# Development of New Synthetic Methods *via* *N*-Heterocyclic Carbene Catalysis

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**in**

## Chemistry

***By***


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*Dedicated*

*to*

*My Family, Teachers and Friends*

# DECLARATION

(*As required under clause I2 of Ordinance IIA of the Central University of Haryana*)

This is to certify that the material embodied in the present work, entitled **"Development of new synthetic methods *via N*-heterocyclic carbene catalysis"**, is based on my original research work. The research work was carried out under the joint supervision of **Dr. Manoj K. Gupta (Supervisor)**, Department of Chemistry, Central University of Haryana and **Dr. Bhoopendra Tiwari (Co-Supervisor)**, Division of Molecular Synthesis & Drug Discovery, Centre of Biomedical Research, SGPGIMS-Campus, Lucknow. This work has not been submitted, in part or full, for any other diploma or degree of any University/ Institution Deemed to be University and College/Institution of National Importance. References from other works have been duly cited at the relevant places.

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***Anil Kumar***

# ABBREVIATIONS

| | | |
|---|---|---|
| *t*-BuOK | : | Potassium *tert*-butoxide |
| EtOH | : | Ethanol |
| $Rb_2CO_3$ | : | Rubidium carbonate |
| $Et_3N$ | : | Triethylamine |
| DIPEA | : | *N*,*N*-Diisopropylethylamine |
| THF | : | Tetrahydrofuran |
| $Cs_2CO_3$ | : | Caesium carbonate |
| rt | : | Room temperature |
| DBU | : | 1,8-Diazabicyclo[5.4. 0]undec-7-ene |
| $K_2CO_3$ | : | Potassium carbonate |
| $CHCl_3$ | : | Chloroform |
| *i*-$Pr_2NEt$ | : | *N*,*N*-Diisopropylethylamine |
| $CH_2Cl_2$ | : | Dichloromethane |
| MS | : | Molecular sieves |
| CsOAc | : | Caesium acetate |
| *i*-PrOH | : | Isopropyl alcohol |
| $CH_3CN$ | : | Acetonitrile |
| MeOH | : | Methanol |
| AcOH | : | Acetic acid |
| *t*-BuOH | : | *tert*-Butyl alcohol |

| | | |
|---|---|---|
| NaOAc | : | Sodium acetate |
| DMF | : | Dimethylformamide |
| KHMDS | : | Potassium bis(trimethylsilyl)amide |
| $CCl_4$ | : | Carbon tetrachloride |
| $MgSO_4$ | : | Magnesium sulfate |
| $K_3PO_4$ | : | Tripotassium phosphate |
| KF | : | Potassium fluoride |
| MTBD | : | 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene |
| DCE | : | 1,2-Dichloroethane |
| EtOAc | : | Ethyl acetate |
| $KHCO_3$ | : | Potassium bicarbonate |
| NaOMe | : | Sodium methoxide |
| $NaHCO_3$ | : | Sodium bicarbonate |
| DME | : | Dimethoxyethane |
| $Ag_2CO_3$ | : | Silver carbonate |
| *t*-AmOH | : | *tert*-Amyl alcohol |
| PCC | : | Pyridinium chlorochromate |
| TFAA | : | Trifluoroacetic anhydride |
| LiHMDS | : | Lithium *bis*(trimethylsilyl)amide |
| $LiAlH_4$ | : | Lithium aluminum hydride |
| DMP | : | Dess-Martin periodinane |
| $Boc_2O$ | : | Di-*tert*-butyl dicarbonate |

| | | |
|---|---|---|
| $Me_3OBF_4$ | : | Trimethyloxonium tetrafluoroborate |
| $HC(OEt)_3$ | : | Triethyl orthoformate |
| PhCl | : | Chlorobenzene |
| NMM | : | *N*-Methylmorpholine |
| TMG | : | 1,1,3,3-Tetramethylguanidine |
| DABCO | : | 1,4-diazabicyclo[2.2.2]octane |
| CsF | : | Cesium fluoride |
| DMAP | : | 4-Dimethylaminopyridine |
| PDC | : | Pyridinium dichromate |
| DMSO | : | Dimethyl sulfoxide |
| TLC | : | Thin-layer chromatography |

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# Chapter 1

## *An Introduction to N-Heterocyclic Carbene (NHC) Catalysis*

### 1.1 Introduction

Carbenes are usually short-lived reactive species containing no formal charge on carbon with a valence of two and have two nonbonding electrons. They are considered as fleeting intermediates in molecular chemistry because they do not follow "octet rule".[1] However, apart from electrophilic nature of these traditional carbenes, there are carbenes known to be nucleophilic in nature, where the divalent carbonic centre is flanked by at least one nitrogen atom within the heterocycle are called *N*-heterocyclic carbenes (NHCs). NHCs have not only become versatile ligands for transition metals, but in last two decades these species encompasses an enormous array to a new set of reactions through polarity reversal (umpolung) reactivity and emerged as powerful organic catalysts in molecular chemistry.[2] This NHC-catalyzed umpolung of the functional group, with the carbonyl carbon atom acting as a transient nucleophile introduced a set of elementary steps that operate via distinct reactive species, including acyl anion, homoenolate and enolate. The benzoin condensation, the coupling of two aldehydes and Stetter reaction, addition of aldehydes to Michael acceptors are most prominent conversions. These transformations utilize acyl anion as the main intermediate. In continuation, NHCs has led to a broad range of annulated or acyclic products through homoenolate and enolate as a reactive intermediate. Furthermore, oxidative NHC catalysis i.e. non umpolung mode of reactivity can be conducted by using inorganic, organic and oxygen as sole oxidants. Additionally, the NHC-catalyzed

radical reaction inspired by the enzymatic catalysis have been developed.[3] Herein, we demonstrate the various important action modes of NHCs (Figure 1.1).

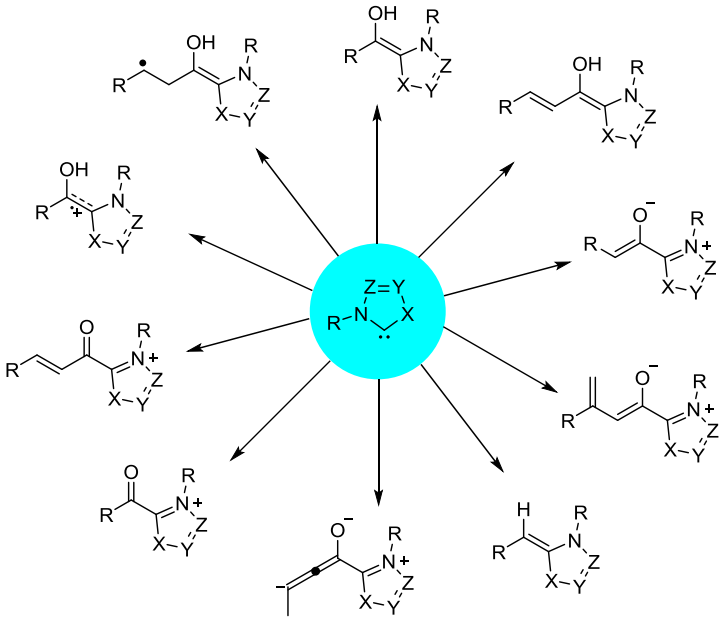
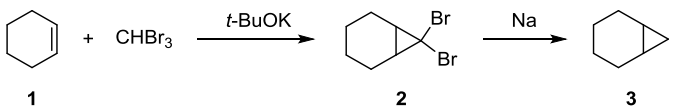


**Figure 1.1** Various important action modes of NHCs

## 1.2 Historical Background of Carbenes

In 1862, A. Geuther made the first statement that dichlorocarbene is a reaction intermediate with a divalent carbon for alkaline hydrolysis of chloroform.[4a] In the year 1897, J. Nef also proposed that Reimer-Tiemann reaction proceeds through dichlorocarbene as the reaction intermediate.[4b] As there was no experimental evidence so carbene moieties were considered as diradicals until 1930s. But in 1954, W. Doering gave the proof of the presence of a dibromomethylene intermediate for the first cyclopropane synthesis (Scheme 1.1).[4c]




**Scheme 1.1** Olefin cyclopropranation *via* methylene intermediate

After this various organic synthesis have been developed which proceed via the methlyene intermediate. These significant developments in this area attracted the chemists to look more closely at this carbene intermediate. First time, carbenes were introduced into the organometallic chemistry by Fisher with a resurgence of interest in 1964.[4d] A carbene is a short lived, highly reactive and neutral species that has a divalent carbon atom with six valence electrons. Although four electrons participate in σ-bonds and two remain at carbene carbon. Since they do not follow "octet rule", carbenes played an important role as transient intermediate in molecular chemistry. Based on the electronic spin they possess, it is necessary to consider both singlet and triplet carbenes (Figure 1.2).[5] In the case of singlet carbene two non bonding electrons at the carbene carbon are paired in highest occupied molecular orbital (HOMO) σ, whereas $p_\pi$ orbital remains vacant. As a result, they are amphiphilic and thus can react as either nucleophilic or electrophilic species. But in the case of triplet carbene two non bonding electrons are in different degenerated $p_x$ and $p_y$ orbital with parallel spins. So they are generally regarded as diradicals due to which triplet carbenes are highly reactive and difficult to isolate. As the total spin of triplet carbene is one so they are paramagnetic in nature and can be observed by electron spin resonance spectroscopy if they persevere long enough.

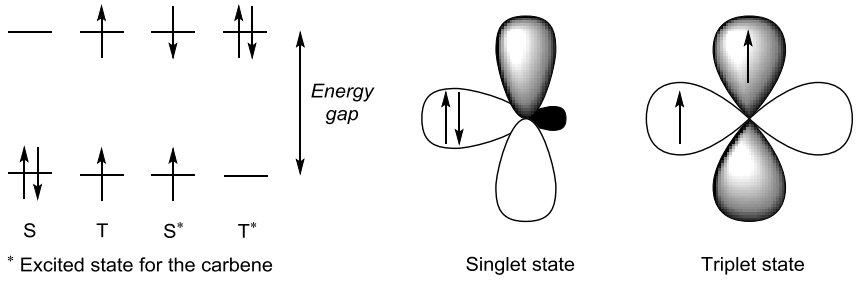



**Figure 1.2** Illustration of different electronic states of carbene

## 1.3 Organometallic Carbene Chemistry

Carbenes have been used to form metal-carbon bond which constitutes the central event in organometallic chemistry. In the 1960s, E. O. Fisher and K. Ölefe have started working on transition metal carbene complexes. In 1964, Fisher discovered the first metal carbene complex.[4d] The dominant bonding in metal carbon bond constituted by Fisher carbenes and transition metal arises from carbene metal σ-donation and metal carbene π-back donation. Fisher carbene complex are electrophilic as π-electrons are usually polarized toward metal resulting an insufficient π-donation from the metal and the adjacent alkoxy substituent. Fisher carbene are associated with low-valent metals and substituents which possess π-donation ability.

On the other hand, Schrock carbenes are poorly stabilized carbenes because they have a minor difference between their singlet and triplet ground state. Therefore they form a covalent metal-carbon bond which typically due to the interaction of triplet state of both carbene and metal center. The metal-carbon bond is known to be a real double bond because π-electrons are almost evenly distributed (Figure 1.3).[1] Consequently, Schrock carbenes are nucleophilic in nature. These carbenes are normally alkyl substituted and interact exclusively with high oxidation state metals.

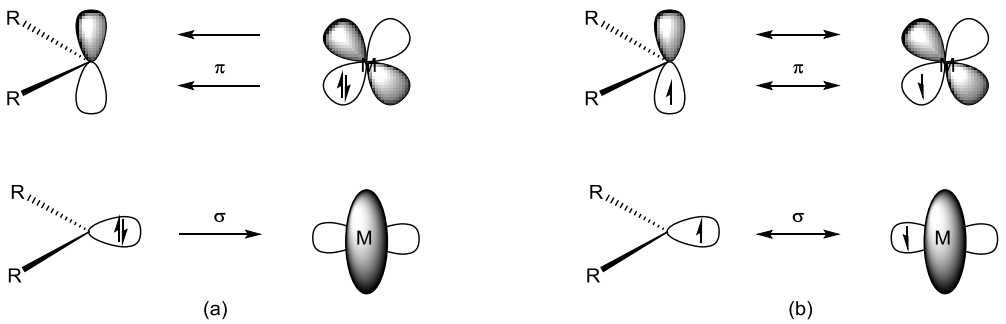


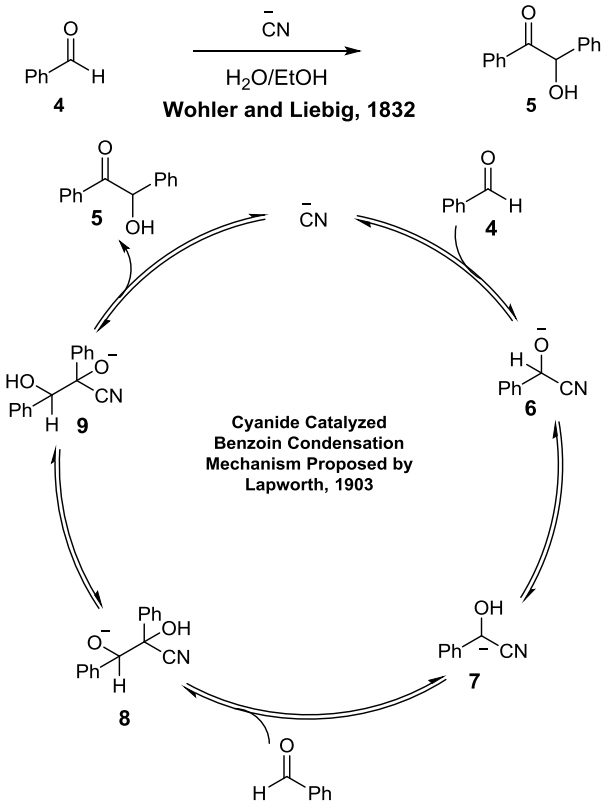

**Figure 1.3** Illustration of the Metal-carbon bonding between (a) Fischer carbenes and (b) Schrock carbenes

## 1.4 Development of NHC-Organocatalysis

In terms of effective chemical transformations like the formation of carbon-carbon bond, organic catalysts are extremely efficient in modern synthetic chemistry. In 1929, Langenback used the word "Organiche Katalysatoren" or organic catalyst.[6a] The term "Organocatalysis" was later described by MacMillan in which a small organic molecule catalyzes a reaction.[6b] Among the plethora of methods developed, Organocatalysis is an effective tool for organic reactions as of low toxicity and atom economy over the transition metal based catalysis which possess some genetic limitations like high cost and toxicity of metal catalyst. Organocatalysis represents a facile reaction course, selectivity, environmentally friendly and offers conversions unprecedented in metal catalysis. The transformations especially the inversion of polarity i.e. umpolung intoduces a new synthetic route by using of NHC Organocatalysis. Catalysis using NHC has appeared as an rewarding research field in organic chemistry. As typical structural features, *N*-heterocyclic carbene also called Arduengo carbenes are highly reactive, neutral species and possess a bivalent carbon atom with an electron sextet.[6c] NHCs are amphiphilic in nature and can behave as both electrophilic and nucleophilic species. As a result they belong to the category of singlet carbene.

The Benzoin condensation catalyzed by NHC has been the focus of intense investigation. In 1832, the initial investigation was carried out from the group of Wöhler and Liebig. They demonstrated cyanide catalyzed self condensation of aromatic aldehyde to provide the corresponding benzoin product.[7a] Hereafter in 1903, Lapworth postulated a mechanism for this condensation reaction (Scheme 1.2).[7b] A key step in

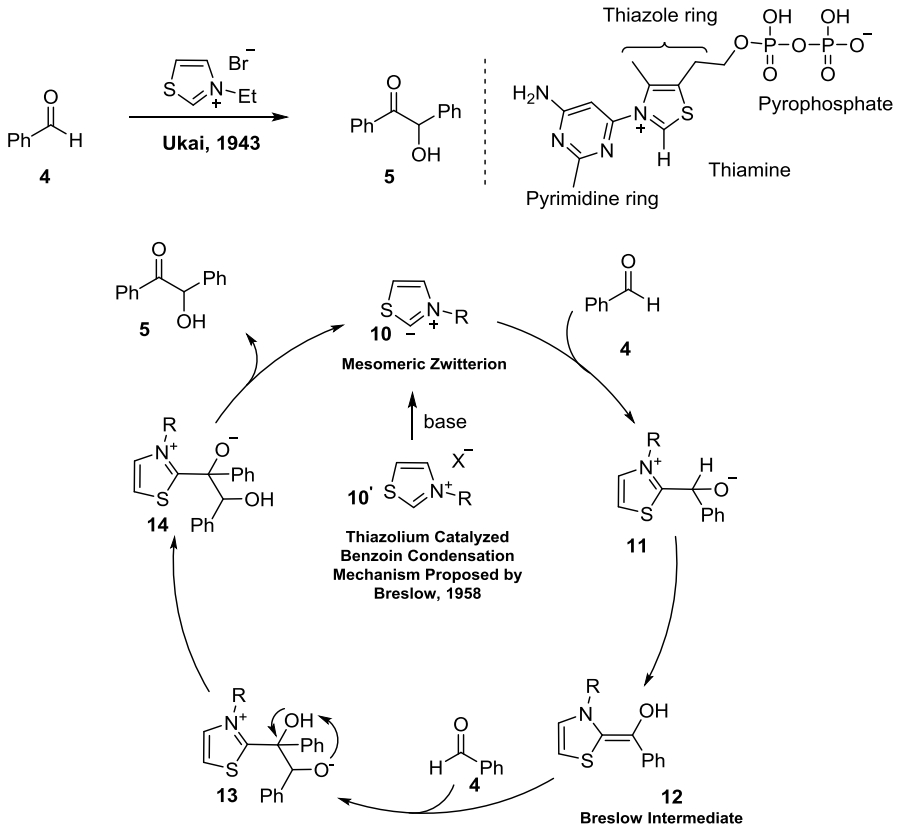
this transformation is the umpolung of aldehyde that is achieved via the formation of carbanion intermediate **7** by addition of cyanide to benzaldehyde followed by protonation through the tetrahedral intermediate **6**. Then, the generated acyl anion intermediate **7** react with another molecule of aldehyde and finally furnish the desired benzoin product **5**.




**Scheme 1.2** Cyanide catalyzed Benzoin condensation

Following on in 1943, Ukai et al. suggested that thiazolium salt could be used as catalyst in benzoin reaction.[8a] Thereafter in 1958, while working on the role of so called coenzyme thiamine (Vitamin B1) Ronald Breslow proposed a mechanistic explanation that implies active part of thiamine could be made of a carbene which could also catalyze the benzoin reaction (Scheme 1.3).[3c] Breslow assumed that *in situ* carbene can

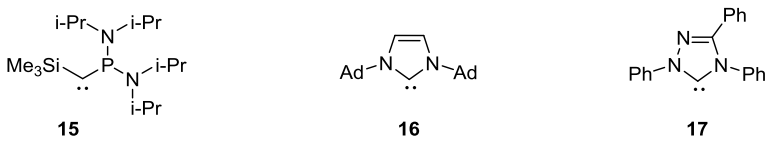
be generated when thiazolium salt is deprotonated at its most acidic position. The key step in the proposed mechanism involves *in situ* generation and addition of carbene **10** to an aldehyde resulting to tetrahedral intermediate **11** followed by proton transfer to give resonance stabilized enaminol type-Breslow intermediate **12**. This nucleophilic acylation reagent **12** reacts with another molecule of aldehyde to deliver the α-hydroxy ketone **5** as the final product and the original carbene catalyst **10** is regenerated.




**Scheme 1.3** Thiamine catalyzed Benzoin condensation

However, from a historical perspective during 1960s first attempt was made to isolate carbene by deprotonation of imidazolium salt with a strong base with the studies of Wanzlick.[8b] But this remained unsuccessful, although carbene could be trapped in the presence of metal fragment whereas in absence of trapping agent only carbene dimers

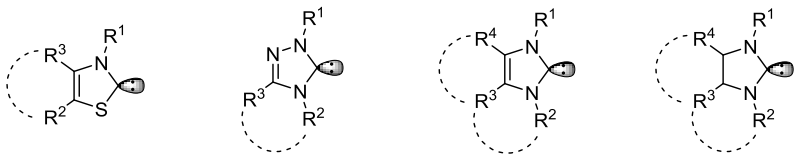
were isolated. The existence of stable carbene was actually reported with the synthesis of phosphinosilylcarbene **15** (Fig. 1.4) by Bertrand and co-workers in 1988.[9a] Furthermore, isolation and characterization of the first crystalline cyclic diaminocarbene **16**, so called NHC was reported by Arduengo et al. in 1991 (Fig. 1.4).[6c] Inspired by this success, Enders et al. studied the triazole heterocycle as an alternative carbene structure with the group of Teles. In 1995, Enders and co-workers reported the synthesis of triazolin-5-ylidene **17** (Fig. 1.4).[9b] Triphenyl triazol-5-ylidene **17** was the first carbene to be commercially available.




**15** **16** **17**

**Figure 1.4** Early *N*-heterocyclic carbenes (Ad = adamantyl)

The area of nucleophilic catalysis comprises a huge range of reactions, with the most popular employing *N*-heterocyclic carbene catalysis. The area of NHCs initially expanded slowly and has been widely utilized as versatile ligands in organometallic chemistry. Since the isolation of stable nucleophilic carbene by Arduengo[6c], Bertrand[9a] and Enders[9b], the NHCs have attracted wide attention from chemical community as they offer an elegant access to a broad range of organic transformations. In general, for these transformations four forms of NHCs are used (Figure 1.5).




**A** **B** **C** **D**

**Figure 1.5** Basic skeleton of *N*-heterocyclic carbenes

Importantly, the stability of NHCs is dependent upon both the electronic and steric factors. Herein, electronic factors include inductive and mesomeric effects and both these contribute to maintain the electro-neutrality of the carbene centre. In terms of inductive effects σ-electron withdrawing substituents favor the singlet state over the triplet state whereas σ-electron donating substituents induce a smaller σ-$p_\pi$ gap which favor a triplet state. Additionally, in the case of mesomeric effect both nitrogen lone pairs interact strongly with the $p_\pi$ orbital of the carbene centre which highlights the different mesomeric forms of NHCs (Figure 1.6). This strong interaction leads to a massive destabilization of the $p_\pi$ orbital resulting in a large σ–$p_\pi$ gap.[1] All these facts conclude that NHCs are not electrophilic but behave like strong nucleophilic species.

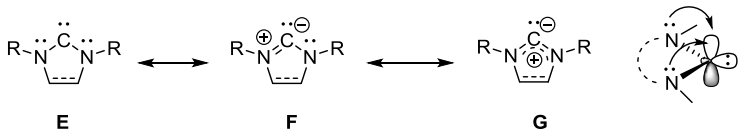



**Figure 1.6** Mesomeric structures of NHCs and stabilization of the singlet ground state

## 1.5 Important Action Modes of NHC

Catalysis of *N*-heterocyclic carbene (NHC) has been shown to provide a number of results which are classified according to the reaction mode and the intermediates produced during the reaction (Figure 1.7). The various reactions through nucleophilic Breslow intermediate (i) with unconventional reaction partners offer transformations unparalleled in metal catalysis. The reaction of Benzoin and Stetter are the two most prominent transformations in the category of traditional umpolung reactions. In the

former transformation addition of *in situ* generated carbene to aldehyde provides acyl anion intermediate, which further combines with another aldehyde molecule to afford α-hydroxy ketones (benzoins). In 1973, Stetter reported for the first time the attachment of acyl anion with Michael acceptor offering efficient access for the synthesis of 1,4-dicarbonyl compounds.[10] On the other hand, a reactive homoenolate intermediate (ii) which possess nucleophilic carbon at β position and can be generated from α,β-unsaturated aldehydes by virtue of NHC catalysis. Additionally, a nucleophilic enolate intermediate (iii) is a result of β-protonation of the homoenolate intermediate. This is a two carbon synthon which typically gives [3+2] and [4+2] annulation reactions and has also been generated from α-halo- or α-aryloxy aldehydes and stable ketenes under NHC catalysis. Furthermore, NHC-bound dienolate intermediate (iv) can be originated from β,β'-disubstituted enals having γ-hydrogen respectively under oxidative NHC-catalysis. Interestingly, enals with leaving group and cyclobutenones also generate dienolate intermediate which participate in formal [4+2] cycloaddition reaction. Notably, an NHC-bound allenoate intermediate (v) induced by the umpolung of ynals bearing a γ-leaving group through NHC-catalyzed internal redox reaction. Basically this allenoate intermediate is a three carbon synthon and commonly deliver [3+2] annulation reactions. The attachment of nucleophillic carbene to Michael acceptors provides the Deoxy-Breslow intermediate (vi), which converts electrophilic β-carbon to nucleophilic carbon. Moreover, the Breslow intermediate can be oxidized to acyl azolium intermediate (vii) by employing external oxidants such as inorganic, $O_2$ and organic oxidants. Likewise, α,β-unsaturated acyl azolium (viii), and α,β-γ,δ-unsaturated acyl

azolium (ix) generated from corresponding enals. Newly, the NHC-catalyzed reaction through radical process (intermediate x and xi) has emerged as a powerful method for various important transformations. Experimental and computational studies also demonstrate that selective formation of each reactive intermediate can be done by controlling the reaction conditions, coupling partner and NHC catalyst.

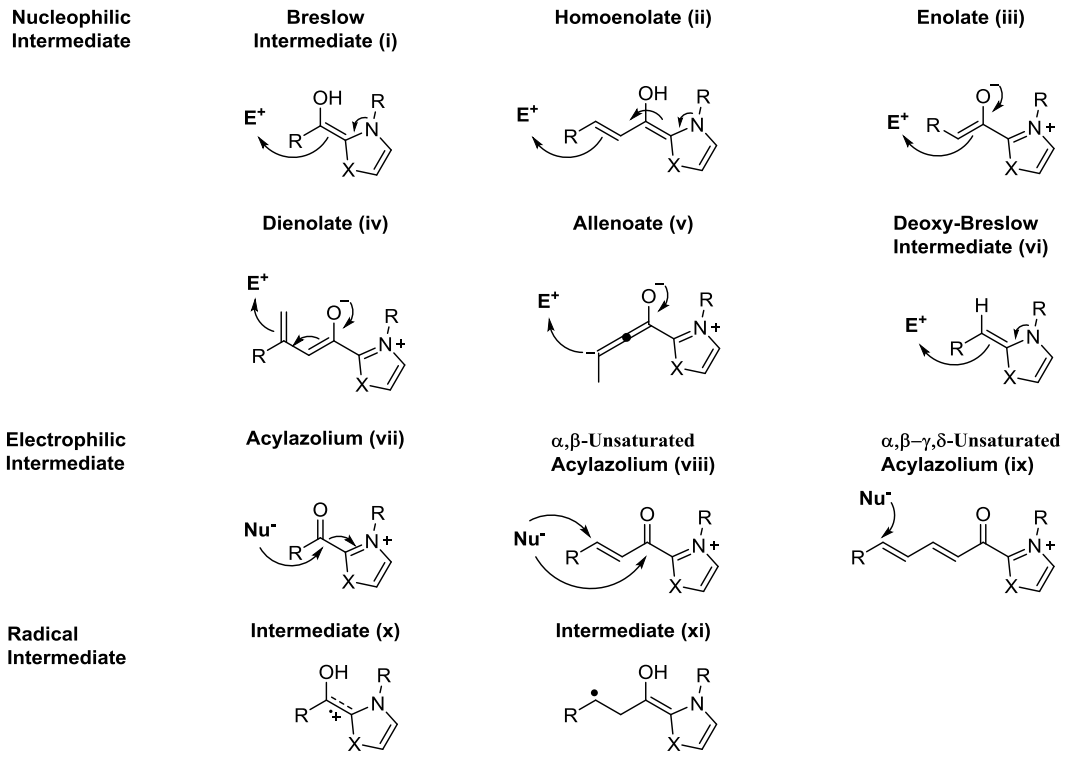



**Figure 1.7** Important action modes of NHC.

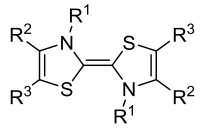
### 1.5.1 Reactions involving NHC-Bound Breslow Intermediate

The NHC-catalyzed polarity inversion of aldehydes through the formation of nucleophilic Breslow intermediate (i), is one of the most studied mode of action in the field of NHC. The transformations such as benzoin condensation (Inter- & Intra-molecular) and Stetter reaction (Intra- & Inter-molecular) are the most marked reactions under the area of NHC-

catalysis. In addition, the hydroacylation reaction of unactivated double and triple bonds catalyzed by NHC through umpolung of aldehydes are well studied.

### (A) Benzoin Condensation

The benzoin condensation catalyzed by NHCs has received substantial attention for several decades because of its employment in the formation of new C-C bonds to access α-functionalized products. In 1832, Wöhler and Liebig reported the self condensation of aromatic aldehyde to produce benzoin by using cyanide as the catalyst (Scheme 1.2).[7a] Later in 1943, Ukai et al. demonstrated self condensation of two same aldehyde so called homo-benzoin condensation employing thiazolium catalyst in existence of base.[8a] Furthermore, Breslow in 1958 suggested a mechanistic explanation for benzoin condensation catalyzed by thiazolium salt (Scheme 1.3).[3c] While an alternative mechanistic model based on the facile formation of carbene dimer (Figure 1.8) was postulated by Lemal and co-workers[11] but finally this could not be stand up to the Breslow mechanistic model.



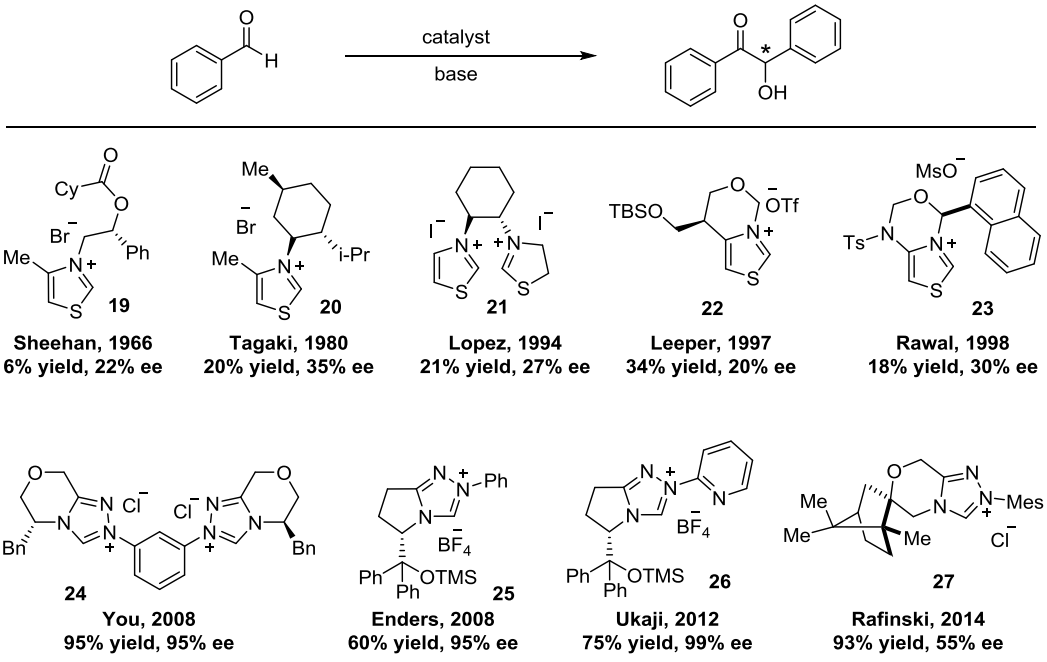

18

**Figure 1.8** Thiazolin-2-ylidene dimer

### (a) Intermolecular Benzoin Condensation

In 1976, Stetter and co-workers were the first to use commercially available thiazolium salt as catalyst for acyloin (aliphatic aldehydes) or benzoin (aromatic aldehydes) condensation on a synthetically useful scale.[12a] Consequently, several chemists have tried best to develop a highly asymmetric version of homo-benzoin reaction that leads to evolution of several chiral NHC precursors. In this context, Sheehan and Hunneman in 1966 reported the first

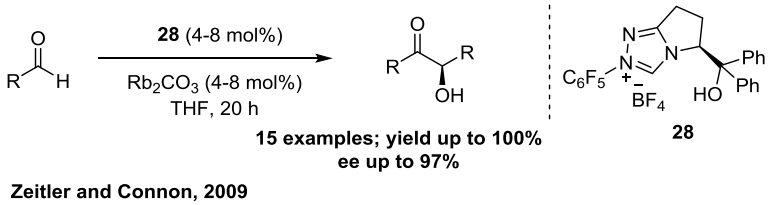
result of asymmetric benzoin condensation employing chiral thiazolium salt **19** as precatalyst and obtained the benzoin in very low yield (6%) and 22% enantiomeric excess (ee).[12b] After this initial report, the effort to increase the efficiency of the homo-benzoin reaction led to the development of a wide variety of various chiral thiazolium and triazolium salt as precatalyst. A assorted series of chiral NHC catalysts, which were employed in asymmetric benzoin condensation is described (Scheme 1.4). The yields and asymmetric induction for benzoin reactions were modest with thiazolium derived NHC-salts (**19-23**) whereas catalyst generated from triazolium based NHC-salts (**24-27**) provided the desired product with increased yields and enantioselectivity.[13] Furthermore, the superiority of triazolium derived NHCs over thiazolium derived counterparts in benzoin condensation was also supported by computational studies.




**Scheme 1.4** Variation of chiral-NHCs for asymmetric homobenzoin condensation

More recently, Connon and Zeitler developed asymmetric benzoin condensation using a triazolium precatalyst **28** which incorporate a hydrogen bond donor providing

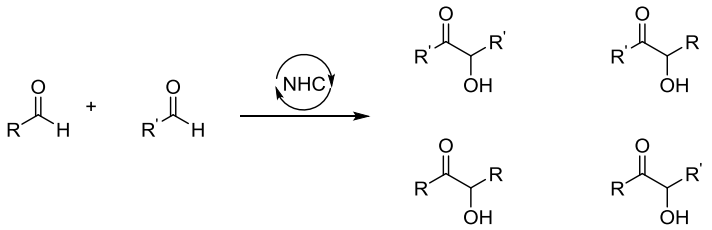
stabilization of secondary interactions in transition state concludes to reach practically fine enantioselectivity.[14]




**Scheme 1.5** Co-operative hydrogen bond assisted enantioselective benzoin condensation

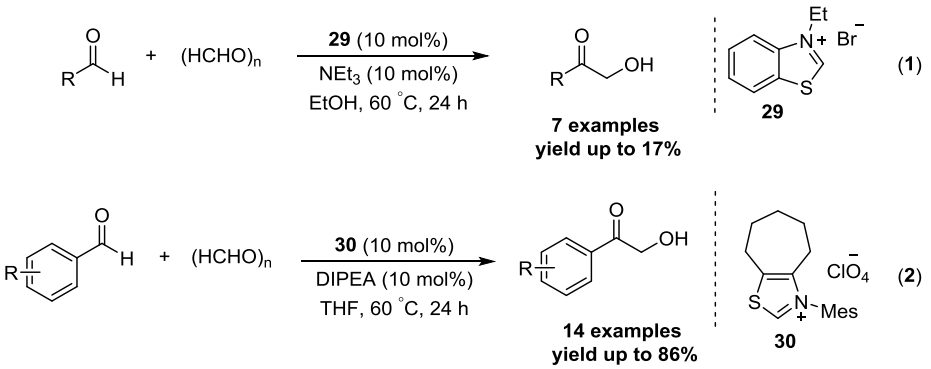
### (b) Intermolecular Cross-Benzoin Reaction

The cross-benzoin reaction is preparation of non-symmetrical products by the cross-coupling of two different aldehydes, wherein one molecule of aldehyde acts as acyl anion equivalent. In this process, a pair of homo-benzoin and cross-benzoin each can be formed providing a mixture with up to eight distinct products including four pair of enantiomers (Scheme 1.6). Notably, a general approach to chemoselective NHC mediated cross-benzoin transformation of electronically and sterically similar aldehydes is still challenging.



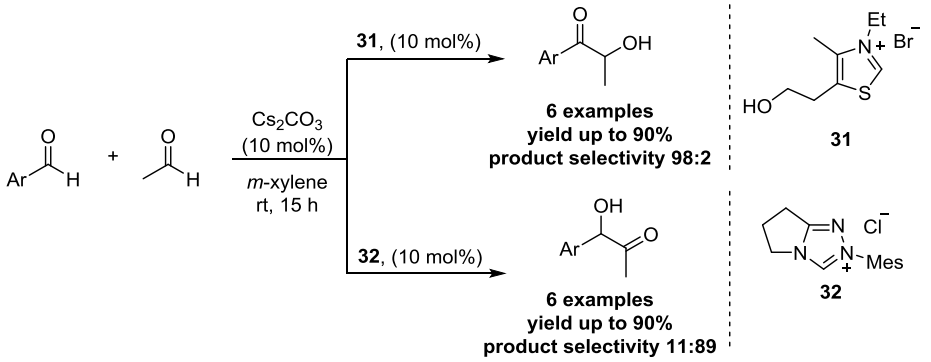

**Scheme 1.6** General intermolecular cross-benzoin reaction

In 1985, Inoue et al. disclosed the NHC mediated cross-benzoin selective transformations of aliphatic and aromatic aldehydes with paraformaldehyde allowing to access α-hydroxy ketones in very low yields (Scheme 1.7, Eq. 1).[15a] Furthermore, Kuhl and Glorius developed thiazolium based catalyst **30** which were used to furnished hydroxy ketone in good to moderate yields (Scheme 1.7, Eq. 2).[15b]




**Scheme 1.7** Cross-benzoin selective reaction

Moreover, Yang and colleagues demonstrated an intermolecular cross-coupling reaction between aromatic aldehydes and acetaldehyde which displayed an exciting variation in reactivity between thiazolium **31** and triazolium **32** derived precursors. The thiazolium-based carbene favored the generation of Breslow equivalent with aromatic aldehydes and successive coupling with aliphatic aldehydes. However, triazolium-based carbene preferentially generate acyl anion intermediate with aliphatic aldehydes followed by addition to aromatic aldehydes (Scheme 1.8).[15c]

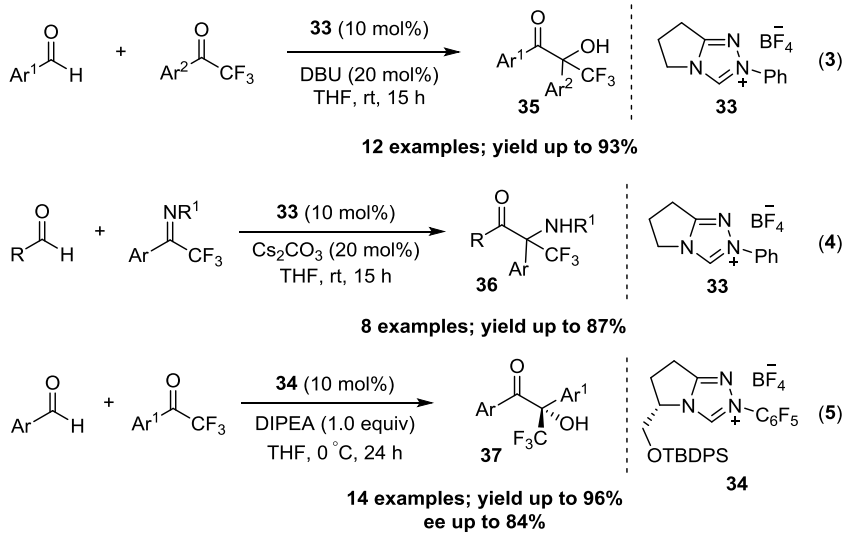



**Scheme 1.8** Catalyst-controlled divergence in cross-benzoin reactions

### (c) Intermolecular Asymmetric Cross-Benzoin Reactions

The expansion of asymmetric cross-benzoin reaction is very challenging because a single catalyst must regulate both chemoselectivity and stereoselectivity. Impressively,

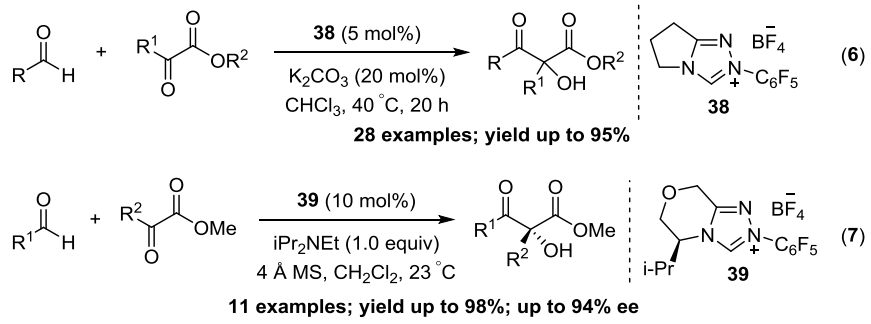
Enders and Henseler disclosed an NHC-catalyzed cross coupling reaction of aryl aldehydes and aryl trifluoromethyl ketones to furnish final product, α-hydroxy-α-trifluoromethyl ketones **35** with high yields and chemoselectivity (Scheme 1.9, Eq. 3).[16a] Herein, the reversibility of the homo-benzoin reactions provides excellent selectivity for the observed cross-benzoin product which has a quaternary stereocentre. Thereafter, they noticed that trifluoromethyl ketimines can also used as electrophiles to broaden the substrate scope (Scheme 1.9, Eq. 4).[16b] Although initial attempts of asymmetric transformation by using a chiral triazolium were not fruitful but latter they were able to overcome this issue by using heteroaromatic aldehyde (acyl donor) in the presence of chiral NHC generated from **34** with aryl trifluoromethyl ketones to furnished the desired trifluoromethylated hydroxy ketones **37** in good yields and enantioselectivity (Scheme 1.9, Eq. 5).[16c]




**Scheme 1.9** Cross-benzoin reaction of aldehydes and trifluoromethyl ketones

Additionally, Connon and Zeitler et al. investigated that α-ketoesters could also be used as electrophilic coupling partner for various aliphatic and aromatic aldehydes which

served as acyl donor for intermolecular cross-benzoin transformation. Remarkably, the authors presented one illustration of an enantioselective product in 48% yield and 76% ee employing chiral NHC-catalyst (Scheme 1.10, Eq. 6).[17a] Furthermore, Gravel and colleagues were successful in broadening the scope of chemoselective and enantioselective version of intermolecular cross-benzoin transformation with aliphatic aldehyde and α-ketoesters. Noticeably, aliphatic α-ketoesters were not compatible under the reaction conditions. The reaction provides the product in good yields and high enantioselectivity by using an electron deficient valine-derived triazolium salt precatalyst **39** (Scheme 1.10, Eq. 7).[17b]

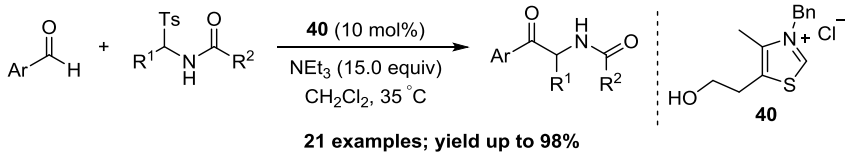



**Scheme 1.10** Cross-benzoin reaction of aldehydes and α-ketoesters

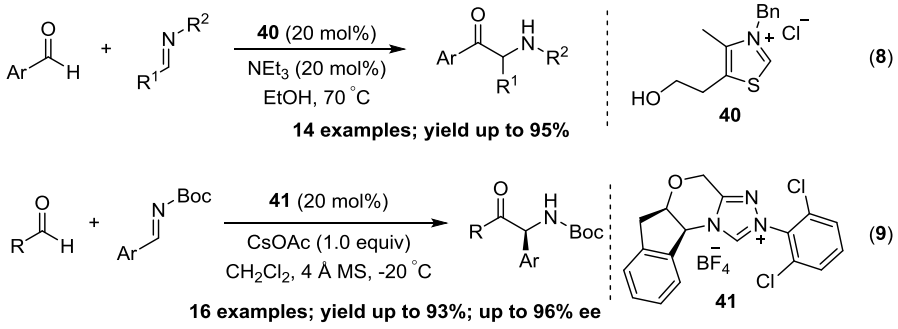
### (d) Intermolecular Cross Aza-Benzoin Reactions

In 2001, Murry and Frantz were first to demonstrate the coupling of acyl anion generated from aldehydes to an imines. They exposed that efficient coupling of Breslow intermediate generated from aldehyde using thiazolium salt **40** as precatalyst and *in situ* formed reactive acylimines by the action of base on the sulfonylamide derivative deliver the desired α-amidoketones in excellent yields (Scheme 1.11).[18a] Subsequently, You and co-workers reported cross-aza benzoin transformation of aryl and hetero-aryl aldehydes with non-activated imines to furnish α-amino ketone products in excellent

yields employing thiazolium precatalyst **40** (Scheme 1.12, Eq. 8).[18b] Notably, the control experiment employing corresponding benzoin (instead of aldehyde) with imines works well which specify that it involves reversible formation of aldehyde homo-benzoin adduct. Later, DiRocco and Rovis disclosed enantioselective cross aza-benzoin reaction of aliphatic aldehyde with N-Boc imines using chiral triazolium salt **41** (Scheme 1.12, Eq. 9).[18c] In this transformation aldehydes acts as acyl donor whereas imines function as receptors. Furthermore, it was observed that addition of NHC to the highly electrophilic N-Boc imines leads to the formation of reversible aza-Breslow intermediates under the reaction conditions and thus cancel out the requirement for a slow addition of highly reactive imines as substrates.

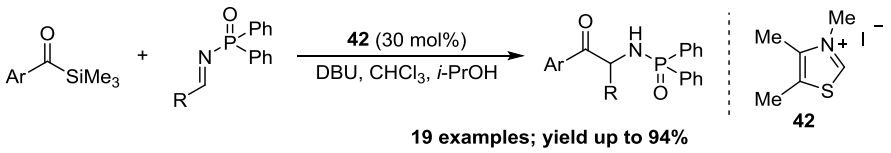



**Scheme 1.11** Cross aza-benzoin reaction of aldehydes and acylimines



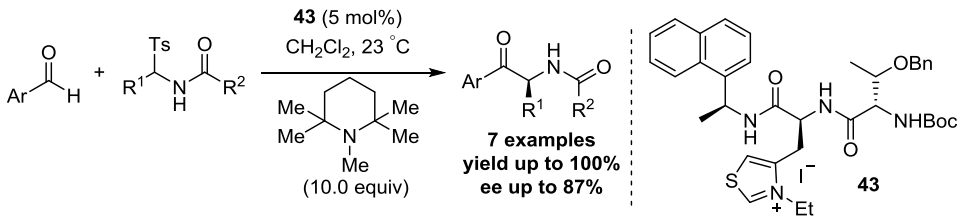

**Scheme 1.12** Cross aza-benzoin reaction of aldehydes and imines

Furthermore, Mattson and Co-workers reported a catalytic cross aza-benzoin transformation using acylsilanes and imines to furnish aminoketones (Scheme 1.13).[19a] Notably, the generated free carbene selectively couples with acyl silanes to generate Breslow intermediate, which then reacts with imines to furnish desired product.




**Scheme 1.13** Cross aza-benzoin reaction of acylsilanes and imines

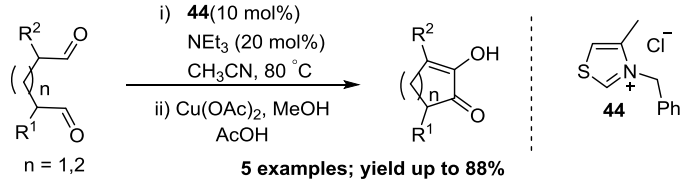
Moreover, Miller et al. in 2005 employed thiazolium-derived chiral salt **43** to expose enantioselective cross aza-benzoin protocol (Scheme 1.14).[19b] The reaction proceeded with generation of Breslow intermediate, which added to masked imines to afford the desired α-amino ketones in excellent yields and good enantioselectivity. This transformation suffers a racemisation of the products resulting a decrease in stereoselectivity under the reaction conditions. This problem was successfully overcome by using a hindered base, pentamethyl piperidine which was inert towards the products and gives the maximum enantioselectivity.




**Scheme 1.14** Enantioselective cross aza-benzoin reaction

### (e) Intramolecular Benzoin Reaction

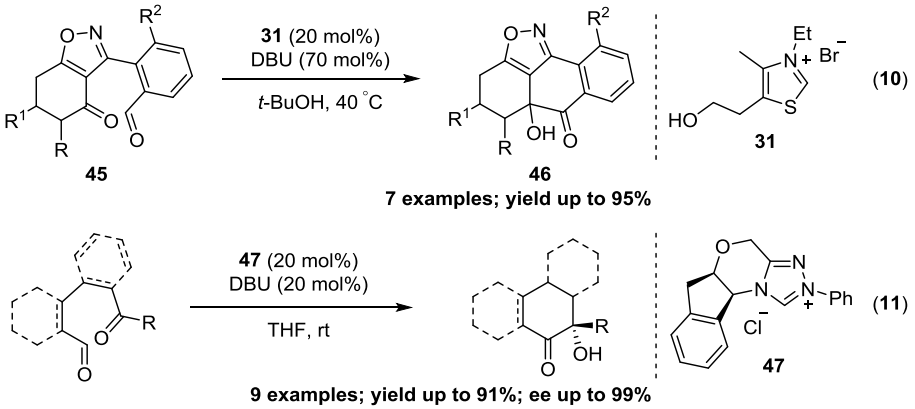
Cookson and Lane demonstrated first intramolecular cross-benzoin condensation in 1976. This report disclosed the formation of 2-hydroxycyclopentanone by the treatment of anhydrous glutaraldehyde with thiazolium salt **44** as precatalyst. The above also endured further oxidation by treatment with Copper (II) acetate affords 2-hydroxycyclopent-2-en-1-one (Scheme 1.15).[20]




**Scheme 1.15** Intramolecular benzoin condensatation

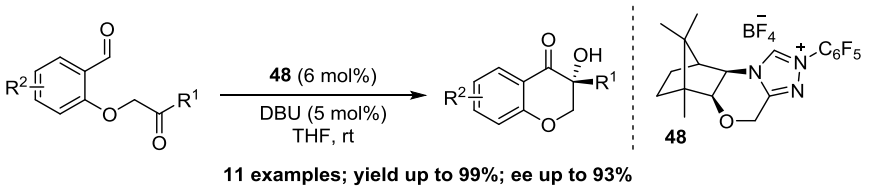
### (f) Intramolecular Cross-Benzoin Reaction

Suzuki and co-workers demonstrated the first intramolecular cross-benzoin condensation of aldehyde and ketone in 2003 (Scheme 1.16, Eq. 10).[21a] This transformation represents the first report on the use of functional group like ketone as an electrophile in non-enzymatic benzoin reaction. Herein, the highly rigid isoxazole-fused cyclohexanone **45** graced with an aryl aldehyde endure a flatten cross-benzoin cyclisation using thiazolium salt **31** as precatalyst to afford a very high stereo- and regioselective polycyclic preanthraquinones analogues **46** in high yields. This efficient protocol authorized the synthesis of orthogonally protected polycyclic quinones using easily accessible starting reagents. Subsequently, they in 2006 advanced enantioselective variant of the same transformation employing an aminoindanol based triazolium catalyst **47** with high yields and excellent enantioselectivity (Scheme 1.16, Eq. 11).[21b]



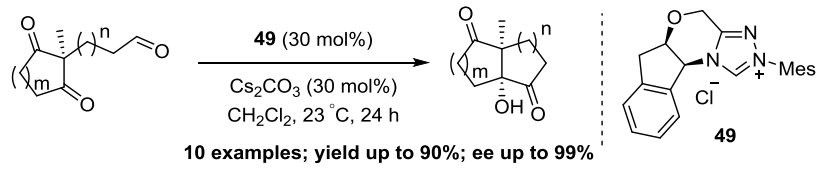

**Scheme 1.16** Intramolecular cross-benzoin condensatation of aldehyde and ketone

Furthermore, You and co-workers developed enantioselective intramolecular heterocoupling between aldehyde and ketone using a camphor-derived triazolium precatalyst **48** for the synthesis of chromanone derivatives possessing a quaternary stereocentre in excellent yields and enantioselectivity (Scheme 1.17).[22a]




**Scheme 1.17** Intramolecular cross-benzoin reaction for chromanone synthesis

In addition, Ema and co-workers developed the synthesis of bicyclic tertiary alcohols possessing a stereogenic centre at both bridgehead carbon *via* an intramolecular crossed benzoin reaction by using the NHC derived from **49** (Scheme 1.18).[22b] Notably, a relatively high loading (30 mol%) of catalyst was crucial for excellent enantioselectivity.

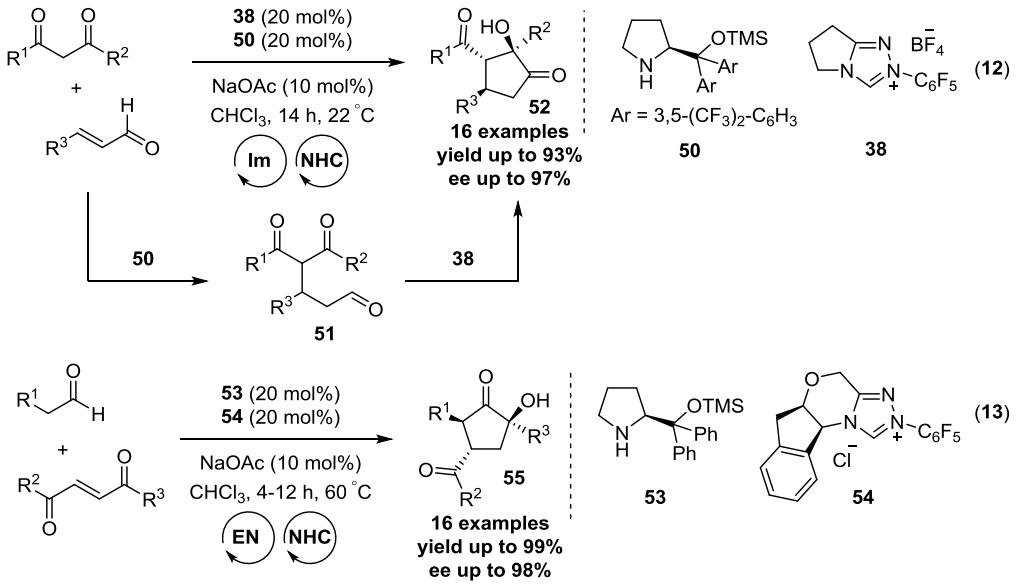



**Scheme 1.18** Intramolecular cross-benzoin reaction to access bicyclic tertiary alcohols

In 2009, Rovis et al. developed a multicatalytic Michael addition-intramolecular benzoin cascade protocol, which leads to the formation of highly functionalized cyclopentanones with excellent enantioselectivity (Scheme 1.19, Eq. 12).[23a] The reaction was initiated with generation of α,β-unsaturated iminium by the reaction of enal and secondary amine catalyst **50**, followed by conjugate nucleophilic addition of diketone, protonation and hydrolysis provides a δ-ketoaldehyde system **51** with release

of **50**. Subsequently, the NHC generated from **38** catalyzes the intramolecular cross-benzoin transformation to furnish desired product **52**. As the NHC precatalyst **38** is achiral so the absolute configuration of reaction is only regulated by secondary amine catalyst **50**. The controlled experiments conclude that Michael addition is reversible but carbene catalyze the intramolecular cross-benzoin process very quickly to furnish final product and thus restrict the destruction of enantioselectivity.

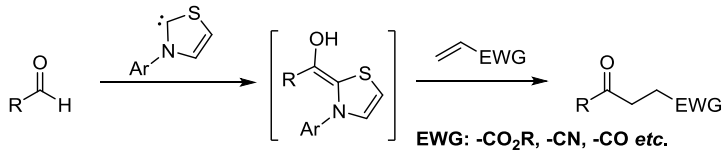
Later, in 2011 they developed a dual enamine-NHC catalytic, conceptually comparable Michael-benzoin cascade reaction (Scheme 1.19, Eq. 13).[23b] The reaction was initiated by the coupling of enolizable aldehyde and secondary amine catalyst **53** to generate enamine, which further combines to an activated Michael acceptor and subsequent hydrolysis gives a δ-ketoaldehyde, which then undergoes intramolecular cross-benzoin condensation employing chiral NHC precatalyst **54** to form the desired highly functionalized cyclopentanol products with excellent enantioselectivity.




**Scheme 1.19** Secondary amine-NHC dual-catalytic, Michael-benzoin cascade reaction

**(B) Stetter Reaction**

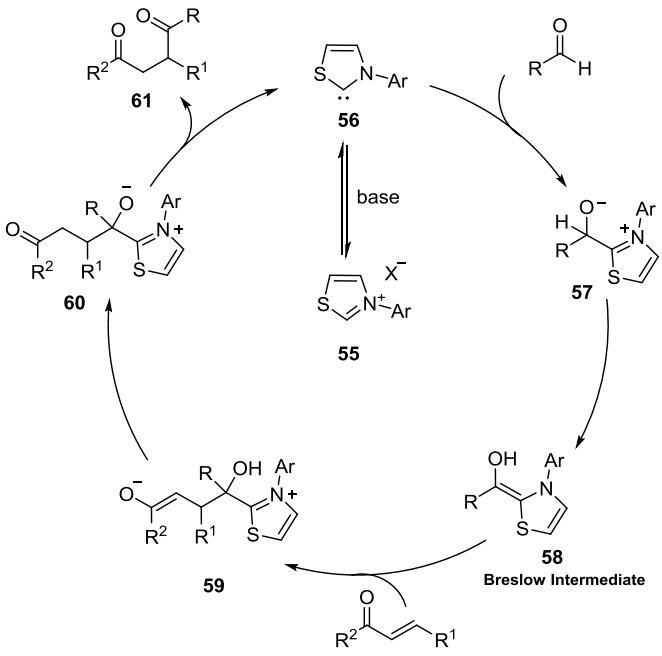
The benzoin condensation was extended to Michael acceptors and thereby significantly increasing the versatility of NHC-catalyzed transformations. In the early of 1970s, Stetter and colleagues reported for the first time the addition of aldehyde to Michael acceptors catalyzed by NHC, giving access to valuable 1,4-bifunctional compounds (Scheme 1.20).[10] In addition, this protocol is precious as it provides abnormal functional group separation and that is not easy to compose by traditional protocols. They succeeded to develop selective conjugate addition reaction using thiazolium-catalyst to cross-couple various aliphatic as well as aromatic aldehydes with different Michael acceptors like α,β-unsaturated esters, ketones, nitriles or sulfones in an intermolecular process. However, the presence of an NHC has been confirmed by the Wanzlick experiments.




**Scheme 1.20** Stetter reaction

Moreover, Arduengo et al. in 1991 isolate and characterize the first stable crystalline NHC to prove that these reactions are catalyzed by NHCs.[6c] A crucial step in the proposed mechanism of Stetter reaction (Scheme 1.21), is nucleophilic addition of *in situ* formed free carbene **56** from azolium precursor **55** to aldehyde, resulting the generation of tetrahedral intermediate **57**, which further transfer proton to the nucleophilic enaminol intermediate commonly known as the Breslow intermediate **58** in a reversible process. This acyl anion intermediate **58** undergoes nucleophilic addition

in irreversible fashion to Michael acceptor to give alkoxide **59** followed by proton transfer to deliver **60** which finally furnished desired 1,4-bifunctional product **61** with regeneration of free carbene**.** In this transformation, the use of chiral NHCs leads to access enantioenriched 1,4-bifunctional compounds. Moreover, Rovis et al. proposed a stepwise mechanistic model for coupling of Breslow intermediate and Michael acceptors.[24a] In addition, they also considered the possibility of a concerted pathway for the same. However, Hawkes and Yates exposed a two-step process for attachment of Breslow intermediate with Michael acceptor, based on DFT calculations.[24b]

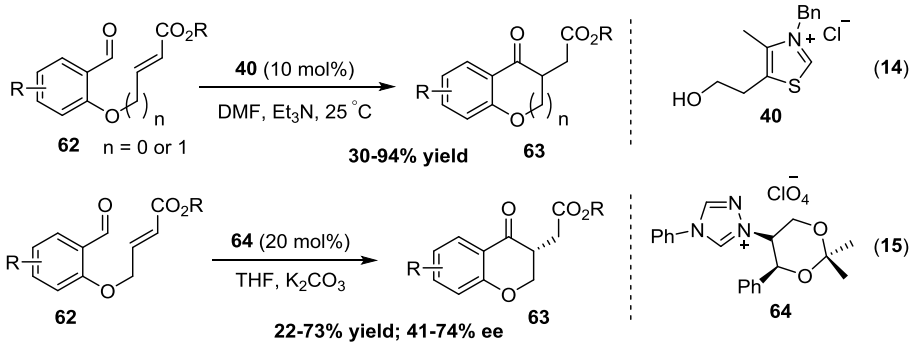



**Scheme 1.21** Catalytic cycle of Stetter reaction

**(a) Intramolecular Stetter Reaction**

In 1995, Ciganek research group reported first general intramolecular Stetter reaction catalyzed by NHC. The intramolecular cyclisation of 2-formyl aryloxy crotonates **62** employing *in situ* produced free carbene from thiazolium salt **40** provides benzo-annulated pyranones **63** (Scheme 1.22, Eq. 14, n = 1).[25a] The reaction of 2-formyl

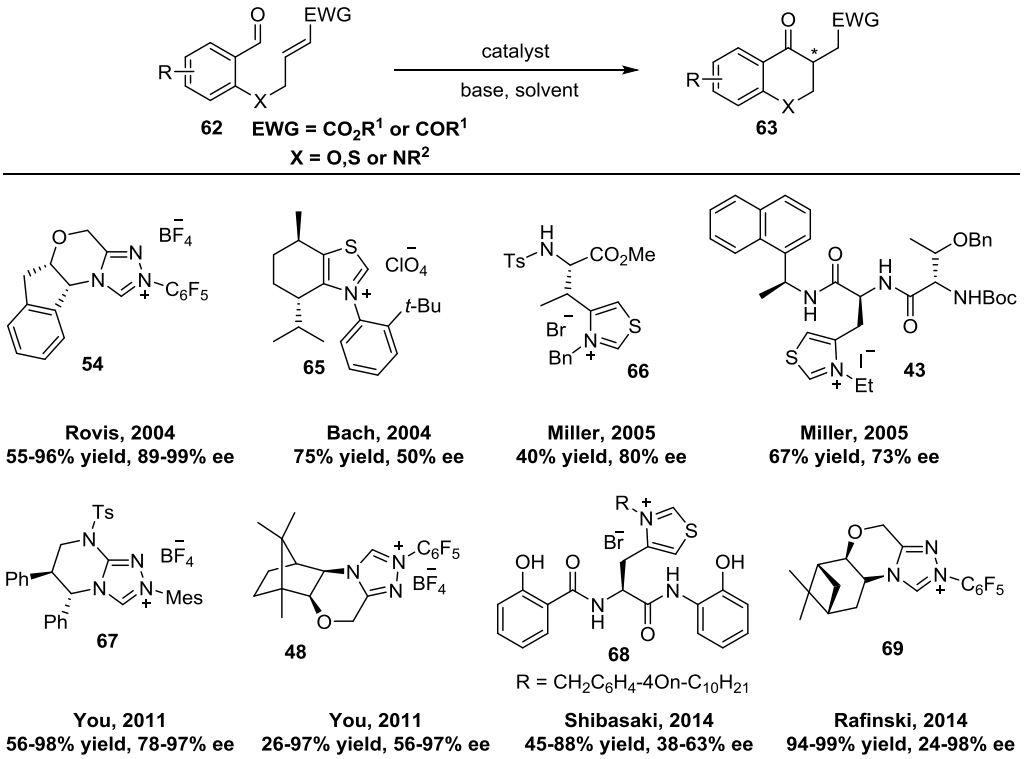
aryloxyacrylates (n = 0) occurred in the absence of base under reflux conditions to afford the furanone derivatives in good yields. The successful formation of **63** from **62** under NHC-catalysis produced a key interest to design various novel chiral NHC precursors that made it possible to establish enantioselective Stetter reaction. In this context, Ender and colleagues in 1996 reported the first enantioselective version of intramolecular Stetter reaction using chiral triazolium salt **64** (Scheme 1.22, Eq. 15).[25b] The various 2-formylaryloxy crotonates **62** endure NHC-catalyzed cyclisation reaction to afford the desired chromanones in average yield and enantioselectivity.



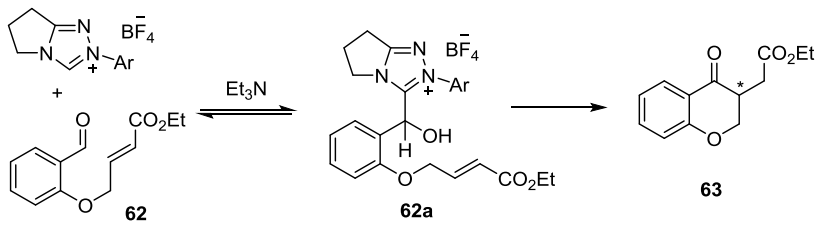

**Scheme 1.22** Seminal intramolecular Stetter reaction

Since the fruitful reports of enantioselective intramolecular Stetter reaction, there has been a significant advancement in this area with a primary focus on the development of new NHC precatalysts. Furthermore, in this context the Rovis, Bach, Miller, You, Shibasaki and Rafinski groups have made great contribution in this arena through developing novel chiral NHC catalysts (Scheme 1.23).[26] The cyclisation of substrate **62** drived from salicylaldehyde furnished chromanone **63** has chosen a typical reaction for comparing the catalytic efficiency. Importantly, Smith and colleagues examine the importance of N-aryl moiety attributed to triazolium based precatalyst in benzoin condensation and Stetter transformation. A variety of tetrahedral intermediates

generated by nucleophilic addition of free carbene on aldehyde **62** were extracted and analyzed. It was determined that formation of **62a** was a reversible process, whereas generation of Stetter product **63** from **62a** was a slow and irreversible process under the reaction condition (Scheme 1.24).[27a] In addition, the best results of intramolecular Stetter reaction was observed by using pentafluoroaryl substituted triazolium precatalyst and triethylamine as a base.

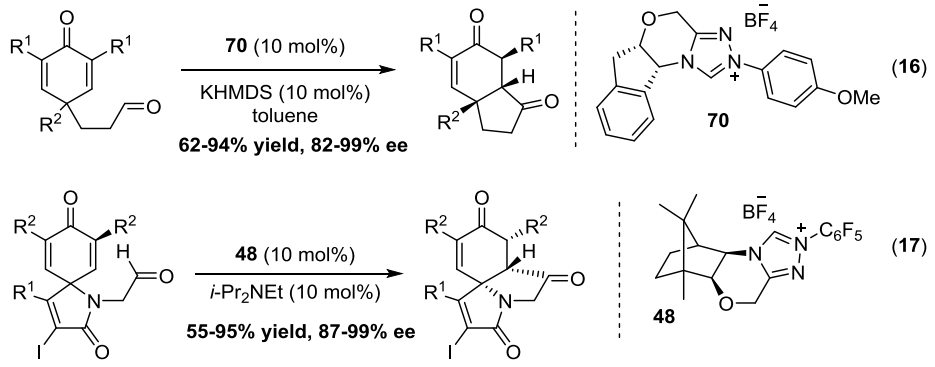



**Scheme 1.23** Variation of chiral-NHCs for asymmetric intramolecular Stetter reaction



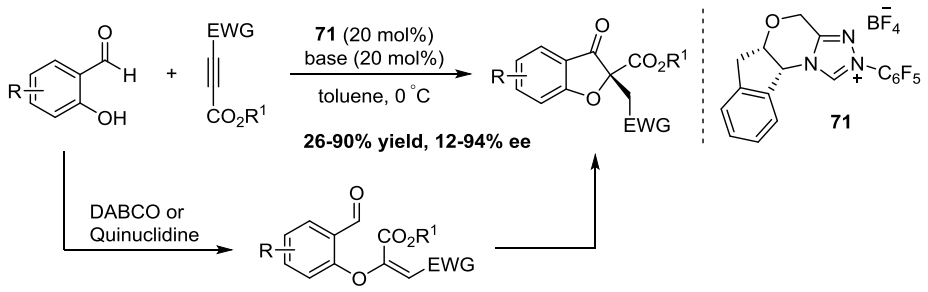

**Scheme 1.24** Aldehyde-NHC adducts isolation for intramolecular Stetter transformation

In 2006, Rovis and Liu reported the carbene catalyzed desymmetrization of cyclohexadienones to furnish hydrobenzofurans by virtue of intramolecular Stetter reaction in good enantioselectivity and diastereoselectivity (Scheme 1.25, Eq. 16).[27b] The carbene generated from the aminoindanol based 4-methoxyaryl-substituted chiral triazolium salt **70** showed the superior reactivity for this intramolecular Stetter reaction. Furthermore, You and colleagues exposed a similar strategy for desymmetrization of cyclohexadienone analogues employing camphor-based triazolium catalyst **48** to access tricyclic carbocycles bearing three contiguous stereocenters with good yields and enantioselectivity (Scheme 1.25, Eq. 17).[27c]



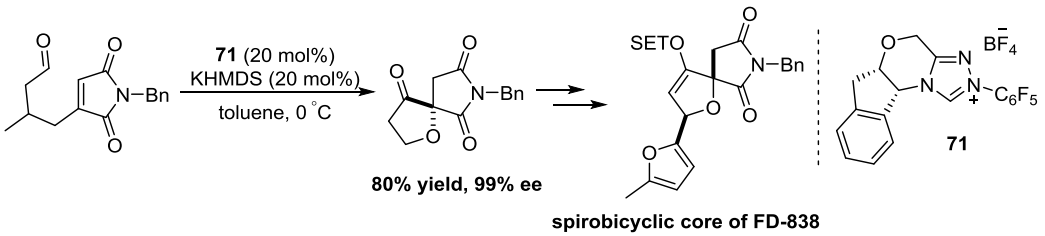

**Scheme 1.25** Desymmetrization of cyclohexadienone derivatives through intramolecular Stetter reaction

In 2010, Rovis et al. reported a sequential one-pot multicatalytic enantioselective reaction of salicylaldehydes with electrophilic alkynes, which proceeds through Michael-intramolecular stetter pathways and furnished benzofuranone derivatives in positive yields and great enantioselectivity. Herein, a base catalyzed the Michael reaction followed by intramolecular stetter reaction catalyzed by chiral NHCs (Scheme 1.26).[28a] In terms of stereoselectivity, the Michael-Stetter one pot technique was found to be preferred over two-step methods.



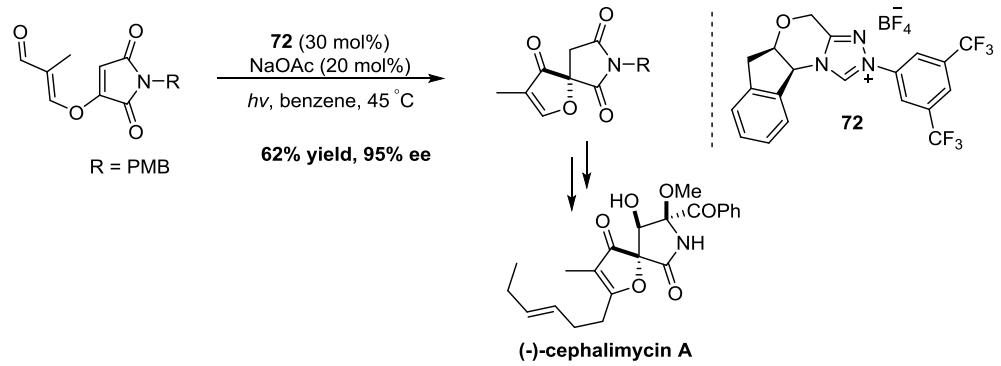

**Scheme 1.26** A cascade oxa-Michael intramolecular Stetter reaction

Recently, Orellana and Rovis developed the enantioselective Stetter transformation for aldehyde bearing an N-benzyl protected maleimide using aminoindanol based chiral NHC **71** to furnish the spirofuranone in 80% yield and 99% ee (Scheme 1.27).[28b] Importantly, this methodology was also elongated for construction of spirocyclic core present in antibiotic FD-838.




**Scheme 1.27** Access to spirobicyclic frame of FD-838 through intramolecular Stetter transformation

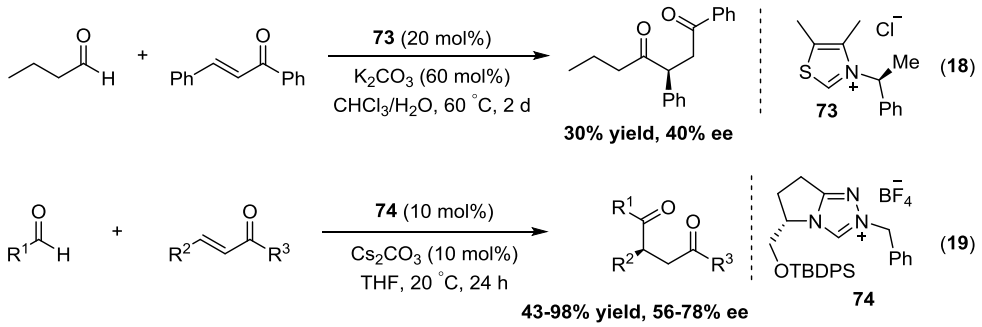
Furthermore, Lathrop and Rovis developed a tandem process involving UV irradiation followed by intramolecular Stetter reaction using chiral triazolium salt **72** of aldehyde derivative to furnish the spirocyclic furanone in moderate yield and exemplary enantioselectivity (Scheme 1.28).[28c] Moreover, this methodology was enforced for the total synthesis of (–)-cephalimycin A.




**Scheme 1.28** A cascade photoisomerization-Stetter reaction

### (b) Intermolecular Stetter Reaction

Even after Stetter's pioneering work in 1970s, a number of new coupling partners in Stetter reaction have been extensively studied.[10] At first, the catalyst designing and reaction procedures have been developed for the enantioselective intramolecular transformations because they diminish reactivity and selectivity issue compared to the intermolecular methodology. Consequently, the advancement on intermolecular Stetter reaction compared to intramolecular Stetter is less due to lower reactivity of β-substituted Michael acceptors in the intermolecular process. However, the recent evolutions on intermolecular Stetter reaction are mainly focused on its enantioselective variant. In 1993, Enders et al. developed the first enantioselective intermolecular Stetter transformation between n-butanal and chalcone using chiral thiazolium catalyst **73** to furnish 1,4-diketone in poor enantioselectivity and yield (Scheme 1.29, Eq. 18).[29a] Recently, they have reported enantioselective intermolecular Stetter methodology of aryl aldehydes and chalcone employing a new carbene drived from triazolium precursor **74** to afford desired products in moderate yields and enantioselectivity (Scheme 1.29, Eq. 19).[29b] Interestingly, the enhancement of enantioselectivity up to 99% ee in product through recrystallization was feasible.



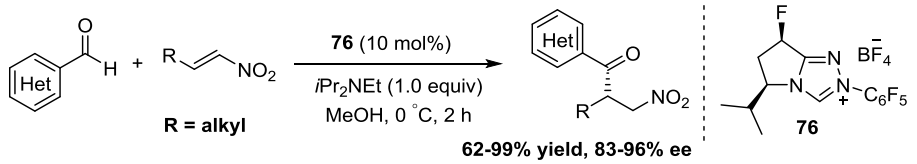

**Scheme 1.29** Asymmetric intermolecular Stetter transformation of aldehyde and chalcone

Independent scrutiny by Rovis and colleagues have made significant progress in the asymmetric intermolecular Stetter reaction. They have disclosed the coupling of glyoxamide analogues derived from morpholine as aldehyde ingredient and alkylidene malonate as Michael acceptor using the phenylalanine based triazolium salt **75** to furnish the desired Stetter product in valuable yield with excellent enantiomeric excess (Scheme 1.30).[30a]


**Scheme 1.30** Asymmetric intermolecular Stetter reaction using alkylidene malonate

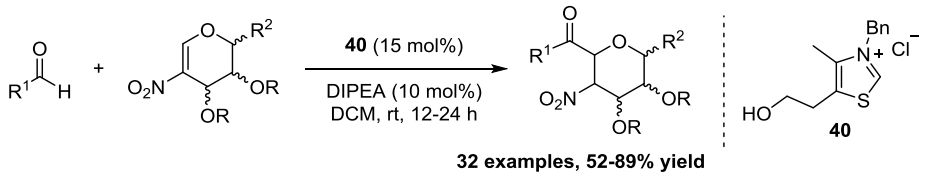
Moreover, Rovis and colleagues developed a general asymmetric intermolecular Stetter method with broad scope by employing hetero-aromatic aldehydes and nitroalkenes as a suitable Michael acceptors in existence of unfamiliar chiral NHC salt **76** (Scheme 1.31).[30b] Importantly, the fluoro and isopropyl substituents in **76** increased the stereoselectivity of the Stetter product. The fluorine effect was further supported by DFT calculations, which showed that fluorine enhanced the electrostatic interaction between acyl anion intermediate and the nitroalkene. The

use of hetero-aromatic aldehyde was necessary to obtain excellent level of reactivity and selectivity.




**Scheme 1.31** Asymmetric intermolecular Stetter reaction using nitroalkene

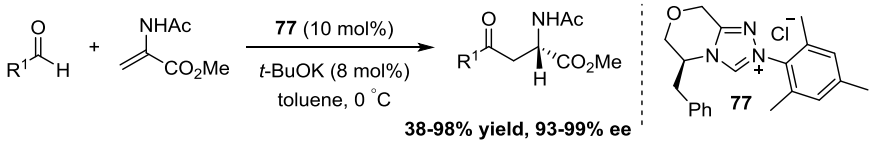
Additionally, Liu and colleagues demonstrated a intermolecular Stetter approach for the reaction of aldehydes with 2-nitroglucal using thiazolium salt **40** to furnish β-selective C-glycoside in moderate yields (Scheme 1.32).[31a] Several (hetero)aromatic aldehydes as well as aliphatic aldehydes afforded the desired Stetter product under the optimized reaction conditions but the nitro-eliminated C-glycosides were accessed when the reaction was carried out in presence of cesium carbonate as the base.




**Scheme 1.32** Intermolecular Stetter reaction using 2-nitroglucal

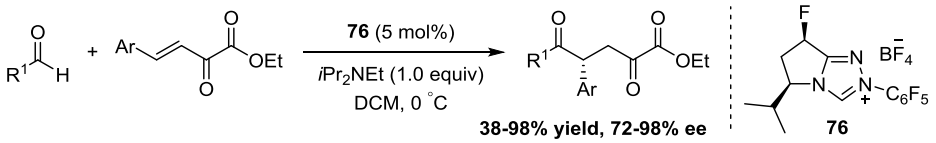
In 2011, Glorius et al. reported an enantioselective variant of intermolecular Stetter transformation by employing aldehyde with *N*-acylamido acrylate as the Michael acceptor in presence of triazolium salt **77** to furnish α-amino acid derivatives in excellent yield and enantioselectivity (Scheme 1.33).[31b] Notably, in this transformation enantioinduction occurred due to enantioselective protonation of enolate intermediate, which was generated by conjugated attachment of the acyl anion with Michael acceptor. In this reaction, the free carbene produced by triazolium salt **77** derived from

L-phenylalaninol delivers best result and low amount of base correlated to the NHC precursor was the secret to successful enantioselectivity.



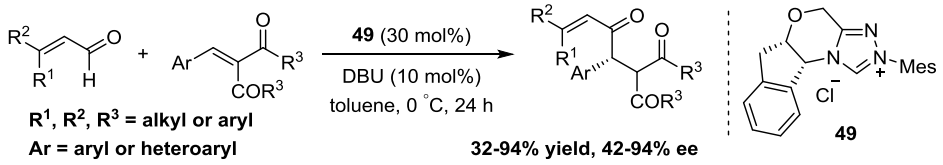

**Scheme 1.33** Asymmetric intermolecular Stetter transformation using *N*-acylamido acrylate

Furthermore, Gravel and co-workers expanded the usage of fluorinated triazolium salt **76** in synthetic chemistry, which was initially matured by Rovis research group.[30b] They employed β,γ-unsaturated α-ketoesters as Michael acceptors to provide enantioselective 1,2,5-tricarbonyl compounds through intermolecular Stetter pathway (Scheme 1.34).[32a] The reaction afforded the desired product in excellent yields and enantioselectivity which were susceptible for a variety of synthetic manipulations.



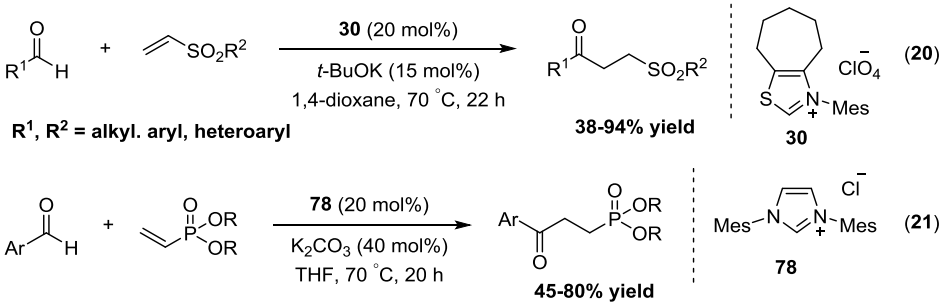

**Scheme 1.34** Asymmetric Stetter reaction employing β,γ-unsaturated α-ketoesters

Moreover, Chi and colleagues developed carbene catalyzed enantioselective intermolecular Stetter transformation between α,β-unsaturated aldehydes and α-acyl chalcones using aminoindanol-derived triazolium salt **49** to furnish desired triketones in reasonable yields with high enantioselectivity (Scheme 1.35).[32b] A wide variety of β-alkyl, β-aryl, and β,β-disubstituted enals worked well and provide corresponding desired product under the reaction condition.




**Scheme 1.35** Asymmetric Stetter reaction of α-acyl chalcones

Furthermore, the NHC-catalyzed highly selective coupling of aldehydes and α,β-unsaturated sulfones through intermolecular Stetter approach was recently reported by Biju research group. The free carbene produced from thiazolium salt **30** catalyzed the reaction to afford γ-keto sulfones in high yields (Scheme 1.36, Eq. 20).[33a] Subsequently, they reported intermolecular Stetter transformation catalyzed by NHC between aldehydes and vinylphosphonates to furnish γ-ketophosphonates in good yields (Scheme 1.36, Eq. 21).[33b] Notably, the imidazolium salt **78** was found to be best catalyst for this transformation.

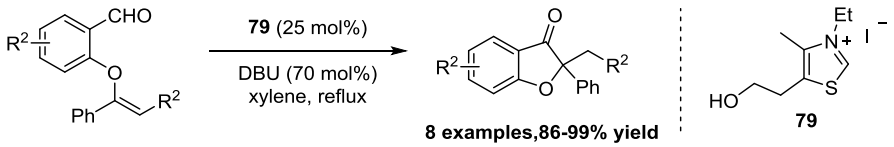



**Scheme 1.36** Intermolecular Stetter reaction using vinylsulfones or vinylphosphonates

### (C) Hydroacylation Reaction of Double and Triple Bonds

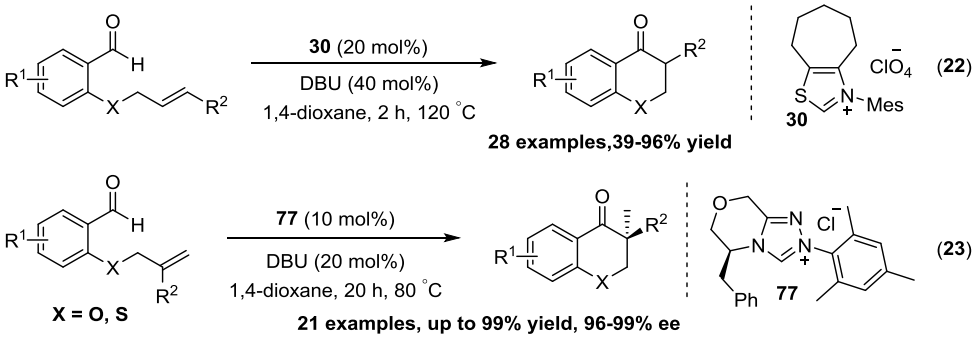
Stetter reaction involves umpolung of aldehydes and subsequent addition of *in situ* formed nucleophilic Breslow intermediate to activated (electron-poor) carbon-carbon multiple bonds. Moreover, the NHC-catalyzed hydroacylation reactions involve umpolung of aldehydes and subsequent addition to unconventional electrophiles for example unactivated

C-C multiple bonds were reported recently. In 2008, She and co-workers demonstrated the NHC-catalyzed intramolecular transformation, which involve nucleophilic addition of Breslow intermediate to enol ethers employing readily available thiazolium salt **79** to furnish benzofuranones in excellent yields (Scheme 1.37).[34a] The proposed mechanism of this transformation involves the intramolecular addition of acyl anion equivalent to C-C double bond of enol ether. Importantly, this was not clear that nucleophilic addition proceeds through concerted or stepwise pathway involving an oxonium species.




**Scheme 1.37** NHC-catalyzed hydroacylation of enol ethers

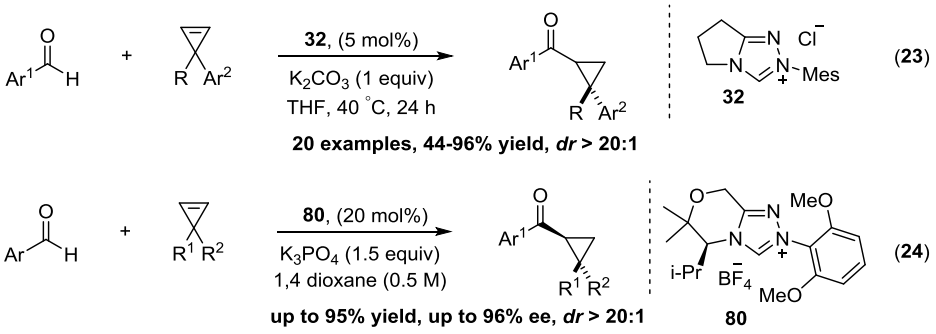
Subsequently, Glorius research group in 2009 developed NHC-mediated intramolecular hydroacylation transformation of unactivated alkenes. In this, the intramolecular cyclization of 2-allyloxy benzaldehydes catalyzed by thiazolium salt **30** furnished desired chromanones in good yields (Scheme 1.38, Eq. 22).[34b] This unique strategy represents the first NHC-organocatalyzed transition-metal-free intramolecular hydroacylation transformation and was also applied to a wide variety of substrates. Furthermore, they uses this approach to synthsize enantioselective chromanones containing all-carbon quaternary centers using chiral triazolium catalyst **77** to access desired product in excellent enantioselectivity (Scheme 1.38, Eq. 23).[34c] Various electronically different 2-allyloxy benzaldehyde derivatives were well tolerated in this reaction.



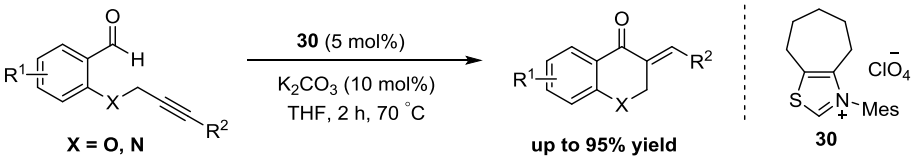

**Scheme 1.38** Hydroacylation reaction of unactivated double bonds catalyzed by NHC

Moreover, Glorius et al. disclosed the first intermolecular hydroacylation transformation of unactivated double bonds. The reaction of aromatic aldehydes and cyclopropenes employing triazolium catalyst **32** furnished the acyl cyclopropanes in moderate yields with high diastereoselectivity under mild conditions (Scheme 1.39, Eq. 23).[35a] Importantly, mechanistic experiments conclude that reaction proceeds through a concerted syn hydroacylation mechanism. Subsequently, they demonstrated the enantioselective intermolecular hydroacylation of cyclopropenes employing electron-affluent chiral triazolium salts **80** possessing substitution at *ortho, ortho'*-postion to deliver the desired acyl cyclopropanes in good yields and enantioselectivity (Scheme 1.39, Eq. 24).[35b]

In 2010, the Glorius group disclosed the intramolecular hydroacylation reaction of unactivated triple bonds. The carbene formed by thiazolium salt **30** catalyzed the reaction of unactivated internal alkynes to afford benzylidene chromanones as a single isomer, which possess synthetically relevant exocyclic olefin group (Scheme 1.40).[36a] Various substrates with electron-donating and-departing groups on both aryl bands were appropriate, providing good yields and also this methodology was further applied to access quinolin-4-ones.

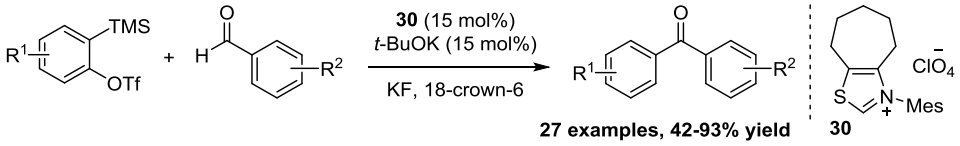



**Scheme 1.39** Hydroacylation of cyclopropenes catalyzed by NHC




**Scheme 1.40** NHC-catalyzed hydroacylation of unactivated internal alkynes

Recently, Biju and Glorius reported a transition-metal-free methodology catalyzed by NHC for intermolecular hydroacylation of arynes. This reaction confess the unusual resistance of nucleophilic carbenes with highly electrophilic arynes. The treatment of various aldehydes with *in situ* generated aryne from 2-trimethylsilylaryl triflate in presence of carbene formed by deprotonation of thiazolium salt **30** using potassium *tert*-butoxide provided numerous aryl ketones in valuable yields (Scheme 1.41).[36b]




**Scheme 1.41** NHC-mediated hydroacylation of arynes

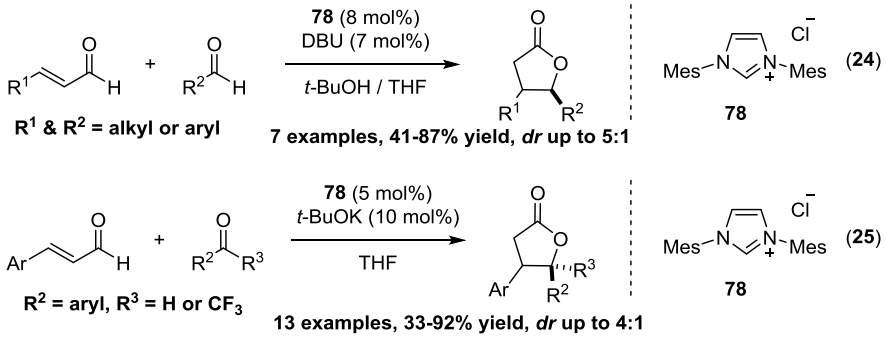
### 1.5.2 Reaction involving NHC-Bound Homoenolate Intermediate

The areas of NHC-organocatalysis remain limited with the Breslow intermediate based reactivity for a very long duration (1943-2004). However, this development has started

to attract more attention of researchers to investigate the various other modes of reactivity by developing new catalyst. Accordingly, the extended Breslow intermediate known as homoenolate intermediate can be generated by employing the α,β-unsaturated aldehydes. Herein, we will focus on the NHC-Bound homoenolate intermediate which considered as a $d^3$-nucleophile and thus constitutes an $a^3$-$d^3$ coupling.

**(a) Functionalization of Enals via Annulative Process**

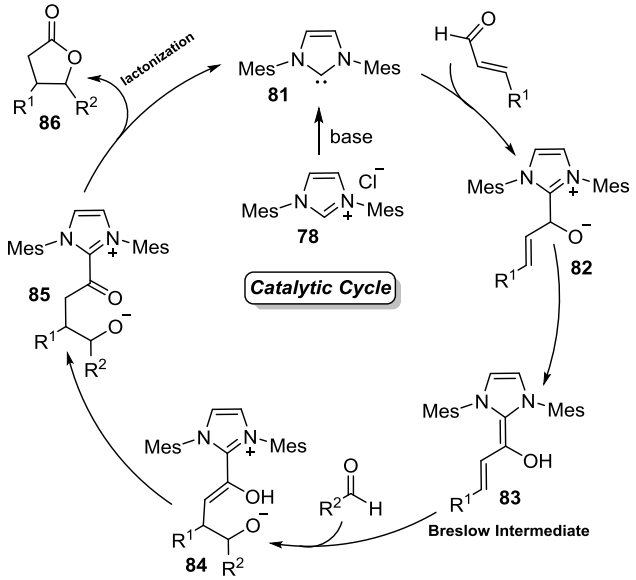
In 2004, the Glorius and the Bode research group independently demonstrated the generation of homoenolate equivalents from α,β-unsaturated aldehydes employing bismesityl imidazolium precatalyst **78**, which further couple with aldehyde leading to the formation of γ-butyrolactones in good yields and diastereoselectivity (Scheme 1.42).[37] Moreover, Glorius research group reported an asymmetric transformation employing trifluoromethyl ketones in place of aldehyde as electrophile.




**Scheme 1.42** Annulation of enals with aldehydes/activated ketones catalyzed by NHC

A plausible mechanistic pathway for this category of conversion is presented in Scheme 1.43. Firstly, the coupling of free carbene and enal in 1,2-fashion generates tetrahedral

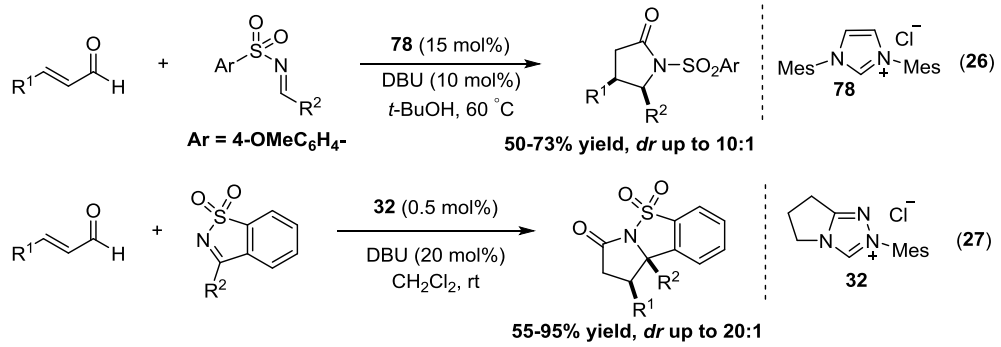
intermediate **82** followed by proton transfer provides conjugated enaminol **83**, usually assigned as homoenolate equivalent. The present $d^3$-nucleophile **83** adds to an electrophile to form the intermediate **84**, which can then tautomerize to give alkoxide intermediate **85** and subsequent intramolecular cyclization provided γ-butyrolactone **86** with regeneration of NHC catalyst.




**Scheme 1.43** Plausible mechanism for γ-butyrolactone synthesis

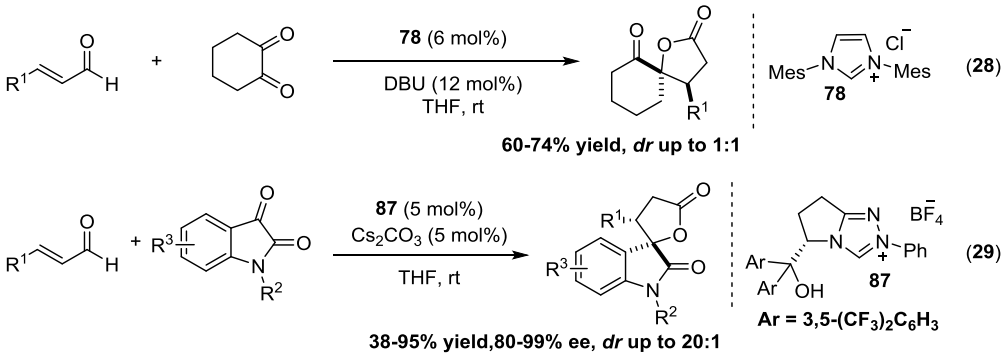
In 2005, Bode and He developed the annulation of enals and N-sulfonyl imines using bismesityl imidazolium precatalyst **78** for the synthesis of γ-lactams in good yields and modest diastereoselectivity (Scheme 1.44, Eq. 26).[38a] A wide range of aromatic enals were tolerated under the reaction condition. However, the variation of imines has limited scope because in several cases the imines underwent irreversible addition to the nucleophilic carbene which leads in cut off the catalytic cycle. Subsequently, they reported the annulation of enals with cyclic sulfonylketimines using catalyst **32** to furnish cis-isomers in quantitative yield with excellent diastereoselectivity (Scheme 1.44, Eq. 27).[38b] The issue associated with irreversible binding of acyclic N-sulfonyl

imines-catalyst was overcome using this cyclic variant. Notably, a wide variety of enals as well as saccharin-derived ketimines were tolerated under the reaction condition.



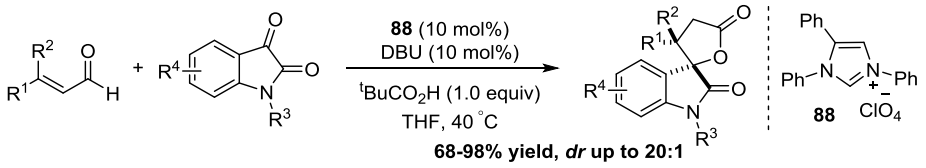

**Scheme 1.44** NHC-catalyzed annulation of enals with imines

In 2006, the Nair research group demonstrated the coupling of homoenolate equivalent generated from enals and 1,2-dicarbonyl to produce spiro γ-lactones in the presence of 1,3-dimesitylimidazol-2-ylidene precatalyst **78**. Notably, 1,2-cyclohexanedione furnished the spirocyclohexanone products in moderate yields with low diastereoselectivity (1:1) (Scheme 1.45, Eq. 28).[39a] In related context, Ye research group developed enantioselective annulation transformation between enals and isatins to afford enantioriched spirooxindole γ-lactone using chiral triazolium precatalyst **87**. The key for excellent diastereo and enantio-selectivity in most cases is the hydrogen-bonding interaction of NHC with the isatins (Scheme 1.45, Eq. 29).[39b]



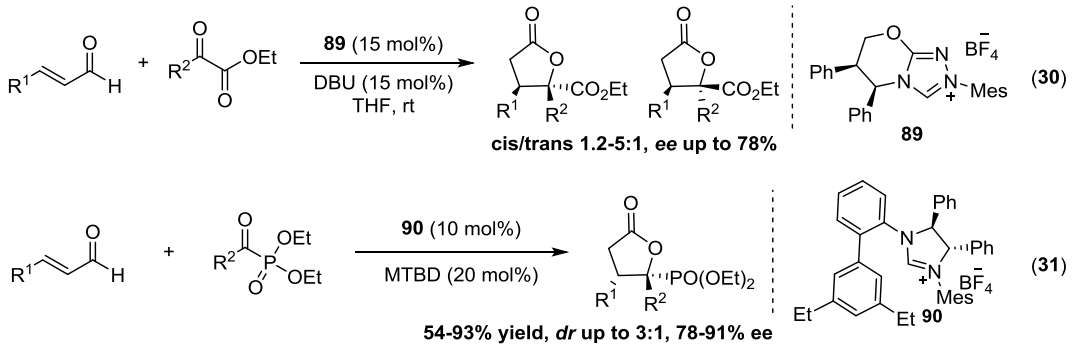

**Scheme 1.45** Annulation of enals with activated ketones catalyzed by NHC

Recently, the Glorius research group developed a dual NHC/ Brønstead acid catalyzed annulation reaction between β,β-disubstituted enals and isatins to produce spirocyclic lactones (Scheme 1.46).[39c] A wide range of aryl and aliphatic substituted enals along with different substitution patterns on isatin moiety were tolerated under the reaction condition. Gratifyingly, the use of Brønstead acid in this transformation increase yield as well as diastereoselectivity.



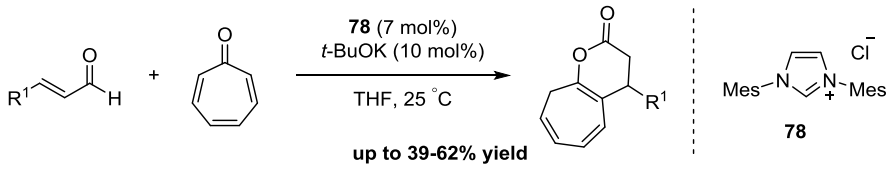

**Scheme 1.46** NHC-catalyzed transformation of β,β-disubstituted enals and isatins

In 2008, You and co-workers exposed that ethyl glyoxalate derivatives with *in situ* generated homoenolate equivalent undergoes annulation transformation using chiral triazolium precatalyst **89** to furnish the γ-lactones in good enantioselectivity for the trans isomer (Scheme 1.47, Eq. 30).[40a] Moreover, Scheidt and colleagues developed an enantioselective homoenolate annulation between enals and acyl phosphonates using chiral imidazolidinium precatalyst **90** to generate γ-lactone in good yields and enantioselectivity (Scheme 1.47, Eq. 31).[40b]




**Scheme 1.47** NHC-catalyzed annulation of β,β-disubstituted enals with isatins

Moreover, Nair and co-workers reported [8+3] annulation between enals and tropone catalyzed by NHC to furnished fused δ-lactone in good yields (Scheme 1.48).[41a] Mechanistically, the transformation advanced by conjugate addition of generated homoenolate equivalent from enals to tropone at more electrophilic position resulting the generation of alkoxide which then undergoes cyclization to furnish the desired product.

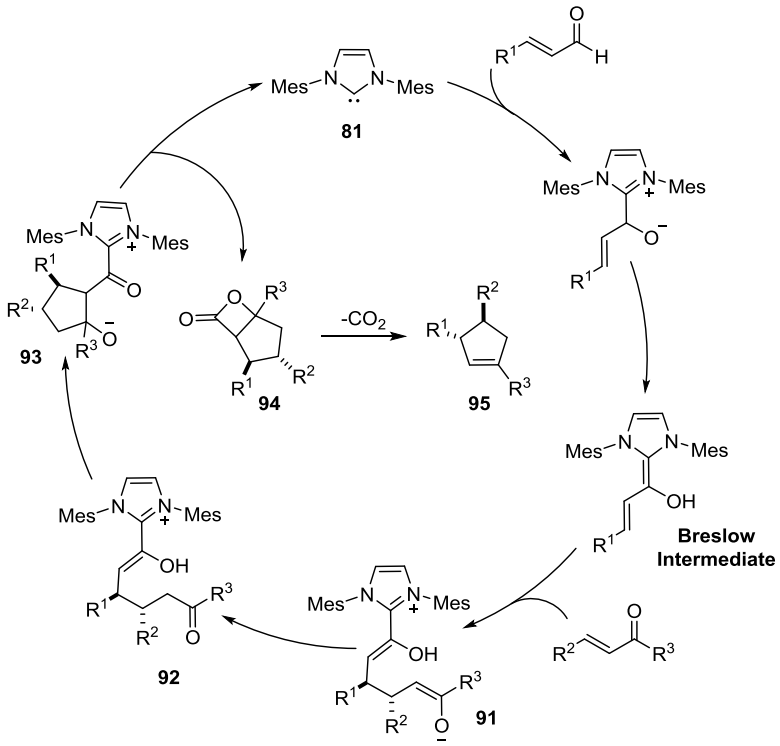



**Scheme 1.48** NHC-mediated transformation of enals with tropone

Apart from heterocycle synthesis, the carbocycles were also synthesized using homoenolate equivalent formed by NHC. In this context, Nair and colleagues in 2006 reported the annulation of enals and chalcones to provide 1,3,4-trisubstituted cyclopentenes (Scheme 1.49).[41b] The transformation concludes in the successful synthesis of cyclopentenes rather than desired cyclopentanones.

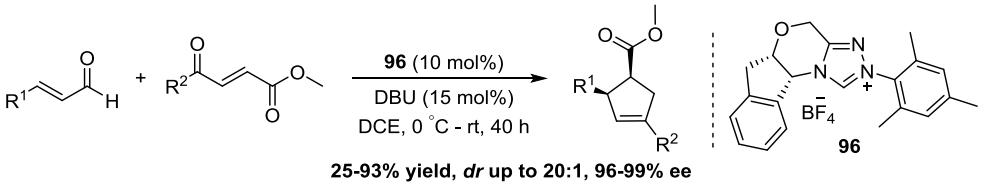
A plausible mechanism suggested that reaction initiates with 1,2-addition of NHC to *trans*-cinnamaldehyde gives rise to the extended Breslow intermediate and subsequent 1,4-addition to chalcone provides the enolate intermediate **91**, which further tautomerize to give ketone **92**. This **92** inttermediate underwent an intramolecular aldol reaction by enol-azolium to produce alkoxide **93**, followed by cyclization of **93** with release of catalyst to give β-lactone **94**, which further decarboxylates to produce the desired cyclopentene product **95** (Scheme 1.50).


**Scheme 1.49** NHC-catalyzed annulation of enals with chalcones



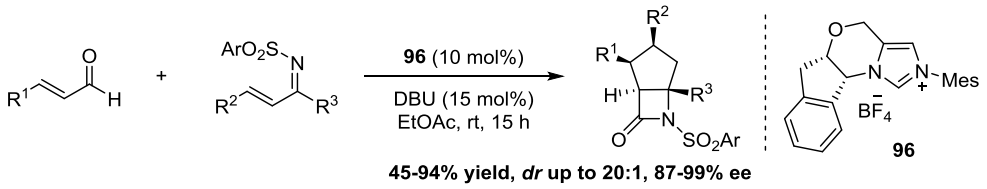

**Scheme 1.50** Plausible mechanism for cyclopentene production

Subsequently, Bode research group developed the enantioselective synthesis of cyclopentenes from enals and 4-oxoenoates using the chiral aminoindanol based triazolium precatalyst **96** (Scheme 1.51).[42a] The transformation furnished the desired product in excellent enantio- and diastereo-selectivity. Importantly, this approach provides cis-isomer in contrast with Nair's approach, which give trans-isomer.



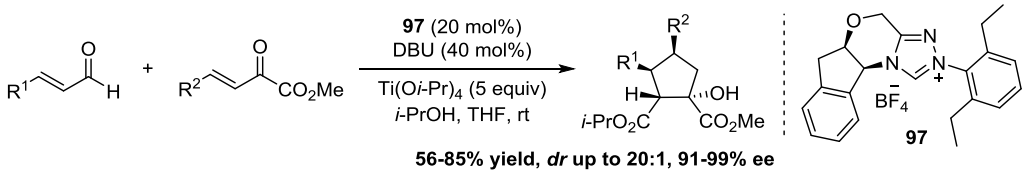

**Scheme 1.51** Annulation of enals and 4-oxoenoates catalyzed by NHC

In 2008, He and Bode demonstrated the conjugate addition of homoenolate to α,β-unsaturated ketimines to access cyclopentane merged β-lactam in high yields and enantioselectivity, and good to excellent diastereoselectivity (Scheme 1.52).[42b] This transformation is noteworthy as it favours the strained β-lactam evolution, in contrast to the chalcone system (Scheme 1.49), which generate the cyclopentenes by decarboxylation. Importantly, a wide variety of enals as well as imines were tolerated under the reaction condition.




**Scheme 1.52** NHC-mediated annulation of enals and ketimines

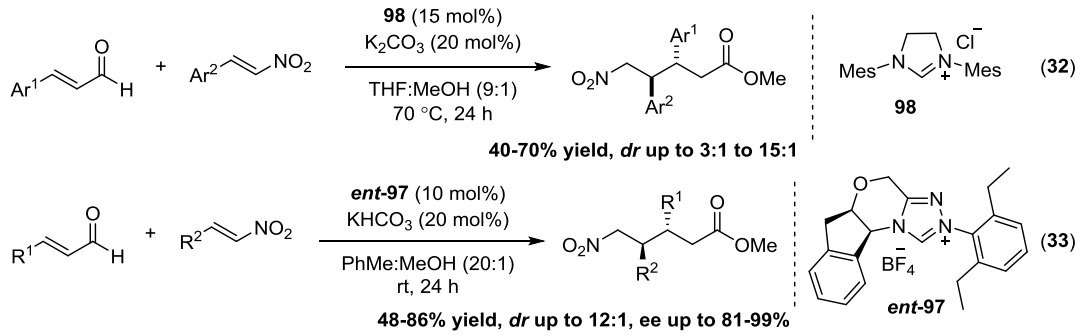
Scheidt et al. in 2011 developed a NHC/Lewis acid catalyzed transformation between enals and α-keto β,γ-unsaturated esters to form highly enantio- and diastereo-selective cyclopentane derivatives in good yields (Scheme 1.53).[42c] In this process linear ester was not formed. Importantly, the enals with alkyl and aryl substitution were well tolerated under the reaction condition but requires the use of aryl esters.




**Scheme 1.53** Annulation of enals and α-keto β,γ-unsaturated esters catalyzed by NHC

**(b) Functionalization of Enals via Non-Annulative Process**

In 2009, Nair and colleagues developed the NHC-mediated homoenolate addition to nitroalkenes to give δ-nitro esters in good yields with moderate diastereoselectivity (Scheme 1.54, Eq. 32).[43a] A wide range of aryl enals as well as nitrostyrene derivatives were well tolerated in the reaction. Moreover, Liu and co-worker exposed the enantioselective homoenolate attachment of enals with nitroalkene using chiral NHC precatalyst ***ent*-97** to furnished desired δ-nitro ester in reasonable yields and enantioselectivity, with moderate to good diastereoselectivity (Scheme 1.54, Eq. 33).[43b] A wide spectrum of aliphatic and aryl enals along with various nitrostyrene analogues, including nitro dienes and nitro enynes worked well in this reaction.

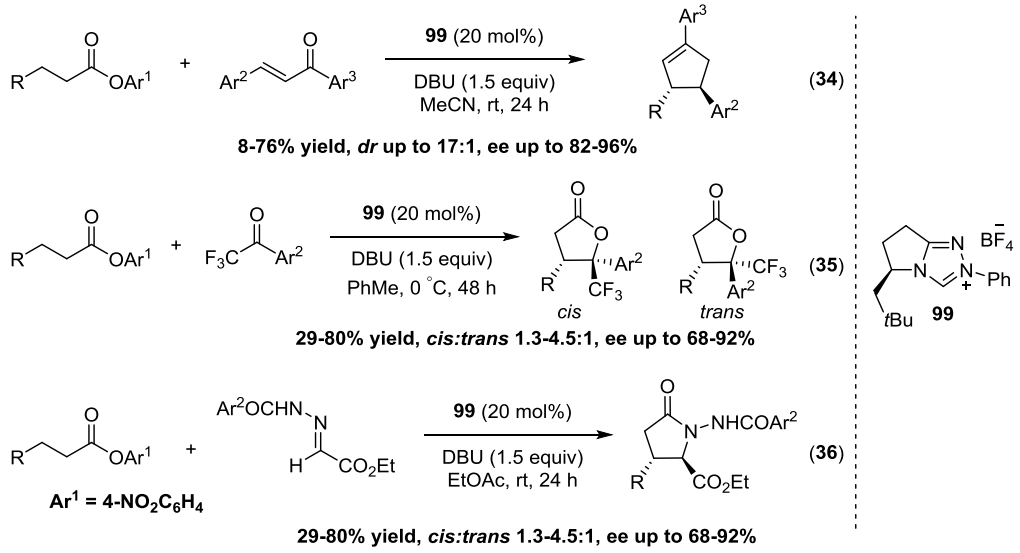



**Scheme 1.54** NHC-catalyzed access to δ-nitro esters

**(c) Alternate Access to Homoenolate Intermediate**

Chi and colleagues in 2013 disclosed that NHC-bound homoenolate intermediate can be generated form substrates other than enals, by employing an efficient bench-stable saturated esters via deprotonation at the $sp^3$ β-carbon (Scheme 1.55, Eq. 34).[44] This reaction affords the desired cyclopentene product in favorable yields and diastereoselectivity, with superb enantioselectivity. As homoenolate precursor, various aryl and aliphatic esters were used and bis-aryl enones were employed as Michael

acceptor. In addition, this homoenolate intermediate has been shown to annulate more electrophiles like trifluoromethyl ketones and hydrazones to furnished enantioenriched γ-lactones and γ-lactams respectively in valuable yields and diastereoselectivity (Scheme 1.55, Eq. 35 and 36).[44] This breakthrough is marked as it functionalizes a typically unreactive β-carbon of saturated ester and thus broadens the scope of NHC-mediated transformations to a field that is commonly associated with metal-mediated C-H activation.




**Scheme 1.55** NHC-catalyzed β-activation of saturated esters

### 1.5.3 Reaction involving NHC-Bound Enolate Intermediate

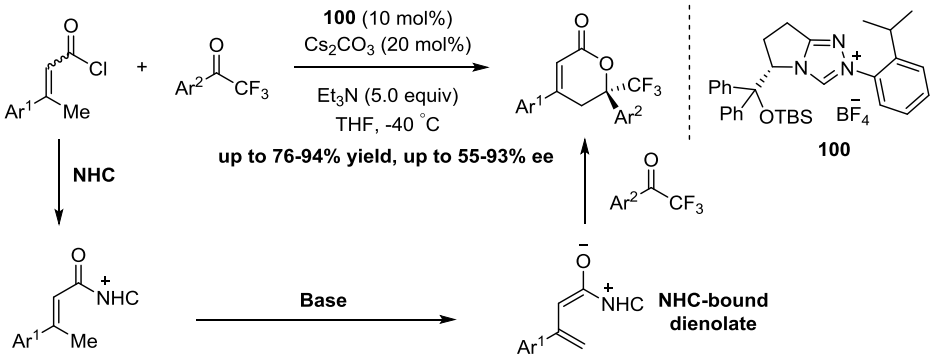
NHC-catalyzed generation and related chemistry of enolate intermediate is disclosed in details in Chapter 2.

### 1.5.4 Reactions involving NHC under Oxidative Conditions

NHC-catalyzed generation of reactive intermediates under oxidative condition and their subsequent reactivity is demonstrated in details in Chapter 3.

### 1.5.5 Reactions involving NHC-Bound Azolium Dienolates

A recent breakthrough in NHC-organocatalysis is the NHC-bound dienolates, which engage in systematic [4+2] cycloaddition transformation by the activation of remote C($sp^3$)-H bond to access six membered heterocycles and carbocycles. In 2011, the Ye research group demonstrated the initial access to catalytically produced NHC-bound dienolates from α,β-unsaturated acyl chlorides, followed by interception with trifluoromethyl ketones to furnish the enantioenriched trifluoromethyl substituted δ-lactones in good yields with excellent enantioselectivity (Scheme 1.56).[45a]

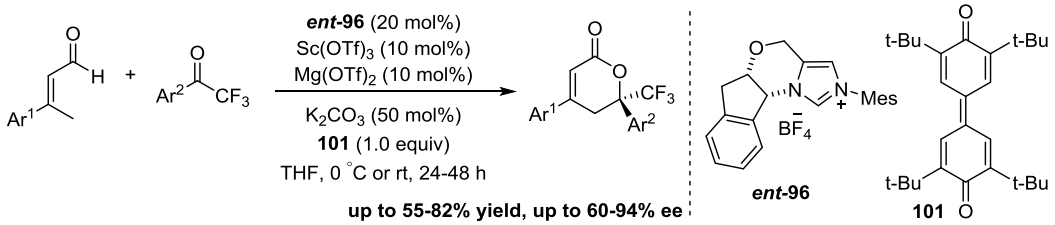



**Scheme 1.56** Generation of NHC-bound dienolate from unsaturated acylchlorides

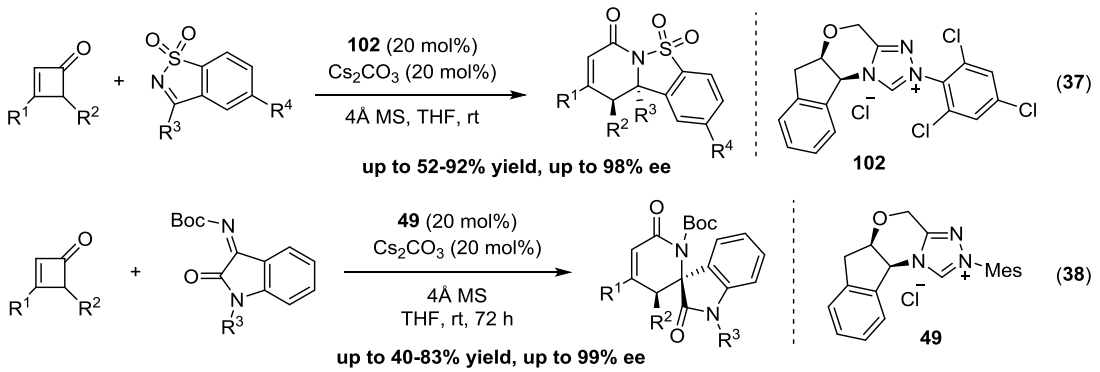
The reaction provide best results with carbene generated from bicyclic triazolium precatalyst **100**, cocatalytic amounts of $Cs_2CO_3$ in excess $Et_3N$. In addition, the other activated ketones such as isatins were also found to be suitable under the optimized condition for the enantioselective synthesis of spirocyclic oxindole-δ-lactones.

In 2012, Chi and co-workers developed the NHC-mediated [4+2] cycloaddition reaction between β,β′-disubstituted enals and trifluoromethyl ketones through NHC-bound dienolate intermediate employing external oxidant **101** (Scheme 1.57).[45b] Importantly, the generally observed homoenolate reactivity in typical NHC-mediated enal reactions

was squashed by inclusion of an additional group at β-carbon of enal. The variation of both the enals and trifluoromethyl ketones worked well under the optimized condition to furnish corresponding desired lactones in positive yields with excellent enantioselectivity. In addition, very high enantioselectivity was obtained with the carbene generated from the chiral triazolium salt ***ent*-96** in combination with Sc/Mg-derived Lewis acid co-catalyst.




**Scheme 1.57** Generation of NHC-bound dienolate from unsaturated aldehyde



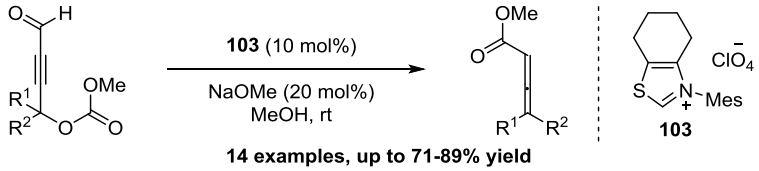

**Scheme 1.58** Generation of NHC-bound dienolate from cyclobutenones

In 2015, the same research group extended the scope to generate NHC-bound dienolate by the use of cyclobutenones (Scheme 1.58).[46] The addition of free carbene generated from the triazolium precatalyst **102/49** to cyclobutenones leads to the formation of NHC-bound dienolate intermediate through a C-C single bond cleavage. This dienolate intermediate further intercept with sulfonyl imines to furnish cyclic lactams in good yields and enantioselectivity (Eq. 37). In addition, the other imines such as isatin imines

were also favorable under the same optimized condition to afford spirolactams in satisfactory yields with superb enantioselectivity (Eq. 38).

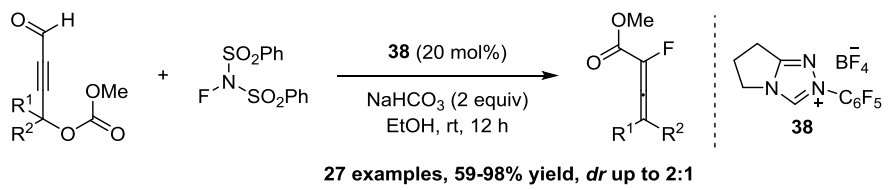
### 1.5.6 Reactions involving NHC-Bound Allenoate Intermediate

In 2012, Sun and colleagues exposed a breakthrough by NHC-mediated internal redox reaction with the isomerization of ynals to allenoates (Scheme 1.59).[47a] Alkynyl aldehydes possessing methyl carbonate at γ-position as a leaving substituent are used as the substrates in the presence of mesityl-substituted thiazolium salt **103** for excellent reactivity. Notably, the variation of alkyl and aryl substituents at the position of $R^1$ and $R^2$ worked well under the optimized condition and provided corresponding allenoates in acceptable yields.



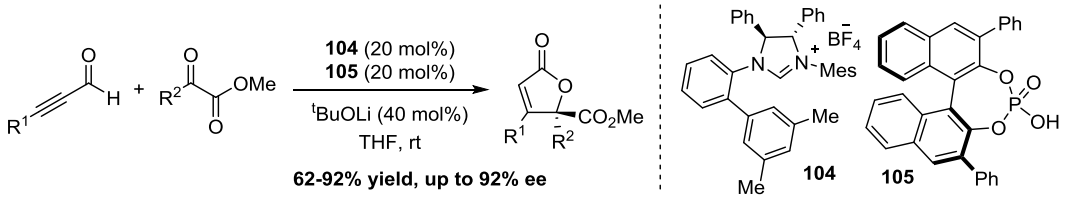

**Scheme 1.59** Generation of NHC-bound allenoates from ynals

Recently, Wang and colleagues developed the NHC-catalyzed synthesis of α-fluoroallenoate by using alkynyl aldehydes as the substrates in the presence of NFSI as a fluorinating source (Scheme 1.60).[47b] The authors proposed that reaction proceeds through a similar cumulenol intermediate, which instead of tautomerization endure nucleophilic addition to NFSI and provides product in pleasant yields with tremendous chemoselectivity.




**Scheme 1.60** NHC-catalyzed α-fluorination of alkynyl aldehydes

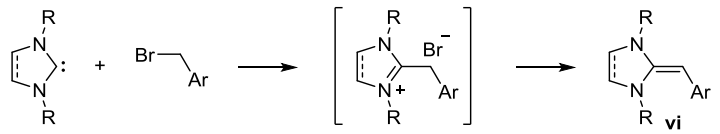
In 2014, Scheidt and co-workers demonstrated a cooperative NHC/Lewis acid mediated enantioselective [3+2] annulation between ynals and α-keto esters to afford γ-butenolides in good to high yields with excellent enantioselectivity (Scheme 1.61).[47c] The reaction afforded best enantioselectivity in the combination of C1-symmetric imidazolidinium precatalyst **104** with C2-symmetric Brønsted acid **105**. A variety of electron-deficient as well as electron-rich aromatic ynals and α-keto esters were tolerated under the reaction condition.




**Scheme 1.61** Synthesis of γ-butenolides catalyzed by cooperative NHC/Chiral Phosphate

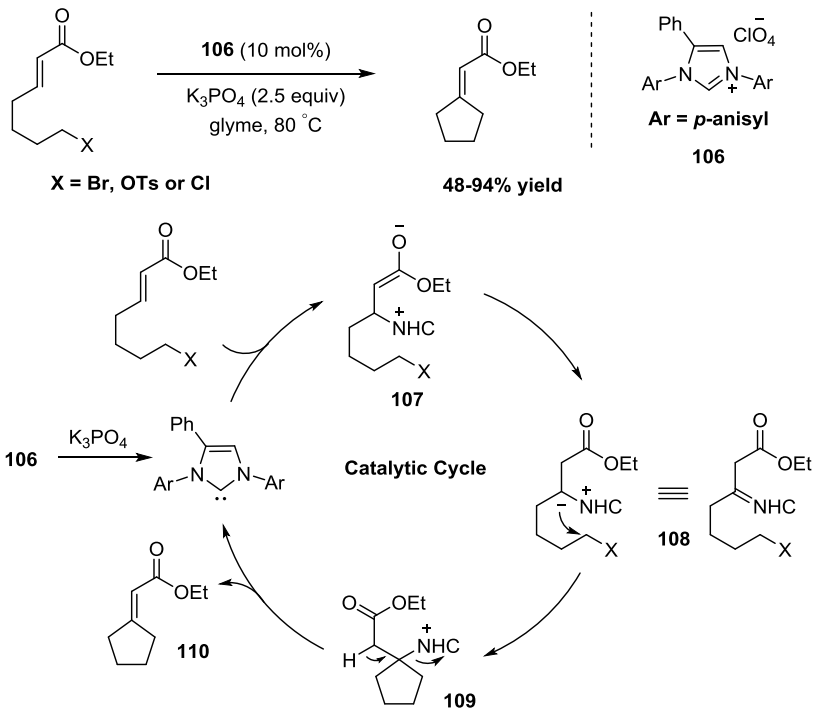
### 1.5.7 Reactions involving NHC-Bound *Deoxy*-Breslow Intermediate

The *umpolung* driven by NHCs is mostly restricted to aldehydes, and the use of other electrophiles has been given minimal attention. In this context, the group of Jacobi von Wangelin reported the isolation of *Deoxy*-Breslow intermediate **vi** through the umpolung of alkyl halides (Scheme 1.62).[48a] Furthermore, Mayr and colleagues performed kinetic measurements to investigate the nucleophilic reactivities of these *deoxy*-Breslow intermediates[48b].




**Scheme 1.62** Generation of *deoxy*-Breslow intermediate by *umpolung* of alkyl halides

In 2006, Fu et al. developed the *umpolung* of Michael acceptors employing NHCs for the intramolecular β-alkylation of α,β-unsaturated esters to afford cyclopentenes (Scheme 1.63).[49a]

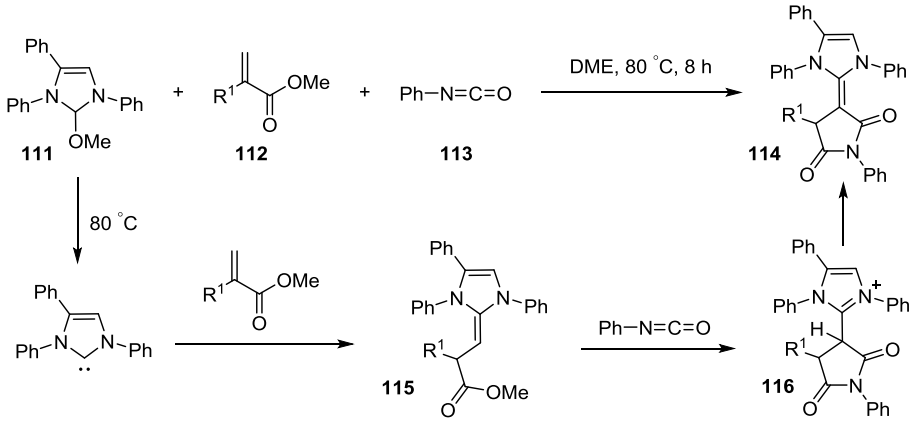



**Scheme 1.63** β-alkylation of α,β-unsaturated esters by *umpolung* of Michael acceptors

It was proposed that transformation advanced with the formation of formal *deoxy*-Breslow intermediate **108** from enolate **107**, which converts the electrophilic β-carbon to nucleophilic and subsequent cyclisation furnished the desired product. This transformation can be regarded as a NHC-catalyzed intramolecular Heck reaction. A variety of Michael acceptors like α,β-unsaturated esters, amides and nitriles worked well in the reaction condition.

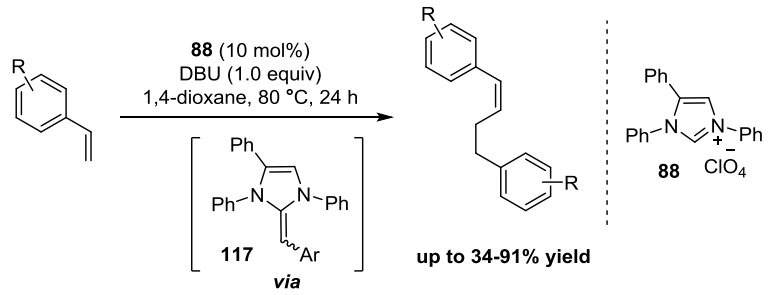
In 2012, Matsuoka et al. reported a tandem one pot three component reaction. The reaction was proceeded with the generation of *deoxy*-Breslow intermediate **115**, by the

addition of NHC to methacrylates **112**, which then undergo annulation with isocyanates **113** to afford urea derivatives **114** in good yields (Scheme 1.64).[49b]




**Scheme 1.64** Multicomponent reaction by *umpolung*/Cyclization cascade

In 2014, the Glorius research group reported the NHC-mediated tail to tail dimerization of activated styrenes in selective manner (Scheme 1.65).[49c]

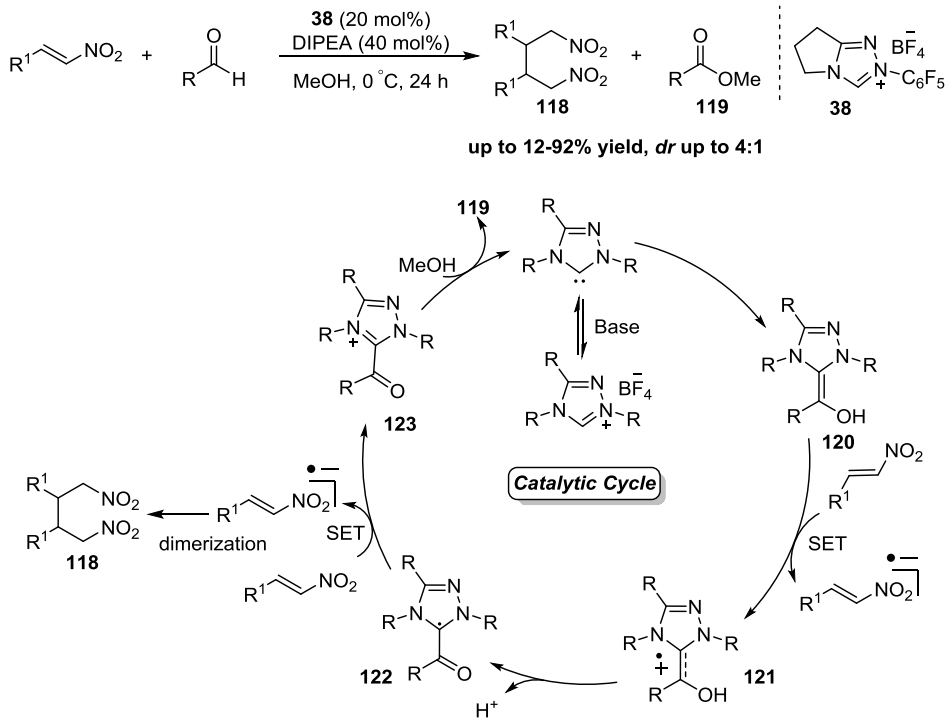



**Scheme 1.65** NHC-catalyzed *umpolung* of styrenes

It was proposed that this protocol proceeds via *deoxy*-Breslow intermediate **117**, which was isolated and characterized successfully. Styrenes bearing electron withdrawing substituent at the *para*-position of the aromatic ring and vinyl pyridines were tolerated under the optimized condition to afford the desired product.

### 1.5.8 Reactions involving Single Electron Transfer Pathways

In 2014, Chi and colleagues reported a NHC-mediated single electron methodology for dimerization of nitroalkenes (Scheme 1.66).[50a]

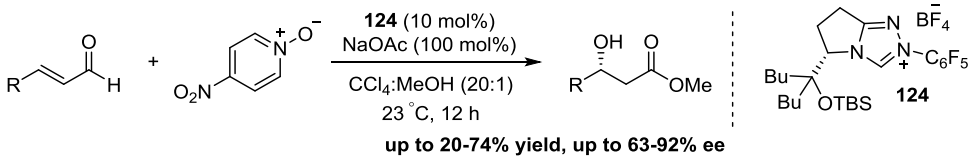



**Scheme 1.66** NHC-catalyzed dimerization of nitroalkenes by single electron transfer pathway

In this reaction the nitroalkene serves as single-electron oxidant and produce radical anion with the Breslow centered radical cation **121**, which then undergoes a deprotonation to give radical acylazolium intermediate **122**, and subsequent release of another single electron in the presence of nitro olefin to generate the acyl azolium intermediate **123**. The radical anion derived from nitroalkene couples with previously formed similar another radical anion and furnished the desired product **118**. The nucleophilic addition of methoxide ion to acylazolium provides ester product **119** with the release of carbene catalyst. Importantly, this proposed pathway is assisted by nitroalkene based radical anion EPR study. A variety of aryl or aliphatic nitroalkenes

with electronically different substitution were well tolerated under optimized condition to afford the dimerized product in moderate to good yields and diastereoselectivity. Interestingly, β,β-disubstituted nitroalkenes were also suitable in this protocol. The aromatic aldehydes were needed as an electron donor in this transformation.

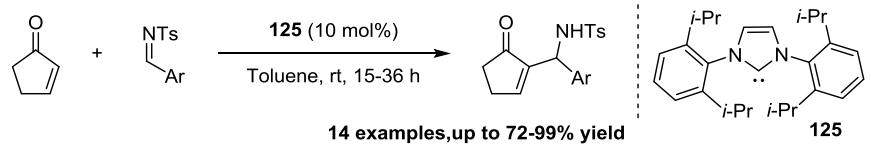
Moreover, White et al. reported β-hydroxylation of enals by single-electron oxidation of Breslow intermediate with the existence of electron deficient nitroarene as the oxidant (Scheme 1.67).[50b] It was found that aromatic and aliphatic enals were suitable to furnish β-hydroxylated products in valuable yields with good enantioselectivity.




**Scheme 1.67** NHC-catalyzed single electron transfer reaction for β-hydroxylation of enals

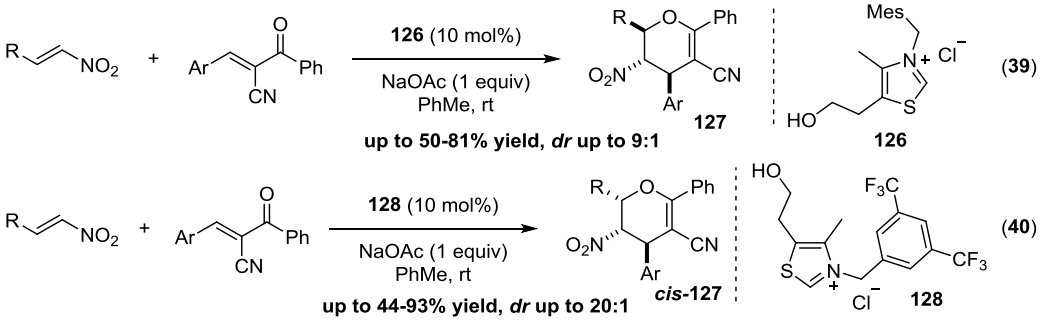
### 1.5.9 Miscellaneous Reactions

In 2007, Ye and colleagues exposed the use of NHCs as a Lewis base to develop the Morita-Baylis-Hillman (MBH) type reaction (Scheme 1.68).[51a] They reported the intermolecular coupling of cyclic enones and N-tosyl aromatic imines using NHC **125** to give the corresponding MBH adduct in good to high yields. In addition, the enantioselective variant was also disclosed, which involve the coupling of cyclopent-2-enone and N-tosylphenylmethanimine to furnish the desired MBH adduct in up to 44% enantioselectivity[51b].



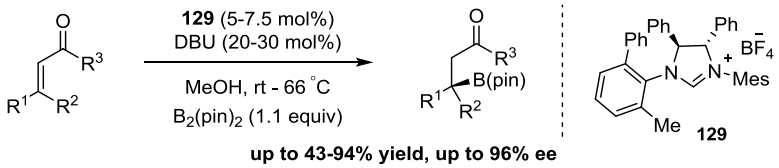

**Scheme 1.68** Morita-Baylis-Hillman transformation catalyzed by NHC

Furthermore, Ye research group in 2013 developed a [4+2] annulation between nitroalkenes and α,β-unsaturated ketone (Scheme 1.69).[52] Mechanistically, the reaction was proceeded through Rauhut-Currier type mechanism, which involve 1,4-addition of nitroalkene-carbene adduct to enone, and subsequent rearrangement of the alkyl azolium by oxygen of the enolate intermediate deliver the desired product. Notably, the use of DABCO or $PPh_3$ instead of catalyst **126** produced only the trace amount of the desired product. In addition, the switch in diastereoselectivity was observed by changing N-substituent of thiazolium salt. The formation of 2,3-trans product **127** is favored in the presence of 2,4,6-trimethylphenyl precatalyst **126** (Eq. 39), whereas electron-deficient 3,5-bis(trifluoromethyl)-phenylthiazolium **128** gives 2,3-cis product selectively (Eq. 40).



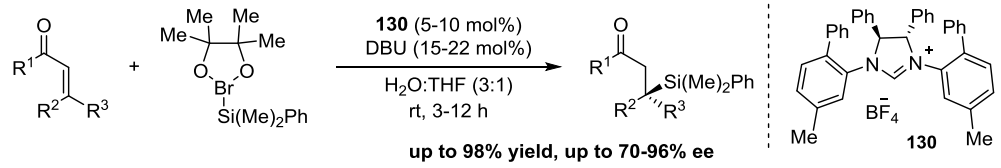

**Scheme 1.69** NHC-mediated [4+2] transformation of nitroalkenes and oxodienes

In 2009, the Hoveyda research group developed the NHC-mediated conjugate addition of boranes to enones to give the β-boronsubstituted ketones[53a]. Numerous Michael acceptors such as enones, enals, enolates and α,β-unsaturated amides were endured in this transformation. Later, they in 2012 developed enantioselective variant of NHC-mediated conjugate borylation using chiral imidazolium precatalyst **129**. This protocol furnished the desire product in admirable yields and enantioselectivity (Scheme 1.70).[53b]




**Scheme 1.70** NHC-mediated conjugate coupling of boranes and enones

In 2011, O'Brien and Hoveyda reported the NHC-catalyzed enantioselective conjugate coupling of silicon and Michael acceptor in a similar fashion to NHC-mediated boron addition. It was believed that the reaction proceeds through the activation of dimethylphenylsilylpinacolatoboron by an NHC catalyst due to high Lewis acidity of boron and thus silicon transfer selectively at β-position of a Michael acceptor (Scheme 1.71).[54] A wide diversity of cyclic enones, acyclic α,β-substituted ketones, lactones, esters and aldehydes worked well as reactants in this protocol to produce β-silylated products in high yields and enantioselectivity. Importantly, the tolerance of enals in this transformation indicates that NHC-catalyst binds exclusively to the complex of silicon-boron instead of aldehyde, resulting to provide products emerging from sense of Breslow intermediate.




**Scheme 1.71** NHC-mediated conjugate attachment of silicones to enones

## 1.6 Conclusion and Central Theme of the Present Work

This chapter has illustrated the various important action modes of NHCs and their reactivity in carbon-carbon and carbon-heteroatom bond forming protocols. From the foregoing discussion, it is clear that the NHC-catalyzed umpolung, non-umpolung and

radical reactivity are attributed to proper selection of the NHC catalyst, coupling partners and reaction conditions. The central theme of this thesis is to utilize NHC-catalysis for the development of new synthetic methods, which can result in the construction of various carbocyclic and heterocyclic derivatives.

NHC-mediated formal [4+2] transformation of α-chloroaldehydes and γ-keto sulfones to access 3,6-disubstituted α-pyrones has been described in the second chapter. The NHC-catalyzed generation of enolate intermediate and their reaction with γ-keto sulfones derivatives affords the desired α-pyrone products. Importantly, the newly formed α-pyrone can be readily converted into a series of value-added molecules via Diels-Alder reaction with a variety of aryne precursors.

Moreover, the compatibility for aerobic oxidation to a diverse family of difficult aldehydes for instance aromatic aldehydes with *ortho*-substitution, terribly electron-affluent aromatic aldehydes and indole-3-carboxaldehydes is one of the challenging task under NHC-organnocatalysis. In view of this, a extremely adequate NHC-mediated protocol for oxidation of aldehydes beneath aerobic condition to furnish analogous carboxylic acids has been discussed in the last chapter of the thesis.

## 1.7 References

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# Chapter 2

## *A Facile Access to 3,6-Disubstituted α-Pyrones via Carbene Catalyzed Formal [4+2] Annulation of α-Chloroaldehydes and γ-Keto Sulfones*

## Part A: Introduction to α-pyrone and preparation of starting reagents

### 2.1 Introduction

The pyrones belongs to a family of six-membered unsaturated cyclic compounds bearing an oxygen atom. This class of compounds exist in two forms like α-pyrone **1** and γ-pyrone **2**. It reveals that γ-pyrone **2** is the vinylogous form of α-pyrone **1** which contains a lactonic structure and many of the chemical properties of these nuclei are similar (Figure 2.1).[1]

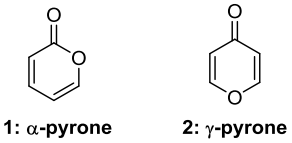



**Figure 2.1** Basic skeleton of pyrones

Importantly, α-pyrones are ubiquitous structural motifs and found in numerous natural products isolated from animals, bacteria, insects, marine organism and plants. They also exhibit interesting biological properties, such as antimicrobial**,** antifungal, enzyme inhibitive, and cytotoxic activities.[2] In this context, nectriapyrone A was isolated from an unidentified fungus acquired from a *Stylotella* sp. Sponge near Taveuni, Fiji by the Crews research group.[3] Moreover, the first metabolite isolated from *Gibberella fujikuroi* furnished gibepyrone A, which exhibit growth inhibitory against *Bacillus subtilis*.[4] Likely, griseulin reveal inhibitory activity against mosquito (*A. eagypti)* and

nematodes (*P. redivivus)* whereas wailupemycins A exhibited inhibitory properties against *E. coli* (Figure 2.2).[5]

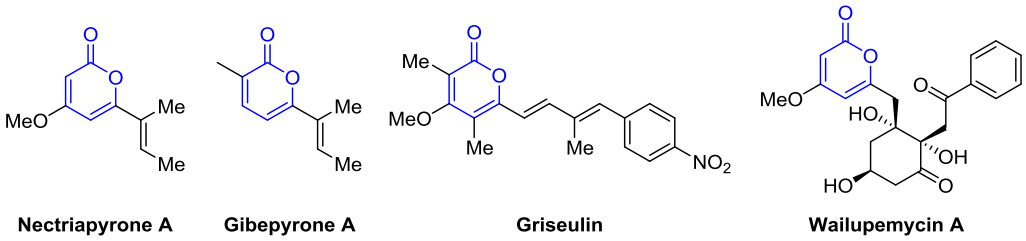



**Figure 2.2** Representative natural products containing α-pyrone motif

Alongside their biological importance, α-pyrone bear multiple reactive sites and can have great utility for the synthesis of sophisticated functional molecules. Importantly, a series of value-added heterocyclic and non-heterocyclic molecules can be accessed starting with simple α-pyrone motif because they show reactivity towards both electrophiles and nucleophiles.[6] In this context, the naturally occurring isocarbostryls such as narciclasine **3**, lycoricidine **4**, and pancratistatin **5** have been isolated from plants of the genus *Amaryllidaceae* and are known to show antiviral and antitumor activities. In addition, *trans*-dihydronarciclasine **6** exhibits two-to ten fold higher potency than pancratistatin against human cancer cell lines and has been isolated from the Chinese medicinal plant *Zephyranthes candida* (Figure 2.3).[7]

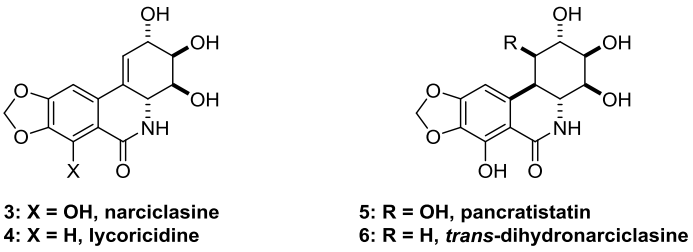


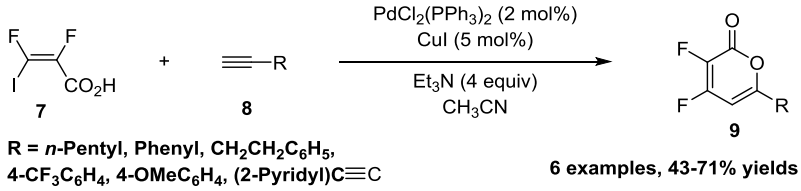

**Figure 2.3** Selected biologically active naturally occurring isocarbostryls

## 2.2 Review of literature

Based on significant importance of α-pyrone as a versatile building block for the construction of various key intermediates in synthetic organic chemistry as well as medicinal chemistry, a novel method affording α-pyrone motif is another synthetic target for an organic chemist. Several synthetic routes to access substituted α-pyrone have been documented in the literature.

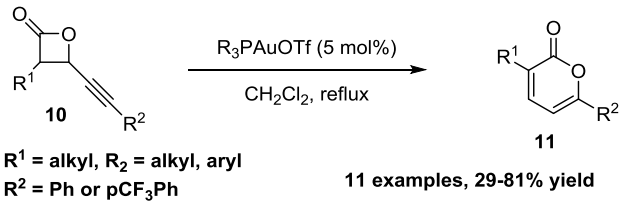
### 2.2.1 General methods for the synthesis of α-pyrone

In 2006, Burton and colleagues demonstrated an efficient protocol for the synthesis of difluorinated α-pyrone employing a Sonogashira alkynylation coupling reaction. This approach involves a reaction of (2E)-2,3-difluorinated-3-iodoacrylic acid **7** and a variety of terminal acetylenes **8** in the presence of $PdCl_2(PPh_3)_2$ in combination with CuI as a co-catalyst to deliver the desired difluorinated α-pyrone **9** in good yields (Scheme 2.1).[8]



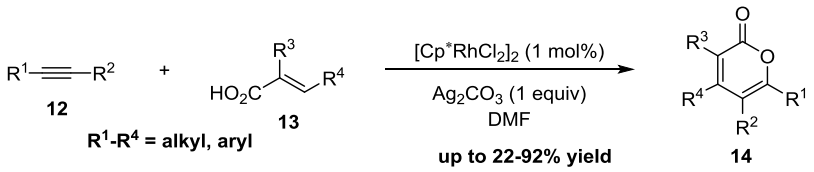

**Scheme 2.1** An approach to difluorinated α-pyrone involving Sonogashira alkynylation

In 2010, the Pale research group reported a two-step procedure to furnish substituted α-pyrones **11** in the presence of gold(1) catalyst through an unprecedented rearrangement of β-alkynylpropiolactones **10**. A wide range of α-pyrone **11** was obtained in two steps with good to high yields (Scheme 2.2).[9]



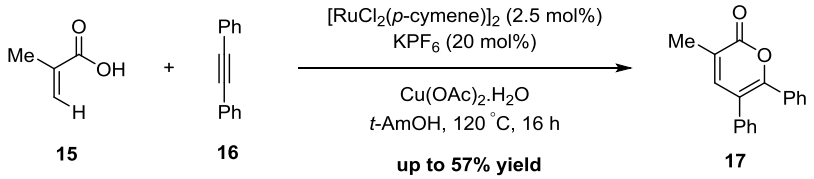

**Scheme 2.2** Gold-catalyzed rearrangement of β-alkynylpropiolactones to access α-pyrone

Moreover, Miura et al. developed a competent construction of α-pyrones **14** using rhodium-catalyzed oxidative coupling of acrylic acids **13** with alkynes **12** in 2009 (Scheme 2.3).[10] This catalytic protocol is also relevant to the coupling with alkenes and 1,3-diynes affording the desired α-pyrones **14** through vinylic C-H bond cleavage of acrylic acids.




**Scheme 2.3** Rhodium-catalyzed oxidative coupling of acrylic acids to access α-pyrone

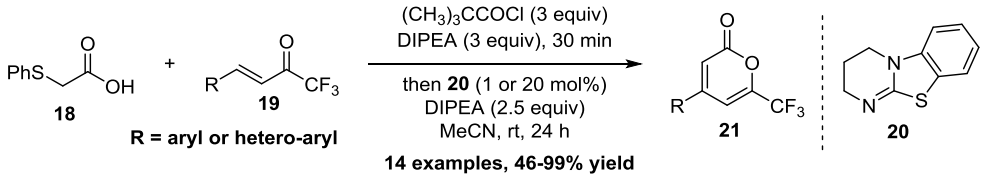
In 2012, Ackerman and colleagues developed a similar cyclization reaction using $[RuCl_2(p\text{-cymene})]_2$ instead of $[Cp^*RhCl_2]_2$. The cationic ruthenium(II) catalyst allowed the direct preparation of α-pyrone **17** in good to high yields through oxidative annulation of alkynes **16** by acrylic acid derivative **15** (Scheme 2.4).[11]




**Scheme 2.4** Ruthenium-catalyzed oxidative annulation of alkynes to access α-pyrone

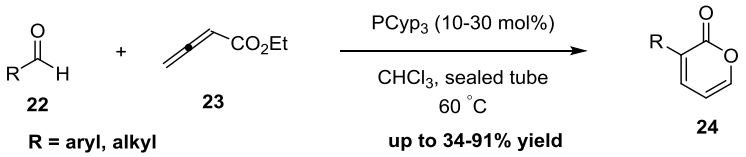
In 2014, Smith and co-workers reported a concise synthesis of di- and trisubstituted α-pyrone **21** from (thiophenyl)acetic acids **18** and α,β-unsaturated trifluoromethyl ketones

**19** through an isothiourea-mediated **20** one-pot Michael addition followed by lactonization and thiol elimination cascade sequence (Scheme 2.5).[12] This approach allows the formation of biologically active compounds in high yields.



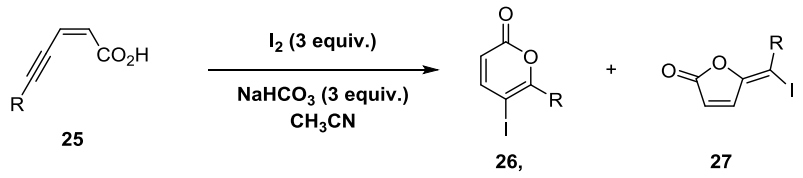

**Scheme 2.5** Isothiourea-catalyzed synthesis of α-pyrone

Moreover, the Kwon research group demonstrated a one-step Phosphine-catalyzed annulation between aldehydes **22** and ethyl allenoate **23** to furnished 6-substituted α-pyrone **24** in moderate to excellent yields (Scheme 2.6).[13] Notably, a variety of aliphatic as well as aromatic aldehydes were well tolerated and delivered the corresponding desired α-pyrone product.



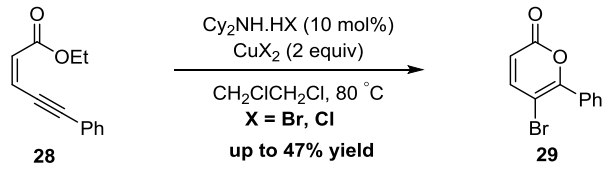

**Scheme 2.6** Phosphine-catalyzed synthesis of 6-substituted α-pyrone

In 2001, Rossi and co-workers demonstrated a Iodolactonization reaction to access α-pyrone even though a selectivity problem is apparent. In this context, the reaction of 5-substituted (Z)-2-en-4-ynoic acids **25** with Iodine and $NaHCO_3$ in $CH_3CN$ or with ICl in $CH_2Cl_2$ provides a mixture of 6-substituted 5-iodo-2(2*H*)-pyranones **26** and (E)-5-(1-iodoylidene)-2(5*H*)-furanones **27** in moderate to good yields, in which the pyranones **26** are the major products (Scheme 2.7).[14]



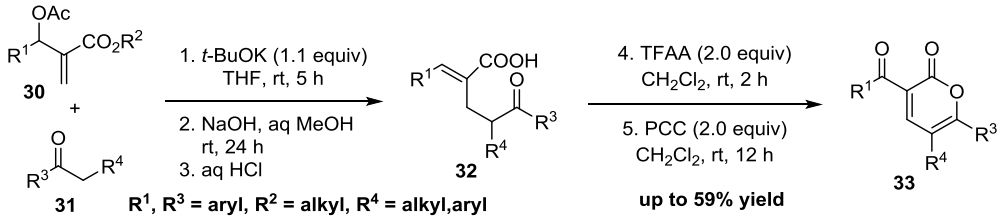

**Scheme 2.7** Iodolactonization strategy for the synthesis of α-pyrone

Furthermore, Li and co-workers developed a $Cy_2NH.HX$ catalytic system to overcome the selectivity problem remaining in the Iodolactonization strategy. The cyclization reaction of (Z)-ethyl 5-phenylpent-2-en-4-ynoate **28** in the presence of $Cy_2NH.HX$ and $CuBr_2$ furnished the desired 5-bromo-α-pyrone **29** in 47% yield (Scheme 2.8).[15] Notably, this approach further extends for various *o*-(alk-1-ynyl)benzoate to furnish the corresponding 4-haloisocoumarins products in good to high yields.



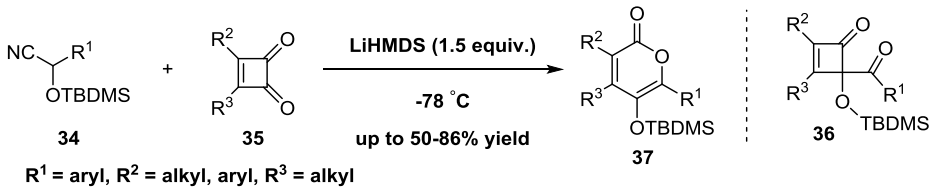

**Scheme 2.8** $Cy_2NH.HX$-catalyzed strategy for the synthesis of α-pyrone

In 2006, Kim and co-workers developed a efficient strategy for the synthesis of 3,5,6-trisubstituted α-pyrone **33** through the sequential introduction of ketone **31** at the primary position of Baylis-Hillman adduct **30** followed by lactonization and the oxidation with PCC (Scheme 2.9).[16]




**Scheme 2.9** Application of Baylis-Hillman reaction for the synthesis of α-pyrone

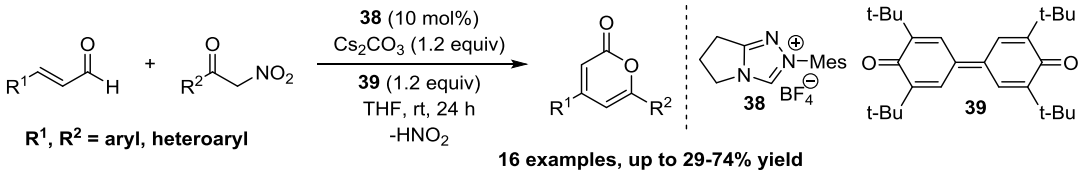
Moreover, Liebeskind and colleagues reported a new approach to deliver highly substituted α-pyrone. The reaction involves the addition of a lithiated *O*-silylated cyanohydrins **34** to a cyclobutenedione **35** followed by intramolecular 1,4-silyl migration and cyanide displacement generates 4-acylcyclobutenone **36**, which undergoes spontaneous ring expansion to furnish desired substituted α-pyrone **37** in good to high yields (Scheme 2.10).[17]




**Scheme 2.10** Application of Baylis-Hillman reaction for the synthesis of α-pyrone

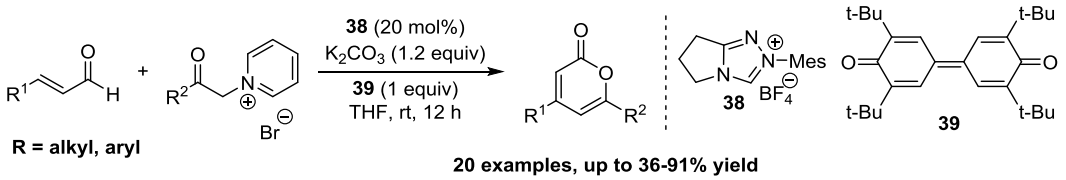
### 2.2.2 NHC-Catalyzed Synthesis of α-Pyrone

Apart from the above discussed methods, the synthesis of 4,6-disubstituted α-pyrone was also reported under the NHC-catalysis. In this context, the Studer research group reported a method for the synthesis of 4,6-disubstituted α-pyrone using aroyl-substituted nitromethanes and enals employing mesityl substituted triazolium precatalyst **38** and bisquinone **39** as an oxidant through Michael addition followed by elimination and lactonization sequence in 2016. Notably, the nitro group in the starting ketone stabilizes the enolate and acts as an ionic leaving group and thus leads to the formation of desired α-pyrone in moderate to good yields (Scheme 2.11).[18a]




**Scheme 2.11** Oxidative NHC-catalyzed synthesis of 4,6-disubstituted α-pyrone using enals and 2-nitroacetophenone

In 2019, the Chi research group demonstrated an NHC-mediated [3+3] cycloaddition transformation of enals with nitrogen ylides applying triazolium precatalyst **38** and bisquinone **39** as an oxidant for the synthesis of 4,6-disubstituted α-pyrone in good to high yields. The prepared 2'-pyridinium acetophenone bromide salts are employed as nitrogen ylide precursors in this approach (Scheme 2.12).[18b]




**Scheme 2.12** Oxidative NHC-catalyzed synthesis of 4,6-disubstituted α-pyrone

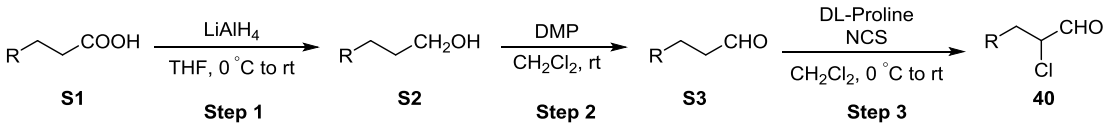
## 2.3 Statement of the Problem

As discussed in the introduction section, several methods have been reported in the literature for the synthesis of substituted α-pyrone. Although, to afford 3,6-disubstituted α-pyrone which are rare, both in nature and synthesis, there is a single gold catalyzed protocol was reported to the best of our knowledge (Scheme 2.2).[9] Therefore, the development of new organocatalytic and operationally simple approach is highly desirable. Notably, in the field of NHC-catalysis both previous approach produce 4,6-disubstituted α-pyrone under oxidative conditions. But, we envisioned the synthesis of 3,6-disubstituted α-pyrone under oxidant free NHC-catalysis. In this context, as per continuation of our ongoing research in territory of *N*-heterocyclic carbene catalysis, herein, we have matured a formal oxidant-free NHC-catalyzed [4+2] annulation between α-chloroaldehydes and γ-ketosulfones. Notably, the reaction proceeds through Michael addition-lactonization-elimination cascade sequence and affords a broad range of 3,6-disubstituted α-pyrone in good to excellent yields.

## 2.4 Preparation of Starting Materials and NHC-Precatalyst

### 2.4.1 Synthesis of α-Chloroaldehydes

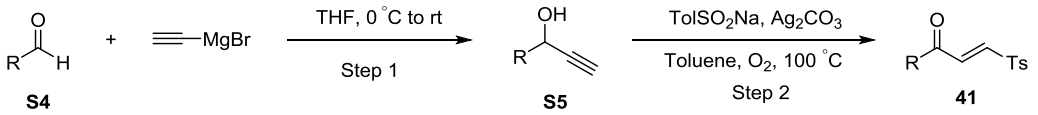
To probe the feasibility of the planed approach, starting substrates α-chloroaldehydes **40** were readily prepared according to the procedure reported previously in the literature.[19] A general route involves the reduction of saturated acid **S1** to corresponding alcohol **S2** using $LiAlH_4$, and subsequent oxidation in presence of Dess-Martin Periodane affords the corresponding aldehydes **S3**. This saturated aldehydes **S3** upon treatment with N-Chlorosuccinimide in presence of DL-Proline as a catalyst furnished the desired α-chloroaldehydes **40** in good yields (Scheme 2.13).




**Scheme 2.13** Synthesis of α-chloroaldehydes

### 2.4.2 Synthesis of γ-Ketosulfones

The starting substrate γ-ketosulfones **41** were readily synthesized following the procedure described previously in the literature.[20] A general approach involves the treatment of the commercially available aldehydes **S4** with ethynlmagnesium bromide for the formation of corresponding propargyl alcohol **S5**. The further reaction of this propargyl alcohol **S5** with sodium sulfinate in presence of silver carbonate as a catalyst provided the desired γ-ketosulfones **41** in good yields (Scheme 2.14).

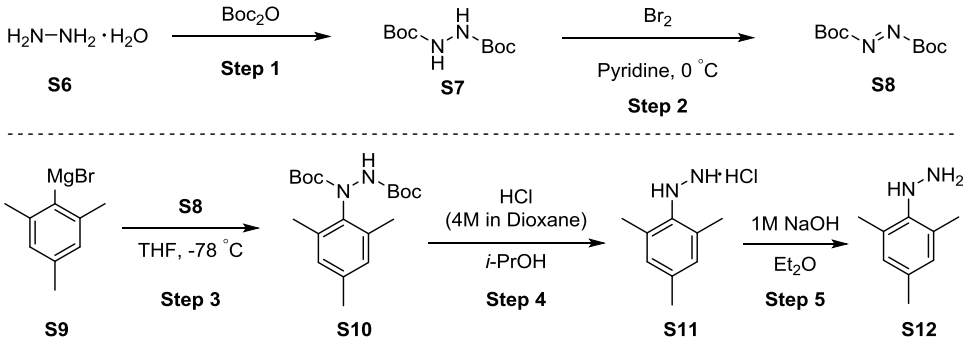



**Scheme 2.14** Synthesis of γ-ketosulfones

### 2.4.3 Synthesis of NHC-Precatalyst

As per our group's ongoing research in space of *N*-heterocyclic carbene catalysis a broad range of NHC-precatalyst have been synthesized by using the literature known protocols. Herein, we describe the synthesis of pyrrolidine based triazolium precatalyst **38** following the procedure reported earlier in the literature.[21]

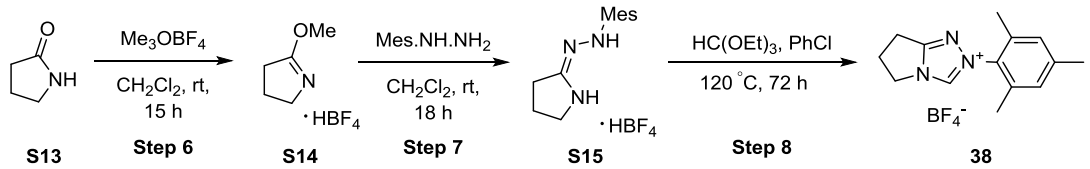
Firstly, this involve the preparation of mesitylhydrazine hydrochloride **S11**, starting from the reaction of hydrazine monohydrate **S6** with di-*tert*-butyl dicarbonate results in the formation of di-tert-butyl hydrazine-1,2-dicarboxylate **S7**, which upon treatment with bromine in presence of pyridine furnished di-*tert*-butyl azodicarboxylate **S8**, and its subsequent reaction with freshly prepared 2-mesitylmagnesium bromide **S9**, followed by Boc-deprotection provides the mesitylhydrazine hydrochloride **S11** which can be stored for a long period. Further reaction of this mesitylhydrazine hydrochloride **S11** with 1M aq. Sodium hydroxide provides free based mesitylhydrazine **S12** in good yields (Scheme 2.15).




**Scheme 2.15** Synthesis of mesitylhydrazine hydrochloride

After the preparation of mesitylhydrazine hydrochloride, we next move towards the preparation of pyrrolidine based NHC-precatalyst **38**. For this, the reaction of pyrrolidin-2-one **S13** with trimethyloxonium tetrafluoroborate provides 5-methoxy-3,4-

dihydro-2H-pyrrole **S14**, which upon further treatment with freshly prepared free based mesitylhydrazine **S12**, and subsequent cyclization using triethylorthoformate in chlorobenzene at 120 °C produces the desired NHC-precatalyst **38** in good yields (Scheme 2.16). Notably, this can be stored for a long period under an inert atmosphere.




**Scheme 2.16** Synthesis of pyrrolidine based NHC-precatalyst

## 2.5 Conclusion

In conclusion, we have synthesized the starting materials such as α-chloroaldehydes **40**, γ-ketosulfones **41** and pyrrolidine based NHC-precatalyst **38** for our designed strategy to access 3,6-disubstituted α-pyrone **42**. As the reaction proceeds through the generation of enolate intermediate in the presence of precatalyst **38** followed by Michael addition-lactonization-elimination cascade sequence. In this context, the detailed study on NHC-catalyzed generation of enolate intermediate and its application to access 3,6-disubstituted α-pyrone is presented in the following sections of part B of this chapter.

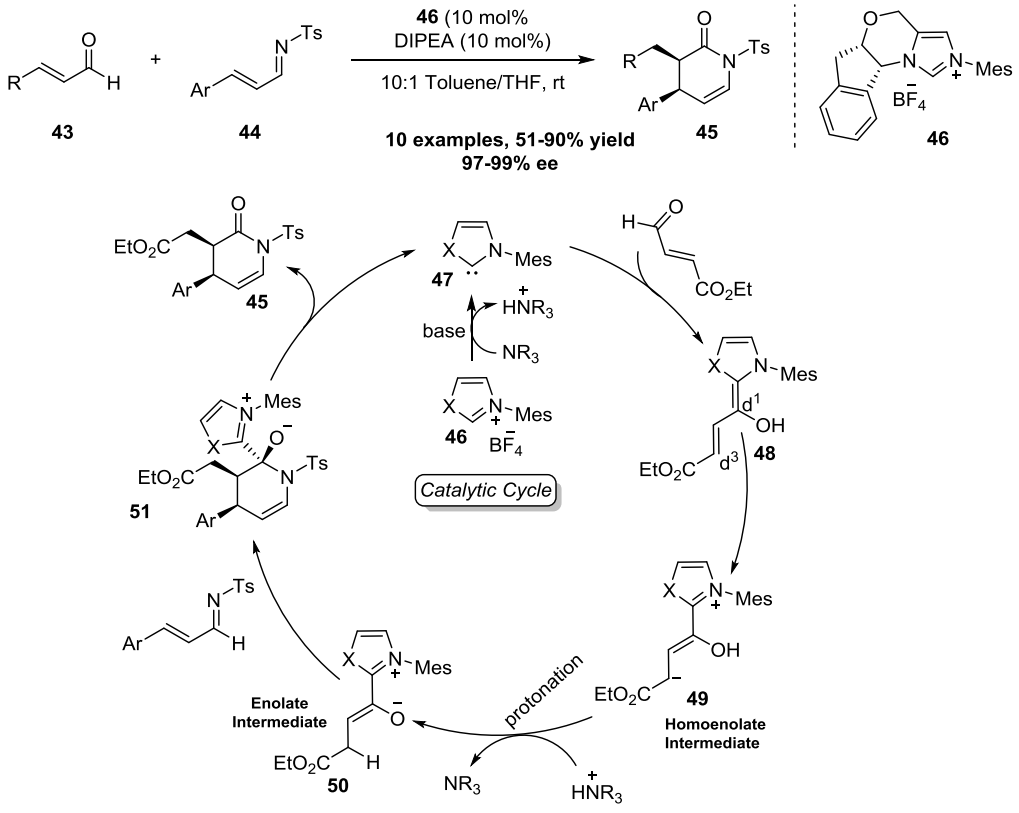
## Part B: Introduction to NHC-Bound Enolate Intermediate and its Application to access 3,6-Disubstituted α-Pyrone

### 2.6 NHC-Bound Enolate Intermediate-An Introduction

The design and development of *N*-heterocyclic carbene (NHC)-organocatalysis has attracted extensive interest in organic synthesis for the rapid construction of biologically and medicinally important molecules from simple starting materials. The NHCs mediated transformation proceeding through umpolung of aldehydes or their synthetic equivalents possess several modes of action such as nucleophilic Breslow intermediate, homoenolate, enolate, and electrophilic acyl azolium, each of which displays different kinds of reactivities.[22] The selective formation of each of these reactive intermediate can be achieved by proper choice of catalyst, substrate and reaction conditions. In this context, the generation of NHC-mediated enolate intermediate has been achieved from enals, α-functionalised aldehydes, ketenes, activated esters etc., which can trapped with electrophile to form a range of important heterocyclic scaffolds through formal cycloadditions.

In 2006, Bode and colleagues developed first approach to produce NHC-mediated nucleophilic enolate intermediate from enals **43**, which then undergo a subsequent hetero Diels-Alder with α,β-unsaturated imines **44** to access dihydropyridinone derivatives **45** in reasonable yields and enantioselectivity as a single *syn*-diastereoisomer (Scheme 2.17).[23] The transformation is postulated to advanced with initial coupling of carbene and enals **43** to generate homoenolate intermediate **49**. The secret to success of these reactions is to control of the unwanted homoenolate pathway and boost of the enolate mode of reactivity by the use of catalytic amount of mild

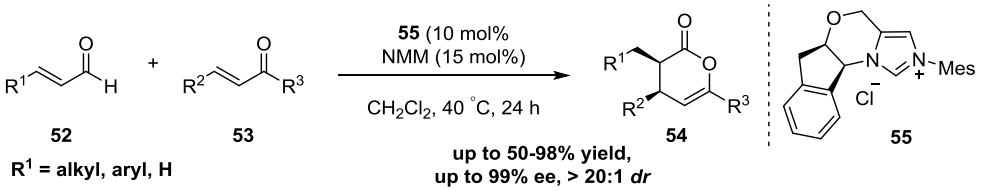
organic base. If the conjugate acid of the catalytic base formed through deprotonation of azolium salt is acidic enough to promote the protonation of homoenolate equivalent then the generation of enolate intermediate **50** take place. Therefore, the success of these reactions is decided by minimizing the competitive reaction pathways. A [4+2] cycloaddition between α,β-unsaturated imines **44** and the enolate equivalent **50** generates the alkoxide **51**, which further releases free carbene to deliver the desired dihydropyridinone derivatives **45** (Scheme 2.17, catalytic cycle).




**Scheme 2.17** NHC-catalyzed generation of enolate intermediate from enals

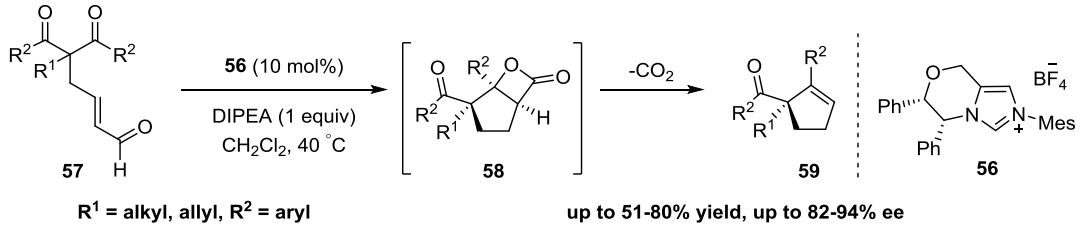
In 2010, Bode et al. developed the highly diastereo- and enantioselective [4+2] annulation of enal **52** and enones **53** using catalytic weak amine base such as *N*-methylmorpholine (NMM) with aminoindanol based triazolium precatalyst **55** to furnish dihydropyran-2-ones **54** (Scheme 2.18).[24] A wide range of alkyl or aryl enals

along with enones having electron deficient substituents were tolerated under the reaction condition and provide the desired product in good to excellent yields.




**Scheme 2.18** NHC-mediated asymmetric construction of dihydropyran-2-ones

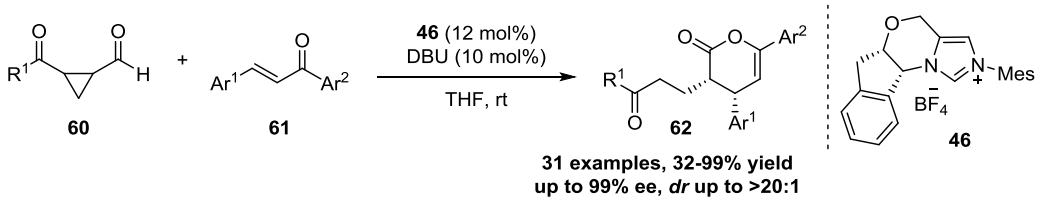
In 2007, Scheidt and colleagues trapped an azolium enolate intermediate from enal **57** followed by desymmetrising aldol addition with a decarboxylation of a β-lactone intermediate **58** to afford functionalised carbocycles **59** in satisfactory yields with excellent enantioselectivity (Scheme 2.19).[25]The scope of this approach was almost restricted to aryl ketones **57**. The use of alkyl ketones granted to afford lactone intermediate **58** in high enantioselectivity with close to diastereoisomeric purity.




**Scheme 2.19** NHC-catalyzed enantioselective synthesis of cyclopentenes

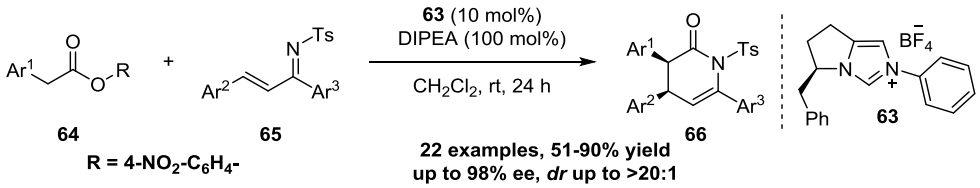
In 2011, Chi and colleagues reported the formal hetero Diels-Alder reaction between formyl cyclopropanes **60** and chalcones **61** for enantioselective synthesis of lactone products **62** in good yields with excellent diastero- and enantioselectivity (Scheme 2.20).[26] This was the first example to access azolium enolate intermediate from formylcyclopropane as starting material. A wide range of chalcones as well as various

aryl derivatives on the formylcyclopropane motif were endured beneath the transformation condition to afford desired product with no reduction in stereocontrol.



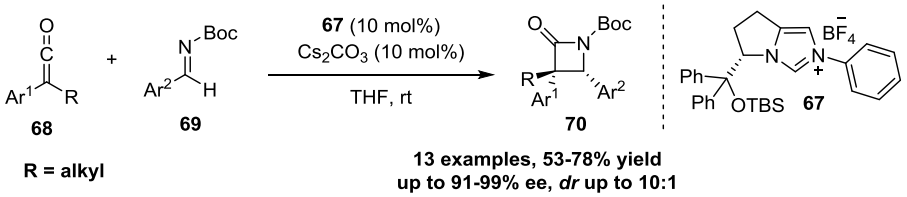

**Scheme 2.20** NHC-catalyzed generation of enolate intermediate from formylcyclopropanes

Furthermore, they have shown that activated carboxylic esters **64** can act as precursors to generate azolium enolates using NHC precursor **63**, which then undergo a formal asymmetric [4+2] annulation with α,β-unsaturated imines **65** to generate the desired dihydropyridinone products **66** in positive yields with valuable diastereo- and enantioselectivity (Scheme 2.21).[27] This approach is currently restricted to the use of arylacetic acid esters.




**Scheme 2.21** NHC-catalyzed generation of enolate intermediate from carboxylate esters

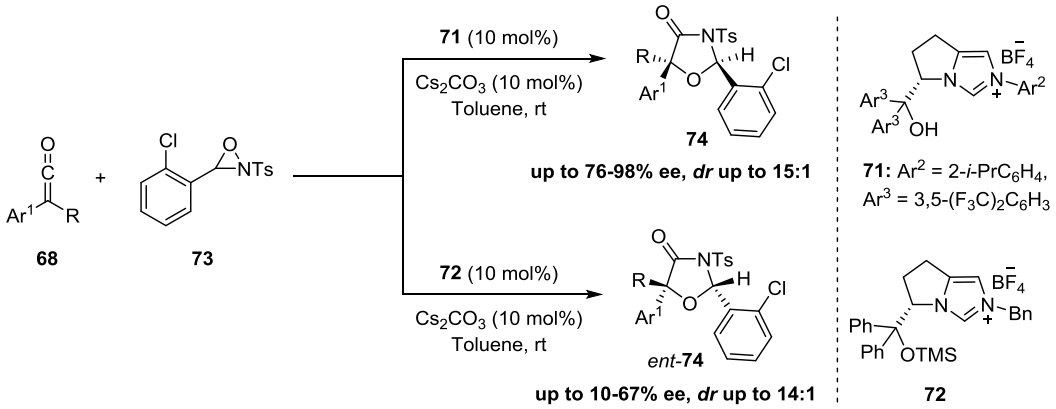
In 2008, Ye and co-workers accessed a ketene derived azolium enolate to develope a precise [2+2] cycloaddition transformation of alkylarylketenes **68** and *N-tert*-butoxycarbonyl imines **69** using (R)-pyroglutamic acid derived precatalyst **67** to furnish the analogous cis-β-lactams **70** in favorable yields with excellent diastereo- and enantioselectivity (Scheme 2.22).[28a] A wide range of ketenes and imines were tolerated under the reaction condition to give corresponding β-lactams.



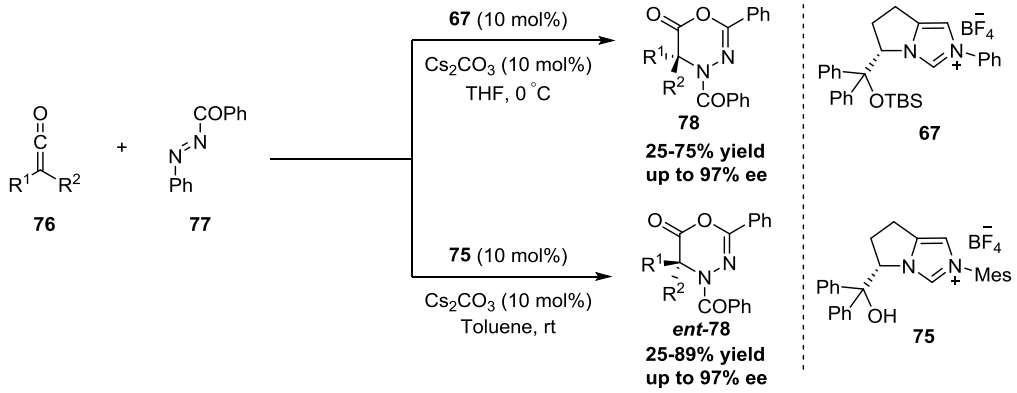

**Scheme 2.22** Generation of azolium enolate intermediate from ketenes

Further, the same group reported the formal [3+2] cycloaddition reaction between ketenes **68** and oxaziridines **73** employing precatalyst **71** for the synthesis of oxazolidin-4-ones **74** in acceptable yields with superb diastero- and enantioselectivity. Importantly, the use of precatalyst **72** furnished opposite stereochemical products, whereas both NHC precatalyst **71** and **72** have identical absolute configurations (Scheme 2.23).[28b] A variety of alkylarylketenes worked well for this transformation.

In 2009, the same research group developed the formal [4+2] cycloaddition reaction between ketenes **76** and *N*-benzoyldiazenes **77** using NHC precatalyst **67** or **75** to give 1,3,4-oxadiazin-6-one **78** in good yields and excellent enantioselectivity (Scheme 2.24).[28c] Importantly, the stereoselectivity of the product could be switched by adjusting the substituents in the NHC-catalyst.

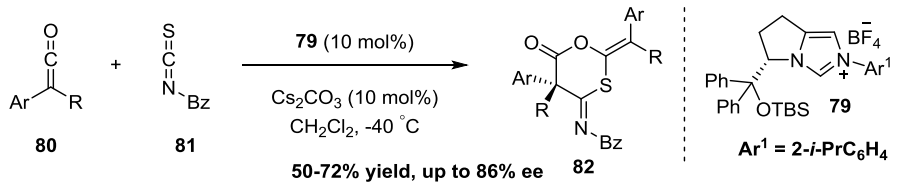



**Scheme 2.23** NHC-mediated [3+2] cycloaddition reaction




**Scheme 2.24** NHC-mediated [4+2] cycloaddition transformation

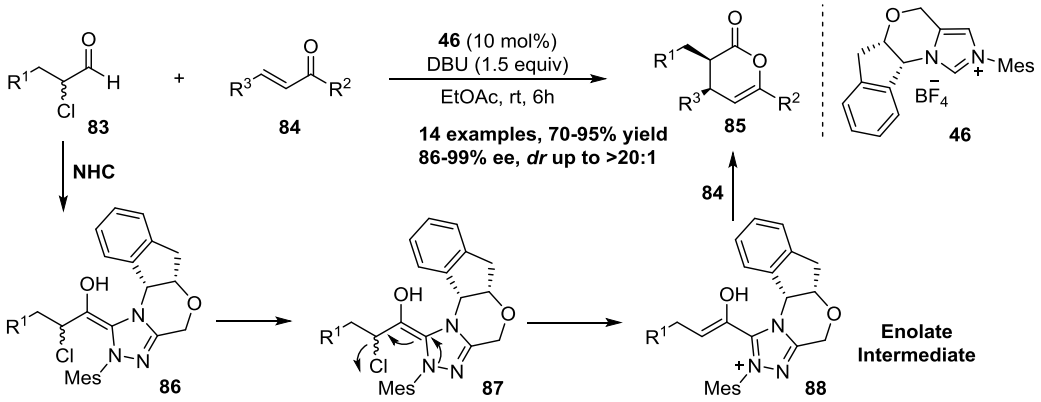
Moreover, Ye and co-workers demonstrated that a formal [2+2+2] pathway could be accessed under NHC-catalysis by employment of ketenes **80** with *N*-benzoylisothiocyanate **81** to afford heterocycles **82** at the reduced reaction temperature of -40 °C (Scheme 2.25).[29] This transformation shows the first asymmetric trimerization of dissimilar ketene equivalents, and provides the desired product in good yields and moderate enantioselectivity.




**Scheme 2.25** NHC-mediated [2+2+2] cycloaddition reaction

Furthermore, the high sensitivity and restricted synthetic diversity of the alkylarylketenes component resulted in the evolution of alternative approach that grant the *in situ* generation of azolium enolate intermediate. In this context, Bode and co-workers succeed to access azolium enolate intermediate **88** from racemic α-chloroaldehydes **83**, which further undergo [4+2] oxodiene Diels-Alder reaction with enones **84** to furnish enantiopure dihydropyranone product **85** (Scheme 2.26).[30] The low

catalyst loading of NHC precursor **46** were used to prepare desired products in excellent yield and high level of diastereo- and enantioselectivity.




**Scheme 2.26** NHC-catalyzed generation of enolate intermediate from α-chloroaldehydes

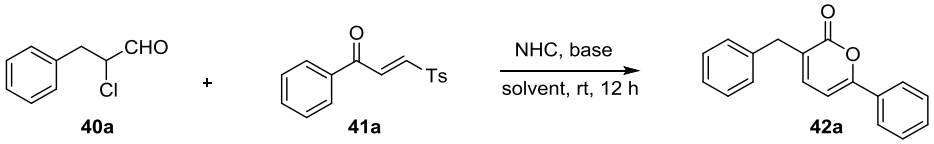
## 2.7 Results and Discussion

### 2.7.1 Optimization Studies

To find an optimal reaction condition, we started our investigation using α-chloroaldehydes **40a** and γ-ketosulfones **41a** as a model substrate (Table 2.1). Initially, the performance of different NHC-precatalyst were assessed using DBU as a base in THF solvent and it was found that imidazolium **89** and thiazolium **90** based catalyst gave inferior results (entry 1-2). However, pyrrolidine derived N-mesityl substituted triazolium precatalyst **38** provided the product **42a** in good yields (entry 4) as compare to N-pentafluorobenzene substituted precatalyst **91** (entry 3). So with NHC-precatalyst **38**, we further screened various bases and it was observed that other organic bases such as TMG and DABCO produced **42a** in reduced yields (entry 5 and 6). Interestingly, the replacement of organic base with inorganic base such as $K_2CO_3$ and $Cs_2CO_3$ provide the desired product **42a** with an improvement in the yield of 65% and 72% respectively (entry 7 and 8). This variation of bases conclude that $Cs_2CO_3$ to be preferred base (entry 8).

Therfore while keeping $Cs_2CO_3$ as a base, we further performed the reaction in different solvents like $CH_3CN$, toluene, $CH_2Cl_2$, chloroform and 1,2-dichloroethane (entry 9-13). It was observed that reaction provides good results in all tested solvents and among various best result with the yield of 94% were obtained while using dichloromethane solvent (entry 11). Notably, a reduction in the production 65% of **42a** was detected while reducing the loading of $Cs_2CO_3$ from 200 mol% to 100 mol% (entry 14). Importantly, the product **42a** was not formed in the absence of NHC-precatalyst **38**, demonstrating its key role in the process (entry 15).

**Table 2.1** Optimization of reaction conditions[a]




| Entry | NHC | Base | Solvent | Yield[b] (%) **42a** |
|---|---|---|---|---|
| 1 | **89** | DBU | THF | 0 |
| 2 | **90** | DBU | THF | 12 |
| 3 | **91** | DBU | THF | 23 |
| 4 | **38** | DBU | THF | 54 |
| 5 | **38** | TMG | THF | 51 |
| 6 | **38** | DABCO | THF | 38 |
| 7 | **38** | $K_2CO_3$ | THF | 65 |
| 8 | **38** | $Cs_2CO_3$ | THF | 72 |
| 9 | **38** | $Cs_2CO_3$ | $CH_3CN$ | 54 |
| 10 | **38** | $Cs_2CO_3$ | toluene | 76 |
| **11** | **38** | **$Cs_2CO_3$** | **$CH_2Cl_2$** | **94** |
| 12 | **38** | $Cs_2CO_3$ | $CHCl_3$ | 91 |
| 13 | **38** | $Cs_2CO_3$ | $(CH_2Cl)_2$ | 90 |
| 14[c] | **38** | $Cs_2CO_3$ | $CH_2Cl_2$ | 65 |
| 15 | - | $Cs_2CO_3$ | $CH_2Cl_2$ | 0 |


[a]Standard reaction condition, unless otherwise specified: **40a** (0.2 mmol), **41a** (0.1 mmol), NHC **38** (20 mol %), $Cs_2CO_3$ (200 mol %), $CH_2Cl_2$ (1.5 mL) at rt for 12 h. [b]Isolated yield of a **42a**.[c]100 mol % of $Cs_2CO_3$ used.

### 2.7.1.1 Characterization of Representative Product 3-benzyl-6-phenyl-2H-pyran-2-one (42a)

The compound **42a** was synthesized by reacting of 2-chloro-3-phenylpropanal **40a** and (E)-1-phenyl-3-tosylprop-2-en-1-one **41a** in presence of 20 mol% NHC-precatalyst **38** using 200 mol% $Cs_2CO_3$ in 1.5 mL of $CH_2Cl_2$ at room temperature for 12 h. The product **42a** was obtained as off white solid in 97% of yield with mp 118-120 $^oC$.

In the $^1H$ NMR of **42a** in $CDCl_3$ at 400 MHz, the appearance of the characteristic peak of protons $\mathbf{H_a}$, $\mathbf{H_b}$ and $\mathbf{H_c}$ at $\delta$ 3.84 (s, 2H), 6.57 (d, $J$ = 6.8 Hz, 1H) and 7.01 (d, $J$ = 6.8 Hz, 1H) in ppm respectively confirmed the formation of desired product **42a** (Figure 2.4). In DEPT-135 NMR spectrum ($CDCl_3$, 100 MHz) the appearance of total 9 signals out of which characteristic peak of $CH_2$ at δ 36.24 ppm confirmed the formation of product **42a** (Figure 2.5).

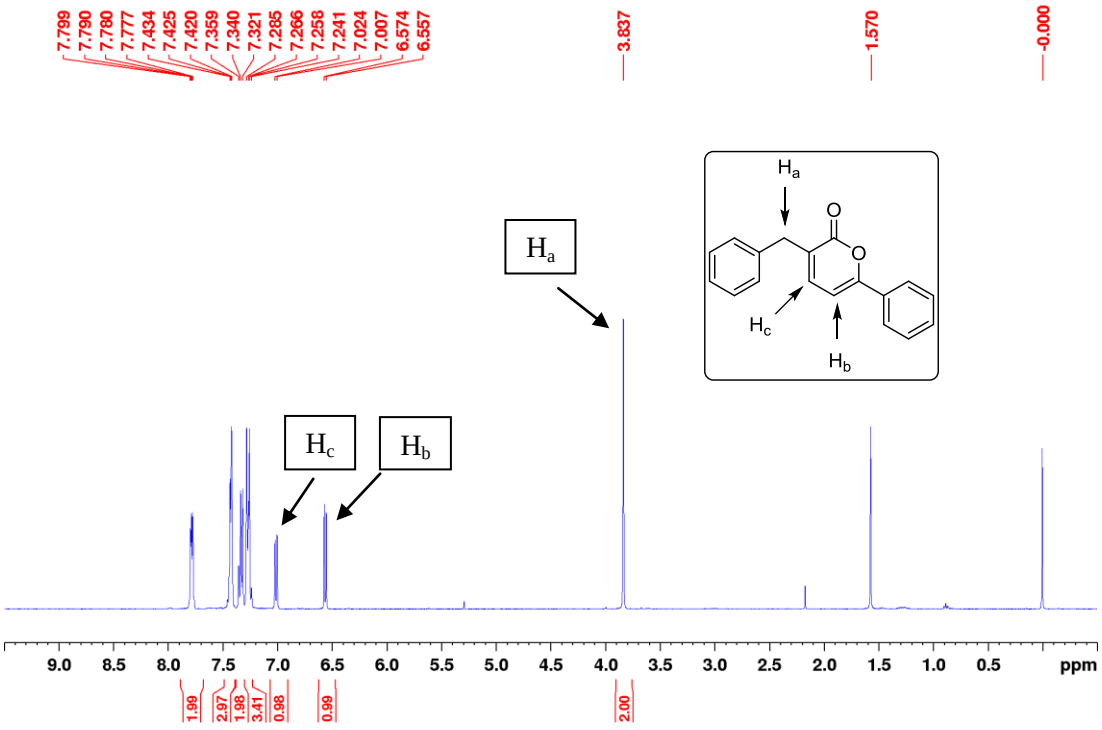



**Figure 2.4** $^1H$ NMR of 3-benzyl-6-phenyl-2H-pyran-2-one (**42a**) in $CDCl_3$ at 400 MHz.

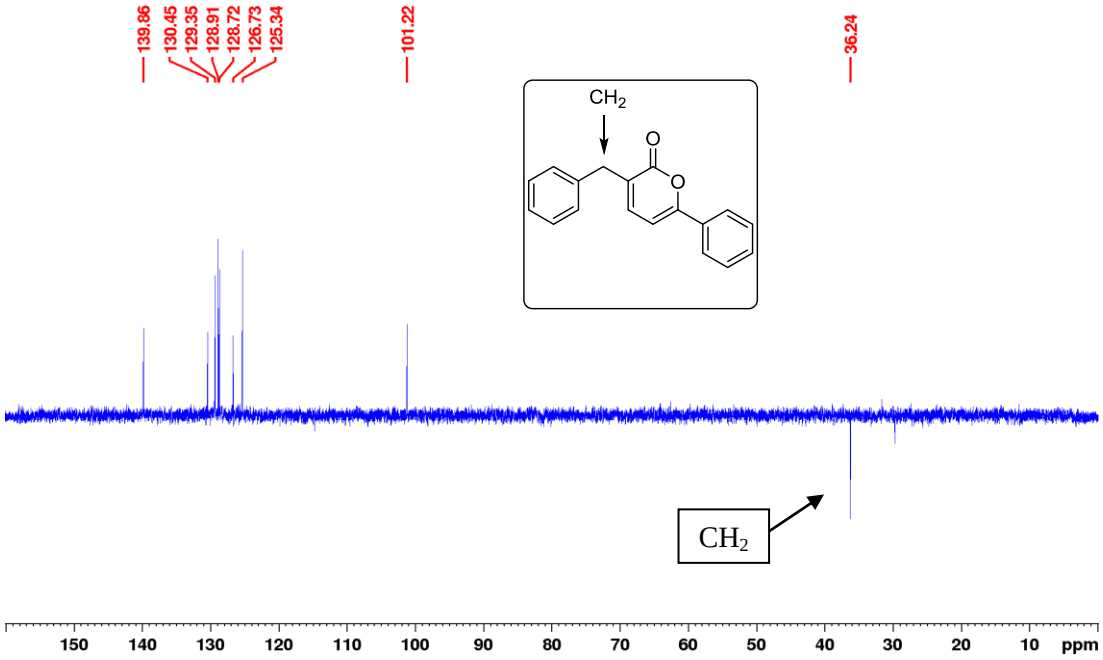



**Figure 2.5** DEPT-135 NMR of 3-benzyl-6-phenyl-2H-pyran-2-one (**42a**) in $CDCl_3$ at 100 MHz

Additionally, in the $^{13}C$ NMR spectrum ($CDCl_3$, 100 MHz), the appearance of four peaks of quaternary $\mathbf{C_q}$ carbon at $\delta$ 127.36, 131.44, 138.05, 158.71 ppm and one for cyclic ester $\mathbf{C_e}$ carbon at $\delta$ 162.78 ppm confirmed the product **42a** (Figure 2.6).

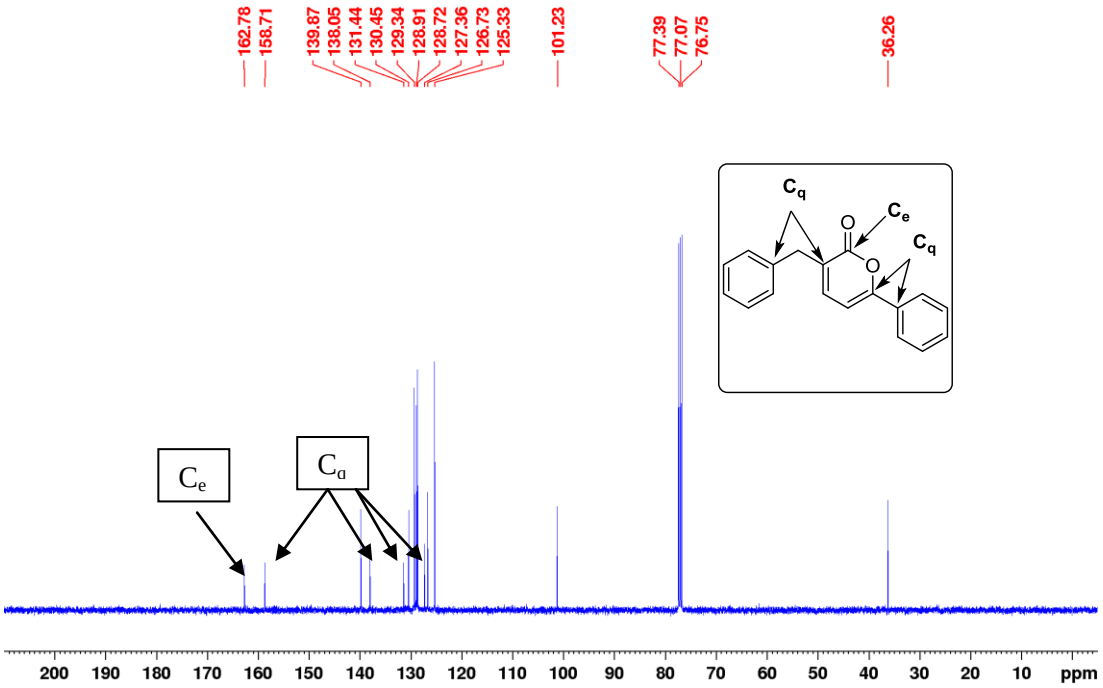


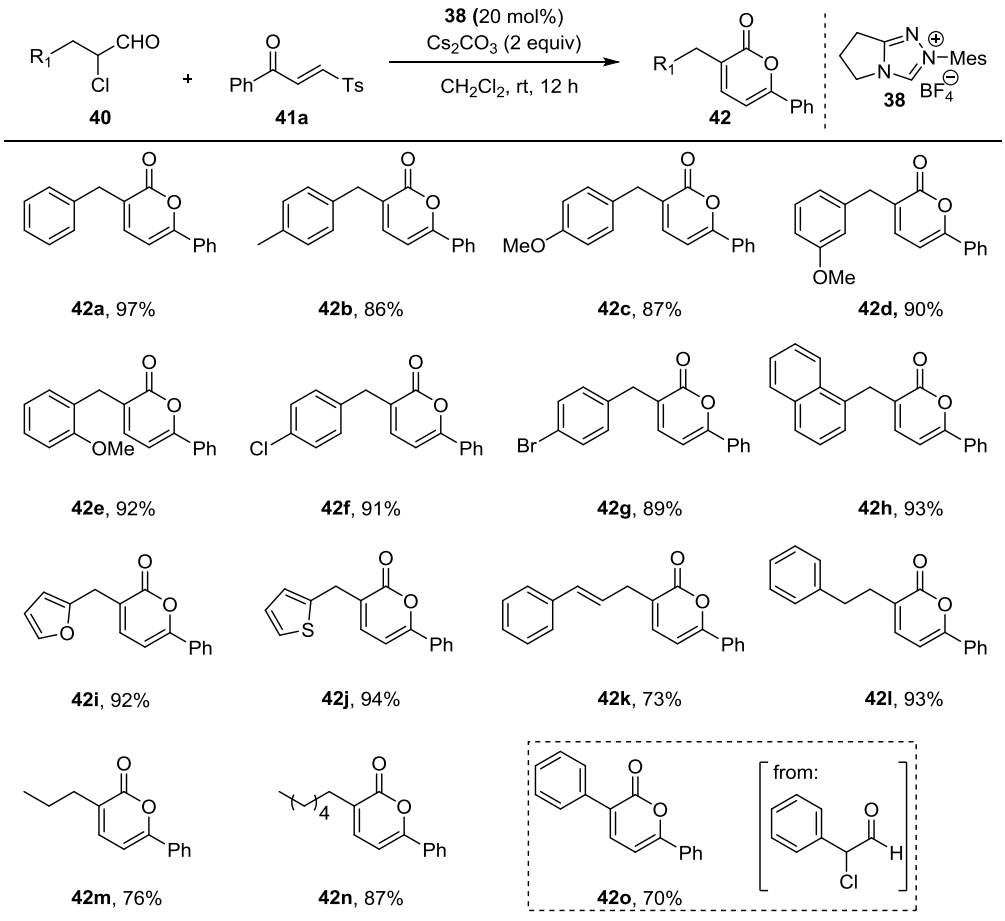

**Figure 2.6** $^{13}C\{1H\}$ NMR of 3-benzyl-6-phenyl-2H-pyran-2-one (**42a**) in $CDCl_3$ at 100 MHz

The appearance of these characteristic protons and carbons established the formation of 3-benzyl-6-phenyl-2H-pyran-2-one **42a**. Its HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{14}NaO_2^+$ 285.0886; found: 285.0884 confirmed its molecular formula to be $C_{18}H_{14}O_2$.

### 2.7.2 Scope of the Reaction for the Synthesis of 3,6-Disubstituted α-Pyrone

After getting the optimized condition (Table 2.1, entry 11) in hand, we then investigated the tolerance of this unique NHC-catalyzed Michael addition-lactonization-elimination cascade reaction with various α-chloro aldehyde **40** derivatives by employing 1-phenyl-3-tosylprop-2-en-1-one **41a** as a model Michael acceptor (Scheme 2.27).

**Scheme 2.27** Scope of α-Chloroaldehydes for the synthesis of 3,6-disubstituted α-pyrone[a,b]



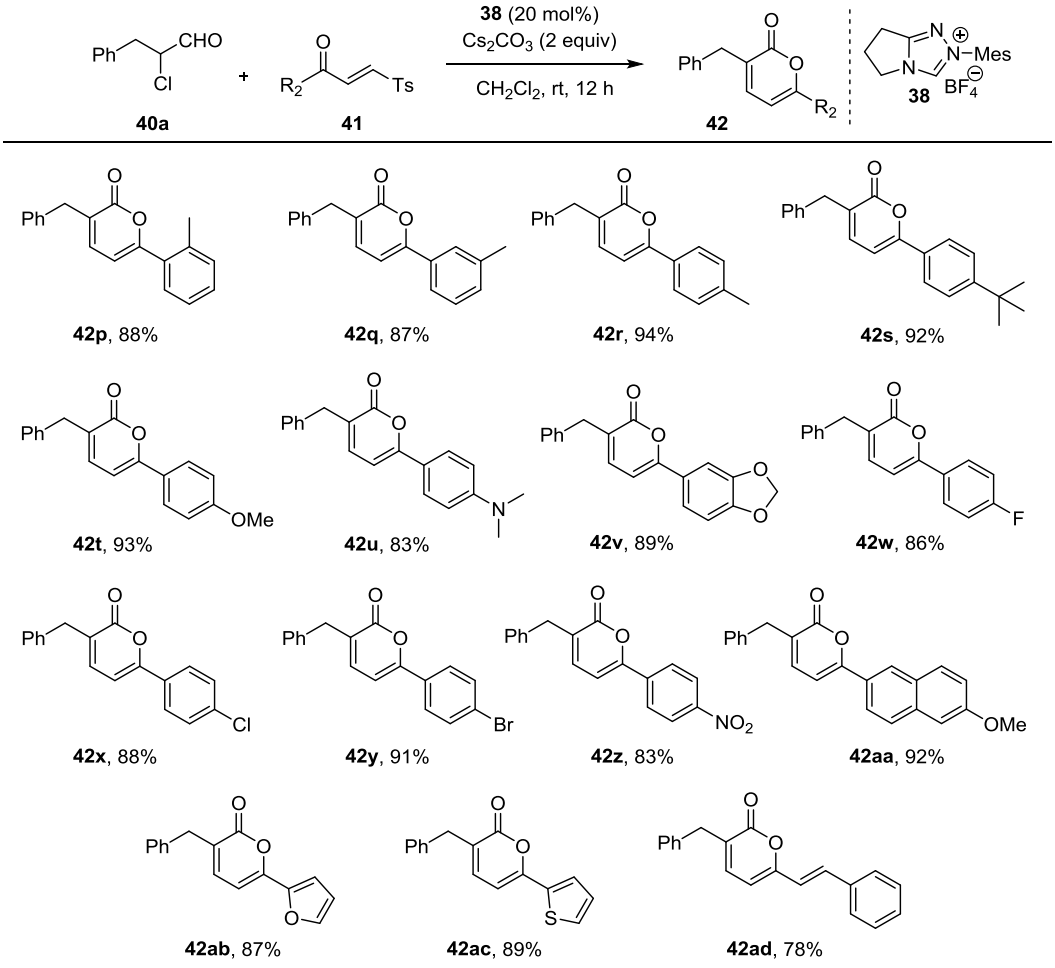

[a]General reaction condition: **40** (0.2 mmol), **41a** (0.1 mmol), NHC **38** (20 mol %), $Cs_2CO_3$ (200 mol %), $CH_2Cl_2$ (1.5 mL) at rt for 12 h. [b]Isolated yields of the product are given.

It was observed that electron-donating substituents at para-, meta- or ortho-position (4-$MeC_6H_4$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$ and 2-$MeOC_6H_4$) as well as electron-withdrawing substituents at para-position (4-$ClC_6H_4$ and 4-$BrC_6H_4$) of the β-aryl-α-chloroaldehyde underwent smooth reaction to furnish the corresponding α-pyrone (**42b-42g**) in good to excellent yields. Interestingly, the replacement of the β-phenyl substituent by a naphthyl or heteroaryl moiety were also well tolerated without affecting chemical yield (**42h-42j**). Notably, this transformation was not limited to this class of aldehydes. In this context, the presence of unsaturated elements were also compatible and thus providing **42k** in 73% yield. In addition, homobenzylic substituted aldehyde with a phenyl ring afforded the desired product **42l** with 93% yield. Pleasingly, aldehydes with linear alkyl substituent such as pentanal and octanal were also amenable, providing the corresponding product (**42m-42n**) in good yields under the optimized condition. Noteworthy, the replacement of the benzyl group by a phenyl group on α-chloroaldehyde **40a** did not affect the outcome of this reaction and corresponding product **42o** was successfully formed in 70% yield under the standard condition.

In view of these interesting results, we further explore the substrate scope by varying the substituents or substitution types on γ-ketosulfones **41** by using 2-chloro-3-phenylpropanal **40a** as a model substrate under the optimized reaction condition (Scheme 2.28). The various electron-donating substituents at ortho-, meta-, or para-position (2-Me, 3-Me, 4-Me, 4-$C(Me)_3$, 4-OMe and 4-$N(Me)_2$) underwent smooth reaction to furnish corresponding 3,6-disubstituted α-pyrone derivatives (**42p-42u**) in 68-80% yields. Notably, an α-pyrone (**42v**) possessing a piperonyl moiety at the $6^{th}$ position were synthesized using this approach. In addition, the introduction of an

electron-withdrawing substituents at para-position (4-F, 4-Cl, 4-Br and 4-$NO_2$) were also tolerated with the catalytic process, leading to the formation of corresponding α-pyrone (**42w-42z**) in 68-76% yields. Gratifyingly, the replacement of aryl units of **41** by the 6-methoxy 2-naphthyl, heteroaryl or cinnamyl units were also tolerated and thus providing the desired product (**42aa-42ad**) in 63-82% yields. More importantly, we next examined the scalability of the reaction with 1g of γ-ketosulfones **41a** and pleasingly, the desired product **42a** was isolated in 89% yield under the optimized reaction condition.

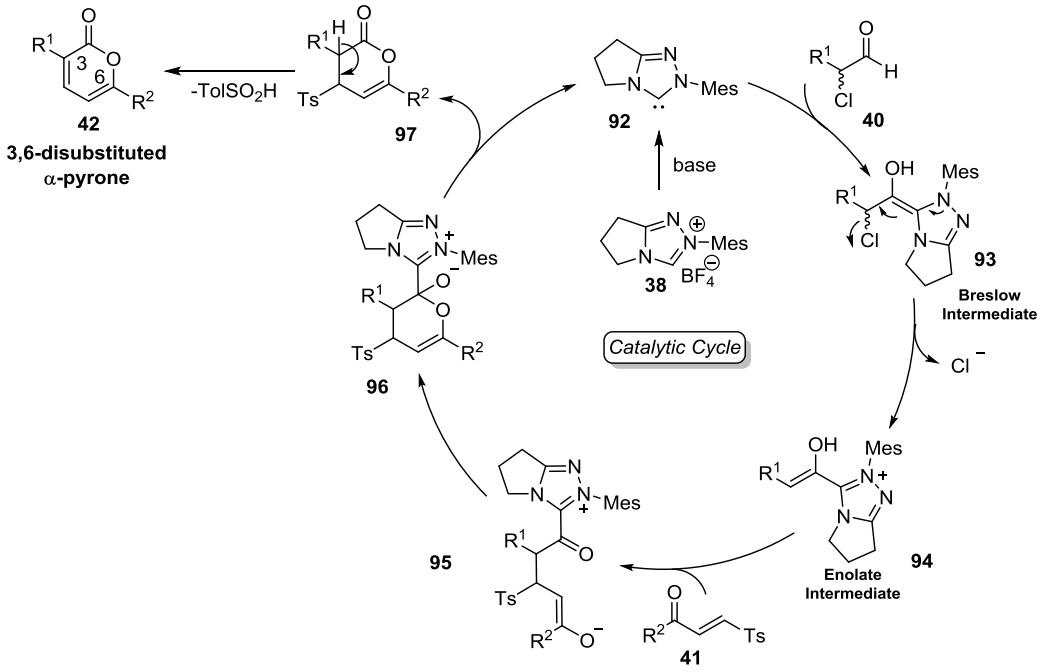
**Scheme 2.28** Scope of γ-ketosulfones for the synthesis of 3,6-disubstituted α-pyrone[a,b]




[a]General reaction condition: **40a** (0.2 mmol), **41** (0.1 mmol), NHC **38** (20 mol %), $Cs_2CO_3$ (200 mol %), $CH_2Cl_2$ (1.5 mL) at rt for 12 h. [b]Isolated yields of the product are given.

### 2.7.3 Proposed Reaction Mechanism

A mechanistic proposal of the transformation is illustrated in Scheme 2.29. Mechanistically, the reaction proceeds with the coupling of carbene **92** with α-chloroaldehyde **40** to generate Breslow intermediate **93**. After leaving of chloride ion an azolium enolate intermediate **94** formed,[30] which undergoes the 1,4-addition to the γ-ketosulfones **41** to produce alkoxide intermediate **95** and subsequent intramolecular cyclisation leads to the formation of sulfone containing dihydropyrone **97** with the release of carbene catalyst. This, dihydropyrone **97** with the release of tosylic acid produced the desired 3,6-disubstituted α-pyrone **42**.

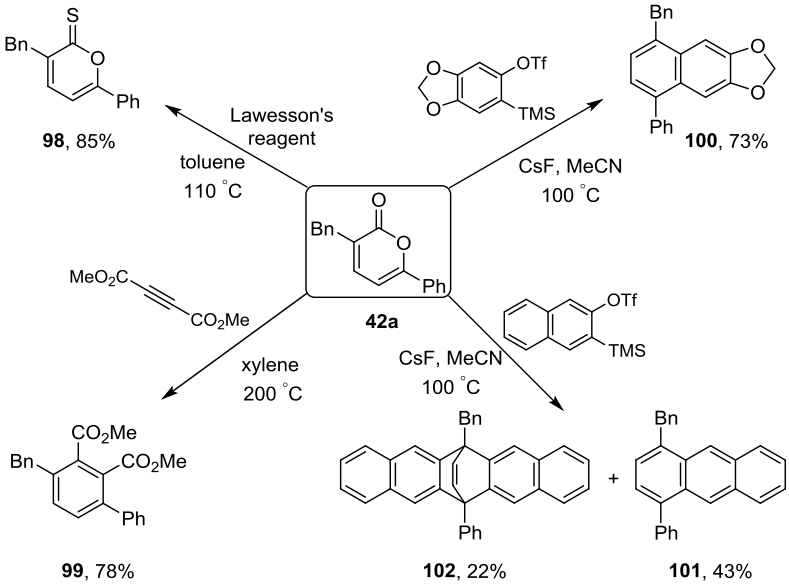



**Scheme 2.29** Plausible mechanism for the formation of 3,6-disubstituted α-pyrone

### 2.7.4 Synthetic Utility of 3,6-Disubstituted α-Pyrone

The synthetic utility of 3,6-disubstituted α-pyrone **42a** were further explored. We examined a series of derivatization to produce synthetically useful building blocks

(Scheme 2.30). In this context, the reaction of **42a** with Lawessons's reagent in dry toluene furnished 3-benzyl-6-phenyl-2H-pyran-2-thione **98** in 85% yield. Moreover, 3,6-disubstituted α-pyrone behaves as stable and reactive diene for Diels-Alder reaction which upon reaction with dienophiles produces cyclo-addition adduct. For instance, the Diels-Alder reaction of **42a** with dimethyl acetylene dicarboxylate produced a highly substituted benzene **99** in 78% yield. In addition, the reaction of **42a** with sesamol based benzyne in acetonitrile furnished a bicyclic adduct, which upon release of $CO_2$ by a retro-Diels-Alder reaction to give 5,8-disubstituted naphtho-1,3-dioxol **100** in 73% yield. Notably, the use of naphthynes instead of sesamol based benzyne delivered a mixture of 1,4-disubstituted anthracene **101** and 6,13-disubstituted ethenopentacene **102** in a relatively low yield.




**Scheme 2.30** Synthetic transformation of 3,6-disubstituted α-pyrone

## 2.8 Conclusion

In conclusion, we have described a NHC-catalyzed formal [4+2] annulation between α-chloro aldehydes and γ-keto sulfones to provide a variety of 3,6-disubstituted α-pyrone

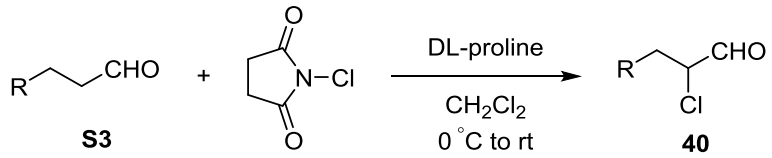
in good to excellent yields. The reaction proceeded through Michael addition followed by lactonization-elimination cascade sequence and provided the desired α-pyrone for a panel of α-chloro aldehydes using γ-ketosulfones as a key Michael acceptor. Notably, the present protocol is attractive due to its operationally simplicity and mild reaction conditions. In addition, we also performed the gram-scale synthesis for 3,6-disubstituted α-pyrone and synthetic utility of the product to access a series of value-added molecules.

## 2.9 Experimental Section

### 2.9.1 General Information and Method

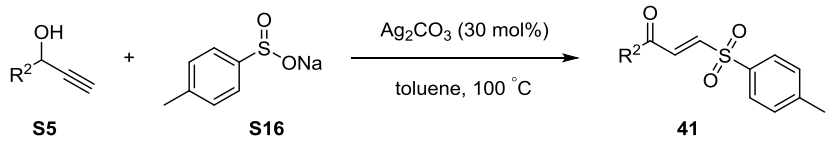
Aldehydes and other fine chemicals were obtained from commercial suppliers and used without purification. Solvents were dried and distilled following the standard procedures. TLC observation was carried out on precoated plates (Merck silica gel 60, $f_{254}$), and the spots were visualized with UV light or by charring the plates dipped in PMA/$KMnO_4$ solution. Flash chromatography was performed using silica gel (230-400 mesh) with distilled solvents. $^{1}H$ and $^{13}C\{^{1}H\}$ NMR for compounds were recorded at 400 MHz instruments and 100 MHz instrument, respectively, using $CDCl_3$ as the solvent unless stated otherwise. Chemical shifts were recorded in parts per million (ppm, δ). $^{1}H$ and $^{13}C\{H\}$ NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sext), septet (sep), doublet of doublet (dd), doublet of triplet (dt), triplet of doublets (td), multiplet (m) etc. High resolution mass spectral analysis (HRMS) was performed on Q-TOF Premier mass spectrometer.

### 2.9.2 General Procedure for the Synthesis of α-Chloro Aldehyde 40[19]




To a stirred solution of aldehyde derivative **S3** (10 mmol, 1 equiv.) in dichloromethane (40mL) at 0 °C was added under argon *DL*-Proline (2 mmol, 0.2 equiv.) and *N*-chlorosuccinimide (NCS, 10 mmol, 1 equiv.). The reaction mixture was stirred at 0 °C for 1 h, and then allowed to reach room temperature and stirred for additional 1.5 h. The reaction was monitored by $^1$H NMR. If the starting aldehyde is not totally consumed, extra NCS was added by small portions until full conversion. The reaction was quenched by addition of pentane (50 mL) and the precipitate was filtered off. The filtrate was concentrated under vacuum and the residue was purified by flash column chromatography on silica gel using hexane/ethyl acetate as eluent to afford the desired α-chloro-aldehyde derivative **40** as a colorless oil.

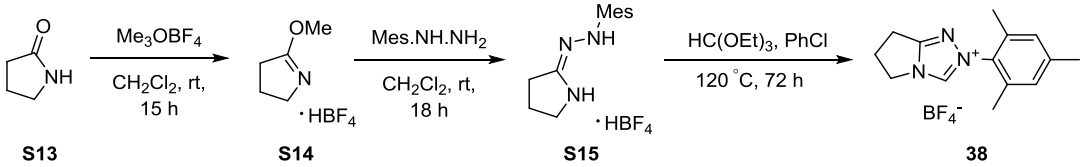
### 2.9.3 General Procedure for the Synthesis of γ-Keto Sulfones 41[20]




A screw-capped reaction vial was charged propargylic alcohol derivative **S5** (0.5 mmol, 1 equiv.) and sodium *p*-methylphenyl sulfinate **S16** (0.75 mmol, 1.5 equiv.) in toluene (2.0 mL) and stirred at room temperature. Subsequently, $Ag_2CO_3$ (0.15 mmol, 0.3 equiv.) was added and the reaction mixture was stirred at 100 °C until the propargylic alcohol **S5** was completely consumed as indicated by thin layer chromatography (TLC). The resulting mixture was concentrated and the residue was

taken up in ethyl acetate. The organic layer was dried over $NaSO_4$ and concentrated. Purification of the crude product by flash column chromatography on silica gel using hexane/ethyl acetate as eluent to afford the desired γ-Keto Sulfones derivative **41** as a colorless solid.

### 2.9.4 Procedure for the Synthesis of NHC-Precatalyst 38

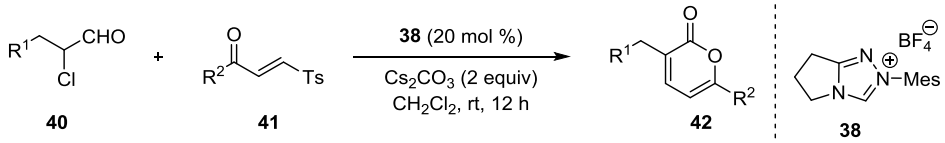



**S13** **S14** **S15** **38**

The triazolium salt **38** was prepared by following the general procedure of Rovis et al.[21b] To a solution of pyrrolidin 2-one (0.52 mL, 6.8 mmol) in anhydrous $CH_2Cl_2$ (25 mL) was added trimethyl oxonium tetrafluoroborate (1.03 g, 6.96 mmol) under argon atmosphere and the mixture was stirred for 18 hrs at room temperature. Then, mesitylhydrazine (1.06 g, 6.96 mmol) was added under inert atmosphere and the resulting orange solution stirred for a further 18 hrs at room temperature. The mixture was then concentrated in vacuo and upon addition of EtOAc (25 mL) the solid hydrazone was formed which was collected by filtration and washed with EtOAc (3 x 10 mL) and then dried under vacuum for several hours provided the hydrazone as an off-white solid (1.06 g) in 51% yield. To this hydrazone chlorobenzene (7 mL) and triethyl ortho-formate (2.89 mL, 17.4 mmol) was added and the mixture was stirred in sealed tube at 120 °C for 72 hours. Then, the mixture was concentrated in vacuo and EtOAc (15 mL) was added and the formed solid was collected by filtration followed by washing with EtOAc (3 x 10 mL). Then the solid was dried under vacuum for several hours to give 2-mesityl-6,7 dihydro-5H-pyrrolo[2,1 *c*] [1,2,4] triazol-2-ium tetrafluoroborate **38** as a an off-white solid (860 mg) in 79% yield.

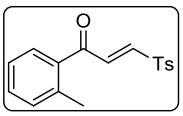
### 2.9.5 General Procedure for the Synthesis of 3,6-Disubstituted α-Pyrone 42

In an oven-dried Schlenk tube equipped with a magnetic stirrer was added under argon the NHC-pre-catalyst **38** (0.02 mmol, 20 mol %) and γ-Keto Sulfone **41** (0.1 mmol). The tube was sealed with a septum, evacuated and refilled with argon (3 cycles). Dichloromethane (1.5 mL), α-chloro aldehyde **40** (0.2 mmol, 2 equiv.), and $Cs_2CO_3$ (0.2 mmol, 2 equiv.) were then added and the reaction mixture was stirred at room temperature for 12 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the residue was subjected to column chromatography using hexane/ethyl acetate as eluent to afford the desired product **42**.




### 2.9.6 Characterization Data

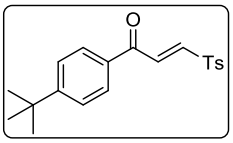
***(E)-1-(o-tolyl)-3-tosylprop-2-en-1-one (41p)***




The title compound was prepared following the general procedure **2.9.3** described above using **S5p** (0.5 mmol, 73 mg, 1.0 equiv.) and **S16** (0.75 mmol, 134 mg, 1.5 equiv.). The product was isolated in 56% yield (84 mg), pale yellow solid, mp 113-115 °C, eluent:(hexane/EtOAc, 90/10); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 2.47 (d, $J$ = 4.0 Hz, 6H), 7.18 (d, $J$ = 16.0 Hz, 1H), 7.27-7.35 (m, 2H), 7.38 (d, $J$ = 8.0 Hz, 2H), 7.45 (t, $J$ = 8.0 Hz, 1H), 7.56-7.65 (m, 2H), 7.82 (d, $J$ = 8.0 Hz, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 21.0, 21.6, 125.9, 128.3, 129.6, 130.2, 132.1, 132.6, 135.6, 135.9, 139.2,

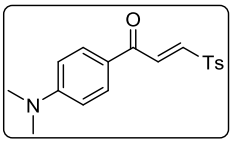
142.0, 145.5, 191.2; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{17}H_{16}NaO_3S^+$ 323.0712; found: 323.0714.

***(E)-1-(4-(tert-butyl) phenyl)-3-tosylprop-2-en-1-one (41s)***




The title compound was prepared following the general procedure **2.9.3** described above using **S5s** (0.5 mmol, 94 mg, 1.0 equiv.) and **S16** (0.75 mmol, 134 mg, 1.5 equiv.). The product was isolated in 53% yield (91 mg), light brown solid, mp 113-115 °C, eluent: (hexane/ EtOAc, 90/10); **$^1$H NMR (400 MHz, CDCl$_3$)**: $\delta$ 1.34 (s, 9H), 2.45 (s, 3H), 7.33 (d, $J$ = 12.0 Hz, 1H), 7.37 (d, $J$ = 8.0 Hz, 2H), 7.52 (d, $J$ = 8.0 Hz, 2H), 7.82 (d, $J$ = 8.0 Hz, 2H), 7.86-7.95 (m, 3H); **$^{13}$C{$^1$H} NMR (100 MHz, CDCl$_3$)**: $\delta$ 21.7, 30.9, 35.3, 126.0, 128.3, 128.9, 130.2, 132.8, 133.5, 135.7, 141.9, 145.5, 158.5, 187.2; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{20}H_{22}NaO_3S^+$ 365.1182; found: 365.1185.

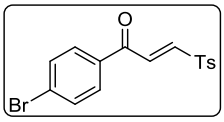
***(E)-1-(4-(dimethylamino) phenyl)-3-tosylprop-2-en-1-one (41u)***




The title compound was prepared following the general procedure **2.9.3** described above using **S5u** (0.5 mmol, 88 mg, 1.0 equiv.) and **S16** (0.75 mmol, 134 mg, 1.5 equiv.). The product was isolated in 61% yield (101 mg), red brown solid, mp 172-174 °C, eluent: (hexane/ EtOAc, 85/15); **$^1$H NMR (400 MHz, CDCl$_3$)**: $\delta$ 2.44 (s, 3H), 3.10 (s, 6H), 6.67 (d, $J$ = 8.0 Hz, 2H), 7.29 (d, $J$ = 16.0 Hz, 1H), 7.36 (d, $J$ = 8.0 Hz, 2H),

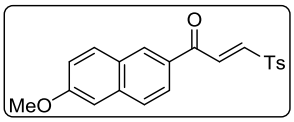
7.82 (d, *J* = 8.0 Hz, 2H), 7.88-7.97 (m, 3H); **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)**: $\delta$ 21.7, 40.0, 110.9, 124.1, 128.2, 130.1, 131.5, 133.6, 136.1, 140.2, 145.2, 154.2, 184.3; **HRMS (ESI-TOF) m/z**: $[M + H]^+$ calcd for $C_{18}H_{20}NO_3S^+$ 330.1158; found: 330.1158.

***(E)-1-(4-bromophenyl)-3-tosylprop-2-en-1-one (41y)***




The title compound was prepared following the general procedure **2.9.3** described above using **S5y** (0.5 mmol, 106 mg, 1.0 equiv.) and **S16** (0.75 mmol, 134 mg, 1.5 equiv.). The product was isolated in 59% yield (108 mg), red brown solid, mp 147-149 °C, eluent: (hexane/ EtOAc, 85/15); **$^{1}H$ NMR (400 MHz, $CDCl_3$)**: $\delta$ 2.46 (s, 3H), 7.35 (d, *J* = 16.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.80-7.88 (m, 5H); **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)**: $\delta$ 21.7, 128.4, 129.9, 130.3, 131.9, 132.4, 134.8, 135.5, 142.8, 145.7, 186.8; **HRMS (ESI-TOF) m/z**: $[M + H]^+$ calcd for $C_{16}H_{14}BrO_3S^+$ 364.9842; found: 364.9836.

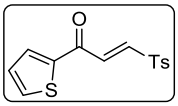
***(E)-1-(6-methoxynaphthalen-2-yl)-3-tosylprop-2-en-1-one (41aa)***




The title compound was prepared following the general procedure **2.9.3** described above using **S5aa** (0.5 mmol, 106 mg, 1.0 equiv.) and **S16** (0.75 mmol, 134 mg, 1.5 equiv.). The product was isolated in 65% yield (119 mg), yellow solid, mp 164-166 °C, eluent: (hexane/EtOAc, 80/20); **$^{1}H$ NMR (400 MHz, $CDCl_3$)**: $\delta$ 2.46 (s, 3H), 3.96 (s, 3H), 7.17 (s, 1H), 7.22-7.27 (m, 1H), 7.35-7.44 (m, 3H), 7.80 (d, *J* = 12.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 16.0

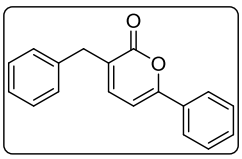
Hz, 1H), 8.44 (s, 1H); **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)**: $\delta$ 21.7, 55.5, 105.9, 120.2, 124.6, 127.6, 127.8, 128.3, 130.2, 131.3, 131.5, 131.5, 132.8, 135.8, 138.0, 141.7, 145.5, 160.5, 186.9; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{21}H_{18}NaO_4S^+$ 389.0818; found: 389.0814.

***(E)-1-(thiophen-2-yl)-3-tosylprop-2-en-1-one (41ac)***




The title compound was prepared following the general procedure **2.9.3** described above using **S5ac** (0.5 mmol, 69 mg, 1.0 equiv.) and **S16** (0.75 mmol, 134 mg, 1.5 equiv.). The product was isolated in 53% yield (77 mg), yellow solid, mp 143-145 °C, eluent: (hexane/EtOAc, 80/20); **$^{1}H$ NMR (400 MHz, $CDCl_3$)**: $\delta$ 2.45 (s, 3H), 7.21 (t, $J$ = 4.0 Hz, 1H), 7.32-7.41 (m, 3H), 7.75 (d, $J$ = 16.0 Hz, 1H), 7.78-7.85 (m, 3H), 7.88 (d, $J$ = 4.0 Hz, 1H); **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)**: $\delta$ 21.7, 128.3, 128.8, 130.2, 132.2, 134.1, 135.5, 136.7, 141.8, 143.7, 145.6, 179.3; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{14}H_{12}NaO_3S_2^+$ 315.0120; found: 315.0121.

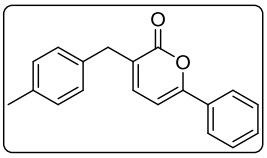
***3-benzyl-6-phenyl-2H-pyran-2-one (42a)***




The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 97% yield (25.4 mg), white solid, mp 118-120 °C, eluent: (hexane/EtOAc, 95/5); **$^{1}H$ NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.84 (s, 2H), 6.57 (d, $J$ = 6.8 Hz, 1H), 7.01 (d, $J$ = 6.8 Hz, 1H), 7.23-7.30 (m, 3H), 7.31-7.37 (m, 2H), 7.40-7.47

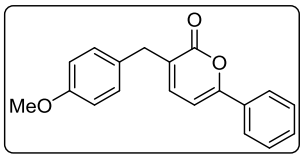
(m, 3H), 7.76-7.82 (m, 2H); **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.2, 101.2, 125.3, 126.7, 127.3, 128.7, 128.8, 129.3, 130.4, 131.4, 138.0, 139.8, 158.6, 162.7; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{18}H_{14}NaO_2^+$ 285.0886; found: 285.0884.

***3-(4-methylbenzyl)-6-phenyl-2H-pyran-2-one (42b)***



The title compound was prepared following the general procedure **2.9.5** described above using **40b** (0.2 mmol, 36.5 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 86% yield (23.8 mg), white solid, mp 145-147 °C, eluent: (hexane/EtOAc, 95/5); **$^{1}H$ NMR (400 MHz, $CDCl_3$)**: $\delta$ 2.34 (s, 3H), 3.80 (s, 2H), 6.56 (d, $J$ = 8.0 Hz, 1H), 7.01 (d, $J$ = 8.0 Hz, 1H), 7.11-7.20 (m, 4H), 7.38-7.47 (m, 3H), 7.74-7.83 (m, 2H); **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)**: $\delta$ 21.0, 35.8, 101.2, 125.3, 127.6, 128.9, 129.2, 129.4, 130.4, 131.4, 134.9, 136.2, 139.7, 158.6, 162.8; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{19}H_{16}NaO_2^+$ 299.1043; found: 299.1042.

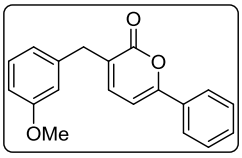
***3-(4-methoxybenzyl)-6-phenyl-2H-pyran-2-one (42c)***




The title compound was prepared following the general procedure **2.9.5** described above using **40c** (0.2 mmol, 39.7 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 87% yield (25.4 mg), white solid, mp 100-102 °C, eluent: (hexane/EtOAc, 90/10); **$^{1}H$ NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.78 (s, 2H), 3.80 (s, 3H), 6.56 (d, $J$ = 8.0 Hz, 1H), 6.88 (d, $J$ = 8.0 Hz, 2H), 7.00 (d, $J$ = 8.0 Hz, 1H), 7.19 (d,

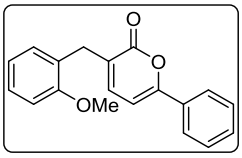
*J* = 8.0 Hz, 2H), 7.39-7.46 (m, 3H), 7.75-7.81 (m, 2H); **$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)**: $\delta$ 35.4, 55.3, 101.2, 114.1, 125.3, 127.8, 128.9, 130.0, 130.3, 130.4, 131.4, 139.6, 158.4, 158.6, 162.8; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{19}H_{16}NaO_3^+$ 315.0992; found: 315.0984.

***3-(3-methoxybenzyl)-6-phenyl-2H-pyran-2-one (42d)***




The title compound was prepared following the general procedure **2.9.5** described above using **40d** (0.2 mmol, 39.7 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 90% yield (26.3 mg), pale yellow solid, mp 80-82 °C, eluent: (hexane/EtOAc, 90/10); **$^1H$ NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.81 (s, 5H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.78-6.84 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.22-7.29 (m, 2H), 7.40-7.47 (m, 3H), 7.76-7.82 (m, 2H); **$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.2, 55.2, 101.2, 112.1, 115.0, 121.7, 125.3, 127.2, 128.9, 129.7, 130.4, 131.4, 139.6, 139.9, 158.7, 159.9, 162.8; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{19}H_{16}NaO_3^+$ 315.0992; found: 315.0985.

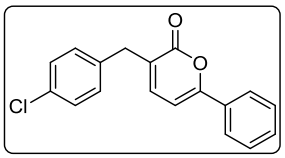
***3-(2-methoxybenzyl)-6-phenyl-2H-pyran-2-one (42e)***




The title compound was prepared following the general procedure **2.9.5** described above using **40e** (0.2 mmol, 39.7 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 92% yield (26.9 mg), pale yellow solid, mp 112-

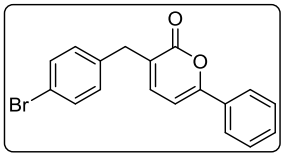
114 °C, eluent: (hexane/EtOAc, 90/10); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.81 (s, 3H), 3.83 (s, 2H), 6.54 (d, $J$ = 8.0 Hz, 1H), 6.87-6.99 (m, 3H), 7.22-7.29 (m, 2H), 7.38-7.46 (m, 3H), 7.74-7.81 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 30.6, 55.3, 101.3, 110.5, 120.7, 125.2, 126.2, 126.7, 128.2, 128.8, 130.2, 131.2, 131.6, 139.3, 157.6, 158.2, 162.9; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{19}H_{16}NaO_3^+$ 315.0992; found: 315.0985.

***3-(4-chlorobenzyl)-6-phenyl-2H-pyran-2-one (42f)***




The title compound was prepared following the general procedure **2.9.5** described above using **40f** (0.2 mmol, 40.6 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 91% yield (27.0 mg), yellow solid, mp 103-105 °C, eluent: (hexane/EtOAc, 92/8); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.80 (s, 2H), 6.58 (d, $J$ = 8.0 Hz, 1H), 7.05 (d, $J$ = 8.0 Hz, 1H), 7.21 (d, $J$ = 8.0 Hz, 2H), 7.30 (d, $J$ = 8.0 Hz, 2H), 7.40-7.47 (m, 3H), 7.75-7.82 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 35.7, 101.1, 125.3, 126.7, 128.8, 128.9, 130.5, 130.6, 131.3, 132.5, 136.5, 140.0, 159.0, 162.6; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{18}H_{13}ClNaO_2^+$ 319.0496; found: 319.0498.

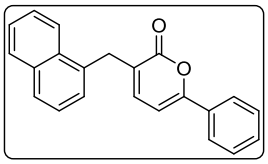
***3-(4-bromobenzyl)-6-phenyl-2H-pyran-2-one (42g)***




The title compound was prepared following the general procedure **2.9.5** described above using **40g** (0.2 mmol, 49.5 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0

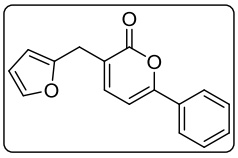
equiv.). The product was isolated in 89% yield (30.4 mg), yellow solid, mp 108-110 °C, eluent: (hexane/EtOAc, 90/10); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.78 (s, 2H), 6.58 (d, $J$ = 8.0 Hz, 1H), 7.05 (d, $J$ = 8.0 Hz, 1H), 7.16 (d, $J$ = 8.0 Hz, 2H), 7.39-7.47 (m, 5H), 7.74-7.82 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 35.7, 101.1, 120.6, 125.3, 126.6, 128.9, 130.5, 130.9, 131.3, 131.7, 137.0, 140.0, 159.0, 162.5; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{18}H_{13}BrNaO_2^+$ 362.9991; found: 362.9986.

***3-(naphthalen-2-ylmethyl)-6-phenyl-2H-pyran-2-one (42h)***



The title compound was prepared following the general procedure **2.9.5** described above using **40h** (0.2 mmol, 43.7 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 93% yield (29.1 mg), yellow solid, mp 80-82 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 4.30 (s, 2H), 6.44 (d, $J$ = 8.0 Hz, 1H), 6.70 (d, $J$ = 8.0 Hz, 1H), 7.39-7.44 (m, 4H), 7.45-7.52 (m, 3H), 7.74-7.80 (m, 2H), 7.82 (d, $J$ = 8.0 Hz, 1H), 7.85-7.92 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 33.1, 101.2, 124.1, 125.3, 125.6, 125.8, 126.4, 126.6, 127.8, 128.1, 128.8, 128.8, 130.4, 131.3, 131.9, 133.8, 133.9, 139.9, 158.4, 162.8; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{22}H_{16}NaO_2^+$ 335.1043; found: 335.1044.

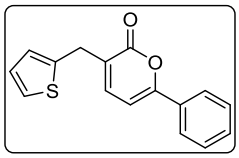
***3-(furan-2-ylmethyl)-6-phenyl-2H-pyran-2-one (42i)***



The title compound was prepared following the general procedure **2.9.5** described above using **40i** (0.2 mmol, 31.7 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The

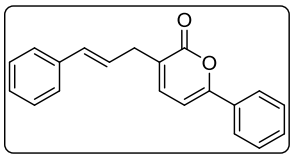
product was isolated in 92% yield (23.2 mg), reddish brown semi solid, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.87 (s, 2H), 6.20 (d, $J$ = 2.8 Hz, 1H), 6.35 (br, 1H), 6.61 (d, $J$ = 8.0 Hz, 1H), 7.14 (d, $J$ = 8.0 Hz, 1H), 7.37 (d, $J$ = 0.8 Hz, 1H), 7.41-7.46 (m, 3H), 7.77-7.82 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 28.6, 101.2, 107.5, 110.5, 124.2, 125.3, 128.9, 130.5, 131.3, 140.1, 141.9, 151.3, 159.0, 162.4; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{16}H_{12}NaO_3^+$ 275.0679; found: 275.0675.

***6-phenyl-3-(thiophen-2-ylmethyl)-2H-pyran-2-one (42j)***




The title compound was prepared following the general procedure **2.9.5** described above using **40j** (0.2 mmol, 34.9 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 94% yield (25.2 mg), reddish brown solid, mp 100-102 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 4.04 (s, 2H), 6.60 (d, $J$ = 8.0 Hz, 1H), 6.93-7.00 (m, 2H), 7.17 (d, $J$ = 8.0 Hz, 1H), 7.20 (d, $J$ = 4.8 Hz, 1H), 7.39-7.46 (m, 3H), 7.76-7.82 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 30.1, 101.2, 124.5, 125.3, 126.4, 126.5, 127.1, 128.8, 130.5, 131.2, 139.9, 140.0, 158.9, 162.4; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{16}H_{12}NaO_2S^+$ 291.0450; found: 291.0449.

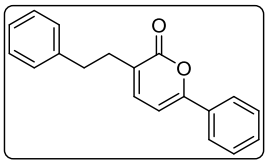
***3-cinnamyl-6-phenyl-2H-pyran-2-one (42k)***




The title compound was prepared following the general procedure **2.9.5** described above using **40k** (0.2 mmol, 38.9 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 73% yield (21.0 mg), yellow solid, mp 101-103 °C,

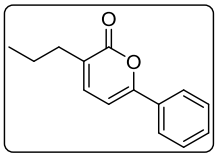
eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.42 (d, $J$ = 6.8 Hz, 2H), 6.34 (dt, $J$ = 16.0, 8.0 Hz, 1H), 6.55 (d, $J$ = 16.0 Hz, 1H), 6.63 (d, $J$ = 8.0 Hz, 1H), 7.19-7.35 (m, 4H), 7.39 (d, $J$ = 8.0 Hz, 2H), 7.41-7.48 (m, 3H), 7.77-7.85 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 33.5, 101.2, 125.3, 125.5, 126.1, 126.2, 127.4, 128.5, 128.9, 130.4, 131.4, 132.9, 137.0, 139.6, 158.8, 162.7; **HRMS (ESI-TOF) m/z**: [M + Na]$^+$ calcd for $C_{20}H_{16}NaO_2^+$ 311.1043; found: 311.1042.

***3-phenethyl-6-phenyl-2H-pyran-2-one (42l)***



The title compound was prepared following the general procedure **2.9.5** described above using **40l** (0.2 mmol, 36.5 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 93% yield (25.7 mg), white solid, mp 115-117 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 2.8 (t, $J$ = 8.0 Hz, 2H), 2.95 (t, $J$ = 8.0 Hz, 2H), 6.55 (d, $J$ = 8.0 Hz, 1H), 7.05 (d, $J$ = 8.0 Hz, 1H), 7.15-7.23 (m, 3H), 7.24-7.32 (m, 2H), 7.39-7.47 (m, 3H), 7.76-7.83 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 32.6, 34.0, 101.1, 125.2, 126.0, 126.6, 128.4, 128.5, 128.8, 130.3, 131.4, 139.8, 141.0, 158.6, 162.8; **HRMS (ESI-TOF) m/z**: [M + Na]$^+$ calcd for $C_{19}H_{16}NaO_2^+$ 299.1043; found: 299.1042.

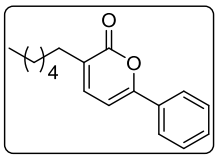
***6-phenyl-3-propyl-2H-pyran-2-one (42m)***



The title compound was prepared following the general procedure **2.9.5** described above using **40m** (0.2 mmol, 24.1 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0

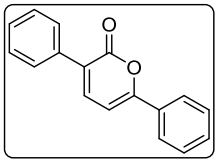
equiv.). The product was isolated in 76% yield (16.3 mg), colorless semi solid, eluent: (hexane/EtOAc, 97/3); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 0.99 (t, $J$ = 8.0 Hz, 3H), 1.65 (sext, $J$ = 8.0 Hz, 2H), 2.49 (t, $J$ = 8.0 Hz, 2.0H), 6.61 (d, $J$ = 8.0 Hz, 1H), 7.20 (d, $J$ = 8.0 Hz, 1H), 7.39-7.47 (m, 3H), 7.77-7.84 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 13.7, 21.2, 32.5, 101.2, 125.2, 127.8, 128.8, 130.3, 131.6, 139.1, 158.4, 163.0; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{14}H_{14}NaO_2^+$ 237.0886; found: 237.0883.

***3-hexyl-6-phenyl-2H-pyran-2-one (42n)***



The title compound was prepared following the general procedure **2.9.5** described above using **40n** (0.2 mmol, 32.5 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0 equiv.). The product was isolated in 87% yield (22.3 mg), colorless semi solid, eluent: (hexane/EtOAc, 97/3); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 0.82-0.94 (m, 3H), 1.20-1.44 (m, 6H), 1.57-1.65 (m, 2H), 2.50 (t, $J$ = 8.0 Hz, 2H), 6.61 (d, $J$ = 6.8 Hz, 1H), 7.19 (d, $J$ = 6.8 Hz, 1H), 7.40-7.47 (m, 3H), 7.77-7.84 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 14.0, 22.6, 27.9, 28.9, 30.5, 31.6, 101.2, 125.2, 128.1, 128.8, 130.2, 131.6, 138.9, 158.3, 163.0; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{17}H_{20}NaO_2^+$ 279.1356; found: 279.1354.

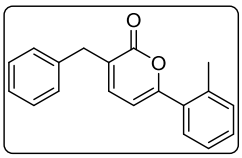
***3,6-diphenyl-2H-pyran-2-one (42o)***



The title compound was prepared following the general procedure **2.9.5** described above using **40o** (0.2 mmol, 30.9 mg, 2.0 equiv.) and **41a** (0.1 mmol, 28.6 mg, 1.0

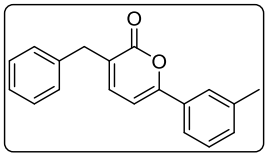
equiv.). The product was isolated in 70% yield (17.4 mg), light yellow solid, mp 153-155 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 6.80 (d, $J$ = 8.0 Hz, 1H), 7.34-7.50 (m, 6H), 7.58 (d, $J$ = 8.0 Hz, 1H), 7.73 (d, $J$ = 8.0 Hz, 2H), 7.84-7.92 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 101.7, 125.5, 125.7, 128.1, 128.4, 128.4, 128.9, 130.7, 131.2, 134.8, 140.3, 159.8, 161.4; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{17}H_{12}NaO_2^+$ 271.0730; found: 271.0727.

***3-benzyl-6-(o-tolyl)-2H-pyran-2-one (42p)***



The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41p** (0.1 mmol, 30.1 mg, 1.0 equiv.). The product was isolated in 88% yield (24.3 mg), yellow solid, mp 107-109 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 2.45 (s, 3H), 3.83 (s, 2H), 6.23 (d, $J$ = 8.0 Hz, 1H), 6.99 (d, $J$ = 8.0 Hz, 1H), 7.20-7.25 (m, 2H), 7.27-7.38 (m, 6H), 7.43 (d, $J$ = 8.0 Hz, 1H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 20.8, 36.2, 105.2, 126.0, 126.7, 127.0, 128.7, 128.9, 129.4, 130.0, 131.2, 132.1, 136.5, 137.9, 139.6, 160.5, 163.0; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{19}H_{16}NaO_2^+$ 299.1043; found: 299.1042.

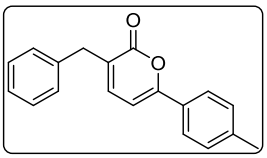
***3-benzyl-6-(m-tolyl)-2H-pyran-2-one (42q)***



The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41q** (0.1 mmol, 30.1 mg, 1.0 equiv.). The

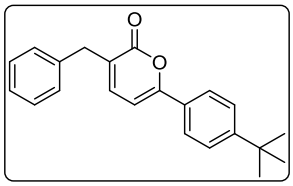
product was isolated in 87% yield (24.1 mg), yellow solid, mp 88-90 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 2.40 (s, 3H), 3.84 (s, 2H), 6.55 (d, $J$ = 8.0 Hz, 1H), 7.00 (d, $J$ = 8.0 Hz, 1H), 7.20-7.37 (m, 7H), 7.57 (d, $J$ = 8.0 Hz, 1H), 7.63 (s, 1H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 21.4, 36.2, 101.1, 122.4, 125.9, 126.7, 127.1, 128.7, 128.7, 129.3, 131.2, 131.3, 138.0, 138.7, 139.9, 158.9, 162.8; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{19}H_{16}NaO_2^+$ 299.1043; found: 299.1042.

***3-benzyl-6-(p-tolyl)-2H-pyran-2-one (42r)***



The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41r** (0.1 mmol, 30.1 mg, 1.0 equiv.). The product was isolated in 94% yield (26.0 mg), yellow solid, mp 102-104 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 2.39 (s, 3H), 3.83 (s, 2H), 6.52 (d, $J$ = 8.0 Hz, 1H), 6.71 (d, $J$ = 8.0 Hz, 1H), 7.20-7.29 (m, 5H), 7.30-7.36 (m, 2H), 7.68 (d, $J$ = 8.0 Hz, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 21.4, 36.2, 100.6, 125.2, 126.6, 126.7, 128.6, 129.3, 129.6, 138.1, 140.0, 140.8, 158.9, 162.8; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{19}H_{16}NaO_2^+$ 299.1043; found: 299.1042.

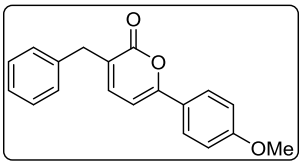
***3-benzyl-6-(4-(tert-butyl) phenyl)-2H-pyran-2-one (42s)***



The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41s** (0.1 mmol, 34.3 mg, 1.0

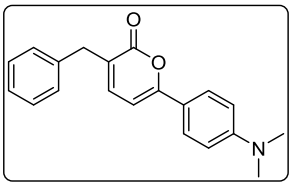
equiv.). The product was isolated in 92% yield (29.3 mg), light yellow solid, mp 129-131 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 1.33 (s, 9H), 3.82 (s, 2H), 6.53 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.21-7.29 (m, 3H), 7.30-7.37 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 31.1, 34.8, 36.2, 100.7, 125.1, 125.8, 126.6, 126.7, 128.6, 128.6, 129.3, 138.1, 140.0, 153.9, 158.9, 162.9; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{22}H_{22}NaO_2^+$ 341.1512; found: 341.1513.

***3-benzyl-6-(4-methoxyphenyl)-2H-pyran-2-one (42t)***




The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41t** (0.1 mmol, 31.6 mg, 1.0 equiv.). The product was isolated in 93% yield (27.2 mg), yellow solid, mp 86-88 °C, eluent: (hexane/EtOAc, 90/10); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.82 (s, 2H), 3.85 (s, 3H), 6.45 (d, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.22-7.29 (m, 3H), 7.30-7.37 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.1, 55.4, 99.8, 114.2, 124.0, 125.8, 126.6, 126.9, 128.6, 129.2, 138.2, 140.2, 158.9, 161.4, 162.9; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{19}H_{16}NaO_3^+$ 315.0992; found: 315.0978.

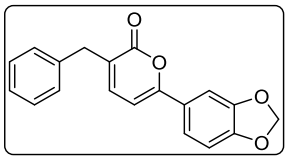
***3-benzyl-6-(4-(dimethylamino) phenyl)-2H-pyran-2-one (42u)***




The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41u** (0.1 mmol, 33.0 mg, 1.0 equiv.). The

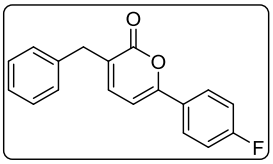
product was isolated in 83% yield (25.3 mg), yellow semi solid, eluent: (hexane/EtOAc, 85/15); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.02 (s, 6H), 3.80 (s, 2H), 6.38 (d, $J$ = 8.0 Hz, 1H), 6.68 (d, $J$ = 8.0 Hz, 2H), 6.97 (d, $J$ = 8.0 Hz, 1H), 7.20-7.35 (m, 5H), 7.67 (d, $J$ = 8.0 Hz, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.1, 40.1, 98.3, 111.6, 118.7, 124.0, 126.5, 126.7, 128.6, 129.2, 138.6, 140.7, 151.6, 160.0, 163.3; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{20}H_{19}NNaO_2^+$ 328.1308; found: 328.1308.

***6-(benzo[d] [1,3] dioxol-5-yl)-3-benzyl-2H-pyran-2-one (42v)***



The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41v** (0.1 mmol, 33.1 mg, 1.0 equiv.). The product was isolated in 89% yield (27.3 mg), yellow solid, mp 133-135 °C, eluent: (hexane/EtOAc, 85/15); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.81 (s, 2H), 6.01 (s, 2H), 6.41 (d, $J$ = 8.0 Hz, 1H), 6.84 (d, $J$ = 8.0 Hz, 1H), 6.98 (d, $J$ = 8.0 Hz, 1H), 7.22 (s, 1H), 7.23-7.29 (m, 3H), 7.30-7.36 (m, 3H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.1, 100.2, 101.6, 105.5, 108.6, 120.1, 125.6, 126.3, 126.6, 128.6, 129.2, 138.1, 140.0, 148.3, 149.6, 158.5, 162.7; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{19}H_{14}NaO_4^+$ 329.0784; found: 329.0784.

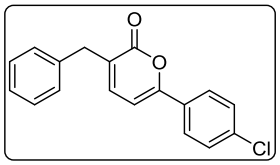
***3-benzyl-6-(4-fluorophenyl)-2H-pyran-2-one (42w)***



The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41w** (0.1 mmol, 30.4 mg, 1.0

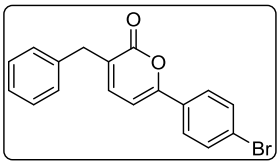
equiv.). The product was isolated in 86% yield (24.1 mg), yellow solid, mp 108-110 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.83 (s, 2H), 6.49 (d, $J$ = 8.0 Hz, 1H), 7.00 (d, $J$ = 8.0 Hz, 1H), 7.11 (t, $J$ = 8.0 Hz, 2H), 7.22-7.29 (m, 3H), 7.30-7.36 (m, 2H), 7.73-7.82 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.2, 100.9 (d, $J$ = 1.2 Hz), 116.0 (d, $J$ = 22.1 Hz), 126.7, 127.2, 127.4 (d, $J$ = 8.3 Hz), 127.7 (d, $J$ = 3.2 Hz), 128.7, 129.3, 137.9, 139.8, 157.8, 162.5, 164.0 (d, $J$ = 250 Hz); **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{18}H_{13}FNaO_2^+$ 303.0792; found: 303.0793.

***3-benzyl-6-(4-chlorophenyl)-2H-pyran-2-one (42x)***




The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41x** (0.1 mmol, 32.1 mg, 1.0 equiv.). The product was isolated in 88% yield (26.1 mg), light yellow solid, mp 106-108 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.83 (s, 2H), 6.55 (d, $J$ = 8.0 Hz, 1H), 7.01 (d, $J$ = 8.0 Hz, 1H), 7.27 (d, $J$ = 8.0 Hz, 3H), 7.31-7.38 (m, 2H), 7.41 (d, $J$ = 8.0 Hz, 2H), 7.72 (d, $J$ = 8.0 Hz, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.2, 101.4, 126.5, 126.8, 127.8, 128.7, 129.2, 129.3, 129.9, 136.5, 137.8, 139.6, 157.5, 162.4; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{18}H_{13}ClNaO_2^+$ 319.0496; found: 319.0498.

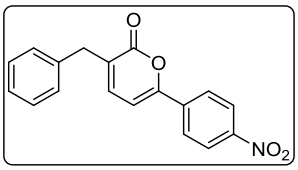
***3-benzyl-6-(4-bromophenyl)-2H-pyran-2-one (42y)***




The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41y** (0.1 mmol, 36.5 mg, 1.0 equiv.). The

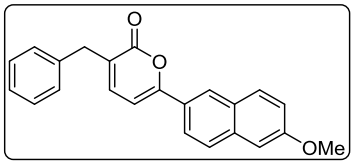
product was isolated in 91% yield (31.0 mg), yellow solid, mp 117-119 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.83 (s, 2H), 6.56 (d, $J$ = 8.0 Hz, 1H), 7.01 (d, $J$ = 8.0 Hz, 1H), 7.27 (d, $J$ = 8.0 Hz, 3H), 7.31-7.38 (m, 2H), 7.57 (d, $J$ = 8.0 Hz, 2H), 7.65 (d, $J$ = 8.0 Hz, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.3, 101.4, 124.9, 126.7, 126.8, 127.9, 128.7, 129.3, 130.3, 132.2, 137.8, 139.6, 157.6, 162.4; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{18}H_{13}BrNaO_2^+$ 362.9991; found: 362.9992.

***3-benzyl-6-(4-nitrophenyl)-2H-pyran-2-one (42z)***




The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41z** (0.1 mmol, 33.1 mg, 1.0 equiv.). The product was isolated in 83% yield (25.5 mg), reddish brown solid, mp 124-126 °C, eluent: (hexane/EtOAc, 85/15); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.86 (s, 2H), 6.72 (d, $J$ = 6.8 Hz, 1H), 7.06 (d, $J$ = 8.0 Hz, 1H), 7.25-7.31 (m, 3H), 7.32-7.39 (m, 2H), 7.96 (d, $J$ = 8.0 Hz, 2H), 7.29 (d, $J$ = 8.0 Hz, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.4, 103.7, 124.2, 125.9, 126.9, 128.8, 129.3, 129.9, 137.0, 137.4, 139.0, 148.5, 155.8, 161.8; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{18}H_{13}NNaO_4^+$ 330.0737; found: 330.0736.

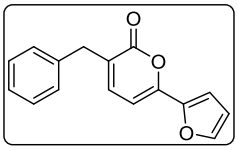
***3-benzyl-6-(6-methoxynaphthalen-2-yl)-2H-pyran-2-one (42aa)***




The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41aa** (0.1 mmol, 36.6 mg, 1.0

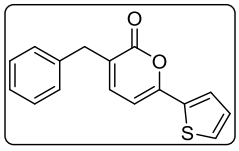
equiv.). The product was isolated in 92% yield (31.5 mg), yellow solid, mp 118-120 °C, eluent: (hexane/EtOAc, 85/15); **$^{1}$H NMR (400 MHz, CDCl$_3$)**: $\delta$ 3.84 (s, 2H), 3.91 (s, 3H), 6.60 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 7.16 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.22-7.30 (m, 3H), 7.30-7.37 (m, 2H), 7.67-7.75 (m, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 8.27 (s, 1H); **$^{13}$C{$^{1}$H} NMR (100 MHz, CDCl$_3$)**: $\delta$ 36.2, 55.3, 100.9, 105.7, 119.7, 122.4, 125.3, 126.2, 126.6, 127.4, 128.4, 128.6, 129.3, 130.4, 135.5, 138.1, 140.0, 158.9, 158.9, 162.9; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{23}H_{18}NaO_3^+$ 365.1148; found: 365.1149.

***3-benzyl-6-(furan-2-yl)-2H-pyran-2-one (42ab)***



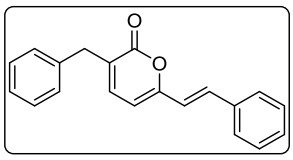
The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41ab** (0.1 mmol, 27.6 mg, 1.0 equiv.). The product was isolated in 87% yield (22.0 mg), reddish brown solid, mp 73-75 °C, eluent: (hexane/EtOAc, 95/5); **$^{1}$H NMR (400 MHz, CDCl$_3$)**: $\delta$ 3.81 (s, 2H), 6.47 (d, *J* = 8.0 Hz, 1H), 6.49-6.53 (m, 1H), 6.95 (d, *J* = 3.2 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.23-7.29 (m, 3H), 7.30-7.36 (m, 2H), 7.47 (s, 1H); **$^{13}$C{$^{1}$H} NMR (100 MHz, CDCl$_3$)**: $\delta$ 36.3, 99.7, 111.0, 112.3, 126.7, 126.9, 128.7, 129.3, 137.9, 139.8, 144.4, 146.5, 150.8, 161.9; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{16}H_{12}NaO_3^+$ 275.0679; found: 275.0679.

***3-benzyl-6-(thiophen-2-yl)-2H-pyran-2-one (42ac)***



The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41ac** (0.1 mmol, 29.3 mg, 1.0 equiv.). The product was isolated in 89% yield (23.9 mg), yellow solid, mp 103-105 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.80 (s, 2H), 6.38 (d, $J$ = 6.8 Hz, 1H), 6.95 (d, $J$ = 8.0 Hz, 1H), 7.07 (t, $J$ = 4.0 Hz, 1H), 7.21-7.28 (m, 3H), 7.29-7.35 (m, 2H), 7.39 (d, $J$ = 8.0 Hz, 1H), 7.53 (d, $J$ = 4.0 Hz, 1H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.3, 100.4, 126.7, 126.7, 128.2, 128.2, 128.7, 129.2, 135.1, 138.0, 139.8, 154.5, 162.0; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{16}H_{12}NaO_2S^+$ 291.0450; found: 291.0450.

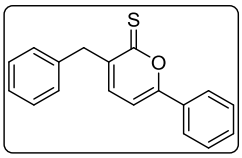
***(E)-3-benzyl-6-styryl-2H-pyran-2-one (42ad)***



The title compound was prepared following the general procedure **2.9.5** described above using **40a** (0.2 mmol, 33.7 mg, 2.0 equiv.) and **41ad** (0.1 mmol, 31.3 mg, 1.0 equiv.). The product was isolated in 78% yield (22.5 mg), yellow solid, mp 118-120 °C, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.82 (s, 2H), 6.07 (d, $J$ = 8.0 Hz, 1H), 6.59 (d, $J$ = 16.0 Hz, 1H), 6.92 (d, $J$ = 6.8 Hz, 1H), 7.22-7.29 (m, 3H), 7.30-7.40 (m, 5H), 7.45 (d, $J$ = 16.0 Hz, 1H), 7.49 (d, $J$ = 8.0 Hz, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 36.3, 105.2, 118.7, 126.7, 127.3, 127.7, 128.7, 128.9, 129.1,

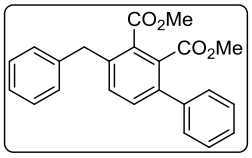
129.3, 134.2, 135.5, 138.0, 139.8, 157.4, 162.5; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{20}H_{16}NaO_2^+$ 311.1043; found: 311.1042.

***3-benzyl-6-phenyl-2H-pyran-2-thione (98)***




The title compound was prepared following the condition of Supuran et al.,[31] a solution of **42a** (0.1 mmol, 26.2 mg, 1.0 equiv.) and Lawesson's reagent (0.12 mmol, 48.5 mg, 1.2 equiv.) in dry toluene (2.0 mL) was refluxed until consumption of the starting material **42a** (TLC monitoring). Then the solvent was removed under vacuo and the obtained residue was purified by silica gel column chromatography to afford the title compound **98** in 85% yield (23.7 mg), yellow solid, mp 105-107 °C, eluent: (hexane/EtOAc, 97/3); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 4.10 (s, 2H), 6.83 (d, $J$ = 8.0 Hz, 1H), 6.89 (d, $J$ = 8.0 Hz, 1H), 7.22-7.30 (m, 3H), 7.31-7.38 (m, 2H), 7.43-7.49 (m, 3H), 7.84-7.89 (m, 2H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 39.9, 105.2, 125.6, 126.7, 128.7, 129.1, 129.5, 130.6, 131.2, 134.9, 137.9, 140.0, 163.9, 197.3; **HRMS (ESI-TOF) m/z**: $[M + H]^+$ calcd for $C_{18}H_{15}OS^+$ 279.0838; found: 279.0841.

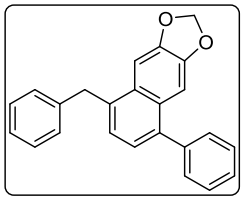
***Dimethyl 4-benzyl-[1,1'-biphenyl]-2,3-dicarboxylate (99)***




The title compound was prepared following the modified conditions of Ziegler et al.,[32] a solution of **42a** (0.1 mmol, 26.2 mg, 1.0 equiv.) and dimethylacetylene dicarboxylate (0.5 mmol, 62 µl, 5.0 equiv.) in xylene (0.2 mL) in a sealed tube was heated to 200 °C

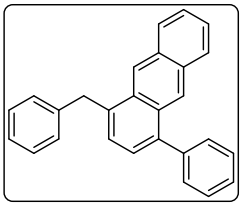
for 72 h. The reaction mixture was cooled to rt and the solvent was removed under vacuo to obtain the crude product which was purified by flash chromatography on silica gel to give **99** in 78% yield (28.1 mg), colorless liquid, eluent: (hexane/EtOAc, 95/5); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 3.57 (s, 3H), 3.77 (s, 3H), 4.17 (s, 2H), 7.18 (d, $J$ = 8.0 Hz, 2H), 7.21 (d, $J$ = 6.8 Hz, 1H), 7.27-7.32 (m, 5H), 7.34-7.42 (m, 4H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 38.9, 52.2, 52.5, 126.4, 127.6, 128.2, 128.3, 128.5, 129.1, 131.9, 132.1, 132.2, 132.2, 138.7, 139.2, 139.7, 139.9, 168.4, 169.0; **HRMS (ESI-TOF) m/z**: $[M + Na]^+$ calcd for $C_{23}H_{20}NaO_4^+$ 383.1254; found: 383.1252.

***5-benzyl-8-phenylnaphtho[2,3-d][1,3]dioxole (100)***



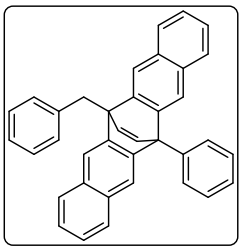
The title compound was prepared following the modified condition of Bronner et al.,[33] a solution of **42a** (0.1 mmol, 26.2 mg, 1.0 equiv.), 6-(trimethylsilyl) benzo[d][1,3] dioxol-5-yl trifluoromethane sulfonate (0.5 mmol, 172 mg, 5.0 equiv.) and CsF (0.5 mmol, 76.0 mg, 5.0 equiv.) in dry $CH_3CN$ (1.0 mL) was heated to 100 °C for 18 h. The reaction mixture was cooled to rt and the solvent was removed under vacuo to obtain the crude product which was purified by flash chromatography on silica gel to give **100** in 73% yield (24.7 mg), off-white solid, eluent: (hexane/EtOAc, 97/3); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 4.37 (s, 2H), 5.96 (s, 2H), 7.26 (s, 1H), 7.20-7.25 (m, 5H), 7.26-7.32 (m, 2H), 7.33 (s, 1H), 7.37-7.50 (m, 5H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 39.7, 101.0, 101.1, 103.1, 125.3, 125.8, 126.1, 127.1, 128.3, 128.5, 128.7, 129.2, 129.5, 130.0, 135.1, 138.6, 140.4, 141.3, 147.3, 147.5; **HRMS (ESI-TOF) m/z**: $[M + H]^+$ calcd for $C_{24}H_{19}O_2^+$ 339.1380; found: 339.1372.

***1-benzyl-4-phenylanthracene (101)***



The title compound was prepared following the modified condition of Bronner et al.,[33] a solution of **42a** (0.1 mmol, 26.2 mg, 1.0 equiv.), 3-(trimethylsilyl)naphthalen-2-yl trifluoromethane sulfonate (0.2 mmol, 70 mg, 2.0 equiv.) and CsF (0.2 mmol, 31.0 mg, 2.0 equiv.) in dry $CH_3CN$ (1.0 mL) was heated to 100 °C for 18 h. The reaction mixture was cooled to rt and the solvent was removed under vacuo to obtain the crude product which was purified by flash chromatography on silica gel to give **101** in 43% yield (14.8 mg), yellow semi solid, eluent: (hexane/$CH_2Cl_2$, 80/20); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$ 4.63 (s, 2H), 7.27-7.36 (m, 6H), 7.37-7.51 (m, 4H), 7.52-7.62 (m, 4H), 7.86 (d, $J$ = 8.0 Hz, 1H), 7.97 (d, $J$ = 8.0 Hz, 1H), 8.48 (s, 1H), 8.64 (s, 1H); **$^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$)**: $\delta$ 39.4, 123.2, 125.4, 125.6, 125.7, 125.9, 126.1, 126.2, 127.3, 128.3, 128.3, 128.5, 128.9, 130.2, 130.8, 130.9, 131.3, 131.3, 136.2, 139.4, 140.4, 141.1; **HRMS (ESI-TOF) m/z**: $[M + H]^+$ calcd for $C_{27}H_{21}^+$ 345.1638; found: 345.1632.

***6-benzyl-13-phenyl-6,13-dihydro-6,13-ethenopentacene (102)***



The title compound was also isolated from the above reaction in 22% yield (10.4 mg), colorless semi solid, eluent: (hexane/$CH_2Cl_2$, 80/20); **$^1$H NMR (400 MHz, $CDCl_3$)**: $\delta$

4.33 (s, 2H), 5.71 (s, 1H), 5.80 (s, 1H), 6.92-7.04 (m, 4H), 7.14 (d, $J$ = 8.0 Hz, 1H), 7.19 (d, $J$ = 8.0 Hz, 2H), 7.27-7.37 (m, 6H), 7.38 (s, 1H), 7.44-7.51 (m, 3H), 7.53-7.68 (m, 5H); **$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)**: $\delta$ 39.2, 50.3, 50.4, 121.4, 121.9, 123.6, 123.9, 125.4, 125.5, 125.5, 126.1, 126.5, 127.1, 127.1, 127.4, 128.4, 128.6, 128.9, 129.5, 131.7, 131.7, 133.7, 136.5, 140.6, 140.8, 141.7, 142.2, 142.5, 143.6, 144.4, 144.8; **HRMS (ESI-TOF) m/z**: $[M + H]^+$ calcd for $C_{37}H_{27}^+$ 471.2107; found: 471.2102.

## 2.10 References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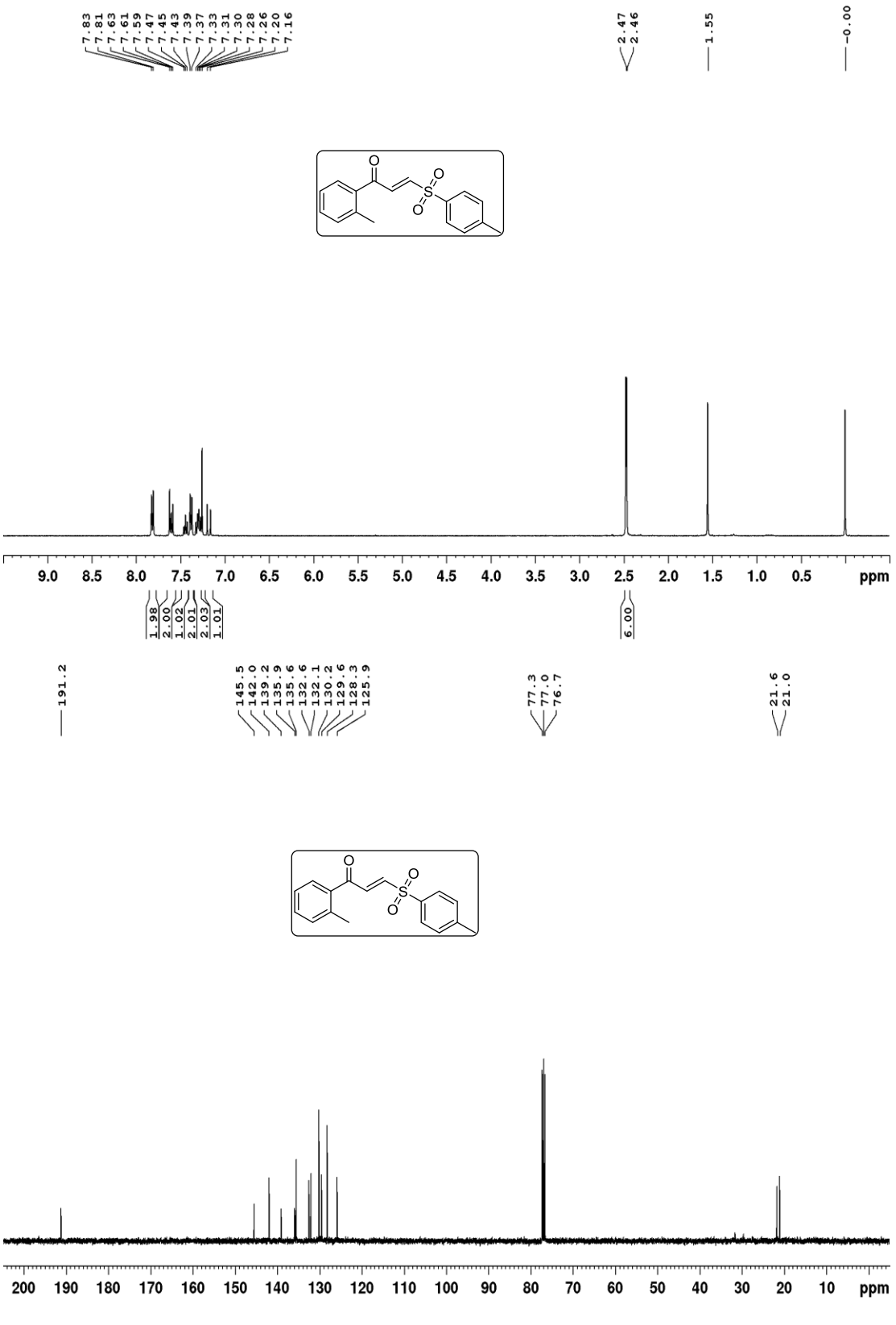
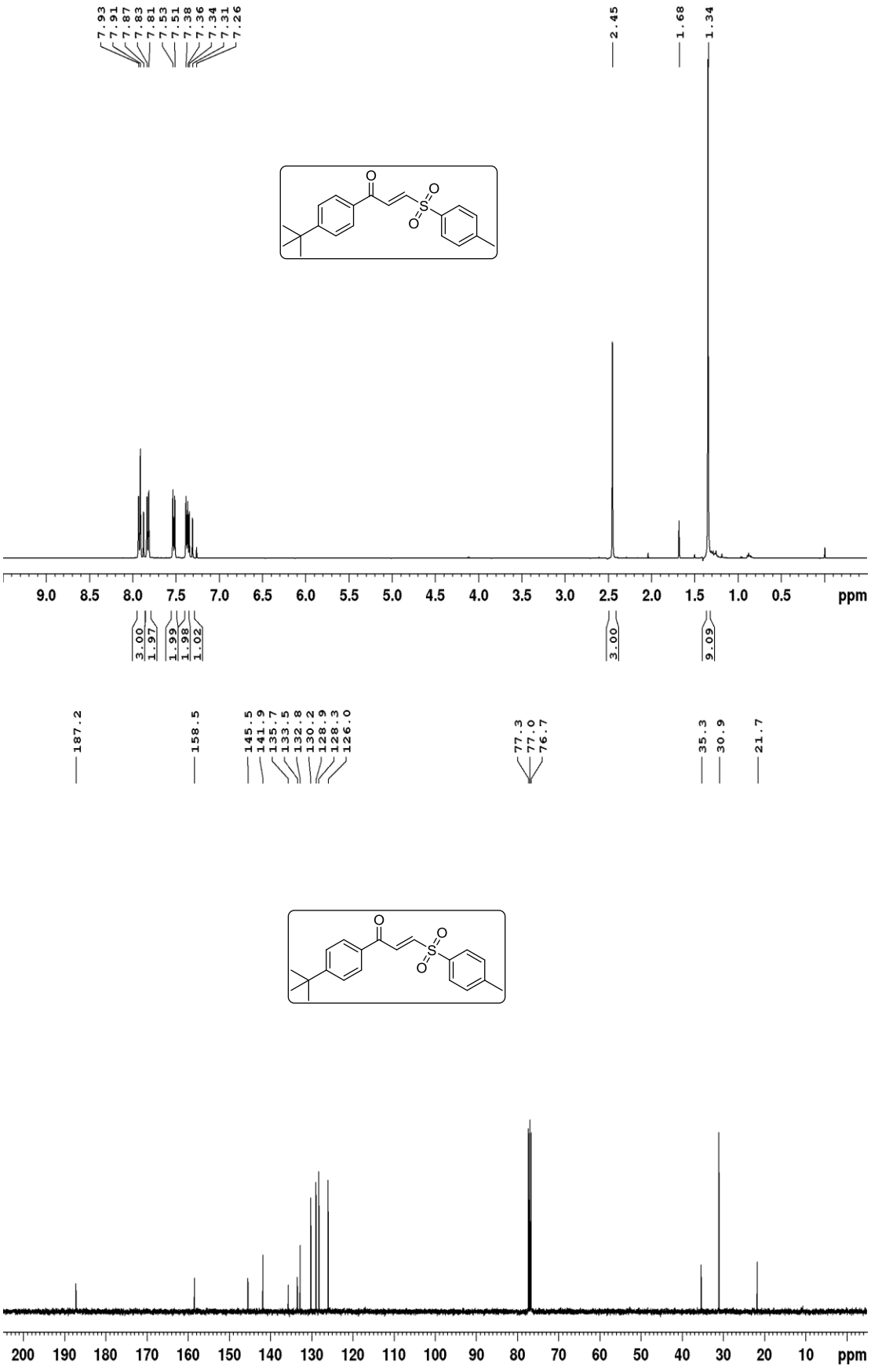
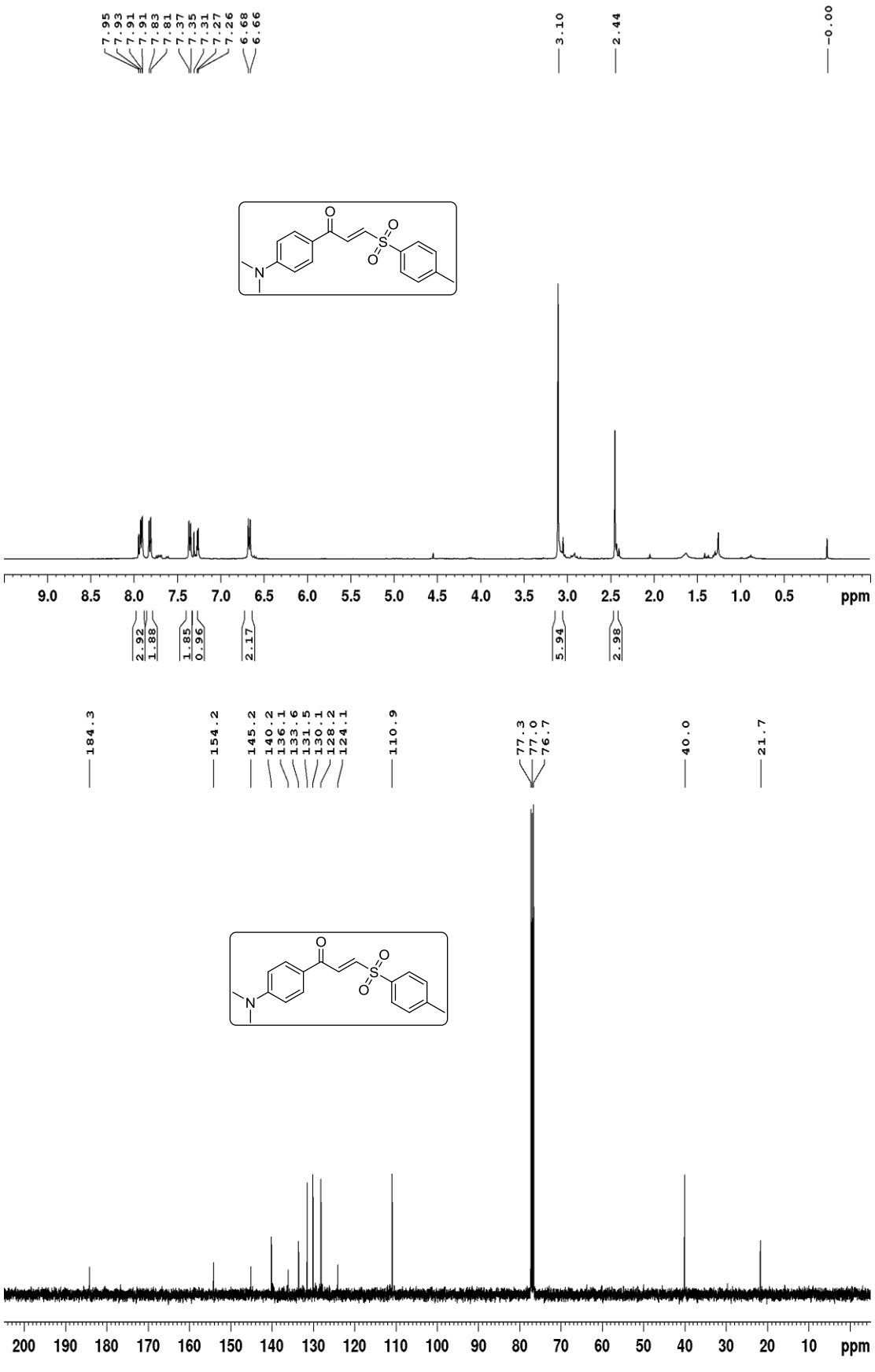
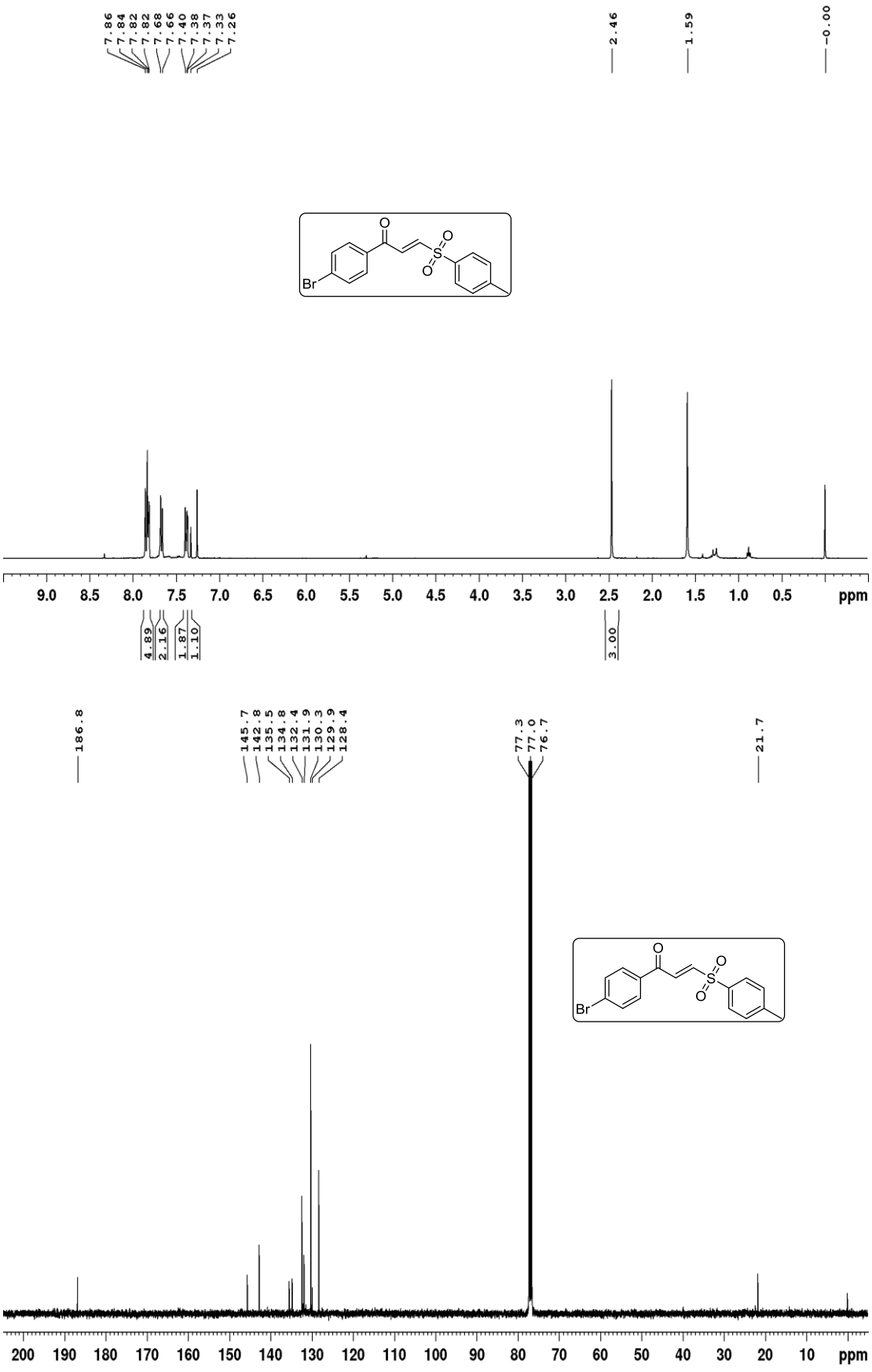
## 2.11 NMR Spectra of New Compounds [$^1$H NMR (400 MHz, $CDCl_3$) and $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$)]




7.93
7.91
7.87
7.83
7.81
7.53
7.51
7.38
7.36
7.34
7.31
7.26
2.45
1.68
1.34
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.00
1.97
1.99
1.98
1.02
3.00
9.09
187.2
158.5
145.5
141.9
135.7
133.5
132.8
130.2
128.9
128.3
126.0
77.3
77.0
76.7
35.3
30.9
21.7
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.95
7.93
7.91
7.91
7.83
7.81
7.37
7.35
7.31
7.27
7.26
6.68
6.66
3.10
2.44
0.00
O
O
S
O
N
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.92
1.88
1.85
0.96
2.17
5.94
2.98
184.3
154.2
145.2
140.2
136.1
133.6
131.5
130.1
128.2
124.1
110.9
77.3
77.0
76.7
40.0
21.7
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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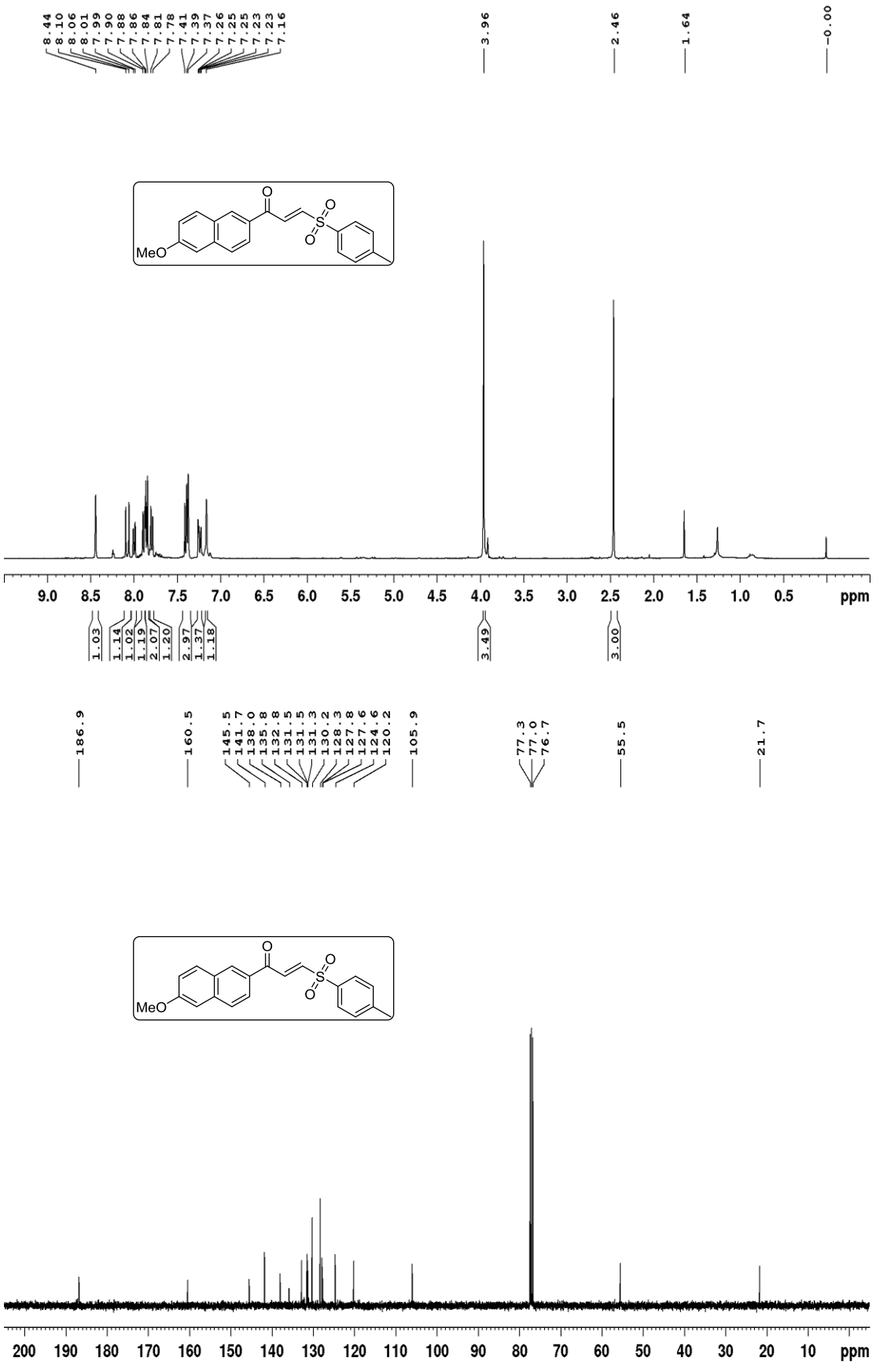
7.82
7.68
7.66
7.40
7.38
7.37
7.33
7.26
2.46
1.59
0.00
Br
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.89
2.16
1.87
1.10
3.00
186.8
145.7
142.8
135.5
134.8
132.4
131.9
130.3
129.9
128.4
77.3
77.0
76.7
21.7
Br
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.44
8.10
8.06
8.01
7.99
7.90
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7.81
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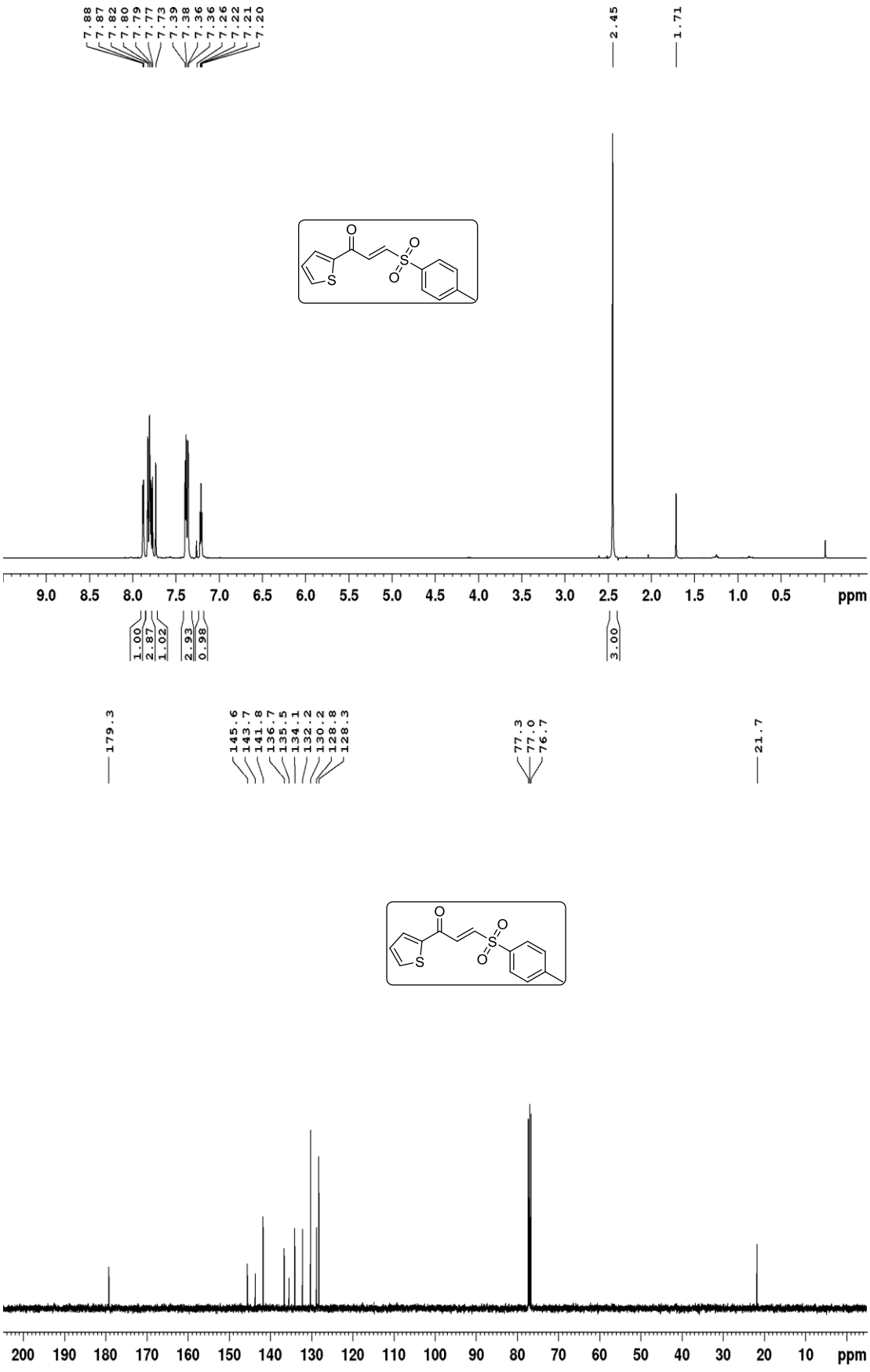
7.37
7.26
7.25
7.25
7.23
7.23
7.16
3.96
2.46
1.64
0.00
MeO
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.03
1.14
1.02
1.19
2.07
1.20
2.97
1.37
1.18
3.49
3.00
186.9
160.5
145.5
141.7
138.0
135.8
132.8
131.5
131.5
131.3
130.2
128.3
127.8
127.6
124.6
120.2
105.9
77.3
77.0
76.7
55.5
21.7
MeO
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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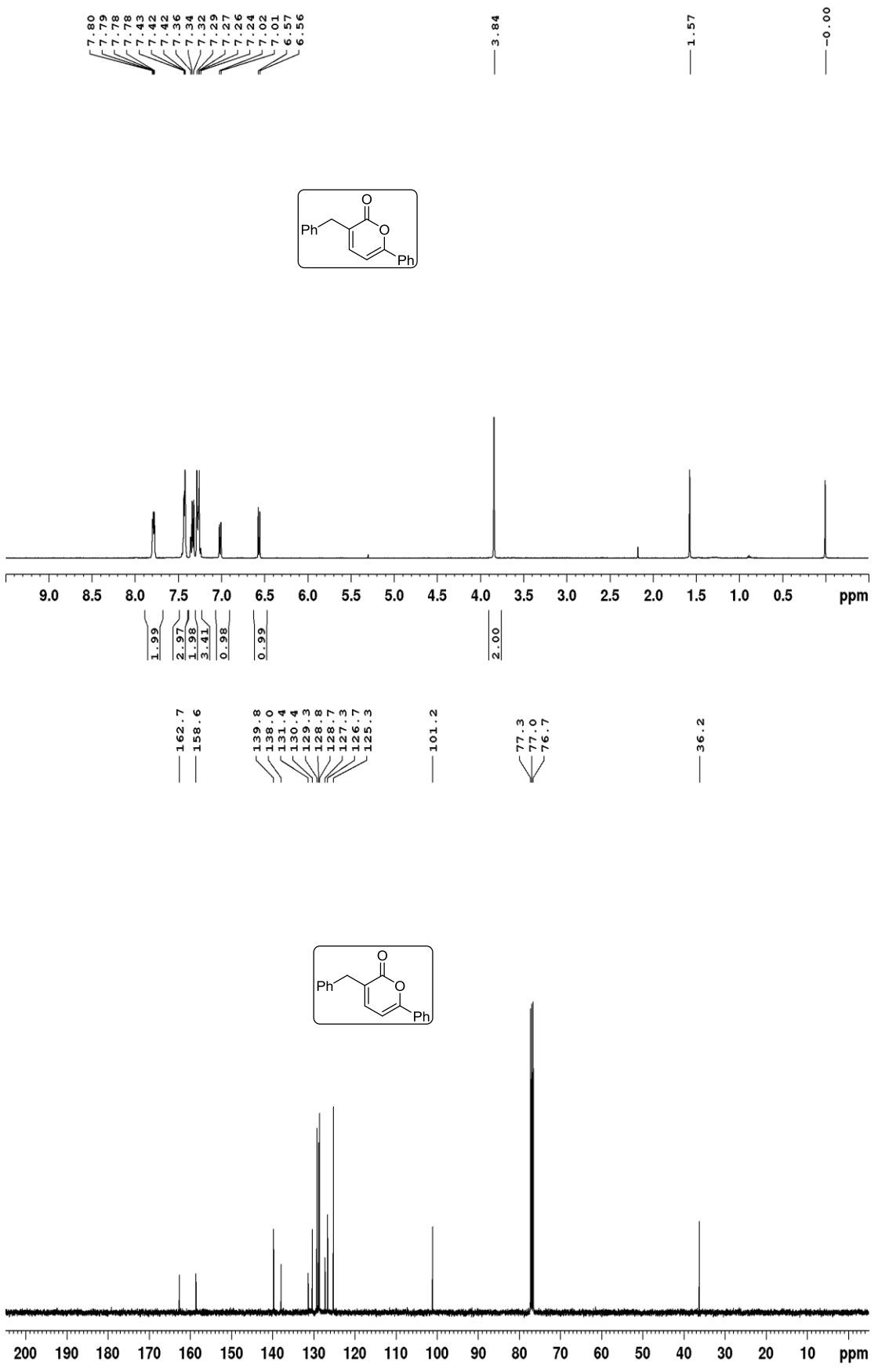
7.87
7.82
7.80
7.79
7.77
7.73
7.39
7.38
7.36
7.26
7.22
7.21
7.20
2.45
1.71
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
2.87
1.02
2.93
0.98
3.00
179.3
145.6
143.7
141.8
136.7
135.5
134.1
132.2
130.2
128.8
128.3
77.3
77.0
76.7
21.7
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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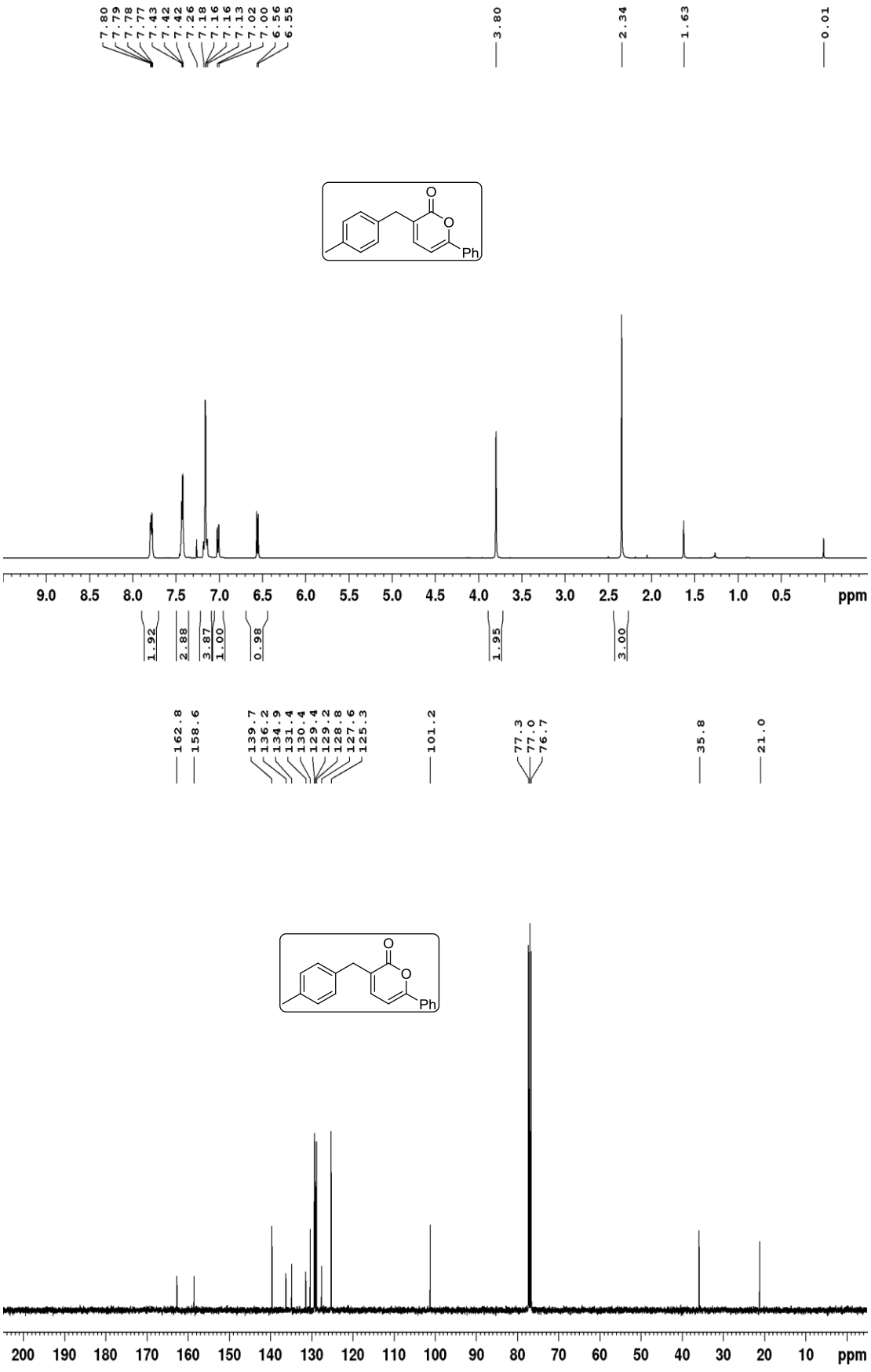
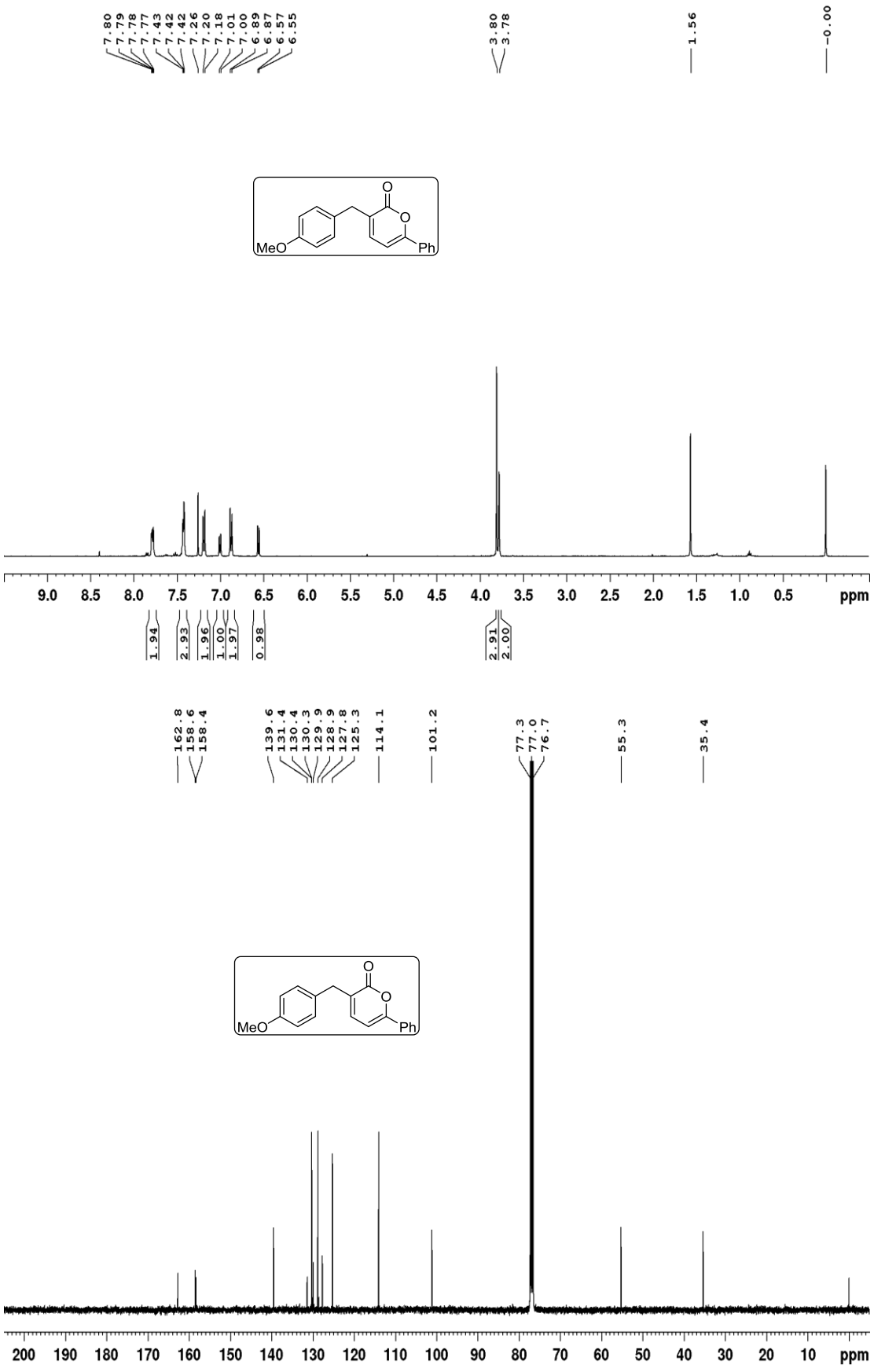
7.79
7.78
7.78
7.43
7.42
7.42
7.36
7.34
7.32
7.29
7.27
7.26
7.24
7.02
7.01
6.57
6.56
3.84
1.57
0.00
O
Ph
O
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.99
2.97
1.98
3.41
0.98
0.99
2.00
162.7
158.6
139.8
138.0
131.4
130.4
129.3
128.8
128.7
127.3
126.7
125.3
101.2
77.3
77.0
76.7
36.2
O
Ph
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.80
7.79
7.78
7.77
7.43
7.42
7.42
7.26
7.18
7.16
7.16
7.13
7.02
7.00
6.56
6.55
3.80
2.34
1.63
0.01
O
O
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.92
2.88
3.87
1.00
0.98
1.95
3.00
162.8
158.6
139.7
136.2
134.9
131.4
130.4
129.4
129.2
128.8
127.6
125.3
101.2
77.3
77.0
76.7
35.8
21.0
O
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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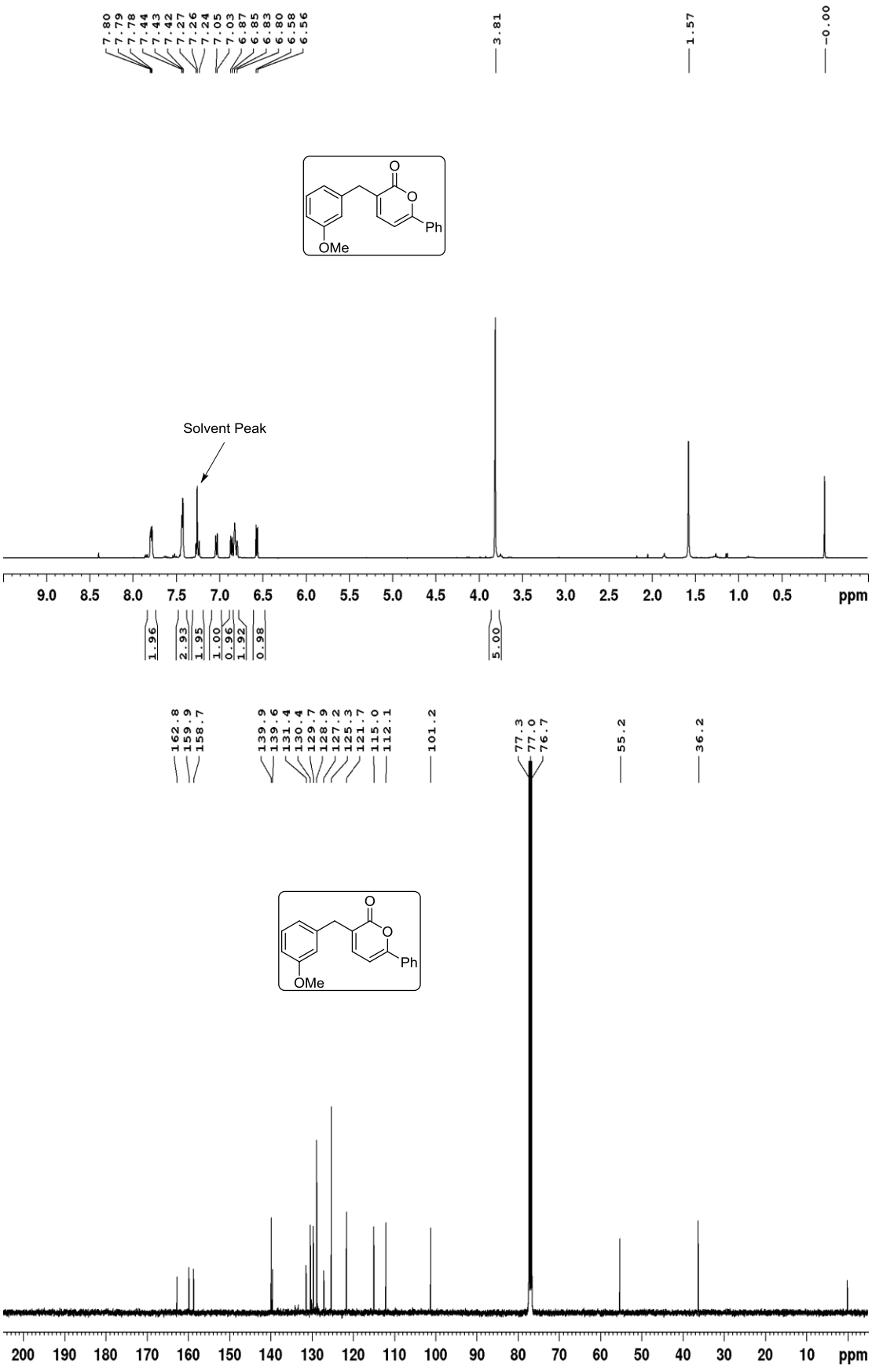
7.79
7.78
7.77
7.43
7.42
7.42
7.26
7.20
7.18
7.01
7.00
6.89
6.87
6.57
6.55
3.80
3.78
1.56
0.00
MeO
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.94
2.93
1.96
1.00
1.97
0.98
2.91
2.00
162.8
158.6
158.4
139.6
131.4
130.4
130.3
129.9
128.9
127.8
125.3
114.1
101.2
77.3
77.0
76.7
55.3
35.4
MeO
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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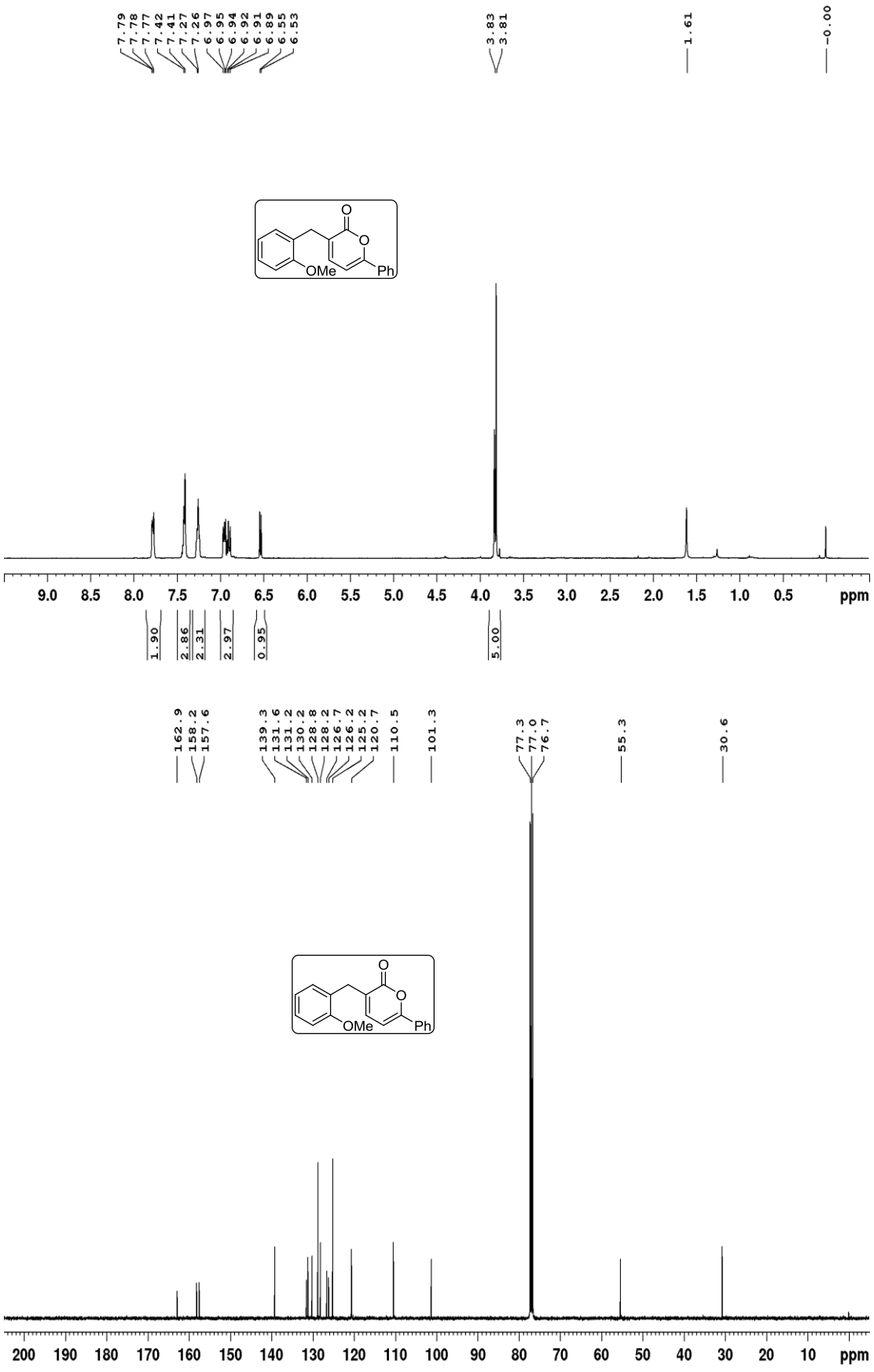
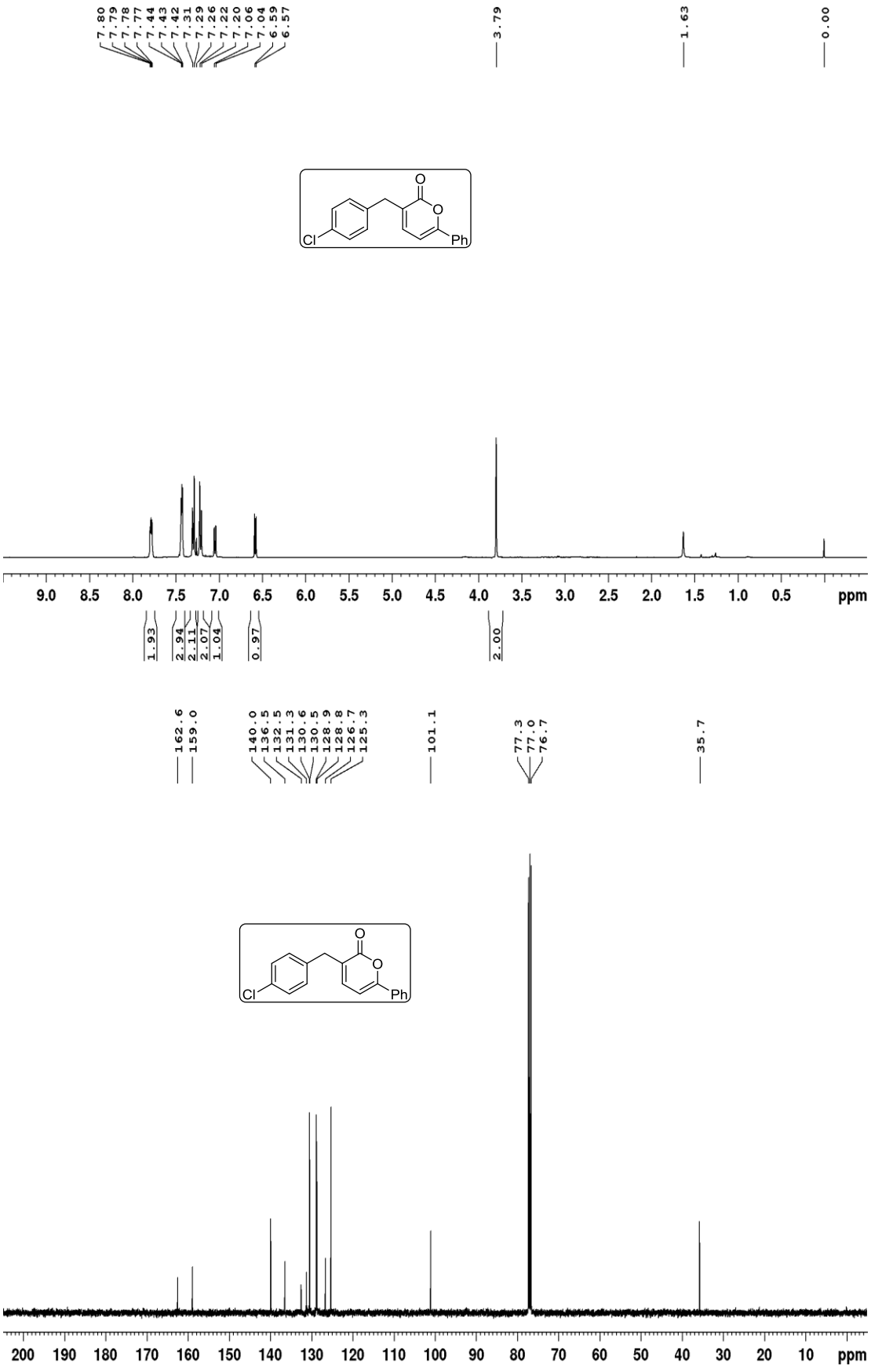
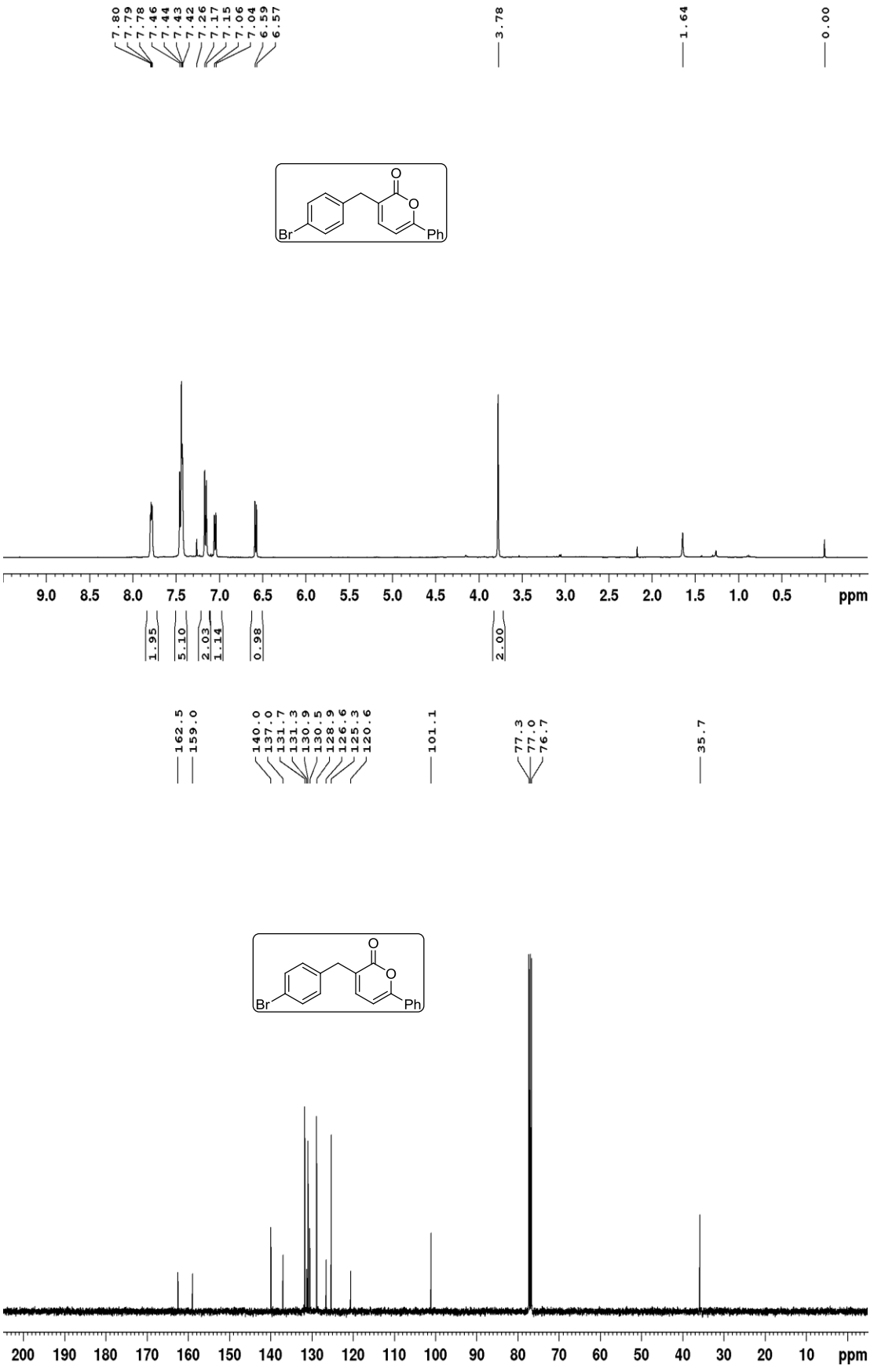
7.79
7.78
7.44
7.43
7.42
7.27
7.26
7.24
7.05
7.03
6.87
6.85
6.83
6.80
6.58
6.56
3.81
1.57
0.00
O
O
Ph
OMe
Solvent Peak
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.96
2.93
1.95
1.00
0.96
1.92
0.98
5.00
162.8
159.9
158.7
139.9
139.6
131.4
130.4
129.7
128.9
127.2
125.3
121.7
115.0
112.1
101.2
77.3
77.0
76.7
55.2
36.2
O
O
Ph
OMe
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.79
7.78
7.77
7.42
7.41
7.27
7.26
6.97
6.95
6.94
6.92
6.91
6.89
6.55
6.53
3.83
3.81
1.61
0.00
O
O
OMe
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.90
2.86
2.31
2.97
0.95
5.00
162.9
158.2
157.6
139.3
131.6
131.2
130.2
128.8
128.2
126.7
126.2
125.2
120.7
110.5
101.3
77.3
77.0
76.7
55.3
30.6
O
O
OMe
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.80
7.79
7.78
7.77
7.44
7.43
7.42
7.31
7.29
7.26
7.22
7.20
7.06
7.04
6.59
6.57
3.79
1.63
0.00
Cl
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.93
2.94
2.11
2.07
1.04
0.97
2.00
162.6
159.0
140.0
136.5
132.5
131.3
130.6
130.5
128.9
128.8
126.7
125.3
101.1
77.3
77.0
76.7
35.7
Cl
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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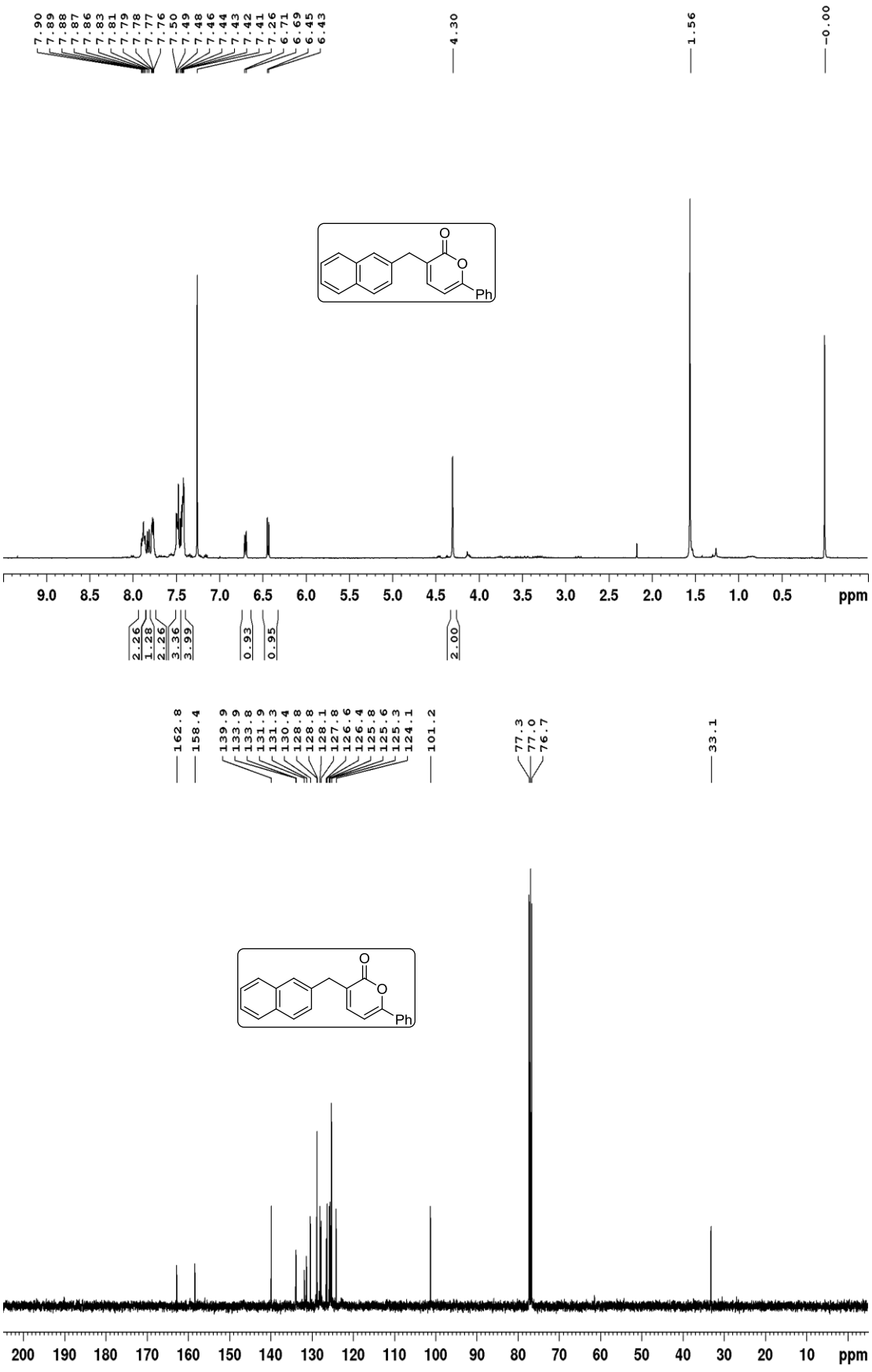
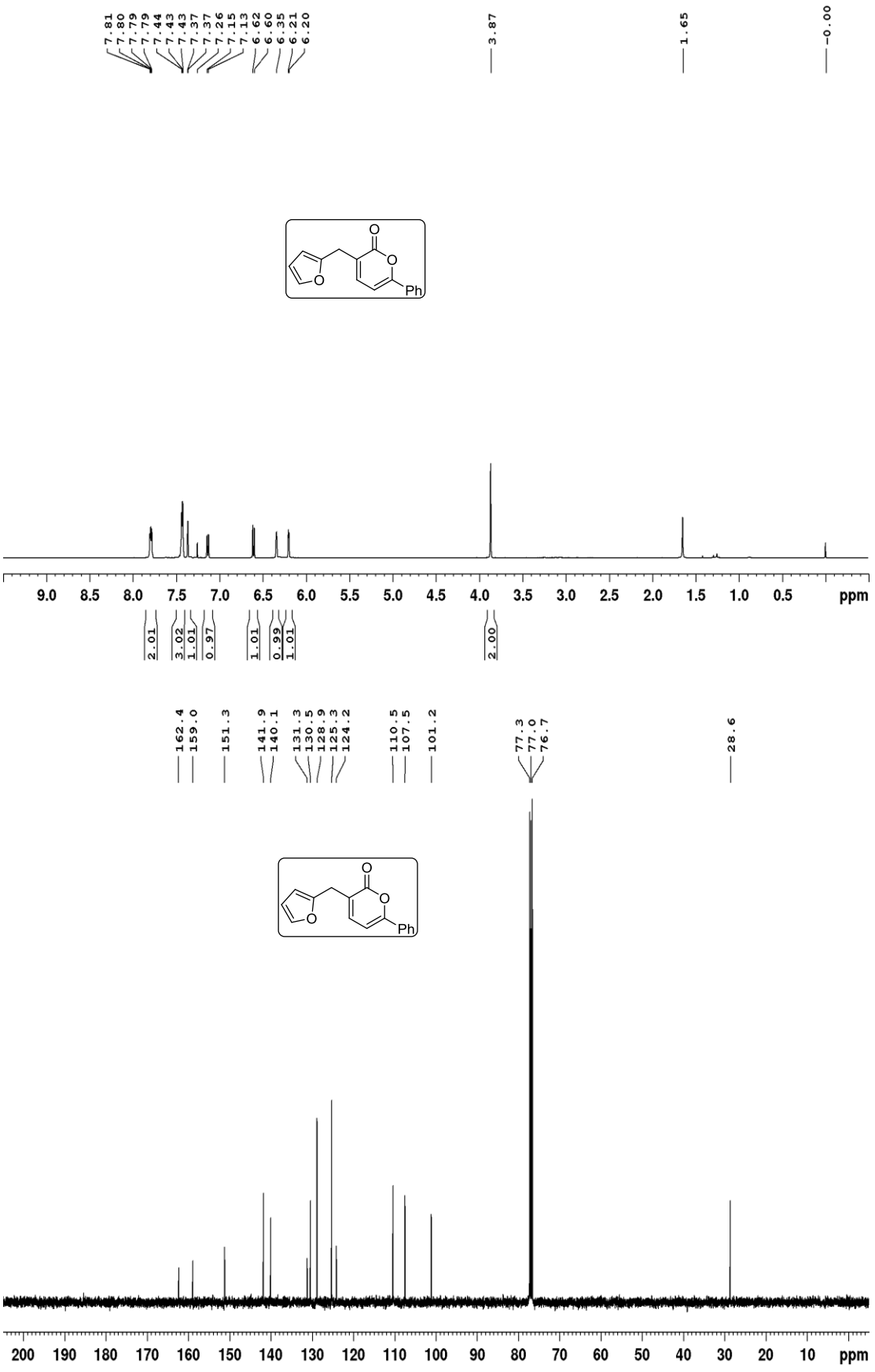
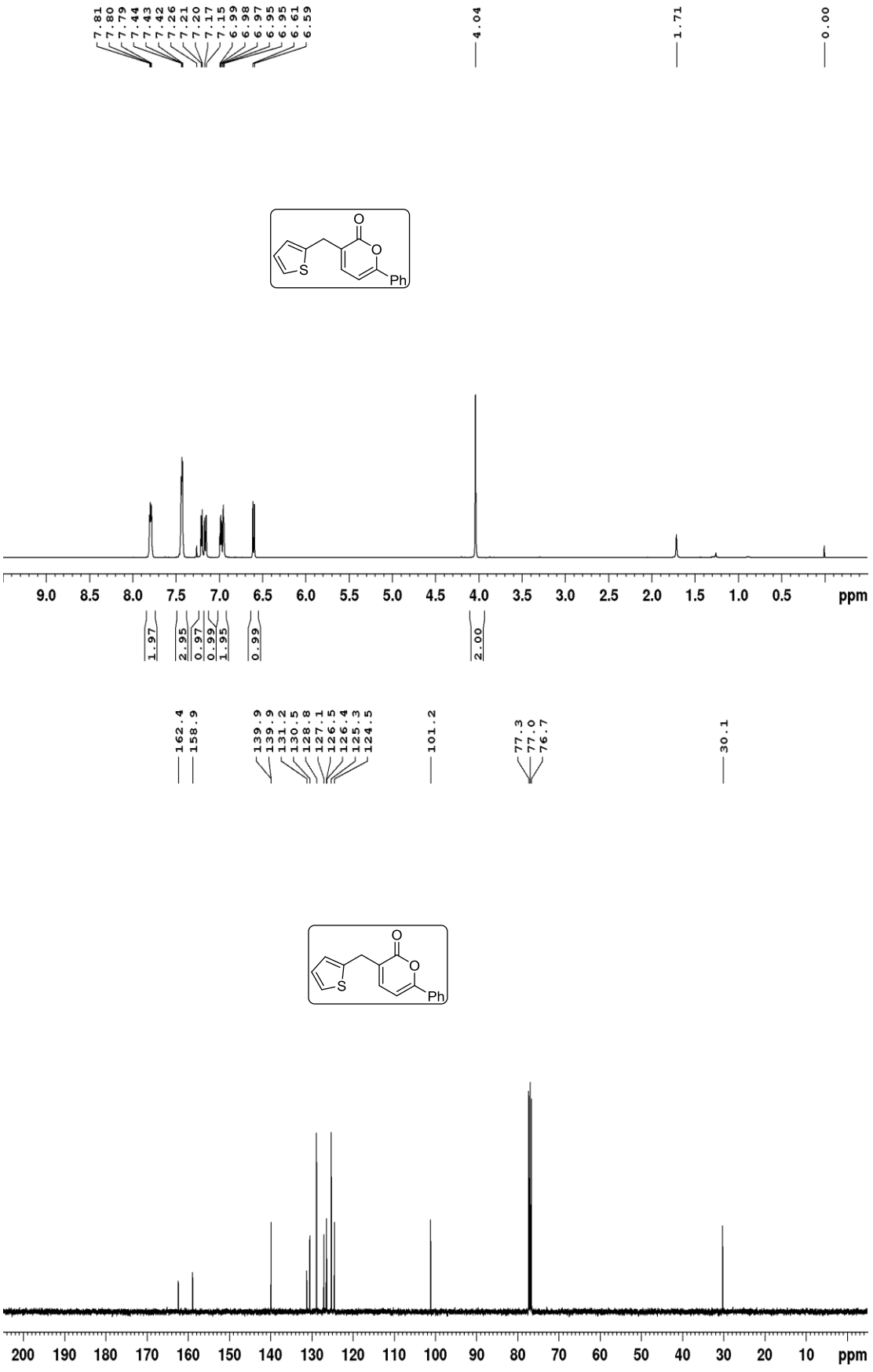
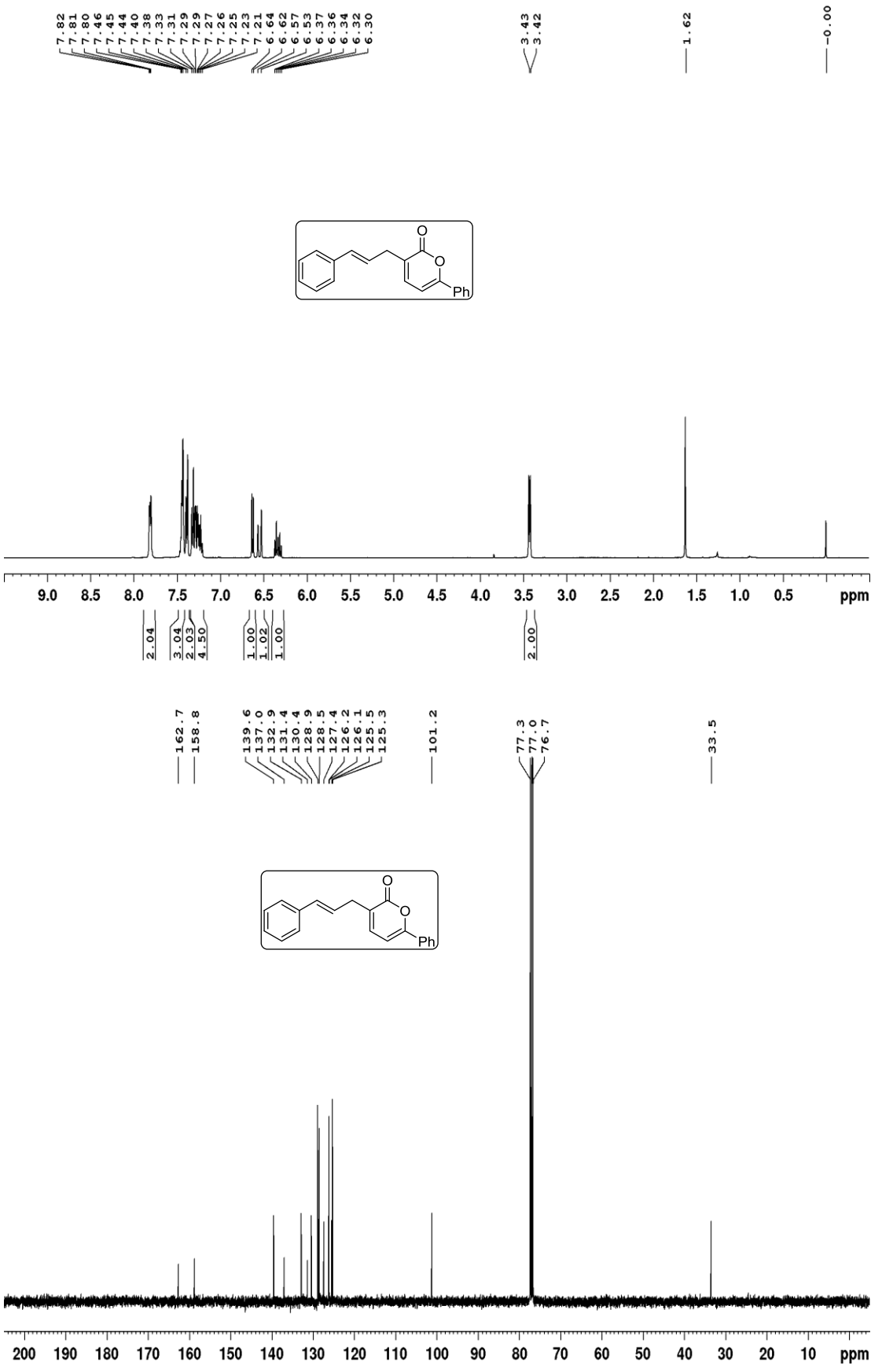
7.79
7.78
7.46
7.44
7.43
7.42
7.26
7.17
7.15
7.06
7.04
6.59
6.57
3.78
1.64
0.00
O
O
Br
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.95
5.10
2.03
1.14
0.98
2.00
162.5
159.0
140.0
137.0
131.7
131.3
130.9
130.5
128.9
126.6
125.3
120.6
101.1
77.3
77.0
76.7
35.7
O
O
Br
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.90
7.89
7.88
7.87
7.86
7.83
7.81
7.79
7.78
7.77
7.76
7.50
7.49
7.48
7.46
7.44
7.43
7.42
7.41
7.26
6.71
6.69
6.45
6.43
4.30
1.56
0.00
O
O
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.26
1.28
2.26
3.36
3.99
0.93
0.95
2.00
162.8
158.4
139.9
133.9
133.8
131.9
131.3
130.4
128.8
128.8
128.1
127.8
126.6
126.4
125.8
125.6
125.3
124.1
101.2
77.3
77.0
76.7
33.1
O
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.81
7.80
7.79
7.79
7.44
7.43
7.43
7.37
7.37
7.26
7.15
7.13
6.62
6.60
6.35
6.21
6.20
3.87
1.65
0.00
O
O
O
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.01
3.02
1.01
0.97
1.01
0.99
1.01
2.00
162.4
159.0
151.3
141.9
140.1
131.3
130.5
128.9
125.3
124.2
110.5
107.5
101.2
77.3
77.0
76.7
28.6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.81
7.80
7.79
7.44
7.43
7.42
7.26
7.21
7.20
7.17
7.15
6.99
6.98
6.97
6.95
6.95
6.61
6.59
4.04
1.71
0.00
O
O
S
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.97
2.95
0.97
0.99
1.95
0.99
2.00
162.4
158.9
139.9
139.9
131.2
130.5
128.8
127.1
126.5
126.4
125.3
124.5
101.2
77.3
77.0
76.7
30.1
O
O
S
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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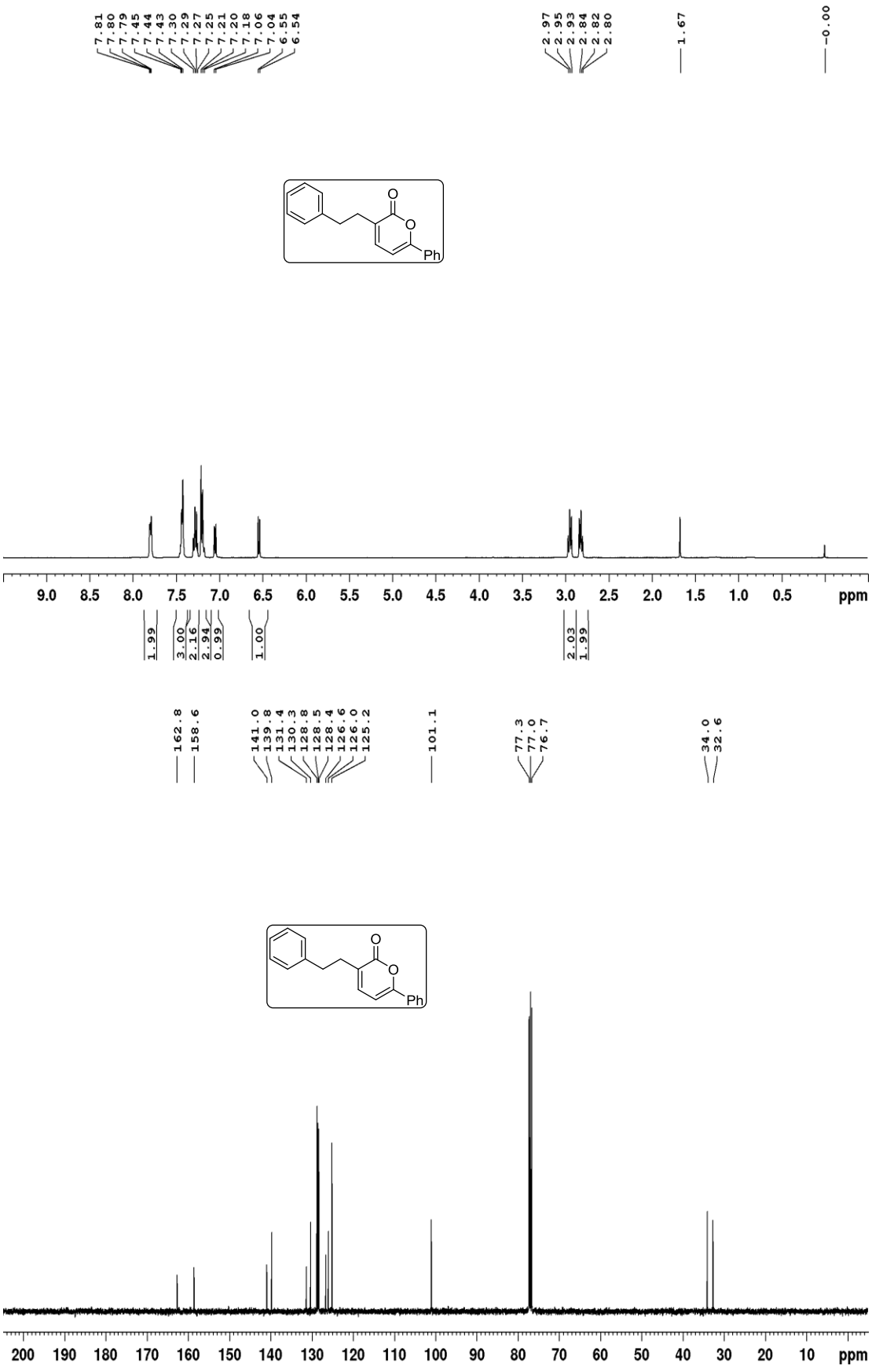
7.80
7.46
7.45
7.44
7.40
7.38
7.33
7.31
7.29
7.29
7.27
7.26
7.25
7.23
7.21
6.64
6.62
6.57
6.53
6.37
6.36
6.34
6.32
6.30
3.43
3.42
1.62
0.00
O
O
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.04
3.04
2.03
4.50
1.00
1.02
1.00
2.00
162.7
158.8
139.6
137.0
132.9
131.4
130.4
128.9
128.5
127.4
126.2
126.1
125.5
125.3
101.2
77.3
77.0
76.7
33.5
O
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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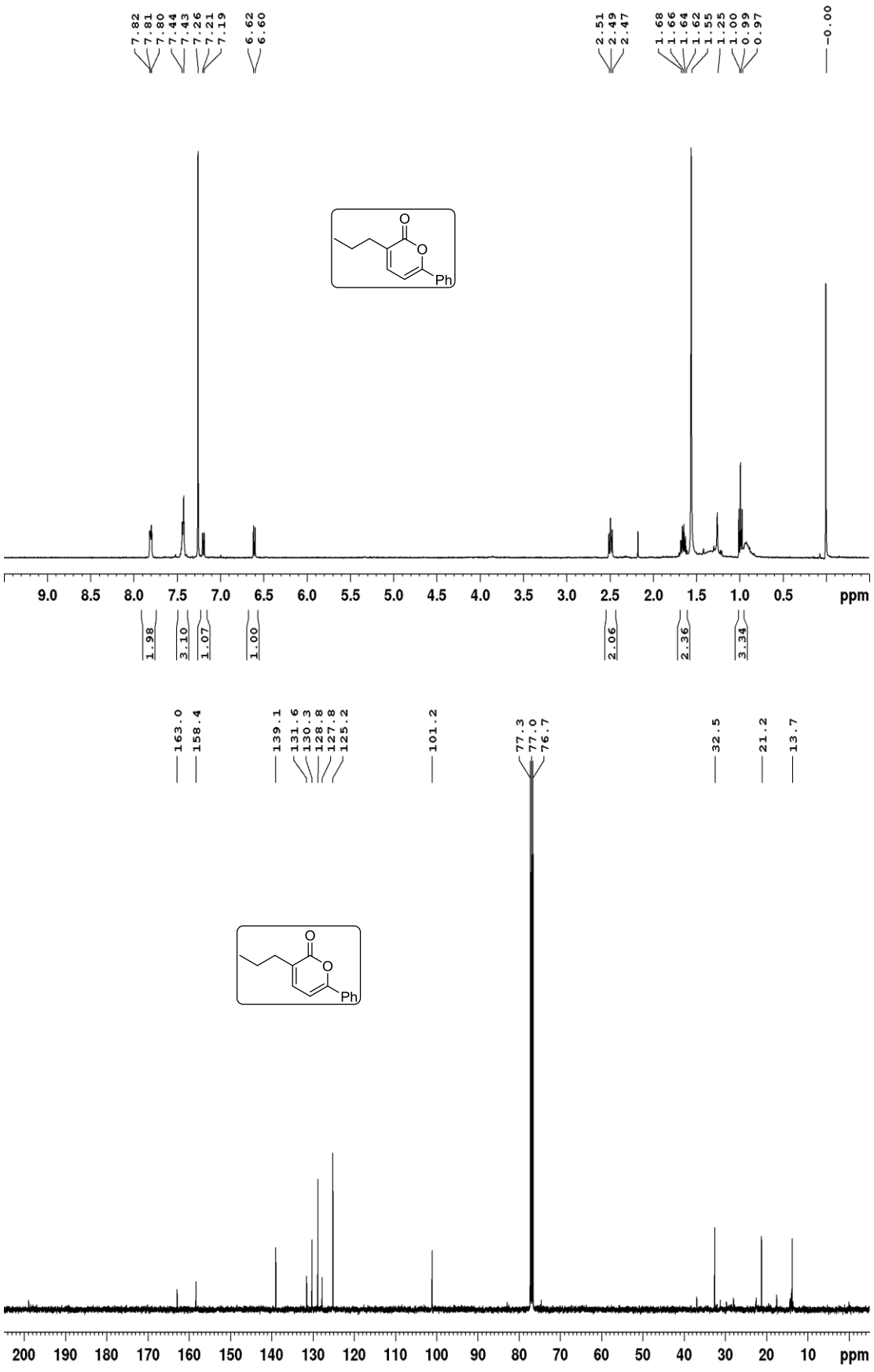
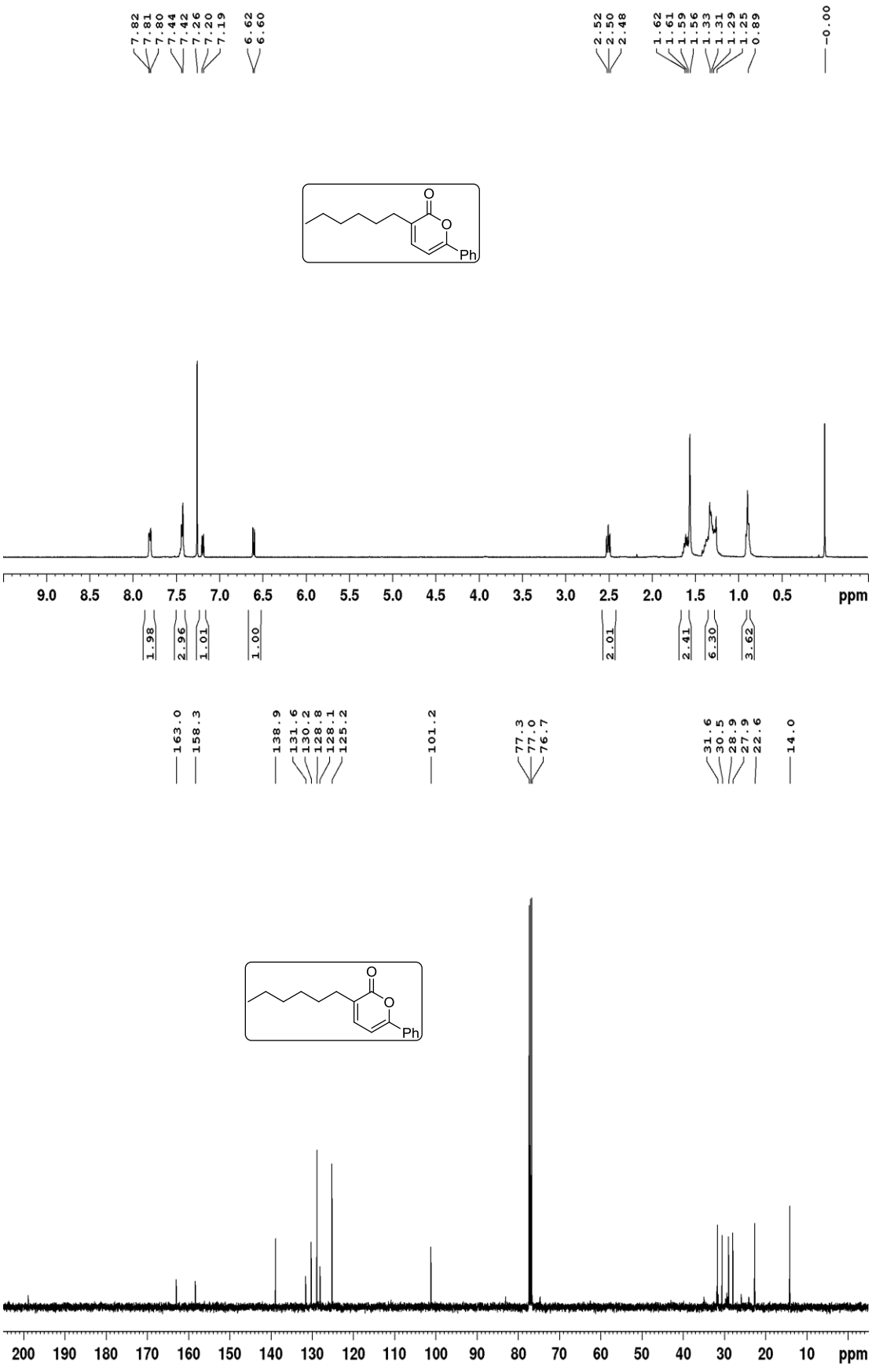
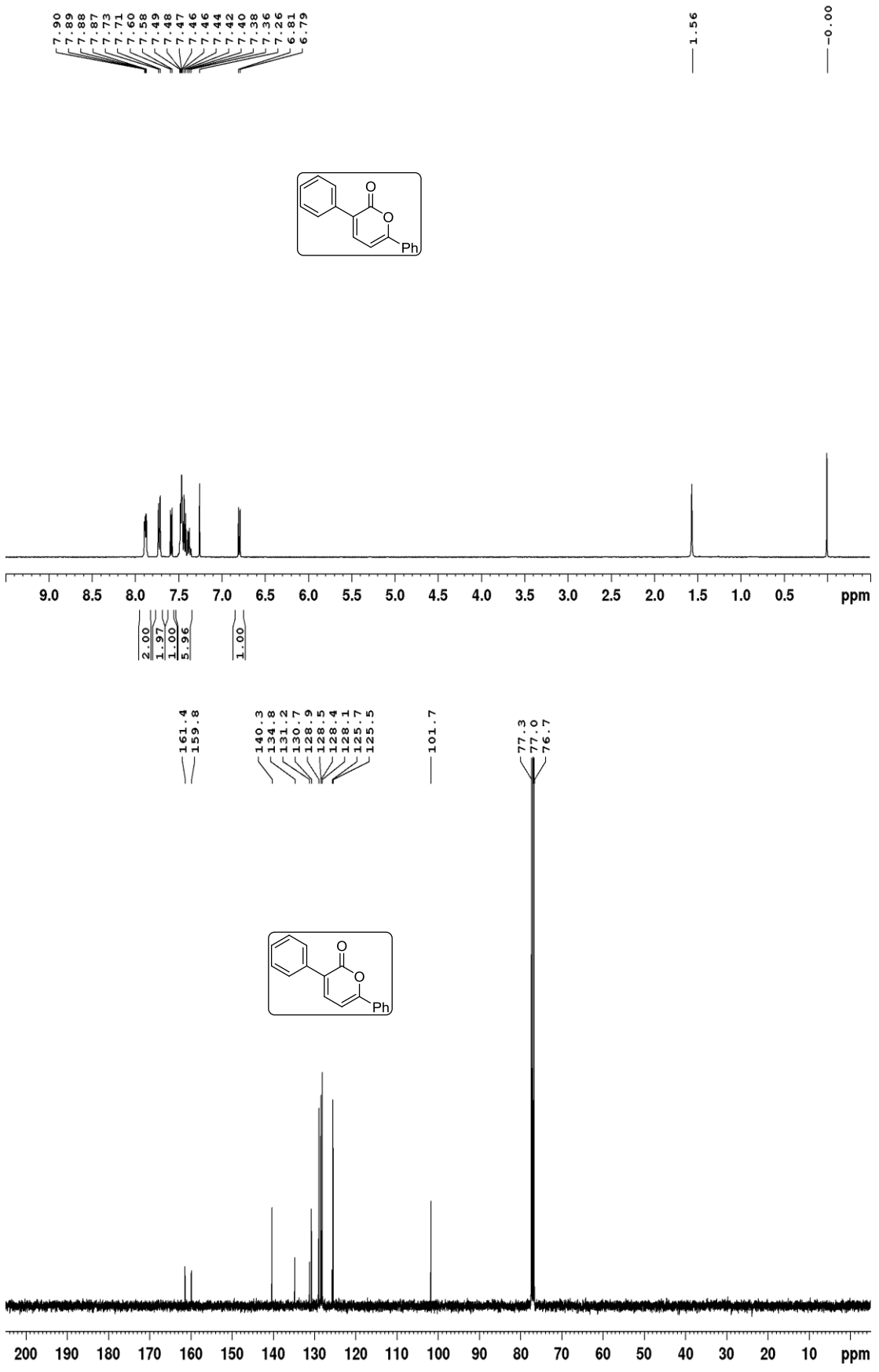
7.80
7.79
7.45
7.44
7.43
7.30
7.29
7.27
7.25
7.21
7.20
7.18
7.06
7.04
6.55
6.54
2.97
2.95
2.93
2.84
2.82
2.80
1.67
0.00
O
O
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.99
3.00
2.16
2.94
0.99
1.00
2.03
1.99
162.8
158.6
141.0
139.8
131.4
130.3
128.8
128.5
128.4
126.6
126.0
125.2
101.1
77.3
77.0
76.7
34.0
32.6
O
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.82
7.81
7.80
7.44
7.43
7.26
7.21
7.19
6.62
6.60
2.51
2.49
2.47
1.68
1.66
1.64
1.62
1.55
1.25
1.00
0.99
0.97
0.00
O
O
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.98
3.10
1.07
1.00
2.06
2.36
3.34
163.0
158.4
139.1
131.6
130.3
128.8
127.8
125.2
101.2
77.3
77.0
76.7
32.5
21.2
13.7
O
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.82
7.81
7.80
7.44
7.42
7.26
7.20
7.19
6.62
6.60
2.52
2.50
2.48
1.62
1.61
1.59
1.56
1.33
1.31
1.29
1.25
0.89
0.00
O
O
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.98
2.96
1.01
1.00
2.01
2.41
6.30
3.62
163.0
158.3
138.9
131.6
130.2
128.8
128.1
125.2
101.2
77.3
77.0
76.7
31.6
30.5
28.9
27.9
22.6
14.0
O
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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7.89
7.88
7.87
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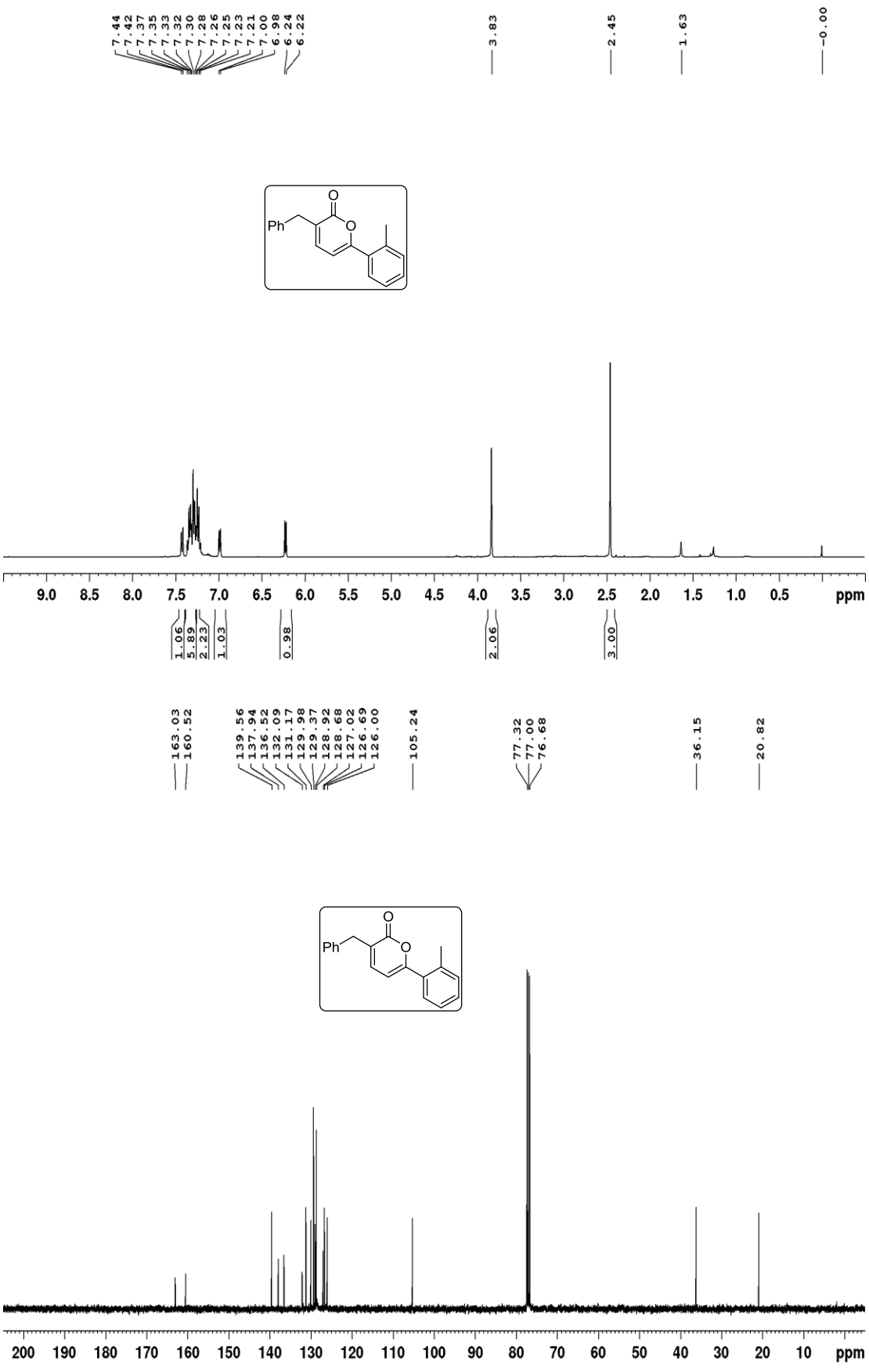
7.71
7.60
7.58
7.49
7.48
7.47
7.46
7.46
7.44
7.42
7.40
7.38
7.36
7.26
6.81
6.79
1.56
0.00
O
O
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.00
1.97
1.00
5.96
1.00
161.4
159.8
140.3
134.8
131.2
130.7
128.9
128.5
128.4
128.1
125.7
125.5
101.7
77.3
77.0
76.7
O
O
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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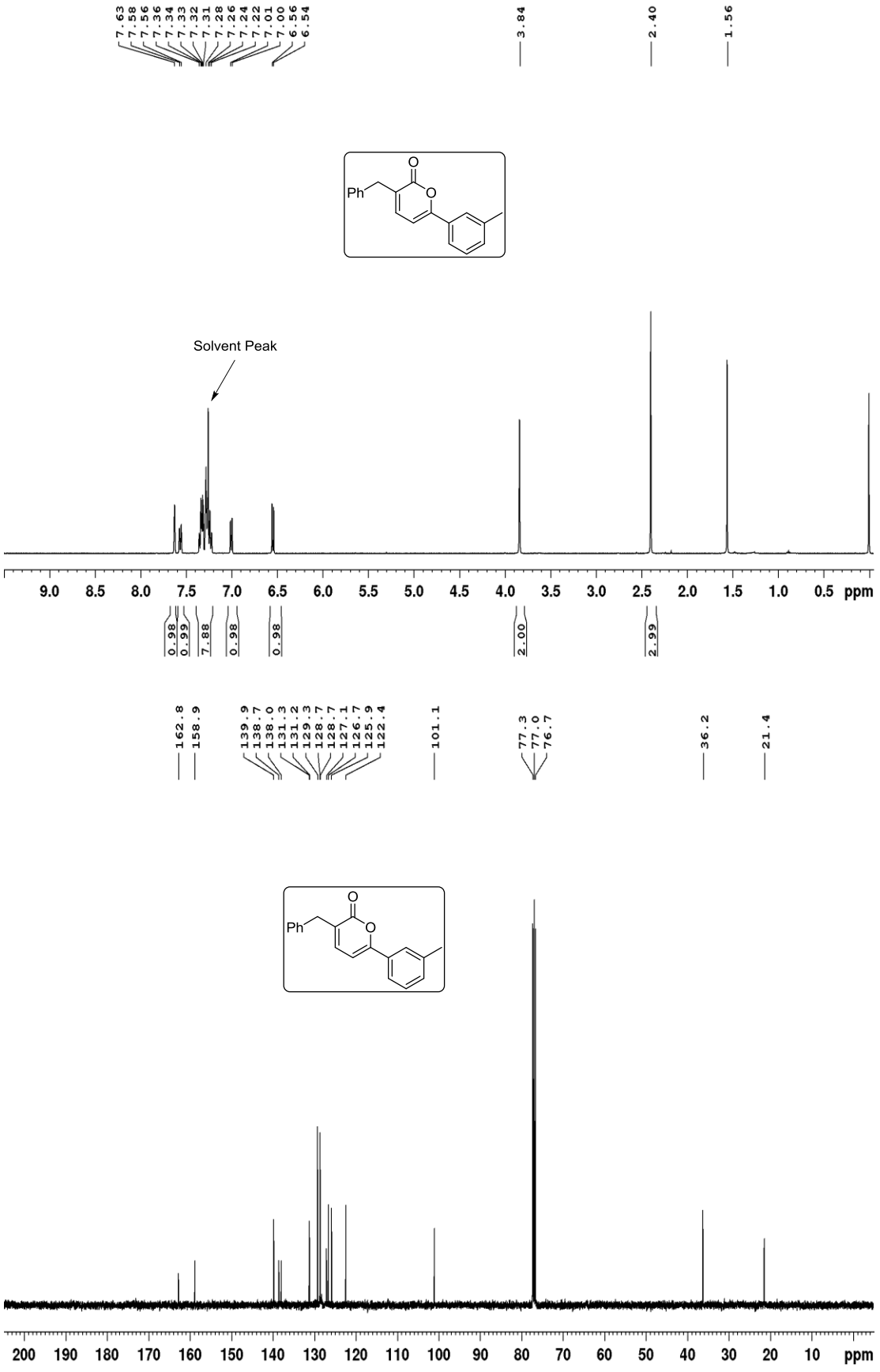
7.42
7.37
7.35
7.33
7.32
7.30
7.28
7.26
7.25
7.23
7.21
7.00
6.98
6.24
6.22
3.83
2.45
1.63
0.00
O
Ph
O
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.06
5.89
2.23
1.03
0.98
2.06
3.00
163.03
160.52
139.56
137.94
136.52
132.09
131.17
129.98
129.37
128.92
128.68
127.02
126.69
126.00
105.24
77.32
77.00
76.68
36.15
20.82
O
Ph
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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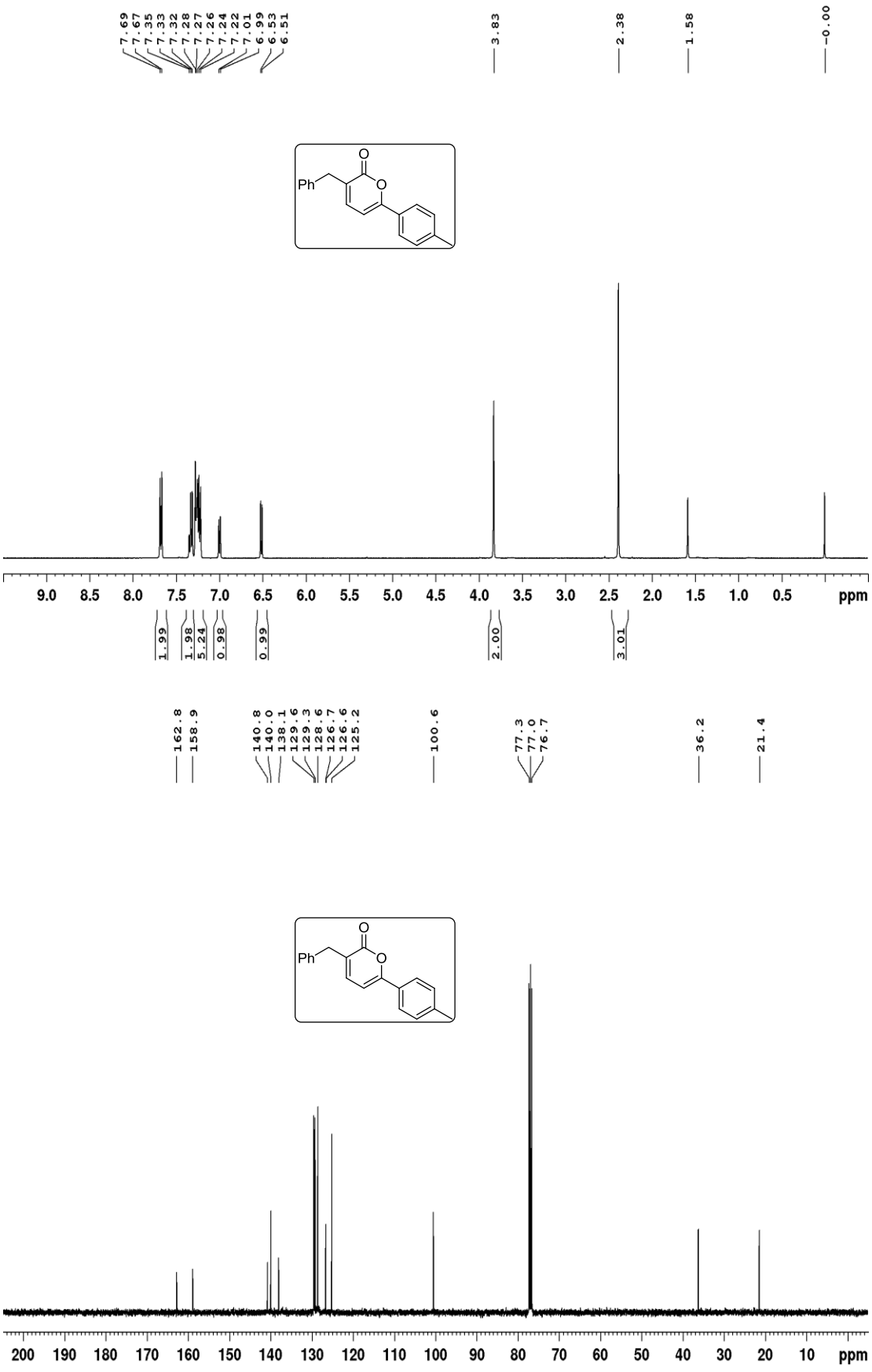
7.58
7.56
7.36
7.34
7.33
7.32
7.31
7.28
7.26
7.24
7.22
7.01
7.00
6.56
6.54
3.84
2.40
1.56
Ph
O
O
Solvent Peak
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.98
0.99
7.88
0.98
0.98
2.00
2.99
162.8
158.9
139.9
138.7
138.0
131.3
131.2
129.3
128.7
128.7
127.1
126.7
125.9
122.4
101.1
77.3
77.0
76.7
36.2
21.4
Ph
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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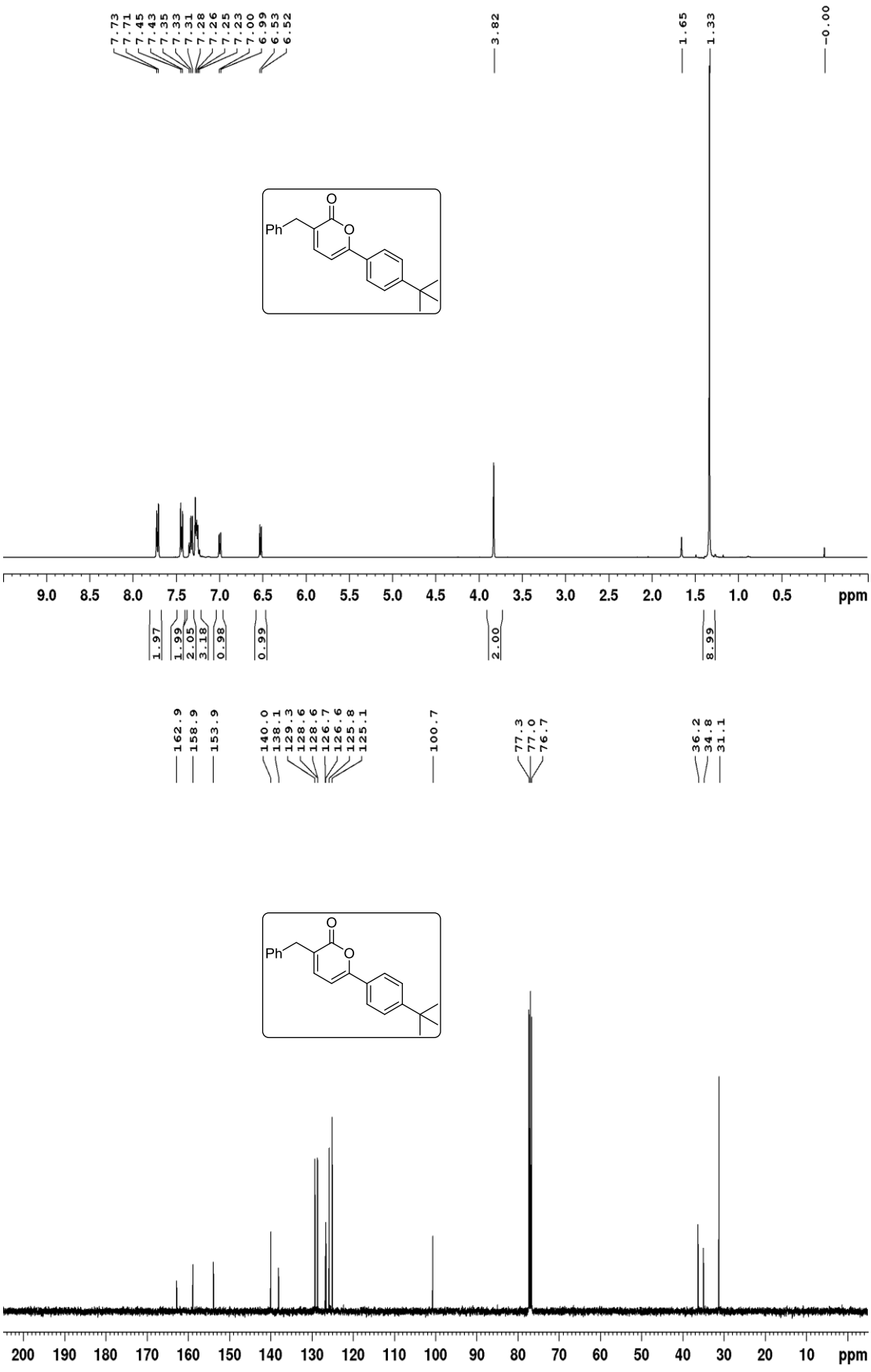
7.67
7.35
7.33
7.32
7.28
7.27
7.26
7.24
7.22
7.01
6.99
6.53
6.51
3.83
2.38
1.58
0.00
Ph
O
O
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.99
1.98
5.24
0.98
0.99
2.00
3.01
162.8
158.9
140.8
140.0
138.1
129.6
129.3
128.6
126.7
126.6
125.2
100.6
77.3
77.0
76.7
36.2
21.4
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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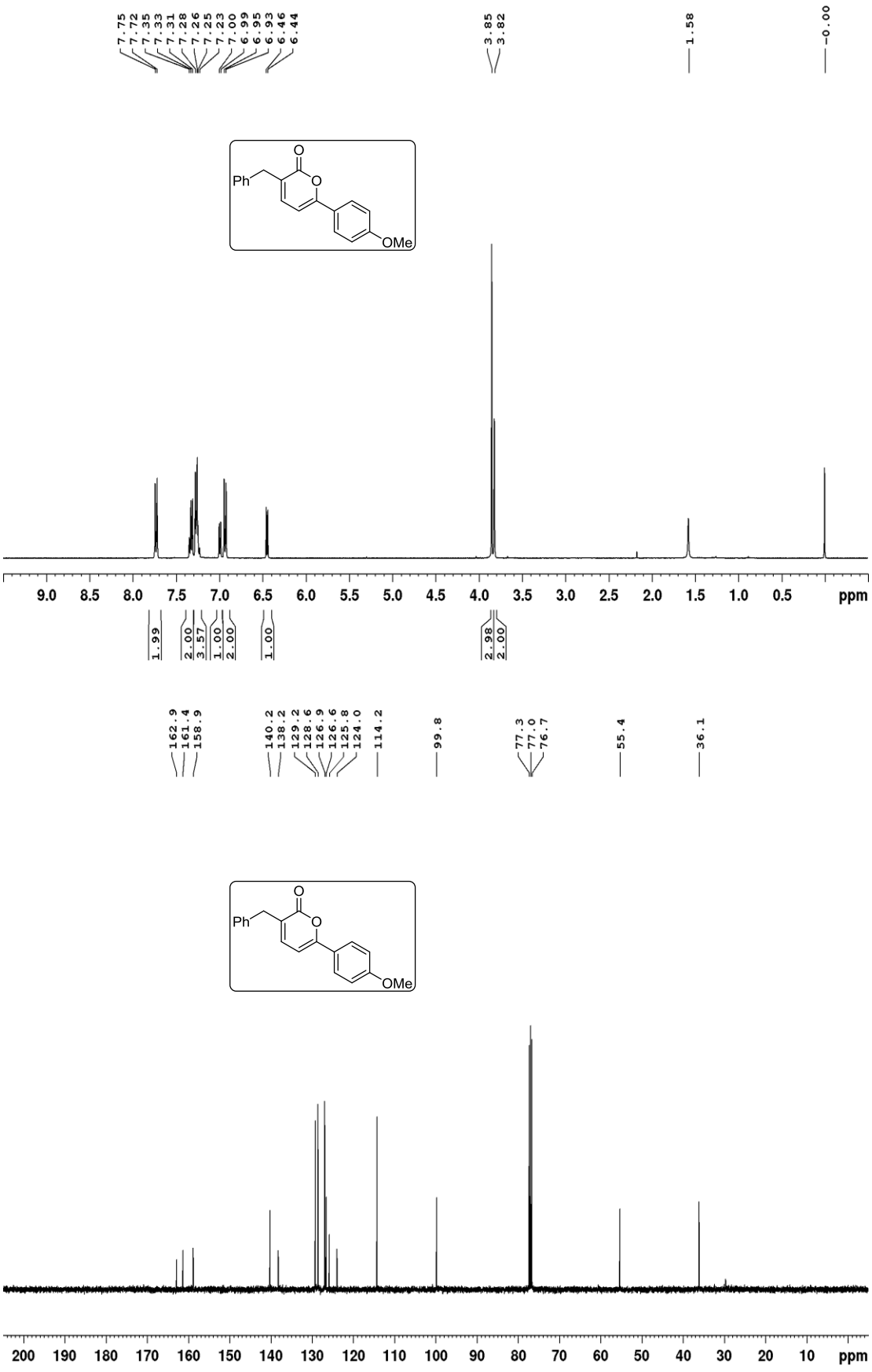
7.71
7.45
7.43
7.35
7.33
7.31
7.28
7.26
7.25
7.23
7.00
6.99
6.53
6.52
3.82
1.65
1.33
0.00
Ph
O
O
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.97
1.99
2.05
3.18
0.98
0.99
2.00
8.99
162.9
158.9
153.9
140.0
138.1
129.3
128.6
128.6
126.7
126.6
125.8
125.1
100.7
77.3
77.0
76.7
36.2
34.8
31.1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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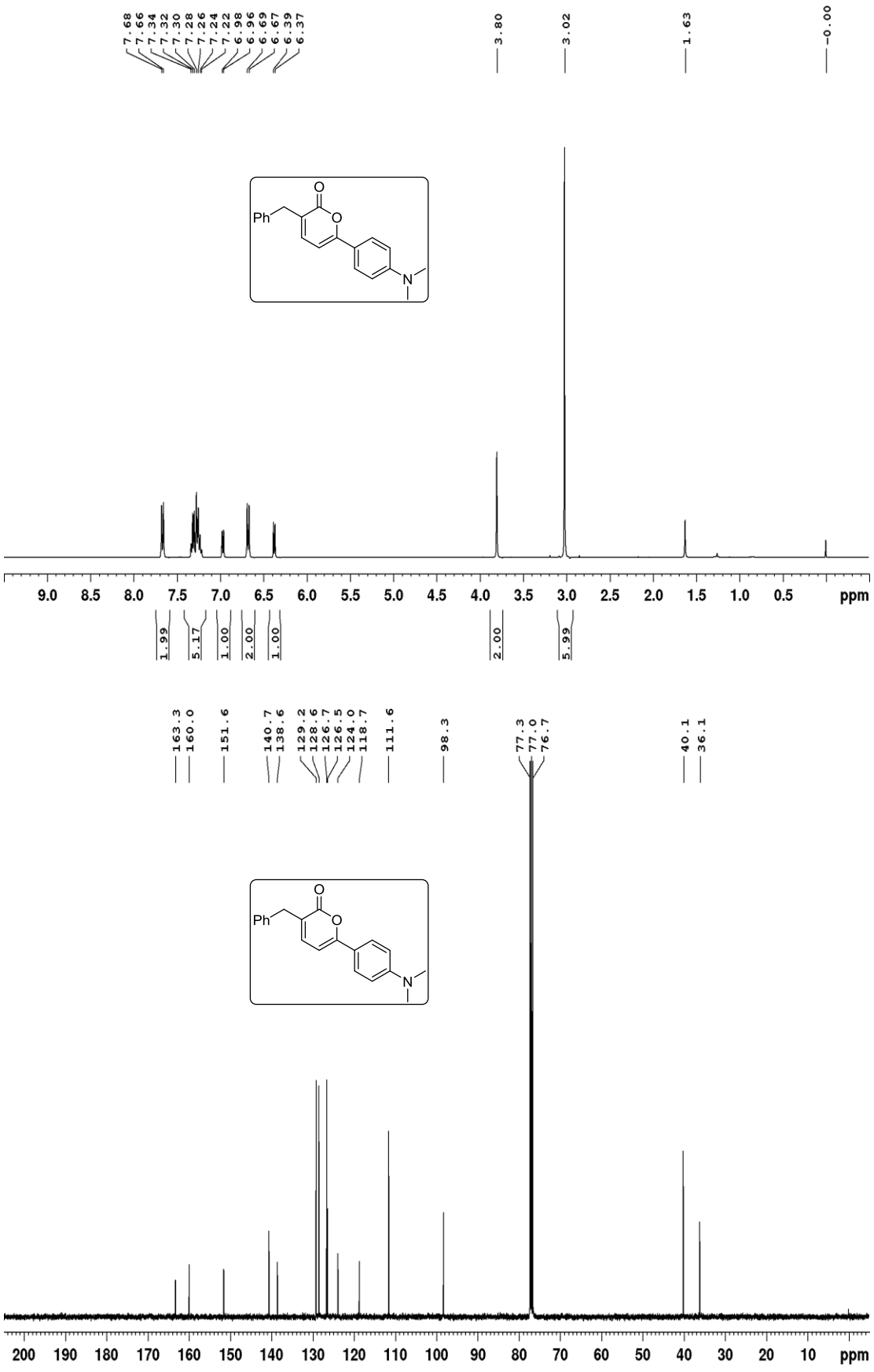
7.72
7.35
7.33
7.31
7.28
7.26
7.25
7.23
7.00
6.99
6.95
6.93
6.46
6.44
3.85
3.82
1.58
0.00
Ph
O
OMe
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.99
2.00
3.57
1.00
2.00
1.00
2.98
2.00
162.9
161.4
158.9
140.2
138.2
129.2
128.6
126.9
126.6
125.8
124.0
114.2
99.8
77.3
77.0
76.7
55.4
36.1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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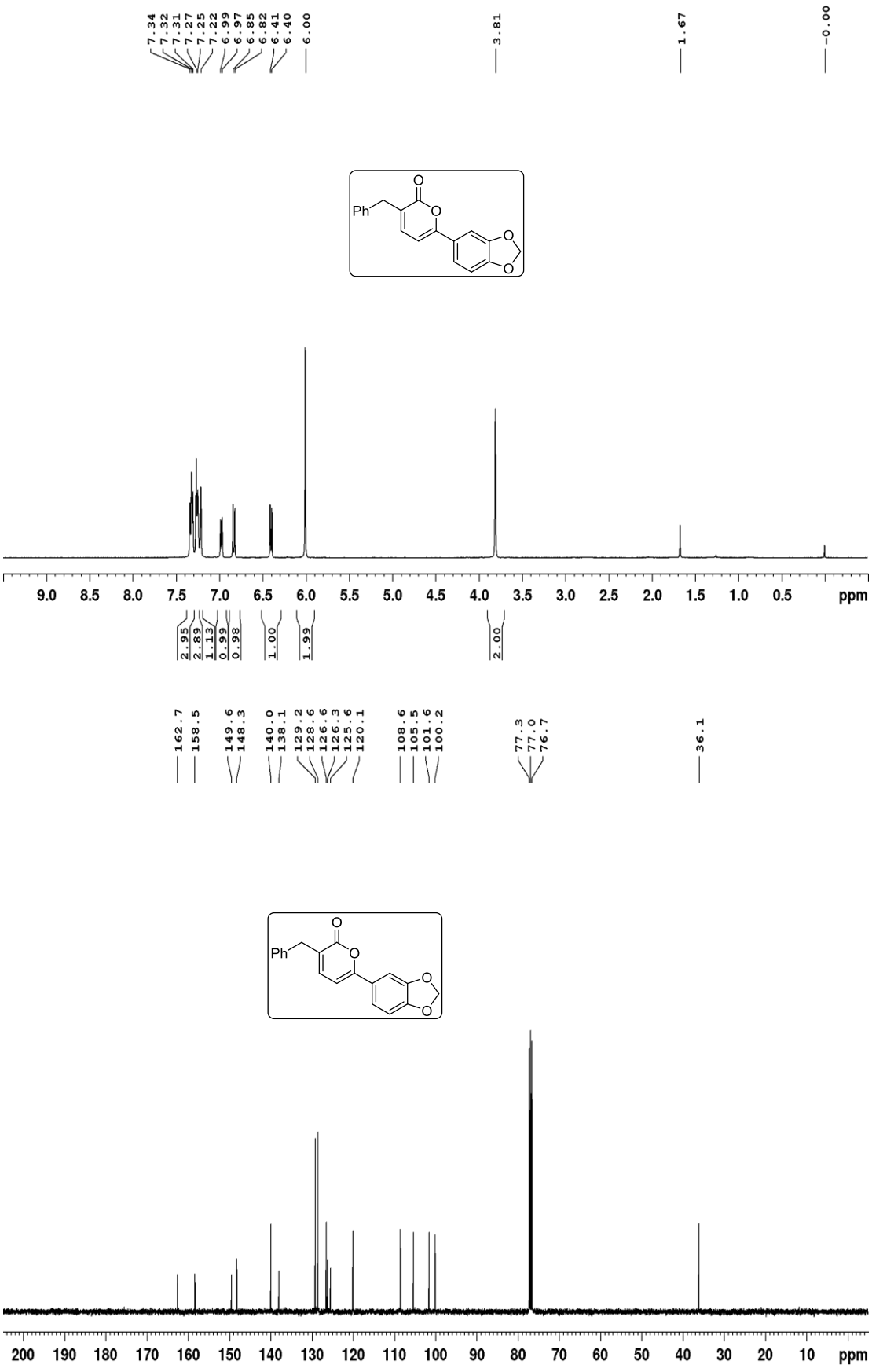
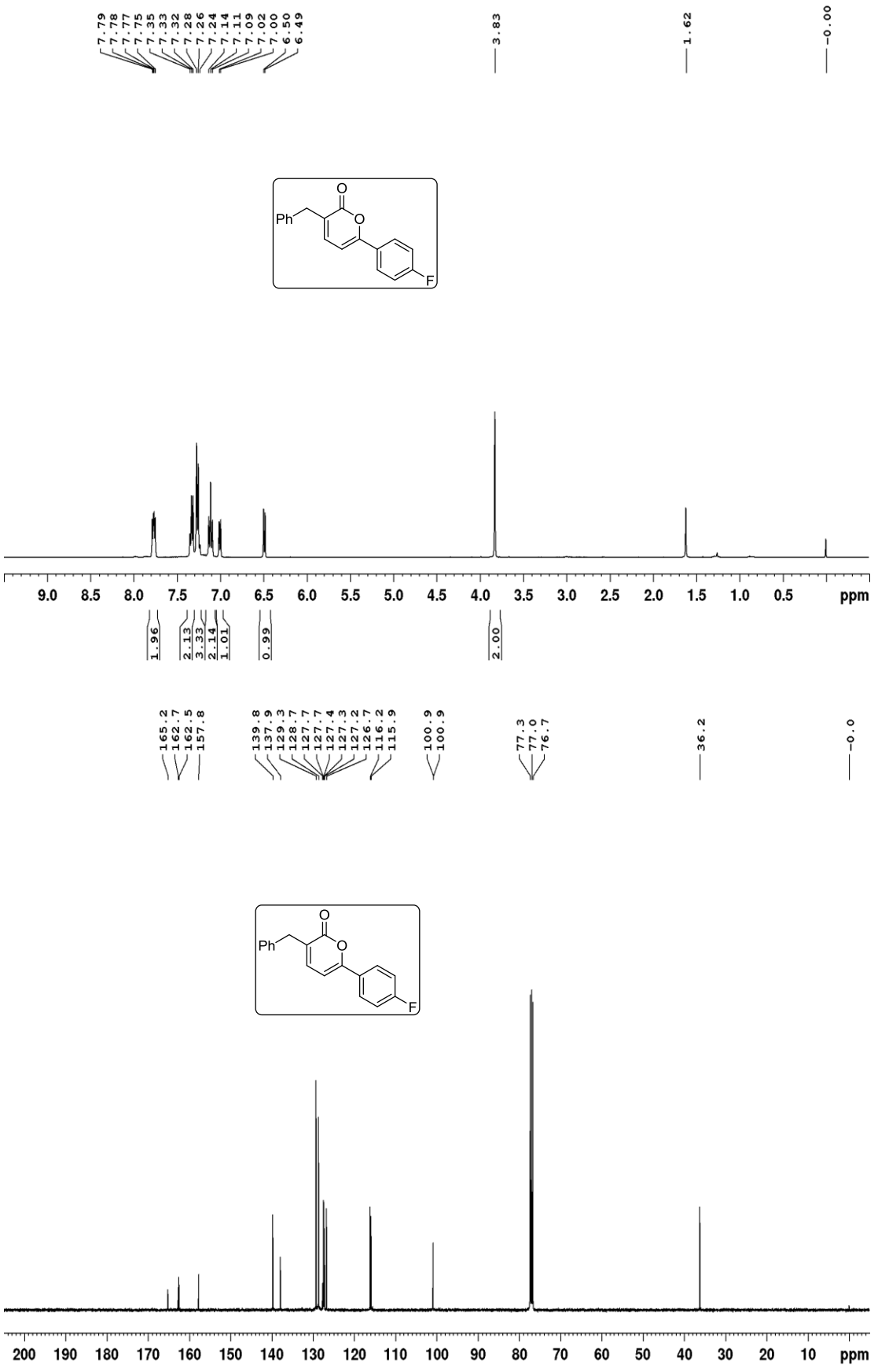
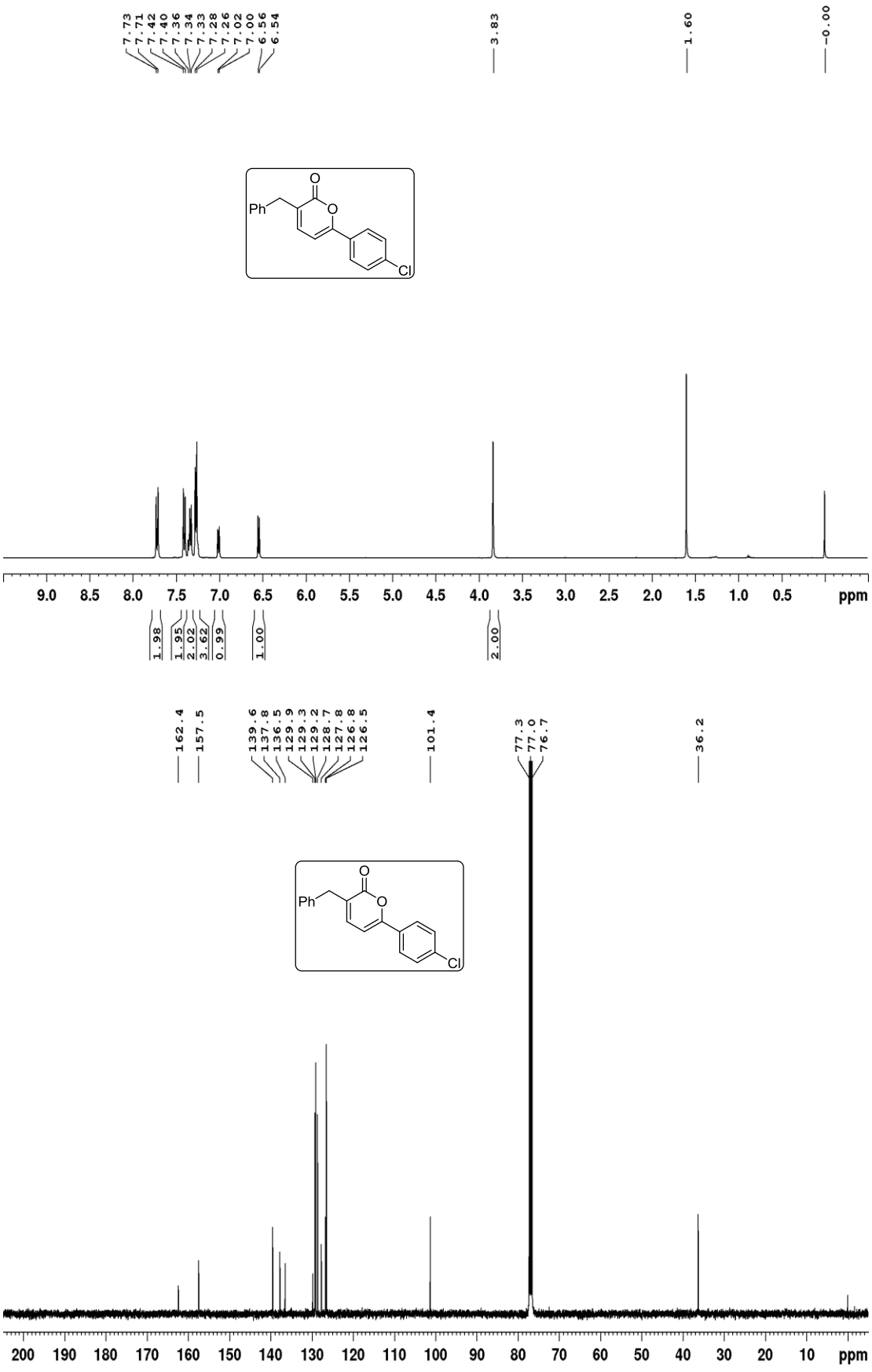
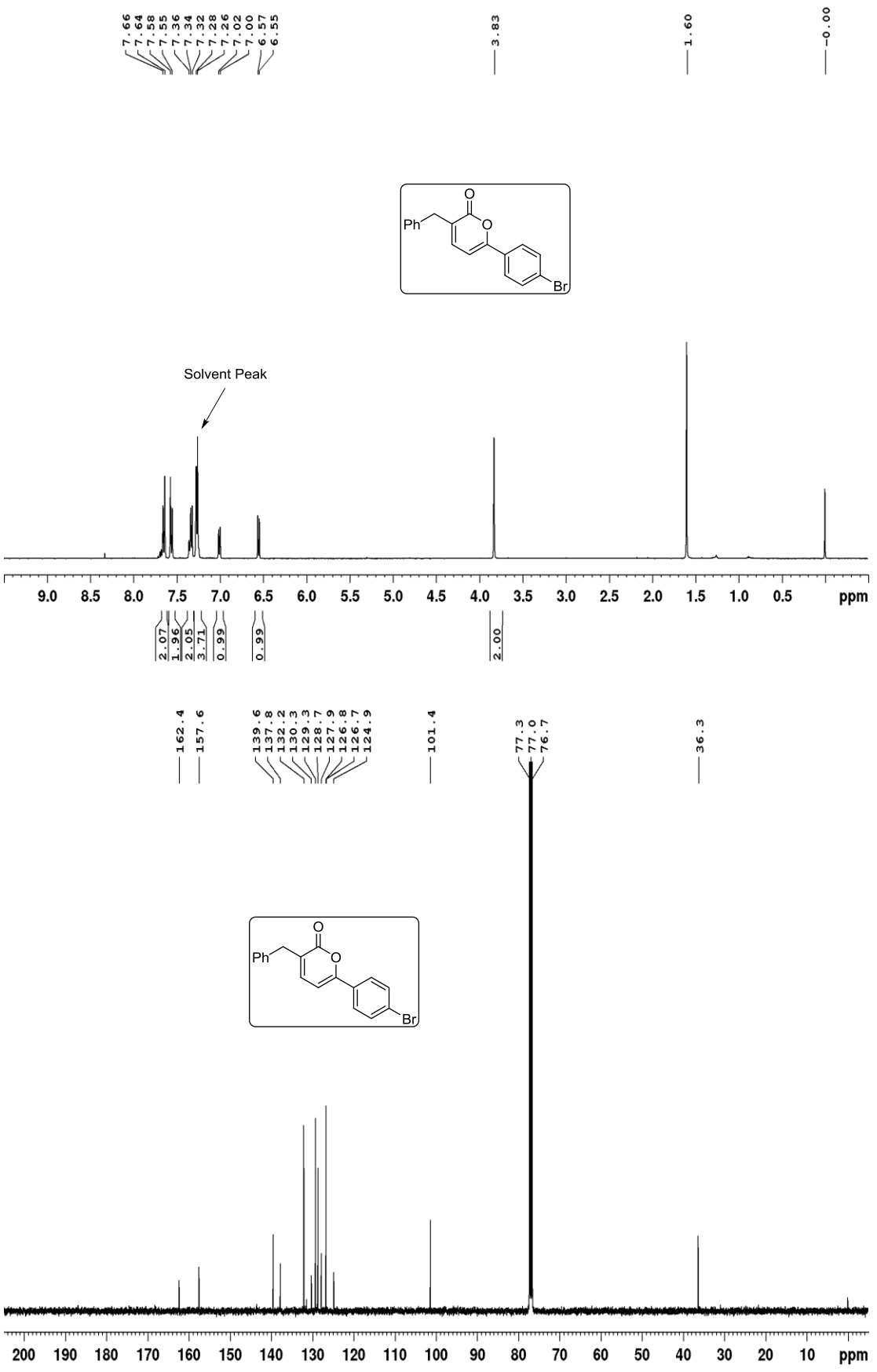
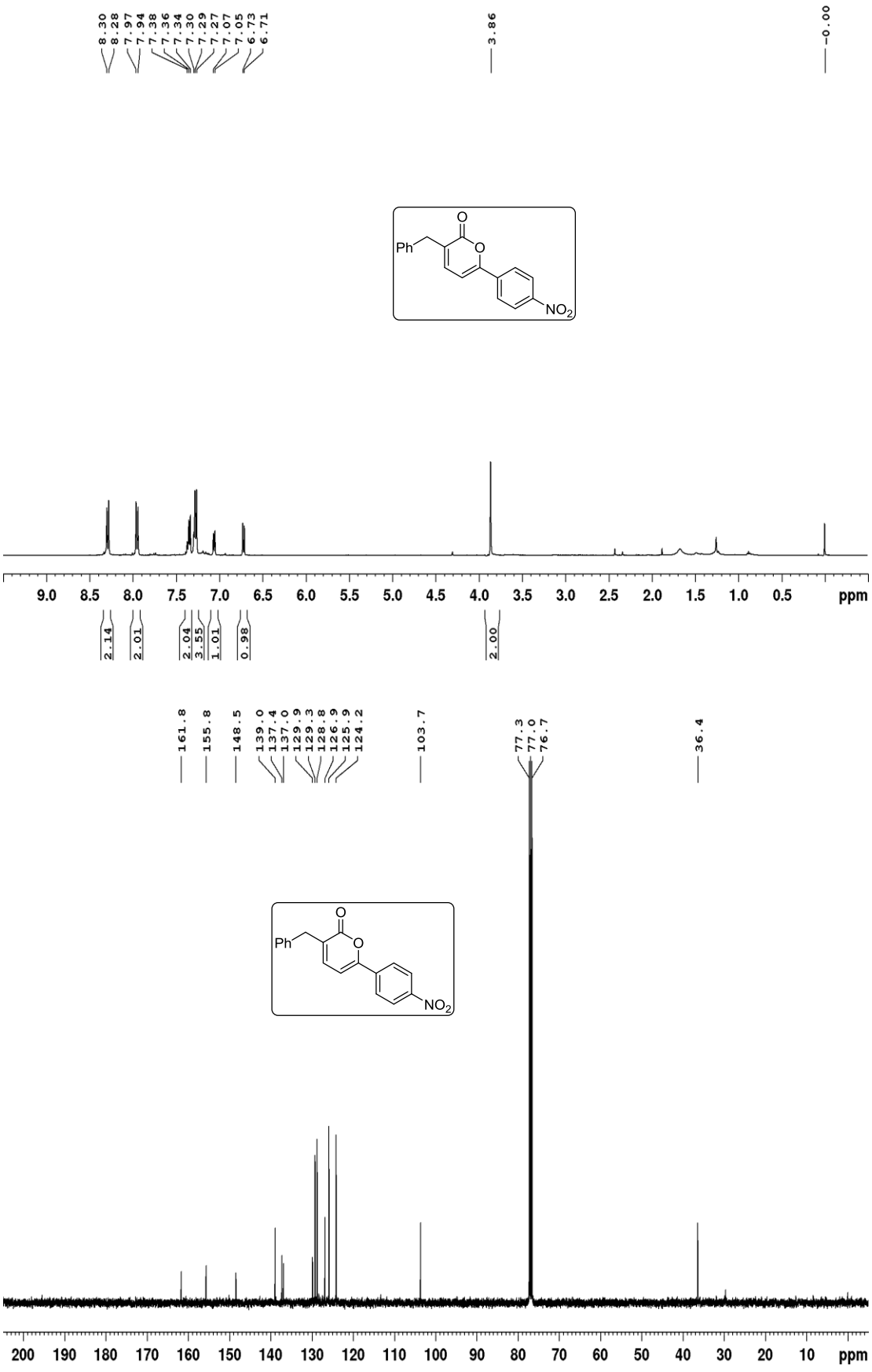
7.66
7.34
7.32
7.30
7.28
7.26
7.24
7.22
6.98
6.96
6.69
6.67
6.39
6.37
3.80
3.02
1.63
0.00
Ph
O
N
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.99
5.17
1.00
2.00
1.00
2.00
5.99
163.3
160.0
151.6
140.7
138.6
129.2
128.6
126.7
126.5
124.0
118.7
111.6
98.3
77.3
77.0
76.7
40.1
36.1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.34
7.32
7.31
7.27
7.25
7.22
6.99
6.97
6.85
6.82
6.41
6.40
6.00
3.81
1.67
0.00
Ph
O
O
O
O
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.95
2.89
1.13
0.99
0.98
1.00
1.99
2.00
162.7
158.5
149.6
148.3
140.0
138.1
129.2
128.6
126.6
126.3
125.6
120.1
108.6
105.5
101.6
100.2
77.3
77.0
76.7
36.1
Ph
O
O
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.79
7.78
7.77
7.75
7.35
7.33
7.32
7.28
7.26
7.24
7.14
7.11
7.09
7.02
7.00
6.50
6.49
3.83
1.62
0.00
Ph
O
O
F
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.96
2.13
3.33
2.14
1.01
0.99
2.00
165.2
162.7
162.5
157.8
139.8
137.9
129.3
128.7
127.7
127.7
127.4
127.3
127.2
126.7
116.2
115.9
100.9
100.9
77.3
77.0
76.7
36.2
0.0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.73
7.71
7.42
7.40
7.36
7.34
7.33
7.28
7.26
7.02
7.00
6.56
6.54
3.83
1.60
0.00
Ph
O
O
Cl
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.98
1.95
2.02
3.62
0.99
1.00
2.00
162.4
157.5
139.6
137.8
136.5
129.9
129.3
129.2
128.7
127.8
126.8
126.5
101.4
77.3
77.0
76.7
36.2
Ph
O
O
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.66
7.64
7.58
7.55
7.36
7.34
7.32
7.28
7.26
7.02
7.00
6.57
6.55
3.83
1.60
0.00
Ph
O
O
Br
Solvent Peak
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.07
1.96
2.05
3.71
0.99
0.99
2.00
162.4
157.6
139.6
137.8
132.2
130.3
129.3
128.7
127.9
126.8
126.7
124.9
101.4
77.3
77.0
76.7
36.3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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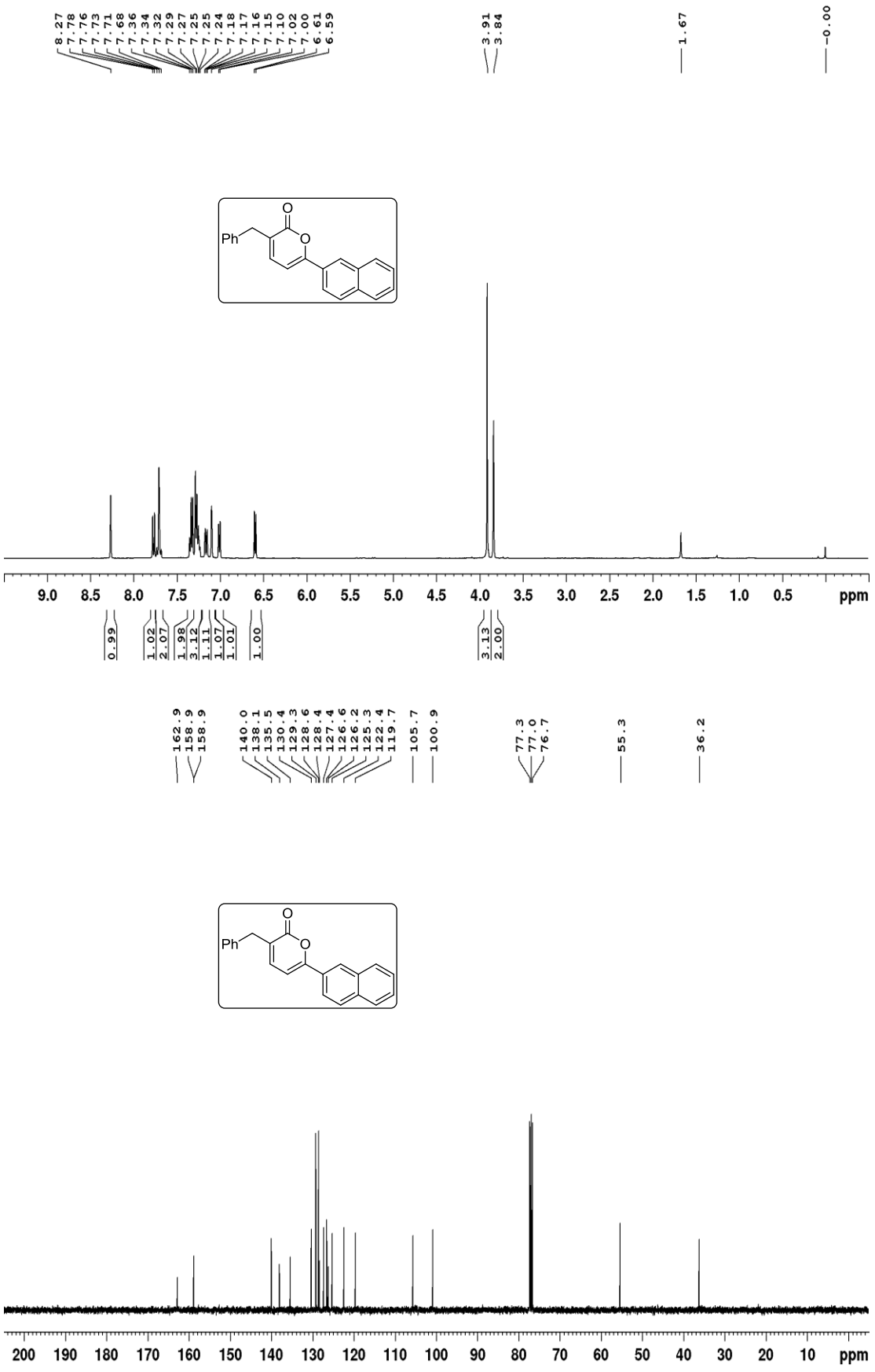
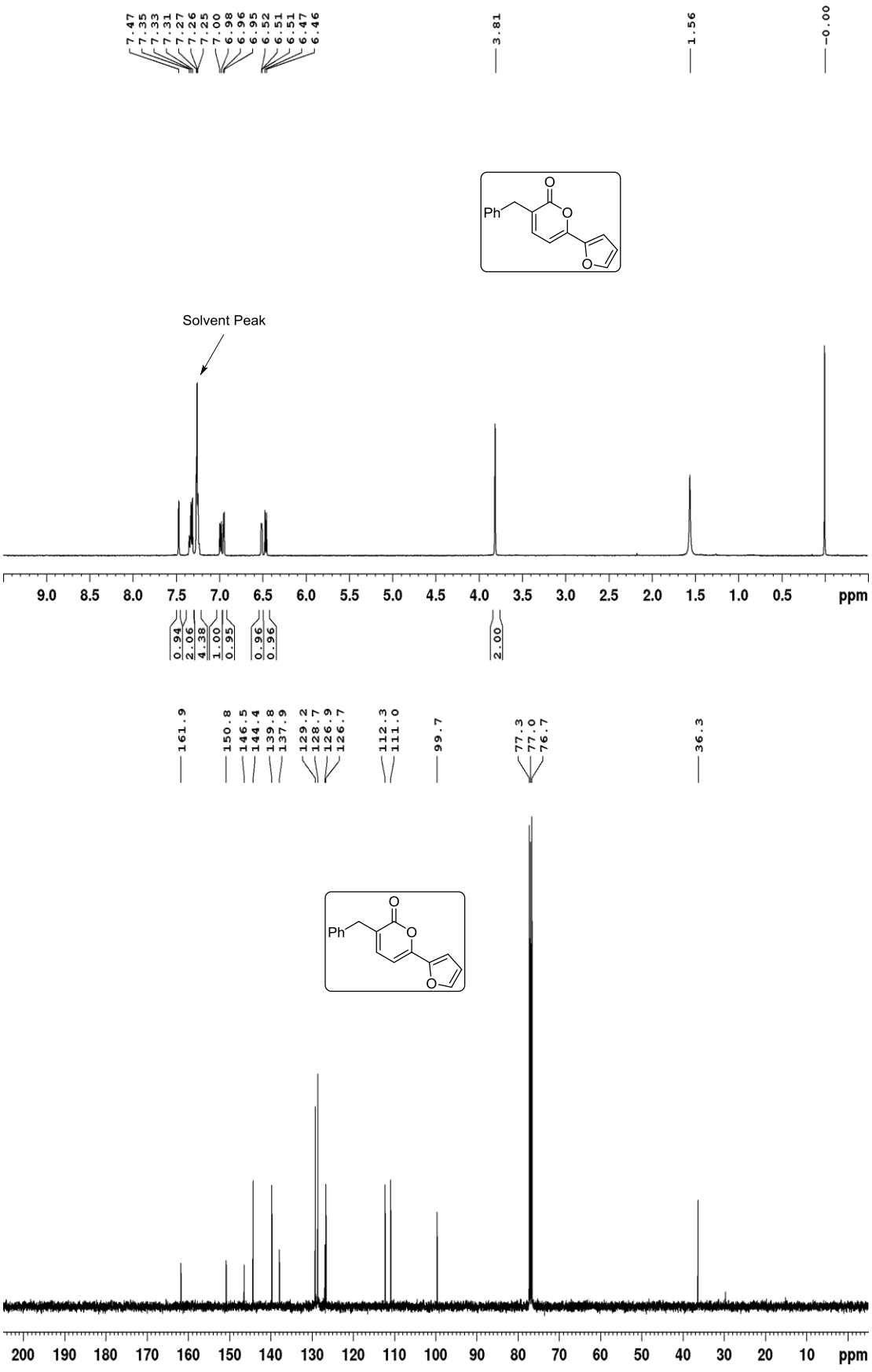
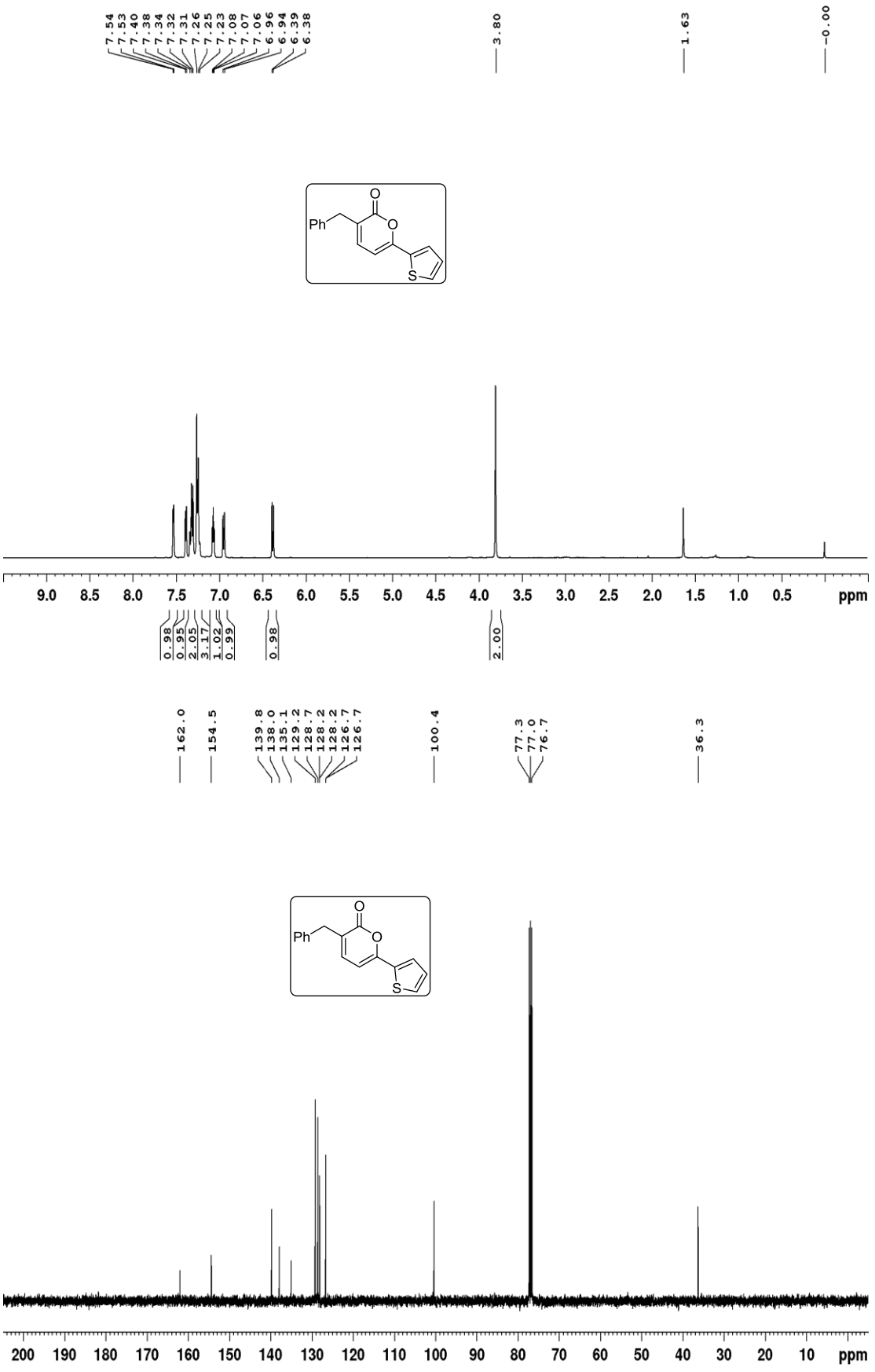
8.28
7.97
7.94
7.38
7.36
7.34
7.30
7.29
7.27
7.07
7.05
6.73
6.71
3.86
0.00
Ph
O
O
NO2
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.14
2.01
2.04
3.55
1.01
0.98
2.00
161.8
155.8
148.5
139.0
137.4
137.0
129.9
129.3
128.8
126.9
125.9
124.2
103.7
77.3
77.0
76.7
36.4
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


8.27
7.78
7.76
7.73
7.71
7.68
7.36
7.34
7.32
7.29
7.27
7.25
7.24
7.18
7.17
7.16
7.15
7.10
7.02
7.00
6.61
6.59
3.91
3.84
1.67
0.00
Ph
O
O
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.99
1.02
2.07
1.98
3.12
1.11
1.07
1.01
1.00
3.13
2.00
162.9
158.9
158.9
140.0
138.1
135.5
130.4
129.3
128.6
128.4
127.4
126.6
126.2
125.3
122.4
119.7
105.7
100.9
77.3
77.0
76.7
55.3
36.2
Ph
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.47
7.35
7.33
7.31
7.27
7.26
7.25
7.00
6.98
6.96
6.95
6.52
6.51
6.51
6.47
6.46
3.81
1.56
0.00
Ph
O
O
O
Solvent Peak
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.94
2.06
4.38
1.00
0.95
0.96
0.96
2.00
161.9
150.8
146.5
144.4
139.8
137.9
129.2
128.7
126.9
126.7
112.3
111.0
99.7
77.3
77.0
76.7
36.3
Ph
O
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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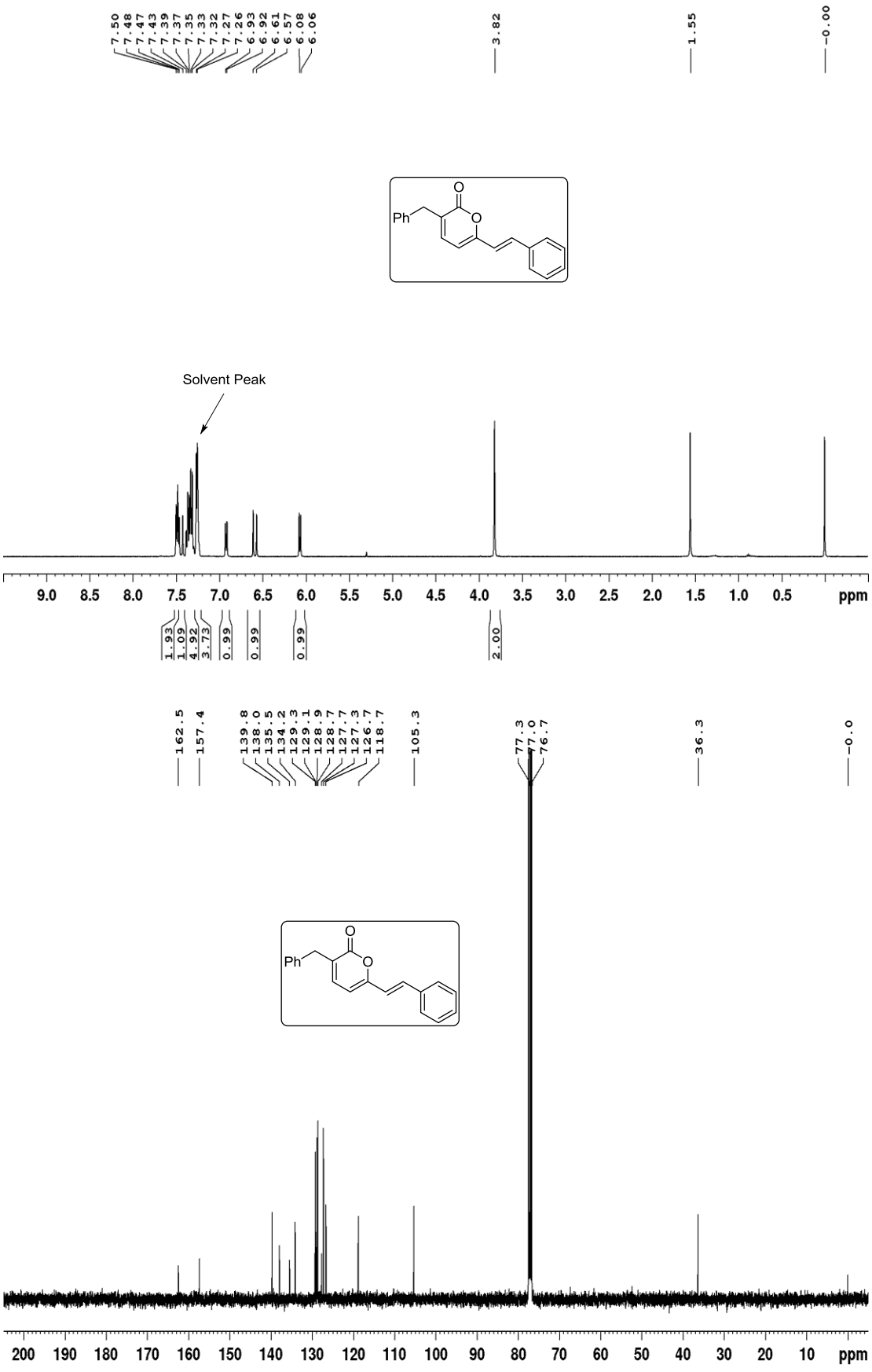
7.53
7.40
7.38
7.34
7.32
7.31
7.26
7.25
7.23
7.08
7.07
7.06
6.96
6.94
6.39
6.38
3.80
1.63
0.00
O
Ph
O
S
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.98
0.95
2.05
3.17
1.02
0.99
0.98
2.00
162.0
154.5
139.8
138.0
135.1
129.2
128.7
128.2
128.2
126.7
126.7
100.4
77.3
77.0
76.7
36.3
O
Ph
O
S
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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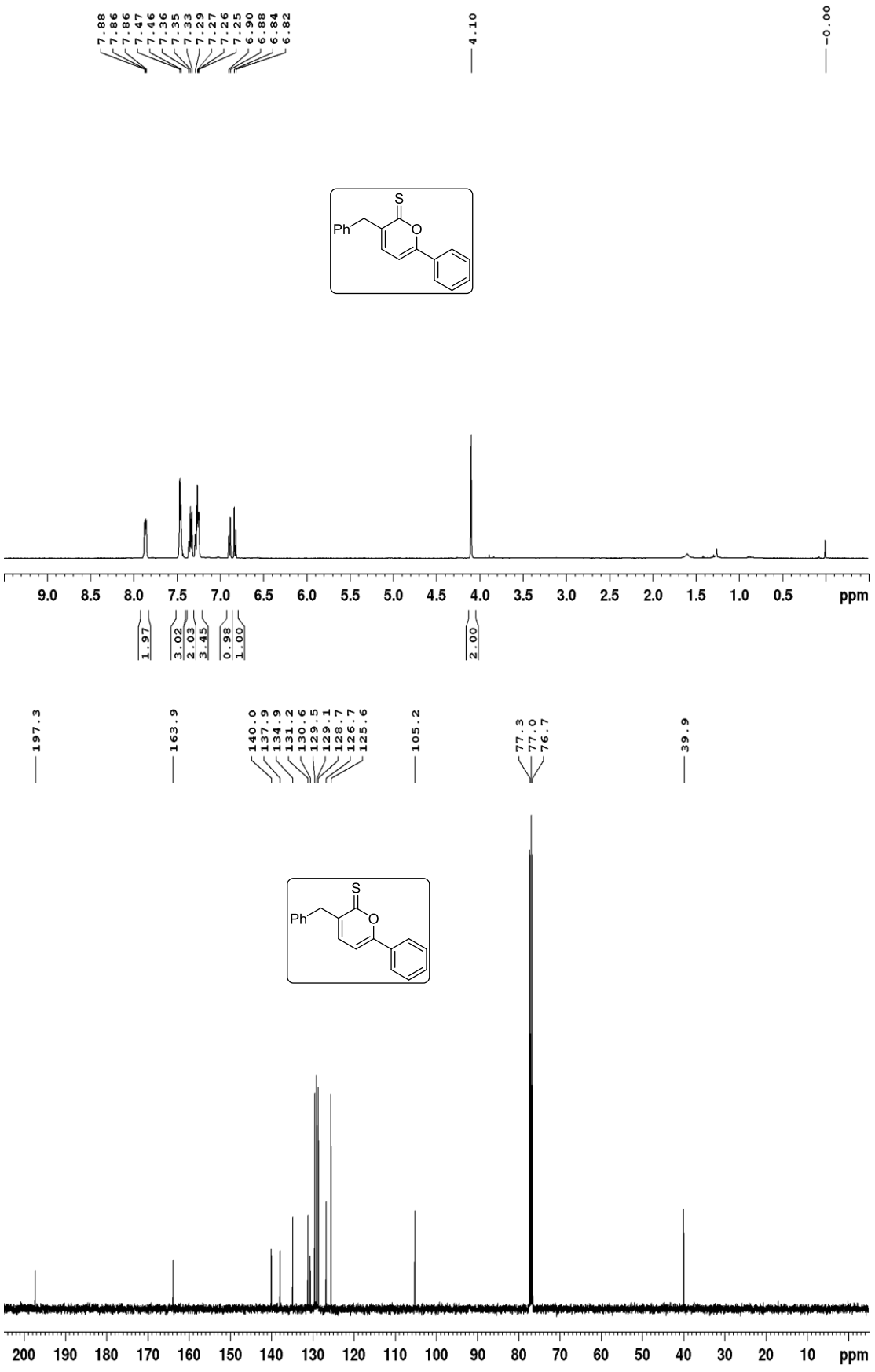
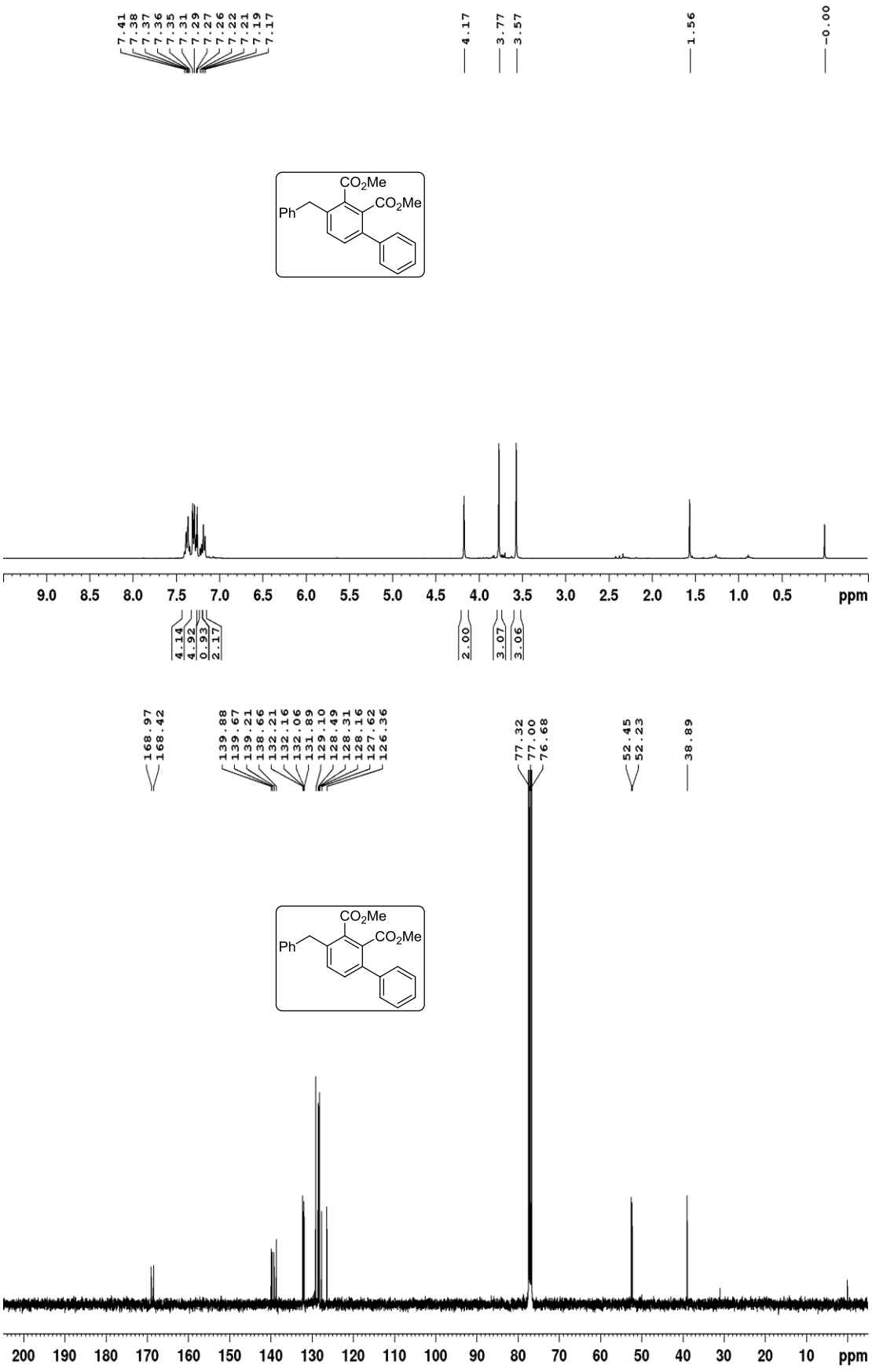
7.48
7.47
7.43
7.39
7.37
7.35
7.33
7.32
7.27
7.26
6.93
6.92
6.61
6.57
6.08
6.06
3.82
1.55
0.00
O
Ph
O
Solvent Peak
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.93
1.09
4.92
3.73
0.99
0.99
0.99
2.00
162.5
157.4
139.8
138.0
135.5
134.2
129.3
129.1
128.9
128.7
127.7
127.3
126.7
118.7
105.3
77.3
77.0
76.7
36.3
0.0
O
Ph
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.88
7.86
7.86
7.47
7.46
7.36
7.35
7.33
7.29
7.27
7.26
7.25
6.90
6.88
6.84
6.82
4.10
0.00
S
Ph
O
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.97
3.02
2.03
3.45
0.98
1.00
2.00
197.3
163.9
140.0
137.9
134.9
131.2
130.6
129.5
129.1
128.7
126.7
125.6
105.2
77.3
77.0
76.7
39.9
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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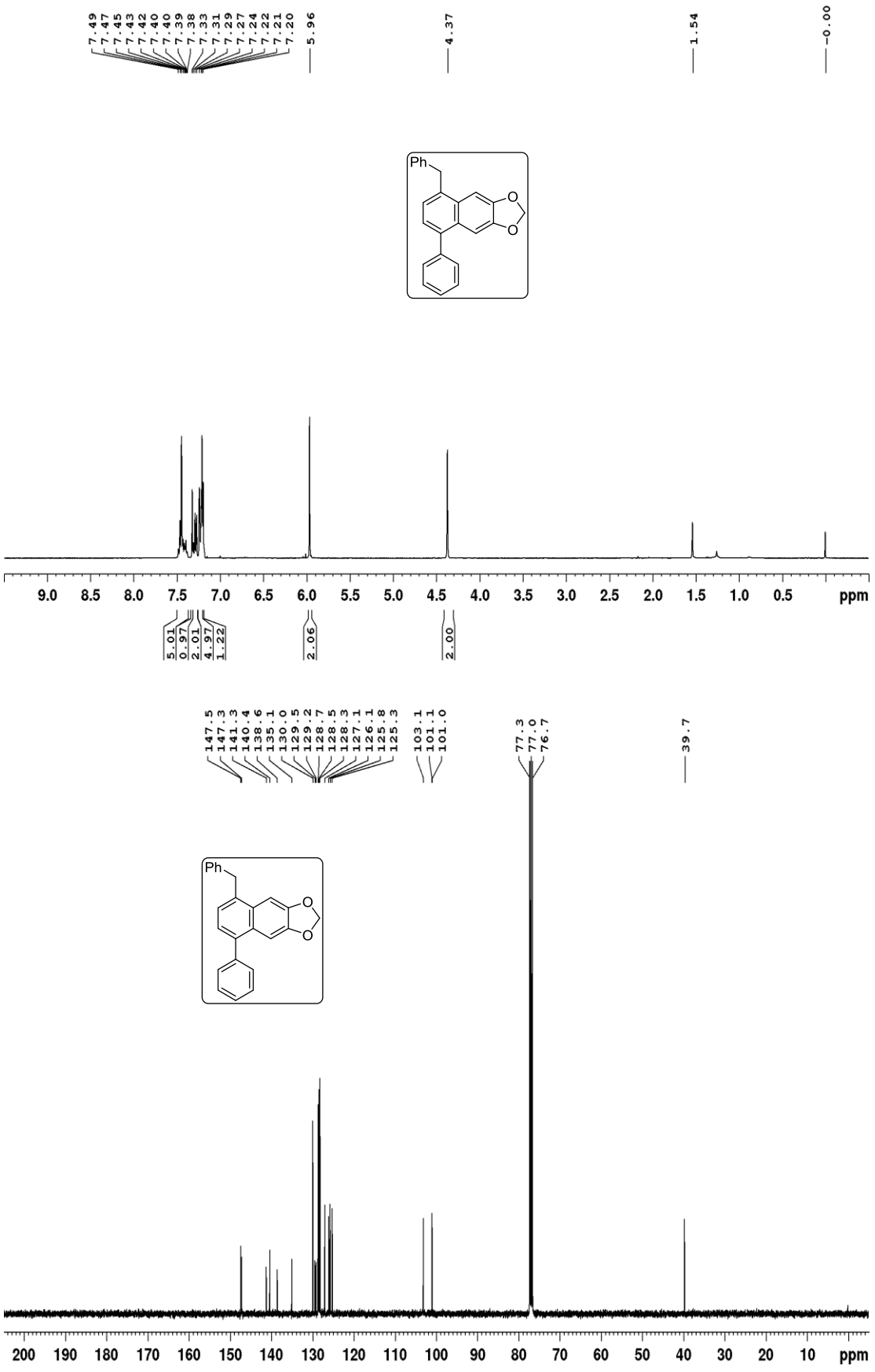
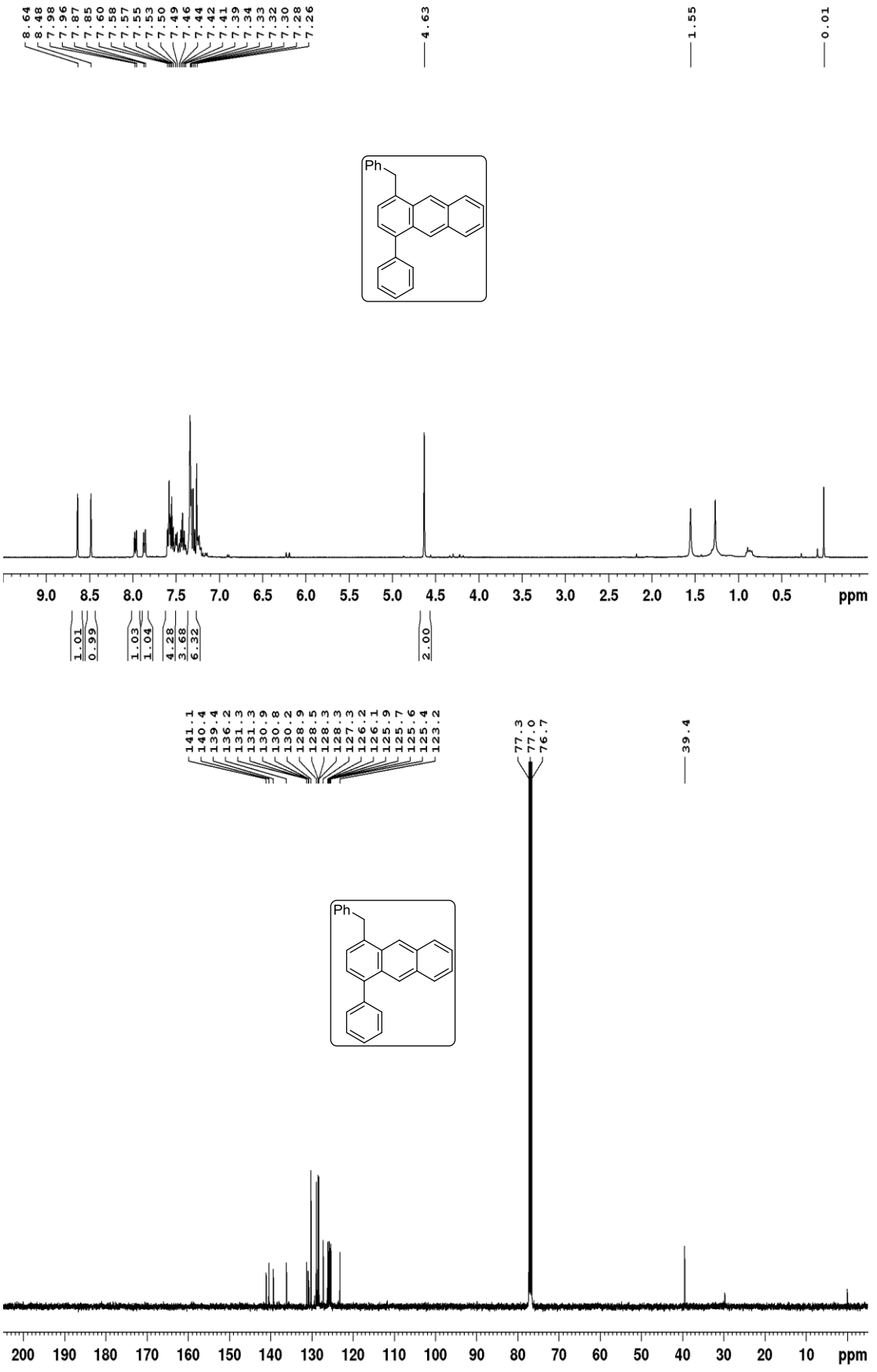
7.38
7.37
7.36
7.35
7.31
7.29
7.27
7.26
7.22
7.21
7.19
7.17
4.17
3.77
3.57
1.56
0.00
CO2Me
CO2Me
Ph
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.14
4.92
0.93
2.17
2.00
3.07
3.06
168.97
168.42
139.88
139.67
139.21
138.66
132.21
132.16
132.06
131.89
129.10
128.49
128.31
128.16
127.62
126.36
77.32
77.00
76.68
52.45
52.23
38.89
CO2Me
CO2Me
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.49
7.47
7.45
7.43
7.42
7.40
7.40
7.39
7.38
7.33
7.31
7.29
7.27
7.24
7.22
7.21
7.20
5.96
4.37
1.54
0.00
Ph
O
O
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.01
0.97
2.01
4.97
1.22
2.06
2.00
147.5
147.3
141.3
140.4
138.6
135.1
130.0
129.5
129.2
128.7
128.5
128.3
127.1
126.1
125.8
125.3
103.1
101.1
101.0
77.3
77.0
76.7
39.7
Ph
O
O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.64
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123.2
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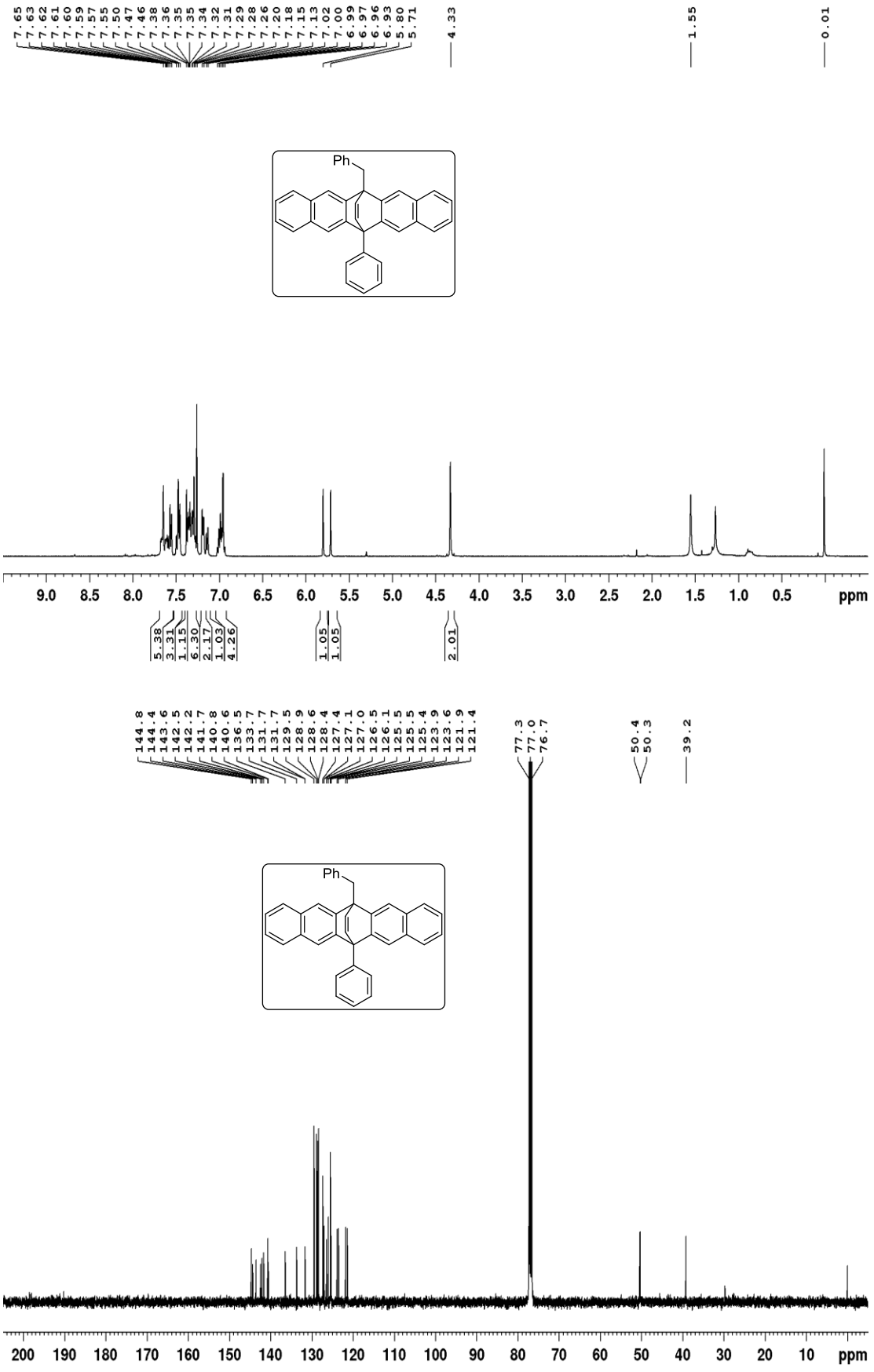
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.65
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6.30
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4.26
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140.8
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136.5
133.7
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131.7
129.5
128.9
128.6
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127.1
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126.5
126.1
125.5
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121.9
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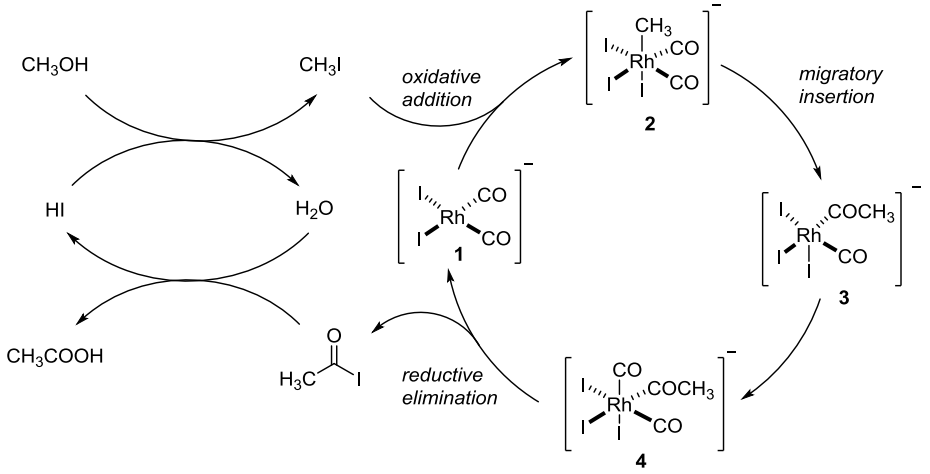
76.7
50.4
50.3
39.2
Ph
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

# Chapter 3

## *A Highly Efficient NHC-Catalyzed Aerobic Oxidation of Aldehydes to Carboxylic Acids*

### 3.1 Introduction

Carboxylic acids are the fundamental and much widely used organic manipulations in synthetic chemistry, both in academic and industrial point of view. They are widely present in nature, and are among the largest common functionalities in organic compounds utilized in industry for the production of pharmaceuticals, agrochemicals, food additives, polymer and solvents.[1] Therefore, the development of mild and efficient methods to access this class of compound is an inviting research space and growing concern in organic chemistry. In routine, such type of substances are produced through oxidation of alcohol or aldehyde under different conditions. In this context, Monsanto and co-workers in 1966 developed the main industrial process for synthesis of acetic acid by carbonylation of methanol catalyzed by rhodium complex in the presence of hydrogen iodide as a co-catalyst (Scheme 3.1).[2]

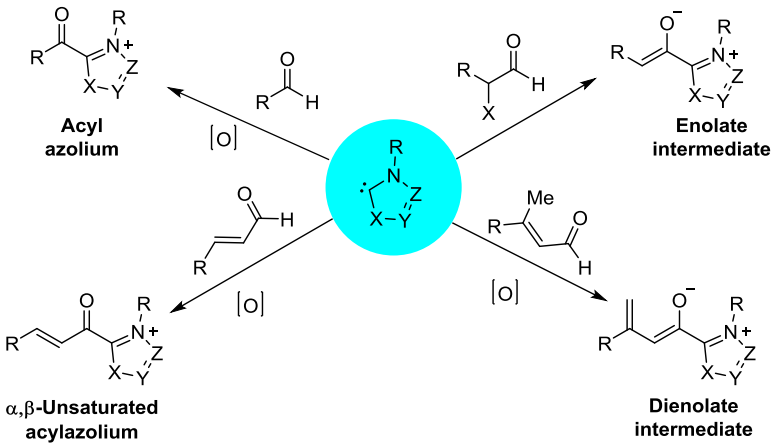



**Scheme 3.1** Monsanto process for synthesis of acetic acid

Mechanistically, the reaction was proposed to proceed with the formation of methyl iodide from methanol and hydrogen iodide. This generated methyl iodide undergoes oxidative addition to rhodium complex **1**, followed by coordination and insertion of carbon monoxide generates an acyl complex **4**, and its subsequent reductive elimination produce the acetyl iodide with the release of active rhodium catalyst. This acetyl iodide reacts with water to furnish acetic acid with restoring HI which can re-enter in the catalytic cycle. Furthermore, this methodology was advanced by the Cativa procedure which differs mainly in the involvement of an iridium based complex and thus provides several advantages such as the suppression of the water gas shift reaction, use of less water in the reaction mixture and the decrease of byproducts like propionic acid.[3]

## 3.2 An Introduction to NHC under Oxidative Conditions

A significant advance has been made in the *N*-heterocyclic carbene (NHC)-organocatalyzed polarity reversal (umpolung) transformations.[4] Besides the NHC-catalyzed umpolung approaches (acyl anion, homoenolate and enolate), NHCs have also been used as catalyst in a variety of nonumpolung transformations. Importantly, NHC-bound acylazolium, α,β-unsaturated acylazolium, and azolium enolate are the important modes of the reactivity which have gained tremendous interest over the past decade. In this context, the acyl azolium intermediate can be accessed by the oxidation of the Breslow intermediate in the presence of external oxidant. Notably, the formation of azolium enolate takes place when acyl azolium contain an α-hydrogen. Furthermore, the α,β-unsaturated acyl azolium and dienolate intermediate can be generated from enal under oxidative NHC-catalysis. In addition, a wide range of α,β-unsaturated carbonyl compounds can produce α,β-unsaturated acyl azolium intermediate, which are incompatible with other organocatalysis (Scheme 3.2).[5]

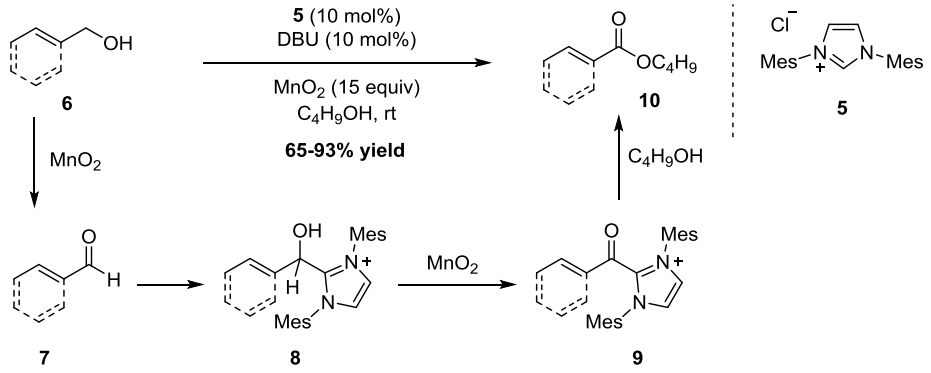



**Scheme 3.2** Important action modes of NHC under non-umpolung mode

Importantly, this versatile α,β-unsaturated acyl azolium intermediate functions as a bis-electrophile granting the addition of several bis-nucleophile in a 1,4-manner, followed by a 1,2-pathway to give a broad range of heterocycles and carbocycles. Herein, the NHC-catalyzed transformation proceeding through nonumpolung mode has been highlighted.

### 3.2.1 NHC-Catalyzed Reaction using Inorganic Oxidant

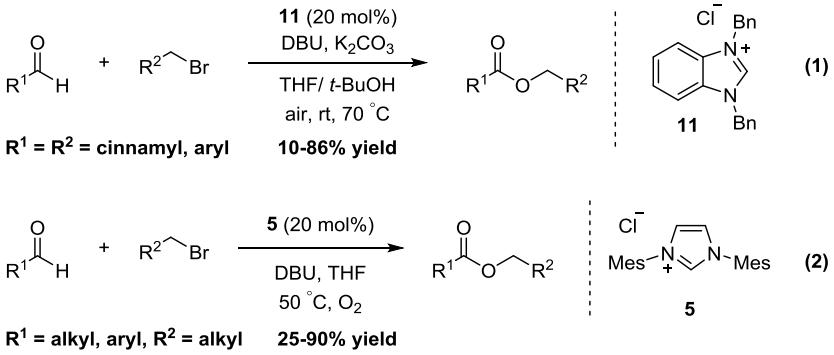
In 2007, Scheidt and colleagues reported first NHC-catalyzed tandem oxidation of numerous allylic, propargylic, or benzylic alcohols applying $MnO_2$ as a moderate oxidant in the presence of imidazolium salt **5** to give corresponding esters in good to excellent yields (Scheme 3.3).[6] This reaction comprises two oxidation steps. Mechanistically, the reaction proceed initially by the oxidation of alcohol to aldehyde **7**, followed by addition of NHC generates Breslow intermediate **8**, which upon further oxidation provides an activated acyl azolium intermediate **9**, that ultimately gets trapped by an alcohol to furnish an ester **10** with the release of carbene catalyst.



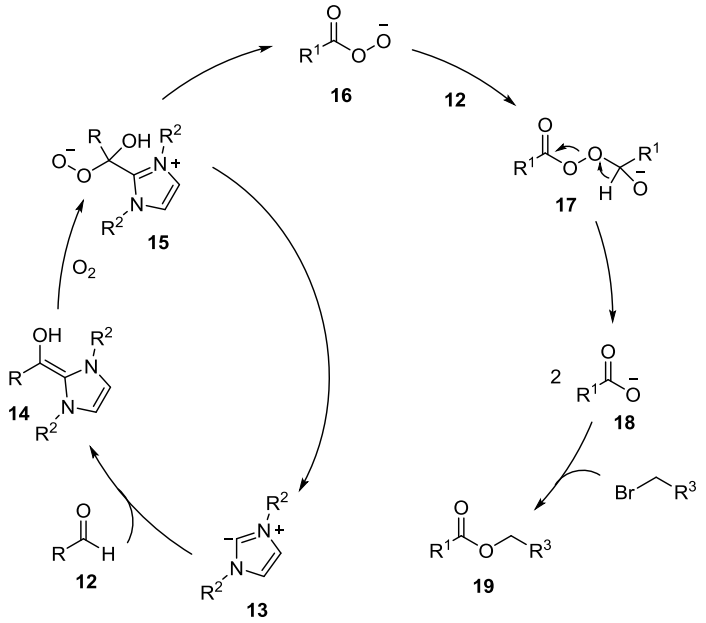

**Scheme 3.3** NHC-catalyzed oxidative esterification reaction

### 3.2.2 NHC-Catalyzed Reaction using Oxygen as Oxidant

In 2011, Liu et al. developed NHC-mediated esterification of cinnamyl and aryl aldehydes using benz-imidazolium catalyst **11** in the presence of diverse cinnamyl or allyl bromides under air as an oxidant (Scheme 3.4, Eq. 1).[7a] The aldehydes with electron-deficient substituent afforded the desire product in better chemical yields. Furthermore, Hui and colleagues extended this similar esterification protocol by using unactivated alkyl bromides in the presence of bulky imidazolium catalyst **5** to afford various esters in valuable yields (Scheme 3.4, Eq. 2).[7b] Detailed mechanistic studies on the aerobic oxidation were conducted to investigate the possible reaction mechanism as exhibited in Scheme 3.5. The transformation proceeds by the addition of free carbene to aldehyde to form Breslow intermediate **14**, which further couples with dioxygen and provide corresponding zwitterionic peroxy intermediate **15**. Subsequently, fragmentation of **15** generates the corresponding peracid intermediate **16** with the release of carbene under basic reaction conditions. This peracid further reacts with another molecule of aldehyde to form hydroxy peroxyl adduct **17** which in turn produces two equivalent of aryl carboxylate **18**, followed by base mediated *O*-alkylation to furnish desired ester **19**.

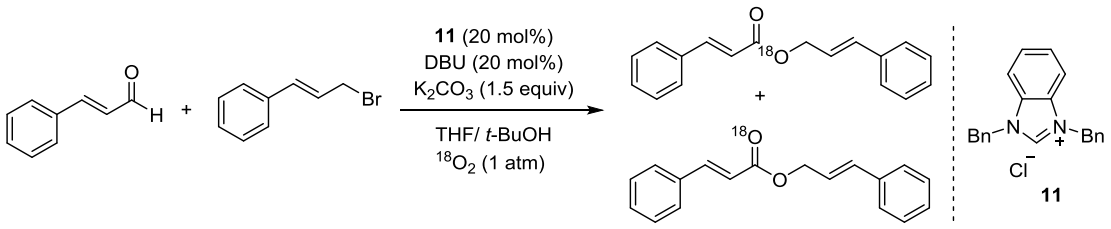



**Scheme 3.4** NHC-catalyzed aerobic oxidation of aldehydes and subsequent alkylation to esters



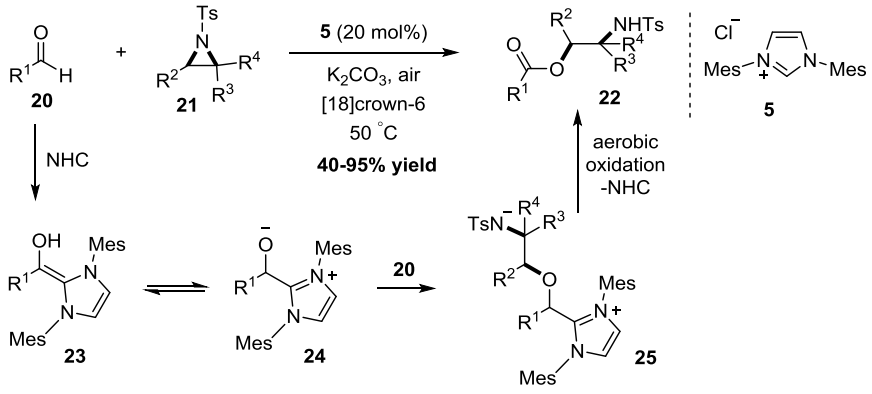

**Scheme 3.5** NHC-catalyzed aerobic oxidation of aldehyde to ester

In addition, Liu and co-workers conducted an isotope-labeling experiments by employing $^{18}O_2$ to support the proposed mechanism. It was observed that NHC-mediated esterification of cinnamaldehyde with cinnamyl bromide in the presence of $^{18}O_2$ atmosphere occurred smoothly to provide ester in 68% yield (Scheme 3.6).[7a] The GC-MS study of the ester product confessed the existence in 1.0:0.8 ratio. This isotopic labeling experiment was in full agreement with the proposed mechanism.



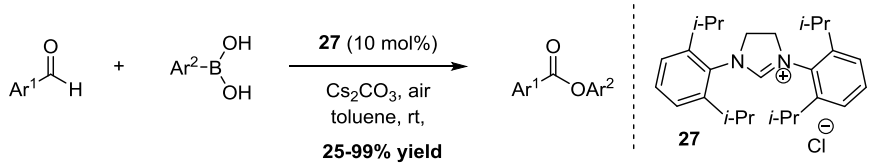

**Scheme 3.6** NHC-catalyzed isotope-labeling experiment for esterification of cinnamaldehyde

In 2006, Chen research group developed NHC-catalyzed aerobic oxidation of aldehydes with aziridines to furnish *O*-acylated and *N*-tosylated 1,2-aminoalcohols in good to excellent yields (Scheme 3.7).[8] Mechanistically, the generation of carboxylate and subsequent aziridine ring opening was rejected as a possible reaction route because the efficient oxidation of aldehydes was not observed in the absence of aziridine under our catalytic system. Moreover, no carboxylate ester was observed after adding methanol, which confirmed that no active acylimidazolium intermediate was formed during the reaction. Therefore, the aziridine ring opening was proposed to occur prior to oxidation of acyl anion by the harder oxygen anion **24** as nucleophile to generate ring-opened intermediate **25**, which further gives the carboxylate compound **22** under aerobic oxidation with the release of carbene catalyst.




**Scheme 3.7** Oxidative NHC-catalyzed ring opening of aziridine with aldehydes

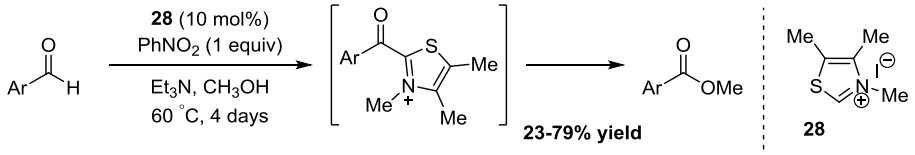
In 2012, Anand and co-workers reported a transition-metal-free protocol for oxidative coupling of aromatic aldehydes with aryl boronic acids using NHC precatalyst **27** to give corresponding esters in favorable yields (Scheme 3.8).[9]




**Scheme 3.8** NHC-mediated oxidative esterification with aryl boronic acids

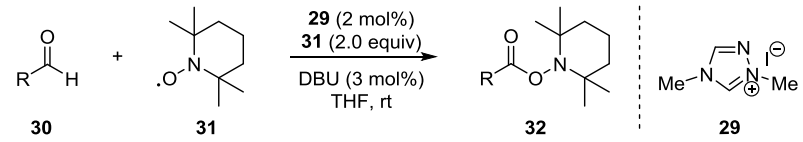
### 3.2.3 NHC-Catalyzed Reaction using Organic Oxidant

Castells and co-workers in 1977, demonstrated first example of NHC-mediated conversion of several aromatic aldehydes to the corresponding carboxylic ester using thiazolium salt precatalyst **28** in the presence of nitrobenzene as an organic oxidant (Scheme 3.9).[10] Importantly, there is no need of external oxidant for the oxidation of 4-nitrobenzaldehyde to get the corresponding 4-nitrobenzoic acid.



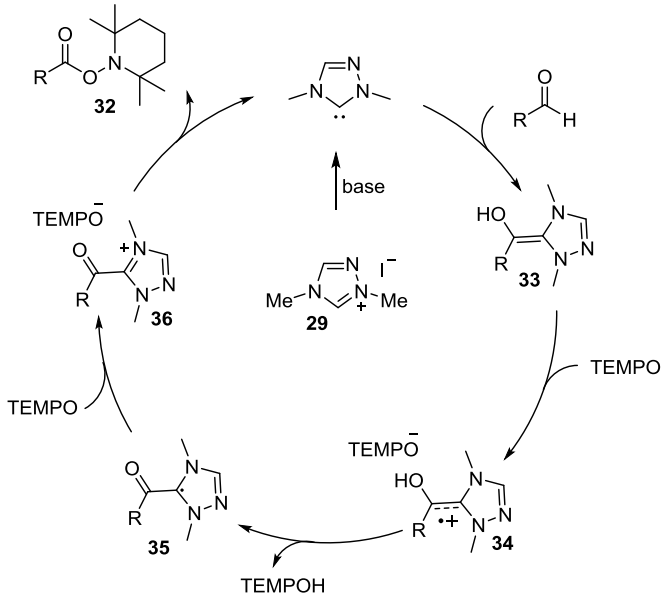

**Scheme 3.9** NHC-catalyzed oxidative conversion of aldehydes to ester

In 2008, the Studer research group reported the biomimetic oxidation of Breslow intermediate by the organic single-electron transfer (SET) oxidant 2,2,6,6-tetramethyl piperidine N-oxyl radical (TEMPO). Various aromatic, hetero-aromatic and aliphatic aldehydes underwent clean oxidation using triazolium precatalyst **29**, DBU and TEMPO (2 equiv) to produce corresponding TEMPO esters **32** in favorable yields (Scheme 3.10).[11] The sluggish reactions were observed for aliphatic aldehydes.




**Scheme 3.10** NHC-catalyzed oxidative conversion of aldehydes to ester

Mechanistically, the transformation proceeds with the formation of Breslow intermediate **33** by reaction of carbene and aldehyde (Scheme 3.11), which then undergoes single-electron transfer to TEMPO to give radical cation **34** and TEMPO$^-$.

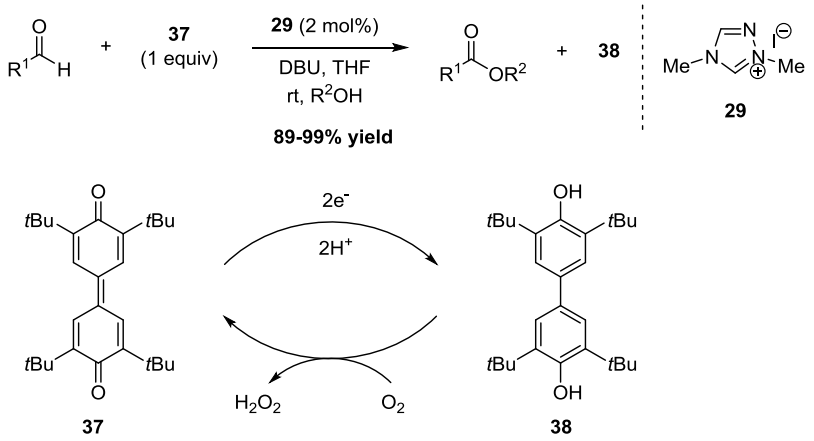



**Scheme 3.11** Plausible mechanism for NHC-catalyzed esterification of aldehydes

An abstraction of proton from **34** by TEMPO$^-$ generates radical **35** and TEMPOH. Another SET from **35** to TEMPO generates acyl azolium intermediate **36**, which on nucleophilic trapping by TEMPO$^-$ furnished the desired ester product **32** with the release of carbene catalyst. The TEMPO esters can easily converted to the corresponding acids or methyl esters under acidic conditions. Additionally, the TEMPO was regenerated by aerobic oxidation, which makes this protocol economically feasible. However, further studies revealed that interception of acyl azolium ion **36** with other

nucleophiles such as alcohols or amines were not successful because trapping of acyl azolium **36** by $TEMPO^-$ is very fast. Therefore, there was a strong demand to find a new SET oxidant which is capable to oxidize Breslow intermediate **33** as well as its reduced form does not show any nucleophilicity.

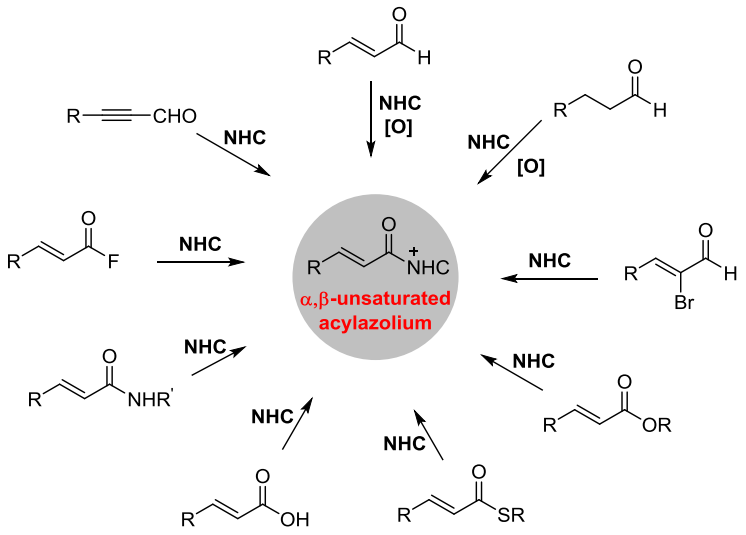
In the related context, they demonstrated the oxidation of various aromatic aldehydes using readily available 3,3',5,5'-tetra-tert-butyldiphenoquinone **37** with NHC-catalyst **29** to give corresponding esters in high yields (Scheme 3.12).[12] The above used organic oxidant acted as a two-electron acceptor and the resultant bisphenol **38** could be quickly separated from the product by column chromatography. Interestingly, the organic oxidant **37** was easily regenerates in near quantitative yield by air oxidation of bisphenol **38**, which renders this approach ecologically and economically attractive.




**Scheme 3.12** NHC-mediated esterification of aldehydes using bisquinone as an oxidant

### 3.2.4 NHC-Catalyzed Reactions *via* α,β-Unsaturated Acylazolium Intermediate

The chemistry of α,β-unsaturated acyl azolium has attracted wide attention from the chemical community. Herein, the important methods to generate α,β-unsaturated acyl azolium intermediate have been described (Scheme 3.13).



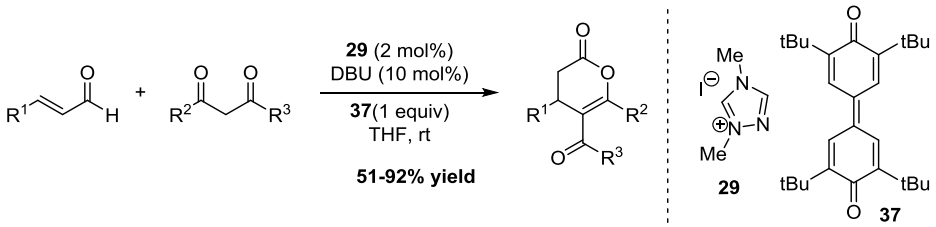

**Scheme 3.13** Methods for the generation of α,β-unsaturated acylazolium

The reaction of enals or saturated aldehydes with NHCs in the presence of external oxidants, the treatment of α-bromoenals or α,β-unsaturated esters with NHCs, the reaction of ynals or α,β-unsaturated acyl fluorides, and the treatment of α,β-unsaturated acids, amides or thioesters with NHCs provide the desired α,β-unsaturated acyl azolium intermediate.

### 3.2.4.1 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from Enals under Oxidative Conditions

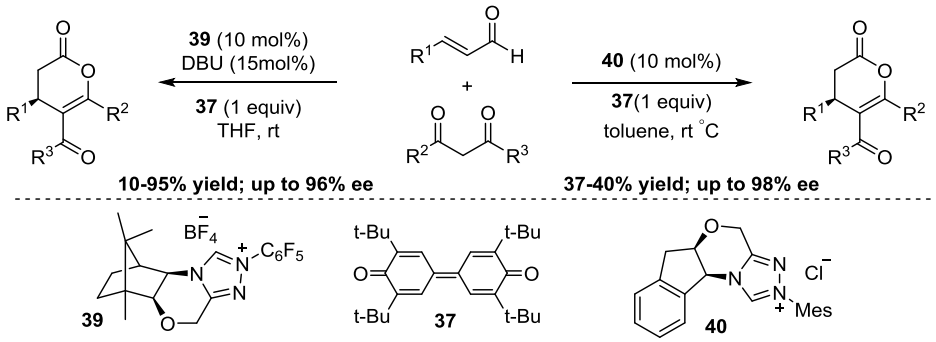
In 2010, Studer and co-workers exposed the conjugate addition of soft carbon nucleophiles such as 1,3-dicarbonyl compounds to catalytically generated α,β-unsaturated acyl azolium intermediate from enals using NHC-precatalyst **29** in the presence of the bisquinone oxidant **37** leads to the formation of functionalized dihydropyranones in good yields (Scheme 3.14).[5a] Various α,β-unsaturated aldehydes as well as nucleophiles like β-diketones or β-keto esters undergoes smooth annulation reaction to give desired products under optimized condition. Moreover, they conducted

more experimental and DFT studies on the mode of addition of nucleophiles to the α,β-unsaturated acyl azolium and concluded that 1,4-addition is more desirable than 1,2-addition.




**Scheme 3.14** Oxidative NHC-mediated access to dihydropyranones

In 2011, You[13] and Xiao[14] research groups independently demonstrated the enantioselective reaction of enals and 1,3-dicarbonyl substrates to produce enantioenriched dihydropyranones derivatives using different chiral NHC precursor with external organic oxidant **37** (Scheme 3.15).

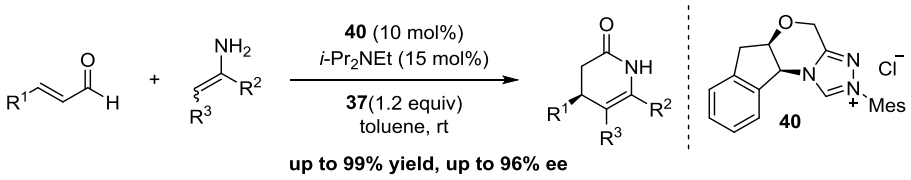



**Scheme 3.15** NHC-catalyzed enantioselective synthesis of dihydropyranones

Notably, D-camphor based triazolium precatalyst **39** in combination with DBU as base and $NaBF_4$ as an additive was applied by You and co-workers to give dihydropyranones in good yields with excellent enantioselectivity. Interestingly, Xiao and co-workers employed aminoindanol based triazolium salt **40** under base free condition to obtain the

desired dihydropyranones in acceptable yields with great selectivity. Additionally, the research group of Xu,[15] Du,[16] Biju,[17] and You[18] reported the annulation reaction of oxidatively generated α,β-unsaturated acyl azolium with a variety of 1,3-bisnucleophile to furnish corresponding dihydropyranones.

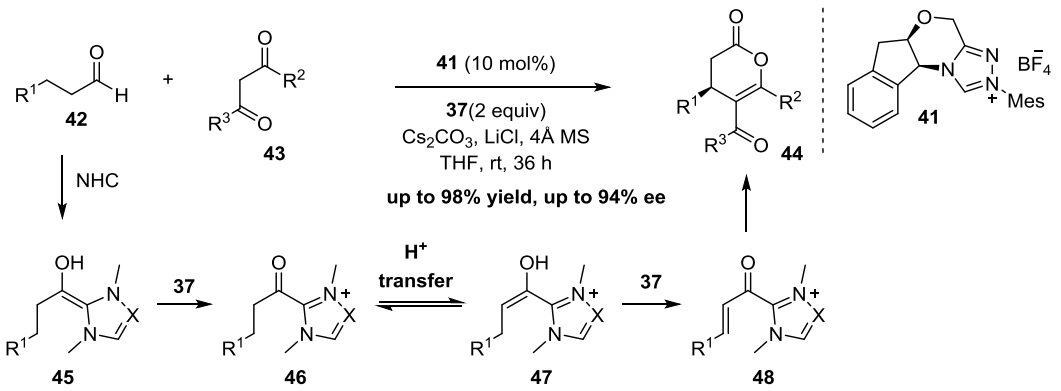
In 2011, Bode et al. exposed NHC-mediated aza-Claisen rearrangement reaction between enals and simple unprotected enamines using chiral triazolium salt **40** in the presence of oxidant **37** to furnish 3,4-dihydropyridinones in positive yields with great enantioselectivity (Scheme 3.16).[19a] Various aliphatic and aromatic enals as well as unprotected enamines containing an electron-withdrawing substituent at β-position were tolerated under the reaction condition. Later, the same research group[19b] as well as Du[20] and Zhong[21] group used other 1,3-bisnucleophiles for the synthesis of dihydropyridinones.




**Scheme 3.16** NHC-catalyzed enantioselective synthesis of dihydropyridinones

### 3.2.4.2 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from Saturated Aldehyde under Oxidative Conditions

In 2013, Chi and colleagues established a special approach for the straight forward functionalization of β-C($sp^3$)-H bond of saturated aldehyde **42** under oxidative NHC catalysis to furnish dihydropyranones **44** in pleasant yields and outstanding ee values (Scheme 3.17).[5b]

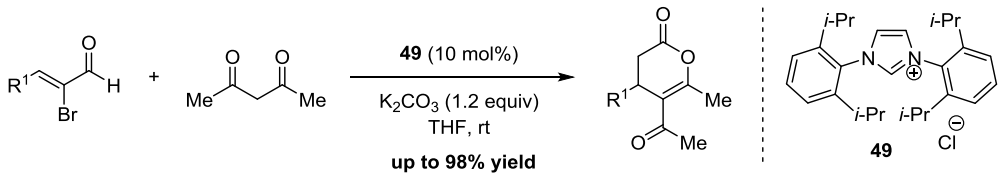



**Scheme 3.17** NHC-catalyzed functionalization of β-C-H bond of saturated aldehydes

Mechanistically, the reaction proceeds by the addition of free carbene generated from triazolium salt **41** to aldehyde **42** to form the Breslow intermediate **45**, which upon oxidation provides NHC-bound saturated acylazolium ion **46** and subsequent proton transfer leads to the formation of an azolium enolate intermediate **47**, followed by an additional oxidation employing excess bisquinone **37** generates the α,β-unsaturated acyl azolium intermediate **48**, which further reacts with 1,3-dicarbonyl substrate and provide desired product. A wide variety of β-aryl-substituted propionaldehydes with both electron-affluent and-deficient along with aryl and alkyl substituted 1,3-dicarbonyl were tolerated under optimized reaction condition.

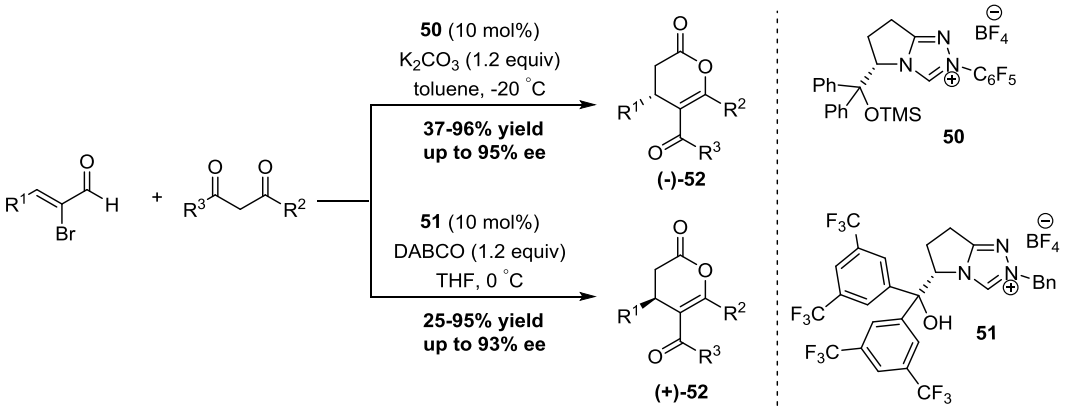
### 3.2.4.3 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from 2-Bromoenals

In 2011, Ye et al. advanced the scope to generate α,β-unsaturated acyl azolium equivalent with introduction of 2-bromoenals as a bench stable precursor. The reaction between these durable reagents and 1,3-dicarbonyl substrates in the presence of achiral imidazolium precatalyst **49** give 3,4-dihydropyrones in high yields (Scheme 3.18).[22]




**Scheme 3.18** NHC-catalyzed synthesis of dihydropyranone using α-bromoenals

Additionally, the NHC-catalyzed highly enantioselective [3+3] annulation reaction between 2-bromoenals and 1,3-dicarbonyl reagents leads to the formation of dihydropyranones **52** in good yields and excellent enantioselectivity (Scheme 3.19).[22]



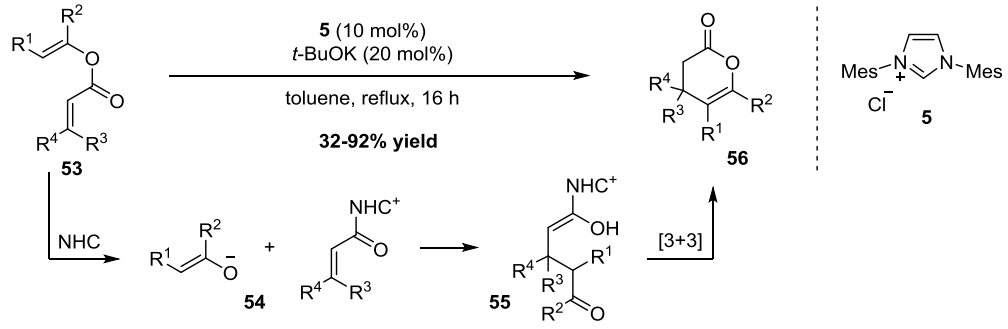

**Scheme 3.19** NHC-catalyzed enantioselective synthesis of dihydropyranone

A broad range of electronically different α-bromo-β-aryl enals as well as aliphatic α-bromoenals and various 1,3-dicarbonyl compound worked well under the optimized condition to afford corresponding desired product. Importantly, both enantiomers of the product could be obtained depending upon the proper choice of catalyst. In this context, the use of NHC generated from triazolium salt **50** having a protected –OH moiety resulted the (-)-**52** enantiomer whereas the employment of triazolium salt **51** containing a free hydroxyl group furnished the (+)-**52** enantiomer. It is interesting to note that a hydrogen bonding interaction between free –OH group of the catalyst and 1,3-dicarbonyl compounds in the transition state promote a high stereoselectivity in the

reaction. Later, the Biju,[23] Enders[24] and Ye[25] research group demonstrated the synthesis of numerous dihydropyranones and dihydropyridinones proceeding by the generation of α,β-unsaturated acyl azolium intermediate from 2-bromoenals.

### 3.2.4.4 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from α,β-Unsaturated Esters

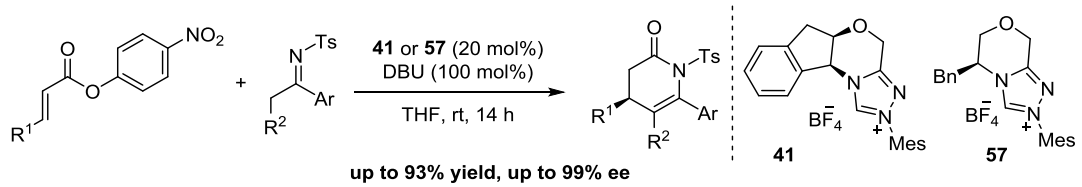
In 2009, Lupton research group exposed NHC-catalyzed fragmentation of α,β-unsaturated enol esters **53** to produce α,β-unsaturated acyl azolium/enolate intermediate **54**, which upon further recombination provide 2,3-dihydropyranones **56** (Scheme 3.20).[26] Notably, a broad range of enol esters including β,β-disubstituted ones endure formal [3+3] annulation reaction to give the corresponding dihydropyranones in high yields.




**Scheme 3.20** NHC-catalyzed annulation of α,β-unsaturated enol esters

In 2013, Chi et al. reported NHC-mediated LUMO activation of α,β-unsaturated esters, followed by a formal [3+3] annulation reaction with imines to furnish enantioenriched dihydropyridinones (Scheme 3.21).[27] The key step for this transformation is the generation of electrophilic α,β-unsaturated acyl azolium intermediate through coupling of NHC catalyst with α,β-unsaturated esters. A variety of substitution on both α,β-unsaturated ester and arylimines were feasible under optimized reaction condition to furnish corresponding desired product in great yields along with excellent enantiomeric

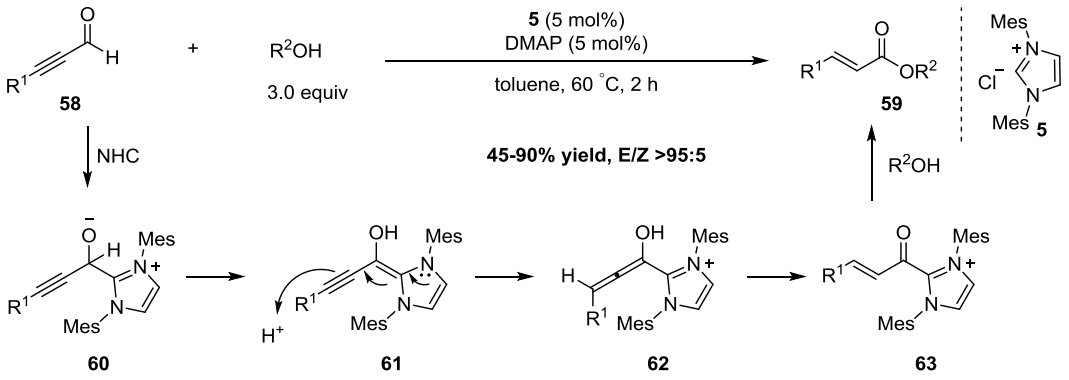
excess. Importantly, the presence of 4-nitro phenyl moiety on the ester component was crucial for this transformation. In addition, the sterically demanding β,β-disubstituted esters were also compatible in this transformation when less sterically blocked triazolium salt **57** was employed.




**Scheme 3.21** NHC-catalyzed enantioselective annulation of α,β-unsaturated ester and imines

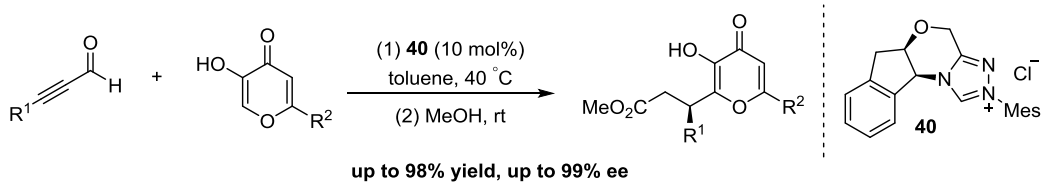
### 3.2.4.5 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from Ynals

In 2006, Zeitler and colleagues exposed NHC-mediated generation of α,β-unsaturated acyl azoliums **63** from propargylic aldehydes **58** in the existence of sterically demanding carbene produced from the imidazolium precatalyst **5** and subsequent interception of **63** with alcohols afford α,β-unsaturated esters **59** (Scheme 3.22).[28] A vast dimension of aliphatic and aromatic ynals along with various primary alcohols were well tolerated under the optimized reaction condition to give the desired corresponding unsaturated esters in good yields. Mechanistically, the reaction was proposed to proceed with the 1,2-addition of *in situ* generated carbene from imidazolium precatalyst **5** to the carbonyl of ynals **58** to from the corresponding tetrahedral intermediate **60**, followed by tautomerization to give unsaturated Breslow intermediate **61** and subsequent β-protonation leads to the formation of allenol intermediate **62**, that further tautomerize rapidly to form α,β-unsaturated acylazolium intermediate **63**, and its interception with alcohols gives the desired unsaturated esters **59**.




**Scheme 3.22** NHC-catalyzed enantioselective annulation of α,β-unsaturated ester and imines

In 2010, Bode and co-workers reported the efficient coupling between ynals and enolic C-nucleophiles like kojic acids employing chiral triazolium precatalyst **40** for highly enantioselective Claisen rearrangements through the intermediacy of catalytically generated α,β-unsaturated acyl azoliums (Scheme 3.23).[29]



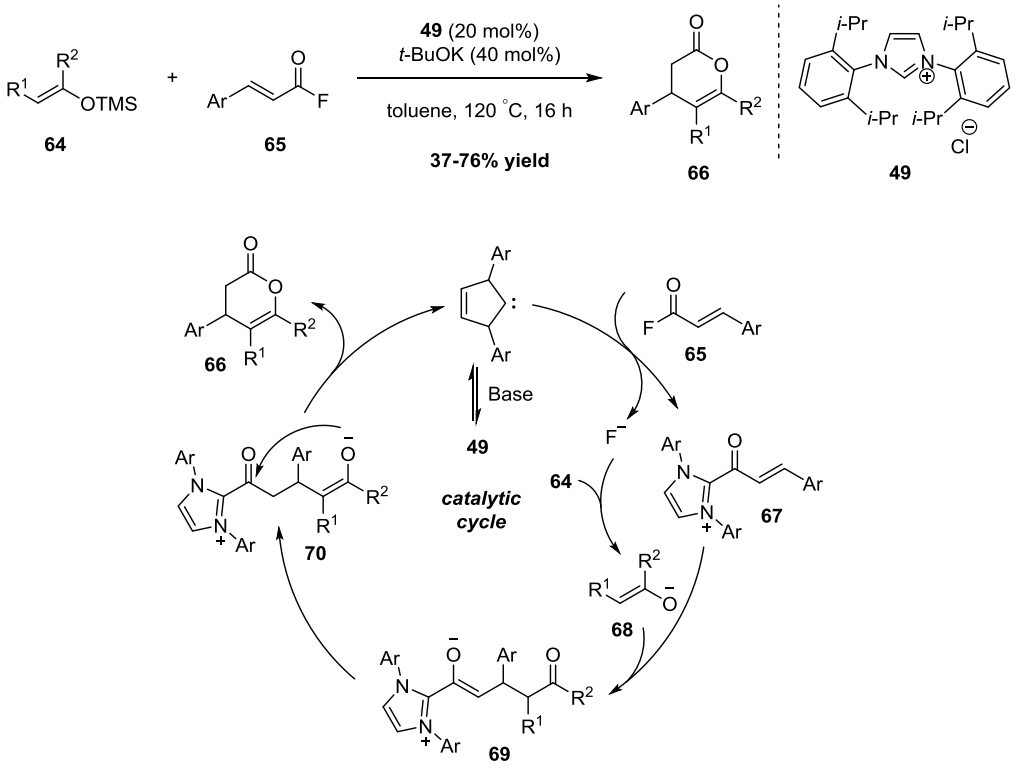

**Scheme 3.23** NHC-catalyzed annulation of ynals with kojic acid *via* Claisen rearrangement

This transformation led to the formation of somewhat unstable dihydropyranones, which further simply stirring in the presence of methanol afford ring-opened product in good yields with excellent enantioselectivity. A wide range of aliphatic and aromatic ynals as well as substituted kojic acids worked well under the reaction condition. Besides kojic acid, the pyruvic esters and β-naphthol provided the corresponding functionalized dihydropyranone under the optimized reaction condition. Remarkably, the counterion of azolium precatalyst behave as mild base for generation of free carbene and thus this protocol was found to succeed even in the absence of external base.

Subsequently, the Xiao research group exposed the efficient NHC-catalyzed coupling of ynals with 1,3-diketones or 1,3-keto esters to afford dihydropyranones.[30]

### 3.2.4.6 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from α,β-Unsaturated Acyl Fluorides

In 2009, the Lupton research group developed NHC-mediated [3+3] annulation reaction between α,β-unsaturated acyl fluorides **65** and TMS enol ethers **64** to afford dihydropyranones **66** in good yields (Scheme 3.24).[26]



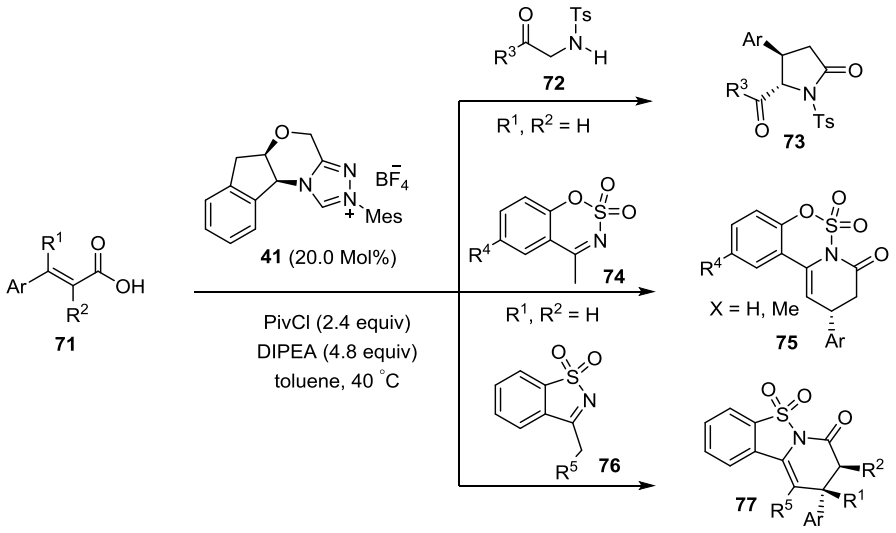

**Scheme 3.24** NHC-catalyzed synthesis of dihydropyranones from unsaturated acyl fluorides

Mechanistically, the reaction proceed with the addition of carbene generated from imidazolium salt **49** to the α,β-unsaturated acyl fluorides to give the α,β-unsaturated acylazolium intermediate **67** with the elimination of fluoride which further deprotects

the enol ether to produce the naked enolate **68** and its subsequent addition to azolium **67** generates the enolate **69**, followed by proton transfer to produce azolium **70**, which undergoes acylation to furnish the desired dihydropyranone derivatives **66** with the elimination of catalyst.

### 3.2.4.7 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from Acids

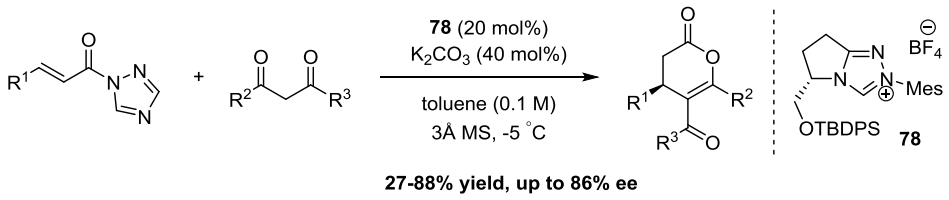
In 2014, Wang, Ye and colleagues disclosed the activation of α,β-unsaturated carboxylic acids **71** to generate α,β-unsaturated acylazolium intermediate employing chiral triazolium precatalyst **41** through the formation of mixed anhydride in the presence of pivaloyl chloride. The interception of this *in situ* generated α,β-unsaturated acylazolium with a variety of 1,2 or 1,3-bisnucleophile furnished five or six-membered heterocycle product (Scheme 3.25).[31] When employing α-amino ketones **72** as 1,2-bisnucleophiles, the reaction afforded the desired γ-butyrolactams **73** in valuable yields and moderate diastereoselectivity with admirable enantioselectivity. In addition, the use of sulfamate-derived cyclic imines **74** as 1,3-bisnucleophile under the same optimized condition leads to the formation of desired tricyclic dihydropyridinone **75** in attractive yields with superb enantioselectivity. Furthermore, the [3+3] cyclocondensation between cyclic imines **76** derived from sultam and α,β-unsaturated acid derived acylazolium furnished the corresponding tricyclic sultams **77** in exemplary yields with magnificent enantioselectivity. Notably, β,β-disubstituted and α,β-disubstituted acids were also found suitable substrate in the transformation and provide corresponding products with quaternary carbon centres or multiple stereogenic centers respectively.




**Scheme 3.25** NHC-catalyzed annulation of α,β-unsaturated acids

### 3.2.4.8 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from Amides

In 2015, Enders research group developed the activation of α,β-unsaturated *N*-acyltriazoles to generate α,β-unsaturated acylazolium intermediate in existence of chiral triazolium precatalyst **78** for the enantioselective synthesis of dihydropyranones *via* [3+3] cycloaddition with 1,3-dicarbonyl compounds (Scheme 3.26).[32] The reaction furnished the desired products in good yields with excellent enantioselectivity.

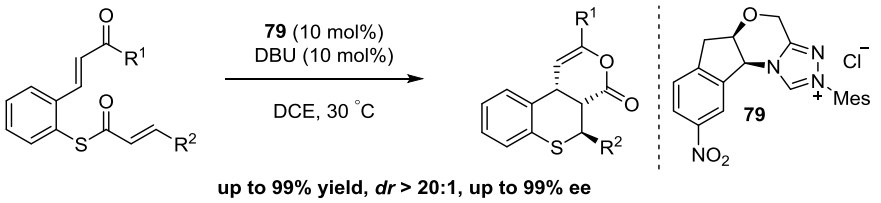



**Scheme 3.26** NHC-mediated asymmetric annulation of α,β-unsaturated amides

### 3.2.4.9 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from Thioesters

In 2017, the Xu research group disclosed the formation of α,β-unsaturated acylazolium intermediate from α,β-unsaturated thioester in the presence of chiral triazolium salt **79**

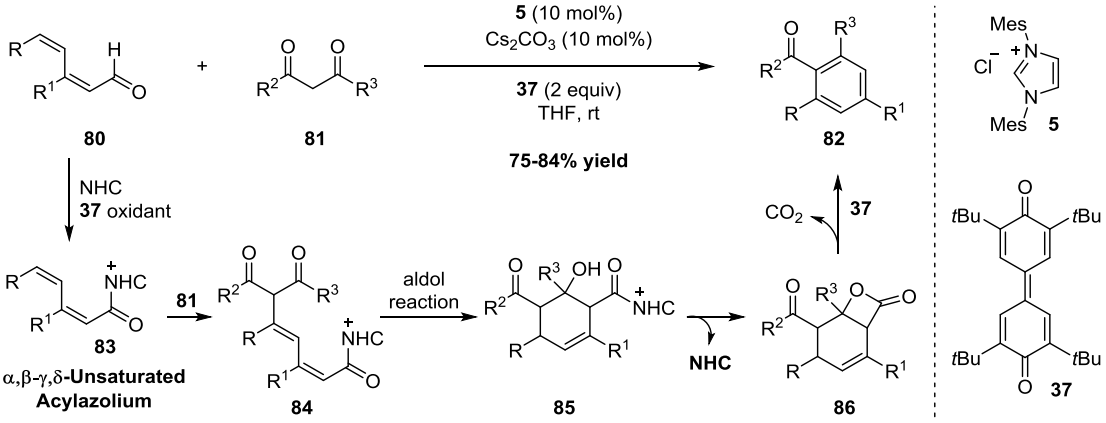
(Scheme 3.27).[33] The reaction proceeds *via* sulpha-Michael/Michael/lactonization sequence to furnished highly substituted thiochroman product in high yield and enantioselectivity.




**Scheme 3.27** NHC-catalyzed generation of α,β-unsaturated acylazoliums from thioesters

### 3.2.5 Reactions *via* α,β-γ,δ-Unsaturated Acylazolium Intermediate

In 2015, the Chi research group demonstrated the activation of the δ-carbon of α,β,γ,δ-diunsaturated aldehydes by controlling the chemoselectivity between the β- and δ-carbon with the introduction of a substituent to block the reactivity of the β-carbon (Scheme 3.28).[34]



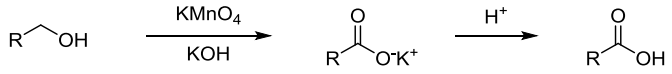

**Scheme 3.28** Generation of α,β-γ,δ unsaturated acylazolium intermediate

This δ-LUMO activated enals react with 1,3-carbonyls under oxidative conditions to furnish multi-substituted arenes **82** in good yields. Mechanistically, the reaction

proceeds with oxidative conversion of unsaturated aldehydes **80** to unsaturated acylazolium intermediate **83**, followed by 1,6-addition of 1,3-diketone leads to the formation of enol intermediate **84**, and a subsequent aldol reaction and lactonization generates bicyclic adduct **86** with the release of carbene catalyst. This bicyclic adduct undergo decarboxylation followed by spontaneous oxidative aromatization using oxidant **37** to furnished the multi-substituted benzene product **82**.

## 3.3 Some Selected Methods for the Synthesis of Carboxylic Acids

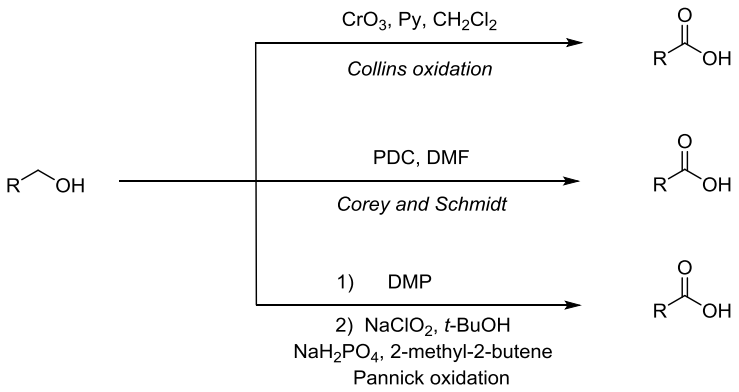
The synthesis of carboxylic acids includes procedures where primary alcohols or aldehydes are oxidized using stoichiometric amount of numerous metal-based oxidants. In 1907, Fournier was the first to propose the oxidation using potassium permanganate ($KMnO_4$) in the presence of strong alkaline aqueous environment (Scheme 3.29).[35a] Although, this methodology limits the scope of the reaction because every alcohol is not soluble in water, therefore addition of an organic co-solvent often helps to resolve out the issue of dissolution of the alcohol in the aqueous permanganate. In addition, a consecutive addition of potassium permanganate is required during reaction to ensure full conversion as it decomposes in water to manganese dioxide ($MnO_2$) and dioxygen.




**Scheme 3.29** Oxidation of alcohol to carboxylic acids using potassium permanganate

Moreover, the Jones oxidation employing chromic trioxide or sodium dichromate in diluted sulfuric acids ($CrO_3/H_2SO_4$/acetone) generates chromic acid *in situ* which acts

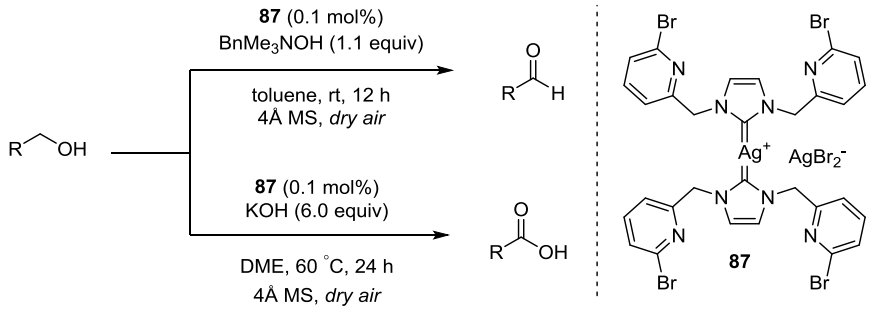
as the oxidant for the transformation, is another traditional method used to prepare carboxylic acids from primary alcohols. However, this protocol was further improved using a complex of chromium (VI) oxide with pyridine called as Collins reagent or pyridinium dichromate (PDC) for the synthesis of carboxylic acid. In addition, a two-step oxidation protocol is also possible to avoid harsh oxidation conditions and functional group incompatibility. Herein, the primary alcohol is first oxidized to an aldehyde using Dess-Martin periodinane (DMP) and consequently undergoes a Pinnick oxidation to deliver the desired carboxylic acid (Scheme 3.30).[35b]




**Scheme 3.30** Traditional methods for the oxidation of alcohol using stoichiometric oxidants

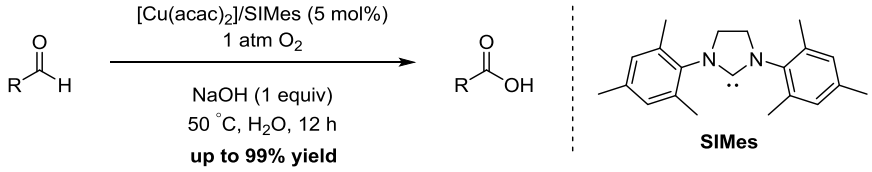
The established oxidation protocols require stoichiometric amounts of these hazardous oxidants and also produce harmful by-products. Therefore, environmentally benign oxidization protocols using molecular oxygen as oxidant provides considerable convenience compared with previously used reagents, such as higher atom economy, practical modesty and furnished water as single by-product. In this context, several metal-based catalytic methods using molecular oxygen as a terminal oxidant have been reported. In this context, the Jiang research group in 2014 demonstrated the selective oxidation of alcohols to aldehydes or carboxylic acids in good to excellent

yields using silver NHC catalyst in the presence of $BnMe_3NOH$ or KOH under dry air (Scheme 3.31).[36]



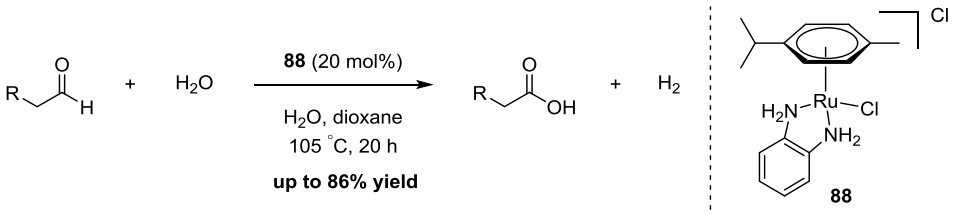

**Scheme 3.31** Silver-NHC catalyzed oxidation of alcohol to aldehydes or acids

In 2016, Li and co-workers developed the first example of copper-catalyzed aerobic oxidation of aldehydes in water, a well-known classic Fehlings reaction, which tolerates a wide range of functional-group and provide desired product in excellent yields (Scheme 3.32).[37]



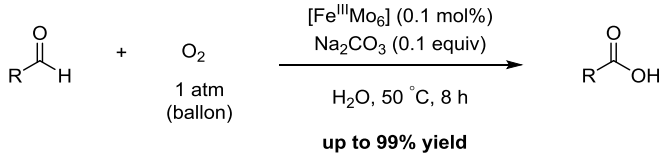

**Scheme 3.32** Copper-NHC mediated aerobic oxidation of aldehydes

Subsequently, Goldberg and co-workers developed the oxidation of aldehydes to carboxylic acids using (para-cymene) ruthenium (II) diamine complexes derived precatalysts in the presence of water as the oxidant. The reaction known as the "aldehyde-water shift" (AWS) and homogeneous precatalyst is highly selective and efficient for both the desired AWS and for conversion of the aldehyde to desired product in good to high yields (Scheme 3.33).[38] A variety of sterically unencumbered aliphatic aldehydes furnished the corresponding carboxylic acid and hydrogen gas.



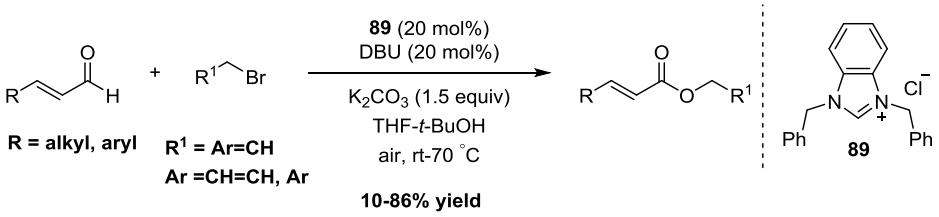

**Scheme 3.33** Ruthenium (II) diamine mediated oxidation of aldehydes using water as oxidant

In 2017, the Wei research group reported the first example of a heterogeneous iron (III)-catalyzed aerobic oxidation of aldehydes in the presence of 1 atmosphere of oxygen as the sole oxidant under mild aqueous conditions (Scheme 3.34).[39] Notably, a broad dimension of functionalized aldehydes furnished desired product in high yields.



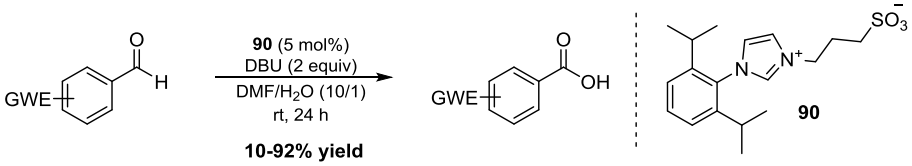

**Scheme 3.34** Iron (III) mediated aerobic oxidation to access acids

However, the development of metal-free organocatalysis provides an alternative approach for various transformation and provides several specific preference over metal-based methodology, including ready availability, vitality in procedure, and improved economic and environmental conditions. Toward this objective, Carbenes (NHCs) have emerged as utmost auspicious catalysts among all organic-molecule based catalysts for oxidation of aldehydes to access analogous carboxylic acids. In this context, the Liu research group in 2011 developed an unanticipated *N*-Heterocyclic carbene-mediated esterification of α,β-unsaturated aldehydes in the existence of air or $MnO_2$ as an oxidant (Scheme 3.35).[7b] A significant efforts have been made on mechanistic studies to investigate the feasible reaction mechanism, based on the isotopic labeling experiment and experimental results.



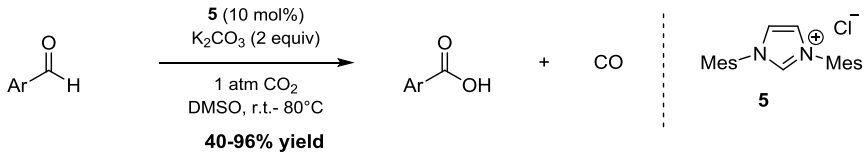

**Scheme 3.35** NHC-catalyzed aerobic esterification of α,β-unsaturated aldehydes

In 2009, Yoshida and colleagues reported a NHC-catalyzed oxidative carboxylation of aryl aldehydes with water in the presence of a sulfoxylalkyl-substituted imidazolium salt **90** (Scheme 3.36).[40] A wide range of aryl aldehydes bearing an electron-withdrawing group were compatible to produce corresponding carboxylic acids with good yields in the absence of oxidant. Additionally, this protocol was further extended to the esters and amides synthesis by using alcohols and amines as the nucleophiles.



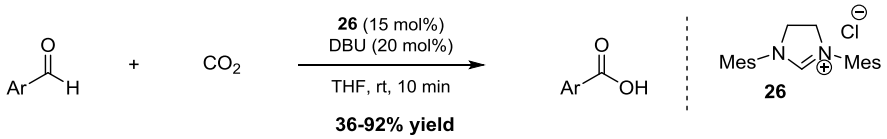

**Scheme 3.36** NHC-catalyzed oxidative carboxylation of aryl aldehydes

In 2010, Zhang research group demonstrated a new economical methodology to oxidize aromatic aldehydes employing carbon dioxide in the presence of mesityl-substituted imidazolium salt **5** under moderate conditions (Scheme 3.37).[41a] The catalytic reduction of carbon dioxide to carbon monoxide using NHCs as organocatalysts and aromatic aldehydes as reductants provides a new approach in utilizing carbon dioxide as renewable "green" source.



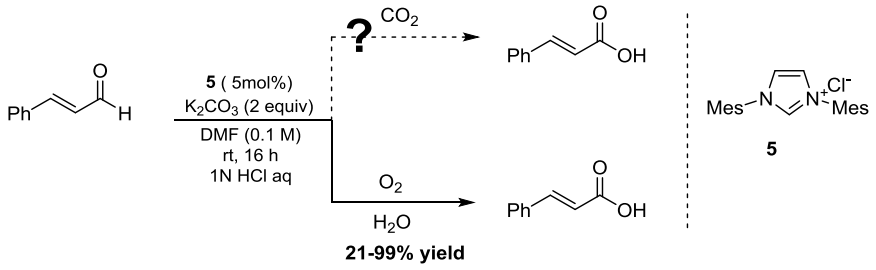

**Scheme 3.37** NHC-catalyzed $CO_2$ splitting reaction with aldehydes

Subsequently, Nair and co-workers exposed a facile NHC-mediated protocol of aldehydes with carbon dioxide for the formation of carboxylic acids under simple conditions (Scheme 3.38).[41b] Importantly, the potential impact in the sequestration of carbon dioxide of the present methodology can't be underestimated, particularly in today's era of global warming.



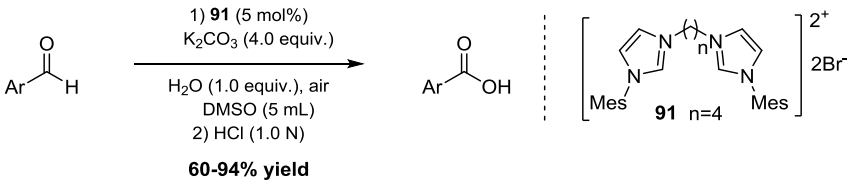

**Scheme 3.38** NHC-catalyzed transformation of aryl aldehydes to acids using $CO_2$

In 2011, the Bode research group carefully investigated NHC-catalyzed oxidation of aldehydes using carbon dioxide as the stoichiometric oxidant. These studies conclude that role of carbon dioxide lies in suppressing side products formed by aldehyde dimerization or oligomerization under the reaction conditions and involves exogenous oxygen as the actual oxidant (Scheme 3.39).[42]



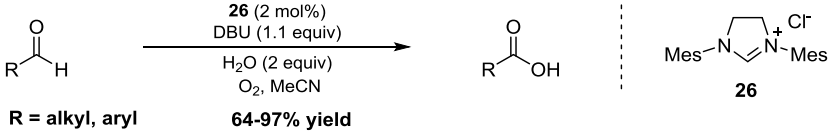

**Scheme 3.39** NHC-catalyzed oxidation of aldehydes to acids using oxygen as oxidant

In 2013, Fu and co-workers reported a highly efficient and convenient reaction for the oxidation of aryl aldehydes using bis-zwitterionic imidazolium salts **91** provides corresponding carboxylic acids in good yields under mild conditions in existence of air as an oxidant (Scheme 3.40).[43] A wide range of aryl aldehydes bearing electron-withdrawing and electron-donating groups were tolerated under the reaction condition.




**Scheme 3.40** Abnormal bis-NHC mediated aerial oxidation of aryl aldehydes

In 2013, Blechert and co-workers demonstrated a terribly selective NHC-mediated aerial oxidation of aldehydes to the corresponding acids or esters in magnificent yields under metal free conditions with low catalyst loading at room temperature (Scheme 3.41).[44] A variety of aldehydes, including α,β-unsaturated, aliphatic and electron-rich substrates were tolerated to deliver the desired corresponding acids as well as ester in valuable yields.

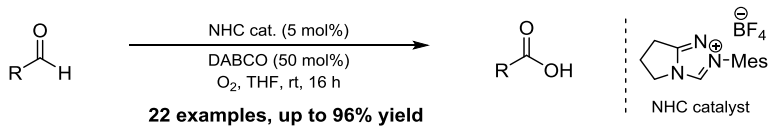



**Scheme 3.41** NHC-catalyzed aerobic oxidation of nonactivated aldehydes

## 3.4 Statement of the Problem

As explained in the earlier segment, aldehydes oxidation in order to provide their carboxylic acid counterpart using numerous metal-based oxidants, several metal-based catalytic methods as well as metal-free organocatalysis are well documented. In addition, the NHC-catalyzed oxidation of aldehydes to acids are studied by several groups, however all methods suffer from one or more drawbacks such as require reaction time of several days, higher temperatures and defined substrate scope like mainly favorable for activated electron-deficient aryl or hetero-aryl aldehydes. Therefore, there is a crucial demand for an adequate, metal-free catalytic and environmentally benign aerobic oxidation technique for problematic substrates such as aryl aldehydes with *ortho*-substitution, immensely electron-affluent aryl aldehydes and

indole-3-carboxaldehydes. In this context, we exposed a eminently competent aerobic oxidation of aryl aldehydes and enals using triazolium based NHC-catalyst with a much shorter reaction time at room temperature (Scheme 3.42). A detailed study of triazolium based NHC-mediated oxidation of aryl aldehydes and enals under aerobic condition is performed and details are presented in this chapter. This study confessed a great yielding process to access carboxylic acid analogues under mild reaction conditions. Moreover, we also have demonstrated this protocol for the gram-scale synthesis.



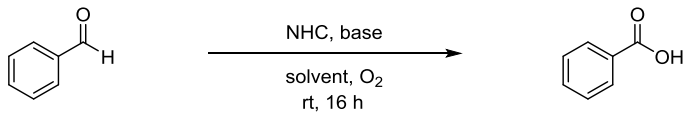

**Scheme 3.42** Proposed methodology

## 3.5 Results and Discussion

### 3.5.1 Optimization Studies

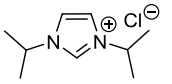
Inspired by the work surrounding this transformation, we initially started a preliminary study employing benzaldehyde **92a** as exemplary substrate beneath an oxygen environment and crucial findings are compiled in Table 3.1. Notably, we conducted a controlled experiment by the treatment of **92a** under the standard condition in the absence of NHC catalyst with a result of no desired formation of product **93a** which confirms the role of NHC catalyst (entry 1). Additionally, other common imidazolium derived NHC precatalyst with either *N*-isopropyl or *N*-Mes group in existence of DABCO as base along with THF as reaction medium produced the desired acid product **93a** in low yield (entries 2-4). Surprisingly, thiazolium based precatalyst **28** was not appropriate to access the desired oxidized product (entry 5). Interestingly, the NHC precatalyst **95** with an *N*-phenyl substituent derived from pyrrolidinone furnished the target product with marginally enhanced yield (entry 6).

**Table 3.1** Optimization of reaction conditions[a]

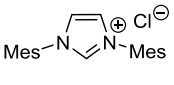



**92a** **93a**

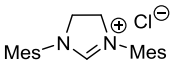
| Entry | Catalyst | Base | Solvent | Yield (%)[b] **93a** |
|---|---|---|---|---|
| 1 | **-** | DABCO | THF | - |
| 2 | **94** | DABCO | THF | <5 |
| 3 | **05** | DABCO | THF | 16 |
| 4 | **26** | DABCO | THF | 25 |
| 5 | **28** | DABCO | THF | <5 |
| 6 | **95** | DABCO | THF | 32 |
| **7** | **96** | **DABCO** | **THF** | **92** |
| 8 | **97** | DABCO | THF | 94 |
| 9 | **96** | DBU | THF | 36 |
| 10 | **96** | $Cs_2CO_3$ | THF | - |
| 11 | **96** | $K_2CO_3$ | THF | - |
| 12 | **96** | t-BuOK | THF | - |
| 13 | **96** | DABCO | DMF | - |
| 14 | **96** | DABCO | DMSO | - |
| 15 | **96** | DABCO | $CH_2Cl_2$ | - |
| 16 | **96** | DABCO | toluene | 73 |
| 17 | **96** | DABCO | $CH_3CN$ | - |
| 18[c] | **96** | DABCO | THF | 93 |
| 19[d] | **96** | DABCO | THF | 89 |
| 20[e] | **96** | DABCO | THF | 72 |
| 21[f] | **96** | DABCO | THF | 54 |
| 22[g] | **96** | DABCO | THF | 76 |



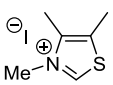

**94**



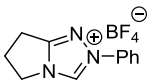

**5**



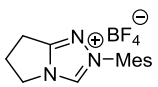

**26**



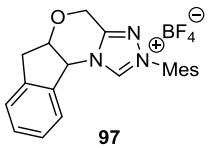

**28**




**95**




**96**




**97**

[a]Reaction conditions: **92a** (0.5 mmol), catalyst **96** (5 mol%), DABCO (50mol%), $O_2$, solvent (3.0 mL), r.t.; unless otherwise specified. [b]Yield of isolated product **93a**. [c]10 mol% of **96** was used. [d]Reaction performed at 50 °C. [e]2 mol% of **96** was used. [f]1 mol% of **96** was used. [g]Reaction under an air atmosphere.

In this precatalyst, changement of the *N*-phenyl substituent by a extra electron-rich *N*-Mes substituent (precatalyst **96**) had an outstanding effect on the output and desired product **93a** was obtained in a magnificent yield of 92% (entry 7). Moreover, the employment of NHC-salt **97** derived from aminoindanol furnished similar results (entry 8). However, considering the accessiblity, expenditure and atom recession the NHC-salt **96** was further used for the optimization analysis.

Furthermore, various bases such as DBU, $Cs_2CO_3$, $K_2CO_3$ and *t*-BuOK furnished either poor or no desired product in the existence of precatalyst **96** in THF as the solvent (entries 9-12). Thereafter, we examined the response of various solvent with the optimum NHC precatalyst **96** and DABCO as base. The targeted acid was produced only in toluene among all the various tested solvents with a diminished yield of 73% (entries 13-17). Importantly, a increase in catalyst load or reaction temperature had no significant change in formation of the desire product (entries 18 and 19). Although, reaction carried out using low catalyst loadings led to diminished yields of the desired product **93a** (entries 20 and 21). Also, reaction carried out under air atmosphere produced the product **93a** in reduced yield of 76% (entry 22).

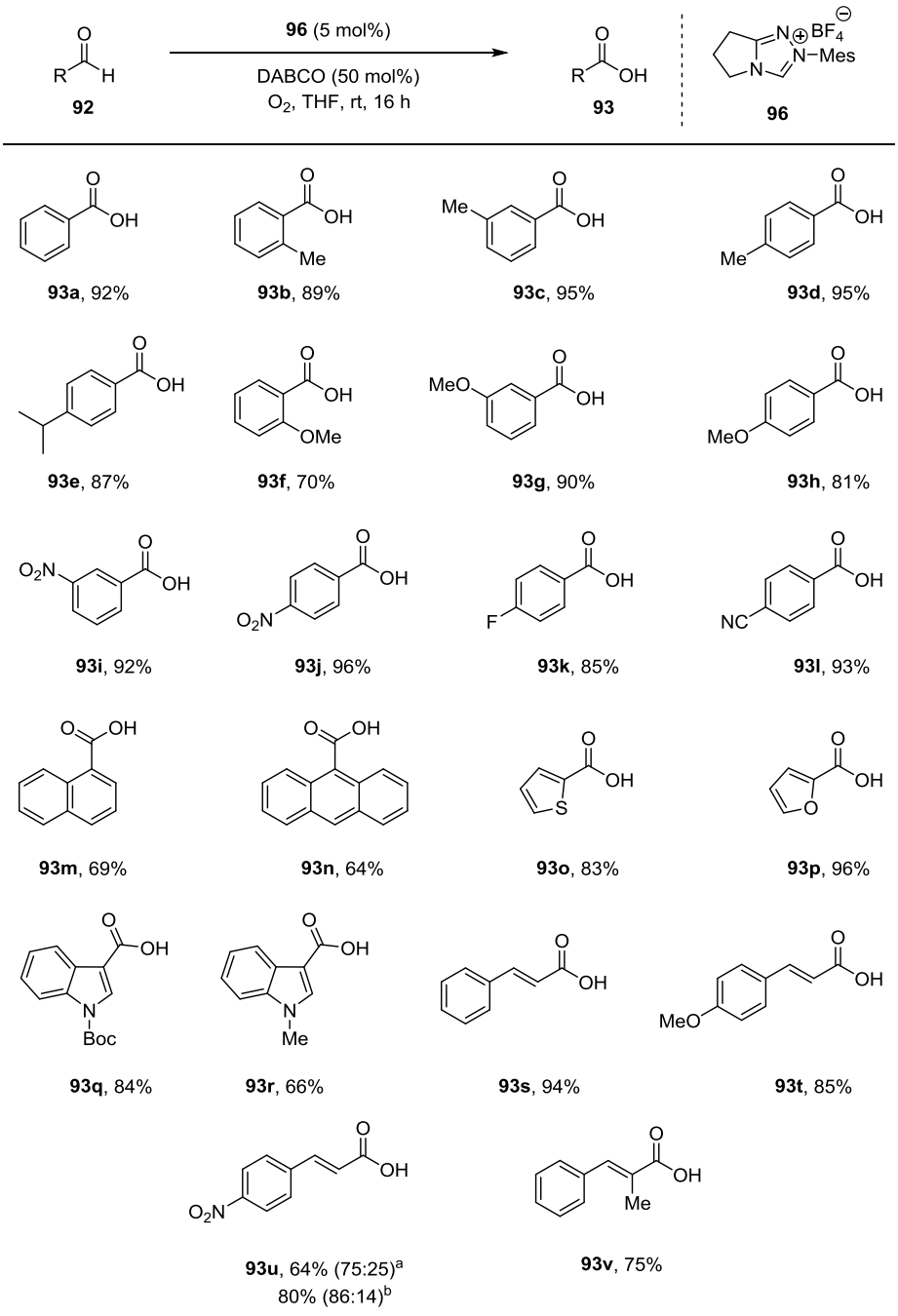
### 3.5.2 Aerobic Oxidation of Aldehydes: Substrate Scope

With this best transformation condition (Table 3.1, entry 7), we further investigated substrate extension of this unique aerobic oxidation protocol (Scheme 3.43). Delightfully, even strongly electron-rich aryl aldehydes are well tolerated resulting to the synthesis of corresponding desired acids **93b-h** in good to high yields. Notably, various electronically different substituents at the *ortho*- positions of aromatic aldehydes behaved inferior than the corresponding *meta*- and *para*-substituted aldehydes (**93b** vs **93c** and **93d**; **93f** vs **93g** and **93h**). Additionally, aryl aldehydes with electron-deficient substituents are well

tolerated affording the analogous desired acids **93i-l** in moderate to exemplary yields. Also, polycyclic aldehydes including 1-naphthaldehyde and anthracene-9-carboxaldehyde resulted in a smooth conversion to the desired products **93m** and **93n** respectively under the optimized reaction condition. Furthermore, it was observed that hetero-aryl aldehydes have no effect in the course of the reaction and leads to the corresponding desired acids **93o-r** in good yields. Importantly, it is worthy of notice that we were initially excited in the synthesis of highly useful synthons such as indole-3-carboxylic acids **93q** and **93r** before commence on this study, with most of the published methods in the literature catalyzed by NHC lacking to deliver an adequate result. Thereafter, we turned our focus to investigate the generality of our approach by examining several enals under our reaction conditions. Pleasingly, when enals with neutral or electron-affluent aryl group at the β-position are subjected into our condition we got corresponding desired acids **93s** and **93t** in excellent yields. Although, an enal with the electron withdrawing substituent at the β-position furnished the product **93u** in moderate yield, but as a combination with respective saturated derivative in a ratio of 75:25. Notably, the employment of catalyst **97** for this substrate under similar reaction conditions provides the similar mixture of products but with a slight improvement in the yield 80% and the ratio 86:14. Furthermore, the substituent at the α-position of enal was well tolerated leading to the formation of product **93v** in 75% yield. Notably, with the employment of an aliphatic aldehyde (1-pentanal) and a enal with β-alkyl-substitution (crotonaldehyde) under optimized reaction condition, a limited transformation into the analogues of desired acid was noticed. Also, as the reaction was not clean and because of inseparable mixture containing an unidentified impurity, it was not possible to isolate the corresponding desired product in pure form. After getting successful results with a variety of aldehydes, we further analyzed the transformation on a 1 gram scope employing benzaldehyde.

Interestingly, the desired product **93a** was isolated in 71% and 87% yield with a 2 mol% and 5 mol% catalyst **(96)** loading over a reaction time of 24 hours, respectively.

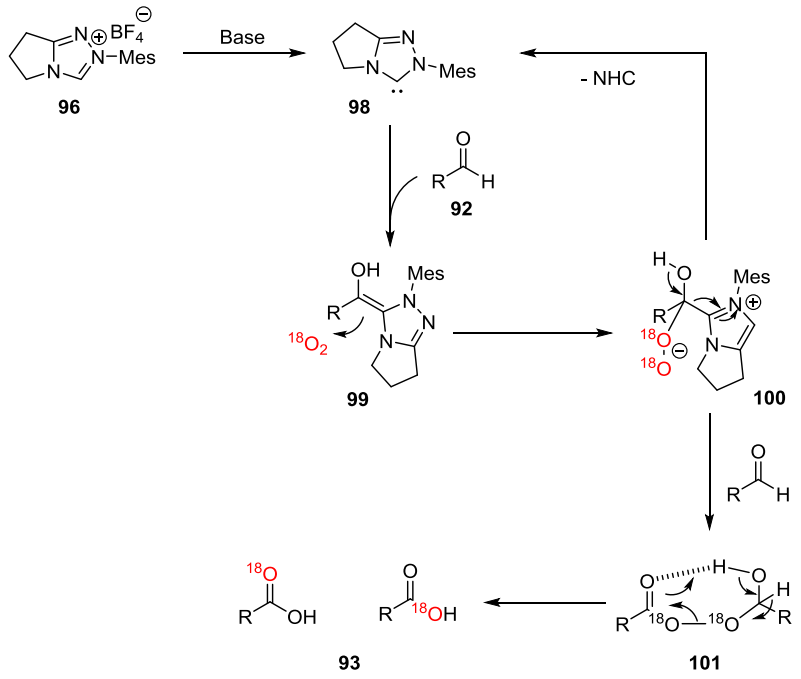
**Scheme 3.43** Substrate scope of aldehydes




Reagents and conditions: **92** (0.5 mmol), precatalyst **96** (5 mol%), DABCO (50 mol%), $O_2$, THF (3.0 mL), r.t., 16 h; unless otherwise specified. Yields are those of isolated products **93**. [a]Ratio of **93u** and its saturated analogue. [b]Precatalyst **97** was employed; ratio of **93u** and its saturated analogue.

### 3.5.3 Plausible Reaction Mechanism

In 2011, Liu and co-workers proposed an oxygen insertion type mechanism for NHC-catalyzed oxidative esterification of aldehydes on the basis of the isotope labeling experiment.[7a] On the basis of this study, a plausible reaction mechanism was proposed as shown in Scheme 3.44.




**Scheme 3.44** Proposed mechanism for the synthesis of carboxylic acids

The transformation initiated *via* the formation of the Breslow equivalent **99** from aldehyde **92** and the NHC **96**. This Breslow intermediate **99** reacts with dioxygen to deliver the corresponding peroxide intermediate **100**, which undergoes the carbene liberation to generate a corresponding deprotonated peracid intermediate which possess doubly $^{18}O$-marked at the peracid moiety. Subsequently, the peracid is commonly known to react with another molecule of aldehyde **92** to generate hydroxy peroxyl adduct **101**, which in turn delivers two equivalent of corresponding acids **93** bearing exactly one labeled O atom.

## 3.6 Conclusion

In closure, we have accomplished a extremely productive NHC-organocatalyzed process for oxidation of different classes of aldehydes in aerobic conditions resulting to the creation of analogous carboxylic acids in good yields under smooth reaction condition. Remarkably, this protocol is suitable for a variety of aldehydes including extremely ambitious electron-affluent aromatic aldehydes, *ortho*-substituted aromatic aldehydes, diverous hetero-aromatic aldehydes, α,β-unsaturated aldehydes and indole-3-carboxaldehydes. Notably, these challenging aldehydes under previously reported NHC-catalyzed protocols provides poor yields or usually unreactive, require high reaction temperature and several days reaction time. Gratifyingly, we have also exposed this synthesis protocol to a gram-scale. In addition, a variety of functional group resistance under moderate reaction condition with high yields of desired acids are the noteworthy ingredient of this current transformation.

## 3.7 Experimental Section

### 3.7.1 General Information

Unless otherwise specified, all reactions were carried out under an $O_2$ atmosphere in a flame-dried reaction vessel. THF was purchased from commercial sources and distilled from Na using benzophenone as an indicator. All aldehydes were purchased from commercial sources and were purified by washing with $NaHCO_3$ after dissolving in dichloromethane or ether, prior to use. Analytical thin layer chromatography was performed on pre-coated plates (Merck silica gel 60, $F_{254}$), and visualization was achieved with shortwave UV light or by dipping in PMA/$KMnO_4$ staining solutions followed by gentle heating. $^1$H NMR spectra were recorded on Bruker Avance III 400 MHz spectrometer using $CDCl_3$ or DMSO-$d_6$ as the solvent at ambient temperature. Chemical shifts (δ) are given in ppm on a scale downfield from TMS, the coupling

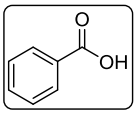
constant *J* are in Hz, and residual solvent signals were used as references. The chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, DMSO-$d_6$ δH = 2.52 ppm). The signal patterns are marked as follows: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet and brs = broad. The $^1$H NMR data of all the isolated products were matched with those disclosed previously in the literature.

### 3.7.2 General Procedure for the NHC-Catalyzed Aerobic Oxidation of Aldehydes

To a flame-dried two neck round bottom flask (25 ml) equipped with a magnetic stir bar was added triazolium precatalyst **96** (0.025 mmol), aldehyde **92** (0.5 mmol), and anhydrous THF (3 ml) subsequently. The reaction vessel was flushed with $O_2$ gas, followed by the addition of DABCO (0.25 mmol). The resultant reaction mixture was kept stirring for 16 h at room temperature under an $O_2$ atmosphere (1 atm, $O_2$ balloon). Upon completion of the reaction as monitored by TLC, the reaction mixture was diluted with EtOAc (10 ml) followed by addition of aqueous 1.0 M NaOH solution. Thereafter, the aqueous layer was extracted, washed with EtOAc (10 ml). Then the aqueous layer was acidified using 3.0 M aqueous HCl solutions (10 ml) and extracted with EtOAc (10 ml) twice. The combined organic fractions were washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give the desired acid in pure form.

### 3.7.3 Spectroscopic Data of Carboxylic Acids

***Benzoic Acid (93a)***[45a]

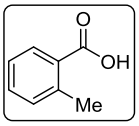



Following the general procedure **3.7.2** described above, the title compound was prepared using benzaldehyde **92a** (0.5 mmol, 53 mg, 1.0 equiv). The product **93a** was isolated in 92% yield (56 mg) as a pale yellow solid.

$R_f$ = 0.4 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 8.17–8.10 (m, 2 H, Ar-H), 7.66–7.59 (m, 1 H, Ar-H), 7.52–7.45 (m, 2 H, Ar-H).

***2-Methylbenzoic acid (93b)***[45b]

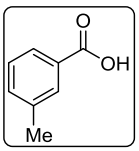



Following the general procedure **3.7.2** described above, the title compound was prepared using 2-methyl benzaldehyde **92b** (0.5 mmol, 60 mg, 1.0 equiv). The product **93b** was isolated in 89% yield (60 mg) as a pale yellow solid.

$R_f$ = 0.4 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, CDCl3)**: δ = 8.07 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.45 (t, *J* = 8.0 Hz, 1 H, Ar-H), 7.28 (t, *J* = 7.2 Hz, 2 H, Ar-H), 2.67 (s, 3 H, CH3).

***3-Methylbenzoic acid (93c)***[45c]

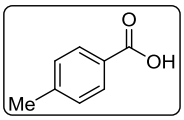



Following the general procedure **3.7.2** described above, the title compound was prepared using 3-methyl benzaldehyde **92c** (0.5 mmol, 60 mg, 1.0 equiv). The product **93c** was isolated in 95% yield (65 mg) as a pale yellow solid.

$R_f$ = 0.4 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 12.04 (br, 1 H, COOH), 7.95-7.93 (m, 2 H, Ar-H), 7.43 (d, 1 H, *J* = 8.0 Hz, Ar-H), 7.37 (t, 1 H, *J* = 8.0 Hz, Ar-H), 2.43 (s, 3 H, $CH_3$).

***4-Methylbenzoic acid (93d)***[45a]

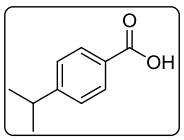



Following the general procedure **3.7.2** described above, the title compound was prepared using 4-methyl benzaldehyde **92d** (0.5 mmol, 60 mg, 1.0 equiv). The product **93d** was isolated in 95% yield (65 mg) as a pale yellow solid.

$R_f$ = 0.4 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 8.02 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.28 (d, *J* = 8.0 Hz, 2 H, Ar-H), 2.44 (s, 3 H, $CH_3$).

***4-Isopropylbenzoic acid (93e)***[39]

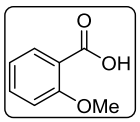



Following the general procedure **3.7.2** described above, the title compound was prepared using 4-methyl benzaldehyde **92e** (0.5 mmol, 74 mg, 1.0 equiv). The product **93e** was isolated in 87% yield (71 mg) as a off-white solid.

$R_f$ = 0.4 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 8.05 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.34 (d, *J* = 8.0 Hz, 2 H, Ar-H), 2.99 (sep, 1 H, *J* = 7.2 Hz, Ar-CH), 1.29 (d, 6 H, *J* = 7.2 Hz, $(CH_3)_2$).

***2-Methoxybenzoic acid (93f)***[45a]

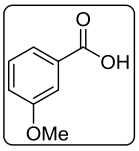



Following the general procedure **3.7.2** described above, the title compound was prepared using 2-methoxy benzaldehyde **92f** (0.5 mmol, 68 mg, 1.0 equiv). The product **93f** was isolated in 70% yield (53 mg) as a pale yellow solid.

$R_f$ = 0.3 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 8.13 (dd, 1 H, $J_1$ = 8.0 Hz, $J_2$ = 1.6 Hz, Ar-H), 7.57-7.52 (m, 1 H, Ar-H), 7.12-7.03 (m, 2 H, Ar-H), 4.05 (s, 3 H, $CH_3$).

***3-Methoxybenzoic acid (93g)***[45a]

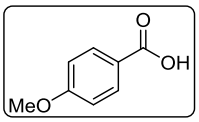



Following the general procedure **3.7.2** described above, the title compound was prepared using 3-methoxy benzaldehyde **92g** (0.5 mmol, 68 mg, 1.0 equiv). The product **93g** was isolated in 90% yield (68 mg) as a pale yellow solid.

$R_f$ = 0.3 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 7.73 (d, 1 H, *J* = 8.0 Hz, Ar-H), 7.64-7.63 (m, 1 H, Ar-H), 7.39 (t, 1 H, *J* = 8.0 Hz, Ar-H), 7.18-7.15 (m, 1 H, Ar-H), 3.87 (s, 3 H, $CH_3$).

***4-Methoxybenzoic acid (93h)***[45a]

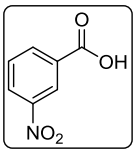



Following the general procedure **3.7.2** described above, the title compound was prepared using 4-methoxy benzaldehyde **92h** (0.5 mmol, 68 mg, 1.0 equiv). The product **93h** was isolated in 81% yield (62 mg) as a pale yellow solid.

$R_f$ = 0.3 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 12.58 (br, 1 H, COOH), 7.89 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.00 (d, *J* = 8.8 Hz, 2 H, Ar-H), 3.82 (s, 3 H, $CH_3$).

***3-Nitrobenzoic acid (93i)***[45a]

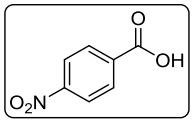



Following the general procedure **3.7.2** described above, the title compound was prepared using 3-nitro benzaldehyde **92i** (0.5 mmol, 76 mg, 1.0 equiv). The product **93i** was isolated in 92% yield (77 mg) as a pale yellow solid.

$R_f$ = 0.3 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, DMSO-$d_6$)**: δ = 8.59 (s, 1 H, Ar-H), 8.45 (d, 1 H, *J* = 8.0 Hz, Ar-H), 8.33 (d, 1 H, *J* = 8.0 Hz, Ar-H), 7.80 (t, 1 H, *J* = 8.0 Hz, Ar-H).

***4-Nitrobenzoic acid (93j)***[45a]

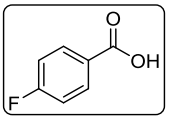



Following the general procedure **3.7.2** described above, the title compound was prepared using 4-nitro benzaldehyde **92j** (0.5 mmol, 76 mg, 1.0 equiv). The product **93j** was isolated in 96% yield (80 mg) as a light yellow solid.

$R_f$ = 0.3 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, DMSO-$d_6$)**: δ = 8.17 (d, *J* = 8.8 Hz, 2 H, Ar-H), 8.32 (d, *J* = 8.8 Hz, 2 H, Ar-H).

***4-Fluorobenzoic acid (93k)***[39]

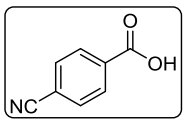



Following the general procedure **3.7.2** described above, the title compound was prepared using 4-fluoro benzaldehyde **92k** (0.5 mmol, 62 mg, 1.0 equiv). The product **93k** was isolated in 85% yield (60 mg) as a white solid.

$R_f$ = 0.4 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, DMSO-$d_6$)**: δ = 13.00 (br, 1 H, COOH), 8.04-7.95 (m, 2 H, Ar-H), 7.30 (t, *J* = 8.8 Hz, 2 H, Ar-H).

***4-Cyanobenzoic acid (93l)***[45a]

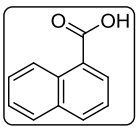



Following the general procedure **3.7.2** described above, the title compound was prepared using 4-cyano benzaldehyde **92l** (0.5 mmol, 66 mg, 1.0 equiv). The product **93l** was isolated in 93% yield (68 mg) as a pale yellow solid.

$R_f$ = 0.3 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, DMSO-$d_6$)**: δ = 13.52 (br, 1 H, COOH), 8.07 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.96 (d, *J* = 8.0 Hz, 2 H, Ar-H).

***1-Napthoic acid (93m)***[39]

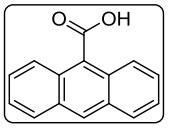



Following the general procedure **3.7.2** described above, the title compound was prepared using 1-napthaldehyde **92m** (0.5 mmol, 78 mg, 1.0 equiv). The product **93m** was isolated in 69% yield (59 mg) as a light yellow solid.

$R_f$ = 0.4 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 9.12 (d, *J* = 8.8 Hz, 1 H, Ar-H), 8.44 (dd, $J_1$ = 7.2 Hz, $J_2$ = 1.2 Hz, 1 H, Ar-H), 8.11 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.93 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.72-7.64 (m, 1 H, Ar-H), 7.62-7.53 (m, 1 H, Ar-H).

***9-Anthracenecarboxylic acid (93n)***[45d]

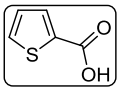



Following the general procedure **3.7.2** described above, the title compound was prepared using anthracene-9-carbaldehyde **92n** (0.5 mmol, 103 mg, 1.0 equiv). The product **93n** was isolated in 84% yield (71 mg) as a yellow solid.

$R_f$ = 0.4 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, DMSO-$d_6$)**: δ = 13.90 (br, 1 H, COOH), 8.72 (s, 1 H, Ar-H), 8.15 (d, *J* = 8.4 Hz, 2 H, Ar-H), 8.08 (d, *J* = 8.0 Hz, 2 H, Ar-H), 7.67-7.53 (m, 4 H, Ar-H).

***2-Thiophenecarboxylic acid (93o)***[39]

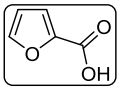



Following the general procedure **3.7.2** described above, the title compound was prepared using thiophene-2-carbaldehyde **92o** (0.5 mmol, 56 mg, 1.0 equiv). The product **93o** was isolated in 83% yield (53 mg) as a white solid.

$R_f$ = 0.3 (20% ethyl acetate in hexane).

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 7.91 (dd, $J_1$ = 3.6 Hz, $J_2$ = 1.2 Hz, 1 H, Ar-H), 7.65 (dd, $J_1$ = 5.2 Hz, $J_2$ = 1.2 Hz, 1 H, Ar-H), 7.15 (dd, $J_1$ = 5.2 Hz, $J_2$ = 1.2 Hz, 1 H, Ar-H).

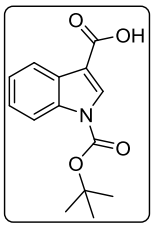
***Furoic acid (93p)***[39]




Following the general procedure **3.7.2** described above, the title compound was prepared using furan-2-carbaldehyde **92p** (0.5 mmol, 48 mg, 1.0 equiv). The product **93p** was isolated in 96% yield (54 mg) as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 9.75 (br, 1 H, COOH), 7.64 (s, 1 H, Ar-H), 7.33 (d, *J* = 3.6 Hz, 1 H, Ar-H), 6.56 (dd, $J_1$ = 3.6 Hz, $J_2$ = 1.6 Hz, 1 H, Ar-H).

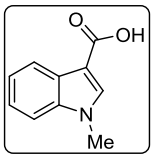
***N-BOC-Indole-3-carboxylic acid (93q)***[45e]




Following the general procedure **3.7.2** described above, the title compound was prepared using *tert*-butyl 3-formyl-1H-indole-1-carboxylate **92q** (0.5 mmol, 123 mg, 1.0 equiv). The product **93q** was isolated in 84% yield (110 mg) as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 8.40 (s, 1 H, Ar-H), 8.25-8.16 (m, 2 H, Ar-H), 7.44-7.33 (m, 2 H, Ar-H), 1.71 (s, 9 H, BOC).

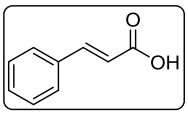
***N-methyl-Indole-3-carboxylic acid (93r)***[45f]




Following the general procedure **3.7.2** described above, the title compound was prepared using *tert*-butyl 1-methyl-1H-indole-3-carbaldehyde **92r** (0.5 mmol, 80 mg, 1.0 equiv). The product **93r** was isolated in 66% yield (63 mg) as a light brown solid.

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 8.25-8.21 (m, 1 H, Ar-H), 7.89 (s, 1 H, Ar-H), 7.40-7.30 (m, 3 H, Ar-H), 3.87 (s, 3 H, $CH_3$).

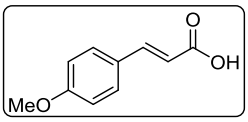
***Trans-Cinnamic acid (93s)***[45g]




Following the general procedure **3.7.2** described above, the title compound was prepared using *trans*-cinnamaldehyde **92s** (0.5 mmol, 66 mg, 1.0 equiv). The product **93s** was isolated in 94% yield (70 mg) as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 11.10 (br, 1 H, COOH), 7.71 (d, *J* = 16 Hz, 1 H, Alkene-H), 7.51-7.41 (m, 2 H, Ar-H), 7.37-7.27 (m, 3 H, Ar-H), 6.37 (d, *J* = 16 Hz, 1 H, Alkene-H).

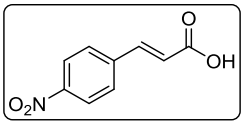
***Trans-4-Methoxycinnamic acid (93t)***[45g]




Following the general procedure **3.7.2** described above, the title compound was prepared using (E)-3-(4-methoxyphenyl)acrylaldehyde **92t** (0.5 mmol, 81 mg, 1.0 equiv). The product **93t** was isolated in 85% yield (76 mg) as a off white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 7.74 (d, *J* = 16 Hz, 1 H, Alkene-H), 7.50 (d, *J* = 8.8 Hz, 2 H, Ar-H), 6.92 (d, *J* = 8.8 Hz, 2 H, Ar-H), 6.31 (d, *J* = 16 Hz, 1 H, Alkene-H), 3.85 (s, 3 H, $CH_3$).

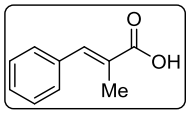
***Trans-4-Nitrocinnamic acid (93u)***[45g]




Following the general procedure **3.7.2** described above, the title compound was prepared using (E)-3-(4-nitrophenyl)acrylaldehyde **92u** (0.5 mmol, 89 mg, 1.0 equiv). The product **93u** was isolated in 80% yield (78 mg) as a off white solid.

**$^1$H NMR (400 MHz, DMSO-$d_6$)**: δ = 12.50 (br, 1 H, COOH), 8.22 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.96 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.68 (d, *J* = 16 Hz, 2 H, Alkene-H), 6.73 (d, *J* = 16 Hz, 2 H, Alkene-H).

***E-α-Methylcinnamic acid (93v)***[45h]




Following the general procedure **3.7.2** described above, the title compound was prepared using (E)-2-methyl-3-phenylacrylaldehyde **92v** (0.5 mmol, 73 mg, 1.0 equiv). The product **93v** was isolated in 75% yield (61 mg) as a white solid.

**$^1$H NMR (400 MHz, $CDCl_3$)**: δ = 11.60 (br, 1 H, COOH), 7.75 (d, 1 H, *J* = 1.2 Hz, Alkene-H), 7.36-7.21 (m, 5 H, Ar-H), 2.05 (d, *J* = 1.2 Hz, 3 H, α- $CH_3$).

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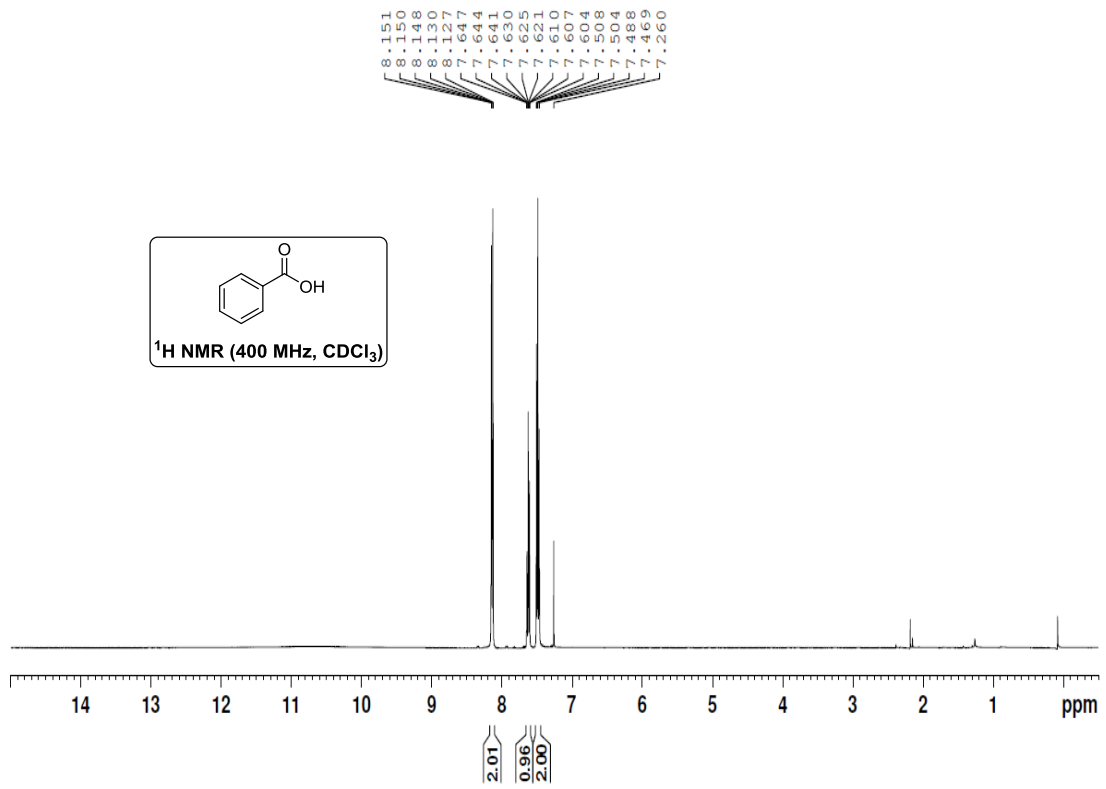
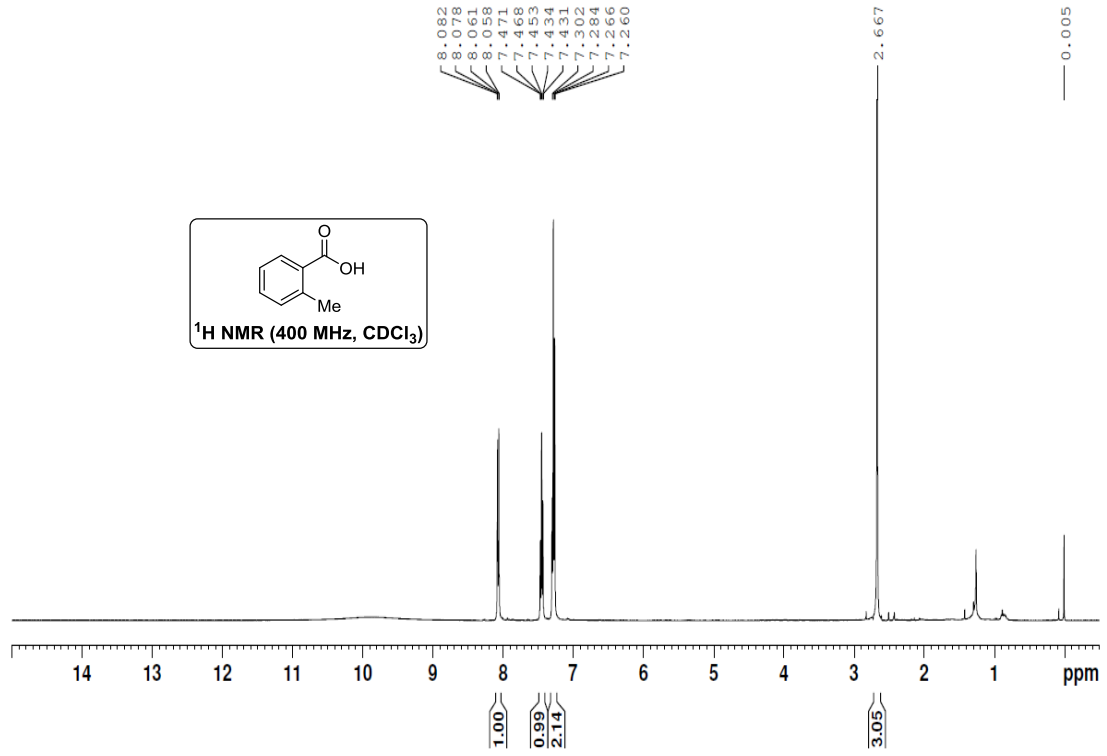
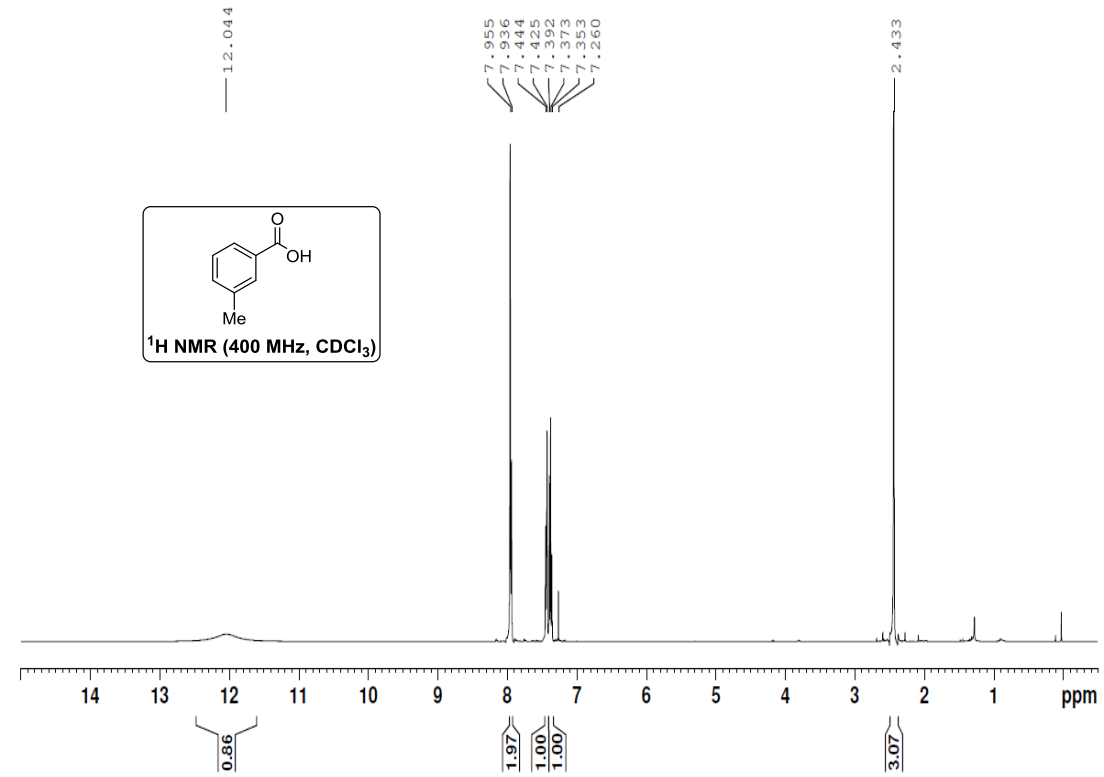
## 3.9 NMR Spectra of Compounds [$^1$H NMR (400 MHz, $CDCl_3$ or DMSO-$d_6$)]

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7.444
7.425
7.392
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7.353
7.260
2.433
O
OH
Me
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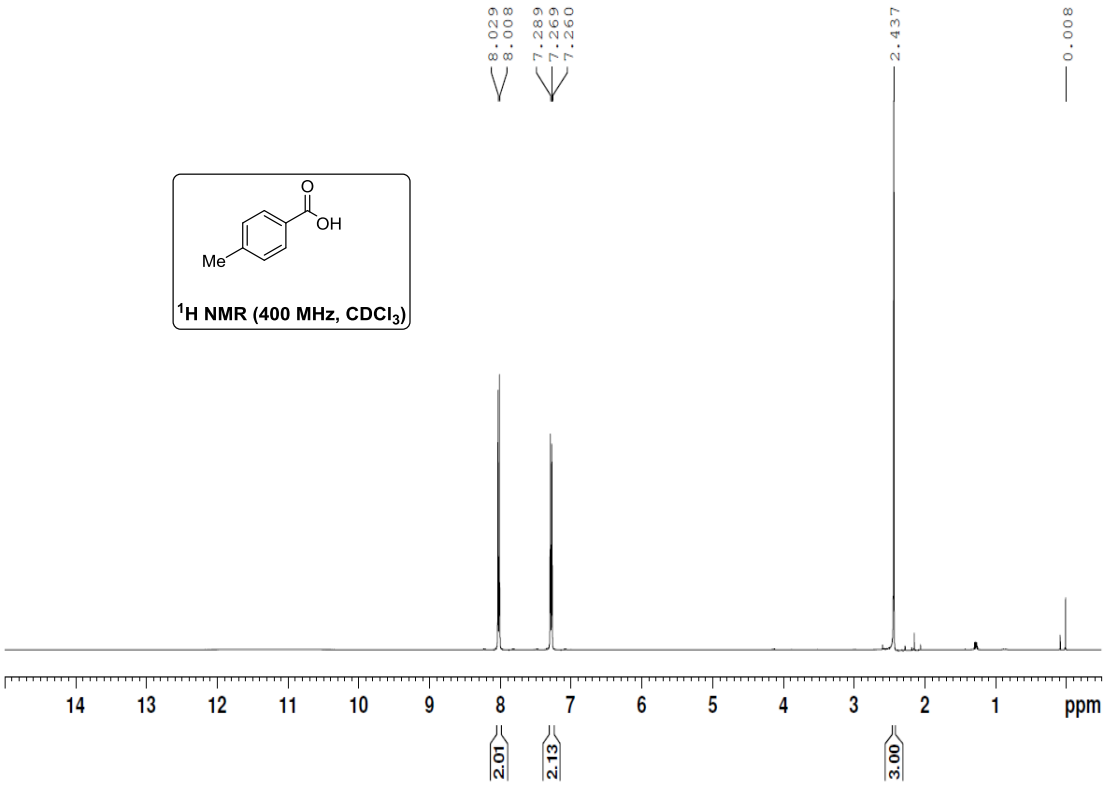
1.97
1.00
1.00
3.07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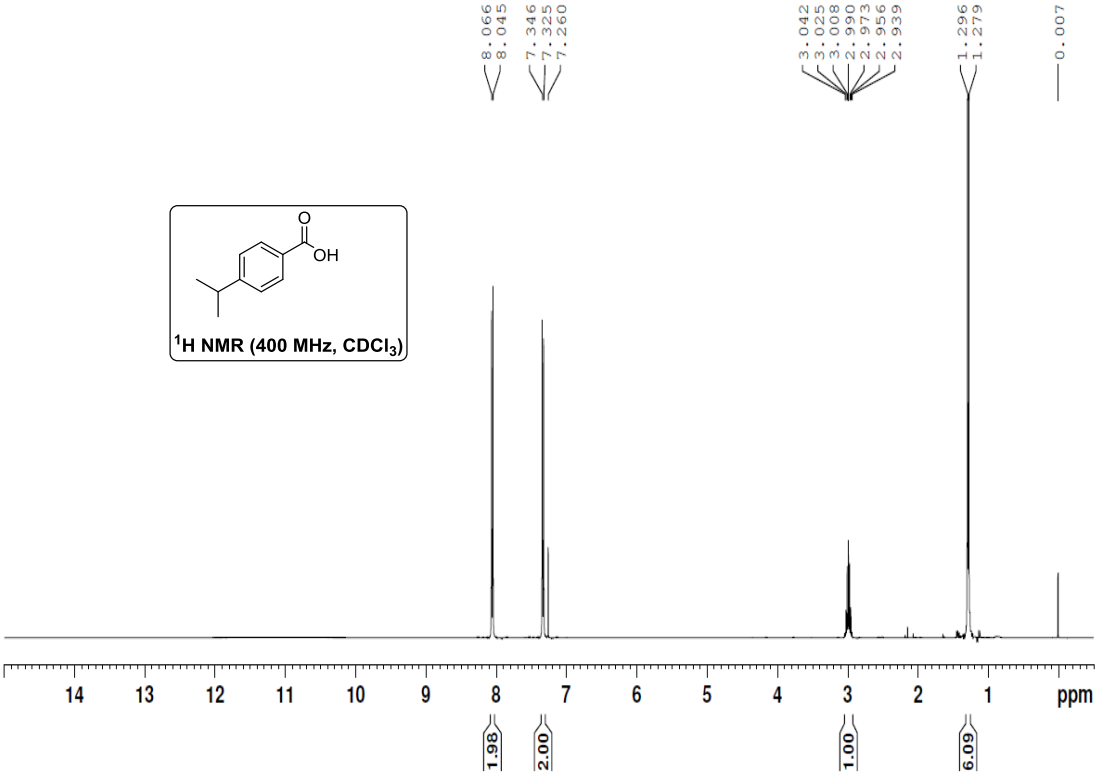
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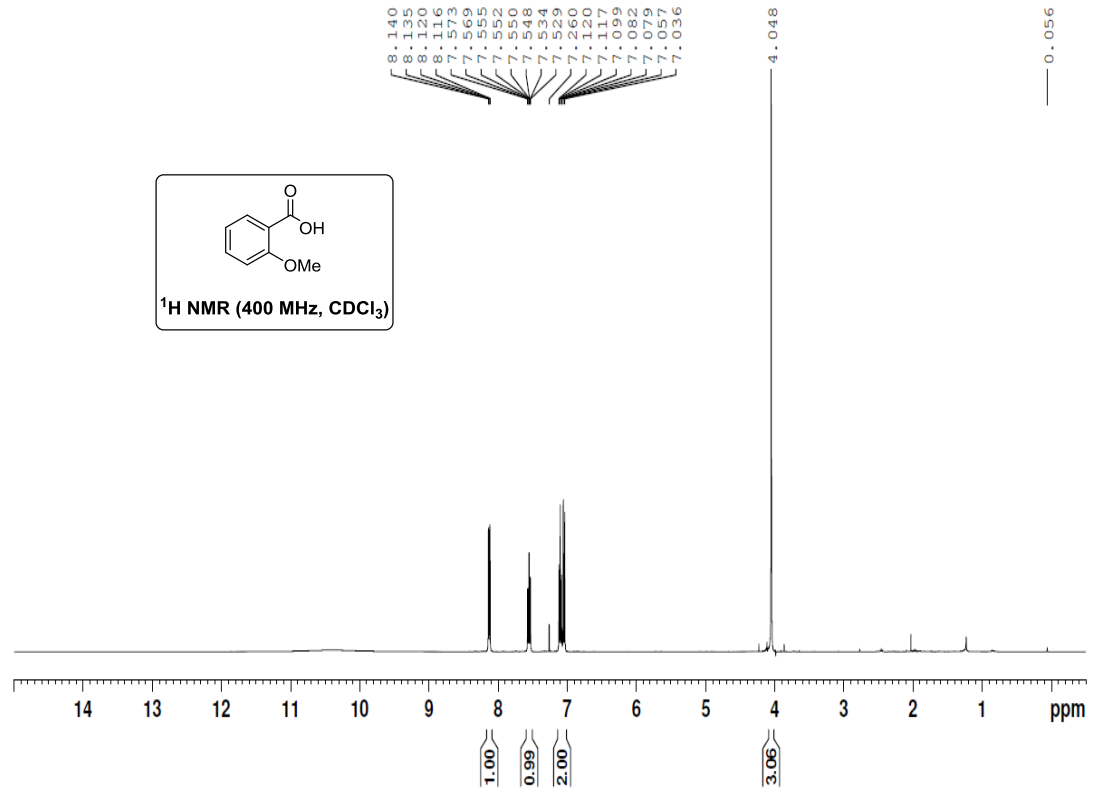
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7.036
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OH
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0.99
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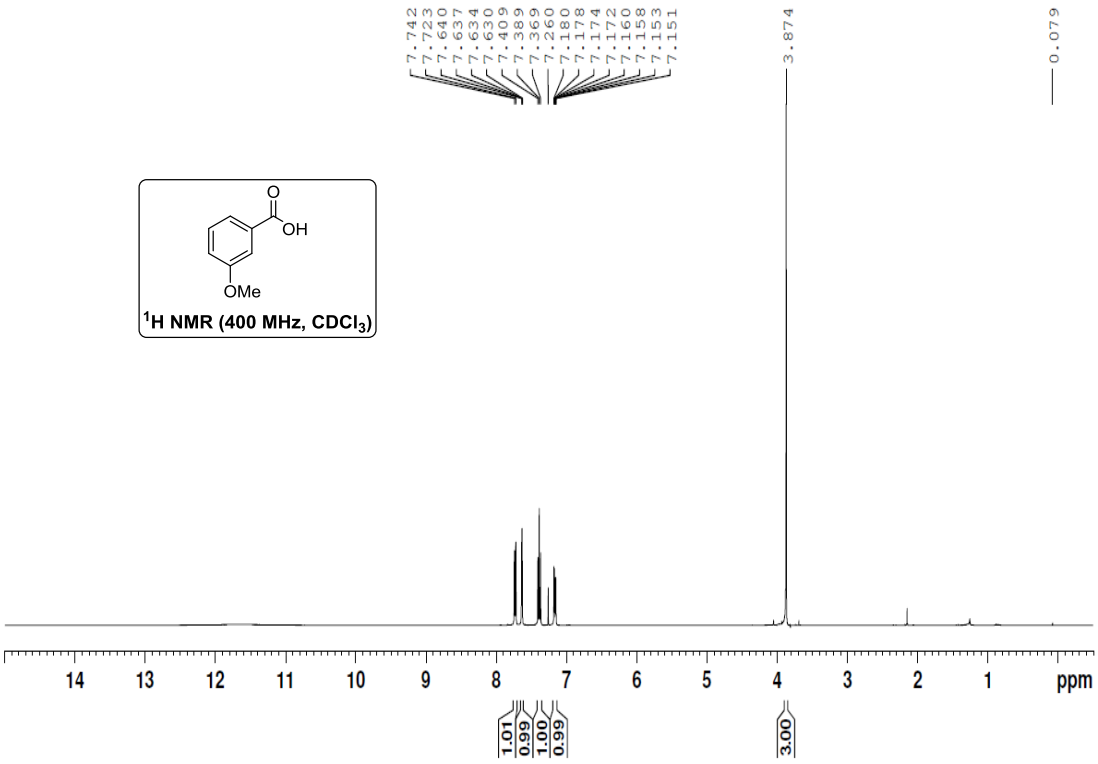
3.06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7.723
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7.634
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7.172
7.160
7.158
7.153
7.151
3.874
0.079
O
OH
OMe
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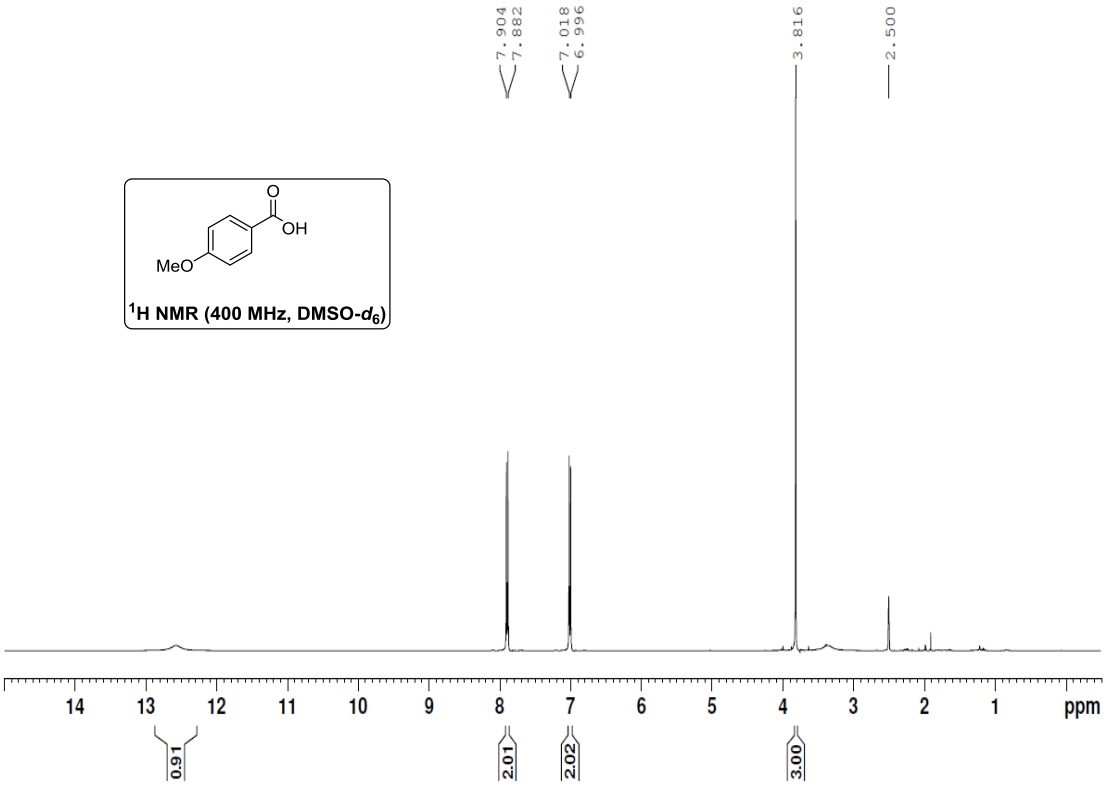
0.99
1.00
0.99
3.00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7.882
7.018
6.996
3.816
2.500
O
OH
MeO
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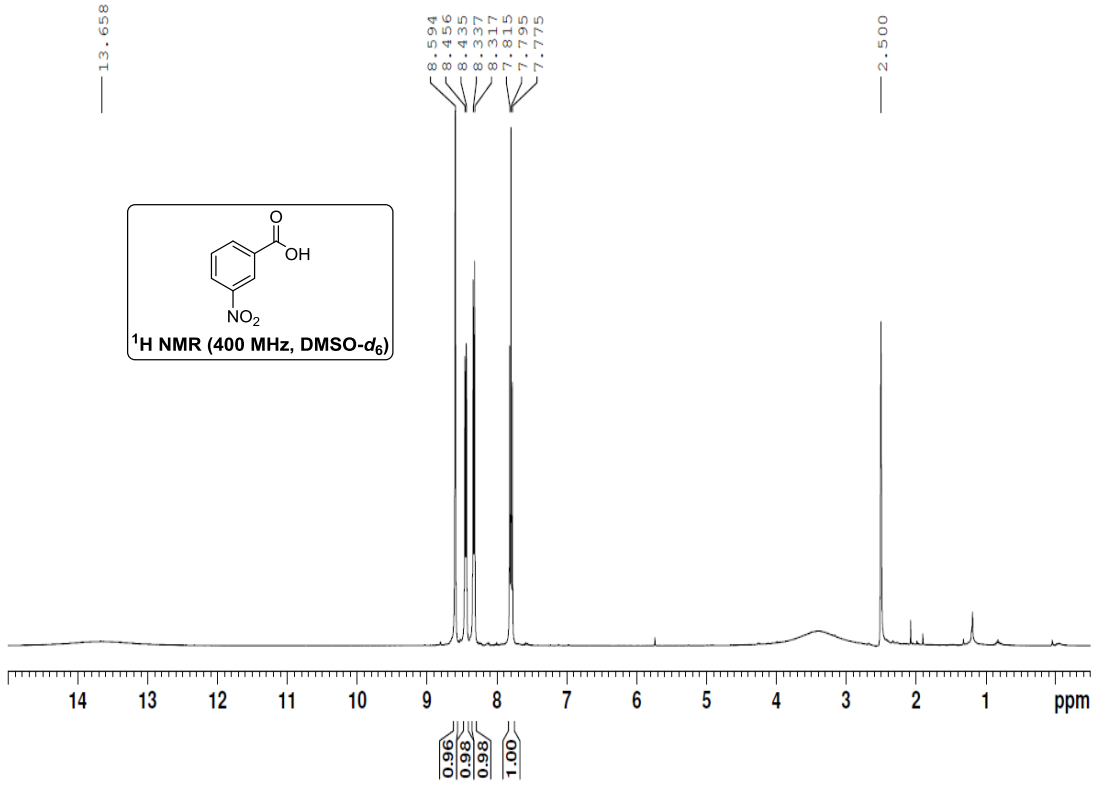
0.91
2.01
2.02
3.00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8.594
8.456
8.435
8.337
8.317
7.815
7.795
7.775
2.500
O
OH
NO2
1H NMR (400 MHz, DMSO-d6)
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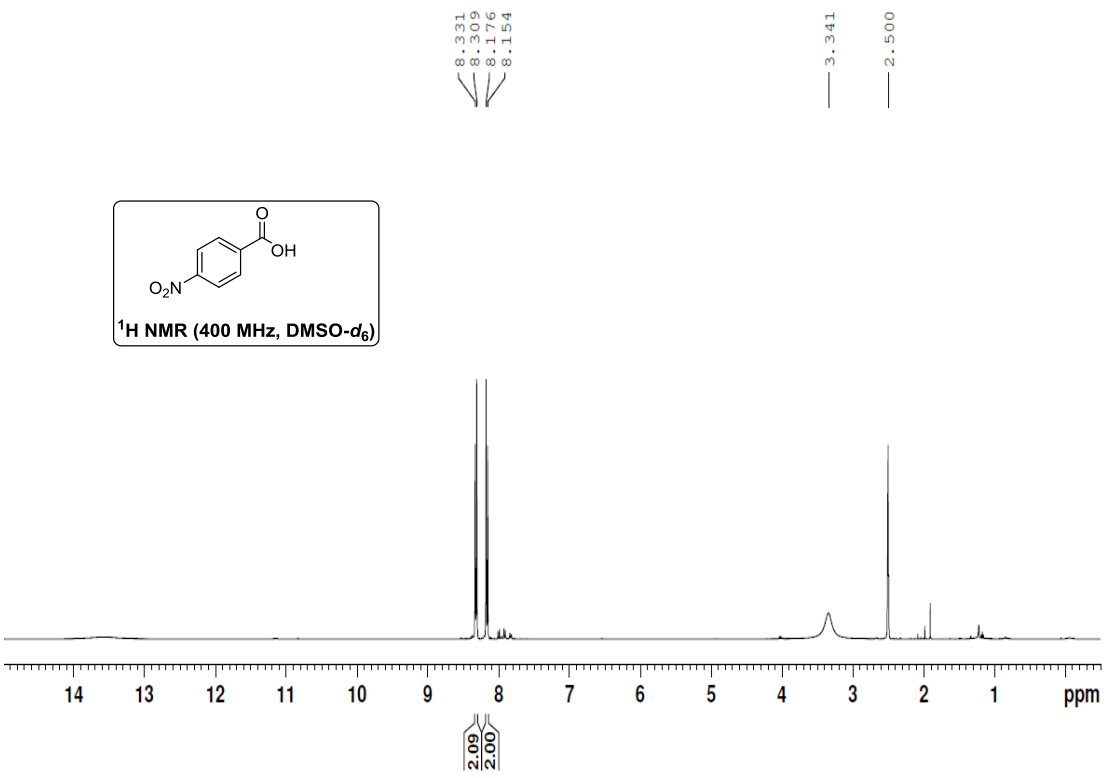
0.96
0.98
0.98
1.00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8.309
8.176
8.154
3.341
2.500
O
OH
O2N
1H NMR (400 MHz, DMSO-d6)
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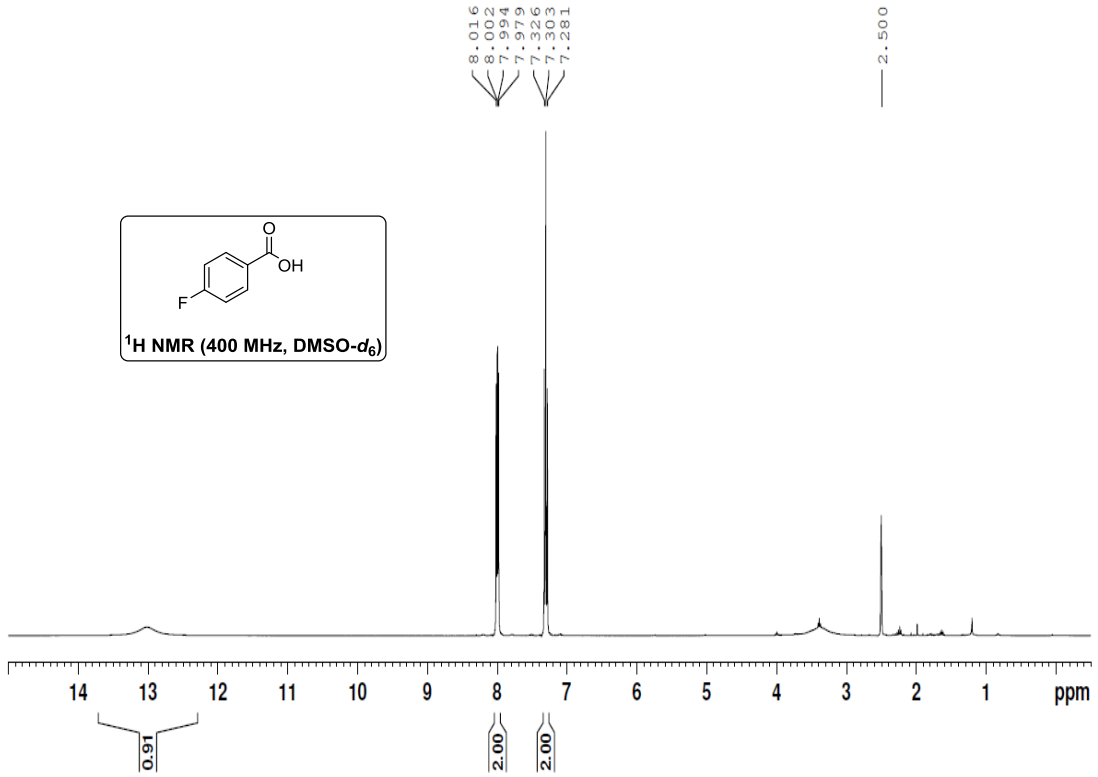
2.09
2.00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8.002
7.994
7.979
7.326
7.303
7.281
2.500
O
OH
F
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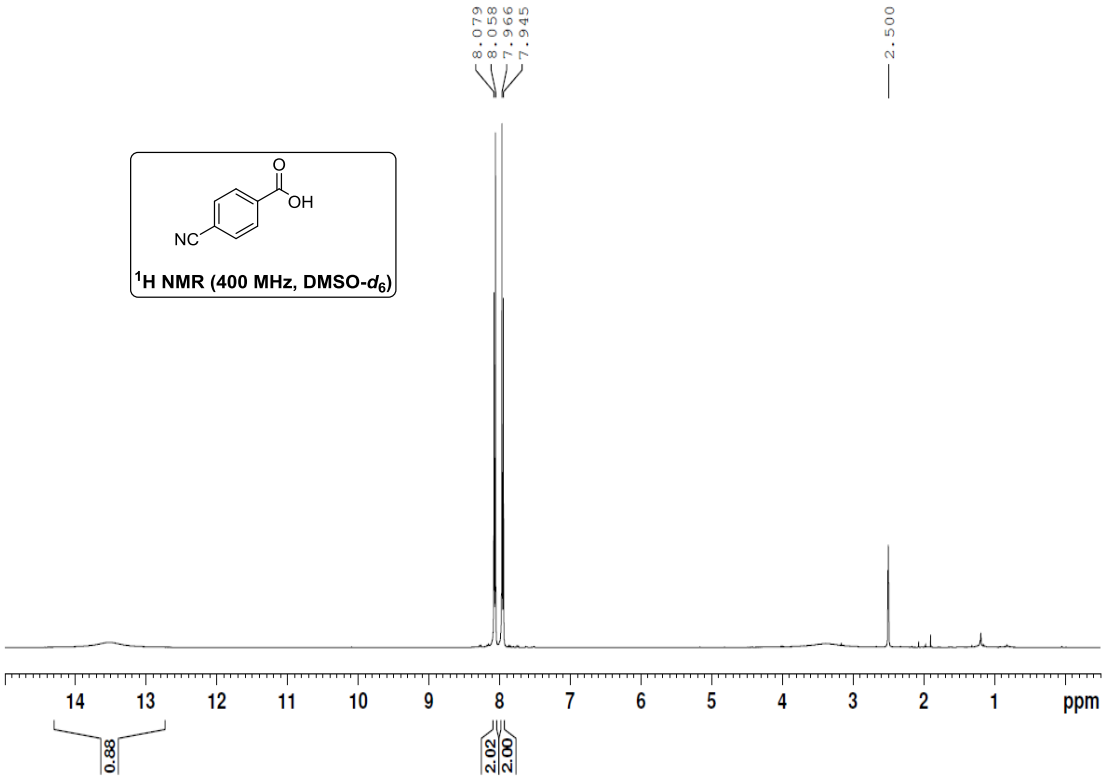
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.91
2.00
2.00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7.945
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OH
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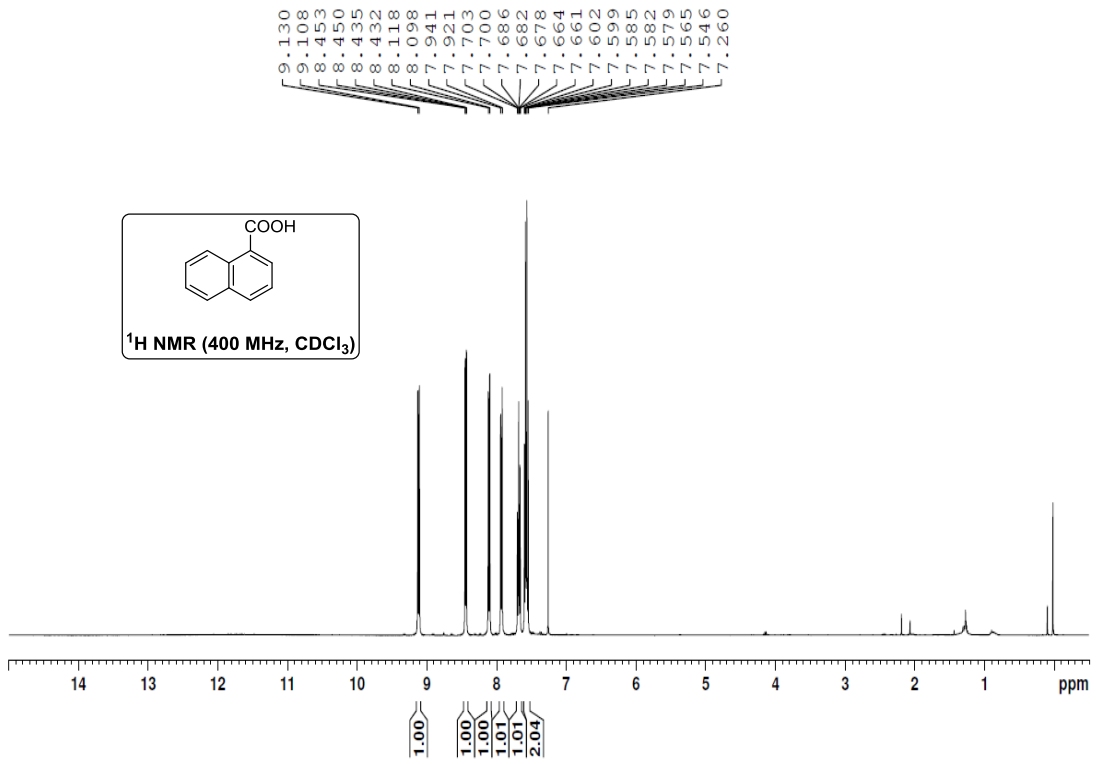
0.88
2.02
2.00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9.108
8.453
8.450
8.435
8.432
8.118
8.098
7.941
7.921
7.703
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7.686
7.682
7.678
7.664
7.661
7.602
7.599
7.585
7.582
7.579
7.565
7.546
7.260
COOH
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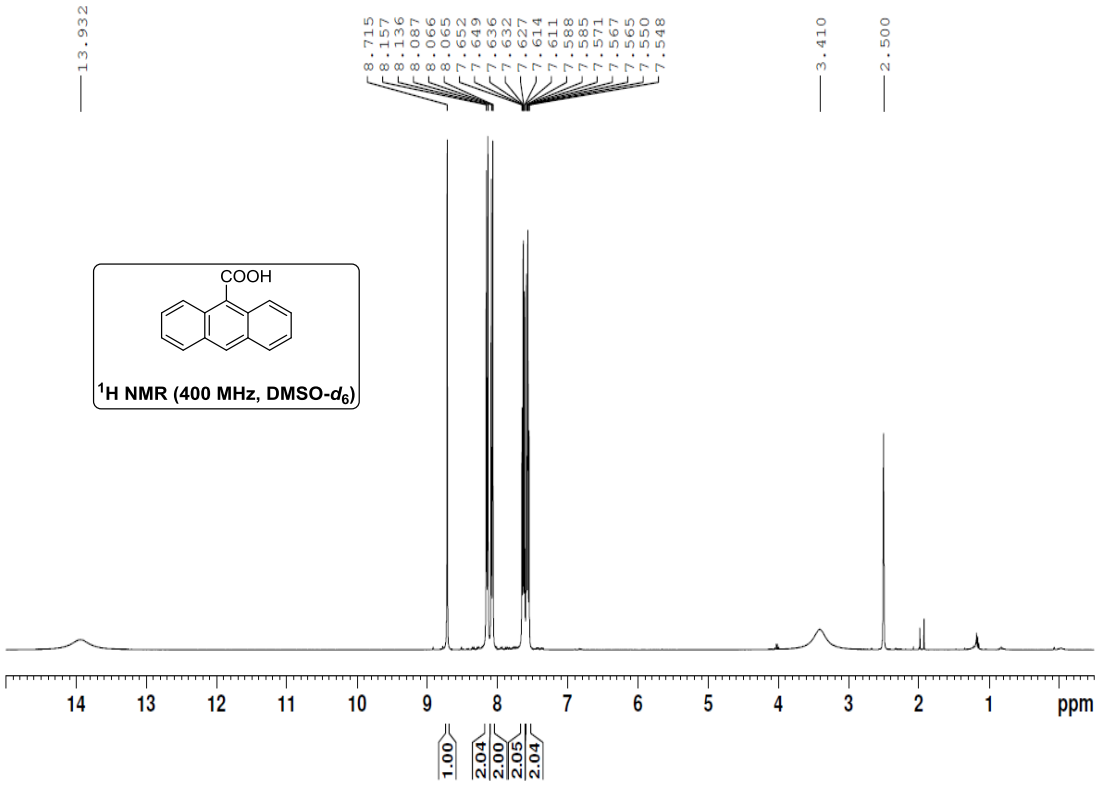
1.00 1.00 1.00 1.01 1.01 2.04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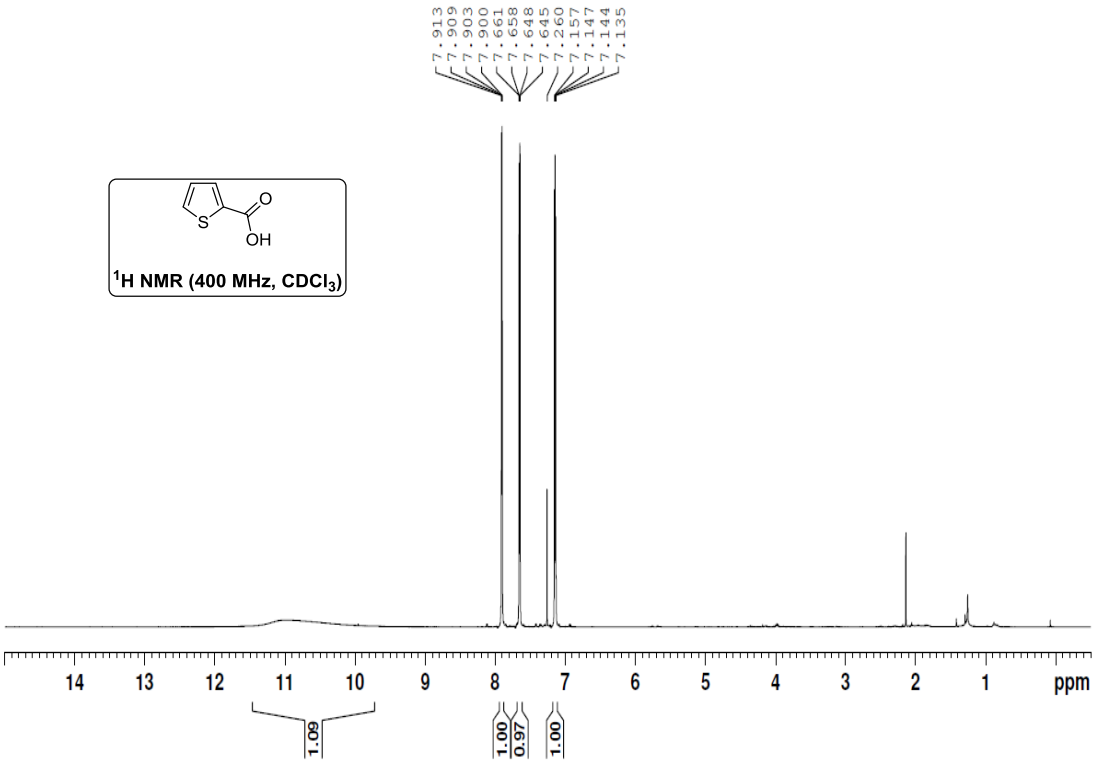
8.715
8.157
8.136
8.087
8.066
8.065
7.652
7.649
7.636
7.632
7.627
7.614
7.611
7.588
7.585
7.571
7.567
7.565
7.550
7.548
3.410
2.500
COOH
$^1$H NMR (400 MHz, DMSO-$d_6$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.00 2.04 2.00 2.05 2.04


7.913
7.909
7.903
7.900
7.661
7.658
7.648
7.645
7.260
7.157
7.147
7.144
7.135
O
S
OH
$^1$H NMR (400 MHz, CDCl$_3$)
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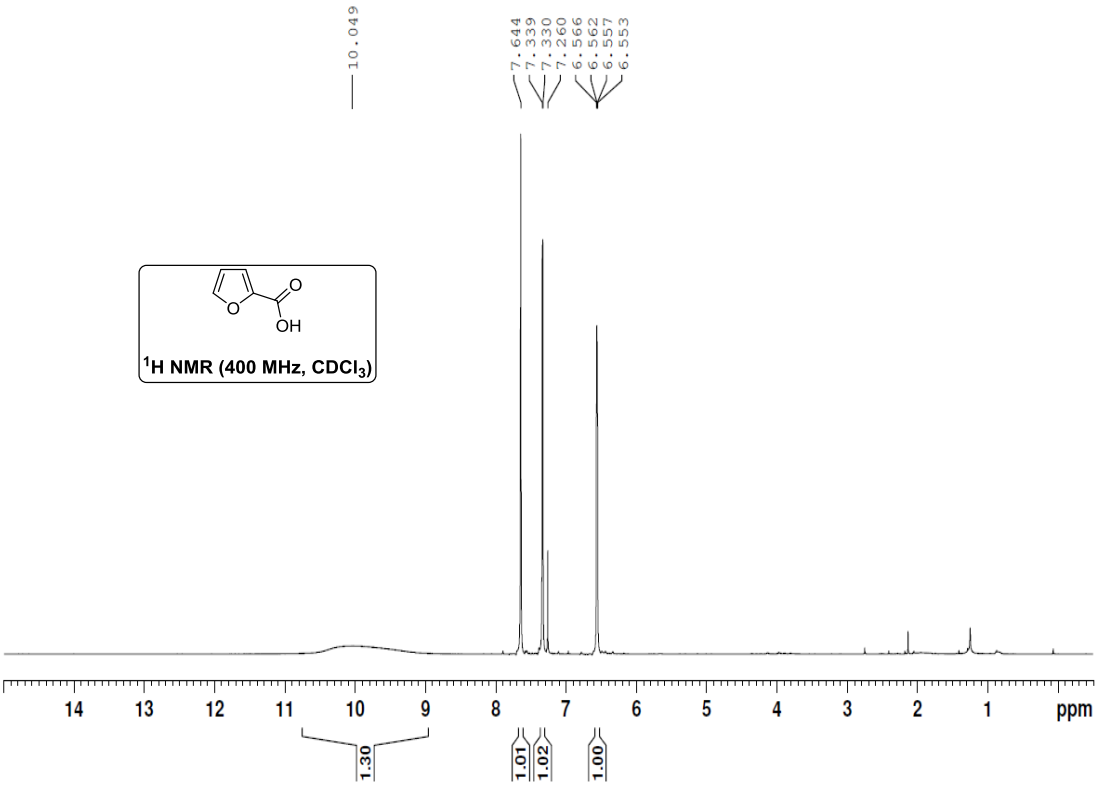
1.09
1.00
0.97
1.00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7.644
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7.330
7.260
6.566
6.562
6.557
6.553
O
O
OH
$^1$H NMR (400 MHz, CDCl$_3$)
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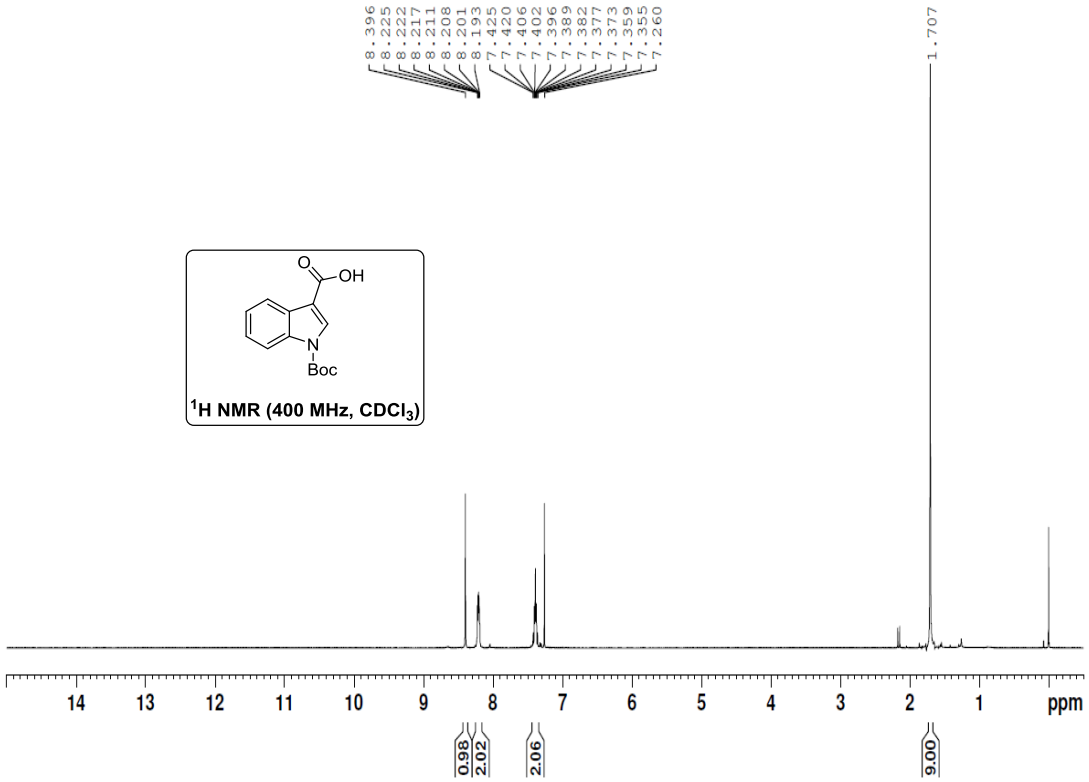
1.30
1.01
1.02
1.00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8.225
8.222
8.217
8.211
8.208
8.201
8.193
7.425
7.420
7.406
7.402
7.396
7.389
7.382
7.377
7.373
7.359
7.355
7.260
1.707
O
OH
N
Boc
$^1$H NMR (400 MHz, CDCl$_3$)
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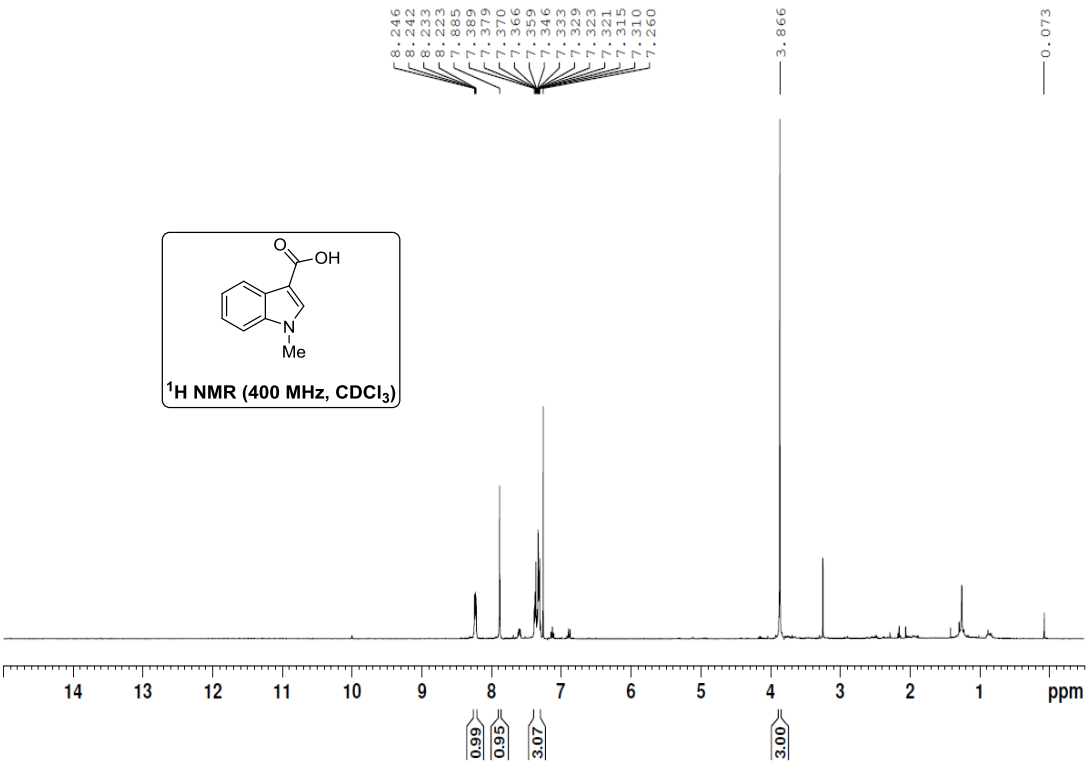
0.98
2.02
2.06
9.00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8.233
8.223
7.885
7.389
7.379
7.370
7.366
7.359
7.346
7.333
7.329
7.323
7.321
7.315
7.310
7.260
3.866
0.073
O
OH
N
Me
$^1$H NMR (400 MHz, CDCl$_3$)
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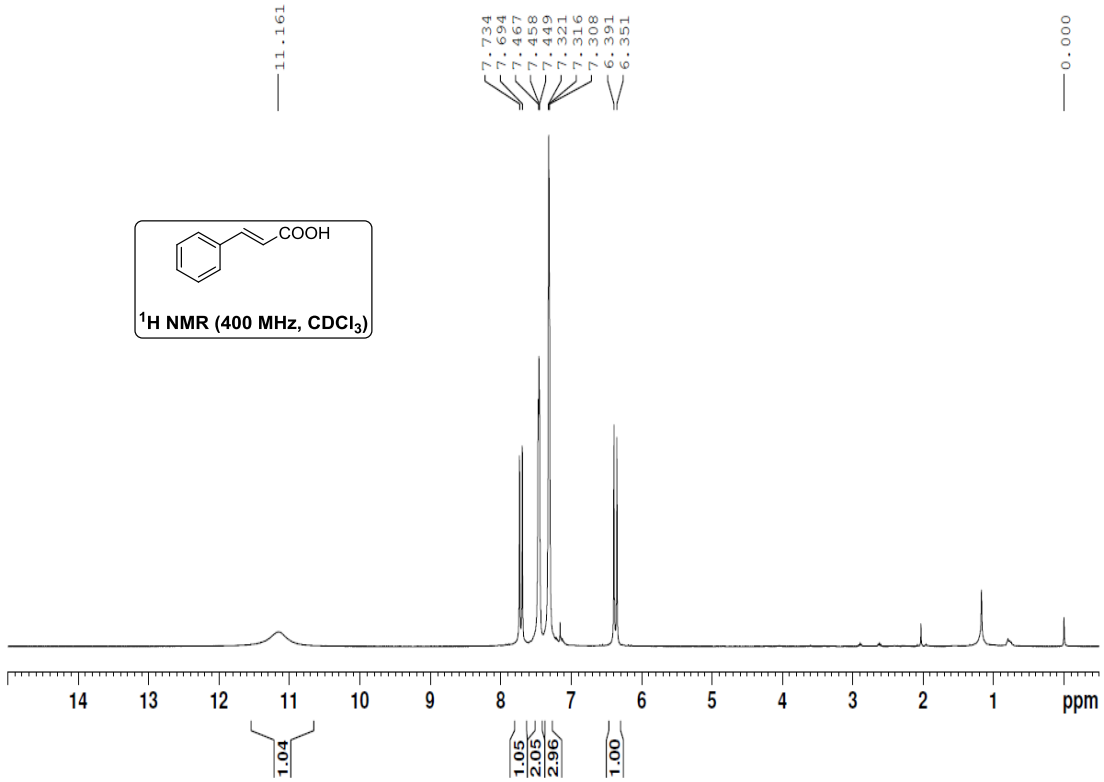
0.99
0.95
3.07
3.00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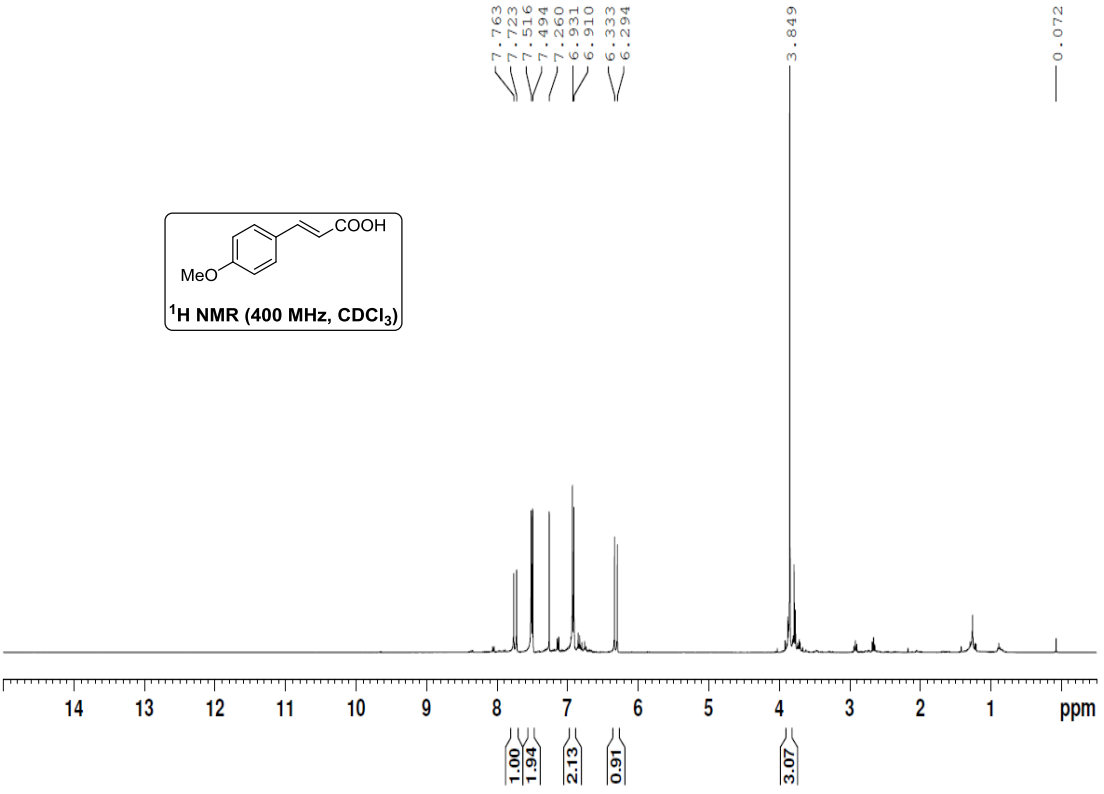
7.694
7.467
7.458
7.449
7.321
7.316
7.308
6.391
6.351
0.000
COOH
$^1$H NMR (400 MHz, CDCl$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.04
1.05
2.05
2.96
1.00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7.516
7.494
7.260
6.931
6.910
6.333
6.294
3.849
0.072
COOH
MeO
$^1$H NMR (400 MHz, CDCl$_3$)
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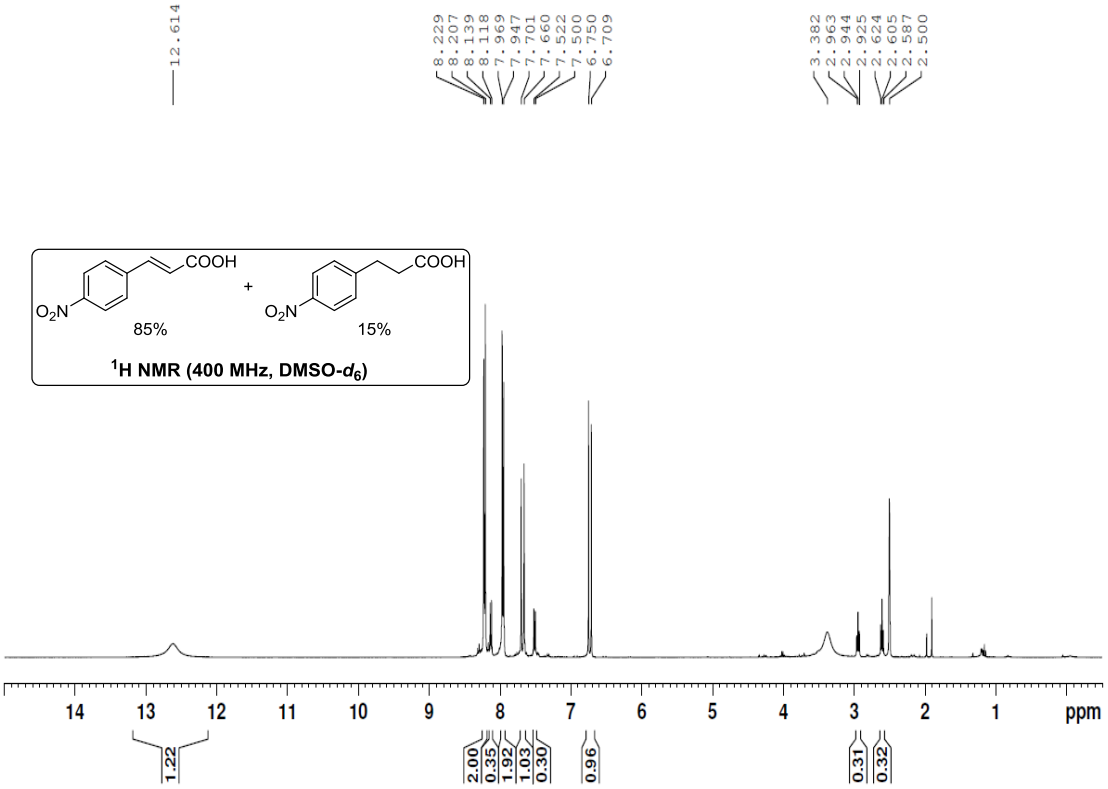
1.00
1.94
2.13
0.91
3.07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8.207
8.139
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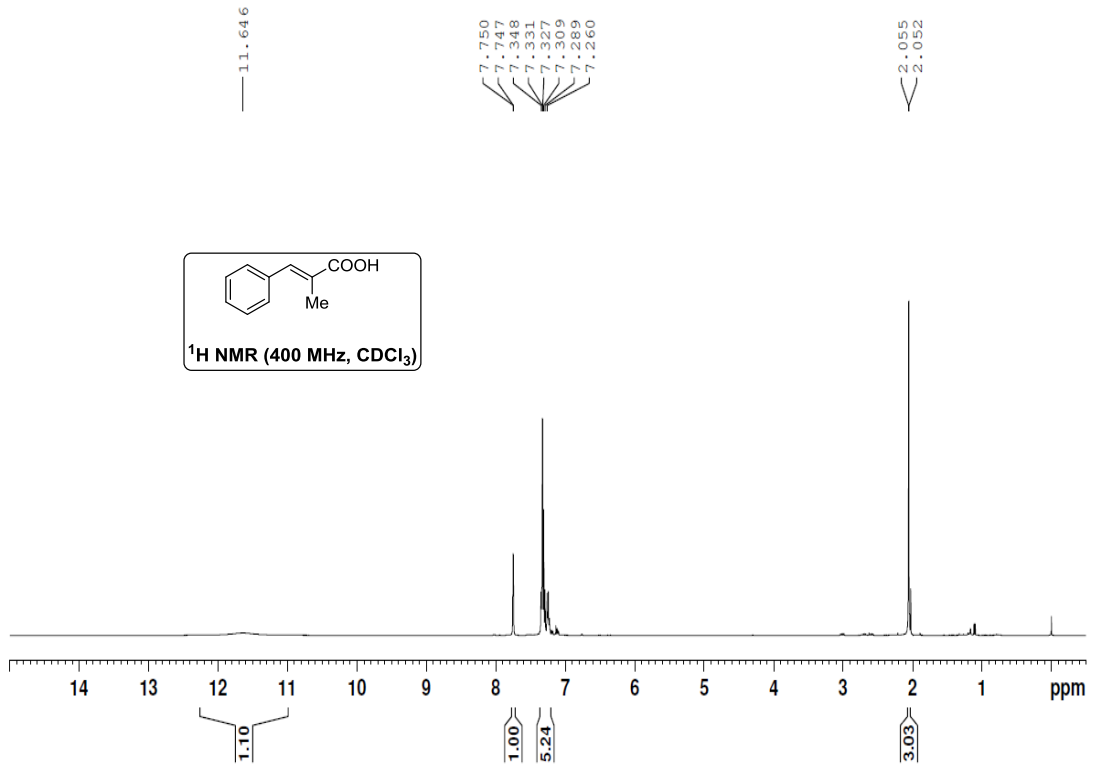
7.969
7.947
7.701
7.660
7.522
7.500
6.750
6.709
3.382
2.963
2.944
2.925
2.624
2.605
2.587
2.500
COOH
O2N
85%
COOH
O2N
15%
1H NMR (400 MHz, DMSO-d6)
ppm
1.22
2.00
0.35
1.92
1.03
0.30
0.96
0.31
0.32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7.750
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7.348
7.331
7.327
7.309
7.289
7.260
2.055
2.052
COOH
Me
1H NMR (400 MHz, CDCl3)
ppm
1.10
1.00
5.24
3.03

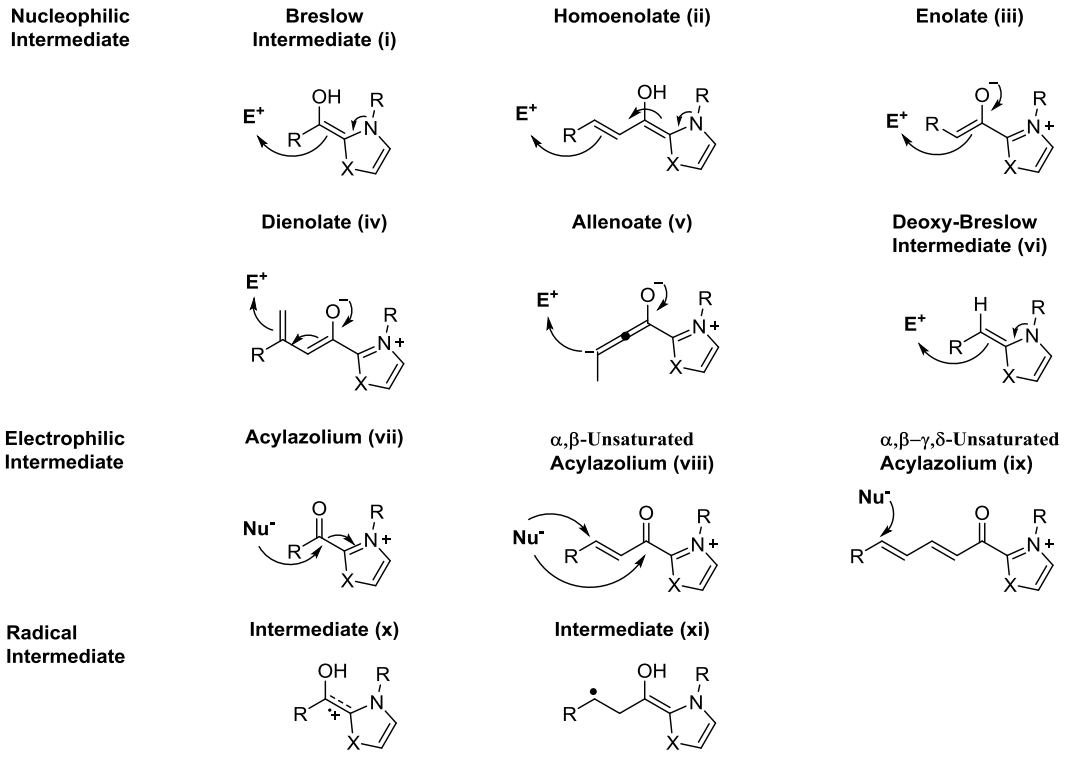
# Summary

The thesis entitled "**Development of new synthetic methods *via* *N*-heterocyclic carbene catalysis**" is divided into three chapters.

**Chapter I: An Introduction to *N*-Heterocyclic Carbene (NHC) Catalysis**

This chapter provides a brief overview about *N*-heterocyclic carbene (NHC)-catalysis and its various reactivity modes (Scheme 1.1). NHC-based organocatalysts have emerged as one of the important synthetic tools for the construction of various carbon-carbon and carbon-heteroatom bonds through umpolung, non-umpolung and radical strategy. NHCs in organocatalysis are typically involves the use of numerous NHC-bound nucleophilic intermediates such as acyl anion, homoenolate, enolate, dienolate, allenoate and deoxy Breslow intermediate (Scheme 1.1). The benzoin condensation and Stetter reaction are the two most prominent reactions, which utilize the acyl anion intermediate (i). Moreover, a variety of acyclic as well as annulated products, mostly in asymmetric form, have been accessed from simple starting materials with the employment of NHC-bound reactive nucleophilic intermediateds (ii-vi). Apart from the umpolung strategies, NHCs are also used as a catalyst for the generation of diverse electrophilic intermediate such as acyl azolium, α,β-unsaturated acyl azolium and α,β-γ,δ-unsaturated acyl azolium (vii-ix) form the corresponding unsaturated carbonyl compounds in the presence of external oxidant. In most of the cases, these important reactive intermediates acts as a bis-electrophile and thus allowing the nucleophilic addition of several bis-nucleophile in a 1,4-fashion followed

by 1,2-pathway for the unconventional construction of various carbocycles and heterocycles which are not suitable in presence of other covalent organocatalysis. In spite of two electron pathway, NHCs are also used in single electron transfer pathway for various important transformation through acyl radical and homoenolate radical intermediate (x and xi). Importantly, these reactive radical intermediates enabled the introduction of sterically bulky substituents, which are not compatible in the well-known two-electron reaction pathway under NHC catalysis.

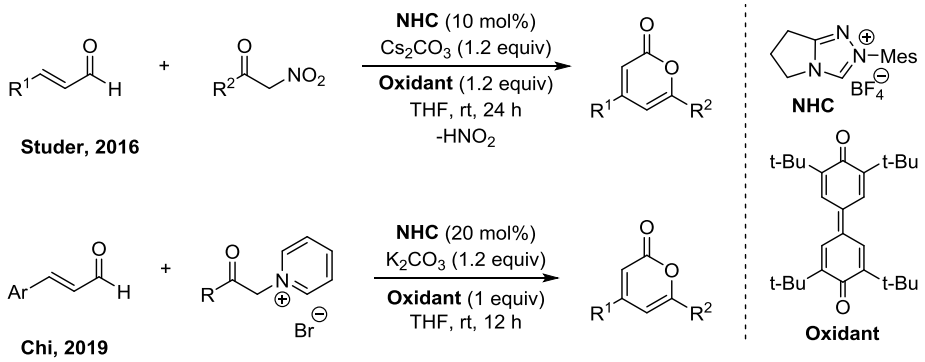



**Scheme 1.1** Various important reactivity modes of NHC

## Chapter II: A Facile Access to 3,6-Disubstituted α-Pyrones *via* Carbene Catalyzed Formal [4+2] Annulation of α-Chloroaldehydes and γ-Keto Sulfones

This chapter is divided into two parts *i.e.* Part-A and Part-B.

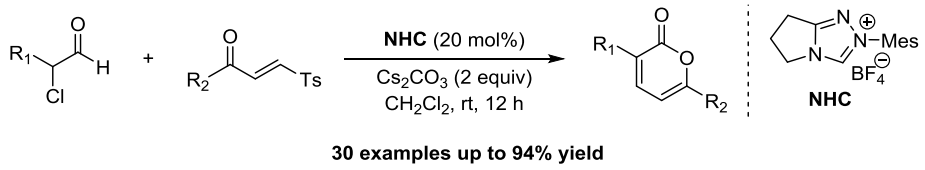
Part A of chapter II entitled *"Introduction to α-pyrones and preparation of starting reagents"* provides a brief sketch about the importance of α-pyrones. The construction of α-pyrone motifs is of great interest due to their utility in the preparation of various key intermediates in synthetic organic chemistry as well as medicinal chemistry. This chapter describes the literature reported methods for the prepation of α-pyrones under metal-based or metal-free catalytic system. Notably, the previous NHC-catalyzed protocols provided 4,6-disubstituted α-pyrones under oxidative conditions (Scheme 1.2). To the best of our knowledge, an NHC-catalytic oxidant-free synthetic method for the synthesis of 3,6-disubstituted α-pyrones has never been reported thus far. Therefore, we envisioned the challenging 3,6-disubstituted α-pyrones under oxidant-free NHC-catalysis using simple starting materials such as α-chloroaldehydes and γ-keto sulfones.




**Scheme 1.2** Synthesis of 4,6-disubstituted α-pyrones using oxidative NHC-catalysis

Part B of chapter II entitled "*Introduction to NHC-bound enolate intermediate and its application to access 3,6-disubstituted α-pyrones*" provides an overview about reactions involving NHC-bound enolate intermediate and its implementation for the synthesis of desired 3,6-disubstituted α-pyrones. The importance and generation of

NHC-bound enolate intermediate from various sources is described in this part. The employment of NHC-bound enolate intermediate for the synthesis of 3,6-disubstituted α-pyrones under oxidant free condition by the reaction of α-chloroaldehydes and γ-keto sulfones has been demonstrated in part B of this chapter (Scheme 1.3). Notably, a broad range of α-chloroaldehydes and γ-ketosulfones were tolerated under the optimized reaction conditions. The use of γ-keto sulfones as a Michael acceptor was key for this unique transformation, enabled the formation of desired α-pyrones in good to excellent yields under transition-metal-free reaction conditions. The present protocol proceeds through Michael addition followed by lactonization and elimination cascade sequence to furnish a variety of 3,6-disubstituted α-pyrones. In addition, this methodology is also demonstrated for the gram-scale synthesis of 3,6-disubstituted α-pyrone. Furthermore, the synthetic utility of the product to afford a variety of value-added molecules in good yields is also explored in this part.

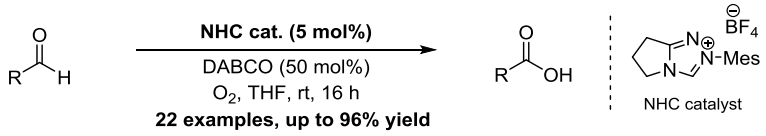



**Scheme 1.3** NHC-catalyzed oxidant-free synthesis of 3,6-disubstituted α-pyrones

## Chapter III: A Highly Efficient NHC-Catalyzed Aerobic Oxidation of Aldehydes to Carboxylic Acids

Carboxylic acids are one of the most privileged structural motifs that is present in various organic compounds used in industry for the production of pharmaceuticals, food additives, agrochemicals, polymer and solvents. This chapter outlined the literature known synthetic methods for the synthesis of carboxylic acids and its

derivatives through metal-based oxidants utilizing stoichiometric amounts, several metal-based or metal-free catalytic methods as well as generation and importance of NHC-bound reactive intermediates under oxidative catalysis. Notably, all the previous reports based on NHC-catalyzed oxidation of aldehydes to acids are suffered from one or more limitations such as limited substrate scope like primarily suitable for activated electron-deficient aryl or hetero-aryl aldehydes, require reaction time of several days and higher temperature. Therefore, an efficient NHC-catalyzed oxidation of aldehydes to carboxylic acids in the presence of oxygen as sole oxidant with a shorter reaction time at room temperature has been developed and described in this chapter (Scheme 1.4).




**Scheme 1.4** NHC-catalyzed aerobic oxidation of aldehydes to carboxylic acids

Pleasingly, the compability of *ortho*-substituted or electron rich aryl aldehydes and indole-3-carboxaldehydes under environmental benign aerobic conditions intensify the novelty of the present protocol. Moreover, this methodology is also extended for gram-scale synthesis under the optimized reaction conditions.

## Conclusion

In this section, the brief description with important characteristic and application of newly developed reactions are described. In addition, the advancement of these protocols and product classes in synthetic organic chemistry are also explained.

# List of Publications

1. **Anil K. Khatana**, Vikram Singh, Manoj K. Gupta, Bhoopendra Tiwari. A highly efficient NHC-catalyzed aerobic oxidation of aldehydes to carboxylic acids. *Synthesis* **2018**, *50*, 4290-4294.

2. Vikram Singh, Ram Subhawan Verma, **Anil K. Khatana**, Bhoopendra Tiwari. Construction of phenanthrenes and chrysenes from β-bromovinylarenes *via* aryne Diels-Alder reaction/aromatization. *J. Org. Chem.* **2019**, *84*, 14161-14167.

3. Atanu Bhaumik, Tazeen Azaz, Vikram Singh, **Anil K. Khatana**, Bhoopendra Tiwari. Carbene/Base-Mediated Redox Alkenylation of Isatins using β-Substituted Organoselenones and Aldehydes. *J. Org. Chem.* **2019**, *84*, 14898-14903.

4. Saumya Verma, Puneet Kumar, **Anil K. Khatana**, Dinesh Chandra, Ajay K. Yadav, Bhoopendra Tiwari, Jawahar L. Jat. Zinc(II)-catalyzed synthesis of secondary amides from ketones *via* Backmann rearrangement using hydroxylamine-*O*-sulfonic acid in aqueous media. *S*ynthesis ***2020***, *52*, 3272-3276.

5. Ram Subhawan Verma, **Anil K. Khatana**, Monika Mishra, Shailesh Kumar, Bhoopendra Tiwari. Access to enantioenriched 4-phosphorylated δ-lactones from β-phosphorylenones and enals *via* carbene organocatalysis. *Chem. Commun.* **2020**, *56*, 7155-7158.

6. Eqvinshi Yadav, **Anil K. Khatana**, Sharol Sebastian, Manoj K. Gupta. DAP derived fatty acid amide organogelators as novel carrier for drug incorporation and pH-responsive release. *New J. Chem*. **2021**, *45*, 415-422.

7. **Anil K. Khatana**, Vikram Singh, Manoj K. Gupta, Bhoopendra Tiwari. A Facile Access to 3,6-Disubstituted α-Pyrones via Carbene Catalyzed Formal [4+2] Annulation of α-Chloroaldehydes and γ-Keto Sulfones. (*Manuscript under preparation).*