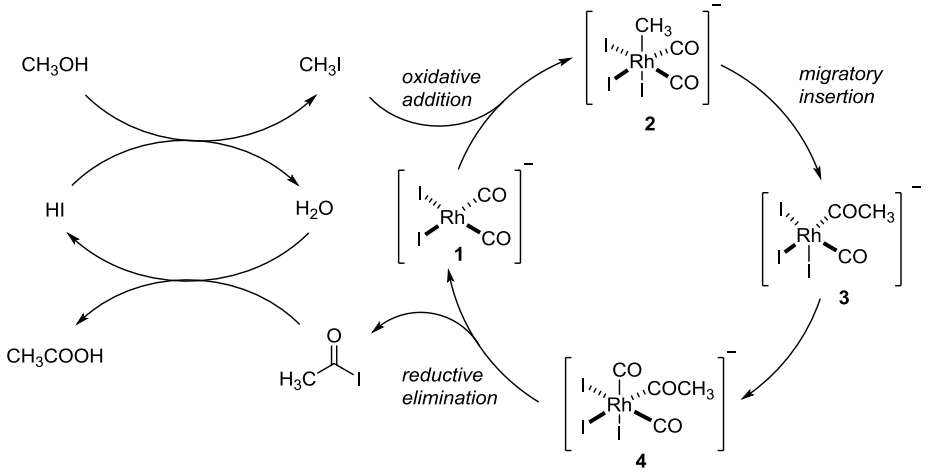
Chapter 3

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]

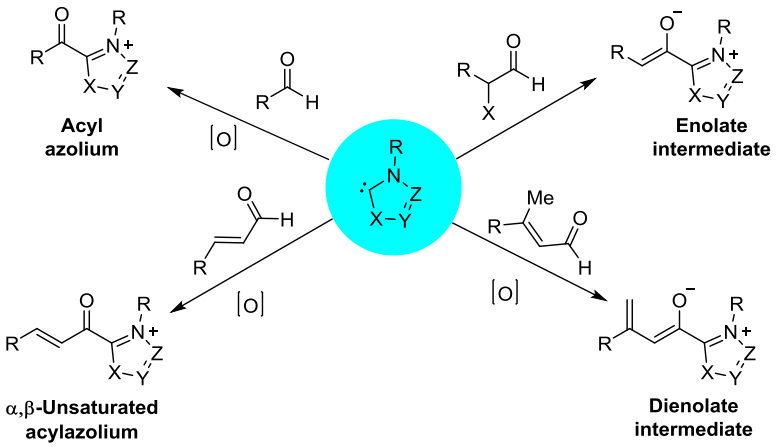


Scheme 3.1 Monsanto process for synthesis of acetic acid

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]

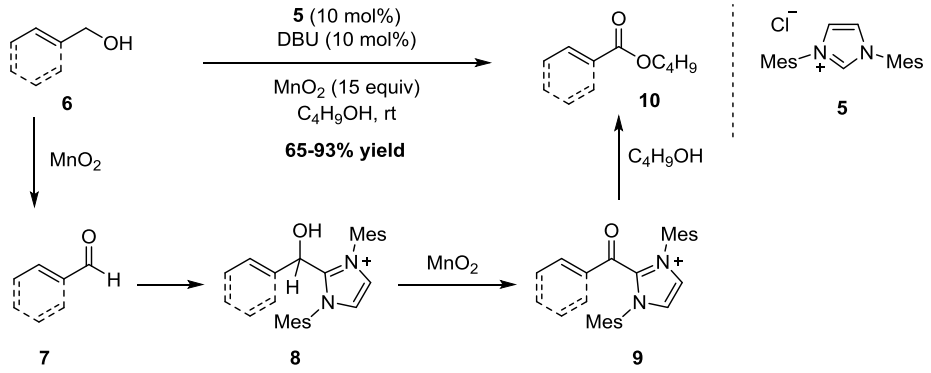


Scheme 3.2 Important action modes of NHC under non-umpolung mode

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

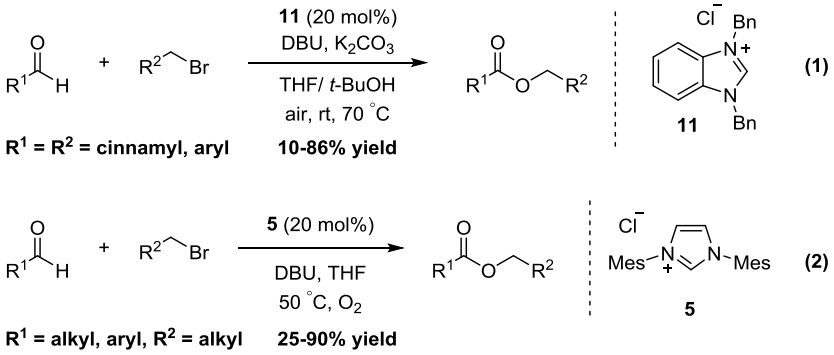
In 2007, Scheidt and colleagues reported first NHC-catalyzed tandem oxidation of numerous allylic, propargylic, or benzylic alcohols applying MnO_2 as a moderate oxidant in the presence of imidazolium salt **5** to give corresponding esters in good to excellent yields (Scheme 3.3).[6] This reaction comprises 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.



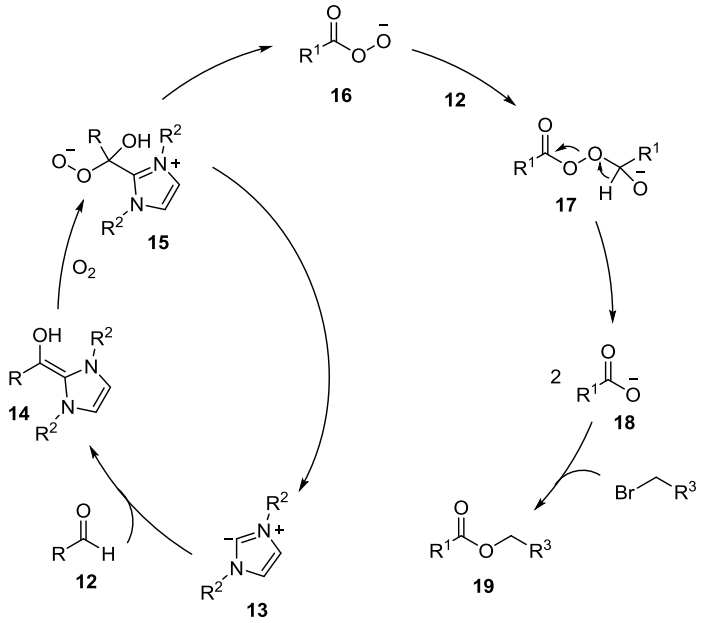
Scheme 3.3 NHC-catalyzed oxidative esterification reaction

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**.

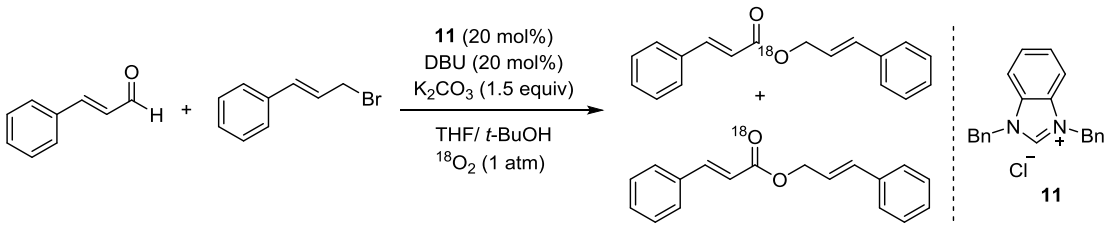


Scheme 3.4 NHC-catalyzed aerobic oxidation of aldehydes and subsequent alkylation to esters



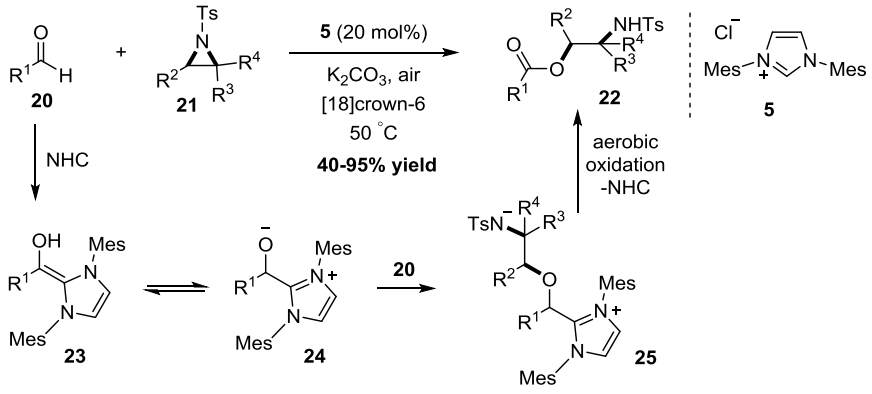
Scheme 3.5 NHC-catalyzed aerobic oxidation of aldehyde to ester

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.



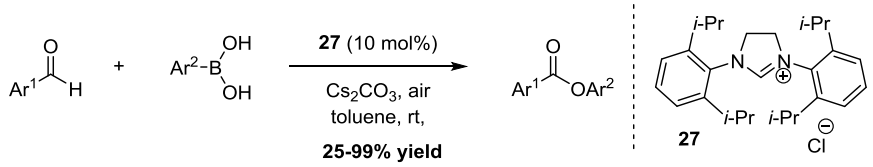
Scheme 3.6 NHC-catalyzed isotope-labeling experiment for esterification of cinnamaldehyde

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

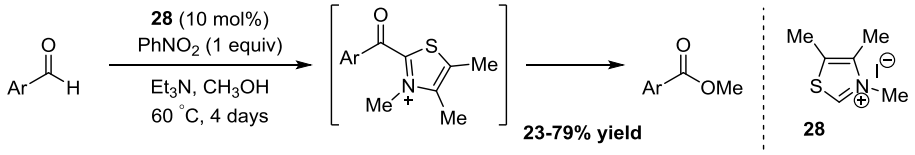
In 2012, Anand and co-workers reported a transition-metal-free protocol for oxidative coupling of aromatic aldehydes with aryl boronic acids using NHC precatalyst **27** to give corresponding esters in favorable yields (Scheme 3.8).[9]



Scheme 3.8 NHC-mediated oxidative esterification with aryl boronic acids

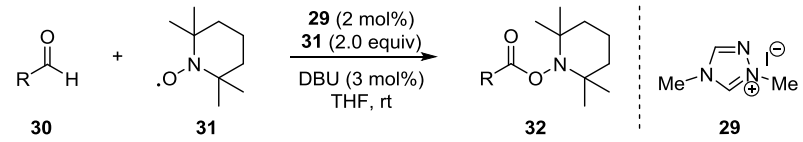
3.2.3 NHC-Catalyzed Reaction using Organic Oxidant

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.



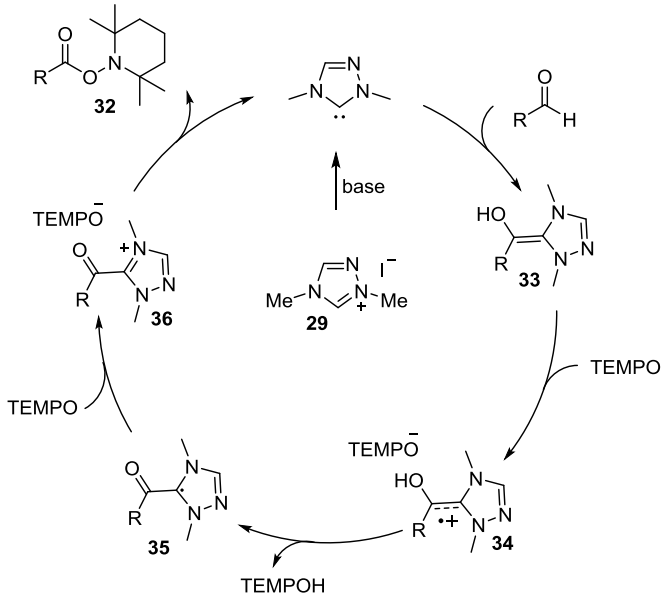
Scheme 3.9 NHC-catalyzed oxidative conversion of aldehydes to ester

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$^-$.

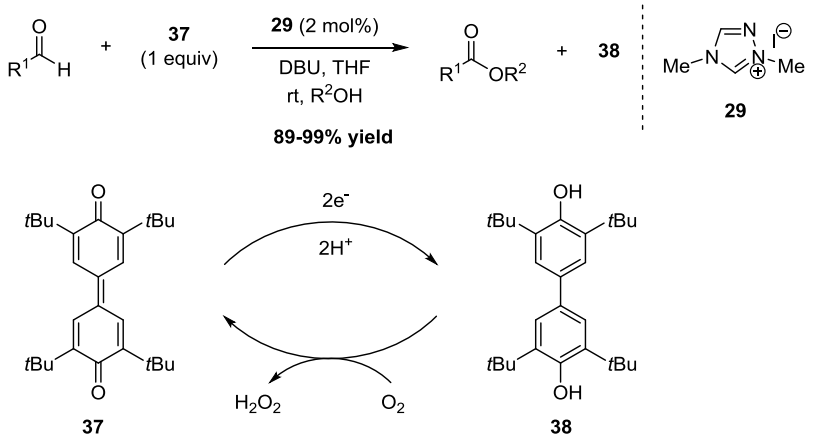


Scheme 3.11 Plausible mechanism for NHC-catalyzed esterification of aldehydes

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.

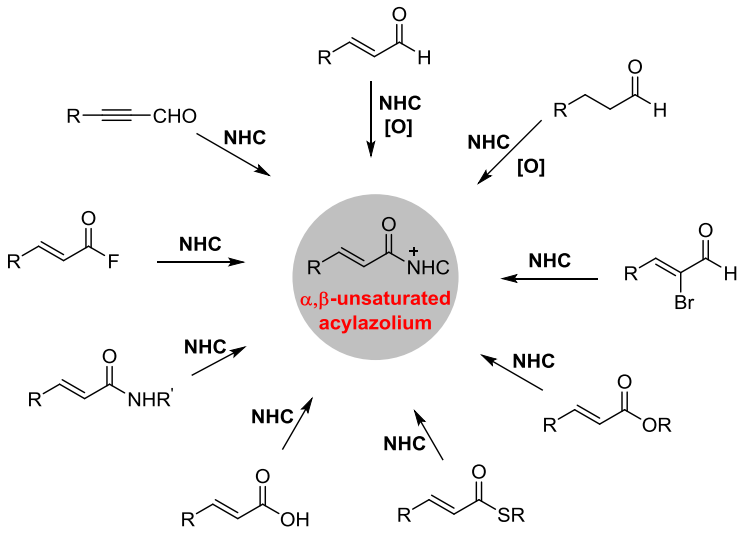
In the related context, they demonstrated the oxidation of various aromatic aldehydes using readily available 3,3',5,5'-tetra-tert-butyldiphenoquinone **37** with NHC-catalyst **29** to give corresponding esters in high yields (Scheme 3.12).[12] The above used organic oxidant acted as a two-electron 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).



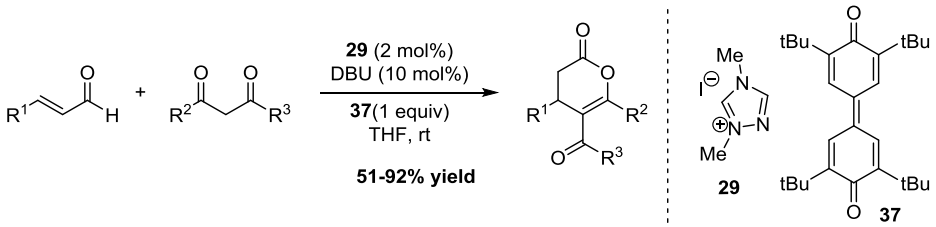
Scheme 3.13 Methods for the generation of α,β-unsaturated acylazolium

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

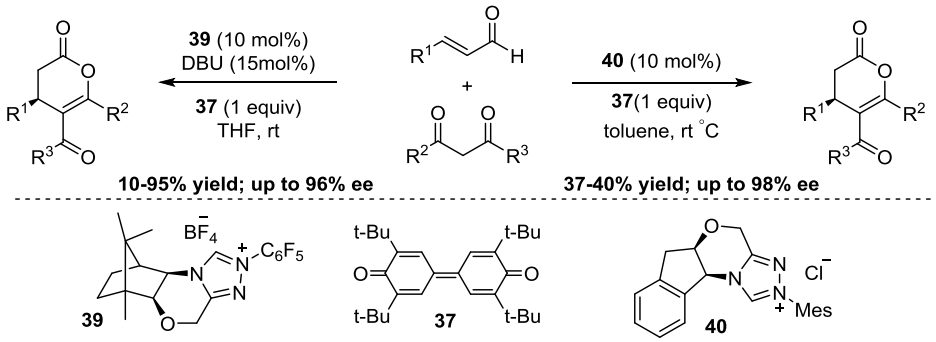
In 2010, Studer and co-workers exposed the conjugate addition of soft carbon nucleophiles such as 1,3-dicarbonyl compounds to catalytically generated α,β-unsaturated acyl azolium intermediate from enals using NHC-precatalyst **29** in the presence of the bisquinone oxidant **37** leads to the formation 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).

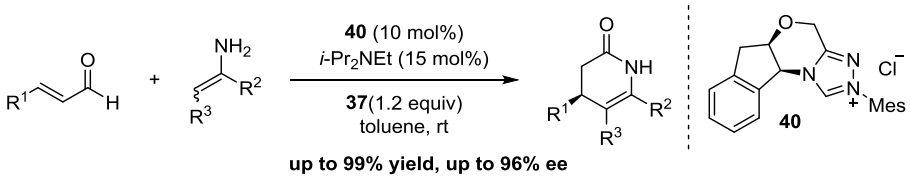


Scheme 3.15 NHC-catalyzed enantioselective synthesis of dihydropyranones

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.

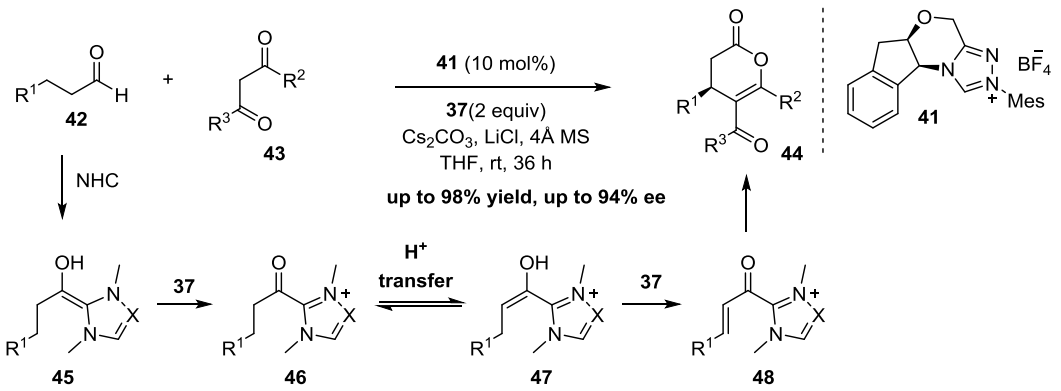
In 2011, Bode et al. exposed NHC-mediated aza-Claisen rearrangement reaction between enals and simple unprotected enamines using chiral triazolium salt **40** in the presence of oxidant **37** to furnish 3,4-dihydropyridinones in positive yields with great enantioselectivity (Scheme 3.16).[19a] Various 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]

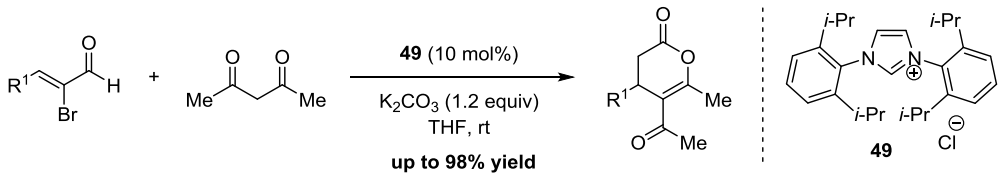


Scheme 3.17 NHC-catalyzed functionalization of β-C-H bond of saturated aldehydes

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.

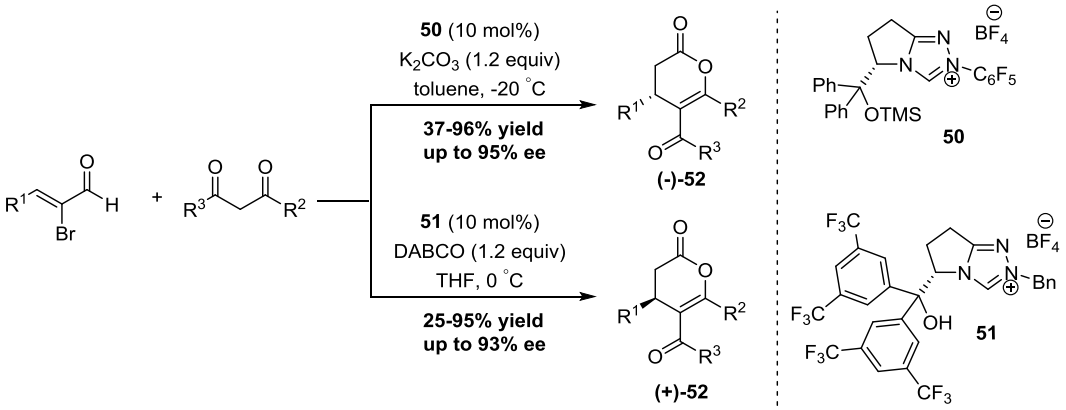
3.2.4.3 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from 2-Bromoenals

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]



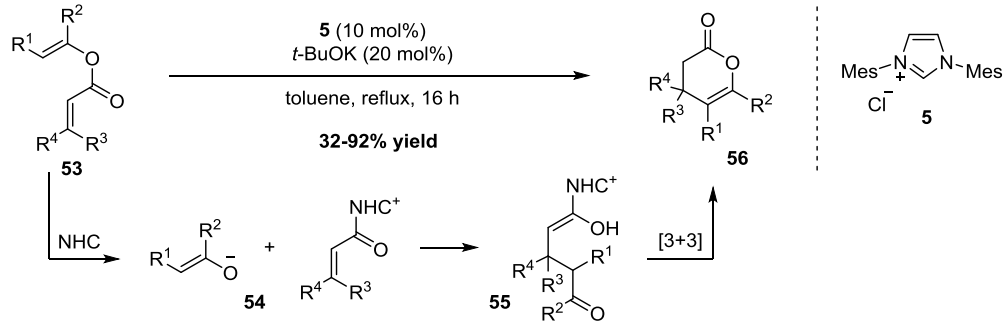
Scheme 3.19 NHC-catalyzed enantioselective synthesis of dihydropyranone

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

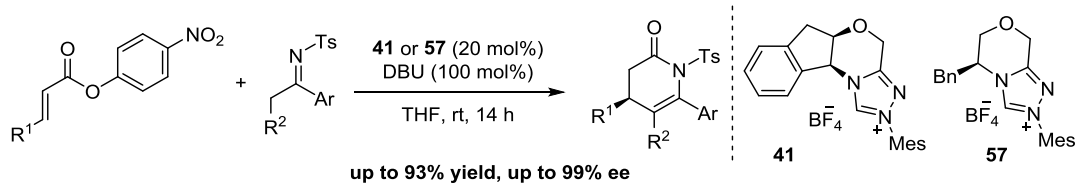
In 2009, Lupton research group exposed NHC-catalyzed fragmentation of α,β-unsaturated enol esters **53** to produce α,β-unsaturated acyl azolium/enolate intermediate **54**, which upon further recombination provide 2,3-dihydropyranones **56** (Scheme 3.20).[26] Notably, a broad range of enol esters including 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

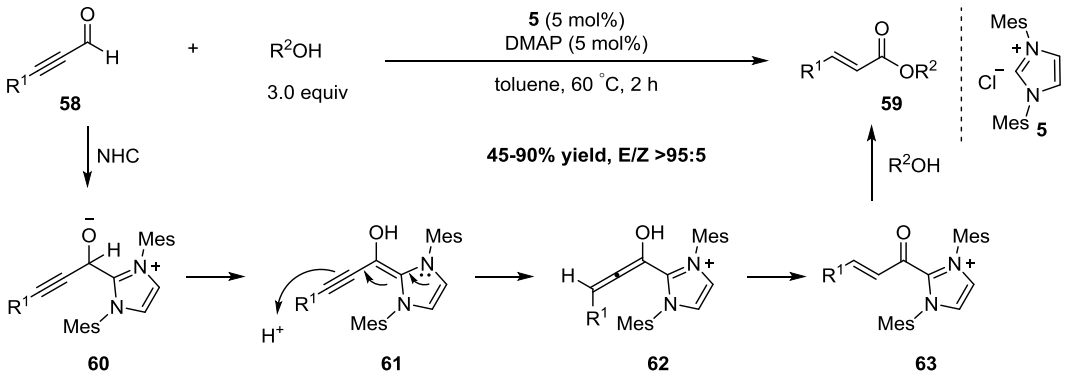
excess. Importantly, the presence of 4-nitro phenyl moiety on the ester component was crucial for this transformation. In addition, the sterically demanding β,β-disubstituted esters were also compatible in this transformation when less sterically blocked triazolium salt **57** was employed.



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

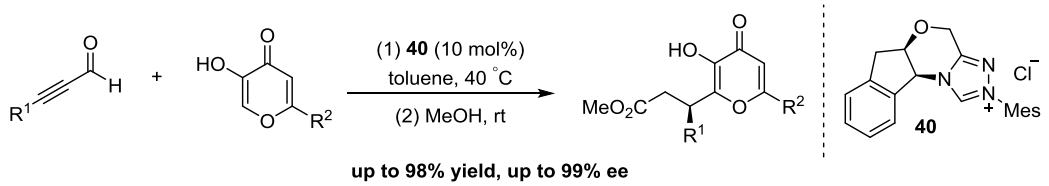
3.2.4.5 NHC-Catalyzed Reaction *via* Generation of α,β-Unsaturated Acyl Azoliums from Ynals

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]



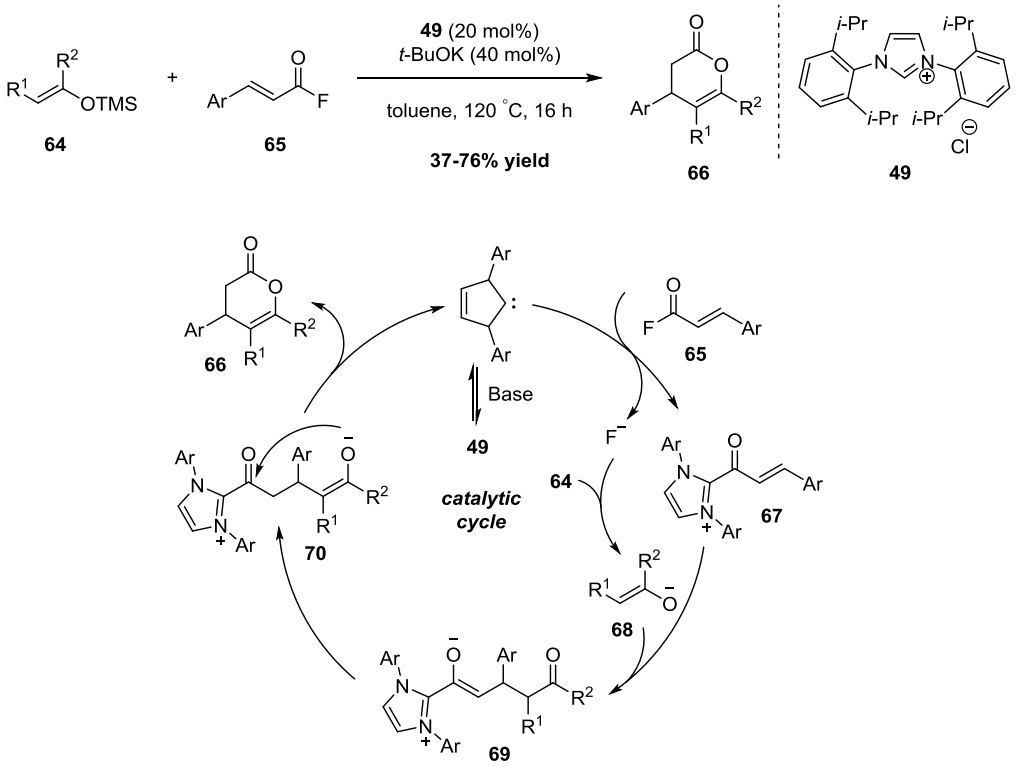
Scheme 3.23 NHC-catalyzed annulation of ynals with kojic acid *via* Claisen rearrangement

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]



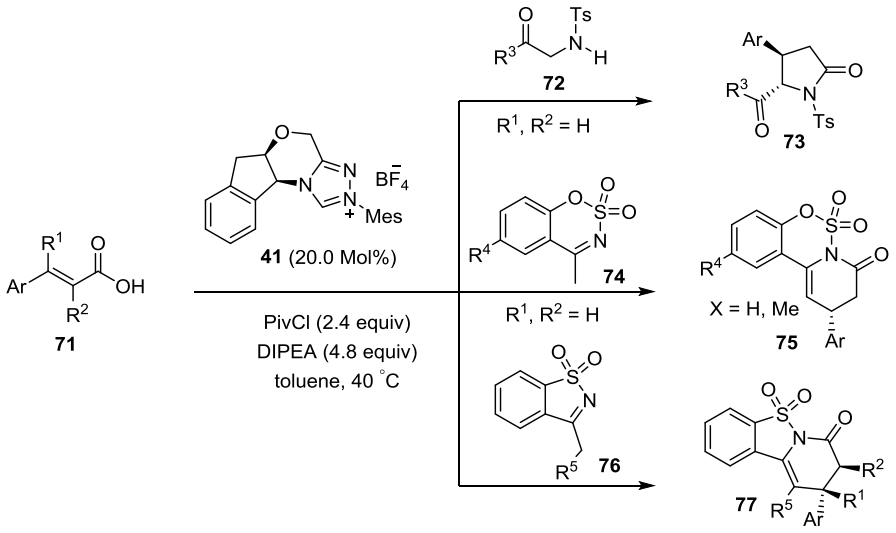
Scheme 3.24 NHC-catalyzed synthesis of dihydropyranones from unsaturated acyl fluorides

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

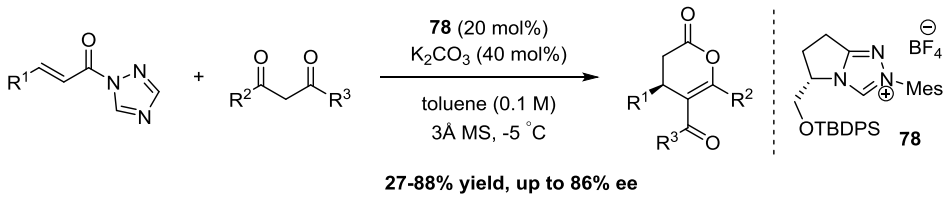
In 2014, Wang, Ye and colleagues disclosed the activation of α,β-unsaturated carboxylic acids **71** to generate α,β-unsaturated acylazolium intermediate employing chiral triazolium precatalyst **41** through the formation of mixed anhydride in the presence of pivaloyl chloride. The interception of this *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.

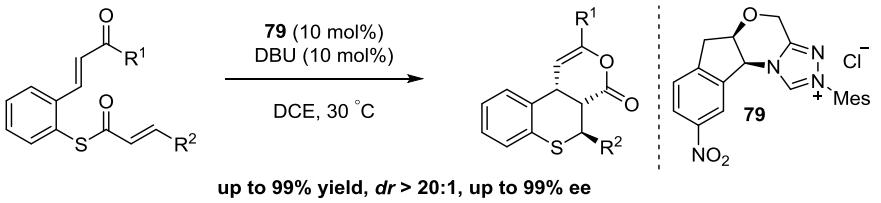


Scheme 3.26 NHC-mediated asymmetric annulation of α,β-unsaturated amides

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**

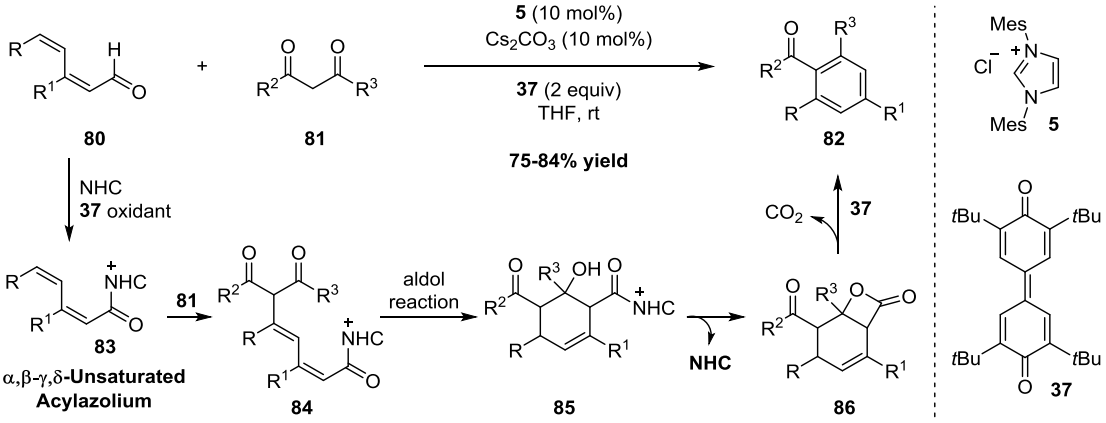
(Scheme 3.27).[33] The reaction proceeds *via* sulpha-Michael/Michael/lactonization sequence to furnished highly substituted thiochroman product in high yield and enantioselectivity.



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]



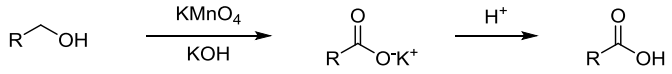
Scheme 3.28 Generation of α,β-γ,δ unsaturated acylazolium intermediate

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

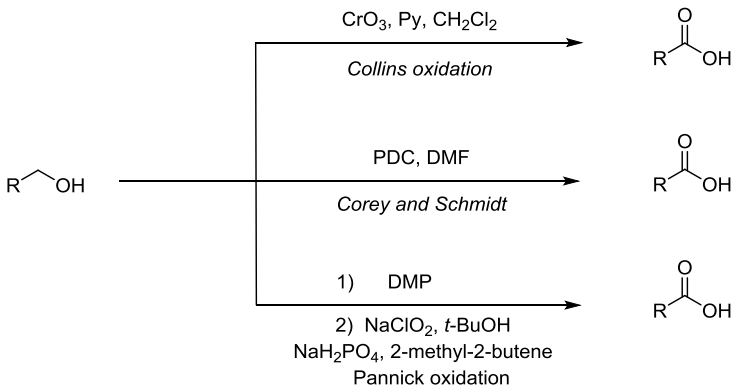
The synthesis of carboxylic acids includes procedures where primary alcohols or aldehydes are oxidized using stoichiometric amount of numerous metal-based oxidants. In 1907, Fournier was the first to propose the oxidation using potassium permanganate ($KMnO_4$) in the presence of strong alkaline aqueous 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

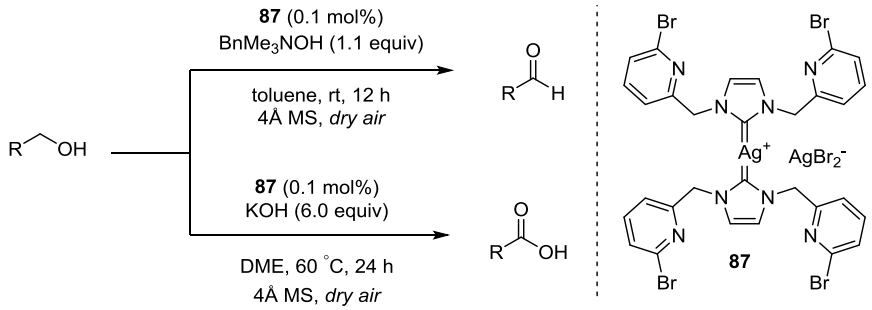
as the oxidant for the transformation, is another traditional method used to prepare carboxylic acids from primary alcohols. However, this protocol was further improved using a complex of chromium (VI) oxide with pyridine called as Collins reagent or pyridinium dichromate (PDC) for the synthesis of carboxylic 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

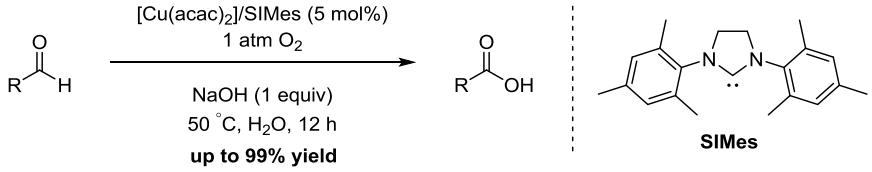
The established oxidation protocols require stoichiometric amounts of these hazardous oxidants and also produce harmful by-products. Therefore, environmentally benign oxidization protocols using molecular oxygen as oxidant provides considerable convenience compared with previously used reagents, such 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]



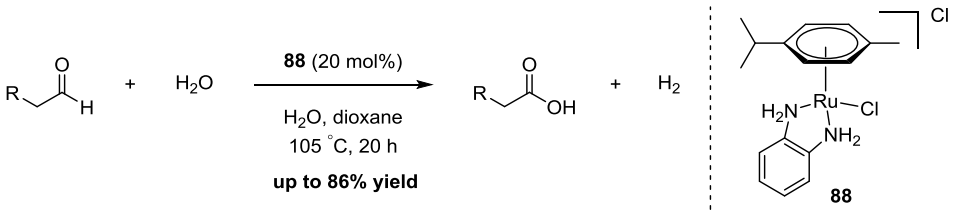
Scheme 3.31 Silver-NHC catalyzed oxidation of alcohol to aldehydes or acids

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]



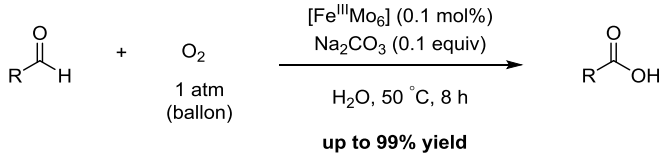
Scheme 3.32 Copper-NHC mediated aerobic oxidation of aldehydes

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.



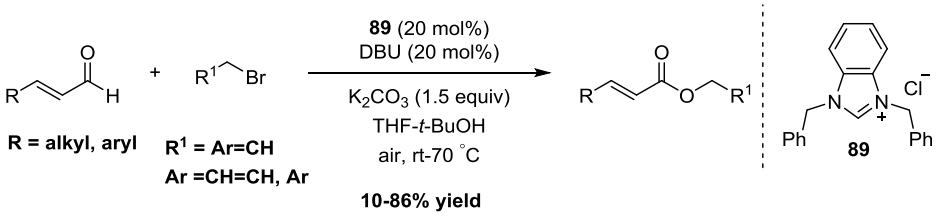
Scheme 3.33 Ruthenium (II) diamine mediated oxidation of aldehydes using water as oxidant

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.



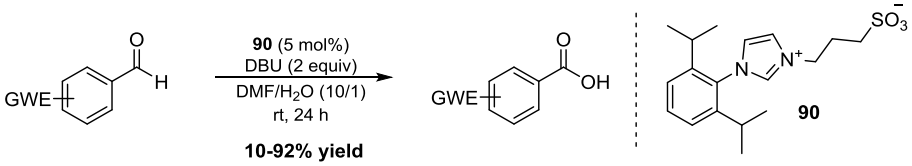
Scheme 3.34 Iron (III) mediated aerobic oxidation to access acids

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.



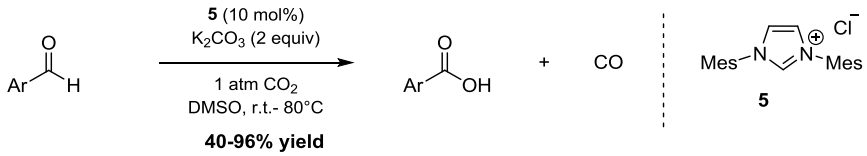
Scheme 3.35 NHC-catalyzed aerobic esterification of α,β-unsaturated aldehydes

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.



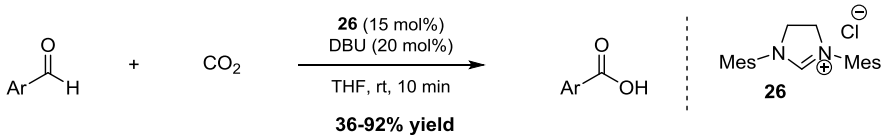
Scheme 3.36 NHC-catalyzed oxidative carboxylation of aryl aldehydes

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.



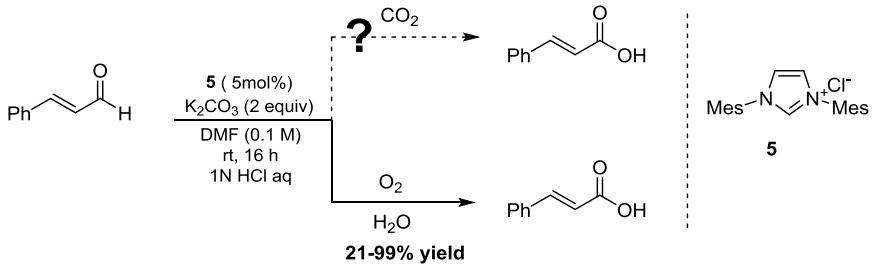
Scheme 3.37 NHC-catalyzed CO_2 splitting reaction with aldehydes

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.



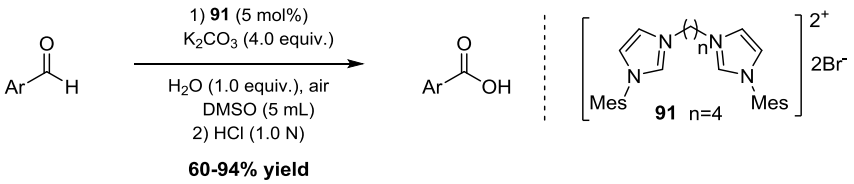
Scheme 3.38 NHC-catalyzed transformation of aryl aldehydes to acids using CO_2

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]



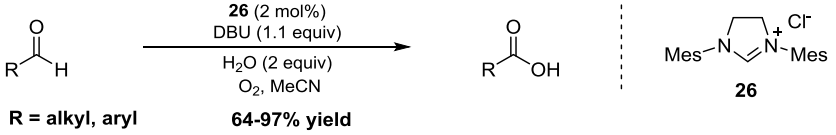
Scheme 3.39 NHC-catalyzed oxidation of aldehydes to acids using oxygen as oxidant

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.

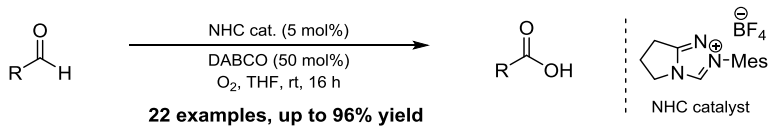


Scheme 3.41 NHC-catalyzed aerobic oxidation of nonactivated aldehydes

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.



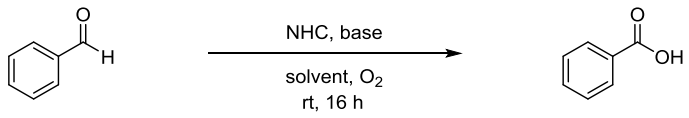
Scheme 3.42 Proposed methodology

3.5 Results and Discussion

3.5.1 Optimization Studies

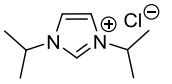
Inspired by the work surrounding this transformation, we initially started a preliminary study employing benzaldehyde **92a** as exemplary substrate beneath an oxygen environment and crucial findings are compiled in Table 3.1. Notably, we conducted a controlled experiment by the treatment of **92a** 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]

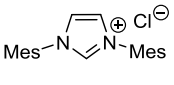


92a **93a**

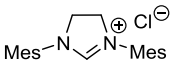
Entry	Catalyst	Base	Solvent	Yield (%)[b] **93a**
1	**-**	DABCO	THF	-
2	**94**	DABCO	THF	<5
3	**05**	DABCO	THF	16
4	**26**	DABCO	THF	25
5	**28**	DABCO	THF	<5
6	**95**	DABCO	THF	32
7	**96**	**DABCO**	**THF**	**92**
8	**97**	DABCO	THF	94
9	**96**	DBU	THF	36
10	**96**	Cs_2CO_3	THF	-
11	**96**	K_2CO_3	THF	-
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



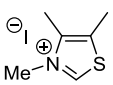
94



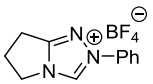
5



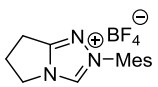
26



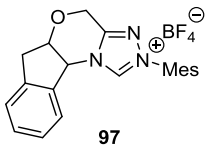
28



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).

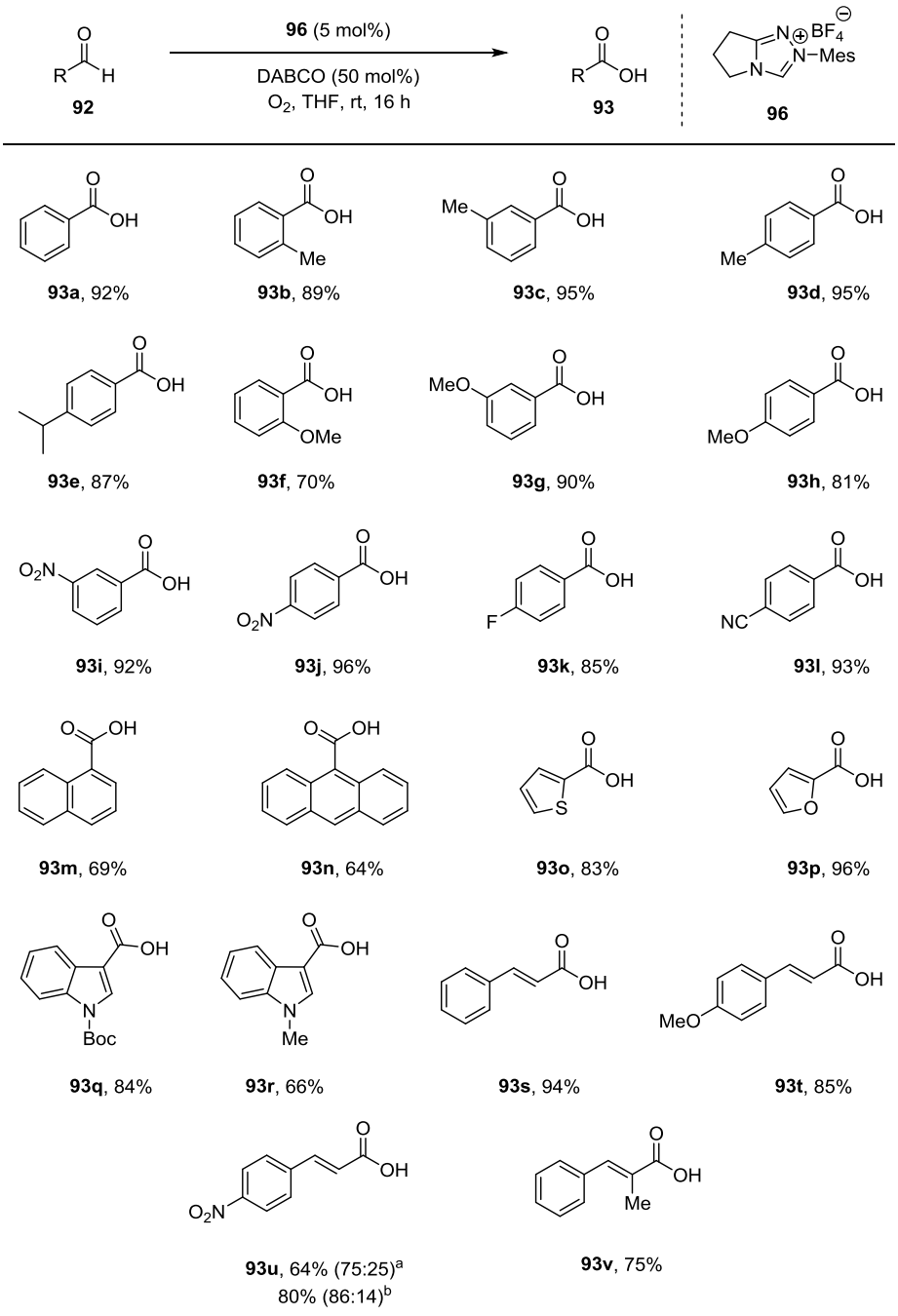
3.5.2 Aerobic Oxidation of Aldehydes: Substrate Scope

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.

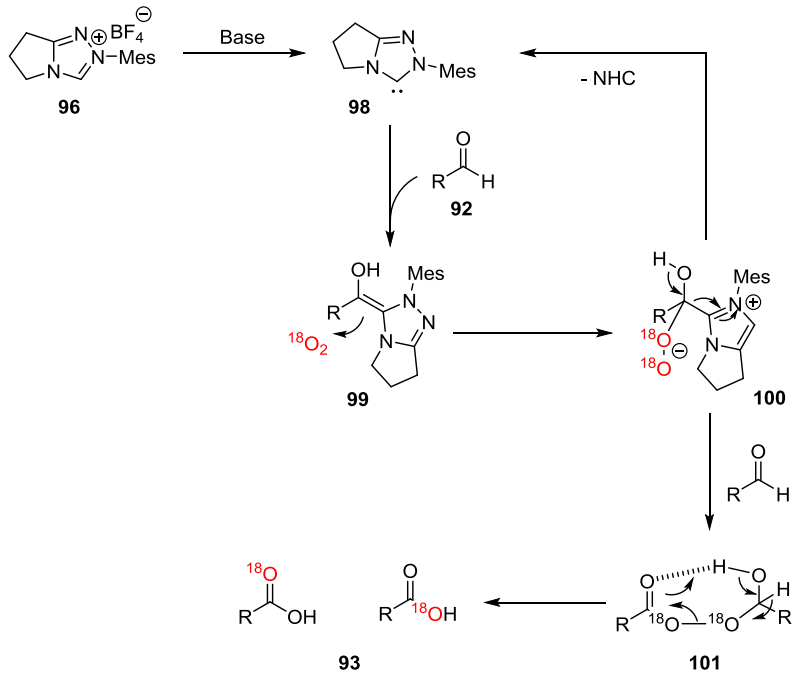
Scheme 3.43 Substrate scope of aldehydes



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

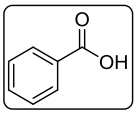
constant *J* are in Hz, and residual solvent signals were used as references. The chemical shifts converted to the TMS scale ($CDCl_3$: δH = 7.26 ppm, DMSO-d_6 δH = 2.52 ppm). The signal patterns are marked as follows: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet and brs = 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]

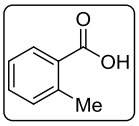


Following the general procedure **3.7.2** described above, the title compound was prepared using benzaldehyde **92a** (0.5 mmol, 53 mg, 1.0 equiv). The product **93a** was isolated in 92% yield (56 mg) as a pale yellow solid.

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]

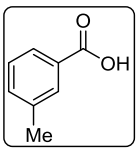


Following the general procedure **3.7.2** described above, the title compound was prepared using 2-methyl benzaldehyde **92b** (0.5 mmol, 60 mg, 1.0 equiv). The product **93b** was isolated in 89% yield (60 mg) as a pale yellow solid.

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]

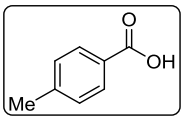


Following the general procedure **3.7.2** described above, the title compound was prepared using 3-methyl benzaldehyde **92c** (0.5 mmol, 60 mg, 1.0 equiv). The product **93c** was isolated in 95% yield (65 mg) as a pale yellow solid.

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]

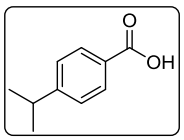


Following the general procedure **3.7.2** described above, the title compound was prepared using 4-methyl benzaldehyde **92d** (0.5 mmol, 60 mg, 1.0 equiv). The product **93d** was isolated in 95% yield (65 mg) as a pale yellow solid.

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]

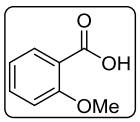


Following the general procedure **3.7.2** described above, the title compound was prepared using 4-methyl benzaldehyde **92e** (0.5 mmol, 74 mg, 1.0 equiv). The product **93e** was isolated in 87% yield (71 mg) as a off-white solid.

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]

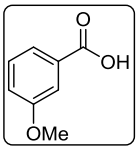


Following the general procedure **3.7.2** described above, the title compound was prepared using 2-methoxy benzaldehyde **92f** (0.5 mmol, 68 mg, 1.0 equiv). The product **93f** was isolated in 70% yield (53 mg) as a pale yellow solid.

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]

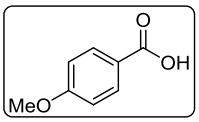


Following the general procedure **3.7.2** described above, the title compound was prepared using 3-methoxy benzaldehyde **92g** (0.5 mmol, 68 mg, 1.0 equiv). The product **93g** was isolated in 90% yield (68 mg) as a pale yellow solid.

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]

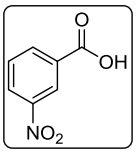


Following the general procedure **3.7.2** described above, the title compound was prepared using 4-methoxy benzaldehyde **92h** (0.5 mmol, 68 mg, 1.0 equiv). The product **93h** was isolated in 81% yield (62 mg) as a pale yellow solid.

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]

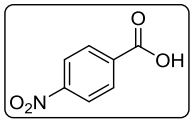


Following the general procedure **3.7.2** described above, the title compound was prepared using 3-nitro benzaldehyde **92i** (0.5 mmol, 76 mg, 1.0 equiv). The product **93i** was isolated in 92% yield (77 mg) as a pale yellow solid.

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]

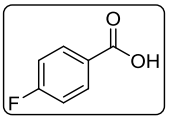


Following the general procedure **3.7.2** described above, the title compound was prepared using 4-nitro benzaldehyde **92j** (0.5 mmol, 76 mg, 1.0 equiv). The product **93j** was isolated in 96% yield (80 mg) as a light yellow solid.

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]

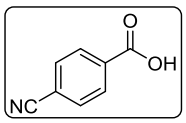


Following the general procedure **3.7.2** described above, the title compound was prepared using 4-fluoro benzaldehyde **92k** (0.5 mmol, 62 mg, 1.0 equiv). The product **93k** was isolated in 85% yield (60 mg) as a white solid.

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]

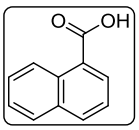


Following the general procedure **3.7.2** described above, the title compound was prepared using 4-cyano benzaldehyde **92l** (0.5 mmol, 66 mg, 1.0 equiv). The product **93l** was isolated in 93% yield (68 mg) as a pale yellow solid.

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]

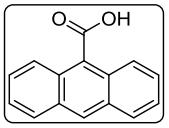


Following the general procedure **3.7.2** described above, the title compound was prepared using 1-napthaldehyde **92m** (0.5 mmol, 78 mg, 1.0 equiv). The product **93m** was isolated in 69% yield (59 mg) as a light yellow solid.

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]

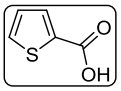


Following the general procedure **3.7.2** described above, the title compound was prepared using anthracene-9-carbaldehyde **92n** (0.5 mmol, 103 mg, 1.0 equiv). The product **93n** was isolated in 84% yield (71 mg) as a yellow solid.

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]

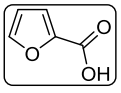


Following the general procedure **3.7.2** described above, the title compound was prepared using thiophene-2-carbaldehyde **92o** (0.5 mmol, 56 mg, 1.0 equiv). The product **93o** was isolated in 83% yield (53 mg) as a white solid.

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).

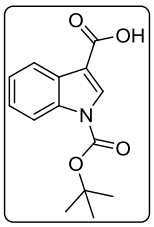
Furoic acid (93p)[39]



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).

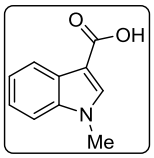
N-BOC-Indole-3-carboxylic acid (93q)[45e]



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).

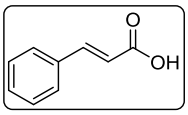
N-methyl-Indole-3-carboxylic acid (93r)[45f]



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).

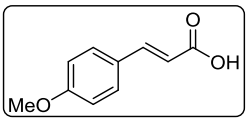
Trans-Cinnamic acid (93s)[45g]



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).

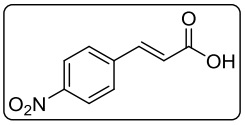
Trans-4-Methoxycinnamic acid (93t)[45g]



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).

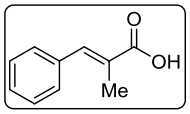
Trans-4-Nitrocinnamic acid (93u)[45g]



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).

3.8 References

1. Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 6th ed.; John Wiley and Sons, Inc: Hoboken, NJ, **2007**.

2. Cheung, H.; Tanke, R. S.; Torrence, G. P. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2000**.

3. Sunley, G. J.; Watson, D. J. *Catal. Today* **2000**, *58*, 293.

4. (a) Seebach, D. *Angew. Chem., Int. Ed.* **1979**, *18*, 239. (b) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (c) Menon, R.; Biju, A. T.; Nair, V. *Chem. Soc. Rev.* **2015**, *44*, 5040.

5. For selected recent reports on NHC-catalyzed generation of α,β-unsaturated acyl azoliums and their reactions, see: (a) De Sarkar, S.; Studer, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9266. (b) Mo, J.; Shen, L.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8588. (c) Mondal, S.; Yetra, S. R.; Patra, A.; Kunte, S. S.; Gonnade, R. G.; Biju, A. T. *Chem. Commun.* **2014**, *50*, 14539. (d) Liang, Z. Q.; Wang, D.-L.; Zhang, H.-M.; Ye, S. *Org. Lett.* **2015**, *17*, 5140. (e) Yetra, S. R.; Mondal, S.; Mukherjee, S.; Gonnade, R. G.; Biju, A. T. *Angew. Chem. Int. Ed.* **2016**, *55*, 268.

6. Maki, B. E.; Chan, A.; Phillips, E. M.; Scheidt, K. A. *Org. Lett.* **2007**, *9*, 371.

7. (a) Maji, B.; Vedachalan, S.; Ge, X.; Cai, S.; Liu, X.-W. *J. Org. Chem.* **2011**, *76*, 3016. (b) Xin, Y.-C.; Shi, S.-H.; Xie, D.-D.; Hui, X.-P.; Xu, P.-F. *Eur. J. Org. Chem.* **2011**, 6527.

8. Liu, Y.-K.; Li, R.; Yue, L.; Li, B.-J.; Chen, Y.-C.; Wu, Y.; Ding, L.-S. *Org. Lett.* **2006**, *8*, 1521.

9. Arde, P.; Ramanjaneyulu, B. T.; Reddy, V.; Saxena, A.; Anand, R. V. *Org. Biomol. Chem.* **2012**, *10*, 848.

10. Castells, J.; Llitjos, H.; Moreno-Manas, M. *Tetrahedron Lett.* **1977**, *18*, 205.

11. Guin, J.; De Sarkar, S.; Grimme S.; Studer, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8727.

12. De Sarkar, S.; Grimme, S. Studer, A. *J. Am. Chem. Soc.* **2010**, *132*, 1190.

13. Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett*. **2011**, *13*, 4080.

14. Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. *Chem. Commun*. **2011**, *47*, 8670.

15. Lu, H.; Liu, J-Y.; Li, C-G.; Lin, J-B.; Liang, Y-M.; Xu, P-F *Chem. Commun*. **2015**, *51*, 4473.

16. Lu, Y.; Tang, W.; Zhang, Y.; Du, D.; Lu, T.; *Adv. Synth. Catal.* **2013**, *355*, 321.

17. Yetra, S. R.; Mondal, S.; Suresh, E.; Biju, A. T. *Org. Lett*. **2015**, *17*, 1417.

18. Li, G.-T.; Gu Q.; You, S.-L. *Chem. Sci.* **2015**, *6*, 4273.

19. (a) Wanner, B.; Mahatthananchai, J.; Bode, J. W. *Org. Lett.* **2011**, *13*, 5378. (b) Kravina, A. G.; Mahatthananchai, J.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9433.

20. Hu, S.; Wang, B.; Zhang, Y.; Tang, W.; Fang, M.; Lu, T.; Du D. *Org. Biomol. Chem*. **2015**, *13*, 4661.

21. Xie, D.; Yang, L.; Lin, Y.; Zhang, Z.; Chen, D. Zeng, X.; Zhong G. *Org. Lett.* **2015**, *17*, 2318.

22. Sun, F.-G.; Sun L.-H.; Ye, S. *Adv. Synth. Catal.* **2011**, *353*, 3134.

23. (a) Yetra, S. R.; Bhunia, A.; Patra, A.; Mane, M. V.; Vanka, K.; Biju, A. T. *Adv. Synth. Catal*. **2013**, *355*, 1089. (b) Yetra, S. R.; Trinadh, K.; Kunte, S.S.; Gonade, R. G.; Biju, A. T. *Org. Lett*. **2013**, *15*, 5202. (c) Yetra, S. R.; Roy, T.; Bhunia, A.; Porwal, D.; Biju, A. T. *J. Org. Chem.* **2014**, *79*, 4245.

24. Ni, Q.; Song, X.; Raabe G.; Enders, D. *Chem. Asian J*. **2014**, *9*, 1535.

25. (a) Gao, Z.-H.; Chen, X.-Y.; Zhang H.-M.; Ye, S. *Chem. Commun.* **2015**, *51*, 12040. (b) Zhang, C.-L.; Wang, D.-L.; Chen K.-Q.; Ye, S. *Org. Biomol. Chem.* **2015**, *13*, 11255.

26. Ryan, S. J.; Candish, L.; Lupton, D. W. J. *Am. Chem. Soc.* **2009**, *131*, 14176.

27. Cheng, J.; Huang Z.; Chi, Y. R.; *Angew. Chem., Int. Ed*. **2013**, *52*, 8592.

28. Zeitler, K. *Org. Lett*. **2006**, *8*, 637.

29. Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc*. **2010**, *132*, 8810.

30. Zhu, Z.-Q.; Xiao, J.-C. *Adv. Synth. Catal*. **2010**, *352*, 2455.

31. Zhang, C.-L.; Wang, Z.-X.; Ye, S. *Angew. Chem., Int. Ed*. **2014**, *53*, 11611.

32. Ni, Q.; Xiong, J.; Song, X.; Raabe, Ge.; Enders D. *Chem. Commun*. **2015**, *51*, 14628.

33. Lu, H.; Zhang, J.-L.; Liu, J.-Y.; Li, H.-Y.; Xu P.-F. *ACS Catal.* **2017**, *7*, 7797.

34. Zhu, T.; Mou, C.; Li, B.; Smetankova, M.; Song, B-A.; Chi,Y. R. *J. Am. Chem. Soc*. **2015**, *137*, 5658.

35. (a) Fournier, H. M. *Comptes Rendus Acad. Sci.* **1907**, 331. (b) Tojo, G.; Fernández, M. *Oxidation of Primary Alcohols to Carboxylic Acids A Guide to Current Common Practice*; **2007**.

36. Han, L.; Xing, P.; Jiang, B. *Org. Lett.* **2014**, *16*, 3428.

37. Liu, M.; Li, C.-J. *Angew. Chem. Int. Ed.* **2016**, *55*, 10806.

38. Brewster, P. T.; Goldberg, M. J.; Tran, C. J.; Heinekey, M. D.; Goldberg, I. K. *ACS Catal.* **2016**, *6*, 6302.

39. Yu, H.; Ru, S.; Dai, G.; Zhai, Y.; Lin, H.; Han, S.; Wei, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 3867.

40. Yoshida, M.; Katagiri, Y.; Zhu, W.-B.; Shishido, K. *Org. Biomol. Chem.* **2009**, *7*, 4062.

41. (a) Gu, L.; Zhang, Y. *J. Am. Chem. Soc.* **2010**, *132*, 914. (b) Nair, V.; Varghese, V.; Paul, R. R.; Jose, A.; Sinu, C. R.; Menon, R. S. *Org. Lett.* **2010**, *12*, 2653.

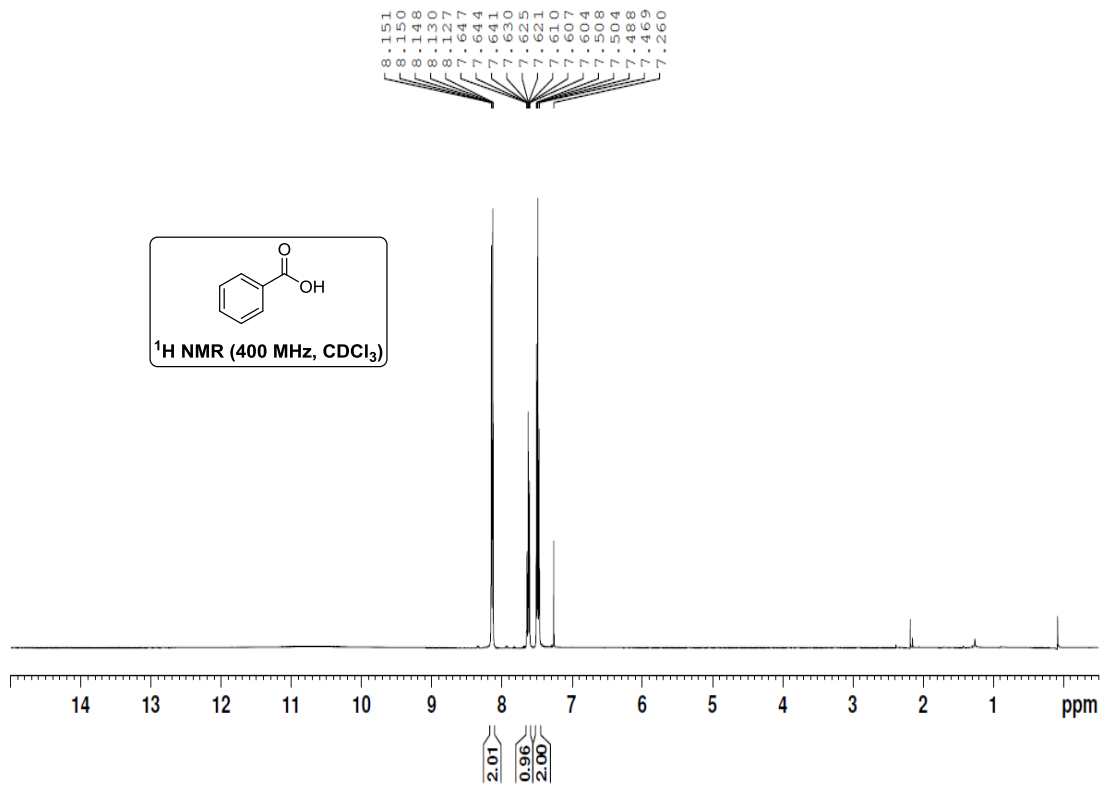
42. Chiang, P.-C.; Bode, J. W. *Org. Lett.* **2011**, *13*, 2422.

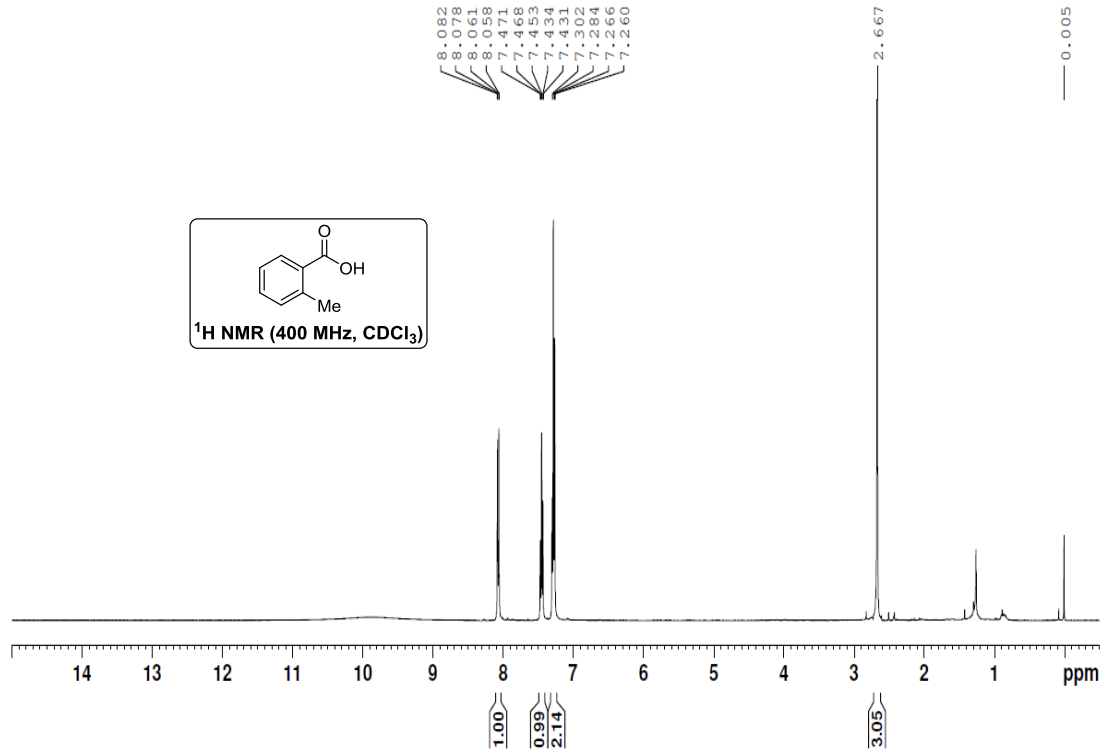
43. Yang, W.; Gou, G.-Z.; Wang, Y.; Fu, W.-F. *RSC Adv.* **2013**, *3*, 6334.

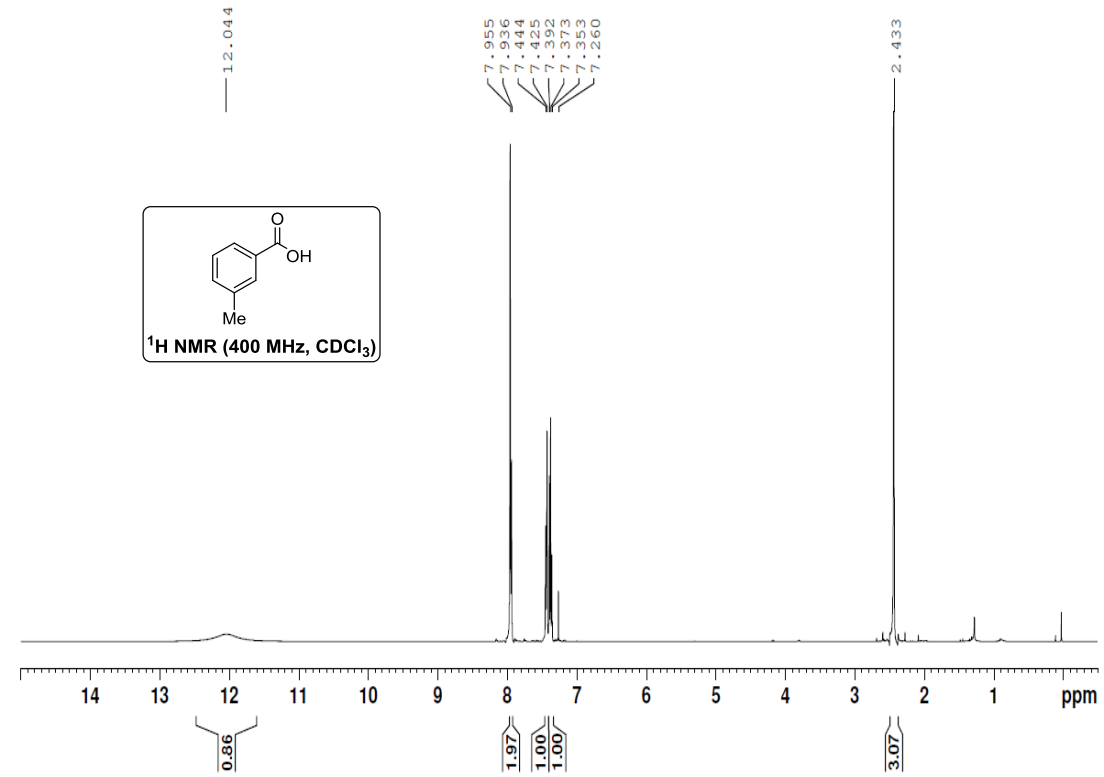
44. Möhlmann, L.; Ludwig, S.; Blechert, S. *Beilstein J. Org. Chem.* **2013**, *9*, 602.

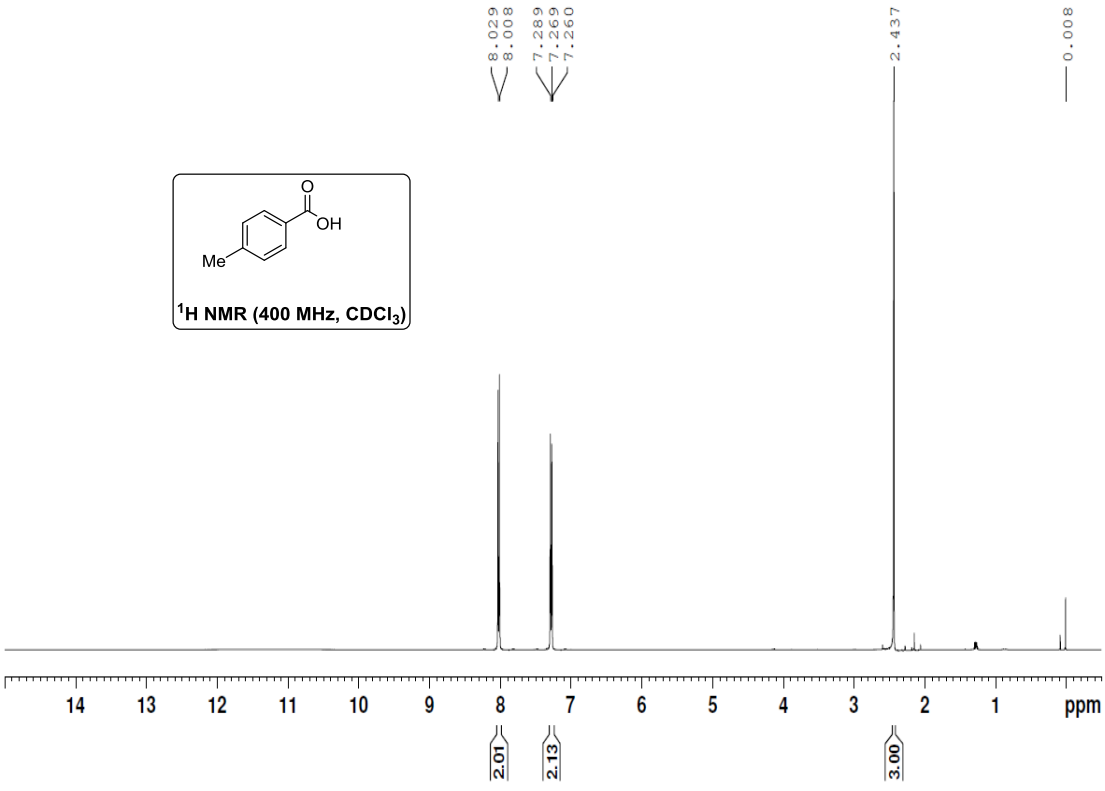
45. For characterization/analytical data of the products, see: (a) Jiang, X.; Ma, S. *Synthesis* **2018**, *50*, 1629. (b) Wu, F. P.; Peng, J. B.; Meng, L. S.; Qi, X.; Wu, X. F. *ChemCatChem* **2017**, *9*, 3121. (c) Hazra, S.; Deb, M.; Elias, A. J. *Green Chem.* **2017**, *19*, 5548. (d) Zheng, R.; Zhou, Q.; Gu, H.; Jiang, H.; Wu, J.; Jin, Z.; Han, D.; Dai, G.; Chen, R. *Tetrahedron Lett.* **2014**, *55*, 5671. (e) Magoulas, G.; Papaioannou, D. *ARKIVOC* **2003**, *(vi)*, 213. (f) Nemoto, K.; Tanaka, S.; Konno, M.; Onozawa, S.; Chiba, M.; Tanaka, Y.; Sasaki, Y.; Okubo, R.; Hattori, T. *Tetrahedron* **2016**, *72*, 734. (g) Nagalakshmi, K.; Diwakar, B. S.; Govindh, B.; Reddy, P. G.; Venu, R.; Bhargavi, I.; Devi, T. J. P.; Murthy, Y. L. N.; Siddaiah, V. *Asian J. Chem.* **2017**, *29*, 1561. (h) Concellon, J. M.; RodriguezSolla, H.; Diaz, P. *J. Org. Chem.* **2007**, *72*, 7974.

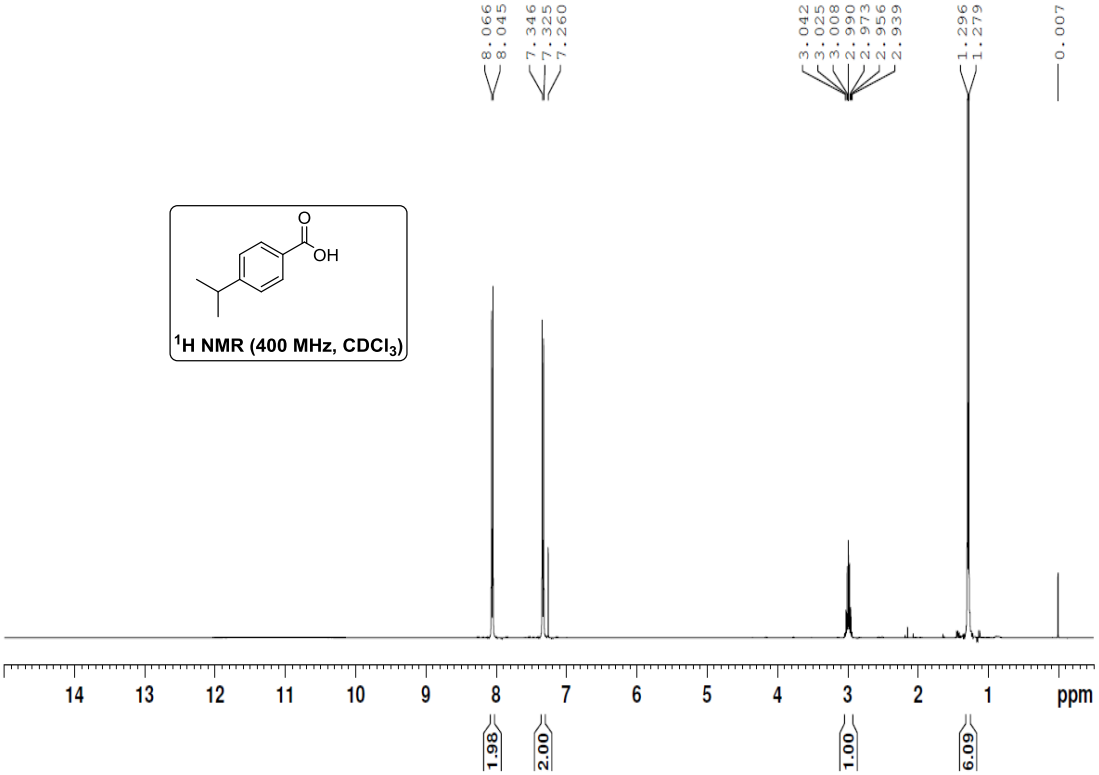
3.9 NMR Spectra of Compounds [^{1}H NMR (400 MHz, $CDCl_3$ or DMSO-d_6)]

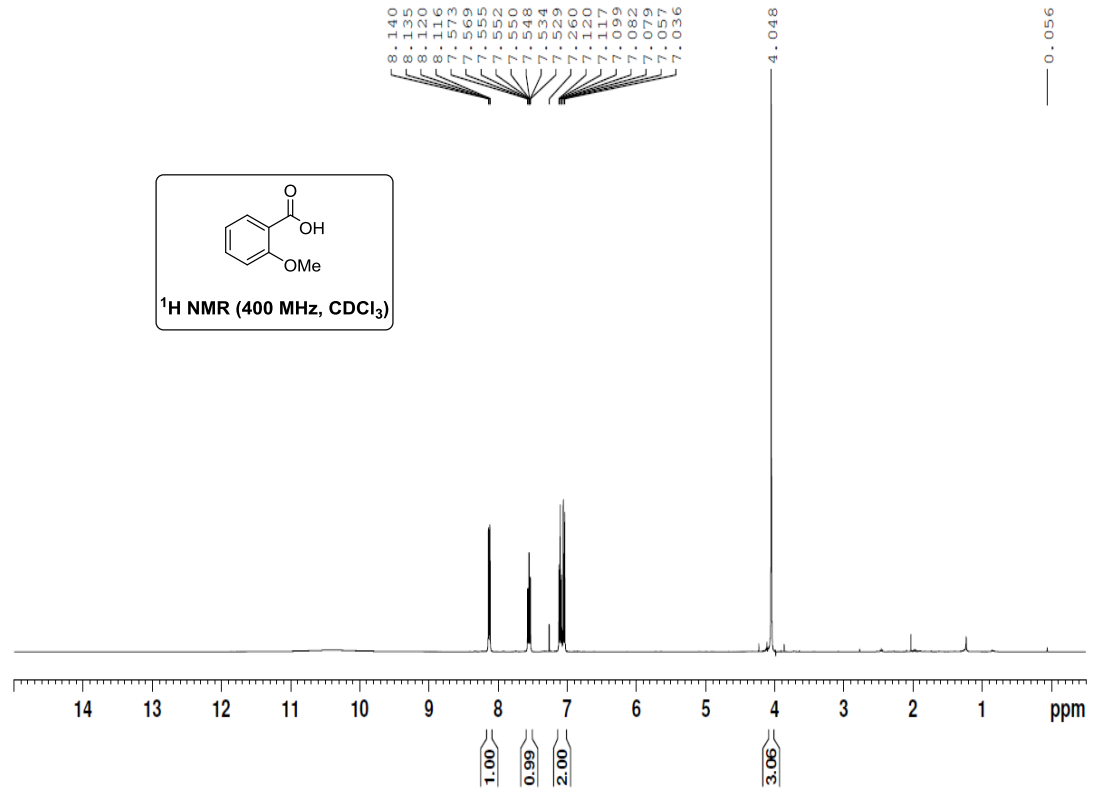


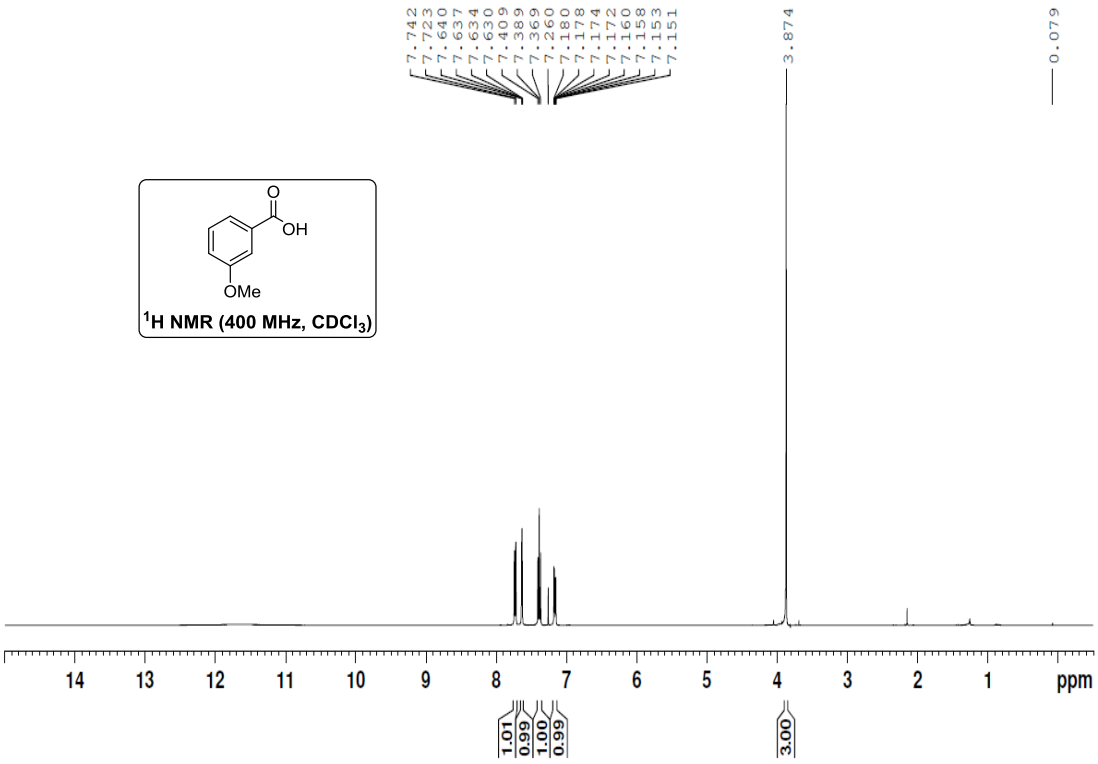


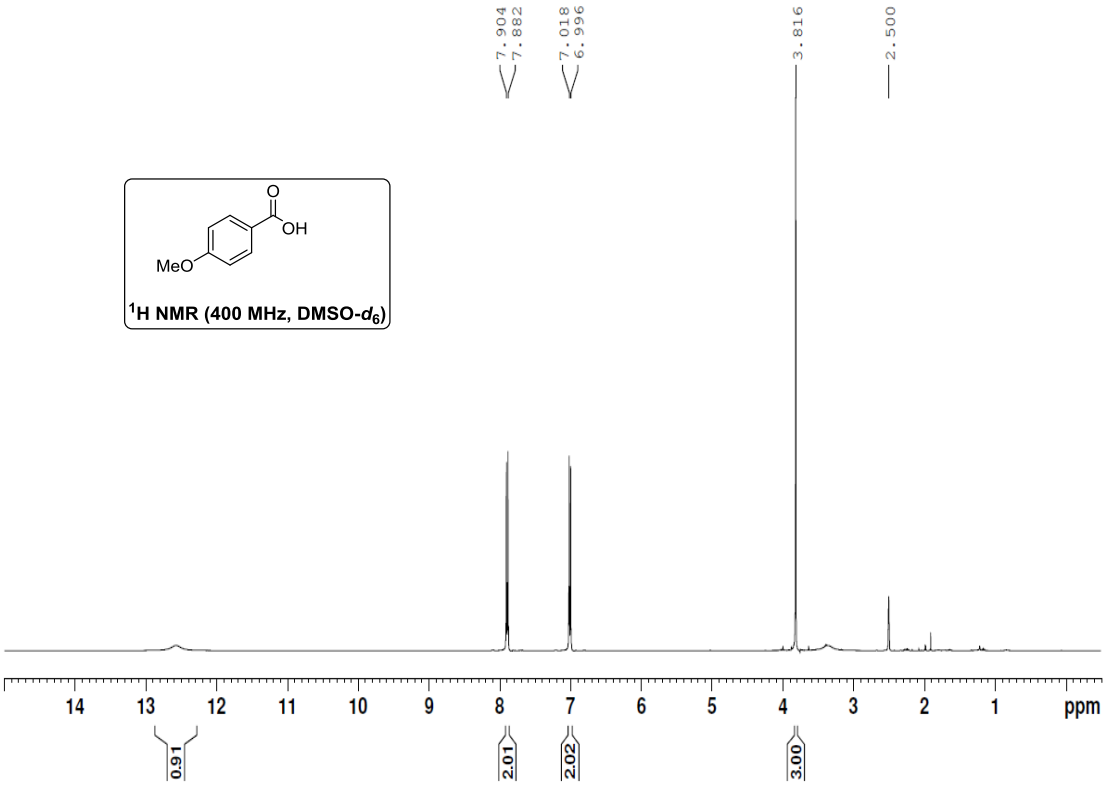

12.044
7.955
7.936
7.444
7.425
7.392
7.373
7.353
7.260
2.433
O
OH
Me
^{1}H NMR (400 MHz, CDCl$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.86
1.97
1.00
1.00
3.07

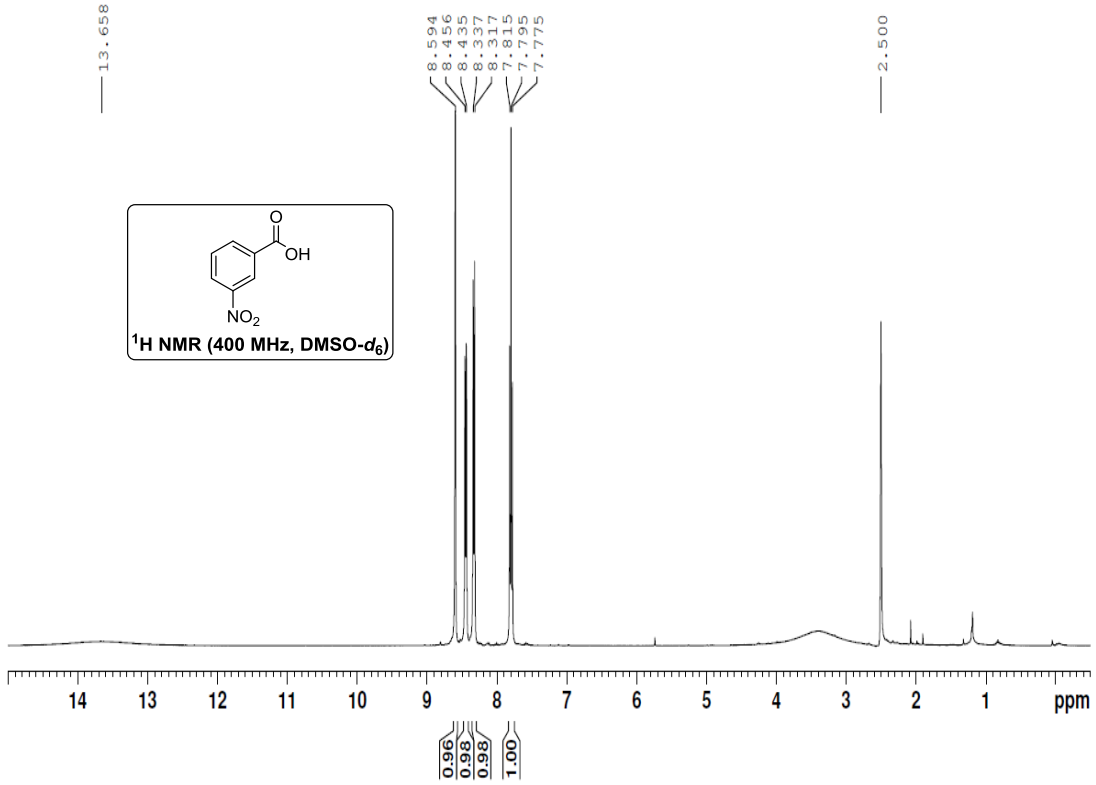

8.029
8.008
7.289
7.269
7.260
2.437
0.008
O
OH
Me
^{1}H NMR (400 MHz, CDCl$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
2.01
2.13
3.00

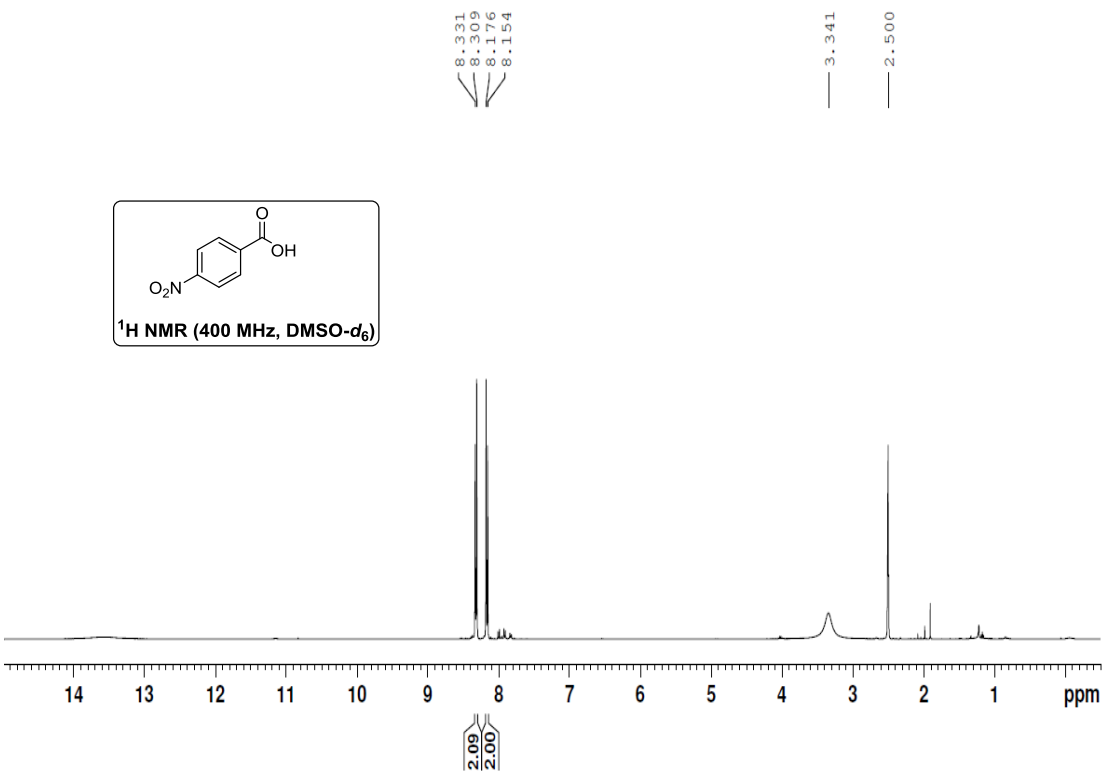

8.066
8.045
7.346
7.325
7.260
3.042
3.025
3.008
2.990
2.973
2.956
2.939
1.296
1.279
0.007
O
OH
^{1}H NMR (400 MHz, CDCl$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.98
2.00
1.00
6.09

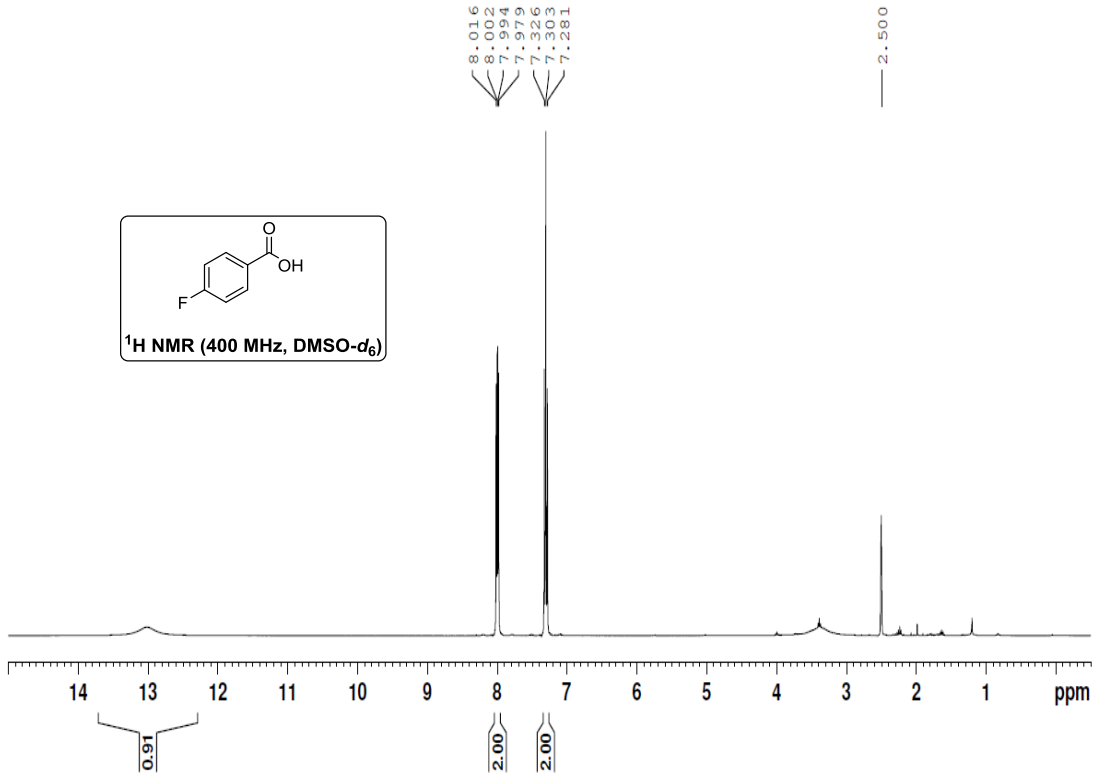

8.140
8.135
8.120
8.116
7.573
7.569
7.555
7.552
7.550
7.548
7.534
7.529
7.260
7.120
7.117
7.099
7.082
7.079
7.057
7.036
4.048
0.056
O
OH
OMe
^{1}H NMR (400 MHz, CDCl$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
0.99
2.00
3.06

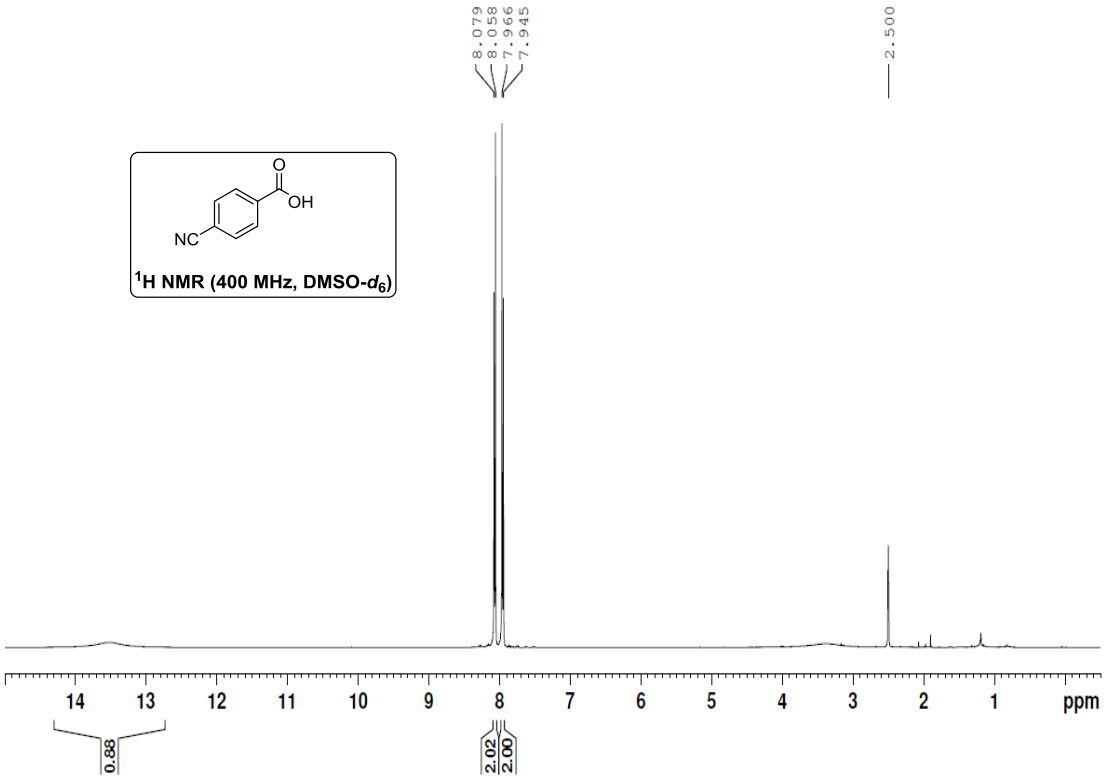

7.742
7.723
7.640
7.637
7.634
7.630
7.409
7.389
7.369
7.260
7.180
7.178
7.174
7.172
7.160
7.158
7.153
7.151
3.874
0.079
O
OH
OMe
^{1}H NMR (400 MHz, CDCl$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.01
0.99
1.00
0.99
3.00

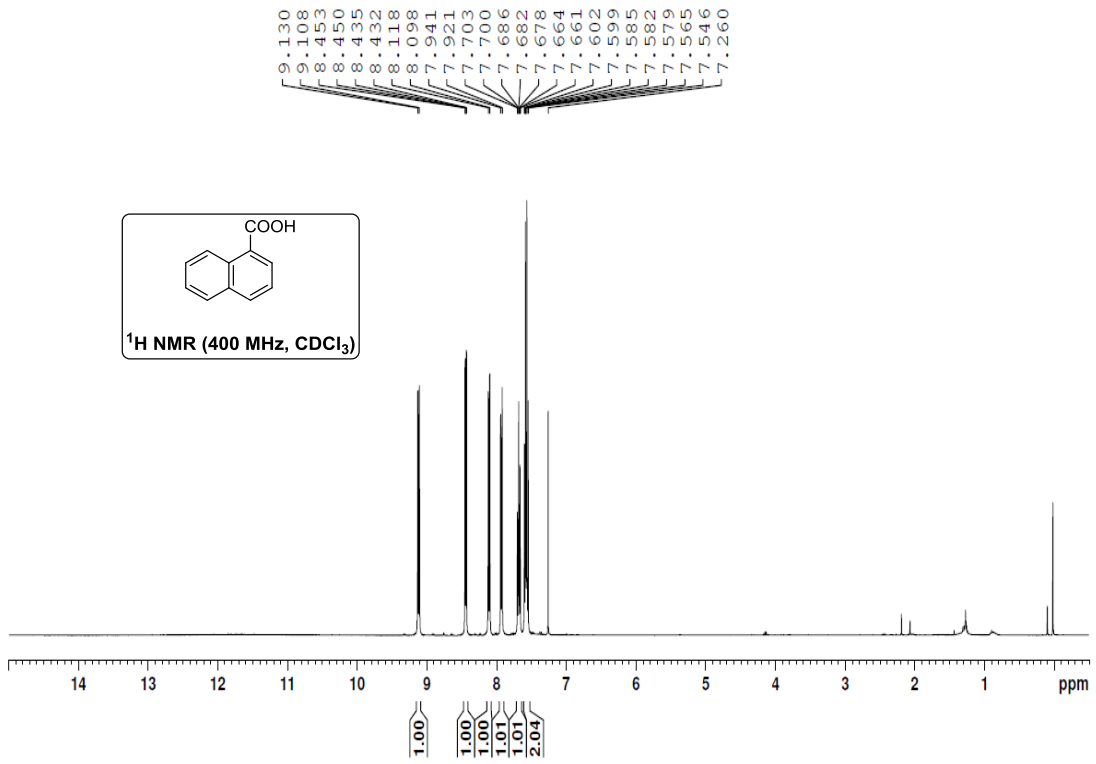

7.904
7.882
7.018
6.996
3.816
2.500
O
OH
MeO
^{1}H NMR (400 MHz, DMSO-d_6)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.91
2.01
2.02
3.00

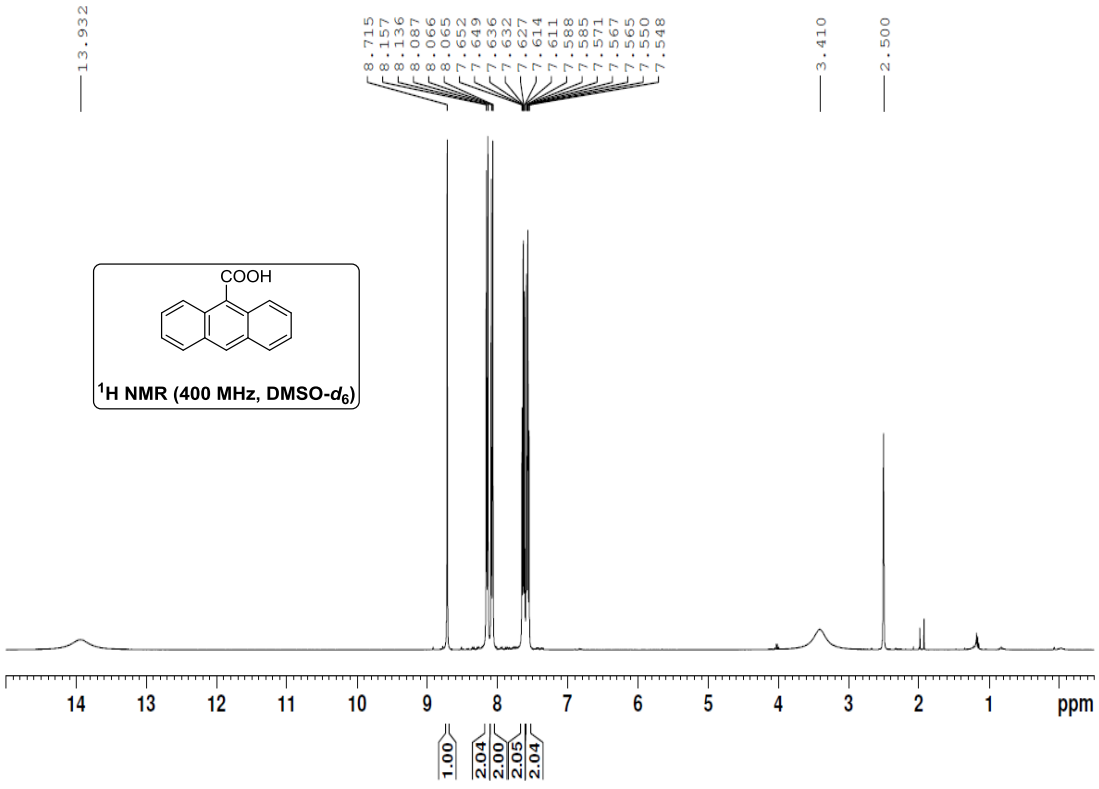

13.658
8.594
8.456
8.435
8.337
8.317
7.815
7.795
7.775
2.500
O
OH
NO2
1H NMR (400 MHz, DMSO-d6)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.96
0.98
0.98
1.00

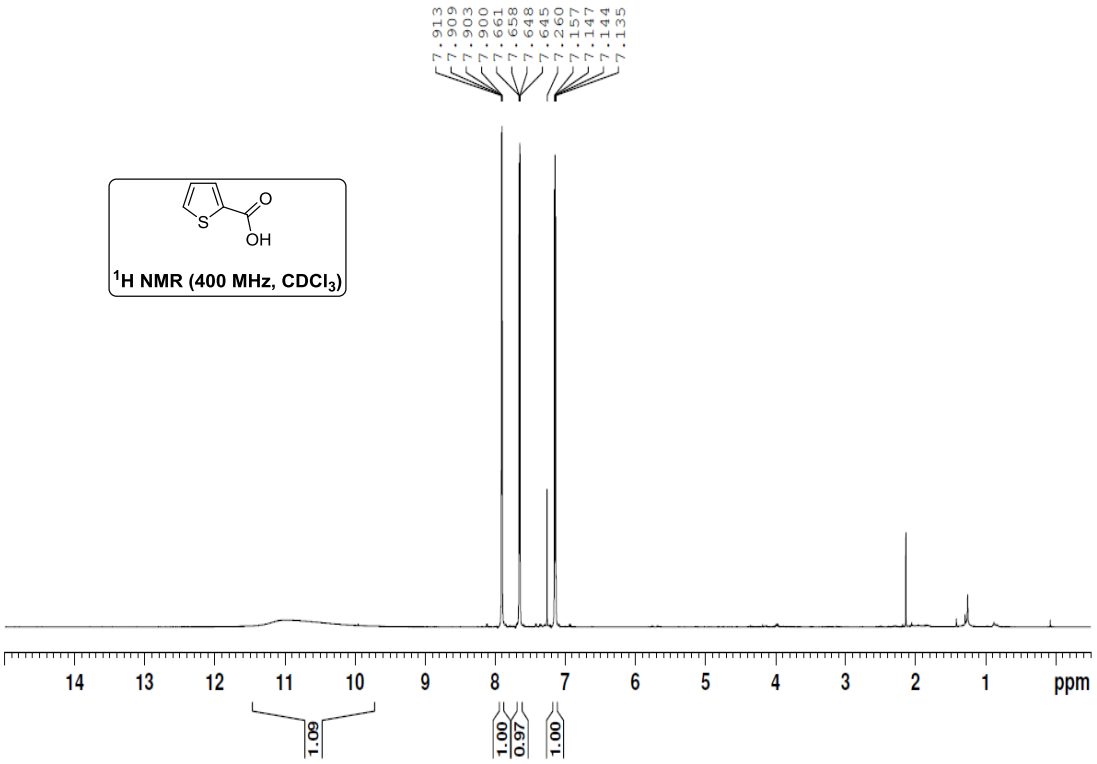

8.331
8.309
8.176
8.154
3.341
2.500
O
OH
O2N
1H NMR (400 MHz, DMSO-d6)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
2.09
2.00

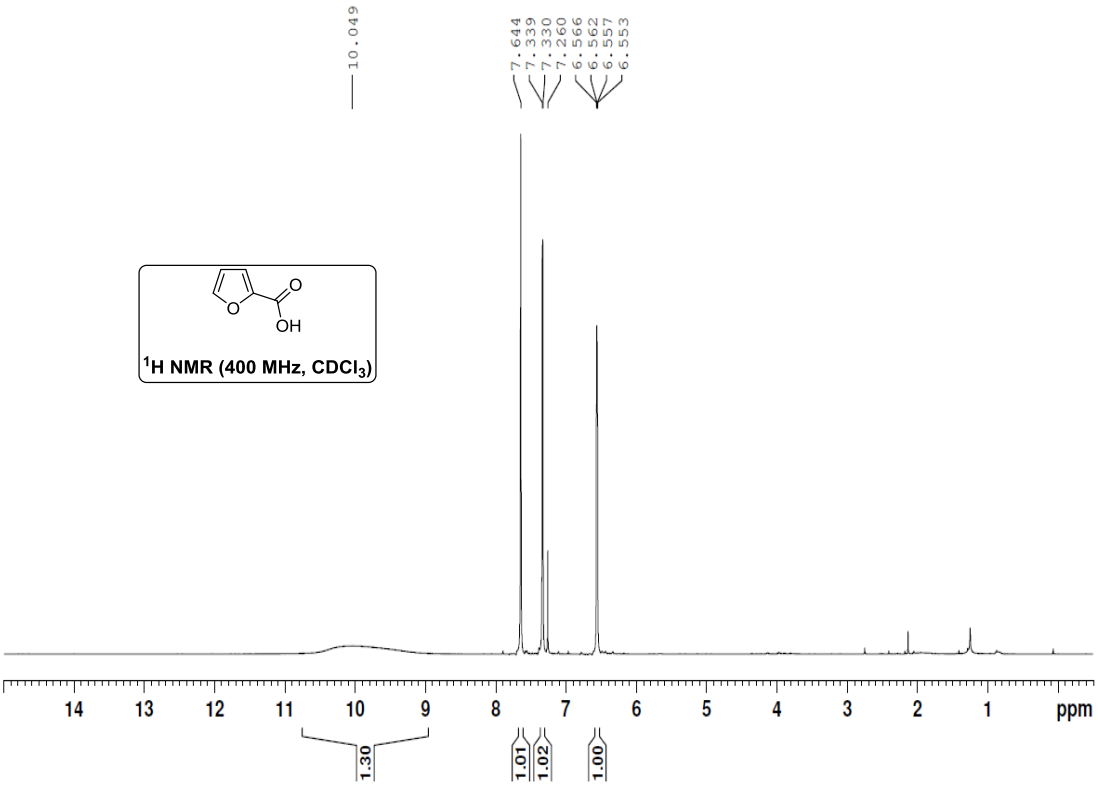

8.016
8.002
7.994
7.979
7.326
7.303
7.281
2.500
O
OH
F
^{1}H NMR (400 MHz, DMSO-d_6)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.91
2.00
2.00

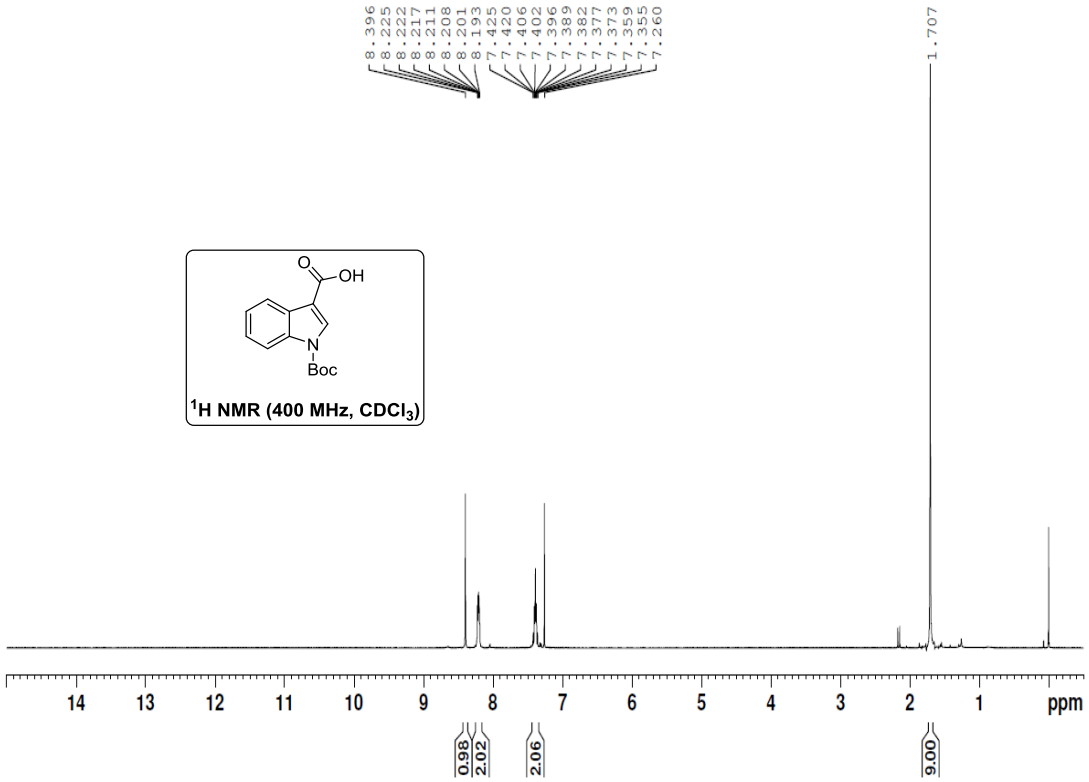

8.079
8.058
7.966
7.945
2.500
O
OH
NC
^{1}H NMR (400 MHz, DMSO-d_6)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.88
2.02
2.00

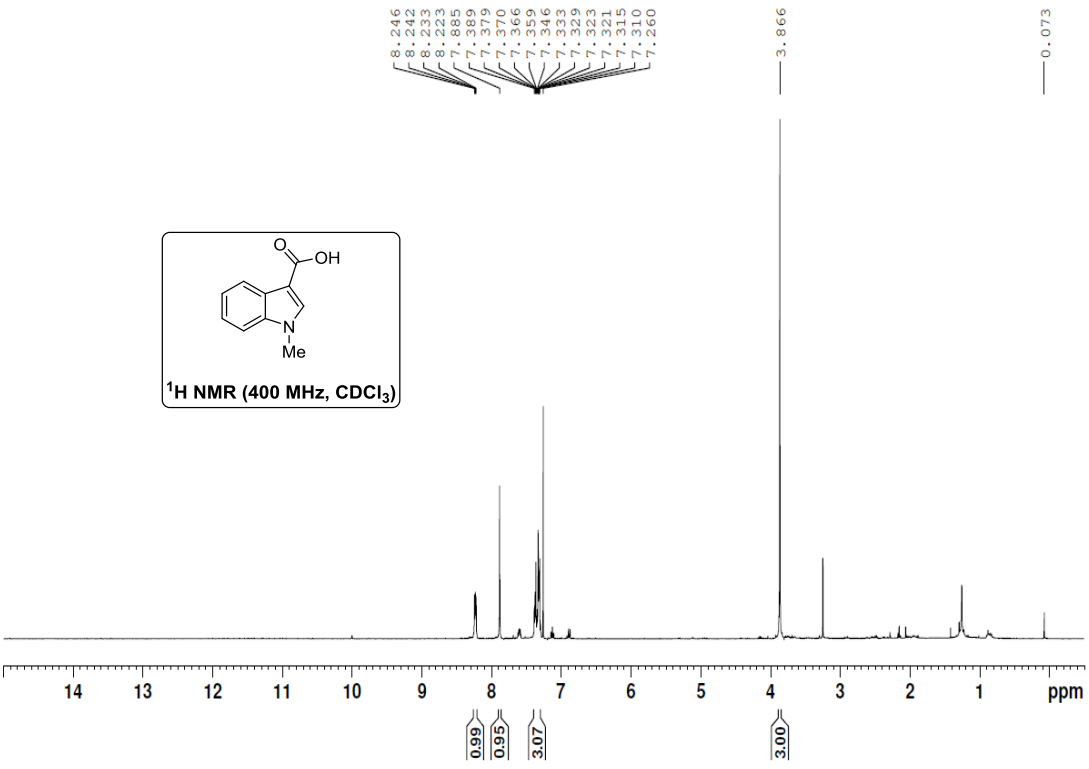

9.130
9.108
8.453
8.450
8.435
8.432
8.118
8.098
7.941
7.921
7.703
7.700
7.686
7.682
7.678
7.664
7.661
7.602
7.599
7.585
7.582
7.579
7.565
7.546
7.260
COOH
^{1}H NMR (400 MHz, CDCl$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.00 1.00 1.00 1.01 1.01 2.04

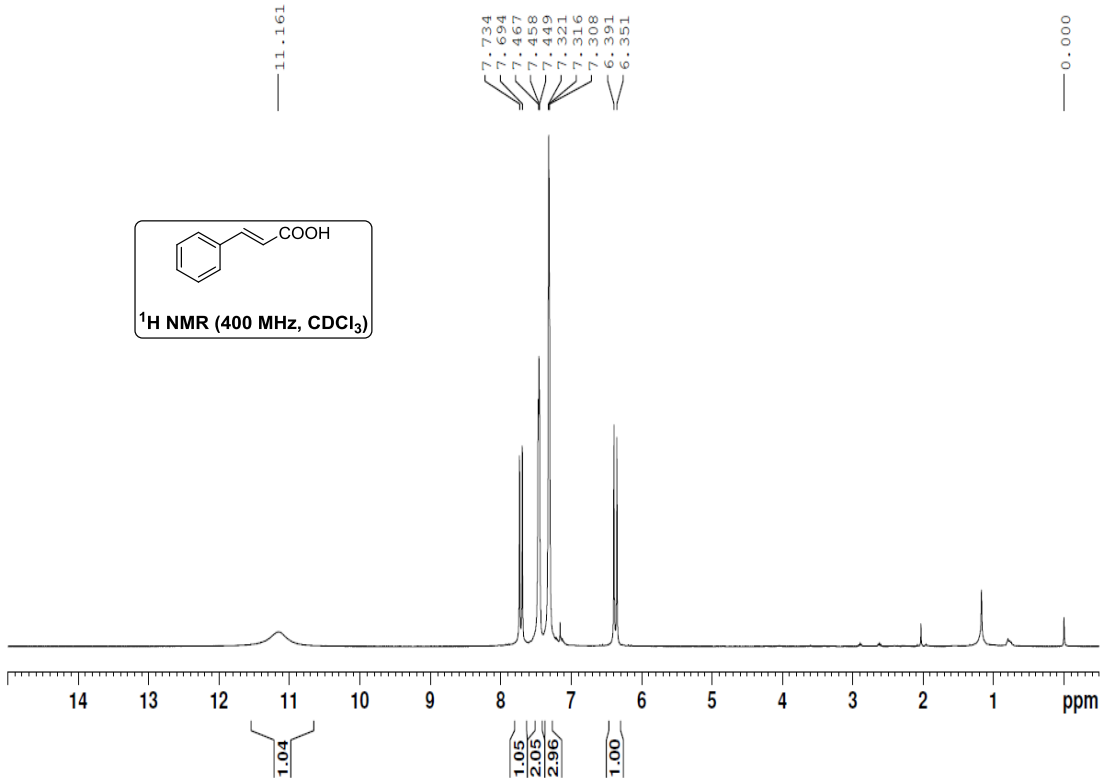

13.932
8.715
8.157
8.136
8.087
8.066
8.065
7.652
7.649
7.636
7.632
7.627
7.614
7.611
7.588
7.585
7.571
7.567
7.565
7.550
7.548
3.410
2.500
COOH
^{1}H NMR (400 MHz, DMSO-d_6)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.00 2.04 2.00 2.05 2.04

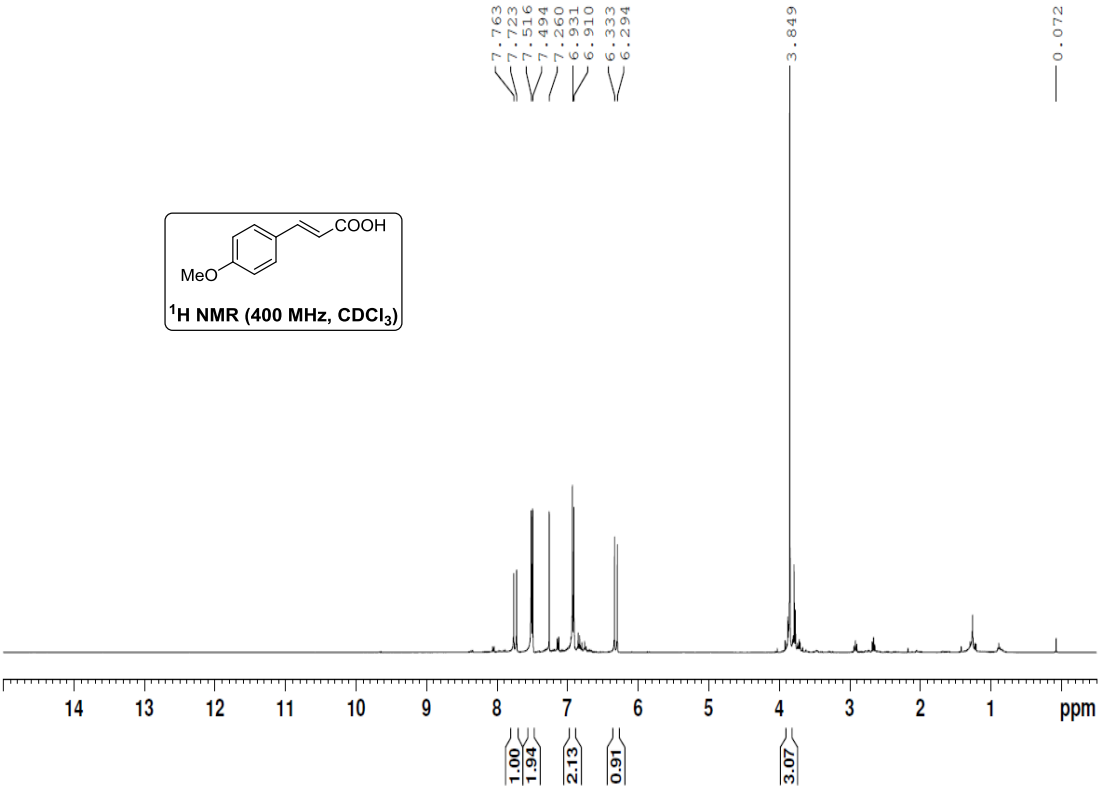

7.913
7.909
7.903
7.900
7.661
7.658
7.648
7.645
7.260
7.157
7.147
7.144
7.135
O
S
OH
^{1}H NMR (400 MHz, CDCl$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.09
1.00
0.97
1.00

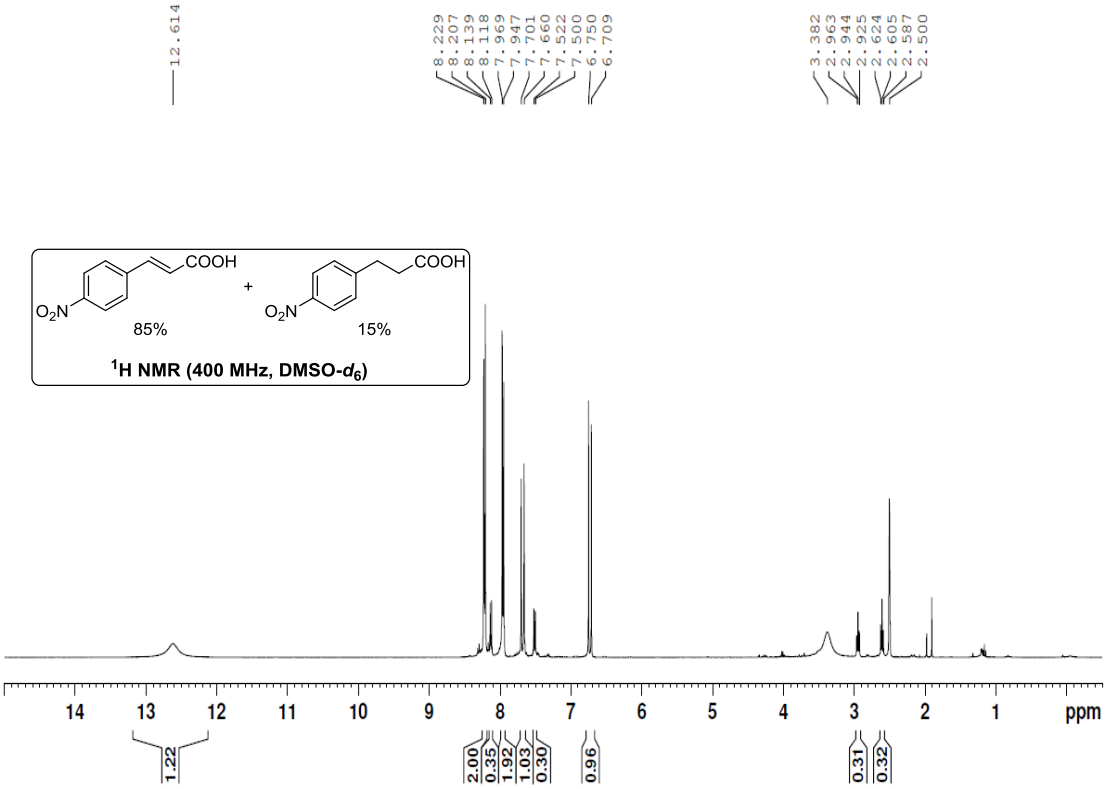

10.049
7.644
7.339
7.330
7.260
6.566
6.562
6.557
6.553
O
O
OH
^{1}H NMR (400 MHz, CDCl$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.30
1.01
1.02
1.00

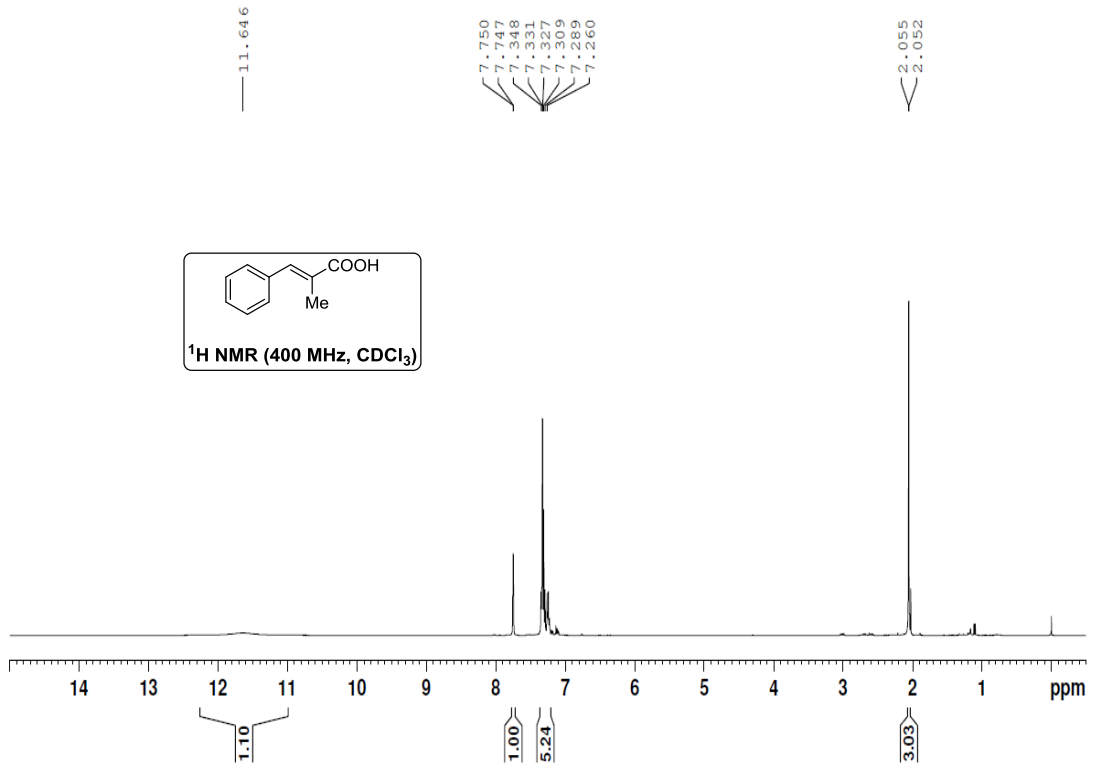

8.396
8.225
8.222
8.217
8.211
8.208
8.201
8.193
7.425
7.420
7.406
7.402
7.396
7.389
7.382
7.377
7.373
7.359
7.355
7.260
1.707
O
OH
N
Boc
^{1}H NMR (400 MHz, CDCl$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.98
2.02
2.06
9.00


8.246
8.242
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$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
0.99
0.95
3.07
3.00


11.161
7.734
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


7.763
7.723
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$_3$)
14 13 12 11 10 9 8 7 6 5 4 3 2 1 ppm
1.00
1.94
2.13
0.91
3.07


12.614
8.229
8.207
8.139
8.118
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


11.646
7.750
7.747
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