyldimethylsilyl})\text{oxy})\text{pent-2-ynal (5.13) (220.0 mg, 1.04 mmol, 1.50 equiv). The flask was sealed with a rubber septum. The resulting solution was heated to 40 °C and stirred for 24 h. Toluene was evaporated and the residue was purified by column chromatography (153 mg, 62 %).} \[\alpha\]^{23}_{D} = +10.7 \text{ (c = 0.9, CHCl}_3; \text{^1H NMR (400 MHz, CDCl}_3): \delta 7.45 \text{ (s, 1H), 3.71–3.66 \text{ (m, 2H), 3.09–3.03 \text{ (m, 1H), 2.88 \text{ (dd, J}_1 = 16.0 \text{ Hz, J}_2 = 1.6 \text{ Hz, 1H), 2.66 \text{ (dd, J}_1 = 16.0 \text{ Hz, J}_2 = 7.2 \text{ Hz, 1H), 1.80–1.76 \text{ (m, 14H), 0.91 \text{ (s, 9H), 0.06 \text{ (s, 6H); ^13C NMR (100 MHz, CDCl}_3): \delta 166.8, 164.3, 117.2, 81.4, 60.5, 35.9, 33.0, 28.2, 25.9, 18.3, –5.3, –5.3; HRMS (ESI) m/z [M+H]}^+: \text{calcd. for C}_{18}\text{H}_{33}\text{O}_5\text{Si: 357.2097, found: 357.2102. 82 % ee as determined by HPLC (IC, 99:1 hexanes:i-PrOH), tr} = 10.2 \text{ and 12.1 mint.} \]
**(S,E)-**tert-butyl-4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3-ethylidene-2-oxo-3,4-dihydro-2H-pyran-5-carboxylate (5.23):

(i) LiN(SiMe$_3$)$_2$ (1.68 mL, 1.68 mmol, 1M in hexane) was added to the solution of 5.22 (0.5 g, 1.4 mmol) in dry THF (5 mL) at -78°C with stirring under nitrogen atmosphere. After 10 min, a solution of MeCHO (0.78 mL, 14.0 mmol) in dry THF (5 mL) was added to this mixture, and stirred for 15 mints. The reaction mixture was quenched with a solution of saturated NH$_4$Cl (2 mL) at room temperature, diluted with EtOAc, washed with sat. NaHCO$_3$, and brine, dried over MgSO$_4$, and concentrated in vacuum to give a residue, which was passed through a silica gel column (Hexane–EtOAc; 3:2) gave a mixture of diastereomers (0.42 g, 75 %) which is used for further steps.

(ii) The above obtained mixture of alcohols (0.42 g, 10.5 mmol) was dissolved in pyridine (8 mL), and to this solution was added MeSO$_2$Cl (0.16 mL, 21.0 mmol) at room temperature with stirring. After 1 h, the reaction mixture was concentrated in vacuum, diluted with EtOAc (20 mL), washed with H$_2$O (2x10 mL), and brine (10 mL), dried over MgSO$_4$, and concentrated in vacuum to give a crude mixture of diastereomers (0.46 g, 85 %).

(iii) The mixture of mesylates (0.46 g, 0.97 mmol) was dissolved THF (5 mL) and added DBU (0.29 mL, 1.95 mmol) and stir at room temperature. After 10 min stirring, the reaction mixture was diluted with EtOAc, washed with sat. NH$_4$Cl, sat. NaHCO$_3$, brine...
and dried over MgSO₄, and concentrated in vacuum to give a mixture of E and Z-
geometrical isomers as viscous oil. The mixture was chromatographed on a silica gel
column. Elution with Hexane-EtOAc (98:2); (0.24 g, 65 %); \([\alpha]^{23}_D = -34.0 \ (c = 0.5, \ CHCl_3)\); \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 7.39 (s, 1H), 7.05 (qd, \(J_1 = 7.2\) Hz, \(J_2 = 0.9\) Hz, 1H), 3.86 (dd, \(J_1 = 7.4\) Hz, \(J_2 = 4.9\) Hz, 1H), 3.62–3.47 (m, 2H), 1.91 (d, \(J = 7.3\) Hz, 3H), 1.82–1.61 (m, 2H), 1.50 (s, 9H), 0.86 (s, 9H), 0.86 (s, 9H), 0.06 (s, 6H); \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta\) 164.2, 162.7, 148.8, 143.2, 127.4, 115.7, 81.4, 59.6, 37.4, 30.2, 28.2, 26.0, 18.2, 14.6, −5.3; HRMS (ESI) m/z [M+H]^+: calcd. for C₂₀H₃₅O₅Si: 383.2260, found: 383.2256.

\([\alpha]^{23}_D = -74.7 \ (c = 1.6, \ CHCl_3)\); \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 7.37 (s, 1H), 6.35 (q, \(J = 7.2\) Hz, 1H), 3.65–3.51 (m, 3H), 1.91 (d, \(J = 7.3\) Hz, 3H), 2.11 (d, \(J = 7.2\) Hz, 3H), 1.94–1.82 (m, 1H), 1.51 (s, 9H), 1.51–1.46 (m, 1H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); HRMS (ESI) m/z [M+H]^+: calcd. for C₂₀H₃₅O₅Si: 383.2260, found: 383.2274.

(3R,E)-2-(tert-butoxycarbonyl)-3-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-ethylidene pentane-1,5-diyl diacetate (5.24):

A magnetically stirred solution of lactone 5.23 (0.1 g, 0.26 mmol) in CH₃OH (1 mL) was cooled to 0 °C then treated with NaBH₄ (1 ml of a 0.1 M solution in CH₃OH). The reaction was stirred at 0 °C for 10 mints then quenched with H₂O (1 ml) and extracted with CH₂Cl₂ (3 x 3 ml). The
combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. The crude reaction mixture was used for acetylation step. The crude reaction mixture was dissolved in CH$_2$Cl$_2$ treated with pyridine (62 mg, 0.63 mL, 0.78 mmol, 3.0 equiv), and then a solution of DMAP (35 mg, 0.28 mmol, 1.1 equiv) in 2 mL of dry CH$_2$Cl$_2$ was slowly added by syringe. Finally, Ac$_2$O (0.1 mg, 0.1 mL, 1.0 mmol, 4.0 equiv) was added dropwise and stir for 2 h. After 2h, the reaction mixture was quenched by adding saturated NH$_4$Cl (5 mL) solution and extract with dichloromethane (5 x 3 mL). The combined organic layer was dried over sodium sulphate and concentrated in vacuo. The residue was purified by column chromatography. Yield: (62 mg, 51 %); [a]$^\text{23}_D$ = −63.0 (c = 0.3, CHCl$_3$);

$^1$H NMR (400 MHz, CDCl$_3$): δ 5.85 (q, J = 7.2 Hz, 1H), 4.54–4.46 (m, 2H), 4.25 (dd, J$_1$ = 10.4 Hz, J$_2$ = 4.4 Hz, 1H), 4.0 (t, J = 10.4 Hz, 1H), 3.56–3.41 (m, 2H), 3.13–3.11 (m, 2H), 2.75–2.71 (m, 2H), 2.07 (s, 3H), 2.02 (s, 3H), 1.73 (d, J = 6.8 Hz, 3H), 1.68–1.61 (m, 2H), 1.51 (s, 9H), 0.86 (s, 9H), 0.06 (s, 6H); HRMS (ESI) m/z [M+H]$^+$: calcd. for C$_{24}$H$_{44}$O$_7$SiNa: 495.2723, found: 495.2719.

**General procedure for DIBAL H reduction:**

To 5 mL flame-dried 10 ml round bottom ester (5.23) flask connected to nitrogen balloon (0.1 g, 0.26 mmol) in 3 mL of dry CH$_2$Cl$_2$. After the mixture was cooled to $-78 \, ^\circ \text{C}$, DIBALH (1.0 M in toluene, 0.28 mL, 0.28 mmol, 1.1 equiv) was added dropwise. After being stirred for 2 h (TLC showed no ester) the reaction mixture was treated with pyridine (62 mg, 0.063 mL, 0.78 mmol, 3.0 equiv), and then a solution of DMAP (35 mg, 0.28 mmol, 1.1 equiv) in 1 mL of dry CH$_2$Cl$_2$ was slowly added. Finally, Ac$_2$O (26 mg, 0.025 mL, 1.0 mmol, 4.0 equiv) was added dropwise, the reaction vessel was packed in a Dewar flask containing dry ice, and the mixture was stirred under an N$_2$ atmosphere for
12 h, the mixture was warmed to –20 °C and the reaction was quenched by adding saturated NH₄Cl (5 mL) solution. The reaction mixture was stirred for 30 mins, allowed to warm to room temperature, and then extracted with CH₂Cl₂ (3 x 5 mL). Aluminium salts formed emulsions, they were disrupted by adding a saturated solution of Rochelle’s salt (10 mL) with vigorous stirring. The combined CH₂Cl₂ extracts were washed with ice-cold 1 N NaHSO₄ (2 x 5 mL), saturated NaHCO₃ (3 mL), and brine (1 mL). After drying (anhydrous Na₂SO₄) and evaporation of CH₂Cl₂ extracts, the residue obtained was purified by flash chromatography on silica gel.

**(S,1E,4E)-2-(tert-butoxycarbonyl)-3-(2-((tert-butyldimethylsilyloxy)ethyl)-4-ethyldiene pent-1-ene-1,5-diyldiacetate (5.26):**

![Chemical Structure](image)

Yield (0.09 g, 75%); [α]⁺²³ D = +53.0 (c = 1.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 8.17 (s, 1H), 5.69 (q, J = 6.8 Hz, 1H), 4.58 (s, 2H), 3.24 (t, J = 7.8 Hz, 1H), 3.60–3.50 (m, 2H), 2.22 (s, 3H), 2.21–2.11 (m, 1H), 2.05 (s, 3H), 2.02–1.94 (m, 1H), 1.51 (s, 9H), 0.86 (s, 9H), 0.06 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 170.8, 166.5, 166.2, 144.2, 135.0, 127.8, 119.2, 80.9, 66.7, 60.8, 34.1, 32.4, 28.1, 25.8, 21.1, 20.7, 18.1, 13.4, –5.1; HRMS (ESI) m/z [M+H]⁺: calcd. for C₂₄H₄₂O₇SiNa: 493.2598, found: 493.2608.

**(S,2E,4E)-tert-butyl-2-(acetoxymethylene)-3-(2-((tert-butyldimethylsilyloxy)ethyl)-4-formylhex-4-enoate (5.25):**

Obtained from Table 5.2, entry 5 condition (16 mg, 15%); [α]⁻²² D = –39.6 (c = 1.2, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 9.41 (s, 1H), 8.10 (s, 1H), 6.63 (q, J = 7.2 Hz, 1H), 4.20 (t, J = 7.8 Hz, 1H), 3.62–3.50 (m, 2H), 2.23 (s, 3H), 2.22–2.11 (m, 1H), 2.05 (d, J = 7.2 Hz, 3H), 2.03–2.01
(m, 1H), 1.49 (s, 9H), 0.90 (s, 9H), 0.04 (s, 6H); **HRMS** (ESI) m/z [M+H]^+: calcd. for C_{22}H_{38}O_{6}SiNa: 449.2245, found: 449.2233.

### Reference Sections


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**CHAPTER 5: N-Heterocyclic Carbene Catalyzed Claisen Rearrangement: An Attempt of Total Synthesis of Oleuropein**
CHAPTER 6

Appendix: Glycosylated Porphyrin Derivatives and Their Photodynamic Activity in Cancer Cells

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Abstract

The present study reports the design and synthesis of nine $C_2$-symmetric 5,15-[bis(arayl)]-10α,20β-[bis(1,2:3,4-di-O-isopropylidene-α-D-galactopyranose-6yl)]porphyrins (6.3-6.11) bearing electron donating or electron withdrawing substituents and a $D_2$-symmetric 5α,10β,15α,20β-tetrakis(1,2:3,4-di-O-isopropylidene-α-D-galactopyranose-6-yl) porphyrin (6.12). In the system we design, the C$_6$ of pyranose sugar is elegantly fused into the porphyrin core as meso carbon, which renders a new type of photodynamic inducers. The biological effects of these derivatives were assessed in HeLa and HCT116 human cancer cells. In particular, the tetra-glycofused structure 6.12 exhibited the highest cellular uptake and photocytotoxicity. Unlike the reported sugar-porphyrin conjugates, which normally localize in mitochondria or endoplasmic reticulum, the unique glycofused pophyrins in this study were dominantly localized in lysosomes. The measurement of the dual fluorescence of annexin V-FITC/PI by flow cytometry revealed that the cell death was caused by apoptosis. Further PARP cleavage study suggested that apoptosis induced by the treatment of compound 6.12 was via caspase-dependent apoptotic pathway in cancer cells.

Introduction

Photodynamic therapy (PDT)$^{[1-6]}$ is a rapidly growing method used to treat various cancers including multidrug resistance$^{[7]}$ (MDR) phenotype tumor cells by using non-toxic photosensitizers (PSs) and innocuous visible light in the presence of molecular oxygen. This technique is based on the generation of cytotoxic reactive oxygen species (ROS) by a PS under light irradiation.$^{[8]}$ Currently, a few potent PSs such as porphyrins,$^{[9-}$
phthalocyanines, perylene, chlorin derivatives are commonly used in photodynamic therapy. They are suitable PSs due to their light absorption in the visible range of spectrum, but early generation of these molecules has obvious drawbacks such as low tissue selectivity, low sensitizing efficiency, low solubility, high systemic toxicity, etc. Therefore, the development of new PS that targets the abnormal cells selectively and generates cytotoxic ROS efficiently is one of the current strategies that are being explored.

Conjugation of porphyrin with cancer cell recognizing biomolecules is an active area receiving much attention, especially the use of biological active sugar motifs as a conjugate. Previous studies described the roles of saccharides in cell recognition, with porphyrin-saccharide derivatives exhibiting much higher binding affinity to human cancer cell lines than their non-saccharide counterparts with the sugar moieties enhancing uptake by cancer cells. Intelligibly, such glycoconjugate porphyrin is thus a potential avenue for targeted photosensitizers towards tumor cells. In this work, we aim to develop a new series of directly linked sugar-porphyrin conjugates and investigate their potential phototoxicity, cellular localization studies, and in vitro apoptotic activities.

### Results and Discussion

#### Rational Design of Glycofused Porphyrins as PSs.

Porphyrin derivatives are commonly used PSs due to their light absorption in the visible range of the spectrum and efficient phototoxicity towards cancer cells. In the past decade, great efforts have been made to search for more efficient photosensitizing molecules by modification of the porphyrin core and peripheral structure of phthalocyanines. Not surprisingly, tumor-recognizing elements, such as monoclonal...
antibodies have also been extensively explored to gain tissue selectivity and reduce systemic toxicity. Synthesis of sugar-porphyrin conjugates were reported sporadically, but in most cases, the biologically active sugars were included into the peripheral structures with a linker between sugar moiety and the photosensitizing core structure (Figure 6.1, structure A). Van Nostrum and co-workers demonstrated the peripheral and axial substitution of phthalocyanines with solketal protected sugar groups (Figure 6.1, structure B) facilitates an increased cellular uptake of cancer cells.\textsuperscript{[16]} The solketal group was thought to act as a targeted micelle, resulting in a higher intracellular concentration of the PS and a concomitant increase in photodynamic effect.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure6_1.png}
\caption{Rational design of new glycofused porphyrin photosensitizers. A, reported photosensitizing porphyrins, R = various groups including sugars; B, glycoconjugated phthalocyanines; C, tolyporphyrin A; D, glycofused porphyrins in this study.}
\end{figure}

This biocompatible sugar unit is used to enhance the cellular uptake through over-expressed glucose transporters in cancer cells.\textsuperscript{[17]} The isopropylidene protecting group renders the compound metabolically stable and increases the cell availability of phthalocyanine conjugate that can be cleaved \textit{in vivo} to form hydrophilic free hydroxyl
The molecular design in this study was also inspired by a naturally occurring sugar-porphyrin conjugate, tolylporphyrin A\textsuperscript{[21]} (Figure 1, structure C). It has a $C_2$ symmetric structural skeleton and the sugar moieties are directly linked to porphyrin. This structural skeleton has the ability to reverse the multidrug resistance (MDR) tumor cells.\textsuperscript{[7,21]} This suggests that conjugating pattern of sugar moieties with porphyrin core also plays an important role for their biological activity. Based on all above and our experience in carbohydrate chemistry and molecular design, we designed the glycofused porphyrins as shown in Figure 1D. In structure D, two para meso positions of porphyrin structure were elegantly fused with the C$_6$ of isopropylidene protected galactose, and the other two para meso postions of the porphyrin structure were still decorated with aryl substitutions (6.3-6.11). The potential efficacy of our design is also strongly supported by Banfi et al. and Ferrand et al. works.\textsuperscript{[9]} They showed that diaryl porphyrin derivatives are more effective than corresponding tetraaryl porphyrin derivatives in inducing photodynamic cell elimination of human colon adenocarcinoma cells. In addition, two para meso positions of porphyrin structure were incorporated with similar sugar units, giving us tetrasugar porphyrin (6.12). We decided to choose galactose as a model sugar because Griegel and co-workers\textsuperscript{[22]} recognized that human retinoblastoma cells express sugar receptors that exhibits a preferential affinity for galactose residues and renders easy assimilation.

**Synthesis of Glycofused Porphyrins.**

Among the various resources from which a porphyrin ring can be constructed, the acid-catalyzed condensation of dipyrrylmethane units with aryl aldehydes represents a widely used route, which we have exploited to obtain *meso* bis-glycosylated
Scheme 6.1. Expedited synthesis of glycofused porphyrin conjugates.

diarylporphyrins in this study. This approach takes advantage of the accessibility of homochiral dinuclear C–glycosyl dipyrromethane unit by a protocol involving the direct condensation of sugar aldehyde with pyrrole (Scheme 6.1). Thus, the condensation of 1,2:3,4-di-O-isopropylidene-α-D-galacto-hexadialdo-1,5-pyranose (6.1) with pyrrole (1:5 molar ratio) and 0.1 equiv of BF₃·Et₂O was effected in dichloromethane at room temperature. The reaction was completed within 1 h, after quenching with NaHCO₃(aq) and flash chromatography, the dipyrromethane sugar unit was obtained in 65% isolated yield. With significant quantity of dipyrromethane sugar in hand, we proceeded to construct the macrocycle. The condensation of the 1,2:3,4-di-O-isopropylidene-5,5-dipyrryl-6-deoxy-α-D-galactopyranose (6.2) with various aromatic aldehydes and sugar aldehyde (6.1) was performed according to the procedures developed by Casiraghi and coworkers. The porphyrin-ring construction was carried out by using various aldehydes with dipyrrol methane (6.2) and BF₃·Et₂O in dry dichloromethane under argon atmosphere. The porphyrinogen intermediate was then oxidized by DDQ and further purification by flash chromatography yielded porphyrins 6.3-6.12 ranging from yields of...
5% to 16% (Scheme 6.1). All the compounds are highly soluble in common organic solvents and deprotection of the isopropylidene group was not performed due to the instability of the compounds even under slightly acidic condition.

**Characterization and Spectral Properties.**

The $^1$H and $^{13}$C NMR spectra of 1,2;3,4-di-O-isopropylidene-5,5-dipyrryl-6-deoxy-$\alpha$-D-galactopyranose ($6.2$) displayed distinct peaks for the pyrrole methyne proton and proton an carbon owing to the diastereotopicity of the two pyrrole units attached at the homochiral sugar fragment. The porphyrin conjugates $6.3$–$6.12$ were subjected to various spectral analyses, including $^1$H NMR, $^{13}$C NMR, mass spectrometry, UV–Vis, and IR spectroscopy. All the compounds are homogeneous and have reliable spectral values. From the $^1$H NMR spectra of all the porphyrin compounds, it was observed that the ring system is highly conjugated and aromatic. In general, the protons at the following positions are responsible for the signals in the indicated regions of the spectra (Fig. 1S):

(a) pyrrole $\beta, \beta'$-protons (10.5 and 8.5 ppm), (b) meso phenyls and other aromatic protons (8.5 to 7.0 ppm), (c) sugar C–5' protons (7.7 to 6.8 ppm), (d) sugar C–1' anomeric proton (6.5 to 6 ppm), (e) other protons on the sugar legs (5.5 to 4.5 ppm), (e) four different methyl groups present in the isopropylidene groups (2.0 to 1.0 ppm), (f) characteristic NH proton (−2 to −3 ppm). The data suggest the slight changes in the chemical shift towards more deshielded region for the sugar methylenic proton as compared to the expected shift because it is directly linked with highly conjugated aromatic system. The diaryl sugar porphyrin ($6.3$–$6.11$) displayed two types of $\beta, \beta'$-pyrrole protons and five signals effect from sugar methylenic protons, thereby proving the presence of $C_2$ symmetry. Also, the integral value of the methylenic proton sugar unit illustrates a highly $C_2$ symmetric nature.
Figure 6.2. Partial $^1$H NMR spectra of compound 6.3, 6.8 and 6.12

Table 6.1. UV & HRMS data of sugar–porphyrin conjugate.

<table>
<thead>
<tr>
<th>Compd</th>
<th>UV–visible spectrum: $\lambda_{max}$ nm (log $\varepsilon$)</th>
<th>HRMS (ESI): m/z (M+H)$^+$ (Calcd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>406 (4.478), 516 (4.136), 549 (3.749), 589 (3.672), 644 (3.549)</td>
<td>919.3948 (919.3918)</td>
</tr>
<tr>
<td>4</td>
<td>419 (4.506), 518 (3.577), 550 (3.103), 590 (3.106), 645 (2.811)</td>
<td>1009.3619 (1009.3620)</td>
</tr>
<tr>
<td>5</td>
<td>416 (4.480), 516 (3.453), 548 (3.051), 590 (2.979), 644 (2.723)</td>
<td>919.3138 (987.3139)</td>
</tr>
<tr>
<td>6</td>
<td>414 (4.540), 518 (4.282), 550 (3.817), 591(3.796), 640 (3.30)</td>
<td>1011.3665 (1011.3673)</td>
</tr>
<tr>
<td>7</td>
<td>414 (4.494), 518 (3.514), 550 (3.412), 590 (3.160), 646 (2.890)</td>
<td>979.4128 (979.4129)</td>
</tr>
<tr>
<td>8</td>
<td>412 (4.533), 516 (4.205), 546 (3.607), 590 (3.768), 644 (3.526)</td>
<td>1039.4347 (1039.4341)</td>
</tr>
<tr>
<td>9</td>
<td>403 (4.538), 516 (4.211), 550 (3.827), 591(3.757), 645 (3.487)</td>
<td>1087.3545 (1087.3564)</td>
</tr>
<tr>
<td>10</td>
<td>405 (4.521), 513 (4.163), 543 (3.422), 586 (3.701), 640 (3.163)</td>
<td>1099.2979 (1099.2976)</td>
</tr>
<tr>
<td>11</td>
<td>412 (4.501), 518 (3.767), 550 (3.480), 591(3.329), 646 (3.089)</td>
<td>931.3044 (931.3047)</td>
</tr>
<tr>
<td>12</td>
<td>406 (4.519), 519 (4.017), 552 (3.381), 591(3.591), 646(3.437)</td>
<td>1223.5266 (1223.5288)</td>
</tr>
</tbody>
</table>
of the compounds. In contrast, compound 6.12 showed eight pyrrole $\beta, $ $\beta'$–protons as a singlet and all the methylene protons of four sugars displayed only five signals which emphasizes the presence of $D_2$ symmetry. Furthermore, comparative NMR diagram illustrates that the partial $^1\text{H}$ NMR spectra of compounds 6.3, 6.8 and 6.12, thereby evidencing the diagnostic signals (Figure 6.2). For compounds 6.3 and 6.8, two types of $\beta, $ $\beta'$ pyrrole protons appeared in the most deshielded aromatic region, but compound 6.12 displayed single peak. Compound 6.3 displayed Ar–H signal next to the $\beta,\beta'$ pyrrole proton, but it disappeared in compound 6.8 due to the replacement of Ar–H by Ar–F. For all the compounds, sugar H–5' appeared in the deshielded region due to ring-current obtained by highly conjugated aromatic system. Successively, anomeric proton followed by the sugar methylene protons appears towards the shielded region. This picture further evidencing compounds 6.3 & 6.8 possess C$_2$–symmetry where as compound 6.12 shows highly D$_2$–symmetry. High resolution mass spectra (HRMS) gave molecular weights which are those expected for the corresponding (M+H)$^+$ formula and it is in good

![Figure 6.3. UV spectra of compound 6.8](image)
agreement (within 0.5 ppm) with the theoretical values (Table 6.1). In the UV–Vis spectra, the Soret bands at 403–419 nm and four Q bands at 500–620 nm showed the characteristic of a porphyrin ring (Table 6.1). For most of the electron donating substituents, the Soret bands were significantly red-shifted compared to the reference porphyrin compound 6.3. In the Q–band region, similar spectral variations were obtained for all electron withdrawing substituents compared to the reference porphyrin compound 6.3.

Cellular Phototoxicity.

**Figure 6.4.** Dose-response curve obtained with compounds 6.5, 6.6, 6.11, and 6.12 in HeLa (A) and HCT116 (B) cells. Cells were photosensitized with 1 μM of each compound and the light dose was varied as indicated. Viability was assessed by MTS assay.

The light dose-dependent phototoxicity of the photosensitizers was investigated in two different human cancer cell lines, HeLa and HCT116 by MTS assay at a concentration of 1 μM. Among the ten compounds studied, four compounds (6.5, 6.6, 6.11, and 6.12) have shown the phototoxic effects in both cancer cell lines (Figure 6.4. A and B). Compound 6.12 is preferentially taken up by HeLa cells over compounds 6.5, 6.6,
and 6.11 while the rest six compounds showed marginal phototoxicity (data not shown). In addition, those compounds exhibited a minor dark cytotoxicity in both cell lines, which maintained more than 90% of survival rate. On the other hand, the control cells irradiated in the absence of the photosensitizer were found to be negligible in cell death. These results suggest that the electron donating substituents present in the para position of the phenyl group, especially p- methoxy (6.5) and p-thiomethoxy (6.6), enhance phototoxicity, compared with the electron withdrawing groups (pentafluoro, p-chloro and p-nitro, 6.8–6.10) and simple phenyl substituent (6.3). Similarly, 3-thiopheneyl group present in compound 6.11 showed good activity due to its electron donating nature. In contrast, the methoxy group present at ortho position of the phenyl ring of compound 6.4

![Cellular uptake](image)

**Figure 6.5.** Cellular uptake. HeLa cells were treated with 1 μM of each compound for 24 h, rinsed, and fixed with 3.7% PFA. Fluorescence images were taken under identical conditions.
and trifluoromethoxy at para position of the phenyl ring of compound 6.7 did not show any activity. However, phenyl group replaced by sugar unit called tetra-sugar porphyrin (6.12) conjugates exhibited quite reasonable phototoxicity. These results further supported that the cancer cells are sensitive to the photosensitizers. The amount of the photosensitizers taken up by the cells was determined by fluorescence microscopy after 24 h treatment. As shown in Figure 6.5, compounds 6.5 and 6.6 were poorly internalized by HeLa cells compared with compounds 6.11 and 6.12. Thus, the extent of uptake of the conjugates is dependent upon the nature of the sugar component and the electron donating nature of the substituent attached at meso position of the porphyrin ring. The cellular uptake of conjugates 6.12 was 3–8 times higher than that of porphyrin 6.5, 6.6 & 6.11 at all time points studied under the same testing condition. It has been postulated that isopropyledine-protected sugar groups from the porphyrin residues play an important role in facilitating cellular uptake, probably through deprotection of solketal group and may contribute to the formation of free hydroxyl group due to the acidic environment of cancer cells.\cite{25}

**Subcellular Localization.**

The precise phototoxic effect of compound 6.12 was evaluated by examining its subcellular localization in Hela cells. To this end, its fluorescence pattern was monitored with the organelle-specific fluorescent probes LysoTracker-Red and MitoTracker-Deep Red by fluorescence microscopy, which target lysosomes and mitochondria, respectively. As shown in Figure 6.6, compound 12 is primarily localized in lysosomes. In addition, the subcellular localization was also examined in HCT116 cells, showing the similar pattern as seen in Hela cells (data not shown). Turk and coworkers reported that apoptosis can be
induced by selectively disrupting lysosome, through the cleavage by papain-like cathepsins independent of caspase activation.\cite{26} Several cathepsins were shown to cleave Bid and assist cytochrome c release from mitochondria in the presence of Bid in vitro, indicating their redundant roles. However, we cannot exclude the possibility that lysosomal proteases can also activate apoptosis other than Bid-mediated apoptotic pathways, prompting us to check the underlying molecular mechanism of the novel PDT compound.

**Studies on PDT Induced Apoptotic Cell Death.**

**Figure 6.6.** Intracellular localization of compounds. Subcellular localization of compound 12 determined by confocal laser scanning microscopy. HeLa cells treated with compound 12 were loaded with specific probes for lysosomes and mitochondria. Compound 12 (green) is shown in the left panels, LysoTracker or MitoTracker (Red) is shown in the middle panels, and an overlay of compound 12 with LysoTracker or MitoTracker (yellow) is shown in the right panels.

\[\text{CHAPTER 6: Appendix: Glycosylated Porphyrin Derivatives and Their Photodynamic Activity in Cancer Cells}\]
In order to delineate cell death mechanism\textsuperscript{[27,28]} in response to the treatment of compound 6.12, standard apoptotic assays were performed. As shown in Figure 6.7, a majority of the non-illuminated cells appeared annexin V–negative section, whereas 80% of the illuminated HeLa cell population was annexin V–positive.

**Studies about Nuclear Condensation and Fragmentation.**

Similar results were obtained from the nuclear condensation and fragmentation analysis. The significant nuclear fragmentation occurred 24 h after light exposure with compound 6.12 in HeLa cells (Figure 6.8). In contrast, cells treated with compound 6.12 without illumination did not exhibit significant changes in nuclear fragmentation analyses (Figure 6.8).

![Figure 6.7](image.png)

**Figure 6.7.** Compound 6.12 with PDT induces apoptotic cell death in HeLa cells. HeLa cells were treated with or without 1 μM compound 6.12 for 24 h and were illuminated with 50 W halogen lamp (0.2 kJ/cm\textsuperscript{2}). After 24 h, cells were co-stained with fluorescent annexin V and propidium iodide and then examined for apoptosis by flow cytometry.
Figure 6.8. Compound 6.12 with PDT induces apoptotic cell death in HeLa cells. Nuclear condensation or fragmentation, one of typical apoptotic features, was assessed by nuclei staining with DAPI after cells were treated with or without 1 µM compound 6.12 with PDT. Images were visualized using a fluorescent microscope and captured with a CCD camera. Arrow indicates normal nuclei.

Figure 6.9. Compound 6.12 with PDT induces apoptotic cell death in HeLa cells. Cells were treated with or without 1 µM compound 6.12 for 24 h and illuminated, and 24 h after irradiation, cells were collected and lysed. The supernatant of the lysate was applied to immunoblotting to detect PARP cleavage. C, untreated cells; D, cells incubated with compound 6.12 without irradiation; 0 and 24, designate time points of cell harvest after irradiation (0.2 kJ/cm²).

CHAPTER 6: Appendix: Glycosylated Porphyrin Derivatives and Their Photodynamic Activity in Cancer Cells
Studies on PARP Cleavage.

Based on our literature and research experience,[29,30] next, we also checked poly(ADP-ribose) polymerase (PARP) cleavage after compound treatment. PARP is a DNA repair enzyme whose expression is triggered by DNA strand breaks, and one of caspase-3 targets. If cells undergo apoptosis, PARP with 113 kD peptide is cleaved into 24 and 89 kD polypeptides by active caspase-3. We found that the treatment with compound 6.12 resulted in a cleavage of 113 kD PARP to 85 kD in HeLa cells, which was most dramatic in cells at 24 h after treatment with PDT (Figure 6.9). The results were consistent with the phototoxicity effect of compound 6.12. Taken together, our data suggest that apoptosis induced by the treatment of compound 6.12 was via caspase-dependent apoptotic pathway in cancer cells.

Conclusions

A series of glycofused porphyrin derivatives with $C_2$ and $D_2$ symmetry, 6.3–6.12 have been designed and efficiently prepared. Their structures were fully confirmed by spectroscopic techniques, and their spectral properties were well characterized. The derivatives 6.5, 6.6, 6.11, and 6.12 showed significant cellular uptake and photocytotoxicity in HeLa cells and HCT116 cells, respectively at a concentration of 1 µM. In particular, the tetra-glycofused structure 6.12 exhibited the highest cellular uptake and photocytotoxicity. Unlike the reported sugar-porphyrin conjugates, which normally localize in mitochondria or endoplasmic reticulum, the unique glycofused porphyrins we designed in this study were dominantly localized in lysosomes. Sugar moieties in our molecules should take credit for the enhanced cellular uptake and also for the lysosome localization. The measurement of the dual fluorescence of annexin V-FITC/PI by flow
cytometry revealed that the cell death was caused by apoptosis. Further PARP cleavage study suggested that apoptosis induced by the treatment of compound 6.12 was via caspase-dependent apoptotic pathway in cancer cells. The in vivo PDT efficacy of compound 6.12 is under investigation in our laboratory.

**Experimental section**

**General:** All the reactions were carried out in a flame or oven dried glassware under an argon or nitrogen atmosphere with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Evaporation of organic solutions was achieved by rotary evaporation with a water bath temperature below 40 °C. Product purification by flash column chromatography was accomplished using silica gel 60 (0.010–0.063 nm). Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates (0.25 mm). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using base solution of potassium permanganate. Porphyrinic compounds were visualized as green emerald spots by dipping in a solution of Ce(III)sulfate (1.0 g), ammonium molybdate (21.0 g), 96% sulfuric acid (31.0 mL), and distilled water (500 mL). IR spectra were recorded using FTIR Restige-21 (Shimadzu). NMR spectra were recorded at room temperature on 300 MHz Bruker ACF 300, 400 MHz Bruker DPX 400, 500 MHz Bruker AMX 500, and 400 MHz JEOL ECA 400 NMR spectrometers. The residual solvent signals were taken as the reference (7.26 ppm for 1H NMR spectra and 77.0 ppm for $^{13}$C NMR spectra in CDCl3). Sometimes the TMS signal at 0.0 ppm was used an internal standard for 1H NMR spectra. Chemical shift ($\delta$) is reported in ppm, coupling constants ($J$) are given in Hz. The following abbreviations classify the multiplicity: $s$ = singlet, $d$ = doublet, $t$ = triplet, $m$ = multiplet or unresolved,
br = broad signal. HRMS (ESI) spectra were recorded on a Finnigan/MAT LCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system.

**Materials:** All solvents were distilled under argon from the following drying agents immediately before use: Dichloromethane was distilled from calcium hydride. Technical grade solvents were used for chromatography and were distilled prior to use. All benzaldehyde were purchased from commercial suppliers and used without further purification. Sugar aldehyde was prepared galactose isopropylidene protection followed by IBX oxidation. BF$_3$·Et$_2$O solution and DDQ were purchased from commercial suppliers and used without further purification. Starting material dipyrryl methane unit (2) was prepared from condensation freshly distilled pyrrole with 1,2:3,4-di-O-isopropylidene-α-D-galacto-hexadialdo-1,5-pyranose (1) purified through silica gel column and perfectly dried. use.

**Synthesis and spectral details of dipyrryl methane:**

**Synthesis of 1,2:3,4-di-O-isopropylidene-5,5-dipyrryl-6-deoxy-α-D-galactopyranose(6.2):**

To a solution of freshly distilled pyrrole (1.35 mL, 19.38 mmol) and 1,2:3,4-di-O-isopropylidene-α-D-galacto-hexadialdo-1,5-pyranose (6.1) (1 g, 3.88 mmol) in CH$_2$Cl$_2$ (100 mL) at ambient temperature with stirring under N$_2$ was added BF$_3$·ethereal solution (48 µL, 0.39 mmol). After 3 h stirring,
the bright orange reaction mixture was quenched by addition of a saturated aqueous NaHCO₃ solution (10 mL) and then diluted with CH₂Cl₂ (100 mL). The organic layer was separated, washed with water (2x50 mL). Then the combined organic layer were dried (MgSO₄), filtered, evaporated, and purified by flash chromatography (7:3 hexane/EtOAc) to give 913 mg (63%) of 6.2 as a white solid; ¹H NMR (300 MHz, CDCl₃): δ 8.83 (s, 1H, NH), 8.49 (s, 1H, NH), 6.71–6.69 (m, 2H, Py–CH), 6.15-6.13 (m, 2H, Py–CH), 6.09 (d, J = 1.1 Hz, 1H, Py–CH), 6.02 (s, 1H, Py–CH), 5.65 (d, J = 5.0 Hz, 1H, Sug–CH), 4.55 (dd, J₁ = 8.0 Hz, J₂ = 2.3 Hz), 4.48 (d, J = 10.0 Hz, 1H, Sug–CH), 4.32 (dd, J₁ = 5.0 Hz, J₂ = 2.3 Hz, 1H, Sug–CH), 4.13 (dd, J₁ = 10.0 Hz, J₂ = 1.3 Hz, 1H), 3.91 (dd, J₁ = 8.0 Hz, J₂ = 1.6 Hz, 1H, Sug–CH), 1.55 (s, 3H, –CH₃), 1.51 (s, 3H, -CH₃), 1.35 (s, 6H, -CH₃); ¹³C NMR (75MHz, CDCl₃): δ 131.0, 129.6, 116.6, 116.5, 109.1, 108.8, 108.1, 107.7, 107.6, 107.0, 96.9, 71.6, 70.8, 70.7, 70.3, 38.1, 25.9, 25.8, 24.8, 24.5; IR (neat): νmax 3417, 1643, 1384, 1213, 717 cm⁻¹; HRMS (ESI): m/z (M+H)⁺ Calcd for C₂₀H₂₇N₂O₅: 375.1920, found: 375.1917.

Synthesis of sugar porphyrin conjugates & spectral details:

General procedure:
To a solution of 1,2:3,4-di-O-isopropylidene-5,5-dipyrryl-6-deoxy-α-D-galactopyranose (6.2) (200 mg, 0.53 mmol) in 250 mL of CH$_2$Cl$_2$ were added sequentially aromatic aldehyde (0.53 mmol) and BF$_3$·ethereal solution (6.7 µL, 0.05 mmol) while a stream of pure argon was passing. The reaction vessel was carefully shielded from light, and stirring was continued for 3 h. Then, triethylamine (7.4 µL, 0.05 mmol) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) (132.90 mg, 0.59 mmol) were added, and the reaction mixture was stirred at room temperature for an additional 3 h. The solvent was evaporated under vacuum, and the resulting dark-violet solid was purified by column chromatography on silica gel to give porphyrin compound as a purple solid (5-16 % yields).

5,15-[Bis(phenyl)]-10α,20β-[bis(1,2:3,4-di-O-isopropylidene-α-D-galactopyranose-6-yl)] porphyrin (6.3):

Prepared according to general procedure using benzaldehyde; Purple solid; (58 mg, 12% yield);

$^1$H NMR (300 MHz, CDCl$_3$): δ 9.69 (d, $J = 4.2$ Hz, 4H, H–β), 8.82 (d, $J = 4.8$ Hz, 4H, H–β), 8.19 (d, $J = 6.3$ Hz, 4H, Ph–CH), 7.79-7.72 (m, 4H, Ph–CH), 7.68 (s, 2H, H–5’), 6.26 (d, $J = 5.1$ Hz, 2H, H–1’), 5.21 (d, $J = 1.2$ Hz, 2H, H–4’), 5.14 (d, $J = 1.8$ Hz, 2H, H–3’), 4.79 (dd, $J_1 = 5.0$ Hz, $J_2 = 2.0$ Hz, 2H, H–2’), 1.86 (s, 6H, –CH$_3$), 1.7 (s, 6H, –CH$_3$), 1.55 (s, 6H, –CH$_3$), 1.19 (s, 6H, -CH$_3$), –2.67 (s, 2H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 162.3, 143.3, 134.5, 131.7, 129.6, 127.5, 126.3, 119.4, 113.7, 109.6, 109.0, 97.8, 71.9, 71.4, 26.8, 25.9, 25.1, 23.4; HRMS (ESI): m/z (M+H)$^+$ Calcd for C$_{54}$H$_{55}$N$_4$O$_{10}$: 919.3918, found: 919.3948;

CHAPTER 6: Appendix: Glycosylated Porphyrin Derivatives and Their Photodynamic Activity in Cancer Cells
**UV–VIS** (CHCl₃) \( \lambda_{\text{max}} \) (log \( \varepsilon \)): 406 (4.478), 516 (4.136), 549 (3.749), 589 (3.672), 644 (3.549); **IR** (neat): \( \nu_{\text{max}} \) 3437, 2989, 1732, 1597, 1483, 1382, 1064, 802 cm⁻¹.

5,15-[Bis(2,6-dimethoxyphenyl)]-10\( \alpha \),20\( \beta \)-[bis(1,2:3,4-di-O-isopropylidene-\( \alpha \)-D-galactopyranose-6-yl)]porphyrin (6.4):

Prepared according to general procedure using 2,6-dimethoxybenzaldehyde; Purple solid; (72 mg, 13% yield); \(^1\text{H NMR} \) (300 MHz, CDCl₃): \( \delta \) 9.59 (s, 4H, H–\( \beta \)), 8.77 (d, \( J = 4.8 \) Hz, 4H, H–\( \beta \)), 7.72 (t, \( J = 8.5 \) Hz, 2H, Ph–CH), 7.64 (s, 2H, H–5’), 7.01–6.99 (m, 4H, Ph–CH), 6.23 (d, \( J = 4.9 \) Hz, 2H, H–1’), 5.26 (d, \( J = 7.8 \) Hz, 2H, H–4’), 5.8 (dd, \( J_1 = 7.8 \) Hz, \( J_2 = 1.9 \) Hz, 2H, H–3’), 4.76 (dd, \( J_1 = 4.9 \) Hz, \( J_2 = 2.0 \) Hz, 2H, H–2’), 3.49 (s, 12H, –OCH₃), 1.84 (s, 6H, –CH₃), 1.70 (s, 6H, –CH₃), 1.52 (s, 6H, –CH₃), 1.21 (s, 6H, –CH₃), 4.76 (dd, \( J_1 = 4.9 \) Hz, \( J_2 = 2.0 \) Hz, 2H, H–2’), 3.49 (s, 12H, –OCH₃), 1.84 (s, 6H, –CH₃), 1.70 (s, 6H, –CH₃), 1.52 (s, 6H, –CH₃), 1.21 (s, 6H, –CH₃), 2.48 (s, 2H, NH); \(^{13}\text{C NMR} \) (125 MHz, CDCl₃): \( \delta \) 160.6, 146.5, 145.2, 130.7, 129.8, 129.5, 121.3, 112.3, 111.3, 109.4, 108.9, 104.2, 97.7, 76.6, 71.9, 71.8, 71.4, 56.0, 26.8, 25.9, 25.1, 23.4; \(^{13}\text{C NMR} \) (125 MHz, CDCl₃): \( \delta \) 160.6, 146.5, 145.2, 130.7, 129.8, 129.5, 121.3, 112.3, 111.3, 109.4, 108.9, 104.2, 97.7, 76.6, 71.9, 71.8, 71.4, 56.0, 26.8, 25.9, 25.1, 23.4; **HRMS** (ESI): m/z (M+H)⁺ Calcd for C₅₉H₆₃N₄O₁₄: 1039.4341, found: 1039.4347; **UV–VIS** (CHCl₃) \( \lambda_{\text{max}} \) (log \( \varepsilon \)): 412 (4.533), 516 (4.205), 546 (3.607), 590 (3.768), 644 (3.526); **IR** (neat): \( \nu_{\text{max}} \) 3435, 2927, 1633, 1469, 1382, 1249, 1109, 1064 cm⁻¹.

5,15-[Bis(4-methoxyphenyl)]-10\( \alpha \),20\( \beta \)-[bis(1,2:3,4-di-O-isopropylidene-\( \alpha \)-D-galactopyranose-6-yl)]porphyrin (6.5):

Prepared according to general procedure using 4-methoxybenzaldehyde; Purple solid; (41 mg, 8% yield); \(^1\text{H NMR} \) (500 MHz, CDCl₃): \( \delta \) 9.67 (s, 4H, H–\( \beta \)), 8.84 (d, \( J = 4.6 \) Hz, 4H, H–\( \beta \)), 8.08 (d, \( J = 8.0 \) Hz, 4H, Ph–CH), 7.66 (s, 2H, H–5’), 7.24 (d, \( J = 7.6 \) Hz, 4H, Ph–CH), 6.25 (d, \( J = 4.8 \) Hz, 2H, H–1’), 5.21 (d, \( J = 7.8 \) Hz, 2H, H–4’), 5.12 (d, \( J = 6.7 \) Hz, 2H, H–4’).
5,15-[Bis(4-(methylthio)phenyl)-10α,20β-[bis(1,2:3,4-di-O-isopropylidene-α-D-galactopyranose-6-yl)]porphyrin (6.6):

Prepared according to general procedure using 4-(methylthio)benzaldehyde; Purple solid; (37 mg, 7% yield); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.70 (d, $J = 3.6$ Hz, 4H, H–β), 8.86 (d, $J = 4.9$ Hz, 4H, H–β), 8.11 (d, $J = 8.1$ Hz, 4H, Ph–CH), 7.69 (s, 2H, H-5′), 7.64 (d, $J = 8.3$ Hz, 4H, Ph–CH), 6.27 (d, $J = 5.0$ Hz, 2H, H–1′), 5.22 (d, $J = 8.2$ Hz, 2H, H–4′), 5.15 (d, $J = 7.8$ Hz, 2H, H–3′), 4.80 (dd, $J_1 = 5.0$ Hz, $J_2 = 1.8$ Hz, 2H, H–2′), 2.78 (s, 6H, –CH$_3$), 1.87 (s, 6H, –CH$_3$), 1.71 (s, 6H, –CH$_3$), 1.56 (s, 6H, –CH$_3$), 1.20 (s, 6H, –CH$_3$), –2.69 (s, 2H, NH); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 140.0, 138.0, 135.1, 134.8, 131.6, 129.6, 125.2, 124.2, 118.8, 113.7, 109.6, 109.0, 107.0, 105.1, 97.8, 71.9, 71.3, 26.7, 25.1, 23.4. HRMS (ESI): m/z (M+H)$^+$ Calcd for C$_{56}$H$_{59}$N$_4$O$_{12}$: 979.4129, found: 979.4128.

UV–VIS (CHCl$_3$) $\lambda_{max}$ (log ε): 414 (4.494), 518 (3.514), 550 (3.412), 590 (3.160), 646 (2.890). IR (neat): $\nu_{max}$ 3435, 2922, 1643, 1462, 1379, 1247, 1174, 1066 cm$^{-1}$.
25.8, 25.1, 23.3, 15.92; HRMS (ESI): m/z (M+H)^+ Calcd for C_{56}H_{99}N_{10}O_{10}S_{2}: 1011.3673, found: 1011.3665; UV–VIS (CHCl_3) \( \lambda_{max} \) (log ε): 414 (4.540), 518 (4.282), 550 (3.817), 591 (3.796), 645 (3.653); IR (neat): \( \nu_{max} \) 3439, 2924, 1643, 1456, 1382, 1257, 1163, 1066 cm\(^{-1}\).

5,15-[Bis(4-trifluoromethoxyphenyl)]-10\( \alpha \),20\( \beta \)[bis(1,2,3,4-di-O-isopropylidene-\( \alpha \)-D-galactopyranose-6-yl)]porphyrin (6.7):

Prepared according to general procedure using 4-trifluoromethoxybenzaldehyde; Purple solid; (29 mg, 5% yield); \(^1\)H NMR (500 MHz, CDCl_3): \( \delta \) 9.71 (s, 4H, H–β), 8.77 (d, \( J = 4.8 \) Hz, 4H, H–β), 8.20 (d, \( J = 8.2 \) Hz, 4H, Ph–CH), 7.67 (s, 2H, H–5'), 7.60 (d, \( J = 7.9 \) Hz, 4H, Ph–CH), 6.25 (d, \( J = 4.9 \) Hz, 2H, H–1'), 5.20 (dd, \( J_1 = 7.9 \) Hz, \( J_2 = 1.5 \) Hz, 2H, H–4'), 5.13 (dd, \( J_1 = 7.8 \) Hz, \( J_2 = 1.9 \) Hz, 2H, H–3'), 4.79 (dd, \( J_1 = 5.0 \) Hz, \( J_2 = 2.0 \) Hz, 2H, H–2'), 1.85 (s, 6H, –CH_3), 1.69 (s, 6H, –CH_3), 1.53 (s, 6H, –CH_3), 1.18 (s, 6H, –CH_3), –2.73 (s, 2H, NH); \(^{13}\)C NMR (100 MHz, CDCl_3): \( \delta \) 149.8, 141.9, 135.5, 130.1, 129.2, 117.9, 114.2, 109.7, 109.1, 97.8, 71.9, 71.3, 26.8, 25.9, 25.1, 23.4; HRMS (ESI): m/z (M+H)^+ Calcd for C_{56}H_{93}N_{10}O_{12}F_6: 1087.3564, found: 1087.3545; UV–VIS (CHCl_3) \( \lambda_{max} \) (log ε): 403 (4.538), 516 (4.211), 550 (3.827), 591 (3.757), 645 (3.487); IR (neat): \( \nu_{max} \) 3435, 2922, 1643, 1382, 1257, 1066, 804 cm\(^{-1}\).

5,15-[Bis(pentafluorophenyl)]-10\( \alpha \),20\( \beta \)[bis(1,2,3,4-di-O-isopropylidene-\( \alpha \)-D-galactopyranose-6-yl)]porphyrin (6.8):

Prepared according to general procedure using pentafluorobenzaldehyde; Purple solid; (64 mg, 11% yield); \(^1\)H NMR (500 MHz, CDCl_3): \( \delta \) 9.86 (s, 4H, H–β), 8.87 (d, \( J = 4.6 \) Hz, 4H, H–β), 7.72 (s, 2H, H–5'), 6.31 (d, \( J = 4.8 \) Hz, 2H, H–1'), 5.26 (d, \( J = 7.7 \) Hz, 2H, H–1'), 4.79 (d, \( J = 5.0 \) Hz, 2H, H–4'), 7.67 (s, 2H, H–5'), 7.60 (d, \( J = 7.9 \) Hz, 4H, Ph–CH), 6.25 (d, \( J = 4.9 \) Hz, 2H, H–1'), 5.20 (dd, \( J_1 = 7.9 \) Hz, \( J_2 = 1.5 \) Hz, 2H, H–4'), 5.13 (dd, \( J_1 = 7.8 \) Hz, \( J_2 = 1.9 \) Hz, 2H, H–3'), 4.79 (dd, \( J_1 = 5.0 \) Hz, \( J_2 = 2.0 \) Hz, 2H, H–2'), 1.85 (s, 6H, –CH_3), 1.69 (s, 6H, –CH_3), 1.53 (s, 6H, –CH_3), 1.18 (s, 6H, –CH_3), –2.73 (s, 2H, NH); \(^{13}\)C NMR (100 MHz, CDCl_3): \( \delta \) 149.8, 141.9, 135.5, 130.1, 129.2, 117.9, 114.2, 109.7, 109.1, 97.8, 71.9, 71.3, 26.8, 25.9, 25.1, 23.4; HRMS (ESI): m/z (M+H)^+ Calcd for C_{56}H_{93}N_{10}O_{12}F_6: 1087.3564, found: 1087.3545; UV–VIS (CHCl_3) \( \lambda_{max} \) (log ε): 403 (4.538), 516 (4.211), 550 (3.827), 591 (3.757), 645 (3.487); IR (neat): \( \nu_{max} \) 3435, 2922, 1643, 1382, 1257, 1066, 804 cm\(^{-1}\).
5,15-[Bis(4-chlorophenyl)]-10α,20β-[bis(1,2;3,4-di-O-isopropylidene-α-D-galactopyranose-6-yl)]Porphyrin (6.9):

Prepared according to general procedure using 4-chlorobenzaldehyde; Purple solid; (36 mg, 7% yield); \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 9.70 (s, 4H, H–β), 8.79 (d, J = 4.6 Hz, 4H, H–β), 8.10 (d, J = 7.0 Hz, 4H, Ph–CH), 7.72 (d, J = 7.0 Hz, 4H, Ph–CH), 7.66 (s, 2H, H–5’), 6.25 (d, J = 4.9 Hz, 2H, H–1’), 5.20 (d, J = 7.7 Hz, 2H, H–4’), 5.13 (d, J = 7.8 Hz, 2H, H–3’), 4.79 (d, J = 4.9 Hz, 2H, H–2’), 1.85 (s, 6H, –CH\(_3\)), 1.69 (s, 6H, –CH\(_3\)), 1.52 (s, 6H, –CH\(_3\)), 1.18 (s, 6H, –CH\(_3\)), –2.74 (s, 2H, NH); \(^13\)C NMR (75 MHz, CDCl\(_3\)): δ 141.7, 135.4, 134.0, 134.0, 131.9, 130.2, 126.6, 117.9, 114.0, 109.6, 109.0, 97.8, 71.9, 71.3, 26.7, 25.8, 25.1, 23.3; HRMS
(ESI): m/z (M+H)$^+$ Calcd for C$_{54}$H$_{53}$N$_6$O$_{10}$Cl$_2$: 987.3139, found: 919.3138; UV–VIS (CHCl$_3$) $\lambda_{\text{max}}$ (log $\varepsilon$): 416 (4.480), 516 (3.453), 548 (3.051), 590 (2.979), 644 (2.723); IR (neat): $\nu_{\text{max}}$: 3439, 2922, 1714, 1643, 1462, 1379, 1068, 702 cm$^{-1}$.

5,15-[Bis(4-nitrophenyl)]-10α,20β-[bis(1,2:3,4-di-O-isopropylidene-$\alpha$-D-galactopyranose-6-yl)]porphyrin (6.10):

Prepared according to general procedure using 4-nitrobenzaldehyde; Purple solid; (32 mg, 6% yield); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.74 (d, $J$ = 3.9 Hz, 4H, H–β), 8.72 (d, $J$ = 4.9 Hz, 4H, H–β), 8.63 (d, $J$ = 8.6 Hz, 4H, Ph–CH), 8.36 (d, $J$ = 8.5 Hz, 4H, Ph–CH), 7.66 (s, 2H, H–5'), 6.25 (d, $J$ = 5.0 Hz, 2H, H–1'), 5.18 (d, $J$ = 9.5 Hz, 2H, H–4'), 5.14 (d, $J$ = 1.8 Hz, 2H, H–3'), 4.80 (dd, $J_1$ = 5.0 Hz, $J_2$ = 1.8 Hz, 2H, H–2') 1.85 (s, 6H, –CH$_3$), 1.69 (s, 6H, –CH$_3$), 1.53 (s, 6H, –CH$_3$), 1.19 (s, 6H, –CH$_3$), –2.72 (s, 2H, NH); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 150.0, 147.7, 135.0, 121.6, 116.8, 114.9, 109.7, 109.1, 97.8, 71.8, 71.3, 26.7, 25.8, 25.0, 23.3. HRMS (ESI): m/z (M+H)$^+$ Calcd for C$_{54}$H$_{53}$N$_6$O$_{14}$: 1009.3620, found: 1009.3619; UV–VIS (CHCl$_3$) $\lambda_{\text{max}}$ (log $\varepsilon$): 419 (4.506), 518 (3.577), 550 (3.103), 590 (3.106), 645 (2.811); IR (neat): $\nu_{\text{max}}$ 3439, 2958, 1714, 1643, 1519, 1462, 1066, cm$^{-1}$.

5,15-[Bis(3-thiophene)]-10α,20β-[bis(1,2:3,4-di-O-isopropylidene-$\alpha$-D-galactopyranose-6-yl)]porphyrin (6.11):

Prepared according to general procedure using 3-formyl thiophene; Purple solid; (24 mg, 5% yield); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.68 (d, $J$ = 3.9 Hz, 4H, H–β), 8.94 (d, $J$ = 4.9 Hz, 4H, H–β), 7.98–7.96 (m, 4H, Ar–CH), 7.70 (dd, $J_1$ = 4.8 Hz, $J_2$ = 3.0 Hz, 4H, H–β),...
7.66 (d, $J = 1.1$ Hz, 2H, $H-5'$), 6.25 (d, $J = 4.9$ Hz, 2H, $H-1'$), 5.20 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.5$ Hz, 2H, $H-4'$), 5.12 (dd, $J_1 = 7.9$ Hz, $J_2 = 2.0$ Hz, 2H, $H-3'$), 4.78 (dd, $J_1 = 5.0$ Hz, $J_2 = 2.0$ Hz, 2H, $H-2'$), 1.86 (s, 6H, $-CH_3$), 1.69 (s, 6H, $-CH_3$), 1.53 (s, 6H, $-CH_3$), 1.18 (s, 6H, $-CH_3$), –2.7 (s, 2H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 162.3, 143.3, 134.8, 131.4, 130.1, 128.1, 122.8, 113.8, 113.7, 109.6, 109.6, 109.0, 97.8, 76.5, 71.9, 71.3, 26.7, 25.9, 25.1, 23.3; HRMS (ESI): m/z (M+H)$^+$ Calcd for C$_{50}$H$_{51}$N$_4$O$_{10}$S$_2$: 931.3047, found: 931.3044; UV–VIS (CHCl$_3$) $\lambda_{max}$ (log $\varepsilon$): 412 (4.501), 518 (3.767), 550 (3.480), 591 (3.329), 646 (3.089); IR (neat): $\nu_{max}$ 3437, 2918, 1643, 1454, 1382, 1255, 1064 cm$^{-1}$.

$5a,10\beta,15a,20\beta$-Tetakis(1,2,3,4-di-$O$-isopropylidene-$\alpha$-$D$-galactopyranose-6-yl)porphyrin (6.12):

Prepared according to general procedure with slight modification. Here, we used instead of aromatic aldehyde another 1,2:3,4-di-$O$-isopropylidene-$\alpha$-$D$-galacto-hexadialdo-1,5-pyranose (1); Purple solid; (104 mg, 16% yield);

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 9.81 (s, 8H), 7.77 (s, 4H, H–5'), 6.32 (d, $J = 4.9$ Hz, 4H, H–1'), 5.28 (d, $J = 8.7$ Hz, 4H, H–4'), 5.18 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.8$ Hz, 4H, H–3'), 4.84 (dd, $J_1 = 5.0$ Hz, $J_2 = 1.9$ Hz, 4H, H–2'), 1.94 (s, 12H, $-CH_3$), 1.85 (s, 12H, $-CH_3$), 1.59 (s, 12H, $-CH_3$), 1.26 (s, 12H, $-CH_3$), –2.88 (s, 2H, NH); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 130.0, 112.5, 109.6, 109.0, 97.7, 76.6, 72.2, 71.9, 71.5, 26.9, 26.1, 25.1, 23.5; HRMS (ESI): m/z...
(M+H)+ Calcd for C_{64}H_{79}N_{4}O_{20}: 1223.5288, found: 1223.5266; \textbf{UV–VIS} (CHCl_{3}) \lambda_{\text{max}} (log ε): 406 (4.519), 519 (4.017), 552 (3.381), 591 (3.591), 646 (3.437); \textbf{IR} (neat): \nu_{\text{max}} 3441, 2989, 2073, 1643, 1382, 1255, 1064, cm^{-1}.

\textbf{Biology Methods and Materials:}\textsuperscript{[33]}

\textbf{Cell Cultures:}

Human cancer cell lines including HCT116 and HeLa were maintained in Dulbecco’s Modified Eagle Medium (DMEM) containing 10% fetal bovine serum and 1% penicillin/streptomycin in a humidified 5% CO_{2} incubator at 37 °C.

\textbf{Photocytotoxicity Assay.}

Cells were seeded onto 96-well plates at a density of about 2 x 10^4 cells per well and incubated in the dark in medium containing 5% serum together with compounds for 24 h at 37°C. Cells were rinsed with phosphate buffered saline (PBS) and then exposed to broad-spectrum green light (480-550 nm) generated by two layers of green cellophane-filtered 50 W halogen lamp using a dose rate of 13 mW/cm^2. Cell viability was determined using the CellTiter 96 Aqueous One Solution Reagent kit (Promega, Medison, WI) according to the manufacturer’s instructions, 24 h after light exposure by measuring absorbance at 490 nm.

\textbf{Intracellular Localization and Image Analysis.}

Cells plated on coverslips in a 6-well plate were incubated with 1 μM of compound for 24 h. For intracellular localization in HeLa cells, cells incubated with compound for 24 h were loaded with 100 nM MitoTracker Deep Red (Molecular Probes) for 15 min or with 100 nM LysoTracker Red (Molecular Probes) for 1 h at 37 °C. The
slides were washed three times with PBS and were visualized by at 60 x magnification on a Zeiss LSM META confocal laser scanning microscopy (Zeiss, Oberkochen, Germany).

**Measurement of Apoptosis.**

Apoptosis was performed as previously described from our group. In brief, cells treated with 1 μM compound were incubated for 24 h and then illuminated. After 24 h, cells were collected and apoptosis was examined by using Annexin V-FLUOS staining kit (Roche, Penzberg, Germany). Cells were counter-stained with propidium iodide followed by fluorescence activated cell sorter (FACS) analysis on a flow cytometer (BD LDR II, BD Biosciences, San Jose, CA). For visualization of apoptotic cells, cells were seeded on coverslips within a 6-well plate. After fixation in 3.7% paraformaldehyde, cells were washed with PBS and permeabilized with 0.2% Triton X-100, washed again with PBS, and mounted by ProLong Gold antifade reagent with DAPI (Molecular probes, Eugene, Oregon). The stained nuclei were observed and photographed under a fluorescence microscope (Nikon Inc., Melville, NY). Apoptosis was measured as the percentage of annexin V-positive and PI-negative cell population. For all experiments, at least 10,000 events were collected per sample.

**Immunoblot Analysis.**

Cells were resuspended in a lysis buffer (20 mM Tris-HCl, pH 7.5, 150 mM NaCl, 0.5% Triton X-100, 1 mM EDTA, 1 mM PMSF) containing protease inhibitors on ice for 40 min. The clear cell lysates were obtained after centrifuging for 15 min at 15,000 rpm. The lysates (30 μg of protein) were resolved by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) and were transferred to nitrocellulose membranes. The membranes were blocked with 5% dry milk in TBS-T (20 mM Tris-HCl, pH 7.5, 140 mM NaCl, and 0.05%
tween-20) and subsequently incubated with primary antibody followed by a goat anti-rabbit or goat anti-mouse IgG conjugated to horseradish peroxidase, and the immunoreactive bands were visualized by the SUPEX Western blotting detection kit (Neuronex, Korea)

References


PUBLICATIONS


7. “N-Heterocyclic carbene catalyzed intramolecular aldehyde-nitrile cross coupling: An
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CONFERENCES


2. “N-Heterocyclic carbene catalyzed intramolecular aldehyde nitrile cross coupling: An easy access to 3-aminochromones.” Seenuvasan Vedachalam and Xue-Wei Liu, “7th WOCJC National Tsing Hua University” Taiwan Sep 4–6, 2010 (Poster, Won best poster award)