"Unexplored Olefin Oxidations with Oxone and Application of *α*-Diazocarbonyl Compounds in the Synthesis of *N*-Heterocycles"

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY (Ph.D.)
IN CHEMISTRY

TO

SAVITRIBAI PHULE PUNE UNIVERSITY

BY

Ravindra S. Phatake

Dr. C. V. Ramana

(Research Guide)

ORGANIC CHEMISTRY DIVISION
CSIR-NATIONAL CHEMICAL LABORATORY
PUNE–411008

January–2017

Dedicated To Friends

DECLARATION

The research work embodied in this thesis has been carried out at CSIR-National Chemical Laboratory, Pune under the supervision of **Dr. C. V. Ramana**, Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune– 411008. This work is original and has not been submitted in part or full, for any degree or diploma of this or any other university.

Organic Chemistry Division
CSIR-National Chemical Laboratory
Pune–411008
January–2016

(Ravindra S. Phatake)

Dr. C. V. Ramana

Phone: +91–20–25902577
+91–20–25903084
E–mail: vr.chepuri@ncl.res.in

CERTIFICATE

This is to certify that the work incorporated in this Ph.D. thesis entitled "**Unexplored Olefin Oxidations with Oxone and Application of *α*-Diazocarbonyl Compounds in the Synthesis of *N*-Heterocycles**" submitted by **Mr. Ravindra S. Phatake** to Savitribai Phule Pune University in fulfillment of the requirements for the award of the Degree of ***Doctor Of Philosophy***, embodies original research work under my supervision. We further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Any research material, text, illustration, table etc., used in the thesis from other sources, have been duly cited and acknowledged.

Ravindra S. Phatake
(Student)

Dr. C. V. Ramana
(Supervisor)

Acknowledgements

I would like to name a few people from the infinite personalities associated in the path of my research career and who have contributed enormously directly or indirectly for the success of the thesis.

It's a great privilege to convey my gratitude to my supervisor **Dr. C. V. Ramana** for his guidance and encouragement throughout my PhD tenure and believe this thesis would never be a success in the absence of his blessings. I would like to take this opportunity to thank other people who involved directly in my PhD career are Dr. Kumar Vanka, Dr. B. L. V. Prasad, Dr. Srinivasa Reddy, Dr. A. Sudalai, Dr. A. Biju, Dr. Pradip Kumar, Dr. Rajesh for their valuable teaching, suggestions in the course-work and colloquium seminars. It is my sole duty to show a token of appreciation to the division of organic chemistry, NMR, HRMS, and director of NCL for providing me all the facilities necessitated for the research work. The CSIR, New Delhi is also acknowledged for the financial supports. I am grateful to the staff members of organic division for their wholehearted help.

I sincerely acknowledge who taught me the *a-b-c-d* of the practical organic chemistry i.e. my senior Dr. Sachin Narute for his vast support from my first day in the lab. I can't forget to acknowledge the senior colleagues viz. Dr. Sunil Kumar Pandey, Dr. Rahul, Dr. Mangesh, Dr. Yadagiri, Dr. Suneel, Dr. Chandrababu, Dr. Yogesh, Dr. Shyam, Dr. Paresh, Dr. Jeetendra, Dr. Atul, Dr. Senthil Kumar, Dr. Suparna and Dr. Narendra for their motivational advices and unconditional supports. My special thanks must go to Dr. Pitambar for his inspirations and all kind of helps. I would like to thank all my colleagues Dinesh, Srinivas, Venkanna, Mahesh S., Mahesh S., Ketan A., Jyothi, Ravindra, Yadav, Manmath for creating merry-cheery environment throughout the clock and maintaining the lab as a family. I sincerely thank to my NCL friends Dr. Ravindra A, Dr. Komal, Dr. Kishor, Dr. Sagar, Dr. Ruby, Dr. Anil, Brijesh, Sanjeev, Amol, Dinesh and Sridhar for their irreplaceable cooperation.

I also consider myself blessed in that I got to spend a major chunk of my time at NCL /Pune with Dr. Sunil, Milind, Shravan, Mahendra, Neeta, Dnyaneshwar, Vivek and Appasaheb. They have always been and will continue to be an inspiration to me. I always enjoy their company and they are my strength for many things. I heartily express all my credits to Marathi group at GJ hostel: Dr. Majid, Dr. Atul, Dr. Satish, Vinita, Taufiq, Santosh, Rohit, Yogesh, and Vaishnavi for energizing at the time of

frustration, supporting at the time of difficulty, and muttering humours at the time of leisure.

I am highly obliged to my teachers at school, college and University level for their motivated teaching, advice, and encouragement.

My family is always source of inspiration and great moral support for me in perceiving my education, I am lucky to having such a beautiful family. The words are insufficient to express my sense of gratitude for my family. Though, I take this opportunity to my sense of gratitude to my parents Mrs. Tarabai (mother) and Mr. Suresh (father) for their tons of love, sacrifice, blessings, unconditional support and encouragement. I express my deep and paramount gratitude to my uncle Prof. V. R. Phatake, for his immeasurable love and affection. Words fall short to thank my brother Mr. Deepak, Mrs. Swati (sister-in-law) and all other members of my family for their never ending encouragement, support and love. I am lucky to have wonderful nephew Shubham (Aum), he has full of happiness, Joy and Curiosity, everlasting cheerfulness in my life. I always enjoy company of all my family members even at short stays at home and finally to the people of my village for their constant encouragements.

Ravindra

ABREVIATIONS

Ac	Acetyl
Ac_2O	Acetic anhydride
AIBN	Azobisisobutyronitrile
aq.	Aqueous
anh.	Anhydrous
Bn	Benzyl
BnBr	Benzyl bromide
DCM	Dichloro methane
DCE	1,2-Dichloro ethane
DEAD	Diethyl azodicarboxylate
DMD/DMDO	Dimethyldioxirane
Cat.	Catalytic
TsCl	Tosyl chloride
Conc.	Concentrated
COSY	Correlation spectroscopy
DIBAL-H	Diisobutylaluminiumhydride
DIPEA	Diisopropylethyl amine
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DET	Diethyl tartrate
DMP	2,2'-Dimethoxypropane
DMF	*N,N*-Dimethylformamide
DMAP	*N,N'*-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
Et_3SiH	Triethylsilyl hydride
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Et_3N	Triethylamine
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
LAH	Lithium aluminum hydride
LiHMDS	Lithium1,1,1,3,3,3-hexamethyldisilazane
LDA	Lithium diisopropyamide
Ms/Mesyl	Methanesulfonyl
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
NMR	Nuclear Magnetic Resonance
NBS	*N*-bromosuccinamide
NMO	*N*-Methylmorpholine N-oxide
NOESY	Nuclear Overhauser Effect Spectroscopy
Pd/C	Palladium on Carbon
p-TSA	*para*-Toluenesulfonic Acid

Ph	Phenyl
Py	Pyridine
PCC	Pryridiniumchlorochromate
PMBCl	*p*-Methoxy benzyl chloride
TBSCl	*tert*-Butyldimethylsilyl chloride
TBAF	*tetra*-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylchlorosilane
t-BuOOH	*tert*-Butyl hydroperoxide
PPh_3	Triphenylphosphine
rt	Room Temperature
sat.	Saturated
TBAI	*tetra*-Butylammonium iodide
Tf_2O	Triflic anhydride
t-BuOK	Potassium tertiary butoxide
TFA	Trifloroacetic acid
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

Abbreviations used for NMR spectral informations:

br	broad	s	singlet
d	doublet	t	triplet
m	multiplet	dd	doublet of doublet
q	quartet	tq	triplet of quartet

GENERAL REMARKS

- ^{1}H NMR spectra were recorded on AV–200 MHz, AV–400 MHz,JEOL AL-400 (400 MHz)and DRX–500 MHz spectrometer using tetramethylsilane(TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AV–50 MHz, AV–100 MHz, JEOL AL-100 (100 MHz)and DRX–125 MHz spectrometer.
- Massspectroscopy was carried out on PI QStar Pulsar (Hybrid Quadrupole-TOFLC/MS/MS) andHigh-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump and alsoEI Mass spectra were recorded on Finngan MAT–1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- All reactions are monitored by Thin Layer Chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F–254) with UV light, I_2, and anisaldehyde in ethanol as developing agents.
- All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 45 °C unless otherwise specified.
- Silica gel (60–120), (100–200), and (230–400) mesh were used for column chromatography.

CONTENTS

ABSTRACT

Research Student	Ravindra S. Phatake
Research Guide	Dr. C. V. Ramana
Title of Thesis	**Unexplored Olefin Oxidations with Oxone and Application of *α*-Diazocarbonyl Compounds in the Synthesis of *N*-Heterocycles**
Registration Number	PGS/Ph.D./8031 dated 08.10.2013 (Title change : PGS/329 dated 22.01.2016)
Date of Registration	17.05.2013
Place of Work	Division of Organic Chemistry CSIR-National Chemical Laboratory, Pune (INDIA)

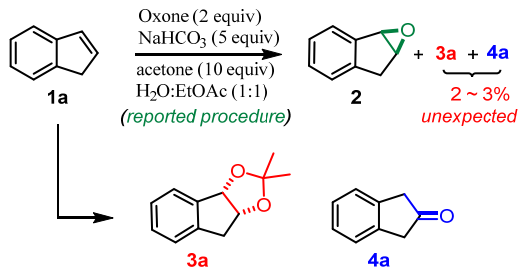
ABSTRACT

The thesis entitled **"Unexplored Olefin Oxidations with Oxone and Application of *α*-Diazocarbonyl Compounds in the Synthesis of *N*-Heterocycles"** is divided into two chapters. The title of the thesis clearly reflects the objective - developing new methods for olefin oxidations and *N*-heterocycles synthesis. The first chapter deals with the Oxone-acetone combination for metal free *syn*-dioxygenation and Wacker-type oxidation of benzo-fused olefins. The second chapter focuses mainly on the simultaneous construction of C–C and C–N bonds employing *α*-diazocarbonyl compounds.

Chapter I: Unexplored Olefin Oxidations with Oxone

Epoxidation, dihydroxylation and oxidation to ketone are the key oxidative transformations of olefins that have been well studied since the beginning of organic synthesis. Until recently, the oxidation of olefins has been mainly reserved for the metal-based reagents. Recently, there is a renewed interest for metal free oxidation methods in the context of strict FDA norms about the trace-metal impurities in the final APIs. In this chapter, presented is an unusual dioxygenation and Wacker-type oxidation employing Oxone-acetone. We have come across these unusual reactions of Oxone accidentally, while carrying out the preparation of the known indene oxide. On multi-gram scales employing the reported procedure using Oxone (Scheme A1) along with the reported epoxide **2**, the acetonide **3a** and 2-indanone **4a** were obtained as the

side products (2 – 3%). Preliminary control experiments revealed that the formation of **3a** and **4a** does not involve epoxide **2** as an intermediate. Prompted by this, we proceeded towards identifying the right conditions that can deliver either of these products exclusively.

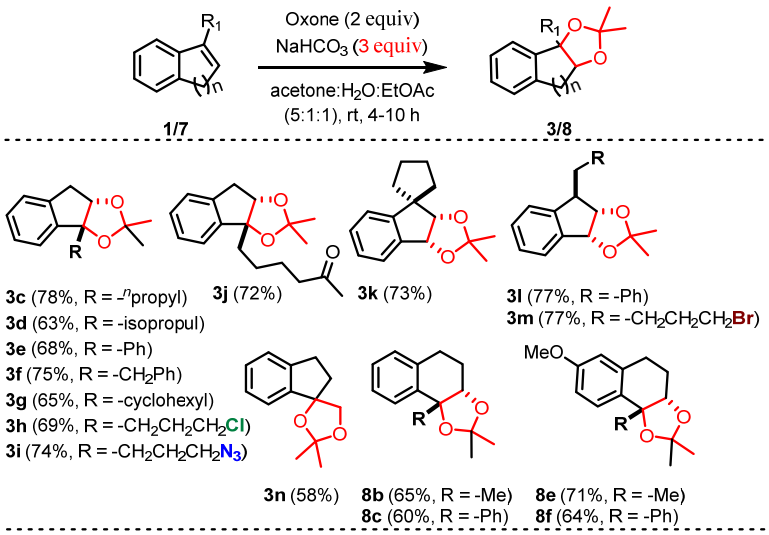


Scheme A1: *Gram Scale Synthesis of Indene Oxide*

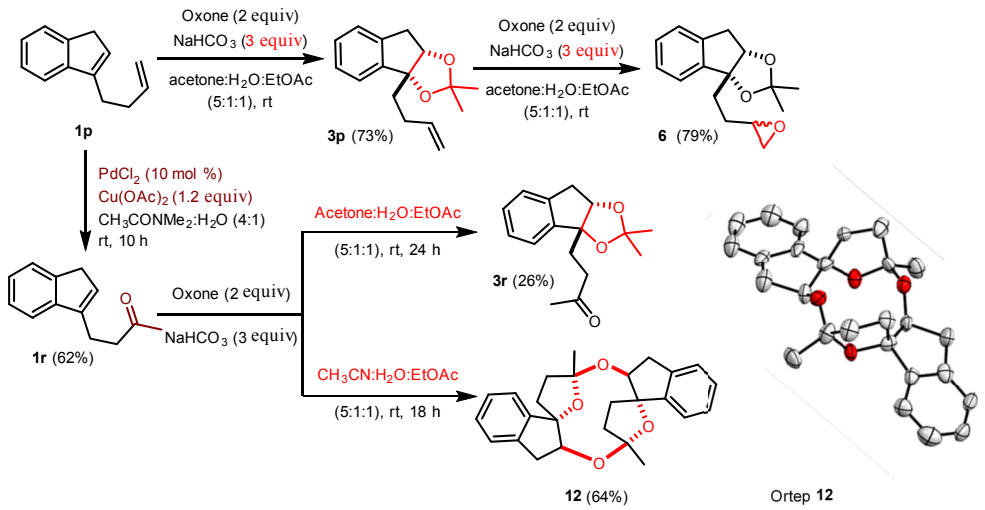
Oxone-Acetone Mediated *Syn*-Dioxygenation of Benzofused Olefins

First, the dioxygenation of indene was examined with all possible variations in the parallel mode for arriving at the right conditions. After exhaustive experimentation we could identify the right conditions to drive the reaction exclusively towards the *syn*-dioxygenation. Control experiments revealed that a 1:1 proportion of ethyl acetate and water with excess acetone is the best solvent combination. The optimized reaction conditions involve the addition of 2 equivalents of powdered Oxone to a stirred slurry of 3 equivalents of sodium bicarbonate ($NaHCO_3$) and 1 equivalent of the indene in a mixture of solvents 5:1:1 (acetone + ethyl acetate + water).

Table A1: *Scope of Oxone-Acetone Mediated Syn-Dioxygenation*



To examine the scope of this novel dioxygenation, a variety of substituted indenes and dihydronaphthalenes have been subjected for the Oxone-oxidation under optimized conditions. In general, all reactions are highly selective towards the *syn*-dioxygenation and gave the corresponding acetonides in good to excellent yields (Table A1).



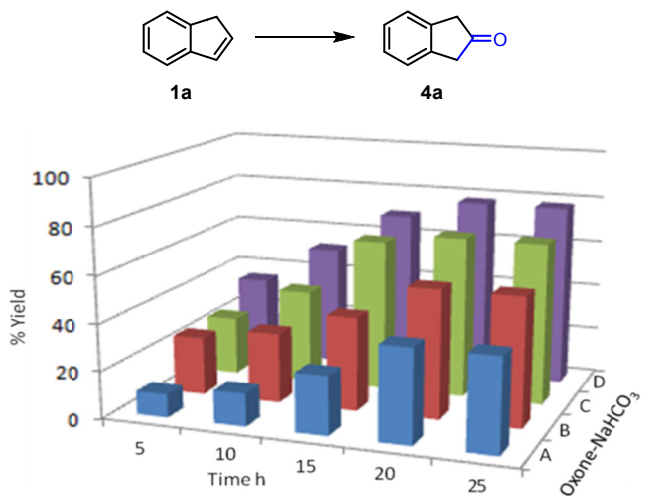
Scheme A2: *Synthesis of Model Substrate* ***1r*** *and its Oxone-Mediated Oxidations*

Next, various control experiments have been carried out to probe the course of the reaction. These experiments have revealed that there is no participation of any trace-metals present in the reagents used and also that the epoxide is not detectable in the entire course of the reaction. In addition, the oxidation of *trans*-/*cis*-stilbenes under current conditions revealed that the dioxygenation mediated by the Oxone-acetone combination is stereospecific. To further probe in this direction, the Oxone-mediated intramolecular-dihydroxylation of the indene derivative **1r** having a pendant ketone has been studied. The successful oxidation of **1r** required acetonitrile as a solvent and provided **12** in good yield. A dimeric acetal structure has been assigned to compound **12** with the help of extensive NMR studies followed by single crystal *X*-ray structural analysis (Scheme A2). With this information in hand and considering the various possibilities that have been speculated in the dioxirane-mediated epoxidations, a tentative mechanism postulating a transition state involving an asynchronous oxygen addition from the dimethyldioxirane (DMDO) to olefin with a certain amount of diradicaloid character (S_E2) and its subsequent cyclization, has been extended for the 1,3-dioxolane formation.

Oxone-Acetone Mediated Wacker-Type Oxidationof Benzofused Olefins

Having established the *syn*-dioxygenation of indene and its related derivatives, next the possibility of selectiveWacker-type oxidation of indene has been examined. It was pertinent to mention here that in our previous dioxygenation optimizations experiments, when 0.5 equiv of Oxone was employed in the presence of 3 equiv of $NaHCO_3$, we noticed the formation of 2-indanone in 35% yield. This important clue has made the further optimization of Wacker-type oxidation quite easy. Parallel experiments comprising of varying the proportions of both oxidant and base with the GC-MS monitoring these reactions has led us to arrive at the optimized conditions quite easily.

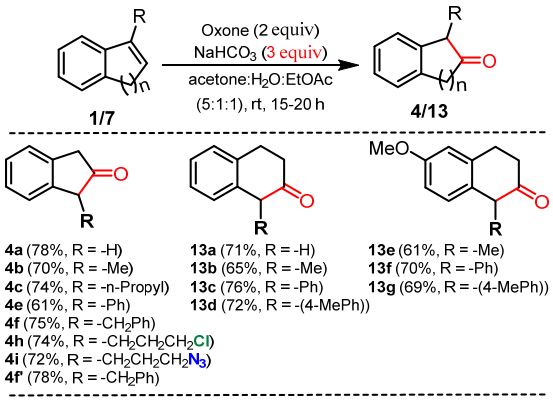
Scheme A3: *Conditions Explored for the Wacker-Type Oxidation*



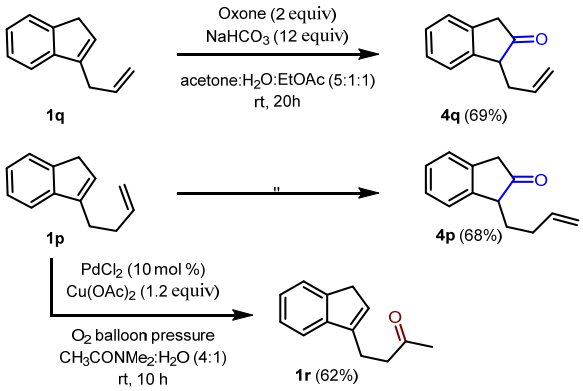
[a] all the reactions were carried out at rt with 0.5 mmol of indene in 2.5 ml acetone and 0.5 ml of (1:1 of H_2O + EtOAc);
[A] Oxone (0.5 equiv), $NaHCO_3$ (3 equiv); [B] Oxone (1.0 equiv), $NaHCO_3$ (6 equiv);
[C] Oxone (1.5 equiv), $NaHCO_3$ (9 equiv); [D] Oxone (2.0 equiv), $NaHCO_3$ (12 equiv).

To this end, the use of 12 equiv of $NaHCO_3$ along with 2 equiv of Oxone was found to be the best combination for the complete conversion of indene **1a** to 2-indanone **4a** in 78% yield at room temperature over a period of 15–20 h. Control experiments revealed that the acetone:H_2O:EtOAc (5:1:1) was the best solvent combination system for the current Wacker-type oxidation.

***Table A2**: Scope of Oxone-Acetone Mediated Wacker-Type Oxidation*



The scope of this reaction has been generalized by employing various substituted indene and dihydronaphthalene derivatives. In general, the reactions proceeded smoothly and provided exclusively corresponding 2-indanones/2-tetralones in good to excellent yields. Gratifyingly, the reaction conditions employed were found to be tolerable for a range of functional groups like chloro and azide without much affecting the yields of the final products (Table A2).



***Scheme A4:** Regioselectivity of Wacker-Type Oxidation*

Subsequently, the dienes 3-(but-3-en-1-yl)-1H-indene (**1p**) and 3-allyl-1H-indene (**1q**) have been subjected for the present oxidation under established conditions to examine the selectivity of the current oxidation method. Interestingly, the oxidation of both dienes **1p** and **1q** occurred in a way such that the internal olefin only got oxidized, resulting in the corresponding indan-2-ones exclusively (Scheme A4). This complementary selectivity clearly explains that the Oxone-acetone mediated oxidation is very selective for the benzo-fused olefins despite the fact that this olefin is sterically hindered.

To conclude, the direct oxidation of indenes and 1,2-dihydronapthalenes resulting in either *syn*-dioxygenation and/or Wacker type oxidation has been accomplished by employing Oxone-acetone and sodium bicarbonate under relatively simple conditions. The control experiments reveal that the current oxidation processes did not occur due to the presence of trace-metal impurities, nor is the epoxide an intermediate in the path of the reaction. In a nutshell, it must be noted that a subtle variation in the reaction conditions either in terms of the solvents employed and/or the amount of base used seems to causes a complete change in the course of the reaction. The current base-driven switching in the reaction path is very unusual and creates substantial opportunities for further exploration.

Chapter II: Application of *α*-Diazocarbonyl Compounds in the Synthesis of *N*-Heterocycles

The simultaneous construction of C–C as well as C–N bonds is one of the important features of nitrogen heterocycles synthesis. The metal-catalyzed directed C–H Activation Annulation (**CHAA**) is one of the recently established approaches for a rapid construction of the *N*-heterocycles. In this chapter, we document the synthesis of various heterocyclic systems exploring the potential of α-diazocarbonyl compounds with the simultaneous formation of C–C and C–N bonds. Described in the first part will be the Ir(III)-catalyzed C−H activation and carbene functionalization reactions for the synthesis of isoquinoline-N-oxides, N-Methoxyisoquinolinediones and N-methoxyisoquinolinones. In the second part, we describe a novel fluoride-mediated dephosphonylation of *α*-diazo-*β*-carbonylphosphonates followed by the (3+2)-cycloaddition of the resulting diazocarbonyl anions with acrylates/arynes to prepare the substituted pyrazolines and indazoles.

Iridium (III)-Catalyzed C–H Activation and Annulation with α-Diazocarbonyl Compounds

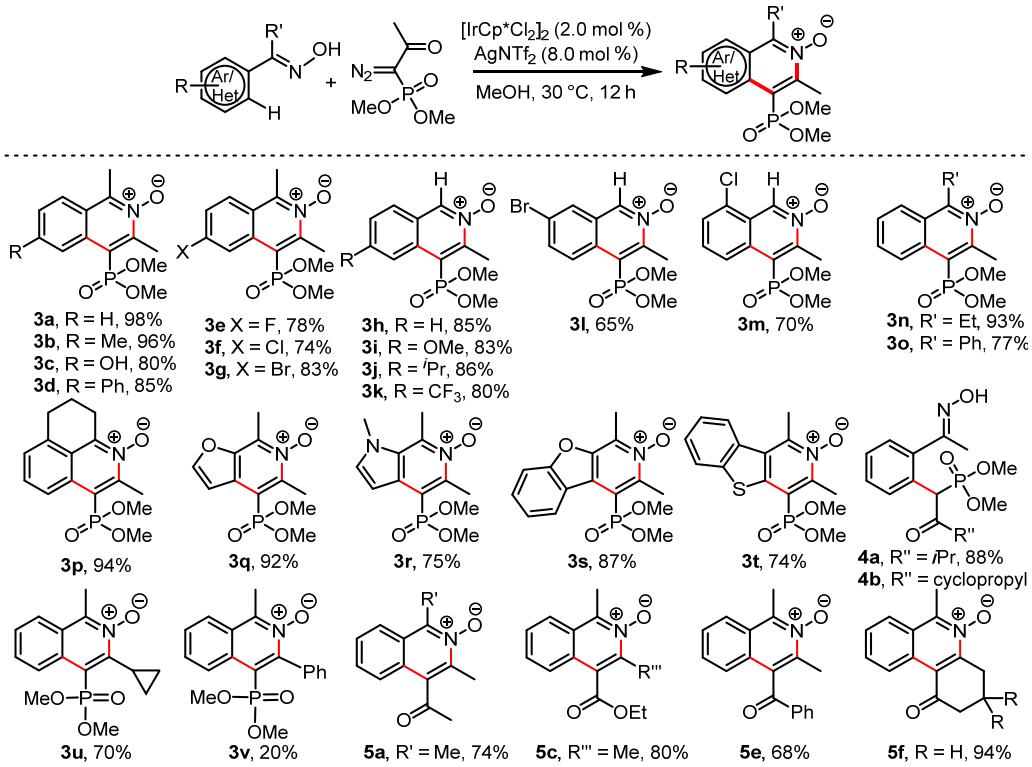
The possibility of direct annulation of heterocyclic units *via* C–H bond transformations is a highly attractive strategy in heterocyclic synthesis. These processes generally comprise of a directing group that facilitates the C–H insertion and annulation of an alkyne/vinyl or allene across the activated C–H bond and the directing groups. A wide range of transition metals such as Co, Pd, Ru, Rh and Ir have been employed in this pursuit. Higher temperatures and the regioselectivity of

alkyne/allene/vinyl ethers insertion are the key issues in these processes. Recently, it has been revealed that α-diazocarbonyl compounds could efficiently replace these unsaturated systems with the desirable regioselectivity and most importantly, at lower-temperatures. However, the reported examples of this C–H activation and annulation with diazo compounds are mainly limited to Rh-catalyzed carbene functionalization. Aiming at the lowering of the reaction temperatures of these processes closely to rt, we were interested to explore the more reactive Ir(III)-complexes.

Our initial explorations in this context started with examining the applicability of the cationic Cp*Ir(III) catalyst prepared from $[IrCp^*Cl_2]_2$ and different silver salts for the synthesis of isoquinoline *N*-oxides from acetophenone oxime **1a** and Ohira-Bestman's diazophosphonate **2a**. After screening various silver salts and different solvents, we could successfully achieve this transformation at 30 °C employing 2 mol% of the $[IrCp^*Cl_2]_2$ and 8 mol% of $AgNTf_2$ in methanol, which resulted in the isolation of the required 4-(dimethoxyphosphoryl)-1,3-dimethylisoquinoline 2-oxide (**3a**) in 95% yield.

Next, the substrate scope of this transformation has been established by employing a wide range of aromatic and heteroaromatic oximes with diverse diazophosphonates. As shown in Table A3, in all the cases, the reactions proceeded smoothly and provided the corresponding isoquinoline *N*-oxides in good to excellent yields.

***Table A3**: Scope of Isoquinoline N-Oxides Synthesis*

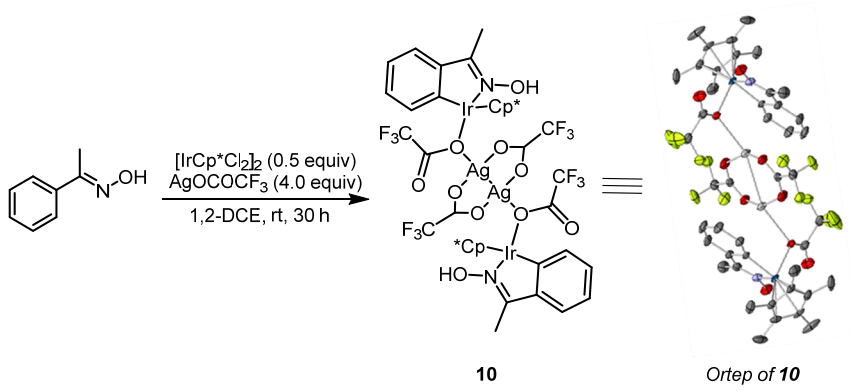


As a part of understanding the mechanistic details of this reaction, the conducted deuterium scrambling experiments revealed the reversibility of the C−H activation step and also indicated that the C−C bond formation to be significantly faster than the C−H activation step. Interestingly, a relatively low value of the primary kinetic isotope effects (KIE) was measured in parallel experiments (KIE = 1.43) and the intramolecular competition reaction (KIE = 1.67). These KIE values indicate that the C−H bond cleavage may not be the rate-limiting step. However, these reactions further experimentation before we can arrive at a final conclusion.

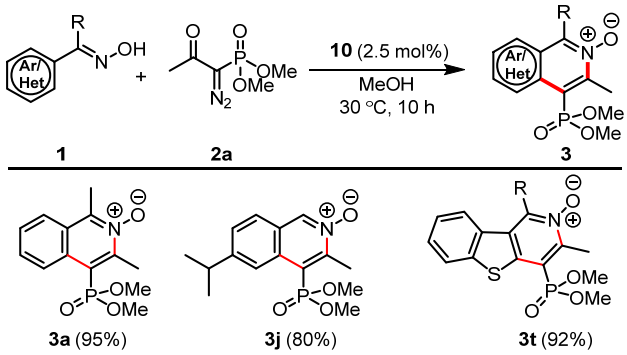
In parallel, we have also conducted the stoichiometric experiments that resulted in the isolation of a dimeric bimetallic cyclometalated Ir(III)/Ag(I) complex (**10**, two iridacycles connected through a dimeric silver bridge). Control experiments revealed that this complex alone catalyses the reaction without any Ag additives resulting in the *N*-oxides with excellent yields. To the best of our knowledge, this is the first isolation of such types of bimetallic Ir-complexes, which can catalyze the C−H activation very efficiently.

Scheme A5: *Synthesis of Complex* ***10*** *and Its Catalytic Activity*

a) Synthesis of Complex ***10***



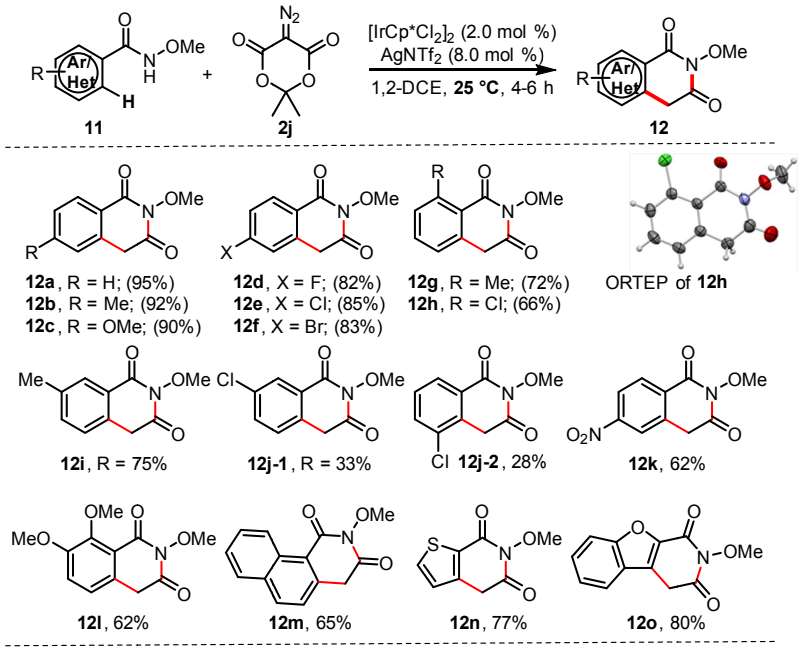
b) Reaction Using Cyclometalated Complexes 10



Ir (III)-Catalyzed Synthesis of *N*-Methoxyisoquinolinediones and *N*-Methoxyisoquinolinone

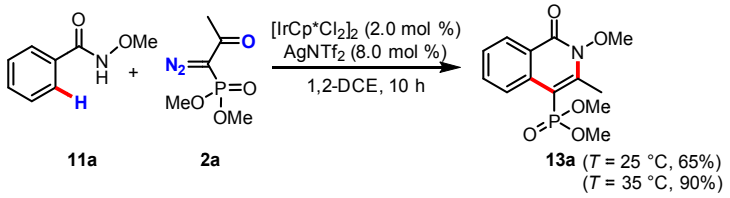
After having this initial success with the Ir(III)-catalytic system in C–H activation cycloannulation for isoquinoline *N*-oxides synthesis, we next explored its potential for building the isoquinolinedione scaffold. Taking *N*-methoxybenzamide **11a** and 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (*α*-diazotized meldrum's acid) **2j** as model substrates, the optimization experiments have been carried out by screening different silver salts and solvents. To this end, the desired *N*-methoxyisoquinolinedione **12a** could be obtained in 92% yield using 2.0 mol % of $[IrCp^*Cl_2]_2$ and 8.0 mol % $AgNTf_2$ in 1,2-dichloroethane (1,2-DCE) at room temperature.

***Table A4**: Ir-Catalyzed N-Methoxyisoquinolinediones Synthesis*



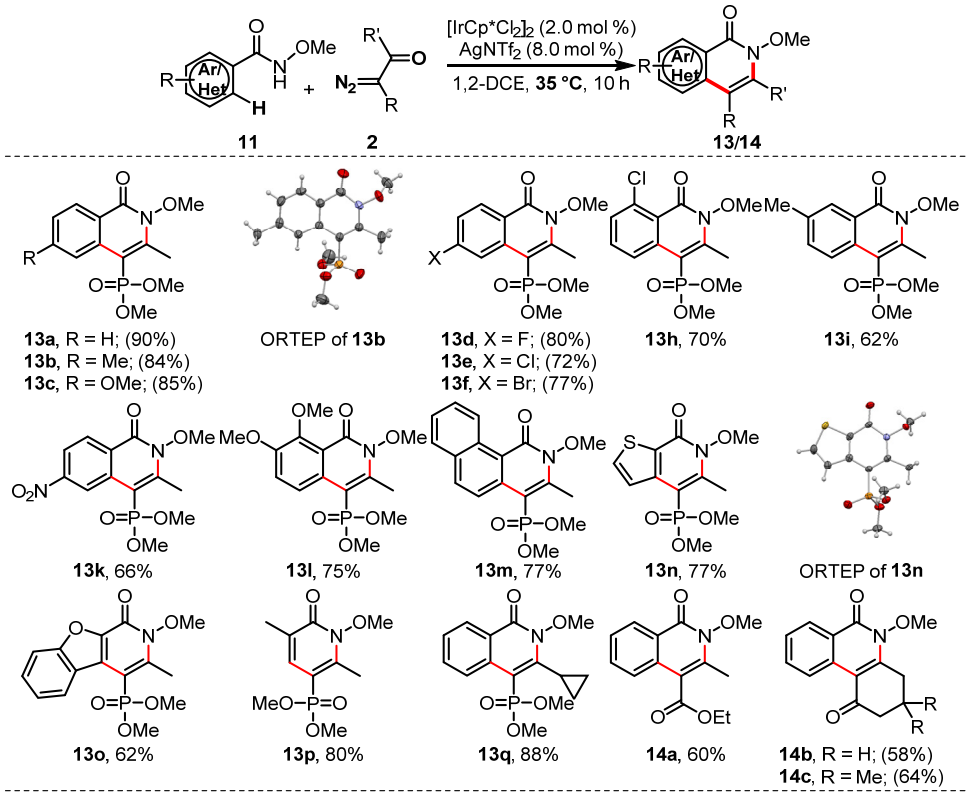
As shown in Table A4, various substituted *N*-methoxybenzamides were treated with *α*-diazotized Meldrum's acid diazophosphonate **2j** to furnish the corresponding *N*-methoxyisoquinolinedione derivatives. Generally, the reactions proceeded smoothly at room temperature regardless of the position as well as electronic nature of the substituents on the aryl ring.

After successful exploration of the aryl and heteroaryl *N*-methoxyisoquinolinedione synthesis, next we focused on extending the present Ir(III)-catalytic system for similar kinds of scaffolds like isoquinolinones (Scheme A6) by switching from the diazotized meldrum acid to diazocarbonyl compounds. As shown in Scheme A6, when employed the Ohira-Bestmann reagent as the diazo partner in the above reaction, the N-methoxyisoquinolinone **13a** was isolated in 65% at rt and in 90% when heated at 35 °C. The steric crowding around the carbonyl group seems to be hindering the imine formation (after the initial C–H functionalization with carbene) and thus the heating of the reaction mixture is warranted for a successful cyclization. Table A5 reveals the scope of this reaction that has been examined by employing a diverse set of oximes and diazocarbonyl compounds.



Scheme A6. *Synthesis of N-methoxyisoquinolinone*

Table A5*: Scope of isoquinoline N-methoxyisoquinolinones synthesis*

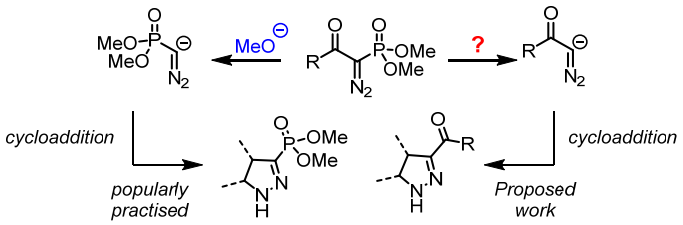


The deuterium scrambling experiments have revealed that unlike with the previous case with free oximes, with O-methylated oxides, the C−H bond activation is largely irreversible [KH/KD = 4.0 for the intermolecular competition reaction] and thus the C−H bond cleavage is most likely the rate-determining step.

To conclude, we have demonstrated that the Ir(III)-catalyzed C–H carbenoid functionalization proceeds under mild conditions (rt – 35 °C) and is superior when compared to the corresponding Rh-catalyzed processes. As a part of this, we have synthesized a wide-range of isoquinoline-*N*-oxides, *N*-Methoxyisoquinolinediones and *N*-methoxyisoquinolinones employing easily available oximes and diazo compounds. Additionally, we have showed that phosphorylated *N*-methoxyisoquinolinone derivatives could be easily synthesized by employing OB reagent as a diazo partner.

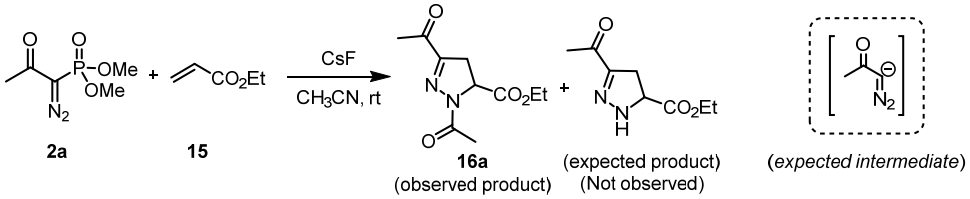
Dephosphonylation of Diazocarbonyl Phosphonates

Diazophosphonates are very well known for a long time because of the foremost famous Ohira-Bestmann Reagent, which is mainly used for one carbon homologation reactions of aldehydes and ketones in organic synthesis. Very recently, *insitu* trapping of the (diazomethyl)phosphonate anion intermediate in a (3 + 2) cycloaddition process has become very popular. The reaction of (diazomethyl)phosphonate anion with conjugated olefins, imines and with alkynes results in the formation of pyrazolyl-/triazolyl phosphonates. The presence of the pyrazoles unit in various marketed drugs and the easy introduction the phosphonate group has led to the rapid exploration of this area. These reactions, including the classical alkynylation with OBR, are generally initiated by the base-mediated deacylation.



Scheme A7. *Proposed Strategies for Novel Pyrazole Synthesis*

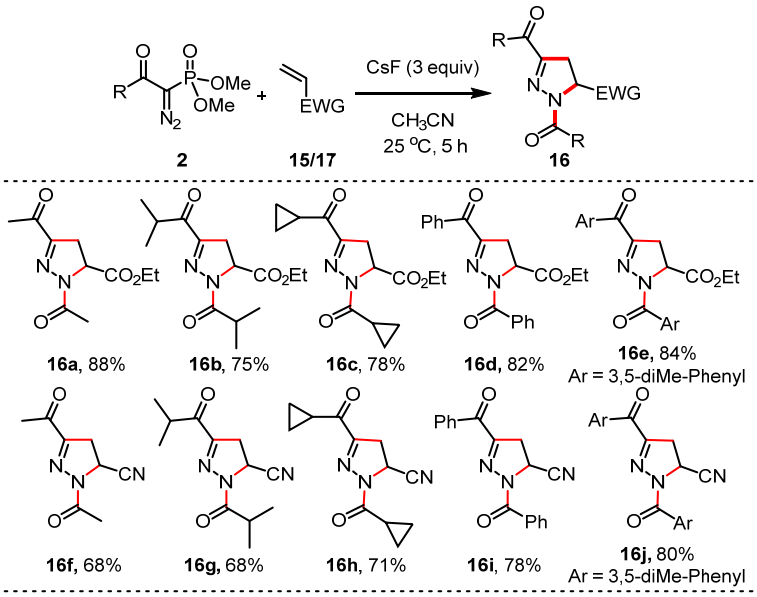
We hypothesized the possibility of retaining the acyl group in place of the phosphonate, which has never been explored, with a preconceived dogma of considering OBR as a surrogate for the (diazomethyl)phosphonate anion. If realized, it should provide an easy approach for the *insitu* generation of anions of diazocarbonyl compounds and also substituent diversity with a provision for synthesis of an *N*-heterocycles library. Considering the size and weak basicity of the fluoride anion when compared to the methoxide anion and the specific affinity of fluoride for the phosphorous centres, we considered it as a complementary base for the dephosphonylation of the OB reagent.



Scheme A8. *Observations from Preliminary Experiments*

Our preliminary screening experiments with different fluoride ion sources revealed the formation of a new product **16a** in 34% yield when CsF was employed as a base. The analysis of the spectral data of **16a** led to the identification of this compound as ethyl 1,3-diacetyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate revealing that the initially formed N–H pyrazole underwent further *N*-acylation by the OBR reagent (Scheme A8). Considering this, further optimization studies have been conducted by varying the amount of OBR **2a** and CsF with respect to the acrylate **15**. To this end, the use of 2.2 equiv of OBR **2a** and 3.0 equiv of CsF in acetonitrile as a solvent at room temperature improved the reaction outcome with the isolation of pyrazole **16a** in 88% yield. Next, as shown in Table A6, the scope of this reaction has been established by employing a wide range of diazo phosphonates containing acyl/aroyl diazophosphonates and ethyl acrylate as well with acrylonitrile as the dipolarophiles. In all the cases, the reactions proceeded smoothly and provided the corresponding pyrazolines in good to excellent yields.

***Table A6**: Scope of Substituted 4,5-Dihydro-1H-Pyrazoles Synthesis*

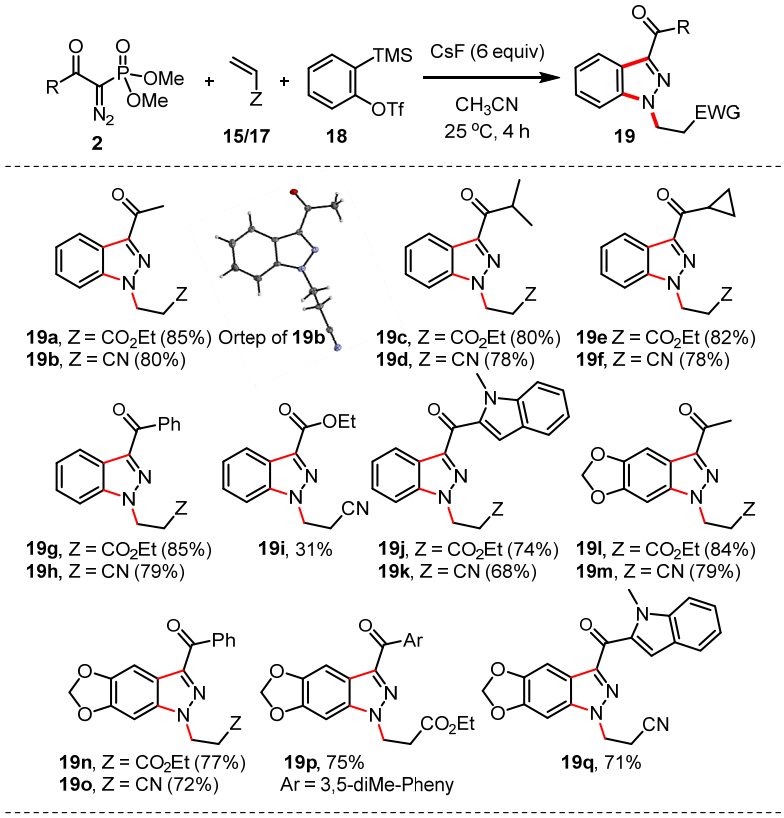


After this initial success with conjugated olefins as the dipolarophiles to trap the intermediate (*α*-acyl)diazomethane anion, we next examined the possibility of trapping the same with *insitu* generated arynes to construct the indazole nucleus. However, considering the earlier reports on the further reactions of the initially formed indazole anions (undergo *N*-arylation with the excess aryne), we speculated on trapping them with acrylates *via* an aza-Michael addition reaction. The optimization

experiments have been conducted by employing the OBR **2a** (1.0 equiv), benzyne precursor **18a** (1.1 equiv), and ethyl acrylate **15** (1.1 equiv) and by varying the concentration of CsF (3 – 6 equiv) in CH_3CN at room temperature. The results with the use of 6 equiv CsF are encouraging - the reaction was completed within 4 h and gave the desired product **19a** that resulted from the expected (3+2) cycloaddition followed by aza-Michael addition, in 85% yield.

With enough information and optimized conditions in hand, the scope and limitations of this current multi-component reaction has been examined employing diverse diazo phosphonates (aliphatic, aromatic and heterocyclic) with aryne precursors and ethyl acrylate/acrylonitrile as the Michael traps (Table A7).

***Table A7**: Scope of 1,3-Disubstituted Indazoles Synthesis*



To conclude, we speculated on the possibility of selective dephosphonylation of the *α*-diazo-*β*-carbonyl phosphonates and realized it successfully under very mild conditions employing fluoride as a base. The derived anions of the (*α*-acyl)diazomethane have been trapped *via* (3+2) cycloadditions with acrylates/acrylonitrile/arynes to furnish 1,3-disubstituted-4,5-dihydro-pyrazoles or indazoles.

CHAPTER I:

Unexplored Olefin Oxidations with Oxone

Introduction

The construction of the C–C and C–hetero atom bonds forms the central dogma of organic synthesis.[1] The majority of the named reactions embodied in the curricula of undergraduate students allow the students to understand the step-by-step progress and the philosophical changes that occurred in the art of organic synthesis during the last two centuries and how molecular synthesis was made easy by innovating with new reactions and developing new reagents.[2] It is certain that the progress made in organic synthesis during the last two centuries is enormous (people from other areas consider that it is a matured science) and we believe that identifying fundamental problems of synthesis is extremely challenging. However, as mentioned previously, even now, the discovery of new methods for the formation of C–C and C–hetero atom bonds is an important endeavor.[3]

Oxidation Reactions

Organic compounds with C–O and C–N bonds are ubiquitous.[1-3] The introduction of these hetero atoms across the growing chain/rings of carbon frameworks is an important aspect. Though it may be mentioned in general oxidation is a process by which a carbon atom gains bonds to more electronegative elements - however, it has been trivially understood as introducing the oxygen or the removal of hydrogens. Interestingly, many of the named oxidations fall under category two that includes the classical alcohol-aldehyde-acid/ester oxidations.[4] The direct inclusion of oxygen atoms into organic molecules has different nomenclature, such as dihydroxylation or carries a suffix such as epoxidation, dioxygenation, or ozonolysis.[5] Oxidation is one of the fundamentally important reactions in biology and chemistry. The direct oxidation of unactivated alkanes is an ever-lasting problem and yet has been not been recognized as a reliable tool in multi-step organic synthesis.[2] On the other hand, the alkene and alkyne groups have served as the right platforms for embroidering the carbon chains with oxygen atoms and, most importantly, with a complete control on the degree of oxidation, regio/diastereo and enantio selectivity.[6]

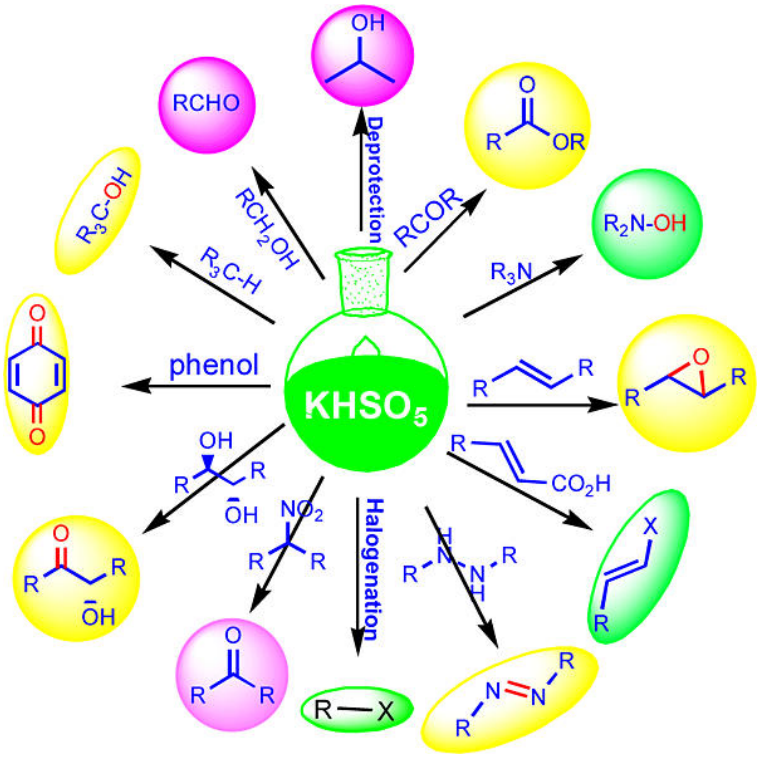
Arguably, the oxidation of alkenes and alkynes has attracted a significant amount of synthetic maneuvers for a long time. In particular, the oxidation of olefins is one of the major topics in the branch of oxidations. Epoxidation, dihydroxylation, and ozonolysis are the three fundamentally important olefin oxidations that are known from the 19th century onwards and the Wacker-oxidation is the one that was

introduced in the latter half of the 20th century.[7] Peroxides and peracids for epoxidation and permanganate or osmium for the dihydroxylation have their own association ever since the science of olefin-oxidation began.[8] However, in the middle of the last century, considering the safety hazards associated with the peroxides/peracids, as expected in the realm of increased the accessibility to various organometallic reagents, there have been tremendous efforts for the catalytic olefin-oxidations employing sustainable oxidants such as aerial oxygen.[9] These reactions have really proven their efficiency on the small scale as well as on large scale. However, in recent years, especially in the pharmaceutical processes, there is an increasing concern over the use of metal-based reactions due to the cost of transition metals, difficulties involved in the complete removal of the metal impurities from the products and toxicity associated with the trace-metals.[10] This has generated a renewed interest on metal free methods for oxidations.[11] Considering the huge volume of work that covers this aspect and pertains to the current work, the following discussion will be dedicated exclusively on oxidations employing Oxone specially mentioned will be those that are original in nature.

Oxone Oxidations in Synthetic Chemistry

Identifying a reagent/catalyst accessible from cheap commercial materials and highly reactive, selective and environmentally benign is always the vision of every chemist. Coming to the oxidations, such an ideal oxidant has not yet been invented. However, Oxone to some extent, appears to fulfill these requirements, and has gained prominence during the past few decades.[12] Oxone is a versatile reagent, having the ability to oxidize numerous functional groups, being easy to handle, non-toxic and soluble in water. It is the oxidant of choice owing to the fact that it is cheap (comparable with hydrogen peroxide and bleach) and commercially available. Oxone salt can be used directly in most of the reactions that proceed *via* dioxirane formation. For the first time in 1979, Edwards and co-workers performed reactions between Oxone and simple ketones (pH 7.5−8.0) to generate dioxiranes.[13] Dioxiranes are three membered ring cyclic peroxides. They transfer oxygen very efficiently, yet are very mild towards a wide range of functional groups. They exhibit chemo-, regio-, diastereo-, and eanantio-selectivities, act catalytically, and can be readily prepared from a suitable ketone (acetone) and potassium monoperoxysulfate.[14] The oxidations

with Oxone in the majority of the cases employ acetone as a solvent and thus the crucial oxidation reactions will be mainly caused by the dimethyldioxirane.[15]



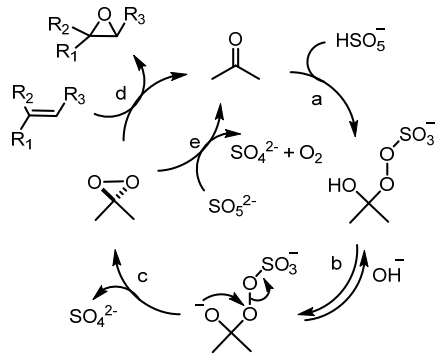
***Scheme 1**. Overview of Oxone Reactions*

Oxone represents a class of oxidants of immense significance for oxidation. In the past several years, Oxone has rapidly grown into one of the most useful oxidant in the arsenal of synthetic organic chemistry. Numerous classes of organic compounds have been oxidized by Oxone (DMD) or similar dioxiranes and some specific behaviors are strictly related to the oxidation mechanism. Because of their versatile reactivity, dioxiranes are today widely adopted as a new class of efficient oxygen-transfer reagents. They are selective in their action, bland towards the oxidation product and capable of performing under mild and strictly neutral conditions. The unique reactivity ranges from the efficient oxy functionalization of unactivated C–H bonds of alkanes under extremely mild conditions,[16] which undoubtedly counts to date among the highlights of the chemistry of dioxiranes. The transfer of an oxygen atom leads to epoxidations and to the oxidation of heteroatoms containing a lone pair of electrons such as amines and sulfides.[15] In fact, the recent discovery that solutions of dioxiranes can be prepared and used to carry out a variety of synthetically useful reactions has set the scene for wide ranging developments of the chemistry of these

interesting cyclic peroxides.[17] Applications in synthesis of the currently popular dimethyldioxirane (DMD) and of methyl(trifluoromethyl)dioxirane (TFD) in isolated form have led to the access to key products that are useful in organic synthesis.[18] This development will include synthetic, physical organic and theoretical aspects; all these reports in chemistry of dimethyldioxirane to date show it to be a very powerful oxidant.[12-16] Our main interest concern the C–O bond forming reactions by using Oxone. In this direction we have tried to summarize the following characteristic reactions reported in literature.

Oxone Epoxidation of Alkenes

Epoxidation is one of the most common reactions in organic chemistry. Starting with epoxides, 1,2-diols and a large number of other 1,2-functionalized compounds can be synthesized. In biology, epoxidation plays an important role in the metabolism of condensed aromatic hydrocarbons in animal organisms.[19] Epoxides, mainly ethylene oxide, propylene oxide and epichlorohydrin are employed in the preparation of epoxy resins. Polymerization of epoxides gives polyethylene glycols or polyoxoalkylenes which, depending on their molecular weights, are used as detergents, lubricants, waxes, and components in hydraulic liquids. Epoxidation of alkenes [unfunctionalized, electron-rich and electron-poor] with either isolated or *insitu* generated dioxiranes has been successfully studied for a long while.[21] The acetone solution of DMD (isol.) is very easy to prepare and used most often because of low cost. If we compare DMD with TFD (methyl(trifluoromethyl)dioxirane), we found that TFD is much more reactive than DMD but still it has very limited applications because of the high cost and volatility of trifluoroacetone.[13,21] The dioxirane generated in solution can accept attack by further caroate ions, yielding the sulphate ion and molecular oxygen. However, in a competitive process, it can then also be attacked by a variety of electron-rich substrates, *viz*., “S”, yielding the oxidation product “SO”. In these reactions, the parent ketone is regenerated; so it returns to the catalytic cycle (Scheme 2).[13,22]

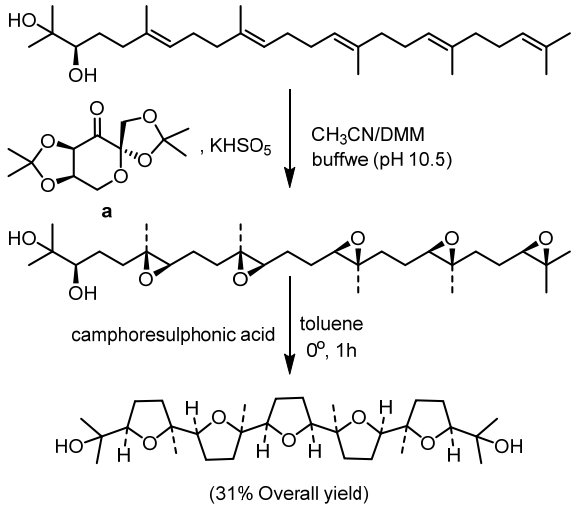


Scheme 2. *Epoxidation Mechanism*

Among the most significant steric and electronic influences, the olefin reactivity and solubility are other important factors affecting the epoxidation. For systematic understanding of alkene epoxidation by using Oxone (dioxirane), we have sorted those into unfunctionalized alkenes, electron-rich/poor alkenes, and alkenes with both electron donors and acceptors.

Epoxidation of Unfunctionalized Alkenes

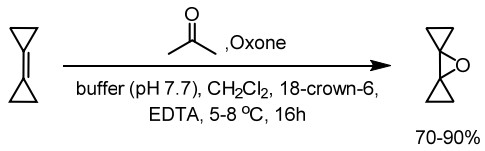
The major study of unfunctionalized alkenes to epoxidation by dioxiranes is mainly focused for the purpose of elucidation of the reaction mechanism. In general, highly substituted alkenes are more reactive and the degree and pattern of alkyl substitution on the double bond controls the reaction rate. The reactivity order is similar to the general electrophilic reagents, which is- *tetra* > *tri* > *di* > *mono*. In these substrates steric factors also play an important role for example, *cis* alkenes are more reactive than the corresponding *trans*-isomer.[23]



Scheme 3. *Synthesis of Glabrescol Analog*

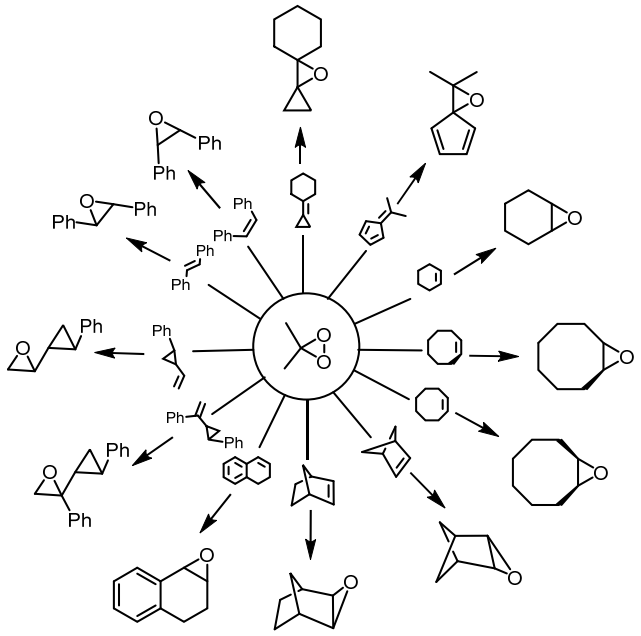
A highlight of this epoxidation protocol was shown by Corey and co-workers in 2000.[24] The author used the Shi's ketone for *insitu* generation of the corresponding dioxirane and it has also been employed for construction of the pentaepoxide of the desired configuration, so that the Glabrescol analog was obtained in 31% overall yield in only two steps. The pentafuran has been used for revision of the Glabrescol structure, a natural product with important biological activity (Scheme 3).

The versatility of Oxone (dioxirane) indicates that it is one of the best epoxidizing reagents among the various reagents available for conducting epoxidations. For the epoxidation of simple alkenes, peracids, especially *m*CPBA, are the most widely used reagents.[25] Although the two oxidants operate mechanistically in a quite similar fashion, steric effects are more pronounced for dioxiranes than for peracids. Compared to other nonmetal-mediated epoxidations [e.g., perhydrates (hexa-fluoracetone/H_2O) and CH_3CN/H_2O_2/HO- (Payne oxidation)], the *insitu* method of dioxiranes offers rewards in terms of reactivity and selectivity. Thus, Weitx-Scheffer conditions (NaOCl, H_2O_2/KOH, t-BuO_2H/KOH) are suited only for electron-poor olefins and *N*-sulfonyloxaziridines are limited to electron-rich enolates and enol ethers.[26] In contrast, dioxiranes oxidize all type of electron-rich and electron-poor double bonds with good selectivities (Scheme 4).



***Scheme 4**. Acid Sensitive Epoxidation*

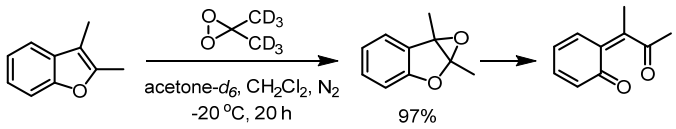
The advantage with the Oxone epoxidations is that the acid-labile groups are compatible. For example, the oxaspiropropane is obtained by epoxidation of the corresponding cyclopropylidene cyclopropene (Scheme 3).[23] Usually, such oxaspiropropane readily rearrange to the respective cyclobutanones. Quite generally, it is observed that the strained double bonds show the highest reactivity towards DMD. The most important advantage of this reaction is for synthetic purpose, seeing as really quantitative yields of epoxides can be readily obtained with either isolated or *insitu* generated dioxiranes. Some typical examples are collectively shown in the following Scheme 5.[23,27]



Scheme 5. *Dioxirane Epoxidation of Unfunctionalized Alkenes*

Epoxidation of Electron-Rich Alkenes

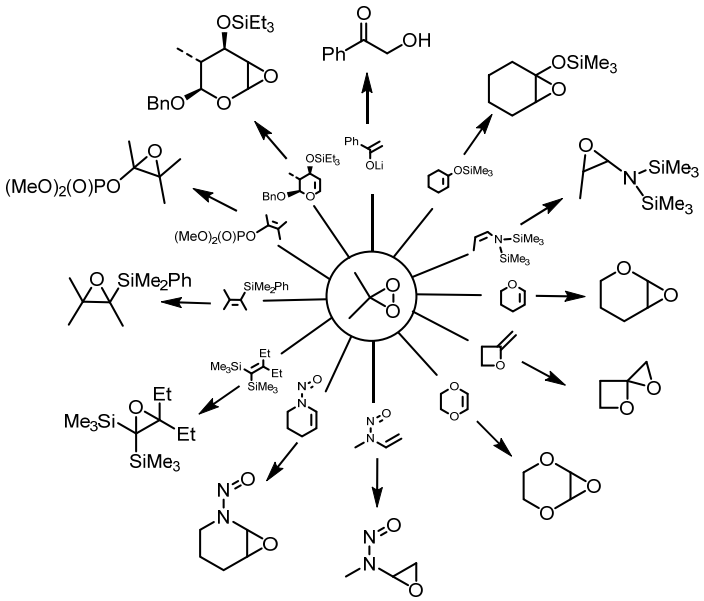
By use of DMD (isol.), a broad variety of electron-rich alkenes are converted into the corresponding epoxides. These reactions have been carried out on large scales with quantitative yields. Even excessively labile examples have been characterized spectroscopically. Electron-rich alkenes are usually more reactive toward oxidation than simple alkenes, and the corresponding epoxides are generally much more labile towards hydrolysis and thermolysis.



Scheme 6. *Dioxirane Epoxidation of 2,3-Dimethylbenzofuran*

In 1991, Adam and co-workers reported a labile epoxide derived from 2,3-dimethylbenzofuran, which even at –20 °C rearranges to the *o*-quinomethide.[28d] Authors characterized this epoxide by ^{1}H NMR spectroscopy, the fully deuterated DMD-d_6 (isol.), prepared in acetone-d_6, was used for the oxidation, and the epoxide was detected at –78 °C (Scheme 6). This emphasizes the importance and convenience if the isolated dioxiranes are employed for the synthesis of exceedingly sensitive substrates. Indeed, the epoxide of 2,3-dimethylfuran, prepared by the epoxidation of

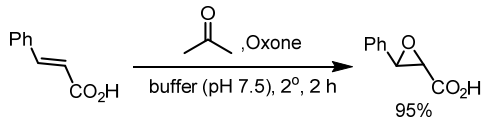
the furan with DMD-d_6 (isol.), could not be detected even at –100 ^{o}C, and only the rearranged product hex-3-ene-2,5-dione was observed. Some typical examples are collectively shown in the following Scheme 7.[28]



***Scheme** 7. Dioxirane Epoxidation of Electron-rich Alkenes*

Epoxidation of Electron-Poor Alkenes

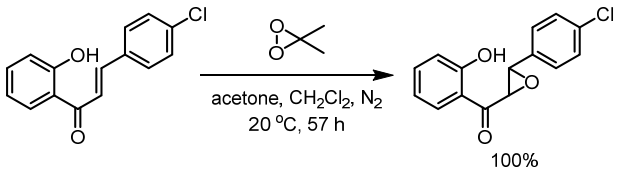
In 1979, Curci and co-workers documented the epoxidation of electron-poor substrates employing the Oxone-acetone combination.[13] The study of *trans*-cinnamic acid epoxidation by DMD (*insitu*) revealed that the resulting epoxides are stable for further hydrolysis and the efficiency of reaction is evident from the quantitative yields obtained (Scheme 8).



***Scheme 8**. Epoxidation of Trans-Cinnamic Acid by Insitu DMD*

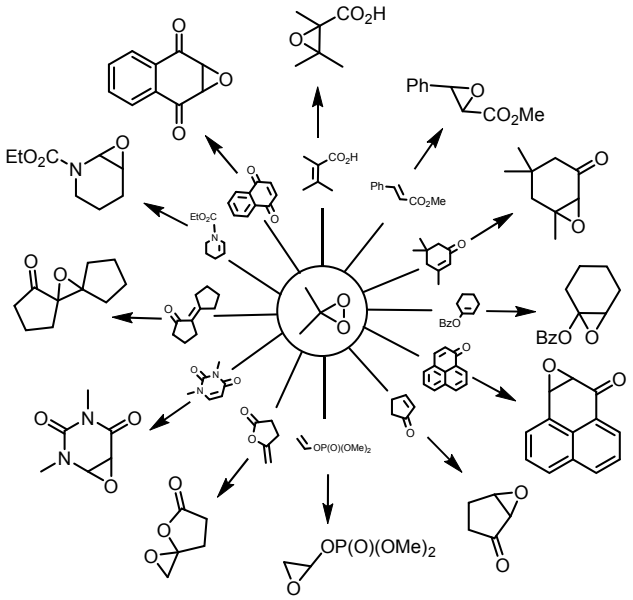
Since the dioxirane is electrophilic and the conjugated alkenes are electron deficient, sometimes, the corresponding epoxidation reactions need much longer time (up to several days) compared to that of electron-rich alkenes (within a few minutes). However, interest continues in this Oxone oxidation of conjugated alkenes, because of the good substrate scope offered, and difficulties for the epoxidation when peracids are employed (require strong basic conditions). However, in some instances, a large

excess of the dioxirane and the conducting of the reactions at elevated temperatures (reflux in acetone) is required in order to get good conversions. Despite this, the Oxone-mediated epoxidations in general are high yielding due to the mild conditions where both hydrolysis and thermolysis of resulting epoxides are negligible. In some epoxidations especially when uncreative electron-poor alkenes are employed, the use of more reactive TFD (*insitu*) gave better results.



Scheme 9. *Dioxirane Epoxidation of α,β-Unsaturated Aryl Ketones*

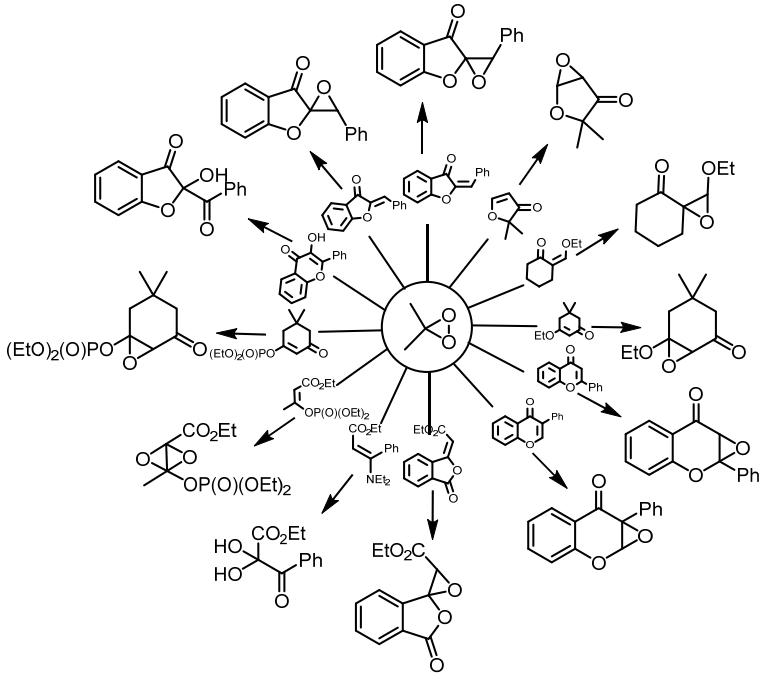
In 1990, Adams and co-workers reported the epoxidation of a number of *α*, *β*-unsaturated ketones and esters that are really difficult to epoxidize with peracids and metal-catalyzed methods.[29b] As shown in Scheme 8, the phenolic group does not require any protection in this process of epoxidation. This till now has not been reported with any other oxidants (Scheme 9). Some typical examples are collectively shown in the following Scheme 10.[13,29]



Scheme 10. *Dioxirane Epoxidation of Electron-Poor Alkenes*

Epoxidation of Alkenes with both Electron Donors and Acceptors

Special classes of olefins such as *β*-alkoxy cyclohexenones, aurones, flavones, and Isoflavones are among the most studied substrates in synthetic chemistry. Their epoxides, which constitute valuable building blocks in natural product synthesis, have been made available for the first time by dioxirane oxidation. The reactivity of these substrates (most of them summarized in Scheme 11) depends on the nature of the substituents, but usually they behave more like the electron-poor substrates, so that at longer reaction times, a large excess of DMD, and elevated temperatures are required for complete conversion. As an example of the *insitu* mode of oxidation, flavone has been epoxidized by TFD in excellent yield.[30]



Scheme 11. *Dioxirane Epoxidation of Alkenes with both Electron Donors and Acceptors*

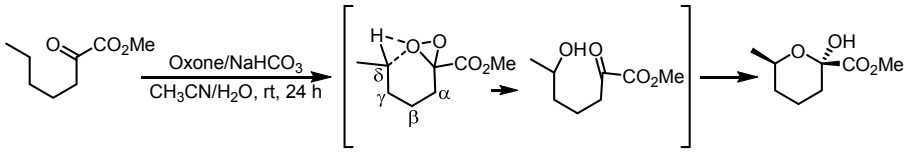
Oxone Oxidation of C−H Bonds

Selective functionalization of saturated hydrocarbons is the Holy Grail for organic chemists and there is a long standing interest to find new ways for unactivated SP^3 C-H oxidations. It has long been of significant importance for both basic research and practical applications in synthetic organic chemistry. With most classical methods of hydrocarbon oxidations, the main problem does not lie much in the particularly low reactivity of the alkane molecules themselves, but rather in the difficulty of achieving selective transformations. Despite several methods being known in literature, there is

still a need for the development of efficient methods for regio- and stereoselective C−H bond activation.[16]

Oxidation of Unactivated C−H Bonds

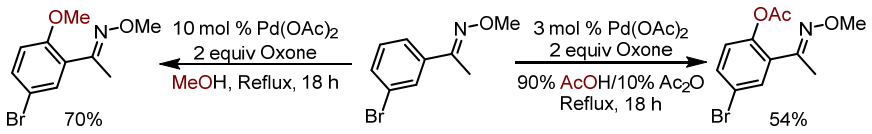
Regioselective oxidation of unactivated C–H bonds has been a challenging problem in organic synthesis. Owing to geometric limitations; intramolecular reactions signify a valuable approach for a regioselective functionalization of C−H bonds. In 1998, Yang and co-workers have reported oxidation of unactivated C−H bonds at the δ site of aliphatic ketones to synthesize tetrahydropyrans (Scheme 12) employing *insitu* generated dioxiranes under mild and neutral conditions.[31] The reaction proceeds with excellent site and stereoselectivity and a preference for tertiary C−H bonds over secondary ones has been noticed.



***Scheme 12**. Selective Oxidation of the δ C-H Bond*

Oxidation of Aromatic C−H Bonds

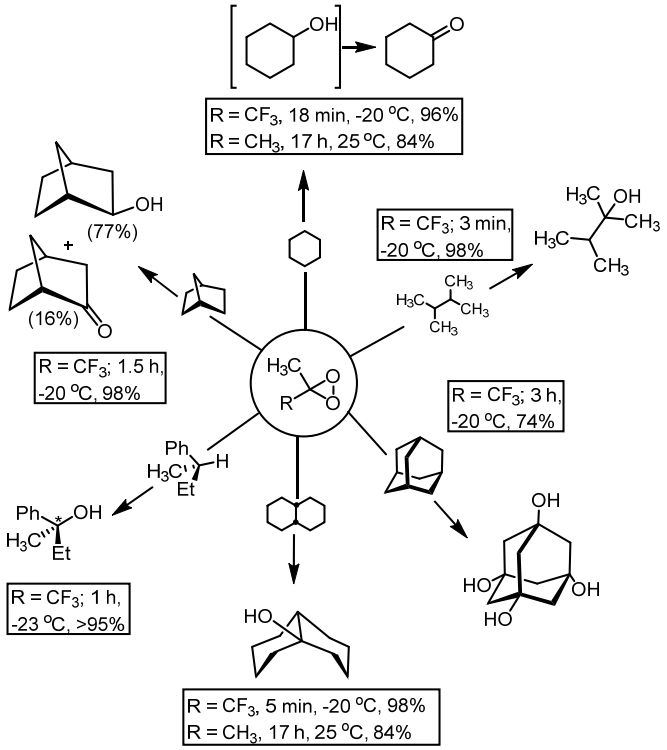
Oxidation reactions by using Oxone are striking because they can be easily, safely, and inexpensively scaled upward. In 2006, Sanford and co-workers reported the acetoxylation reaction of *O*-methyl oximes employing $Pd(OAc)_2$ and Oxone as a co-oxidant on 15 g scale. Remarkably, only 3 mol % of $Pd(OAc)_2$ was enough for large-scale oxidations and the catalyst loading could potentially be reduced even further, albeit with longer reaction times. Depending upon the solvent employed acetic acid or methanol either acetoxy or methoxy groups have been placed on the *ortho*-position to oxime. In addition, a wide variety of functional groups, such as halides, nitriles, ethers, enolizable oxime ethers, amides, and benzylic C−H bonds, were tolerated under these oxidizing reaction conditions (Scheme 13).[32]



***Scheme 13**. Oxidation of Aromatic C−H Bonds Using Oxone*

Oxidation of Hydrocarbon Unactivated C−H Bonds

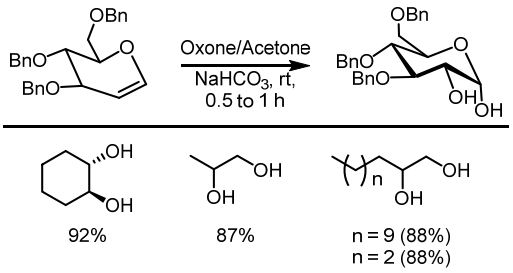
Alkanes containing functional compounds are somewhat rare for oxidation reactions. Several groups have addressed the many problems associated with the reactivity and the selective conversions. Organometallic compounds cover the major areas of research regarding catalytic alkane oxidation. However, several problems remain to be addressed. In this regard a few representative cases demonstrate the key feature of dioxirane reactivity, *i.e.,* its efficiency to give selective *O*-atom insertions into alkane and cycloalkane C-H bonds under extremely mild conditions so that even simple "unactivated" hydrocarbons can be oxy-functionalized (Scheme 14). The inspection of Scheme 14 suggests that these oxidations generally require reaction times of hours and excess oxidant, employing DMD. But it covers a very broad range of cyclic and acyclic hydrocarbons with a very high yield and selectivity in the product formation. Interestingly, the more powerful TFDO is capable of carrying out these transformations often in a matter of minutes and with unchanged selectivity.[14a,16,33]



***Scheme 14**. Dioxirane-Mediated Oxidation of Hydrocarbon C−H Bonds*

Dihydroxylation of Olefins

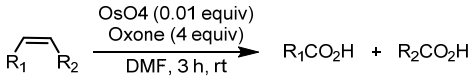
In 2003, Vankar and co-workers reported a new method for conversion of glycals and non-carbohydrate substrates into the respective 1,2-diols, using a mixture of Oxone and acetone in good yields. Interestingly, among the non-carbohydrate substrates, cyclohexene gave a good yield of the diol, but stilbene provided an epoxide, and in some cases the reaction was incomplete. It is known that formation of epoxides and their subsequent ring opening occurs better with glycals as substrates. This is why glycals are more nucleophilic than simple olefins, and the corresponding epoxides are thus more reactive toward ring opening (Scheme 15).[34]



***Scheme 15**. Synthesis of 1,2-diols using Oxone/Acetone*

Oxidative Cleavage of Olefins

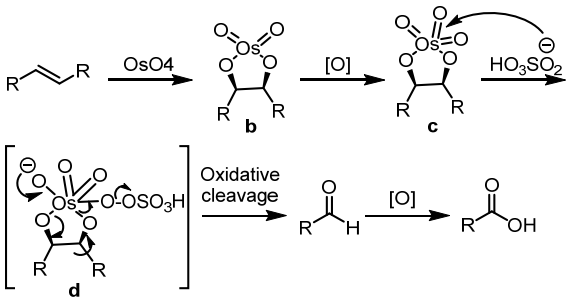
Out of existing several methodologies for oxidative cleavage of olefins the two mainly studied are: (i) transformation of olefins into 1,2-diols followed by cleavage with $NaIO_4$ or other oxidants and (ii) ozonolysis, in which the olefin is directly cleaved into a variety of functionalized products depending on the workup conditions. In 2001, Borhan and co-workers have reported the selective oxidative cleavage of various olefins providing carboxylic acids or ketones using catalytic amounts of OsO_4 and Oxone in DMF as solvent (Scheme 16).[35]



***Scheme 16**. Oxidation of Olefins*

In this process of oxidation (olefins to carboxylic acids), it is believed that Oxone functions in three distinctive oxidizing roles: (1) it oxidizes the initially formed osmate back to Os(VIII), (2) it promotes oxidative cleavage to form an intermediate aldehyde, and (3) it independently oxidizes the aldehyde to the carboxylic acid. There is a certain amount of debate as to the exact mechanism about the oxidative cleavage

proposals, which have been made as to the intermediacy of an osmate ester that undergoes the oxidative cleavage.

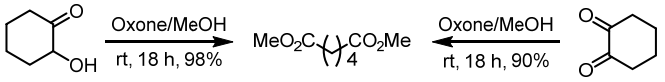


***Scheme 17**. Oxidation of Olefins to Carboxylic Acid*

Scheme 16 shows the proposed mechanism, in which the initially formed osmate **b** is oxidized by Oxone to furnish **c**, which is subsequently attacked by the same reagent written differently to yield intermediate **d**. Fragmentation of **d** regenerates OsO_4 and produces two aldehydes, which can undergo further oxidation to yield carboxylic acids (Scheme17). [35]

Oxidative Cleavage of Carbonyl Compounds

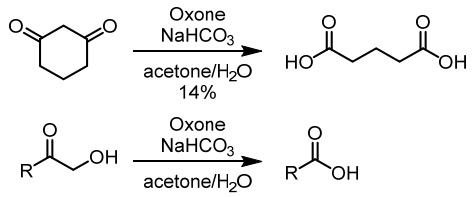
In 2004, Borhan and co-workers reported a methodology to oxidatively cleave *α*-hydroxyketones and *α*- or *β*-diones to diesters using Oxone in methanol as a solvent. Interestingly, oxidation of *α*-hydroxyketones and *α* or any diones in methanol as solvent afforded good to excellent yields of methyl diesters (Scheme 18). Successful screening for cyclic and acyclic *β*-diones affords the desired dimethyl esters in good yields.[36]



***Scheme 18**. Oxidative Cleavage of Dicarbonyls and α-Hydroxyketones with Oxone*

In another study, Ashford and Crega reported the oxidative degradation of 1,3-dicarbonyl compounds and *α*-hydroxy ketones to carboxylic acids using Oxone (Scheme 19). In preliminary results of the oxidative cleavage of 1,3-dicarbonylcompounds and α-hydroxy ketones the author reported that the oxalate derivatives as well as simple malonic esters can be oxidized to carboxylic acids. In a further study, it was also found that the reaction works equally well for aliphatic and aromatic 1,3-diketones. Even the simple symmetrical biaryl diketone undergoes clean

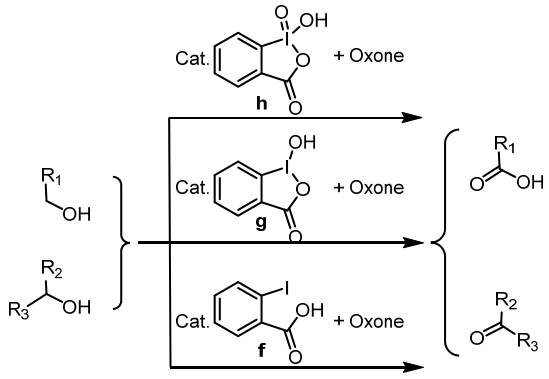
conversion to benzoic acid. On the other hand, the cyclic alkyl diketones afforded the corresponding dicarboxylic acid.[37]



Scheme 19. *Reaction of 1,3-Dicarbonyls and α-Hydroxyketones with Oxone*

Oxidation of Functional Groups

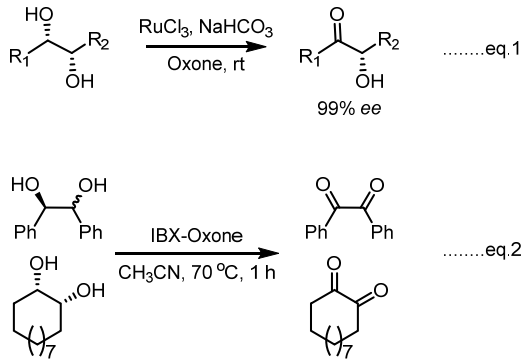
In 1999, Santagostino and co-workers reported a user-friendly methodfor the preparation of IBX (**h**) from 2-iodo-benzoic acid (**f**) employing Oxone in hot water.[38] Inspired by this report in 2005, Vinod and co-workers described the first catalytic use of 2-iodobenzoic acid (**f**) in the presence of Oxone as a co-oxidant for the oxidation of primary and secondary alcohols in aqueous acetonitrile. Oxidation of primary alcohols into the corresponding carboxylic acids is very easy, but it could not be selectively oxidized to the corresponding aldehydes. Secondary alcohols were oxidized to the corresponding ketones, and no Bayer−Villiger oxidation products were observed (Scheme 20).[38]



Scheme 20. *IBX-Catalyzed Oxidations of Alcohols with Oxone*

This Oxone-mediated oxygen-transfer process is very versatile and it was best exemplified by oxidation of vicinal diols. In 2004, Plietker reported the development of the first catalytic, regio- and chemoselective oxidation of vicinal diols to acyloins using $RuCl_3$ and Oxone (Scheme 21, eq. 1). This catalytic oxidation by $RuCl_3$ and Oxone protocol proved to be useful for dehydrogenation of enantiomerically enriched

glycols. Various α-hydroxy ketones were obtained with full retention of enantiopurity and a predictable absolute configuration.[39]



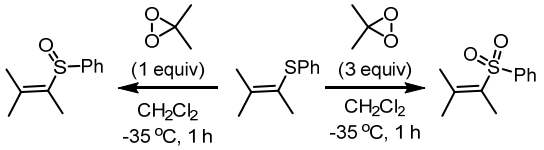
***Scheme 21**. Oxidation of Vicinal Diols*

In a further study, Ishihara's group (2009) reported that benzylic sec, sec-1,2-diol and aliphatic sec,sec-1,2-diol could be oxidized to diketones in moderate to high yields using the IBX-Oxone system (Scheme 21, eq. 2). On the other hand, the study explains that the oxidation of aliphatic diols gave oxidative cleavage products. In the non-aqueous solvent system, the desired carbonyl products were obtained in nearly pure form, by simple filtration of mainly wastes derived from Oxone and the washing with water to take away catalyst derivatives.[40]

Complimentary Oxidations with Oxone

Selectivity is a crucial feature in planning a synthetic sequence, in which a key step may utilize an oxidation by Oxone on multifunctionalized substrates. The reactivity of Oxone has always been important for its incontestable nature in organic synthesis and it is one of the multitalented reagents with the number of opportunities and flexibility for use in oxidation reactions. There are several instances in the literature where Oxone showed unusual reactivity and unexpected products formation that depended on a number of factors such as a small change in the concentration of reagent or additive, and a change in solvent. On the other hand two different substrates under the same reaction conditions result in completely different products. In general, the oxidations with Oxone are carried out in aqueous conditions and preferentially under mild reaction conditions. Generally, oxidations by the electrophilic DMD take place at the site of higher electron density and lower steric demand. Good regioselectivity has been observed in heteroatom oxidations and C-H

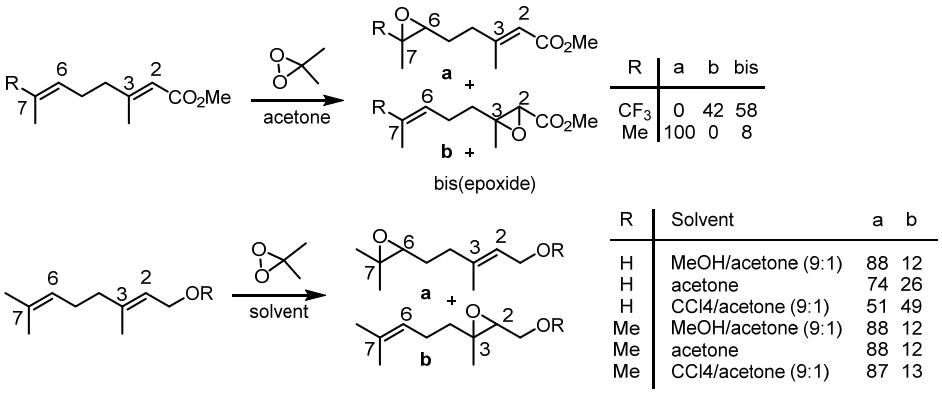
insertions. Here, we have summarized some of those important reactions showing the characteristic properties of Oxone oxidations.



***Scheme 22**. Equivalent Dependent Relative Oxidations of Sulfide*

Murray and co-workers have carried out comprehensive studies on the reactivity of dioxiranes using pure solutions of dioxiranes. In 1987, they reported an interesting observation where the product selectivity depended on the concentration of the reagent used for the reaction. Simple sulfides react with DMD to selectively sulfoxides or sulfones. The reactions are actually instantaneous at room temperature (Scheme 22).[41]

The regioselectivity is mainly dictated by electronic effects in DMD epoxidations; good examples have been shown by different groups. In 1993, Curci and co-workers,[42] followed immediately in 1994 by Bovicelli and co-workers,[43] and in 1996 Adam and co-workers,[44] all developed one of the fantastic applications of Oxone for the regio-, chemo-, stereo-, and diastereoselective epoxidation reactions. Messeguer's group reported on how the site selectivity of epoxidation of internal dienes varies depending upon the substituents present on the olefin. For example, the oxidation of geranic acid with DMDO results exclusively in the formation of unconjugated olefin. On the other hand when one of the terminal methyl groups is replaced with a trifluoromethyl group, the selectivity drops dramatically (Scheme 23).

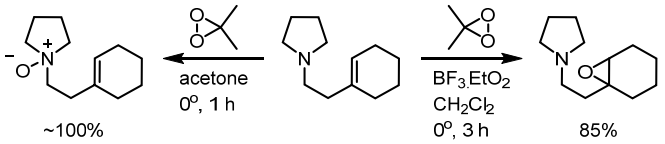


R	a	b	bis
CF_3	0	42	58
Me	100	0	8

R	Solvent	a	b
H	MeOH/acetone (9:1)	88	12
H	acetone	74	26
H	CCl4/acetone (9:1)	51	49
Me	MeOH/acetone (9:1)	88	12
Me	acetone	88	12
Me	CCl4/acetone (9:1)	87	13

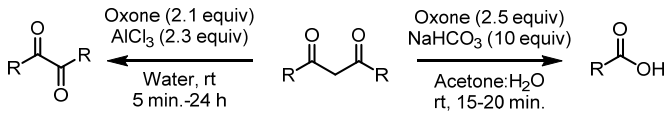
***Scheme 23**. Regioselectivity in DMD Epoxidation*

In another example on the epoxidation of geraniol, it has been shown that the allylic –OH group offers intramolecular hydrogen bonding. For example, selectivity in the epoxidation of geraniol by DMD in protic versus aprotic solvents was shown to shift toward the 2,3-epoxide (from 88:12 in 9:1 MeOH/acetone to 51:49 in 9:1 CCl_4/acetone). In aprotic medium (CCl_4/acetone), the allylic hydroxy group of geraniol stabilizes the transition state structure through hydrogen bonding with the dioxirane and, consequently, the less nucleophilic 2,3-double bond competes more efficiently in the epoxidation. In the protic medium (9:1 MeOH/acetone), methanol engages in the hydrogen bonding with the dioxirane and the substrate, thus reducing the role of the allylic hydroxy group.[45]



Scheme 24. *Chemoselectivity in DMD Oxidation*

In 1995, Messeguer and co-workers have reported the chemoselective oxidation of tertiary amines bearing alkenes. In general, reactions loading to the epoxidation of a substrate with a double bond in the presence of heteroatom functionality (sulphide or amide) are not practical without protection. The author have reported a particular example of substrate, with selectivity of product either epoxide formation or *N*-oxide formation reactions (Scheme 24).[46]

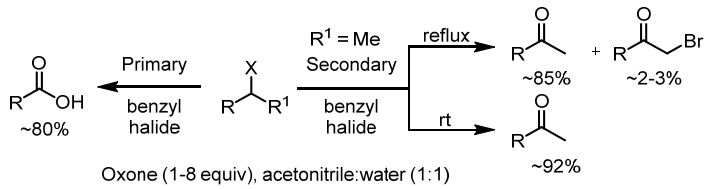


Scheme 25. *Oxidative Degradations by Using Oxone*

In 2001, Ashford and co-workers developed a novel method for oxidative degradation of 1,3-dicarbonyl compounds and *α*-hydroxy ketones into the analogous carboxylic acids by using Oxone.[47] Further in 2013, Smonou and co-workers in continued their study for the reactions of *β*-keto esters and 1,3-diketones with Oxone.[48] In this report the authors have developed another highly efficient, mild, practical, and convenient method for the synthesis of simple *α*-keto esters and 1,2-diketones using inexpensive, non-toxic reagents in the aqueous medium (Scheme 25).

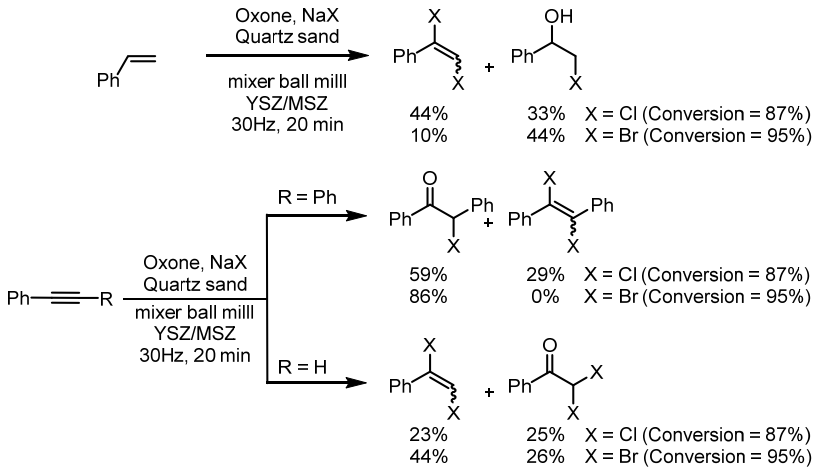
***Scheme 26**. Oxidation of Aldehydes to Carboxylic Acids/Esters*

In 2003, Borhan and co-workers reported a simple protocol for the oxidation. These reactions may possibly be important alternatives to traditional metal-mediated oxidations. Here the author has reported the oxidation of aldehydes to carboxylic acids utilizing Oxone as the sole oxidant. Conversion of aldehydes into their corresponding ester products by using alcoholic solvents is also reported (Scheme 26).[49]



***Scheme 27**. Oxidation of Primary and Secondary Halides*

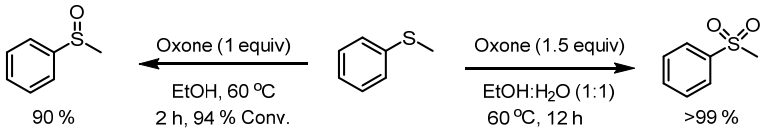
In 2012, Moorthy and co-workers found that Oxone can be employed directly for oxidation of a number of benzyl halides. In a detailed study the authors reported the conversion of activated primary and secondary halides to the corresponding acids and ketones, respectively. The rate of oxidation completely depends on the medium employed for the reaction and different rates were observed for differently-substituted substrates (Scheme 27).[50]



***Scheme 28**. Selectivity for Solid-State Halogenation*

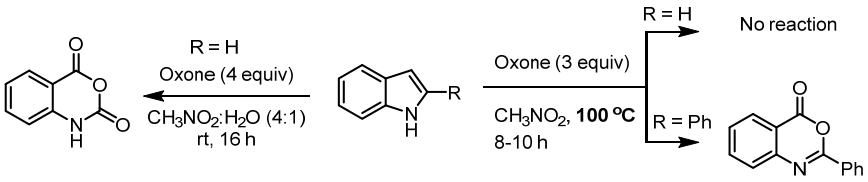
Later, in 2012 Stolle and co-workers reported another efficient method for the formation of aryl chlorides and bromides by using Oxone and NaX (X = Cl, Br) using the ball mill technique. In this report it was very clearly observed that apart from

halogenation of aromatics, unsaturated functional groups like alkenyl and alkynyl groups, which were tagged to a phenyl ring, were accessible for halogenation. For example the halogenation of styrene and phenyl acetylene provided 1,2-dibromostyrene. In addition, the oxidation products 2,2-dibromo-1-phenylethan-1-ol or 2,2-dibromo-1-phenylethanone were formed respectively. If at all possible, activated substrates are halogenated, whereby bromination afforded superior product yields than chlorination (Scheme 28).[51]



Scheme 29. *Solvent-Controlled Oxidations of Sulfoxide or Sulfone*

In 2012, He and co-workers revisited the reactions of sulfoxide or sulfone in a more selective and controlled fashion. The authors have claimed good result for solvent-controlled oxidative sulfoxidation high conversion as well as tunable chemo-selectivity. The striking feature is the selective oxidation to the sulfoxide or sulfone can be achieved by changing the solvent and using Oxone as a reagent, under safe and mild conditions without any additional reagent (Scheme 29).[52]



Scheme 30. *Oxidations of Indoles*

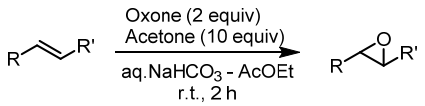
Recently, in 2013 Guan and co-workers reported a novel and efficient method for the oxidation of 2-arylindoles to synthesize 2-arylbenzoxazinones utilizing Oxone as the sole oxidant.[53] In this study the authors reported the requirement of 2-aryl for this observation. In addition to this work a very recent study of Grundt and co-workers (2013), overcame the problem of a compulsory 2-aryl group in indole system and developed a new method for the synthesis of biologically important isatoic anhydrides by using Oxone under very mild conditions (Scheme 30).[54]

This selective compilation of oxidations with Oxone *inter alia* with dioxiranes reveal its broad spectrum utility, tolerance for a wide-range of groups and arguably the reactions proceed at ambient temperatures. Despite a voluminous amounts of work

documented there are still opportunities for further exploration with Oxone. In the preceding section, we document two unusual and complementary Oxone-acetone mediated oxidations of benzofused olefins such as indenes and dihydronaphthalenes resulting in either *syn*-dioxygenation or a Wacker-type oxidation.

Present Work

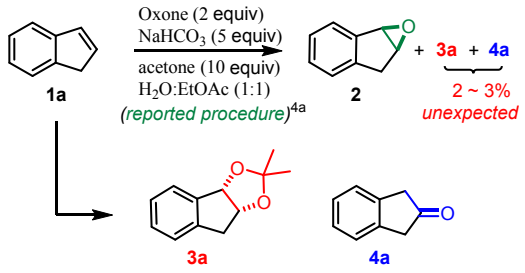
Epoxidation, dihydroxylation, and oxidation to ketone are some of the important oxidative transformations of olefins, where Oxone has been widely employed for epoxidations.[12-16] The 1,2-diol unit is one of the most ubiquitous moieties in natural products, pharmaceuticals and has arguably attracted a significant amount of synthetic maneuvers for a long time.[55] The *syn-/anti*-dihydroxylation of alkenes has been considered as a simple approach for the installation of these 1,2-diol units, which in general has been mainly reserved for the metal-based reagents.[9] OsO_4, introduced by Criegee, is the most commonly employed catalyst for the *syn*-dihydroxylation of olefins and has been central to many developments in this area.[56] The toxicity of osmium, taken together with its volatility, has led to the exploration of several other metals for this purpose. However, in general, the metal based *syn*-dihydroxylations have limitations in terms of the waste generated and also because of the difficulties involved in the complete removal of the metal impurities from the products.[10] Thus, the metal free method for the dihydroxylation of alkenes is the most desired alternative and renewed interest has been shown in this field in recent years.[57] Phthaloyl peroxide is the first reagent that has been employed for the metal free direct dihydroxylations by Greene.[58] Though the reaction is stereospecific and documented as early as in 1956, the problems associated with instability/explosive nature of the reagent and the poor product yields have been dealt with only recently by introducing cyclic acyl peroxides by Tomkinson and co-workers.[17] The closely related more reactive cyclic peroxides, the dioxiranes, have been widely employed for the epoxidations. The one-pot combination of olefin epoxidation and the subsequent opening leading to vicinal-diols has also been well established with the dioxiranes.[34] However, it results either in *trans*-dihydroxylation products or a diastereomeric mixture depending upon the conditions. In spite of the myriad methods available, advantageous methodologies in terms of selectivity, availability of starting material, operational simplicity, functional-group tolerance, environmental sustainability and economy are in constant demand.



***Scheme 31**. Epoxidation of Olefins Using Oxone*

Metal-Free *Syn*-Dioxygenation of the Benzo-Fused Olefins Employing Oxone

Our entry in this area was accidental, while preparing a well known indene oxide on multi-gram scales by employing the Oxone. In 2002, Hashimoto and co-workers reported a practical and efficient process for epoxidation of aromatic olefins using Oxone in a two-phase system (ethyl acetate-water). The reported method is suitable for large-scale synthesis and covers diverse aromatic olefin substrates (Scheme 31).[59] In our study, while following the exact reported protocol for large scale epoxidation of indene, under prescribed conditions, along with the required epoxide **2**, we always ended up with some side products (2–3%). Since the reactions are conducted on more than 20 g, we were able to isolate both the products as well as white solids (**3a** & **4a**) and both have been characterized by using ^{1}H & ^{13}C NMR (Scheme 32).



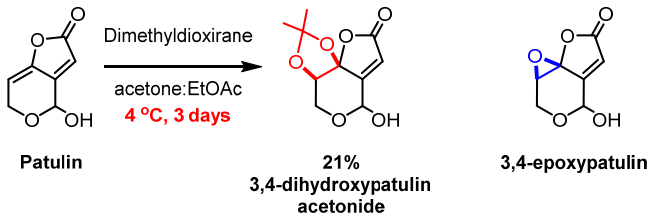
***Scheme 32**. Gram Scale Synthesis of Indene Oxide*

Coming to the compound **3a**, in the ^{1}H NMR spectrum, all the four aromatic protons resonated at δ 7.39–7.42 (m, H), δ 6.37–6.50 (m, 3H) ppm and another two protons at δ 5.54 (d, J = 5.6 Hz, 1H) & 4.99 (ddd, J = 2.2, 4.2, 5.6 Hz, 1H) ppm while sharing a similar coupling constant value 5.6 Hz, which clearly suggests the vicinal coupling of these two protons. Remaining signals at δ 3.14 (dd, J = 2.2, 4.2 Hz, 2H) are characteristic of CH_2 protons in the five membered indene ring system. Finally we characterized specific two singlets with the value of δ 1.40 (s, 3H) & 1.21 (s, 3H). These two signals clearly tell us the presence of acetonide in the current compound. In the ^{13}C NMR spectrum of compound **3a**, the four aromatic carbons (CH) resonated at δ 128.9 (CH), 125.7 (CH), 127.2 (CH) and 125.4 (CH) ppm as doublets. Similarly, two quaternary aromatic carbons resonated at δ 141.4 (C) &140.9 (C) ppm as singlet. The characteristic signal for the acetonide quaternary carbon resonated at δ 110.7 (C) as a singlet. Additionally, it was confirmed by comparing the recorded NMR data with the reported one.[60] It is somewhat more exciting for us to find the more surprising structure of **3a**, with the additional curiosity of the characterization of

another white solid compound (**4a**) being done. Similar to the first compound, in ^{1}H NMR spectrum of compound **4a**, all the four aromatic protons resonated at δ 7.26–7.31 (m, 4H) ppm and there was another only one singlet that resonated at δ 3.57 ppm integrating for four protons. In ^{13}C NMR spectrum of compound **4a**, a characteristic signal indicating the presence of a carbonyl group was seen at δ 215.3 as a singlet. There is only one CH_2 peak noticed at δ 44.1. This information quickly revealed that the compound is 2-indanone **4a** and that the data recorded exactly matched with the earlier reported data.[61]

After having the confirmed structures for these two side products in hand, we are more interested to understand the genesis of their formation. Initial experiments by continuing the reaction for longer times did not offer any improvement in the side products formation. This revealed that the epoxide **2** is not converting in to these side products **3a**/**4a** and that may be happening independently. Intrigued by this, we carried out an extensive literature search that revealed a couple of reports showing the formation of such acetonides along with the expected epoxides in the Oxone-acetone oxidation. However, none were seen for the direct oxidation of an olefin to ketone (Wacker-type oxidation).

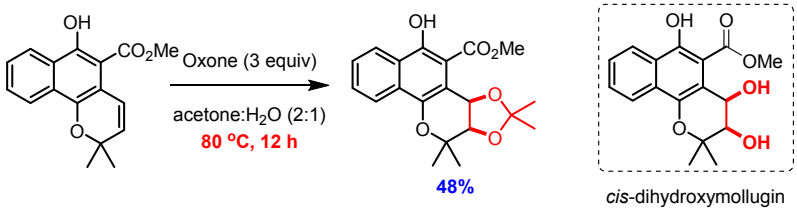
In 2000, White and co-workers, for the first time came across this unusual reactivity with DMDO while doing the well-known dihydroxylation reaction. For the preparation of 3,4-epoxypatulin, the reaction of patulin with dimethyldioxirane in acetone was sluggish and yielded a compound that was assigned the structure of 3,4-dihydroxypatulin acetonide (Scheme 33).[62]



***Scheme 33**. Synthesis of Patulin Analogues*

Later on, in 2008, De Kimpe and co-workers reported the *syn*-dihydroxylation as a side reaction during the epoxidation by using Oxone for the synthesis of 3,4-dihydroxymollugin (Scheme 34). In this report, the authors studied this reaction with all possible variations but clearly mention that this is a very specific substrate that yielded the dihydroxylation product. In the mechanistic proposal for the dioxirane-

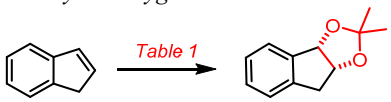
mediated formation of 3,4-dihydromollugin acetonide, the authors presumed two different mechanistic possibilities, i. radical cyclization, and ii. *via* epoxide opening.[63]



Scheme 34. *Synthesis of 3,4-Dihydroxymollugin*

In both the examples, the reaction has been considered as an unusual event and thus had been limited to a single substrate. The formation of the acetonide is most readily rationalized as possibly arising from epoxide that reacts with acetone in the presence of a trace amount of acid. However, the intermediacy of a dioxyl radical, mooted by Murray and considered by others, cannot be expelled, and may be preferred in reactions with less-reactive double bonds.[41] Intrigued by this observation and in anticipation of the developing metal free dioxygenation and/or Wacker-type oxidation, the possibility of selective oxidation of indene **1a** with Oxone has been explored.

Table 1. *Conditions Explored for the Syn-Dioxygenation*



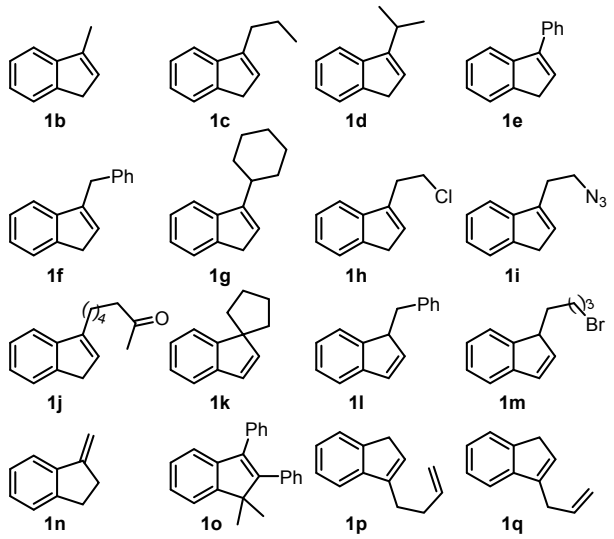
Sr. No.	Oxone (equiv)	$NaHCO_3$ (equiv)	Organic Solvent	TBAI[b] (equiv)	% of Conversion	% Yield[c] (**3a**)
1	0.5	1	EtOAC	-	10	--
2	0.5	2	EtOAC	-	25	20[d]
3	0.5	3	EtOAC	-	40	--[e]
4	1	3	EtOAC	-	40	12[d]
5	2	3	EtOAC	-	100	82
6	2	3	EtOAC	0.1	100	80
7	2	3	DCM	-	60	50
8	2	3	DCM	0.1	66	55
9	2	3	Toluene	-	75	60
10	2	3	Toluene	0.1	78	62
11	2	2	EtOAC	-	90	71
12	3	3	EtOAC	-	100	83
13	4	3	EtOAC	-	100	70[d]
14	4	5	EtOAC	-	100	55[d]

*[a] all the reactions are carried out at rt with 0.5 mmol of indene in 2.5 ml acetone and 0.5 ml of (1:1 of H_2O + solvent); [b] TBAI = n-$Bu_4N^+I^-$; [c] isolated yield; [d] mixture of products (**2**+**3a**+**4a**); [e]* ***4a*** *was obtained in 35% isolated yield.*

At the outset, the dioxygenation of **1a** was examined with all achievable discrepancies in parallel mode for arriving at the right conditions (Table 1). After exhaustive experimentation; we could recognize the right circumstances to impel the reaction absolutely towards the *syn*-dioxygenation. Somewhat surprisingly, unlike with the epoxidation where the acetone had been used as the reagent, in the optimized conditions for the *syn*-dihydroxylation, the acetone was found to be the solvent. Otherwise, both the base and Oxone were employed in almost the same molar fractions, similar to the case of epoxidation. Control experiments revealed that a 1:1 proportion of ethyl acetate and water with acetone is the best combination of solvent. Other organic solvents like toluene and dichloromethane are not found to be that good. We expect that by the use of phase transfer catalysts will increase the speed of product formation in the reaction, but in the current transformation the use of TBAI [n-$Bu_4N^+I^-$] has no such effect on the reaction. The optimized reaction conditions involve the addition of 2 equivalents of powdered Oxone to a stirred slurry of 3 equivalents of sodium bicarbonate ($NaHCO_3$) and 1 equivalent of indene (**1a**) in a mixture of solvents 5:1:1 (acetone + ethyl acetate + water). With simple indene, the reaction was completed in 4 h and the required **3a** was formed as the sole product in 82% yield. With this condition, the single product formation takes place with complete consumption of the starting material. Mainly the solvent system and equivalents of Oxone/base is important, a slight change (increase or decrease) in amount of Oxone/base changes the product formation swiftly. In most of the cases, we find the inseparable mixture of products. Amazingly, even the rate of conversion is very less. We find that the use of 0.5 equivalents of Oxone with 3.0 equivalents of sodium bicarbonate at the current solvents system 5:1:1 (acetone + ethyl acetate + water) gives the single product ketone **4a**, albeit in low yields.

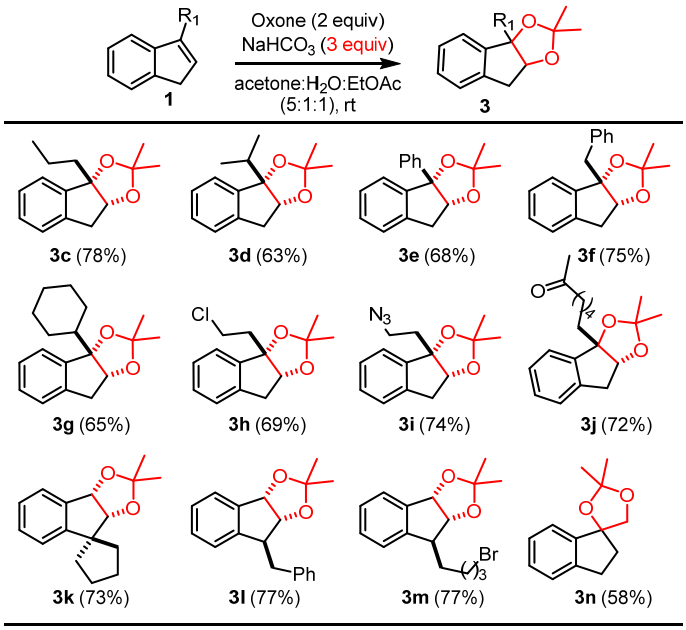
These initial results on solvent-driven reactivity change are remarkable with substantial opportunities for further exploration. Further scope of this *syn*-dioxygenation reaction has been generalized by employing various substituted indene derivatives (Table 2, detailed procedures for synthesis are given in the experimental section).

***Table 2**. Prepared Different Substituted Indene Derivatives*

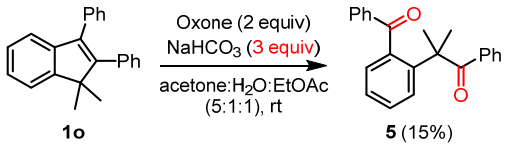


In general, the reactions are highly selective towards the *syn*-dioxygenation and the corresponding acetonides were isolated in excellent yields. A wide range of indenes mainly having the substituent variations on olefin have been tested for the reactions. The substrates having simple long chain n-propyl (**1c**) and iso-propyl (**1d**), similarly cyclohexyl (**1g**) work well and gave the corresponding products **3c**, **3d** and **3g** in good yields. The simple phenyl (**1e**) substituent on the olefin also finds compatibility for the current transformation (**3e**). In addition, the indene derivatives containing sensitive functional groups such as chloro (**1h**), azide (**1i**), carbonyl (**1j**) and bromo (**1m**) on the side chains are also compatible under current conditions and gave the corresponding products (**3h**–**3j** and **3m**) in good to excellent yields. Substituent like benzyl at 1- or 3- positions of indene (**1f**, **1l**) has no effect on the reaction and resulted in corresponding acetonides with good yields. The spiro[cyclopentane-1,1'-indene] (**1k**) and 1-methylene-2,3-dihydro-1*H*-indene (**1n**) were also found to be compatible under these conditions and gave the corresponding acetonides **3k** and **3n** in very good yields (Table 3).

Table 3. *Scope of Oxone-Acetone Mediated Syn-Dioxygenation*

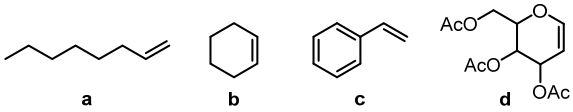


The reaction of tetra substituted 1,1-dimethyl-2,3-diphenyl-1*H*-indene (**1o**) deserves a special mention. The reaction of **1o** was sluggish and after a long time gave exclusively the diketo derivative **5** (15%) as the main product (Scheme 35).



Scheme 35*. Reaction of Tetra Substituted Indene**1o***

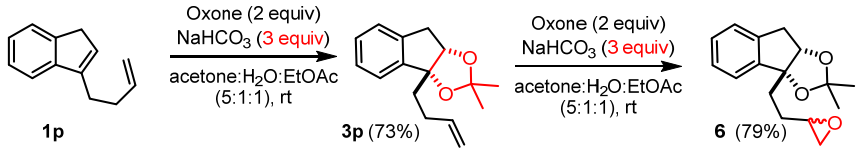
Next, we intended to examine the scope of this reaction with simple acyclic and cyclic olefins. The easily availableoct-1-ene (**a**), cyclohexene (**b**), styrene (**c**) and triacetylglucal (**d**) have been subjected for the oxidation under the current conditions. In all the cases the usual epoxidation was the main event (Scheme 36) and in case of triacetylglucal, the corresponding diol was isolated in moderate yields.



Scheme 36*. Other Olefins Screened for Current Reaction*

Following the disappointment with the simple olefin substrates, we intended to check the selectivity of this reaction. For this purpose, we planned a substrate

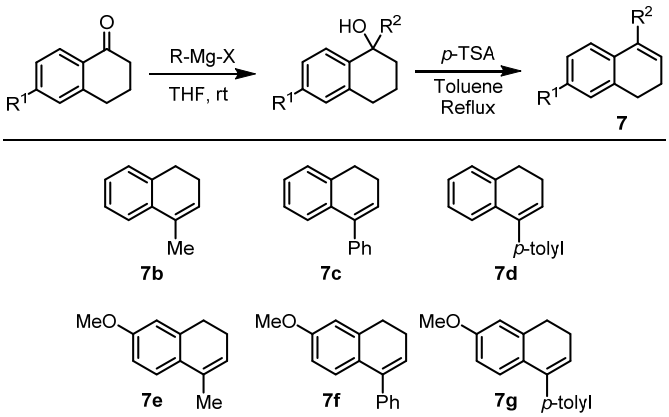
containing both benzo-fused cyclic as well as pendent alkenyl group at C_2, 3-(but-3-en-1-yl)-1*H*-indene (**1p**). Substrate **1p** was synthesised by a simple two-step sequence that comprises of adding 3-butenyl magnesium bromide to indene and then dehydration of the resulting alcohol. Next, the diene **1p** has been subjected for Oxone-acetone mediated dioxygenation. Under our conditions, the internal olefin reacted exclusively leaving the pendant alkenyl unit intact and provided the corresponding acetonide **3p** in good yield (Scheme 37). The exclusive formation of the acetonide from **1p** with Oxone clearly indicated that this process is much faster than the epoxidation and that the indenyl olefin is much more reactive than the pendant terminal alkene. When **3p** was treated again with Oxone under the same conditions, the corresponding diastereomeric mixture of epoxides **6** was isolated in 79% yield. These observations epoxidation of simple olefins and exclusive formation of acetonide in the case of **3p**, reveal that the current reactivity of dioxirane was limited only with the activated cyclic olefins.



***Scheme 37**. Controlled Experiment for Regio-Specific Reactivity*

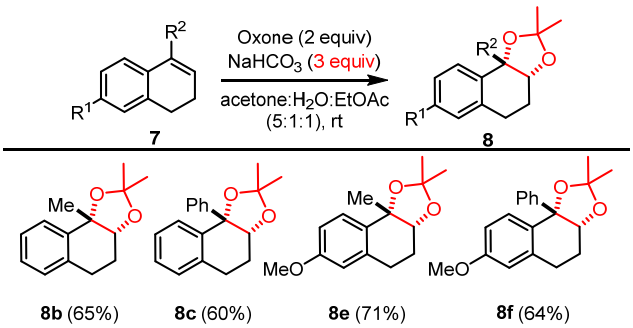
Having known the specific requirements for the current reaction output with Oxone, we next proceeded for testing with the related dihydronaphthalene derivatives. We synthesised differently substituted dihydronaphthalene derivatives **7b**–**7g**, by using the known two step protocol (Scheme 38) starting from alpha-tetralone derivatives (the detailed procedures are given in the experimental section).

Scheme 38. *Synthesis of Dihydronaphthalene Derivatives*



The *syn*-dioxygenation of these synthesized dihydronaphthalene derivatives **7b**, **7c**, **7e** and **7f** have been examined under our conditions. The oxidation of the dihydronaphthalenes having a substituent on the olefin like methyl (**7b**) and phenyl (**7c**) proceeded smoothly and provided the corresponding acetonides **8b** and **8c** in good yields . Also, the dihydronaphthalenes **7e** and **7f** containing the substituent on olefin as well a *p*-methoxy on the aromatic ring are also compatible and provided the requisite acetonide products **8e** and **8f** in good yields (Scheme 39).

Scheme 39. *Syn-Dioxygenation of Dihydronaphthalene Derivatives*

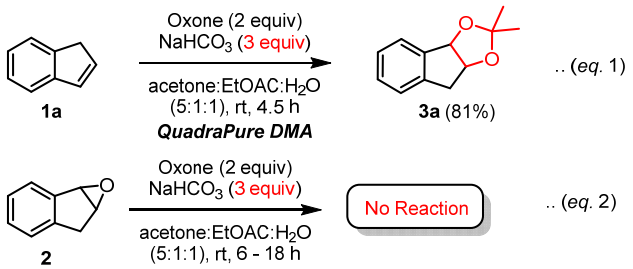


Mechanistic Investigation

To this end, we could conclude that the Oxone-acetone combination can be employed for the direct conversion of olefins to acetonides provided they are cyclic and fused to aromatic rings. This is a limitation and as we mentioned the current reaction works with very specific substrates. This reactivity is quite abnormal and demands a detailed study to understand what paves the path for the current products. In this regard, we carried out specific control experiments followed by model studies in order to gain mechanistic insight in to the present reaction.

Our first concern in this whole process was to know the possibility of this oxidation resulting from the catalysis by trace metal impurities present in the $NaHCO_3$ or Oxone. As shown in Scheme 40, eq. 1, the Oxone-acetone mediated dioxygenation reaction has been examined under similar conditions in the presence of QuadraPure™ DMA (1:1 w/w with respect to the indene) a known scavenger for metals such as Pd, Cu(I), Cu(II), Ni, Pt, etc.[64] The reaction proceeded as usual without any interference from the added metal scavenger, thus ruling out that this oxidation reaction could be the result of trace metal impurities in the $NaHCO_3$ or Oxone.

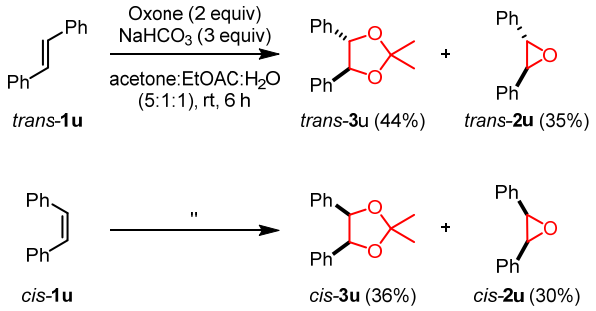
Next, we examined the possibility of the current reaction involving an intermediate epoxide. In this regard, indene oxide **2** was subjected for oxidation under current conditions which revealed that it was intact. This confirmed that epoxide is not an intermediate in this transformation (Scheme 40, eq. 2).



Scheme 40**. A Controlled Experiment to Examine the Involvement of Trace Metal Impurities and Epoxide **2

Stereospecific Oxidation of *cis*-/*trans*-Stilbenes

Next, when it became apparent that the epoxide is not responsible for the current reaction outcome, we proceeded to know the stereospecific nature of the reaction. In this context, we planned to use *cis*- and *trans*-stilbenes to check the reaction feasibility and, if reaction worked then the stereospecificity of the dihydroxylation process. When these two substrates were subjected for the oxidation under the current conditions, the reactions in both the cases were sluggish and gave a mixture of epoxide and acetonide products. Interestingly, both epoxidation and syn-dioxygenation reactions are completely stereospecific. The *trans*-stilbene gave exclusively the corresponding *trans*-acetonide and *trans*-epoxide in moderate yields. Similarly, the *cis*-stilbene gave the corresponding *cis*-acetonide and *cis*-epoxide (Scheme 41).



***Scheme 41**. Synthesis of 3,4-Dihydroxymollugin*

All the products resulting from the stilbene-oxidations have been characterised and identified by using ^{1}H NMR. The ^{1}H NMR of the *cis*- and *trans*-acetonides display quite different patterns. For example, the two methyl groups from acetonide seem to be resonating as one singlet (for six protons) in case of *trans* and two separate singlets (for three protons each) in case of the *cis*-acetonide. For *trans*-acetonide ^{1}H NMR: δ 1.67 (s, 6H), 4.78 (s, 2H), 7.21−7.23 (m, 3H), 7.30−7.32 (m, 6H), 7.35 (d, J = 3.3 Hz, 1H) ppm; For *cis*-acetonide ^{1}H NMR: δ 1.62 (s, 3H), 1.83 (s, 3H), 5.49 (br.s, 2H), 6.90−7.23 (m, 10H) ppm. This observed stereospecific 1,3-dioxlane formation evidently reveals that the epoxide is not involved as an intermediate in this process.[65]

GC Analysis for the Reaction of Indene to Acetonide

Also, the monitoring of the dihydroxylation of indene **1a** with GC has disclosed that there were no detectable amounts of indene oxide **2a** during the entire

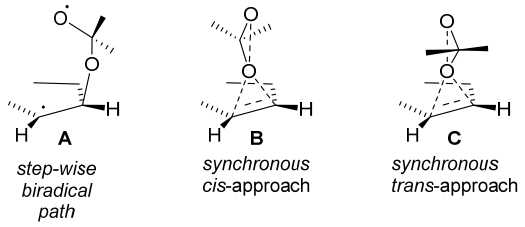
course of this reaction. The reaction has been analysed with the help of GC for every 30 minutes until the complete consumption of the starting indene (see the experimental section for details).

Intramolecular Oxidation with Proposed Substrate 1r

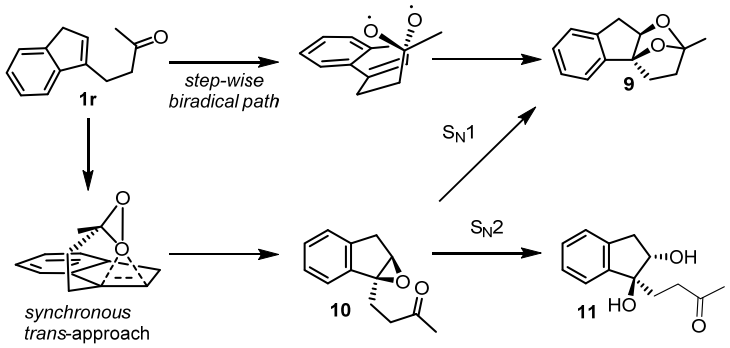
At this stage, it becomes apparent that the current deoxygenation with Oxone-acetone combination is unique and proceeds independently without any epoxide intermediate involvement and that the reactions are stereospecific. This suggests that the nature of the intermediate dioxirane involved is solvent dependent since the same indene undergoes epoxidation when employed in different conditions.

In general, there are two possible mechanistic proposals that have been in debate for oxygen transfer from the dimethyldioxirane (DMDO) to olefin. These are - i. a step-wise diradical pathway or ii. a non-polar concerted path (Fig 1).[66-68] Although the possibility of the first path has been criticized, theoretical calculations have indicated that in such a case, the formation of a 1,3-dioxolane would be preferred both thermodynamically and kinetically.[67d] Coming to the more accepted concerted path, a spiro butterfly transition state involving the nucleophilic approach of olefin with the O–O bond of the DMDO [*cis*- or *trans*- approach depending upon the relative orientation of the *gem*-dimethyl group of DMDO with respect to the bulky substituent of the olefin, (Fig 1)] along with an S_N2 type of coordinate has been proposed.[67]

Figure 1. *Proposed Transition States for DMDO*

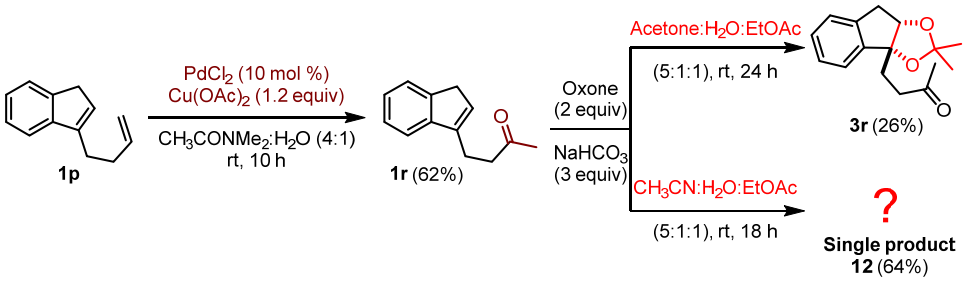


For gaining additional mechanistic insights in this current transformation, we planned to employ indene derivative **1r** for intramolecular oxidation as a model substrate. The outcome of the intramolecular Oxone-mediated oxidation of indene **1r** is expected to be significant.



Scheme 42**. Possible Outcome of Oxidation of Indene **1r

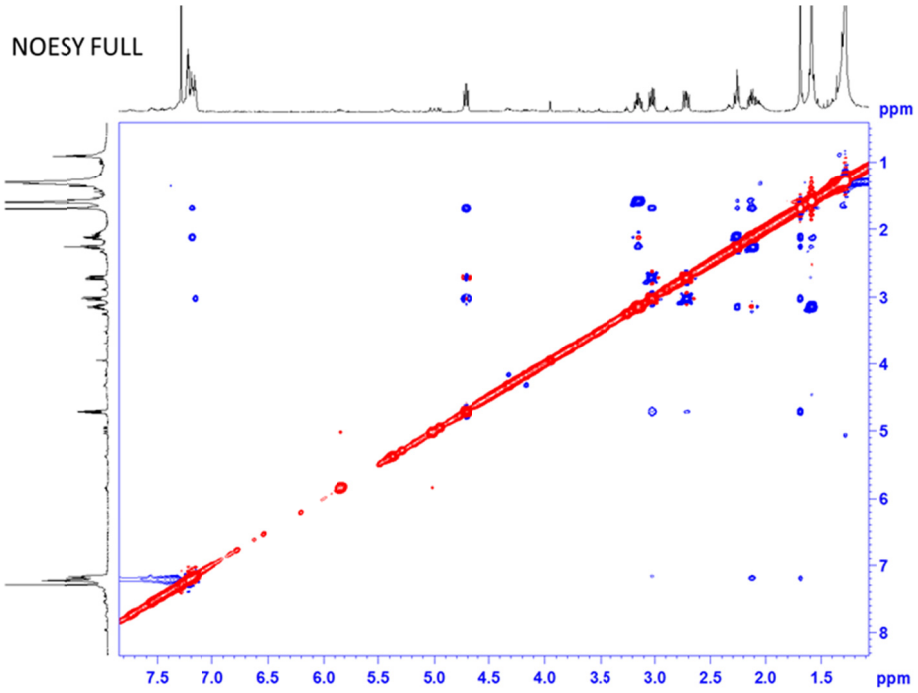
Considering these earlier mechanistic proposals (Scheme 42), two products are expected from the oxidation of **1r** either i. bridged bicyclicketal **9** or ii. *trans*-diol **11**/its derivatives. The bicyclic ketal **9** is expected through a stepwise diradical mechanism. A concerted process should provide the intermediate epoxide **10** that subsequently opens in S_N2 fashion leading to the *trans*-diol **11**. The bicyclic ketal **9** is also expected from the intermediate epoxide **10** through an S_N1 mechanism for its opening [formation of a benzylic cation (3° carbocation) from the epoxide **10** should be even more facile when compared with the indene epoxide **2** (2° carbocation)]. Thus, the formation of the *trans*-diol **11**/its derivatives should rule out both the possible step-wise processes for the 1,3-dioxolane formation.



***Scheme 43.** Synthesis of Model Substrate **1r** and its Oxone-Mediated Oxidation*

Scheme 43 describes the synthesis of the model substrate **1r** and its subsequent Oxone-mediated oxidation. The Wacker oxidation of the indene derivative **1p** having a pendant but-3-enyl proceeded selectively at the terminal olefin and provided **1r**. The intramolecular oxidation reaction of the model substrate **1w** with Oxone in acetone is very sluggish and provided very less yield of acetonide product **3r** along with some other mixture of products. Under similar conditions and when acetone was replaced with acetonitrile, the reaction proceeded smoothly with

formation of a single product **12** in good yield. The newly formed compound **12** was characterized with ^{1}H NMR: ***δ*** 1.55 (t, *J* = 4.0 Hz, 2H), 1.65 (s, 3H), 2.12 (dt, *J* = 5.0, 8.5 Hz, 1H), 2.25 (dd, *J* = 7.2, 12.1 Hz, 1H), 2.71 (dd, *J* = 10.3, 14.6 Hz, 1H), 3.02 (dd, *J* = 7.2, 15.0 Hz, 1H), 3.15 (dt, *J* = 7.7, 13.1 Hz, 1H), 4.7 (dd, *J* = 7.9, 10.2 Hz, 1H), 7.12–7.16 (m, 2H), 7.17–7.20 (m, 2H). The ^{13}C NMR of the compound **12** clearly indicated the presence of a ketal carbon (*δ* 107.9 ppm about 3 ppm deviation from a similar [2,2,1]-bridged bicyclic ketal), both the NMR's are in agreement for the presence of bicyclic ketal **9** as a product. However, mass spectrometry shows that the observed value for the product is (HRMS (ESI+)) 427.1880. This is exactly twice than of the bicyclic ketal **9**. Further to this, the NOESY analysis of compound **12** indicated a *trans*-diol configuration present in the formed product, which is not possible in bicyclic ketal **9** (Figure 2).



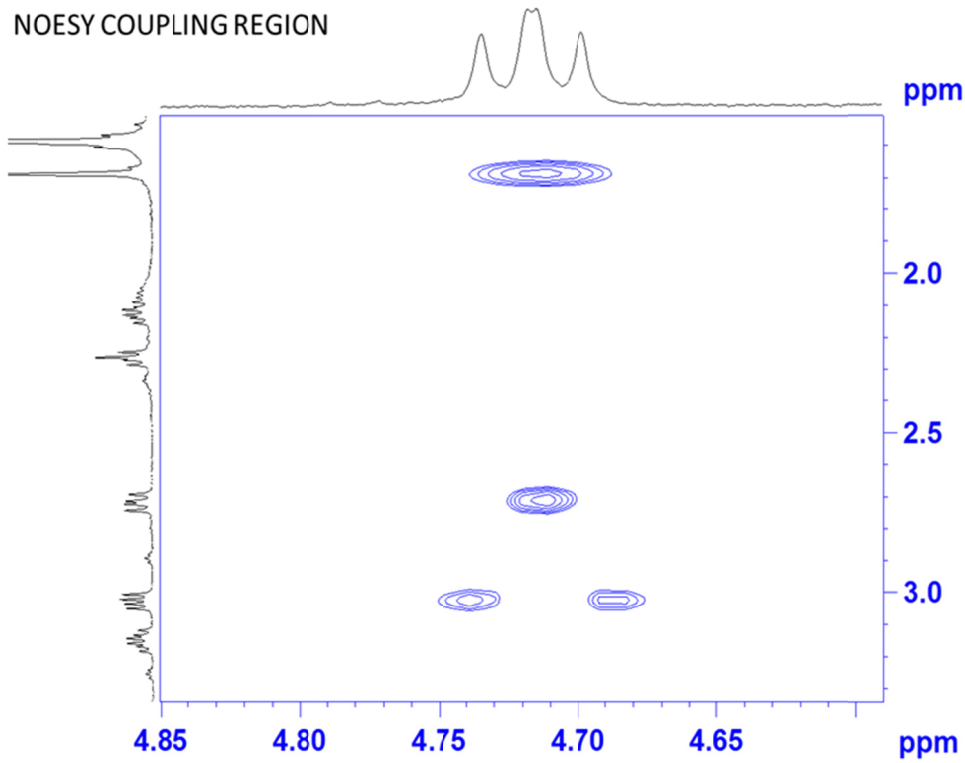
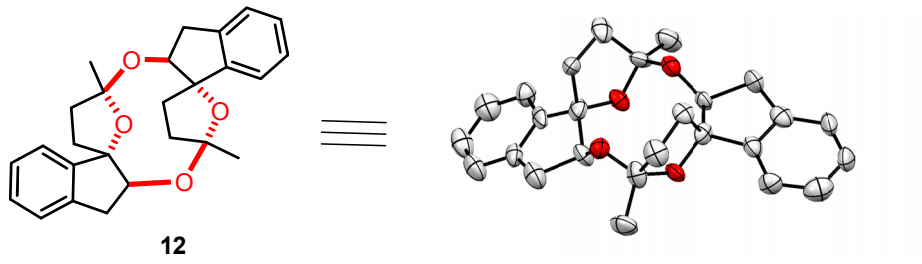


Figure 2**. NOESY Spectrum of Compound **12

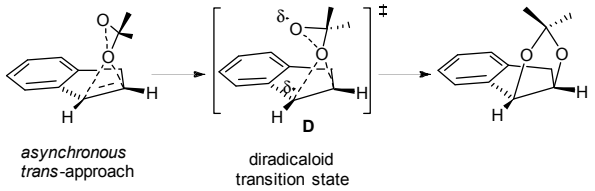
Finally, the single crystal *X*-ray structural analysis has led us to assign a dimeric acetal structure to compound **12** (Figure 3). The formation of dimeric acetal **12** with a *trans*-diol configuration clearly indicates that the epoxide **10** is an intermediate in this process and that its opening occurred in an S_N2 fashion. It clearly ruled out the possibility of a step-wise diradical pathway for the *syn*-dihydroxylation of indene/dihydronaphthalene derivatives. In addition, it also ruled out the S_N1 path for the 1,3-dioxolane formation in case of the intermolecular reactions.

Figure 3.** Molecular Structure of Dimeric Acetal **12



With this information in hand, we have proposed the following tentative mechanism for the intermolecular Oxone-acetone mediated 1,3-dioxolane formation

(Scheme 44). In the first step, the transition state involved for the interaction of DMDO with the olefin is *trans*-asynchronous. This was founded upon the proposals of the group of Bach and Houk who suggested that when the olefin carbons are electronically biased, the oxygen transfer occurs in an asynchronous transition state and that there is a certain amount of diradicaloid character (SE_2) in the TS.[68] Due to the possible stabilization at the benzylic center in the diradicaloid transition state, the second carbon-oxygen bond formation seems to be competing with the oxygen-oxygen bond cleavage. In case of **1r**, an intramolecular *trans*-asynchronous approach of oxygen to olefin is sterically challenged (the incoming oxygen needs to be oriented close to the *β*-carbon) and thus, the epoxide **10** was formed through a *trans*-synchronous oxygen transfer.

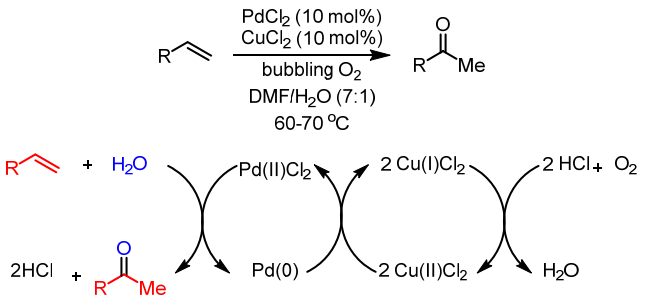


Scheme 44: *Postulated Mechanism*

In conclusion, this work demonstrates the versatility of Oxone for the metal free oxidative functionalization of olefins. The current studies reveal that apart from their well-established epoxidation, with a simple variation in reaction conditions, the metal-free syn-dioxygenation of the benzo-fused cyclic olefins employing Oxone is possible. Although, there is a limitation with respect to the substrates, currently, this Oxone-mediated *syn*-dioxygenation is a significant step in the area of metal-free dihydroxylations and will provide a fresh impetus for further developments.

Metal-Free Wacker-Type Oxidation of the Benzo-Fused Olefins Employing Oxone

Since the beginning of organic synthesis, we can find the significant utility of olefins in different type of oxidation reactions. Among these, the oxidation of olefins directly to carbonyl compounds such as aldehydes and ketones has its own industrial and academic significance. The conversion of olefins to carbonyl compounds has been mainly dealt with by employing the complexes of metals such Hg, Pd, Pt, Au, Ru and Cu. The Wacker oxidation that uses palladium in combination with copper in the presence of an oxidant is one of the most useful and fundamental reactions in organic synthesis (Scheme 45). Several modifications have been carried out in recent years that emphasizes mainly on the use of green solvents and oxidant free reaction conditions to achieve an effective environment benign method. However, methods that employ less hazardous, cost-effective and metal free oxidation techniques are still warranted.



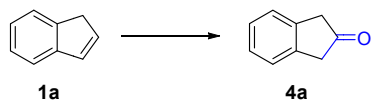
Scheme 45. *Wacker Oxidation and Mechanism*

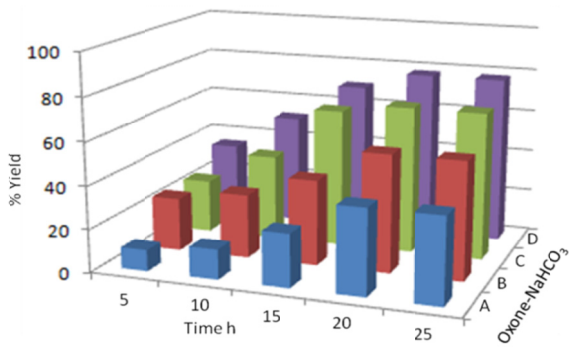
During our preceding investigations on the dioxygenation of indene **1a**, it has been found that the indan-2-one **4a** was isolated as a single product in 35% yield. The exact condition for this oxidation is 0.5 equiv of Oxone in the presence of 3 equiv of $NaHCO_3$ in 5:1:1 (acetone + ethyl acetate + water) solvents system. In order to explore this extraordinary reactivity of Oxone, we start to find a suitable reaction conditions for the exclusive formation of 2-indanone **4a**. With the knowledge of previous condition for dioxygenation and exclusive **4a** formation (Table 1), we put forward some logical experimentation.

Optimisation experiments have been conducted by varying the proportions of both oxidant and base. The progress and the nature of the intermediates involved in this process have been analysed with the help of GC-MS. In general, a noticeable change in the consumption of starting material with the product formation was

observed with the variation especially in the amounts of base employed. Finally, we have realized that the use of 12 equiv of $NaHCO_3$ along with 2 equiv of Oxone was the best combination for the complete conversion (Scheme 46). Under these optimized conditions, complete consumption of indene **1a** takes place with 78% yield of the 2-indanone **4a** at room temperature over the period of 15–20 h. However, no further improvement was observed by increasing the quantity of either oxidant and/or base. Also, prolonging the reaction for longer durations has no effect. Control experiments revealed that the acetone+H_2O+EtOAc (5:1:1) employed for *syn*-dioxygenation was also found to be the best solvent combination system for the current Wacker-type oxidation.

Scheme 46. *Conditions Explored for the Wacker-Type Oxidation*

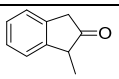
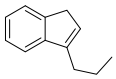
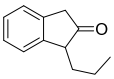
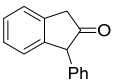
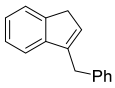
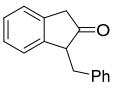
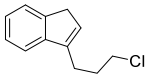
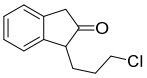
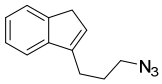
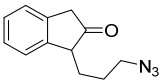
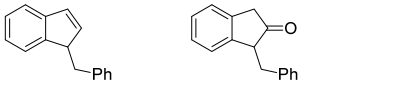




[a] all the reactions were carried out at rt with 0.5 mmol of indene in 2.5 ml acetone and 0.5 ml of (1:1 of H_2O + EtOAc); [A] Oxone (0.5 equiv), $NaHCO_3$(3 equiv); [B] Oxone (1.0 equiv), $NaHCO_3$(6 equiv); [C] Oxone (1.5 equiv), $NaHCO_3$(9 equiv); [D]Oxone (2.0 equiv), $NaHCO_3$(12 equiv).

With the best conditions in hand for the exclusively Wacker-type oxidation, we next planned to explore the scope of different indene derivatives for the present reaction. For this purpose, already synthesized indene derivatives from Table 4 have been selected. In general, the reactions proceeded smoothly and provided exclusively corresponding 2-indanones in good yields.

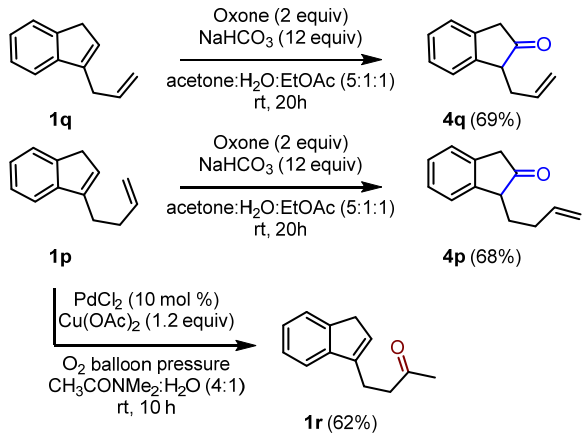
***Table 4**. Scope of Wacker-Type Oxidation*[a]

Entry	Substrate	Product	Yield[b] (%)
1	 **1b**	 **4b**	70
2	 **1c**	 **4c**	74
3	 **1e**	 **4e**	61
4	 **1f**	 **4f**	75
5	 **1h**	 **4h**	74
6	 **1i**	 **4i**	72
7	 **1l**	**4f**	78

As shown in Table 4, the indenes were having aliphatic substitution on olefin like methyl (**1b**), *n*-propyl (**1c**) are compatible and gave the corresponding ketones **4b** & **4c**. Similarly, indenes having aromatic substitution on olefin like **1d** (phenyl) underwent this Wacker-type oxidation smoothly and provided **4d** in very good yields. As indicated in the Table 4, the substitution at the C-3 (**1b**–**1d**) and at the C-1 position (**1l**) of indene has little effect on the outcome of the reaction (in terms of yields and the regioselectivity). This suggested that the reaction is highly regioselective in nature. As expected, the C-1 substituted indene **1l** (1-benzyl-1*H*-indene) and the C-3 substituted **1f** (3-benzyl-1*H*-indene) led to the formation of 1-benzyl-1*H*-inden-2(3H)-one (**4f**). Delightfully, a wide range of functional groups like chloro (**1h**) and azide (**1i**) were found to be tolerant under the reaction current reaction conditions employed.

Next, the Wacker-type of oxidation of 1-allylindene (**1q**) and 1-(but-3-enyl) indene **1p** has been studied to understand the specific reactivity for this Wacker-type oxidation. Interestingly, the oxidation of both dienes **1p** and **1q** occurred in a way

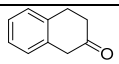
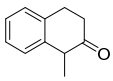
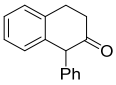
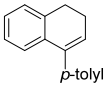
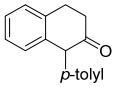
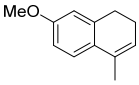
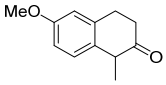
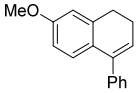
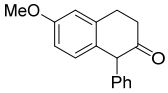
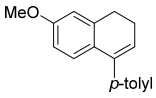
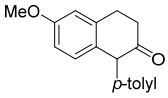
such that the internal olefins only got oxidized, resulting in the corresponding indan-2-ones **4p** and **4q** exclusively (Scheme 47). In this case also, the exclusive formations of the indan-2-ones with Oxone evidently specify that this process is much faster than the epoxidation. Another point is the reactivity of two different olefins; it proves that the indenyl olefin is much more reactive than the pendant terminal alkenes. As already noticed in scheme 39, when **1p** was exposed to the Pd-catalyzed Wacker oxidation, the exclusive oxidation of the external olefin occurs without disturbing the internal olefin. This complementary selectivity clearly explains that the Oxone-acetone mediated Wacker-type oxidation is very selective for the benzo-fused olefins despite the fact that this olefin is sterically hindered.



Scheme 47. *Selectivity Study for Metal-Catalyzed and Metal Free Reactions*

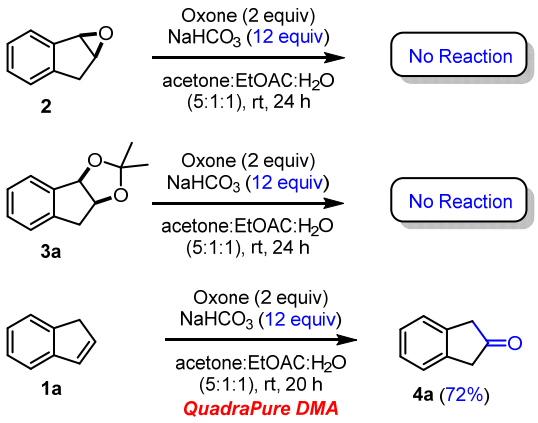
Next, the oxidation of previously synthesized 1,2-dihydronaphthalenes (**7b**–**7g**) has been conducted to increase the current Oxone-mediated Wacker-type oxidation. As shown in Table 5, in all the cases, the reaction proceeded efficiently and provided the corresponding 2-tetralones with complete regioselectivity. Placing the substitution either on olefin (**7b**–**7d**) or/and aromatic nucleus (**7e**–**7g**) has no dramatic effect on the outcome of the reaction and the corresponding ketones were obtained in very good yields (**8b**–**8g**). It is worth mentioning here that tetralones **8d** and **8e** have been prepared earlier in the context of the synthesis of an ABCD tetracyclic Bruceantin precursor and a 2 step protocol has been employed.

***Table 5**. Scope of Wacker-Type Oxidation*[a]

Entry	Substrate	Product	Yield[b] (%)
1	 **7a**	 **8a**	71
2	 **7b**	 **8b**	65
3	 **7c**	 **8c**	76
4	 **7d**	 **8d**	72
5	 **7e**	 **8e**	61
6	 **7f**	 **8f**	70
7	 **7g**	 **8g**	69

Experiment to Examine the Concern of Trace Metal Impurities, Epoxide 2/Acetonide 3a

Similar to the acetonide study, in this reaction too, we conducted some preliminary control experiments. At first, both epoxide **2** and acetonide **3a** have been exposed to the present conditions for a longer period. It has been found that both **2** and **3a** are intact, which indicated that either epoxide or the acetonide are not involved as intermediates in the current transformation. Indeed, the GC-MS monitoring of this reaction during the optimization studies has clearly indicated that none of these intermediates are present. Next, similar to last time, in this case as well, the oxidation of **1a** has been conducted employing excess QuadraPure^{TM} DMA [a known scavenger for metals such as Pd, Cu(I), Cu(II), Ni, Pt etc.] as an additive in the reaction medium. As shown in Scheme 47, there was no interference from this added metal scavenger and there was no change either in the time or the yield of the product. This control experiment has precisely ruled out the possible involvement of traces of metal impurities present in the $NaHCO_3$ or Oxone (Scheme 48).



Scheme 48. *Controlled Experiments for Trace Metal Impurities, Epoxide* ***2****/Acetonide* ***3a***

To conclude, we documented the direct oxidation of indenes and 1,2-dihydronapthalenes respectively to the corresponding 2-indanones and 2-tetralones employing Oxone-acetone and sodium bicarbonate under relatively simple conditions. The control experiments primarily reveal that the current reaction is similar to the acetonide formation and did not occur due to the presence of trace-metal impurities, nor is the epoxide an intermediate in the path of the reaction. In a nutshell, it must be noted that a subtle variation in the reaction conditions either in terms of the solvents employed and/or the amount of bases used seems to causes a complete change in the course of the reaction. The current base-driven switching in reaction path is very unusual and creates substantial opportunities for further exploration.

Experimental Section

General Procedure for synthesis of substituted indenes[69] (1): NaH (1.2 equiv) was added to suspension of indene (1.0 equiv) and alkyl bromide (1.1 equiv) in DMF at 0 °C and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with cold water at 0 °C and portioned between water and ethyl acetate. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2×50 mL). The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column (ethyl acetate and pet ether as eluent) to afford substituted indene (85-95%, Table 2).

General Procedure for synthesis of substituted indenes (1)/dihydronaphthalenes[69] (7): Magnesium shavings (1.5 equiv) were stirred in THF and I_2 (trace) was added. Halo-compound (R-X, 1.3 equiv) was added dropwise to the mixture; the reaction was exothermic, and the mixture was stirred for 20 min. Indanone/Tetralone derivative (1.0 equiv) was then added, (exothermic), the reaction was stirred for 5–10 h. Water (30 mL) was slowly added, (exothermic), the product was extracted with DCM (2×100 mL), dried over magnesium sulphate and the solvent removed to yield the tertiary alcohol as a red-brown oil. This alcohol was dissolved in toluene and *p*-toluenesulphonic acid (1.1 equiv) was added. The reaction was heated under reflux for 1 h after which time it was cooled to ambient temperature and washed with water (2×20 mL), dried over magnesium sulphate and the solvent removed to give brown oil. This was then purified by column chromatography on silica, using ethyl acetate/hexane (3%) to yield the product (Table 2, Scheme 38).

General procedure for *syn*-dioxygenation: To a solution of indene (**1**, 1 equiv) in acetone (5 mL, for 1 mmol indene) were added ethyl acetate (1 mL), water (1 mL) and solid $NaHCO_3$ (3 equiv) and the reaction mixture was stirred for 10 min. To this was added solid Oxone (2 equiv) and contents were stirred at room temperature for 4-10 h. After completion of the reaction, the excess acetone evaporated under reduced pressure and remaining reaction mixture portioned between water and ethyl acetate (20 mL each). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 20 mL). Combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel

column (ethyl acetate and pet ether as eluent) to afford the corresponding acetonide (**3**).

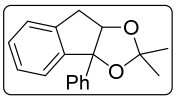
2,2-Dimethyl-8,8a-dihydro-3aH-indeno[1,2-d][1,3]dioxole (3a): The general procedure was followed using indene (**1a**) (200 mg, 0.86 mmol) as a substrate procured **3a** (270 mg, 82%) as a white solid; R_f 0.3 (5% ethyl acetate/pet. ether); mp: 65-68 °C**;** IR ($CHCl_3$)ν: 3018, 2934, 1608, 1460, 1372, 1216, 1056, 1018, 863, 758, 668 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21 (s, 3H), 1.40 (s, 3H), 3.14 (dd, J = 2.2, 4.2 Hz, 2H), 4.99 (ddd, J = 2.2, 4.2, 5.6 Hz, 1H), 5.54 (d, J = 5.6 Hz, 1H), 7.20–7.28 (m, 3H), 7.39–7.42 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 25.9 (CH_3), 27.5 (CH_3), 37.8 (CH_2), 79.4 (CH), 84.0 (CH), 110.7 (C), 125.4 (CH), 125.7 (CH), 127.2 (CH), 128.9 (CH), 140.9 (C), 141.4 (C) ppm.

2,2-Dimethyl-3a-propyl-8,8a-dihydro-3aH-indeno[1,2-d][1,3]dioxole (3c): The general procedure was followed using 3-propyl-1H-indene (**1c**) (100 mg, 0.52 mmol) as a substrate procured **3c** (108 mg, 78%) as a colorless liquid; R_f 0.3 (5% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 3026, 2984, 2933, 1607, 1459, 1368, 1247, 1126, 1057, 910, 848, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, J = 7.3 Hz, 3H), 1.05 (s, 3H), 1.19 (ddq, J = 5.3, 7.3, 12.5 Hz, 1H), 1.36–1.39 (m, 1H), 1.42 (s, 3H), 1.86 (ddd, J = 2.2, 4.7, 12.6 Hz, 1H), 1.94 (ddd, J = 2.2, 4.7, 12.6 Hz, 1H), 3.07 (d, J = 2.4 Hz, 2H), 4.61 (t, J = 2.4 Hz, 1H), 7.16–7.20 (m, 1H), 7.24–7.27 (m, 2H), 7.33–7.35 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.4 (CH_3), 17.5 (CH_2), 27.5 (CH_3), 27.8 (CH_3), 37.1 (CH_2), 39.9 (CH_2), 83.5 (CH), 93.8 (C), 110.0 (C), 124.1 (CH), 125.3 (CH), 127.1 (CH), 128.4 (CH), 140.0 (C), 145.4 (C) ppm; HRMS (ESI+): calcd. for $C_{15}H_{20}O_2Na^+$ 255.1356, found 255.1351.

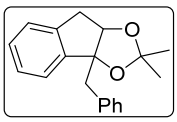
3a-Isopropyl-2,2-dimethyl-8,8a-dihydro-3aH-indeno[1,2-d][1,3]dioxole (3d): The general procedure was followed using 3-isopropyl-1H-indene (**1d**) (100 mg, 0.52 mmol) as a substrate procured **3d** (87 mg, 63%) as a colorless liquid; R_f 0.3 (5% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 3025, 2962, 2933, 1606, 1471, 1378, 1368, 1243, 1219, 1165, 1094, 1059, 907, 849, 751 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 6H), 1.41 (s, 3H), 2.29 (pent, J = 7.0, 13.8 Hz, 1H), 3.04 (d, J = 4.0 Hz, 2H), 4.63 (dd, J = 1.6, 4.0 Hz, 1H), 7.20 (d, J = 6.8 Hz, 1H), 7.22–7.28 (m, 2H), 7.34 (d, 6.9 Hz, 1H); ^{13}C-NMR

(125 MHz, $CDCl_3$): δ = 17.4 (CH_3), 17.5 (CH_3), 27.6 (CH_3), 28.0 (CH_3), 34.5 (CH), 38.3 (CH_2), 81.7 (CH), 96.9 (C), 110.1 (C), 124.6 (CH), 125.2 (CH), 127 (CH), 128.4 (CH), 140.8 (C), 144.5 (C) ppm; HRMS (ESI+): calcd. for $C_{15}H_{20}O_2Na^+$ 255.1356, found 255.1353.

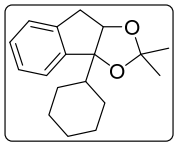
2,2-Dimethyl-3a-phenyl-8,8a-dihydro-3aH-indeno[1,2-d][1,3]dioxole (3e): The general procedure was followed using 3-phenyl-1H-indene (**1e**) (100 mg, 0.52 mmol) as a substrate procured **3e** (94 mg, 68%) as a white solid; R_f 0.3 (5% ethyl acetate/pet. ether); mp: 58-59 °C; IR ($CHCl_3$)ν: 3018, 2932, 1601, 1447, 1372, 1216, 1053, 851, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (s, 3H), 1.54 (s, 3H), 3.19 (d, J = 17.3 Hz, 1H), 3.28 (dd, J = 4.6, 17.3 Hz, 1H), 4.70 (d, J = 4.6 Hz, 1H), 7.20–7.25 (m, 5H), 7.27–7.33 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.9 (CH_3), 27.7 (CH_3), 36.8 (CH_2), 87.3 (CH), 95.2 (C), 111.0 (C), 125.2 (CH), 125.5 (3CH), 127.3 (CH), 127.7 (CH), 128.3 (2CH), 128.6 (CH), 140.6 (C), 142.4 (C), 145.7 (C) ppm; HRMS (ESI+): calcd. for $C_{18}H_{18}O_2Na^+$ 289.1199, found 289.1204.



3a-Benzyl-2,2-dimethyl-8,8a-dihydro-3aH-indeno[1,2-d][1,3]dioxole (3f): The general procedure was followed using 3-benzyl-1H-indene (**1f**) (100 mg, 0.48 mmol) as a substrate procured **3f** (102 mg, 75%) as a white solid; R_f 0.3 (5% ethyl acetate/pet. ether); mp: 77–79 °C; IR ($CHCl_3$)ν: 3066, 3017, 2988, 1604, 1454, 1380, 1216, 1056, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.05 (s, 3H), 1.22 (s, 3H), 2.65 (dd, J = 4.8, 17.2 Hz, 1H), 2.95 (d, J = 17.2 Hz, 1H), 3.11 (d, J = 13.7 Hz, 1H), 3.23 (d, J = 13.8 Hz, 1H), 4.59 (d, J = 4.8 Hz, 1H), 7.04 (dd, J = 3.7, 7.4 Hz, 2H), 7.11 (dd, J = 3.8, 5.5 Hz, 1H), 7.17–7.20 (m, 3H), 7.23–7.25 (m, 2H), 7.32 (dd, J = 2.3, 5.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 27.2 (CH_3), 27.8 (CH_3), 36.4 (CH_2), 43.7 (CH_2), 82.8 (CH), 93.4 (C), 110.3 (C), 124.3 (CH), 125.3 (CH), 126.5 (CH), 127.1 (CH), 127.8 (2CH), 128.5 (CH), 130.5 (2CH), 136.1 (C), 140.3 (C), 145.1 (C) ppm; HRMS (ESI+): calcd. for $C_{19}H_{20}O_2Na^+$ 303.1356, found 303.1351.

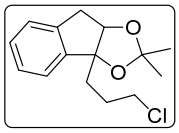


3a-Cyclohexyl-2,2-dimethyl-8,8a-dihydro-3aH-indeno[2,1-d][1,3]dioxole (3g): The general procedure was followed using 3-cyclohexyl-1H-indene (**1g**) (100 mg, 0.50 mmol) as a substrate procured **3g** (89 mg, 65%) as a colorless liquid; R_f 0.3 (5% ethyl acetate/pet. ether); IR ($CHCl_3$)ν:

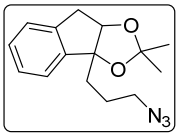


3070, 2984, 2928, 1732, 1605, 1451, 1377, 1367, 1244, 1175, 1058, 848, 752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.92–0.97 (m, 2H), 0.99 (s, 3H), 1.07–1.15 (m, 2H), 1.24–1.28 (m, 2H), 1.40 (s, 3H), 1.66 (d, J = 9.7 Hz, 2H), 1.79 (d, J = 13.4 Hz, 1H), 1.93 (tt, J = 3.0, 12.1 Hz, 1H), 2.04 (d, J = 12.9 Hz, 1H), 3.0 (d, J = 3.9 Hz, 2H), 4.86 (dd, J = 1.8, 3.3 Hz, 1H), 7.19 (dd, J = 2.2, 7.1 Hz, 1H), 7.24–7.27 (m, 2H), 7.34 (dd, J = 2.2, 7.1 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 26.2 (CH_2), 26.4 ($2CH_2$), 27.5 (CH_2), 27.6 ($2CH_2$), 28.1 (CH_3), 38.1 (CH_2), 44.6 (CH), 81.9 (CH), 96.5 (CH), 110.0 (C), 124.6 (CH), 125.1 (CH), 127.0 (CH), 128.3 (CH), 140.8 (C), 144.9 (C) ppm; HRMS (ESI+): calcd. for $C_{18}H_{24}O_2Na^+$ 295.1669, found 295.1668.

3a-(3-Chloropropyl)-2,2-dimethyl-8,8a-dihydro-3aH-indeno[1,2-d][1,3]dioxole (3h): The general procedure was followed using 3-(3-chloropropyl)-1H-indene (**1h**) (100 mg, 0.52 mmol) as a substrate procured **3h** (96 mg, 69%) as a yellow liquid; R_f 0.3 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 3065, 2956, 1711, 1604, 1457, 1396, 1295, 1018, 770, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (s, 3H), 1.40 (s, 3H), 1.70–1.82 (m, 1H), 1.90–2.06 (m, 3H), 3.07 (d, J = 2.5 Hz, 2H), 3.36–3.41(m, 1H), 3.50–3.55(m, 1H), 4.59 (dd, J = 2.5, 3.9 Hz, 1H), 7.22 (dd, J = 2.7, 7.6 Hz, 1H), 7.26 (dd, J = 2.7, 5.6 Hz, 2H), 7.34 (dd, J = 2.5, 7.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.5 (CH_3), 27.8 (CH_3), 33.7 (CH_2), 34.8 (CH_2), 37.0 (CH_2), 45.1 (CH_2), 83.5 (CH), 93.1 (C), 110.4 (C), 124.1 (CH), 125.5 (CH), 127.3 (CH), 128.7 (CH), 139.9 (C), 144.8 (C) ppm; HRMS (ESI+): calcd. for $C_{15}H_{19}O_2ClNa^+$ -H_2O 271.0860, found 271.0861.



3a-(3-Azidopropyl)-2,2-dimethyl-3a,8a-dihydro-8H-indeno[1,2-d][1,3]dioxole (3i): The general procedure was followed using 3-(3-azidopropyl)-1H-indene (**1i**) (100 mg, 0.50 mmol) as a substrate procured **3i** (102 mg, 74%) as a yellow liquid; R_f 0.3 (10% ethyl acetate/pet. ether); H^1 NMR (400MHz): δ = 1.03 (s, 3H), 1.40 (s, 3H), 1.45–1.56 (m, 1H), 1.66–1.77 (m, 1H), 1.84–1.91 (m, 1H), 1.92–2.00 (m, 1H), 3.07 (d, J = 2.8 Hz, 2H), 3.22–3.33 (m, 2H), 4.59 (t, J = 2.5 Hz, 1H), 7.18–7.20 (m, 1H), 7.22–7.28 (m, 2H), 7.31–7.34 (m, 1H); ^{13}C NMR (100 MHz): δ = 24.0 (CH_2), 27.5 (CH_3), 27.8 (CH_3), 34.5 (CH_2), 37.0 (CH_2), 51.6 (CH_2), 83.2 (CH), 93.2 (C), 110.4 (C), 124.1 (CH), 125.5 (CH), 127.3 (CH), 128.7 (CH), 134.0 (C), 144.8 (C) ppm; HRMS (ESI+): calcd. for $C_{15}H_{19}O_2N_3Na^+$ 296.1369, found 296.1369.



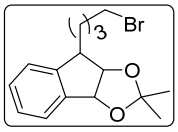
7-(2,2-Dimethyl-8,8a-dihydro-3aH-indeno[2,1-d][1,3]dioxol-3a-yl)heptan-2-one (3j): The general procedure was followed using 7-(1H-inden-3-yl)heptan-2-one (**1j**) (100 mg, 0.44 mmol) as a substrate procured **3j** (93 mg, 72%) as a colorless liquid; R_f 0.3 (10% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 3024, 2985, 2934, 1716, 1459, 1368, 1245, 1220, 1055, 1017, 853, 754 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 3H), 1.10–1.19 (m, 1H), 1.23–1.31(m, 2H), 1.34–1.39 (m, 1H), 1.41 (s, 3H), 1.49–1.57 (m, 2H), 1.79–1.94 (m, 2H), 2.10 (s, 3H), 2.39 (t, J = 7.2 Hz, 2H), 3.06 (d, J = 3.0 Hz, 2H), 4.59 (t, J = 2.6 Hz, 1H), 7.20 (dd, J = 2.9, 7.0 Hz, 1H), 7.26 (dd, J = 2.6, 6.7 Hz, 2H), 7.34 (dd, J = 2.9, 7.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 23.5 (CH_2), 23.9 (CH_2), 27.4 (CH_3), 27.8 (CH_3), 29.4 (CH_2), 29.8 (CH_3), 37.1 (CH_2), 37.4 (CH_2), 43.5 (CH_2), 83.5 (CH), 93.6 (C), 110.0 (C), 124.1 (CH), 125.3 (CH), 127.1 (CH), 128.4 (CH), 140.0 (C), 145.2 (C), 209.1 (C) ppm; HRMS (ESI+): calcd. for $C_{19}H_{26}O_3Na^+$ 325.1774, found 325.1774.

2',2'-Dimethyl-3a',8a'-dihydrospiro[cyclopentane-1,8'-indeno[2,1-d][1,3]dioxole] (3k): The general procedure was followed using spiro[cyclopentane-1,1'-indene] (**1k**) (100 mg, 0.52 mmol) as a substrate procured **3k** (101 mg, 73%) as a colorless liquid; R_f 0.3 (5% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 2933, 1746, 1606, 1455, 1369, 1242, 1155, 1073, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.41 (s, 3H), 1.54–1.59 (m, 2H), 1.62–1.69 (m, 1H), 1.72–1.78 (m, 1H), 1.83–1.87 (m, 4H), 4.46 (d, J = 5.3 Hz, 1H), 5.58 (d, J = 5.3 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.2 (CH_2), 25.4 (CH_2), 26.5 (CH_3), 27.6 (CH_3), 33.5 (CH_2), 41.7 (CH_2), 57.1 (C), 82.6 (CH), 87.6 (CH), 111.2 (C), 123.0 (CH), 125.2 (CH), 127.2 (CH), 129.0 (CH), 141.0 (C), 149.2 (C) ppm; **HRMS (ESI+):** calcd. for $C_{16}H_{20}O_2Na^+$ 267.1356, found 267.1353.

8-Benzyl-2,2-dimethyl-8,8a-dihydro-3aH-indeno[1,2-d][1,3]dioxole (3l): The general procedure was followed using 1-benzyl-1H-indene (**1l**) (100 mg, 0.48 mmol) as a substrate procured **3l** (134 mg, 77%) as a colorless liquid; R_f 0.3 (5% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 3027, 2985, 2925, 1603, 1454, 1370, 1210, 1059, 866, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (s, 3H), 1.36 (s, 3H), 2.88 (d, J = 7.5 Hz, 2H), 3.68 (t, J = 7.5, 5.4 Hz, 1H), 4.67 (d, J = 5.4 Hz, 1H), 5.41 (d, J = 5.4 Hz, 1H), 6.97 (dd, J = 1.8, 6.6 Hz,

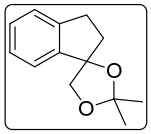
1H), 7.11 (dd, J = 1.5, 7.8 Hz, 2H), 7.21–7.25 (m, 3H), 7.26–7.29 (m, 2H), 7.39 (dd, J = 2.1, 7.1 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.1 (CH_3), 27.5 (CH_3), 40.8 (CH_2), 50.9 (CH), 83.0 (CH), 84.5 (CH), 110.7 (C), 125.4 (CH), 125.6 (CH), 126.3 (CH), 127.7 (CH), 128.4 (2CH), 128.7 (CH), 129.2 (2CH), 139.0 (C), 141.6 (C), 144.2 (C) ppm; HRMS (ESI+): calcd. for $C_{19}H_{20}O_2Na^+$ 303.1356, found 303.1351.

8-(4-Bromobutyl)-2,2-dimethyl-8,8a-dihydro-3aH-indeno[1,2-d][1,3]dioxole (3m): The general procedure was followed using 3-(4-bromobutyl)-1H-indene (**1m**) (100 mg, 0.52 mmol) as a substrate procured **3m** (107 mg, 77%) as a brown liquid; R_f 0.3 (5% ethyl acetate/pet. ether);



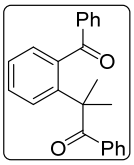
IR ($CHCl_3$)ν: 2984, 2931, 1606, 1456, 1371, 1248, 1208, 1049, 867, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 3H), 1.41 (s, 3H), 1.48–1.52 (m, 1H), 1.54–1.60 (m, 2H), 1.63–1.68 (m, 1H), 1.86–1.93 (m, 2H), 3.28 (dd, J = 5.4, 8.8 Hz, 1H), 3.42 (t, J = 6.8 Hz, 2H), 4.63 (dd, J = 1.1, 5.6 Hz, 1H), 5.57 (d, J = 5.6 Hz, 1H), 7.21 (d, J = 7.3 Hz, 1H), 7.28 (dd, J = 1.4, 7.3 Hz, 1H), 7.32 (dt, J = 1.3, 7.3 Hz, 1H), 7.42 (d, J = 7.3 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.9 (CH_2), 26.0 (CH_3), 27.5 (CH_3), 32.7 (CH_2), 33.4 (CH_2), 33.8 (CH_2), 50.1 (CH), 83.2 (CH), 85.4 (CH), 111.0 (C), 125.1 (CH), 125.8 (CH), 127.6 (CH), 129.1 (CH), 141.0 (C), 144.9 (C) ppm; HRMS (ESI+): calcd. for $C_{16}H_{21}BrO_2Na^+$ 347.0617, found 347.0615.

2',2'-Dimethyl-2,3-dihydrospiro[indene-1,4'-[1,3]dioxolane] (3n): The general procedure was followed using 1-methylene-2,3-dihydro-1H-indene (**1n**) (100 mg, 0.78 mmol) as a substrate procured **3n** (91 mg, 58%) as a colorless liquid; R_f 0.3 (5% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 3018,



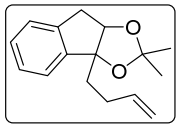
2934, 1608, 1460, 1372, 1216, 1056, 1018, 863, 758, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (s, 3H), 1.56 (s, 3H), 2.28–2.31 (m, 1H), 2.34–2.41 (m, 1H), 2.89 (dt, J = 7.7, 16.1 Hz, 1H), 4.99 (ddd, J = 4.4, 7.7, 16.1 Hz, 1H), 4.02 (d, J = 8.5 Hz, 1H), 4.12 (d, J = 8.5 Hz, 1H), 7.24–7.31 (m, 3H), 7.41–7.44 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 26.7 (CH_3), 27.1 (CH_3), 29.4 (CH_2), 36.6 (CH_2), 74.2 (CH_2), 90.1 (C), 109.7 (C), 123.4 (CH), 124.8 (CH), 127.0 (CH), 128.6 (CH), 143.2 (2C) ppm; GC-HRMS (+EI): calcd. for $C_{13}H_{16}O_2^+$ 204.1145, found 204.1149.

2-(2-Benzoylphenyl)-2-methyl-1-phenylpropan-1-one (5): The general procedure was followed using 1,1-dimethyl-2,3-diphenyl-1H-indene (**1o**) (100 mg, 0.34 mmol) as a substrate procured **5** (17 mg, 15%) as a

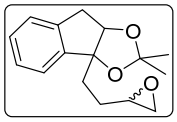


colorless liquid; R_f 0.5 (20% ethyl acetate/pet. ether); IR ($CHCl_3$)v: 3025,2962, 2933, 1606, 1716, 1685, 1368, 1243, 1219, 1165, 1094, 1059, 907, 849, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 6H), 7.16 (t, J = 8.0 Hz, 2H), 7.23 (dd, J = 1.3, 7.5 Hz, 1H), 7.27–7.33 (m, 4H), 7.50 (t, J = 7.8 Hz, 1H), 7.51–7.53 (m, 2H), 7.55–7.58 (m, 3H), 7.63 (d, J = 7.78 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 29.0 ($2CH_3$), 51.68 (C), 125.7 (CH), 127.4 (CH), 127.8 (2CH), 128.11 (2CH), 129.8 (2CH), 130.1 (CH), 130.3 (2CH), 130.7 (CH), 131.5 (CH), 132.9 (CH), 136.1 (C), 137.2 (C), 137.5 (C), 144.9 (C), 197.8 (C), 202.1 (C) ppm.

3a-(But-3-enyl)-2,2-dimethyl-8,8a-dihydro-3aH-indeno[2,1-d][1,3]dioxole (3p): The general procedure was followed using 3-(but-3-en-1-yl)-1H-indene (**1p**) (100 mg, 0.59 mmol) as a substrate procured **3p** (105 mg, 73%) as a colorless liquid; R_f 0.3 (8% ethyl acetate/pet. ether); IR ($CHCl_3$)v: 3074, 2984, 2931, 1641, 1607, 1459, 1369, 1245, 1166, 1058, 911, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (s, 3H), 1.42 (s, 3H), 1.90–1.94 (m, 1H), 1.95–1.97 (m, 1H), 2.00–2.05 (m, 1H), 2.11–2.19 (m, 1H), 3.08 (d, J = 2.6 Hz, 2H), 4.63 (t, J = 2.6 Hz, 1H), 4.94 (dd, J = 1.7, 10.1 Hz, 1H), 5.01 (dd, J = 1.7, 17.1 Hz, 1H), 5.82 (m, 1H), 7.19–7.22 (m, 1H), 7.24–7.28 (m, 2H), 7.33–7.35 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 27.5 (CH_3), 27.8 (CH_3), 28.5 (CH_2), 36.6 (CH_2), 37.1 (CH_2), 83.4 (CH), 93.5 (C), 110.2 (C), 114.6 (CH_2), 124.2 (CH), 125.4 (CH), 127.2 (CH), 128.5 (CH), 138.0 (C), 140.1 (C), 145.1 (C) ppm; HRMS (ESI+): calcd. for $C_{16}H_{20}O_2Na^+$ 267.1356, found 267.1353.

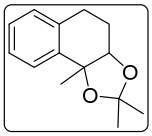


2,2-Dimethyl-3a-(2-(oxiran-2-yl)ethyl)-3a,8a-dihydro-8H-indeno[1,2-d][1,3]dioxole (6): (Diastereomeric mixture with 50:50 percent) The general procedure was followed using 3a-(but-3-enyl)-2,2-dimethyl-8,8a-dihydro-3aH-indeno[2,1-d][1,3]dioxole (**3p**) (110 mg, 0.54 mmol) as a substrate procured **6** (110 mg, 79%) as a colorless liquid; R_f 0.5 (20% ethyl acetate/pet. ether); IR ($CHCl_3$)v: 3074, 2984, 2931, 1641, 1607, 1459, 1369, 1245, 1166, 1058, 911, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.03 (s, 1.5H), 1.04 (s, 1.5H), 1.40 (s, 1.5H), 1.41 (s, 1.5H), 1.42–1.46 (m, 0.5H), 1.46–1.50 (m, 0.5H), 1.57–1.64 (m, 0.5H), 1.71–1.78 (m, 0.5H), 1.93–2.00 (m, 1H), 2.00–2.12 (m, 1H), 2.41 (dd, J = 2.7, 4.9 Hz, 0.5H), 2.48 (dd, J = 2.7, 4.9 Hz, 0.5H), 2.71 (t, J = 4.4 Hz, 0.5H), 2.74 (t, J = 4.4 Hz, 0.5H), 2.88–2.92 (m, 1H), 3.03–3.07 (m, 1H), 3.07–3.10 (m, 1H), 4.58–4.59 (m, 1H), 7.19–7.21 (m, 1H), 7.23–7.25 (m, 1H), 7.25–7.28



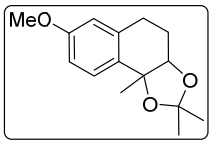
(m, 1H), 7.32–7.33 (m, 0.5H), 7.33–7.35 (m, 0.5H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 27.3 (CH_2), 27.4 (CH_2), 27.5 ($2CH_3$), 27.8 ($2CH_3$), 33.2 (CH_2), 33.5 (CH_2), 37.0 (CH_2), 37.1 (CH_2), 47.0 ($2CH_2$), 52.0 (CH), 52.1 (CH), 83.3 (CH), 83.6 (CH), 93.1 (2C), 110.3 (2C), 124.1 (2CH), 125.4(2CH), 127.3 (2CH), 128.6 (2CH), 139.9 (C), 140.1 (C), 144.7 (C), 144.9 (C) ppm; HRMS (ESI+): calcd. for $C_{16}H_{20}O_3Na^+$ 283.1305, found 283.1303.

2,2,9b-Trimethyl-3a,4,5,9b-tetrahydronaphtho[2,1-d][1,3]dioxole (8b): The general procedure was followed using 4-methyl-1,2-dihydronaphthalene (**7b**) (100 mg, 0.69 mmol) as a substrate procured **8b** (99 mg, 65%) as a colorless liquid; R_f 0.3 (5% ethyl acetate/pet. ether); IR ($CHCl_3$)ν: 3022, 2982, 2870, 1492, 1439, 1367, 1255, 1237, 1107, 1090, 1001, 847, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (s, 3H), 1.42 (s, 3H), 1.57 (s, 3H), 1.90–1.98 (m, 1H), 2.21–2.28 (m, 1H), 2.64 (m, 1H), 3.04 (ddt, J = 4.5, 5.3 Hz, 1H), 4.17 (dd, J = 1.4, 7.7 Hz, 1H), 7.06 (d, J = 1.4, 7.5 Hz, 1H), 7.17 (dt, J = 1.4, 7.3 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 23.7 (CH_3), 24.1 (CH_2), 27.1 (CH_3), 27.3 (CH_3), 25.6 (CH_3), 79.0 (CH), 79.1 (C), 108.0 (C), 126.5 (CH), 126.9 (CH), 127.8 (CH), 127.9 (CH), 135.0 (C), 140.2 (C) ppm; HRMS (ESI+): calcd. for $C_{14}H_{18}O_2Na$



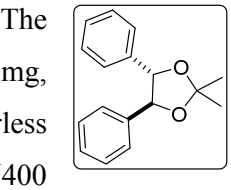
2,2-Dimethyl-9b-phenyl-3a,4,5,9btetrahydronaphtho[2,1-d][1,3]dioxole (8c): The general procedure was followed using 4-phenyl-1,2-dihydronaphthalene (**7c**) (100 mg, 0.49 mmol) as a substrate procured **8c** (82 mg, 60%) as a colorless solid; R_f 0.3 (5% ethyl acetate/pet. ether); mp: 95-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.60 (s, 3H), 2.05 (ddt, J = 1.6, 5.2, 13.6 Hz, 1H), 2.17–2.24 (m, 1H), 2.75 (dd, J = 4.9, 16.1 Hz, 1H), 3.20 (dt, J = 5.2, 12.4 Hz, 1H), 4.19 (d, J = 4.9 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.15 (d, J = 6.8 Hz, 2H), 7.19 (d, J = 6.8 Hz, 1H), 7.24–7.28 (m, 1H), 7.29–7.30 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 22.9 (CH_2), 23.4 (CH_2), 27.0 (CH_3), 27.5 (CH_3), 80.5 (CH), 83.9 (C), 108.7 (C), 126.6 (3CH), 127.1 (CH), 127.2 (CH), 127.7 (CH), 127.9 (2CH), 130.5 (CH), 136.1 (C), 139.3 (C), 144.5 (C) ppm; HRMS (ESI+): calcd. for $C_{19}H_{20}O_2Na^+$ 303.1356, found 303.1353.

7-Methoxy-2,2,9b-trimethyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]dioxole (8e): The general procedure was followed using 7-

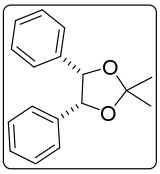


methoxy-4-methyl-1,2-dihydronaphthalene (**7e**) (100 mg, 0.57 mmol) as a substrate procured **8e** (101 mg, 71%) as a colorless liquid; R_f 0.3 (10% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (s, 3H), 1.41 (s, 3H), 1.54 (s, 3H), 1.94 (td, J = 5.0, 13.4 Hz, 1H), 2.25 (d, J = 13.4 Hz , 1H), 2.58 (dd, J = 5.0, 16.4 Hz, 1H), 3.06 (ddt, J = 5.0, 12.2 Hz, 1H), 3.77 (s, 3H), 4.13 (m, 1H), 6.56 (s, 1H), 6.79 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 8.5 Hz 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 24.1 (CH_2), 24.3 (CH_2), 27.3 ($3CH_3$), 55.12 (CH_3), 79.0 (C), 79.1 (CH), 107.8 (C), 112.0 (CH), 113.1 (CH), 129.1 (CH), 132.7 (C), 136.5 (C), 158.3 (C) ppm; GC-HRMS (+EI): calcd. for $C_{15}H_{20}O_3^+$ 248.1407, found 248.1425.

7-Methoxy-2,2-dimethyl-9b-phenyl-3a,4,5,9b-tetrahydronaphtho[1,2-d][1,3]dioxole (8f): The general procedure was followed using 7-methoxy-4-phenyl-1,2-dihydronaphthalene (**7f**) (100 mg, 0.42 mmol) as a substrate procured **8f** (84 mg, 64%) as a white solid; R_f 0.3 (15% ethyl acetate/pet. ether); H^1 NMR (500MHz) δ: 1.14 (s, 3H), 1.59 (s, 3H), 2.21 (ddd, J = 5.1, 13.2 Hz, 1H), 2.20 (d, J = 14.2 Hz, 1H), 2.58 (dd, J = 5.0, 16.8 Hz, 1H), 3.06 (ddd, J = 5.5, 13.3 Hz, 1H), 3.79 (s, 3H), 4.17 (s, 1H), 6.56 (s, 1H), 6.69 (dd, J = 2.2, 8.2 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 7.2–7.3 (m, 1H), 7.27–7.30 (m, 4H); ^{13}C NMR (125 MHz) δ: 23.1 (CH_2), 23.8 (CH_2), 27.1 (CH_3), 27.5 (CH_3), 55.8 (CH_3), 80.5 (CH), 83.5 (C), 108.6 (C), 111.5 (CH), 113.4 (CH), 126.6 (2CH), 127.1 (CH), 127.9 (2CH), 131.7 (CH), 137.5 (2C), 144.7 (C), 158.4 (C) ppm; HRMS (ESI+): calcd. for $C_{20}H_{22}O_3Na^+$ 333.1461, found 333.1458.



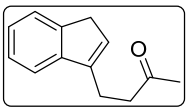
(4S,5S)-2,2-Dimethyl-4,5-diphenyl-1,3-dioxolane (*trans*-3s): The general procedure was followed using *trans*-stilbene (*trans*-**1s**) (100 mg, 0.56 mmol) as a substrate procured *trans*-**3s** (62 mg, 44%) as a colorless liquid; R_f 0.3 (5% ethyl acetate/pet. ether); mp: 65-68 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 6H), 4.78 (s, 2H), 7.21−7.23 (m, 3H), 7.30−7.32 (m, 6H), 7.35(d, J = 3.3 Hz, 1H) ; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.2 ($2CH_3$), 85.4 (2CH), 109.4 (C), 126.7 (4CH), 128.2 (2CH), 128.4 (4CH), 136.7 (2C) ppm.



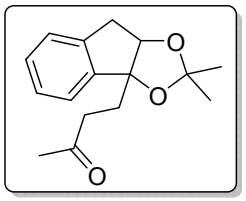
(4S,5R)-2,2-Dimethyl-4,5-diphenyl-1,3-dioxolane(*cis*-3s): The general procedure was followed using *cis*-stilbene (*cis*-**1s**) (100 mg, 0.55 mmol) as a substrate procured *cis*-**3s** (51 mg, 36%) as a colorless liquid; R_f 0.3 (5% ethyl acetate/pet. ether); mp: 65-68 °C; ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 1.62 (s, 3H), 1.83 (s, 3H), 5.49 (br.s, 2H), 6.90−7.23 (m, 10H) ppm.

4-(1H-Inden-3-yl)butan-2-one (1r): To a solution of 3-(but-3-en-1-yl)-1H-indene (**1p**) (100 mg, 0.58 mmol) in DMA:H_2O (8:1) (10 mL) was added copper acetate(128.0 mg, 0.71 mmol) and Palladium Chloride (10.41 mg, 0.058 mmol) stir the reaction mixture at room temperature for 2hrs at oxygen atmosphere. After completion of the reaction, reaction mixture extracted with water and ethyl acetate (3×50 mL). The organic layer was dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by silica gel column (ethyl acetate and pet ether as eluent) to afford **1r** (70 mg, 64%) as a yellow syrup; R_f0.5 (15% ethyl acetate/pet. ether);^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 3H), 2.85 (s, 4H), 3.34 (s, 2H), 6.21 (s, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.7 (CH_2), 29.9 (CH_3), 37.7 (CH_2), 41.9 (CH_2), 118.8 (CH), 123.8 (CH), 124.7 (CH), 126.1 (CH), 128.0 (CH), 143.0 (C), 144.4 (C), 144.9 (C), 208.1 (C) ppm; HRMS (ESI+):calcd. for $C_{13}H_{15}O^+$ 187.1114, found 187.1117.



4-(2,2-Dimethyl-8,8a-dihydro-3aH-indeno[1,2-d][1,3]dioxol-3a-yl)butan-2-one (3r):- The general procedure B was followed using 4-(1H-inden-3-yl)butan-2-one (**1r**) (100 mg, 0.59 mmol) as a substrate procured **3r** (36 mg, 26%) as a colorless liquid; R_f 0.4 (20 ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 3H), 1.40 (s, 3H), 2.04–2.10 (m, 1H), 2.12 (s, 3H), 2.015–2.21 (m, 1H), 2.42–2.50 (m, 1H), 2.55–2.63 (m, 1H), 3.07 (d, J = 2.5 Hz, 2H), 4.54 (t, J = 2.5 Hz, 1H), 7.19–7.21 (m, 1H), 7.24–7.27 (m, 2H), 7.32–7.34 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 27.5 (CH_3), 27.8 (CH_3), 29.7 (CH_2), 29.9 (CH_3), 36.9 (CH_2), 38.6 (CH_2), 83.6 (CH), 92.8 (C), 110.4 (C), 124.2 (CH), 125.5 (CH), 127.3 (CH), 128.7 (CH), 140.0 (C), 144.7 (C), 207.9 (C) ppm; HRMS (ESI+): calcd. for $C_{16}H_{20}O_3Na^+$ 283.1302, found 283.1305.

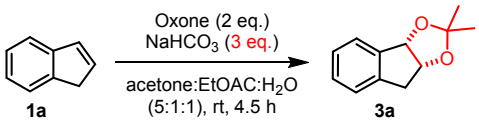


7,16-Dimethyl-5,5a,8,9,14,14a,17,18-octahydro-7H,16H-7,9a:16,18a diepoxydiindeno[2,1-b:2',1'-h][1,7]dioxacyclododecine (12): To a solution of 4-(1H-inden-3-yl)butan-2-one (**1r**) (100 mg, 0.54 mmol) in acetonitrile (10 mL) was added ethyl acetate (2 mL), water (2 mL), $NaHCO_3$ (135.3 mg, 1.61 mmol) and the

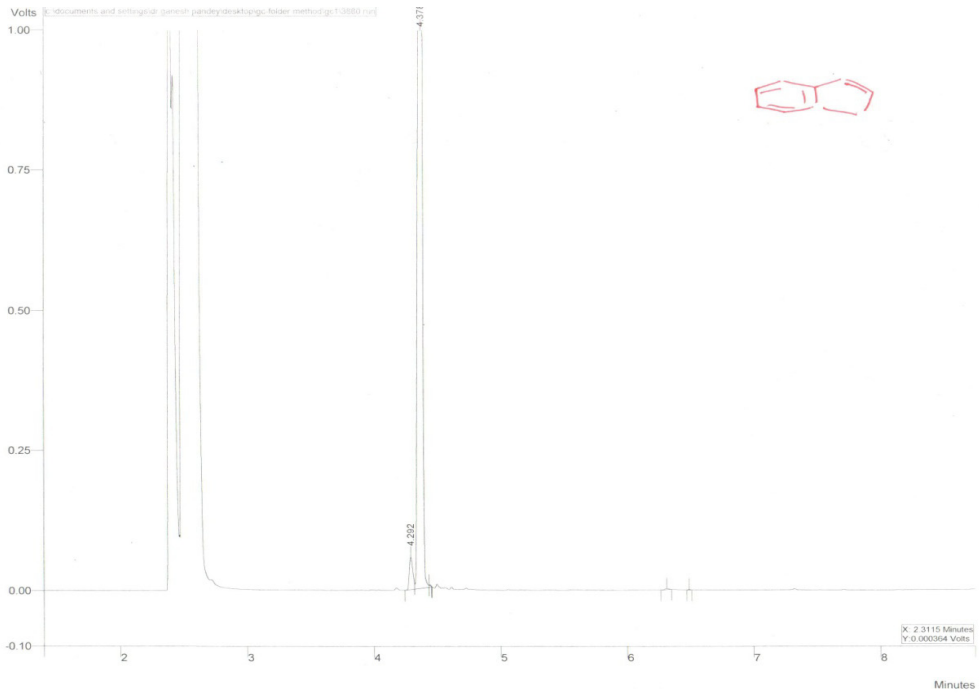
reaction mixture was stirr for 10 min then solid oxone was added (660.1 mg, 1.07 mmol), stirr the reaction mixture at room temperature for 10 h. After completion of the reaction, reaction mixture extracted with water and ethyl acetate (3×50 mL). The organic layer was dried over sodium sulphate and evaporated under reduced pressure. The crude product was purified by silica gel column (ethyl acetate and pet ether as eluent) to afford **12** (65 mg, 64%) as a white solid; R_f0.3 (5% ethyl acetate/pet. ether);mp: 141-145 °C; IR ($CHCl_3$)v: 2982, 2935, 1607, 1461, 1381, 1214, 1134, 1082, 1015, 937, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.55 (t, J = 4.0 Hz, 2H), 1.65 (s, 6H), 2.12 (dt, J = 5.0, 8.5 Hz, 2H), 2.25 (dd, J = 7.2, 12.1 Hz,2H), 2.71 (dd, J = 10.3, 14.6 Hz,2H), 3.02 (dd, J = 7.2, 15.0 Hz, 2H), 3.15 (dt, J = 7.7, 13.1 Hz, 2H), 4.7 (dd, J = 7.9, 10.2 Hz, 2H), 7.12–7.16 (m, 4H), 7.17–7.20 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 23.4 ($2CH_3$), 29.6 ($2CH_2$), 37.1 ($2CH_2$), 38.3 ($2CH_2$), 77.1 (2CH), 94.3 (2C), 107.9 (2C), 122.5 (2CH), 124.1 (2CH), 124.6 (2CH), 127.7 (2CH), 136.8 (2C), 146.7 (2C) ppm; HRMS (ESI+): calcd. for $C_{26}H_{28}O_4Na^+$ 427.1880, found 427.1875.

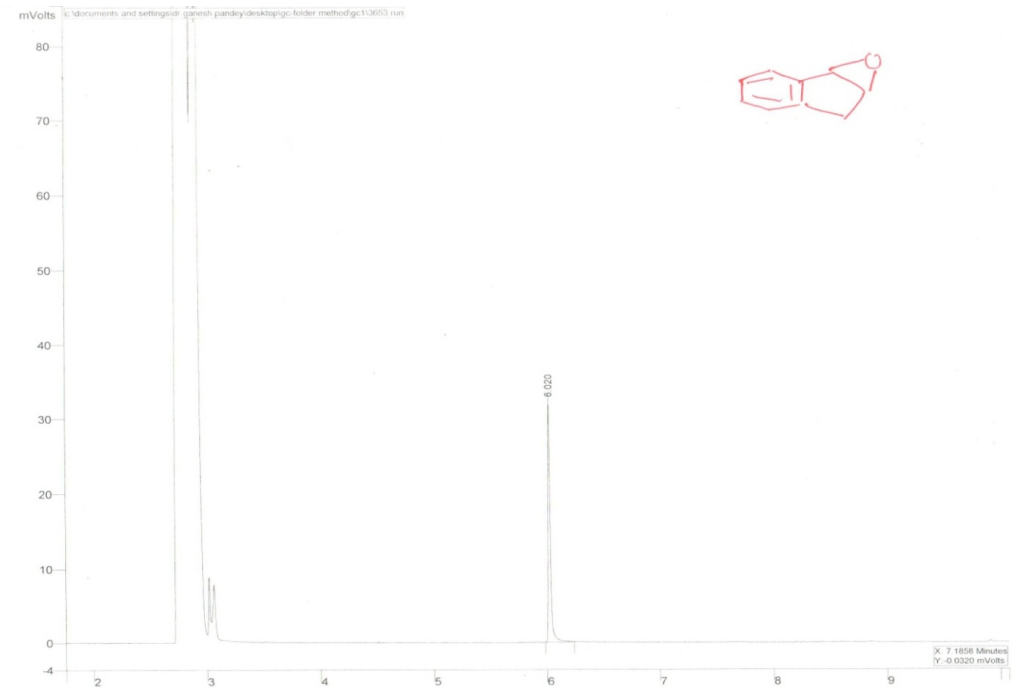
GC analysis for the reaction of indene to acetonide

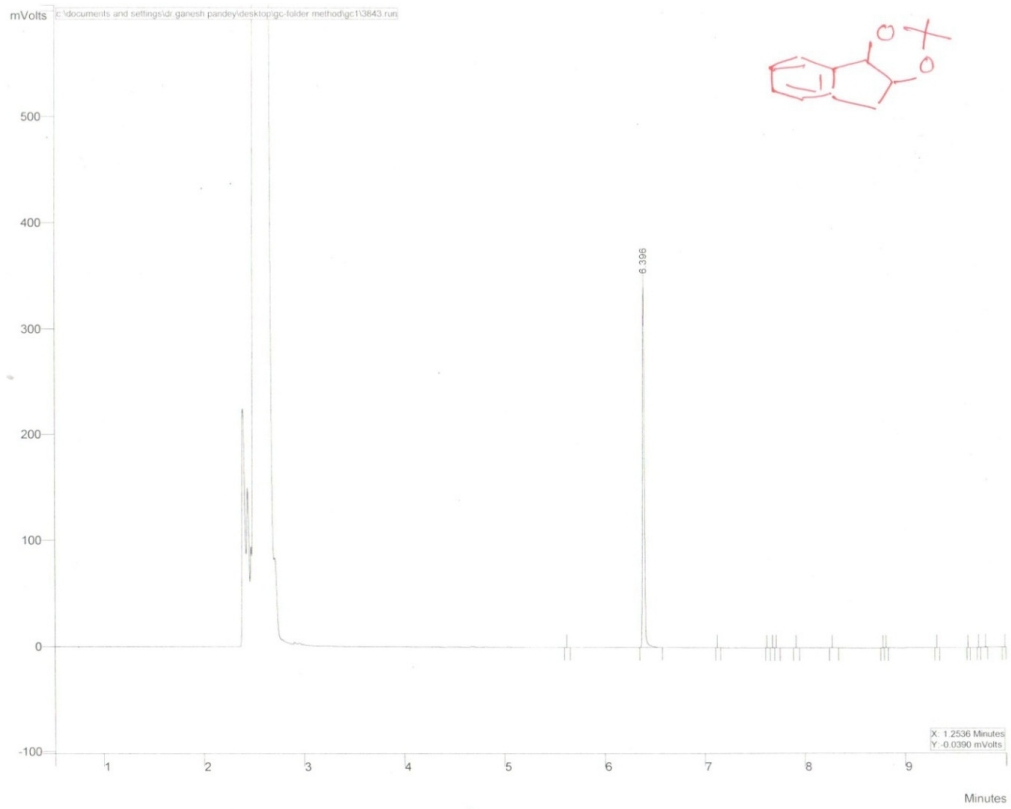
The reaction has been analysed with the help GC for every 30 minutes until the complete consumption of the starting indene. Selected GC chromatograms are given in the next pages (time is mentioned on spectra)

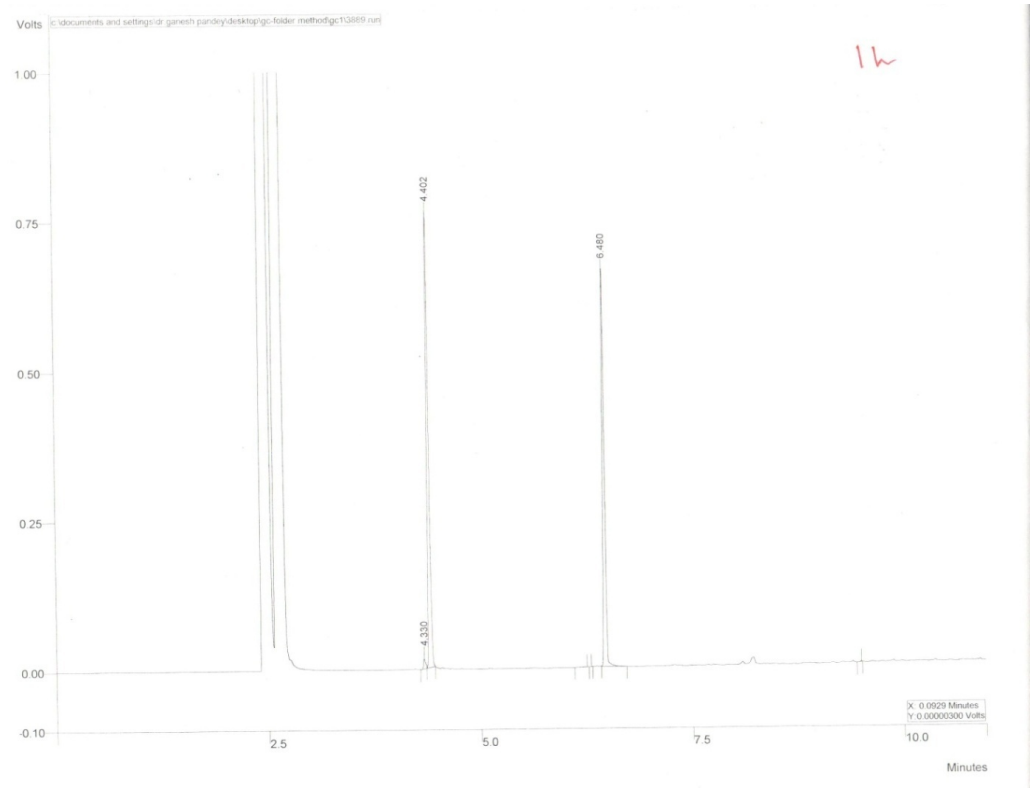


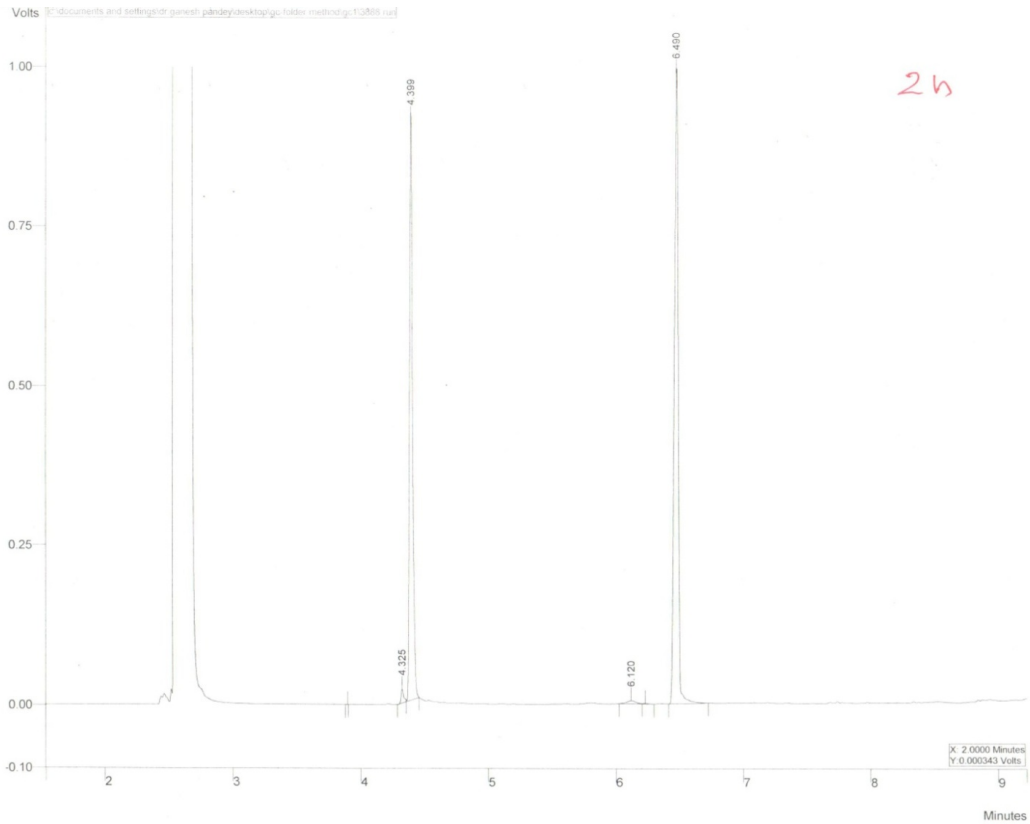
Instrument Use:	Varian CP-3800
Column:	HP-5 (30m×0.25µm ×0.25 mm)
Detector:	FID (temp. 280 ^{o}C)
Injector temp.:	280 ^{o}C
Column Cond.:	80 ^{o}C (1 min) to 280 ^{o}C (5 min)
Column Flow:	1.0 mL/min.
Carrier Gas:	N_2
Sample Dissolved:	Ethyl Acetate

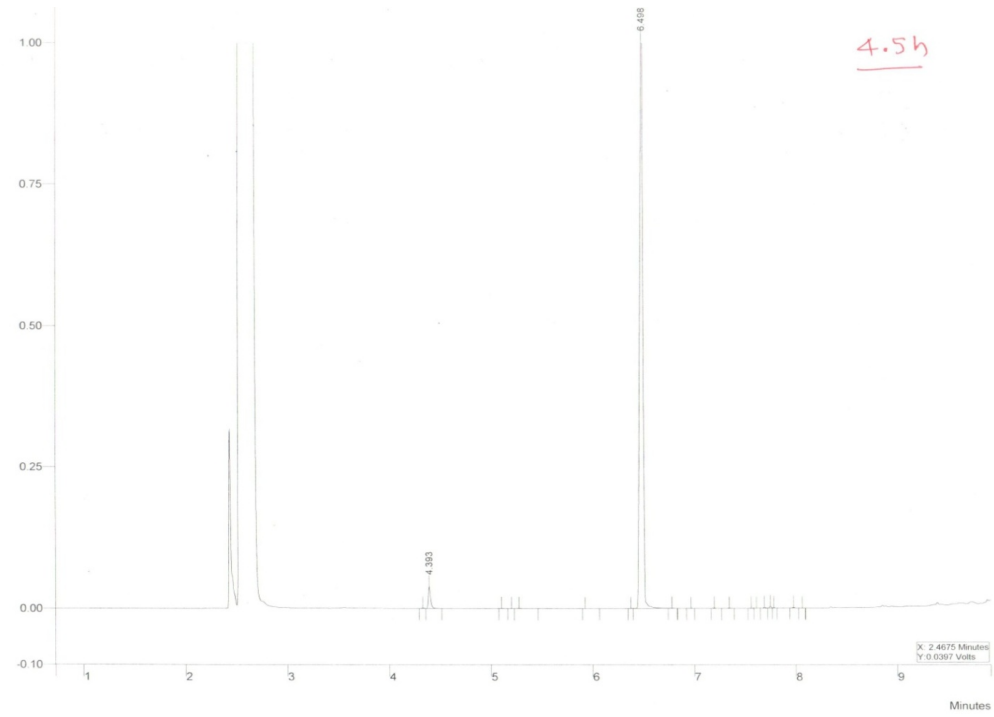

Volts
1.00
0.75
0.50
0.25
0.00
-0.10
4.371
4.292
2
3
4
5
6
7
8
X: 2.3115 Minutes
Y: 0.000364 Volts
Minutes


mVolts
80
70
60
50
40
30
20
10
0
-4
6.020
2
3
4
5
6
7
8
9
X: 7.1858 Minutes
Y: -0.0320 mVolts


mVolts
c:\documents and settings\dr.ganesh pandey\desktop\gc-folder method\gc1\3843.run
6.396
X: 1.2536 Minutes
Y: -0.0390 mVolts
Minutes

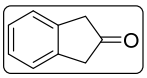

Volts
c:\documents and settings\dr.ganesh pandey\desktop\gc-folder method\gc1\3869.run
1h
4.402
6.480
4.330
X: 0.0929 Minutes
Y: 0.00000300 Volts
Minutes


Volts
1.00
0.75
0.50
0.25
0.00
-0.10
4.399
6.490
4.325
6.120
2h
X: 2.0000 Minutes
Y: 0.000343 Volts
2
3
4
5
6
7
8
9
Minutes

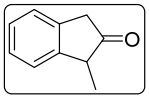

1.00
0.75
0.50
0.25
0.00
-0.10
6.498
4.393
4.5h
X: 2.4675 Minutes
Y: 0.0397 Volts
1
2
3
4
5
6
7
8
9
Minutes

General procedure for Wacker-type oxidation: To a solution of indene (1 equiv) in acetone (10 mL, for 1 mmol indene) were added ethyl acetate (2 mL), water (2 mL) and solid $NaHCO_3$ (3 equiv) and the reaction mixture was stirred for 10 min. To this was added solid Oxone (0.5 equiv) and contents were stirred at room temperature for 15-18 h. After completion of the reaction, the excess acetone evaporated under reduced pressure and remaining reaction mixture portioned between water and ethyl acetate (20 mL each). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 x 20 mL). Combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column (ethyl acetate and pet ether as eluent) to afford the corresponding ketone.

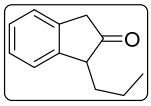
1,3-Dihydro-2H-inden-2-one_(4a): The general procedure was followed using 1H-indene (**1a**) (100 mg, 0.86 mmol) as a substrate procured **4a** (89 mg, 78%) as a white solid; R_f 0.3 (15% ethyl acetate/pet. ether); H^1 NMR (200MHz) : δ = 3.57 (s, 4H), 7.26–7.31 (m, 4H) ppm; ^{13}C NMR (50 MHz) : δ= 44.1 ($2CH_2$), 125.1 (2CH), 127.4 (2CH), 137.8 (2C), 215.3 (C) ppm.



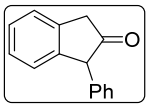
1-Methyl-1,3-dihydro-2H-inden-2-one (4b): The general procedure was followed using 3-methyl-1H-indene (**1b**) (100 mg, 0.52 mmol) as a substrate procured **4b** (79 mg, 70%) as a colorless solid; R_f 0.3 (15% ethyl acetate/pet. ether); H^1 NMR (200MHz) : δ = 1.33 (t, J = 2 Hz, 3H), 2.42 (m, 1H), 3.13 (t, J = 4 Hz, 2H), 7.04–7.37 (m, 4H) ppm.



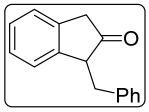
1-Propyl-1,3-dihydro-2H-inden-2-one (4c): The general procedure was followed using 3-propyl-1H-indene (**1c**) (100 mg, 0.63 mmol) as a substrate procured **4c** (83 mg, 74%) as a colorless liquid; R_f 0.3 (10% ethyl acetate/pet. ether); H^1 NMR (200MHz) : 0.922 (t, J = 7.4 Hz, 3H), 1.28–1.42 (m, 2H), 1.81–1.91 (m, 2H), 5.76 (t, J = 5.7 Hz, 1H), 3.52 (s, 2H), 7.26–7.31 (m, 4H) ppm.



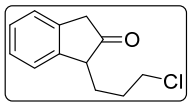
1-Phenyl-1,3-dihydro-2H-inden-2-one (4e): The general procedure was followed using 3-phenyl-1H-indene (**1e**) (100 mg, 0.77 mmol) as a substrate procured **4e** (66 mg, 61%) as a colorless solid; R_f 0.3 (15% ethyl acetate/pet. ether); H^1 NMR (200MHz) : δ = 3.62 (s, 2H), 4.63 (s, 1H), 7.04–7.16 (m, 3H), 7.20–7.36 (s, 6H) ppm; ^{13}C NMR (50 MHz) : δ = 44.1 ($2CH_2$), 125.0 (2CH), 127.4 (2CH), 137.7 (2C), 215.2 (C) ppm.



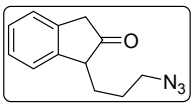
1-Benzyl-1,3-dihydro-2H-inden-2-one (4f): The general procedure was followed using 3-benzyl-1H-indene (**1f**) (100 mg, 0.48 mmol) as a substrate procured **4f** (81 mg, 75%) as a colorless solid; R_f 0.3 (15% ethyl acetate/pet. ether); H^1 NMR (200MHz) : 2.93–3.04 (m, 1H), 3.19–3.54 (m, 3H), 3.74–3.80 (m, 1H), 6.92–6.96 (m, 1H), 7.04–7.09 (m, 2H), 7.16–7.21 (m, 6H) ppm.



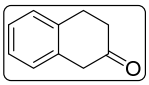
1-(3-Chloropropyl)-1,3-dihydro-2H-inden-2-one (4h): The general procedure was followed using 3-(3-chloropropyl)-1H-indene (**1h**) (100 mg, 0.5 mmol) as a substrate procured **4h** (80 mg, 74%) as a yellow liquid; R_f 0.3 (15% ethyl acetate/pet. ether); H^1 NMR (500MHz) : δ = 1.75–1.90 (m, 2H), 1.94–2.02 (m, 1H), 2.05–2.12 (m, 1H), 3.48–3.59 (m, 5H), 7.26–7.31(m, 4H); ^{13}C NMR (125 MHz) : δ = 28.7 (CH_2), 29.0 (CH_2), 43.4 (CH_2), 44.8 (CH_2), 51.8 (CH), 124.4 (CH), 124.9 (CH), 127.5 (CH), 127.6 (CH), 136.8 (C), 140.4 (C), 217.5 (C) ppm; HRMS (ESI+): calcd. for $C_{12}H_{13}OClNa^+$ 231.0547, found 231.0548.



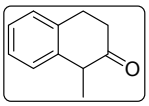
1-(3-Azidopropyl)-1,3-dihydro-2H-inden-2-one (4i): The general procedure was followed using 3-(3-azidopropyl)-1H-indene (**1i**) (100 mg, 0.50 mmol) as a substrate procured **4i** (78 mg, 72%) as a yellow liquid; R_f 0.3 (15% ethyl acetate/pet. ether); H^1 NMR (500MHz) : δ = 1.57–1.71 (m, 2H), 1.91–1.99 (m, 1H), 2.01–2.09 (m, 1H), 3.12–3.31 (m, 2H), 3.42–3.63 (m, 3H), 7.14–7.56 (m, 4H); ^{13}C NMR (125 MHz) : δ = 25.5 (CH_2), 28.3 (CH_2), 43.4 (CH_2), 51.3 (CH_2), 52.2 (CH), 124.4 (CH), 124.9 (CH), 127.6 (2CH), 136.8 (C), 141.3 (C), 217.5 (C) ppm; HRMS (ESI+): calcd. for $C_{12}H_{13}ON_3Na^+$ 238.0951, found 238.0952.



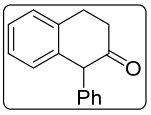
3,4-Dihydronaphthalen-2(1H)-one (8a): The general procedure was followed using 1,2-dihydronaphthalene (**7a**) (100 mg, 0.77 mmol) as a substrate procured **8a** (80 mg, 71%) as a colorless liquid; R_f 0.4 (15% ethyl acetate/pet. ether); H^1 NMR (200MHz) : 1.12–1.88 (m, 1H), 2.40–2.46 (m, 1H), 2.50–2.63 (m, 1H), 2.74–2.92 (m, 1H), 3.78 (t, J = 3.5 MHz, 1H), 3.89 (d, J = 4.3 MHz, 1H), 7.11–7.15 (m, 1H), 7.20–7.34 (m, 2H), 7.41–7.45 (m, 1H) ppm.



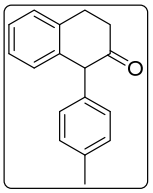
1-Methyl-3,4-dihydronaphthalen-2(1H)-one (8b): The general procedure was followed using 4-methyl-1,2-dihydronaphthalene (**7b**) (100 mg, 0.69 mmol) as a substrate procured **8b** (72 mg, 65%) as a colorless solid; R_f 0.3 (15% ethyl acetate/pet. ether)**; H^1 NMR (200MHz) : 1**.32 (d, J = 6 Hz, 3H), 1.91 (d, J = 6 Hz, 1H), 2.51–3.0 (m, 4H), 6.81–7.33 (m, 4H), ppm.



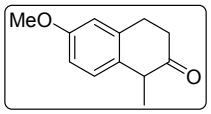
1-Phenyl-3,4-dihydronaphthalen-2(1H)-one (8c): The general procedure was followed using 4-phenyl-1,2-dihydronaphthalene (**7c**) (100 mg, 0.49 mmol) as a substrate procured **8c** (70 mg, 65%) as a colorless solid, melting point 163-166 ^{o}C; R_f 0.3 (15% ethyl acetate/pet. ether); H^1 NMR (200MHz) : 2.60–2.68 (m, 1H), 2.73–2.90 (m, 1H), 3.10–3.33 (m, 2H), 4.81 (s, 1H), 7.04–7.49 (m, 9H) ppm.



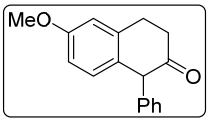
1-(p-Tolyl)-3,4-dihydronaphthalen-2(1H)-one (8d): The general procedure was followed using 4-(p-tolyl)-1,2-dihydronaphthalene (**7d**) (100 mg, 0.45 mmol) as a substrate procured **8d** (77 mg, 72%) as a colorless liquid; R_f 0.3 (15% ethyl acetate/pet. ether); H^1 NMR (500MHz) : δ = 2.31 (s, 3H), 2.53–2.61 (m, 1H), 2.67–2.75 (m, 1H), 2.98–3.05 (m, 1H), 3.08–3.15 (m, 1H), 4.71 (s, 1H), 6.98 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H), 7.18–7.24 (m, 1H), 7.27 (d, J = 4.4 Hz, 2H); ^{13}C NMR (125 MHz) : δ = 21.0 (CH_3), 28.2 (CH_2), 37.0 (CH_2), 59.5 (CH), 127.2 (CH), 127.3 (CH), 127.4 (CH), 127.9 (2CH), 129.4 (CH), 129.5 (CH), 129.6 (CH), 134.5 (C), 136.7 (C), 137.0 (2C), 209.9 (C) ppm; HRMS (ESI+): calcd. for $C_{17}H_{16}ONa^+$ 259.1093, found 259.1093.



6-Methoxy-1-methyl-3,4-dihydronaphthalen-2(1H)-one (8e): The general procedure was followed using 4-phenyl-1,2-dihydronaphthalene (**7e**) (100 mg, 0.57 mmol) as a substrate procured **8e** (67 mg, 61%) as a colorless oil; R_f 0.3 (20% ethyl acetate/pet. ether); H^1 NMR (200MHz) : 1.41 (t, J = 5 Hz, 3H), 2.63 (dd, J = 2, 3 Hz, 2H), 3.20 (dd, J = 2, 3 Hz, 2H), 3.81 (s, 3H), 6.94–7.89 (m, 3H) ppm.

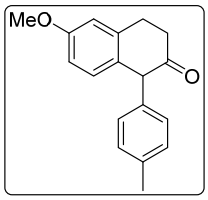


6-Methoxy-1-phenyl-3,4-dihydronaphthalen-2(1H)-one (8f): The general procedure was followed using 7-methoxy-4-phenyl-1,2-dihydronaphthalene (**7f**) (100 mg, 0.42 mmol) as a substrate procured **8f** (77 mg, 72%) as a colorless liquid; R_f 0.3 (15% ethyl acetate/pet. ether);

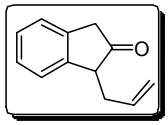


H^1 NMR (500MHz) : δ = 2.56–2.62 (m, 1H), 2.71–2.77 (m, 1H), 2.98–3.04 (m, 1H), 3.09–3.15 (m, 1H), 3.85 (s, 3H), 4.73 (s, 1H), 6.80–6.84 (m, 2H), 6.96 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 7.1 Hz, 2H), 7.28 (t, *J* = 6.6 Hz, 1H), 7.33 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (125 MHz) : δ = 28.4 (CH_2), 36.7 (CH_2), 55.3 (CH_3), 59.0 (CH), 112.8 (CH), 113.1 (CH), 127.1 (CH), 128.4 (C), 128.5 (2CH), 128.6 (2CH), 130.6 (CH), 137.9 (C), 138.2 (C), 158.8 (C), 209.8 (C) ppm; HRMS (ESI+): calcd. for $C_{17}H_{16}O_2Na^+$ 275.1043, found 275.1040.

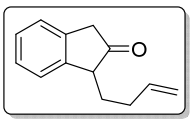
6-Methoxy-1-(p-tolyl)-3,4-dihydronaphthalen-2(1H)-one (8g): The general procedure was followed using 7-methoxy-4-phenyl-1,2-dihydronaphthalene (**7g**) (100 mg, 0.40 mmol) as a substrate procured **8g** (73 mg, 69%) as a colorless liquid; R_f 0.3 (15% ethyl acetate/pet. ether); H^1 NMR (500MHz) δ: 2.31 (s, 3H),2.51–2.57 (m, 1H), 2.66–2.72 (m, 1H), 2.94–3.00 (m, 1H), 3.04–3.10 (m, 1H), 3.82 (s, 3H), 4.66 (s, 1H), 6.79 (dd, *J* = 2.5, 8.4 Hz, 1H), 6.82 (d, *J* = 2.52 Hz, 1H), 6.93 (d, *J* = 8.16 Hz, 1H), 6.98(d, *J* = 7.94 Hz, 2H), 7.11 (d, *J* = 8.14 Hz, 2H); ^{13}C NMR (125 MHz) δ: 21.0 (CH_3), 28.4 (CH_2), 36.8 (CH_2), 55.3 (CH_3), 58.7 (CH), 112.8 (CH), 113.1 (CH), 128.4 (2CH), 128.6 (C), 129.4 (2CH), 130.6 (CH), 134.9 (C), 136.8 (C), 138.1 (C), 158.7 (C), 209.9 (C) ppm; HRMS (ESI+): calcd. for $C_{18}H_{18}O_2Na^+$ 289.1199, found 289.1199.



1-Allyl-1,3-dihydro-2H-inden-2-one (4q): The general procedure was followed using 3-allyl-1H-indene (**1q**) (100 mg, 0.64 mmol) as a substrate procured **4q** (76mg, 69%) as a colorless liquid; R_f 0.3 (15% ethyl acetate/pet. ether); NMR (200MHz) : δ = 2.51–2.78 (m, 2H), 3.49–3.57 (m, 3H), 4.98–5.11 (m, 2H), 5.61–5.82 (m, 1H), 7.26–7.35(m, 4H); ^{13}C NMR (50 MHz) : δ = 35.7 (CH_2), 43.4 (CH_2), 52.6 (CH), 117.8 (CH_2), 124.8 (2CH), 127.4 (CH), 127.5 (CH), 134.4 (CH), 136.8 (C), 141.5 (C), 217.1 (C) ppm.

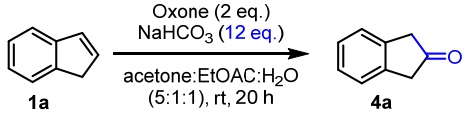


1-(But-3-en-1-yl)-1,3-dihydro-2H-inden-2-one (4p): The general procedure was followed using 3-(but-3-en-1-yl)-1H-indene (**1p**) (100 mg, 0.59 mmol) as a substrate procured **4p** (74mg, 68%) as a colorless liquid; R_f 0.3 (15% ethyl acetate/pet. ether); ^1H NMR (200 MHz, $CDCl_3$): *δ* = 1.92–2.03 (m, 2H), 2.04–2.14 (m, 2H), 3.48 (d, *J* = 5.2 Hz, 1H), 3.53 (s, 2H), 4.92–5.08 (m, 2H), 5.69–5.75 (m, 1H), 7.28–7.32 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$): *δ*



= 30.3 (CH_2), 30.6 (CH_2), 43.5 (CH_2), 52.2 (CH), 115.4 (CH_2), 124.5 (CH), 124.9 (CH), 127.4 (CH), 127.5 (CH), 137.0 (CH), 137.8 (C), 141.9 (C), 217.9 (C) ppm; HRMS (ESI+):calcd. for $C_{13}H_{14}ONa^+$ 209.0993, found 209.0937.

GC analysis for the reaction of indene to Ketone: Similar to acetonide, in ketone reaction also we analyze the reaction mixture at certain time interval and find out the ketone formation is a direct process, there is no epoxide intermediate (time mentioned on spectra)



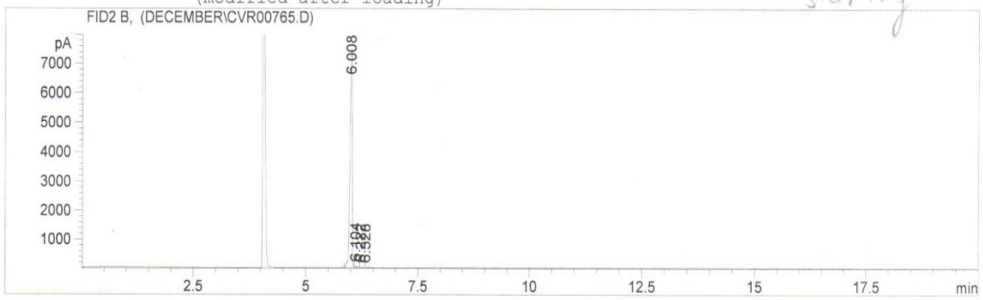
Instrument Use:	Agilent 6890N
Column:	HP-5 (30m×0.25μm ×0.25 mm)
Detector:	FID (temp. 300 ^{o}C)
Injector temp.:	280 ^{o}C
Column Cond.:	80 ^{o}C (1 min) to 300 ^{o}C (10 min)
Column Flow:	1.0 mL/min.
Carrier Gas:	N_2
Sample Dissolved:	Dichloromethane

```
Data File C:\HPCHEM\1\DATA\DECEMBER\CVR00765.D                    Sample Name: RR-01

  100 Deg (1min) 20Deg/min 280 Deg (10 min) 6890N Agilent
   DET-300 DEG INJ.280 DEG.COL: HP-5
  Sample is dissolved in DCM

  ==================================================================
  Injection Date  : 12/17/2013 12:09:54 AM
  Sample Name     : RR-01                        Location : Vial 2
  Acq. Operator   : Dr.BORIKAR                        Inj :   1
                                                Inj Volume : Manually
  Acq. Method     : C:\HPCHEM\1\METHODS\REGFID.M
  Last changed    : 12/17/2013 12:06:24 AM by Dr.BORIKAR
                    (modified after loading)
  Analysis Method : C:\HPCHEM\1\METHODS\REGFID.M
  Last changed    : 12/17/2013 12:51:17 AM by Dr.BORIKAR
                    (modified after loading)
```

starting



ata File C:\HPCHEM\1\DATA\DECEMBER\CVR00766.D

Sample Name: RR-02

100 Deg (1min) 20Deg/min 280 Deg (10 min) 6890N Agilent
DET-300 DEG INJ.280 DEG.COL: HP-5
Sample is dissolved in DCM

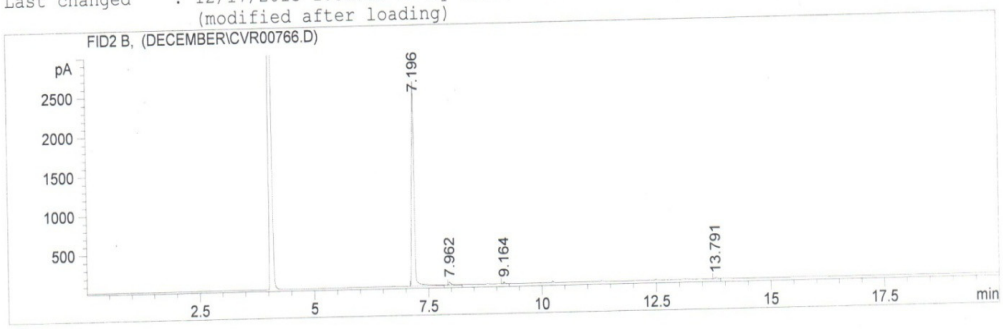
==========

Injection Date : 12/17/2013 12:52:35 AM
Sample Name : RR-02
Acq. Operator : Dr.BORIKAR

Location : Vial 2
Inj : 1
Inj Volume : Manually

Acq. Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/17/2013 12:51:17 AM by Dr.BORIKAR
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/17/2013 1:51:32 AM by Dr.BORIKAR
(modified after loading)

product



Data File C:\HPCHEM\1\DATA\DECEMBER\CVR00770.D

Sample Name: RR-02-A

100 Deg (1min) 20Deg/min 280 Deg (10 min) 6890N Agilent
DET-300 DEG INJ.280 DEG.COL: HP-5
Sample is dissolved in DCM

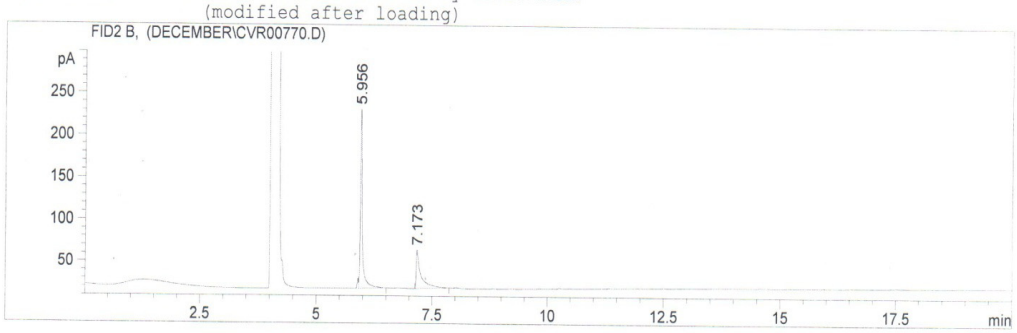
==========

2h

Injection Date : 12/17/2013 2:55:01 AM
Sample Name : RR-02-A
Acq. Operator : Dr.BORIKAR

Location : Vial 2
Inj : 1
Inj Volume : Manually

Acq. Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/17/2013 2:50:53 AM by Dr.BORIKAR
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/17/2013 3:39:05 AM by Dr.BORIKAR
(modified after loading)



Data File C:\HPCHEM\1\DATA\DECEMBER\CVR00778.D Sample Name: RR-02-D-1

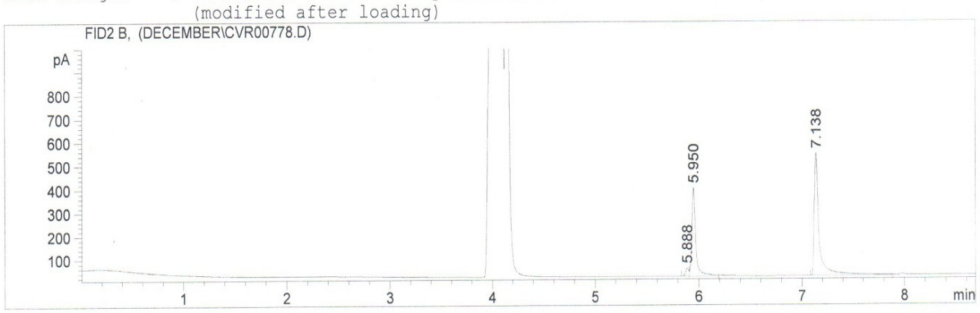
100 Deg (1min) 20Deg/min 280 Deg (10 min) 6890N Agilent
DET-300 DEG INJ.280 DEG.COL: HP-5
Sample is dissolved in DCM

6h

==========

Injection Date : 12/18/2013 3:44:35 AM
Sample Name : RR-02-D-1 Location : Vial 2
Acq. Operator : Dr.BORIKAR Inj : 1
Inj Volume : Manually

Acq. Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/18/2013 3:42:17 AM by Dr.BORIKAR
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/18/2013 3:54:00 AM by Dr.BORIKAR
(modified after loading)



Data File C:\HPCHEM\1\DATA\DECEMBER\CVR00780.D Sample Name: RR-02-D-3

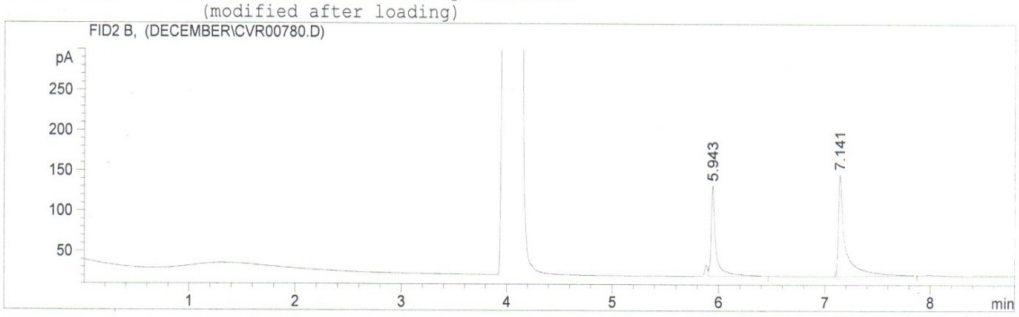
100 Deg (1min) 20Deg/min 280 Deg (10 min) 6890N Agilent
DET-300 DEG INJ.280 DEG.COL: HP-5
Sample is dissolved in DCM

8h

==========

Injection Date : 12/18/2013 4:09:33 AM
Sample Name : RR-02-D-3 Location : Vial 2
Acq. Operator : Dr.BORIKAR Inj : 1
Inj Volume : Manually

Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/18/2013 4:06:17 AM by Dr.BORIKAR
(modified after loading)



Data File C:\HPCHEM\1\DATA\DECEMBER\CVR00772.D Sample Name: RR-02-F

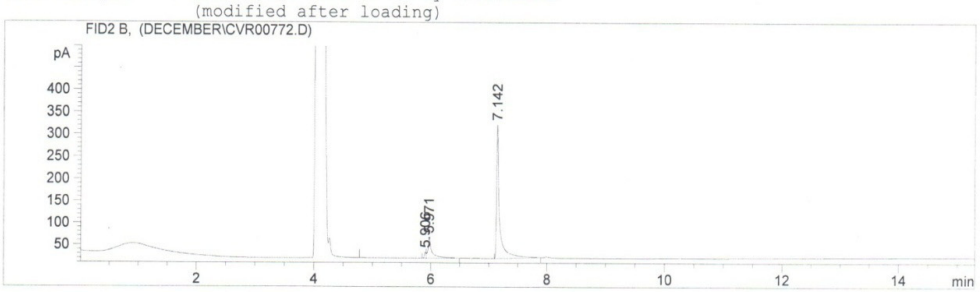
100 Deg (1min) 20Deg/min 280 Deg (10 min) 6890N Agilent
DET-300 DEG INJ.280 DEG.COL: HP-5
Sample is dissolved in DCM

15h

==========

Injection Date : 12/17/2013 4:16:15 AM
Sample Name : RR-02-F Location : Vial 2
Acq. Operator : Dr.BORIKAR Inj : 1
Inj Volume : Manually

Acq. Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/17/2013 3:39:05 AM by Dr.BORIKAR
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/17/2013 4:31:49 AM by Dr.BORIKAR
(modified after loading)



Data File C:\HPCHEM\1\DATA\DECEMBER\CVR00774.D Sample Name: RR-02-H

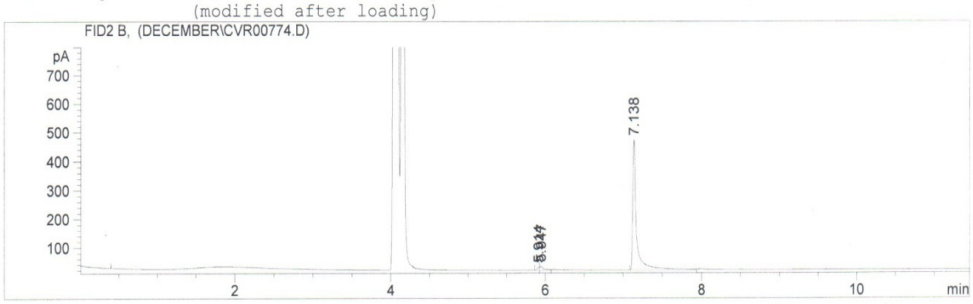
100 Deg (1min) 20Deg/min 280 Deg (10 min) 6890N Agilent
DET-300 DEG INJ.280 DEG.COL: HP-5
Sample is dissolved in DCM

20h

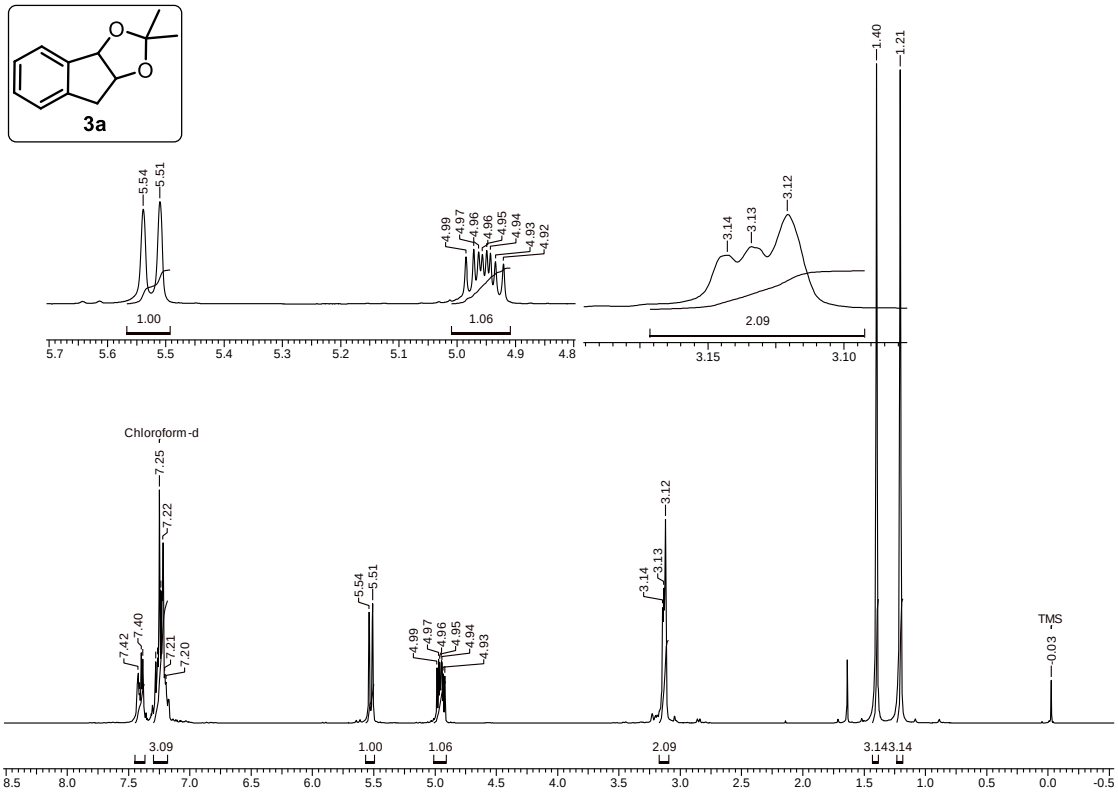
==========

Injection Date : 12/17/2013 4:49:42 AM
Sample Name : RR-02-H Location : Vial 2
Acq. Operator : Dr.BORIKAR Inj : 1
Inj Volume : Manually

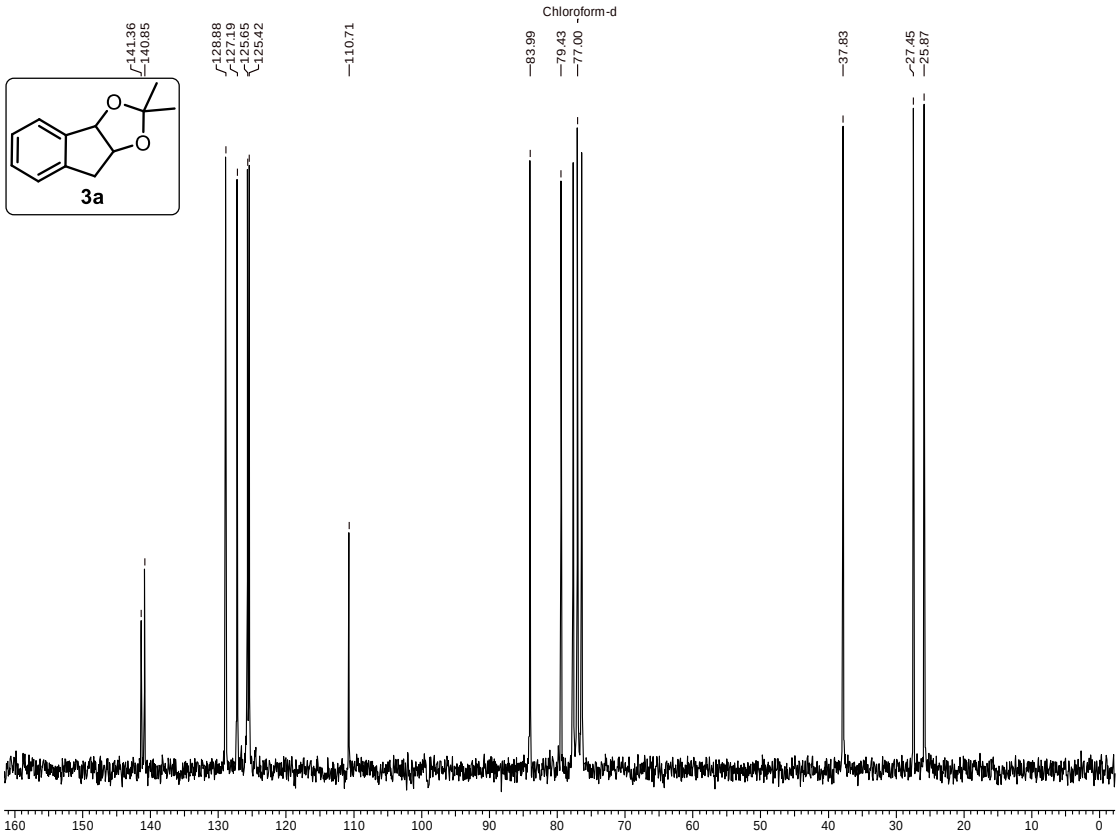
Acq. Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/17/2013 4:46:06 AM by Dr.BORIKAR
(modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\REGFID.M
Last changed : 12/17/2013 5:02:41 AM by Dr.BORIKAR
(modified after loading)



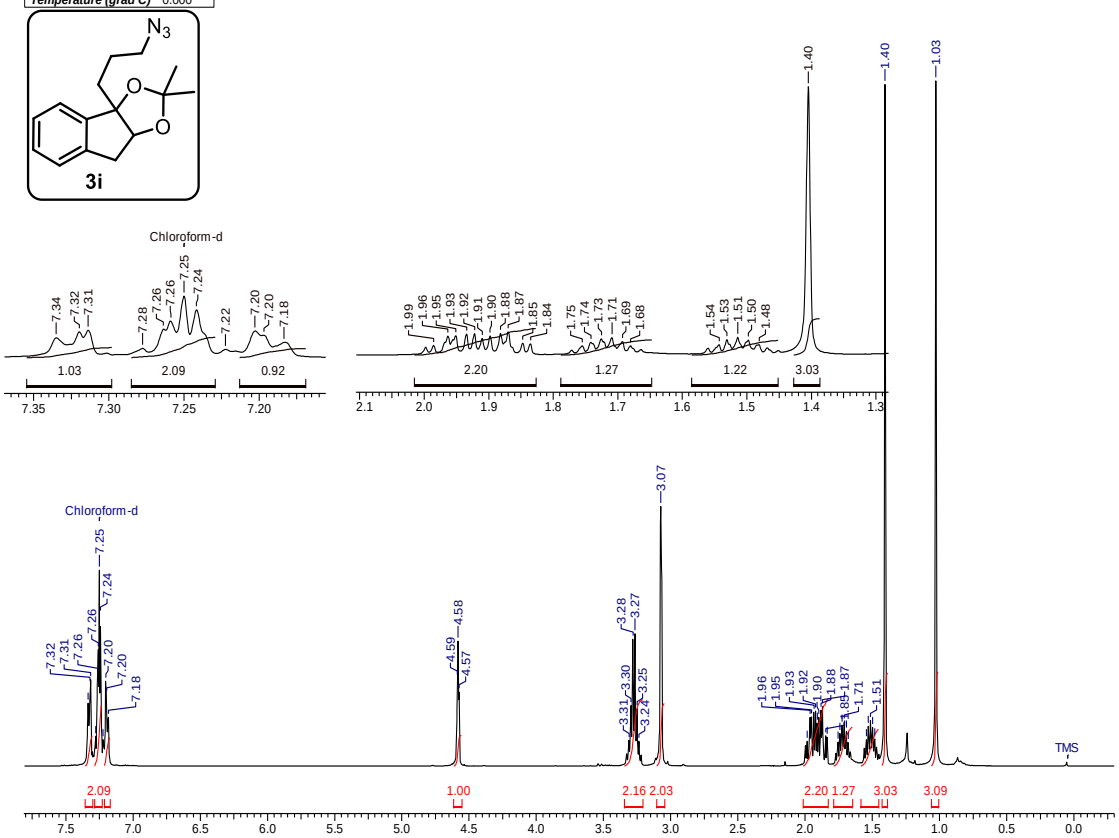
Acquisition Time (sec) 7.9167	***Comment***	Ravindra/11178		***Date***	08/11/2011 02:14:28		
Frequency (MHz) 200.13	***Nucleus***	1H	***Original Points Count*** 32768	***Points Count***	32768	***Sweep Width (Hz)***	4139.07
Temperature (grad C) 0.000							



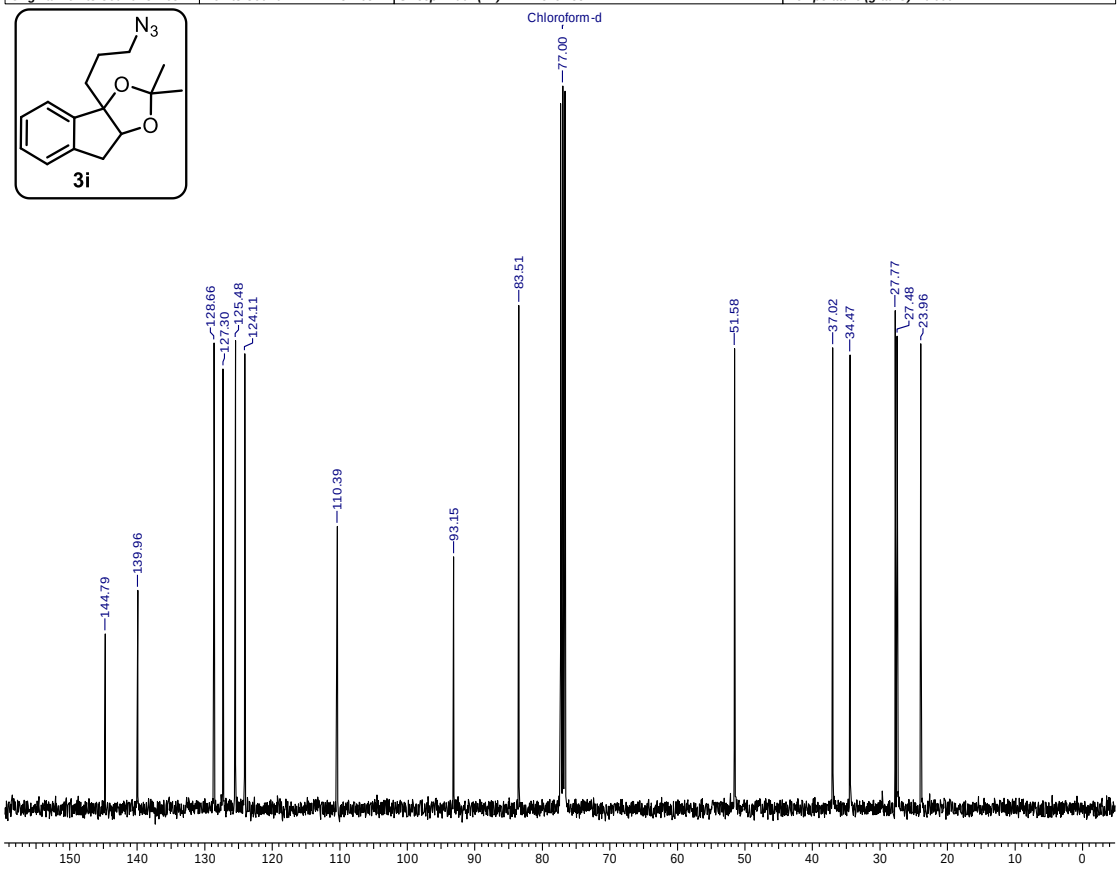
Acquisition Time (sec) 2.7329	***Comment***	Ravindra/11178		***Date***	11/11/2011 09:06:28		
Frequency (MHz) 50.32	***Nucleus***	13C	***Original Points Count*** 32768	***Points Count***	32768	***Sweep Width (Hz)***	11990.41
Temperature (grad C) 0.000							



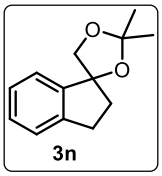
Acquisition Time (sec)	3.9846	**Comment**	Ravindra		**Date**	24/08/2013 17:19:08	
Frequency (MHz)	400.13	**Nucleus**	1H	**Original Points Count** 32768	**Points Count**	32768	**Sweep Width (Hz)** 8223.68
Temperature (grad C)	0.000						

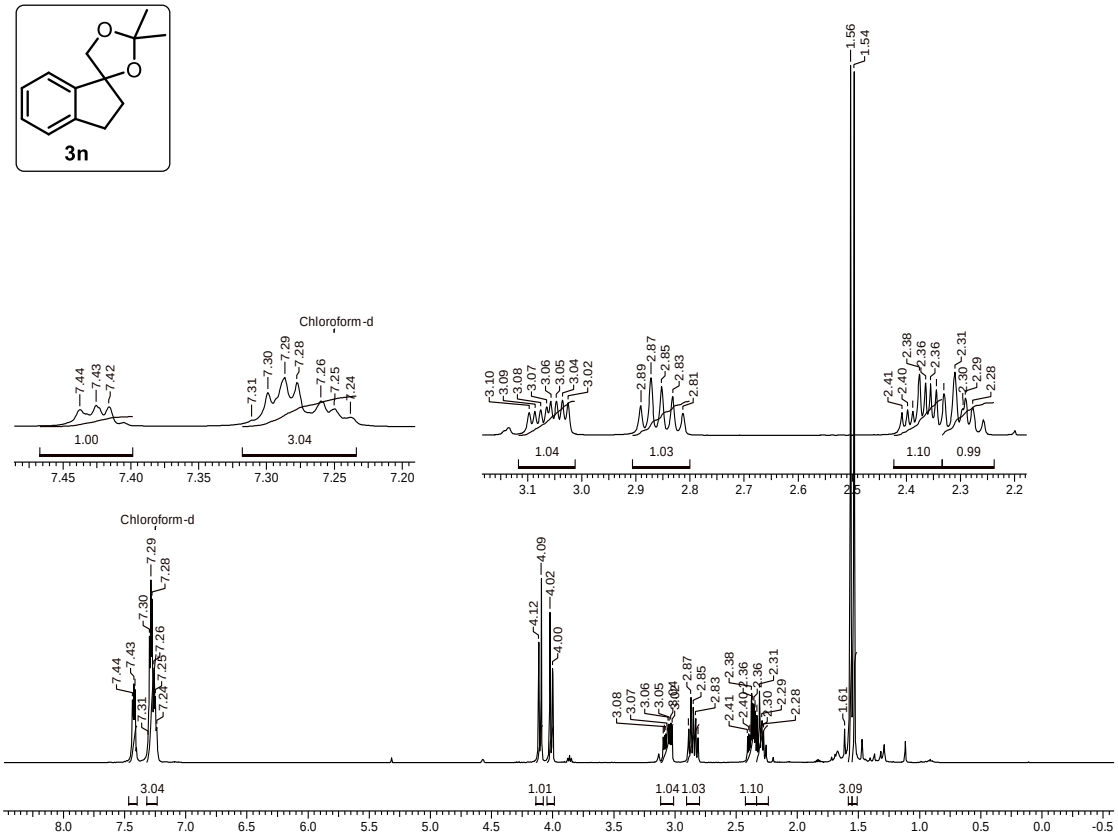


Acquisition Time (sec)	1.2976	**Date**	24/08/2013 17:31:56		**Frequency (MHz)**	100.61	**Nucleus** 13C
Original Points Count	32768	**Points Count**	32768	**Sweep Width (Hz)** 25252.53			**Temperature (grad C)** 0.000

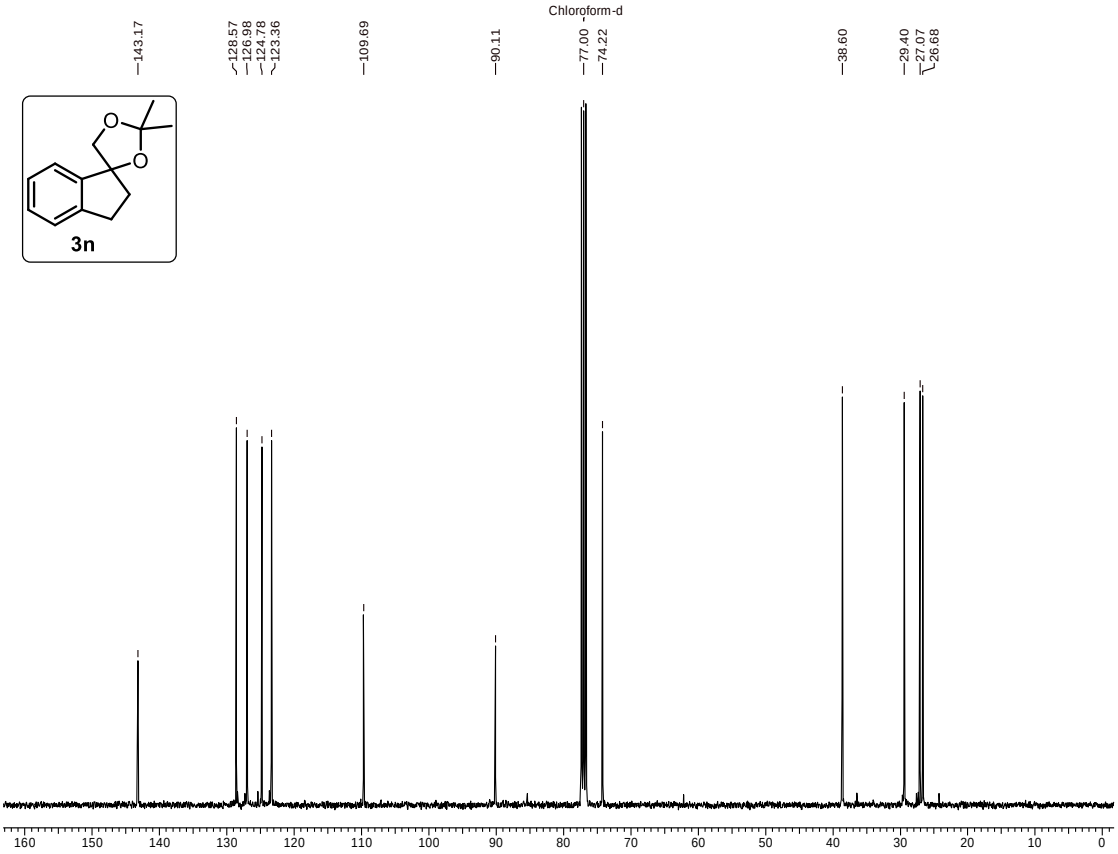


Acquisition Time (sec) 3.9846	***Comment***	Ravindra		***Date***	26/04/2013 13:43:06		
Frequency (MHz) 400.13	***Nucleus***	1H	***Original Points Count*** 32768	***Points Count***	32768	***Sweep Width (Hz)***	8223.68
Temperature (grad C) 0.000							

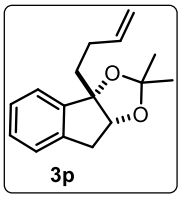


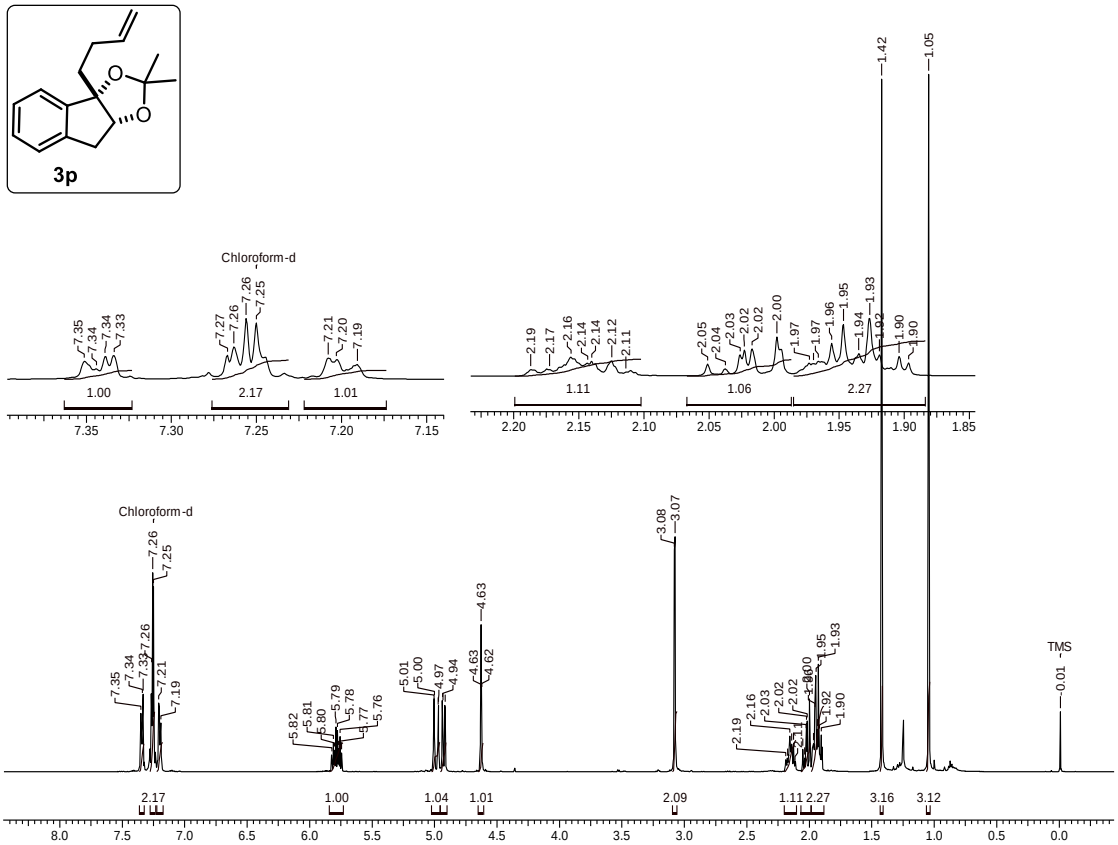


Acquisition Time (sec) 1.2976	***Date***	26/04/2013 13:42:44		***Frequency (MHz)***	100.61	***Nucleus***	13C
Original Points Count 32768	***Points Count***	32768	***Sweep Width (Hz)*** 25252.53			***Temperature (grad C)*** 0.000	

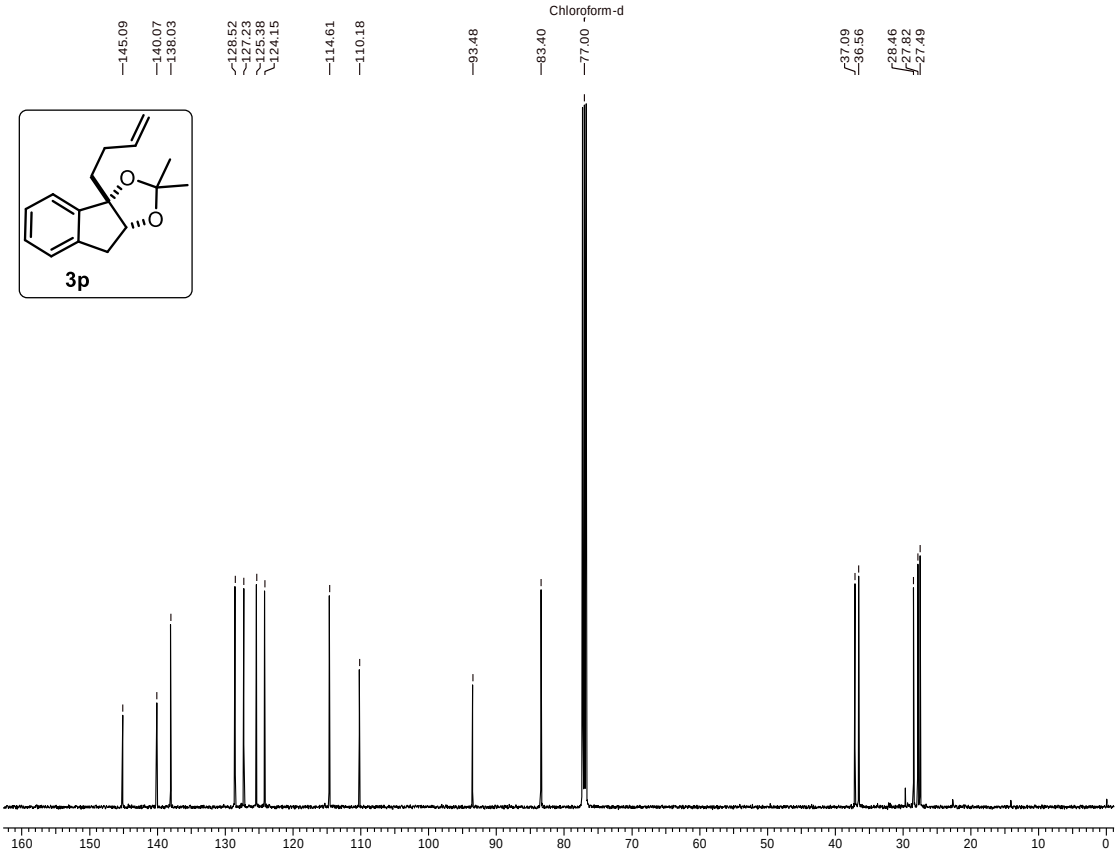


Acquisition Time (sec) 3.2768	***Comment***	Sachin G		***Date***	22/09/2012 15:34:30		
Frequency (MHz) 500.13	***Nucleus***	1H	***Original Points Count*** 32768	***Points Count***	32768	***Sweep Width (Hz)***	10000.00
Temperature (grad C) 0.000							

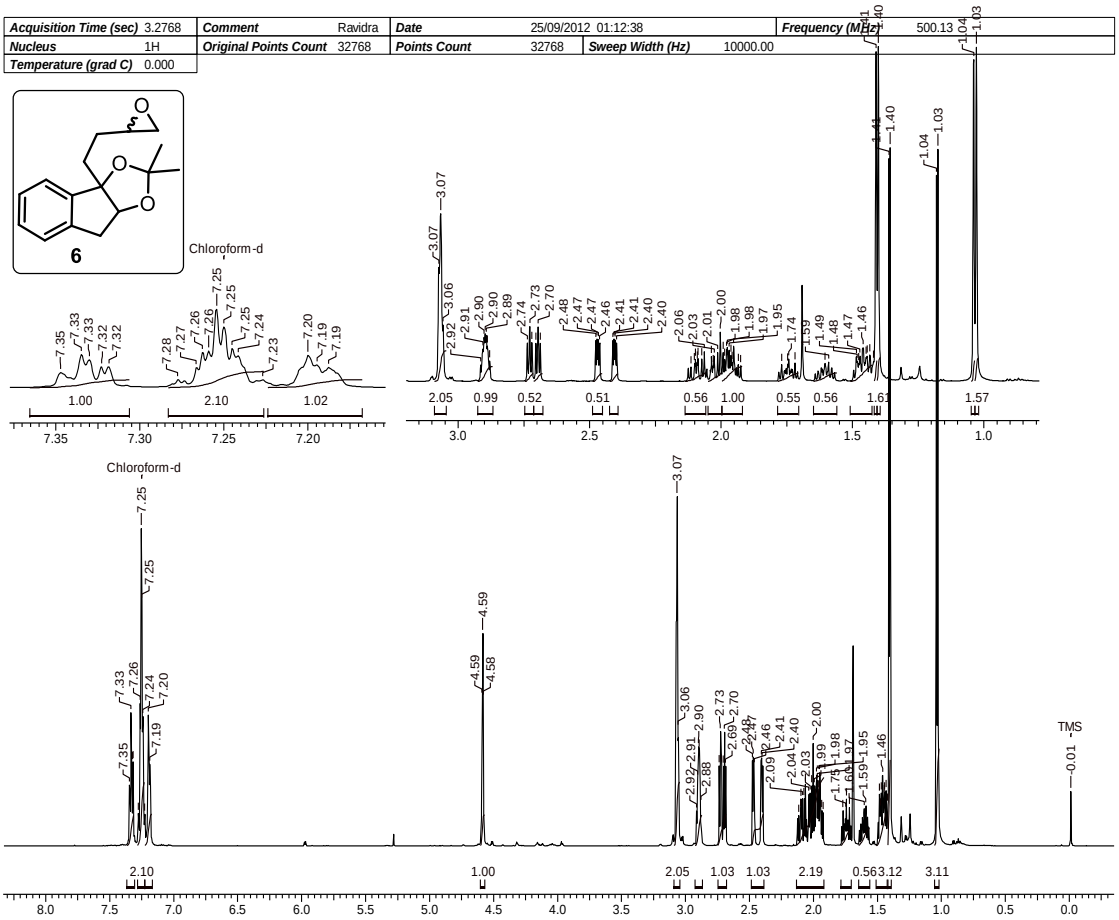




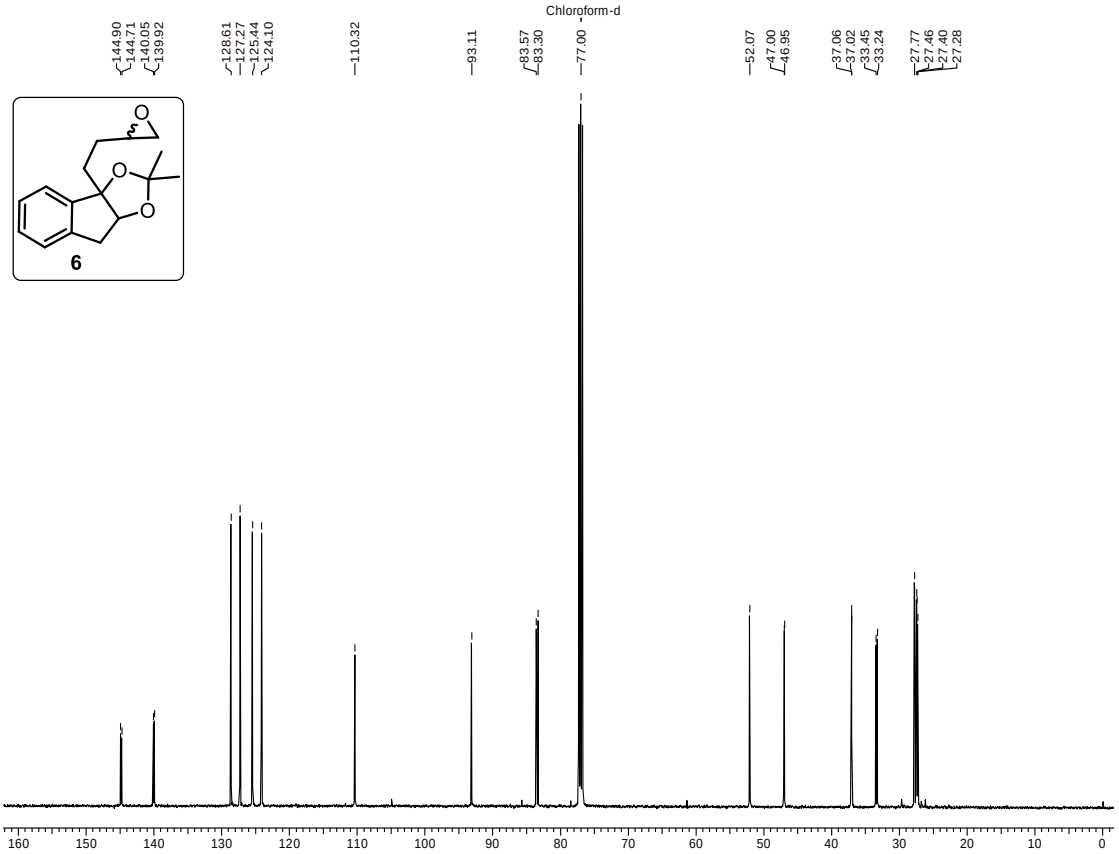
Acquisition Time (sec) 1.0486	***Date***	22/09/2012 18:36:24		***Frequency (MHz)***	125.76	***Nucleus***	13C
Original Points Count 32768	***Points Count***	32768	***Sweep Width (Hz)***	31250.00		***Temperature (grad C)***	0.000



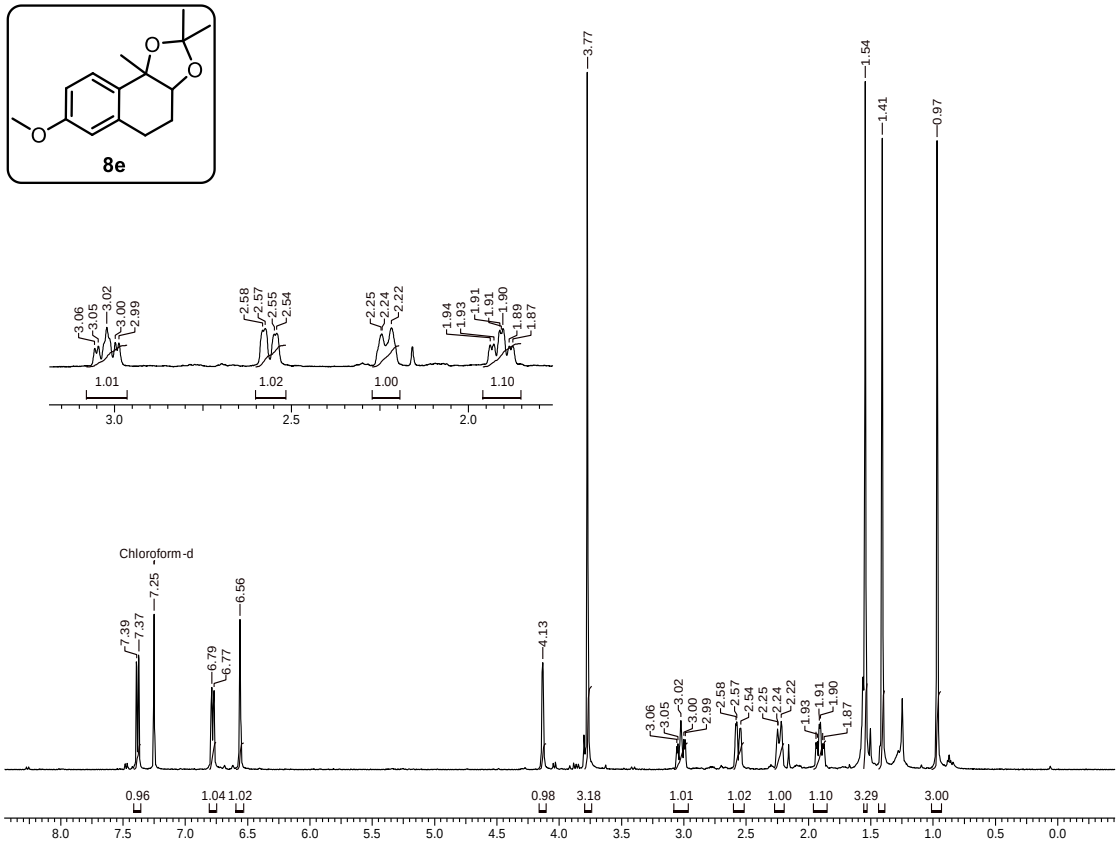
Acquisition Time (sec)	3.2768	**Comment**	Ravidra	**Date**	25/09/2012 01:12:38	**Frequency (MHz)**	500.13
Nucleus	1H	**Original Points Count**	32768	**Points Count**	32768	**Sweep Width (Hz)**	10000.00
Temperature (grad C)	0.000						



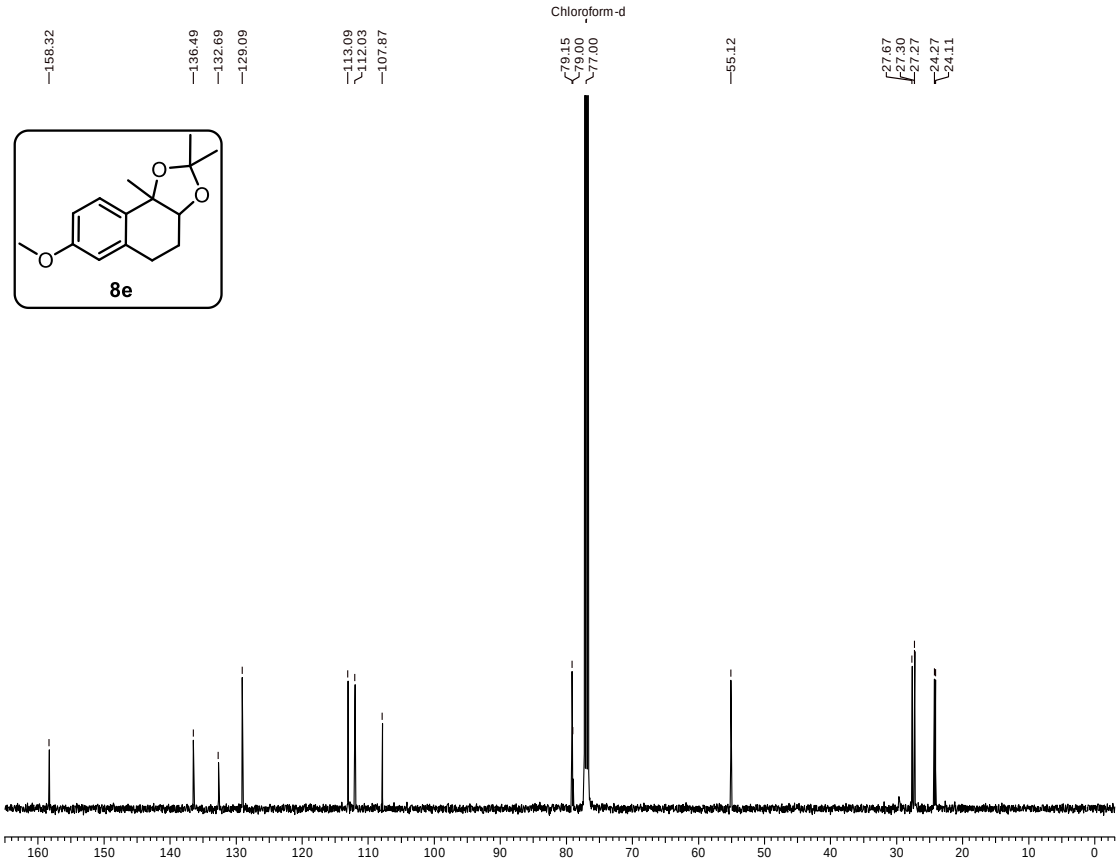
Acquisition Time (sec)	1.0486	**Date**	25/09/2012 01:12:20	**Frequency (MHz)**	125.76	**Nucleus**	13C
Original Points Count	32768	**Points Count**	32768	**Sweep Width (Hz)**	31250.00	**Temperature (grad C)**	0.000



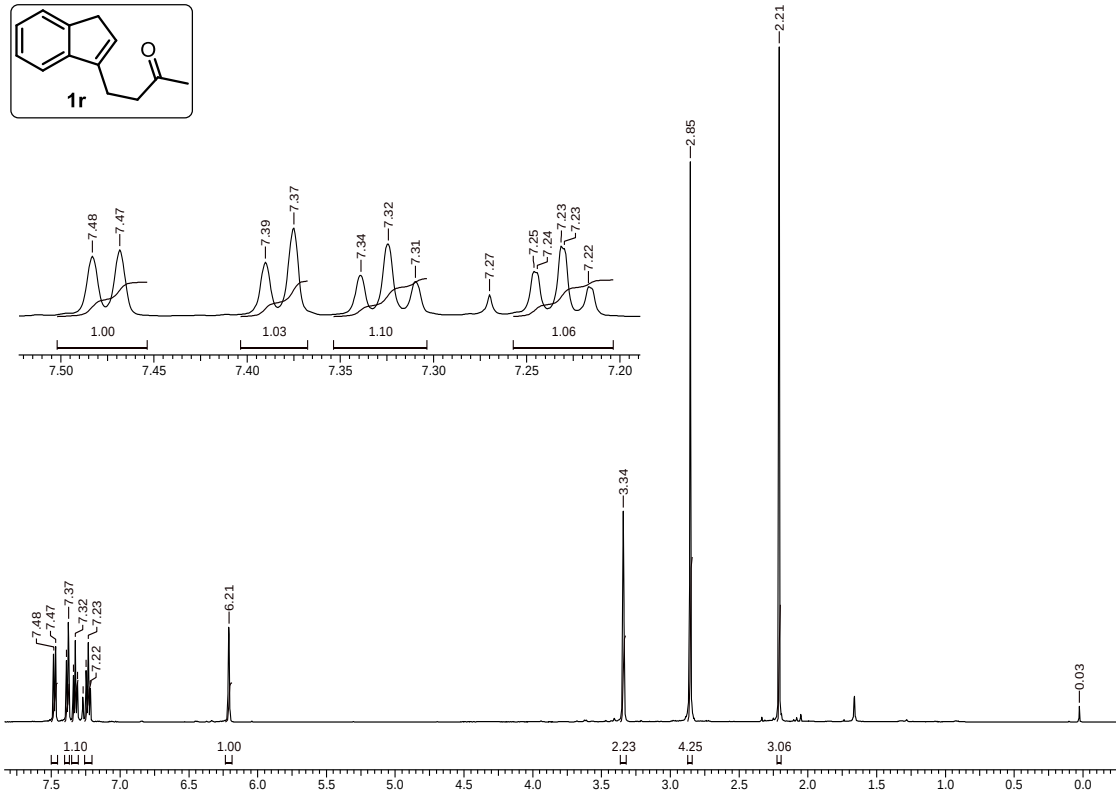
Acquisition Time (sec) 3.2768	***Comment***	Ravindra		***Date***	21/04/2013 14:14:12		
Frequency (MHz) 500.13	***Nucleus***	1H	***Original Points Count*** 32768	***Points Count***	32768	***Sweep Width (Hz)***	10000.00
Temperature (grad C) 0.000							



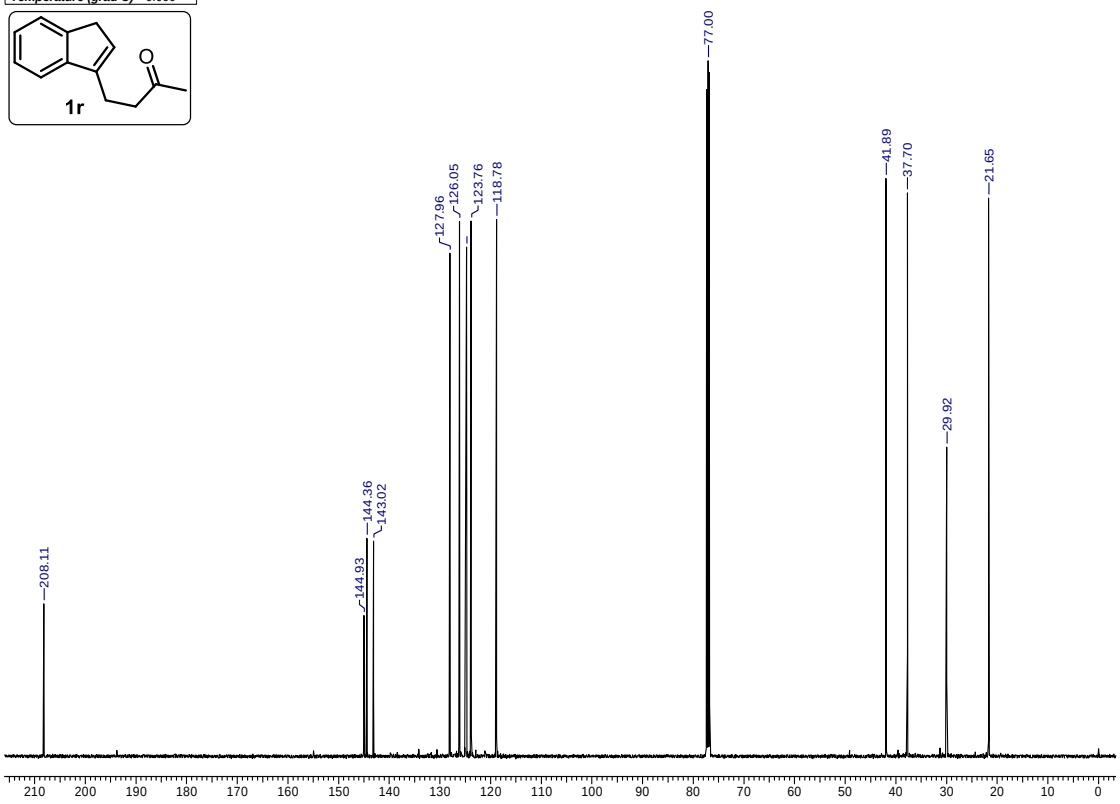
Acquisition Time (sec) 1.0486	***Date***	21/04/2013 16:15:08		***Frequency (MHz)***	125.76	***Nucleus***	13C
Original Points Count 32768	***Points Count***	32768	***Sweep Width (Hz)*** 31250.00			***Temperature (grad C)*** 0.000	



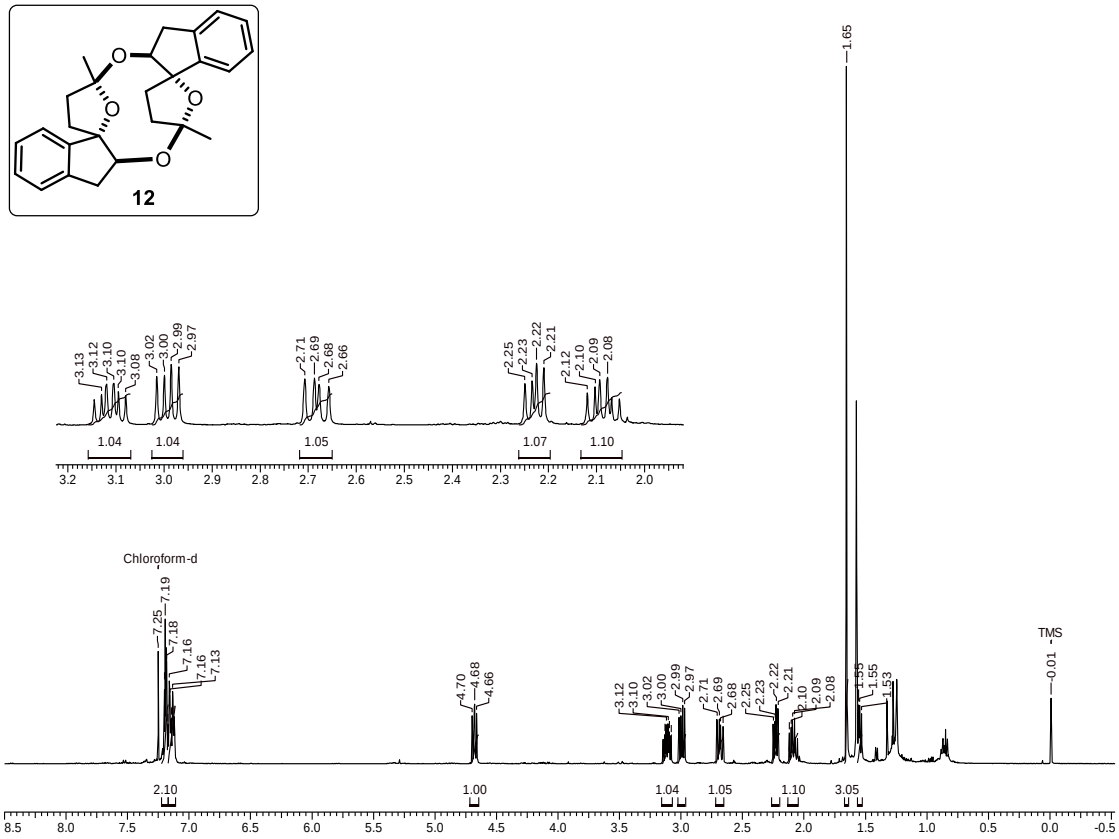
Acquisition Time (sec)	1.6384	**Comment**	RAVINDRA 1H		**Date**	10 May 2014 15:39:12	
Frequency (MHz)	500.13	**Nucleus**	1H	**Number of Transients** 64	**Original Points Count**	16384	**Points Count** 32768
Solvent	CHLOROFORM-d			**Sweep Width (Hz)** 9999.70	**Temperature (grad C)**	26.400	



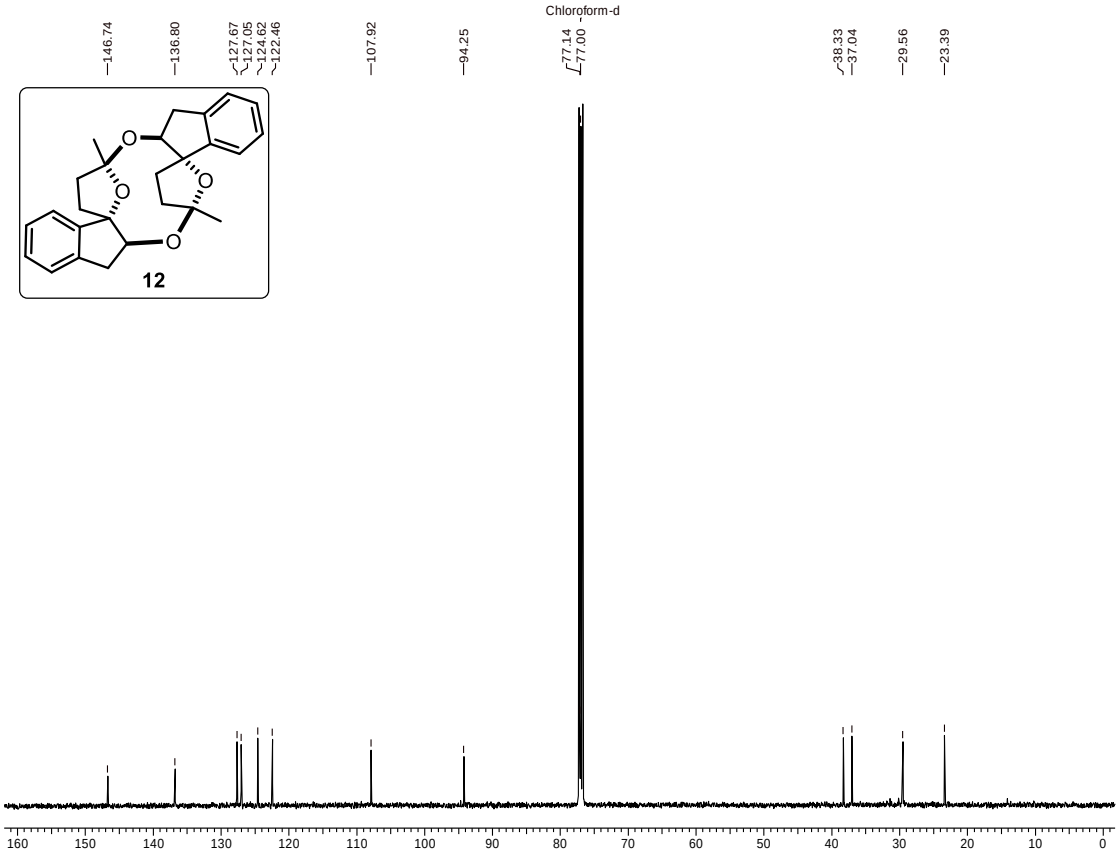
Acquisition Time (sec)	1.1010	**Comment**	13C	**Date**	11/05/2014 00:12:48		**Frequency (MHz)** 125.76
Nucleus	13C	**Original Points Count**	32768	**Points Count**	32768	**Sweep Width (Hz)**	29761.90
Temperature (grad C)	0.000						



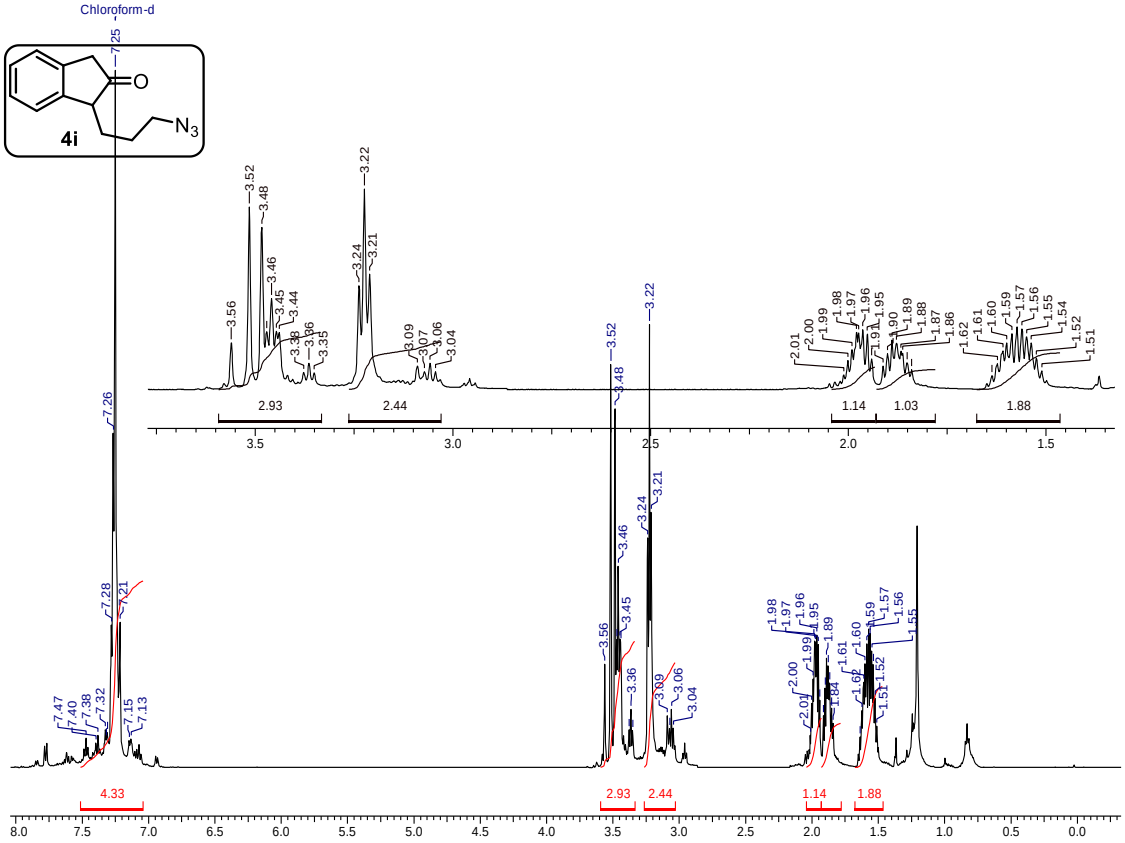
Acquisition Time (sec) 3.2768	***Comment***	Ravindra		***Date***	04/10/2012 17:07:58		
Frequency (MHz) 500.13	***Nucleus***	1H	***Original Points Count*** 32768	***Points Count***	32768	***Sweep Width (Hz)***	10000.00
Temperature (grad C) 0.000							



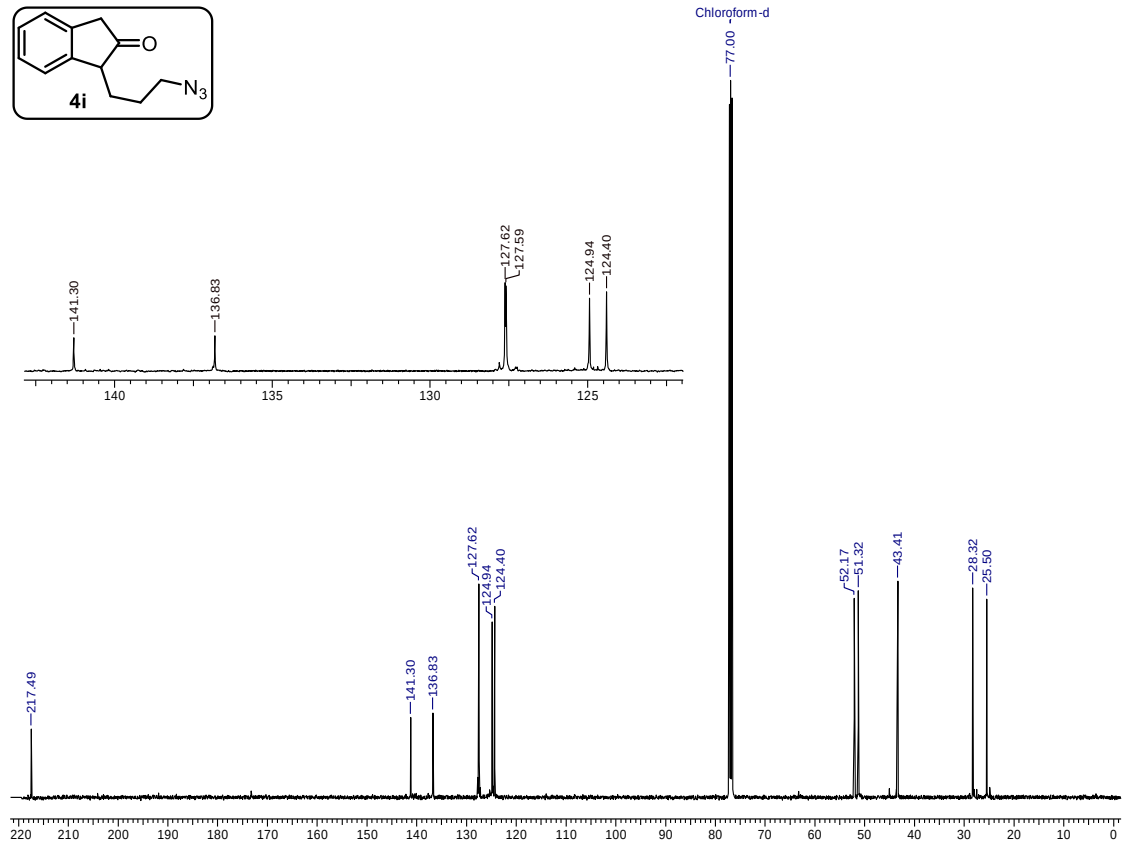
Acquisition Time (sec) 1.0486	***Date***	04/10/2012 18:16:36		***Frequency (MHz)***	125.76	***Nucleus***	13C
Original Points Count 32768	***Points Count***	32768	***Sweep Width (Hz)*** 31250.00			***Temperature (grad C)***	0.000



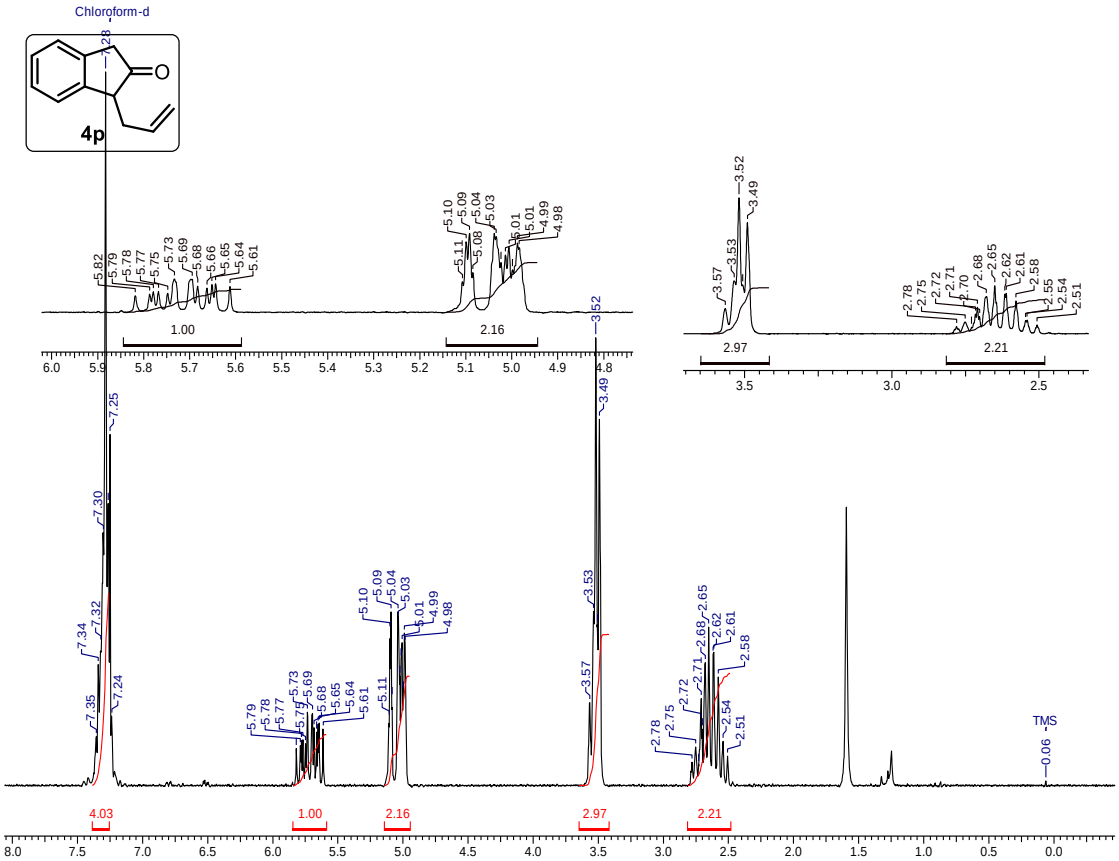
Acquisition Time (sec) 2.0031	***Comment*** Ravindra 1H			***Date*** 22 Aug 2013 15:43:28			
Frequency (MHz) 500.13	***Nucleus*** 1H	***Number of Transients*** 64		***Original Points Count*** 20031		***Points Count*** 32768	
Solvent CHLOROFORM-d		***Sweep Width (Hz)*** 9999.70		***Temperature (grad C)*** 22.000			



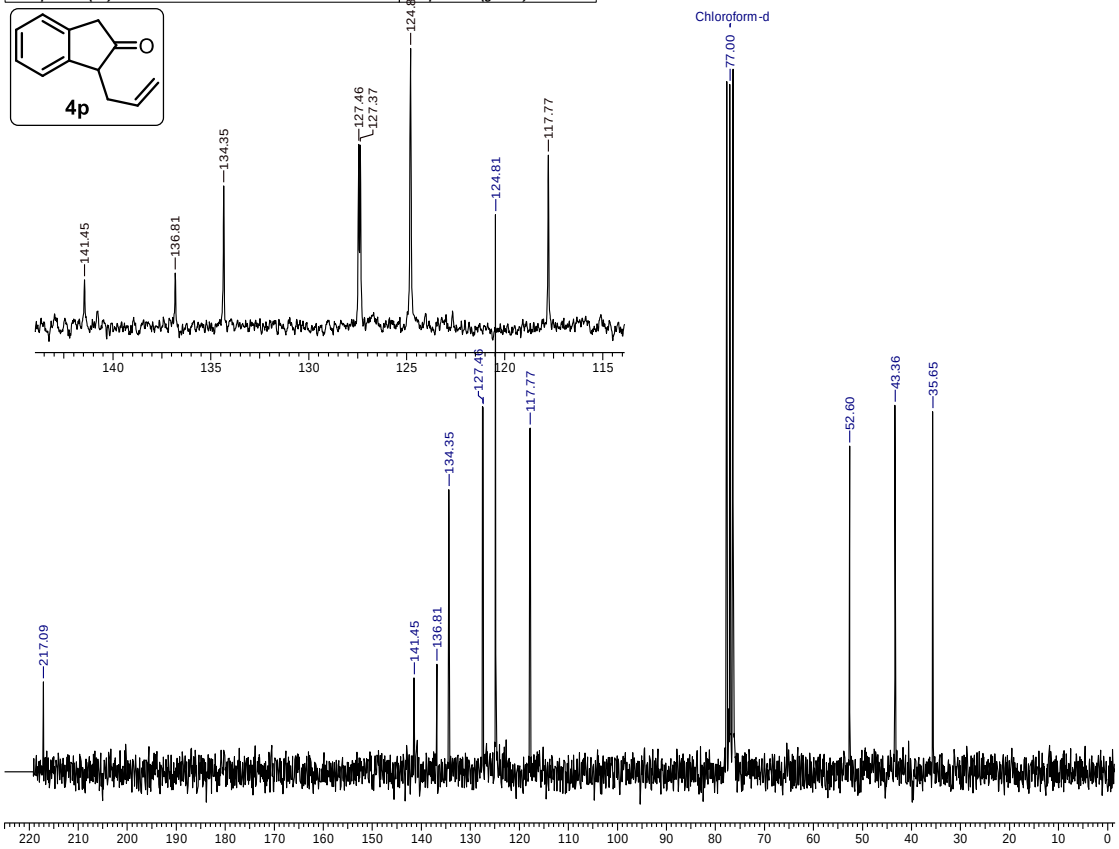
Acquisition Time (sec) 1.0486	***Comment*** 13C	***Date*** 22 Aug 2013 18:38:24				***Frequency (MHz)*** 125.76	
Nucleus 13C	***Number of Transients*** 2507	***Original Points Count*** 32768		***Points Count*** 32768		***Solvent*** CHLOROFORM-d	
Sweep Width (Hz) 31249.05	***Temperature (grad C)*** 22.800						



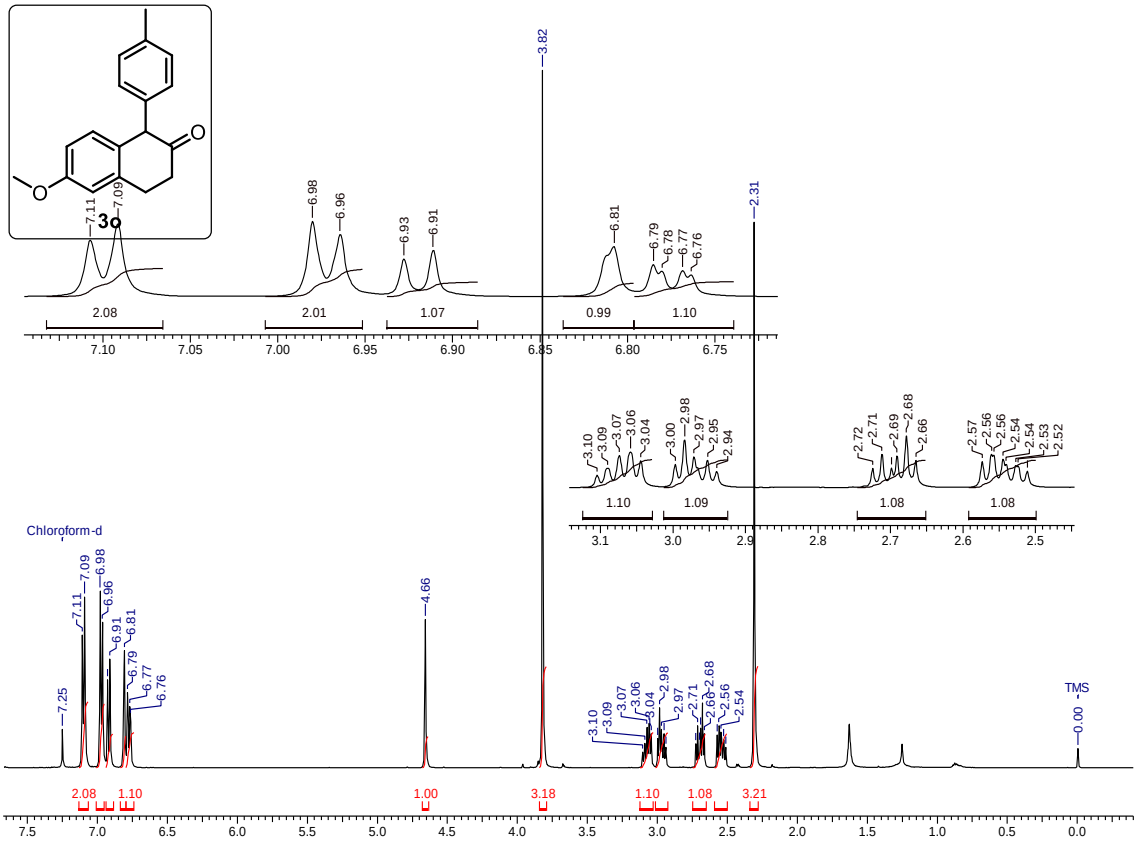
Acquisition Time (sec)	7.9167	**Comment**	ravindra	**Date**	02/07/2013 12:14:30	**Frequency (MHz)**	200.13
Nucleus	1H	**Original Points Count**	32768	**Points Count**	32768	**Sweep Width (Hz)**	4139.07	**Temperature (grad C)**	0.000



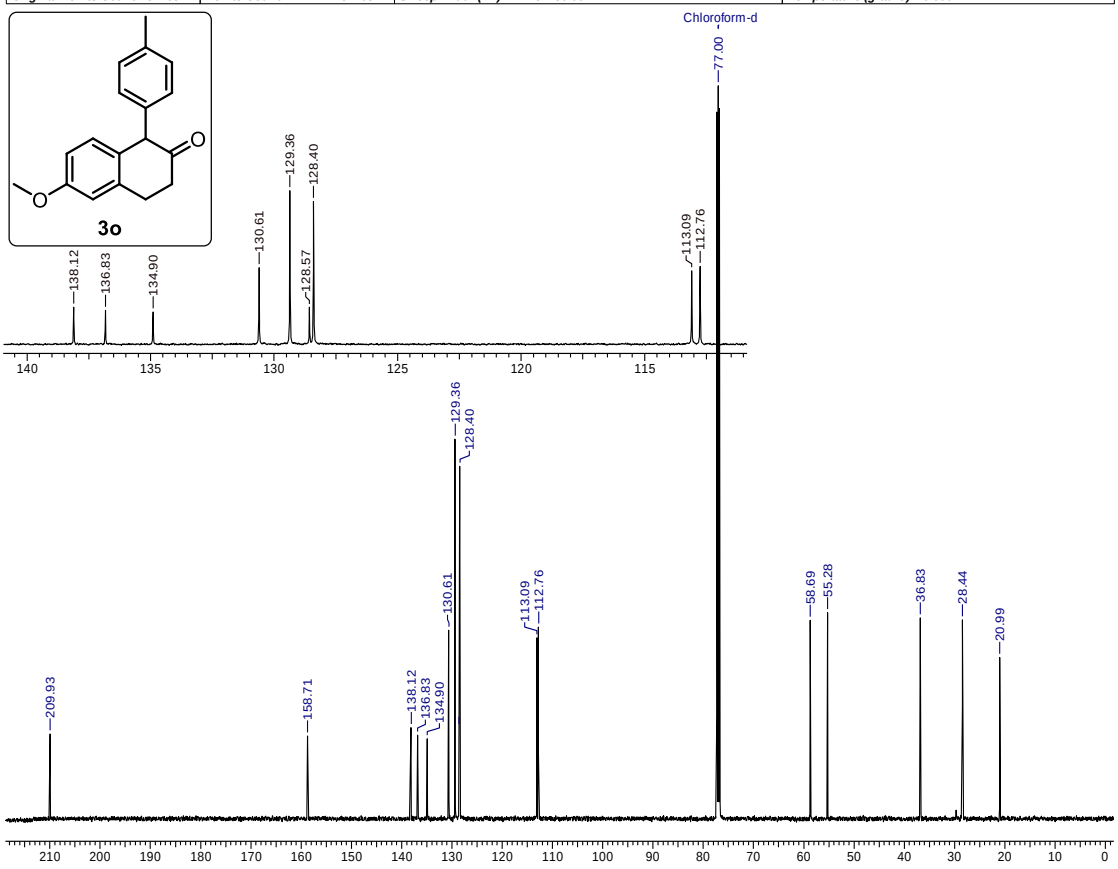
Acquisition Time (sec)	0.6832	**Comment**	ravindra	**Date**	08 Jul 2013 06:47:36	**Frequency (MHz)**	50.32
Nucleus	13C	**Number of Transients**	600	**Original Points Count**	8192	**Points Count**	32768	**Solvent**	CHLOROFORM-d
Sweep Width (Hz)	11990.04			**Temperature (grad C)**	27.000		



Acquisition Time (sec) 3.2768	**Comment**	Ravindra		**Date**	15/08/2013 15:54:48		
Frequency (MHz) 500.13	**Nucleus**	1H	**Original Points Count** 32768	**Points Count**	32768	**Sweep Width (Hz)**	10000.00
Temperature (grad C) 0.000							



Acquisition Time (sec) 1.0486	**Date**	15/08/2013 15:55:32		**Frequency (MHz)**	125.76	**Nucleus**	13C
Original Points Count 32768	**Points Count**	32768	**Sweep Width (Hz)**	31250.00		**Temperature (grad C)**	0.000



References

1. a) Masel, R. I. Chemical Kinetics and Catalysis; *Wiley-Interscience: New York*, **2001**. b) Behr, A. Organometallic Compounds and Homogeneous Catalysis: Ullmann's Encyclopedia of Industrial Chemistry; *Wiley-VCH: Weinheim*, **2002**. c) Elschenbroich, C. Organometallics; *Wiley-VCH: Weinheim*, **2006**.
2. a) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. Angew. Chem., Int. Ed. **2000**, *39*, 4414. b) Eisenstadt, A.; Ager, D. J. In Fine Chemicals through Heterogeneous Catalysis; Sheldon, R. A., van Bekkum, H., Eds.; Wiley-VCH: Weinheim, **2001**. c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Angew. Chem., Int. Ed. **2005**, *44*, 4442. d) Corbet, J.-P.; Mignani, G. *Chem.* Rev. **2006**, *106*, 2651. e) Magano, J.; Dunetz, J. R. Chem. Rev. **2011**, *111*, 2177. f) Crawley, M. L.; Trost, B. M.; Shen, H. C. Selected Applications of Transition Metal-Catalyzed Carbon−Carbon Cross-Coupling Reactions in the Pharmaceutical Industry; Wiley-VCH: Weinheim, **2012**.
3. a) Pal, S.; Khan, M. A.; Bindu, P.; Dubey, P. K. *Beilstein J. Org. Chem.* **2007**, *3*. b) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960. c) Xie, J.; Jiang, H. L.; Cheng, Y. X.; Zhu, C. J. *Chem. Comm.* **2012**, *48*, 979. d) Song, G. Y.; Wang, F.; Li, X. W. *Chem. Soc. Rev.* **2012**, *41*, 3651. e) Sun, C. L.; Shi, Z. J. *Chem. Rev.* **2014**, *114*, 9219. f) Roscales, S.; Csaky, A. G. *Chem. Soc. Rev.* **2014**, *43*, 8215-8225.
4. a) Carey, F. A.; Sundberg, R. J. Advanced Organic Chemistry; 3rd ed.; *Plenum: New York,* **1990** pp 624. b) March, J. Advanced Organic Chemistry; 4th ed.; *Wiley: New York,* **1992** pp 734. c) Backvall, J.-E., Ed. Modern Oxidation Methods; *Wiley-VHC*: *Weinheim, Germany*, **2004**; d) March, J. Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (3rd ed.), *Wiley: New York*, ISBN: 0-471-85472-7, **1985**. (b) Gabriel, T.; Marcos, F. Oxidation of Alcohols to Aldehydes and Ketones, *Springer*, *New York,* ISBN: 0-387-23607-4, **2006**.
5. a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.*, **1973**, 95 (18). b) Florent, J.-C.; Monneret, C. Glycoscience: Chemistry and Chemical Biology I–III (Deoxygenation, Chapter 2), *Springer*, pp 231-251, **2001**. c) Yudin A. K. Aziridines and Epoxides in Organic Synthesis, *Wiley:* ISBN: 978-3-527-

31213-9, **2006**. d) Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990.

6. Bloch, D., R. Organic Chemistry Demystified (2 ed.), *McGraw-Hill*, p. 57. ISBN 978-0-07-176797-2, **2012**.
7. a) Elschenbroich, C. ‘‘Organometallics”, *Wiley-VCH: Weinheim*. ISBN 978-3-527-29390-2, **2006**. b) Takacs, J. M.; Jiang, X. T. *Curr. Org. Chem.* **2003**, *7*, 369-396.
8. a) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976,** *17*, 1973. b) Schroder, M. *Chem. Rev.* **1980**, *80*, 187. c) Comprehensive Organic Synthesis; Trost, B. M. Ed.; Pergamon: Oxford, UK, **1991**; Vol. 7, pp 437. d) Lohray, B. B. *Tetrahedron Asymm.* **1992,** *3*, 1317. e) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994,** *94*, 2483.
9. a) Begley, J.; Mohamed, S. E.; Whiting, D. A.; Dsouza, F.; Hatam, N. A. R. *J. Chem. Soc. Perkin Trans. 1* **1983**, 883. b) Wang, Y. P.; Xing, Y. L.; Zhang, Q.; O'Doherty, G. A. *Chem. Commun.* **2011**, *47*, 8493. c) Georges, Y.; Allenbach, Y.; Ariza, X.; Campagne, J. M.; Garcia, J. *J. Org. Chem.* **2004**, *69*, 7387. d) Sergeeva, E. V.; Rozenberg, V. I.; Antonov, D. Y.; Vorontsov, E. V.; Starikova, Z. A.; Fedyanin, I. V.; Hopf, H. *Chem. Eur. J.* **2005,** *11*, 6944.
10. a) Naota, T.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599. b) Plietker, B. *Synthesis* **2005**, 2453. c) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, 1725. d) Christie, S. D. R.; Warrington, A. D. *Synthesis* **2008**, 1325. e) Bataille, C. J. R.; Donohoe, T. J. *Chem. Soc. Rev.* **2011**, *40*, 114. f) Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, *40*, 4912. g) Talsi, E. P.; Bryliakov, K. P. *Coord. Chem. Rev.* **2012**, *256*, 1418. h) Saisaha, P.; de Boer, J. W.; Browne, W. R. *Chem. Soc. Rev.* **2013**, *42*, 2059. i) Wu, W. Q.; Jiang, H. F. *Acc. Chem. Res.* **2012**, *45*, 1736.
11. a) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. b) Vedrenne, E.; Wallner, O. A.; Vitale, M.; Schmidt, F.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 165. b) Hudlicky, T.; Reed, J. W. *Synlett* **2009**, 685. c) Kang, Y. B.; Gade, L. H. *J. Am. Chem. Soc.* **2011**, *133*, 3658. d) Rawling, M. J.; Tomkinson, N. C. O. *Org. Biomol. Chem.* **2013**, *11*, 1434-1440.
12. a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. b) Hussain, H.; Green, I. R.; Ahmed, I. *Chem. Rev.* **2013**, *113*, 3329.

13. Edwards, J. O.; Pater, R. H.; Curci, R.; DiFuria, F. Photochem. Photobiol. **1979**, 30, 63.
14. a) Baeyer, A. V.; Villiger, V. *Ber*. **1899**, *32*, 3625. b) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811-22. c) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847-59. d) Travis, B. R.; Ciaramitaro, B. P.; Borhan, B. *Eur. J. Org. Chem*. **2002**, 3429.
15. a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. b) Adam, W.; Hadjiarapoglou, L. *Top. Curr. Chem*. **1993**, *164*, 45.
16. Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1-9.
17. a) Griffith, J. C.; Jones, K. M.; Picon, S.; Rawling, M. J.; Kariuki, B. M.; Campbell, M.; Tomkinson, N. C. O. *J. Am. Chem. Soc.* **2010**, *132*, 14409. b) Jones, K. M.; Tomkinson, N. C. O. *J. Org. Chem.* **2012**, *77*, 921. c) Picon, S.; Rawling, M.; Campbell, M.; Tomkinson, N. C. O. *Org. Lett.* **2012**, *14*, 6250.
18. a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem*. **1985**, *50*, 2847-2853. b) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem*. **1987**, *52*, 699. c) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem*. **1988**, *53*, 3890-3891.
19. a) Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677. b) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. H. J. *Chem. Rev.* **2006**, *106*, 2734. c) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Ripin, D. H. B. *Chem. Rev.* **2006**, *106*, 2943. d) de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575. e) Wang, Y. P.; Xing, Y. L.; Zhang, Q.; O'Doherty, G. A. *Chem. Commun.* **2011**, *47*, 8493.
20. Adam, W.; Saha-Möller, C. R.; Zhao, C.-G., Dioxirane Epoxidation of Alkenes, In *Organic Reactions*; John Wiley & Sons, Inc.: **2004**.
21. a) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem*. **1980**, *45*, 4758. b) Jeyaraman, R.; Murray, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 2462. c) Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber*. **1991**, *124*, 227.
22. Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem*. **1995**, *67*, 811.
23. a) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett*. **1987**, *28*, 3311. b) Hofland, A.; Stcinberg, H.; de Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 350. c) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc*. **1973**, *95,* 5321.

24. Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc*. **2000**, *122,* 4831.
25. McDonald, R. N.; Steppel, R. N.; Dorsey, J. E. *Org. Synth.*, **1988**, *6*, 276.
26. Weitz, E.; Scheffer, A. *Chem. Ber.* **1921**, *54*, 2327.
27. a) Adam, W.; Hadjiarapoglou, L. *Top. Chem. Chem*. **1993**, *164*, 45. b) Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem*. **1988**, *53*, 3437. c) Adam, W.; Curci, R.; D'Accolti, L.; Dinoi, A,; Fusco, C.; Gasparrini, F.; Kluge, R.; Schulz, M.; Smerz, A. K.; Veloza, L. A.; Weinkotz, S.; Winde, R. *Chem. Eur. J.* **1997**, *3*, 105. d) Adam, W.; Frohling, B.; Peters, K.; Weinkotz, S. *J. Am. Chem. Soc*. **1998**, *120,* 8941.
28. a) Adam, W.; Hadjiarapoglou, L.; Jager, V.; Klicic, J.; Seidel, B.; Wang, X. *Chem, Ber*. **1991**, *124*, 2361. b) Adam, W.; Hadjiarapoglou, L.; Wang, X. *Tetrahedron Lett*. **1989**, *30*, 6497. c) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett*. **1974**, *15*, 4317. d) Adam, W.; Hadjiarapoglou, L.; Mosandl, T.; Saha-Moller, C. R.; Wild, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 200. e) Adam, W.; Bialas, J.; Hadjiarapoglou, L.; Sauter, M. Chem. Ber. 1992, 125, 231. f) Sauter, M.; Adam, W. *Acc. Chem. Res.* **1995**, *28*, 289.
29. a) Patai, S.; Rappoport, Z. In The Chemistry of Alkenes; Ed.; *Wiley: New York*, **1964**, Vol. 1, pp. 512-517. b) Adam, W.; Hadjiarapoglou, L.; Nestler, B. *Tetrahedron Lett*. **1990**, *31*, 331. c) Piers, E.; Boulet, S. L. *Tetrahedron Lett*. **1997**, *38*, 8815. d) Porter, M. J.; Skidmore, J. *J. Chem. Soc., Chem. Commun*. **2000**, 1215.
30. a) Adam, W.; Hadjiarapoglou, L.; Levai, A. *Synthesis* **1992**, 436. b) Adam, W.; Glosch, D.; Hadjiarapoglou, L.; Patonay, T. *Tetrahedron Lett*. **1991**, *32*, 1041. c) Adam, W.; Glosch, D.; Hadjiarapoglou, L.; Patonay, T. *J. Org. Chem*. **1991**, *56*, 7292.
31. Yang, D.; Wong, M. K.; Wang, X. C.; Tang, Y. C *J. Am. Chem. Soc*. **1998**, *120*, 6611.
32. Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett*. **2006**, *8*, 1141.
33. a) Hull, L. A.; Budhai, L. *Tetrahedron Lett*. **1993**, *34*, 5039. b) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc*. **1989**, *111*, 6749. c) Dinoi, A.; Curci, R.; Carloni, P.; Damiani, E.; Stipa, P.; Greci, L. *Eur. J. Org. Chem.* **1998**, *1*, 871.
34. Rani, S.; Vankar, Y. D. *Tetrahedron Lett*. **2003**, *44*, 907.

35. a) Travis, B. R.; Narayan, R. S.; Borhan, B. *J. Am. Chem. Soc*. **2002**, *124*, 3824. b) Lee, K.; Kim, Y. H.; Han, S. B.; Kang, H.; Park, S.; Seo, W. S.; Park, J. T.; Kim, B.; Chang, S. *J. Am. Chem. Soc.* **2003**, *125*, 6844.
36. a) Yan, J.; Travis, B. R.; Borhan, B. *J. Org. Chem*. **2004**, *69*, 9299. b) Crispin, D. J.; Vanstone, A. E.; Whitehurst, J. S. *J. Chem. Soc.* **1970**, 10. c) Tamura, Y.; Annoura, H.; Kondo, H.; Fuji, M.; Yoshida, T.; Fujioka, H. *Chem. Pharm. Bull*. **1987**, *35*, 2305.
37. Ashfor Miller, d, S. W.; Grega, K. C. *J. Org. Chem.* **2001**, *66*, 1523.
38. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
39. Plietker, B. *Org. Lett*. **2004**, *6*, 289.
40. Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251.
41. Murray, R. W.; Jeyaraman, R.; Pillay, M. K. *J. Org. Chem.* **1987**, *52*, 746.
42. Messeguer, A.; Fusco, C.; Curci, R. *Tetrahedron* **1993**, *49*, 6299.
43. Bovicell, P.; Lupattelli, P.; Mincione, E. *J. Org. Chem.* **1994**, *59*, 4304.
44. Adam, W.; Smerz, A. K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581.
45. Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703.
46. Ferrer, M.; Sanchezbaeza, F.; Messeguer, A.; Diez, A.; Rubiralta, M. *J. Chem. Soc., Chem. Commun.* **1995**, 293.
47. Ashford, S. W.; Grega, K. C. *J. Org. Chem.* **2001**, *66*, 1523.
48. Stergiou, A.; Bariotaki, A.; Kalaitzakis, D.; Smonou, I. *J. Org. Chem.* **2013**, *78*, 7268.
49. Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5*, 1031.
50. Parida, K. N.; Jhulki, S.; Mandal, S.; Moorthy, J. N. *Tetrahedron* **2012**, *68*, 9763.
51. Schmidt, R.; Stolle, A.; Ondruschka, B. *Green Chem.* **2012**, *14*, 1673.
52. Yu, B.; Liu, A. H.; He, L. N.; Li, B.; Diao, Z. F.; Li, Y. N. *Green Chem.* **2012**, *14*, 957.
53. Lian, X. L.; Lei, H.; Quan, X. J.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. *Chem. Commun.* **2013**, *49*, 8196.
54. Nelson, A. C.; Kalinowski, E. S.; Czerniecki, N. J.; Jacobson, T. L.; Grundt, P. *Org. Biomol. Chem.* **2013**, *11*, 7455.
55. a) Singh H. S. in Organic Synthesis by Oxidation with Metal Compounds; Mijs, W. J., De Jonge, C. R. H. I., Eds.; Plenum: New York, **1986**. b)

Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677. c) Fu, G. C.; in Modern Carbonyl Chemistry (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, pp. 69-91. d) Katsuki, T. Asymmetric Oxidation Reactions: A Practical Approach in Chemistry; Oxford University Press: Oxford, **2001**. e) Weissermel, K.; Arpe H.-J. Industrial Organic Chemistry, 4th ed.; Wiley-VCH: Federal Republic of Germany, **2003**. pp 152-153 and pp 277-278.

56. a) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976,** *17*, 1973. b) Schroder, M. *Chem. Rev.* **1980**, *80*, 187. c) Comprehensive Organic Synthesis; Trost, B. M. Ed.; Pergamon: Oxford, UK, **1991**; Vol. 7, pp 437–448. d) Lohray, B. B. *Tetrahedron Asymm.* **1992,** *3*, 1317. e) Kolb, H. C.; Vannieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994,** *94*, 2483.
57. a) Rosatella, A. A.; Afonso, C. A. M. *Adv. Synth. Catal.* **2011**, *353*, 2920. b) Schwarz, M.; Reiser, O. *Angew. Chem. Int. Ed.* **2011**, *50*, 10495. c) Yuan, C. X.; Axelrod, A.; Varela, M.; Danysh, L.; Siegel, D. *Tetrahedron Lett.* **2011**, *52*, 2540.
58. a) Greene, F. D. *J. Am. Chem. Soc.* **1956,** *78*, 2246. b) Greene, F. D. *J. Am. Chem. Soc.* **1956,** *78*, 2250. c) Greene, F. D.; Rees, W. W. *J. Am. Chem. Soc.* **1958,** *80*, 3432. d) Greene, F. D. *J. Am. Chem. Soc.* **1959,** *81*, 1503. e) Greene, F. D.; Rees, W. W. *J. Am. Chem. Soc.* **1960,** *82*, 890.
59. Hashimoto, N.; Kanda, A. *Org. Proc. Res. Dev.* **2002**, *6*, 405.
60. Kotsuki, H.; Kataoka, M.; Nishizawa, H. *Tetrahedron Lett.* **1993,** *34*, 4031.
61. Nakatani, K. *Tetrahedron Lett.* **1987**, *28*, 165.
62. Ghisalberti, E. L.; Hargreaves, J. R.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **2000**, *53*, 995.
63. Mudiganti, N. V. S.; Claessens, S.; Habonimana, P.; De Kimpe, N. *J. Org. Chem.* **2008**, *73*, 3867.
64. Hinchcliffe, A.; Hughes, C.; Pears, D. A.; Pitts, M. R. *Org. Proc. Res. Dev.* **2007**, *11*, 477.
65. Solladie-Cavallo, A.; Choucair, E.; Balaz, M.; Lupattelli, P.; Bonini, C.; Di Blasio, N. *Eur. J. Org. Chem.***2006**, 3007.
66. Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* 2006, *39*, 1.
67. (a) Annese, C.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gandolfi, R.; Curci, R. *J. Am. Chem. Soc.***2008**, *130*, 1197. (b) Angelis, Y.; Zhang, X. J.; Orfanopoulos,

M. *Tetrahedron Lett.***1996**, *37*, 5991. (c) Adam, W.; Curci, R.; Daccolti, L.; Dinoi, A.; Fusco, C.; Gasparrini, F.; Kluge, R.; Paredes, R.; Schulz, M.; Smerz, A. K.; Veloza, L. A.; Weinkotz, S.; Winde, R. *Chem. Eur. J.***1997**, *3*, 105. (d) Bach, R. D.; Glukhovtsev, M. N.; Gonzalez, C.; Marquez, M.; Estevez, C. M.; Baboul, A. G.; Schlegel, H. B. *J. Phys. Chem. A***1997**, *101*, 6092.

68. (a) Liu, J.; Houk, K. N.; Dinoi, A.; Fusco, C.; Curci, R. *J. Org. Chem.***1998**, *63*, 8565. (b) Bravo, A.; Fontana, F.; Fronza, G.; Minisci, F.; Zhao, L. H. *J. Org. Chem.***1998**, *63*, 254. (c) Bravo, A.; Fontana, F.; Fronza, G.; Minisci, F.; Serri, A. *Tetrahedron Lett.***1995**, *36*, 6945. (d) Curci, R.; Dinoi, A.; Fusco, C.; Lillo, M. A. *Tetrahedron Lett.***1996**, *37*, 249.

69. a) Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron* **1982**, *38*, 2403. b) Adamczyk, M.; Watt, D. S.; Netzel, D. A. *J. Org. Chem.* **1984**, *49*, 4226. c) Dehmlow, E. V.; Bollmann, C. *Tetrahedron Lett.* **1991**, *32*, 5773. d) Wu, X.; Chen, J.; Ji, M.; Varady, J.; Levant, B.; Wang, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5813.

CHAPTER II:

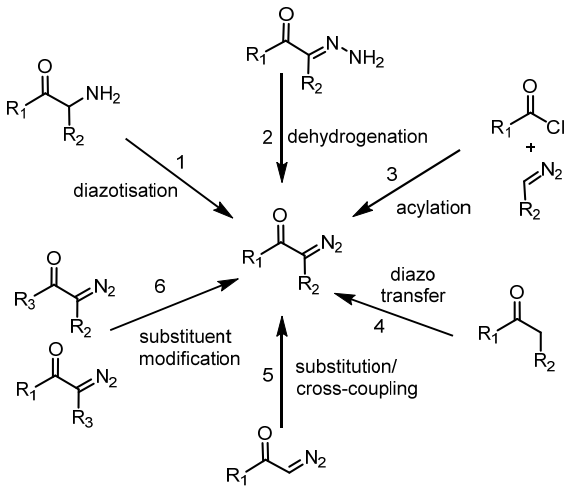
Application of *α*-Diazocarbonyl Compounds in the Synthesis of *N*-Heterocycles

Introduction

This part of our work is centered on the synthesis of *N*-heterocycles by using *α*-diazocarbonyl compounds. In this context, we wish to provide a brief overview on the synthesis and utility of *α*-diazocarbonyl compounds pertaining to the advances that have been documented mainly during the last two-decades.

α-Diazocarbonyl Compounds

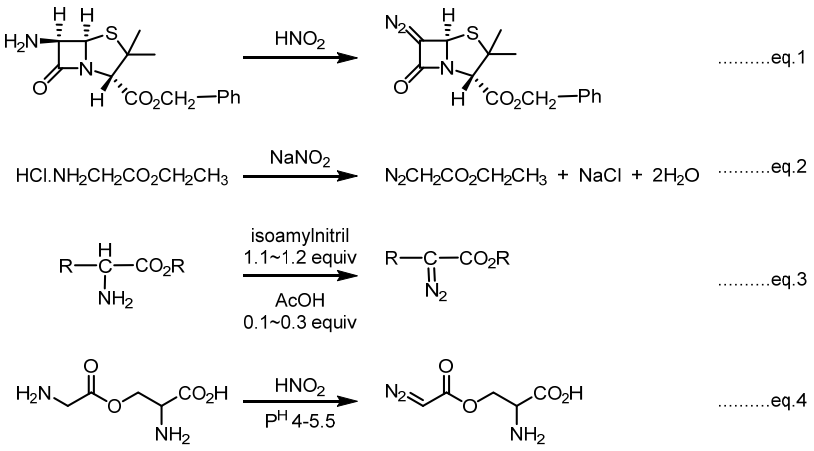
The *α*-Diazocarbonyl compounds have a long history in organic chemistry. In 1883, the work of Curtius on diazotization of natural *α*-amino acids was the first recorded synthesis of a *α*-diazocarbonyl compound (ethyl diazoacetate was first synthesized from glycine).[1] After that, in 1912, Wolf discovered the rearrangement of diazocarbonyl compounds, which now bears his name.[2] Simple diazocarbonyl compounds became readily accessible only in the late 1920s, through the breakthrough work done by Arndt and Eistert and by Bradley and Robinson.[3] The acylation of diazomethane with an acid chloride to prepare *α*-diazo ketones reported by these groups led to a rapid expansion of this area and this method remains the single most significant route to acyclic terminal *α*-diazo ketones. The transfer of diazo group to active methylene compounds is another important method that allows the synthesis of both terminal and internal diazocarbonyl compounds.[4] Even several well-documented methods already exist; diazocarbonyl synthesis leftovers an active research area. This is mainly driven by the need to improve safety by minimizing risks in handling reagents while extending the ability to access new molecules through chemoselective synthesis. The established routes to diazocarbonyl compounds (Scheme 1)[5] are (1) amine diazotization, (2) modification of oximes, hydrazones, and tosyl hydrazones, (3) acylation of diazoalkanes, and (4) diazo transfer to an acid derivative or a ketone. The first two are still well-practised. However, there have been no noteworthy recent innovations in these methods. Coming to the routes 3 and 4 that comprise of diazoalkane acylation and diazo transfer, there is a need to advance with new reagents and procedures. To this list we can now add approaches whereby a diazocarbonyl compound is transformed into another one withholding the diazo function. These include (5) substitution and cross-coupling at the diazo carbon and (6) substituent modification at the relevant branch of the diazocarbonyl group. Selecting the most suitable synthetic approach usually depends on the nature of the substituents attached to the diazocarbonyl group.



***Scheme 1**. Synthesis of α-Diazocarbonyl Compounds*

Diazotization of *α*-Amino Acids

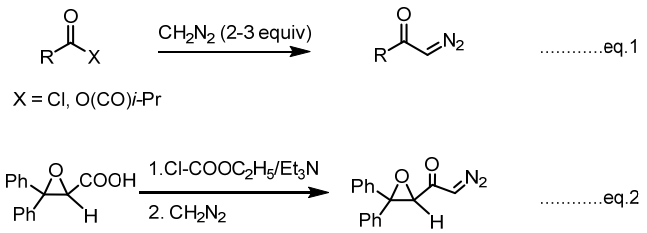
Despite several recent advances that will be described below, still diazotization is the choice of method for production of the synthetically versatile 6-diazopenicillanates (Scheme 2, eq. 1)[6a-b] and of ethyl diazoacetate (Scheme 2, eq. 2)[6c] from 6-aminopenicillanic acid esters and glycine ethyl ester respectively**.** A further opportunity of the diazotization progress to simpler and more convenient synthesis of the higher amino acids such as alanine, phenylalanine, isoleucine, and methionine is also possible (Scheme 2, eq. 3)[6d] Isoamyl nitrite is the preferred diazotization agent. The antibiotic azaserine, active against certain tumors, could be prepared by diazotizing the corresponding *O*-glycylserine (Scheme 2, eq. 4).[6e]



***Scheme 2**. Additional Room of the Diazotization*

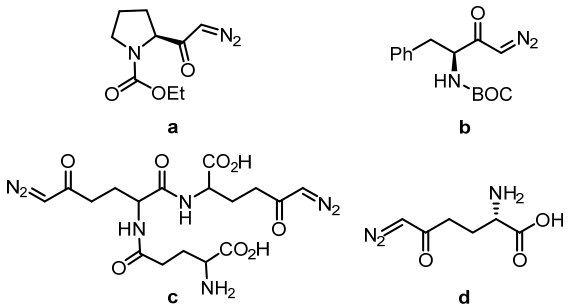
Acylation of Diazoalkanes

Acylation of diazomethane is the most generally used route to acyclic terminal diazoketones. The process is frequently referred to as the Arndt−Eistert reaction, which involves addition of an acyl chloride to ethereal diazomethane (at least 1-2 equiv excess) at or below 0 ^{o}C; extensive purification of the product is generally avoidable (Scheme 3, eq. 1).[3,4]



***Scheme** 3. Acylation of Diazoalkanes*

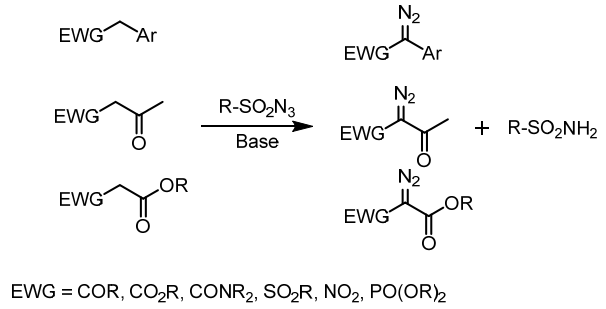
Anhydrides are also suitable acylating agents for diazomethane. An appropriate procedure involves the treatment of a carboxylic acid with dicyclohexyl carbodiimide to form the anhydride which is then allowed to react with ethereal diazomethane. A convenient *in situ* procedure to form mixed anhydrides is also available involving anhydride formation between the carboxylic acid and a chloroformate, followed by treatment with diazomethane. For example, 3-(diazoacetyl)-2,2-diphenyloxirane has been synthesized by this route (Scheme 3, eq. 2).[7] This route has also been applied for the production of homochiral α-diazo ketones from *N*-protected amino-acids, proline, and phenylalanine, furnishing diazo ketone **a** and **b**, respectively.[8] Acylation of higher diazoalkanes with acyl chlorides and anhydrides is also possible, although less efficiently than with diazomethane. Numerous synthetic intermediates containing the diazoethyl group have been obtained in this way.



Recently, Pettit and Nelson[9] designed a special apparatus for the synthesis of terminal diazocarbonyl compounds in dealing with the total synthesis of the azotomycin and 6-diazo-5-oxo-L-norleucine (**d**, commonly known as DON)–anticancer constituents isolated from the *Streptomyces ambofuciens*. This apparatus contains a separate compartment for the activation of carboxylic acid groups in ether by treating with oxalylchloride, triethylamine in the presence of a catalytic amount of dimethyl formamide and the resulting acyl chloride solution is then filtered into ethereal diazomethane at -78 ^{o}C.

Diazo-Transfer Reactions

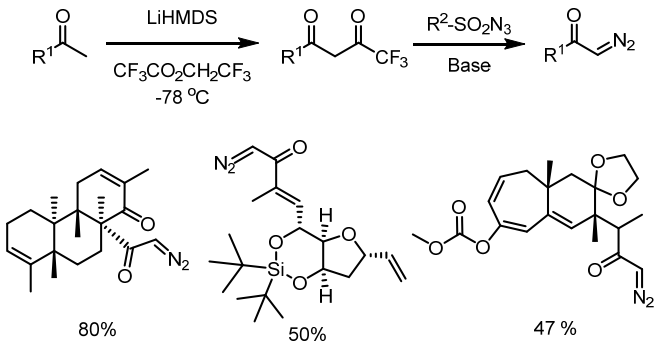
In 1967, Regitz and co-workers introduced a highly useful diazo transfer technique, which is the best amongst various available routes. This technique overcomes obvious limitations of diazoalkane acylation, which is not applicable to cyclic *α*-diazoketones. Diazo transfer is now the standard route for cyclic *α*-diazoketones as well as acyclic systems that are not accessible by acyl-transfer processes. In the broadest sense, diazo transfer refers to the transfer of a complete diazo group from a donor to an acceptor, which, for *α*-diazocarbonyl products must therefore be an acid or ketone derivative. Formation of diazocarbonyl compounds *via* diazo transfer is valid to a wide range of active methylene compounds, normally ketones and carboxylic acid derivatives. Diazo transfer is most regularly carried out with a sulfonyl azide in the presence of a base (Scheme 4).[10]



***Scheme 4**. Diazo Transfer–Preparation of Diazocarbonyl Compounds*

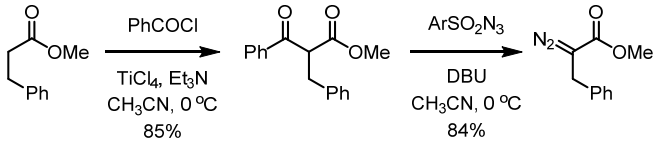
The standard Regitz procedure usually fails in cases where the methylene group is activated by a single carbonyl group. In 1990, Danheiser's group reported a two-step process for diazo-transfer to simple ketones that have no additional electron-withdrawing/aromatic groups at the *β*-position. This process involves a trifluoroacetyl

activation followed by a diazo transfer reaction (Scheme 4).[11] This methodology is particularly interesting for preparing α, β-unsaturated diazoketones that are difficult to prepare by regular methods such as direct acylation due to competing dipolar cycloaddition of the conjugated double bond.



Scheme 5. *Trifluoroacetylation/Detrifluoroacetylation Diazo Transfer*

Even though the scope of this protocol has been mainly restricted to simple α, β-unsaturated ketones in addition to aromatic methyl ketones, recent reports have demonstrated the utility of this transformation for more complex intermediates in natural product synthesis (Scheme 5). This Danheiser methodology is also useful for converting carboxylic esters to the corresponding diazocarbonyl compounds. More recently, Taber's group developed a new procedure that overcomes the issue of the required strongly basic and cryogenic conditions that may sometimes be problematic.[12] Activation of the ester by a titanium chloride-mediated benzoylation followed by diazo group transfer under mild conditions was proposed (Scheme 6).

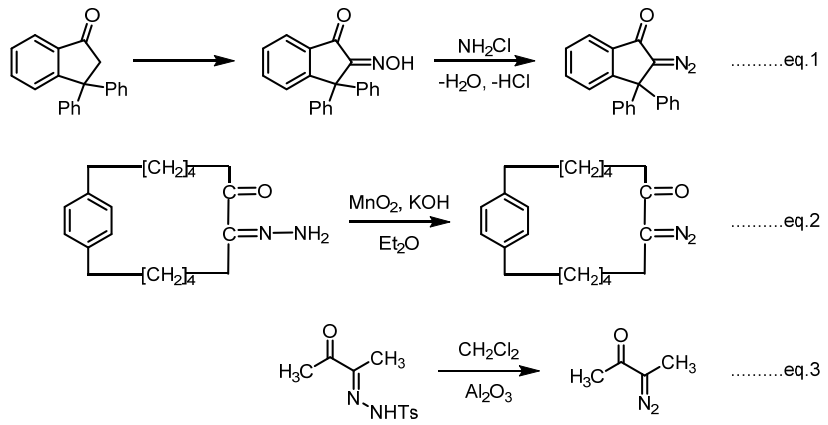


Scheme 6. *Benzoylation/Debenzoylation Diazo Transfer*

Other Routes to α-Diazocarbonyl Compounds

The Forster reaction, which involves oxime formation at the α-methylene position of a ketone followed by treatment with chloramine resulting in the desired diazocarbonyl compound (Scheme 7, eq. 1)[13a] is one of the earlier methods reported in this context. Similarly, the dehydrogenation of hydrazones by using MnO_2 and KOH

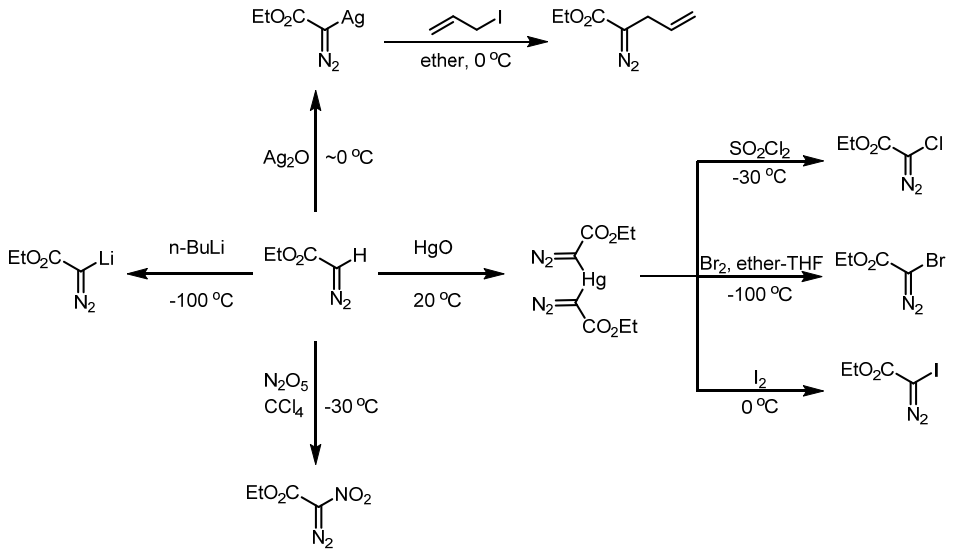
(Scheme 7, eq. 2) [13b] and the Bamford-Stevens tosyl hydrazone decomposition using aluminium oxide (Scheme 7, eq. 3) [13c] also fall under this category. These procedures are mainly used for preparing the cyclic diazoketones that have been subjected for the ring expansion and contraction studies.



***Scheme** 7. Other Routes to α-Diazocarbonyl Compounds*

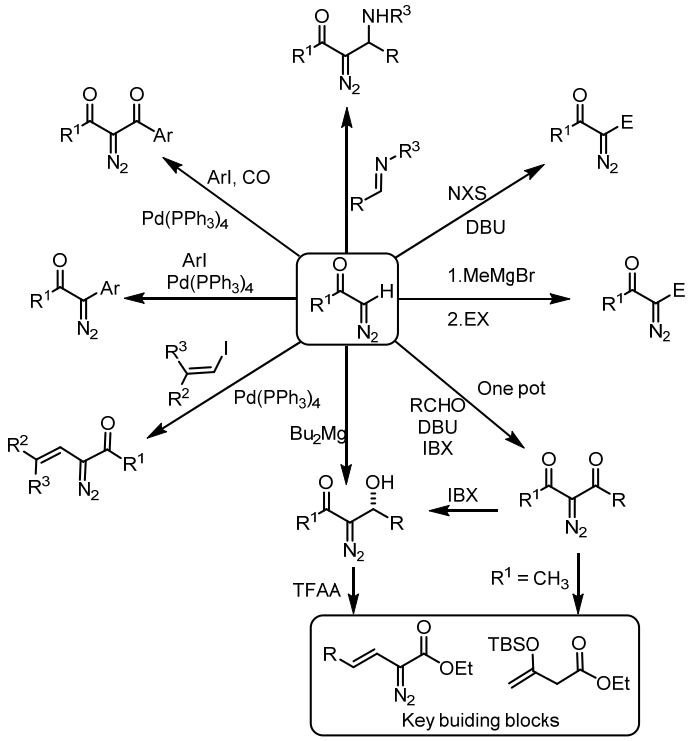
Chemical Modification of *α*-Diazocarbonyl Compounds

In general, electrophilic reagents substitute the hydrogen atom attached to the diazo carbon. In addition, the conversion of diazoalkanes into their metallated derivatives offers better reactivity as they readily undergo transmetallation and alkylation reactions. Halogenation can be carried out directly, as well as through mercury or silver derivatives. Nitration can be achieved directly at low temperature by treatment with dinitrogen pentoxide. These reactions make possible the introduction of carbon moieties, including some rather complicated groups and especially unsaturated groups into the existing diazocarbonyl compounds (Scheme 8).[14]



Scheme 8. *Substitution Reactions of α-Diazocarbonyl Compounds*

Transformation of one diazocarbonyl compound into another with retention of the diazo functionality has continued to be an active research area and has progressed significantly in recent years. These transformation methods showed potential in the C–C coupling of diazocarbonyls with aldehydes, imines, chloroformate, pyrocarbonates, and sulfonyl chlorides. Electrophilic halogenation, palladium catalyzed C–C couplings have been reported recently in large numbers (Scheme 9).[15]



***Scheme 9**. Scope of Functionalization of Diazocarbonyl Compounds*

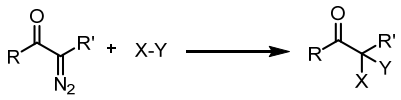
Development in this field has now reached a stage that justifies the statement that the diazoalkane substitution is one of the best approaches for the functionalized diazoalkanes synthesis. Synthetic applications of these reactions have been greatly extended in the chemistry of heterocycles, cyclobutadienes, oxepines, thepines or cyclooctatetraenes, which is indicative of a diverse secondary chemistry.

Diazocarbonyl Reactions in Synthesis

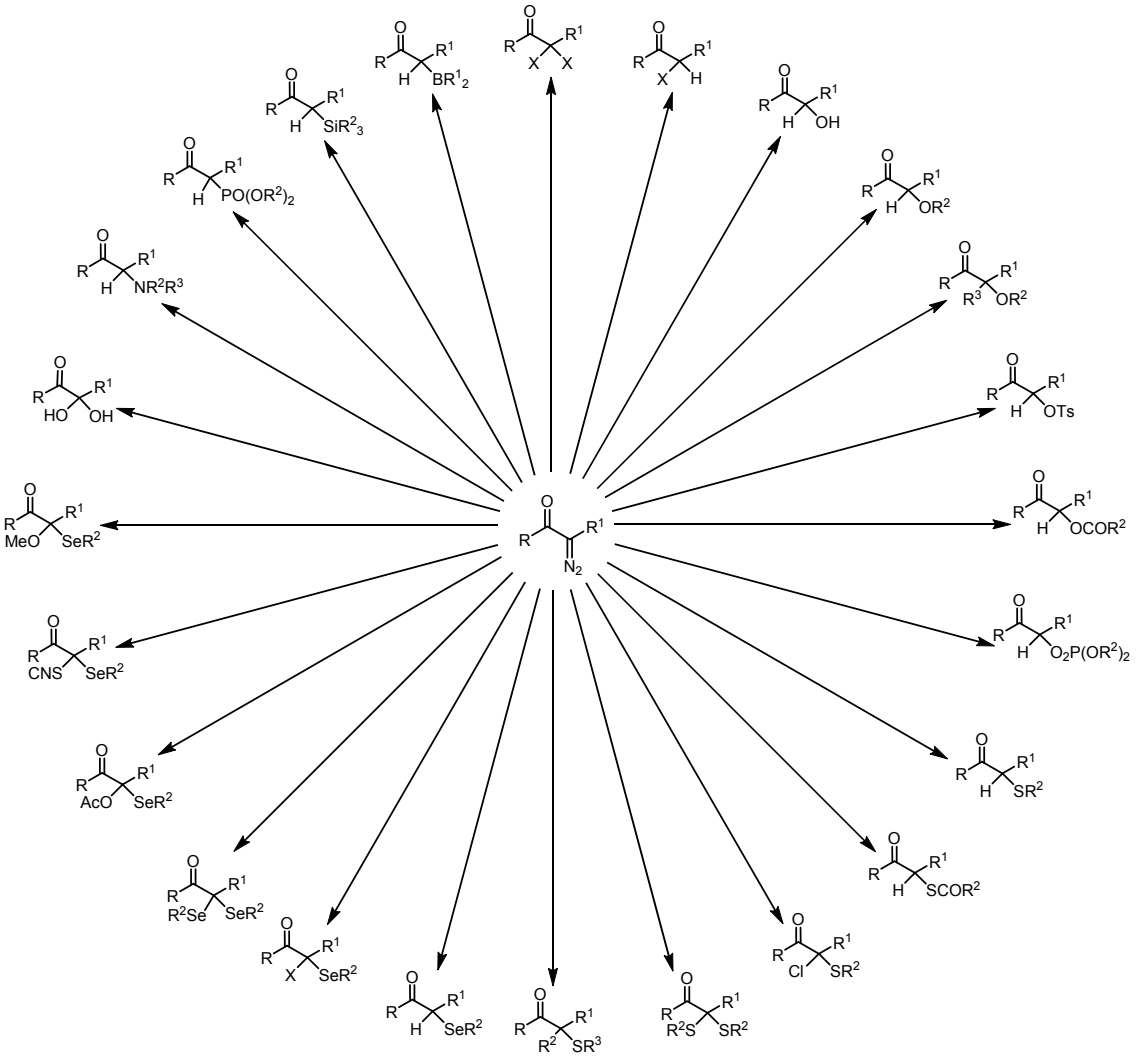
Diazocarbonyl compounds are quite famous for their exceptional flexibility and ambiphilic nature in organic synthesis. The loss of nitrogen, which can be brought about thermally, photochemically, or catalytically has a significant role in the reaction of diazocarbonyl. Reactive intermediates of diazocarbonyl consist of free carbenes, carbenoids (metal-bound carbenes), carbonyl ylides and diazonium cations, which are mainly formed by stoichiometric reactions with many Bronsted acids and electrophiles, and catalytically with numerous transition metals and their salts. It is seen that each intermolecular process complements its intramolecular counterpart. The success of intramolecular processes has maintained the high level of interest in diazocarbonyl compounds. The most operational reactions of diazocarbonyls are cyclopropanation, Wolf rearrangement, insertion into unactivated C–H bonds, aromatic cycloaddition, *α,α*-substitution, dipolar addition, acid-catalyzed cyclization of unsaturated substrates, dimerization, electrophilic aromatic substitution, oxidation and ylide formation followed by sigmatropic rearrangement. Another most extensively studied and most important application of *α*-diazocarbonyl compound is for the generation of metal carbene species. Here, the diazocompounds reacts with a transition metal catalyst, followed by dinitrogen discharge. These metal carbenes have a broad spectrum of reactivity, and can typically undergo cyclopropanation C–H, O–H, S–H and N-H bond insertion, 1,2-shift, ylide formation and aromatic cycloadditions.

***α,α*-Substitution Reactions**

α,α-substitution reactions of the *α*-diazocarbonyls entail the diazo group being replaced by two new substituents. In these substitution reactions, mechanistically there exists a broad spectrum of processes ranging from uncatalyzed electrophilic attack on the diazocarbonyl group to carbene, carbenoid, or ylide formation in situations where thermolysis, photolysis, or metal ion catalysis is employed.

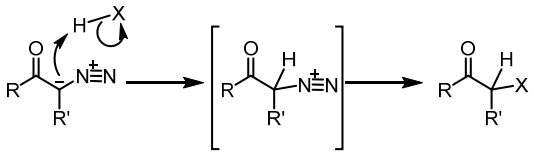


This area of research has been much more explored and all the information is available for reactions in which **X–Y** is molecular halogen, or where **X** is a hydrogen atom and **Y** a halogen or oxygen, nitrogen, phosphorus, sulphur, selenium, or a silicon-based group. The process represents a quite general approach to the regiospecific mono- or di-functionalization of a ketone, in many cases under essentially neutral conditions. For expediency in the following they have been collected in Scheme 10.[4a]



Scheme 10. *α,α-Substitution Reactions of α-Diazocarbonyl Compounds*

Comprehensive study was done for displacement of nitrogen from *α*-diazocarbonyls by using halogens (chlorine, bromine, and iodine) to furnishing *α,α*-dihalogenated products (X–Y = F_2, $C1_2$, Br_2, I_2). It has been also studied by using mixed halides such as IBr and IC1. Diazo ketones react very rapidly with hydrogen halides to form the corresponding *α*-haloketone. The hydrogen iodide is an exception to this. The mechanisms of these reactions are probably very similar to that of halogen substitution with the initial electrophilic attack on the diazocarbonyl group furnishing a diazonium ion from which nitrogen is displaced by halide ion in an S_N2 process.[16a]



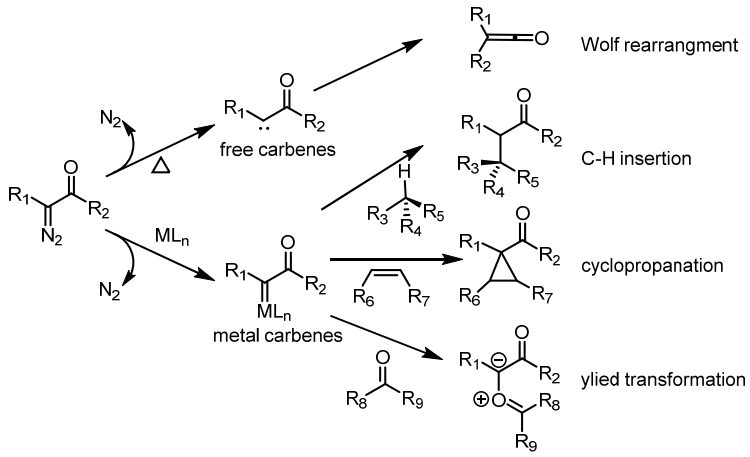
The addition of water and alcohols to *α*-diazocarbonyl compounds has seen several inventions for *α,α*-substitution in contemporary organic synthesis (X–Y = H–OH, H–OR, H–OCOR, H–OSO_2R, H–$OP(O)(OR)_2$). Such additions can be carried out by either Bronsted or Lewis acids, notably dilute sulfuric acid and boron trifluoride. Later it has been suggested that metal salts offer greater advantages in terms of selectivity and efficiency.[16b]

The synthesis of *α*-ketosulfonates from diazoketones by adding sulfonic acids is one of the classical examples in this regard. Methane-/ethane/trifluoromethane-/camphorsulfonic acids and a variety of substituted benzenesulfonic acids have all been employed in this pursuit and these reactions generally proceed rapidly at room temperature without external catalysis.

The major advantage of this process is that it offers a versatile handle for introducing various sulphur-containing substituents next to ketones and esters (X–Y = H–SR, CI–SR, RS–SR).[16c] Photolysis processes lead to carbene insertion into the S–H bonds producing ethyl (ethylthio) acetate. Likewise, using AIBN as a radical initiator under thermal conditions, the sulfenylated product is obtained in very high yield. The organo selenium reagents also participate with similar ease in the *α,α*-substitution reactions of diazocarbonyls (X–Y = H–SeR, CI–SeR, Br–SeR, I–SeR, F–SeR, RSe–SeR).[16d] Similarly, other important substitutions where X–Y = H–NR^1R^2, H–SiR_3, R–BR_2, work very well for producing *α*-amino ketones, *α*-silyl carbonyl adducts, *α*-alkylated carbonyl compounds respectively.[4a,16]

Carbene Reactions of *α*-Diazocarbonyl Compounds

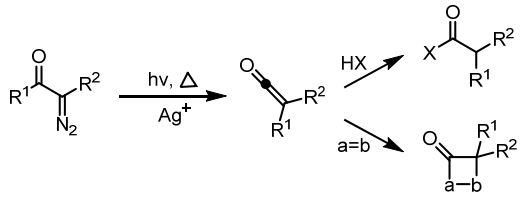
Diazocarbonyls are always a useful source of carbenes because the electron-withdrawing carbonyl group stabilizes the diazo dipole, which is absent in diazomethane. Diazocarbonyl compounds are very easily decomposed to carbenes by heat, light or metal. Decomposition of diazocarbonyl compounds leads to highly reactive carbene species, either free or metal stabilized that undergo a wide array of transformations including cyclopropanation, C–H insertion, ylide reactions, and the Wolff rearrangement.[2] Numerous useful scaffolds such as cyclopropanes, cycloalkanones, and *β*-lactams could be synthesized from diazocarbonyl compounds *via* carbene reactions (Scheme 11).



***Scheme 11**. Carbene Reactions of α-Diazocarbonyl Compounds*

The thermal and metal mediated rearrangements are known from as early as 1902.[17] However, the higher temperatures required for the thermal decomposition of *α*-diazocarbonyl compounds (180 ^{o}C) leads to several side reactions/rearrangements. At the same time, the transition metals greatly lower the temperature by formation of a stable metal-carbene intermediate. However, these metal carbenes are so stable; they don't undergo regular rearrangement and lead to a variety of side products,

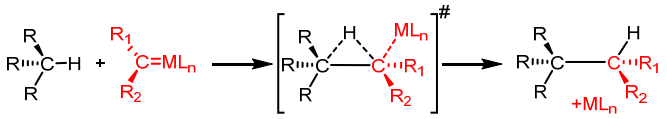
In this context, in 1951, Gross and co-workers reported the first example of the photolytic Wolf rearrangement.[18] *α*-Diazo ketones have two absorption bands, an allowed π→π* transition at 240–270 nm, and a formally forbidden π→σ* transition at 270–310 nm. Medium or low-pressure mercury arc lamps can excite these respective transitions (Scheme 12).



Scheme 12. *The Wolff Rearrangement*

C–H Insertion Reactions

The carbene insertion into C–H bonds documented in 1942 by Meerwein, Rathjen and Werner continues to attract the attention of synthetic chemists.[19] Over several decades, there is significant attention on the utilization of diazocarbonyl compounds as precursors in carbon-carbon bond forming reactions. The insertion process can be either intermolecular or intramolecular and both demonstrate a broad range of applications in synthesis. However, when compared to intramolecular the intermolecular C–H insertion has attracted less attention because of low selectivity and competition from intramolecular reactions. Intramolecular insertion of keto carbenes into unactivated C–H bonds has assumed strategic importance in organic synthesis. Sometime it allows transformations that would otherwise be difficult to achieve (Scheme 13).



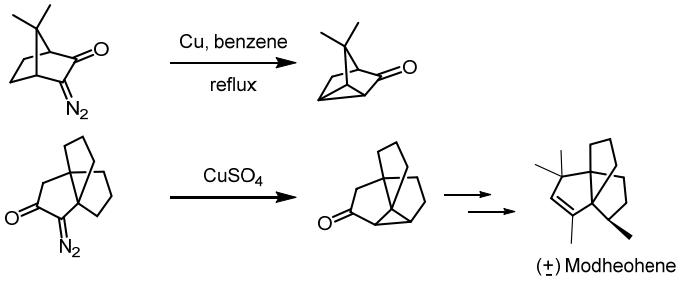
Scheme 13. *Mechanism for C-H Insertion Reaction*

One of the well-studied applications of the intramolecular carbene insertion reaction is the construction of cyclic rings with ring sizes varying from three to six. In these process, the ring size and the regioselectivity depends upon the type of diazo function, the degree of substitution on the carbon where insertion takes place and steric and electronic factors.

Intramolecular C–H Insertion: Three-Membered Ring Formation

In some special cases the geometrical rigidity of structures favours intramolecular C–H insertion, resulting in the formation of three-membered ring compounds. For example, catalytic conversion of diazocamphor into cyclocamphanone involves the cyclopropyl ring formation *via* C–H insertion. It has

also been used in the stereo controlled synthesis of racemic Modheohene (Scheme 14).[20]

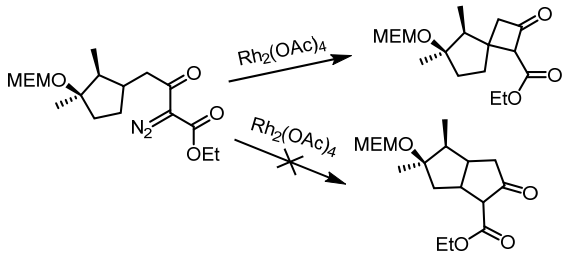


***Scheme 14**. Three-Membered Ring Formation*

Intramolecular C–H Insertion: Four-Membered Ring Formation (Carbocycles/Heterocycles)

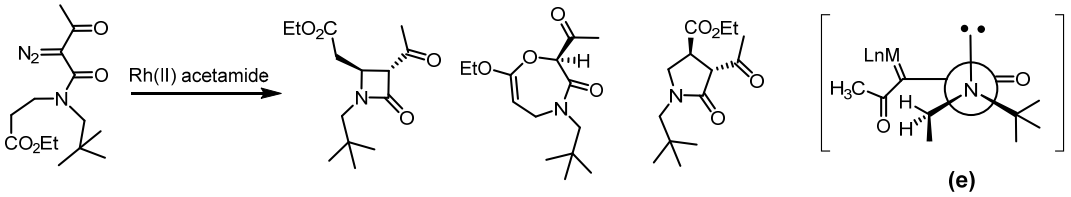
A wide range of four-membered heterocycles are accessible but only a few examples of four-membered carbocycle formation, *via* intramolecular C–H insertion have been reported. Most of the cases of carbocycles are usually observed as low-yield products along with five-membered ring formation. However, in some examples, with appropriate substrate design, moderate yields of cyclobutanone products can be obtained. The intramolecular C–H insertion reaction of carbenes or carbenoids derived from α-diazo esters and α-diazo amides gives β-lactones, β-lactam and 1,2-azaphosphetidine. In the case of heterocyclic systems, the preference for four-membered ring formation is probably due to the activation of the adjacent oxygen atom and the intrinsic conformational bias of metallocarbenoid species formed from diazomalonates.

Coming to a four-membered carbocycle formation, the work of Cane and co-workers is worth mentioning. This group documented the synthesis of a bicycle[4.3.0]-octanone derivative by annulation of a spirocyclobutanone *via* intramolecular C–H insertion. In the substrate employed, the combined 1,3-interactions of the MEM ether and the secondary methyl group hinder the approach of the carbenoid to the secondary C–H bond, there by directing attack to the opposite face of the cyclopentane ring on which only a tertiary hydrogen atom is accessible, thus leading to spirocyclobutanone (Scheme 15).[21]



Scheme 15. *Four-Membered Carbocyclic Ring Formation*

Another report from Doyle and co-workers indicated that catalytic breakdown of diazo acetoacetamide forms not only the *β*-lactam, but also the carbonyl ylide derived product and the *γ*-lactam insertion product (Scheme 16).[22] Though switching the electronically selective rhodium(II) acetamidate as catalyst, the *β*-lactam product was the main insertion product. The accomplishment of the above transformation was recognized to be an activating control on the C–H bond neighbouring to the amide nitrogen atom, and conformational preferences that placed the reacting C–H bond in close proximity to the carbenoid centre, as shown in Scheme 16 (**e**).[22]

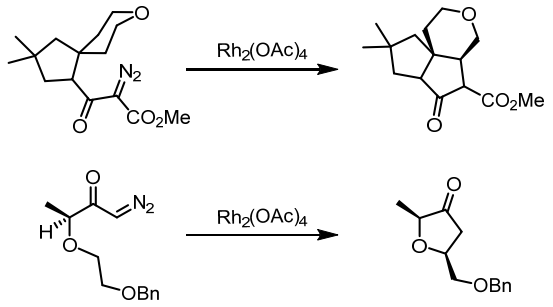


Scheme 16. *Four-Membered Heterocyclic Ring Formation*

Intramolecular C–H Insertion: Five-Membered Ring Formation (Carbocycles/Heterocycles)

The carbenoid C–H insertion approach is widely used for preparation of the cyclopentane ring, which is an important structural unit of natural products. This strategy is particularly useful because the diazocarbonyl precursors are readily available. Most methods for five-membered carbocycle construction depend on the joining together of previously functionalized carbon atoms. If a heteroatom is present in the molecule, the preference for C–H bond insertion always goes into that C–H bond which is alpha to the heteroatom. Adams and co-workers have described that even in case of ether oxygen; it promotes this type of regioselectivity in carbenoid C–H insertion. The C–H bond next to the ether oxygen is the ideal site of insertion compared to the usual "unactivated" aliphatic carbon-hydrogen bond (Scheme 17).[23]

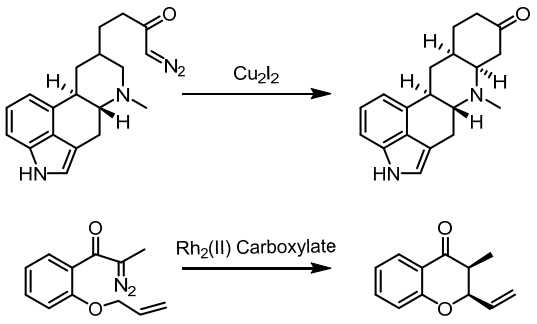
This area signifies one of the most useful employments of intramolecular diazocarbonyl reactions.



***Scheme 17**. Five-Membered Ring Formation*

Intramolecular C–H Insertion: Six-Membered Ring Formation (Carbocycles/Heterocycles)

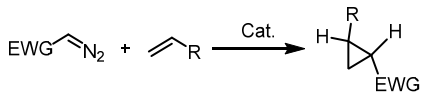
Competition for regioselectivity between six-membered and five-membered carbenoid C–H insertion strongly depends on the type of diazocarbonyl precursor. In case of freely rotating aliphatic chains, five-membered ring formation predominates. Conversely, if a δ-carbon hydrogen bond is activated by one flanking heteroatom, the C–H insertion results in a six-membered ring formation (Scheme 18).[24]



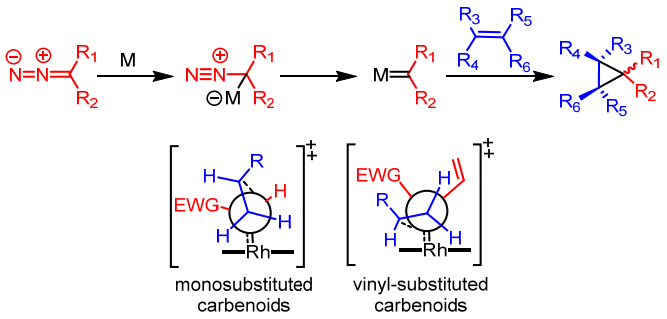
***Scheme 18**. Six-Membered Ring Formation*

Cyclopropanation of Alkene

Exercise of α-diazocarbonyl compounds for cyclopropanation of olefins is one of the most meticulously studied conversions in organic chemistry.[25] The cyclopropane ring itself is found in a number of natural products. [25b] Its biological significance and synthetic utility has received considerable attention over the past several decades.

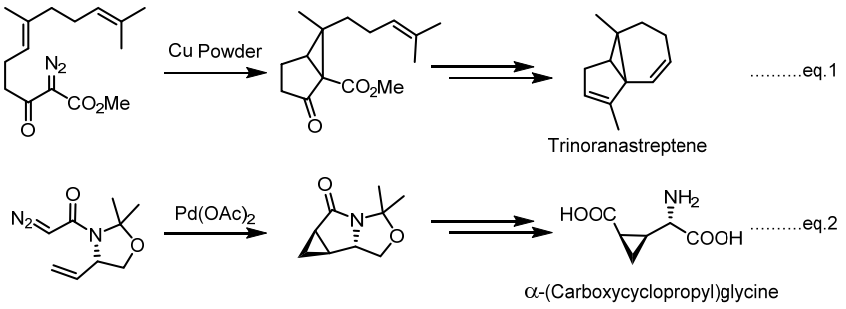


The decomposition of diazocarbonyl compounds in the presence of alkenes by using different transition metal catalysts has provided a facile and powerful means of constructing cyclopropanes. The formation of a metal carbene intermediate by attack of the diazo compound on the metal center produces a zwitterionic metal alkyl complex, which ousts nitrogen gas. Concerted addition of the metal carbene to the olefin generates the observed cyclopropane product. The configuration of the olefin is retained throughout the process. However, metal carbenes with heterotopic faces may generate a mixture of diastereomers (Scheme 19). Among the various transition metals used for cyclopropanation, counting rhodium, ruthenium, and cobalt, the copper catalysts occupy a special place, particularly for intermolecular reactions.[26]



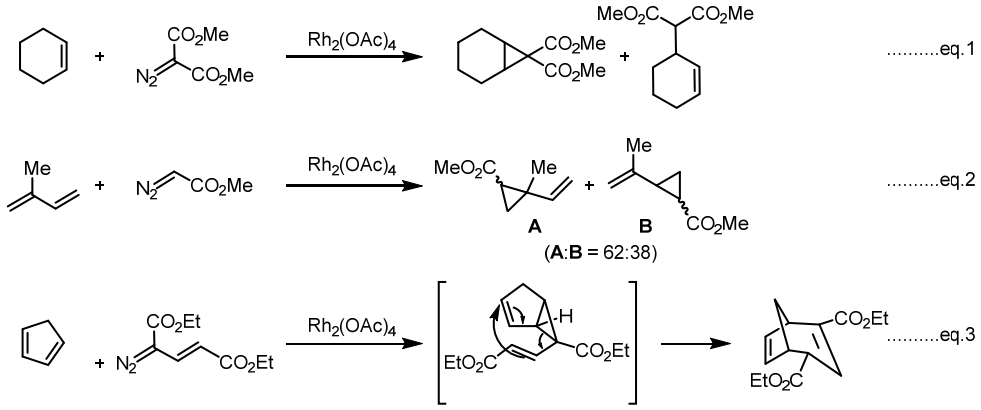
***Scheme 19**. Prevailing Mechanism*

The configuration of the product is decided by the path of approach of the olefin to the metal carbene. In reactions of mono substituted metal carbenes with terminal olefins, the olefin likely approaches "end-on" (with the carbon-carbon double bond of the olefin nearly parallel to the metal-carbon double bond of the carbene) with the olefin R group pointed away from the substituent of the carbene. A second transition state model has been proposed for reactions of vinyl-substituted carbenes. In this model, the olefin approaches "side-on" (with the carbon-carbon double bond of the olefin perpendicular to the metal-carbon double bond of the carbene) with the olefin R group far from the vinyl group (Scheme 19).[26]



***Scheme 20**. Intramolecular Cyclopropanation*

In 1988, Kang and co-workers published the first total synthesis of Trinoranastreptene having an unprecedented tricyclo[5.3.0.0]decane ring system. As shown in Scheme 20 (eq. 1), the bicyclo[3.1.0]hexane derivative was synthesized from the corresponding diazocarbonyl precursor employing the Rh-catalyst and was transformed into Trinoranastreptene.[27a] Similarly, Yamanoi and Ohfune groups have employed intramolecular cyclopropanation in their synthesis of naturally occurring *α*-(Carboxycyclopropy1)glycine (Scheme 20, eq. 2).[27b]



***Scheme 21**. Intermolecular Cyclopropanation*

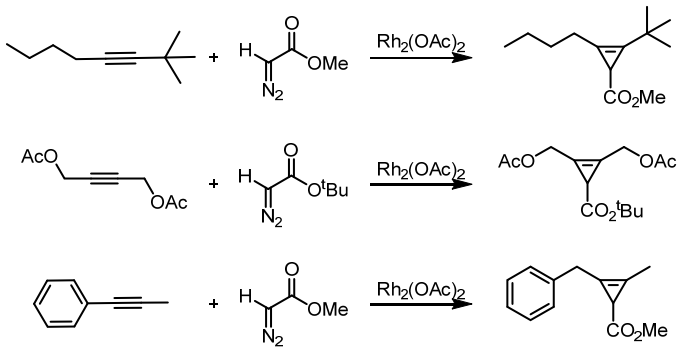
Compared to the intramolecular reactions, the intermolecular cyclopropanation reactions employing diazocarbonyl compounds are more recent. Rhodium carboxylate complexes, such as dirhodium tetraacetate, are most commonly used to catalyze this transformation. Diazocarbonyl compounds substituted with two electron-withdrawing groups, such as diazomalonates, are prone to experiencing side reactions under cyclopropanation conditions (3 + 2) Cycloaddition and C–H insertion side products have been observed during these reactions (Scheme 21, eq. 1). [28] Doyle and co-workers (1982) have reported the cyclopropanation of isoprene with ethyl diazoacetate with a striking preference for the more substituted double bond (Scheme

21, eq. 2).[28] In case of vinyl diazoacetates, Davies and co-workers (1987) found that when it reacts with dienes, it forms divinyl cyclopropanes, which undergo Cope rearrangement to afford cycloheptadienes (Scheme 21, eq. 3).[28]

Cyclopropanation of Alkynes

Analogous to alkene, alkynes also undergo cyclopropanation with α-diazocarbonyl compounds leading to the formation of cyclopropene products. These cyclopropenes are endowed with high strain energy and are enormously reactive synthetic intermediates that often not isolable, although exceptions do exist.

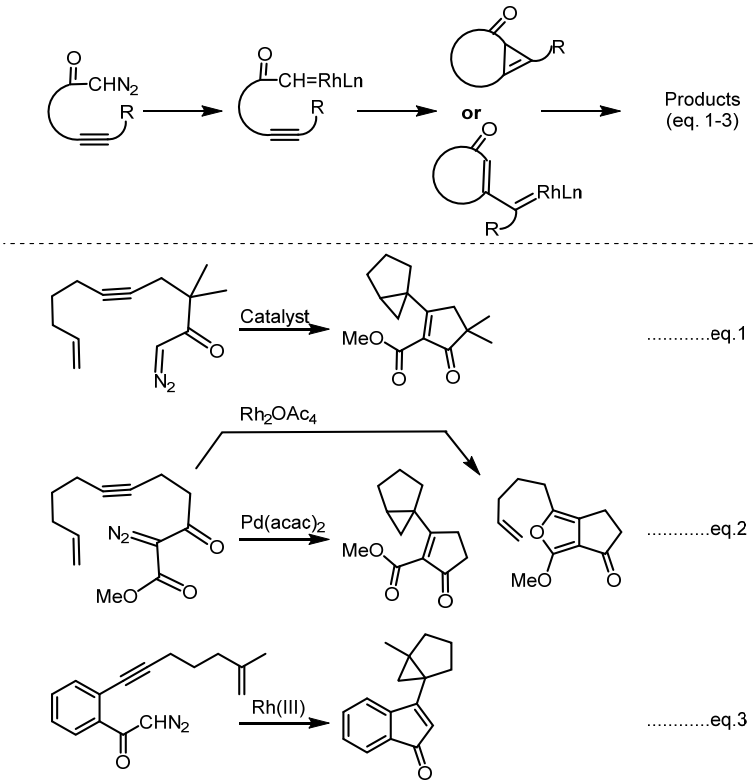
Early examples on the cyclopropanation of alkynes were documented in 1964, by Doering and Pomerantz, employing the photolysis of diazoacetate. Currently, this can be achieved by employing various metal complexes. Copper catalysts often required higher temperatures, which thereby exposed the primary reaction products to thermal or catalytic ring opening. On the other hand, the rhodium(II) carboxylates, because of selectivity and mild reaction conditions, have become the catalysts of choice in this pursuit. Selected examples of cyclopropanation of alkynes are shown in Scheme 22.[29]



***Scheme 22**. Intermolecular Cycopropenation*

Coming to the intramolecular cyclopropanation of alkynes, this has been potentially utilised for the construction of polycyclic molecules from acyclic precursors. In general, the resulting cyclopropene intermediates rearrange to vinyl carbenes that can take part in additional reactions with proximal functional groups. The seminal contributions from Hoye and Padwa have revealed that these cascade processes were initiated by formation of a metal carbene from the diazocarbonyl group. There are two possible paths for the formation of α-vinyl carbenoids. In the first path, the metal carbenoid adds to the alkyne and produces α-vinyl carbenoid

directly *via* insertion and the second proceeds *via* addition resulting in a highly strained cyclopropene intermediate. Hoye's work clearly showed that metallated species are involved in the product-determining steps. The type of products and yields are largely depends on metals used for reaction. The behaviour of the substrate in Scheme 23 eq. 2 illustrates the catalyst dependence on the fate of the vinyl carbenoid. While the use of Pd leads to efficient cyclopropanation of the distal double bond, Rh catalyzes the formation of a fused furan system, presumably from interception of the vinyl carbenoid by the ester carbonyl oxygen atom (Scheme 23).[30]

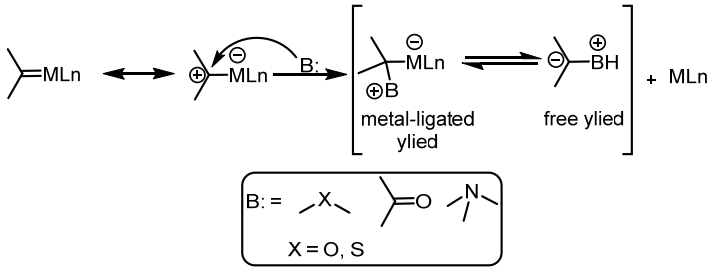


***Scheme 23**. Intramolecular Cycopropenation*

Ylide Formation Reaction

Because of the highly electrophilic nature of carbenes that have originated from diazocarbonyl compounds, they react with the suitably placed heteroatoms [as Lewis Bases (B:)] leading to the ylide formation. The carbenoids react with functional groups such as ethers, sulfides, amines and carbonyl compounds and provide oxonium, sulfur, nitrogen, and carbonyl ylides respectively. The generated adduct either dissociate from the catalytic species to form a "free ylide" or react as a metal-ligated ylide complex (Scheme 24). These ylides are highly reactive and readily

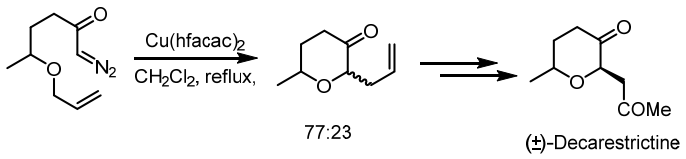
undergo further reactions, both inter- and intramolecularly, to give stable products. The most common reactions of catalytically generated ylides include [2,3]-sigmatropic rearrangement of allyl-substituted intermediates, [1,2]-insertion or Stevens rearrangement (typical of oxonium, sulfur, and nitrogen ylides), and dipolar cycloaddition (typical of carbonyl ylides).[2,4b,31]



***Scheme 24**. Ylide Formation*

Oxonium Ylides

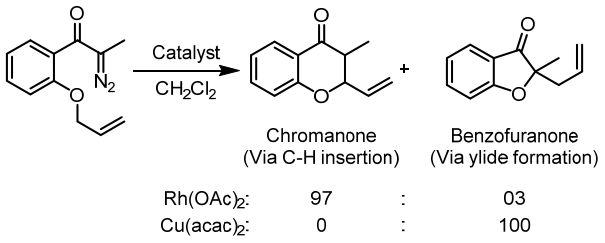
Oxonium ylides are very well known for their sigmatropic rearrangements to form new C−C bonds. Cyclic oxonium ylides have potential for the synthesis of five-, six-, and eight-membered oxygen heterocycles. In 1986, the first rhodium-catalyzed oxonium ylides formation from α-diazoketones and α-diazo-β-ketoesters was reported. Another early report by Clark and co-workers, exemplify that the application of [2,3]-sigmatropic rearrangement of oxonium ylides in total synthesis in the preparation of (±)-Decarestrictine. The copper catalyzed cyclization of a *α*-diazoketone substrate is the main step involved in this synthesis (Scheme 25).[32]



***Scheme 25**. Synthesis of Decarestrictine*

[2,3]-Sigmatropic Rearrangement of Oxonium Ylides

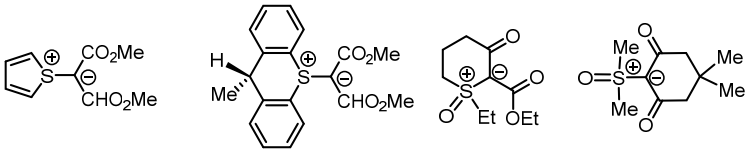
Rhodium(II) carboxylates are the catalysts of choice for the formation of oxonium ylides. In intramolecular cyclic oxonium ylide reactions, there is always the competing C−H insertion process. As shown in Scheme 26, the selectivity can be controlled by the choice of catalyst. Copper complexes generally provide the ylide-derived product while rhodium species are typically found to favour C−H insertion.[33]



Scheme 26. *Chromanone vs Benzofuranone Formation*

Sulfonium Ylides

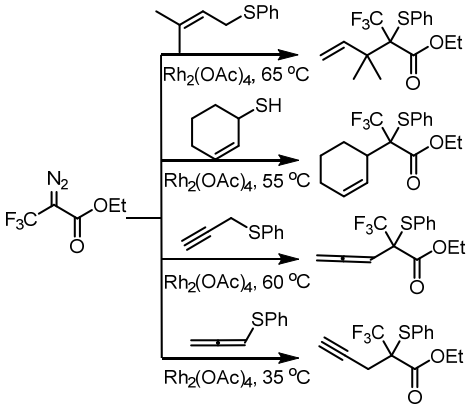
The Porter (1978) and Tamura (1981) groups have independently reported the isolation of sulfonium ylides generated from thiophene and thioxanthene respectively. Unlike oxonium ylides, the isolation of sulfur ylides is possible if the ylide carbon is flanked by two stabilizing electron-withdrawing groups and if the ylide generated is not prone to subsequent rapid rearrangement reactions (Scheme 27). Similarly, the reaction of sulfoxides with metal carbenoids also produces stable sulfur ylides.[34]



Scheme 27. *Stable Sulfur Ylides*

[2,3]-Sigmatropic Rearrangement of Sulfonium Ylide

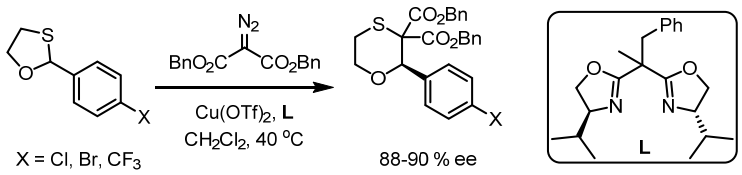
One of the common reactions of sulfonium ylides is the [2,3]-sigmatropic rearrangement. A wide range of copper and rhodium complex have been employed for sulfonium ylide [2,3]-sigmatropic rearrangements. Scheme 28 provides the compilation of selected examples in this context.[35]



Scheme 28. *[2,3]-Sigmatropic Rearrangements of Sulfur Ylides*

[1,2]-Stevens Rearrangement of Sulfonium Ylide

One pot formation of sulfur ylides and successive [1,2]-Stevens rearrangement has been applied as a key C−C bond forming strategy. In 2009, Tang and co-workers reported the first example of a catalytic asymmetric [1,2]-Stevens rearrangement of sulfur ylides. In this work, optically active 1,4-oxathianes were prepared in high yields and with excellent stereoselectivities by reaction of 1,3-oxathiolanes and diazomalonates in the presence of various copper bisoxazoline catalysts. Optimal results were achieved for reaction with dibenzyl-substituted diazomalonates, 1,3-oxathiolanes with an electron-withdrawing group substituted (X = Cl, Br, CF_3) benzene ring, and a copper catalyst generated from $Cu(OTf)_2$ and ligand (L) (Scheme 29).[36]



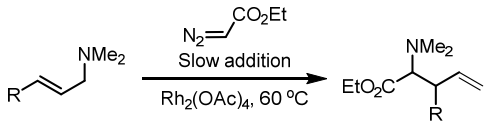
***Scheme 29**. Catalytic Asymmetric [1,2]-Stevens Rearrangement*

Ammonium Ylides

As compared to oxygen and sulfur ylides, ammonium ylides generated from metal carbenoids are fewer in the literature. The main reason for this is the strongly Lewis basic nature of the nitrogen atom of the amine precursors that can complex tightly to the transition metal, often rendering the catalyst inactive. However, the synthetic potential of nitrogen ylides has been exhibited for both inter- and intramolecular processes.[37]

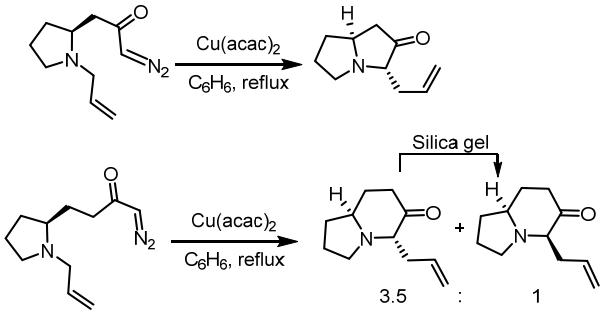
[2,3]-Sigmatropic Rearrangement of ammonium ylides

Doyle and co-workers have reported the rhodium-catalyzed [2,3]-sigmatropic rearrangement of ammonium ylides as an efficient method for the synthesis of substituted homoallylamines (Scheme 30).[38]



***Scheme 30**. [2,3]-Sigmatropic Rearrangement of Ammonium Ylides*

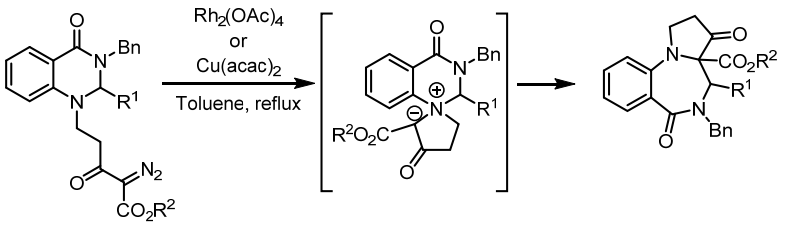
Recently, Clark and co-workers reported the synthesis of bicyclic amines *via* ammonium ylides. While the formation of a five-membered ring occurred with a high diastereoselectivity, the homologous six-membered products were obtained as a mixture of *cis* and *trans* isomers indicating the involvement of two diastereomeric ylide intermediates (Scheme 31).[39]



***Scheme 31**. Formation of Five- and Six-Membered Rings*

[1,2]-Stevens Rearrangement of ammonium ylides

Because the rhodium(II) catalyst complexes strongly with nitrogen ylides the available examples for the intermolecular generation/[1,2]-rearrangement have been limited mainly to the use of copper powder. This rearrangement has been successfully applied for the synthesis of several biologically active compounds, including the cephalotaxine ring skeleton, isoindolobenzazepine alkaloids, and the novel pyrrolo[1,2-a][1,4]-benzodiazepinone system (Scheme 32).[40]

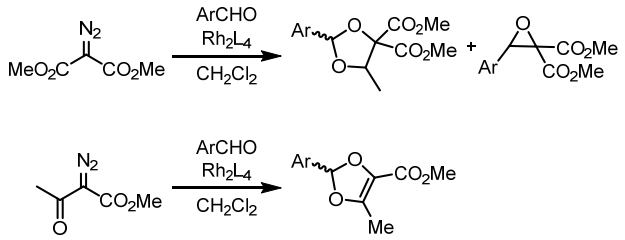


***Scheme 32**. Synthesis of the Pyrrolo[1,2- α][1,4]benzodiazepinone Ring System*

Carbonyl Ylide 1,3-Dipolar Cycloaddition

The addition of metal carbenoids to carbonyl groups leads to the formation of carbonyl ylides that can undergo cyclization to epoxides, hydride transfer and 1,3-dipolar cycloadditions (Scheme 33).[41] The formation of ylides may be intra- or intermolecular. As is the case with onium ylides, the reactions can take place either *via* a free ylide, in which case the catalyst has no influence on the stereochemical

outcome of the reaction, or *via* a metal ylide, in which case asymmetric induction due to the influence of a chiral catalyst is possible.

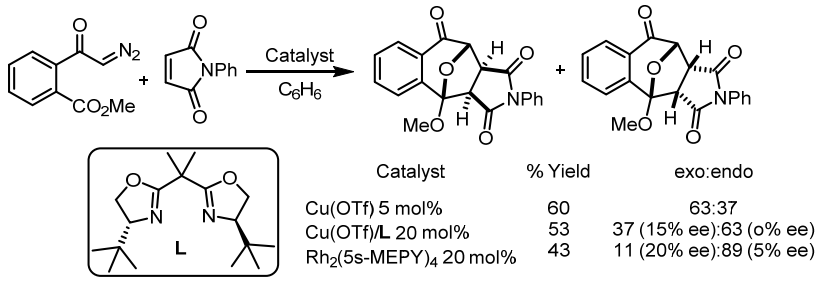


Scheme 33. *Formation of Dioxolanes, Epoxides, and Dioxolenes*

The nature of the diazocompound has a strong influence on the reaction pathway. While dimethyl diazomalonate reacted with aldehydes to form dioxolane and/or epoxide, in ratios that were dependent on the electronic nature of the aldehyde, methyl diazoacetoacetate reacted with electron-rich and electron-poor aldehydes to form the dioxolene products exclusively, through intramolecular trapping of the ylide (Scheme 33). [41]

Tandem Intramolecular Ylide Formation/Intermolecular Cycloaddition

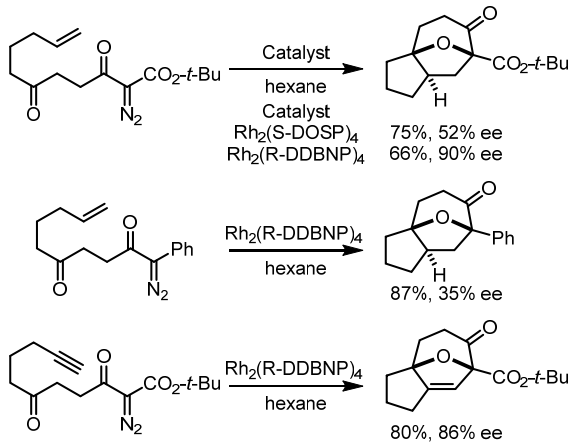
In 1998, Suga and Ibata reported for the first time an example of asymmetric induction in an intermolecular carbonyl ylide cycloaddition reaction. The aromatic diazo compound reacts with maleimides and the *exo*/*endo*-selectivity was seen to be strongly influenced by the catalyst. $Rh_2(OAc)_4$ and CuCl gave predominantly *exo* selectivity, while more Lewis acidic Cu(OTf) or CuCl combined with $Yb(OTf)_3$ gave greater *endo*-selectivity. Reactions with $Rh_2(5(S)\text{-MEPY})_4$ or Cu(OTf)−bisoxazoline afforded low levels of enantioselectivity (Scheme 34).[42]



Scheme 34. *Intramolecular Ylide Formation and Reaction with N-Phenylmaleimide*

Tandem Intramolecular Ylide Formation/Intramolecular Cycloaddition

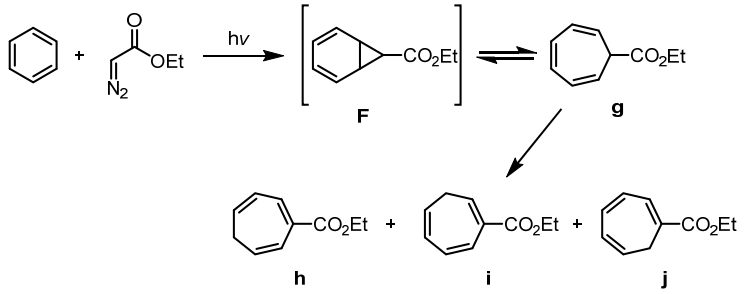
In 1997, Hodgson and co-workers reported the first example for catalyst controlled asymmetric induction in a carbonyl ylide (3 + 2) cycloaddition. A diazoketoester containing remote ketone and alkene groups was shown to undergo intramolecular ylide formation and cycloaddition in the presence of $Rh_2(DOSP)_4$ to afford the tricyclic adduct with an enantiomeric excess of 52% (Scheme 35).[43] It was subsequently demonstrated by the same group that the enantioselectivity could be improved to 90% ee by using $Rh_2(DDBNP)_4$ (Scheme 35).[43]



***Scheme 35**. Catalyst-Controlled Asymmetric Induction*

Reactions with Aromatics

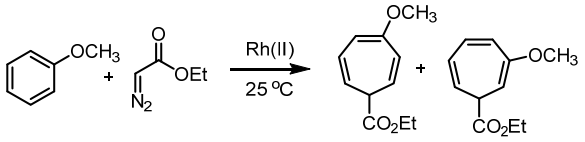
In 1883, for the first time, Curtius reported the synthesis of ethyl diazoacetate (EDA).[1] Quickly after the Curtius report, Buchner[44] reported the reactions with alkenes, alkynes, and aromatics that were to prolong for 30 or more years. In preliminary results, Buchner reported thermal decomposition of EDA in benzene, furnishing a single product (norcaradiene structure). After careful re-examination of the reaction and formed products, in 1956, the Doering group reported that the Buchner reaction in its original form produces four cycloheptatrienyl esters (Scheme 36).[45]



***Scheme 36**. Reaction of EDA with Benzene*

The Buchner reaction always ends with the complex mixtures of cycloheptatrienyl esters, which usually were neither separated nor individually recognized. Interestingly either thermal or photochemical decomposition of diazo acetate was seen to occur, with the reactions to a great extent proceeding with a similar outcome. The existing explanation of both processes is that carbethoxycarbene addition to benzene proceeds *via* an unstable norcaradiene intermediate (**f**) which is in mobile equilibrium with the more stable cycloheptatriene tautomer (**g**); the remaining products (**h-j**) being isomers of (**g**) formed by thermally or photochemically induced sigmatropic rearrangement.[46]

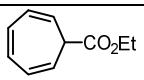
In 1980, a Belgian group documented a systematic investigation on the rhodium catalysed carbene insertions across various aromatic substrates. The most common problems in the thermal and photochemical reactions were solved swiftly. It has been observed that the thermal reaction of **EDA** with anisole led to seven products (35% yield). On the other hand, the same with rhodium trifluoroacetate gave exclusively two products in 73% yield (Scheme 37).[47]

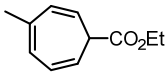
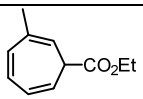
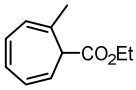
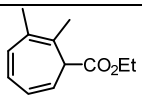
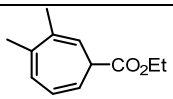
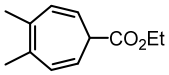
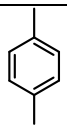
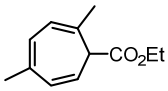
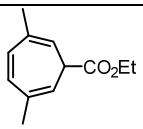
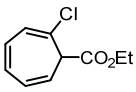
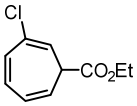
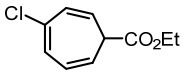
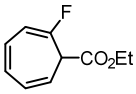
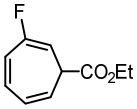
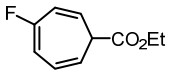


***Scheme 37**. Reaction of EDA with Anisole*

In general, rhodium(II)-catalyzed decomposition of alkyl diazoacetates in a large excess of aromatic substrate at room temperature produces kinetically controlled cycloheptatrienyl esters in excellent yield. In case of anisole, though the methoxy substituent clearly exerts a directive result in favour of the 4-isomers, both products of the latter (Scheme 37) reaction are kinetically controlled unconjugated esters, neither of which was even detected in the thermal reactions. A summary of the interaction of diazoacetate on several aromatics with **EDA** is shown in Table **1**.[47]

***Table 1:** Reactions of Ethyl Diazoacetate with Aromatics*

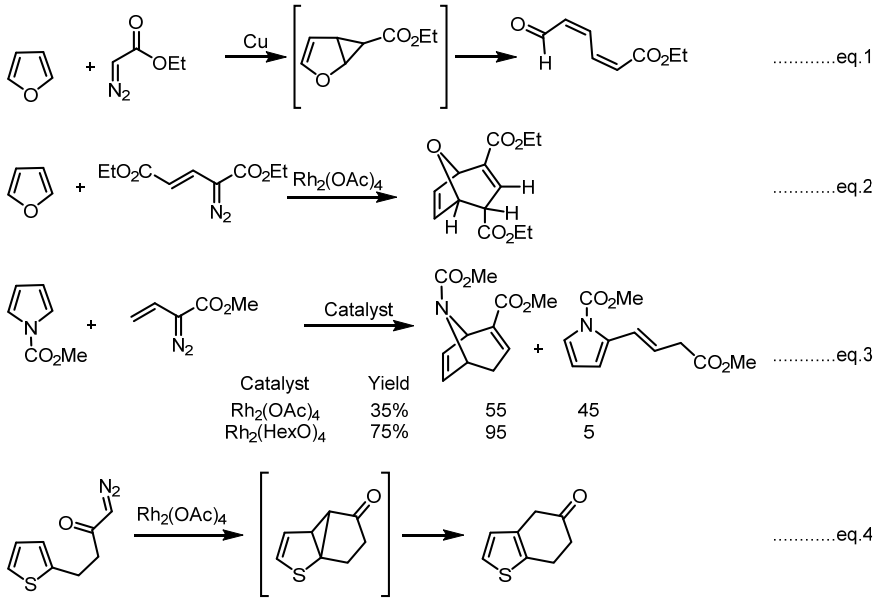
Precursor	Products
	 100%

	 56%	 23%	 17%
	 43%	 39%	 18%
	 85%	 10%	
	 5%	 15%	 80%
	 8%	 12%	 80%

Heteroaromatic Compounds

Similar to simple aromatics (benzene), other aromatics (heteroaromatic) such as furan, pyrrole, and thiophene have found relevance in reactions with diazocarbonyls. Early in 1958, Novac and Sorm have reported that cyclopropanation of furan with ethyl diazoacetate is possible by using copper catalysis, but that the primarily produced cycloadduct undergoes a ready ring-opening process to afford the *Z*, *E*-diene adducts (Scheme 39, eq. 1).[48]

Afterwards, in 1985, the Davies group reported the reaction of furans with vinyl diazoesters that led to a (4 + 3) cycloaddition.[49] It has been argued that unlike with the simple vinyl carbenes that have a strong propensity for intramolecular reactions, the corresponding metal carbenoid complexes are stable and undesirable intramolecular side reactions should therefore be minimized. As shown in Scheme 38, the rhodium(II)acetate catalysed decomposition of vinyl diazo ester in the presence of furan at room temperature gave the bicyclic adduct (Scheme 38, eq. 2) as the major product resulting from aa stereospecific (4 + 3) cycloaddition between a vinyl carbenoid and a furan.[49]



Scheme 38. *Reactions with heteroaromatic*

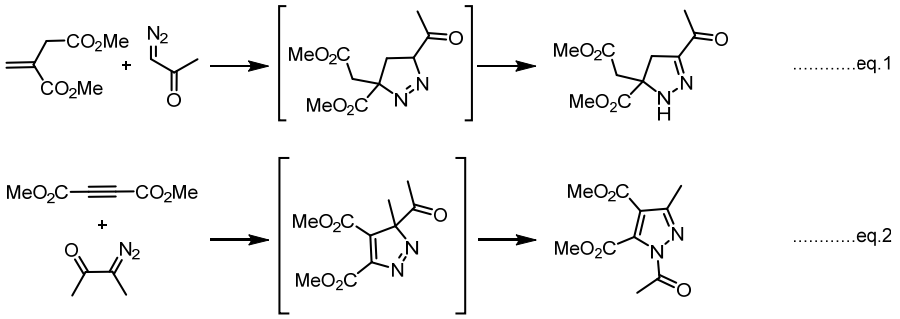
Extensive work on these cycloaddition reactions by Davies group continued with other heteroaromatic substrates. Similar to furan, reaction of *N*-acylated pyrrole with a vinyl diazocarbonyl having a single electron-withdrawing group resulted in the construction of a tropane skeleton *via* a (4 + 3) cycloaddition.[50] The reaction outcome was strongly catalyst dependent, with rhodium(II) hexanoate in hexane furnishing a much higher conversion than rhodium(II) acetate in dichloromethane (Scheme 38, eq. 3). The reaction between thiophenes and diazocarbonyls also has been known for several years. Rhodium-(II) salts are mainly used as catalysts for these reactions. Ylide formation, Cyclopropanation, and C-H insertion are the general possible processes. Inter-and intramolecular versions are well known for this and the outcome of the reaction totally depends upon the diazocarbonyl precursors and reaction conditions (Scheme 38, eq. 4).[51]

Cycloaddition Reactions of Diazocarbonyls

Cycloaddition is another appealing work done in the chemistry of *α*-diazocarbonyls. These compounds are highly capable for numerous inter-and intramolecular cycloadditions, which may occur directly onto the diazocarbonyl precursor with retention of nitrogen or *via* the keto carbenoid functionality as a 1,3-dipole.[52]

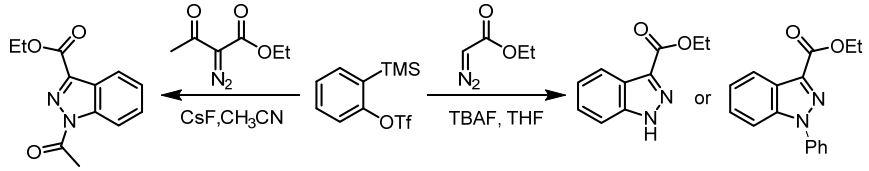
Diazocarbonyl Compounds as 1,3-Dipoles in the (3 + 2) Cycloadditions

α-Diazocarbonyl undergo a wide variety of 1,3-dipolar (3 + 2) cycloaddition reactions with conjugated double bonds or double bonds as a part of a strained ring system, without loss of nitrogen to furnish Δ^1-pyrazolines. For example, the reaction of dimethyl itaconate and 1-diazo-2-propanone furnishes the Δ^1-pyrazoline. This undergoes spontaneous tautomerization to afford the Δ^2-pyrazolinein good yield (Scheme 39, eq. 1).[53a] Similarly, carbon-carbon triple bonds conjugated with carbonyls also participate well in these1,3-dipolar cycloaddition reactions. 2-Diazo-3-butanone reacts with dimethyl acetylene dicarboxylate to form the unstable pyrazolenine, which undergoes an acetyl migration leading to N(2)-substituted pyrazole (Scheme 39, eq. 2).[53b]



***Scheme 39**. Diazocarbonyl (3+2)-Cycloadditions with Olefin/Alkyne*

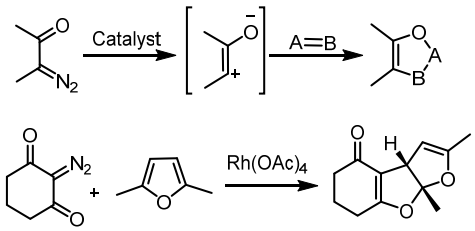
Further in 2007, Larock and co-workers extended this concept of 1,3-dipolar (3 + 2) cycloaddition reaction of diazo compounds for indazoles synthesis. It involves the reaction of diazo compounds with *o*-silylaryl triflates (aryne precursor) in the presence of cesium fluoride to afford the corresponding (3+2) cycloadducts in good to excellent yields. Diazo compounds bearing hydrogen undergo tautomerization to the corresponding 1*H*-indazoles. At the same time the use of an excess of the aryne precursor affords excellent yields of *N*-aryl-1*H*-indazoles. Diazo compounds with carbonyl groups attached to the diazo carbon undergo acyl migration to form the corresponding 1-acylindazoles (Scheme 40).[54]



***Scheme 40**. Diazocarbonyl (3 + 2) Cycloadditions with Aryne*

Cycloaddition with Participation of Both the Carbenic Carbon and the Carbonyl Oxygen Atoms

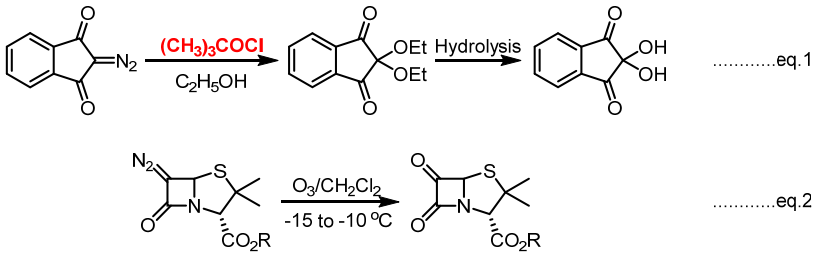
The (3 + 2) cycloaddition reactions of carbenes and carbenoids derived from α-diazocarbonyl compounds, involving the participation of both carbenic carbon and carbonyl oxygen with multiple bonds furnishing di-/tetrahydrofurans, are also documented well. The possibility of thermal rearrangement of initial formed products has also been speculated for the net formation dihydrofuran (Scheme 41).[55]



Scheme 41. *Diazocarbonyl (3 + 2)-Cycloaddition Reactions for Heterocycles*

Oxidations of Diazocarbonyl Compounds

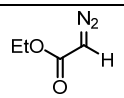
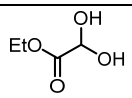
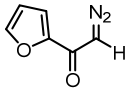
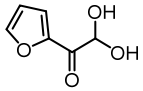
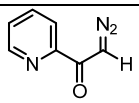
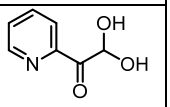
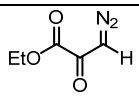
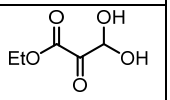
Oxidation of the diazo function of α-diazocarbonyl is one of the interesting areas. Various reagents are available for oxidation. The nature of the product depends on the choice of oxidant and the substitution pattern on the substrate.[56] Peroxy acids react with disubstituted diazo ketones to form 1,2-diketones which may react further with this oxidant. ^{t}-Butyl hypochlorite in ethanol oxidizes 2-diazoindanedione to a trione monoketal which on hydrolysis furnishes ninhydrin hydrate (Scheme 42, eq. 1).[56a] Oxidation of primary diazo ketones with ozone can lead to products resulting from C–H bond cleavage of the initially formed glyoxal. However, when this complication is absent, as with 6-diazo-APA (Scheme 42, eq. 2)[56b] cleavage by ozone to the α-diketone can be very efficient.



Scheme 42. *Oxidation of the Diazo*

These synthetically useful diazocarbonyl oxidation reactions are more noticeably studied through the use of dioxiranes, mainly dimethyldioxirane (DMD).This oxidant is readily available (easy to prepare and distilled as a dilute solution in acetone), converts diazo ketones into diketones or glyoxals in a high state of purity since there are no byproducts other than nitrogen and acetone. Glyoxals are generally isolated in hydrated form (Table 2). Predominantly important are the diazo ketones with oxidizable heterocyclic substituents where the reaction occurs exclusively at the diazo group.[57]

Table 2. *Oxidation of Diazocarbonyls by DMD*

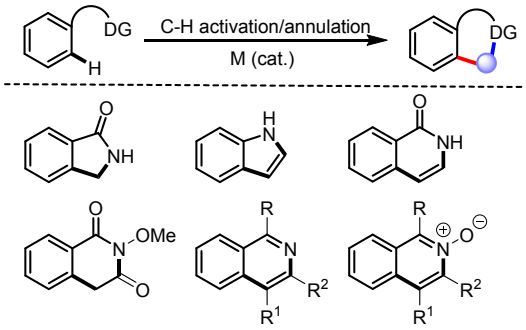
Diazocarbonyls	Products
	
	
	
	

Present Work

Though it may not be unwise not to feel so, however a long standing association with organic molecules reveals that oxygen is enriched in those compounds that mainly deal with energy and stability, while the compounds with nitrogen are associated with the finer aspects such as beauty and defense. The cyclic compounds containing nitrogen atoms are trivially called as heterocycles, which prevail over a diverse range of natural products and pharmaceutically active compounds.[58] The array of applications of nitrogen heterocycles is very extensive and this has geared them up as one of the prime classical divisions of organic chemistry. The account of the improvement of modern science for heterocyclic chemistry is marked by spectacular increases in the variety of compounds, products, and synthesis paths.[58]

The formation of C–N bonds is one of the central aspects of organic synthesis, especially in the heterocyclic ring constructions. Since the beginning, this has been tackled elegantly and there are more than hundred name reactions that deal directly with the C–N bond formations.[59] Also, more than 90% of the currently prescribed drugs have a nitrogen atom. Thus, the heterocyclic synthesis is an evergreen and extremely important area in organic synthesis. The approaches for the construction of these nitrogen heterocycles mainly involve the use of C–N bond forming reactions such as reductive amination, nucleophilic substitution, or dipolar cycloaddition for ring closures.[58-60]

The simultaneous construction of C–C as well as C–N bonds is one of the important aspects of nitrogen heterocycles synthesis. The cycloaddition reactions have always been opted for first in this pursuit because of their efficiency, along with the desirable step and atom economies.[61] In recent years, the use of metal-catalyzed C–C and C–N bond forming reactions comprising of C–H Activation–Annulation (**CHAA**)) for the construction of the *N*-heterocycles (Scheme 43) have gained wide popularity in a short span of time.[62] When these CHAA processes comprise of multicomponent couplings generating several bonds, rings and/or stereocenters in a single process, they allow a simple access to complex heterocyclic systems that can find applications in medicinal chemistry and drug discovery.[63]



Scheme 43. *CHAA Reaction for N-Heterocycles*

The transition metal catalyzed C−H activation/annulation reaction is one of the straightforward approaches for the synthesis of *N*-heterocyclic compounds.[62] Diverse cross-coupling partners such as alkenes, alkynes, and allenes have been systematically explored for the synthesis of various *N*-heterocyclic compounds.[64] In this context, it is quite reasonable to find the diazo compounds as multipurpose coupling partners in C−H activation/annulation reactions considering their ease of carbene generation and insertion into C–H bonds.[65]

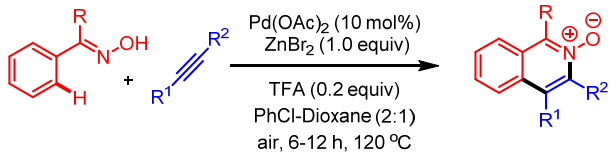
In 2012, Yu and co-workers have reported the first example of a Rh(III)-catalyzed C−H functionalization of arenes with diazomalonates.[66] Following this, the possibility of use diazocarbonyl compounds in Rh(III)-catalyzed C−H activation and annulation cascade has been aptly explored by several research groups.[64-67] Although substantial progress has been made in this type of C−H functionalization, they are, mainly limited to Rh(III)-complexes. In recent years, Cp*Ir(III) has been explored for C−H carbenoid functionalization, with a good number of reports on the C−H alkylation reaction.[68,69] In this regard, we have been interested to explore the Cp*Ir(III) catalyst for a directed C−H activation and annulation employing *α*-diazocarbonyl compounds, especially for synthesizing isoquinolines, isoquinolinediones, and isoquinolinones.

Iridium (III)-Catalyzed Synthesis of Isoquinoline *N*-Oxides

The heterocyclic *N*-oxide derivatives represent an important structural unit found in various natural products, pharmaceutical agents, and chiral ligands.[70] The chemistry and application of heterocyclic *N*-oxides have always received much attention due to their usefulness as synthetic intermediates and their biological importance. The traditional synthesis of *N*-oxides involves the direct oxidation of parent heterocycles with a stoichiometric amount of peroxides or peracids.[71] The major limitations of these methods are the prerequisite of a completely fabricated

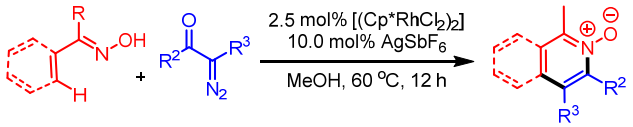
heterocyclic unit and the compatibility of the sensitive functional groups present on the substrate. The use of transition-metal catalyzed transformations had, to some extent, addressed the oxidation under mild conditions. In recent times, C−H activation approaches are preferred over the traditional methods, especially in the context of the synthesis of *N*-oxide derivatives.[64] There is considerable literature dealing with the metal catalyzed reactions for the *N*-oxide of isoquinoline and pyridine derivatives but only a few references are available concerning the C−H activation and annulation cascade.[65]

In 2013, Huang and co-workers have documented the inaugural entry for the oxime directed C–H activation annulation reaction for the selective synthesis of isoquinoline *N*-oxides.[72] In this study, they showed that the palladium catalyzed acid assisted reaction undergoes concerted metallation deprotonation followed by carbopalladation and transmetallation to yield polysubstituted isoquinoline *N*-oxides. However, the requirement of high temperature and a stoichiometric amount of acids and alkyne scope are the major limitations of this approach (Scheme 44).



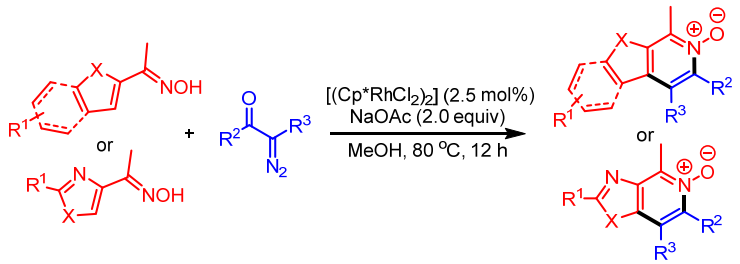
Scheme 44. *Palladium Catalyzed N-Oxide Synthesis*

Recently, the Glorius group reported the first Rh(III)-catalyzed intermolecular C-H activation annulation reaction using vinyl or aryloximes and diazo compounds for the synthesis of pyridine and isoquinoline *N*-oxides (Scheme 45).[73]



Scheme 45. *Rhodium-(III) Catalyzed N-Oxide Synthesis*

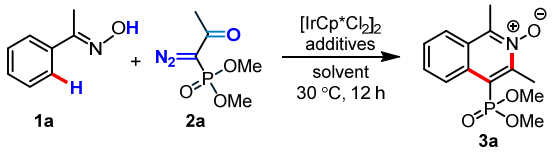
Following the Glorius group report, in 2015, Yao and co-workers showed the replacement of aryloximes with heterocycle-fused oximes to get heterocycle-fused pyridine *N*-oxides using a Rh(III)-catalyst for the C–H activation and annulation reaction (Scheme 47).[74]



Scheme 47. *Rhodium-(III) Catalyzed N-Oxide Synthesis*

As per our intention to develop the Cp*Ir(III) catalyst system and inspired with these literature reports; we envisioned the feasibility of directed C−H activation and annulation by using a *α*-diazocarbonyl compounds as a coupling partner to furnish a variety of *N*-heterocycles. Instead of altering the directing group for the current proposal, we plan to move forward with existing reported aryl and heteroaryl oximes in order to check the feasibility of the Cp*Ir(III) catalyst system. As a first step in this direction, acetophenone oxime **1a** and Ohira-Bestman's diazophosphonate **2a** have been selected as model substrates to screen the reaction parameters. After performing a few optimization experiments, we were pleased to find that the reaction proceeded very well by employing 2 mol% of the $[IrCp^*Cl_2]_2$ and 8 mol% of $AgNTf_2$ in methanol at 30 °C (Table 3, entry 2) and the required N-oxide **3a** was obtained in 95% yield. The effect of solvent is found to be very crucial. Among, various solvents screened, methanol is the best solvent, and all other solvents (CF_3CH_2OH, 1,2-DCE, THF, acetonitrile, toluene and dioxane) were ineffective for the reaction (Table 3, entries 1–9). Various silver salts such as $AgNTf_2$, $AgSbF_6$, AgOAc, $AgBF_4$, $AgOC(O)CF_3$, $LiNTf_2$ are screened for the current transformation and $AgNTf_2$ turned out to be the most effective in combination with the Cp*Ir(III) catalyst system (Table 3, entries 10–16). Interestingly, under similar conditions, a [Cp*Rh(III)] catalytic system was found to be less efficient (55% crude yield) and a $[Ru(p\text{-Cymene})Cl_2]_2$ catalytic system was found to be non-functioning for current transformation (Table 3, entries 17–18). Furthermore, when the reaction was carried out in the absence of the Ir(III)-complex under similar reaction conditions, no trace of product formation was observed. Similarly, a control experiment conducted in the absence of silver salts (the formation of **3a** was very negligible, Table 3, entries 14 and 15) showed that their presence is essential. Thus, these controlled experiments revealed that both Ir(III) and silver salts were essential for bringing the current C–H activation and annulation reaction.

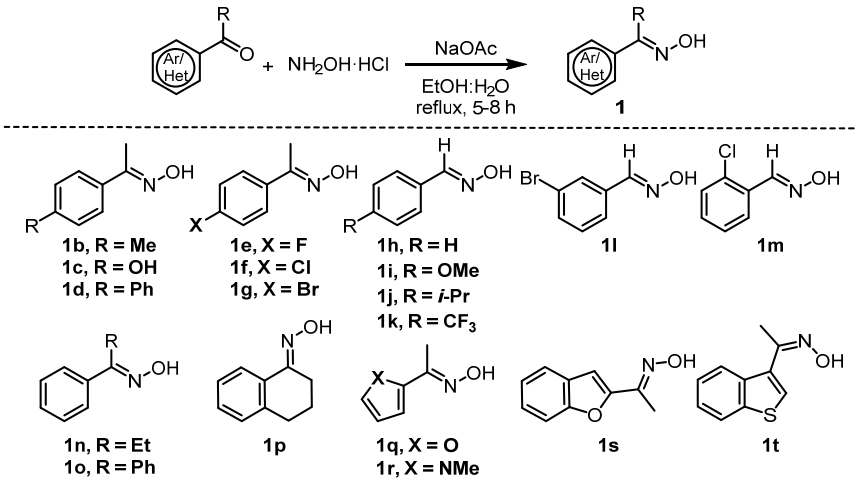
Table 3. *Optimization of Reaction Parameters*[a]



Entry	Catalyst (mol %)	Additives (mol %)	Solvent	Yield %
1	$[IrCp^*Cl_2]_2$ (4.0)	$AgNTf_2$ (16.0)	Methanol	98
2	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	Methanol	99 (95)
3	$[IrCp^*Cl_2]_2$ (1.0)	$AgNTf_2$ (4.0)	Methanol	60
4	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	CF_3CH_2OH	<5
5	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	1,2-DCE	<5
6	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	THF	<5
7	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	Acetonitrile	<5
8	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	Toluene	<5
9	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	Dioxane	<5
10	$[IrCp^*Cl_2]_2$ (2.0)	$AgSbF_6$ (8.0)	Methanol	88
11	$[IrCp^*Cl_2]_2$ (2.0)	$AgBF_4$ (8.0)	Methanol	83
12	$[IrCp^*Cl_2]_2$ (2.0)	AgOAc (8.0)	Methanol	20
13	$[IrCp^*Cl_2]_2$ (2.0)	$AgOC(O)CF_3$ (8.0)	Methanol	72
14	--	$AgNTf_2$ (8.0)	Methanol	NR
15	$[IrCp^*Cl_2]_2$ (2.0)	--	Methanol	8
16	$[IrCp^*Cl_2]_2$ (2.0)	$LiNTf_2$ (8.0)	Methanol	10
17	[RhCp*Cl2]2 (2.0)	AgSbF6 (8.0)	Methanol	55
18	[Ru(*p*-Cymene)Cl2]2 (2.0)	AgNTf2 (8.0)	Methanol	<5

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.2 equiv), in methanol (1mL) at 30 °C for 12 h.
[b]^{1}HNMR yield (CH_2Br_2 as an internal standard); isolated yield in parentheses.

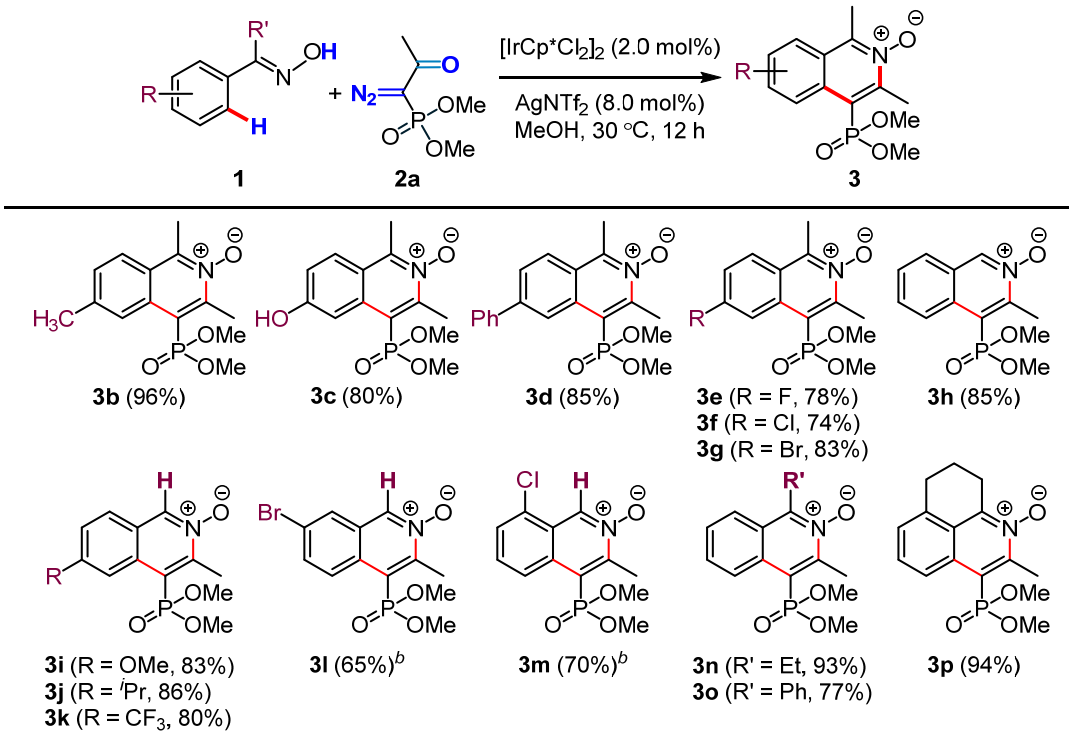
After optimizing the reaction conditions, the next plan was to expand the scope of the current reaction to arrive at a diverse set of isoquinoline *N*-oxides. The first set of substrates (aryl and heteroaryl oximes) has been synthesized following the reported methods: by refluxing a ketone or aldehyde with $NH_2OH{\cdot}HCl$ and NaOAc in ethanol followed by simple recrystallization to give the pure solid oximes in quantative yields (Scheme 46).[75]



Scheme 46. *Synthesis of Aryl and Heteroaryl Oximes*

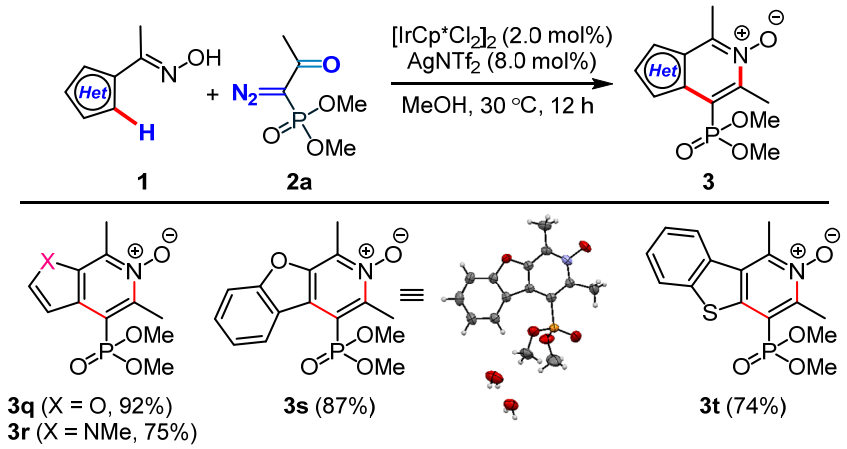
Next, after having a set of oxime substrates and optimized reaction conditions in hand, we examined the substrate scope of this transformation. A variety of aromatic oximes with different substituents react with Ohira-Bestman's diazophosphonate **2a** leading to the corresponding isoquinoline *N*-oxides in good yields (Scheme 47). Substrates bearing electron-donating groups like simple methyl (**1b**) and even free hydroxyl groups (**1c**) at the *para* position of oximes are work very well and provide the corresponding *N*-oxide products (**3b**, **3c**) in excellent yields. Similarly, oximes containing electron-withdrawing groups like phenyl (**1d**) or halogens substituted oximes (**1e**–**1g**) at *para* positions were found to be compatible under the present conditions (**3d**–**3g**).

Scheme. 47 *Substrate Scope of Aryl Oximes*[a]



Subsequently, the scope of the reaction was extended to benzaldehyde oxime derivatives **1h**–**1m**. We were gratified to find that not only benzaldehyde oxime, but also substrates with electron donating substituents (*p*-methoxy (**1i**), *p-iso*-propyl (**1j**)), and electron withdrawing substituents [*p*-CF_3(**1k**), *o*-Cl (**1m**)] were found to be compatible and provided the requisite *N*-oxide products in excellent yield (**3i-3k**, **3m**). The reactions with substrates bearing substitution at *meta*- (*m*-Br, **1l**) and *ortho*- (*o*-Cl, **1m**) positions were found to be sluggish under standard reaction conditions. However, the reaction yields could be increased to considerable amounts upon increasing the reaction temperature to 60 °C. It is important to mention here that the reaction goes selectively at the sterically less bulky position with these substrates having *meta*-substituents (**3l**). Further, the effect of substitution on the methyl side of acetophenone oxime was studied. For instance, reactions of Ohira-Bestman's diazophosphonate **2a** with propiophenone oxime (**1n**) proceeded smoothly and furnished the cyclised product **3n** in 93% yield. Similarly, under the standard conditions, the reaction of oximes derived from benzophenone (**1o**) and *α*-tetralone (**1p**) provided the corresponding cyclised products **3o** and **3p** respectively in excellent yields.

Scheme 48. *Scope of Heteroaryl Oximes*[a]



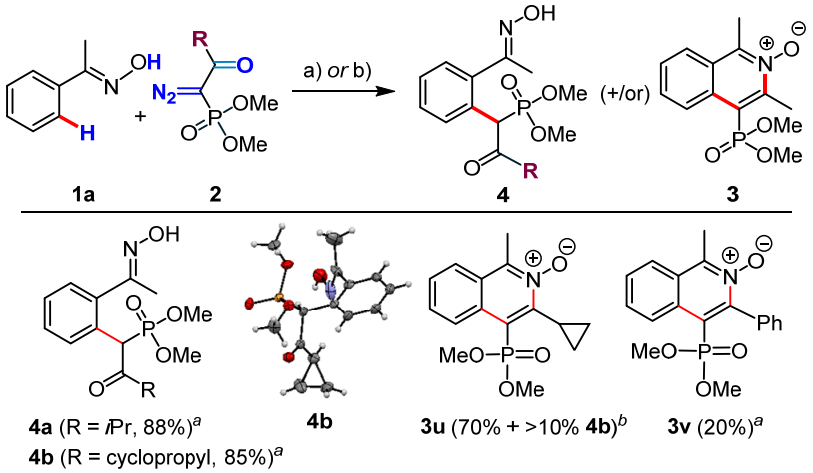
[a]*Reaction conditions: oxime (0.15 mmol),* ***2a*** *(1.2 equiv), in methanol (1mL) at 30 °C for 12 h.*

After successful conversion of aryl oximes to isoquinoline-*N*-oxide derivatives, next the feasibility of heteroaryl oxime derivatives was studied. We were pleased to see that the reaction of 1-(furan-2-yl)ethanone oxime (**1q**) with Ohira-Bestman's diazophosphonate **2a** under standard reaction conditions gave the desired 4-(dimethoxyphosphoryl)-5,7-dimethylfuro[2,3-c]pyridine 6-oxide (**3q**) in 92% yield (Scheme 48). Similarly, other heteroaromatic oximes derived from *N*-methylpyrrole (**1r**), benzofuran (**1s**), and benzothiophene (**1t**) were found to be compatible under these conditions and gave the desired **3r**–**3t**. Additionally, the structure of **3s** was confirmed by X-ray crystallographic analysis.

With the established oxime scope in hand, we next intended to explore the scope of diazo compounds. Interestingly, when simple dimethyl (1-diazo-3-methyl-2-oxobutyl)phosphonate (**2b**) was used as a substrate, only the alkylated product **4a** was observed in excellent yield, without further cyclization (Scheme 49). Along similar lines, the cyclopropyl substituted diazo compound (**2c**) also gave the alkylated product **4b** exclusively in high yield. The molecular structure of **4b** was unambiguously established with the help of single crystal X-ray structural analysis. At this stage we hypothesized that maybe the higher energy barrier for the keto-enol isomerization is the reason for the isolation of the alkylated products and presumed that the increase in the reaction temperature is required to push the reaction to the final cyclised products. In fact, when the reaction was carried out at 60 °C, the cyclised *N*-oxide product **3u** was obtained as the major product (70%) along with a minor amount of alkylated product **4b**. This observation indicates that the overall

reaction goes *via* alkylation followed by cyclization to give the isoquinoline *N*-oxide product. Interestingly, when phenyl substituted diazo compound (**2d**) was used under standard conditions, only the cyclised product **3v** was obtained in poor yield. The poor yield may be due to steric bulkiness of the diazo compounds.

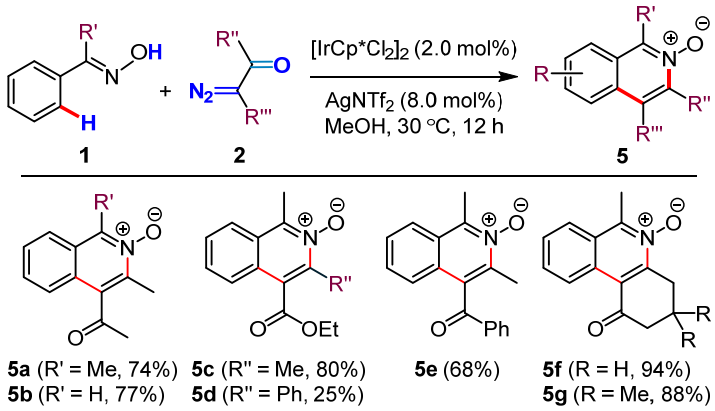
Scheme 49. *Scope of Diazo Compounds*



Reaction conditions: ***1a*** *(0.15 mmol), diazo compounds****2*** *(1.2 equiv), in methanol (1mL) [IrCp*Cl2]2 (2.0 mol%), AgNTf2 (8.0 mol%), a) 30 °C, 12 h; b) 60 °C, 12 h.*

In order to further extend the generality of our reaction, the diazo compounds without a phosphonate group have been synthesized and screened (Scheme 50). The reaction of 3-diazopentane-2,4-dione (**2e**) proceeded smoothly with both acetophenone oxime **1a** and benzaldehyde oxime **1h** to furnish 4-acetyl-3-methylisoquinoline-2-oxide derivatives **5a** and **5b** respectively in very good yield. Similarly, the reaction of ethyl-2-diazo-3-oxobutanoate (**2f**) with acetophenone oxime**1a** gave the desired product **5c** in 80% yield. As observed earlier, with the sterically bulky ethyl 2-diazo-3-oxo-3-phenylpropanoate (**2g**), the product **5d** was obtained in poor yields. Furthermore, when the reaction was performed with sterically unsymmetrical 2-diazo-1-phenylbutane-1,3-dione (**2h**), cyclization occurred exclusively with the less sterically hindered carbonyl group to give **5e** in good yields. Further extending the scope of the present reaction, cyclic diazo compounds like 2-diazocyclohexane-1,3-dione (**2i**) and 2-diazo-5,5-dimethylcyclohexane-1,3-dione (**2j**) were found to be very efficient coupling partners to afford the corresponding tricyclic products **5f** and **5g** in excellent yield.

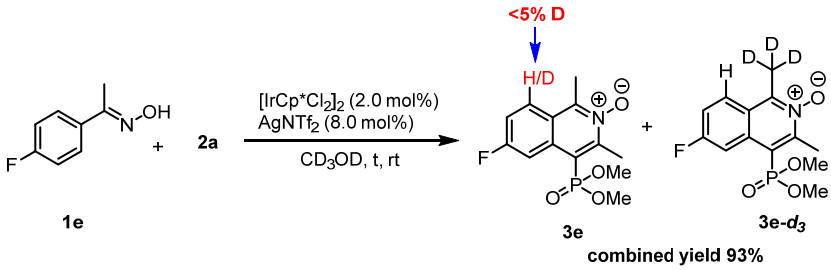
Scheme 50. *Scope of Diazo Compounds*



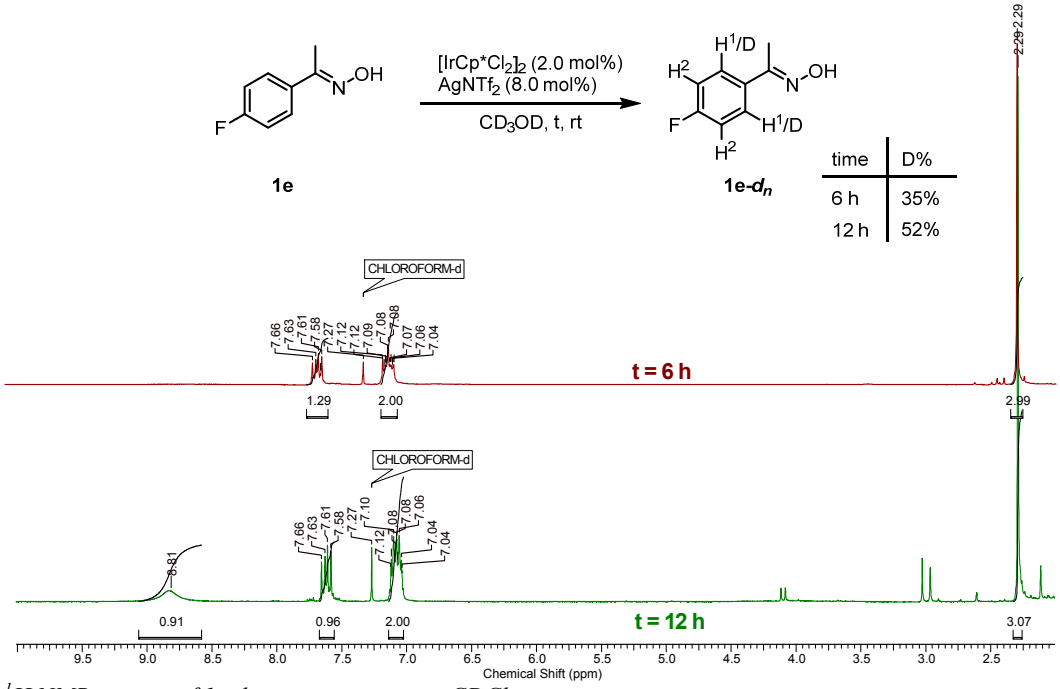
[a]*Reaction conditions:* ***1*** *(0.15 mmol), diazo compounds* ***2*** *(1.2 equiv), in methanol (1mL) at 30 °C for 12 h.*

Mechanistic Studies

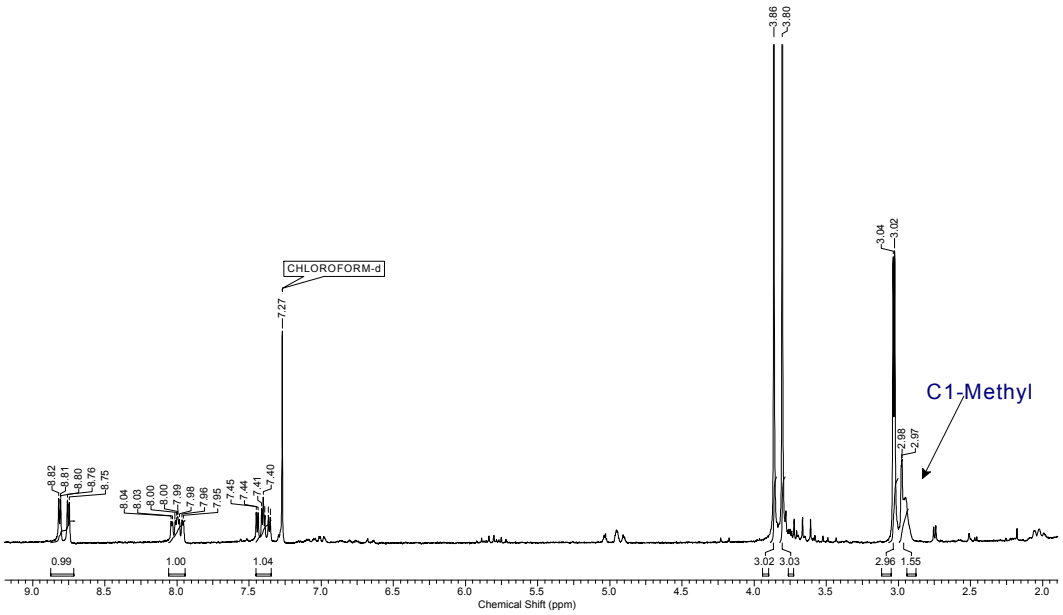
To gain some mechanistic insight, a set of preliminary control experiments have been carried out. A notable deuterium scrambling was observed when the reaction was performed in CD_3OD in the absence of the diazo compound indicating the reversibility of the C–H activation step. When the same experiment was performed in the presence of 1.2 equiv of diazo compound **2a**, after 14 h of reaction **3g** was isolated in 93% yield. Analysis of **3g** by ^{1}H NMR and ESI-MS showed no deuterium incorporation of the *ortho* proton, suggesting the C–C bond formation to be significantly faster than the back reaction of the C–H activation step.[76]



Deuterium Exchange Study in absence of Diazo compound



^{1}H NMR spectra of 1e-d_n at mention time in $CDCl_3$

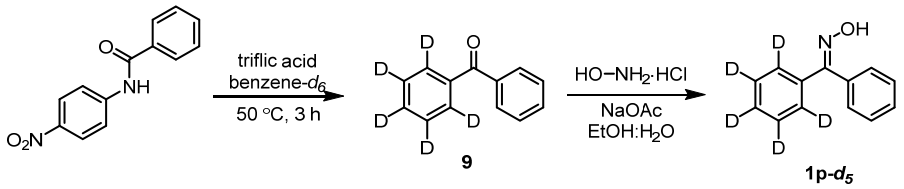


*^{1}H NMR spectra of **3e-d_n** in $CDCl_3$.*

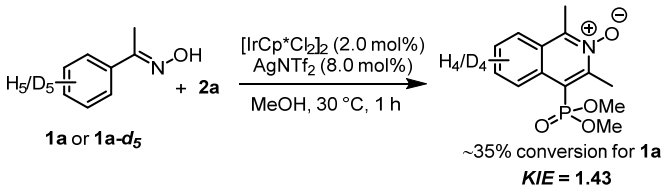
Study of Kinetic Isotop Effect

A relatively significant level of primary kinetic isotope effects (*KIE* = 1.45) was measured in parallel experiments. Interestingly, similar kinetic isotope effects (*KIE* = 1.67) were observed for the intramolecular competition reaction. Although it is not convincing at the present stage, these *KIE* values indicate that the C–H bond cleavage may be the the rate-limiting step.[77]

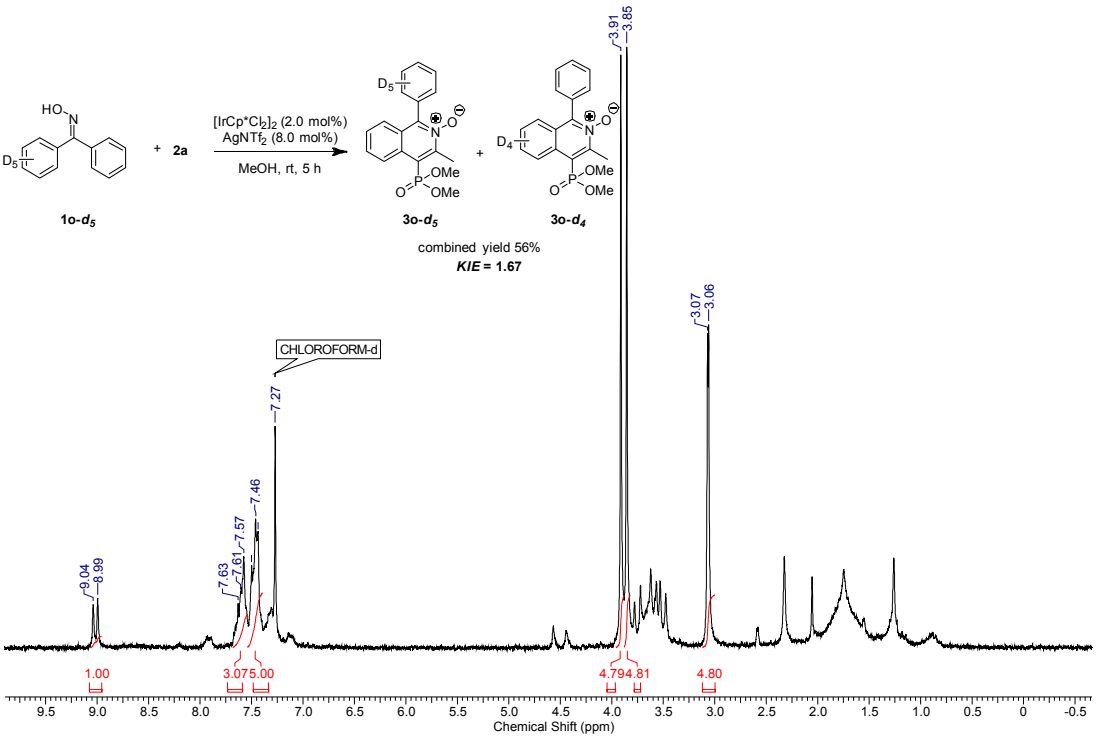
Synthesis of Compound 1p-*d*$_5$



Parallel Experiments



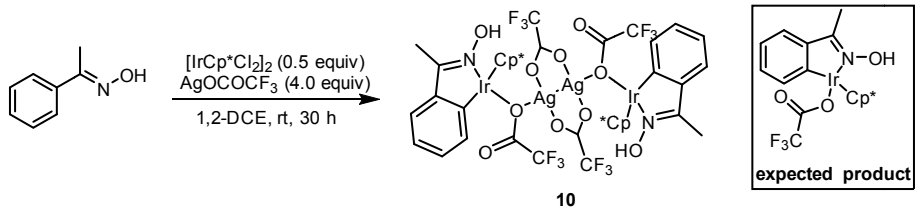
Intramolecular Compititive Experiments



*NMR spectra of **3o-d$_5$** and **3o-d$_4$** in CDCl$_3$.*

Preparation of Cyclometalated Complex 10

After treatment of acetophenone oxime **1a** with $[IrCp^*Cl_2]_2$ and excess of silver trifluoroacetate in 1,2-dichloroetane, a stable cyclometalated Ir(III) complex was obtained. Initially, we assumed this to be the monomeric Ir(III) complex. However, X-ray crystallography analysis of the complex revealed that, the complex contains two cyclometallated Iridacycles that are bridged with a binuclear silver complex (Figure 1). The occurrence of such binuclear silver carboxylate species have been documented in the literature.[78] However, to the best of our knowledge, this is the first isolation of such types of bimetallic Ir-complexes. Further, Ir-complex **10** was used as the catalyst for selected (hetero) aryl oximes to furnish **3a**, **3j** and **3t** in good to excellent yields (Scheme 51). The complex alone catalyzes the reaction without any Ag-additives to give 95% of **3a**, which indicates the relevance of the C–H activation reaction. However, we were supersised to see the previous results with the same Ag-salts results in lower yield (Table 1, entry 13).This is the first such type of bimetallic Ir-complex that can catalyze the C–H activation very efficiently.[78]



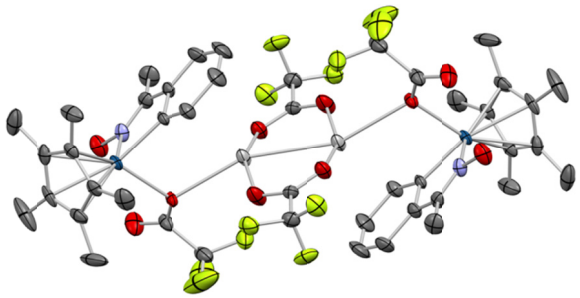
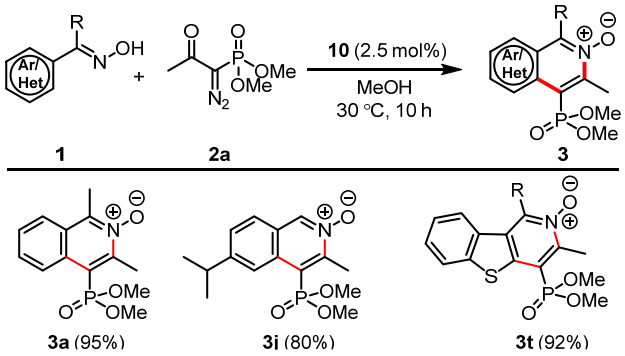


Figure 1. *ORTEP of **10**, Hydrogen Atoms are Omitted for Clarity.*

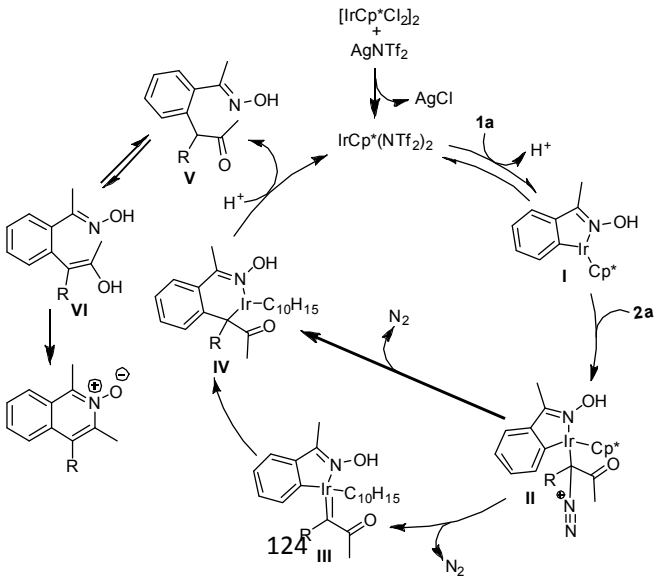
Reaction Using Cyclometalated Complexes 10



Scheme 51. *Reaction Using Cyclometalated Complexes*

Proposed Catalytic Cycle

Based on the above observed data, and precedent literature reports, a mechanistic pathway has been proposed. The first step is the generation of a cationic Ir(III) species from $[IrCp^*Cl_2]_2$ with the $AgNTf_2$ additive, which facilitates the key C−H bond activation to afford a five-membered iridacyclic intermediate **I**. The diazonium intermediate **II** may form by the coordination of the diazo compound with **I**. Generation of the carbene intermediate **III** is assumed to take place before the subsequent migratory insertion of carbene to C–Ir bond leading to **IV**. Alternatively, intramolecular 1,2-migratory insertion of the aryl group would give **IV**. Next, protonolysis of **IV** delivers the alkylated product **V**, which is supposed to be in equilibrium with the corresponding enol intermediate **VI**. Finally, intermediate **VI** undergoes dehydration either *via* 6π electro cyclization or nucleophilic cyclization to give the desired product **3a**.[79]



In summary, we have developed iridium-catalyzed addition of (hetero)aryl C–H bonds to the diazo compound to furnish isoquinoline and hereto aromatic fused pyridine *N*-oxide derivatives. The present reaction is mild, does not require any external base or oxidants and releases environment friendly water and nitrogen as the by-products. During the course of mechanistic investigations, we have isolated a rare dimer bimetallic species containing two iridacyclic units, which catalyzes the reaction without any additives.

Iridium (III)-Catalyzed Synthesis of *N*-Methoxyisoquinolinediones

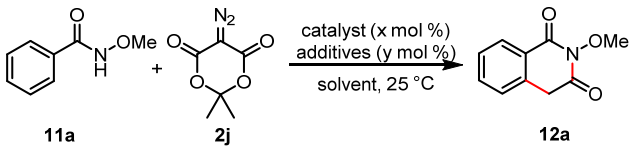
Continuing our efforts to develop a mild and efficient Ir(III)-catalytic system for the synthesis of *N*-heterocyclic compounds *via* the C–H carbenoid functionalization strategy we next focused on building the isoquinolinedione scaffold. Recently in 2015, Yi and co-workers have reported the Rh(III)-catalyzed carbene insertion C–H annulation approach synthesis of diverse *N*-methoxyisoquinolinedione *via* Rh(III)-catalyzed carbene insertion C–H annulation approach (Scheme 52).[80]

Scheme 52. *Synthesis of N-Methoxyisoquinolinedione*

Considering the widespread applications of isoquinolinedione heterocyclic units in medicinal chemistry such as aldose reductase (ALR2) inhibition, antitumor activity against the human pancreatic carcinoma cell line, potent and selective inhibition of cyclin-dependent kinase 4, and Lck kinase we were interested in developing a mild C–H functionalization method for a rapid synthesis of the key scaffold.[81] Encouraged with the recent report using Rh(III), and with the aim of extending the Ir(III)-catalyzed C–H functionalization, we have undertaken the C–H functionalization of benzamides with *α*-diazotized Meldrum's acid in the presence of air at room temperature to afford *N*-methoxyisoquinolinediones.

At the beginning of our studies, *N*-methoxybenzamide **11a** and 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (α-diazotized meldrum's acid) **2j** were taken as model substrates for reaction optimization. Different solvents were screened (MeOH, THF, dioxane and DCE) out of which DCE was found to be the best solvent for the current transformation (Table 4, entry 1-4).

Table 4. *Optimization of Reaction Conditions*[a]



Entry	Catalyst (mol %)	Additives (mol %)	Solvent	Time (h)	Yield[b] (%)
1	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	MeOH	10	25
2	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	THF	10	58
3	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	Dioxane	10	72

4	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	DCE	10	93
5	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	DCE	5	95 (90)
6	$[IrCp^*Cl_2]_2$ (2.0)	$AgSbF_6$ (8.0)	DCE	5	80
7	$[IrCp^*Cl_2]_2$ (2.0)	$AgBF_4$ (8.0)	DCE	5	72
8	$[IrCp^*Cl_2]_2$ (2.0)	AgOAc (8.0)	DCE	5	45
9	$[IrCp^*Cl_2]_2$ (2.0)	$AgOC(O)CF_3$ (8.0)	DCE	5	61
10	$[IrCp^*Cl_2]_2$ (1.0)	$AgNTf_2$ (4.0)	DCE	5	68
11	$[IrCp^*Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	DCE	1	60
12	$[IrCp^*Cl_2]_2$ (2.0)	$LiNTf_2$ (8.0)	DCE	5	15
13	$[IrCp^*Cl_2]_2$ (2.0)	None	DCE	5	12
14	None	$AgNTf_2$ (8.0)	DCE	5	0
15	$[RhCp^*Cl_2]_2$ (2.0)	$AgSbF_6$ (8.0)	DCE	5	<5
16	$[RhCp^*Cl_2]_2$ (2.0)	$AgSbF_6$ (8.0)	THF	5	<5
17	[Ru(*p*-Cymene)$Cl_2]_2$ (2.0)	$AgNTf_2$ (8.0)	DCE	5	<5

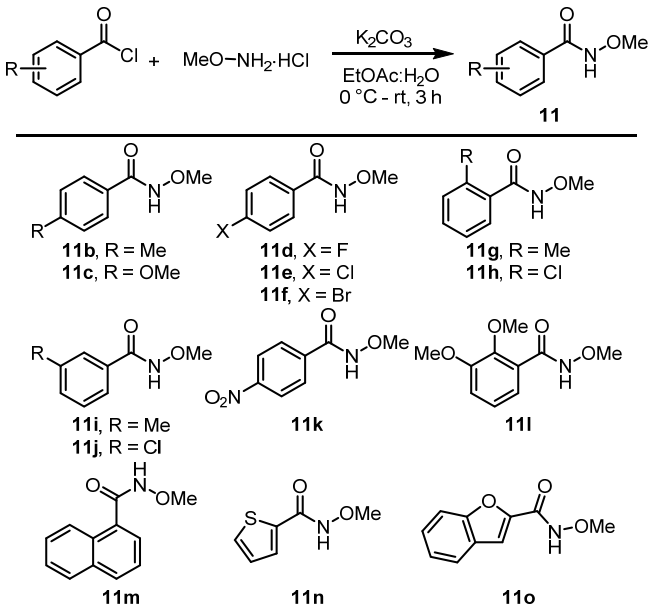
[a]Reaction conditions: **11a** (0.15 mmol), **2j** (1.1 equiv),with catalyst and additives in solvent (1 mL) at 25 °C. [b] Crude yield was mentioned based on ^1H NMR (CH_2Br_2 as an internal standard); isolated yield in parentheses.

The reaction efficiency decreased to 68% when the catalyst loading was reduced to 1.0 mol % (Table 4, entry 10). Also, interrupting the reaction after 1 hour, gave only 60% of product **12a** (Table 4, entry 11). In the absence of either Ir-catalyst or silver additive, only trace amount of product formation was noticed (Table 4, entries 13-14). Very poor yield was obtained when $LiNTf_2$ was used in lieu of the silver species (Table 4, entry 12). Among various silver additives like$AgNTf_2$, $AgSbF_6$, AgOAc, $AgBF_4$ and $AgOC(O)CF_3$ screened, $AgNTf_2$ was found to have the best combination with Ir-catalyst (Table 4, entries 5-9). Interestingly, commonly used Rh-and Ru-catalytic systems were found to be ineffective under present conditions (Table 4, entries 6–7). Surprisingly, reaction with other *N*-substituted benzamides like *N*-(*tert*-butyl)benzamides, *N*-methylbenzamide or *N*-hydroxybenzamide were found to be sluggish. After screening various reaction parameters, we were pleased to observe that the desired *N*-methoxyisoquinolinedione **12a** could be obtained in 92% yield using 2.0 mol % of $[IrCp^*Cl_2]_2$ and 8.0 mol % $AgNTf_2$ in 1,2-dichloroethane (1,2-DCE) at room temperature.

With the best conditions in hand, we next examined the scope of substituted benzamides for the present reaction. For this, various substituted *N*-methoxybenzamides have been synthesized by the using reported procedure (Scheme 53): To a solution of K_2CO_3 in a mixture of EtOAc/H_2O (2:1) was added *O*-

methylhydroxylamine hydrochloride. The resulting solution was cooled to 0°C, followed by dropwise addition of the benzoyl chloride. The reaction mixture was warmed to room temperature and stirred overnight. The organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The pure products were obtained by flash column chromatography.[82]

Scheme 53. *Synthesis of substituted Benzamides*



After having a variety of substituted benzamides in hand, we proceeded for the scope of the reaction. Various substituted *N*-methoxybenzamides were treated with α-diazotized Meldrum's acid diazophosphonate **2j** to furnish the corresponding *N*-methoxyisoquinolinedione derivatives (Scheme 54). Generally, the reaction proceeded very smoothly at room temperature regardless of the position as well as electronic nature of the substituents on the aryl ring. Benzamides having electron donating groups such as methyl (**11b**), methoxy (**11c**) at the *para* position worked well and gave the products in high yield (**12b**, **12c**). Similarly electron withdrawing groups like halogens (**11d**–**11f**) at *para* position furnished the corresponding products (**12d**–**12f**). However, the benzamides bearing a strongly electron withdrawing nitro group (**11k**) resulted in slightly lower yield (**12k**). Similarly, benzamides with an *ortho*-substituent such as methyl (**11g**), chloro (**11h**) were found to be quite compatible and gave the desired product in good yields (**12g**, **12h**). It was observed that substitution at the *meta*-position plays a crucial role in controlling the

regioselectivity of the present C–H annulation. For instance, when *m*-methyl benzamide was used (**11i**), C–H activation occurred predominantly at the less hindered position and gave exclusively product **12i**. On the other hand the *m*-chloro benzamide (**11j**) gave the mixture of regiomers (**12j-i** and **12j-ii**) in 1.2:1 ratio. Also, 2,3-dimethoxybenzamide (**11l**) and polyaromatic naphthalene benzamide (**11m**) were found to be compatible under present reaction conditions with good yields (**12l** & **12m**).

Scheme 54. *Benzamide Substrate Scope*[a]

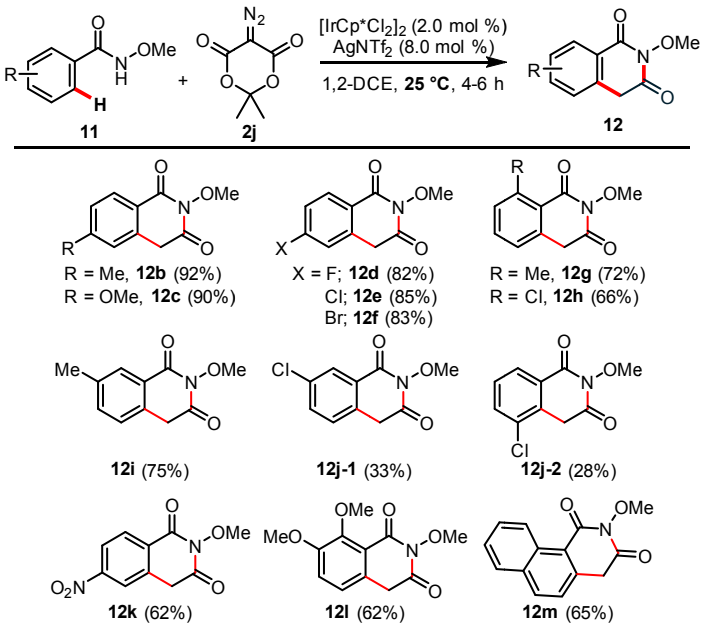
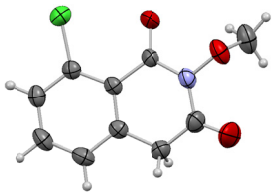
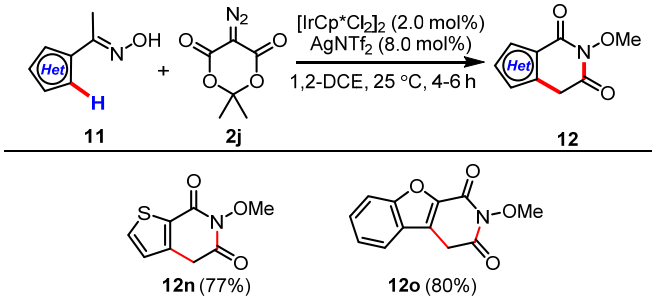


Figure 3. *Ortep Diagram of* ***12h***



After successful conversion of *N*-methoxybenzamides to *N*-methoxyisoquinolinedione derivatives, next, the feasibility of heterocyclic amide derivatives was studied.

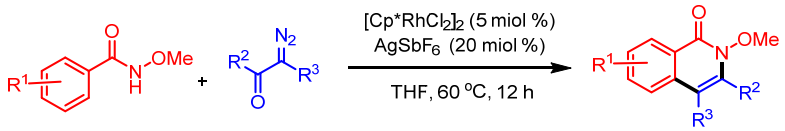
Scheme 55. *Heterocyclic Amide Substrate Scope*[a]



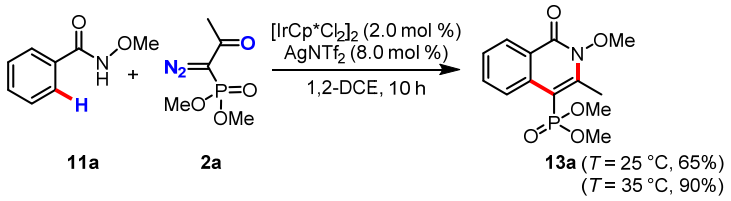
We were pleased to see that the reaction of *N*-methoxythiophene-2-carboxamide (**11n**) and *N*-methoxybenzofuran-2-carboxamide (**11o**) with Meldrum's acid diazophosphonate **2j** under standard reaction conditions gave the desired6-methoxythieno[2,3-c]pyridine-5,7(4H,6H)-dione (**12n**) and 2-methoxybenzofuro[2,3-c]pyridine-1,3(2H,4H)-dione (**12o**) respectively in high yields (Scheme 55).

Iridium (III)-Catalyzed Synthesis of *N*-methoxyisoquinolinone

After successful exploration of the aryl and heteroaryl *N*-methoxyisoquinolinedione synthesis, we next focused on extending the present Ir(III)-catalytic system for the synthesis of related isoquinolinones. Isoquinolinones and pyridinonesare important structural units that is present in many natural products. In addition, isoquinolinone is a privileged scaffold that has been used widely in the drug discovery programs related to cancer, HIV and cardiac diseases.[83] Due to this diverse biological activity, the synthesis of isoquinolinones has received much attention in recent years. Typical methods include the base-promoted condensation of 2-(bromomethyl)benzonitrile, the rearrangement of 2-(2-benzofuranyl)benzonitriles, the double metalation of arylbenzamides, the cyclization of 2-chloro benzonitriles and *β*-ketoesters, and Ugi and Heck reactions. Among the several reported methods, the cyclization of aryl amides and alkynes catalyzed by transition metals is the most accepted. In this context, the recent report of Wang and co-workers employing a Rh(III)-catalyzed C–H annulation of benzamides with the diazo compounds (Scheme 56)[84] is interesting and has been identified as a suitable system for exploring with the Ir-catalysts.



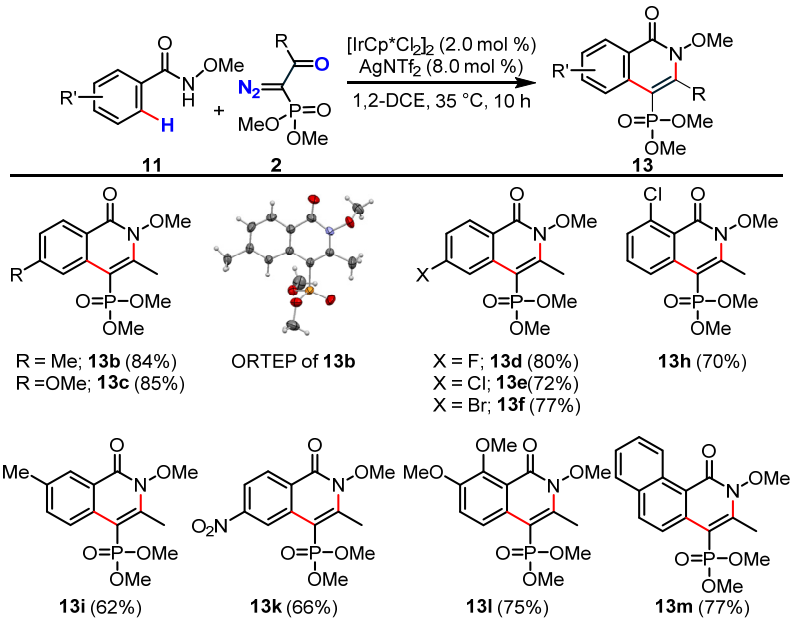
Scheme 56. *Wang Report for Isoquinolinone*



Scheme 57. *Synthesis of N-Methoxyisoquinolinone*

As foretold, the treatment of *N*-methoxybenzamide (**11a**) with the Ohira-Bestmann's diazo phosphonate **2a** under present Ir(III)-catalytic conditions afforded the desired *N*-methoxyisoquinolinone **13a** in 65% yield. Surprisingly, the product yield was increased up to 90% by running the reaction at a slightly higher temperature (35 °C) for 10 hours (Scheme 57). Upon slightly altering with same conditions by simple change in temperature, we received ample results for our proposed reaction (finally the reaction proceeded very well by using 2 mol% of the $[IrCp^*Cl_2]_2$ and 8 mol% of $AgNTf_2$ in 1,2-DCE at 35 °C).

Scheme 58. *Scope of N-Methoxyisoquinolinone Synthesis*[a]

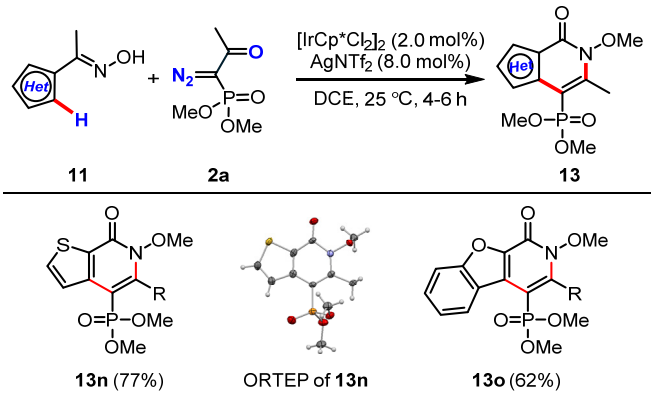


[a]*Reaction conditions:* ***11*** *(0.15 mmol),* ***2a*** *(1.2 equiv), in 1,2-DCE (1 mL). Isolated yields are given.*

With these optimized conditions in hand, the scope of this reaction has been examined by employing a variety of benzamides. As shown in Scheme 58, the current annulation reaction is compatible with the benzamides havingboth electron-donating

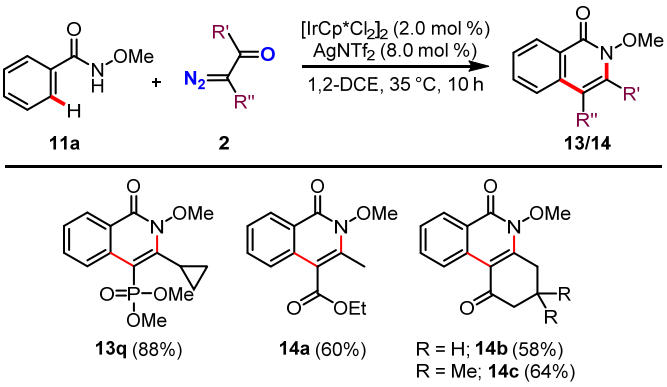
[methyl (**11b**), methoxy (**11c**)] and electron-withdrawing groups (halogens, **11d–11f**) present on the *para* position of *N*-methoxybenzamide. The compounds underwent C–H activation-annulations smoothly to furnish the corresponding *N*-methoxyisoquinolinone derivatives (**13b–13f**) in good to very good yields. Also, the reaction of benzamide **11k** bearing a strong electron withdrawing nitro group proceeded smoothly and gave the corresponding product **13k**. At the same, time *o*-chloro (**11h**) and *m*-methyl (**11i**) *N*-methoxybenzamides gave the corresponding *N*-methoxyisoquinolinone in comparable yields (**13h** & **13i**). Next, the amides derived from 2,3-dimethoxybenzoic acid (**11l**) and naphthalene-1-carboxylic acid (**11m**) were also found to be compatible with the present conditions (**13l** & **13m**).

Scheme 59. *Scope of N-Methoxy-Heterocyclic-Carboxamides*[a]



After successful conversion of aryl *N*-methoxybenzamides to *N*-methoxyisoquinolinone derivatives, next the feasibility of heteroaryl *N*-methoxybenzamides derivatives was studied. We were pleased to see that the reaction of *N*-methoxythiophene-2-carboxamide (**11n**) with Ohira-Bestman's diazophosphonate **2a** under standard reaction conditions gave the desired heterocyclic *N*-methoxyisoquinolinone **13n** in 77% yield (Scheme 59). The structure of **13n** was confirmed by X-ray crystallographic analysis. Similarly, *N*-methoxybenzofuran-2-carboxamide (**11o**) was found to be compatible under these conditions and gave the desired product **13o**.

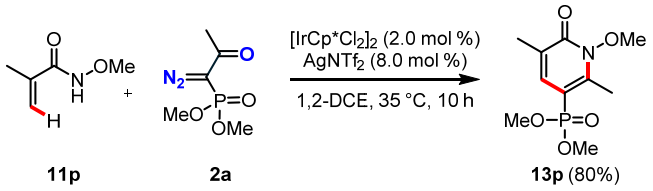
Scheme 60. *Scope of Diazo Compounds*[a]



In order to further extend the generality of our reaction, we then explored the substituent effect on the diazo compound by changing the carbonyl substituent. Likewise, the treatment of the cyclopropyl substituted diazo compound (**2c**) gave the expected product **13q** in high yield. Similarly, the diazo compounds without a phosphonate group have been screened, in order to afford various *N*-methoxyisoquinolinonederivatives (Scheme 60). In case of ethyl 3-diazo-2,4-dioxopentanoate (**2f**), the product **14a** was obtained in good yield. Equally, the cyclic α-diazocarbonyl compounds like 2-diazocyclohexane-1,3-dione (**2i**) and 2-diazo-5,5-dimethylcyclohexane-1,3-dione (**2j**) furnished the corresponding tetrahydrophenanthridinone derivatives (**14b**, **14c**) in good yields.

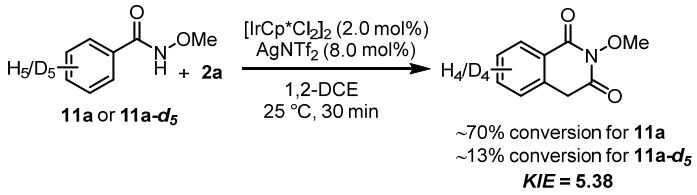
Further, the scope of reaction was examined with an acyclic amide. The treatment of *N*-methoxymethacrylamide (**11p**) with Ohira-Bestmann's diazo phosphonate **2a** under the standard conditions gave the corresponding pyridinone (**13p**) in high yield. Successful formation of pyridinone proves the generality of this reaction (Scheme 61).

Scheme 61. *Reaction of N-Methoxymethacrylamide*

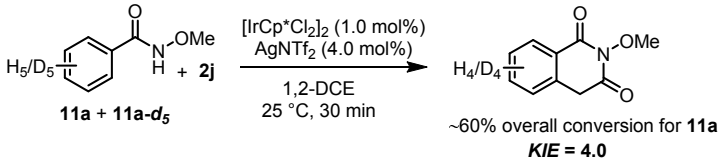


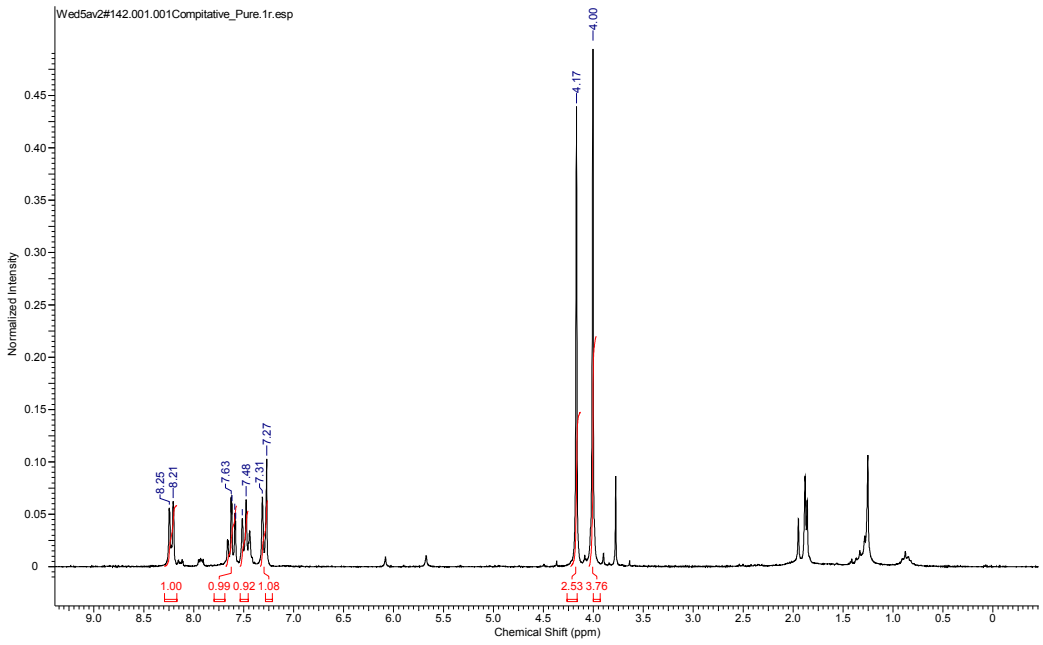
Mechanistic Investigation

Next, in order to understand the course of this reaction, a series of preliminary experiments were carried out. The simple benzamide **11a** and its deuterated analogue **11a-d$_5$** have been subjected for the annulation separately and in competition with the diazo compounds **2a**. A significant level of primary kinetic isotope effects (*KIE* = 5.38) were measured in parallel experiments. Interestingly, similar kinetic isotope effects (*KIE* = 4.0) were observed in the intermolecular competition reaction. Together, these studies suggested that C–H bond cleavage is most likely the rate determining step.[77]



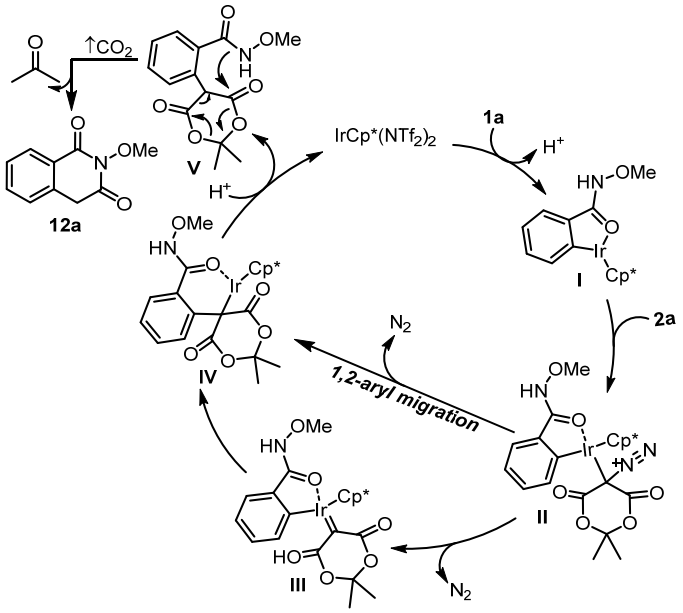
Competitive Experiments





*^{1}H NMR spectra of **3a-d$_5$** and **3a-d$_4$** in $CDCl_3$*

Based on the experimental results and precedent literature reports, a plausible catalytic pathway is proposed.[79] First, a cationic [Cp*Ir(III)] species will react with benzamide through the key C–H bond cleavage step to form the five-membered iridacyclic intermediate **I**. Coordination of the diazo compound with **I** will afford the diazonium species **II** and then the release of N_2 will form the Ir-carbene species **III**. Subsequent migratory insertion of carbene to the Ir–C bond would form the six-membered iridacyclic intermediate **IV**. Alternatively, intermediate **IV** will form *via* intramolecular 1,2-migratory insertion of the aryl group. Next, protonation of **IV** delivers the alkylated intermediated **V** and regenerates the reactive [Cp*Ir(III)] species. Intermediate **V** then undergoes annulations *via* tandem addition, elimination, decarboxylation and protonation to furnish the desire product **12a**.

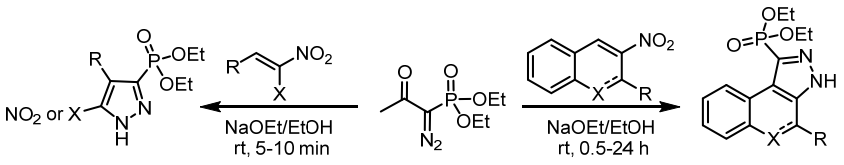


Fluoride-Mediated Dephosphonylation of *α*-Diazo-*β*-carbonyl Phosphonates

In 1971, Seyferth–Gilbert developed a reliable and operationally simple reagent which is widely employed in organic synthesis for the homologation of an aryl ketone (or aldehyde) to give corresponding terminal or internal alkynes.[85] Further in 1996, Bestmann and co-workers circumvented the disadvantage of Seyferth–Gilbert protocols like the use of strong bases, low temperatures and inert gas techniques by employing dimethyl-1-diazo-2-oxopropylphosphonate as a stable precursor for dimethyl (diazomethyl)phosphonate. This diazophosphonate has been named as the Ohira-Bestmann reagent.[86] Because of its simple one step preparation, commercially availability and mild conditions employed; this reagent has become a very popular for a one carbon homologation of various aldehydes. It is noteworthy that this mild method for generating alkyne provides a highly general solution to the fundamental problems that are associated with the traditional methods.[87]

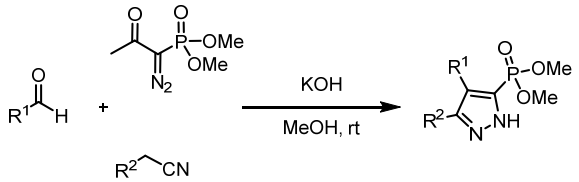
The OBR is characterized by a fully functionalized diazomethane having pendant acyl and phosphonyl groups on the central carbon. The alkynylation of aldehydes that encashes the carbene reactivity of the OB reagent comprises a net loss of all the three functional units around the central carbon. Besides its established and widespread utility in alkynes synthesis, the diverse functionality present in OBR provides an opportunity for its chemoselective functionalization. Thus, the selective manipulation of this reagent to retain some of these functional units in the end products is an attractive application that has been attempted nowadays.[88] Most recent striking work by using diazo-phosphonates is the trapping of the (diazomethyl)phosphonate anion intermediate and its utilization by apparent (3 + 2)cycloaddition process with conjugated olefins and imines and with alkynes, resulting in the formation of pyrazolyl-/triazolyl phosphonates.[89] The presence of the pyrazole unit in various marketed drugs and the easy introduction of the phosphonate group has led to the rapid exploration of this area.[90]

In 2007, Namboothiri and co-workers reported the inaugural entry in this area with a report on 1,3-dipolar cycloaddition of the in situ generated anion of diethyl 1-diazomethylphosphonate with conjugated nitro alkenes providing regioisomerically pure phosphonyl pyrazoles (Scheme 62).[89a]



Scheme 62. *Synthesis of Phosphonyl pyrazoles*

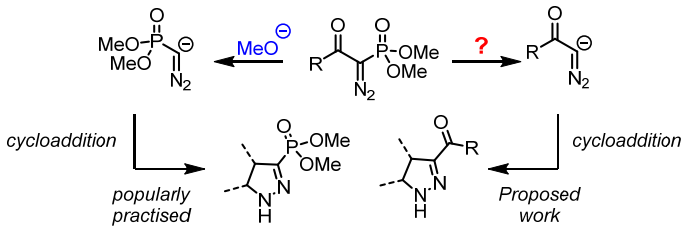
In 2010, Smietana and co-worker developed a simple process that comprises of using Ohira-Bestmann reagent in a multicomponent reaction comprising of condensation of aldehydes with alkyl nitrile and the cycloaddition of the diazophosphonate anion derived from the OBR and subsequent decynation leading to the 4,5-disubstituted pyrazole-3-phosphate derivatives. After these primary reports, convincing progress has been made in this area. The easy introduction of a phosphate group into the pharmaceutically important pyrazole scaffold was indeed a major attraction for the cycloadditions of the phosphonate derived from the OBR reagent (Scheme 63).[89b]



Scheme 63. *Access to Phosphonyl Pyrazole from Aldehydes*

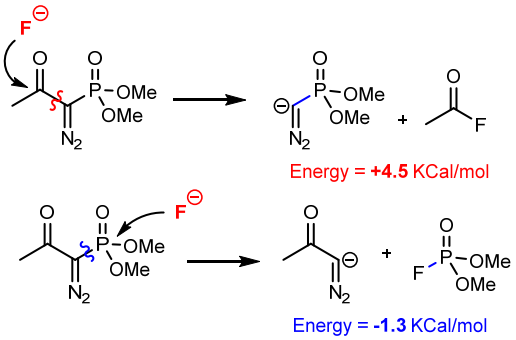
From a large number of reports with the OBR, it is clear that OBR trivially loses the acyl group with the phosphonate group carried forward in the end products. On the other hand, in the classical alkynylation, the OBR loses all the pendant groups on the central carbon by the end of the alkyne construction. On the other hand, in the annulation reactions that have been documented above, OBR selectively loses the diazo group. In this context, we wondered about another possible reactivity pathway of OBR that seems to be never explored, retaining the acyl group in place of the phosphonate group. This is an attractive proposal especially when employed in combination with (3 + 2) cycloaddition, where it provides more substituent diversity and a provision for further functionalization. Remarkably, this aspect has never been explored with a preconceived dogma of considering OBR as a surrogate for the (diazomethyl)phosphonate anion. Inspired by literature reports and in continuation of our interest on α-diazocarbonyls for *N*-heterocycle synthesis, we started a program on

examining the possibility of displacing of the phosphonate group in place of acyl (Scheme 64).



Scheme 64. *Proposed Strategies for Pyrazole Synthesis*

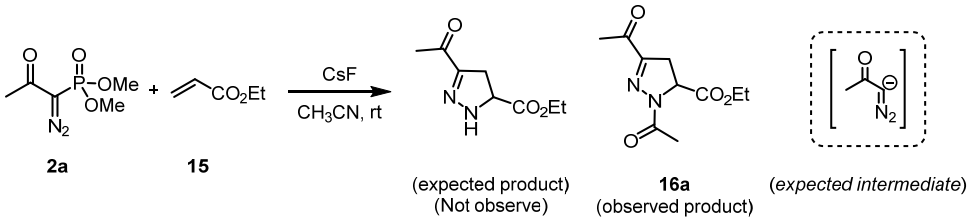
Our plan for the selective C–P bond cleavage in OBR is about choosing an appropriate base that can selectively react with the phosphorous centre. In this context, we have considered fluoride as a possible mediator considering its smaller size, weak basicity (*pKa* of HF = 3.5, MeOH~15.5 and *tert*-BuOH~18) and, importantly, because of its affinity for a phosphorous center.[91] Indeed, preliminary DFT calculations of the reactions involving the fluoride ion mediated displacement of either acyl or the phosphonyl groups revealed that the latter process is an endothermic process (ΔE = –1.3 kcal/mol) and is preferred over the former (ΔE = +4.3 kcal/mol) (Scheme 65).



Scheme 65. *Preliminary DFT Calculations*

Having this information in hand, the preliminary experiments were conducted by employing stoichiometric amounts of OBR (**2a**), ethyl acrylate (**15**) and cesium fluoride in acetonitrile at room temperature. Despite the reaction being sluggish, the formation of a new product in substantial amounts was observed. The chromatographic purification of this incomplete reaction led to isolation of this new product **16a** in 34% yield (Table 5, entry 1). The analysis of the spectral data of **16a** led to the identification of this compound as ethyl 1,3-diacetyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate, thus endorsing the validity of our hypothesis, although the intended initial N-H pyrazole underwent further *N*-acylation by the OBR reagent

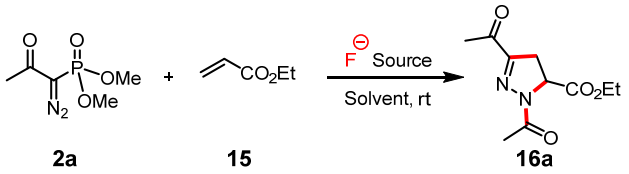
(Scheme 66). The *N*-acylation with OBR has been not yet documented. However, it can be expected considering basicity of the Δ^2-pyrazoline [pKa ~ 15][92] which is close to that of methanol [pKa ~ 15.5] and corroborating with the *N*-acylation of pyrrolidine with ethyl diazoacetoacetate.[93] Considering this, further optimization studies have been conducted by varying the amount of OBR (**2a**) and CsF with respect to the acrylate **15**.



Scheme 66. *Observations from Preliminary Experiments*

Subsequent experimentation with varying concentrations of reagents/base revealed that the use of 2.2 equiv of OBR **2a** and 3.0 equiv of CsF in acetonitrile as a solvent improved the reaction outcome with the isolation of pyrazole **16a** in 88% yield (Table 5, entry 4). The use of other fluoride sources such as tetra butyl ammonium fluoride (TBAF) and KF/18-crown-6 were not beneficial (Table 5, entry 8–10). Also, the reactions carried out below room temperature were not efficient (Table 5; entry 6–7). Instead of acetonitrile, the use of other solvents (such as THF) reduced the product formation (Table 5; entry 7–10). It is important to mention here that during the whole optimization study, we were unable to trap or isolate the free N–H pyrazole intermediate.

Table 5. *Observations During Reaction Optimization*[a]



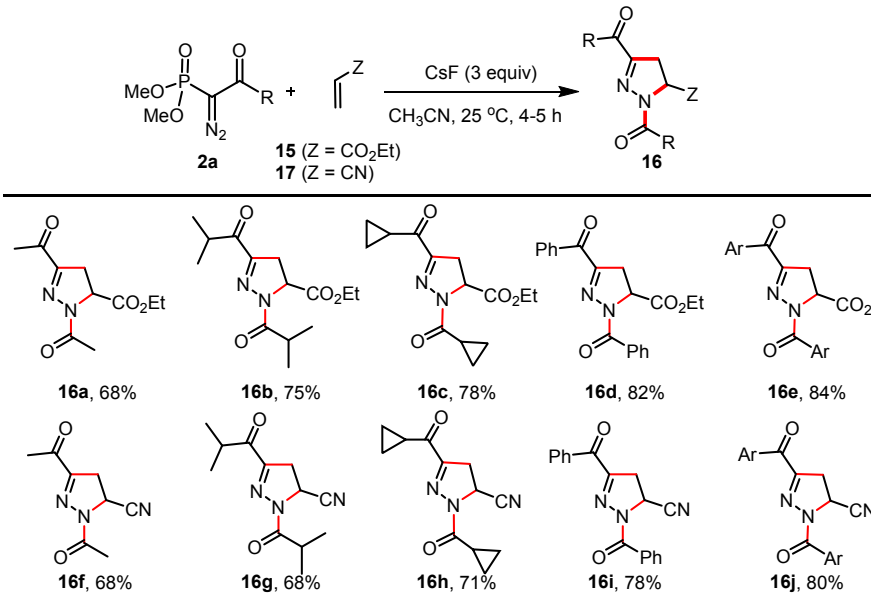
Sr. No	BOR, **2a** (equiv)	$F^{\ominus}$ Source (equiv)	Solvent	**16a** Yield[b] (%)
1	1.1	CsF (2.0)	CH_3CN	34
2	1.1	CsF (3.0)	CH_3CN	35
3	2.2	CsF (2.0)	CH_3CN	61
4	2.2	CsF (3.0)	CH_3CN	88
5	3.0	CsF (5.0)	CH_3CN	89
6[c]	2.2	CsF (3.0)	CH_3CN	50
7[d]	2.2	CsF (3.0)	THF	75

8	2.2	TBAF (3.0)	THF	39
9	2.2	TBAF (5.0)	THF	57
10	2.2	KF (3.0) & 18-crown-6 (3.0)	THF	42

[a]All reactions were carried out on approximately a 0.3 mmol scale at a 0.08 M concentration. All reagent and substrate addition was done at room temperature (25 °C), stirred for the next 4-5 h. [b]Isolated yields. [c]Reaction addition and stirring continued at -10 °C for 10 h. [d]Substrate addition at room temp., and stirred at 60 °C for 5 h.

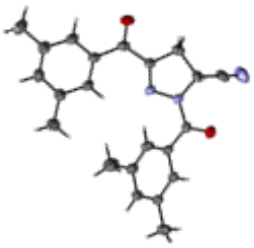
Once we had the optimized reaction conditions in hand, we proceeded further to expand the scope of the reaction and build a library of novel substituted 4,5-dihydro-pyrazoles (Scheme 67). In this context, a wide range of diazo phosphonates containing aliphatic (*i*so-propyl (**2b**), cyclopropyl (**2c**)), aromatic (phenyl (**2d**), 3,5-dimethylphenyl (**2l**)), heteroaromatic [2-(*N*-methylindolyl] (**2m**) and carboxyl groups (**2k**) have been prepared and employed in the current reaction using ethyl acrylate as the dipolarophile. It was found that the reactions with the substrates having an aliphatic group next to carbonyl, such as –Me (**2a**), -*i*-propyl (**2b**), and –cyclopropyl (**2c**) provided corresponding products **16a–16c** in good to excellent yields. Also, substrates having aromatic groups such as phenyl (**2d**) and 3,5-dimethyl-phenyl (**2l**), reacted smoothly and gave the corresponding products in excellent yields. However, the reactions with indole-derived (**2m**) and with diazophosphonate having the carboxylate group (**2k**) were found to be sluggish and gave complex reaction mixtures. In parallel, we have also examined the compatibility of acrylonitrile **17** as a dipolarophile in the current reaction. The reactions with acrylonitrile also proceeded smoothly with all aliphatic and aromatic substrates giving **16f–16j** in very good yields. The structure of **16j** was confirmed by single crystal X-ray diffraction studies (Figure 5).

Scheme 67. *Scope of 4,5-Dihydro-Pyrazole Synthesis*[a]

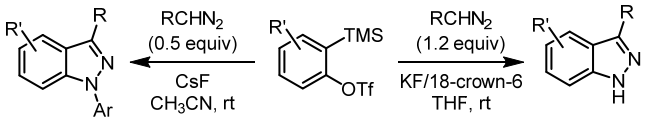


[a]*Reaction conditions:* ***15*** *(2.2 equiv),* ***2a*** *(0.25 mmol), in CH_3CN (1 mL). Ar = 3,5-diMe-phenyl.*

Figure 5. *Ortep Diagram of* ***16j***

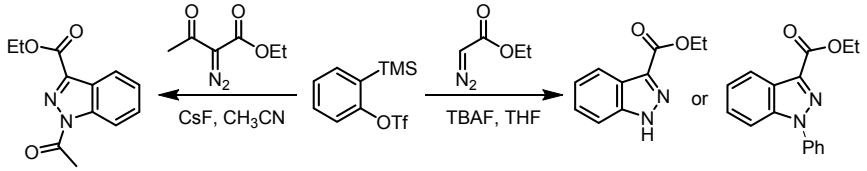


After this initial success, we next examined the possibility of extending the scope of the current transformation for indazoles synthesis employing aryne intermediates as dipolarophiles.[94,95] In 2007, Yamamoto[94a] and Larock[95a] groups reported the synthesis of indazoles employing a 1,3-dipolar cycloaddition of benzynes with diazomethane derivatives (Scheme 68). In these reports, CsF or KF have been employed for the *in situ* generation of arynes that subsequently undergoes a (3 + 2) cycloaddition with the diazo compound. As shown in the Scheme 70, either N–H or N–aryl indazoles are obtained depending upon the conditions and reaction stoichiometry.



***Scheme 68**. Synthesis of Indazoles*

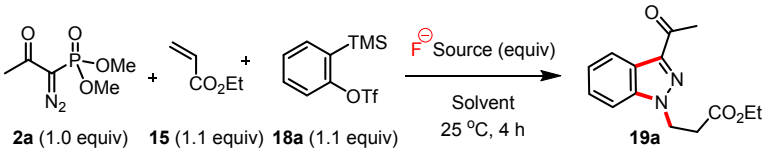
The *N*-functionalization of the initially formed N–H indazole is a competing reaction and requires another equivalent of aryne precursor for a successful product outcome. Interestingly, when ethyl diazoacetoacetate was employed, the resulting cycloaddition products underwent acyl migration to afford 1-acylindazole-3-carboxylate (Scheme 41).



***Scheme 41**. Diazocarbonyl (3 + 2)Cycloadditions with Aryne*

These earlier reports revealed that efficient trapping of the *insitu* generated indazolyl anion is warranted for a successful outcome. This indeed has revealed the possibility of developing a three-component process involving the OBR reagent. Accordingly, we planned the synthesis of 1,3-disubstituted indazoles by (3 + 2) cycloaddition of *insitu* generated aryne and (*α*-acyl)diazomethane anion and the trapping of intermediate N–H indazole *via* an aza-Michael addition reaction employing conjugated olefins. In this regard, the initial experiments were carried out by employing the OBR **2a** (1 equiv), benzyne precursor **18a** (1.1 equiv), and ethyl acrylate **15** (1.1 equiv) and by varying the concentration of CsF (3 – 6 equiv) in CH_3CN at room temperature. The results with the use of 6 equiv CsF are encouraging and the reaction was completed within 4 h and gave the desired product **19a**in 85% yield. As observed earlier, the change of the fluoride source from CsF to TBAF and KF/18-crown-6 led to a large decline in the yield of isolated **19a** from 85% to 36-57% (Table 6, entry 7 & 8).

***Table 6.** Optimization for Indazoles*[a]



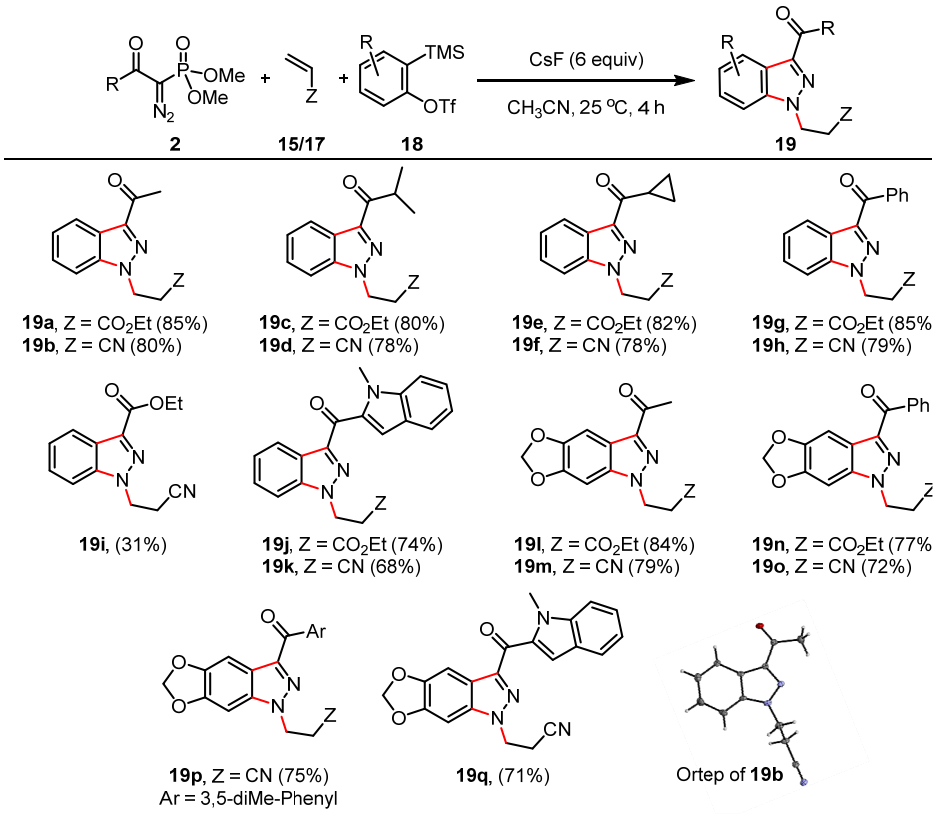
entry	Fluoride(equiv)	solvent	**19a**Yield[b] %
1	CsF (3.0)	CH_3CN	<30
2	CsF (5.0)	CH_3CN	76

3	CsF (6.0)	CH_3CN	85
4	CsF (8.0)	MeCN	84
5	TBAF (3.0)	THF	<5
6	TBAF (6.0)	THF	30
7[c]	TBAF (6.0)	THF	36
8	KF (6.0) &18-Crown-6(6.0)	THF	57

[a] All reactions were carried out on approximately a 0.5 mmol scale at a 0.08 M concentration. [b] Isolated yields. [c] All reagent and substrate addition done at -10 ^{o}C and stirred it for 30 min. with the same temperature latter kept it at room temperature for next 4-5 h.

With the adequate results in hand, the scope and limitations of this one-pot (3 + 2) cycloaddition followed by the aza-Michael addition process has been examined employing diverse diazo phosphonates, aryne precursors and ethyl acrylate/acrylonitrile as the Michael traps. We were pleased to observe that a wide range of diazo phosphonates containing both aliphatic [*i*so-propyl (**2b**), cyclopropyl (**2c**)] and aromatic [phenyl (**2d**), 3,5-dimethylphenyl (**2l**)] groups underwent this multicomponent process very smoothly to furnish the corresponding 1,3-disubstituted indazole derivatives (**19a**–**19h**) in good to excellent yields. The structure of **19b** was confirmed by single crystal X-ray diffraction studies. Next, the compatibility of various phosphonate derivatives under the current conditions was examined. In case of ethyl diazophosphonoacetate **2k**, the reactions were sluggish and the yields were found to be poor. Interestingly, with the indole derived phosphonate **2m** that failed in the previous case, the reaction proceeded smoothly and provided the corresponding product **19j** in very good yields. Furthermore, the reaction of substituted aryne precursor **18b** under standard conditions gave the corresponding indazoles in high yields. In all the cases aliphatic (**2a**), aromatic (**2d** & **2l**) and heteroaromatic (**2m**) compounds, the reactions proceeded with equal ease and gave excellent yields. In addition to the ethyl acrylate, the reactions employing acrylonitrile **17** as a Michael acceptor also proceeded smoothly and the corresponding products were obtained in very good yields (Scheme 69).

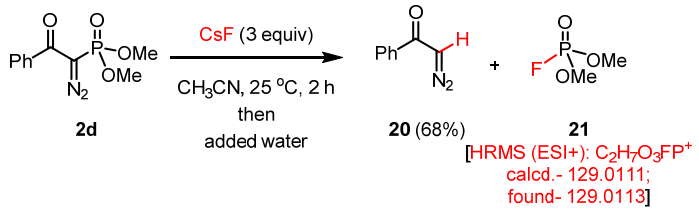
Scheme 69. *Scope of 1,3-Disubstituted Indazole Synthesis*[a]

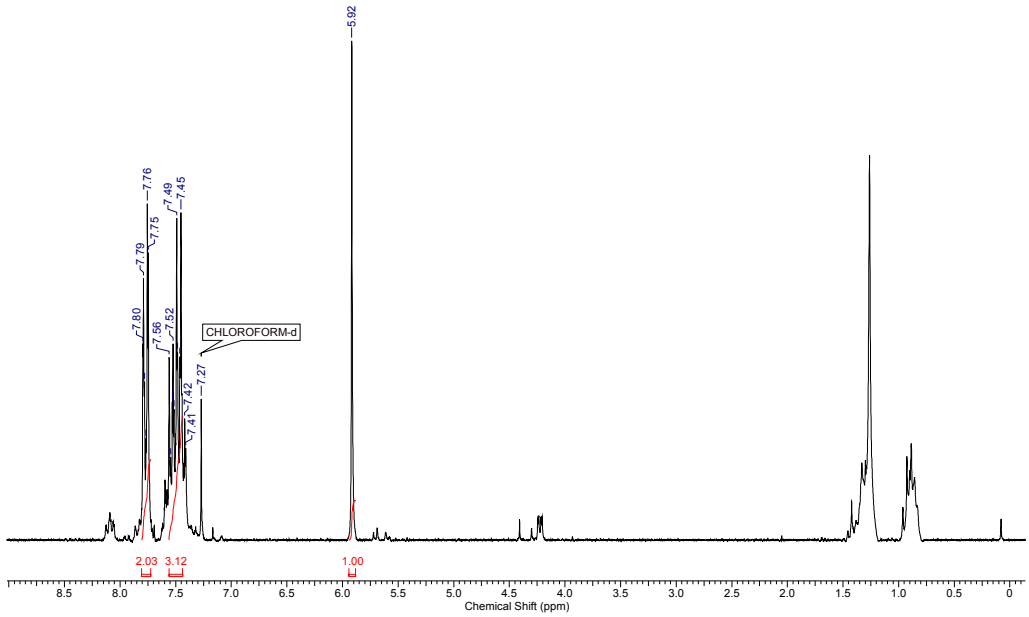


Mechanistic Investigation

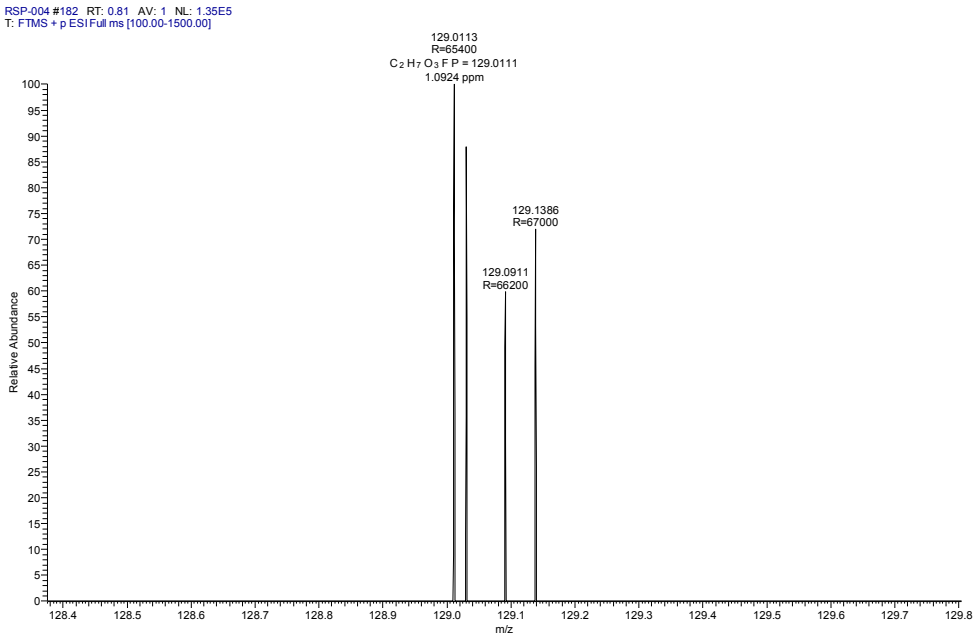
After having proving our hypothesis on selective dephosphonylation of the OBR reagent and the trapping of acyl diazo intermediates with alkenes and arynes, we next proceeded for gaining some insights on the course of the reactions and providing some experimental validation for our hypothesis. First, for endorsing our hypothesis of fluoride mediated C–P bond cleavage, the reaction of the OBR with CsF alone has been examined. Only diazo phosphonate (**2d**) was taken with CsF (3.0 equiv) in acetonitrile and the reaction mixture stirred for 2 h. The crude reaction mixture was subjected for HRMS. The data clearly shows the mass for newly formed dimethyl phosphorofluoridate (**21**) [(HRMS (ESI+): calcd. for $C_2H_7O_3FP^+$ 129.0111, found 129.0113]. Further, the same reaction was quenched by adding water, as envisaged we were able to isolate 2-diazo-1-phenylethan-1-one (**20**) as a single product in 68% yield. The formation of **20** and **21** are the key evidences that revealed that the reaction is succeeding *via* the C–P bond cleavage. This fluoride mediated cleavage *insitu* generates the 1,3-dipolar species, which further proceeds for cycloaddition to form the

corresponding pyrazole/indazole. After having this initial information, finding the *N*-acylation of pyrazoles by the OB reagent has become the next concern.



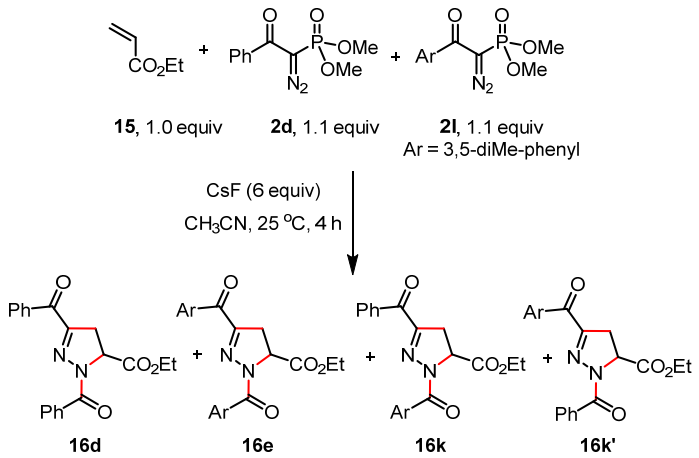


^{1}H NMR of crude reaction mixture (20)



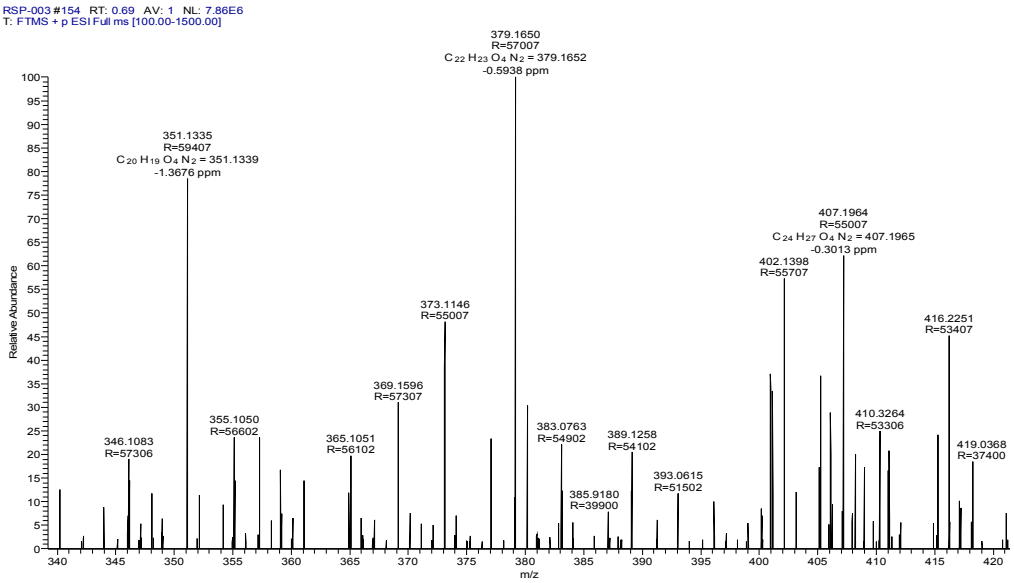
HRMS Spectrum for crude reaction mixture (21)

In this context, the competing experiments comprising of the reaction of two different diazo phosphonates **2d** and **2l** (1.1 equiv of each) with ethyl acrylate **15** has been conducted and the crude mixture was analysed with the help of HRMS.



From this it became apparent that all possible crossover products have been formed. This clearly suggested that the fluoride mediated C–P bond cleavage is the first step followed by the (3 + 2) cycloaddition and the *N*-acylation of resulting pyrazoles with OBR or the Aza-Michael reaction of intermediate indazoles with conjugated olefins.

HRMS Spectra for Cross-over experiment

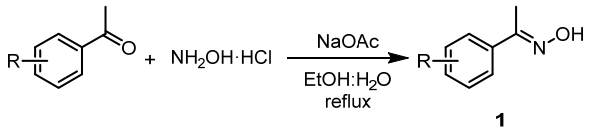


In summary, the selective dephosphonylation of the *α*-diazo-*β*-carbonyl phosphonates has been executed successfully under mild conditions employing CsF as the base. The derived anion of the (*α*-acyl)diazomethane has been trapped either *via*

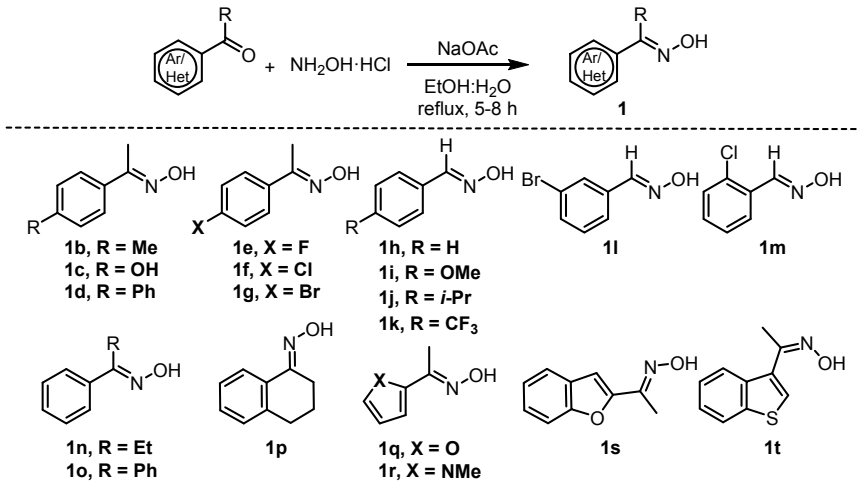
its (3 + 2) cycloadditions with acrylates/acrylonitrile to furnish 1,3-disubstituted-4,5-dihydro-pyrazoles or with *insitu* generated aryne intermediates to synthesize 1,3-disubstituted-indazole derivatives. New reactivity of OBR for one pot *N*-acylation of pyrazole is reported.

General Procedure for the Preparation of Starting Materials

Preparation of Oximes (1)[75]

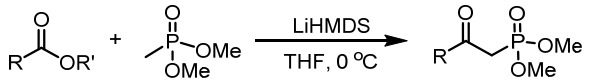


A mixture of ketone or aldehyde (5.0 mmol), $NH_2OH{\cdot}HCl$ (7.5 mmol, 0.522 g), NaOAc (12.5 mol, 1.03 g), in 4 mL ethanol and 12 mL water were placed in a 50 mL round-bottom flask with a reflux condenser. Then the reaction flask was heated to reflux and the reaction progress was monitored by TLC. After the reaction, the contents were poured into a 250 mL beaker and cooled to 0 °C. After cooling, the precipitate was filtered with suction, and the crude product was thoroughly washed with water and dried under vacuum. Recrystallization of the crude product with ethanol, gives the pure solid oximes in quantative yields.



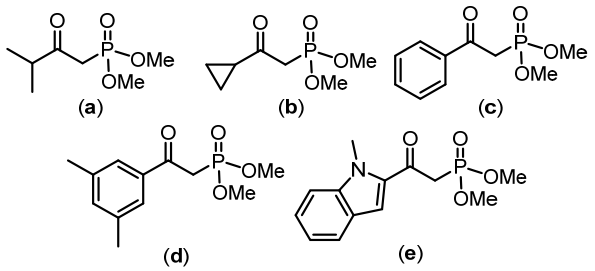
Scheme 46. *Synthesis of aryl and heteroaryl oximes*

Preparation of *β*-Ketophosphonates[96]

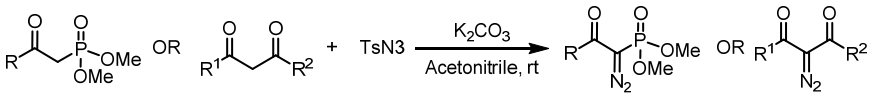


The reactions are carried out employing 1 g of starting ester. To a solution of LiHMDS (2.2 equiv) in THF (1.0 M) cooled in an ice bath, was added methyl dimethyl phosphonate (1.1 equiv). To this mixture was added the ester (either neat or dissolved in a minimal amount of THF) drop-wise, maintaining the internal

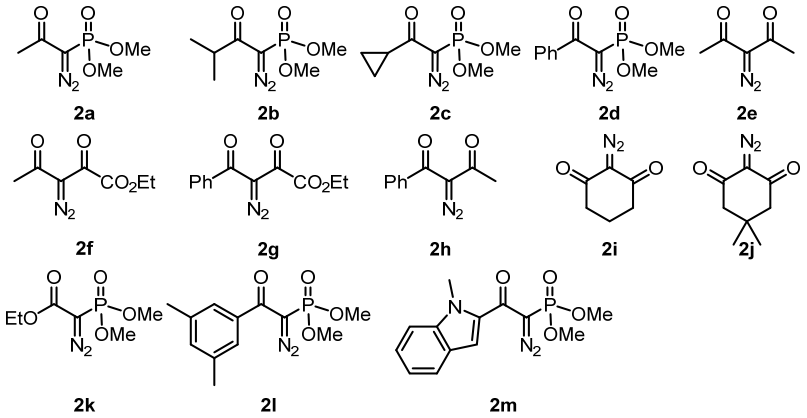
temperature of the reaction below 5°C. The reaction was stirred at 0°C until complete consumption of the ester as determined by TLC. The mixture was partitioned between sat. NH_4Cl and EtOAc, the aqueous layer was extracted with EtOAc (10 mL x 3). The combined organic layer was washed with water (10 mL x 2), brine (10 mL x 2), dried over Na_2SO_4 and the solvent removed in *vacuo*. Crude product as such used for further reaction.



Preparation of Diazo Substrates (2)[97]



The procedure reported by Riu[2] & Munoz/Taber[3] groups has been used to prepare **2a**–**2f**. To a stirred solution of phosphonate (3.0 mmol) and TsN_3 (712 mg, 3.6 mmol) in acetonitrile (10 mL) was added K_2CO_3 (624 mg, 4.52 mmol) and the resulting mixture was stirred at room temperature for overnight. The reaction mixture was filtered through a pad of *Celite* and washed with EtOAc (10 mL x 3). The solvent was evaporated under reduce pressure and the residue was purified by flash column chromatography using EtOAc/petroleum ether as eluent to furnish the pure diazo compound.



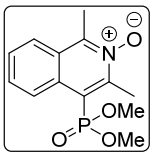
Scheme 70. *Synthesis of Diazo substrates*

General procedure for Substrate Scope of isoquinoline 2-oxide (3)

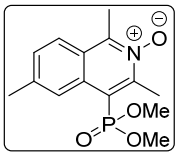
To a screw capped vial with a spin vane triangular-shaped Teflon stir bar were added (hetero)aryl oxime (0.15 mmol), diazo compound (0.18 mmol), $[IrCp^*Cl_2]_2$ (2.0 mol%, 2.4 mg), $AgNTf_2$ (8.0 mol%, 4.7 mg), and solvent (1.0 mL) under air. The reaction mixture was stirred at 30 °C for 12 h. The reaction mixture was filtered through a pad of celite and then washed with CH_2Cl_2 (5 mL x 3). Solvents were removed under reduced pressure and the residue was purified by column chromatography (MeOH/dichloromethane) to obtain the pure product.

Spectroscopic data of Synthesized Compounds

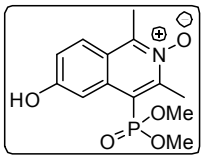
4-(Dimethoxyphosphoryl)-1,3-dimethylisoquinoline 2-oxide (3a): Following the general procedure compound **3a** was obtained in 95% as white solid; R_f 0.2 (90% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.96 (s, 3H), 3.02 (d, J = 2.2 Hz, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 7.58–7.64 (m, 2H), 7.98 (dt, J = 2.4, 7.9 Hz, 1H), 8.95 (dd, J = 2.4, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4 (CH_3), 17.4 (CH_3), 52.7 (CH_3), 52.7 (CH_3), 118.3 (d, J = 186.3 Hz, C), 124.3 (CH), 126.8 (d, J = 3.0 Hz, CH), 127.1 (d, J = 15.1 Hz, C), 128.2 (CH), 129.3 (d, J = 9.6 Hz, C), 129.4 (CH), 150.1 (C), 153.2 (d, J = 18.6 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{13}H_{17}NO_4P$ $[M+H]^+$: 282.0890, found: 282.0881.



4-(Dimethoxyphosphoryl)-1,3,6-trimethylisoquinoline 2-oxide (3b): Following the general procedure compound **3b** was obtained in 96% as brown sticky solid; R_f 0.2 (90% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.54 (s, 3H), 2.95 (s, 3H), 3.02 (d, J = 2.2 Hz, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 7.45 (d, J = 8.9 Hz, 1H), 7.88 (dd, J = 2.0, 8.9 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4 (CH_3), 17.5 (CH_3), 22.3 (CH_3), 52.6 (CH_3), 52.7 (CH_3), 117.4 (d, J = 185.1 Hz, C), 124.0 (CH), 125.5 (d, J = 15.2 Hz, C), 125.9 (d, J = 2.8 Hz, CH), 129.3 (d, J = 10.0 Hz, C), 130.3 (CH), 139.7 (C), 149.3 (C), 153.1 (d, J = 18.1 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{14}H_{19}NO_4P$ $[M+H]^+$: 296.1046, found: 296.1043.

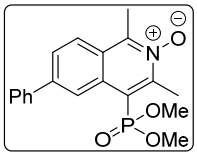


4-(Dimethoxyphosphoryl)-6-hydroxy-1,3-dimethylisoquinoline 2-oxide (3c):



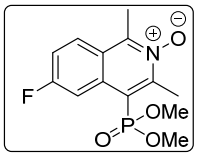
Following the general procedure compound **3c** was obtained in 80% as yellow sticky solid; R_f 0.3 (5% methanol/dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87 (d, J = 1.9 Hz, 3H), 2.92 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 7.22 (dd, J = 2.2, 9.2 Hz, 1H), 8.07 (dd, J = 2.8, 9.2 Hz, 1H), 8.03 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7 (CH_3), 25.7 (CH_3), 52.5 (CH_3), 52.6 (CH_3), 108.1 (d, J = 2.8 Hz, CH), 110.9 (d, J = 186.7 Hz, CH), 119.1 (CH), 120.5 (d, J = 11.0 Hz, C), 126.2 (CH), 140.3 (d, J = 13.5 Hz, C), 157.9 (d, J = 14.0 Hz, C), 160.3 (C), 162.0 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{13}H_{17}NO_5P$ $[M+H]^+$: 298.0839, found: 298.0837.

4-(Dimethoxyphosphoryl)-1,3-dimethyl-6-phenylisoquinoline 2-oxide (3d):



Following the general procedure compound **3d** was obtained in 85% as light yellow solid; R_f 0.3 (95% ethyl acetate/pet. ether); mp: 134–139 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.98 (s, 3H), 3.05 (d, J = 2.2 Hz, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 7.42 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.4 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.9 Hz, 1H), 7.04 (dd, J = 2.0, 8.9 Hz, 1H), 9.29 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.4 (CH_3), 17.5 (CH_3), 52.7 (CH_3), 52.7 (CH_3), 118.2 (d, J = 185.2 Hz, C), 124.0 (2CH), 126.3 (d, J = 15.2 Hz, C), 127.3 (2CH), 127.4 (CH), 128.2 (CH), 129.1 (2CH), 129.2 (d, J = 26.5 Hz, CH), 139.7 (C), 141.2 (C), 149.0 (d, J = 3.0 Hz, C), 153.6 (d, J = 17.8 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{21}NO_4P$ $[M+H]^+$: 358.1203, found: 358.1198.

6-Fluoro-4-(dimethoxyphosphoryl)-1,3-dimethylisoquinoline 2-oxide (3e):



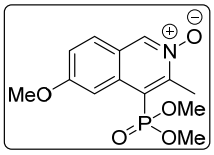
Following the general procedure compound **3e** was obtained in 78% as light brown solid; R_f 0.3 (95% ethyl acetate/pet. ether); mp: 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 (d, J = 1.4 Hz, 3H), 3.00 (d, J = 2.2 Hz, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 7.40 (ddd, J = 2.7, 4.6, 7.6 Hz, 1H), 8.00 (ddd, J = 1.9, 3.7, 5.6 Hz, 1H), 8.77 (dd, J = 2.7, 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6 (CH_3), 17.6 (CH_3), 52.8 (CH_3), 52.8 (CH_3), 111.75 (dd, J = 2.8, 25.7 Hz, CH), 117.9 (dd, J = 5.6, 186.1 Hz, C), 118.5 (d, J = 25.8 Hz, C), 124.6 (d, J = 15.1 Hz, C), 126.8 (d, J = 9.3 Hz, CH), 130.4 (t, J = 10.0 Hz, C), 149.1 (C), 154.4 (d, J = 17.2 Hz, C), 163.5 (d, J = 251.2 Hz, C) ppm; HRMS (ESI+): calcd. for $C_{13}H_{16}FNO_4P$ $[M+H]^+$: 300.0795, found: 300.0793.

6-Chloro-4-(dimethoxyphosphoryl)-1,3-dimethylisoquinoline 2-oxide (3f): Following the general procedure compound **3f** was obtained in 74% as brown sticky solid; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (s, 3H), 3.01 (d, J = 2.2 Hz, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 7.57 (dd, J = 1.9, 9.1 Hz, 1H), 7.91 (dd, J = 2.2, 9.1 Hz, 1H), 9.25 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5 (CH_3), 17.6 (CH_3), 52.8 (CH_3), 52.9 (CH_3), 117.6 (d, J = 185.7 Hz, C), 125.5 (d, J = 1.5 Hz, CH), 125.8 (d, J = 15.2 Hz, C), 126.1 (d, J = 2.2 Hz, CH), 129.1 (CH), 129.4 (d, J = 9.3 Hz, C), 135.5 (C), 149.0 (C), 154.4 (d, J = 17.4 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{13}H_{16}NO_4ClP$ $[M+H]^+$: 316.0505, found: 316.0497.

6-Bromo-4-(dimethoxyphosphoryl)-1,3-dimethylisoquinoline 2-oxide (3g): Following the general procedure compound **3g** was obtained in 83% as light yellow solid; R_f 0.3 (95% ethyl acetate/pet. ether); mp: 146–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (s, 3H), 3.01 (d, J = 2.2 Hz, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 7.70 (dd, J = 1.9, 9.1 Hz, 1H), 7.83 (dd, J = 2.2, 9.1 Hz, 1H), 9.25 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (CH_3), 17.6 (CH_3), 52.8 (CH_3), 52.9 (CH_3), 117.6 (d, J = 185.6 Hz, C), 124.0 (C), 125.4 (CH), 125.8 (d, J = 14.6 Hz, C), 129.3 (d, J = 2.4 Hz, CH), 129.6 (d, J = 9.6 Hz, C), 131.7 (CH), 149.1 (C), 154.4 (d, J = 17.3 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{13}H_{16}NO_4BrP$ $[M+H]^+$: 359.9995, found: 359.9992.

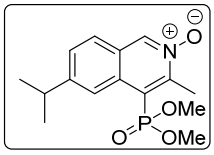
4-(Dimethoxyphosphoryl)-3-methylisoquinoline 2-oxide (3h): Following the general procedure compound **3h** was obtained in 85% as yellow oil; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (d, J = 2.4 Hz, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 7.57–7.61 (m, 1H), 7.63–7.67 (m, 1H), 7.70–7.72 (m, 1H), 8.93 (d, J = 8.4 Hz, 1H), 9.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7 (CH_3), 52.8 (CH_3), 52.9 (CH_3), 121.2 (d, J = 182.7 Hz, C), 125.2 (d, J = 1.9 Hz, CH), 126.5 (d, J = 2.9 Hz, CH), 128.1 (d, J = 15.7 Hz, C), 128.6 (CH), 129.8 (d, J = 9.6 Hz, C), 130.0 (CH), 139.4 (CH), 153.8 (d, J = 18.2 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{12}H_{15}NO_4P$ $[M+H]^+$: 268.0733, found: 268.0726.

4-(dimethoxyphosphoryl)-6-methoxy-3-methylisoquinoline 2-oxide (3i):



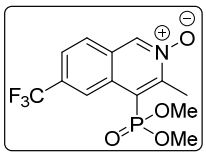
Following the general procedure compound **3i** was obtained in 83% as brown oil; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (t, J = 2.5 Hz, 3H), 3.80 (d, J = 2.7 Hz, 3H), 3.83 (d, J = 2.7 Hz, 3H), 3.96 (d, J = 4.0 Hz, 3H), 7.24 (dt, J = 2.4, 8.8 Hz, 1H), 7.63 (dt, J = 2.4, 9.1 Hz, 1H), 8.56 (s, 1H), 8.91 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.0 (CH_3), 52.7 (CH_3), 52.8 (CH_3), 55.6 (CH_3), 105.2 (d, J = 2 Hz, CH), 119.2 (d, J = 183.1 Hz, C), 121.8 (CH), 123.6 (d, J = 16.3 Hz, C), 126.9 (CH), 132.6 (d, J = 10.7 Hz, C), 139.5 (CH), 153.6 (d, J = 17.7 Hz, C), 161.0 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{13}H_{17}NO_5P$ $[M+H]^+$: 298.0839, found: 298.0829.

4-(Dimethoxyphosphoryl)-6-isopropyl-3-methylisoquinoline 2-oxide (3j):

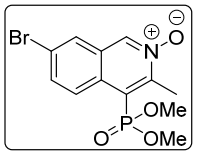


Following the general procedure compound **3j** was obtained in 86% as yellow oil; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J = 6.9 Hz, 6H), 3.00 (d, J = 2.2 Hz, 3H), 3.14 (quin, J = 6.9, 13.2 Hz, 1H), 3.81 (s, 3H), 3.84 (s, 3H), 7.51 (d, J = 8.5 Hz, 1H), 7.66 (dd, J = 2.1, 8.5 Hz, 1H), 8.77 (s, 1H), 8.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7 (CH_3), 23.54 ($2CH_3$), 34.8 (CH), 52.7 (CH_3), 52.8 (CH_3), 120.6 (d, J = 183.0 Hz, C), 123.1 (d, J = 2.4 Hz, CH), 125.2 (d, J = 1.8 Hz, CH), 126.7 (d, J = 16.5 Hz, C), 128.3 (CH), 130.3 (d, J = 9.4 Hz, C), 139.3 (d, J = 2.6 Hz, CH), 151.21 (C), 153.5 (d, J = 18.1 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{15}H_{21}NO_4P$ $[M+H]^+$: 310.1203, found: 310.1201.

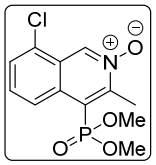
4-(Dimethoxyphosphoryl)-3-methyl-6-(trifluoromethyl) isoquinoline 2-oxide (3k): Following the general procedure compound **3k** was obtained in 80% as yellow oil; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00 (d, J = 2.2 Hz, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 7.77 (dd, J = 1.2, 8.7 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 9.03 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.81 (CH_3), 53.1 (CH_3), 53.1 (CH_3), 120.5 (C), 122.3 (d, J = 6.0 Hz, C), 124.5 (d, J = 2.9 Hz, CH), 124.6 (d, J = 4.8 Hz, CH), 126.0 (CH), 128.5 (d, J = 9.5 Hz, C), 129.4 (d, J = 15.7 Hz, C), 131.2 (d, J = 33.4 Hz, C), 138.8 (CH), 155.4 (d, J = 16.8 Hz, C) ppm; HRMS (ESI$^+$):calcd. for $C_{13}H_{14}F_3NO_4P$ $[M+H]^+$: 359.9992, found: 359.9995.



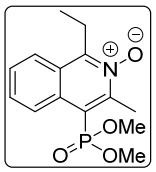
7-bromo-4-(dimethoxyphosphoryl)-3-methylisoquinoline 2-oxide (3l): Following the general procedure compound **3l** was obtained in 65% as yellow sticky solid; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.97 (d, J = 2.3 Hz, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 7.70 (dd, J = 2.3, 9.5 Hz, 1H), 7.86 (t, J = 2.3 Hz, 1H), 8.88 (s, 1H), 8.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8 (CH_3), 52.9 (CH_3), 53.0 (CH_3), 121.5 (d, J = 182.5 Hz, C), 123.0 (CH), 126.7 (CH), 128.1 (d, J = 9.6 Hz, C), 128.4 (CH), 129.4 (d, J = 15.6 Hz, C), 133.0 (CH), 138.1 (C), 154.2 (d, J = 17.3 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{12}H_{14}BrNO_4P$ $[M+H]^+$: 345.9838, found: 345.9839 and 347.9812 (isomeric).



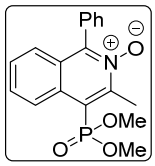
8-Chloro-4-(dimethoxyphosphoryl)-3-methylisoquinoline 2-oxide (3m): Following the general procedure compound **3m** was obtained in 70% as yellow oil; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.01 (d, J = 2.4 Hz, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 7.55 (dd, J = 7.2, 8.9 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 8.93 (d, J = 8.9 Hz, 1H), 9.44 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 16.9 (CH_3), 52.9 (CH_3), 53.0 (CH_3), 121.6 (d, J = 184.6 Hz, C), 125.5 (d, J = 2.6 Hz, CH), 126.2 (d, J = 16.8 Hz, C), 128.8 (CH), 129.0 (d, J = 3.7 Hz, C), 129.3 (CH), 130.7 (d, J = 10.2 Hz, C), 136.9 (d, J = 2.9 Hz, CH), 154.7 (d, J = 17.1 Hz, C) ppm; HRMS (ESI+): calcd. for $C_{13}H_{16}NO_4ClP$ $[M+H]^+$: 316.0500, found 316.497.



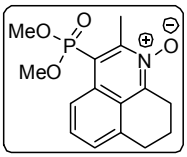
4-(Dimethoxyphosphoryl)-1-ethyl-3-methylisoquinoline 2-oxide (3n): Following the general procedure compound **3n** was obtained in 93% as yellow oil; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (t, J = 7.6 Hz, 3H), 3.04 (d, J = 2.2 Hz, 3H), 3.54 (q, J = 7.6, 15.0 Hz, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 7.63–7.63 (m, 2H), 7.94–7.96 (m, 1H), 8.96–8.96 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.6 (CH_3), 17.4 (CH_3), 21.0 (CH_2), 52.7 (CH_3), 52.7 (CH_3), 118.4 (d, J = 185.2 Hz, C), 123.8 (d, J = 2.1 Hz, CH), 126.6 (d, J = 15.1 Hz, C), 126.9 (d, J = 2.9 Hz, CH), 128.2 (CH), 128.39 (CH), 138.8 (C), 146.3 (C), 153.5 (d, J = 18.6 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{14}H_{19}NO_4P$ $[M+H]^+$: 296.1046, found: 296.1039.



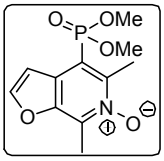
4-(Dimethoxyphosphoryl)-3-methyl-1-phenylisoquinoline 2-oxide (3o): Following the general procedure compound **3o** was obtained in 77% as yellow sticky solid; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (d, J = 2.3 Hz, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 7.43–7.51 (m, 4H), 7.55–7.66 (m, 4H), 9.03 (d, J = 8.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.2 (CH_3), 52.8 (CH_3), 52.9 (CH_3), 120.2 (d, J = 184.1 Hz, C), 126.1 (CH), 126.4 (d, J = 2.3 Hz, CH), 128.0 (CH), 128.1 (C), 128.8 (2CH), 129.1 (CH), 129.3 (C), 129.4 (CH), 129.6 (2CH), 131.6 (C), 149.3 (C), 154.2 (d, J = 18.0 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{18}NO_4NaP$ $[M+Na]^+$: 366.0866, found 366.0861.



Dimethyl (1-hydroxy-2-methyl-8,9-dihydro-7H-1l4-benzo[de]quinolin-3yl)phosphonate (3p): Following the general procedure compound **3p** was obtained in 94% as brown oil; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14 (quin, J = 6.1, 12.7 Hz, 2H), 3.00–3.02 (m, 5H), 3.37 (t, J = 6.1 Hz, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 7.33 (d, J = 6.7 Hz, 1H), 7.51 (dd, J = 6.7, 8.6 Hz, 1H), 8.71 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0 (CH_3), 21.1 (CH_2), 26.7 (CH_2), 29.6 (CH_2), 52.5 (CH_3), 52.6 (CH_3), 118.0 (d, J = 186.0 Hz, C), 124.3 (d, J = 1.9 Hz, CH), 125.1 (d, J = 15.5 Hz, C), 126.2 (CH), 128.9 (d, J = 9.7 Hz, C), 129.2 (CH), 135.7 (C), 149.9 (C), 153.0 (d, J = 18.5 Hz, C) ppm; HRMS (ESI$^+$):calcd. for $C_{15}H_{19}NO_4P$ $[M]^+$: 308.1046, found: 308.1042.



4-(Dimethoxyphosphoryl)-5,7-dimethylfuro[2,3-c]pyridine 6-oxide (3q): Following the general procedure compound **3q** was obtained in 92% as brown solid; R_f 0.3 (95% ethyl acetate/pet. ether); mp: 139–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 (d, J = 0.9 Hz, 3H), 2.82 (d, J = 1.9 Hz, 3H), 3.78 (s, 3H), 3.81 (s, 3H) 7.39 (d, J = 2.2 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3 (CH_3), 16.7 (CH_3), 52.8 (2CH_3), 108.8 (CH), 113.2 (d, J = 193.6 Hz, C), 127.7 (d, J = 9.7 Hz, C), 139.0 (C), 149.1 (d, J = 4.8 Hz, C), 149.1 (CH), 149.3 (d, J = 4.8 Hz, C) ppm; HRMS (ESI$^+$): calcd. for $C_{11}H_{15}NO_5P$ $[M+H]^+$: 272.0682, found: 272.0673.



4-(Dimethoxyphosphoryl)-1,5,7-trimethyl-1H-pyrrolo[2,3-c]pyridine 6-oxide (3r): Following the general procedure compound **3r** was obtained in 75% as brown sticky solid; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.20 (s, 3H), 2.23 (s, 3H), 3.60 (s, 3H), 3.72 (d, J = 5.2 Hz, 3H), 3.74 (d, J = 5.2 Hz, 3H), 6.38 (d, J = 2.8 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.8 (CH_3), 29.5 (d, J = 3.8 Hz,CH_3), 35.4 (CH_3), 53.3 (d, J = 6.8 Hz, CH_3), 53.6 (d, J = 6.8 Hz, CH_3), 100.1 (d, J = 3.7 Hz, CH), 122.8 (d, J = 7.6 Hz, C), 123.6 (C), 124.1 (CH), 128.7 (d, J = 11.4 Hz, C), 142.7 (C), 149.2 (C) ppm; HRMS (ESI$^+$):calcd. for $C_{12}H_{18}N_2O_4P$ $[M+H]^+$: 285.0999, found: 285.0996.

4-(Dimethoxyphosphoryl)-1,3-dimethylbenzofuro[2,3-c]pyridine 2-oxide (3s): Following the general procedure compound **3s** was obtained in 87% as brown solid; R_f 0.3 (95% ethyl acetate/pet. ether); mp: 139–142 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.86 (s, 3H), 3.03 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 7.43 (t, J = 7.7 Hz, 1H), 7.56–7.63 (m, 2H), 8.74 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$):δ12.5 (CH_3), 16.6 (CH_3), 52.8 (CH_3), 52.9 (CH_3), 111.7 (CH), 114.3 (d, J = 192.2 Hz, C), 121.9 (C), 122.6 (d, J = 8.1 Hz, C), 123.9 (CH), 126.3 (CH), 129.4 (CH), 139.1 (C), 150.7 (d, J = 19.6 Hz, C), 150.4 (d, J = 20.6 Hz, C), 157.8 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{15}H_{17}NO_5P$ $[M+H]^+$: 322.0839, found: 322.0832.

4-(Dimethoxyphosphoryl)-1,3-dimethylbenzo[4,5]thieno[3,2-c]pyridine 2-oxide (3t): Following the general procedure compound **3t** was obtained in 74% as white solid; R_f 0.3 (95% ethyl acetate/pet. ether); mp: 146–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (d, J = 1.8 Hz, 3H), 3.28 (d, J = 0.9 Hz, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 7.53–7.60 (m, 2H), 7.90–7.95 (m, 1H), 8.34–8.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2 (CH_3), 17.7 (CH_3), 53.1 (CH_3), 53.2 (CH_3), 115.8 (d, J = 191.8, C), 122.7 (CH), 124.7 (CH), 125.3 (CH), 127.8 (CH), 130.7 (d, J = 15.2, C), 132.4 (C), 141.7 (d, J = 7.1, C), 141.8 (C), 148.4 (C), 150.1 (d, J = 19.6 Hz, C); HRMS (ESI$^+$): calcd. for $C_{15}H_{17}NO_4PS$ $[M+H]^+$: 338.0610, found: 338. 0599.

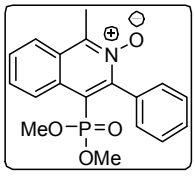
Dimethyl (E)-(1-(2-(1-(hydroxyimino)ethyl)phenyl)-3-methyl-2-oxobutyl)phosphonate (4a): Following the general procedure compound **4a** was obtained in 88% as yellow oil; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H), 1.77 (quin, J = 6.7, 13.5 Hz, 1H), 2.41 (s, 3H), 3.39 (d, J = 11.0 Hz, 3H), 3.66 (d, J = 11.2 Hz, 3H), 3.89 (d, J = 25.0 Hz, 1H), 7.17–7.19 (m, 1H), 7.23–7.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 15.7 (CH_3), 16.8 (CH_3), 33.4 (d, J = 12.2 Hz, CH), 46.6 (d, J = 136.5 Hz, CH), 52.90 (d, J = 7.2 Hz, CH_3), 53.52 (d, J = 6.4 Hz, CH_3), 124.8 (d, J = 3.2 Hz, CH), 127.4 (d, J = 8.4 Hz, C), 128.5 (d, J = 3.8 Hz, CH), 129.4 (d, J = 3.4 Hz, CH), 130.0 (C), 130.4 (d, J = 6.3 Hz, CH), 138.7 (C), 184.6 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{15}H_{23}NO_5P$ $[M+H]^+$: 328.1308, found: 328.1306.

Dimethyl (2-cyclopropyl-1-(2-(1-(hydroxyimino)ethyl)phenyl)-2-oxoethyl)phosphonate (4b): Following the general procedure compound **4b** was obtained in 85% as yellow oil; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.31–0.42 (m, 2H), 0.58–0.63 (m, 1H), 0.83–0.89 (m, 1H), 1.22–1.28 (m, 2H), 2.49 (s, 3H), 3.53 (d, J = 11.1 Hz, 3H), 3.72 (d, J = 11.1 Hz, 3H), 4.14 (d, J = 23.2 Hz, 1H), 7.37–7.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.66 (2CH_2), 14.1 (CH_3), 18.0 (d, J = 14.3 Hz, CH), 50.54 (d, J = 136.6 Hz, CH), 53.00 (d, J = 7.4 Hz, CH_3), 53.43 (d, J = 6.7 Hz, CH_3), 125.5 (CH), 127.3 (d, J = 8.2 Hz, C), 127.9 (C), 128.4 (d, J = 3.5 Hz, CH), 129.3 (d, J = 3.2 Hz, CH), 130.9 (d, J = 5.7 Hz, CH), 155.4 (C), 204.1 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{15}H_{21}NO_5P$ $[M+H]^+$: 326.1152, found: 326.1151.

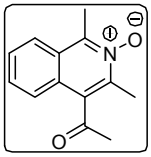
3-Cyclopropyl-4-(dimethoxyphosphoryl)-1-methylisoquinoline 2-oxide (3u): Following the general procedure compound **3u** was obtained in 70% as yellow sticky solid; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00–1.02 (m, 1H), 1.29–1.31 (m, 2H), 2.37–2.41 (m, 1H), 2.93 (s, 3H), 3.64–3.74 (m, 1H), 3.81 (d, J = 2.3 Hz, 3H), 3.84 (d, J = 2.3 Hz, 3H), 7.59–7.61 (m, 2H), 7.92–7.94 (m, 1H), 8.55–8.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.66 (2CH_2), 14.1 (CH_3), 18.0 (d, J = 14.3 Hz, CH), 50.5 (d, J = 136.6 Hz, CH), 53.0 (d, J = 7.4 Hz, CH_3), 53.4 (d, J = 6.7 Hz, CH_3), 125.5 (CH), 127.3 (d, J = 8.2 Hz, C), 127.9 (C), 128.4 (d, J = 3.5 Hz, CH), 129.3 (d, J

= 3.2 Hz, CH), 130.9 (d, J = 5.7 Hz, CH), 155.4 (C), 204.1 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{15}H_{19}NO_4P$ $[M+H]^+$: 308.1046, found: 308.1044.

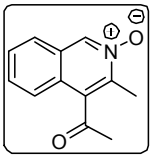
4-(Dimethoxyphosphoryl)-1-methyl-3-phenylisoquinoline 2-oxide (3v): Following the general procedure compound **3v** was obtained in 20% as yellow sticky solid; R_f 0.3 (95% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 (s, 3H), 3.49 (s, 3H), 3.51 (s, 3H), 7.39–7.42 (m, 2H), 7.48–7.53 (m, 3H), 7.67–7.71 (m, 2H), 8.02–8.05 (m, 1H), 8.89–8.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 52.7 (CH_3), 52.8 (CH_3), 121.5 (d, J = 188.9 Hz, C), 124.2 (CH), 127.8 (d, J = 3.8 Hz, CH), 127.9 (2CH), 128.4 (C), 128.6 (d, J = 5.7 Hz, C), 128.9 (CH), 129.1 (d, J = 6.7 Hz, CH), 129.7 (2CH), 134.1 (C), 149.4 (C), 151.8 (d, J = 16.3 Hz, C), ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{19}NO_4P$ $[M+H]^+$: 344.1046, found: 344.1061.



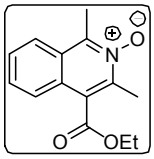
4-Acetyl-1,3-dimethylisoquinoline 2-oxide (5a): Following the general procedure compound **5a** was obtained in 74% as yellow solid; R_f 0.3 (90% ethyl acetate/pet. ether); mp: 137–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H), 2.64 (s, 3H), 2.91 (s, 3H), 7.50–7.62 (m, 3H), 7.97 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 15.6 (CH_3), 32.8 (CH_3), 123.6 (CH), 124.0 (C), 124.3 (CH), 127.5 (C), 128.3 (CH), 128.8 (CH), 133.3 (C), 140.4 (C), 145.8 (C), 202.7 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.1019, found: 216.1019.



4-acetyl-3-methylisoquinoline 2-oxide (5b): Following the general procedure compound **5b** was obtained in 77% as colorless oil; R_f 0.3 (90% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.58 (s, 3H), 2.68 (s, 3H), 7.52–7.55 (m, 1H), 7.59–7.62 (m, 2H), 7.74–7.78 (m, 1H), 8.93 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0 (CH_3), 32.7 (CH_3), 123.2 (CH), 124.9 (C), 125.3 (CH), 128.4 (C), 128.9 (CH), 129.8 (CH), 135.7 (C), 136.6 (CH), 141.1 (C), 202.2 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{12}H_{12}NO_2$ $[M+H]^+$: 202.0863, found: 202.0863.

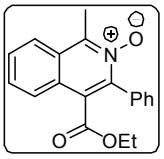


4-(Ethoxycarbonyl)-1,3-dimethylisoquinoline 2-oxide (5c): Following the general procedure compound **5c** was obtained in 80% as yellow solid; R_f 0.3 (90% ethyl acetate/pet. ether); mp: 102–106 °C. ^{1}H

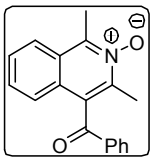


NMR (400 MHz, $CDCl_3$): δ 1.49 (t, J = 7.2 Hz, 3H), 2.67 (s, 3H), 2.93 (s, 3H), 4.59 (q, J = 7.2, 14.5 Hz, 2H), 7.57–7.63 (m, 2H), 7.71–7.73 (m, 1H), 7.79 (dd, J = 2.2, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 14.2 (CH_3), 16.1 (CH_3), 62.3 (CH_2), 124.1 (CH), 124.3 (CH), 125.0 (C), 126.1 (C), 127.3 (C), 128.3 (CH), 128.8 (CH), 143.5 (C), 146.6 (C), 166.5 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1125, found: 246.1122.

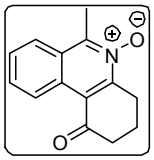
4-(Ethoxycarbonyl)-1-methyl-3-phenylisoquinoline 2-oxide (5d): Following the general procedure compound **5d** was obtained in 25% as white sticky solid; R_f 0.3 (90% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, J = 7.1 Hz, 3H), 2.96 (s, 3H), 4.13 (q, J = 7.3, 14.2 Hz, 2H), 7.47–7.50 (m, 3H), 7.51–7.53 (m, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 8.03 (t, J = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.5 (CH_3), 13.7 (CH_3), 62.0 (CH_2), 124.2 (CH), 125.0 (CH), 125.2 (C), 127.6 (C), 128.1 (2CH), 128.3 (C), 129.0 (CH), 129.2 (CH), 129.3 (CH), 129.9 (2CH), 132.0 (C), 144.9 (C), 147.1 (C), 165.7 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{19}H_{18}NO_3$ $[M+H]^+$: 308.1281, found: 308.1275.



4-Benzoyl-1,3-dimethylisoquinoline 2-oxide (5e): Following the general procedure compound **5e** was obtained in 68% as white sticky solid; R_f 0.3 (90% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 3.01 (s, 3H), 7.45–7.51 (m, 4H), 7.60–7.63 (m, 1H), 7.65–7.68 (m, 1H), 7.87 (d, J = 7.8 Hz, 2H), 8.03 (d, J = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 16.1 (CH_3), 124.2 (CH), 124.7 (CH), 125.8 (C), 127.4 (C), 128.4 (CH), 128.7 (CH), 129.2 (2CH), 129.8 (2CH), 130.8 (C), 134.7 (CH), 136.4 (C), 142.1 (C), 146.2 (C), 195.0 (C) ppm; HRMS (ESI$^+$): calcd. for $C_{18}H_{16}NO_2$ $[M+H]^+$: 278.1176, found: 278.1173.

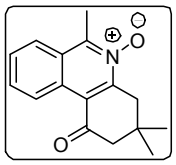


6-Methyl-1-oxo-1,2,3,4-tetrahydrophenanthridine 5-oxide (5f): Following the general procedure compound **5f** was obtained in 94% as brown solid; R_f 0.3 (90% ethyl acetate/pet. ether); mp: 158–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 6H), 2.65 (s, 2H), 2.99 (s, 3H), 3.32 (s, 2H), 7.66 (dd, J = 1.6, 6.6 Hz, 1H), 7.72 (dd, J = 1.6, 6.6 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 9.34 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (CH_3), 28.4 (2CH_3), 31.8 (C), 39.5 (CH_2), 53.3 (CH_2), 122.1 (C), 123.9 (CH), 125.7 (C), 126.2 (CH),



127.3 (C), 128.5 (CH), 130.4 (CH), 150.7 (C), 152.5 (C), 199.4 (C) ppm; HRMS (ESI^+): calcd. for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1019, found: 228.1018.

3,3,6-Trimethyl-1-oxo-1,2,3,4-tetrahydrophenanthridine 5-oxide (5g): Following the general procedure compound **5g** was obtained in 88% as brown sticky solid; R_f 0.3 (90% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (quin, J = 6.3, 13.0 Hz, 2H), 2.78 (t, J = 6.3 Hz, 2H), 2.95 (s, 3H), 3.41 (t, J = 6.3 Hz, 2H), 7.62 (dt, J = 1.5, 7.5 Hz, 1H), 7.68 (dd, J = 1.2, 7.2 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 9.29 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 20.4 (CH_2), 25.7 (CH_2), 39.6 (CH_2), 122.8 (C), 123.8 (CH), 125.9 (C), 126.2 (CH), 127.2 (C), 128.4 (CH), 130.4 (CH), 150.4 (C), 154.0 (C), 199.1 (C) ppm; HRMS (ESI^+): calcd. for $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1332, found: 256.1332.



X-Ray Crystallographic Information

Single-crystal X-ray data of **3s**, **4b** and **10** were collected on a Bruker KAPPA APEX II CCD Duo diffractometer, using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from total 36 frames. The X-ray data acquisition was monitored by APEX 2 program suit. All the data were corrected for Lorentz-polarization and absorption effects using SAINT and SADABS programs integrated in APEX 2 package. The structures were solved by direct methods and refined by full matrix least squares, based on F^2, using SHELX-97. Molecular diagrams were generated using Mercury programs. Geometrical calculations were performed using SHELXTL and PLATON. The H atoms for the **3s**, **4b** and **10** were placed in geometrically idealized positions (C-H = 0.93 and C-H = 0.97 Å for the phenyl and methylene H atoms) and constrained to ride on their parent atoms [Uiso(H) = 1.2 Ueq(C)].

Table 7. *Crystal Data of Compounds 4c, 6, and 18*

Crystal Data	**Compound 3s**	**Compound 4b**	**Complex 10**
Formula	$C_{15}H_{20}NO_7P$	$C_{15}H_{20}NO_5P$	$C_{44}H_{46}Ag_2F_{12}Ir_2N_2O_{10}$
Mr	357.29	325.29	1590.97
Crystal Size, mm	0.34 x 0.27 x 0.21	0.34 x 0.25 x 0.10	0.27 x 0.26 x 0.16
Temp. (K)	296(2) K	296(2)	296(2)
Crystal Syst.	Triclinic	Monoclinic	Monoclinic
Space Group	*P-1*	$P2_1/c$	$P2_1/c$
a/Å	7.016(4)	9.3895(5)	13.09250(9)
b/Å	11.027(4)	11.8119(6)	11.36750(8)
c/Å	11.187(4)	16.7592(8)	17.09390(12)
$\alpha/^0$	107.843(4)	90	90
$\beta/^0$	94.401(7)	119.122(3)	90.4080(10)
$\gamma/^0$	92.67(2)	90	90
V/Å3	819.3(6)	1623.76(14)	2544.00(3)
Z	2	4	2
*D*calc/g cm^{-3}	2,1.448	1.331	2.077

μ/mm^{-1}	0.206	0.191	16.867
F(000)	376	688	1520
Ab. Correct.	multi-scan	multi-scan	multi-scan
Tmin/ Tmax	0.9581/0.9334	0.9811	0.1733
2Θmax		0.9378	0.0922
Total reflns.	10386	25469	41944
Unique reflns.	2772	2848	4680
Obs. reflns.	2256	2691	
h, k, l (min, max)	(-8, 8) (-13, 13) (-13, 12)	(-11, 11) (-14, 14) (-19,19)	(-15, 15) (-13, 13) (-20, 20)
R_{int}	0.0587	0.0448	0.0766
No. of para	237	203	332
R1 [*I*> 2σ(*I*)]	0.0507	0.0789	0.0419
wR2[*I*> 2σ(*I*)]	0.1070	0.1551	0.1099
R1 [all data]	0.0663	0.0829	0.0462
wR2 [all data]	0.1142	0.1573	0.1139
goodness-offit	1.058	1.178	1.070
$\Delta\rho_{max}$,$\Delta\rho_{min}$ (eÅ^{-3})	0.221, -0.319	1.332, -0.545	0.920, -1.941
CCDC no.		**1431589**	**1432093**

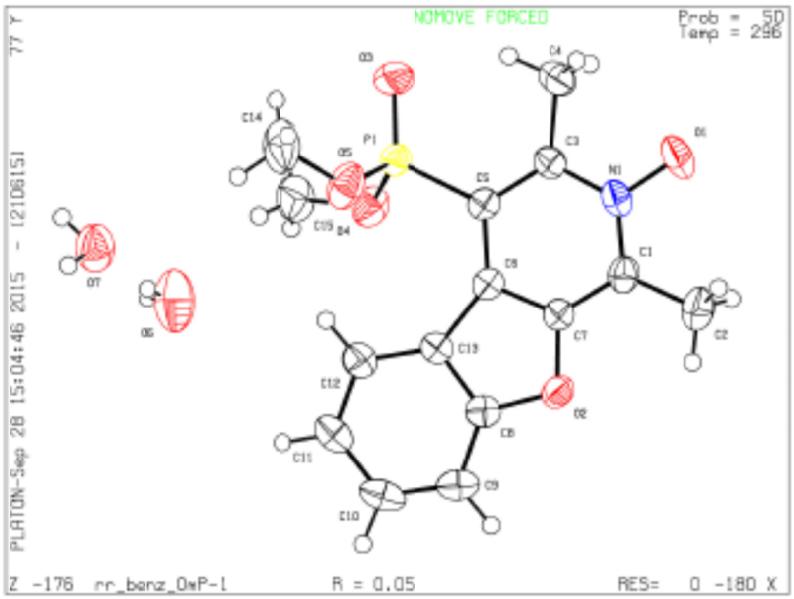


***Figure 6**. ORTEP of Compound **3s**.*

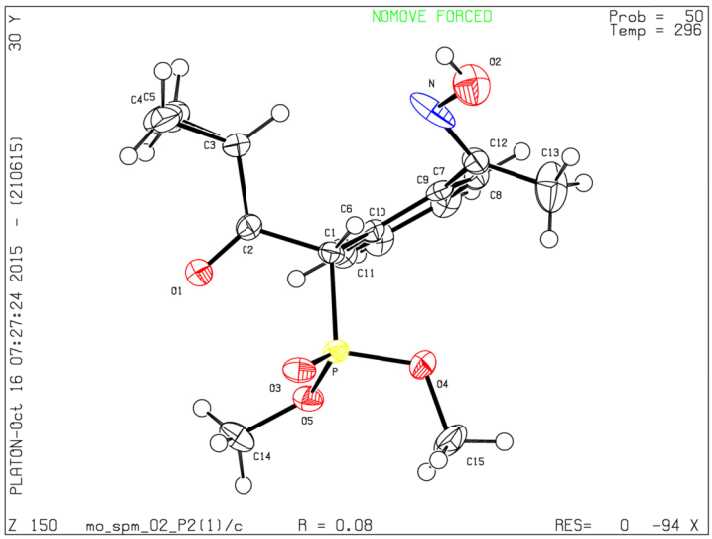


***Figure 7**. ORTEP of Compound **4b**.*

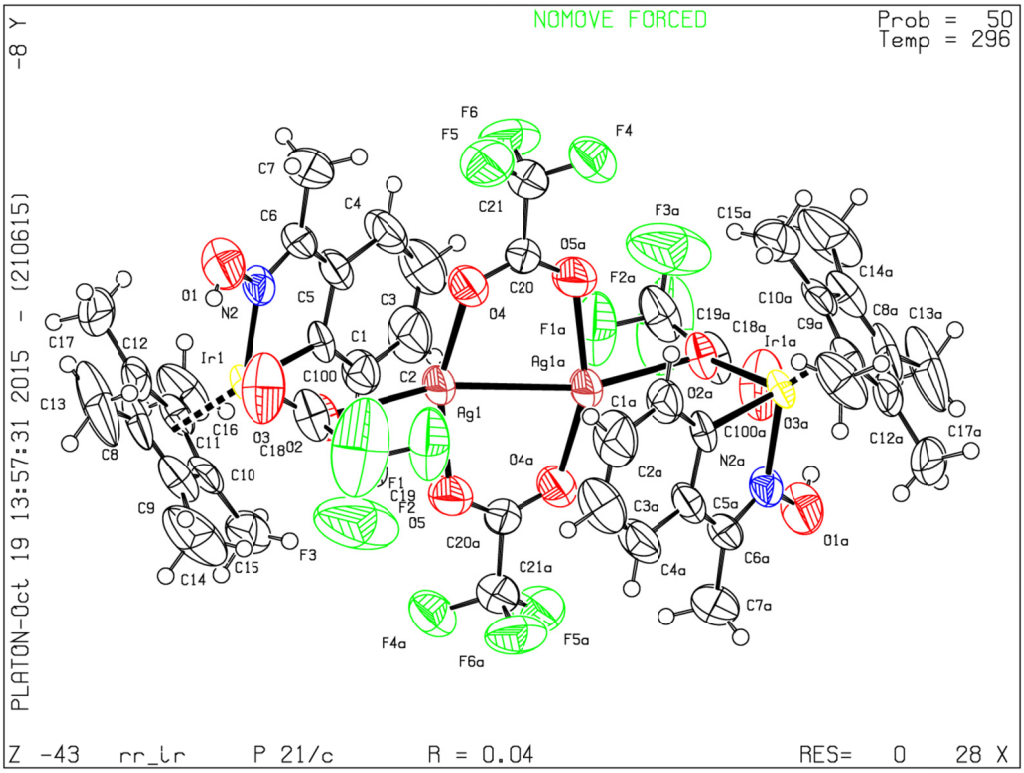
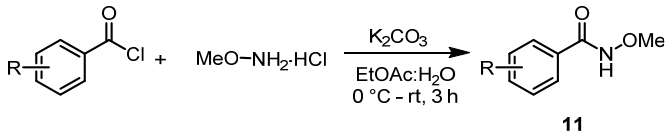
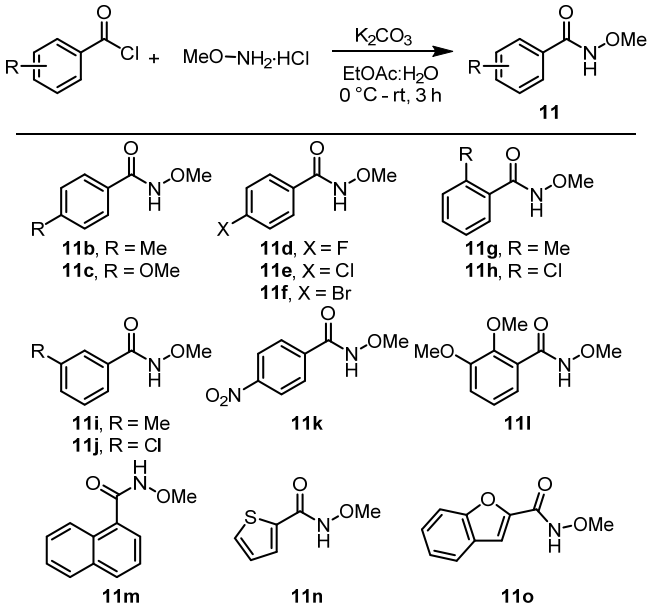


***Figure 8**. ORTEP of Complex **10**.*

Preparation of amides (11)[82]



To a solution of K_2CO_3 (6.0 mmol, 2.0 equiv) in a mixture of EtOAc/H_2O (30 mL, 2:1) was added *O*-methylhydroxylamine hydrochloride (3.6 mmol, 1.2 equiv). The resulting solution was cooled to 0°C, followed by drop wise addition of the benzoyl chloride (3.0 mmol, 1.0 equiv). The reaction mixture was warmed to room temperature and stirred for overnight. The organic phase was separated and the aqueous phase was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The pure products were obtained by flash column chromatography.



Scheme 55. *Synthesis of substituted benzamides*

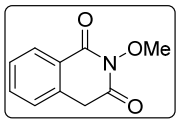
General procedure for Substrate Scope of *N*-Methoxyisoquinolinedione (12)

To a screw capped vial with a spin vane triangular-shaped Teflon stir bar were added (hetero)aryl oxime (0.15 mmol), diazo compound (0.17 mmol), $[IrCp^*Cl_2]_2$ (2.0 mol%, 2.4 mg), $AgNTf_2$ (8.0 mol%, 4.7 mg), and 1,2-dichloroethane (1.0 mL) under air. The reaction mixture was stirred at room temperature for 5 h. After completion of the reaction, the reaction mixture was filtered through a pad of celite and then washed

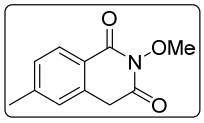
with EtOAc (5 mL x 3). Solvents were removed under reduced pressure and the residue was purified by column chromatography (EtOAc/Petroleum ether) to obtain the desired pure products.

Spectroscopic data of Synthesized Compounds

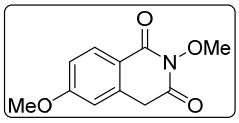
2-Methoxyisoquinoline-1,3(2H,4H)-dione (12a): Following the general procedure compound **12a** was obtained in 90% yield (26.0 mg) as yellow solid; R_f 0.4 (50% ethyl acetate/pet. ether); mp: 130-106 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.95 (s, 3H), 4.13 (s, 2H), 7.25 (s, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.55–7.61 (m, 1H), 8.15 (d, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.4, 64.0, 125.0, 127.3, 127.8, 128.9, 133.1, 133.9, 161.1, 165.5; HRMS (ESI+): calcd. for $C_{10}H_{10}O_3N$ $[M+H]^+$: 192.0655, found: 192.0654.



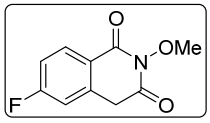
2-Methoxy-6-methylisoquinoline-1,3(2H,4H)-dione (12b): Following the general procedure compound **12b** was obtained in 92% yield (28.3 mg) as yellow solid; R_f 0.4 (50% ethyl acetate/pet. ether); mp: 150-153 °C; ^{1}H ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42 (s, 3H), 3.98 (s, 3H), 4.10 (s, 2H), 7.08 (s, 1H), 7.26 (s, 1H), 8.08 (d, J = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.7, 37.4, 64.1, 122.6, 127.8, 129.0, 129.1, 133.1, 145.2, 161.2, 165.7; HRMS (ESI+): calcd. for $C_{11}H_{12}O_3N$ $[M+H]^+$: 206.0812, found: 206.0813.



2,6-Dimethoxyisoquinoline-1,3(2H,4H)-dione (12c): Following the general procedure compound **12c** was obtained in 90% yield (30 mg) as yellow solid; R_f 0.3 (60% ethyl acetate/pet. ether); mp: 135-137 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 3H), 3.97 (s, 3H), 4.10 (s, 2H), 6.70 (s, 1H), 6.96 (dd, J = 8.9, 2.4 Hz, 1H), 8.11 (d, J = 8.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.6, 55.6, 64.1, 111.6, 114.5, 117.8, 131.2, 135.4, 160.8, 164.1, 165.5; HRMS (ESI+): calcd. for $C_{11}H_{12}O_4N$ $[M+H]^+$: 222.0761, found: 222.0761.

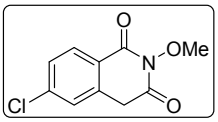


6-Fluoro-2-methoxyisoquinoline-1,3(2H,4H)-dione (12d): Following the general procedure compound **12d** was obtained in 82% yield (25.6 mg) as yellow solid; R_f 0.3 (50% ethyl acetate/pet. ether); mp: 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.98 (s, 3H), 4.15 (s, 2H), 6.95–7.03 (m, 1H), 7.17 (td, J = 8.5, 2.3 Hz, 1H), 8.23 (dd, J = 8.9, 5.7 Hz, 1H); ^{13}C NMR

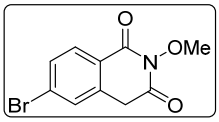


(100 MHz, $CDCl_3$): δ 37.4, 64.2, 114.2 (d, J = 22.8 Hz), 115.9 (d, J = 22.8 Hz), 121.6 (d, J = 1.9 Hz), 132.0 (d, J = 9.6 Hz), 136.0 (d, J = 9.6 Hz), 160.2, 164.8 (d, J = 13.4 Hz), 167.3; HRMS (ESI+): calcd. for $C_{10}H_9O_3NF$ $[M+H]^+$: 210.0561, found: 210.0561.

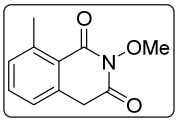
6-Chloro-2-methoxyisoquinoline-1,3(2H,4H)-dione (12e): Following the general procedure compound **12e** was obtained in 85% yield (28.8 mg) as yellow solid; R_f 0.3 (50% ethyl acetate/pet. ether); mp: 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.35 (br. s., 2H), 3.91 (s, 3H), 7.26 (d, J=1.7 Hz, 1H), 7.38 (dd, J = 8.6, 1.7 Hz, 1H), 8.06 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.7, 64.0, 123.4, 127.3, 128.5, 130.4, 134.6, 134.7, 140.6, 160.5, 165.1; HRMS (ESI+): calcd. for $C_{10}H_9O_3NCl$ $[M+H]^+$: 226.0265, found: 226.0265.



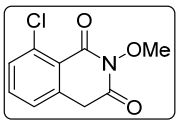
6-Bromo-2-methoxyisoquinoline-1,3(2H,4H)-dione (12f): Following the general procedure compound **12f** was obtained in 83% yield (33.6 mg) as yellow solid; R_f 0.3 (50% ethyl acetate/pet. ether); mp: 205-208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 3H), 4.14 (s, 2H), 7.48 (s, 1H), 7.61 (d, J = 8.6 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.1, 64.2, 124.1, 129.3, 130.4, 130.6, 131.6, 134.8, 160.5, 164.7; HRMS (ESI+): calcd. for $C_{10}H_9O_3NBr$ $[M+H]^+$: 269.9760, found: 269.9760.



2-Methoxy-8-methylisoquinoline-1,3(2H,4H)-dione (12g): Following the general procedure compound **12g** was obtained in 72% yield (22.2 mg) as yellow solid; R_f 0.4 (50% ethyl acetate/pet. ether); mp: 142-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.79 (s, 3H), 4.00 (s, 3H), 4.14 (s, 2H), 7.13 (d, J = 7.3 Hz, 1H), 7.22–7.30 (m, 1H), 7.41–7.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 37.8, 64.0, 123.1, 125.6, 131.6, 132.9, 134.4, 143.3, 161.6, 165.2; HRMS (ESI+): calcd. for $C_{11}H_{12}O_3N$ $[M+H]^+$: 206.0812, found: 206.0813.

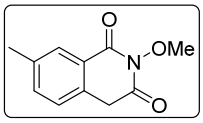


8-Chloro-2-methoxyisoquinoline-1,3(2H,4H)-dione (12h): Following the general procedure compound **12h** was obtained in 66% yield (22.4 mg) as yellow solid; R_f 0.3 (50% ethyl acetate/pet. ether); mp: 140-143 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.98 (s, 3H), 4.16 (s, 2H), 7.18–7.24 (m, 1H), 7.47–7.52 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 37.8, 64.1, 122.0, 126.4,

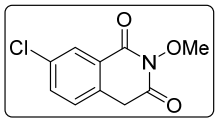


131.8, 133.6, 136.0, 136.7, 158.8, 164.2; HRMS (ESI+): calcd. for $C_{10}H_9O_3NCl$ $[M+H]^+$: 226.0265, found: 226.0265.

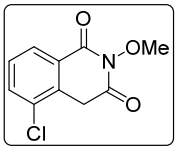
2-Methoxy-7-methylisoquinoline-1,3(2H,4H)-dione (12i): Following the general procedure compound **12i** was obtained in 75% yield (23.2 mg) as yellow solid; R_f 0.4 (50% ethyl acetate/pet. ether); mp: 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.99 (s, 3H), 4.11 (s, 2H), 7.17 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 8.02 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 37.2, 64.1, 124.9, 127.2, 129.1, 130.2, 135.0, 138.0, 161.3, 165.7; HRMS (ESI+): calcd. for $C_{11}H_{12}O_3N$ $[M+H]^+$: 206.0812, found: 206.0813.



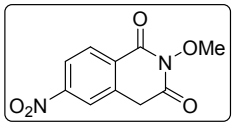
7-Chloro-2-methoxyisoquinoline-1,3(2H,4H)-dione (12j-i): Following the general procedure compound **12j-i** was obtained in 33% yield (11.2 mg) as yellow solid; R_f 0.3 (50% ethyl acetate/pet. ether); mp: 142-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (s, 3H), 4.14 (s, 2H), 7.25 (d, J = 8.2 Hz, 1H), 7.55–7.61 (m, 1H), 8.20 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.1, 64.2, 126.8, 128.8, 128.8, 131.4, 134.2, 134.4, 160.1, 164.9; HRMS (ESI+): calcd. for $C_{10}H_9O_3NCl$ $[M+H]^+$: 226.0265, found: 226.0267.



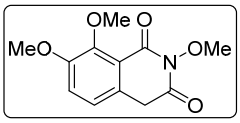
5-Chloro-2-methoxyisoquinoline-1,3(2H,4H)-dione (12j-ii): Following the general procedure compound **12j-ii** was obtained in 28% yield (9.4 mg) as yellow solid; R_f 0.3 (50% ethyl acetate/pet. ether); mp: 140-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01 (s, 3H), 4.15 (s, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.68 (dd, J = 8.0, 1.1 Hz, 1H), 8.18 (dd, J = 7.8, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.2, 64.2, 127.0, 127.8, 129.0, 131.3, 133.0, 134.4, 160.2, 164.3; HRMS (ESI+): calcd. for $C_{10}H_9O_3NCl$ $[M+H]^+$: 226.0265, found: 226.0266.



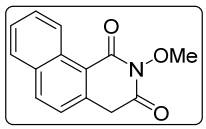
2-Methoxy-6-nitroisoquinoline-1,3(2H,4H)-dione (12k): Following the general procedure compound **12k** was obtained in 62% yield (22.0 mg) as yellow solid; R_f 0.3 (60% ethyl acetate/pet. ether); mp: 210-213 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (s, 3H), 4.30 (s, 2H), 8.20 (s, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.45 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.4, 64.4, 122.6, 122.8, 130.1, 130.9, 134.7, 150.9, 159.5, 164.1; HRMS (ESI+): calcd. for $C_{10}H_9O_5N_2$ $[M+H]^+$: 237.0506, found: 237.0507.



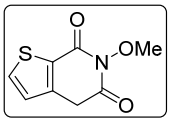
2,7,8-Trimethoxyisoquinoline-1,3(2H,4H)-dione (12l): Following the general procedure compound **12l** was obtained in 62% yield (23.3 mg) as pale yellow solid; R_f 0.3 (70% ethyl acetate/pet. ether); mp: 157-159 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.93 (s, 3H), 3.97 (s, 3H), 4.05 (s, 2H), 6.97 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 36.9, 56.3, 61.4, 64.0, 117.8, 119.1, 123.1, 125.5, 151.1, 153.1, 158.9, 165.3; HRMS (ESI+): calcd. for $C_{12}H_{14}O_5N$ $[M+H]^+$: 252.0866, found: 226.0867.



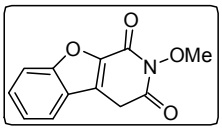
2-Methoxybenzo[h]isoquinoline-1,3(2H,4H)-dione (12m): Following the general procedure compound **12m** was obtained in 65% yield (23.5 mg) as yellow solid; R_f 0.4 (50% ethyl acetate/pet. ether); mp: 185-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.07 (s, 3H), 4.28 (s, 2H), 7.30 (d, J = 8.2 Hz, 1H), 7.59–7.64 (m, 1H), 7.74 (ddd, J = 8.6, 7.0, 1.4 Hz, 1H), 7.87–7.92 (m, 1H), 8.07 (d, J = 8.2 Hz, 1H), 9.67 (d, J = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.5, 64.1, 119.2, 124.5, 126.1, 126.9, 128.8, 129.6, 131.6, 133.0, 135.5, 135.6, 161.9, 164.9; HRMS (ESI+): calcd. for $C_{14}H_{12}O_3N$ $[M+H]^+$: 242.0812, found: 242.0812.



6-Methoxy-3a,7a-dihydrothieno[2,3-c]pyridine-5,7(4H,6H)-dione (12n): Following the general procedure compound **12n** was obtained in 77% yield (22.8 mg) as yellow solid; R_f 0.3 (60% ethyl acetate/pet. ether); mp: 165-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.00 (s, 3H), 4.09 (s, 2H), 7.02 (d, J = 5.0 Hz, 2H), 7.76 (d, J = 5.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.6, 64.3, 126.5, 128.0, 135.1, 139.9, 156.9, 165.8; HRMS (ESI+): calcd. for $C_8H_8O_3NS$ $[M+H]^+$: 198.0219, found: 198.0219.



2-Methoxybenzofuro[2,3-c]pyridine-1,3(2H,4H)-dione (12o): Following the general procedure compound **12o** was obtained in 80% yield (27.8 mg) as brown solid; R_f 0.3 (60% ethyl acetate/pet. ether); mp: 200-202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (s, 3H), 4.19 (s, 2H), 7.39–7.44 (m, 1H), 7.55–7.60 (m, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31, 65, 113, 121, 122, 124, 125, 127, 129, 140, 157, 165; HRMS (ESI+): calcd. for $C_{12}H_{10}O_4N$ $[M+H]^+$: 232.0604, found: 232.0604.

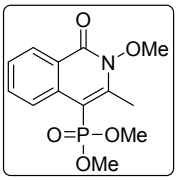


General procedure for Substrate Scope of *N*-Methoxyisoquinolinone (13)

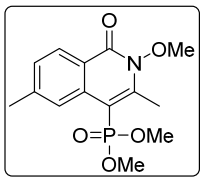
To a screw capped vial with a spin vane triangular-shaped Teflon stir bar were added (hetero)aryl oxime (0.15 mmol), diazocompound (0.17 mmol), $[IrCp^*Cl_2]_2$ (2.0 mol%, 2.4 mg), $AgNTf_2$ (8.0 mol%, 4.7 mg), and 1,2-dichloroethane (1.0 mL) under air. The reaction mixture was stirred at 35 °C for 10 h. After completion of the reaction, the reaction mixture was filtered through a pad of celite and then washed with EtOAc (5 mL x 3). Solvents were removed under reduced pressure and the residue was purified by column chromatography (EtOAc/Petroleum ether) to obtain the desired pure products.

Spectroscopic data of Synthesized Compounds

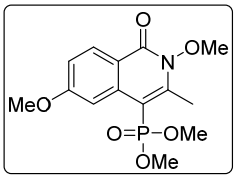
Dimethyl (2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13a): Following the general procedure compound **13a** was obtained in 90% yield (40.1 mg) as white solid; R_f 0.3 (70% ethyl acetate/pet. ether); mp: 108-110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.98 (d, J = 2.1 Hz, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 4.10 (s, 3H), 7.49 (t, J = 7.5 Hz, 1H), 7.66–7.73 (m, 1H), 8.32 (d, J = 8.5 Hz, 1H), 8.45 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.4 (d, J = 1.9 Hz), 52.3 (d, J = 5.6 Hz), 63.7, 99.7 (d, J = 199.1 Hz), 125.4 (d, J = 14.4 Hz), 126.0, 126.5, 127.6, 132.8, 134.8 (d, J = 9.5 Hz), 151.1 (d, J = 23.2 Hz), 158.3; HRMS (ESI+): calcd. for $C_{13}H_{17}O_5NP$ $[M+H]^+$: 298.0839, found: 298.0838.



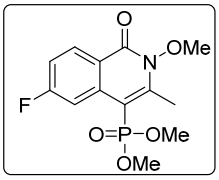
Dimethyl (2-methoxy-3,6-dimethyl-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13b) Following the general procedure compound **13b** was obtained in 84% yield (39.3 mg) as white solid; R_f 0.3 (70% ethyl acetate/pet. ether); mp: 113-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H), 2.93 (d, J = 2.2 Hz, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 4.06 (s, 3H), 7.25–7.33 (m, 1H), 8.11 (s, 1H), 8.31 (dd, J = 8.3, 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5 (d, J = 2.3 Hz), 22.4, 52.3 (d, J = 5.4 Hz), 63.7, 98.9 (d, J = 198.2 Hz), 123.2 (d, J = 14.5 Hz), 125.7 (d, J = 1.9 Hz), 127.6, 128.1, 134.8 (d, J = 9.7 Hz), 143.5, 151.0 (d, J = 23.2 Hz), 158.2; HRMS (ESI+): calcd. for $C_{14}H_{19}O_5NP$ $[M+H]^+$: 312.0995, found: 312.0995.



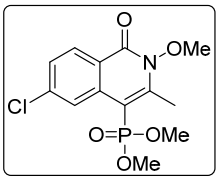
Dimethyl (2,6-dimethoxy-3-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13c) Following the general procedure compound **13c** was obtained in 85% yield (41.8 mg) as white solid; R_f 0.3 (70% ethyl acetate/pet. ether); mp: 128-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (d, J = 1.5 Hz, 3H), 3.75–3.77 (m, 3H), 3.77–3.81(m, 3H), 3.91(s, 3H), 4.07 (s, 3H), 7.05 (dd, J = 8.8, 1.7 Hz, 1H), 7.88 (d, J = 2.0 Hz, 1H), 8.34 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6 (d, J = 2.3 Hz), 52.3 (d, J = 5.5 Hz), 55.4, 63.8, 98.4 (d, J = 199.2 Hz), 108.0, 115.6, 119.1 (d, J = 14.4 Hz), 137.0 (d, J = 9.3 Hz), 151.5 (d, J = 22.3 Hz), 158.0, 162.0; HRMS (ESI+): calcd. for $C_{14}H_{19}O_6NP$ $[M+H]^+$: 328.0945, found: 328.0943.



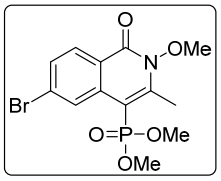
Dimethyl (6-fluoro-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13d): Following the general procedure compound **13d** was obtained in 80% yield (38.0 mg) as white solid; R_f 0.3 (60% ethyl acetate/pet. ether); mp: 129-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (s, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 4.07 (s, 3H), 7.57 (d, J = 8.6 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6, 52.3 (d, J = 5.4 Hz), 63.8, 98.7 (dd, J = 3.1, 199.3 Hz), 111.9 (d, J = 25.0 Hz), 115.2 (d, J = 23.8 Hz), 122.0 (d, J = 14.3 Hz), 130.6 (d, J = 10.7 Hz), 137.2 (dd, J = 9.2, 11.7 Hz), 152.2 (d, J = 22.7 Hz), 157.6, 166.3 (d, J = 252.0 Hz); HRMS (ESI+): calcd. for $C_{13}H_{16}O_5NFP$ $[M+H]^+$: 316.0745, found: 316.0744.



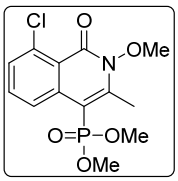
Dimethyl (6-chloro-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13e): Following the general procedure compound **13e** was obtained in 72% yield (35.8 mg) as white solid; R_f 0.3 (60% ethyl acetate/pet. ether); mp: 142-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 4.07 (s, 3H), 7.57 (d, J = 8.6 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6, 52.5 (d, J = 5.4 Hz), 63.8, 98.5 (d, J = 199.6 Hz), 124.1 (d, J = 14.1 Hz), 128.4, 128.8, 129.2, 129.9, 1.36.3 (d, J = 9.3 Hz), 152.1 (d, J = 22.5 Hz), 157.8; HRMS (ESI+): calcd. for $C_{13}H_{16}O_5NClP$ $[M+H]^+$: 332.0449, found: 332.0449.



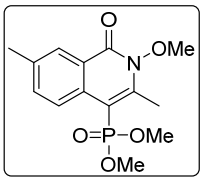
Dimethyl (6-bromo-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13f): Following the general procedure compound **13f** was obtained in 77% yield (43.5 mg) as yellow solid; R_f 0.3 (60% ethyl acetate/pet. ether); mp: 137-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.93 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 4.07 (s, 3H), 7.57 (d, J = 8.6 Hz, 1 H), 8.26 (d, J = 8.3 Hz, 1 H), 8.53 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.6, 52.5 (d, J = 5.5 Hz), 63.8, 98.5 (d, J = 199.5 Hz), 124.1 (d, J = 13.9 Hz), 128.4, 128.8, 129.2, 129.9, 1.36.3 (d, J = 9.2 Hz), 152.1 (d, J = 22.5 Hz), 157.8; HRMS (ESI+): calcd. for $C_{13}H_{16}O_5NBrP$ $[M+H]^+$: 375.9944, found: 375.9947.



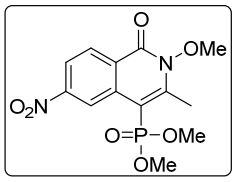
Dimethyl (8-chloro-2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13h): Following the general procedure compound **13h** was obtained in 70% yield (34.8 mg) as pale yellow solid; R_f 0.3 (60% ethyl acetate/pet. ether); mp: 102-105 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.91 (d, J = 2.1 Hz, 3H), 3.72 (s, 3H), 3.77 (s, 3H), 4.05 (s, 3H), 7.42–7.55 (m, 2H), 8.26 (dd, J = 6.9, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7, 52.4 (d, J = 5.7 Hz), 63.7, 98.3 (d, J = 200.8 Hz), 121.8 (d, J = 14.5 Hz), 125.0, 129.8, 132.1, 135.1 (d, J = 3.0 Hz), 137.9 (d, J = 10.3 Hz), 152.1 (d, J = 22.2 Hz), 156.3; HRMS (ESI+): calcd. for $C_{13}H_{16}O_5NClP$ $[M+H]^+$: 332.0449, found: 332.0449.



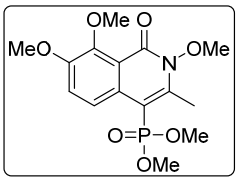
Dimethyl (2-methoxy-3,7-dimethyl-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13i): Following the general procedure compound **13i** was obtained in 62% yield (29.0 mg) as white solid; R_f 0.3 (70% ethyl acetate/pet. ether); mp: 120-122 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 17 H), 2.94 (d, J=2.3 Hz, 16 H), 3.73 (s, 17 H), 3.78 (s, 17 H), 4.07 (s, 17 H), 7.48 (dd, J=8.7, 1.8 Hz, 5 H), 8.18 (d, J=8.7 Hz, 6 H), 8.23 (br. s., 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 21.0, 52.2 (d, J = 5.1 Hz), 63.7, 99.0 (d, J = 199.5 Hz), 125.3 (d, J = 14.2 Hz), 125.9, 127.1, 132.4 (d, J = 9.3 Hz), 134.3, 136.7, 150.0 (d, J = 23.7 Hz), 158.3; HRMS (ESI+): calcd. for $C_{14}H_{19}O_5NP$ $[M+H]^+$: 312.0995, found: 312.0992.



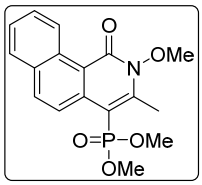
Dimethyl (2-methoxy-3-methyl-6-nitro-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13k): Following the general procedure compound **13k** was obtained in 66% yield (34.0 mg) as pale yellow solid; R_f 0.3 (80% ethyl acetate/pet. ether); mp: 157-159 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.00 (d, J = 2.3 Hz, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.13 (s, 3H), 8.23 (dd, J = 8.8, 2.3 Hz, 1H), 8.58–8.61 (m, 1H), 9.32 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7 (d, J = 1.7 Hz), 52.7 (d, J = 5.9 Hz), 64.0, 99.8 (d, J = 201.3 Hz), 120.2, 122.3, 129.1 (d, J = 13.5 Hz),, 129.6, 135.8 (d, J = 8.7 Hz), 150.4, 153.2 (d, J = 22.1 Hz), 157.2; HRMS (ESI+): calcd. for $C_{13}H_{16}O_7N_2P$ $[M+H]^+$: 343.0690, found: 343.0688.



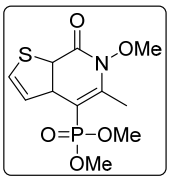
Dimethyl (2,7,8-trimethoxy-3-methyl-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13l): Following the general procedure compound **13l** was obtained in 75% yield (40.2 mg) as light yellow oil; R_f 0.3 (80% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.89 (d, J = 2.4 Hz, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 4.05 (s, 3H), 7.31 (d, J = 9.2 Hz, 1H), 8.08 (d, J = 9.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.9, 52.4 (d, J = 5.7 Hz), 63.7, 99.1 (d, J = 200.5 Hz), 119.2 (d, J = 14.0 Hz), 123.3 (d, J = 2.7 Hz), 126.9, 127.2, 127.9, 128.6, 131.4, 133.8, 137.4 (d, J = 9.5 Hz), 151.8 (d, J = 22.8 Hz), 158.5; HRMS (ESI+): calcd. for $C_{15}H_{21}O_7NP$ $[M+H]^+$: 358.1050, found: 358.1049.



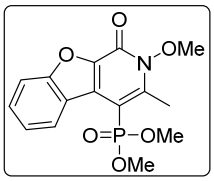
Dimethyl (2-methoxy-3-methyl-1-oxo-1,2-dihydrobenzo[h]isoquinolin-4-yl)phosphonate (13m): Following the general procedure compound **13m** was obtained in 77% yield (40.2 mg) as brown sticky solid; R_f 0.3 (60% ethyl acetate/pet. ether); mp: 107-109 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.05 (d, J = 2.1 Hz, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 4.15 (s, 3H), 7.63 (td, J = 7.4, 1.1 Hz, 1H), 7.75 (ddd, J = 8.7, 7.0, 1.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 8.04 (d, J = 9.2 Hz, 1H), 8.38 (d, J = 9.2 Hz, 1H), 10.10 (d, J = 8.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.4 (d, J = 1.9 Hz), 52.3 (d, J = 5.6 Hz), 63.7, 99.7 (d, J = 199.1 Hz), 125.4 (d, J = 14.4 Hz), 126.0, 126.5, 127.6, 132.8, 134.8 (d, J = 9.5 Hz), 151.1 (d, J = 23.2 Hz), 158.3; HRMS (ESI+): calcd. for $C_{17}H_{19}O_5NP$ $[M+H]^+$: 348.0995, found: 348.0995.



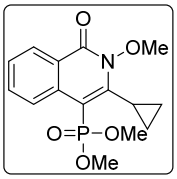
Dimethyl (6-methoxy-5-methyl-7-oxo-3a,6,7,7a-tetrahydrothieno[2,3-c]pyridin-4-yl)phosphonate (13n): Following the general procedure compound **13n** was obtained in 77% yield (35.0 mg) as white solid; R_f 0.3 (70% ethyl acetate/pet. ether); mp: 108-111 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.87 (d, J = 2.1 Hz, 3H), 3.75 (s, 3H), 3.77 (s, 3H), 4.10 (s, 3H), 7.71 (d, J = 5.5 Hz, 1H), 7.75 (d, J = 5.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.1 (d, J = 1.9 Hz), 52.4 (d, J = 5.4 Hz), 64.0, 98.3 (d, J = 201.8 Hz), 126.2, 128.9 (d, J = 16.6 Hz), 133.6, 143.3 (d, J = 9.7 Hz), 150.5 (d, J = 22.4 Hz), 154.7; HRMS (ESI+): calcd. for $C_{14}H_{15}O_5NPS$ $[M+H]^+$: 304.0403, found: 304.0402.



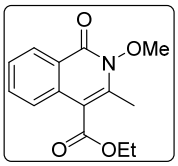
Dimethyl (2-methoxy-3-methyl-1-oxo-1,2-dihydrobenzofuro[2,3-c]pyridin-4-yl)phosphonate (13o): Following the general procedure compound **13o** was obtained in 62% yield (31.4 mg) as pale yellow solid; R_f 0.3 (70% ethyl acetate/pet. ether); mp: 189-192 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.05 (d, J = 2.0 Hz, 3H), 3.78 (s, 3H), 3.84 (s, 3H), 4.18 (s, 3H), 7.35–7.47 (m, 1H), 7.57 (td, J = 7.7, 1.3 Hz, 1H), 7.65–7.74 (m, 1H), 8.39 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1, 52.5 (d, J = 5.7 Hz), 64.3, 95.3 (d, J = 206.3 Hz), 112.5, 122.1, 123.7, 125.6, 127.2 (d, J = 8.3 Hz), 129.1, 142.8 (d, J = 18.6 Hz), 150.3 (d, J = 24.8 Hz), 151.1, 157.2; HRMS (ESI+): calcd. for $C_{15}H_{17}O_6NP$ $[M+H]^+$: 338.0788, found: 338.0786.



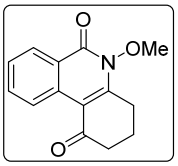
Dimethyl (3-cyclopropyl-2-methoxy-1-oxo-1,2-dihydroisoquinolin-4-yl)phosphonate (13q): Following the general procedure compound **13q** was obtained in 88% yield (42.7 mg) as yellow oil; R_f 0.3 (70% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96–1.01 (m, 2H), 1.23–1.28 (m, 2H), 2.19–2.29 (m, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 4.12 (s, 3H), 7.44–7.50 (m, 1H), 7.65 (ddd, J = 8.5, 7.1, 1.8 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 8.40 (dt, J = 8.1, 1.7 Hz, 1H);; ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.5, 12.8 (d, J = 3.7 Hz), 52.5 (d, J = 5.8 Hz), 64.2, 102.9 (d, J = 204.2 Hz), 125.7 (d, J = 14.3 Hz), 126.1 (d, J = 2.8 Hz), 126.7, 127.5, 132.5, 134.8 (d, J = 8.7 Hz), 154.5 (d, J = 20.2 Hz), 158.5; HRMS (ESI+): calcd. for $C_{15}H_{19}O_5NP$ $[M+H]^+$: 324.0995, found: 324.0995.



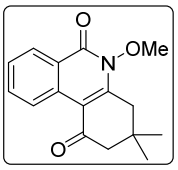
Ethyl 2-methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (14a): Following the general procedure compound **14a** was obtained in 60% yield (23.6 mg) as light yellow oil; R_f 0.4 (40% ethyl acetate/pet. ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (t, J = 7.3 Hz, 3H), 2.54–2.57 (m, 3H), 4.09 (s, 3H), 4.47 (q, J = 6.9 Hz, 2H), 7.48 (ddd, J = 7.9, 5.2, 3.0 Hz, 1H), 7.65–7.71 (m, 2H), 8.41–8.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 14.9, 61.7, 63.8, 109.6, 123.8, 125.3, 126.6, 127.8, 132.8, 133.1, 140.7, 158.2, 166.8; HRMS (ESI+): calcd. for $C_{14}H_{16}O_4N$ $[M+H]^+$: 262.1074, found: 262.1071.



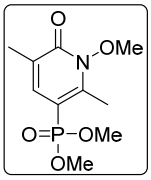
5-Methoxy-3,4-dihydrophenanthridine-1,6(2H,5H)-dione (14b): Following the general procedure compound **14b** was obtained in 58% yield (21.2 mg) as white solid; R_f 0.3 (40% ethyl acetate/pet. ether); mp: 130-134 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.18–2.23 (m, 2H), 2.63–2.67 (m, 2H), 3.17 (t, J = 6.1 Hz, 2H), 4.12 (s, 3H), 7.47–7.52 (m, 1H), 7.71–7.75 (m, 1H), 8.41 (dd, J = 8.0, 1.1 Hz, 1H), 9.24 (d, J = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.6, 24.8, 38.8, 64.1, 109.8, 125.0, 126.3, 127.1, 127.3, 133.3, 133.7, 153.1, 158.5, 196.1; HRMS (ESI+): calcd. for $C_{14}H_{14}O_3N$ $[M+H]^+$: 244.0968, found: 244.0968.



5-Methoxy-3,3-dimethyl-3,4-dihydrophenanthridine-1,6(2H,5H)-dione (14c): Following the general procedure compound **14c** was obtained in 64% yield (26.0 mg) as light yellow solid; R_f 0.4 (50% ethyl acetate/pet. ether); mp: 126-128 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (s, 6H), 2.53 (s, 2H), 3.03 (s, 2H), 4.11 (s, 3H), 7.51 (td, J = 7.6, 1.1 Hz, 1H), 7.75 (ddd, J = 8.6, 7.1, 1.6 Hz, 1H), 8.43 (dd, J = 8.1, 1.1 Hz, 1H), 9.28 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 31.8, 38.3, 52.5, 64.1, 108.8, 125.0, 126.2, 127.1, 127.4, 133.1, 133.7, 151.4, 158.7, 196.3; HRMS (ESI+): calcd. for $C_{16}H_{18}O_3N$ $[M+H]^+$: 272.1281, found: 272.1280.



Dimethyl (1-methoxy-2,5-dimethyl-6-oxo-1,6-dihydropyridin-3-yl)phosphonate (13p): Following the general procedure compound **13p** was obtained in 80% yield (31.5 mg) as light yellow oil; R_f 0.3 (40% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.15 (s, 3H), 2.66 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 4.06 (s, 3H), 7.46 (d, J = 11.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.3 (d, J = 2.9 Hz), 16.7, 52.8 (d, J = 5.5



Hz), 63.6, 100.2 (d, J = 207.4 Hz), 128.1 (d, J = 14.8 Hz), 137.6 (d, J = 8.2 Hz), 150.8 (d, J = 20.7 Hz), 159.3; HRMS (ESI+): calcd. for $C_{10}H_{17}O_5NP$ $[M+H]^+$: 262.0839, found: 262.0837.

X-Ray Crystallographic Information

General information

Single-crystal X-ray data of **12h**, **13b** and **13n** were collected on a Bruker KAPPA APEX II CCD Duo diffractometer, using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from total 36 frames. The X-ray data acquisition was monitored by APEX 2 program suit. All the data were corrected for Lorentz-polarization and absorption effects using SAINT and SADABS programs integrated in APEX 2 package. The structures were solved by direct methods and refined by full matrix least squares, based on F^2, using SHELX-97. Molecular diagrams were generated using Mercury programs. Geometrical calculations were performed using SHELXTL and PLATON. The H atoms for the **12h**, **13b** and **13n** were placed in geometrically idealized positions (C-H = 0.93 and C-H = 0.97 Å for the phenyl and methylene H atoms) and constrained to ride on their parent atoms [Uiso(H) = 1.2 Ueq(C)].

Table 8. *Crystal Data of Compounds* ***12h, 13b,*** *and* ***13n***

Crystal Data	**Compound 12h**	**Compound 13b**	**Compound 13n**
Formula	C_{10} H_8 Cl N O_3	C15 H18 O5 P	C11 H14 N O5 P S
Mr	225.62	309.26	303.26
Crystal Size, mm	0.498 x 0.325 x 0.124	0.42 x 0.35 x 0.124	0.35 x 0.25 x 0.15
Temp. (K)	296(2) K	296(2) K	150(2) K
Crystal Syst.	Monoclinic	Triclinic	Monoclinic
Space Group	P 21/c	P-1	P2(1)/c
a/Å	9.2286(6)	8.0151(6)	9.0499(5)
b/Å	12.6651(9)	9.9592(8)	9.3721(6)
c/Å	8.3177(6)	10.3467(8)	16.1145(10)
$\alpha/^0$	90	69.516(4)	90
$\beta/^0$	96.240(3)	72.945(4)	105.5360(10)
$\gamma/^0$	90	89.454(4)	90
V/Å3	966.42(12)	735.66(10)	1316.84(14)
Z	4	2	4
*D*calc/g cm^{-3}	1.551	1.396	1.530
μ/mm^{-1}	0.379	0.206	0.383
F(000)	464	326	632
Ab. Correct.	multi-scan	multi-scan	multi-scan
Tmin/ Tmax	2.742 to 28.345	2.893 to 28.459°	2.34 to 24.98

2Θmax			
Total reflns.	30222	18852	11778
Unique reflns.	2406	3680	2318
Obs. reflns.			
h, k, l (min, max)	-12, 12 -16, 16 -11, 11	-10, 10 -13, 13 -13, 13	-10, 10 -11, 11 -19, 18
R_{int}	0.0507	0.0519	0.0207
No. of para	137	195	176
R1 [*I*> 2*σ*(*I*)]	0.0511	0.0624	0.0295
wR2[*I*> 2*σ*(*I*)]	0.1419	0.1707	0.0753
R1 [all data]	0.0697	0.1036	0.0312
wR2 [all data]	0.1560	0.1925	0.0765
goodness-offit	1.024	1.220	0.975
$\Delta\rho_{max}$,$\Delta\rho_{min}$ (eÅ^{-3})	0.550 and -0.239	0.672 and -0.377	0.380 and -0.289
CCDC no.			

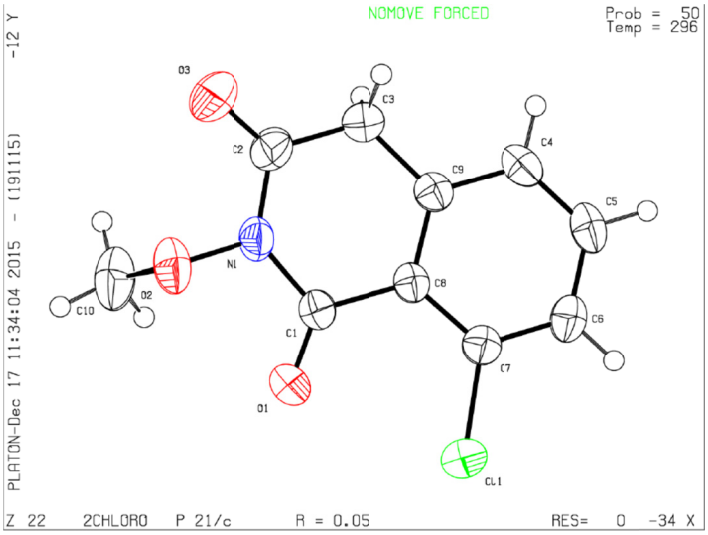


Figure 9. *ORTEP structure of compound* ***12h***

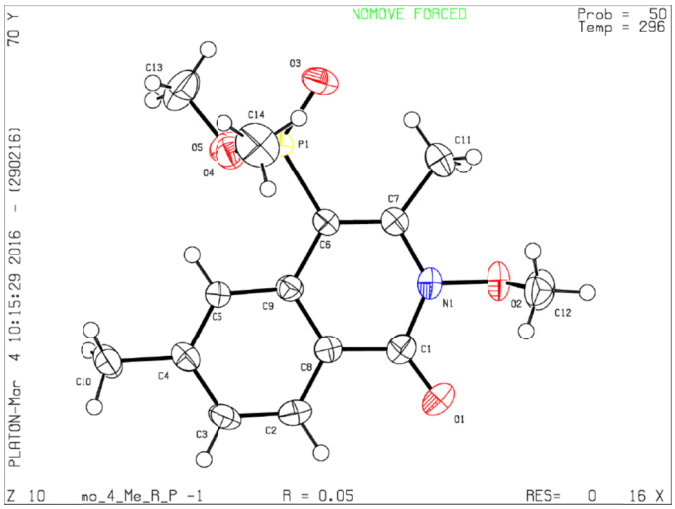


Figure 10. *ORTEP diadram of compound* ***13b***.

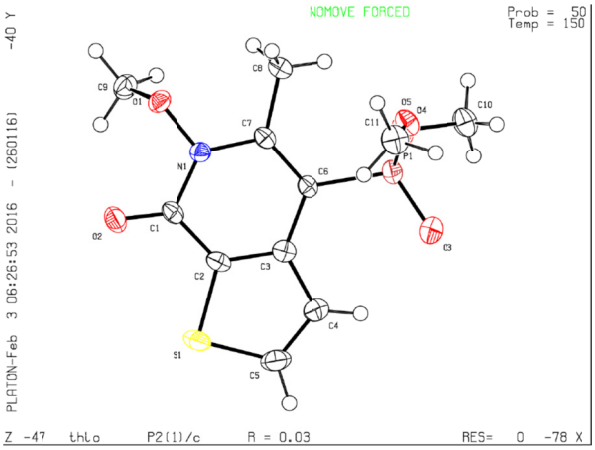
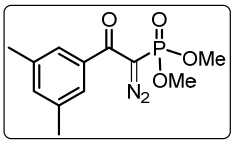
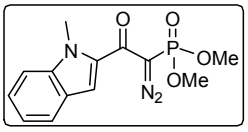


Figure 10. *ORTEP diagram of compound* ***13n***

Dimethyl (1-diazo-2-(3,5-dimethylphenyl)-2-oxoethyl)phosphonate (2l): Following the general procedure compound **2l** was obtained in 88% yield as pale yellow solid; R_f 0.4 (50% ethyl acetate/petroleum ether); mp: 75-80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 6H), 3.92 (s, 3H), 3.95 (s, 3H), 7.27 (s, 1H), 7.36 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.2, 54.0, 54.1, 124.9. 134.1, 136.7, 138.4, 187.7 (d, J = 8.8 Hz)ppm; HRMS (ESI+): calcd. for $C_{12}H_{16}N_2O_4P^+$ 283.0842, found 283.0842.



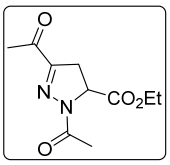
Dimethyl (1-diazo-2-(1-methyl-1H-indol-2-yl)-2-oxoethyl)phosphonate (2m): Following the general procedure compound **2m** was obtained in 72% yield as dark brown sticky solid; R_f 0.4 (60% ethyl acetate/petroleum ether); mp: 66-70 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 3.91 (s, 3H), 3.96 (s, 3H), 7.16–7.19 (m, 2H), 7.39 (d, J = 3.7 Hz, 2H), 7.70 (d, J = 7.9 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 31.7, 54.0, 54.1, 109.0, 110.2, 121.0, 122.8, 125.6, 125.8, 132.4 (d, J = 5.7 Hz), 139.5, 178.0 (d, J = 9.5 Hz) ppm; HRMS (ESI+): calcd. for $C_{13}H_{15}N_3O_4P^+$ 308.0795, found 308.0794.



General Procedure for the CsF-Mediated Dephosphonylation and Cycloaddition with Ethyl Acrylate or Acrylonitrile

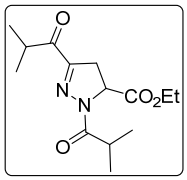
To a flame-dried two necked RB flask equipped with a magnetic stir bar was added dry CsF (114 mg, 0.75 mmol, 3 equiv). The RB flask was evacuated and backfilled with argon and CH_3CN (1.0 mL). To this, were added dimethyl diazo compounds (**2**, 0.55 mmol, 2.2 equiv), ethyl acrylate (**15,** 0.25 mmol, 1.0 equiv) and stirred at 25 °C for 2–6 h. After completion of the reaction (2–6 h) as indicated by TLC, solvent was evaporated and the crude residue was purified by silica gel column chromatography to afford 4,5-dihydro-pyrazole **16**.

Ethyl 1,3-diacetyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate (16a): Following the general procedure compound **16a** was obtained in 88% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H), 2.43 (s, 3H), 2.50 (s, 3H), 3.11 (dd, J = 6.3, 19.0 Hz, 1H), 3.38 (dd, J = 13.0, 19.0

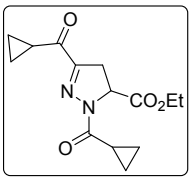


Hz, 1H), 4.25 (dd, J = 7.2, 14.3 Hz, 2H), 4.95 (q, J = 6.2, 13.0 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.0, 21.2, 25.7, 35.3, 58.8, 62.1, 152.6, 169.2, 169.9, 193.9 ppm; HRMS (ESI+): calcd. for $C_{10}H_{14}N_2O_4Na^+$ 249.0846, found 249.0851.

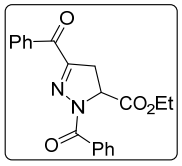
Ethyl 1,3-diisobutyryl-4,5-dihydro-1*H*-pyrazole-5-carboxylate (16b): Following the general procedure compound **16b** was obtained in 75% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (s, 3H), 1.20–1.22 (m, 6H), 1.24–1.30 (m, 6H), 3.11 (dd, J = 6.4, 18.8 Hz, 1H), 3.37 (dd, J = 9.8, 18.6 Hz, 1H), 3.43 (dd, J = 6.9, 13.7 Hz, 1H), 3.59 (q, J = 6.9, 13.7 Hz, 1H), 4.18–4.26 (m, 2H), 4.94 (dd, J = 6.4, 13.0 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0, 18.4, 18.6, 18.7, 18.8, 31.8, 35.2, 36.1, 58.5, 61.9, 151.1, 169.3, 176.4, 200.3 ppm; HRMS (ESI+): calcd. for $C_{14}H_{22}N_2O_4Na^+$ 305.1472, found 305.1467.



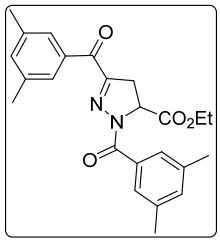
Ethyl 1,3-di(cyclopropanecarbonyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate (16c): Following the general procedure compound **16c** was obtained in 78% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94–1.00 (m, 2H), 1.04–1.08 (m, 2H), 1.10–1.16 (m, 2H), 1.17–1.21 (m, 2H), 1.23–1.26 (m, 3H), 2.71 (sept., J = 4.6Hz, 1H), 2.98 (sept., J = 4.6 Hz, 1H), 3.14 (dd, J = 6.4, 18.8 Hz, 1H), 3.41 (dd, J = 12.8, 18.8 Hz, 1H), 4.16–4.25 (m, 2H), 4.96 (dd, J = 6.4, 12.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 9.2, 9.3, 11.7, 12.3, 12.4, 14.0, 17.0, 35.3, 59.0, 61.9, 152.9, 169.3, 173.2, 195.9 ppm; HRMS (ESI+): calcd. for $C_{14}H_{18}N_2O_4Na^+$ 301.1159, found 301.1155.



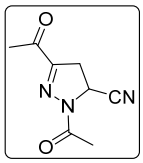
Ethyl 1,3-dibenzoyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate (16d): Following the general procedure compound **16d** was obtained in 82 % yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (t, J = 7.1 Hz, 3H), 3.39 (dd, J = 6.3, 18.8 Hz, 1H), 3.67 (dd, J = 12.9, 18.8 Hz, 1H), 4.27–4.32 (m, 2H), 5.21 (dd, J = 6.3, 12.9 Hz, 1H), 7.41–7.46 (m, 4H), 7.53–7.60 (m, 2H), 7.79 (d, J = 8.0 Hz, 2H), 8.19 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.1, 36.3, 59.1, 62.1, 127.8, 128.3, 130.1, 130.3, 131.9, 132.5, 133.5, 135.4, 153.0, 167.6, 169.3, 186.6 ppm; HRMS (ESI+): calcd. for $C_{20}H_{19}N_2O_4^+$ 351.1339, found 351.1338.



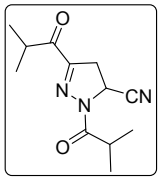
Ethyl 1,3-bis(3,5-dimethylbenzoyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate (16e): Following the general procedure compound **16e** was obtained in 84% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.35 (t, J = 7.3 Hz, 3H), 2.31 (s, 6H), 2.35 (s, 6H), 3.36 (dd, J = 6.5, 18.5 Hz, 1H), 3.64 (dd, J = 13.0, 18.5 Hz, 1H), 4.27–4.32 (m, 2H), 5.17 (dd, J = 6.5, 13.0 Hz, 1H) 7.16 (s, 1H), 7.21 (s, 1H), 7.56 (s, 2H), 7.80 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.1, 21.2, 21.3, 36.3, 59.0, 62.1, 127.6, 128.0, 132.6, 133.3, 135.1, 135.5, 137.4, 137.8, 153.2, 168.2, 169.4, 168.8 ppm; HRMS (ESI+): calcd. for $C_{24}H_{27}N_2O_4M^+$ 407.1965, found 407.1960.



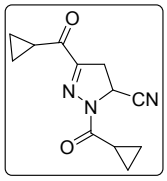
1,3-Diacetyl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile (16f): Following the general procedure compound **16f** was obtained in 68% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.44 (s, 3H), 2.52 (s, 3H), 3.47 (d, J = 9.6 Hz, 2H), 5.18 (t, J = 9.6 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 21.3, 25.7, 36.2, 46.0, 115.7, 152.7, 169.4, 193.0 ppm; HRMS (ESI+): calcd. for $C_8H_{10}N_3O_2^+$ 180.0768, found 180.0771.



1,3-Diisobutyryl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile (16g): Following the general procedure compound **16g** was obtained in 68% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (d, J = 7.1 Hz, 3H), 1.23 (d, J = 7.1 Hz, 6H), 1.28 (d, J = 7.1 Hz, 3H), 3.34 (sept., J = 7.1 Hz, 1H), 3.44 (d, J = 9.5 Hz, 2H), 3.54 (sept., J = 7.1Hz, 1H), 5.13 (t, J = 9.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.5, 18.6, 18.7, 32.3, 36.2, 36.4, 45.9, 115.9, 151.2, 176.0, 195.5 ppm; HRMS (ESI+): calcd. for $C_{12}H_{18}N_3O_2^+$ 236.1394, found 236.1393.

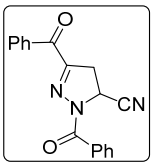


1,3-Di(cyclopropanecarbonyl)-4,5-dihydro-1*H*-pyrazole-5-carbonitrile (16h): Following the general procedure compound **16h** was obtained in 71% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00–1.05 (m, 2H), 1.08–1.13 (m, 2H), 1.22–1.27 (m, 4H), 2.57–2.62 (m, 1H), 2.87–2.93 (m, 1H), 3.47 (d, J =

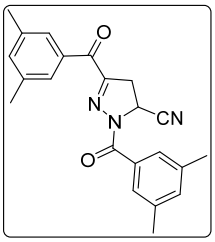


9.6 Hz, 2H), 5.17 (d, J = 9.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 9.8, 9.9, 11.9, 12.6, 12.8, 17.2, 36.2, 46.2, 115.9, 152.8, 172.9, 195.2 ppm; HRMS (ESI+): calcd. for $C_{12}H_{13}N_3O_2Na^+$ 254.0900, found 254.0898.

1,3-Dibenzoyl-4,5-dihydro-1*H*-pyrazole-5-carbonitrile (16i): Following the general procedure compound **16i** was obtained in 78% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.66–3.77 (m, 2H), 5.40 (dd, J = 7.4, 11.7 Hz, 1H), 7.43–7.48 (m, 4H), 7.57–7.63 (m, 2H), 7.99 (d, J = 8.0 Hz, 2H), 8.17 (d, J = 8.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 37.1, 46.5, 116.0, 128.0, 128.4, 130.2, 130.3, 131.3, 132.6, 133.9, 134.9, 153.0, 167.0, 185.8 ppm; HRMS (ESI+): calcd. for $C_{18}H_{13}N_3O_2^+$ 303.1001, found 303.1001.



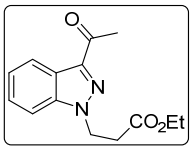
1,3-Bis(3,5-dimethylbenzoyl)-4,5-dihydro-1*H*-pyrazole-5-carbonitrile (16j): Following the general procedure compound **16j** was obtained in 80% yield as white solid; R_f 0.4 (50% ethyl acetate/petroleum ether); mp: 176-180 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 6H), 2.36 (s, 6H), 3.62–3.75 (m, 2H), 5.38 (dd, J = 7.5, 11.8 Hz, 1H), 7.21 (s, 1H), 7.25 (s, 1H), 7.59 (s, 2H), 7.79 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ21.2, 21.3, 37.1, 46.6, 116.1, 127.8, 128.0, 131.4, 134.1, 135.0, 135.6, 137.7, 138.1, 153.1, 167.6, 186.0 ppm; HRMS (ESI+): calcd. for $C_{22}H_{21}N_3O_2Na^+$ 382.1526, found 382.1523.



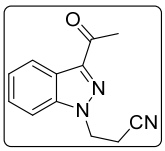
General procedure for Substrate Scope of Indazoles (19)

To a flame-dried two necked RB flask equipped with a magnetic stir bar was added dry CsF (230 mg, 1.5 mmol, 6 equiv). Then the RB flask was evacuated and backfilled with argon. To this, were added CH_3CN (1.5 mL), diazo compound **2** (0.25 mmol, 1.0 equiv), ethyl acrylate or acrylonitrile **15**/**17** (0.27 mmol, 1.1 equiv) and the aryne precursor **18** (0.27 mmol, 1.1 equiv). Subsequently the mixture was stirred at 25 °C for 2–5 h under argon atmosphere. The solvent was evaporated and the crude residue was purified by silica gel column chromatography to afford corresponding indazole derivative **5**.

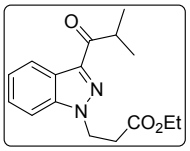
Ethyl 3-(3-acetyl-1H-indazol-1-yl)propanoate (19a): Following the general procedure compound **19a** was obtained in 86% yield as colorless sticky solid; R_f 0.4 (50% ethyl acetate/petroleum ether);mp: 79-82 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 (t, J = 7.1 Hz, 3H), 2.71 (s, 3H), 3.07 (t, J = 6.9 Hz, 2H), 4.15 (dd, J = 7.1, 14.2 Hz, 2H), 4.75 (t, J = 6.9 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 8.37 (d, J = 8.3 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.1, 26.8, 34.2, 44.7, 61.0, 109.4, 122.6, 123.0, 123.7, 127.0, 140.9, 142.7, 170.8, 194.8 ppm; HRMS (ESI+): calcd. for $C_{14}H_{16}O_3N_2Na^+$ 283.1053, found 283.1053.



3-(3-Acetyl-1H-indazol-1-yl)propanenitrile (19b): Following the general procedure compound **19b** was obtained in 77% yield as colorless solid; R_f 0.4 (50% ethyl acetate/petroleum ether); mp: 122-125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.72 (s, 3H), 3.12 (t, J = 7.0 Hz, 2H), 4.75 (t, J = 7.0 Hz, 2H), 7.36–7.39 (m, 1H), 7.49–7.53 (m, 2H), 8.40 (d,J = 8.1 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.4, 26.8, 44.7, 108.6, 116.7, 122.7, 123.3, 124.1, 127.7, 140.8, 143.5, 194.6 ppm; HRMS (ESI+): calcd. for $C_{12}H_{11}ON_3Na^+$ 236.0794, found 236.0795.

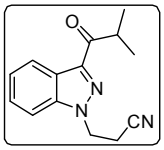


Ethyl 3-(3-isobutyryl-1H-indazol-1-yl)propanoate (19c): Following the general procedure compound **19c** was obtained in 80% yield as colorless thick oil;R_f 0.4 (50% ethyl acetate/petroleum ether; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J = 7.3 Hz, 3H), 1.27 (bs, 6H), 3.07 (t, J = 6.7 Hz, 2H), 3.25 (quint., J = 6.7 Hz, 1H), 4.15 (dd, J = 7.3, 14.0 Hz, 2H), 4.75 (t, J = 7.3 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 8.39

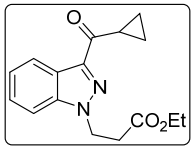


(d, J = 7.9 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.1, 19.0, 34.2, 36.3, 44.7, 61.0, 109.3, 123.1, 123.6, 126.9, 140.9, 141.3, 170.8, 201.3 ppm; HRMS (ESI+): calcd. for $C_{16}H_{20}N_2O_3Na^+$ 311.1366, found 311.1364.

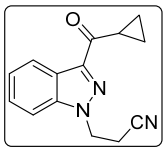
3-(3-Isobutyryl-1H-indazol-1-yl)propanenitrile (19d): Following the general procedure compound **19d** was obtained in 78% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (bs, 3H), 1.28 (bs, 3H), 3.09 (t, J = 7.0 Hz, 2H), 3.39 (sept., J = 6.9Hz, 1H), 4.73 (t, J = 7.0 Hz, 2H), 7.33–7.37 (m, 1H), 7.47–7.48 (m, 2H), 8.38–8.40 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.4, 19.0, 36.4, 44.7, 108.6, 116.7, 123.3, 123.5, 124.0, 127.6, 140.8, 142.1, 201.1 ppm; HRMS (ESI+): calcd. for $C_{14}H_{15}N_3ONa^+$ 264.1107, found 264.1105.



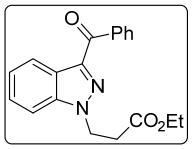
Ethyl 3-(3-(cyclopropanecarbonyl)-1H-indazol-1-yl)propanoate (19e): Following the general procedure compound **19e** was obtained in 82% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04–1.07 (m, 2H), 1.21 (t, J = 6.9 Hz, 3H), 1.29–1.31 (m, 2H), 3.09 (t, J = 6.9 Hz, 2H), 3.25 (sept., J = 4.2 H), 4.15 (dd, J = 7.3, 14.5 Hz, 2H), 4.78 (t, J = 6.9 Hz, 2H), 7.34 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 8.37 (d, J = 8.1 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 11.3, 14.1, 17.2, 34.3, 44.8, 61.0, 109.3, 125.5, 123.0, 123.6, 127.0, 140.9, 143.0, 170.9, 196.6 ppm; HRMS (ESI+): calcd. for $C_{16}H_{18}N_2O_3Na^+$ 309.1210, found 309.1206.



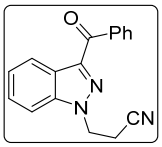
3-(3-(Cyclopropanecarbonyl)-1H-indazol-1-yl)propanenitrile (19f): Following the general procedure compound **19f** was obtained in 78% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (sext.,J = 3.8Hz, 2H), 1.10 (quint.,J = 3.8 Hz, 2H),3.13 (t, J = 6.9 Hz, 2H), 3.24 (sept., J = 4.2 Hz, 1H), 4.77 (t, J = 7.3 Hz, 2H), 7.38 (quint.,J = 4.6Hz, 1H), 7.51 (d, J = 3.4 Hz, 2H), 8.40 (d, J = 8.0 Hz, 1H);^{13}C-NMR (125 MHz, $CDCl_3$): δ11.5, 17.4, 18.4, 44.8, 108.6, 116.7, 122.7, 123.4, 124.0, 127.7, 140.8, 143.8, 196.5 ppm; HRMS (ESI+): calcd. for $C_{14}H_{13}N_3ONa^+$ 262.0951, found 262.0949.



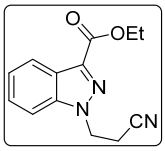
Ethyl 3-(3-acetyl-1H-indazol-1-yl)propanoate (19g): Following the general procedure compound **19g** was obtained in 88% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.19 (t, J = 7.1 Hz, 3H), 3.09 (t, J = 6.8 Hz, 2H), 4.13 (dd, J = 7.1, 14.3 Hz, 2H), 4.80 (t, J = 6.9 Hz, 2H), 7.40 (td, J = 0.9, 7.6 Hz, 1H), 7.48–7.54 (m, 3H), 7.58–7.63 (m, 2H), 8.32–8.83 (m, 2H), 8.47 (dt, J = 1.1, 8.4 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.0, 34.3, 44.8, 61.0, 109.4, 123.2, 123.7, 124.5, 127.2, 128.1, 130.6, 132.4, 137.9, 140.5, 142.2, 170.8, 188.4; HRMS (ESI+): calcd. for $C_{19}H_{18}O_3N_2Na^+$ 345.1210, found 345.1210.



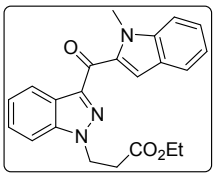
3-(3-Benzoyl-1H-indazol-1-yl)propanenitrile (19h): Following the general procedure compound **19h** was obtained in 79% yield as white solid; R_f 0.4 (50% ethyl acetate/petroleum ether); mp: 114-117 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.12 (t, J = 6.8 Hz, 2H), 4.80 (t, J = 7.0 Hz, 2H), 7.40–7.44 (m, 1H), 7.52–7.56 (m, 4H), 7.61–7.68 (m, 1H), 8.33 (d, J = 8.0 Hz, 2H), 8.49 (d, J = 8.4 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.4, 44.8, 108.6, 116.8, 123.6, 124.1, 124.6, 127.8, 128.2, 130.5, 132.7, 137.6, 140.4, 143.0, 188.4 ppm; HRMS (ESI+): calcd. for $C_{17}H_{13}ON_3Na^+$ 298.0951, found 298.0950.



Ethyl 1-(2-cyanoethyl)-1H-indazole-3-carboxylate (19i): Following the general procedure compound **19i** was obtained in 31% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52 (t, J = 7.1 Hz, 3H), 3.10 (t, J = 6.9 Hz, 2H), 4.57 (q, J = 7.1, 14.3 Hz, 2H), 4.79 (t, J = 6.9 Hz, 2H), 7.39 (dt, J = 1.2, 7.3 Hz, 1H), 7.5–7.56 (m, 2H), 8.25 (d, J = 8.3 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.5,18.6, 44.9, 61.3, 109.0, 116.7, 122.6, 123.6, 123.7, 127.7, 136.7, 140.8, 162.3 ppm; HRMS (ESI+): calcd. for $C_{13}H_{13}N_3O_2Na^+$ 266.0900, found 266.0901.

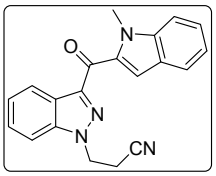


Ethyl 3-(3-(1-methyl-1H-indole-2-carbonyl)-1H-indazol-1-yl)propanoate (19j): Following the general procedure compound **19j** was obtained in 74% yield brown thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (t, J = 7.0 Hz, 3H), 3.13 (t, J = 6.7 Hz, 2H), 4.17 (q, J = 7.2, 14.3 Hz, 2H), 4.20 (s, 3H), 4.83 (t, J = 6.5 Hz, 2H), 7.17–7.20 (m, 1H), 7.36–7.40 (m, 1H), 7.41–7.43 (m, 1H), 7.44–7.46 (m, 1H),7.48–7.52 (m, 1H),7.60 (d, J = 8.54 Hz, 1H), 7.79 (dt, J = 1.1,

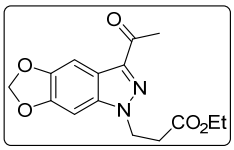


8.0 Hz, 1H), 7.89 (s, 1H), 8.47 (dt, J = 1.1, 8.2 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.1, 32.2, 34.3, 44.8, 61.0, 109.4, 110.2, 115.1, 120.5, 123.0, 123.2, 123.5, 124.3, 125.7, 126.3, 127.1, 134.8, 140.3, 140.6, 143.0, 170.8, 180.8 ppm; HRMS (ESI+): calcd. for$C_{22}H_{21}O_3N_3Na^+$ 398.1475, found 398.1475.

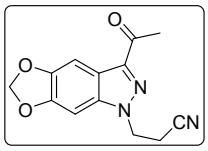
3-(3-(1-Methyl-1H-indole-2-carbonyl)-1H-indazol-1-yl)propanenitrile (19k): Following the general procedure compound **19k** was obtained in 68% yield as brown thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.18 (t, J = 6.9 Hz, 2H), 4.20 (s, 3H), 4.85 (t, J = 6.9 Hz, 2H), 7.15–7.23 (m, 1H), 7.37–7.45 (m, 3H), 7.54–7.57 (m, 2H), 7.80 (dt, J = 1.1, 8.0 Hz, 1H), 7.89 (t, J = 3.7 Hz, 1H), 8.50 (dt, J = 1.1, 8.4 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.6, 32.3, 44.8, 108.7, 110.3, 115.5, 116.8, 120.6, 122.4, 123.4, 123.9, 124.4, 126.0, 126.3, 127.8, 134.6, 140.4, 140.5, 144.0, 180.5 ppm; HRMS (ESI+): calcd. for $C_{20}H_{16}ON_4Na^+$ 351.1216, found 351.1216.



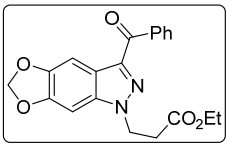
Ethyl 3-(3-acetyl-1H-[1,3]dioxolo[4,5-f]indazol-1-yl)propanoate (19l): Following the general procedure compound **19l** was obtained in 84% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, J = 7.2 Hz, 3H), 2.65 (s, 3H), 3.03 (t, J = 6.7Hz, 2H), 4.16 (q, J = 7.2, 14.3 Hz, 2H), 4.61 (t, J = 6.7 Hz, 2H), 6.05 (s, 2H), 6.88 (s, 1H), 7.64 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.1, 26.6, 34.1, 44.9, 61.0, 88.9, 99.7, 101.8, 117.7, 137.7, 142.5, 146.6, 149.3, 170.8, 194.8 ppm; HRMS (ESI+): calcd. for $C_{15}H_{16}O_5N_2Na^+$ 327.0951, found 327.0943.



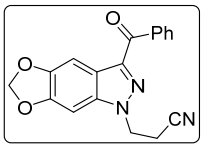
3-(3-acetyl-1H-[1,3]dioxolo[4,5-f]indazol-1-yl)propanenitrile(19m): Following the general procedure compound **19m** was obtained in 74% yield as white solid; R_f 0.4 (50% ethyl acetate/petroleum ether); mp: 169-173 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.66 (s, 3H), 3.08 (t, J = 6.9 Hz, 2H), 4.61 (t, J = 6.9 Hz, 2H), 6.07 (s, 2H), 6.82 (s, 1H), 7.67 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.3, 26.6, 44.9, 88.3, 100.1, 102.1, 116.7, 117.8, 137.7, 143.3, 146.9, 149.8, 194.6 ppm; HRMS (ESI+): calcd. for $C_{13}H_{11}O_3N_3Na^+$ 280.0693, found 280.0688.



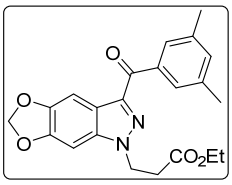
Ethyl 3-(3-benzoyl-1H-[1,3]dioxolo[4,5-f]indazol-1-yl)propanoate (19n): Following the general procedure compound **19n** was obtained in 77% yield as colorless thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ1.22 (t, J = 7.1 Hz, 3H), 3.05 (t, J = 6.4 Hz, 2H), 4.15 (q, J = 7.1, 14.3 Hz, 2H), 4.66 (t, J = 6.6 Hz, 2H), 6.08 (s, 2H), 6.93 (s, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.76 (s, 1H), 8.31 (d, J = 7.7 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.1, 34.2, 45.0, 61.1, 88.9, 100.0, 101.9, 119.8, 128.1, 130.6, 132.3, 137.4, 138.0, 142.0, 146.7, 149.4, 170.8, 188.5 ppm; HRMS (ESI+): calcd. for $C_{20}H_{18}O_5N_2Na^+$ 389.1108, found 389.1107.



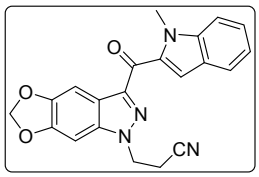
3-(3-Benzoyl-1H-[1,3]dioxolo[4,5-f]indazol-1-yl)propanenitrile (19o): Following the general procedure compound **19o** was obtained in 72% yield as white solid; R_f 0.4 (50% ethyl acetate/petroleum ether); mp: 103-107 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.08 (t, J = 7.1 Hz, 2H), 4.66 (t, J = 7.1 Hz, 2H), 6.10 (s, 2H), 6.87 (s, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.77 (s, 1H), 8.30 (d, J = 7.7 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.4, 45.0, 88.2, 100.3, 102.1, 116.7, 119.9, 128.2, 130.5, 132.6, 137.2, 137.7, 142.8, 147.0, 149.9, 188.4 ppm; HRMS (ESI+): calcd. for $C_{18}H_{13}O_3N_3Na^+$ 342.0849, found 342.0848.



Ethyl 3-(3-(3,5-dimethylbenzoyl)-1H-[1,3]dioxolo[4,5-f]indazol-1-yl)propanoate (19p): Following the general procedure compound **19p** was obtained in 71% yield as white solid; R_f 0.4 (50% ethyl acetate/petroleum ether); mp: 94-98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (t, J = 7.3 Hz, 3H), 2.42 (s, 6H), 3.05 (t, J = 7.1 Hz, 2H), 4.14 (q, J = 7.2, 14.2 Hz, 2H), 4.66 (t, J = 7.3 Hz, 2H), 6.07 (s, 2H), 6.93 (s, 1H), 7.23 (s, 1H), 7.73 (s, 1H), 7.86 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 14.1, 21.4, 34.2, 44.9, 61.0, 88.9, 100.0, 101.9, 119.7, 128.3, 134.1, 137.4, 137.6, 138.0, 142.2, 146.6, 149.4, 170.8, 189.1 ppm; HRMS (ESI+): calcd. for $C_{22}H_{23}O_5N_2^+$ 395.1601, found 395.1592.



3-(3-(1-Methyl-1H-indole-2-carbonyl)-1H-[1,3]dioxolo[4,5-f]indazol-1-yl)propanenitrile (19q): Following the general procedure compound **19q** was obtained in 71% yield as yellow thick oil; R_f 0.4 (50% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.12 (t, J = 6.8 Hz, 2H), 4.17 (s, 3H), 4.69 (t, J = 6.9 Hz, 2H), 6.10 (s, 2H), 6.87 (s, 1H), 7.19 (t,J = 7.1 Hz, 1H), 7.39–7.45 (m, 2H), 7.74–7.77 (m, 2H), 7.88 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 18.5, 32.2, 45.0, 88.3, 100.1, 102.1, 110.2, 115.3, 116.8, 119.6, 120.6, 123.4, 125.9, 126.3, 134.6, 137.3, 140.4, 143.7, 146.8, 149.9, 180.6 ppm; HRMS (ESI+): calcd. for $C_{21}H_{16}O_3N_4Na^+$ 395.1115, found 395.1114.



X-Ray Crystallographic Information

General information

Single-crystal X-ray data of **16j** and **19b** were collected on a Bruker SMART APEX II CCD diffractometer, using graphite-monochromatized (MoKα radiation λ = 0.71073 Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from total 36 frames. The X-ray data acquisition was monitored by APEX2 program (Bruker, 2006). All the data were corrected for Lorentz-polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). The structures were solved by direct methods and refined by full matrix least squares, based on F^2, using SHELX-97. Molecular diagrams were generated using Mercury programs. Geometrical calculations were performed using SHELXTL and PLATON. ORTEP views of two compounds were drawn with 30% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii.

Table 9. *Crystal Data of Compounds* ***16j****, and* ***19b***

Crystal Data	**Compound 16j**	**Compound 19b**
Formula	$C_{22}H_{21}N_3O_2$	$C_{12}H_{11}N_3O$
Mr	359.42	213.24
Crystal Size, mm	0.40 x 0.32 x 0.25	0.41 x 0.30 x 0.16
Temp. (K)	296(2) K	150(2)
Crystal Syst.	Monoclinic	Monoclinic
Space Group	$P2_1/c$	$P2_1/c$
a/Å	11.1909(9)	8.798(2)
b/Å	21.865(2)	17.333(4)
c/Å	8.6529(2)	7.162(2)
$\alpha/^0$	90	90
$\beta/^0$	112.255(6)	99.138(9)
$\gamma/^0$	90	90
V/Å3	1159.6(3)	1078.3(5)
Z	4	4
Dcalc/g cm^{-3}	1.314	1.218
μ/mm^{-1}	0.080	0.080

F(000)	760.0	448.0
Ab. Correct.	multi-scan	multi-scan
Tmin/ Tmax	0.9689/0.9804	0.9650/0.9861
2Θmax	25.00	24.99
Total reflns.	13647	7736
Unique reflns.	3464	1912
Obs. reflns.	2134	1562
h, k, l (min, max)	(-13, 13) (-25, 26) (-10, 10)	(-10, 10) (-18, 20) (-8, 8)
R_{int}	0.0875	0.0571
No. of para	248	146
R1 [$I > 2\sigma(I)$]	0.1070	0.1026
wR2[$I > 2\sigma(I)$]	0.1935	0.2150
R1 [all data]	0.1710	0.1197
wR2 [all data]	0.2162	0.2232
goodness-of fit	1.175	1.129
$\Delta\rho_{max}$,$\Delta\rho_{min}$ (eÅ^{-3})	0.210, -0.209	0.460, -0.326
CCDC no.	**1506272**	**1506273**

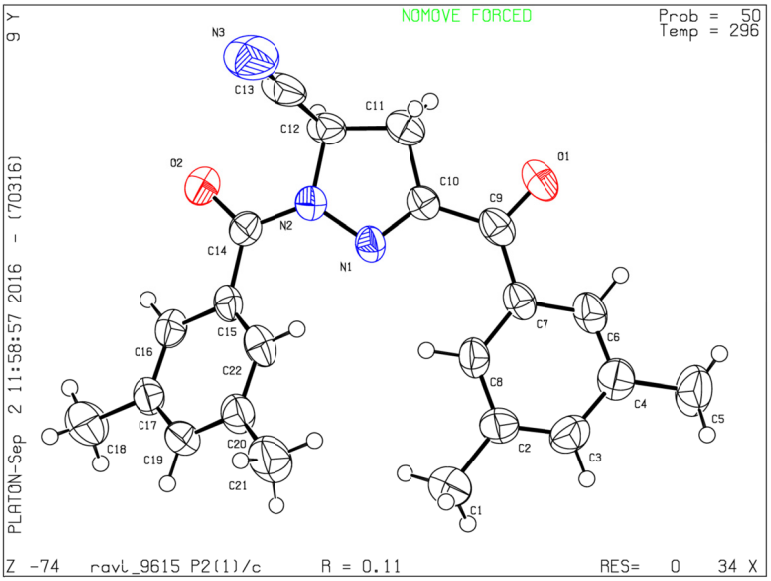


Figure 12. *ORTEP structure of corpound* ***16j***

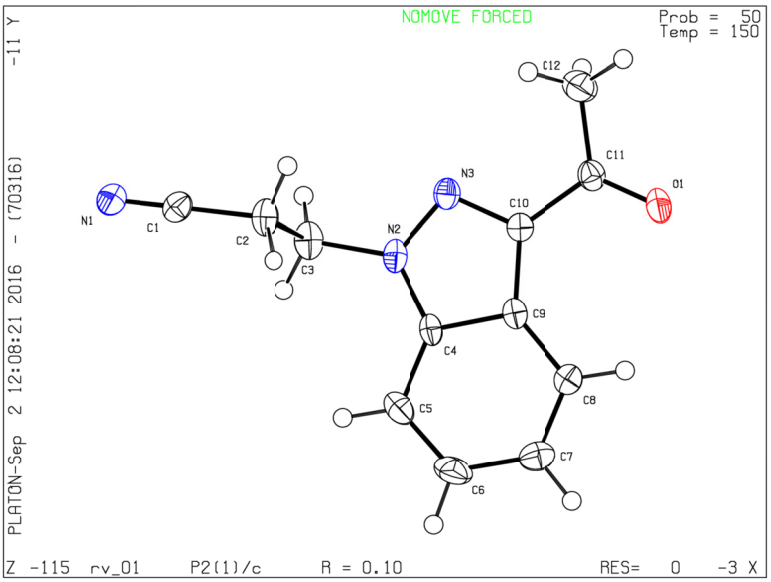
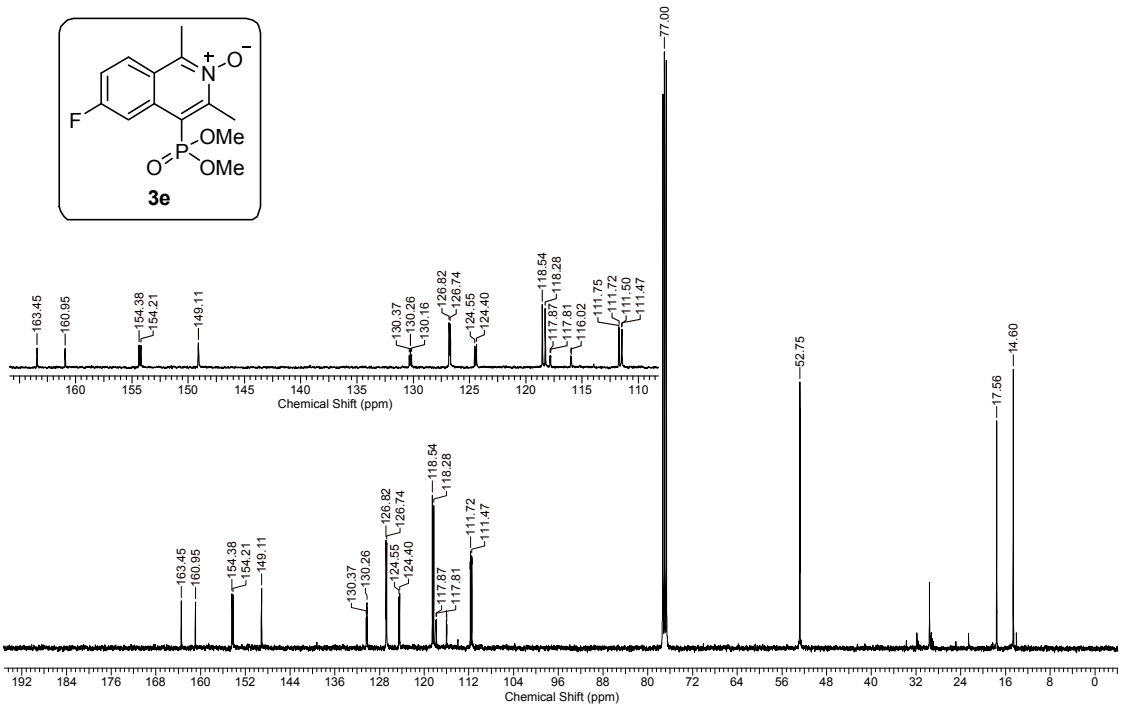
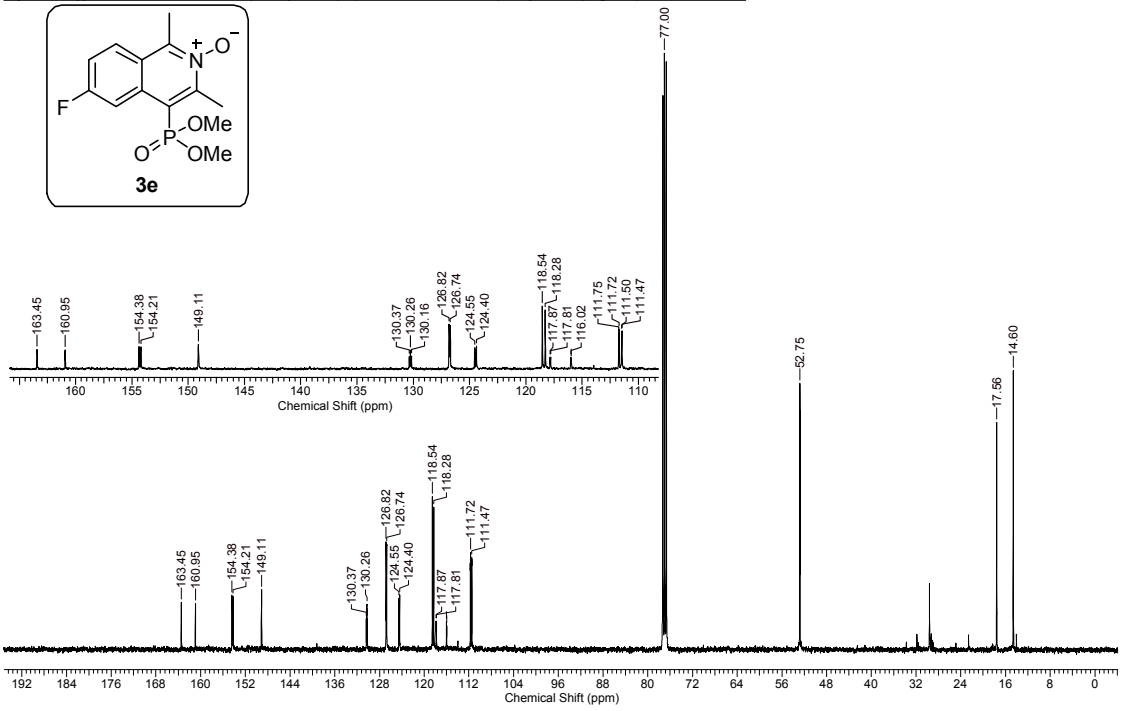


Figure 13. *ORTEP structure of corpound* ***19b***

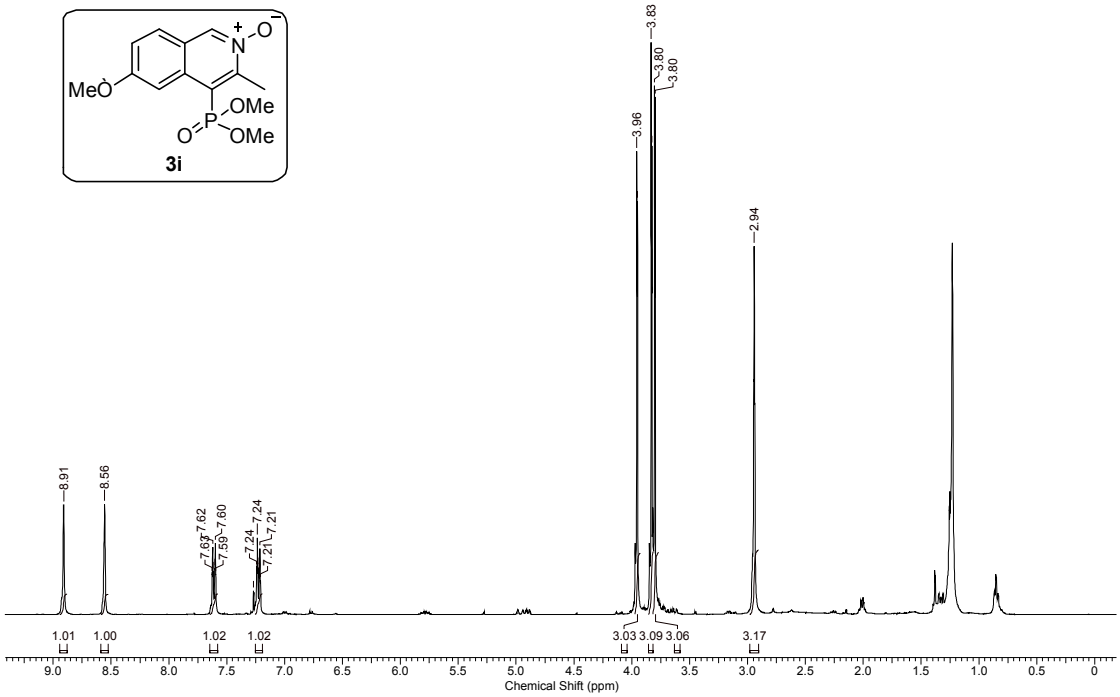
Acquisition Time (sec)	1.0434	***Comment***	Pitambar	***Date***	08 Aug 2015 07:40:52		
Date Stamp	07 Aug 2015 15:23:00			***File Name***	\\agni\nmr_data\JEOL_400\2015\August 2015 liquid\Thu2ECX400#016_CARBON-3.jdf		
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	1500	***Origin***	ECX 400
Original Points Count	26214	***Owner***	delta	***Points Count***	26214	***Pulse Sequence***	single_pulse_dec
Receiver Gain	60.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10039.3311
Spectrum Type	STANDARD	***Sweep Width (Hz)***	25124.29	***Temperature (degree C)***	22.400		



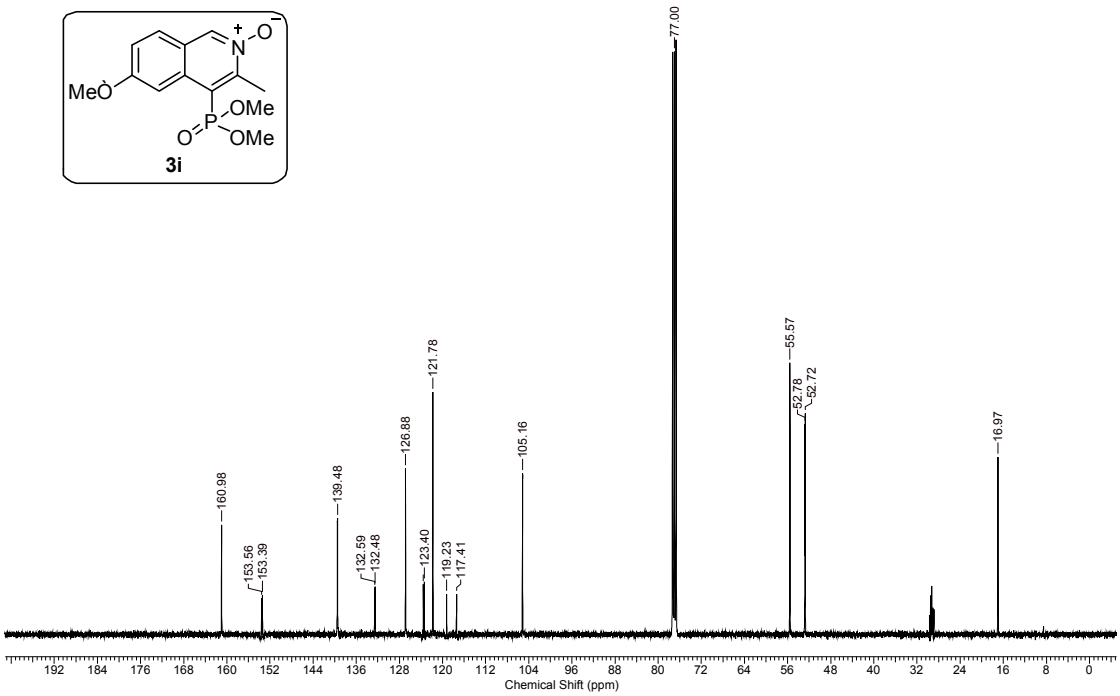
Acquisition Time (sec)	1.0434	***Comment***	Pitambar	***Date***	08 Aug 2015 07:40:52		
Date Stamp	07 Aug 2015 15:23:00			***File Name***	\\agni\nmr_data\JEOL_400\2015\August 2015 liquid\Thu2ECX400#016_CARBON-3.jdf		
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	1500	***Origin***	ECX 400
Original Points Count	26214	***Owner***	delta	***Points Count***	26214	***Pulse Sequence***	single_pulse_dec
Receiver Gain	60.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10039.3311
Spectrum Type	STANDARD	***Sweep Width (Hz)***	25124.29	***Temperature (degree C)***	22.400		



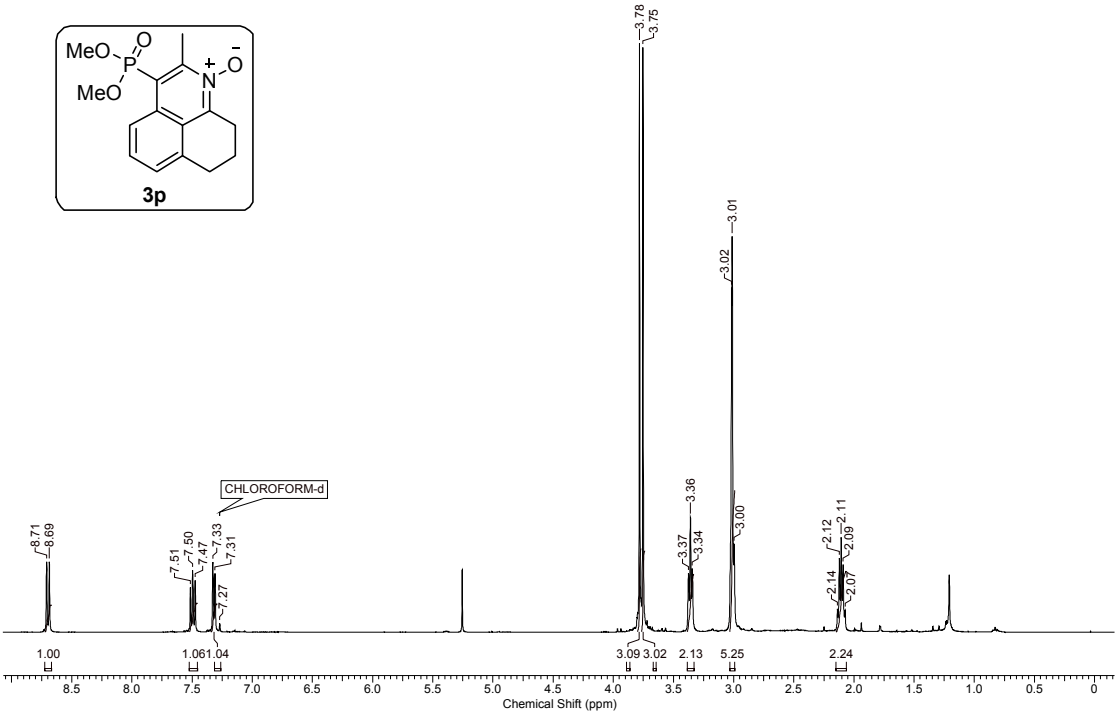
Acquisition Time (sec)	2.1838	***Comment***	Goudappagouda	***Date***	08 Oct 2015 01:25:50
Date Stamp	07 Oct 2015 09:35:59				
File Name	\\agni\nmr_data\JEOL_400\2015\October_2015_Liquid\Wed 7.10.15\Tue2ECX400#007_PROTON-3.jdf			***Frequency (MHz)***	399.78
Nucleus	1H	***Number of Transients***	128	***Origin***	ECX 400
Original Points Count	13107	***Owner***	delta	***Points Count***	13107
Pulse Sequence	single_pulse.ex2	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2007.4668	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6001.85
Temperature (degree C)	21.900				



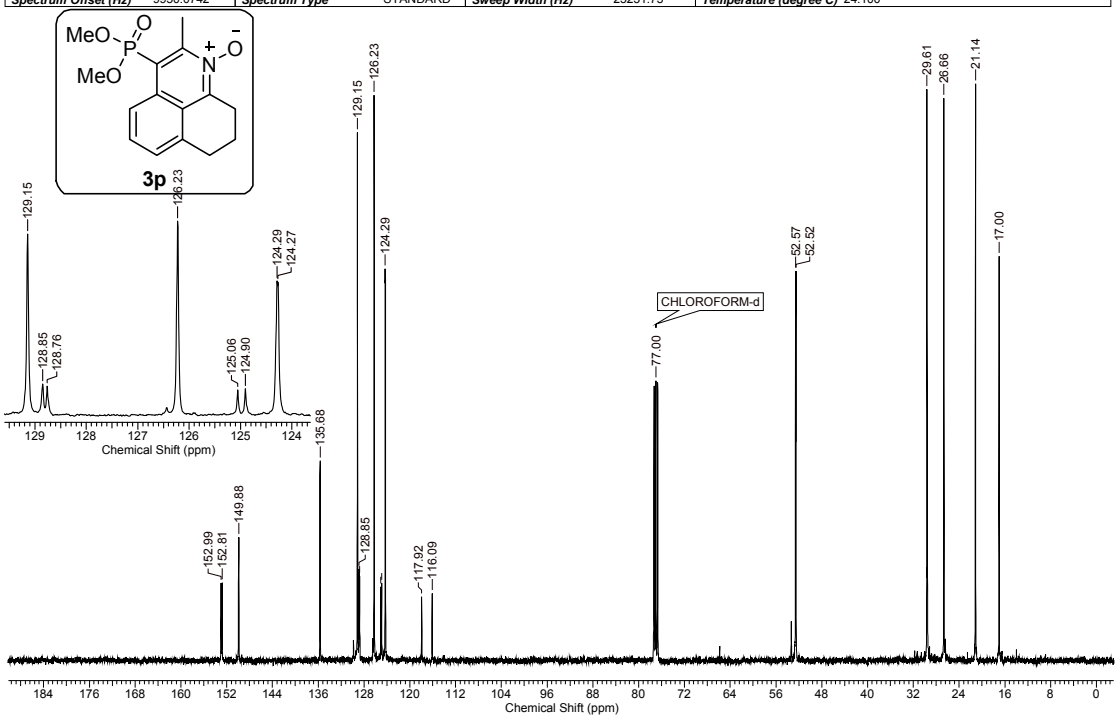
Acquisition Time (sec)	1.0434	***Comment***	Goudappagouda	***Date***	08 Oct 2015 02:43:53
Date Stamp	07 Oct 2015 10:22:41				
File Name	\\agni\nmr_data\JEOL_400\2015\October_2015_Liquid\Wed 7.10.15\Tue2ECX400#007_CARBON-3.jdf			***Frequency (MHz)***	100.53
Nucleus	13C	***Number of Transients***	1200	***Origin***	ECX 400
Original Points Count	26214	***Owner***	delta	***Points Count***	26214
Pulse Sequence	single_pulse_dec	***Receiver Gain***	60.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10039.3311	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25124.29
Temperature (degree C)	22.400				



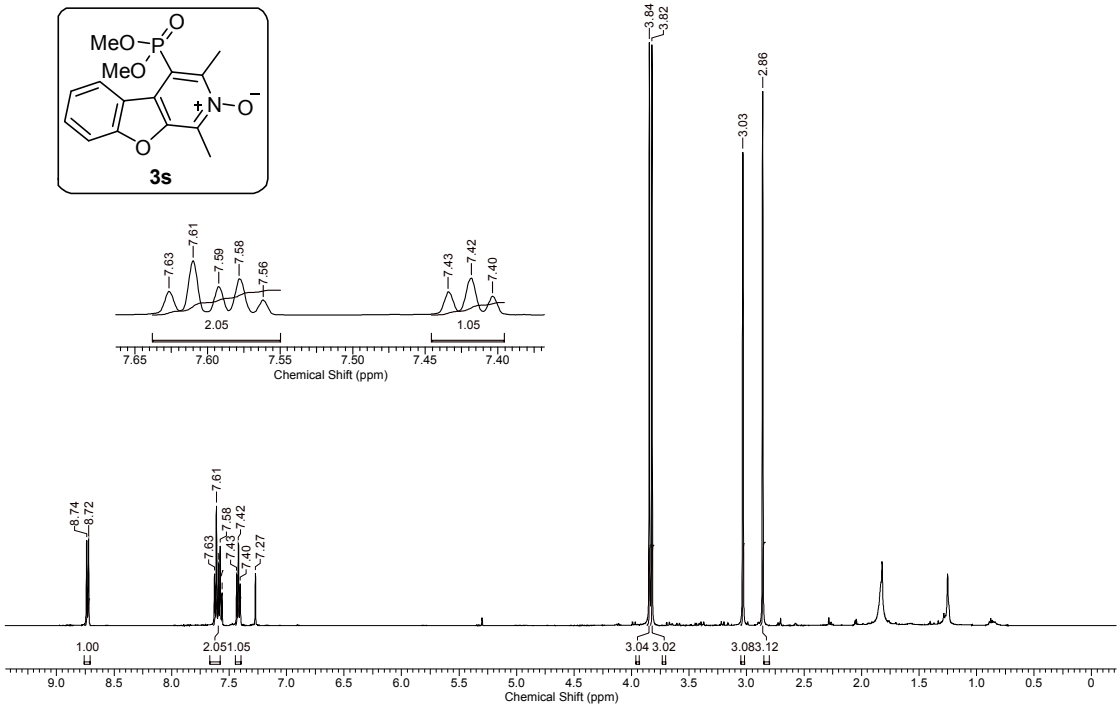
Acquisition Time (sec)	2.0447	***Comment***	Vivek 1H	***Date***	17 Jul 2015 12:41:44		
Date Stamp	17 Jul 2015 12:41:44			***File Name***	\\agni\nmr_data\AV400\July_15_400\Fri3av400#014\1\PDATA\1\1r		
Frequency (MHz)	400.13	***Nucleus***	1H	***Number of Transients***	64	***Origin***	spect
Original Points Count	16384	***Owner***	Administrator	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	90.50	***SW(cyclical) (Hz)***	8012.82	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2395.0613	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	8012.58	***Temperature (degree C)***	23.200



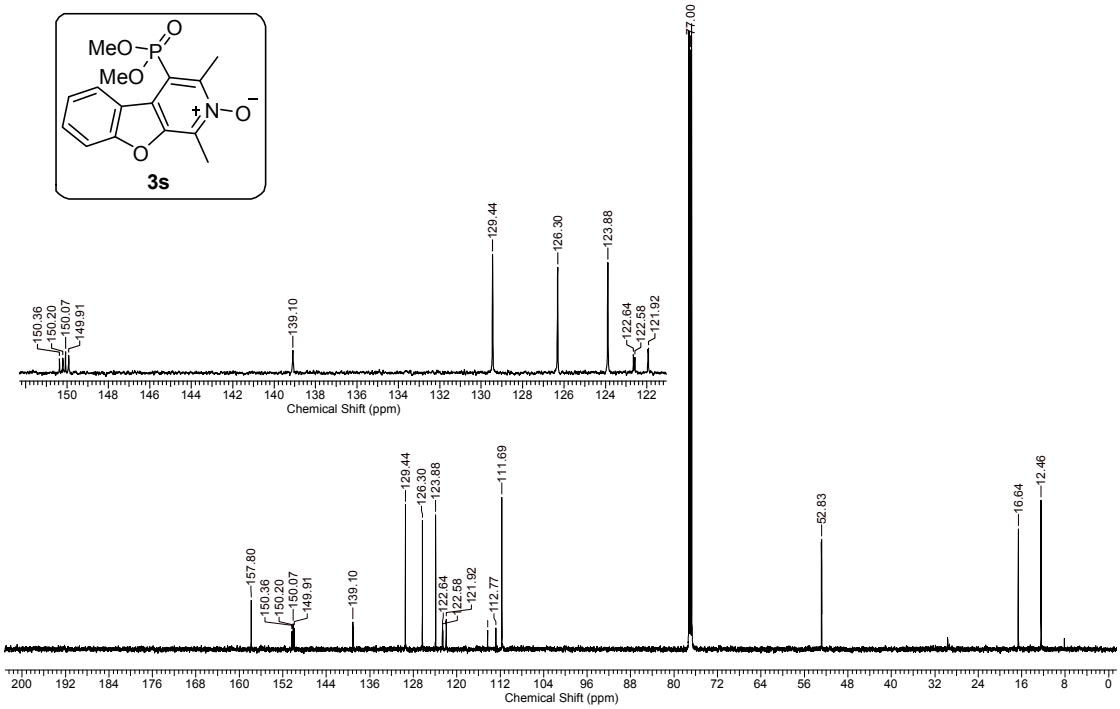
Acquisition Time (sec)	0.6488	***Comment***	13C	***Date***	17 Jul 2015 13:50:00		
Date Stamp	17 Jul 2015 13:50:00			***File Name***	\\agni\nmr_data\AV400\July_15_400\Fri3av400#014\3\PDATA\1\1r		
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	1947	***Origin***	spect
Original Points Count	16384	***Owner***	root	***Points Count***	32768	***Pulse Sequence***	zgpg
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	25252.53	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	9950.0742	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25251.75	***Temperature (degree C)***	24.100



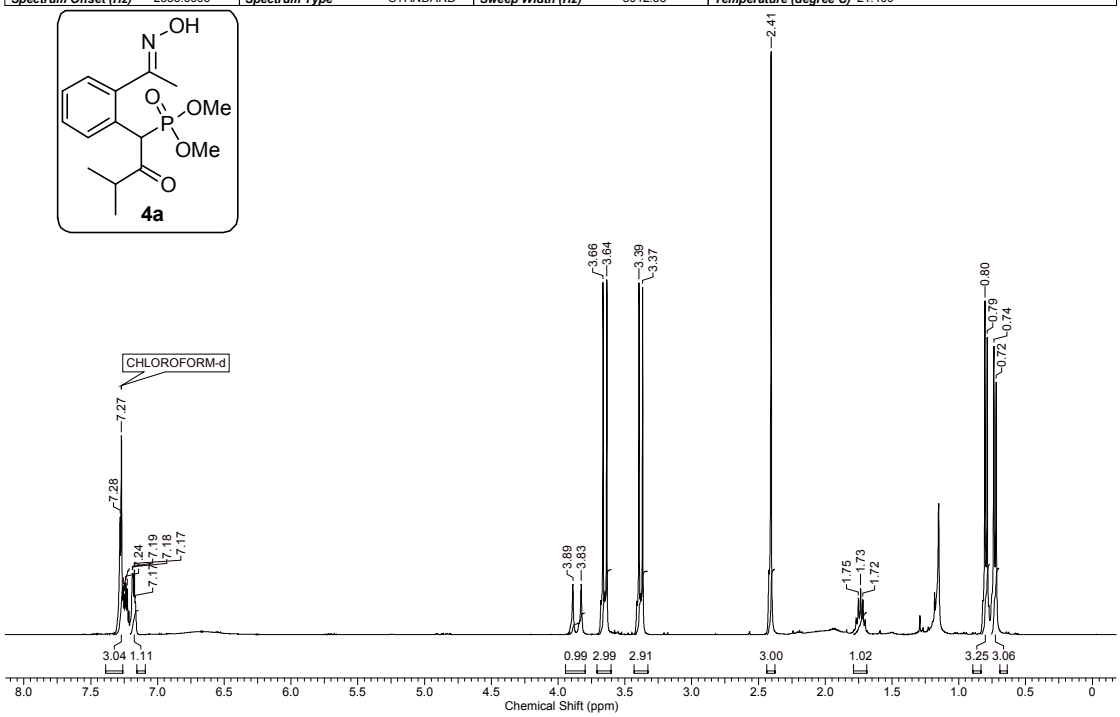
Acquisition Time (sec)	1.6000	***Comment***	Raju 1H	***Date***	24 Jul 2015 09:25:52		
Date Stamp	24 Jul 2015 09:25:52			***File Name***	\\agni\nmr_data\AV_500\July_15_500\Fri4av500#001\1\PDATA\1\1r		
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	32	***Origin***	spect
Original Points Count	16000	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	287.00	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2491.9937	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.800



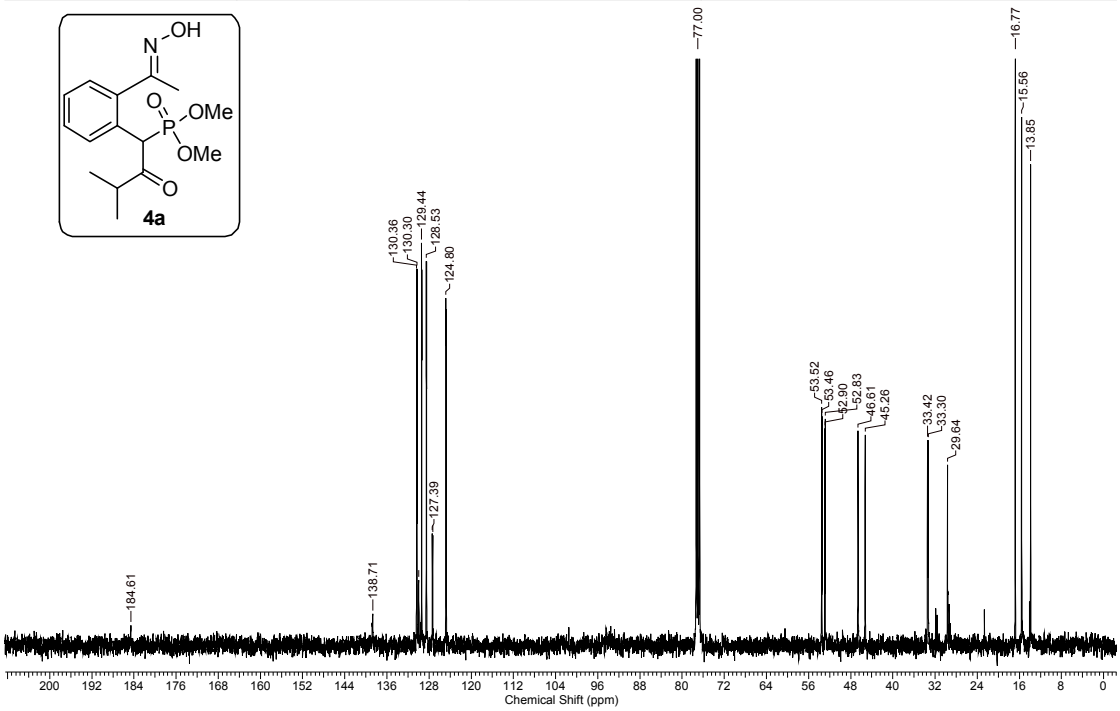
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	24 Jul 2015 10:27:44		
Date Stamp	24 Jul 2015 10:27:44			***File Name***	\\agni\nmr_data\AV_500\July_15_500\Fri4av500#001\3\PDATA\1\1r		
Frequency (MHz)	125.76	***Nucleus***	13C	***Number of Transients***	1580	***Origin***	spect
Original Points Count	20480	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	31250.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12558.2012	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	26.000



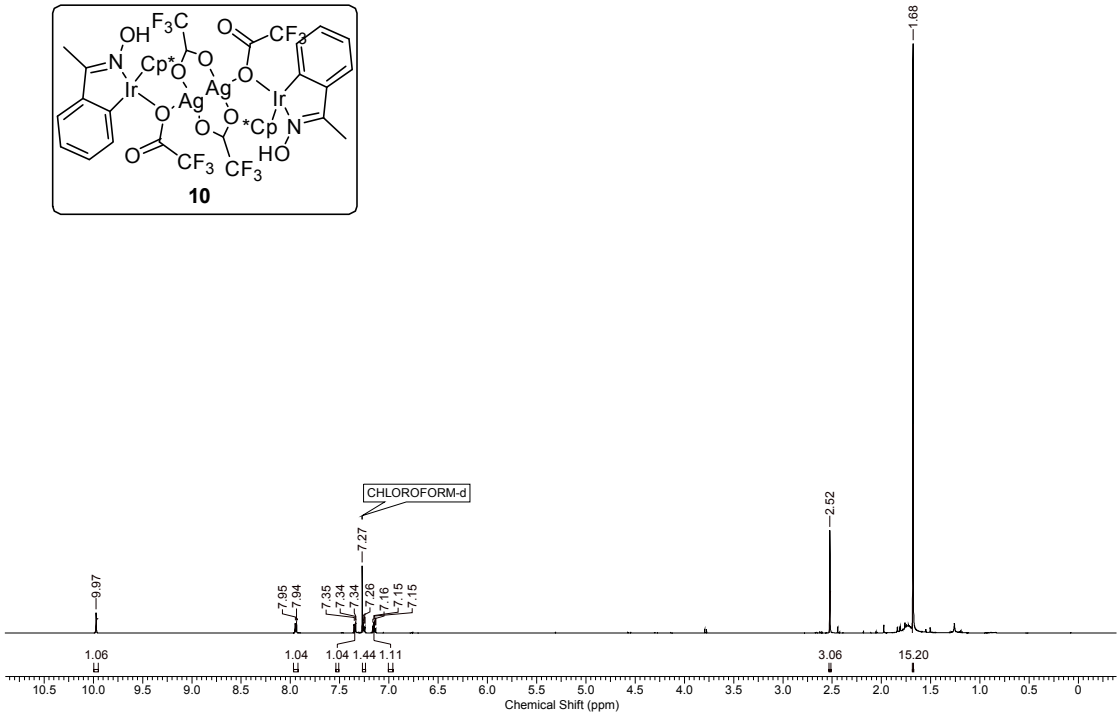
Acquisition Time (sec)	2.0447	***Comment***	Vivekj 1H	***Date***	28 Aug 2015 12:33:12		
Date Stamp	28 Aug 2015 12:33:12			***File Name***	\\agni\nmr_data\AV400\Aug_15_400\Fri5av400#015\1\PDATA\1\1r		
Frequency (MHz)	400.13	***Nucleus***	1H	***Number of Transients***	64	***Origin***	spect
Original Points Count	16384	***Owner***	Administrator	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	128.00	***SW(cyclical) (Hz)***	8012.82	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2356.6699	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	8012.58	***Temperature (degree C)***	21.400



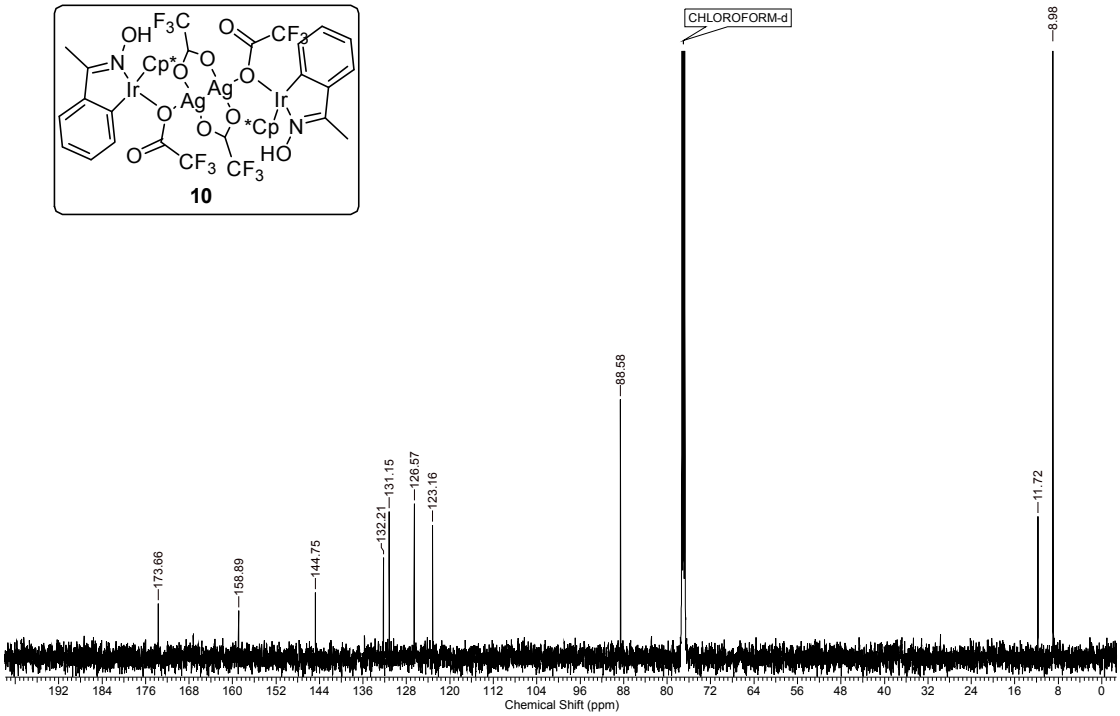
Acquisition Time (sec)	0.6488	***Comment***	13C	***Date***	28 Aug 2015 13:28:40		
Date Stamp	28 Aug 2015 13:28:40			***File Name***	\\agni\nmr_data\AV400\Aug_15_400\Fri5av400#015\3\PDATA\1\1r		
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	1060	***Origin***	spect
Original Points Count	16384	***Owner***	root	***Points Count***	32768	***Pulse Sequence***	zgpg
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	25252.53	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	9955.4688	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25251.75	***Temperature (degree C)***	22.300



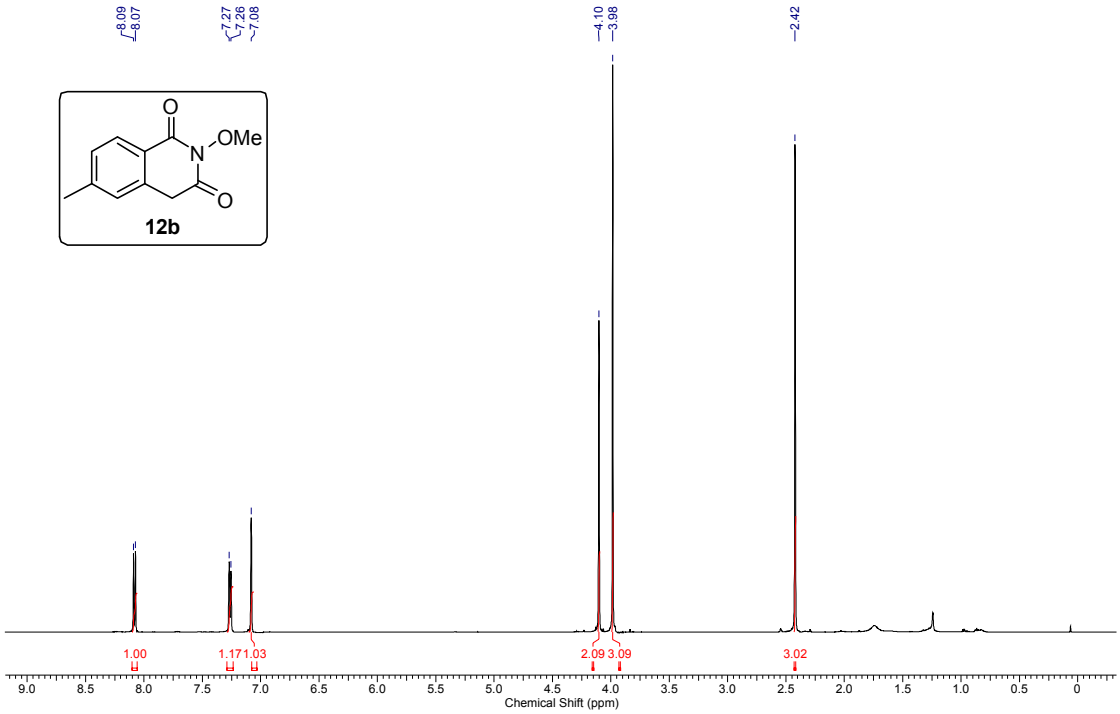
Acquisition Time (sec)	1.6000	***Comment***	Ravindra 1H	***Date***	18 Sep 2015 12:59:12		
Date Stamp	18 Sep 2015 12:59:12			***File Name***	I:\pendrive back up\Applications\Fri3av500#009 complex\1\PDATA\1\1r		
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	128	***Origin***	spect
Original Points Count	16000	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	456.00	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2492.2988	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	26.000



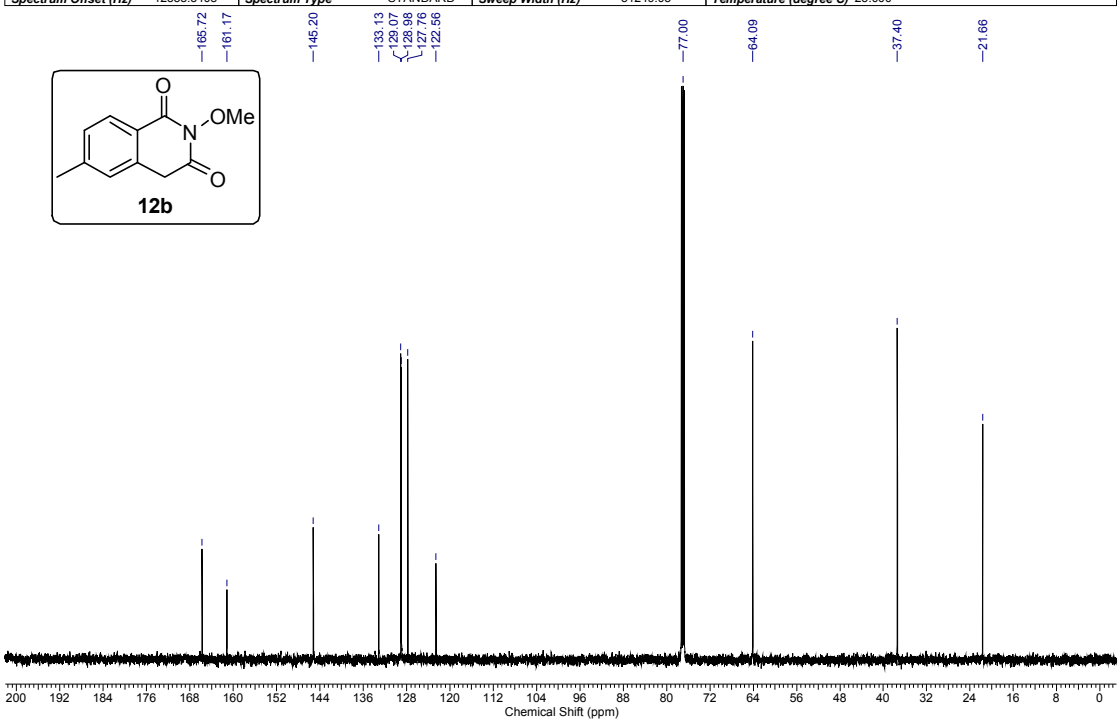
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	18 Sep 2015 14:03:12		
Date Stamp	18 Sep 2015 14:03:12			***File Name***	I:\pendrive back up\Applications\Fri3av500#009 complex\3\PDATA\1\1r		
Frequency (MHz)	125.76	***Nucleus***	13C	***Number of Transients***	1162	***Origin***	spect
Original Points Count	20480	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	31250.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12559.1543	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	25.900



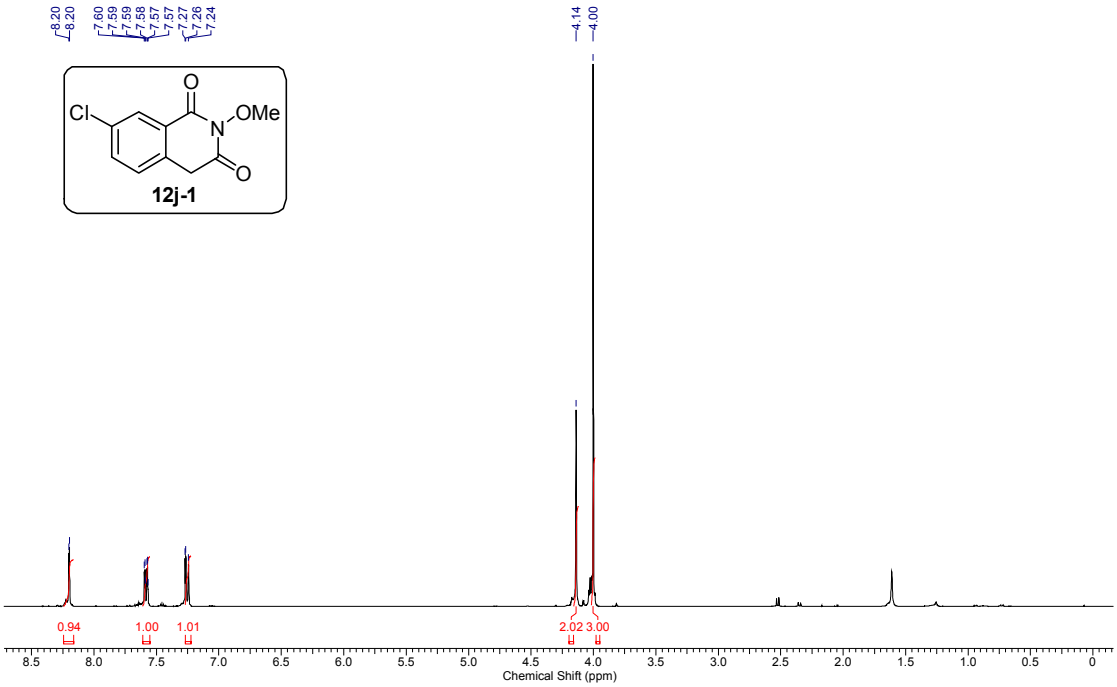
Acquisition Time (sec)	1.6000	***Comment***	Ravindra 1H	***Date***	26 Nov 2015 11:14:24		
Date Stamp	26 Nov 2015 11:14:24			***File Name***	\\agni\nmr_data\AV_500\Nov_15_500\Thu4av500#002\1\PDATA\1\1r		
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Origin***	spect
Original Points Count	16000	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	181.00	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2490.7729	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	24.900



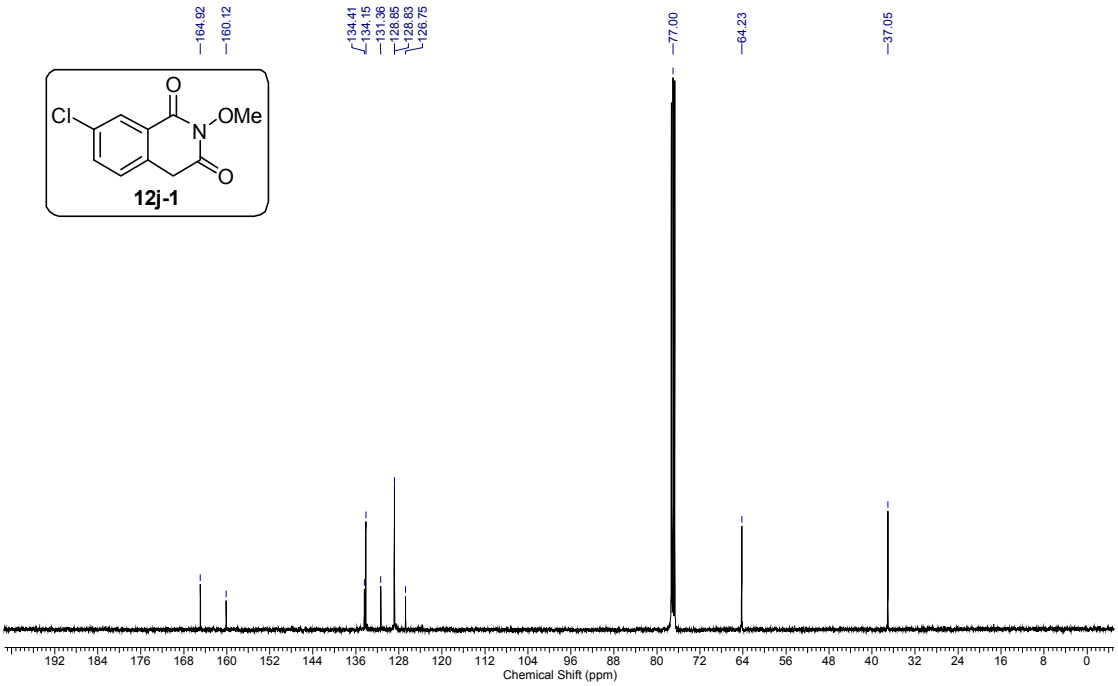
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	26 Nov 2015 11:27:12		
Date Stamp	26 Nov 2015 11:27:12			***File Name***	\\agni\nmr_data\AV_500\Nov_15_500\Thu4av500#002\3\PDATA\1\1r		
Frequency (MHz)	125.76	***Nucleus***	13C	***Number of Transients***	261	***Origin***	spect
Original Points Count	20480	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	1440.00	***SW(cyclical) (Hz)***	31250.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12555.3408	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	25.000



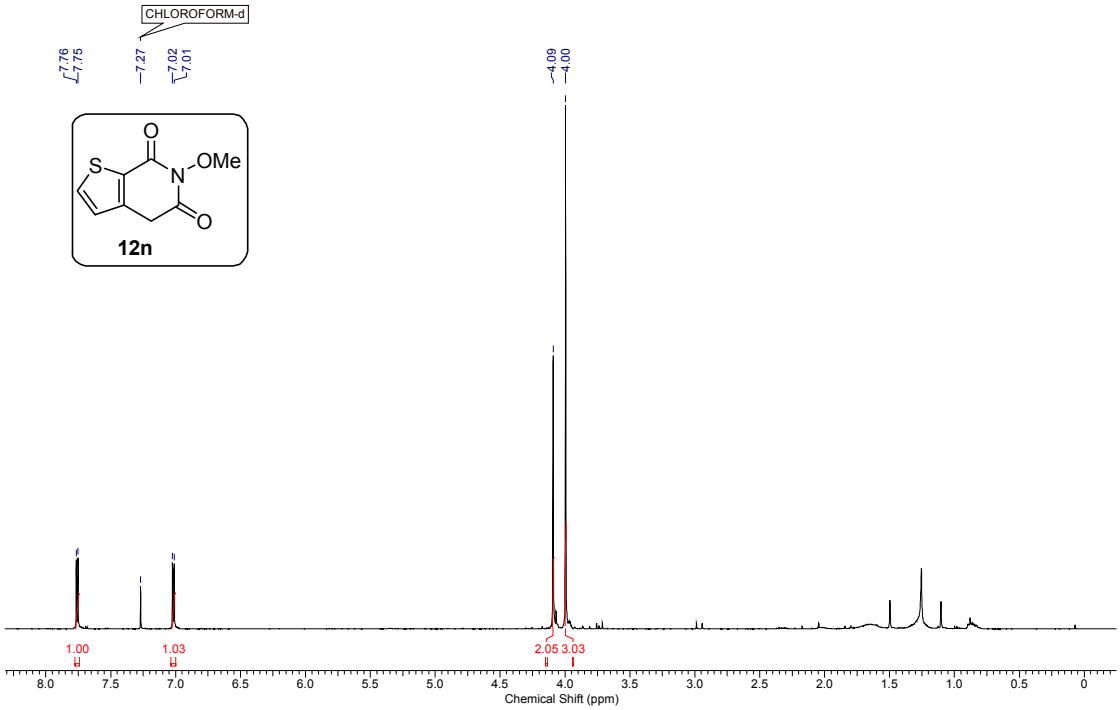
Acquisition Time (sec)	2.1838	***Comment***	Pitambar	***Date***	22 Nov 2015 16:04:01		
Date Stamp	22 Nov 2015 05:59:56			***File Name***	\\agni\nmr_data\JEOL_400\2015\Nov_2015_Liquid\Fri3ECX400#021_PROTON-3.jdf		
Frequency (MHz)	399.78	***Nucleus***	1H	***Number of Transients***	64	***Origin***	ECX 400
Original Points Count	13107	***Owner***	delta	***Points Count***	13107	***Pulse Sequence***	single_pulse.ex2
Receiver Gain	44.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	2007.4668
Spectrum Type	STANDARD	***Sweep Width (Hz)***	6001.85	***Temperature (degree C)***	23.600		



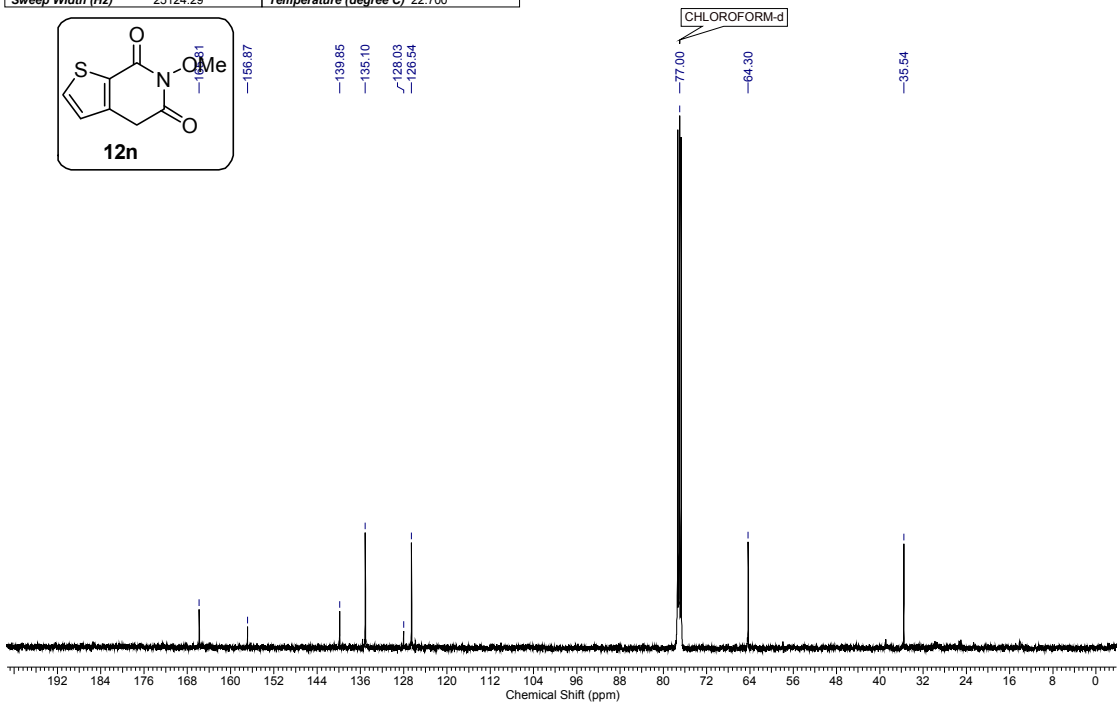
Acquisition Time (sec)	1.0434	***Comment***	Pitambar	***Date***	23 Nov 2015 00:12:42		
Date Stamp	22 Nov 2015 07:34:09			***File Name***	\\agni\nmr_data\JEOL_400\2015\Nov_2015_Liquid\Fri3ECX400#021_CARBON-3.jdf		
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	2400	***Origin***	ECX 400
Original Points Count	26214	***Owner***	delta	***Points Count***	26214	***Pulse Sequence***	single_pulse_dec
Receiver Gain	60.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10043.1650
Spectrum Type	STANDARD	***Sweep Width (Hz)***	25124.29	***Temperature (degree C)***	24.000		



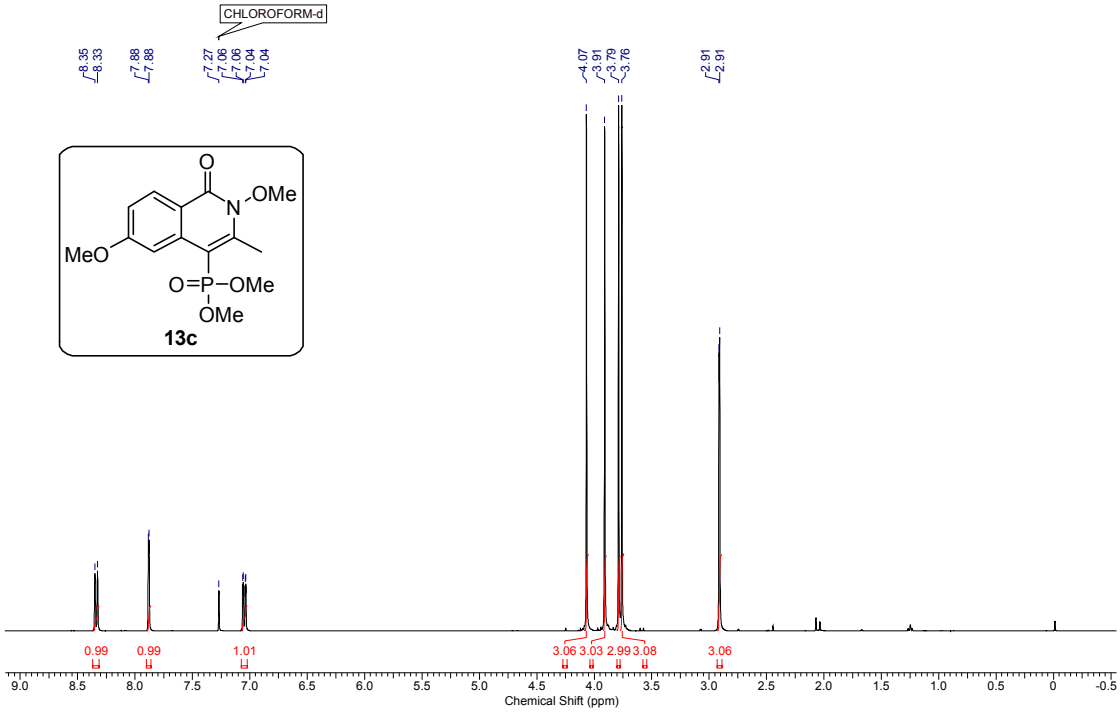
Acquisition Time (sec)	2.1838	***Comment***	Ravindra	***Date***	12 Jan 2016 12:26:12		
Date Stamp	12 Jan 2016 02:18:38			***File Name***	\\172.16.2.4\nmr_data\Jeol_400_new\Liquid Jan 16\Mon3ECX400#002_PROTON-3.jdf		
Frequency (MHz)	399.78	***Nucleus***	1H	***Number of Transients***	44	***Origin***	ECX 400
Original Points Count	13107	***Owner***	delta	***Points Count***	13107	***Pulse Sequence***	single_pulse.ex2
Receiver Gain	42.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	2007.4668
Spectrum Type	STANDARD	***Sweep Width (Hz)***	6001.85	***Temperature (degree C)***	22.400		



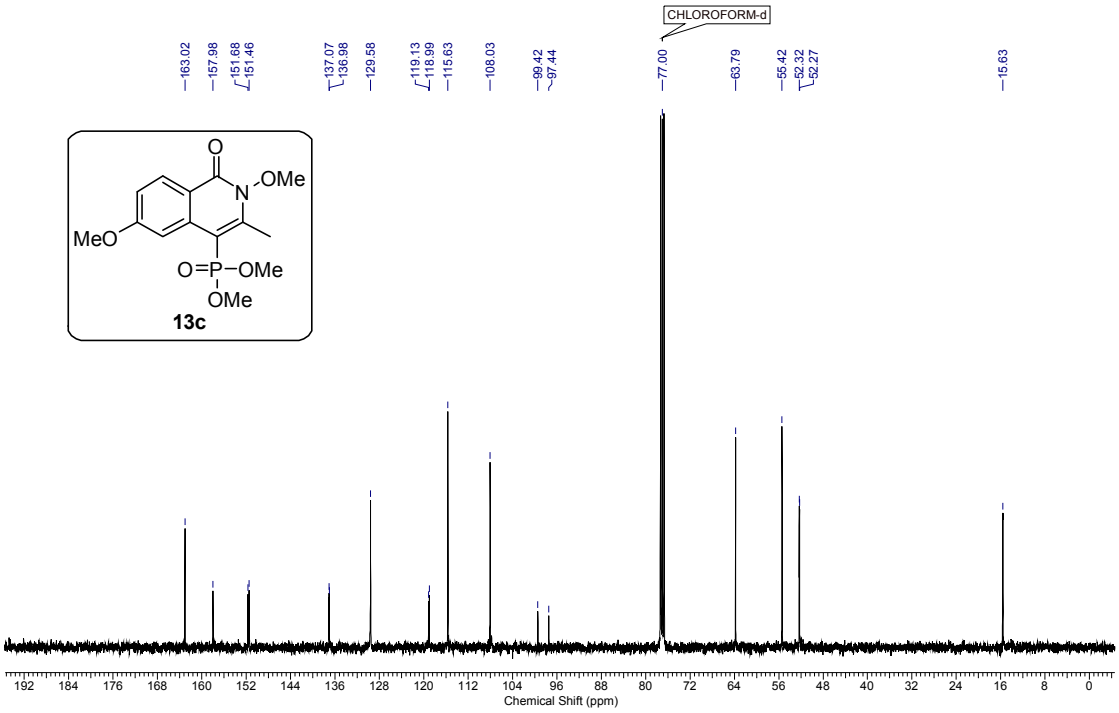
Acquisition Time (sec)	1.0434	***Comment***	Ravindra	***Date***	14 Jan 2016 15:54:45		
Date Stamp	14 Jan 2016 05:31:22						
File Name	\\172.16.2.4\nmr_data\Jeol_400\2016_JEOL_400\JAN_16_JEOL_400\Liquid Jan 16\Wed3ECX400#018_CARBON-3.jdf						
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	1200	***Origin***	ECX 400
Original Points Count	26214	***Owner***	delta	***Points Count***	26214	***Pulse Sequence***	single_pulse_dec
Receiver Gain	60.00	***Solvent***	CHLOROFORM-d	***Spectrum Offset (Hz)***	10042.2061	***Spectrum Type***	STANDARD
Sweep Width (Hz)	25124.29	***Temperature (degree C)***	22.700				



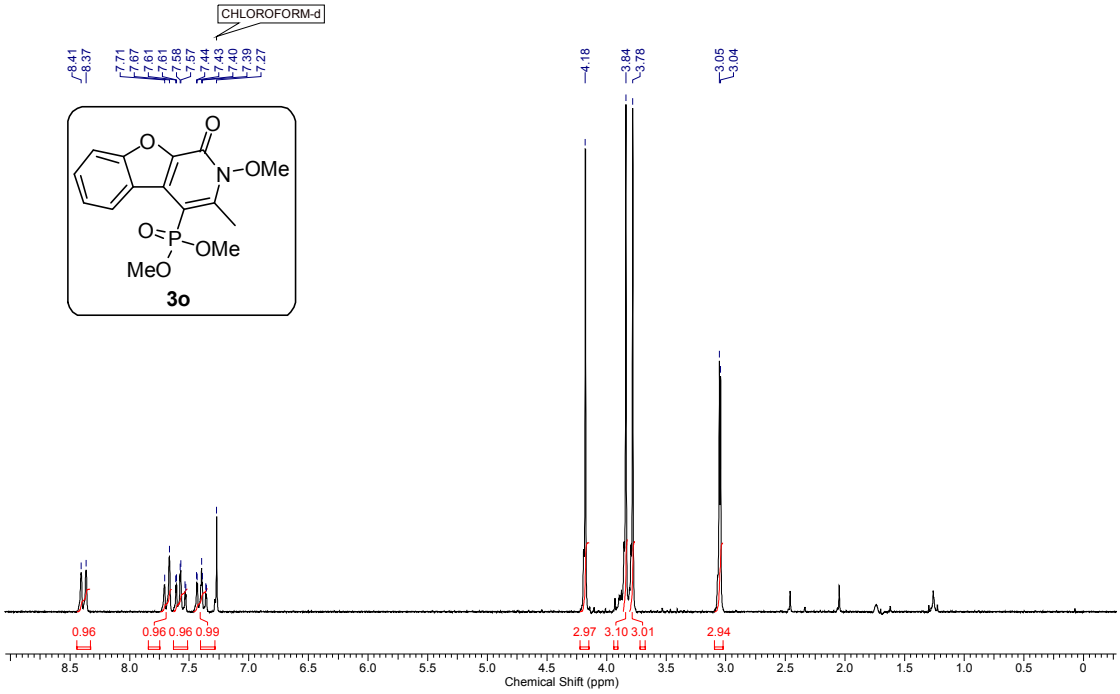
Acquisition Time (sec)	2.0447	***Comment***	Pitamber 1H	***Date***	30 Nov 2015 11:22:48		
Date Stamp	30 Nov 2015 11:22:48			***File Name***	\\agni\nmr_data\AV400\Nov_15_400\Mon5av400#008\1\PDATA\1\1r		
Frequency (MHz)	400.13	***Nucleus***	1H	***Number of Transients***	64	***Origin***	spect
Original Points Count	16384	***Owner***	Administrator	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	228.00	***SW(cyclical) (Hz)***	8012.82	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2395.0613	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	8012.58	***Temperature (degree C)***	22.500



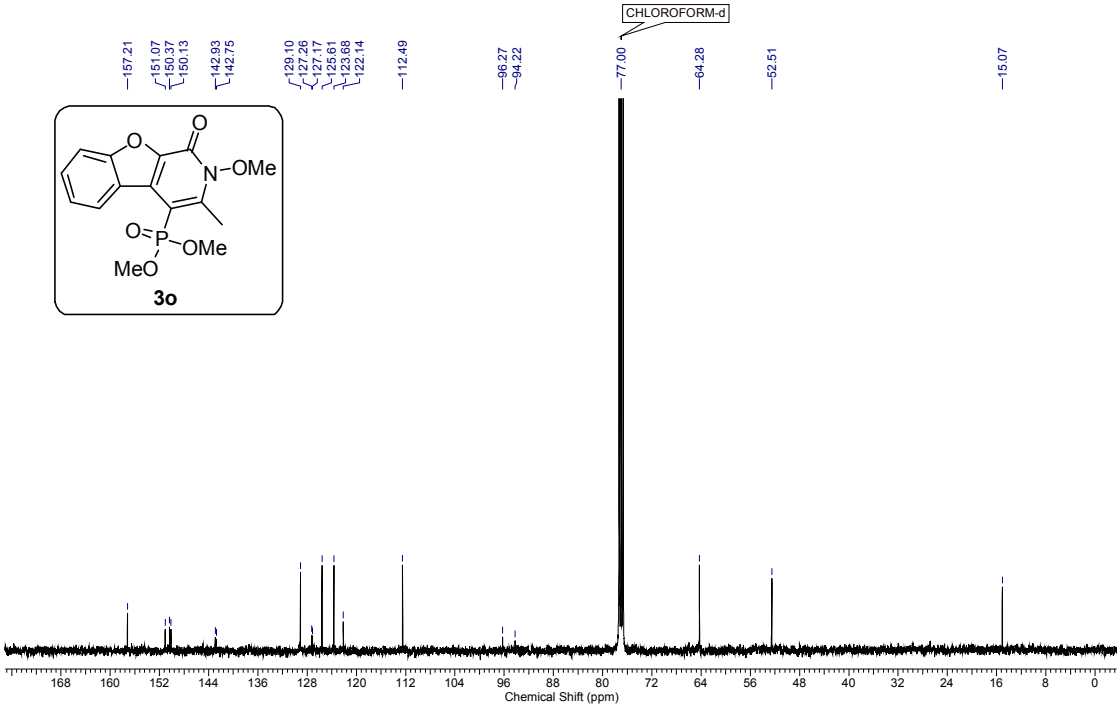
Acquisition Time (sec)	0.6488	***Comment***	13C	***Date***	30 Nov 2015 11:44:08		
Date Stamp	30 Nov 2015 11:44:08			***File Name***	\\agni\nmr_data\AV400\Nov_15_400\Mon5av400#008\3\PDATA\1\1r		
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	823	***Origin***	spect
Original Points Count	16384	***Owner***	root	***Points Count***	32768	***Pulse Sequence***	zgpg
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	25252.53	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10056.4238	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25251.75	***Temperature (degree C)***	22.900



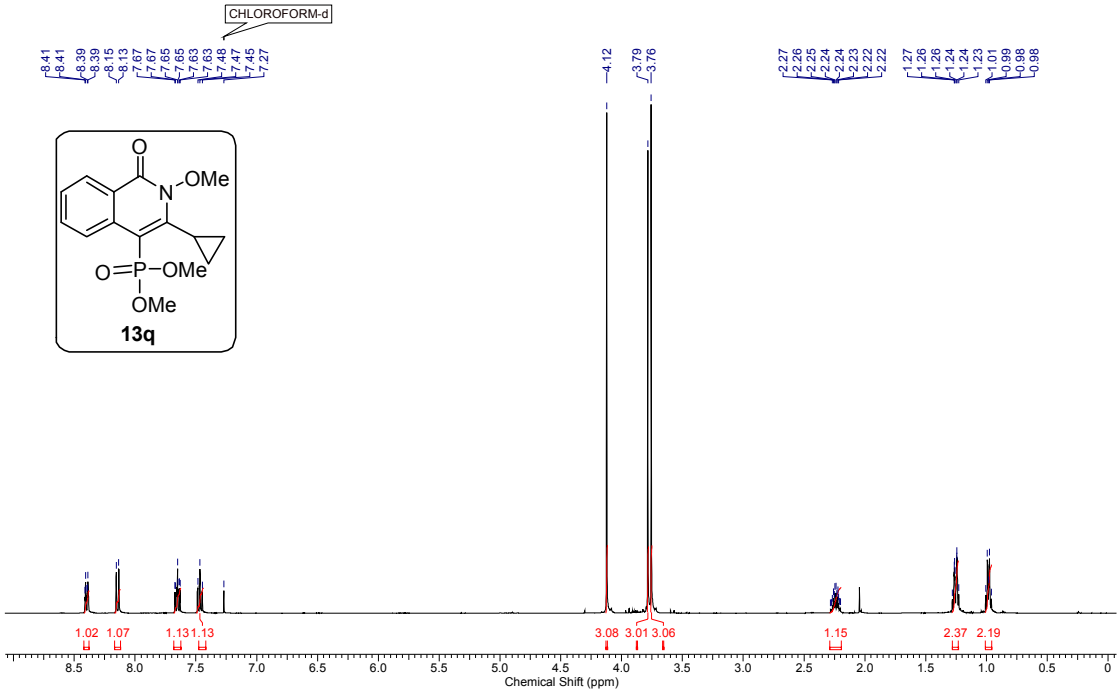
Acquisition Time (sec)	3.9584	***Comment***	Ravindra	***Date***	06 Feb 2016 13:37:12		
Date Stamp	06 Feb 2016 13:37:12						
File Name	\\172.16.2.4\nmr_data\AV200\2016#AV200\FEB_16#AV200\data\Administrator\nmr\Sat1av2#002\1\PDATA\1\1r						
Frequency (MHz)	200.13	***Nucleus***	1H	***Number of Transients***	4	***Origin***	av200
Original Points Count	16384	***Owner***	Administrator	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	1149.40	***SW(cyclical) (Hz)***	4139.07	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	1229.1581	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	4138.95	***Temperature (degree C)***	27.000



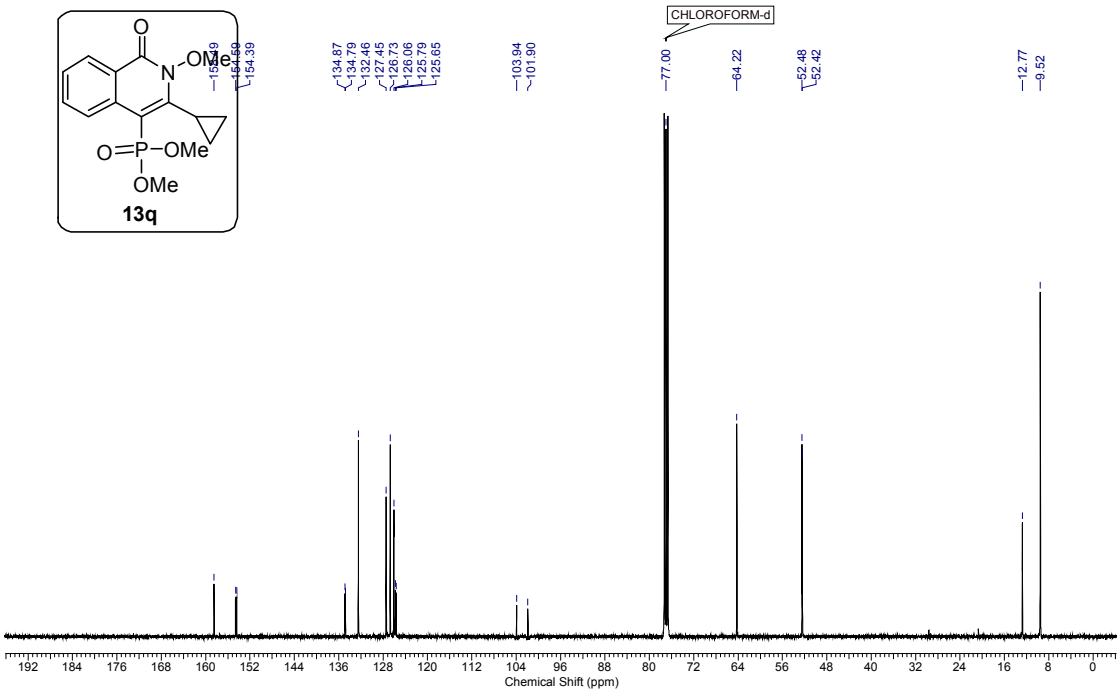
Acquisition Time (sec)	1.0434	***Comment***	Ravindra	***Date***	12 Jan 2016 13:59:54		
Date Stamp	12 Jan 2016 03:21:03			***File Name***	\\172.16.2.4\nmr_data\Jeol_400_new\Liquid Jan 16\Mon3ECX400#003_CARBON-3.jdf		
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	1200	***Origin***	ECX 400
Original Points Count	26214	***Owner***	delta	***Points Count***	26214	***Pulse Sequence***	single_pulse_dec
Receiver Gain	60.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10043.1650
Spectrum Type	STANDARD	***Sweep Width (Hz)***	25124.29	***Temperature (degree C)***	22.600		



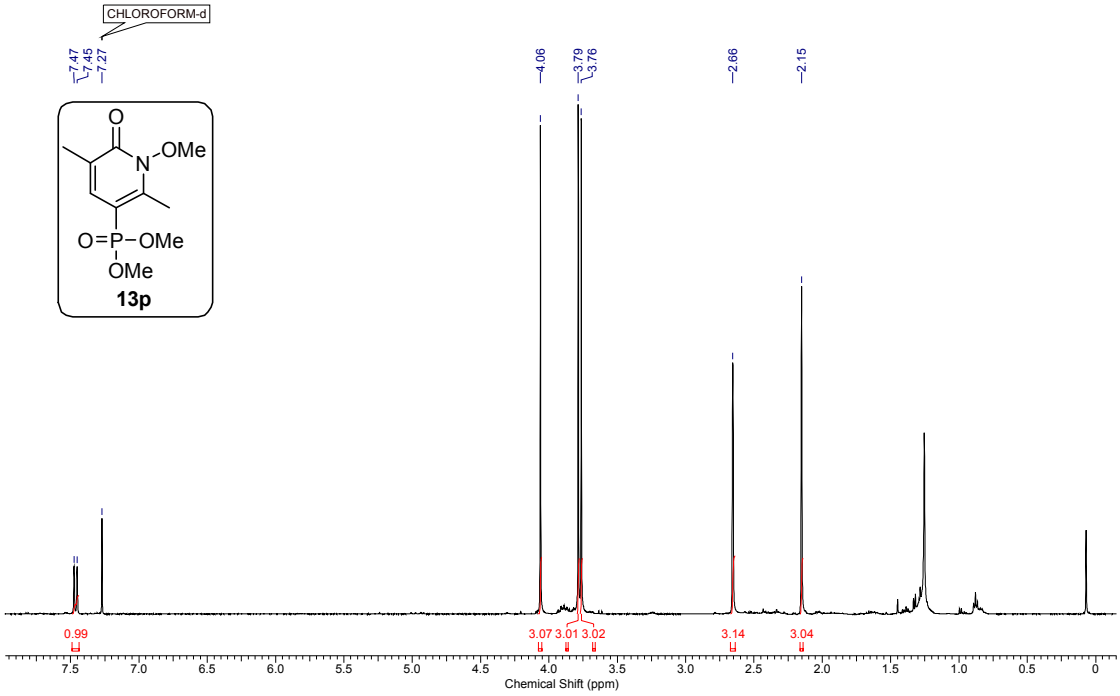
Acquisition Time (sec)	2.1838	***Comment***	Ravindra	***Date***	17 Nov 2015 00:07:32		
Date Stamp	16 Nov 2015 08:15:39						
File Name	F:\pitambar\Research\3rd methodology_Amide\NMR\ketodiazo\simple+cyclo phos\Mon3ECX400#001_PROTON-3.jdf						
Frequency (MHz)	399.78	***Nucleus***	1H	***Number of Transients***	128	***Origin***	ECX 400
Original Points Count	13107	***Owner***	delta	***Points Count***	13107	***Pulse Sequence***	single_pulse.ex2
Receiver Gain	30.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	2007.4668
Spectrum Type	STANDARD	***Sweep Width (Hz)***	6001.85	***Temperature (degree C)***	22.700		



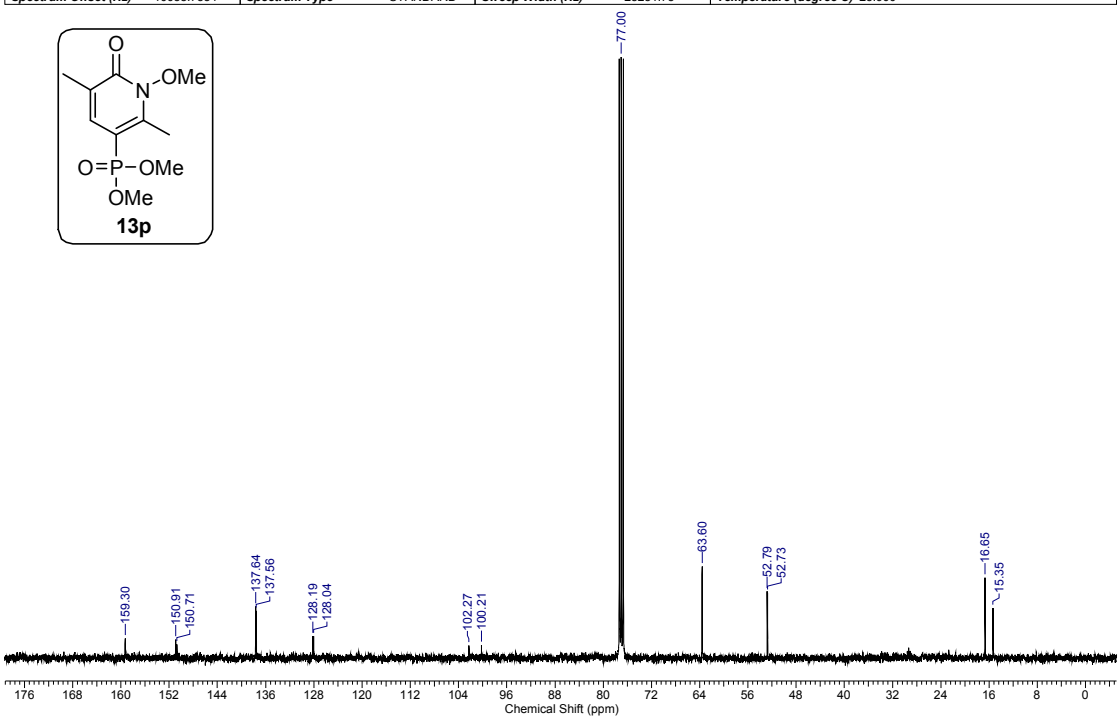
Acquisition Time (sec)	1.0434	***Comment***	Ravindra	***Date***	17 Nov 2015 02:04:10		
Date Stamp	16 Nov 2015 09:33:11						
File Name	F:\pitambar\Research\3rd methodology_Amide\NMR\ketodiazo\simple+cyclo phos\Mon3ECX400#001_CARBON-3.jdf						
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	2000	***Origin***	ECX 400
Original Points Count	26214	***Owner***	delta	***Points Count***	26214	***Pulse Sequence***	single_pulse_dec
Receiver Gain	60.00	***Solvent***	CHLOROFORM-d	***Spectrum Offset (Hz)***	10039.3311	***Spectrum Type***	STANDARD
Sweep Width (Hz)	25124.29	***Temperature (degree C)***	23.300				



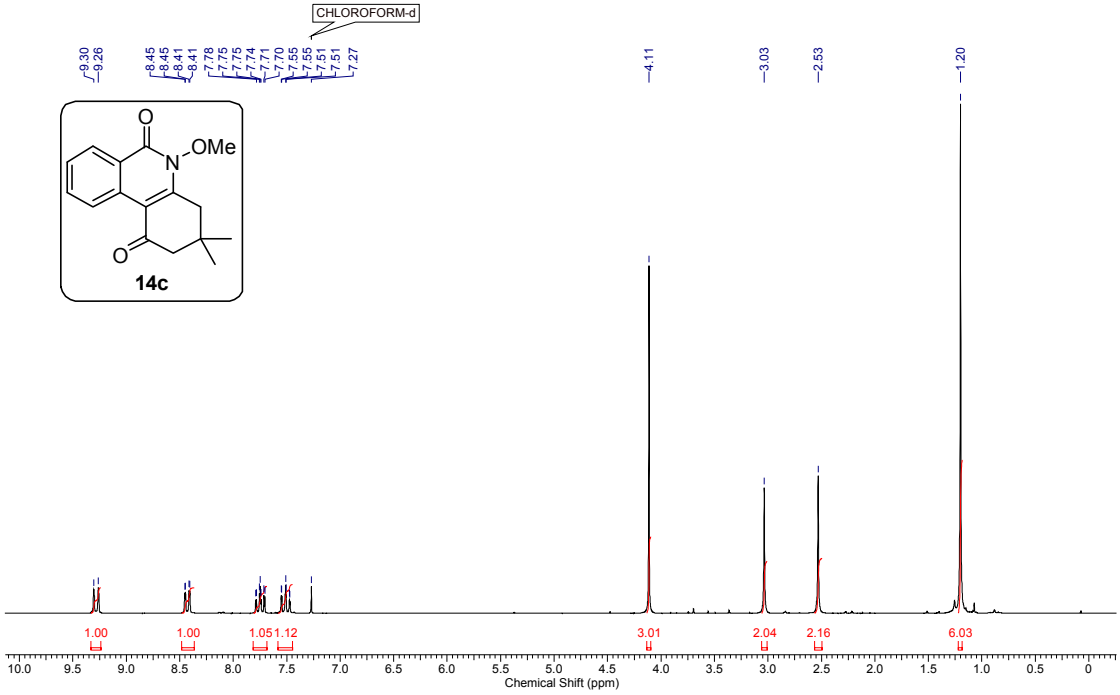
Acquisition Time (sec)	1.2800	***Comment***	Ravindra 1H	***Date***	10 Feb 2016 12:48:16
Date Stamp	10 Feb 2016 12:48:16				
File Name	\\172.16.2.4\nmr_data\AV500\2016_AV500\FEB_16_AV500\Wed2av500#009\1\PDATA\1\1r			***Frequency (MHz)***	500.13
Nucleus	1H	***Number of Transients***	32	***Origin***	spect
Original Points Count	16000	***Owner***	nmr	***Points Count***	32768
Pulse Sequence	zg30	***Receiver Gain***	322.00	***SW(cyclical) (Hz)***	12500.00
Solvent	CHLOROFORM-d	***Spectrum Offset (Hz)***	3492.7031	***Spectrum Type***	STANDARD
Sweep Width (Hz)	12499.62	***Temperature (degree C)***	25.000		



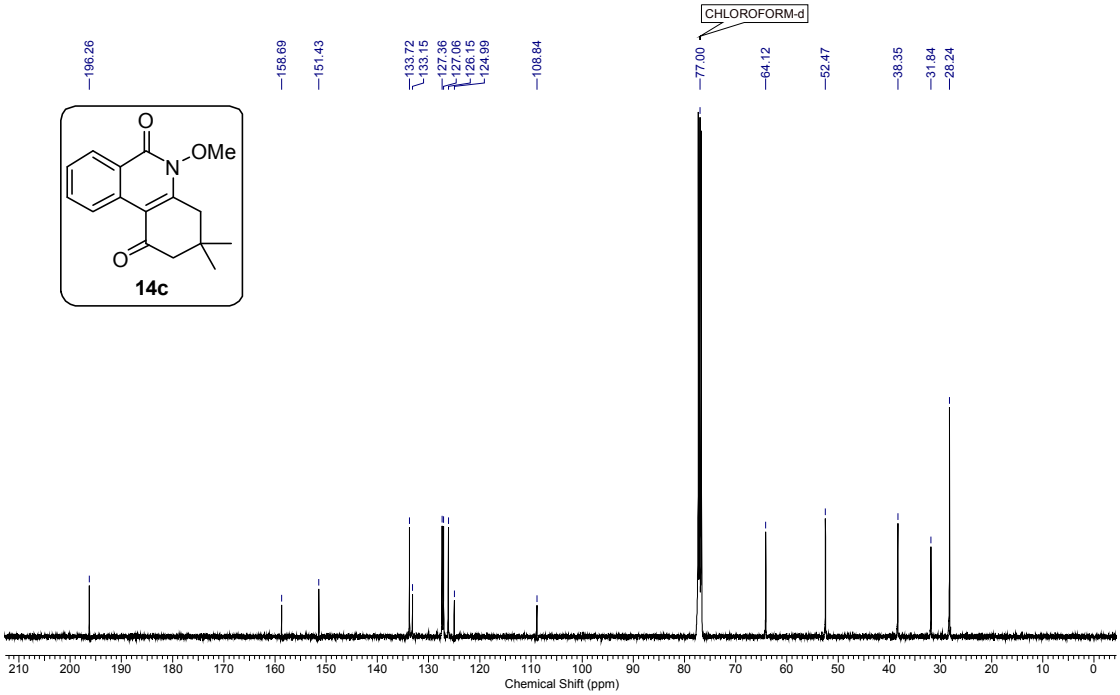
Acquisition Time (sec)	0.6488	***Comment***	13C	***Date***	12 Feb 2016 20:07:36		
Date Stamp	12 Feb 2016 20:07:36			***File Name***	\\172.16.2.4\nmr_data\AV400\Feb_16_400\Fri2av400#019\3\PDATA\1\1r		
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	1152	***Origin***	spect
Original Points Count	16384	***Owner***	root	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	25252.53	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10058.7354	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25251.75	***Temperature (degree C)***	23.900



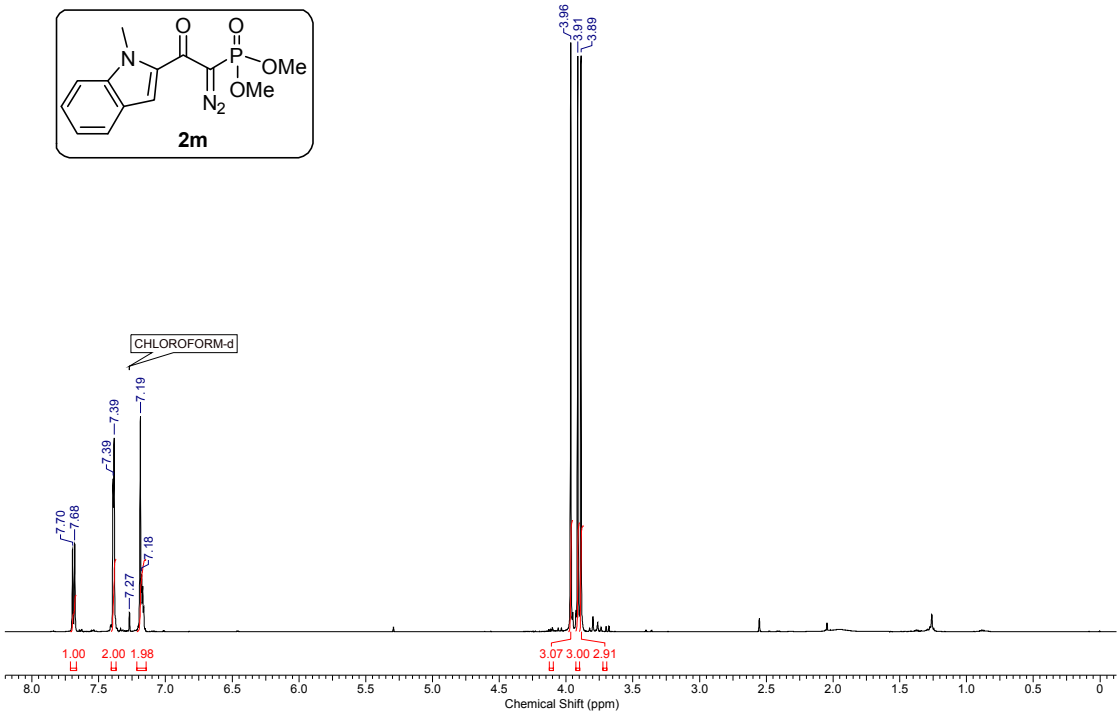
Acquisition Time (sec)	3.9584	***Comment***	Ravindra	***Date***	13 Nov 2015 22:41:12
Date Stamp	13 Nov 2015 22:41:12				
File Name	\\agni\nmr_data\AV200\NOV_15#AV200\data\Administrator\nmr\Fri2av2#130\1\PDATA\1\1r			***Frequency (MHz)***	200.13
Nucleus	1H	***Number of Transients***	32	***Origin*** av200	***Original Points Count*** 16384
Owner	Administrator	***Points Count***	32768	***Pulse Sequence*** zg30	***Receiver Gain*** 574.70
SW(cyclical) (Hz)	4139.07	***Solvent***	CHLOROFORM-d		***Spectrum Offset (Hz)*** 1229.2844
Spectrum Type	STANDARD	***Sweep Width (Hz)***	4138.95	***Temperature (degree C)*** 27.000	



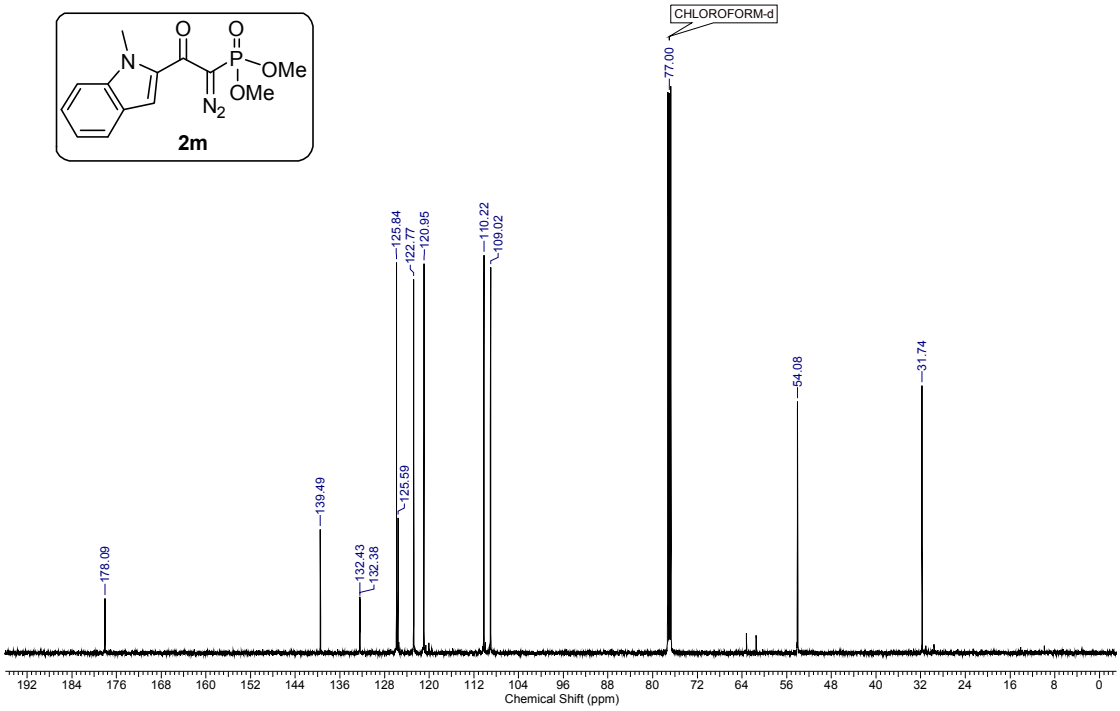
Acquisition Time (sec)	1.0434	***Comment***	Ravindra	***Date***	17 Nov 2015 04:26:58		
Date Stamp	16 Nov 2015 12:16:55						
File Name	F:\pitambar\Research\3rd methodology_Amide\NMR\ketodiazo\simple+dimethylcyclohexanone\Mon3ECX400#002_CARBON-3.jdf						
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	2000	***Origin***	ECX 400
Original Points Count	26214	***Owner***	delta	***Points Count***	26214	***Pulse Sequence***	single_pulse_dec
Receiver Gain	60.00	***Solvent***	CHLOROFORM-d	***Spectrum Offset (Hz)***	10042.2061	***Spectrum Type***	STANDARD
Sweep Width (Hz)	25124.29	***Temperature (degree C)***	23.400				



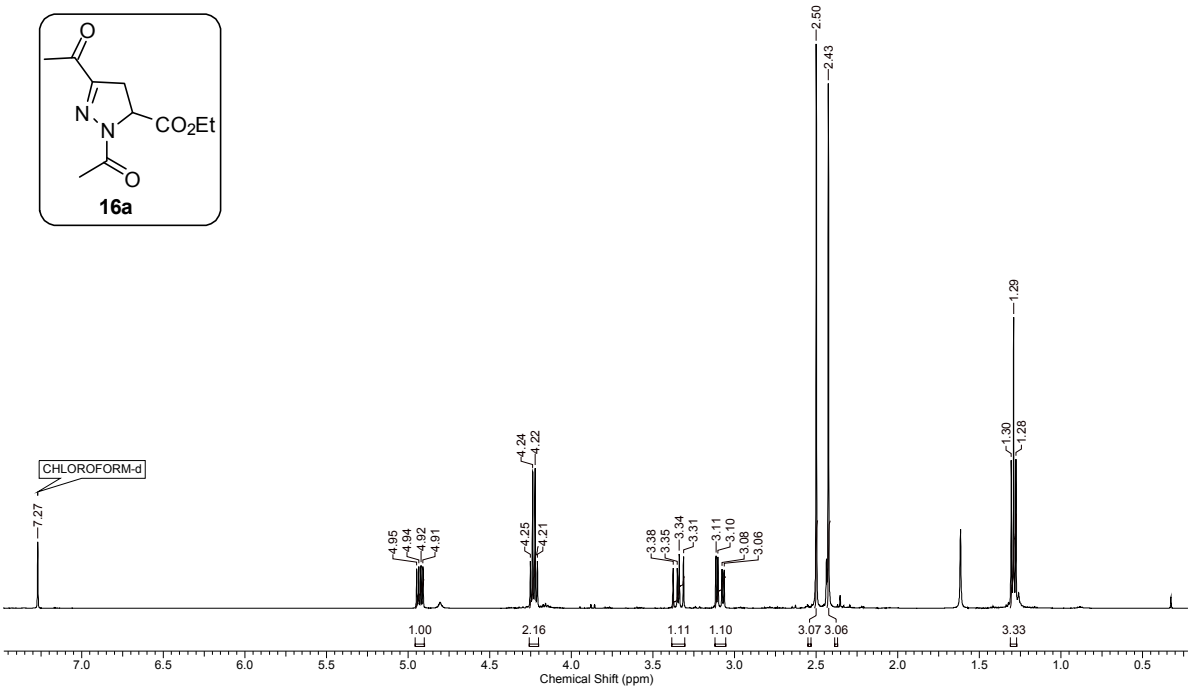
Acquisition Time (sec)	1.6000	***Comment***	VIvek 1H	***Date***	17 Mar 2015 12:31:12		
Date Stamp	17 Mar 2015 12:31:12			***File Name***	\\agni\nmr_data\AV_500\Mar_15_500\Tue3av500#012\1\PDATA\1\1r		
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Origin***	spect
Original Points Count	16000	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	161.00	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2491.6885	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	26.300



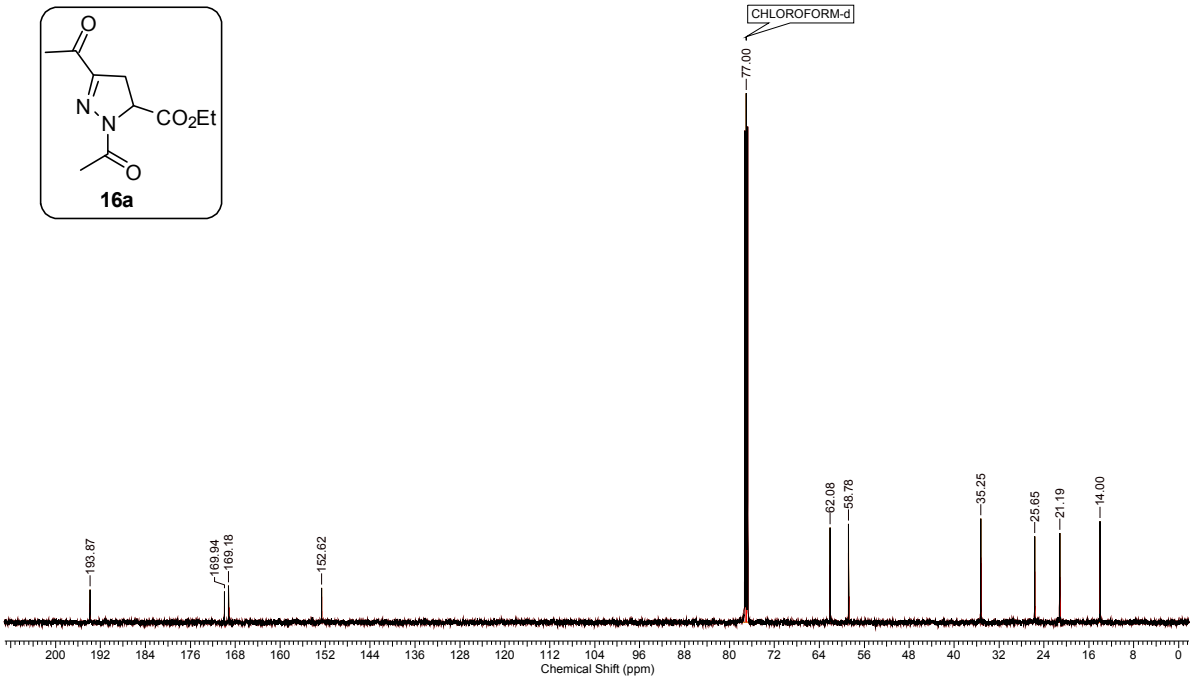
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	17 Mar 2015 14:07:12		
Date Stamp	17 Mar 2015 14:07:12			***File Name***	\\agni\nmr_data\AV_500\Mar_15_500\Tue3av500#012\3\PDATA\1\1r		
Frequency (MHz)	125.76	***Nucleus***	13C	***Number of Transients***	1980	***Origin***	spect
Original Points Count	20480	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	1290.00	***SW(cyclical) (Hz)***	31250.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12553.4326	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	27.300



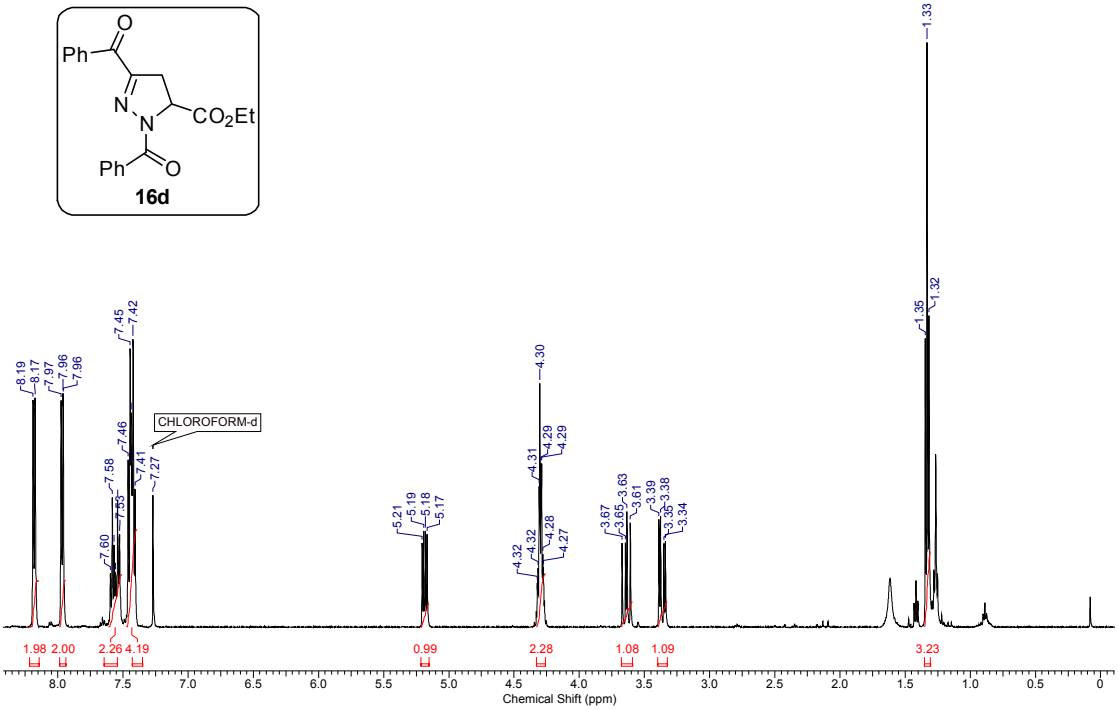
Acquisition Time (sec)	1.6000	***Comment***	Ravindra 1H	***Date***	12 May 2015 16:04:48				
Date Stamp	12 May 2015 16:04:48			***File Name***	\\agni\nmr_data\AV_500\May _15_500\Tue3av500#009\1\PDATA\1\1r				
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	64	***Origin***	spect	***Original Points Count***	16000
Owner	nmr	***Points Count***	32768	***Pulse Sequence***	zg30	***Receiver Gain***	362.00	***SW(cyclical) (Hz)***	10000.00
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2491.6885	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70
Temperature (degree C)	28.300								



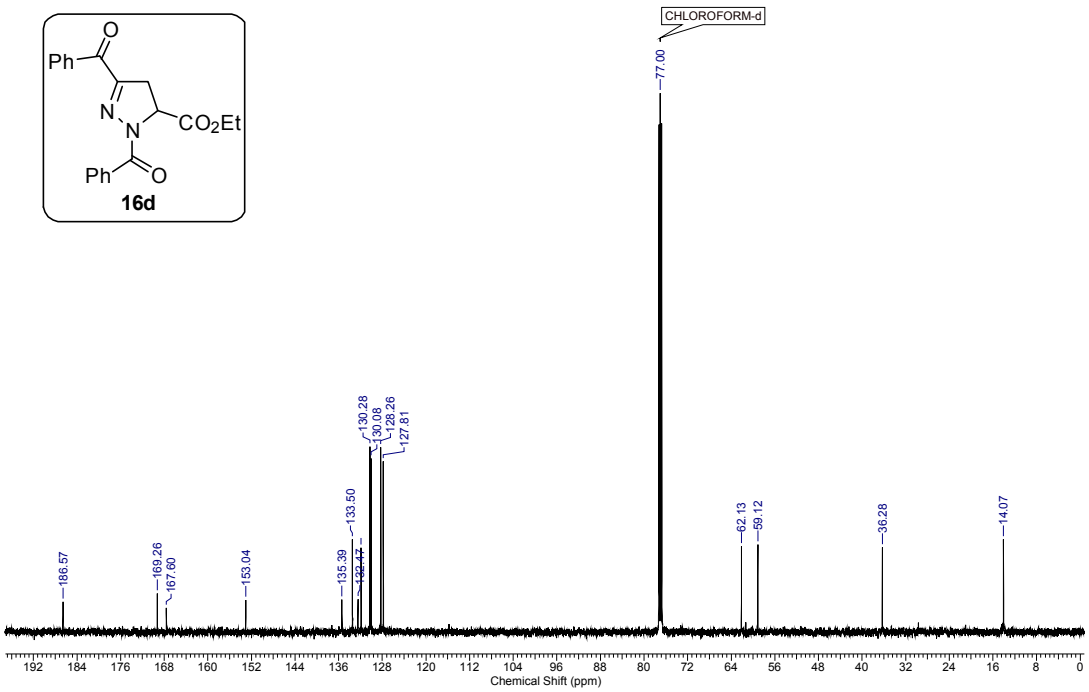
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	12 May 2015 17:02:24				
Date Stamp	12 May 2015 17:02:24			***File Name***	\\agni\nmr_data\AV_500\May _15_500\Tue3av500#009\3\PDATA\1\1r				
Frequency (MHz)	125.76	***Nucleus***	13C	***Number of Transients***	1265	***Origin***	spect	***Original Points Count***	20480
Owner	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30	***Receiver Gain***	1290.00	***SW(cyclical) (Hz)***	31250.00
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	12560.1094	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	31249.05
Temperature (degree C)	28.700								



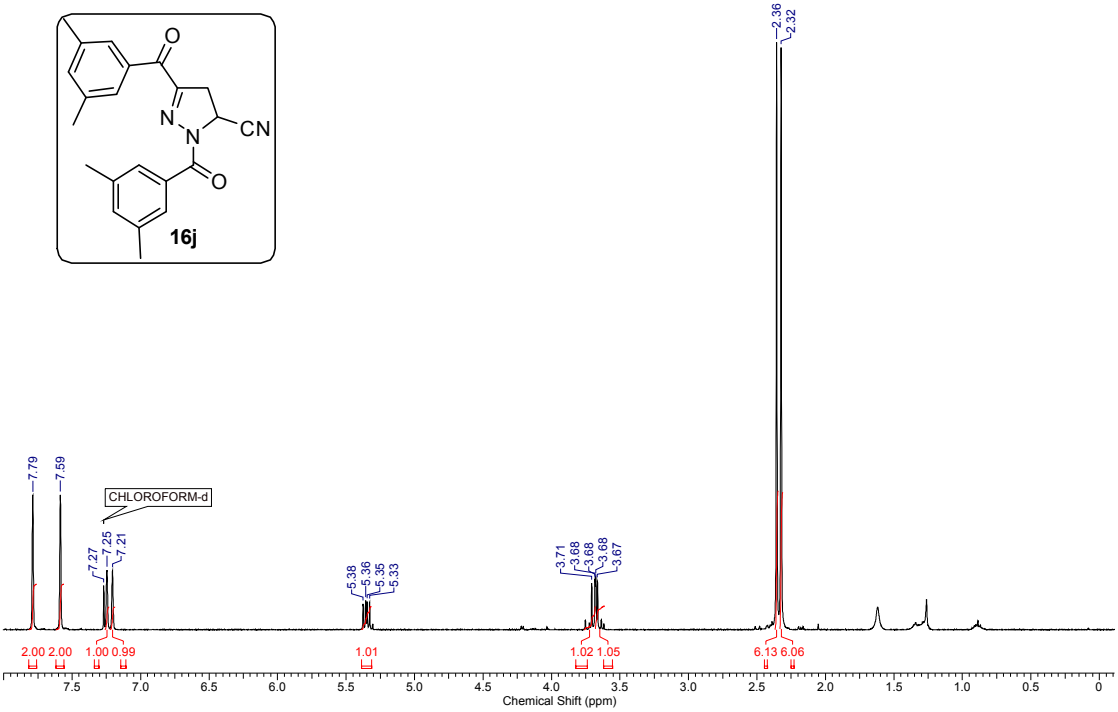
Acquisition Time (sec)	1.6000	***Comment***	vinod 1H	***Date***	20 May 2015 12:25:04		
Date Stamp	20 May 2015 12:25:04			***File Name***	\\agni\nmr_data\AV_500\May _15_500\Wed4av500#009\1\PDATA\1\1r		
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	16000	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	287.00	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2491.3833	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	28.400



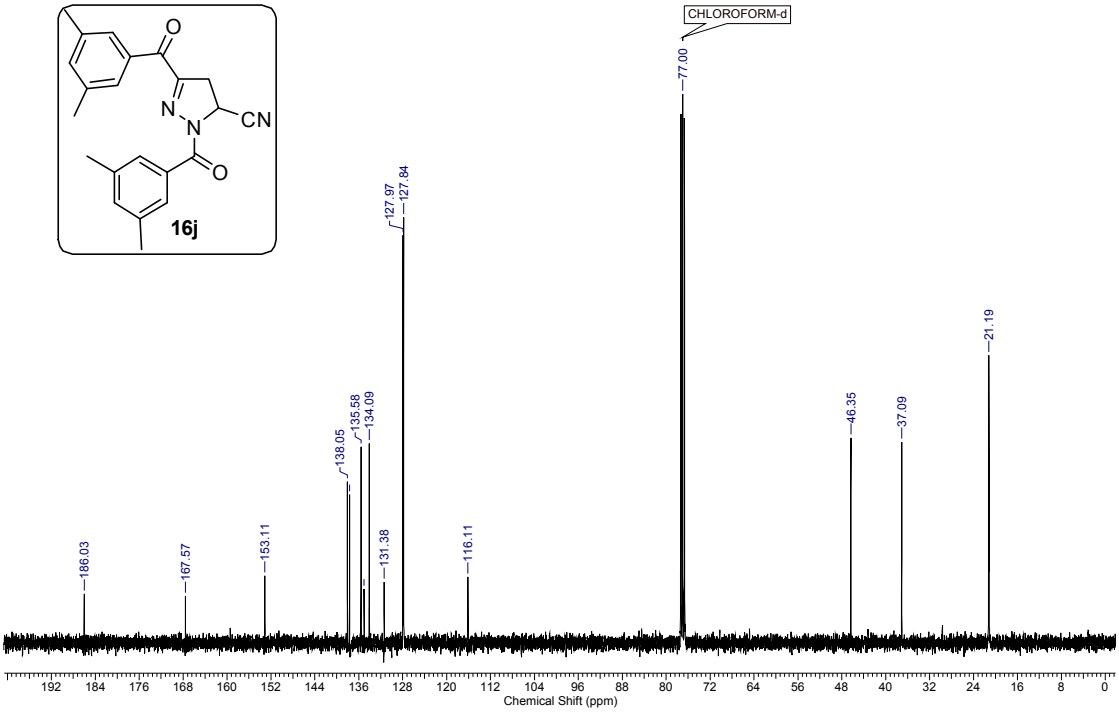
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	20 May 2015 12:33:36		
Date Stamp	20 May 2015 12:33:36			***File Name***	\\agni\nmr_data\AV_500\May _15_500\Wed4av500#009\3\PDATA\1\1r		
Frequency (MHz)	125.76	***Nucleus***	13C	***Number of Transients***	380	***Origin***	spect
Original Points Count	20480	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	1290.00	***SW(cyclical) (Hz)***	31250.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12560.1094	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	28.800



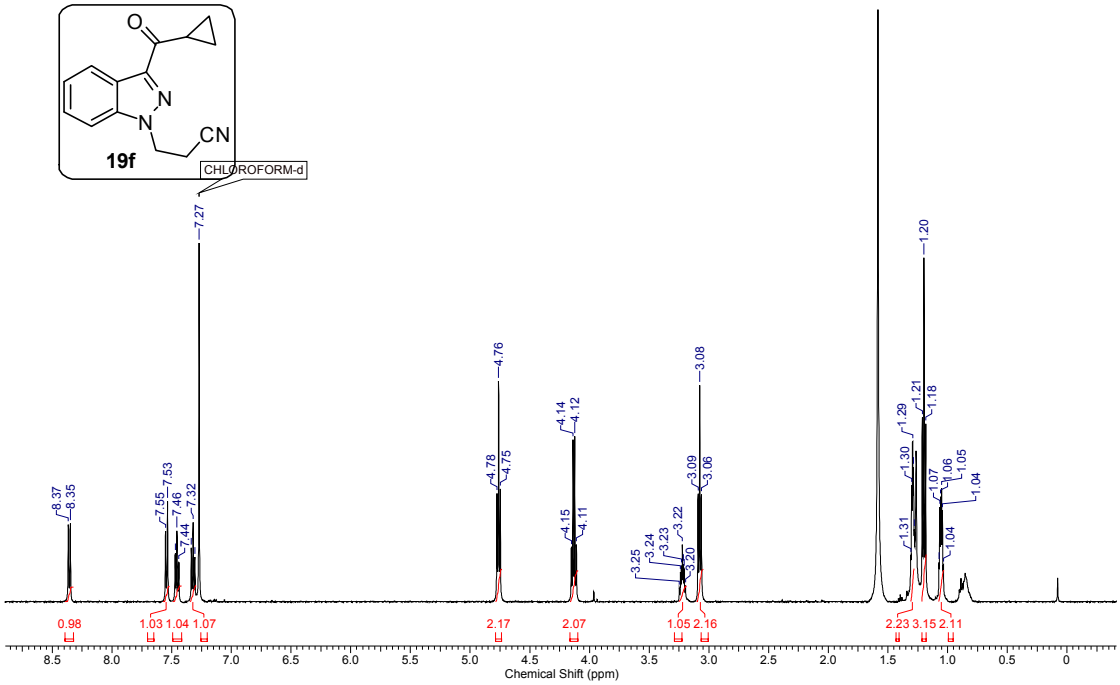
Acquisition Time (sec)	2.0447	***Comment***	vivek 1H	***Date***	12 Jun 2015 15:08:56		
Date Stamp	12 Jun 2015 15:08:56			***File Name***	\\agni\nmr_data\AV400\June_2015\Fri2av400#021\1\PDATA\1\1r		
Frequency (MHz)	400.13	***Nucleus***	1H	***Number of Transients***	16	***Origin***	spect
Original Points Count	16384	***Owner***	Administrator	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	362.00	***SW(cyclical) (Hz)***	8012.82	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2394.8169	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	8012.58	***Temperature (degree C)***	21.400



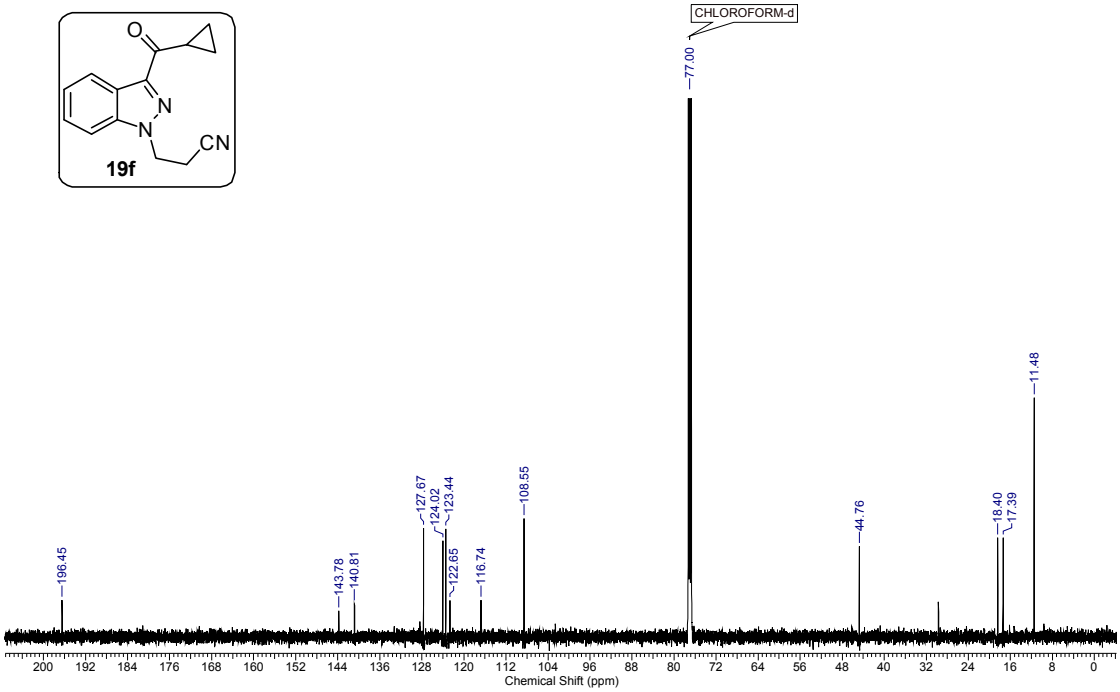
Acquisition Time (sec)	0.6488	***Comment***	13C	***Date***	12 Jun 2015 15:21:44		
Date Stamp	12 Jun 2015 15:21:44			***File Name***	\\agni\nmr_data\AV400\June_2015\Fri2av400#021\3\PDATA\1\1r		
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	337	***Origin***	spect
Original Points Count	16384	***Owner***	root	***Points Count***	32768	***Pulse Sequence***	zgpg
Receiver Gain	2050.00	***SW(cyclical) (Hz)***	25252.53	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	9957.0107	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	25251.75	***Temperature (degree C)***	21.900



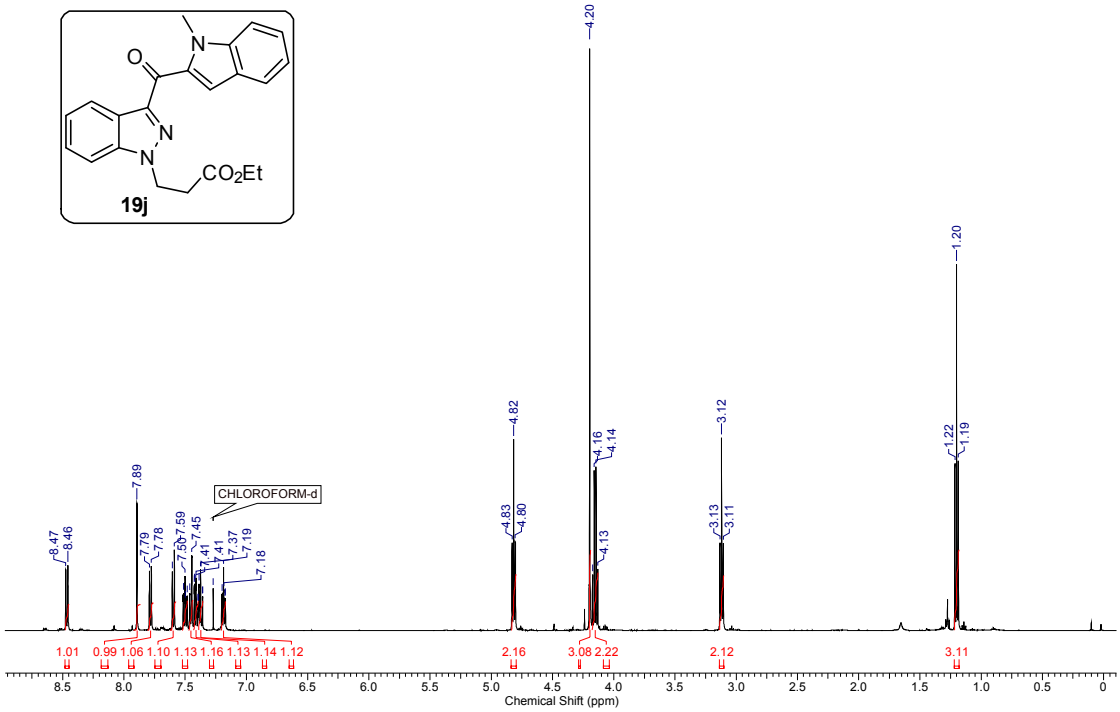
Acquisition Time (sec)	1.2800	***Comment***	Ravindra 1H	***Date***	14 Sep 2016 14:43:44		
Date Stamp	14 Sep 2016 14:43:44						
File Name	\\172.16.2.4\nmr_data\AV500\2016_AV500\Sep_16_AV500\Wed3av500#013_11178\1\PDATA\1\1r					***Frequency (MHz)***	500.13
Nucleus	1H	***Number of Transients***	9	***Origin***	spect	***Original Points Count***	16000
Owner	nmr	***Points Count***	32768	***Pulse Sequence***	zg30	***Receiver Gain***	575.00
SW(cyclical) (Hz)	12500.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	3492.3218
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12499.62	***Temperature (degree C)***	24.900		



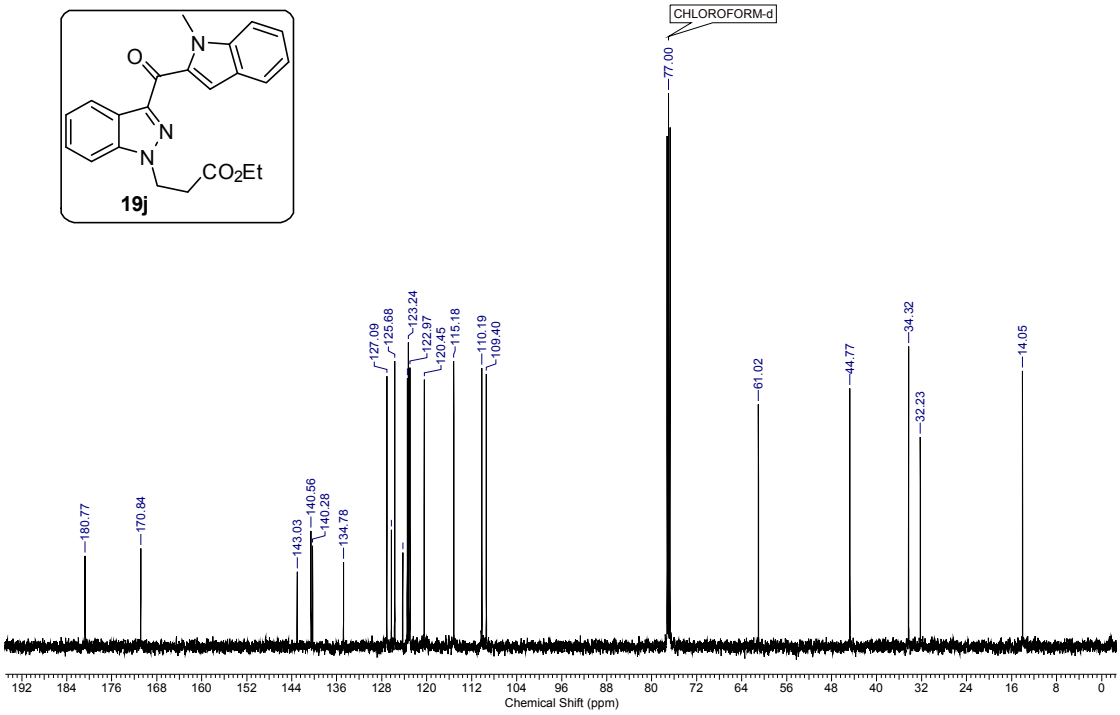
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	14 Sep 2016 14:37:20		
Date Stamp	14 Sep 2016 14:37:20						
File Name	\\172.16.2.4\nmr_data\AV500\2016_AV500\Sep_16_AV500\Wed3av500#012_11178\3\PDATA\1\1r					***Frequency (MHz)***	125.76
Nucleus	13C	***Number of Transients***	2431	***Origin***	spect	***Original Points Count***	20480
Owner	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30	***Receiver Gain***	2050.00
SW(cyclical) (Hz)	31250.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	12561.0615
Spectrum Type	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	25.000		



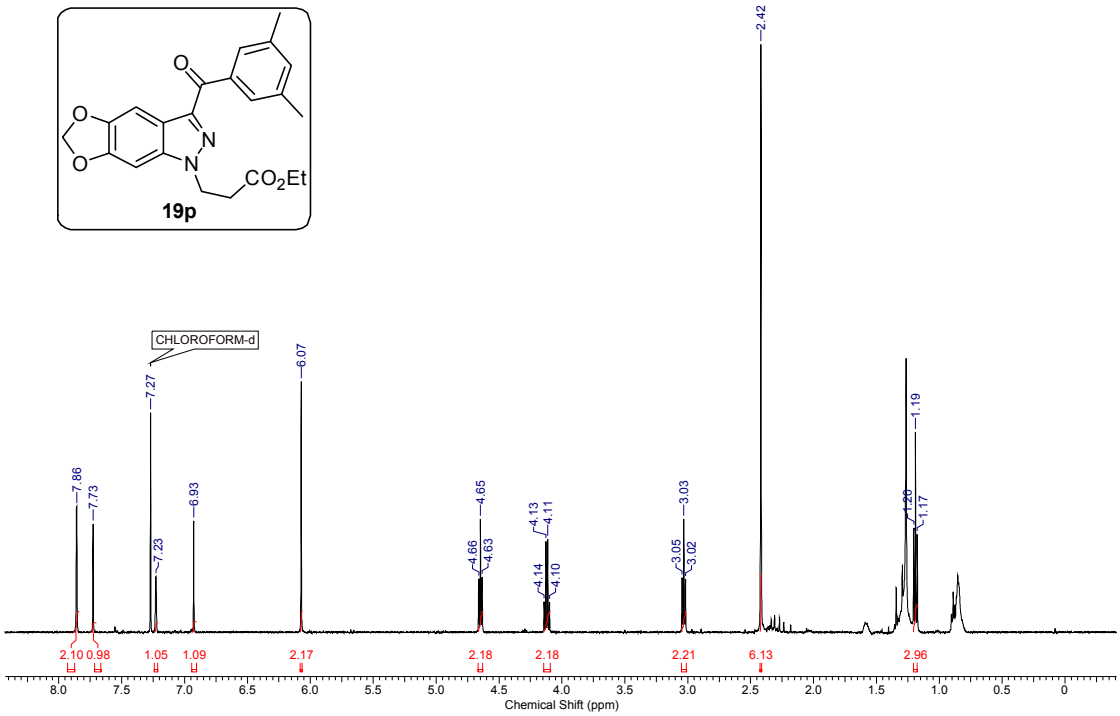
Acquisition Time (sec)	1.6000	***Comment***	Ravindra 1H	***Date***	24 Feb 2015 16:47:12		
Date Stamp	24 Feb 2015 16:47:12			***File Name***	\\agni\nmr_data\AV_500\Feb_15_500\Tue4av500#007\1\PDATA\1\1r		
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	32	***Origin***	spect
Original Points Count	16000	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	161.00	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2491.9937	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	25.400



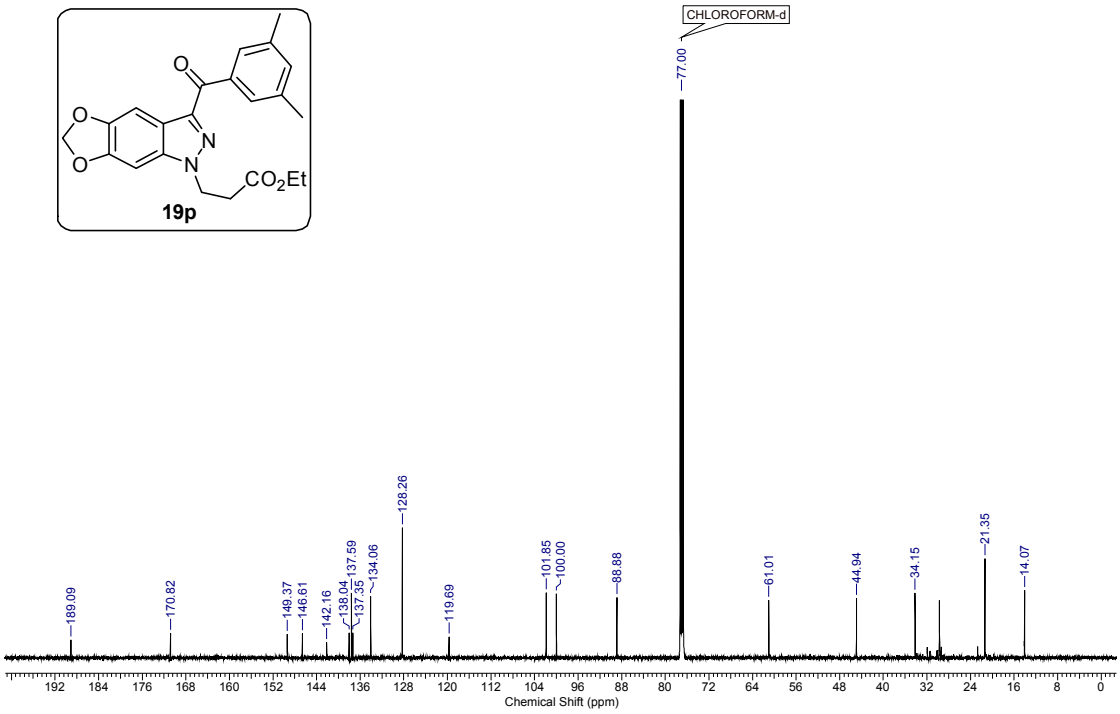
Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	24 Feb 2015 16:51:28		
Date Stamp	24 Feb 2015 16:51:28			***File Name***	\\agni\nmr_data\AV_500\Feb_15_500\Tue4av500#007\3\PDATA\1\1r		
Frequency (MHz)	125.76	***Nucleus***	13C	***Number of Transients***	249	***Origin***	spect
Original Points Count	20480	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	1290.00	***SW(cyclical) (Hz)***	31250.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12555.3408	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	26.100



Acquisition Time (sec)	1.6000	***Comment***	vivek 1H	***Date***	23 Apr 2015 20:12:16		
Date Stamp	23 Apr 2015 20:12:16			***File Name***	\\agni\nmr_data\AV_500\April_15_500\Thu4av500#026\1\PDATA\1\1r		
Frequency (MHz)	500.13	***Nucleus***	1H	***Number of Transients***	128	***Origin***	spect
Original Points Count	16000	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zg30
Receiver Gain	406.00	***SW(cyclical) (Hz)***	10000.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2491.9937	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	9999.70	***Temperature (degree C)***	27.700



Acquisition Time (sec)	0.6554	***Comment***	13C	***Date***	24 Apr 2015 10:00:00		
Date Stamp	24 Apr 2015 10:00:00			***File Name***	\\agni\nmr_data\AV_500\April_15_500\Thu4av500#026\3\PDATA\1\1r		
Frequency (MHz)	125.76	***Nucleus***	13C	***Number of Transients***	19498	***Origin***	spect
Original Points Count	20480	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg30
Receiver Gain	1290.00	***SW(cyclical) (Hz)***	31250.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	12562.0156	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	31249.05	***Temperature (degree C)***	27.300



References

1. Curtius, T. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230.
2. a) L. Wolff, *Justus Liebigs Ann. Chem.* **1902**, *325*, 129. b) Kirmse, W. *Eur. J. Org. Chem.* **2002**, *2002*, 2193.
3. a) Anrdt, F.; Eistert, B.; Part.de, W. *Ber. Dtsch. Chem. Ges.* **1927**, *60B,* 1364. b) Amdt, F.; Amende, J. *Ber. Dtsch. Chem. Ges.* **1928**, *61B*, 1122. c) Arndt, F.; Eistert, B.; Amende, J. *Ber. Dtsch. Chem. Ges.* **1928**, 61B, 1949. d) Bradley, W.; Robinson, R. J. *Chem. Soc.* **1928**, 1310.
4. a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. b) Doyle, M. P.; McKervey, M. A.; Ye, T. Modern Catalytic Methods for Organic Synthesis with Diazo Compounds; John Wiley & Sons: New York, **1998**.
5. Maas, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 8186.
6. a) Giddinge, P. J.; John, D. L; Thomas, E. J. *Tetrahedron Lett.* **1980**, *21*,395. b) Hauser, D.; Sigg, H. P. *Helu. Chim. Acta* **1967**, *50*, 1327. c) Searle, N. **E. *Organic Syntheses;*** Wiley: New York, **1963;** Collect. Vol. IV, p **424.** d) Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* **1976**, *31,* 227. e) Ehrlich, J.; Anderaon,L. E.; Coffey, G. L.; Nilleges, A. B.; Knudsen, M. P.; Koepsell, H. J.; Kohberger, D. L.; Oyaaa, J. E. *Nature* **1954**, 71.
7. a) Zwanenburg, B.; Thijs, L. *Tetrahedron Lett.* **1974**, *9*, 2459. b) Thijs, L.; Smeets, F. L. M.; Gillissen, P. J. M.; Harmsen, J.; Zwanenburg, B. *Tetrahedron* **1980**, *36*, 2141.
8. Ye, T.; McKervey, M. A. *Tetrahedron* **1992**, *48*, 8007.
9. a) Wilds, A. L.; Meader, A. L. J. *Org. Chem.* **1948**, *13*, 763. b) Pettit, G. R.; Nelson, P. S. *J. Org. Chem.* **1983**, *48*, 741. c) Pettit, G. R.; Nelson, P. S. J. *Org. Chem.* **1986**, *51*, 1282.
10. Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.
11. a) Abad, A.; Agulló, C.; Cuñat, A. C.; de Alfonso Marzal, I.; Navarro, I.; Gris, A. *Tetrahedron* **2006**, *62*, 3266. b) Arthuis, M.; Beaud, R.; Gandon, V.; Roulland, E. *Angew. Chem., Int. Ed.* **2012**, *51*, 10510. c) Shibuya, G. M.; Enquist, J. A.; Stoltz, B. M. *Org. Lett*. **2013**, *15*, 3480.
12. Taber, D. F.; Sheth, R. B.; Joshi, P. V. *J. Org. Chem.* **2005**, *70*, 2851.

13. a) Cava, M. P.; Litle, R. L.; Napier, D. R. *J. Am. Chem. Soc.* **1958**, *80*, 2257. b) Allinger, N. L.; Freiberg, L. A. *J. Org. Chem.* **1962**, *27*, 1490. c) Muchowski, **J.** M. *Tetrahedron Lett.* **1966**, 1773.
14. Fink, J.; Regitz, M. *Synthesis* **1985**, 569.
15. Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981.
16. a) Taylor, T. W. J.; Foracey, L. A. *J. Chem. Soc.* **1930**, 2272. b) Giddings, P. J.; John, D. I.; Thomas, E. J. *Tetrahedron Lett.* **1978**, 995. c) Ando, W. h The Chemistry of Diatoniumc;nd Diazogroups; Patai, S., *Ed.; John Wiley BE Sons: New York,* **1978**; Chapter 9, p 445. d) Pellicciari, R.; Curini, M.; Ceccherelli, P.; Fringuelli, R. *J. Chem. Soc., Chem. Commun.* **1979**, 440.
17. Ovalles, S. R.; Hansen, J. H.; Davies, H. M. L. *Org. Lett.* **2011**, *13*, 4284.
18. Horner, L.; Spietschka, E.; Gross, A. W. *Justus Liebigs Ann. Chem.* **1951**, *573*, 17.
19. Meerwein, H.; Rathjen, H.; Wemer, H. *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 1610.
20. a) Yates, P.; Danishefsky, S. *J. Am. Chem. Soc.* **1962**, *84*, 879. b) Wrobel, J.; Takahashi, K.; Honkan, V.; Lannoye, G.; Cook, J. M.; Bertz, S. H. *J. Org. Chem.* **1983**, *48*, 139.
21. Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295.
22. Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820.
23. a) Taber, D. F.; Schuchardt, J. L. *J. Am. Chem. Soc.***1986**, *107*, 5289. b) Adama, J.; Poupart, M. A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753.
24. a) Ballabio, M.; Malatesta,V.; Ruggieri, D.; Temperilli, A. *Gazz. Chim. Ital.* **1988**, *118,* 375. b) McKervey,M. A.;Ye,T. *J. Chem. Soc., Chem. Commun.* **1992**, 823.
25. a) Burke, **S.** D.; Grieco, P. A. *Org. React. (N.Y.)* **1979**, *26*, 361. b) Hatch, C. E., In, Baum, J. S. *J. Org. Chem.* **1980**, *45*, 3281.
26. a) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348. b) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, **1998**, pp. 163-220. c) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919.

27. a) Kang, **S.** H.; Kim, W. J.; Chae, Y. B. *Tetrahedron Lett.* **1988**, *29*, 5169. b) Yamanoi, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 1181.
28. a) Pirrung, M. C.; Zhang, J.; Lackey, K.; Sternbach, D. D.; Brown, F. *J. Org. Chem.* **1995**, *60*, 2112. b) Davies, H. M. L.; Clark, T. J.; Church, L. A. *Tetrahedron Lett.* **1989**, *30*, 5057. c) Davies, H.; Smith, H.; Korkor, O. *Tetrahedron Lett.* **1987**, *28*, 1853. d) Doyle, M.; Dorow, R.; Tamblyn, W.; Buhro, W. *Tetrahedron Lett.* **1982**, *23*, 2261.
29. a) Protopopova, M. N.; Shapiro, E. A. *Ruas. Chem. Rev.* **1989**, *58*, 667. b) Shapiro,E. A.; Lun'kova, ***G.*** V.;Nefedov, A. 0.; Dolgii, I. E.;Nefedov, O. M. *Izu. Akad. Nauk SSSR, Ser. Khim.* **1981**, 2535. c) Donaldson, W. A.; Hughes, R. P. *J. Am. Chem. Soc.* **1982**, 104, 4846. d) Dowd, P.; Garner, P.; Schappert, R.; Imgartinger, H.; Goldman, A. *J. Org. Chem.* **1982**, *47*, 4240.
30. a) Hoye, T. R.; Dinamore, C. J.; Johnson, D. S.; Korkowski, P. F. J. *Org. Chem.* **1990**, 55, 4518. b) Padwa, A.; Krumpe, K. E.; Gareau, Y.; Chiacchio, U. *J. Org. Chem.* **1991**, *56*, 2523.
31. Padwa, A.; Hornbuckle, S. F. *Chem. Rev*. **1991**, *91*, 263.
32. a) Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron* **1966**, *22*, 3393. b) Ando, W.; Kondo, S.; Nakayama, K.; Ichibori, K.; Kohoda, H.; Yamato, H.; Imai, I.; Nakaido, S.; Migita, T. *J. Am. Chem. Soc.* **1972**, *94*, 3870. c) Friedrich, K.; Jansen, U.; Kirmse, W. *Tetrahedron Lett.* **1985**, *26*, 193. d) Nozaki, H.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1965**, *6*, 2563.
33. Ye, T.; Garcia, C. F.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1373.
34. a) Gillespie, R. J.; Murray-Rust, J.; Murray-Rust, P.; Porter, A. E. A. *J. Chem. Soc., Chem. Commun.* **1978**, 83. b) Tamura, Y.; Mukai, C.; Nakajima, N.; Ikeda, M.; Kido, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 212. c) Moody, C. J.; Slawin, A. M. Z.; Taylor, R. J.; Williams, D. J. *Tetrahedron Lett.* **1988**, *29*, 6009. d) Moody, C. J.; Taylor, R. J. *Tetrahedron* **1990**, *46*, 6525.
35. Shi, G.; Xu, Y.; Xu, M. *Tetrahedron* **1991**, *47*, 1629.
36. Qu, J.-P.; Xu, Z.-H.; Zhou, J.; Cao, C.-L.; Sun, X.-L.; Dai, L.-X.; Tang, Y. *Adv. Synth. Catal*. **2009**, *351*, 308.
37. Felthouse, T. R. *Prog. Inorg. Chem.* **1982**, *29*, 73.
38. Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094.

39. Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Blake, A. J.; Cooke, P. A.; Street, L. *J. Chem. Soc., Perkin Trans. 1* **2001**, *0*, 3325.
40. Mucedda, M.; Muroni, D.; Saba, A.; Manassero, C. *Tetrahedron* **2007**, *63*, 12232.
41. Russell, A. E.; Brekan, J.; Gronenberg, L.; Doyle, M. P. *J. Org. Chem.* **2004**, *69*, 5269.
42. Suga, H.; Ishida, H.; Ibata, T. *Tetrahedron Lett.* **1998**, *39*, 3165.
43. a) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Tetrahedron Lett.* **1997**, *38*, 6471−6472. b) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Chem. Commun.* **1999**, 2185. c) Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem. - Eur. J.* **2001**, *7*, 4465. d) Hodgson, D. M.; Selden, D. A.; Dossetter, A. G. *Tetrahedron: Asymmetry* **2003**, *14*, 3841. e) Hodgson, D. M.; Labande, A. H.; Pierard, F. Y. T. M.; Expósito Castro, M. Á. *J. Org. Chem.* **2003**, *68*, 6153.
44. a) Buchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.* **1886**, *18*, 2371. b) Buchner, E. *Liebigs Ann. Chem.* **1893**, 273, 214; **1894**, 27, 3250; **1896**, 29,106; **1897**, 30, 632; **1898**, 31, 2241.
45. von E. Doering, W.; Laber, G.; Vonderwahl, R.; Chamberlain, N. F.: Williams, R. B. *J. Am. Chem. Soc.* **1966**, 78, 5448.
46. a) Buchner, E.; Papandieck, A. *Liebigs Ann. Chem.* **1893**, *273*, 233. b) Buchner, E.; Lingg, F. *Ber. Dtsch. Chem. Ges.* **1898**, 31, 402. c) Braren, W.; Buchner, E. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 684. d) Buchner, E.; Lehmann, L. *Ber. Dtsch. Chem. Ges.* **1902**, *35,* 35.
47. a) Anciaux, A. J.; Demonceau, A.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyesil, Ph. *J. Chem. Soc., Chem. Commun.* **1980**,765. b) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssil, Ph. *J. Org. Chem.* **1981**, *46*, 873.
48. Novac, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1968**, *23*, 1126.
49. Davies, H. M. L.; Clark, D. M.; Smith, T. K. *Tetrahedron Lett.* **1986**, *26*, 5659.
50. Davies, H. M. L.; Saikali, E.; Young, W. B. J. *Org. Chem.* **1991**, 56, 5696.
51. a) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1986**, *51*, 5036. b) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299.

52. Regitz, M.; Heydt, H. In *1,3-Dipolar Cycloaddition Chemistry;* Padwa, A., Ed.; John Wiley & Sons, Inc.: New York, 1984, Vol. 1, p 393.
53. a) Ghandour, N. El.; Soulier, J. C. *R. Acad. Sci. Paris* **1971**, *272*, 243. b) Franck-Neumann, M.; Buchecker, C. *Tetrahedron Lett.* **1972**, 937; **1976**, 2069.
54. Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219.
55. Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. ***J. Am. Chem. Soc*** **1977**, *99*, 4778.
56. a) Bailey, P. S.; Reader, A. M.; Koleaker, P.; White, H. M.;Barborak, J. C. *J.* ***Org. Chem.*** **1966**, 30, 3042. b) Ursini, A.; Pellicciari, R.; Tamburini, B.; Carlesso, R.; Gaviraghi, G. *Synthesis* **1992**, 363.
57. a) Murray, R. W.; Jeyaraman, J. *J.* ***Org. Chem.*** **1986**, *50*, 2847. b) Adam, W.; Bialas, J.; Hadjiarapoglou, L. ***Chem. Ber.*** **1991**, *124*, 2377. c) Darkins, P.; McCarthy, N.; McKervey, M. A.; Ye,T. *J.* ***Chem.*** *SOC., Chem. Commun.* **1993**, 1222.
58. a) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265. b) Martins, P.; Jesus, J.; Santos, S.; Raposo, L. R.; Roma-Rodrigues, C.; Baptista, P. V.; Fernandes, A. R. *Molecules* **2015**, *20*, 16852. c) Yusuf, M.; Jain, P. *Arab. J. Chem.* **2014**, *7*, 525. d) Dua, R.; Shrivastava, S.; Sonwane S. K.; Srivastava S. K. *Advan. Biol. Res.* **2011**, *5* 120. e) Baumann, M.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265. f) Lauria, A.; Delisi, R.; Mingoia, F.; Terenzi, A.; Martorana, A.; Barone, G.; Almerico, A. M. *Eur. J. Org. Chem.* **2014**, *2014*, 3289
59. a) Bariwal, J.; Van der Eycken, E. *Chem. Soc. Rev.* **2013**, *42*, 9283. b) hin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040. c) Hartwig, J. F. *Nature* **2008**, *455*, 314. d) Abel-Magid, A. F.; Mehrman, S. J. *Org. Proc. Res. Devel.* **2006**, *10*, 971. e) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.
60. a) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. b) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2015**, *116*, 12564. c) Wen, Q.; Lu, P.; Wang, Y. *RSC Adv.* **2014**, *4*, 47806.
61. a) Fisera, L.; Ondrus, V.; Kuban, J.; Micuch, P.; Blanarikova, I.; Jager, V. *J. Heterocycl. Chem.* **2000**, *37*, 551. b) Pearson, W. H. *Pure Appl.*

Chem **2002**, *74*, 1339. c) Kanemasa, S. *Synlett* **2002**, 1371. d) Padwa, A.; Pearson, W. H., *Chem. Heterocycl. Comp*., **2002**, *59*. e) Lashgari, N.; Ziarani, G. M. *Arkivoc* **2012**, 277-320.

62. a) Zhou, S.; Wang, J.; Zhang, F.; Song, C.; Zhu, J. *Org. Lett.* **2016**, *18*, 2427-2430. b) Wan, J.-P.; Li, Y.; Liu, Y. *Org. Chem. Front.* **2016**, *3*, 768. c) Mei, T. S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J. Q. *Synthesis* **2012**, *44*, 1778. d) Huang, H. W.; Cai, J. H.; Deng, G. J. *Org. Biomol. Chem.* **2016**, *14*, 1519. e) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31. f) Engle, K. M.; Mei, T. S.; Wasa, M.; Yu, J. Q. *Acc. Chem. Res.* **2012**, *45*, 788. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. g) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. h) Zhu, C.; Wang, R.; Falck, J. R. *Chem. –Asian J.* **2012**, *7*, 1502. i) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. j) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. k) Wencel-Delord J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. l) Jeffreya J. L.; Sarpong, R. *Chem. Sci.* **2013**, *4*, 4092. m) Yan, G.; Wu, X.; Yang, M. *Org. Biomol. Chem.* **2013**, *11*, 5558. n) Rouquet, G. Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. o) Pan, S.; Shibata, T. *ACS Catal.* 2013, 3, 704. p) Jun, C. H.; Park, J. W. *Top. Curr. Chem.* **2014**, *346*, 59. q) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. r) Kuhl, N.; Schröder N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443.

63. a) Mayer, S. C.; Banker, A. L.; Boschelli, F.; Di, L.; Johnson, M.; Kenny, C. H.; Krishnamurthy, G.; Kutterer, K.; Moy, F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3641. b) Wang, B.-R. K.-J.; Li, H.; Li, Y.; Mei, Q.-B.; Zhang, S.-Q. *Med. Chem. Res.* **2014**, *23*, 1340. c) Malamas, M. S.; Hohman, J. T. C.; Millent, J. *J. Med. Chem.* **1994**, *37*, 2043. d) Snow, R. J.; Cardozo, M. G.; Morwick, T. M.; Busacca, C. A.; Dong, Y.; Eckner, R. J.; Jacober, S.; Jakes, S.; Kapadia, S.; Lukas, S.; Panzenbeck, M.; Peet, G. W.; Peterson, J. D.; Prokopowicz, A. S.; Sellati, R.; Tolbert, R. M.; Tschantz, M. A.; Moss, N. *J. Med. Chem.* **2002**, *45*, 3394. e) Xia, B.; Ma, W.; Zheng, B.; Zhang, X.; Fan, B. *Eur. J. Med. Chem.* **2008**, *43*, 1489. f) Reux, B.; Nevalainen, T.; Raitio, K. H.; Koskinen, A. M. P. *Bioorg. Med. Chem.* **2009**, *17*, 4441. g) Rajanarendar, E.; Raju, S.; Reddy, M. N.; Krishna, S. R.; Kiran, L. H.; Reddy, A. R. N.; Reddy, Y. N. *Eur. J. Med. Chem.* **2012**, *50*, 274.

64. a) Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, 924. b) Yeom, H.-S.; Lee, Y.; Leeb, J.-E.; Shin, S. *Org. Biomol. Chem.* **2009**, *7*, 4744. c) Ding, Q.; Wang, D.; Sang, X.; Lin, Y.; Peng, Y. *Tetrahedron* **2012**, *68*, 8869. d) Wang, H.; Zhu, M.; Ye, S.; Wu, J. *RSC Adv.* **2013**, *3*, 13626. e) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. f) Hashiguchi, B. G.; Bischof, S. M.; Konnick, M. M.; Periana, R. A. *Acc. Chem. Res.* **2012**, *45*, 885. g) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. h) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. i) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. j) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. k) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.* **2014**, *114*, 8775. l) Kuhl, N.; Schroder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. m) Yang, L.; Huang, H. *Chem. Rev.* **2015**, *115*, 3468. n) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. o) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308.

65. a) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486. b) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560. c) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236. d) Xia, Y.; Zhang, Y.; Wang, J. *ACS Catal.* **2013**, *3*, 2586. e) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 7986.

66. Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565.

67. a) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364. b) Yu, X.; Yu, S.; Xiao, J.; Wan, B.; Li, X. *J. Org. Chem.* **2013**, *78*, 5444. c) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. d) Cui, S.; Zhang, Y.; Wang, D.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3912. e) Hu, F.; Xia, Y.; Ye, F.; Liu, Z.; Ma, C.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1364. f) Shi, J.; Yan, Y.; Li, Q.; Xu, H. E.; Yi, W. *Chem. Commun.* **2014**, *50*, 6483. g) Lam, H.-W.; Man, K.-Y.; Chan, W.-W.; Zhou, Z.; Yu, W.-Y. *Org. Biomol. Chem.* **2014**, *12*, 4112. h) Liang, Y.; Yu, K.; Li, B.; Xu, S.; Song, H.; Wang, B. *Chem. Commun.* **2014**, *50*, 6130. i) Ye, B.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 7896. j) Son, J.-Y.; Kim, S.; Jeon, W. H.; Lee, P. H. *Org. Lett.* **2015**, *17*, 2518. k) Chen, X.; Hu, X.; Bai, S.; Deng, Y.; Jiang, H.; Zeng, W. *Org. Lett.* **2016**, *18*, 192. And

reference there in. l) Li, B.; Jiao, P.; Zhong, H.; Huang, J. *Synlett* **2013**, *24*, 2431.

68. a) Ryu, J.; Kwak, J.; Shin, K.; Lee, D.; Chang, S. *J. Am. Chem. Soc.* **2013**, *135*, 12861. b) Itoh, M.; Hirano, K.; Satoh, T.; Shibata, Y.; Tanaka, K.; Miura, M. *J. Org. Chem.* **2013**, *78*, 1365. c) Pan, S.; Wakaki, T.; Ryu, N.; Shibata, T. *Chem. –Asian J.* **2014**, *9*, 1257. d) Ai, W.; Yang, X.; Wu, Y.; Wang, X.; Li, Y.; Yang, Y.; Zhou, B. *Chem.–Eur. J.* **2014**, *20*, 17653. f) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780. g) Pan, C.; Jin, N.; Zhang, H.; Han, J.; Zhu, C. *J. Org. Chem.* **2014**, *79*, 9427. h) Shin, K.; Chang, S. *J. Org. Chem.* **2014**, *79*, 12197. i) Ai, W.; Wu, Y.; Tang, H.; Yang, X.; Yang, Y.; Li, Y.; Zhou, B. *Chem. Commun.* **2015**, *51*, 7871. j) Chen, H.; Huestis, M. P. *ChemCatChem* **2015**, *7*, 743. k) Lee, D.; Chang, S. *Chem.–Eur. J.* **2015**, *21*, 5364. l) Hou, W.; Yang, Y.; Ai, W.; Wu, Y.; Wang, X.; Zhou, B.; Li, Y. *Eur. J. Org. Chem.* **2015**, 395. m) Wu, Y.; Yang, Y.; Zhou, B.; Li, Y. *J. Org. Chem.* **2015**, *80*, 1946. n) Wang, H.; Xie, F.; Qi, Z.; Li, X. *Org. Lett.* **2015**, *17*, 920. o) Suzuki, C.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2015**, *17*, 1597. (p) Zhou, T.; Li, L.; Li, B.; Song, H.; Wang, B. *Org. Lett.* **2015**, *17*, 4204.
69. a) Ai, W.; Yang, X.; Wu, Y.; Wang, X.; Li, Y.; Yang, Y.; Zhou, B. *Chem. –Eur. J.* **2014**, *20*, 17653. b) Xia, Y.; Liu, Z.; Feng, S.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 223. c) Zhang, S.-S.; Jiang, C. –Y.; Wu, J. –Q.; Liu, X.-G.; LI, Q.; Huang, Z.-S. Li, D.; Wang, H. *Chem. Commun.* **2015**, *51*, 10240.
70. a) Nicholas, G. M.; Blunt, J. W.; Munro, M. H. G. *J. Nat. Prod.* **2001**, *64*, 341. b) Donnell, G. O.; Poeschl, R.; Zimhony, O.; Gunaratnam, M.; Moreira, J. B. C.; Neidle, S.; Evangelopoulos, D.; Bhakta, S.; Malkinson, J. P.; Boshoff, H. I.; Lenaerts, A.; Gibbons, S. *J. Nat. Prod.* **2009**, *72*, 360. c) Derdau, V.; Laschat, S.; Hupe, E.; Kçnig, W. A.; Dix, I.; Jones, P. G. *Eur. J. Inorg. Chem.* **1999**, 1001. d) Malkov, A. V.; Kocovsky, P. *Eur. J. Org. Chem.* **2007**, 29. e) Takenaka, N.; Sarangthem, R. S.; Captain, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 9708. f) Chen, J.; Takenaka, N. *Chem. –Eur. J.* **2009**, *15*, 7268.
71. a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. b) Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, 1991. c) Youssif, S. *ARKIVOC* **2001**, *2001 (i)*, 242.
72. Li, B.; Jiao, P.; Zhong, H.; Huang, J. *Synlett* **2013**, *24*, 2431.

73. Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204.
74. Sun, P.; Wu, Y.; Yang, T.; Wu, X.; Xu, J.; Lin, A.; Yao, H. *Adv. Synth. Catal.* **2015**, *357*, 2469–2473.
75. Zhang, G.; Wen, X.; Wang, Y.; Mo, W.; Ding, C. *J. Org. Chem.* **2011**, *76*, 4665.
76. a) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. b) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908.
77. Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, 51, 3066.
78. a) Boutadla, Y.; Davies, D. L.; Jones, R. C.; Singh, K. *Chem. -Eur. J.* **2011**, *17*, 3438. b) Watanabe, M.; Kashiwame, Y.; Kuwata, S.; Ikariya, T. *Eur. J. Inorg. Chem*. **2012**, *2012*, 504. (c) Patel, P.; Chang, S. *Org. Lett.* **2014**, *16*, 3328.
79. a) Zhang, S.-S.; Jiang, C.-Y.; Wu, J.-Q.; Liu, X.-G.; Li, Q.; Huang, Z.-S.; Li, D.; Wang, H. *Chem. Commun.* **2015**, *51*, 10240. b) Xia, Y.; Liu, Z.; Feng, S.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 223. c) Chan, W.-W.; Lo, S.-F.; Zhou, Z.; Yu, W.-Y. *J. Am. Chem. Soc.* **2012**, *134*, 13565. d) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364. e) Shin, K.; Park, S.-W.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 8584. f) Dateer, R. B.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4908.
80. Shi, J.; Zhou, J.; Yan, Y.; Jia, J.; Liu, X.; Song, H.; Xu, H. E.; Yi, W. *Chem. Commun.* **2015**, *51*, 668.
81. a) Mayer, S. C.; Banker, A. L.; Boschelli, F.; Di, L.; Johnson, M.; Kenny, C. H.; Krishnamurthy, G.; Kutterer, K.; Moy, F. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3641. b) Wang, B.-R. K.-J.; Li, H.; Li, Y.; Mei, Q.-B.; Zhang, S.-Q. *Med. Chem. Res.* **2014**, *23*, 1340. c) Malamas, M. S.; Hohman, J. T. C.; Millent, J. *J. Med. Chem.* **1994**, *37*, 2043. d) Snow, R. J.; Cardozo, M. G.; Morwick, T. M.; Busacca, C. A.; Dong, Y.; Eckner, R. J.; Jacober, S.; Jakes, S.; Kapadia, S.; Lukas, S.; Panzenbeck, M.; Peet, G. W.; Peterson, J. D.; Prokopowicz, A. S.; Sellati, R.; Tolbert, R. M.; Tschantz, M. A.; Moss, N. *J. Med. Chem.* **2002**, *45*, 3394.

82. Fukui, Y.; Liu, P.; Liu, Q.; He, Z.-T.; Wu, N.-Y.; Tian, P.; Lin, G.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 15607.

83. a) Hufford, C. D.; Oguntimein, B. O. *J. Nat. Prod.* **1982**, *45*, 337. b) Matsui, T.; Sugiura, T.; Nakai, H.; Iguchi, S.; Shigeoka, S.; Takada, H.; Odagaki, Y.; Nagao, Y.; Ushio, Y.; Ohmoto, K.; Iwamura, H.; Yamazaki, S.; Arai, Y.; Kawamura, M. *J. Med. Chem.* **1992**, *35*, 3307. c) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624. d) Pettit, G. R.; Meng, Y.; Herald, D. L.; Graham, K. A. N.; Pettit, R. K.; Doubek, D. L. *J. Nat. Prod.* **2003**, *66*, 1065. e) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059.

84. Shi, L.; Yu, K.; Wang, B. *Chem. Commun.* **2015**, *51*, 17277.

85. Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379.

86. Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

87. a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 448. b) Gilbert, J. C.; Blackburn, B. K. *J. Org. Chem.* **1986**, *51*, 3656. c) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. e) Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G. *J. Org. Chem.* **1996**, *61*, 2540. f) Roth, G. J.; Liepold, B.; Muller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59. g) Jepsen, T. H.; Kristensen, J. L. *J. Org. Chem.* **2014**, *79*, 9423.

88. a) Zhan, M.; Zhang, S.; Zhang, W.-X.; Xi, Z. *Org. Lett.* **2013**, *15*, 4182-4185; b) Pramanik, M. M. D.; Chaturvedi, A. K.; Rastogi, N. *Chem. Commun.* **2014**, *50*, 12896-12898; c) Ye, F.; Wang, C.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11625-11628; d) Mykhailiuk, P. K. *Eur. J. Org. Chem.* **2015**, 7235-7239; e) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981-10080; f) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366-5412; g) Chen, X.; Xie, Y.; Xiao, X. S.; Li, G. Q.; Deng, Y. F.; Jiang, H. F.; Zeng, W. *Chem. Commun.* **2015**, *51*, 15328-15331; h) Pramanik, M. M. D.; Rastogi, N. *Org. Biomol. Chem.* **2016**, *14*, 1239-1243; i) Matheis, C.; Krause, T.; Bragoni, V.; Goossen, L. J. *Chem. Eur. J.* **2016**, *22*, 12270-12273.

89. a) Muruganantham, R.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2007**, *9*, 1125. b) Mohanan, K.; Martin, A. R.; Toupet, L.; Smietana, M.; Vasseur, J. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 3196. c) Verma, D.; Mobin, S.;

Namboothiri, I. N. N. *J. Org. Chem.* **2011**, *76*, 4764. d) Kumar, R.; Verma, D.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2012**, *14*, 4070. e) Mohapatra, S.; Bhanja, C.; Jena, S.; Chakroborty, S.; Nayak, S. *Synth. Commun.* **2013**, *43*, 1993. f) Pramanik, M. M. D.; Kant, R.; Rastogi, N. *Tetrahedron* **2014**, *70*, 5214. g) Ahamad, S.; Gupta, A. K.; Kant, R.; Mohanan, K. *Org. Biomol. Chem.* **2015**, *13*, 1492. h) Gupta, A. K.; Ahamad, S.; Gupta, E.; Kant, R.; Mohanan, K. *Org. Biomol. Chem.* **2015**, *13*, 9783. i) Kamal, A.; Sastry, K. N. V.; Chandrasekhar, D.; Mani, G. S.; Adiyala, P. R.; Nanubolu, J. B.; Singarapu, K. K.; Maurya, R. A. *J. Org. Chem.* **2015**, *80*, 4325. j) Mykhailiuk, P. K. *Angew. Chem. Int. Ed.* **2015**, *54*, 6558. k) Shelke, A. M.; Suryavanshi, G. *Org. Biomol.Chem.* **2016**, *13*, 8669. l) Aronoff, M. R.; Gold, B.; Raines, R. T. *Tetrahedron Lett.* **2016**, *57*, 2347.

90. a) Regan, J.; Breitfelder, S.; Cirillo, P.; Gilmore, T.; Graham, A. G.; Hickey, E.; Klaus, B.; Madwed, J.; Moriak, M.; Moss, N.; Pargellis, C.; Pav, S.; Proto, A.; Swinamer, A.; Tong, L.; Torcellini, C. *J. Med. Chem.* **2002**, *45*, 2994. b) Mowbray, C. E.; Burt, C.; Corbau, R.; Gayton, S.; Hawes, M.; Perros, M.; Tran, I.; Price, D. A.; Quinton, F. J.; Selby, M. D.; Stupple, P. A.; Webster, R.; Wood, A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5857. c) Winters, M. P.; Subasinghe, N.; Wall, M.; Beck, E.; Brandt, M. R.; Finley, M. F. A.; Liu, Y.; Lubin, M. L.; Neeper, M. P.; Qin, N.; Flores, C. M.; Sui, Z. H. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2053.
91. a) Ogilvle, K. K.; Beaucage, S. L. *Nucleic Acids Res.***1979**, *7*, 805. b) b) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429. c) Kanemasa, S.; Araki, T.; Kanai, T.; Wada, E. *Tetrahedron Lett.* **1999**, *40*, 5059. d) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr.Opin.Drug Discovery Dev.* **2008**, *11*, 803. e) Murai, T.; Inaji, S.; Takenaka, T. *Heteroat. Chem.* **2009**, *20*, 255. f) Hawkins, M. J.; Powell, E. T.; Leo, G. C.; Gauthier, D. A.; Greco, M. N.; Maryanoff, B. *Org. Lett.* **2006**, *8*, 3429. g) Abid, I.; Gosselin, P.; Mathe-Allainmat, M.; Abid, S.; Dujardin, G.; Gaulon-Nourry, C. *J. Org. Chem.* **2015**, *80*, 9980. h) Hameed, A.; Alharthy, R. D.; Iqbal, J.; Langer, P. *Tetrahedron* **2016**, *72*, 2763.
92. a) Elguero, J.; Gonzalez, E.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1969**, 2054. b) Alkorta, I.; Gonzalez, E.;, Jagerovic, N.; Elguero, J.; Flammang, R. *J. Phys. Org. Chem.* **2000**, *13*, 372.

93. a) West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051. b) Padwa, A.; Dean, D. C.; Fairfax, D. J.; Xu, Simon L. *J. Org. Chem.* 1993, 58, 4646. c) Heydt, H. *Science of Synthesis* **2004**, *27*, 843.
94. a) Jin, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3323. b) Spiteri, C.; Keeling, S.; Moses, J. E. *Org. Lett.* **2010**, *12*, 3368. c) Wu, C. R.; Fang, Y. S.; Larock, R. C.; Shi, F. *Org. Lett.* **2010**, *12*, 2234. d) Li, P.; Zhao, J. J.; Wu, C. R.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340. e) Li, P.; Wu, C. R.; Zhao, J.; Rogness, D. C.; Shi, F. *J. Org. Chem.* **2012**, *77*, 3149. f) Wang, C. D.; Liu, R. S. *Org. Biomol. Chem.* **2012**, *10*, 8948.
95. a) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219. b) Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191.
96. a) R. R. Milburn, K. McRae, J. Chan, J. Tedrow, R. Larsen and M. Faul, *Tetrahedron Lett.*, 2009, **50**, 870. b) K. M. Maloney and J. Y. L. Chung, *J. Org. Chem.*, 2009, **74**, 7574.
97. a) Meffre, P.; Hermann, S.; Durand, P.; Reginato, G.; Riu, A. *Tetrahedron* **2002**, *58*, 5159. b) Koskinen, A. M. P.; Muñoz, L. *J. Chem. Soc., Chem. Commun.* **1990**, 652.

LIST OF PUBLICATIONS:

PEER-REVIEWED PUBLICATIONS

- "Oxone–acetone mediated *syn*-dioxygenation of benzo-fused olefins" Ravindra S. Phatake, Chepuri V. Ramana, *Tetrahedron Lett*. **2015**, *56*, 2183.
- "Oxone–acetone mediated Wacker-type oxidation of benzo-fused olefins" Ravindra S. Phatake, Chepuri V. Ramana, *Tetrahedron Lett*. **2015**, *56*, 3868.
- "Ir(III)-Catalyzed Synthesis of Isoquinoline *N*-Oxides from Aryloxime and α-Diazocarbonyl Compounds" Ravindra S. Phatake, Pitambar Patel, and Chepuri V. Ramana, *Org. Lett*. **2016**, *18*, 292.
- "Ir(III)-Catalyzed Carbenoid Functionalization of Benzamides: Facile Synthesis of *N*-Methoxyisoquinolinediones and *N*-Methoxyisoquinolinones" Ravindra S. Phatake, Pitambar Patel, and Chepuri V. Ramana, *Org. Lett.* **2016**, *18,* 292.
- Fluoride-Mediated Dephosphonylation of *α*-Diazo-*β*-carbonyl Phosphonates Ravindra S. Phatake, Venkannababu Mullapudi, Vivek C. Wakchaure, and Chepuri V. Ramana, *Org. Lett*. **2017**, *ASAP* (**DOI**: 10.1021/acs.orglett.6b03573).
- **Patent**: "Oxone-Acetone Mediated Metal Free Preparation of *Syn*-Diols" Chepuri V. Ramana, Ravindra S. Phatake, **2015**, WO2014207766 A9.

ChemSpider Synthetic Pages:

- "Triflic Acid Catalyzed Cyclization of trans-Cinnamaldehyde to 3- phenyl-1Hindene"
  Ravindra Phatake, Sachin Gholap, *CSSP*-764, **2014**, DOI: 10.1039/SP764.
- "Esterification of 2-bromo-3-phenylpropanoic acid"
  Ravindra Phatake, *CSSP*-765, **2014**, DOI: 10.1039/SP765.
- "Acid Catalyzed Furan Ring Transposition"
  Ravindra Phatake, Jamsheena V., *CSSP*-768, **2014**, DOI: 10.1039/SP768.
- "Syn-dioxygenation of 7-methoxy-4-methyl-1, 2-dihydronaphthalene" Ravindra Phatake, *CSSP*-785, **2015**, DOI: 10.1039/SP785.

Erratum