Domino Jeffery Heck Reaction Followed by Aldol Condensation: An Efficient Strategy for the Synthesis of Functionalized Acroleins

A Project Report

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Master of Science

By

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INDIAN INSTITUTE OF TECHNOLOGY, HYDERABAD

Declaration

I declare that this written submission represents my ideas in my own words, and where others' ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be a cause for disciplinary action by the Institute and can also evoke penal action from the sources that have thus not been properly cited, or from whom proper permission has not been taken when needed.

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This thesis entitled **"Domino Jeffery Heck Reaction Followed by Aldol Condensation: An Efficient Strategy for the Synthesis of Acroleins"** by Kailash Kumar Shaw is approved for the degree of Master of Science from IIT Hyderabad.

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Dedicated

To

MY FAMILY

Abstract

Synthetic protocols like domino or sequential one-pot are considered to be valuable techniques in organic synthesis as they are devoid of intermediate isolation.[1] These one-pot processes involve multiple steps to be catalyzed sequentially by a metal complex or sequential addition of reagents to drive a set of reactions. In recent years the transition metal catalysis mainly that of palladium and copper are found to be the most powerful platform in order to perform such kind of transformations.

Taking this advantage of transition metals, in the present context we have described a few efficient strategies for the synthesis of substituted acroleins from the simple and readily accessible iodoarenes and allylic alcohols by using palladium acetate and triethylamine as catalyst and base respectively.

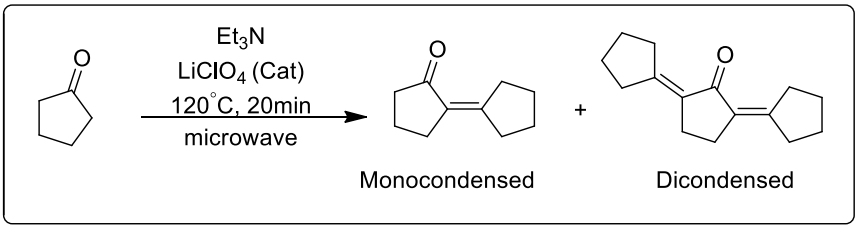
Contents

A Domino Jeffery Heck Reaction Followed by Aldol Condensation: An Efficient Strategy for the Synthesis of Functionalized Acroleins.

1.1 INTRODUCTION:

Domino one-pot synthetic methods[1] are highly acknowledged in the synthetic organic[2] field as they involve construction of more than one bond without isolating the intermediates. These methods have the additional advantage of minimizing the solvents and the waste produced. They help in the improving on the yield and also save on the time required for the isolation[2]. Therefore, such a method when employed for the synthesis of commercially useful materials is highly adaptable[3].

Aldol reaction is one of the most important reaction for the construction of C–C bonds in the synthetic organic chemistry[4]. The resulting β-hydroxycarbonyl compound has the core functional moiety present in various synthetic intermediates. Aldol reaction is often a significant key step in the synthesis of many biologically important compounds[4]. Self-condensation of aldehydes is a well-known process[5]. It involves a carbonyl group that acts both as the electrophile and the nucleophile in an aldol condensation. Aldehydes are generally reported to be more facile for self-condensation as compared to the ketones probably due to the steric factors. Hence, self-condensation for aldehydes is possible even in the mild acidic or basic conditions. Self-condensation can be intermolecular or intramolecular thus resulting in the formation of α,β-unsaturated aldehydes. For example, in one of the reports Lalit Kumar Sharma et al reported the condensation of cyclopentanone to give mono and di-condensed product[6]. Cyclopentanone in the presence of triethylamine along with catalytic $LiClO_4$ resulted in monocondensed alpha, beta un-saturated carbonyl compounds as major product with 68% yield and slight isolated the di-condensed product as a minor product with about 17% yield (Scheme 1)[6].



Scheme 1: Representative example of self-condensation

Synthetic Applications:

Acroleins[7], the α,β-unsaturated aldehydes, have been reported to show commercial utility as synthetic precursors of many useful compounds. In the recent times there has been a consistent demand for studying newer strategies for the preparation of such synthetic precursors[8] like acroleins as their bi-functionality is highly exploited for the synthetic purposes. Acrolein, also popularly known as propenal, is the smallest unsaturated aldehyde. Acrolein is known to have some basic advantages in synthesis of various commercially important and valued compounds[9] namely methionine, (by using methanethiol followed by the Strecker synthesis), polyester resin, 1,2,6-hexanettiol, pentaeerythritol (Figure 1). It also forms the basic building block[8] in Skraup synthesis for quinolone formation which is one of the most abundantly used heteroaromatic compound. Many industries like medicinal, agricultural, forestry and pesticide are dependent on the acrolein as it forms a major component for the biocide preparation[10]. Disinfectants like glutaraldehyde are also prepared from acrolein. Acrolein is also used for the synthesis of acrylic acid which is also a very commonly used precursor in the synthetic organic chemistry. Acrylic acid is used in preparation of important compounds like superabsorbent, plastic, paints and coatings[11]. Acrolein can also be used as a chemical precursor in different type of reactions like oxidation, reduction, Heck, aldol reactions etc[12].

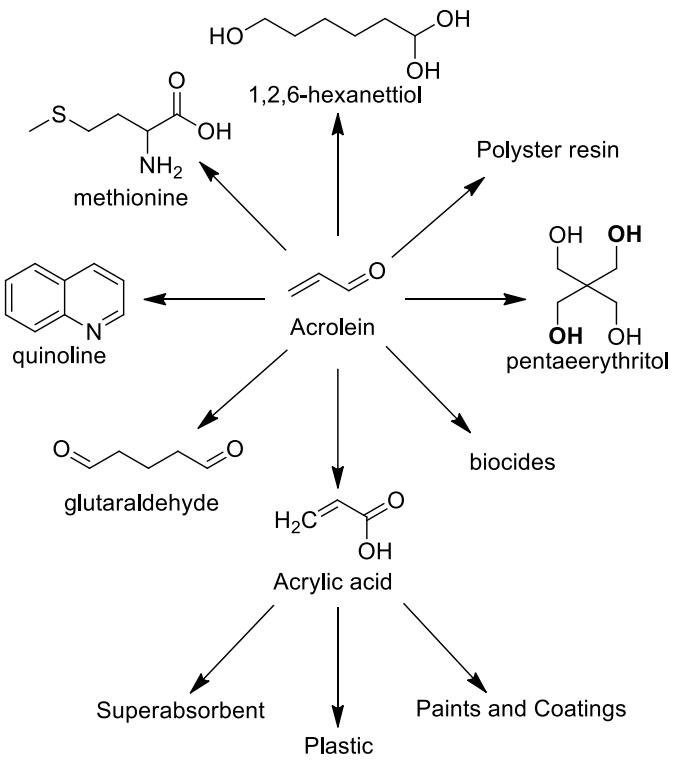
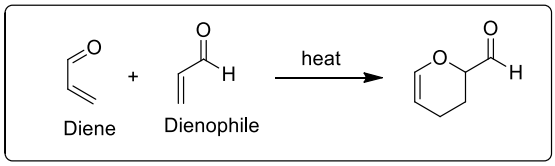


Figure 1: Utility of acrolein

Acrolein is also utilized as a diene in Diels-alder reaction[13] which is a powerful tool in organic synthesis to construct carbon-carbon bond (Scheme 2)[14].



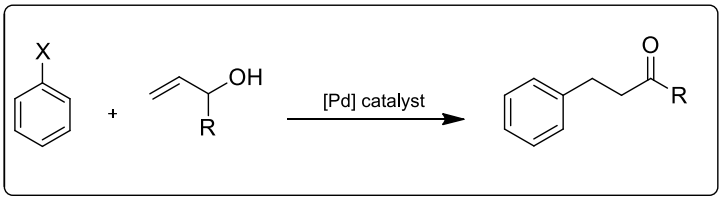
Scheme 2: Acrolein as diene

Acrolein co-polymers are utilized in photography, textile treatment, paper industry, as builders in laundry and as coatings for aluminum and steel panels. Some other modified acroleins act as scavengers of sulfides in oil-field floodwater systems and also to crosslink protein collagen in the leather tanning industry.

Background studies

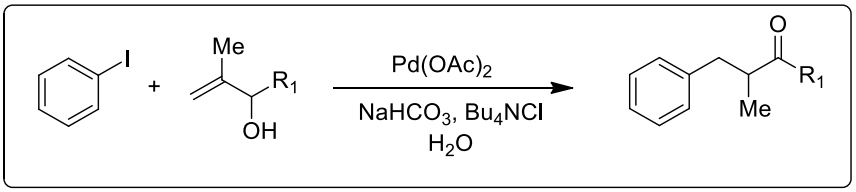
Heck reaction[15] has become one of the powerful tools in organic chemistry for C–C bond formation employing palladium for the coupling reactions. In particular, palladium catalyzed

coupling reaction of aryl halides with olefins has been versatile and well-studied. The particular case when allylic alcohols are employed, β-aromatic carbonyl compounds are usually obtained due to palladium-catalyzed reaction of aryl halides. Jeffery et al modified the classical Heck coupling and reported an efficient strategy for synthesizing highly selective beta aromatic carbonyl compounds with allylic alcohols by using palladium acetate as catalyst in the presence of a base and ammonium salt under inert conditions. The typical reaction conditions of Jeffery-Heck involve the reaction of aryl halides with allylic alcohols in presence of palladium catalyst for the preparation of aryl aldehydes and ketones (Scheme 3). But these conditions were manipulated in a number of ways and thus led to the various modifications.



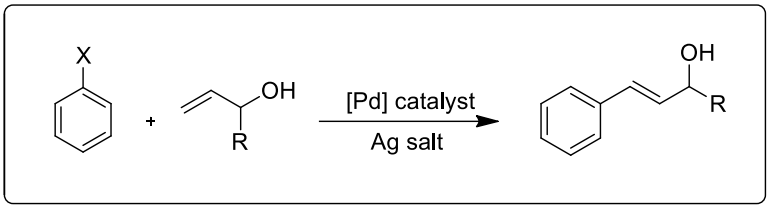
Scheme 3: Representative example of Jeffery-Heck reaction.

Accounting to the further advances accomplished, the use of water as a reaction medium for transition metal catalyzed reactions is very attractive in organic synthesis for both economic and safety reasons. Bumagin et al investigated the coupling reactions of aryl halides with boronic acids and the arylation of water insoluble olefins under neat water in the presence of palladium acetate. The reactions proceeded under mild conditions with very good yields. Here the palladium-catalyzed arylation of allylic alcohols with aryl iodides in neat water without any organic co-solvent (Scheme 4) are shown as follows, a highly selective beta aromatic carbonyl compounds are obtained. Having a closer insight into the reactivity patterns of the aryl halides and the scope of the reaction conditions it was studied by Bumagin et al that the aryl iodides reacted more efficiently when compared to the corresponding aryl bromides. This method was also worked well for aryl iodides having both electron withdrawing as well as donating groups.



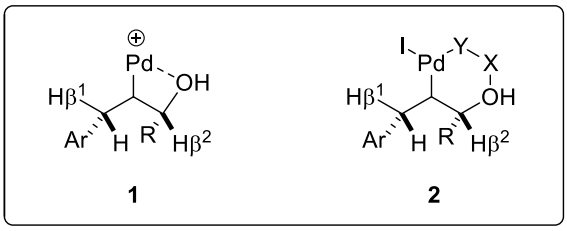
Scheme 4: Palladium-catalyzed arylation of allylic alcohols in water.

Further exploitation of the Jeffery-Heck reaction was also done by Jeffery by employing various additives such as silver salts in stoichiometric amounts to affect the course of the reaction. This modification interestingly led to the formation of cinnamyl alcohols under mild conditions (Scheme 5).



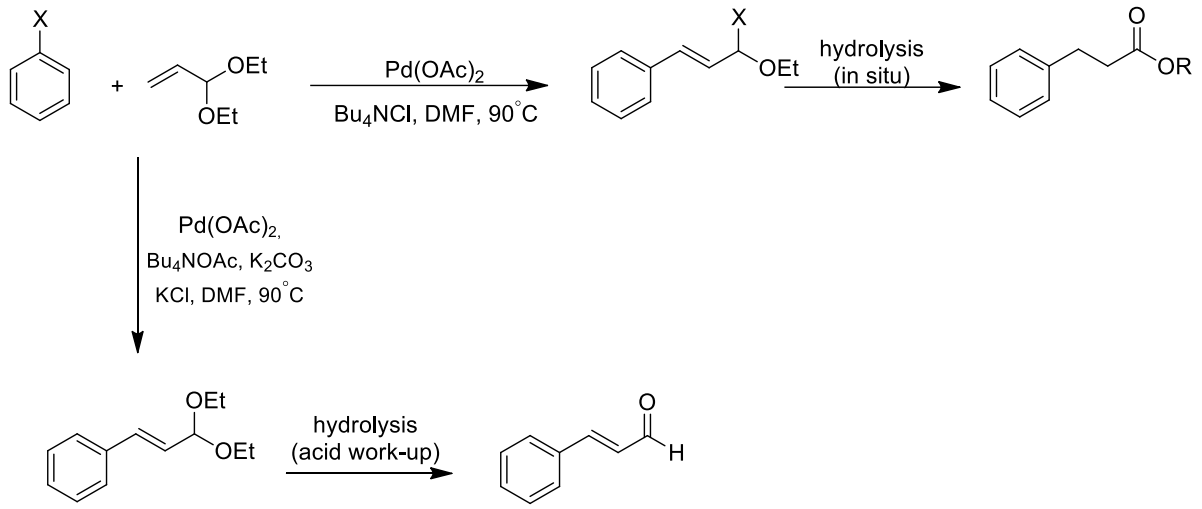
Scheme 5: Arylation of allylic alcohols forming cinnamyl alcohols

In yet another modification, Kang et al showed high regioselectivity preference using diphenyliodoniumtetrafluoroborate as the arylating agent under milder conditions as room temperature. Here, as well as in scheme 4, electron-deficient Pd(II) center played a key role in the formation of the carbopalladation intermediate (Scheme 6)[16].



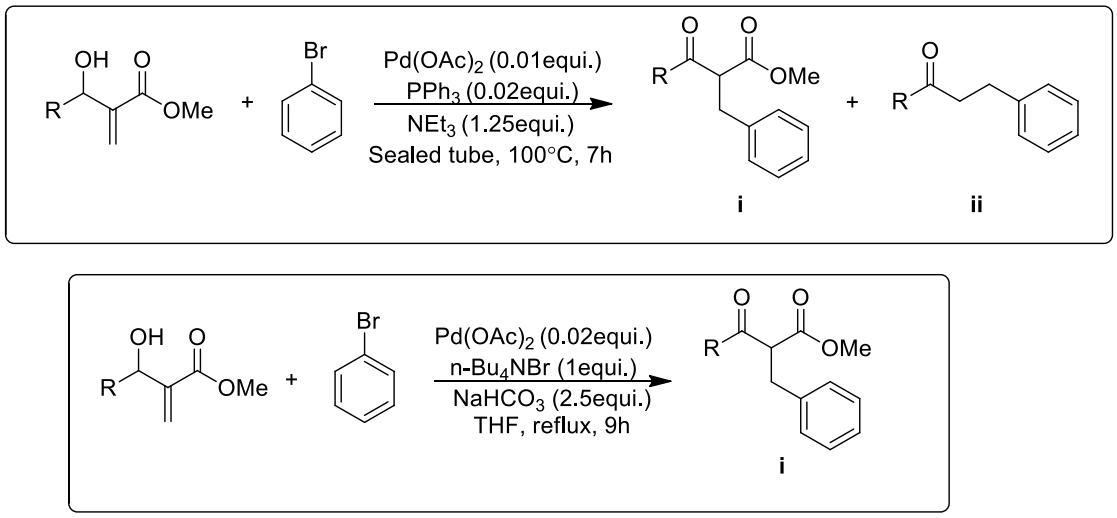
Scheme 6: Palladacycle formation for regioselectivity.

Further studies on the Heck reaction showed that the slight variation in the reaction conditions, in particular the ammonium salt alterations led to completely varied products. This was elaborated by Muzart et al when aryl halides and acrolein diethyl acetal was used, it resulted in formation of either cinnamaldehydes or 3-arylpropanoate esters based on the quaternary salt employed[17, 18]. In the presence of acetate anions and tetrabutylammonium cations in the reaction, esters were hydrolyzed to the corresponding acids (Scheme 7).



Scheme 7: Role of quaternary salt in Pd-catalysed arylation reaction

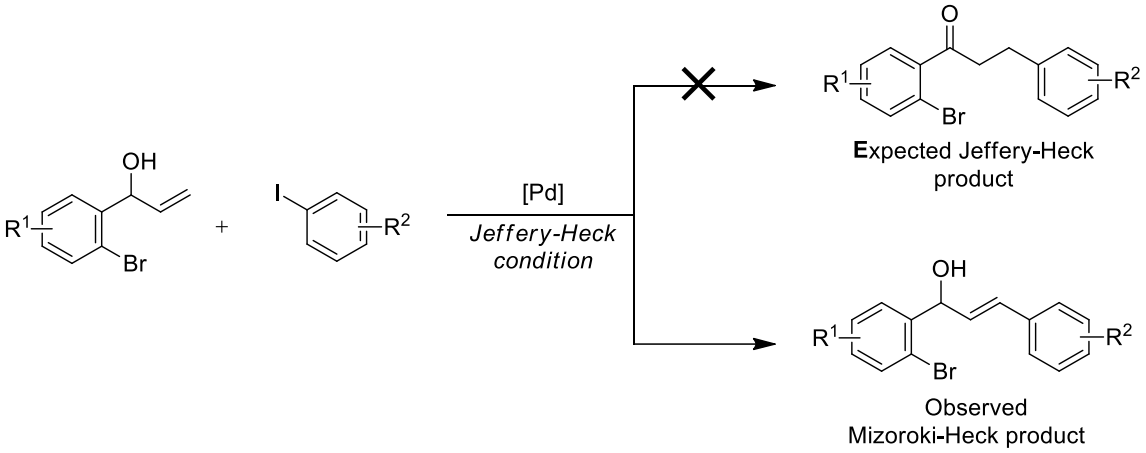
In 1984, Jeffery et al worked out that stoichiometric quantities of ammonium salts afforded the Heck arylation of allylic alcohols[19]. To check the product selectivity, he performed the reaction in the presence and absence of stoichiometric amounts of ammonium halides and indeed the results were astounding by the formation of sole Jeffery-Heck ketone[20] **i** as the product in the presence of quaternary ammonium salt (Scheme 8)[21, 22].



Scheme 8: Role of quaternary ammonium salt in Jeffery-Heck product formation

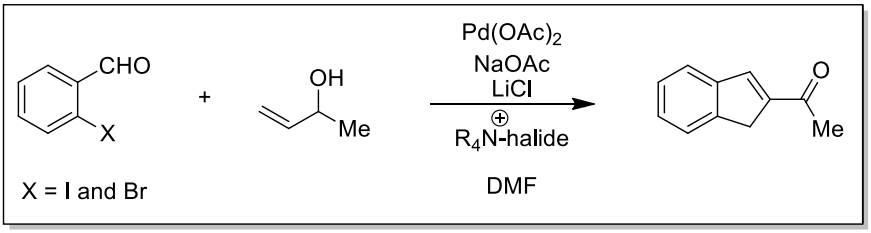
Being immensely interested in domino transition-metal catalysis[23], our group targeted synthesis of dihydrochalcones by employing [Pd]-catalyzed cross-coupling of aryl halides with allylic alcohols under traditional Jeffery-Heck conditions (Scheme 9). Surprisingly, instead of the standard Jeffery-Heck product i.e. β-aryl carbonyls, the reaction exclusively formed the β-aryl

allylic alcohol and was isolated as the sole product[24]. Based on the careful study of the literature, it was revealed that the usual Heck followed by double bond isomerization to give the carbonyl compounds is observed in particular for the substrates having no *ortho*-substituents on the aromatic ring of the allylic alcohols. Hence in the presence of *ortho*-bromo substituent, due to the bulky nature of the bromine group, the aromatic moiety confines the rotation around C-C bond of the PdCH−CH(OH)Ar intermediate, thus leading to Mizoroki-Heck product (Scheme 9).



Scheme 9: Synthesis of dihydrochalcones by [Pd]-catalyzed cross-coupling of aryl halides with allylic alcohols

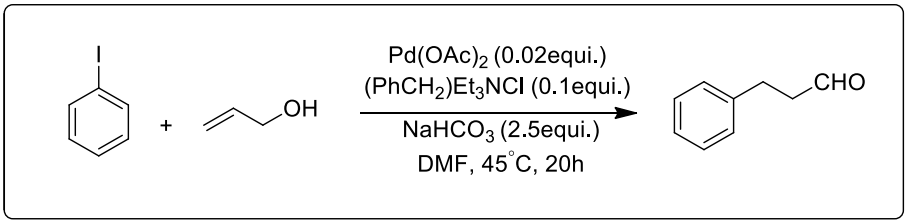
Another very interesting result was observed by Tu et al during the synthesis of 2-acyl-1H-indenes via one-pot palladium-catalysed tandem Heck-aldol reaction[25]. *O*-halogenated benzaldehydes were treated with prop-2-en-1-ols in a one-pot palladium-catalysed arylation, using tetrabutylammonium chloride and LiCl as additives, and it resulted in unusual 2-acyl-1H-indenes (Scheme 10)[26]. This was explained on the basis of tandem Heck–aldol sequence. The reaction initially underwent the usual Jeffery-Heck reaction followed by the intramolecular aldol condensation resulting in the indene formation[26].



Scheme 10: Indene formation by tandem Heck–aldol reaction

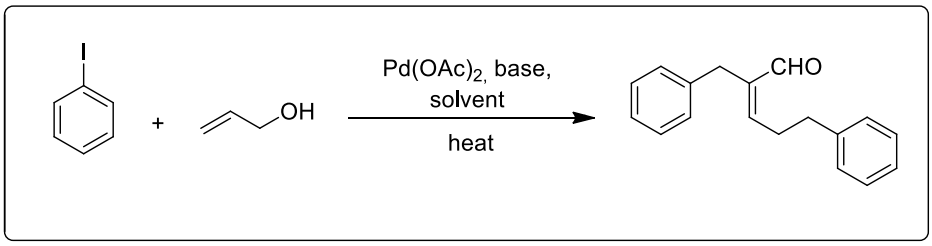
Hence, keeping in view the significant role played by the reaction conditions and the substrate substituents we planned to extend the study of Jeffery-Heck reaction under some unique diversified

conditions. We initiated our study by performing the reaction between the iodoarene and simple allyl alcohol in the presence of palladium acetate, sodium bicarbonate and quaternary ammonium salts to result in the formation of corresponding aldehyde[27].



Scheme 11: Typical Jeffery-Heck[28] reaction of iodoarene and allyl alcohol.

Under slightly modified conditions, by varying base to trimethylamine in the absence of quaternary salt, the reaction when performed at a higher temperature of 100 ^{o}C led to formation of altogether novel α,β-unsaturated aldehyde.



Scheme 12: Unusual α,β-unsaturated aldehyde formation.

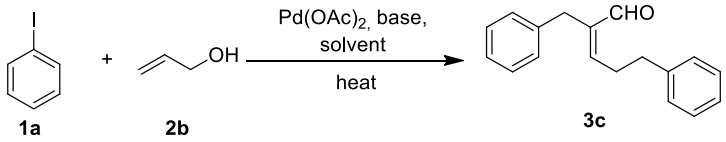
This result was quite astonishing as it varied from the classical Jeffery product. But this can be explained on the basis that as the reaction conditions varied and in the absence of the quaternary salt, the Jeffery Heck product might have undergone the typical intermolecular aldol condensation reaction in-situ and thus formed the unexpected tandem Heck-aldol product **xx**.

RESULTS AND DISCUSSION

To find out the best optimized reaction conditions for the formation of **3**, iodobenzene **1a** was chosen as model and reacted with the allyl alcohol **2** (Scheme 13) under different reaction conditions in the presence of base using $Pd(OAc)_2$ as a catalyst and the results are summarized in Table 1.

Initially, the reaction when performed in various solvents like methanol, ethanol and toluene using $Pd(OAc)_2$ in catalytic quantity with triethylamine as base did not result in the formation of the required product **3a** (Table 1, entries 1, 2 & 3). Later we moved over to use DIPEA as the base and in the presence of DMF solvent at highly increased temperature but the result was not satisfying and led to an unclean drag on TLC (Table 1, entry 4). This made us realize that probably the temperature conditions were too harsh for the highly reactive aldehyde to sustain. Hence we switched back to use triethylamine in DMF at 80 ^oC and fortunately it resulted in the formation of the required Heck-aldol product although in moderate yields (Table 1, entry 5). Upon a meager increase in the temperature to 100 ^oC and maintaining the other conditions standard, the yield of **3a** was improvised to a moderate level (Table 1, entry 6). In an aim to further increase the yield, we tried DIPEA in CH_3CN solvent at 100 ^oC, but the reaction did not prove to be of any benefit in improving the yield (Table 1, entry 7).

Thus, the best optimized reaction conditions for the formation of the product **3a** were identified as given in table 1, entry 6. It was then aimed to check the scope and the feasibility of the reaction by applying the optimized conditions to the various other aryl halides **1**.



Entry	Catalyst (5 mol %)	Base (equiv)	Solvent (mL)	Temerature (°C)	Time (h)	Yield (%)[a]
1.	$Pd(OAc)_2$	Et_3N	MeOH	60	24	-
2.	$Pd(OAc)_2$	Et_3N	EtOH	70	24	-
3.	$Pd(OAc)_2$	Et_3N	toluene	110	24	-
4.	$Pd(OAc)_2$	DIPEA	DMF	140	15	-
5.	$Pd(OAc)_2$	Et_3N	DMF	80	24	66
6.	$Pd(OAc)_2$	Et_3N	DMF	100	24	73
7.	$Pd(OAc)_2$	DIPEA	CH_3CN	110	24	69

Table 1: Optimization conditions for the preparation of substituted acroleins: [a] Isolated yields of the pure product.

Scope and limitations of the method:

The scope and limitation of the method was determined when the best optimized reaction conditions were employed on different iodoarenes with ally alcohol and the results obtained are depicted in the table 2. The methodology was found to be highly amenable and resulted in various substituted acroleins **3**.

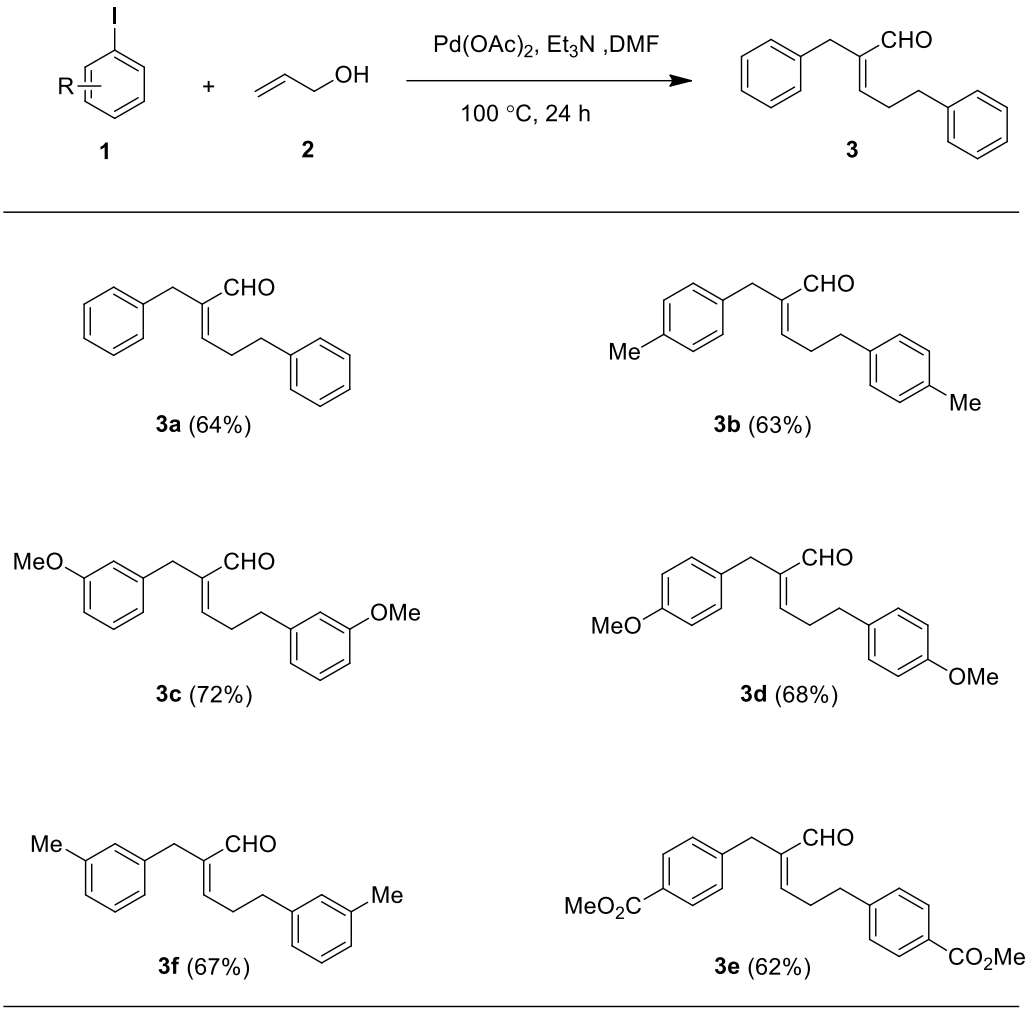


Table 2: Table of acroleins **3** formed from the arylation of aryl iodides **1** and ally alcohol **2**.

Plausible mechanism of the substituted acroleins (3)

The plausible mechanism of the reaction initially involves the insertion of palladium catalyst to form the pallada complex A, which would form complex B, upon coupling/addition of allyl alcohol **2**. The complex B is expected to undergo the internal rotation in a usual Heck manner to give palladium complex C. Further, the reductive elimination generates back the palladium catalyst *insitu* and also generates the corresponding aldehyde D. The resulting aldehyde D is

expected to further undergo intermolecular condensation reaction to result in the tandem Jeffery-Heck-aldol product **3a**.

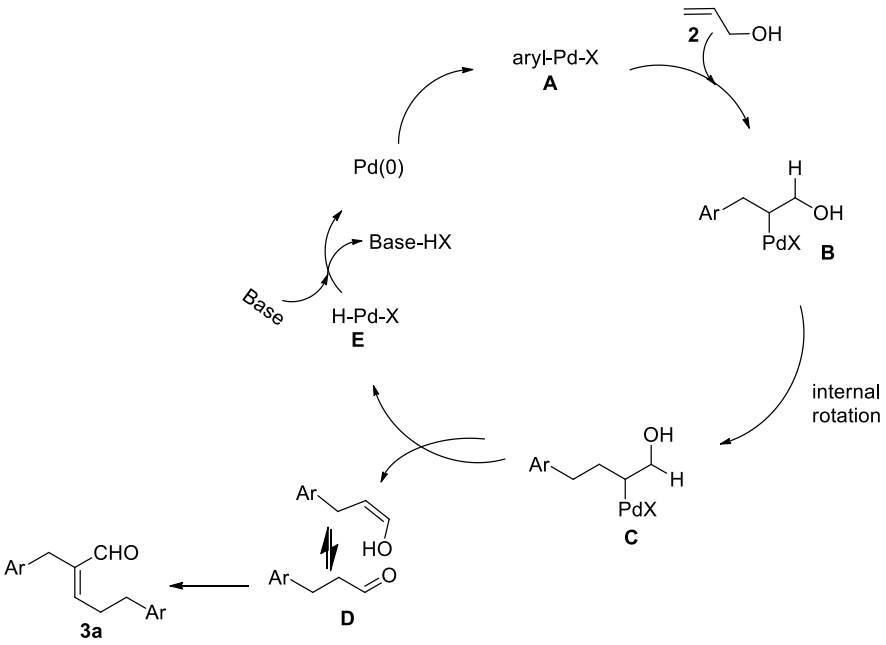


Figure 2: Plausible mechanism of formation of **3a**.

CONCLUSION:

In summary, we have developed a one-pot method for the synthesis of functionalized acroleins via C-C bond formation between aryl iodides and allylic alcohols using the unusual and modified Jeffery-Heck protocol. Interestingly, under our researched conditions the Jeffery-Heck product generated further underwent a self-aldol reaction and thus furnished the substituted acroleins with good yields. These (acroleins) showed significant utility as good chemical precursors in organic synthesis of various commercial compounds.

To best of our knowledge, this domino one-pot Jeffery-Heck followed by aldol condensation was not reported in the literature and further developments in this protocol are needed to be researched especially in order to improve upon the yields and the scope of the reaction.

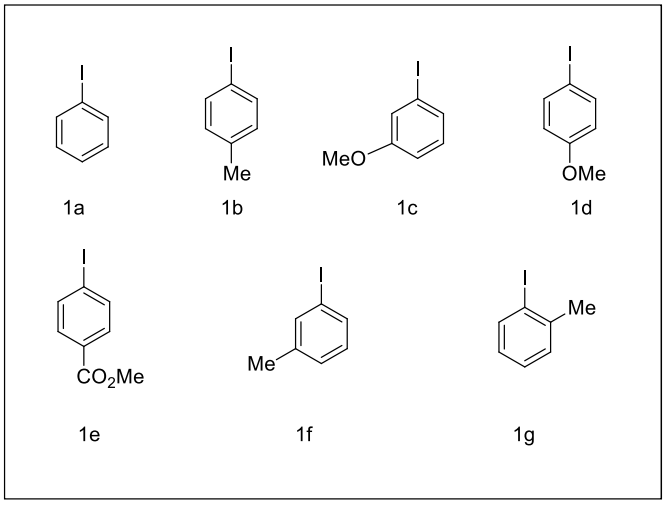
1.6 EXPERIMENTAL SECTION:

General: IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H =0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{13}C NMR, the nature of carbons (C, CH, CH_2 and CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH_2) and q = quartet (for CH_3). In the ^{1}H-NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui =quintet, sept = septet, dd = doublet of doublet, m = multiplet and br. s = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C CPD and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF electron spray ionization (ESI) mode and atmospheric pressure chemical ionization (APCI) modes. All small scale dry reactions were carried out using Schlenk tubes under inert atmosphere. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate as eluents. Reactions were generally run under argon or a nitrogen atmosphere. Solvents were distilled prior to use; petroleum ether with a boiling range of 60 to 80 °C was used. N, N-Dimethylformamide (DMF) was dried over CaH_2 and triethylamine was distilled. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

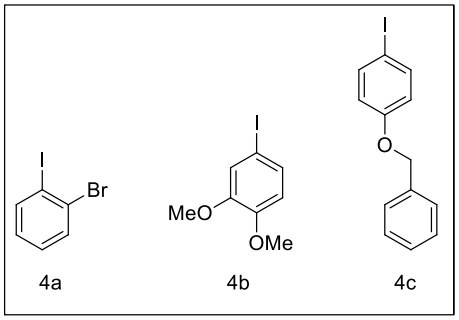
GP-1 (General procedure for preparation of (2*Z*)-2-benzyl-5-phenylpent-2enal): In an oven dried Schlenk tube, when aromatic iodobenzene **1** (100 mg, 0.42-0.49 mmol), allyl alcohol **2** (0.17-, 0.2 ml,45 mmol) and dry N, N-Dimethylformamide (DMF) (0.4 mL) were added followed by base triethylamine (0.34 mL, 1.25 mmol) and catalyst $Pd(OAc)_2$ at room temperature under nitrogen atmosphere. The reaction mixture was stirred at room temperature and then heated in an oil bath at 90 °C for 24 h and monitored by TLC. Then, the mixture was quenched by the addition of aqueous $NaHCO_3$ solution and then extracted with ethyl acetate (3 × 15 mL). The organic layer

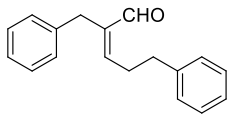
was washed with saturated NaCl solution, dried (Na_2SO_4) and filtered. Evaporation of the solvent under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the acrolein **3** (60-70%).

The following iodo compounds **1a-1g**, which are used as starting materials, are commercially available.



The following iodo compounds **4a–4c**, which have been prepared were reported in literature.





3a

(2*Z*)-2-benzyl-5-phenylpent-2-enal (3a):

GP-1 was carried out with iodobenzene **1a** (100 mg, 0.49 mmol), allyl alcohol **2a** (142 mg, 2.45 mmol), triethylamine (247 mg, 2.45 mmol) and palladium acetate (5.5 mg, 5 mol%) followed

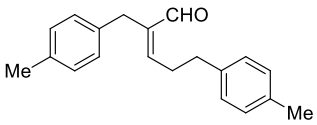
by DMF (0.4 mL) at 90 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to petroleum ether/ethyl acetate, 95:5) furnished the acrolein derivative **3a** (30 mg, 64%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 97:3), R_f(**1a**)=0.70, R_f(**3a**)=0.35, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3027, 2921, 1639, 1680, 1453, 1136, 909, 883, 732 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=9.41 (s, 1H, CHO), 7.27 (dd, 2H, *J*=7.3 and 7.3 Hz, Ar-H), 7.24–7.03 (m, 8H, Ar-H), 6.59 (dd, 1H, *J*=7.3 and 6.4 Hz, C*H*=CCHO), 3.55 (s, 2H, ArCH_2CCHO), 2.80–2.60 (m, 4H, ArCH_2CH_2) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=194.5 (d, CHO), 154.7 (d, *C*H=CCHO), 142.7 (s, CH=*C*CHO), 140.4 (s, Ar-C), 139.0 (s, Ar-C), 128.5 (d, 2C, 2 × Ar-CH), 128.4 (d, 2C, 2 × Ar-CH), 128.3 (d, 2C, 2 × Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 126.3 (d, Ar-CH), 126.0 (d, Ar-CH), 34.4 (t, Ar*C*H_2CCHO), 31.0 (t, CH_2), 29.6 (t, CH_2) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{18}H_{19}O]^+$=$[M+H]^+$: 251.1430; found 251.1427.



3b

(2Z)-2-(4-methylbenzyl)-5-(4-methylphenyl) pent-2-enal (3b):

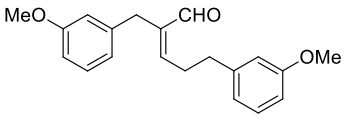
GP-1 was carried out with iodotoluene **1b** (100 mg, 0.46 mmol), allyl alcohol **2a** (133 mg, 2.3 mmol), triethylamine (232 mg, 2.3 mmol) and palladium acetate (5.1 mg, 5 mol%) followed by DMF (0.4 mL) at 90 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to petroleum ether/ethyl acetate, 95:5) furnished the acrolin derivative **3b** (40 mg, 63%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 97:3), R_f(**1b**)=0.72, R_f(**3b**)=0.36, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2919, 2850, 1683, 1514, 1138, 1108, 1021, 801, 721 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=9.42 (s, 1H, CHO), 7.00–6.80 (m, 8H, Ar-H), 6.59 (dd, 1H, *J*=7.3 and 6.4 Hz, C*H*=CCHO), 3.53 (s, 2H, ArCH_2CCHO), 2.80–2.65 (m, 4H, ArCH_2CH_2), 2.32 (s, 3H, ArCH_3), 2.28 (s, 3H, ArCH_3) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=194.7 (d, CHO), 154.7 (d, *C*H=CCHO), 142.9 (s, CH=*C*CHO), 137.4 (s, Ar-C), 136.0 (s, Ar-C), 135.9 (s, Ar-C), 135.5 (s, Ar-C), 129.2 (d, 2C, 2 × Ar-CH), 129.1 (d, 2C, 2 × Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 128.1 (d, 2C, 2 × Ar-CH), 34.0 (t, Ar*C*H_2CCHO), 31.1 (t, CH_2), 29.2 (t, CH_2), 21.0 (q, ArCH_3), 20.9 (q, ArCH_3) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{20}H_{26}NO]^+$=$[M+NH_4]^+$: 296.2009; found 296.2012.



3c

(2*Z*)-2-(3-methoxybenzyl)-5-(3-methoxyphenyl) pent-2 enal (3c):

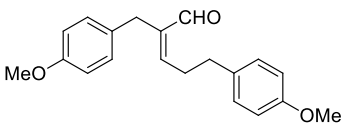
GP-1 was carried out with 3-iodoanisole **1c** (100 mg, 0.43 mmol), allyl alcohol **2a** (124 mg, 2.14 mmol), triethylamine (216 mg, 2.14 mmol) and palladium acetate (4.9 mg, 5 mol%) followed by DMF (0.4 mL) at 90 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to petroleum ether/ethyl acetate, 94:6) furnished the acrolin derivative **3c** (48 mg, 72%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 97:3), R_f(**1c**)=0.65, R_f(**3c**)=0.32, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2924, 2835, 1682, 1583, 1454, 1258, 1150, 778 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=9.44 (s, 1H, CHO), 7.20 (dd, 1H, *J*=8.3 and 7.8 Hz, Ar-H), 7.14 (dd, 1H, *J*=7.8 and 7.8 Hz, Ar-H), 6.80–6.65 (m, 6H, Ar-H), 6.61 (dd, 1H, *J*=7.3 and 6.4 Hz, C*H*=CCHO), 3.78 (s, 3H, ArOCH_3), 3.75 (s, 3H, ArOCH_3), 3.56 (s, 2H, ArCH_2CCHO), 2.80–2.65 (m, 4H, ArCH_2CH_2) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=194.5 (d, CHO), 159.7 (s, Ar-C), 159.6 (s, Ar-C), 154.8 (d, *C*H=CCHO), 142.6 (s, CH=*C*CHO), 142.0 (s, Ar-C), 140.6 (s, Ar-C), 129.6 (d, Ar-CH), 129.4 (d, Ar-CH), 120.7 (d, Ar-CH), 114.2 (d, Ar-CH), 114.1 (d, Ar-CH), 111.5 (d, Ar-CH), 111.4 (d, Ar-CH), 55.1 (2 × q, 2C, 2 × ArOCH_3), 34.4 (t, Ar*C*H_2CCHO), 30.9 (t, CH_2), 29.6 (t, CH_2) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{20}H_{23}O_3]^+$=$[M+H]^+$: 311.1642; found 311.1637.



3d

(2Z)-2-(4-methoxybenzyl)-5-(4-methoxyphenyl) pent-2-enal (3d):

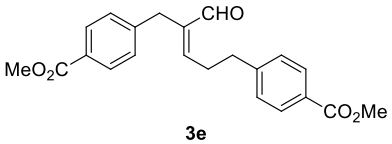
GP-1 was carried out with 4-iodoanisole **1d** (100 mg, 0.43 mmol), allyl alcohol **2a** (124 mg, 2.14 mmol), triethylamine (216 mg, 2.14 mmol) and palladium acetate (4.8 mg, 5 mol%) followed by DMF (0.4 mL) at 90 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to petroleum ether/ethyl acetate, 94:6) furnished the acrolin derivative **3d** (45 mg, 68%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate 97:3), R_f(**1d**)=0.65, R_f(**3d**)=0.32, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=2921, 2850, 1678, 1601, 1246, 1174, 957, 808 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=9.41 (s, 1H, CHO), 7.05 (d, 2H, *J*=8.8 Hz, Ar-H), 7.00 (d, 2H, *J*=8.8 Hz, Ar-H), 6.82 (d, 2H, *J*=8.8 Hz, Ar-H), 6.75 (d, 2H, *J*=8.8 Hz, Ar-H), 6.57 (dd, 1H, *J*=7.3 and 6.4 Hz, C*H*=CCHO), 3.79 (s, 3H, $ArOCH_3$), 3.75 (s, 3H, $ArOCH_3$), 3.49 (s, 2H, ArCH_2CCHO), 2.80–2.60 (m, 4H, ArCH_2CH_2) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=194.7 (d, CHO), 158.1 (s, Ar-C), 157.9 (s, Ar-C), 154.6 (d, *C*H=CCHO), 143.1 (s, CH=*C*CHO), 132.5 (s, Ar-C), 131.1 (s, Ar-C), 129.3 (d, 2C, 2 × Ar-CH), 129.2 (d, 2C, 2 × Ar-CH), 113.9 (d, 2C, 2 × Ar-CH), 113.8 (d, 2C, 2 × Ar-CH), 55.2 (2 × q, 2C, 2 × $ArOCH_3$), 33.6 (t, Ar*C*H_2CCHO), 31.2 (t, CH_2), 28.7 (t, CH_2) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{20}H_{23}O_3]^+$=$[M+H]^+$: 311.1642; found 311.1647.



3e

(Z)-dimethyl 4,4'-(2-formylpent-2-ene-1,5-diyl) dibenzoate (3e):

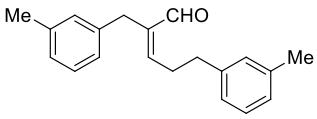
GP-1 was carried out with 4-iodomethylbenzoate **1e** (100 mg, 0.38 mmol), allyl alcohol **2a** (110 mg, 1.90 mmol), triethylamine (224 mg, 1.90 mmol) and palladium acetate (4.3 mg, 5 mol%) followed by DMF (0.4 mL) at 90 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to petroleum ether/ethyl acetate, 92:8) furnished the acrolin derivative **3e** (54 mg, 72%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 95:5), R_f(**1e**)=0.70, R_f(**3e**)=0.35, UV detection].

IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3027, 2921, 1639, 1680, 1453, 1136, 909, 883, 732, 696, 617 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=9.43 (s, 1H, CHO), 7.93 (d, 2H, *J*=8.3 Hz, Ar-H), 7.87 (d, 2H, *J*=8.3 Hz, Ar-H), 7.17 (d, 2H, *J*=8.3 Hz, Ar-H), 7.12 (d, 2H, *J*=8.3 Hz, Ar-H), 6.61 (dd, 1H, *J*=7.3 and 7.3 Hz, C*H*=CCHO), 3.89 (s, 3H, $COOCH_3$), 3.87 (s, 3H, $COOCH_3$), 3.59 (s, 2H, ArCH_2CCHO), 2.82–2.60 (m, 4H, ArCH_2CH_2) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): δ=194.1 (d, CHO), 166.9 (s, O=C–O), 166.8 (s, O=C–O), 154.3 (d, *C*H=CCHO), 145.5 (s, CH=*C*CHO), 144.2 (s, Ar-C), 142.3 (s, Ar-C), 129.9 (d, 2C, 2 × Ar-CH), 129.8 (d, 2C, 2 × Ar-CH), 128.4 (s, Ar-C), 128.3 (d, 2C, 2 × Ar-CH), 128.2 (d, 2C, 2 × Ar-CH), 128.1 (s, Ar-C), 52.0 (q, COO*C*H_3), 51.9 (q, COO*C*H_3), 34.3 (t, Ar*C*H_2CCHO), 30.6 (t, CH_2), 29.6 (t, CH_2) ppm.

HR-MS (ESI$^+$): m/z calculated for $[C_{22}H_{23}O_5]^+$=$[M+H]^+$: 367.1540; found 367.1534.



3f

(2*Z*)-2-benzyl-5-phenylpent-2-enal (3f):

GP-1 was carried out with 3-iodotoluene **1f** (100 mg, 0.45 mmol), allyl alcohol **2a** (142 mg, 2.45 mmol), triethylamine (247 mg, 2.45 mmol) and palladium acetate (5.5 mg, 5 mol%) followed by DMF (0.4 mL) at 90 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 97:3 to petroleum ether/ethyl acetate, 95:5) furnished the acrolin derivative **3f** (31 mg, 67%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate 90:10), R_f(**1f**)=0.70, R_f(**3f**)=0.35, UV detection].

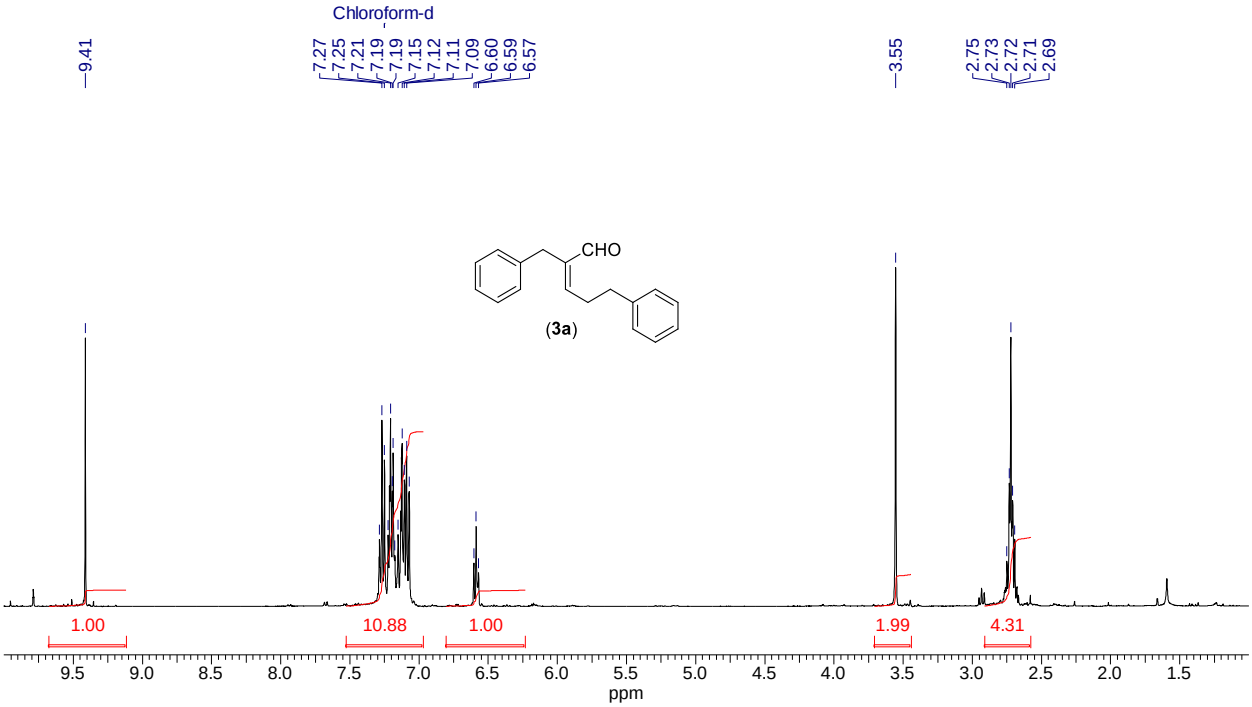
IR (neat; MIR-ATR, 4000–600 cm^{-1}): ν_{max}=3341, 2923, 2855, 1723, 1682, 1639, 1512, 1458, 777, 698 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=9.44 (s, 1H, CHO), 7.18 (dd, 1H, *J*=7.8 and 7.3 Hz, Ar-H), 7.12 (dd, 1H, *J*=7.3 and 7.3 Hz, Ar-H), 7.06–6.80 (m, 6H, Ar-H), 6.61 (dd, 1H, *J*=7.3 and 6.4 Hz, C*H*=CCHO), 3.55 (s, 2H, ArCH_2CCHO), 2.80–2.60 (m, 4H, ArCH_2CH_2), 2.32 (s, 3H, ArCH_3), 2.28 (s, 3H, ArCH_3) ppm.

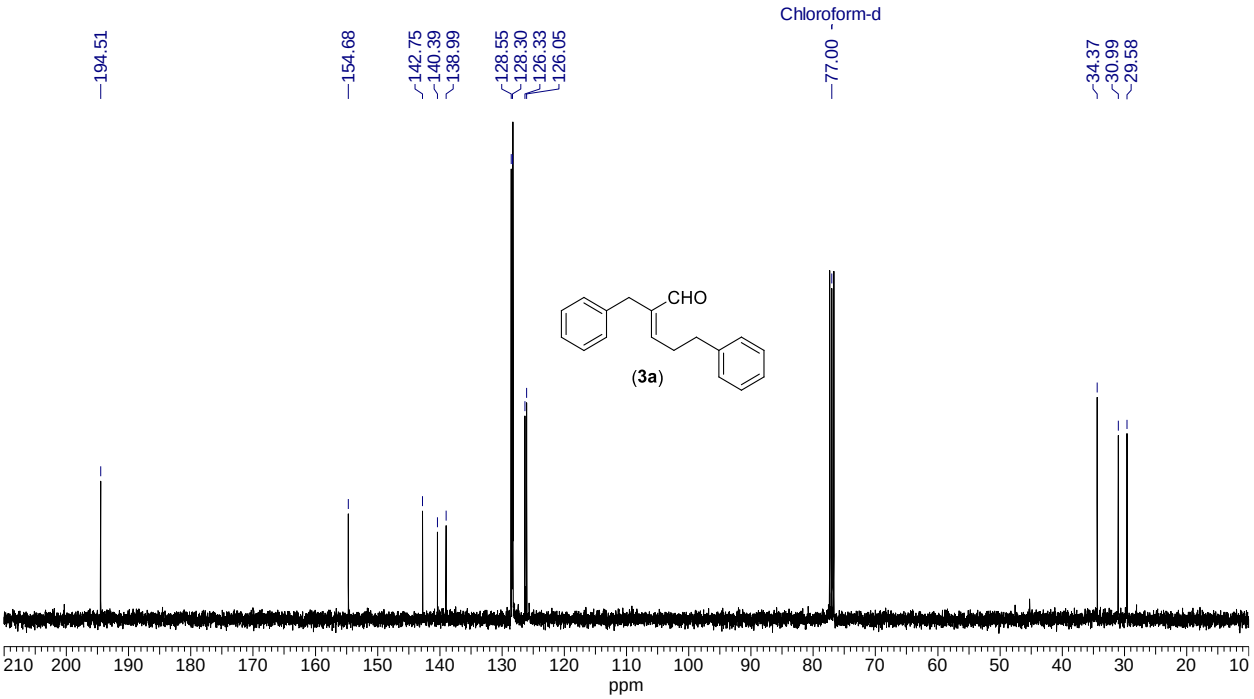
^{13}C NMR ($CDCl_3$, 100 MHz): δ=194.7 (d, CHO), 154.9 (d, *C*H=CCHO), 142.7 (s, CH=*C*CHO), 140.4 (s, Ar-C), 139.0 (s, Ar-C), 138.2 (s, Ar-C), 138.0 (s, Ar-C), 129.1 (d, Ar-CH),

129.0 (d, Ar-CH), 128.5 (d, Ar-CH), 128.3 (d, Ar-CH), 127.1 (d, Ar-CH), 126.8 (d, Ar-CH), 125.3 (d, Ar-CH), 125.2 (d, Ar-CH), 34.3 (t, Ar*C*H_2CCHO), 31.1 (t, CH_2), 29.5 (t, CH_2) 21.4 (2 × q, 2C, 2 × ArCH_3) ppm.

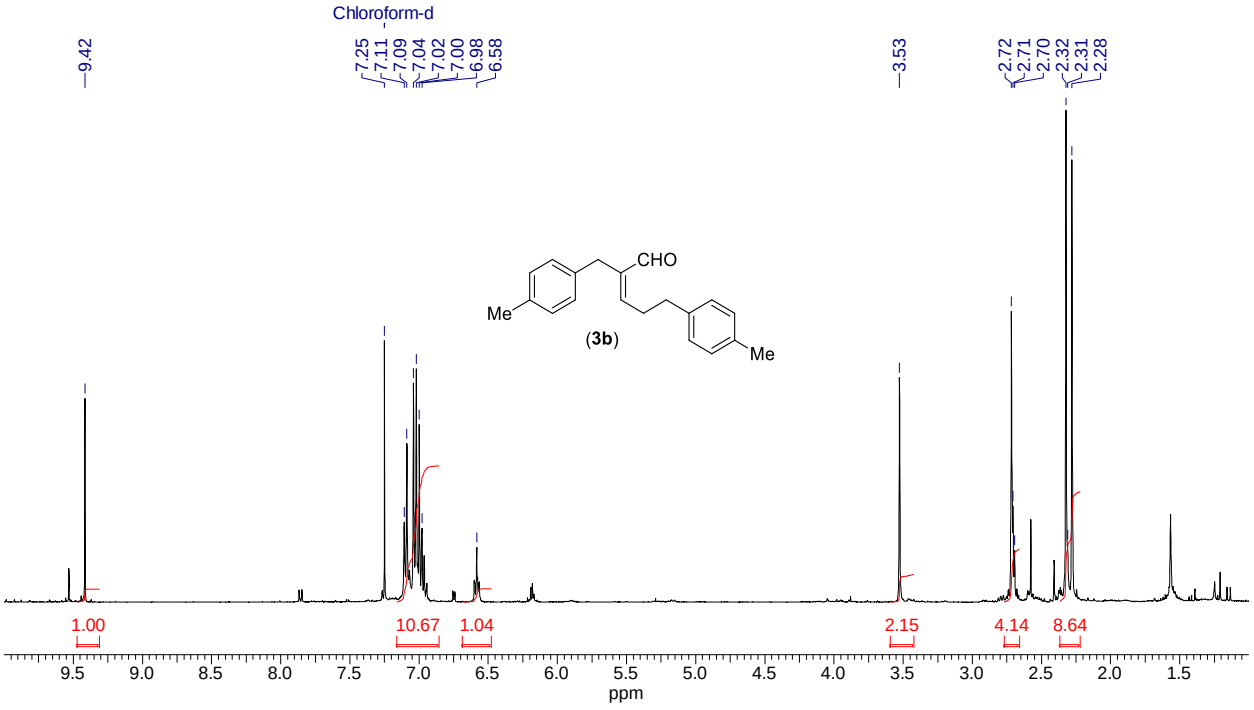
HR-MS (ESI$^+$): m/z calculated for $[C_{20}H_{26}NO]^+$=$[M+NH_4]^+$: 296.2009; found 296.2002.



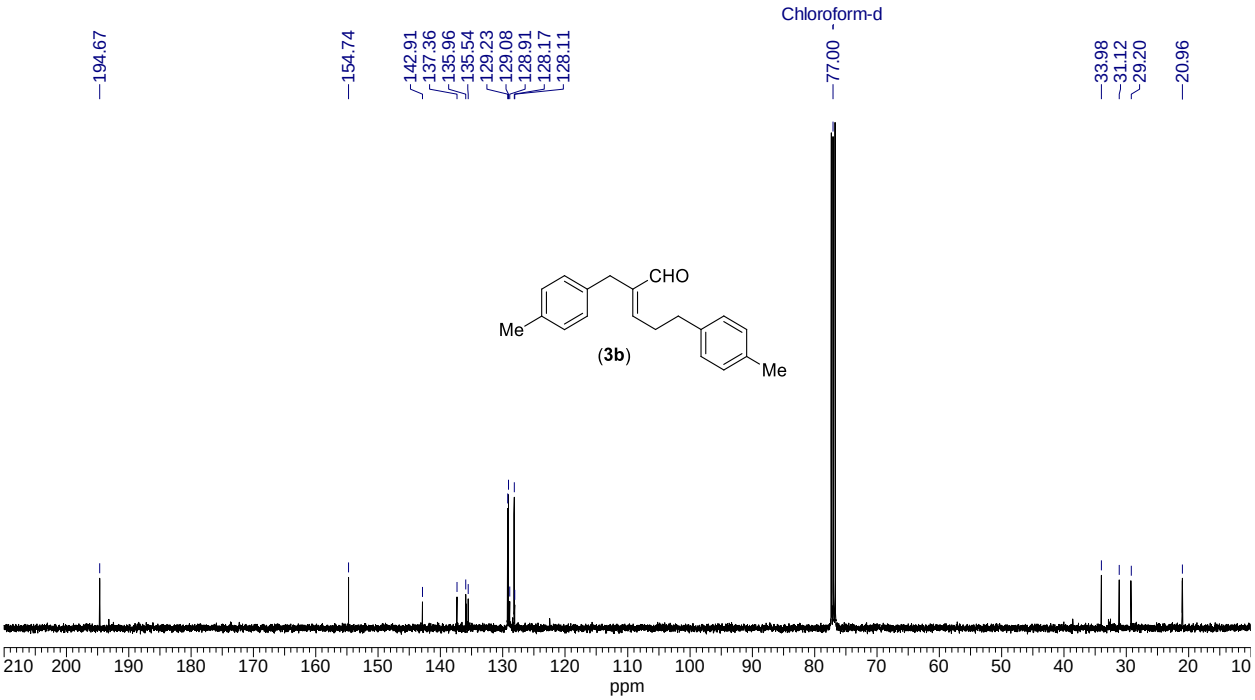
^{1}H NMR (400 MHz) spectrum of **3a** in $CDCl_3$



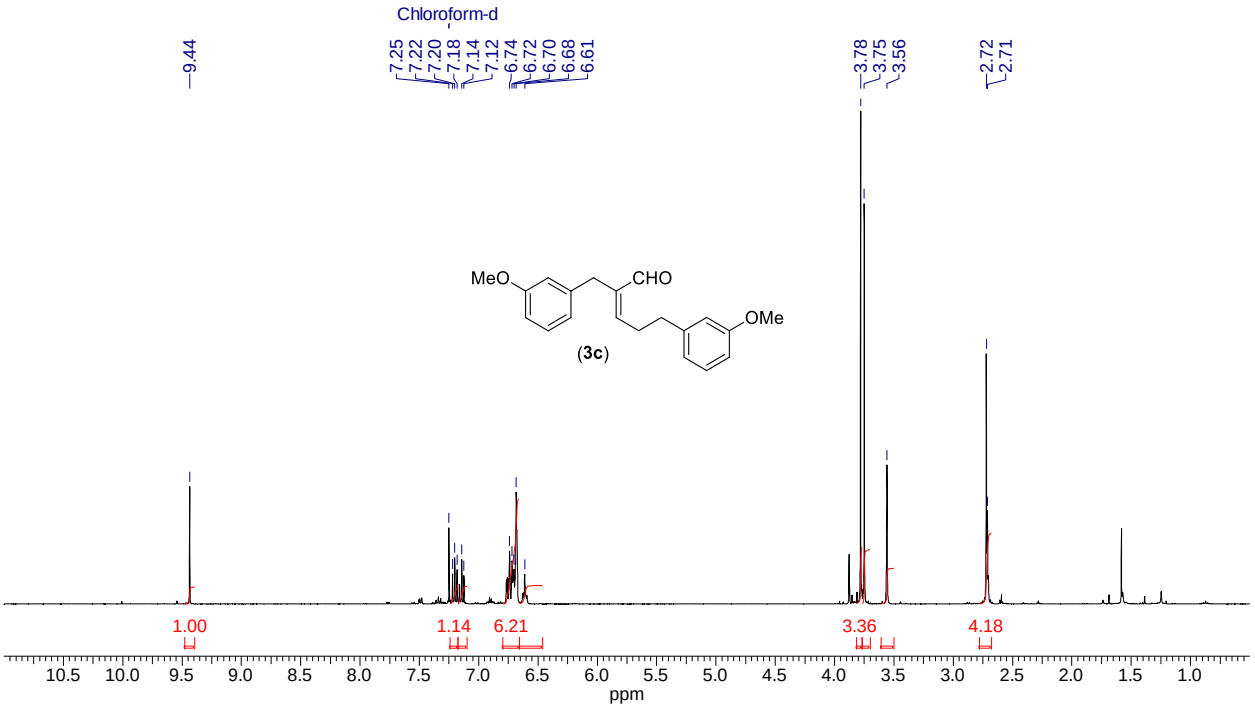
^{13}C NMR (100 MHz) spectrum of **3a** in $CDCl_3$



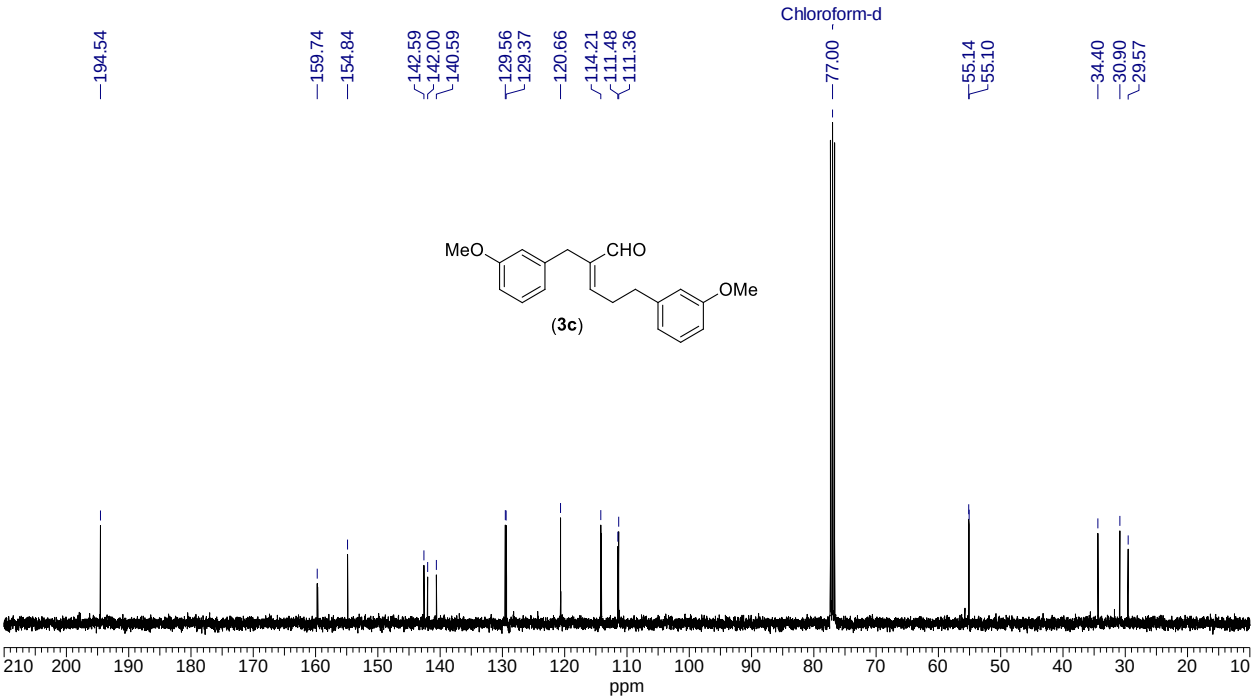
^{1}H NMR (400 MHz) spectrum of **3b** in $CDCl_3$



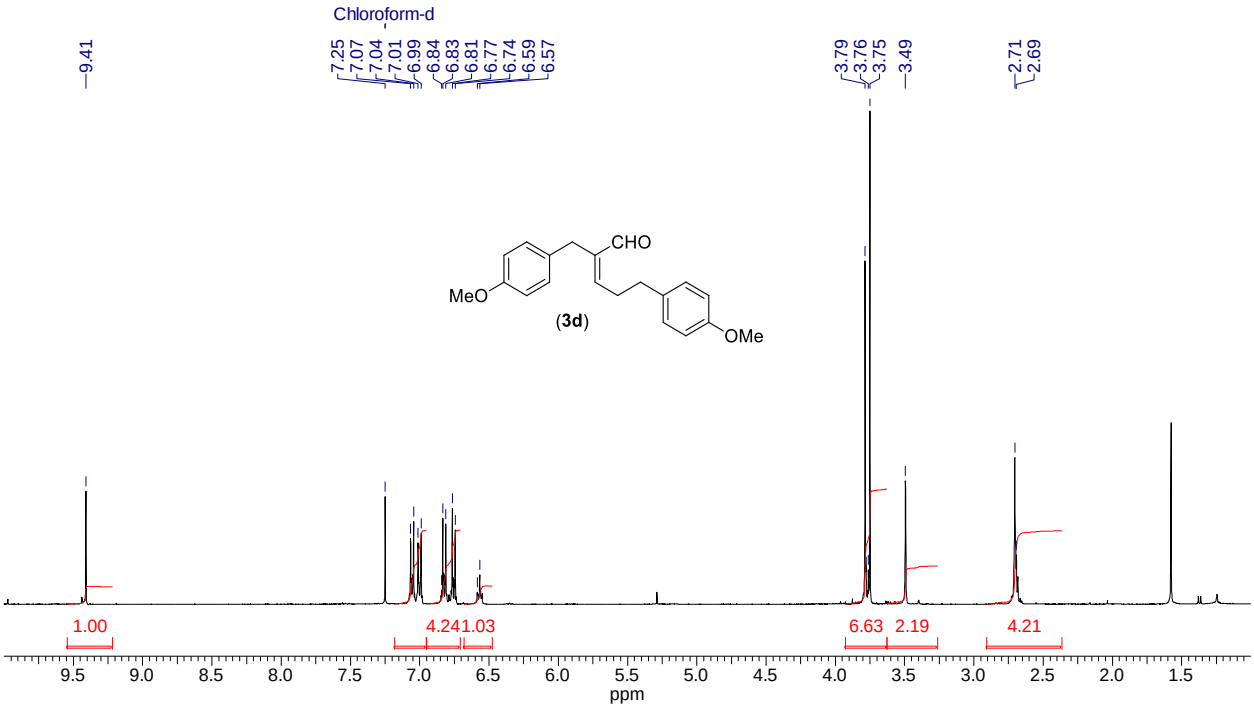
^{13}C NMR (100 MHz) spectrum of **3b** in $CDCl_3$



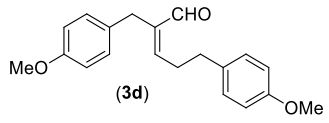
^{1}H NMR (400 MHz) spectrum of **3c** in $CDCl_3$

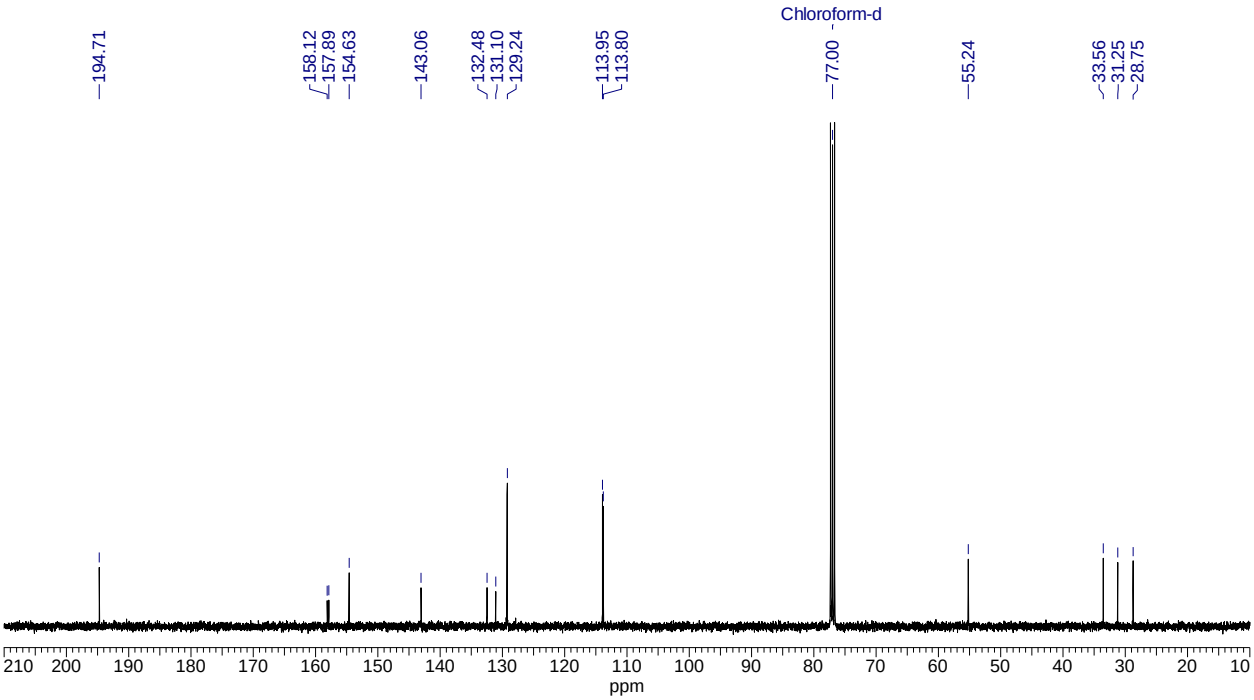


^{13}C NMR (100 MHz) spectrum of **3c** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of **3d** in $CDCl_3$





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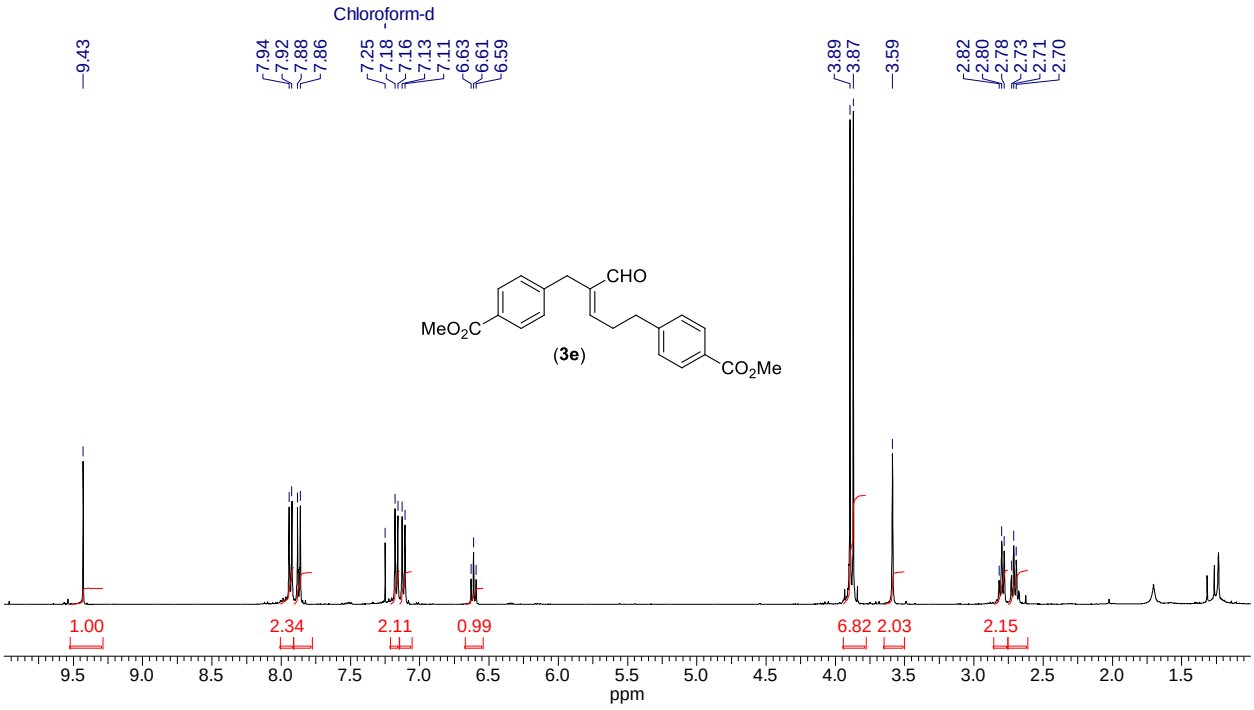
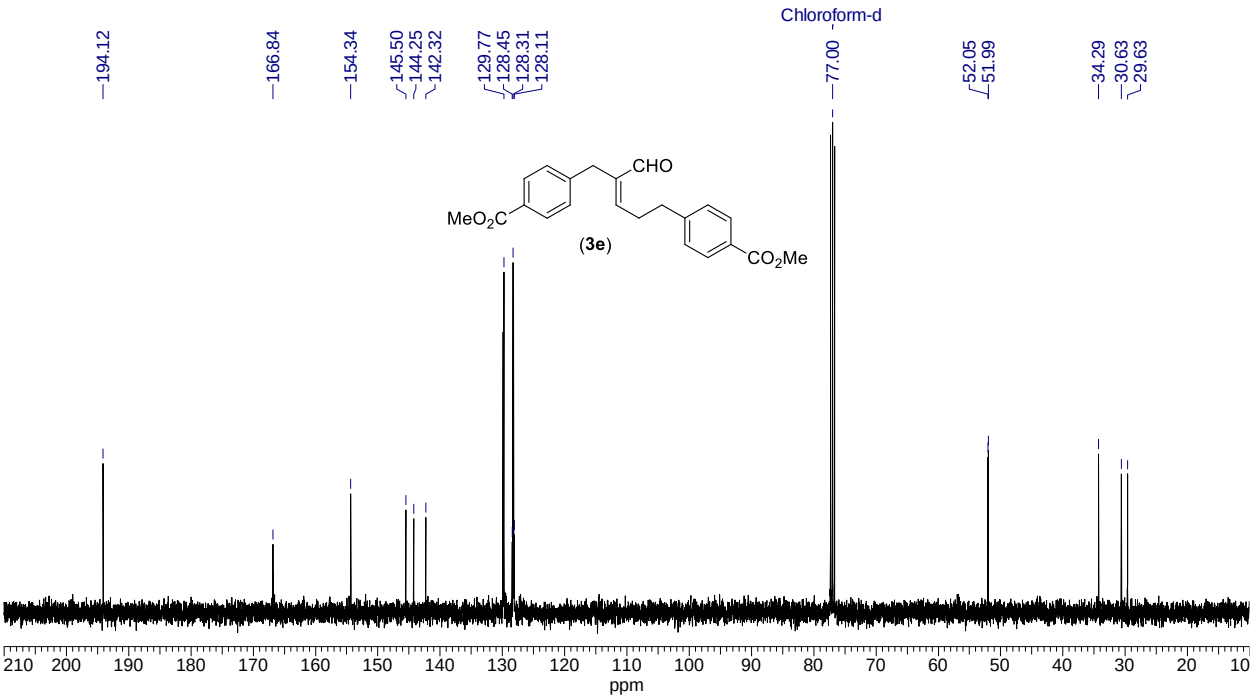
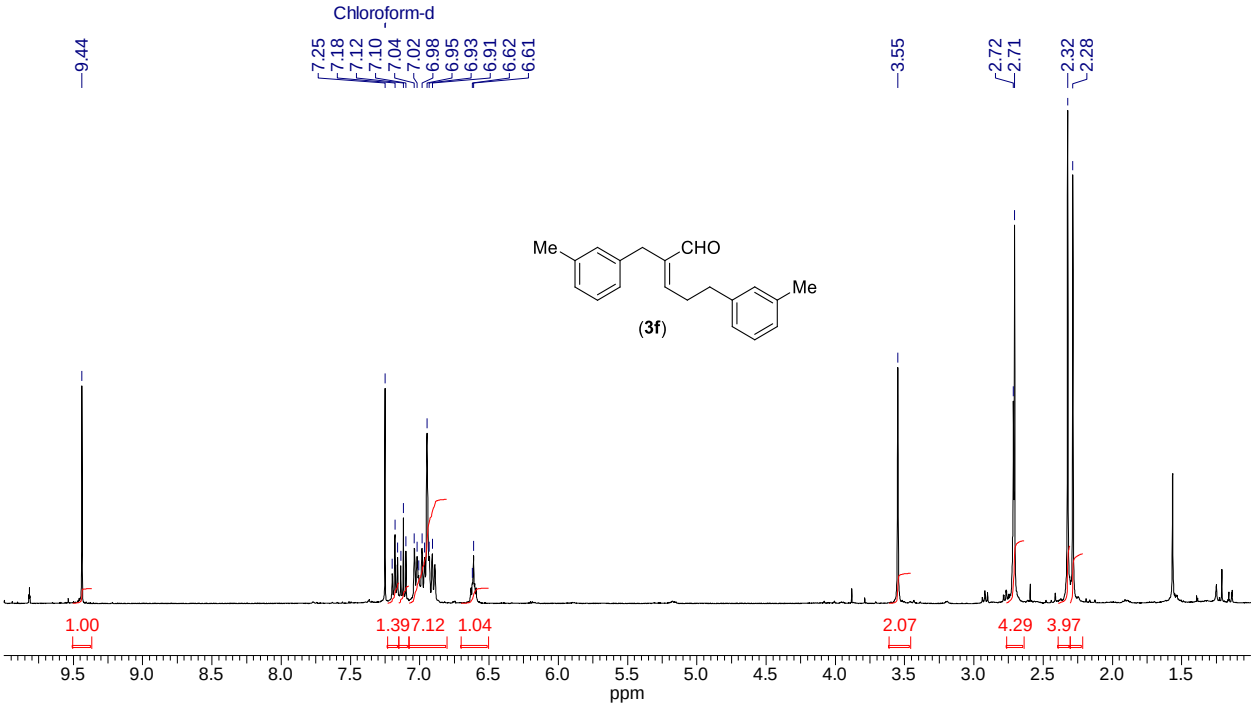


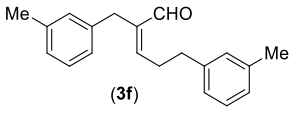
^{1}H NMR (400 MHz) spectrum of **3e** in $CDCl_3$

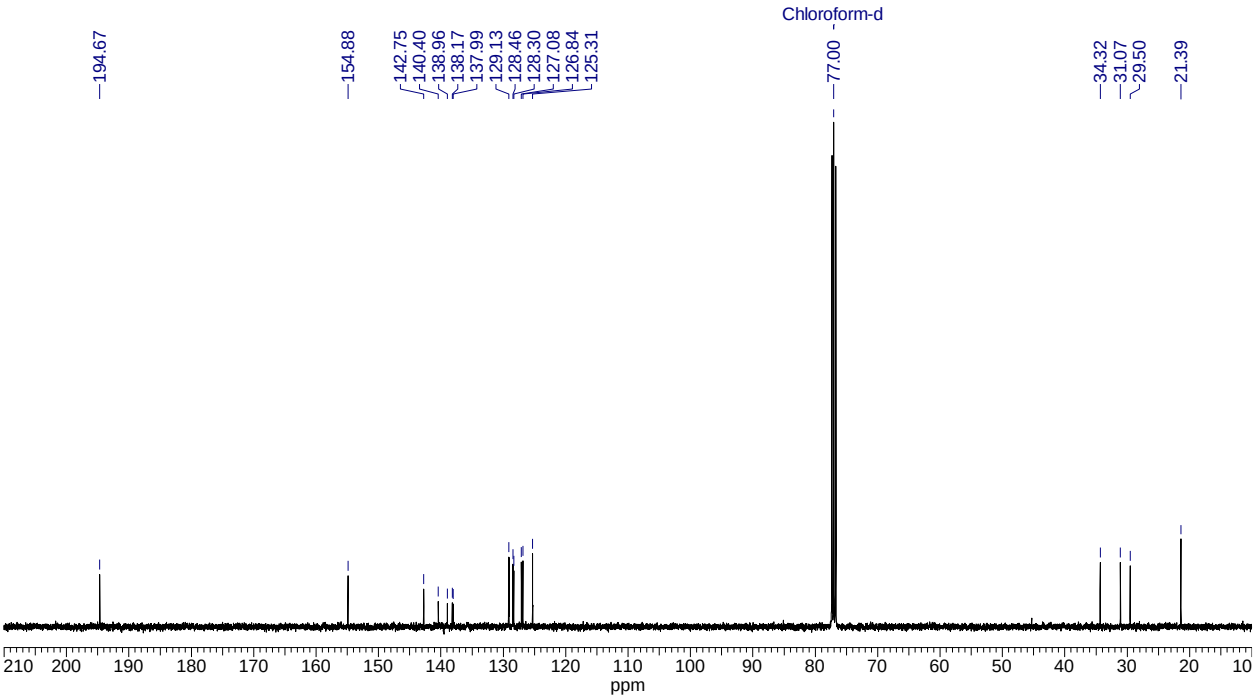


^{13}C NMR (100 MHz) spectrum of **3e** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of **3f** in $CDCl_3$





^{13}C NMR (100 MHz) spectrum of **3f** in $CDCl_3$

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