Max-Planck-Institut
für molekulare Physiologie

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dortmund

Development of Novel Oxidative Annulations *via* C–H Bond Functionalization

Dissertation

For the achievement of the academic degree of the
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By

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Entwicklung neuer Methoden zur oxidativen Anellierung *via* C–H Bindungsfunktionalisierung

Dissertation

zur Erlangung des akademischen Grades eines
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M. Sc. Srimanta Manna

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Declaration/Erklärung

The work presented in this thesis was carried out at the Max Planck Institute of Molecular Physiology and the Faculty of Chemistry and Chemical Biology Technical University Dortmund, Germany, between July, 2013 and April, 2017 under the supervision of Dr. Andrey P. Antonchick and Prof. Dr. Herbert Waldmann.

Die vorliegende Thesis wurde am Max-Planck-Institut für molekulare Physiologie und der Fakultät Chemie und Chemische Biologie der Technischen Universität Dortmund, Deutschland, im Zeitraum von Juli 2013 bis April 2017 unter der Aufsicht von Dr. Andrey P. Antonchick und Prof. Dr. Herbert Waldmann angefertigt.

Dortmund, 2017

Srimanta Manna

Dedicated to My Parents
and Sisters

List of publications

Parts of this work were already published in following journal:

1) **Metal-Free Oxidative Dehydrogenative Diels-Alder Reaction for Selective Functionalization of Alkylbenzenes**
S. Manna, A. P. Antonchick, *Chem. Eur. J.* **2017**, *23*, 7825-7829.

2) **(1+1+1) Cyclotrimerization in Cyclopropanes Synthesis**
S. Manna, A. P. Antonchick, *Angew. Chem.* **2016**, *128*, 5376-5379; *Angew. Chem. Int. Ed.* **2016**, *55*, 5290-5293.

3) **Copper-Catalyzed (2+1) Annulation of Acetophenones with Maleimides: Direct Synthesis of Cyclopropanes**
S. Manna, A. P. Antonchick, *Angew. Chem.* **2015**, *127*, 15058-15061; *Angew. Chem. Int. Ed.* **2015**, *54*, 14845-14848.

4) **Hypervalent Iodine (III) in Direct Oxidative Amination of Arenes with Heteroaromatic Amine**
S. Manna[$], P. O. Serebrennikova[$], I. A. Utepova, A. P. Antonchick, O. N. Chupakhin, *Org. Lett.* **2015**, *17*, 4588-4591.

5) **Copper(I)-Catalyzed Radical Addition of Acetophenones to Alkynes in Furan Synthesis**
S. Manna, A. P. Antonchick, *Org. Lett.* **2015**, *17*, 4300-4303.

6) **Regioselective Annulation of Nitrosopyridine with Alkynes: Straightforward Synthesis of *N*–Oxide-Imidazopyridines**
S. Manna, R. Narayan, C. Golz, C. Strohmann, A. P. Antonchick, *Chem. Commun.* **2015**, *51*, 6119-6122.

7) **Metal-Free Annulation of Arenes with 2-Aminopyridine Derivatives: The Methyl Group as a Traceless Non-Chelating Directing Group**
S. Manna, K. Matcha, A. P. Antonchick, *Angew. Chem*. **2014**, *126*, 8302-8305; *Angew. Chem. Int. Ed*, **2014**, *53*, 8163-8166.

8) **Organocatalytic Oxidative Annulation of Benzamide Derivatives with Alkynes**
S. Manna, A. P. Antonchick, *Angew. Chem*. **2014**, *126*, 7452-7455; *Angew. Chem. Int. Ed*, **2014**, *53*, 7324-7327.

9) **Radical Trideuteromethylation with Deuterated Dimethyl Sulfoxide in the Synthesis of Heterocycles and Labelled Building Blocks**
R. Caporaso, S. Manna, S. Zinken, A. R. Kochnev, E. R. Lukyanenko, A. V. Kurkin, A. P. Antonchick, *Chem. Commun.* **2016**, *52*, 12486-12489.

10) **Hypervalent Iodine (III) in Direct Carbon–Hydrogen Bond Functionalization**
R. Narayan, S. Manna, A. P. Antonchick, *Synlett* **2015**, *26*, 1785-180

11) **Sustainable Oxidative Metal-Free Annulation**
L. Bering, S. Manna, A. P. Antonchick, *Chem. Eur. J.*, **2017**, DOI: 10.1002/chem.201702063

[$]Both authors contributed equally to this work

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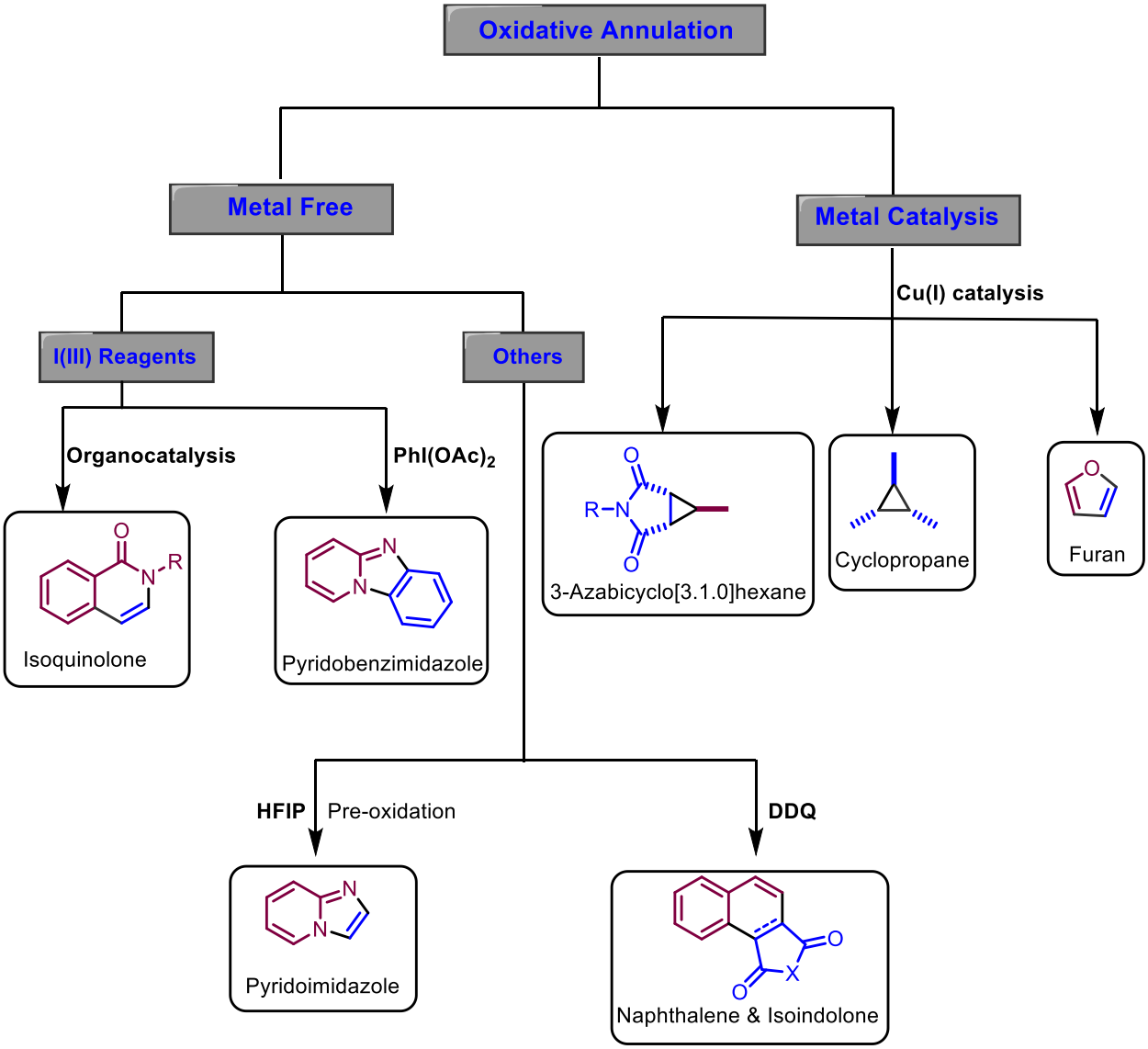
Abstract

A major goal of the synthetic chemists is the development of methods which can be used for the synthesis of target molecules from simple building blocks. In this context, annulation reactions are considered one of the most efficient methods in organic synthesis due to the formation of at least two bonds in a single step. It has been widely used in many fields such as pharmaceuticals, materials and natural products synthesis. Among them, oxidative annulation *via* C–H bond functionalization is one of the great interests due to the construction of cyclic molecules from non-functionalized precursors. These methods could be utilized in the aforementioned fields since they are efficient, mild and step-economic.



In the present study, syntheses of "privileged scaffolds" were described *via* oxidative annulation of C–H bonds functionalization. The main focus of this thesis has been directed

towards the development of new methods for the biologically relevant heterocycles and carbocycles synthesis employing simple building blocks. The presented work is divided into two parts, the first part dealing with metal-free conditions including hypervalent iodine reagents and DDQ and the second part with the copper-catalyzed acetophenone functionalization.

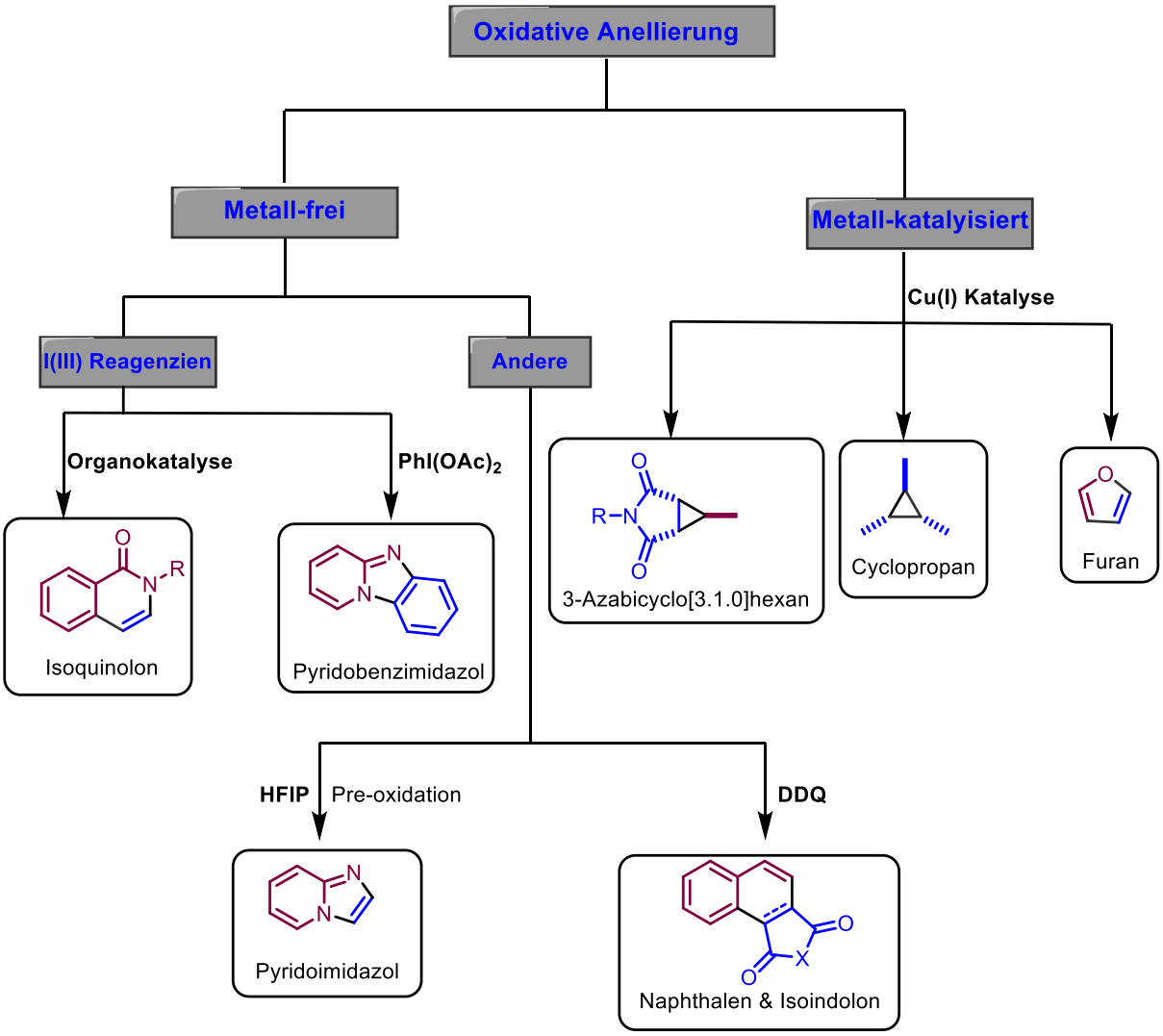
To accomplish our goal, iodobenzene catalyzed oxidative annulation of benzamide derivatives with alkynes was developed for the synthesis of isoquinolone scaffolds. Furthermore, syntheses of pyrido[1,2-*a*]benzimidazoles and *N*-heteroaryl anilines were achieved using $PhI(OAc)_2$ as oxidant. In addition, methyl group of arenes as a traceless directing group in the synthesis of benzo[4,5]imidazo[1,2-*a*]quinolone derivatives was demonstrated. Highly regioselective syntheses of *N*-oxide imidazopyridines were described by annulation of nitrosopyridine derivatives with alkynes and alkenes. Furthermore, an oxidative Diels-Alder reaction of alkylbenzenes and electron-deficient alkenes were investigated under metal-free conditions. In addition, first time dehydrogenative nitration of alkylbenzenes was demonstrated using DDQ as oxidant.

In the second part of this work, copper(I)-catalyzed syntheses of cyclopropanes *via* oxidative annulation of acetophenones with electron-deficient alkenes were investigated. The developed reaction represents copper(I)-catalyzed stereoselective 3-azabicyclo[3.1.0]hexane synthesis. The reaction mechanism revealed that cyclopropanation underwent *via* a novel radical addition onto the electron-deficient alkenes. Furthermore, syntheses of strain cyclopropanes were demonstrated from three acetophenone derivatives to access fully substituted cyclopropanes. It is remarkable that (1+1+1) cyclotrimerization was developed for the first time in the synthesis of small saturated carbocycles employing acetophenones. This method allowed the straightforward synthesis of strain cyclopropanes. A step forward in this direction a copper(I)-catalyzed radical addition of acetophenone to electron-deficient alkynes for the synthesis of furans were demonstrated under oxidative reaction conditions. The developed method provided polysubstituted furan derivatives from various acetophenones.

All synthesized compounds were submitted to the COMAS for various cell-based assays to identify potential inhibitors of the hedgehog signaling pathway, Wnt signaling pathway and autophagy.

Kurzfassung

Ein obergeordnetes Ziel von Chemikern ist die Entwicklung neuer Methoden, welche für die Darstellung von Zielmolekülen aus einfachen Synthesebausteinen genutzt werden können. Bedingt durch die Formierung von wenigstens zwei neuen chemischen Bindungen in einem Schritt werden Anellierungsreaktionen in diesem Kontext als ein hoch effizienter Ansatz in der organischen Chemie verstanden. Anellierung ist daher eine häufig genutzte Strategie zur Darstellung von Naturstoffen und pharmazeutisch relevanten Molekülen. Oxidative Anellierungs *via* C-H Bindungsfunktionalisierung ist von besonderem Interesse, auf Grund der Konstruktion cyclischer Moleküle ausgehend von nichtfunktionalisierten Startmaterialien. Diese Methoden können in den zuvor genannten Feldern genutzt werden, da sie sich durch besonders milde Reaktionsbedingungen, hohe Effizienz und Syntheseschrittökonomie auszeichnen.



In den vorliegenden Studien wurde die Synthese privilegierter Gerüstmoleküle *via* oxidativer

Anellierung durch C-H Bindungsfunktionalisierung beschrieben. Schwerpunkt lag dabei auf der Entwicklung neuer Methoden zur Synthese biologisch relevanter Heterocyclen und Carbocyclen ausgehend von einfachen Synthesebausteinen. Die präsentierte Arbeit gliedert sich dabei in zwei Teile. Der erste Teil beinhaltet Metall-freie Reaktionen durch den Einsatz von hypervalenten Iodreagenzien und DDQ und der zweite Teil die kupferkatalysierte direkte C-H Bindungsfunktionalisierung.

Um dieses Ziel zu erreichen wurde die Iodbenzol katalysierte oxidative Anellierung zur Synthese des Isoquinolongerüsts ausgehend von Benzamid und Alkynen entwickelt. Darüber hinaus wurde die Synthese von Pyrido[1,2-*a*]benzimidazolen und *N*-heteroaryl Anilinen durch den Einsatz von $PhI(OAc)_2$ als Oxidationsmittel erzielt. Zusätzlich wurde die Methylgruppe von Arenen als spurlose dirigierende Gruppe zur Synthese von Benzo[4,5]imidazo[1,2-*a*]quinolonen demonstriert. Die hoch regioselektive Synthese von Imidazopyridin *N*-Oxiden wurde durch die Anellierung von Nitrosopyridinen mit Alkynen und Alkenen erzielt. Weiterhin wurde die Metall-freie oxidative Diels-Alder Reaktion von Alkylbenzol und elektronenarmen Alkenen untersucht. Basierend auf den gewonnenen Erkenntnissen wurde zusätzlich zum ersten Mal die dehydrogenative Nitrierung von Alkylbenzolen doch die Verwendung von DDQ als Oxidationsmittel demonstriert.

Im zweiten Teil dieser Arbeit wurde die Kupfer(I)-katalysierte Synthese von Cyclopropanen *via* oxidativer Anellierung von Acetophenonen mit elektronenarmen Alkenen untersucht. Die entwickelten Reaktionen beinhalten die Kupfer(I)-katalysierte und stereoselektive Synthese von 3-Azabicyclo[3.1.0]hexan. Studien des Reaktionsmechanismus zeigten, dass die Cyclopropanierung durch radikalische Addition an elektronenarmen Alkene erfolgte. Weiterhin wurde die Synthese von gespannten Cyclopropanen ausgehend von drei Acetophenonderivaten entwickelt, wodurch hoch substituierte Cyclopropane zugänglich wurden. Die (1+1+1) Cyclotrimerisierung repräsentiert das erste Beispiel für die direkte Synthese von kleinen, gesättigten Carbocyclen durch den Einsatz von Acetophenonen. Ein weiterer Schritt gelang durch die Kupfer(I)-katalysierte radikalische Addition von Acetophenonen an elektronenarme Alkyne zur Synthese von Furanen unter oxidativen Reaktionsbedingungen. Die neuentwickelte Reaktion erlaubt die Synthese polysubstituierter Furanderivate ausgehen von verschiedenen Acetophenonen.

Alle synthetisierten Verbindungen wurden im COMAS in verschiedenen Zell-basierten Assays getestet, wodurch verschiedene Inhibitoren des Hedgehog Signalweges, des Wnt Signalweges und Autophagie identifiziert wurden.

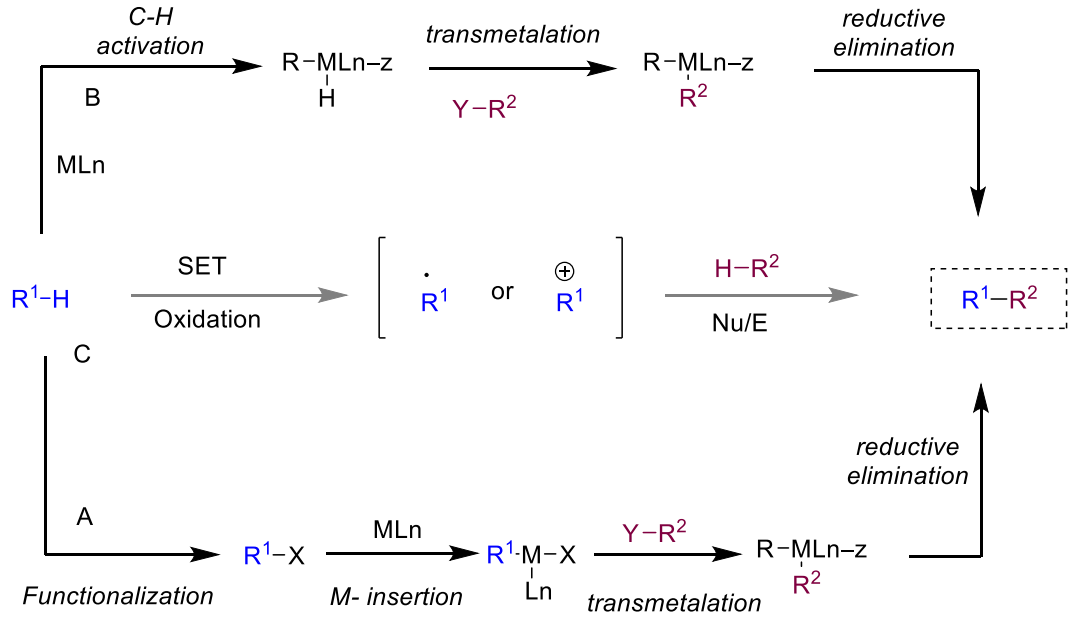
Chapter 1

General Introduction

1.1 Introduction

Carbon-carbon or carbon-heteroatom (C–X = N, O, S etc.) bond formation *via* carbon-hydrogen (C–H) bond functionalization is one of the greatest interests in modern organic chemistry.[1-4] Carbon-hydrogen bonds are ubiquitous in nature.[5-11] Therefore, C–H bond functionalization appears to be one of the most powerful routes to install different functionalities and emerged as a great tool in the last few decades in many fields such as medicinal chemistry, pharmaceutical and natural product synthesis.[4] Among various C–H activation pathways, oxidative cross-coupling reactions have found great advantage to enable C–C and C–X bond formation. Functionalization of C–H bond is considered to be the most challenging and elusive to the synthetic chemists.[12] The oxidative *cross-dehydrogenative-coupling* (CDC) reaction became highly attractive method in the synthesis of complex architectures.[7, 13-15] There were several breakthrough methods for CDC, which were developed by using transition metal (TM) catalysts or under metal-free conditions.[16] It has great benefits in the context of non-functionalization of the precursors, step and an atom economical processes,[17] and least amount of chemical waste production.[18-19] Due to their prime advantages in organic synthesis, the direct construction of C–C and C–heteroatom bonds by functionalization of C–H bonds have been extensively studied.[20]

1.2 Background of Cross-Coupling Reaction



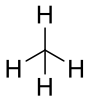
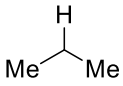
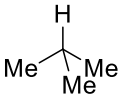
Scheme 1.1. Oxidative C–H bond functionalization *vs* classic cross-coupling.

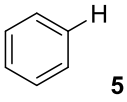
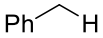
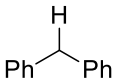
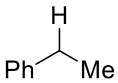
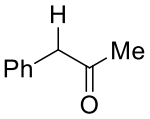
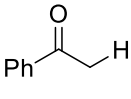
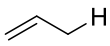
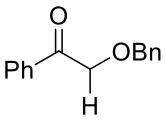
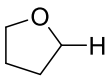
In general, three types of mechanisms are hypothesized for the oxidative coupling reactions in the literature (Scheme 1.1).[21-24] In the type A, first metal insertion takes place with organic halide/pseudohalide as coupling partners followed by transmetalation with functionalized substrate and a subsequently reductive elimination provides coupling product.[23] For type B, reaction proceeds *via* metal-catalyzed C–H bond activations with organometallic reagents. Normally, this type of reaction takes place in three steps: electrophilic substitution, transmetalation and reductive elimination. The reaction in type C is oxidative cross-coupling between two different C–H bonds. Generally, in this reaction mechanism the radical, radical cationic or cationic species were generated *via* single electron transfer (SET) process followed by *in-situ* oxidation of radical species which reacts with nucleophilic or electrophilic substrate to generate coupling product after elimination of hydrogen atom (Scheme 1.1).[25-26]

1.3 Oxidative Cross-Coupling *via* C–H Bond Functionalization

In the last century, several cross-coupling reactions were developed in the organic chemistry and widely used in many fields.[27-30] However, the major drawback of the cross-coupling reactions includes the requirement of functionalized substrates, higher temperatures, additives and stoichiometric amount of metal salts. Therefore, the major goal of synthetic chemists has been always to minimize the chemical waste in the cross-coupling reaction without compromising the efficiency of the process. At the beginning of the 20th century, oxidative C–H bond functionalization was just a dream to the chemists. Later on, several attractive oxidative cross-coupling reactions were slowly emerged using transition metals.[5] Nevertheless, oxidative coupling reaction was considered as a green process and sustainable method due to step-atom economical nature and less amount of chemical waste production.[4] In the recent years, several types of C–H bond functionalization has been reported such as C(sp^3)–H, C(sp^2)–H and C(sp)–H. Among them, functionalization of C(sp^3)–H bonds are considered to be the most challenging because of its poor acidity in nature and filled high-energy orbitals which readily interact with empty orbitals of the metal.[31] However, oxidative coupling of C(sp^2)–H or C(sp)–H bond is relatively easier than inert C(sp^3)–H bond, since the bond dissociation energy (BDE) of C(sp^3)–H is higher than other types of C–H bond. The bond dissociation energy of various types of bonds is highlighted in Scheme 1.2.[32]

Various C-H bond

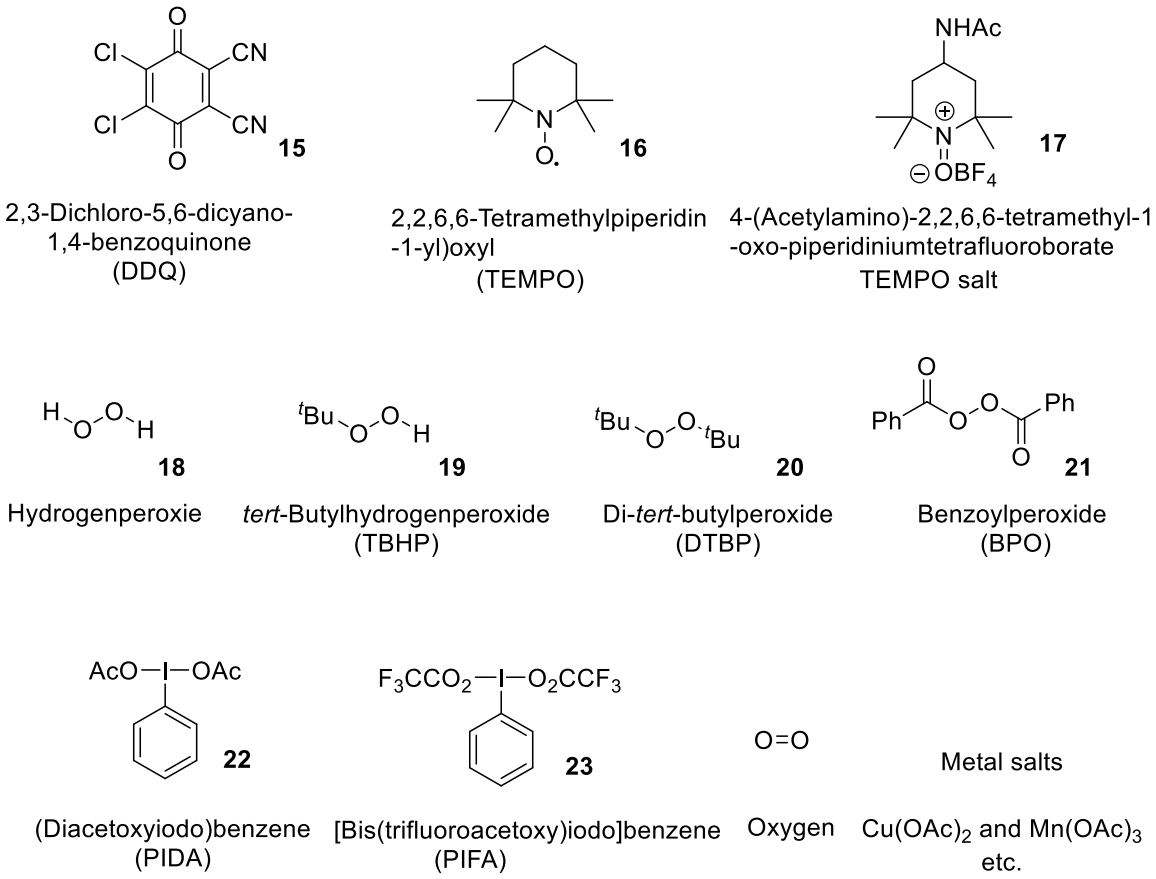
Substrate				
	1	**2**	**3**	**4**
BDE (kcal mol^{-1})	104.8	101.1	98.6	96.5

Entry	Substrate	BDE (kcal mol^{-1})	Entry	Substrate	BDE (kcal mol^{-1})
1	 **5**	112.3	6	 **10**	88.5
2	 **6**	84.5	7	 **11**	85.4
3	 **7**	82.3	8	 **12**	85.2
4	 **8**	93.0	9	 **13**	88.2
5	 **9**	84.8	10	 **14**	92

Scheme 1.2. Bond dissociation energy of various C–H bonds.

1.4 Oxidants for C–H Bond Functionalization

In the last few decades, various oxidants were successfully used for the oxidative C–H bond functionalization such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (**15**), 2,2,6,6-tetramethylpiperidine 1-oxyl (**16**), TEMPO salts (**17**), peroxides, hypervalent iodine (III) reagents[33] such as $PhI(OAc)_2$ (**22**) and $PhI(OCOCF_3)_2$ (**23**), molecular oxygen[34] and various metal salts. They are considered as a milder oxidant in modern synthetic organic synthesis (Scheme 1.3).[35] These oxidants are also widely used in the oxidative cross-coupling and annulation reactions.[36-44]

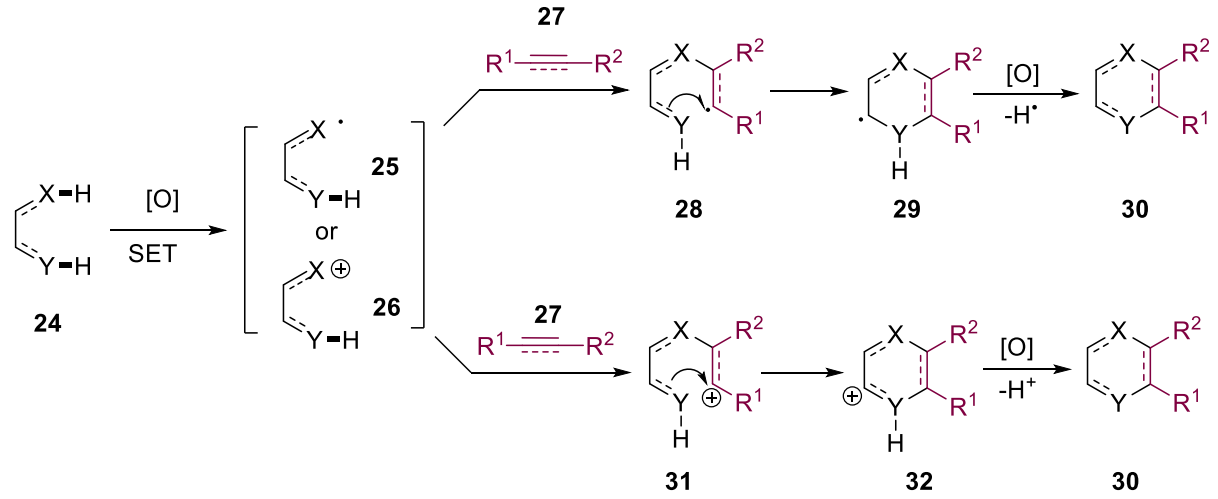


Scheme 1.3. Various oxidants for C–H bond functionalization.

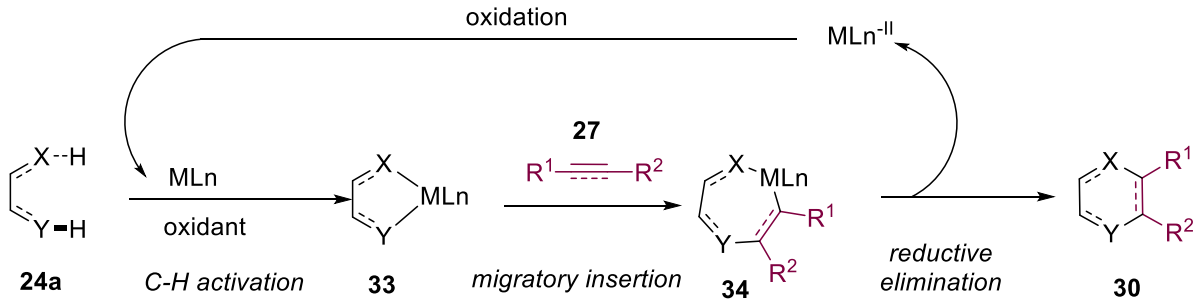
1.5 Various Routes of Oxidative Annulation Reaction

In general, three types of mechanisms of oxidative annulation reactions has been described in the literature (Scheme 1.4). In the first step, the radical species **25** or cation species **26** are generated *via* oxidation of C–H bond in the presence of oxidant.[6] Afterwards, the nucleophilic or electrophilic addition to the alkene or alkyne affords a radical intermediate **28** which subsequently undergoes intramolecular cyclization to deliver radical intermediate **29**. Finally, the oxidation of the radical species followed by hydrogen abstraction provides the desired product **30**. On the other hand, after the addition of cationic species **26** onto alkene or alkyne leads to formation of cationic intermediate **31** which subsequently intramolecular cyclization to form the intermediate **32**.[45] The intermediate **32** undergoes over oxidation followed by hydrogen elimination affording the desired product **30**. For the metal-catalyzed oxidative annulation, most common mechanism has been shown in Scheme 1.4.[46] Initially, the metalocyclic intermediate **33** was generated *via* C–H activation followed by migratory insertion to the alkene or alkyne. Eventually, reductive elimination of metal provides the annulated product **30** (Scheme 1.4). The active metal species is regenerated *via* oxidation.

Radical/ Cationic Intermediate Oxidative Annulation



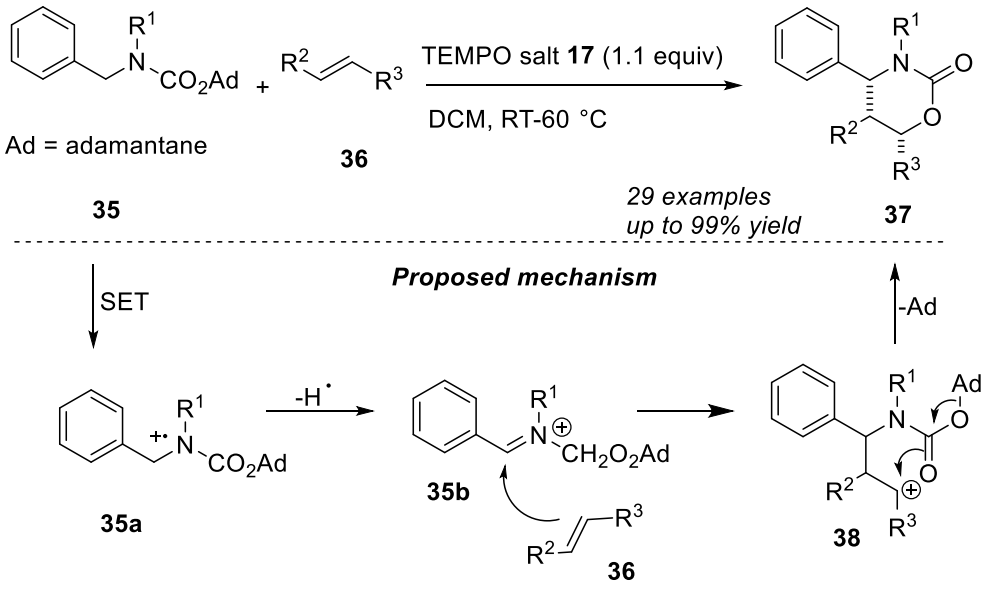
Metal catalyzed Oxidation annulation



Scheme 1.4. Reaction mechanism of oxidative annulation.

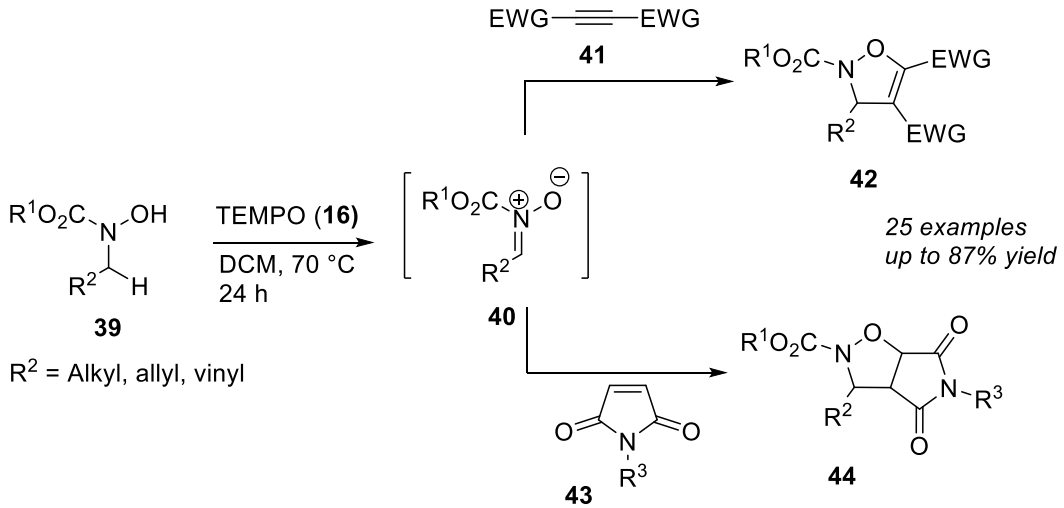
1.6 TEMPO Salt/ TEMPO Mediated Oxidative Annulation

Several C–H bond functionalizations have been reported in the last decades using stable *N*–oxyl radical as mild oxidant such as TEMPO radical.[47-50] TEMPO radical (**18**) was first reported by Lebedev and Kazarnovskii in 1959 and used as a versatile oxidant in organic synthesis. Recently, Carcía Manchéno and co-workers developed TEMPO oxoammonium salt (**17**) mediated (4+2) oxidative annulation of *N*-benzylcarbamates (**35**) with simple olefins (**36**) (Scheme 1.5).[48] According to the proposed reaction mechanism, single-electron oxidation of amine followed by hydrogen atom abstraction generates iminium ion intermediate (**35a**). Afterwards, iminium ion (**35b**) undergoes electrophilic addition to the olefin to furnish the carbocation intermediate **38** which is trapped by nucleophilic oxygen of carbamate to produce the desired product **37**.



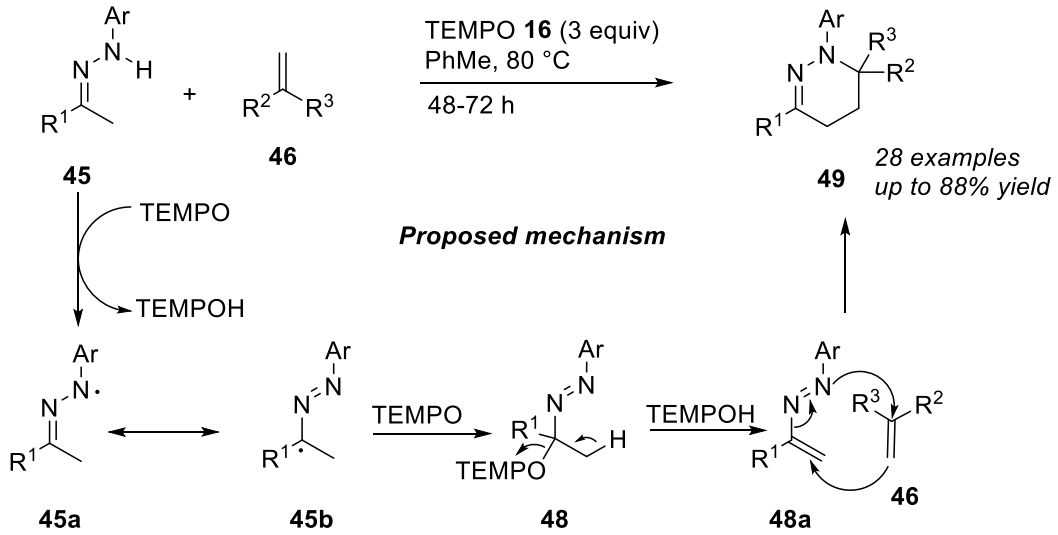
Scheme 1.5. Oxidative annulation of *N*-benzylcarbamate with alkene.

In 2015, Carcía Manchéno and co-workers reported first 2,2,6,6-tetramethylpiperidine 1-oxyl (**16**) mediated C(sp^3)–H bond functionalization for the oxidative annulation.[47] The annulation reaction of alkyne (**41**) and maleimide (**43**) underwent through the nitrone intermediate (**40**) which was generated from alkyl, allyl or benzyl *N*-carbamoyl *N*-hydroxylamine in the presence of TEMPO as oxidant (Scheme 1.6).



Scheme 1.6. Oxidative annulation of alkene.

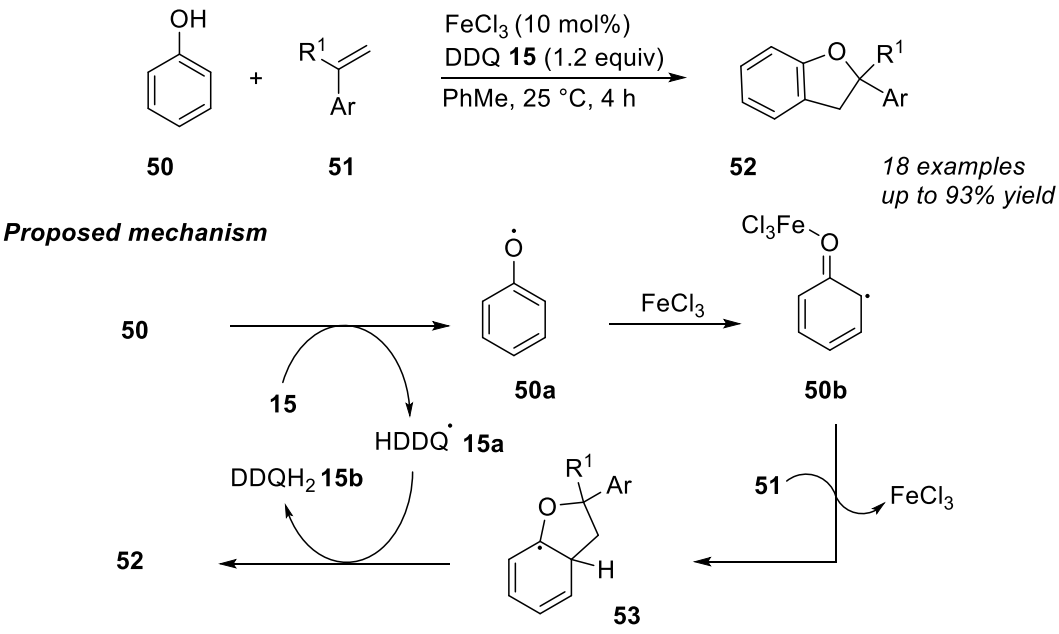
Very recently, Han and co-workers disclosed an elegant TEMPO (**16**) mediated intermolecular oxidative aza-Diels-Alder reaction *via* functionalization of ketohydrazone (Scheme 1.7).[51] According to the mechanism proposed by the authors, 2 equivalents of TEMPO (**16**) required for transformation to achieve the desired product **49**. At the beginning the radical species **45a** was formed by hydrogen atom abstraction from **45** by TEMPO radical.



Scheme 1.7. Oxidative aza-Diels-Alder reaction.

It was found that the intermediate **45a** was stabilized *via* resonance to generate the intermediate **45b**. The intermediate **48a** was formed *via* oxidation of the intermediate **45b** with 1 equivalent of TEMPO and subsequently undergoes [4+2] cycloaddition with **46** to provide the product **49**.

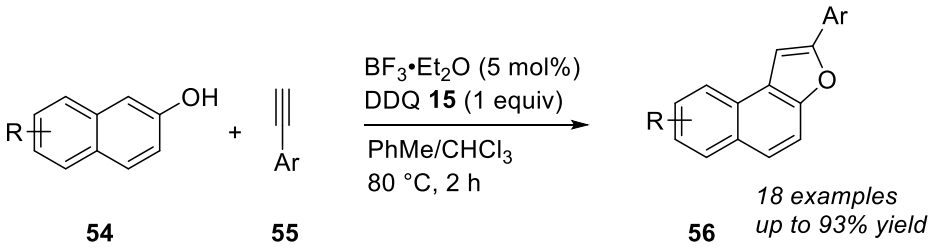
1.7 DDQ Mediated Oxidative Annulation



Scheme 1.8. Oxidative annulation of phenol with alkene.

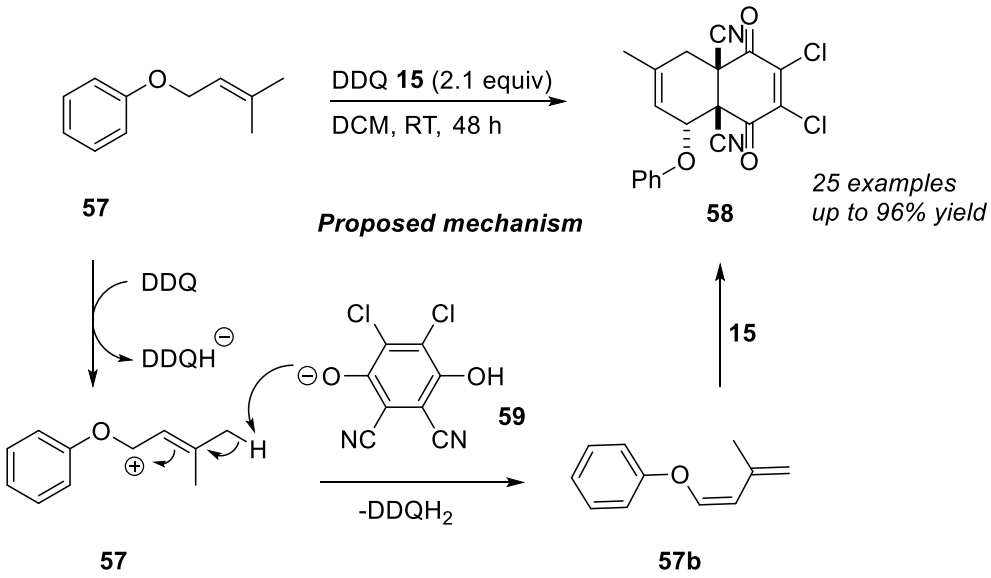
In the last decades, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (**15**) was successfully used for the oxidative annulation reactions.[52-58] Recently, the group of Lei described a novel $FeCl_3$-catalyzed oxidative annulation of phenol derivatives (**50**) with olefins (**51**) employing DDQ (**15**) as oxidant (Scheme 1.8).[53] Based on their mechanistic studies, the authors proposed a

plausible reaction mechanism of DDQ mediated oxidative alkene annulation with phenol. First, DDQ reacted with phenol to form radical species (**50a**) which led to furnish the intermediate **50b**. Afterwards, the intermediate **50b** could react with alkene to generate the intermediate **53** which undergoes oxidation with **15a** to produce the target product **52**.



Scheme 1.9. Oxidative annulation of 2-naphthol with alkyne.

In 2016, Liu *et al*. reported the first successfully DDQ (**15**) mediated oxidation annulation of 2-naphthol derivative (**54**) with terminal alkyne (**55**) under metal-free conditions (Scheme 1.9). The reaction was found to be extremely versatile with various 2-naphthols and alkynes. The mechanistic studies suggested that a novel radical oxidative annulation underwent *via* C–C coupling and C–O intramolecular cyclization under developed reaction conditions.[54] First, 2-naphthol was oxidized by DDQ to form 2-naphthol radical in the presence of BF_3. Afterwards, the 2-naphthol radical was attacked to generate the vinyl radical of alkyne which undergoes cyclization *via* oxygen atom and followed by oxidation of radical species providing the product **56**.



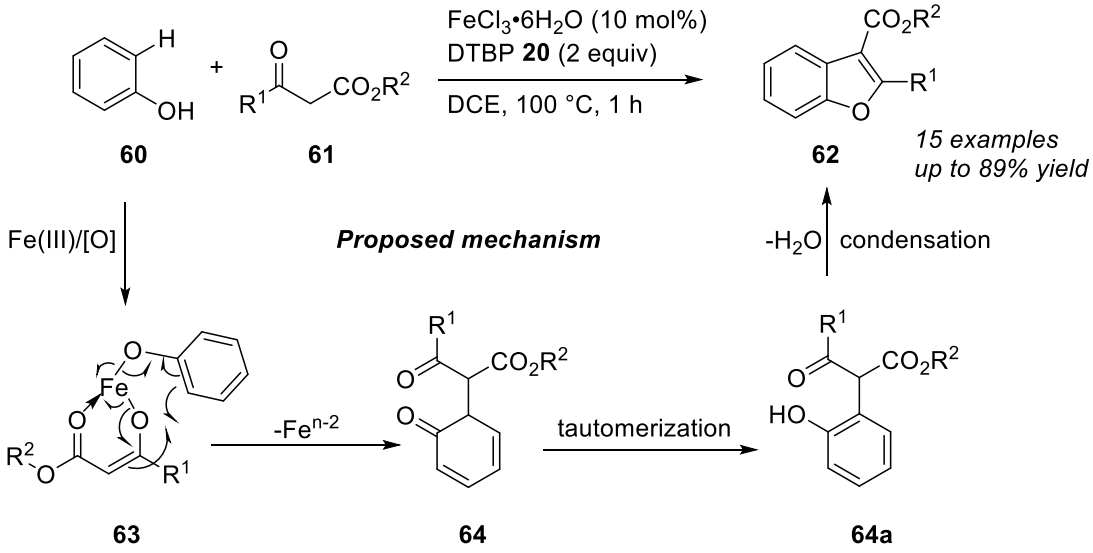
Scheme 1.10. Oxidative annulation of prenyl derivative with alkene.

Later, in 2015 Zhou and co-workers reported the DDQ (**15**) mediated dehydrogenative Diels-Alder reaction of prenyl derivative (**57**) under metal-free conditions (Scheme 1.10).[52]

The developed reaction tolerated under oxidative annulation of various prenyl derivatives with DDQ. The mechanistic studies indicated that the dehydrogenative Diels-Alder reaction underwent through isoprene intermediate which was generated *via* oxidation of prenyl derivative in the presence of DDQ.

1.8 Peroxide Mediated Oxidative Annulation

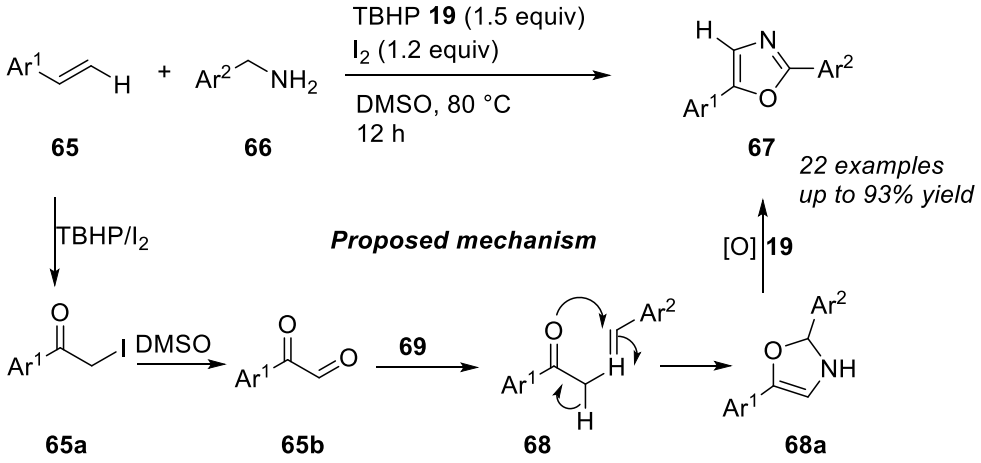
Recently, various peroxides were used for the oxidative annulation to build diverse annulated products including furan, oxazole and nitrogen-based heterocycles.[59-67] In 2009, Li and co-workers described the synthesis of polysubstituted benzofurans (**62**) through Fe-catalyzed tandem oxidative annulation between phenols (**60**) and *β*-ketoester derivatives (**61**) using DTBP (**20**) as oxidant (Scheme 1.11).[68] Proposed reaction mechanism has been shown in the Scheme 1.11. The intermediate **63** was formed after reaction of $FeCl_3$ with phenol and *β*-ketoester which produce the intermediate **64** after reductive elimination of iron species. The intermediate **64a** could be formed *via* tautomerization of intermediate **64**. Subsequently, the product **62** was formed by condensation of the intermediate **64a**.



Scheme 1.11. Oxidative annulation of phenol with alkene.

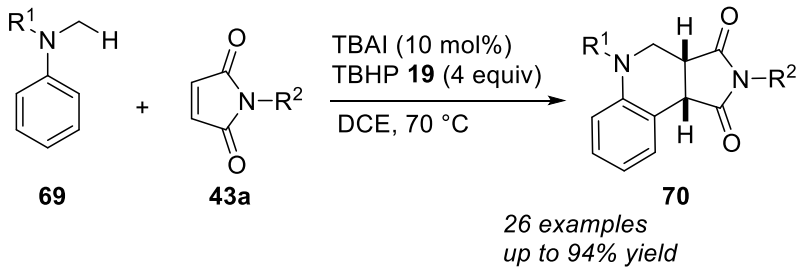
In 2010, Jiang and co-workers disclosed oxidative annulation of easily accessible benzylamine derivatives (**66**) with alkenes (**65**) in the synthesis of oxazole derivatives (**67**) employing *tert*-butyl hydroperoxide (**19**) as oxidant in combination with molecular iodine (Scheme 1.12).[60] The proposed reaction mechanism of the oxazole synthesis has been described in the Scheme 1.12. Mechanistically, it was proposed that the intermediate **65a** was formed in the presence of I_2 in combination with TBHP. The intermediate could undergo oxidation to generate the intermediate **65b**. Upon reaction with benzylamine, produce the

intermediate **68**. After attacking of the lone pair of oxygen to the imine intermediate furnish the substrate **68a**. Afterward, oxidation of the intermediate **68a** provided the target product **67**.



Scheme 1.12. Oxidative annulation of benzylamine with alkene.

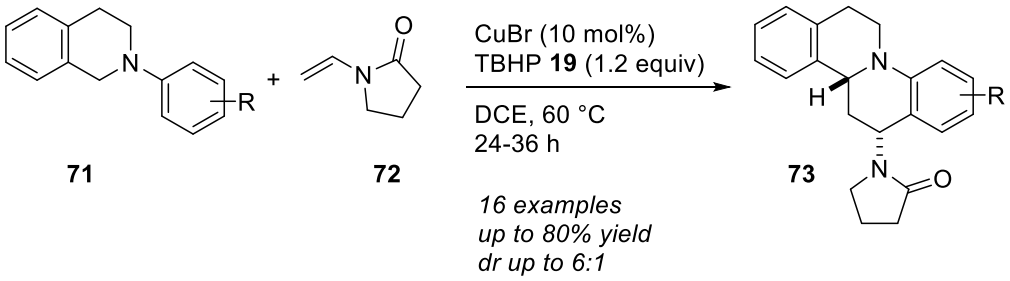
In 2016, Antonchick and Song published an elegant oxidative annulation between tertiary anilines (**71**) and alkenes (**72*)*** employing tetrabutylammonium iodide (TBAI) as a catalyst and *tert*-butyl hydroperoxide (**21**) as oxidant under metal-free conditions (Scheme 1.12).[66] The reported method showed functionalization of diverse tertiary anilines with different alkenes to build a wide range of substrate scopes. The mechanistic studies suggested that the oxidative annulation reaction proceeded *via* the formation of *α*-aminoalkyl radical. It is formed by *tert*-butoxyl radical which generates *in-situ* reaction between *tert*-butyl hydroperoxide and iodide ion. The *α*-aminoalkyl radical could attack the alkene to form radical intermediate followed by cyclization and hydrogen abstraction providing the product **70**.



Scheme 1.13. Oxidative annulation of tertiary aniline with alkene.

In the recent years several Povarov type oxidative annulation has been developed using various oxidant *via* C–H bond functionalization.[69-73] Very recently, Seidel and co-workers established copper(I) bromide catalyzed oxidation [4+2] cycloadditions of *N*-aryl amines with

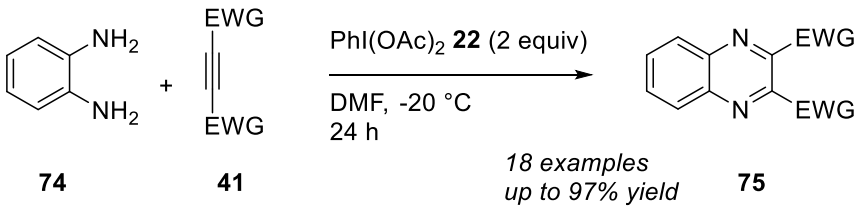
alkenes to achieve polycyclic amines derivatives (Scheme 1.14).[74] According to the described mechanism by the authors, the reaction underwent *via* iminium ion intermediate which was formed by oxidation of *N*-aryl amines with *tert*-butyl hydroperoxide in the presence of copper(I) bromide.



Scheme 1.14. Oxidative Povarov type annulation in synthesis of polycyclic amine.

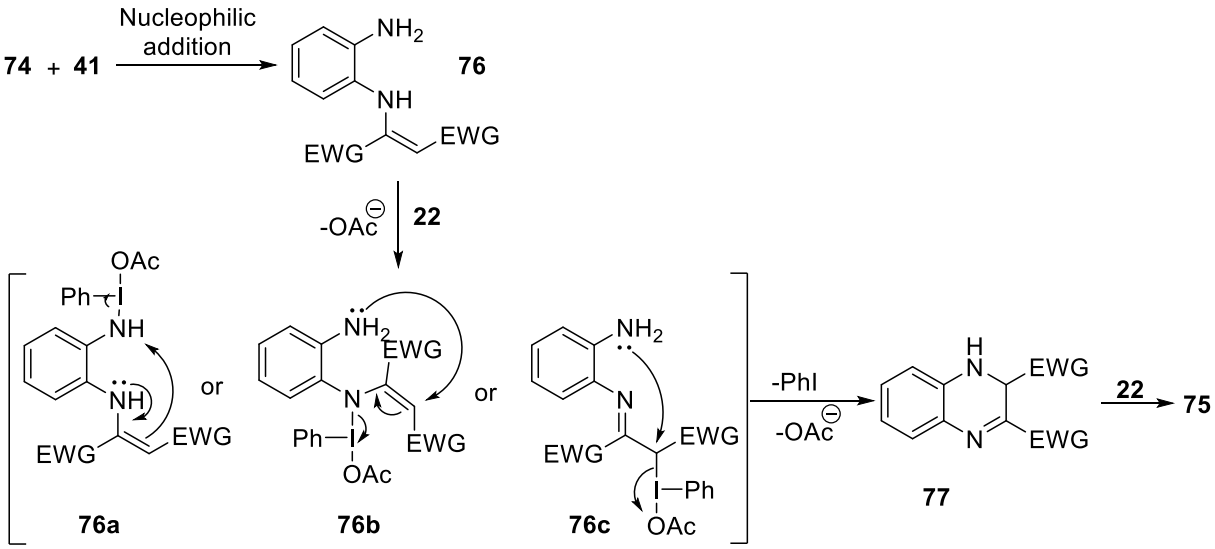
1.9 Hypervalent Iodine (III) Mediated Oxidative Annulation

Application of hypervalent iodine (III) reagents has seen explosive growth in the last few decades due to its versatile oxidizing ability, easy availability and environmentally benign nature.[75-76] Hypervalent iodine (III) reagents have found great success in the development of novel methods and widely used for oxidative amination, cross-dehydrogenative coupling (CDC) reaction and various oxidation processes.[77-91] Recently, Antonchick group developed several oxidative intramolecular and intermolecular amination reactions employing hypervalent iodine (III) reagents from simple building blocks.[79, 87, 89-90]



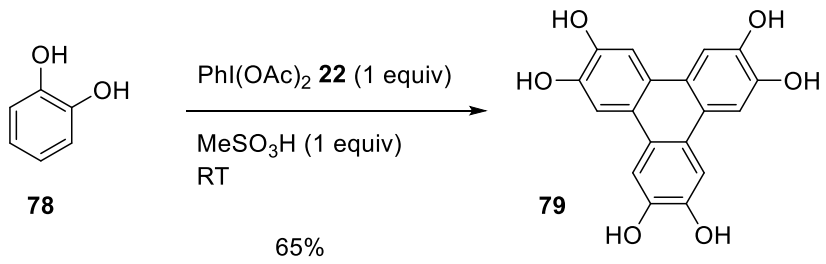
Scheme 1.5. Oxidative annulation of phenol with alkene.

In 2013, the group of Minakata and Takeda first developed hypervalent iodine (III) mediated oxidative annulation of *o*-phenyldiamines (**74**) with electron-deficient alkynes (**41**) in the synthesis of quinoxaline derivatives (Scheme 1.15).[92] According to authors proposed reaction mechanism, *o*-phenyldiamine (**74**) could react with electron-deficient alkyne to generate three probable intermediates **76a**, **76b** or **76c** which subsequently undergoes intramolecular cyclization followed by oxidation, providing the desired product **75** (Scheme 1.16).



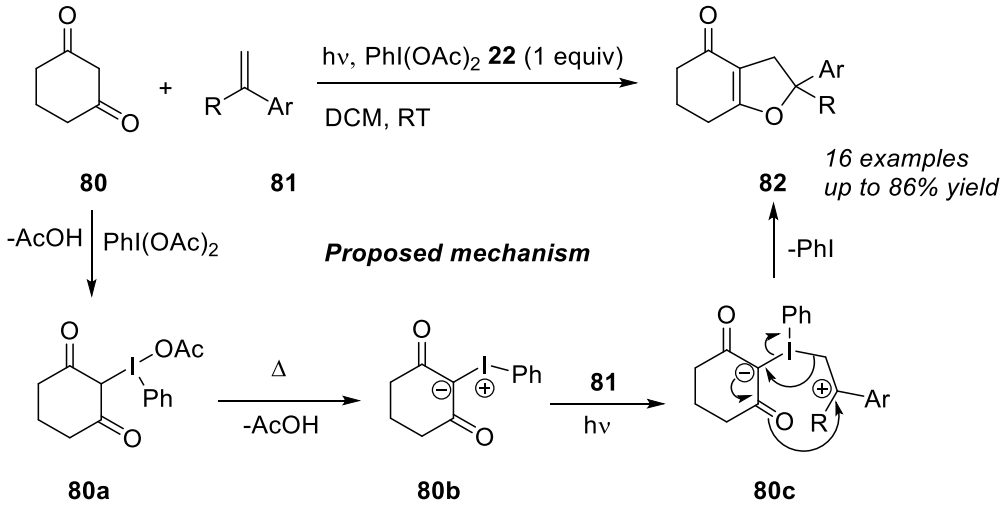
Scheme 1.16. Proposed mechanism of quinoxaline synthesis.

In 2009, Kita and co-workers reported an oxidative trimerization of catechol (**78**) to hexahydroxytriphenylene (**79)** using hypervalent iodine (III) reagents as oxidant (Scheme 1.17).[93] The reaction proceeded under mild reaction conditions and resulted in the formation of useful hexahydroxytriphenylene (**79**).



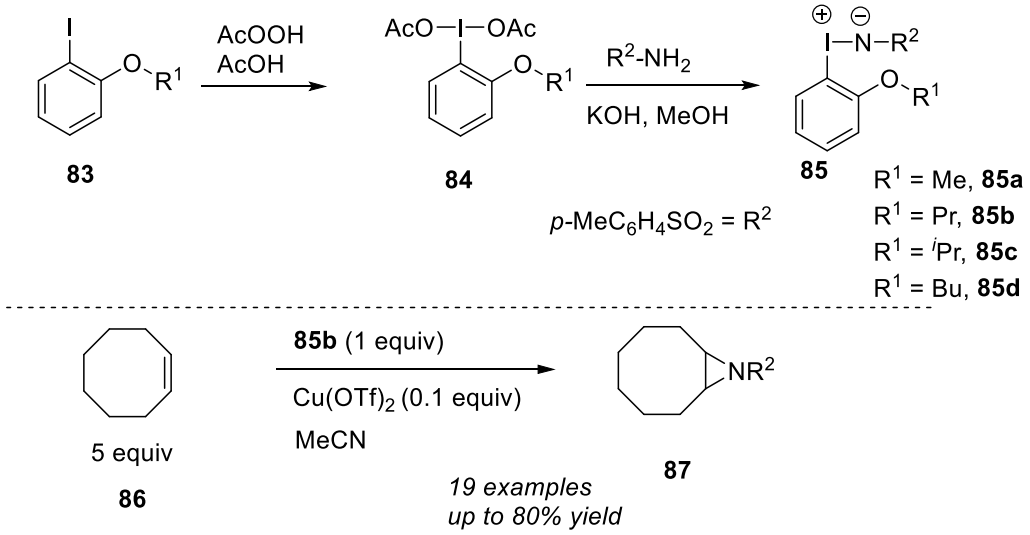
Scheme 1.17. Hypervalent iodine (III) mediated oxidative annulation of catechol.

In 2013, Hadjiarapoglou and co-worker published a novel method for the synthesis of fused dihydrofuran (**82**) from 1,3-cyclohexanedione (**80**) and alkene (**81**) using iodobenzene diacetate (**22)** under photochemical activation (Scheme 1.18).[94] The reaction mechanism suggested that a tandem cycloaddition underwent *via* C–C bond formation and C–O bond cyclization under the developed reaction conditions. In the proposed mechanism for $PhI(OAc)_2$ mediated oxidative annulation, first 1,3-cyclohexanedione reacted with $PhI(OAc)_2$ to form the intermediate **80a** which led to produce the intermediate **80b** after losing acetic acid. The intermediate **80b** could be reacted with alkene to generate the intermediate **80c** followed by reductive elimination of iodobenzene proving the desired product **82** (Scheme 1.18).



Scheme 1.18. Hypervalent iodine (III) mediated (3+2) oxidative annulation.

Very recently, Zhdankin and co-workers developed a catalytic aziridination of alkene (**86**) using hypervalent iodine (III) reagents (**85**) (Scheme 1.19).[95] It could be utilized as a nitrene precursors based on *ortho*-alkoxyiodobenzene for aziridine (**87**) synthesis. Alkoxyphenyliminoiodanes reagent were generated from hypervalent iodine (III) reagents.

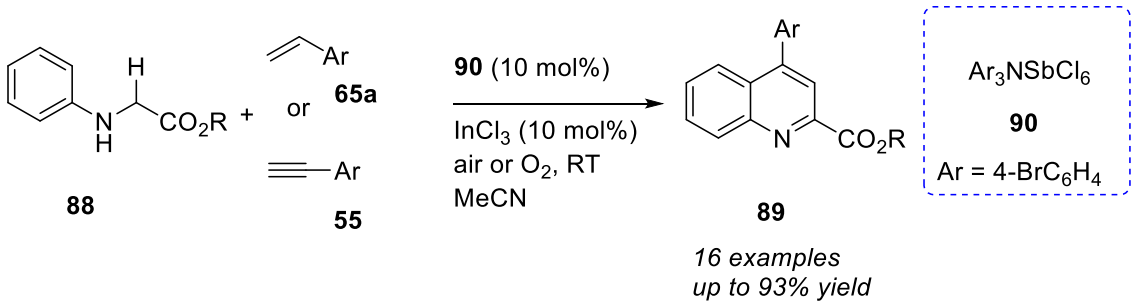


Scheme 1.19. Aziridination of alkene.

1.10 Molecular Oxygen as Oxidant for Oxidative Annulation

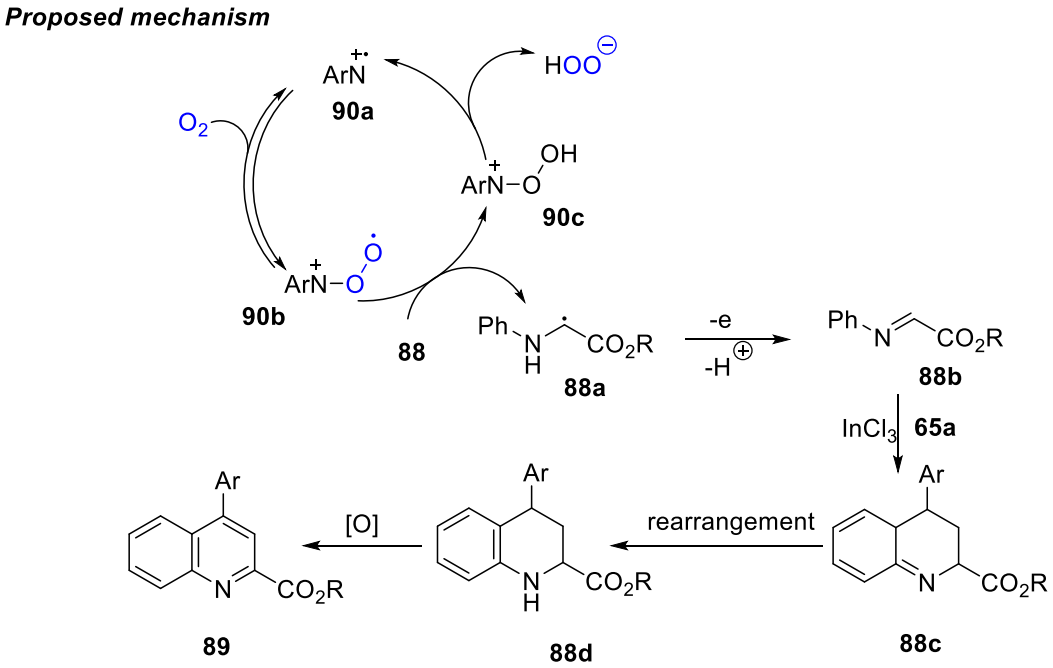
Recently, the application of molecular oxygen has attracted great attention as oxidant for the oxidative coupling reaction due to its green nature and abundance compared to the metal oxidants or peroxides.[35] Oxidative coupling reaction using molecular oxygen as oxidant has not much explored due to poor reactivity and less selectivity. Albeit, there are some methods for oxidative annulation reaction using molecular oxygen as oxidant.[96-97] In 2012, the group

of Jia and Wang reported the synthesis of substituted quinolines (**89**) between glycine derivatives (**88**) and styrenes (**65a**) or alkynes (**55**) in combination with tris(4-bromophenyl)aminium hexachloroantimonate (**90**) as a catalyst under oxygen atmosphere (Scheme 1.20).[98]



Scheme 1.20. Oxygen mediated oxidative annulation.

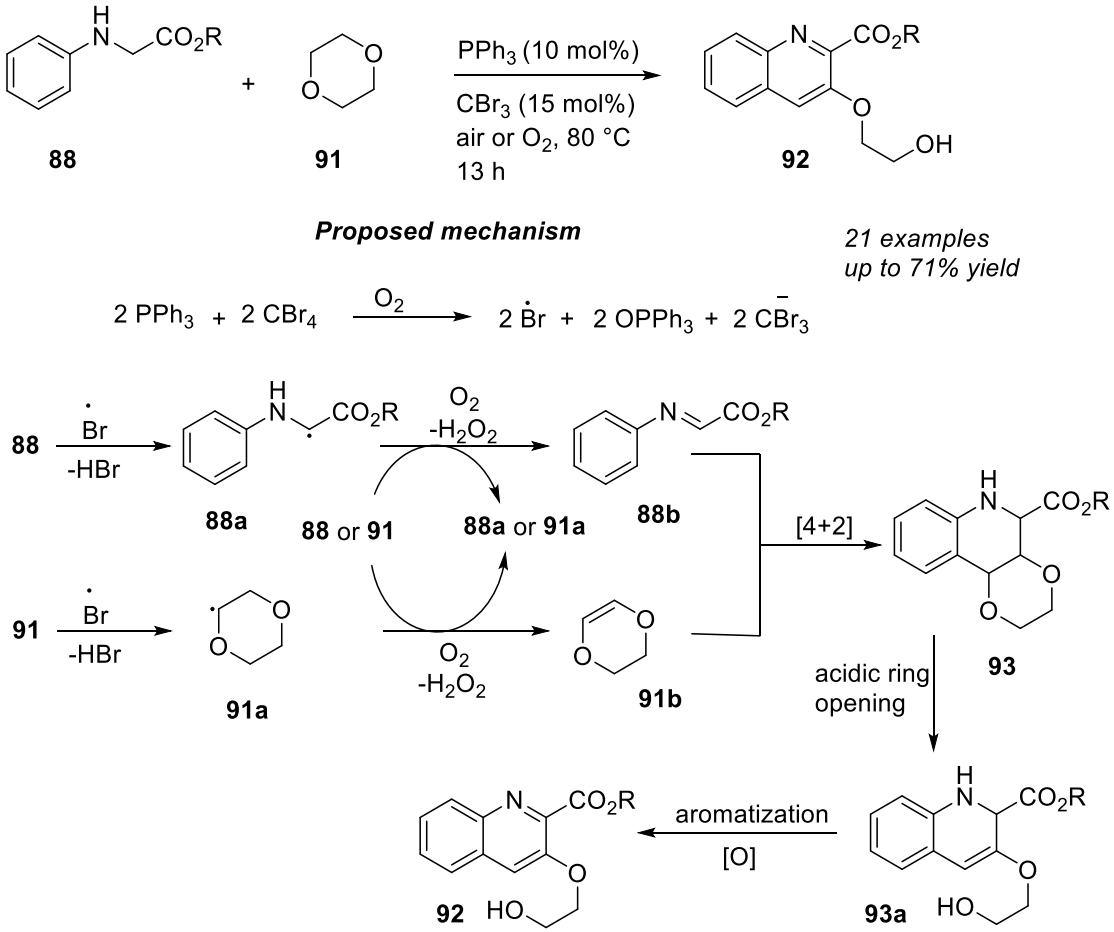
According to the proposed mechanism by the authors, first oxygen could react with $TBPA^{+\bullet}$ to produce the peroxide intermediate (Scheme 1.21). The peroxide intermediate abstracts hydrogen atom from glycine derivative to generate intermediate **88a** and $TBPA^{+\bullet}$ was regenerated after fragment of peroxide. The intermediate **88b** was generated *via* oxidation of



Scheme 1.21. Proposed mechanism of oxygen mediated oxidative annulation.

the intermediate **88a** which undergoes Povarov type reaction with alkene to furnish the intermediate **88c**. Finally, the desired product **89** was formed *via* rearrangement of intermediate **88c** followed by oxidation of intermediated **88d**.

In 2016, Hua and co-workers disclosed double oxidative dehydrogenative annulation between glycine derivatives (**88**) and dioxane (**91**) under oxygen atmosphere (Scheme 1.22).[99] Quinoline derivatives could be obtained from various glycine derivatives. According to the proposed reaction mechanism by the authors, first bromine radical was formed after nucleophilic attacks of PPh_3 to CBr_4 (Scheme 1.22). The bromine radical abstracts hydrogen atom from the glycine derivative to form the radical intermediate **88a** which undergoes over

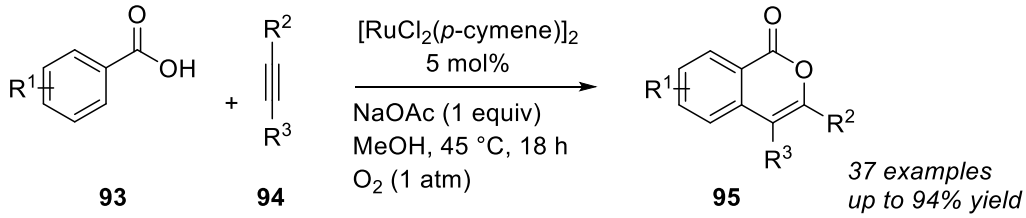


Scheme 1.22. Oxidative annulation of glycine derivative with dioxane.

oxidation in the presence of oxygen, giving an intermediate **88b**. Similarly, 2,3-dihydro-1,4-dioxine (**91b**) was formed after reaction of dioxane (**91**) with bromine radical and followed by oxidation of radical species with molecular oxygen. The intermediate **88b** undergoes [4+2] cycloaddition with intermediate **91b** to afford intermediate **93** which producing the intermediate **93a** after acidic ring-opening. Finally, aromatization of intermediate **93a** in presence of oxidant provided the target product **92**.

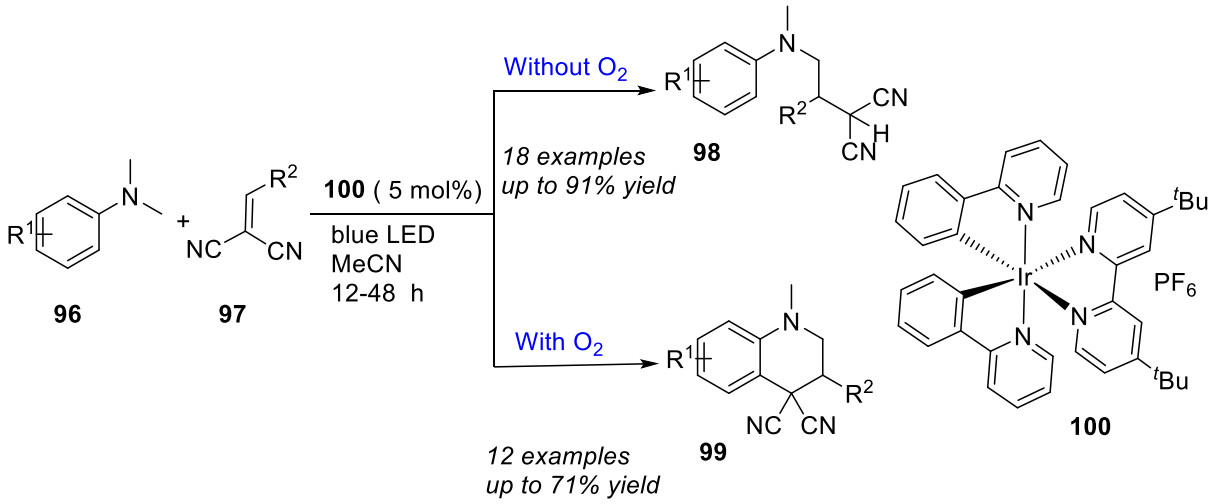
In 2015, Ackermann and co-workers reported as unprecedented ruthenium-catalyzed oxidative annulation of benzoic acid derivative (**93**) and alkyne (**94**) with molecular oxygen as

the sole oxidant (Scheme 1.23).[100] According to the mechanism proposed by the authors, acetic acid is crucial for the re-oxidation of Ru(0) by the molecular oxygen.



Scheme 1.23. Oxidative annulation benzoic acid with alkyne.

In 2013, Rueping and co-workers reported an elegant oxidative annulation of alkene (**97**) and aryl tertiary aniline derivative (**96**) with combination of molecular oxygen and visible-light photoredox catalysis (Scheme 1.24).[101] In the absence of oxygen, only intermolecular radical addition onto the electron-deficient alkene took place and observed liner product **98** formation. In contrast, intermolecular annulation occurred in the presence of molecular oxygen, and provided the desired annulated product **99**. The mechanistic investigations suggested that reaction underwent through radical intermediate and molecular oxygen promoted the cyclization *via* oxidation of radical species (Scheme 1.24). On the other hand, in absence of oxygen acyclic product **99** was formed.

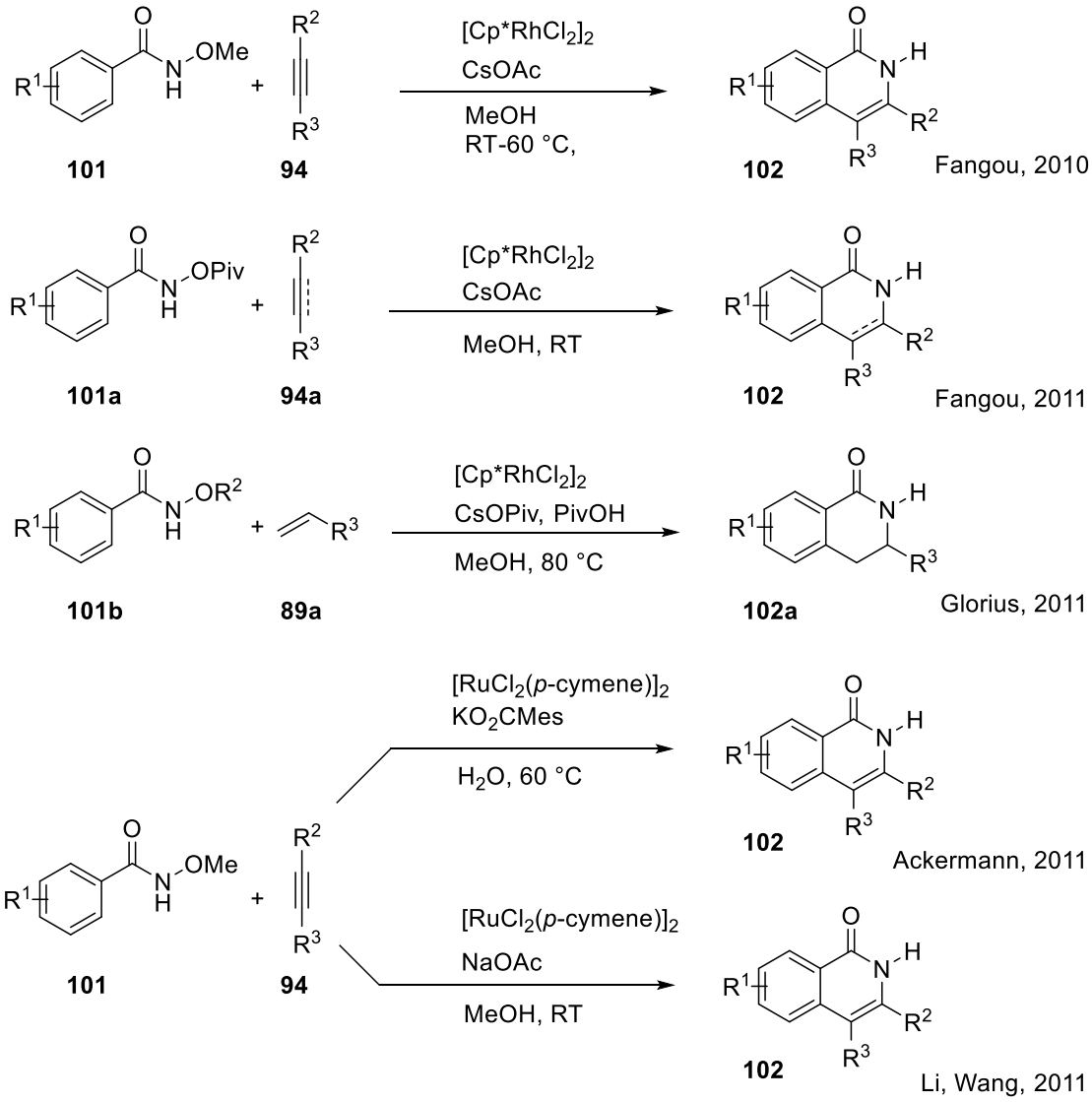


Scheme 1.24. Photocatalyzed oxidative annulation.

1.11 Directing Groups as Internal Oxidants for Oxidative Annulation

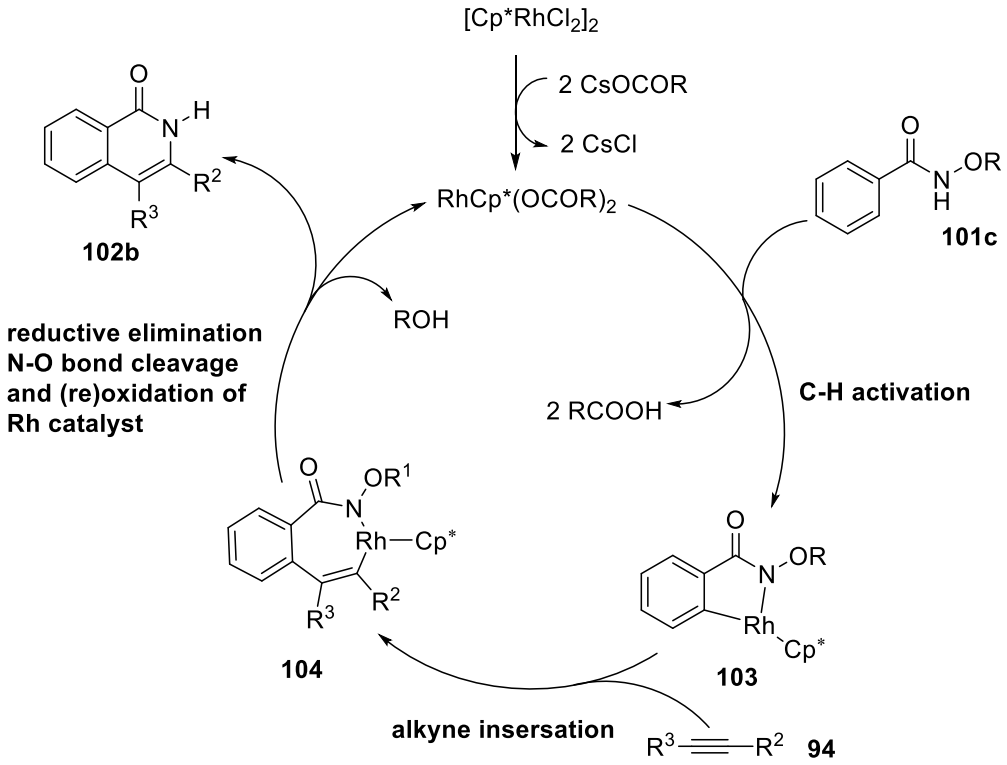
In the last few decades, several transition-metals catalyzed oxidative annulation were developed employing directing groups as internal oxidants (Scheme 1.25). In 2010, Fagnou and co-workers discovered the pioneering work of alkyne (**94**) annulations with using amides directing groups as internal oxidants through C–H bond activation and N–O bond

cleavages.[102-104] Afterwards, Fagnou groups as well as Glorius and Rovis groups reported Rh(III)-catalyzed oxidative annulation of benzamide derivative (**101**) with alkyne (**94**) or alkene (**89a**) with oxidizing directing groups as internal oxidant (Scheme 1.25).[105-106] In 2011, Ackermann group as well as Li and Wang groups developed ruthenium-catalyzed an oxidative annulation between benzamide derivative (**101**) and alkyne (**94**) using directing group as internal oxidant.[107-108]



Scheme 1.25. Oxidative annulations using directing groups as internal oxidants.

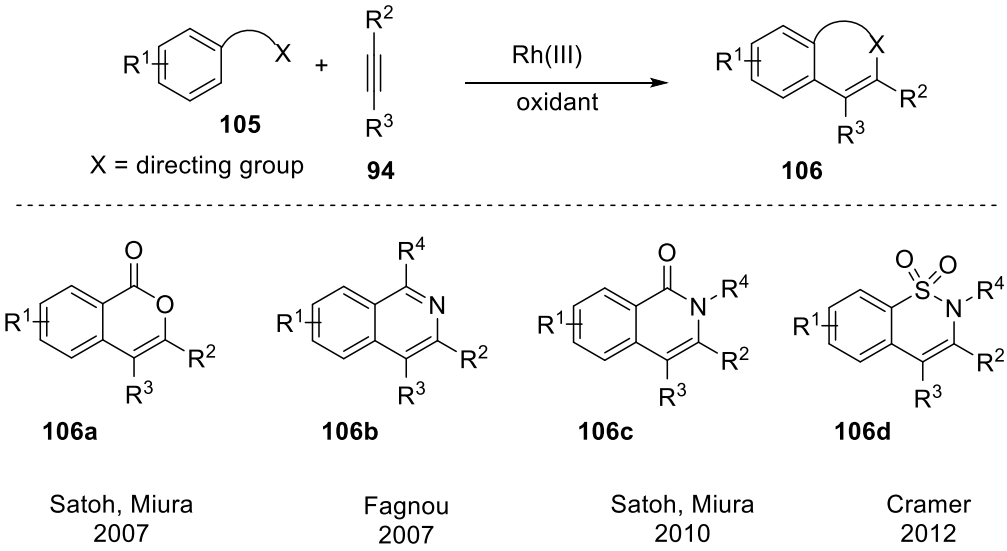
The catalytic cycle of Rh(III)-catalyzed oxidative alkyne annulations using directing groups as internal oxidants has been shown in the Scheme 1.26. Initially, the metallocycle intermediate was generated *via* C–H activation of benzamide (**101c**). The intermediate (**103**) undergoes the alkyne insertion to form seven-member rhodium complex (**104**). Afterwards, reductive elimination and N–O bond cleavage in the presence of acid, delivering the product (**102b**) and recycling Rh (III) catalyst.[109]



Scheme 1.26. Proposed mechanism of Rh-catalyzed oxidative alkyne annulation.

1.12 Metal Salt as Oxidants for Oxidative Annulation

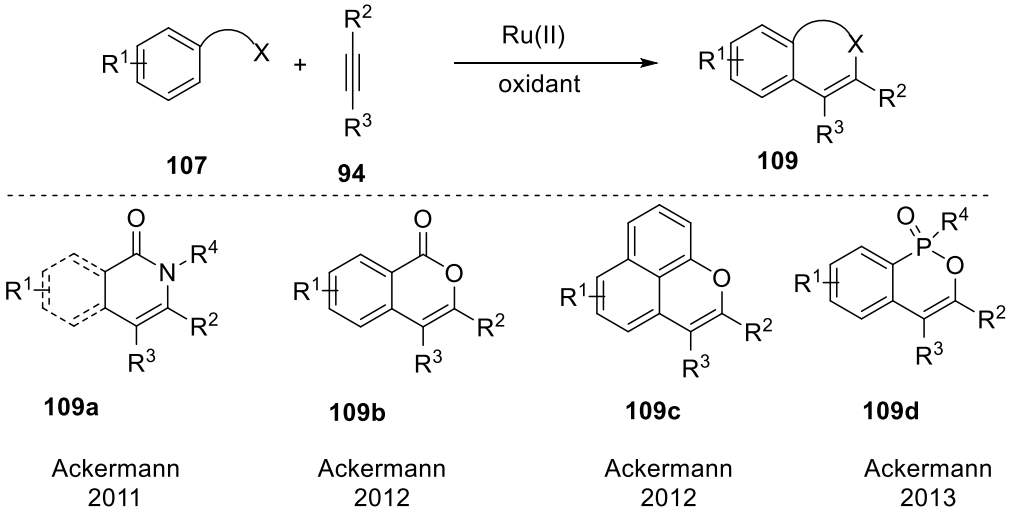
The combination of late transition-metal complexes as catalyst and metal salts as oxidants was widely used in the field of C–H activation (Scheme 1.27) In this context, several novel



Scheme 1.27. Oxidative annulation of alkyne in the presence metal oxidant

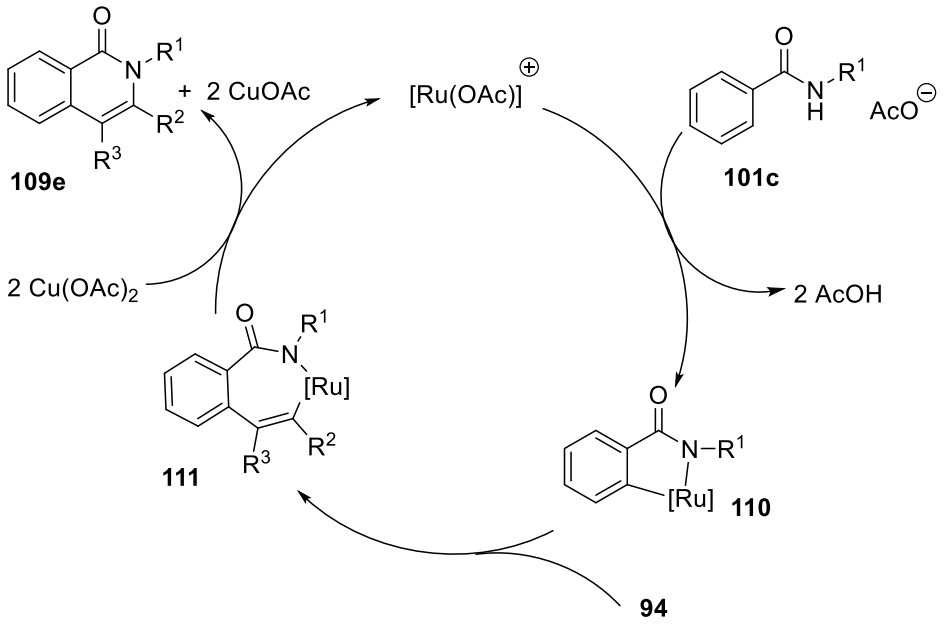
methods have been reported in the last decades for the oxidative annulation of alkyne with benzoic acid, amine or amide derivatives.[110-115] In 2007, Satoh and co-workers reported rhodium-catalyzed oxidative annulation of benzoic acid with alkyne using $Cu(OAc)_2 \cdot H_2O$ as

oxidant.[112] Later, groups of Ackermann, Satoh, Miura and Cramer independently demonstrated transition metal catalyzed oxidative annulation of alkyne **94** with various substrates in the presence of metal salt as oxidant.[111, 114-115]



Scheme 1.28. Ru(II)-catalyzed oxidative annulation of alkyne.

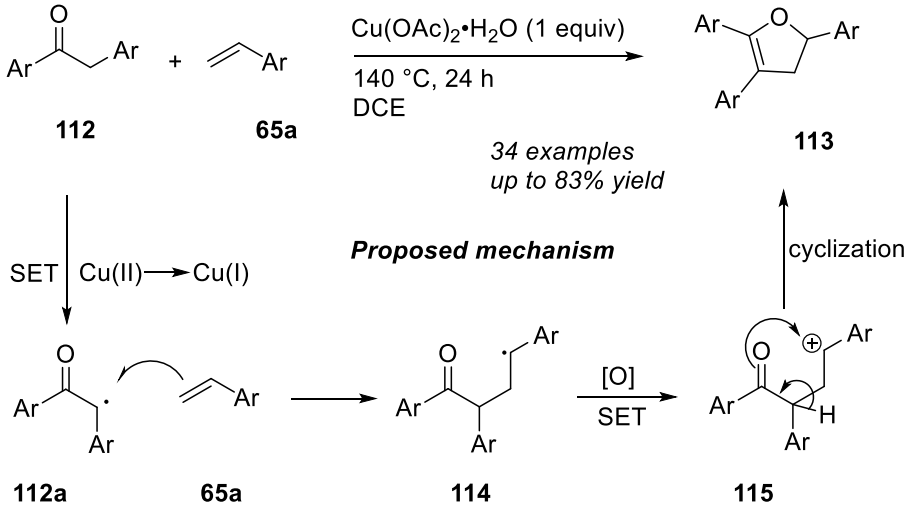
Recently, Ackermann and co-workers reported several elegant oxidative annulation methods employing ruthenium(II)-catalysts for oxidative annulation of alkynes (Scheme 1.28).[115] Later, Wang and co-workers also disclosed ruthenium(II)-catalyzed oxidative annulation of alkynes with benzamides.



Scheme 1.29. Proposed mechanism for Ru-catalyzed oxidative alkyne annulation.

Thus, the catalytic cycle of Rh-catalyzed alkyne annulation has been shown in the Scheme 1.29. Irreversible cycloruthenated complex (**110**) was generated in the presence of acetate.

Intermediate (**110**) undergoes the alkyne insertion to form seven-member ruthenium complex (**111**), which upon reductive elimination producing the desired isoquinolone **109e**.[115]



Scheme 1.30. $Cu(OAc)_2$ mediated oxidative annulation.

In 2014, Maiti and co-workers reported as unprecedented oxidative annulation between aryl ketones (**112**) and aromatic olefins (**89**) using $Cu(OAc)_2$ as oxidant (Scheme 1.30).[110] According to authors proposed mechanism, the reaction underwent *via* aryl ketone radical (**112a**) pathway. The reaction was followed by a novel oxidative annulation *via* radical C–C formation and C–O cyclization to achieve 2,3-dihydrofurans derivatives **113**.

Chapter 2

Aim of the Project

Chapter 2. Aim of the Project

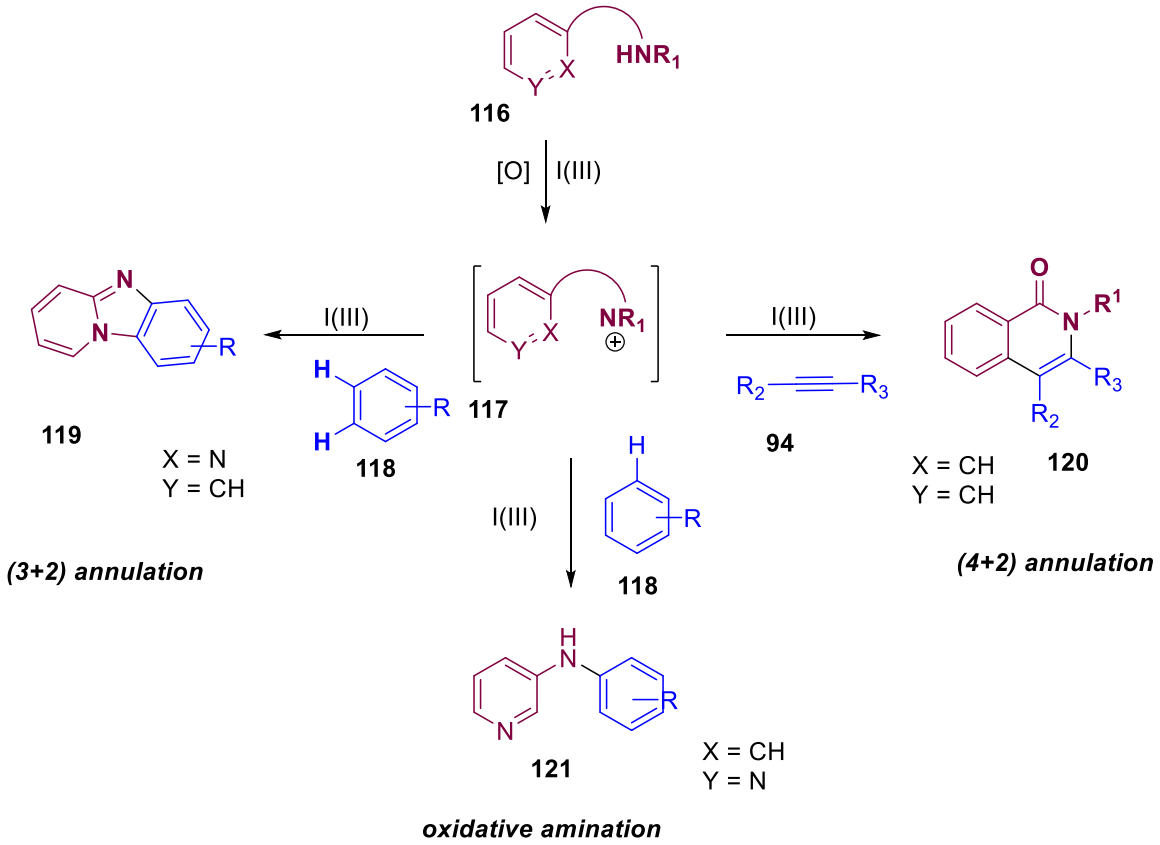
2.1 Overview of the Projects

Selective C–H bond functionalization for the construction of novel carbon–carbon or carbon–heteroatom bond is one of the most challenging tasks.[116-117] In the recent years, direct C–H bonds functionalization are considered as a mild, efficient and step-economic method using non-prefunctionalized coupling partners. Therefore, development of novel methods for the synthesis privileged scaffolds using simple building blocks would be highly interesting methods. Among them, oxidative annulation reaction *via* C–H bond functionalization is of great interest due to the formation of cyclic molecules from at least two acyclic molecules in single process.[116, 118] These methods could be used in the synthesis of biologically relevant compounds since they are efficient and step economic method.

The aim of this work is the development of new methods for the "privileged scaffolds" syntheses using hypervalent iodine (III) reagents, metal-free conditions and copper catalyst *via* C–H bonds functionalization. The nitrogen-containing heterocycles such as isoquinolones and pyrido[1,2-*a*]benzimidazoles and *N*-arylated pyridine scaffolds could be synthesized using hypervalent iodine (III) reagents. Further, various carbocycles such as 1,4-phenanthraquinones and cyclopropanes could be developed employing novel C–H bonds functionalization. Furthermore, synthesis of furan derivatives was subjected under oxidative conditions *via* acetophenones functionalization.

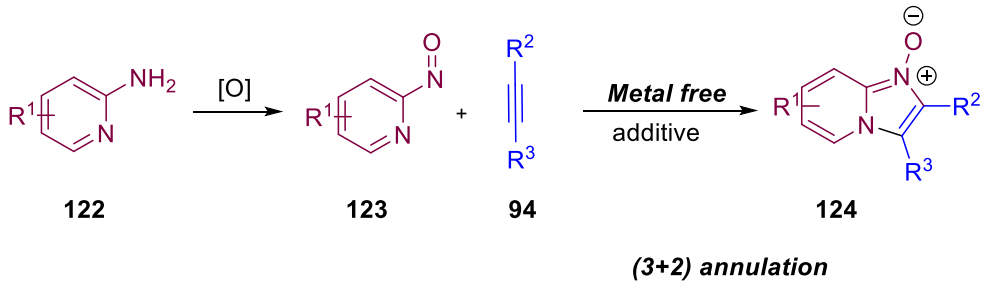
2.2 Hypervalent Iodine (III) Mediated Oxidative Annulation

Hypervalent iodine (III) mediated C–H bond functionalization has emerged over the last few decades as an attractive tool in synthetic organic chemistry.[119] One of the potential uses of this class of reagents is the construction of heterocycles *via* oxidative C–H bond functionalization.[120] Nitrogen-containing heterocycles are ubiquitous in natural products and drug molecules. Therefore, synthesis of nitrogen-based heterocycles under metal-free conditions is highly desirable. I(III) reagents were used to generate nitronium ion intermediate with protected amines for oxidative amination. Our approach to generate the aforementioned heterocycles is to generate a nitronium ion *in-situ* from the corresponding amines followed by trapping of these intermediates with suitable nucleophiles. Our hypothesis could be investigated with different aminopyridines or protected amides and various nucleophiles such as simple arenes or alkynes under hypervalent iodine (III) mediated in the synthesis of nitrogen-based heterocycles (Scheme 2.1).



Scheme 2.1. Hypervalent iodine (III) mediated oxidative annulation and amination.

In the course of these studies, we were also interested to develop a new method for the synthesis of pyridobenzimidazoles under metal-free conditions since pyridobenzimidazoles represents important scaffolds for biologically studies and drug molecules. Therefore, synthesis of pyridobenzimidazole derivatives would be highly demanding under mild and efficient metal-free conditions (Scheme 2.2).

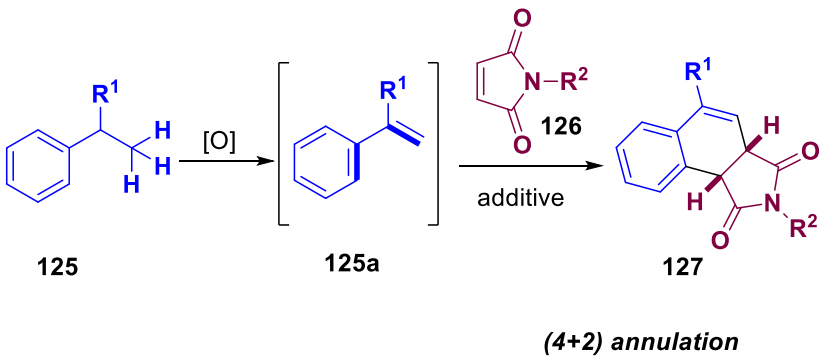


Scheme 2.2. Synthesis of pyridobenzimidazole scaffold.

2.3 Metal-Free Oxidative Dehydrogenative Diels-Alder Reaction

Carbon-hydrogen (C–H) bonds functionalization represents one of the most fundamental and efficient methods in organic synthesis. In the last decades, the construction C–C bond *via* functionalization of C–H has attracted great attention due the employment of simple building blocks.[121] In this regards, we moved to oxidative dehydrogenative Diels-Alder (DDA)

reaction of alkylbenzenes with alkenes *via* C(sp^3)–H bond functionalization. Over the last few decades, Diels-Alder reaction has found utilizing of diene-dienophile chemistry to obtain unsaturated carbocycles. Despite its importance in organic synthesis, dehydrogenative Diels-Alder (DDA) reactions paid great attention recently due to atom economy. Nevertheless, the synthesis of carbocycles by functionalization of unactivated C–H bonds remains a prime challenge to the chemists. Therefore, the development of new methods in this direction would be highly desirable.[122]



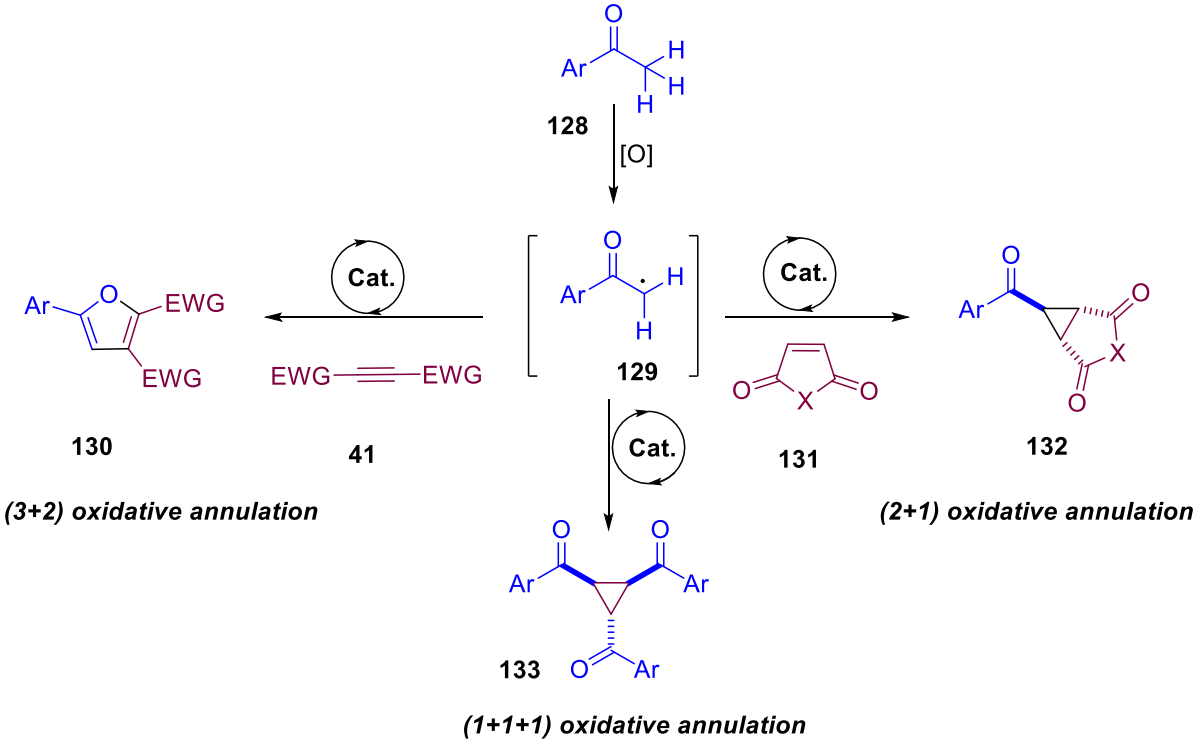
Scheme 2.3. Dehydrogenative Diels-Alder reaction.

However, metal-free dehydrogenative Diels-Alder reactions of alkylbenzenes with electron-deficient alkenes have never been investigated. We envisioned that dehydrogenative Diels-Alder reaction of simple alkylbenzenes might lead to interesting heterocycles and carbocycles.

2.4 Copper-Catalyzed Oxidative Annulation of Acetophenones

Finally, we were curious about the oxidative annulation of acetophenones with alkenes and alkynes that might be used for the synthesis of cyclopropanes and furans. Cyclopropanes[123] and furans[124] are among the most versatile and important classes of compounds and present in many natural products and biologically active drug molecules.[125] Traditionally, cyclopropanes are synthesized through the Simmon-Smith reaction[126-131], Michael-initiated ring closure reaction[132-135] and metal-carbene intermediates employing various transition metal or metal-free conditions.[136] In addition prior methods employed prefunctionalized precursors and drastic reaction conditions. Therefore, the development of cyclopropanes using mild conditions and user friendly chemicals would be a highly desirable. During studies on cyclopropanation, it was found that cyclopropanes were formed *via* acetophenones radical addition to the alkenes intermediate. From these studies, we envisaged that the new route to

multisubstituted furans *via* acetophenone radical addition to alkynes would be highly



Scheme 2.4. Synthesis of cyclopropanes and furans.

interesting route. To the best of our knowledge, synthesis of furan derivatives *via* direct annulation of simple acetophenones with alkynes has never investigated. Moreover, an efficient method for the synthesis of polysubstituted furans *via* acetophenones functionalization would be highly demanded.

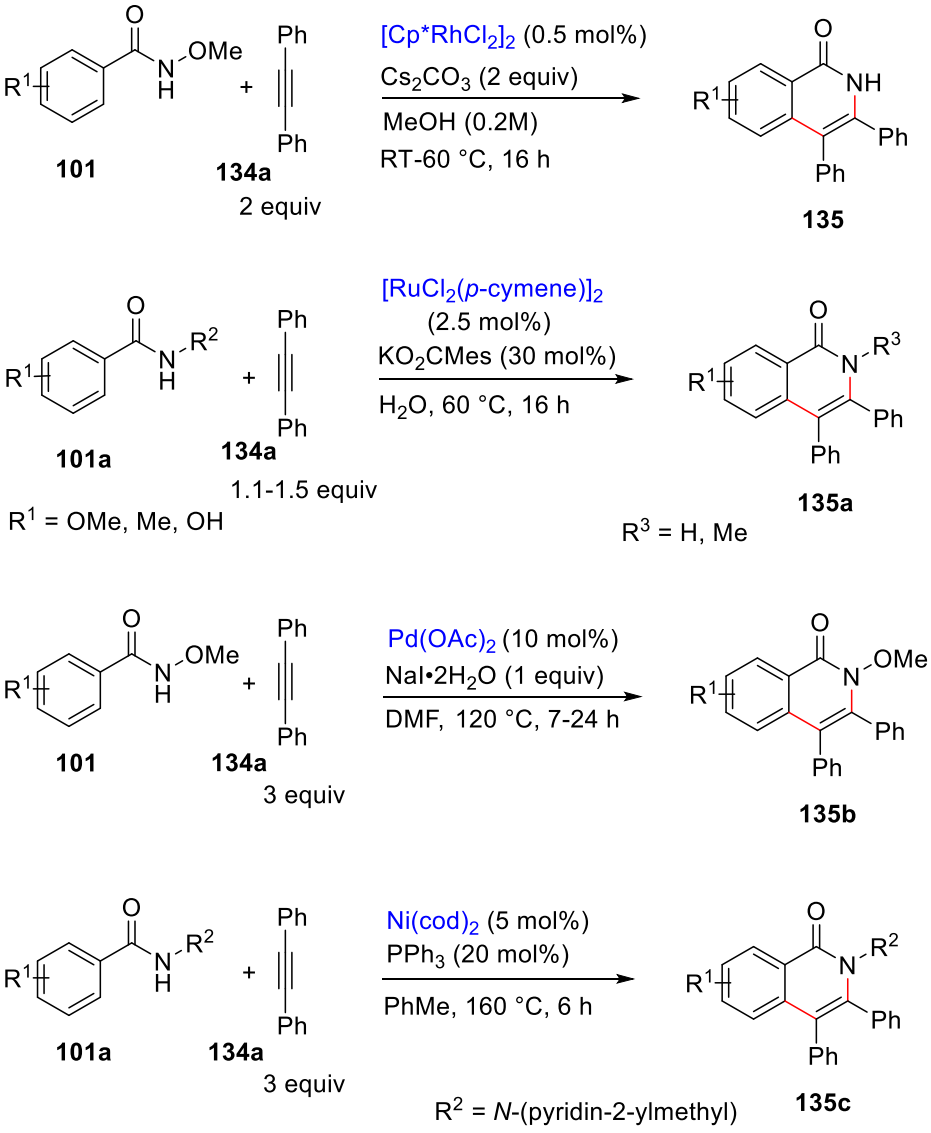
Chapter 3

Iodobenzene-Catalyzed Oxidative Annulation of Benzamide Derivatives with Alkynes

(This part already published: S. Manna, A. P. Antonchick, *Angew. Chem*. **2014**, *126*, 7452-7455; *Angew. Chem. Int. Ed*, **2014**, *53*, 7324-7327.)

3.1 Introduction

C–H bond amination has emerged over the last few decades and became an attractive field to build molecular diversities employing simple starting materials.[137-138] They are extensively used in the synthesis of biologically relevant drug molecules[139-140] and natural products synthesis.[141] In the last century, syntheses of nitrogen-containing heterocycles were well established by transition metal (TM) catalysts using prefunctionalized precursors.[142] Nevertheless, metal-free methods in the synthesis of heterocycles are becoming more interesting field due to atom economic and environmentally friendly nature in modern chemistry. However, the development of new method for the synthesis of nitrogen-based heterocycles such as isoquinolone employing cheaper and user friendly hypervalent iodine (III) reagents *via* C–H bond amination is highly demanded.[119]



Scheme 3.1. Transition metal catalyzed directed quinolones synthesis.

In the last decades, several methods to isoquinilones synthesis were reported using transition metal catalyst such as Rh, Ru, Ni and Pd applying different approaches (Scheme 3.1). [102-108, 115, 143] First, Fagnou and co-workers were initiated the annulation of benzamides with alkynes for the synthesis of isoquinolone derivatives employing Rh-catalyst *via* direct C–H bond activation using directing group as an internal oxidant.[102-104] Very recently, Ackermann and co-workers disclosed Ru-catalyzed an efficient approach to annulation of *N*-hydroxybenzamides, *N*-methoxybenzamides, *N*-methylbenzamides and alkynes for the demonstration of isoquinolines.[108, 115] Pd-catalyzed synthesis of isoquinolines was developed by Huang and co-workers employing atmospheric oxygen as an external oxidant for this transformation.[144] Chatani and co-workers independently developed first nickel catalyzed chelation-assisted cycloaddition of benzamides with alkynes for the synthesis of isoquinolones scaffolds where alkyne was used as an internal oxidant in this transformation.[145] However, reported methods require higher temperature, external oxidant or internal oxidant and longer reaction time in the synthesis of isoquinolone scaffolds. It is notable that metal-free method for isoquinolones synthesis has never been investigated. Therefore, a mild, efficient and organocatalytic conditions for the synthesis of isoquinolone scaffolds would be highly desirable.

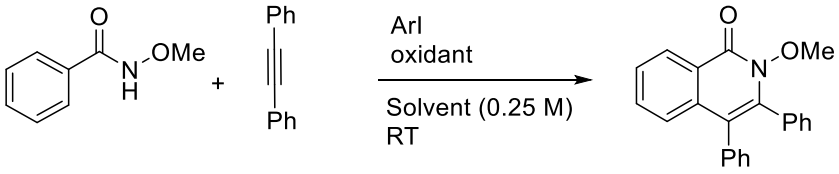
3.2 Results and Discussion

3.3 Studies on the Optimization of Reaction Conditions

We initiated our optimization studies with *N*-methoxybenzamide (**136a**) and commercially available diphenylacetylene (**134a**) in the presence of $PhI(OAc)_2$ (**22**) as oxidant in HFIP as a solvent at room temperature for 12 h and the desired product **137a** was obtained in 40% yield (Table 3.3.1). Encouraged by the initial result, we then started the optimization of isoquinolone scaffold synthesis with iodobenzene (**138**) as a catalyst and 3-chloroperbenzoic acid as oxidant. We found that the catalytic amount of iodobenzene (**138**) was effective for this transformation. After screening several oxidants for *in-situ* generation of hypervalent iodine (III) with PhI (**138**), we found that peracetic acid was to be the best oxidant to provide the desired product **137a** in 68% yield. Later, we examined the oxidative annulation with $PhI(OCOCF_3)_2$ (**23**) instead of **138** and peracetic acid to obtain good conversion. We did not obtain our target product **137a** in the presence of stoichiometric amounts of $PhI(OCOCF_3)_2$ (**23**). Afterwards, we tested different solvents for the oxidative annulation. Pleasingly we found that HFIP was to be the best solvent and provided the desired product **137a** in 68%

yield (Table 3.3.1, entry 3). The annulated product **137a** was not observed in MeOH, EtOAc, $CHCl_3$ or DCE as a solvent. After screening several solvents, various iodobenzene

Table 3.3.1. Optimization of reaction conditions for isoquinolone synthesis.[a]



136a **134a** **137a**

Entry	Solvent	ArI (mol%)	Oxidant	Yield (%)
1[b,c]	HFIP	-	$PhI(OAc)_2$,	40
2[d]	HFIP	**PhI (138)**	*m*CPBA	52
3	HFIP	**138**	AcOOH	68
4	HFIP	**138**	DTBP	n.d.
5	HFIP	**138**	H_2O_2	n.d.
6	CF_3CH_2OH	**138**	AcOOH	44
7	HFIP	-	$PhI(OCOCF_3)_2$	n.d.
8	HFIP:DCM (1:1)	**138**	AcOOH	41
9	$CHCl_3$	**138**	AcOOH	n.d.
10	MeOH	**138**	AcOOH	44
11	DCE	**138**	AcOOH	n.d.
12	HFIP	4-$MeOC_6H_4I$ (**138b**)	AcOOH	5
13	HFIP	4-MeC_6H_4I (**138c**)	AcOOH	20
14	HFIP	4-$NO_2C_6H_4I$ (**138d**)	AcOOH	n.d.
15[e]	HFIP	**138**	AcOOH	64
16[f]	HFIP	**138**	AcOOH	78
17[g]	HFIP	**138**	AcOOH	73
18[h]	HFIP	**138**	AcOOH	55

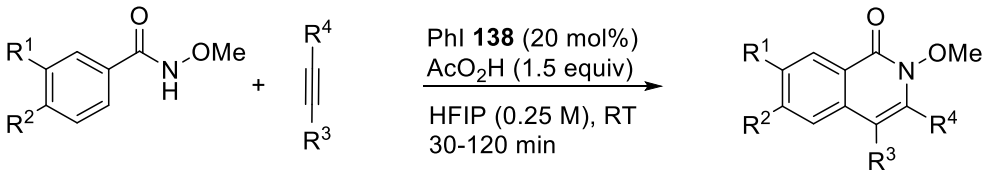
[a] Reaction conditions: **136a** (0.15 mmol), **134a** (0.18 mmol), ArI (10-20 mol%) in solvent (0.25 M) for 30 min. [b] Reactrion was carried out for 12 h. [c] $PhI(OAc)_2$ (2 equiv) used. [d] *m*-CPBA (1.5 equiv) used. [e] catalyst **138e** (2,2',6.6'-tetramethylbiphenyl) 10 mol% was used. [f] Peracetic acid was added portion wise. [g] 1.5 equiv AcOOH was used. [h] 15 mol% catalyst was used. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. DCE = 1,2-dichloroethane. n.d. = not detected.

derivatives were anticipated in combination with peracetic acid at ambient temperature in HFIP solvent to achieve the best yield. The iodobenzene (**138**) was found to be the best catalyst and provided the desired product **137a** in 73% yield. Dramatically yield was increased to 78% while 1.5 equivalents peracetic acid was added by portion wise. Notably, improvement of yield did not observe when the amount of peracetic acid was increased or decreased under the same reaction conditions.

3.4 Scope of Iodobenzene-Catalyzed Oxidative Annulation

With the optimal reaction conditions in hand, we next explored the scope of reaction with various substituted alkynes **134** with *N*-methoxybenzamide derivatives **136** (Table 3.4.1). We found that the reaction was very facile and provided the desired products in good to excellent yield. The reaction of alkyne bearing electron-withdrawing as well as electron-donating

Table 3.4.1. Scope of different alkynes.[a]



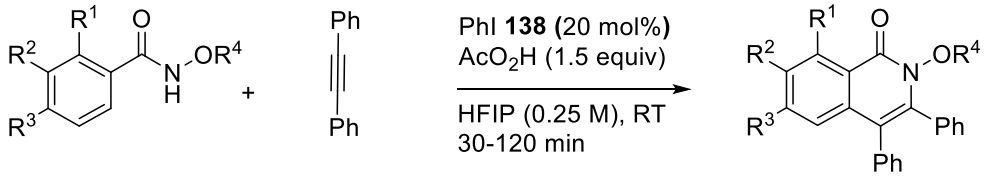
136 **134** **137**

Entry	R^1	R^2	R^3	R^4	Product	Yield (%)
1	H	H	Ph	Ph	**137a**	78
2	OMe	OMe	4-MeC_6H_4	4-MeC_6H_4	**137b**	82
3	H	H	3-MeC_6H_4	3-MeC_6H_4	**137c**	60
4[b]	OMe	OMe	Ph	4-$CF_3C_6H_4$	**137d**	53
5[b]	H	H	Ph	4-$CF_3C_6H_4$	**137e**	71
6[c]	OMe	OMe	Ph	4-FC_6H_4	**137f**	61 (2:1)
7[c]	H	H	Ph	4-FC_6H_4	**137g**	53 (2:1)
8[b]	H	H	Ph	4-$NO_2C_6H_4$	**137h**	50
9[d]	OMe	OMe	4-$MeOC_6H_4$	Ph	**137i**	50
10	H	H	Ph	H	**137j**	n.d.
11	H	H	CH_2Cl	CH_2Cl	**137k**	n.d.
12	H	H	Cycloheyl	H	**137l**	n.d.

[a] Reaction conditions: **137** (0.15 mmol), **134** (0.18 mmol), 20 mol% **139** in HFIP (0.25 M) at RT for 30-120 min. [b] 25 mol% catalyst loading. [c] Yield of mixture of isomers were shown in the table. [d] $PhI(OAc)_2$ (1.5 equiv) used instead of catalytic conditions. n.d. = not detected.

groups at the *para*-position on the aryl part of diphenylacetylene were well tolerated and afforded cyclized products in good yield. Various functional groups such as trifluoromethyl, fluoro, nitro and methoxy on the aryl part were tolerated under mild reaction conditions and delivered the desired products (**137b-137h**) in good to moderate yield. With *para* substituted

Table 3.4.2. Scope of different benzamides.[a]



136(a-o) **134a** **139**

Entry	R^1	R^2	R^3	R^4	Product	Yield (%)
1	H	H	H	C_6H_{17}	**139a**	81
2	H	H	H	nBu	**139b**	85
3	H	H	H	^{i}Pr	**139c**	76
4[b]	H	H	H	$PhCH_2$	**139d**	56
5	H	H	H	2-Methylallyl	**139e**	75
2	H	OMe	OMe	Me	**139f**	64
9	Me	H	H	Me	**139g**	68
10[c]	H	Me	H	Me	**139h**	65 (3:1)
6	H	H	Me	Me	**139i**	74
7	H	H	^{t}Bu	Me	**139j**	69
8	H	H	Ph	Me	**139k**	65
11[c]	H	OCF_3	H	Me	**139l**	54 (5:4)
12	H	H	H	Ph	**139m**	n.d.
13	H	H	H	Me	**139n**	n.d.
14	H	H	OMe	Me	**139o**	n.d.
15	H	H	SMe	Me	**139p**	n.d.

[a] Reaction conditions: **136** (0.15 mmol), **134a** (0.18 mmol), 20 mol% PhI **138** in HFIP (0.25 M) at RT for 30-120 min. [b] 10 mol% **138e** catalyst, 5 equiv TFA and 2 equiv AcOH were used and run up to 4 h. [c] Major isomer has shown in the Table. n.d. = not detected.

unsymmetrical alkynes such as methoxy, nitro and trifluoromethyl group; regioselectively delivered single isomer and the structures were established based on NOE analysis. Notably,

methyl group in the *meta* and *para*-position of diphenylacetylene worked well and afforded the isoquinolone derivatives (**137b** and **137c**) in moderate to good yields.

After explored the scope of alkynes, a wide range of *N*-alkoxy group of benzamide derivatives were also investigated with simple diphenylacetylene (**134a**) under developed reaction conditions (Table 3.4.2). We observed long chain aliphatic groups such as octane and *n*-butane could be produced the annulated products **139a** and **139b** under organocatalytic reaction conditions in excellent yield. The reaction of **134a** with *N*-isopropyloxy benzamide also provided the desired product **139c** in 76% yield without any difficulty. The benzyloxybenzamide as a substrate was also investigated and obtained the desired product **139d** in 56% yield. *N*-((2-Methylallyl)oxy)benzamide produced the desired product **139e** in 75% yield without oxidation of terminal alkene. We next turned our attention to the different benzamide derivatives for the synthesis of isoquinolone scaffolds. The electron-rich 3,5-methoxybenzamide selectively reacted with **134a** under our optimal reaction condition and provided the corresponding product **139f** in 64% yield. Notably, the reaction of diphenylacetylene (**134a**) with methyl substituted benzamideamides led to form target products **139h** and **139i** in moderate to good yield. Pleasingly, we found that *para*-substituted electron-rich benzamides reacted smoothly with diphenylacetylene (**134a**) and afforded the desired isoquinolones **139i-139k** in good yield. *para*-Substituted methoxy and thiomethyl groups of *N*-methoxybenzamide did not gave the desired product under developed reaction conditions. Phenyl substituted benzamide slowly reacted to give corresponding isoquinolone **139k** in 65% yield. Unfortunately, strong electron-withdrawing benzaamide derivatives did not give the desired product. *N*-Methylbenzamide and *N*-phenylbenzamide did not give yield under developed reaction conditions.

3.5 Determination of the Regioisomers

3.5.1 1-D NOE Experiments for Product 137i

NOE experiment was performed to identify regioisomer of product **137i** (Figure 3.1). According to the NOE analysis, $\mathbf{H^b}$ correlated with proton $\mathbf{H^a}$ and proton $\mathbf{H^c}$ after irradiation of proton $\mathbf{H^b}$. Proton $\mathbf{H^b}$ on irradiation shows no correlation with $\mathbf{OMe^a}$ which indicated that $\mathbf{H^b}$ is far from $\mathbf{OMe^a}$ group. After irradiation of proton $\mathbf{H^c}$, there was correlation with proton $\mathbf{H^b}$ and $\mathbf{OMe^b}$ and no correlation observed with $\mathbf{OMe^a}$. NOE experimental result suggested that Ph group close to N–OMe group.

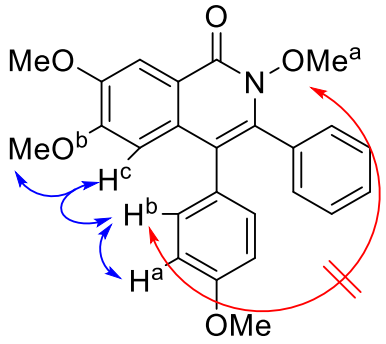


Figure 3.1. Identification of regioisomer of product **137i** by NOE experiments.

3.5.2 1-D NOE Experiments for Product 137d

Similarly, NOE experiment was carried out for product **137d** (Figure 3.2) to identify regioisomer. Upon irradiation of proton **H**^{a} which correlated with proton **H**^{b} and **OMe**^{a}. Proton **H**^{d} on irradiation does not correlation with proton **H**^{c} which indicated that **H**^{c} is close to **H**^{d} of 4-methoxybenzene group. Upon irradiation of proton O**Me**^{a} which shows correlation with proton **H**^{a} and no correlation with proton **H**^{d}. NOE studies suggested that **Ph** group far to N–OMe group.

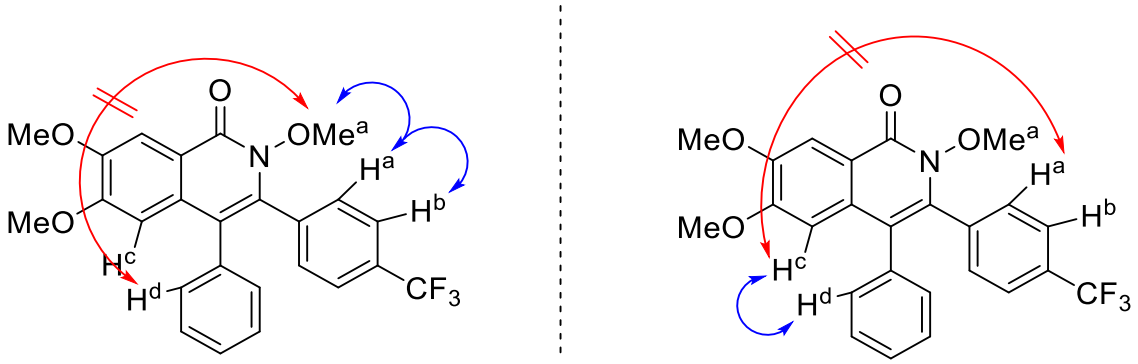
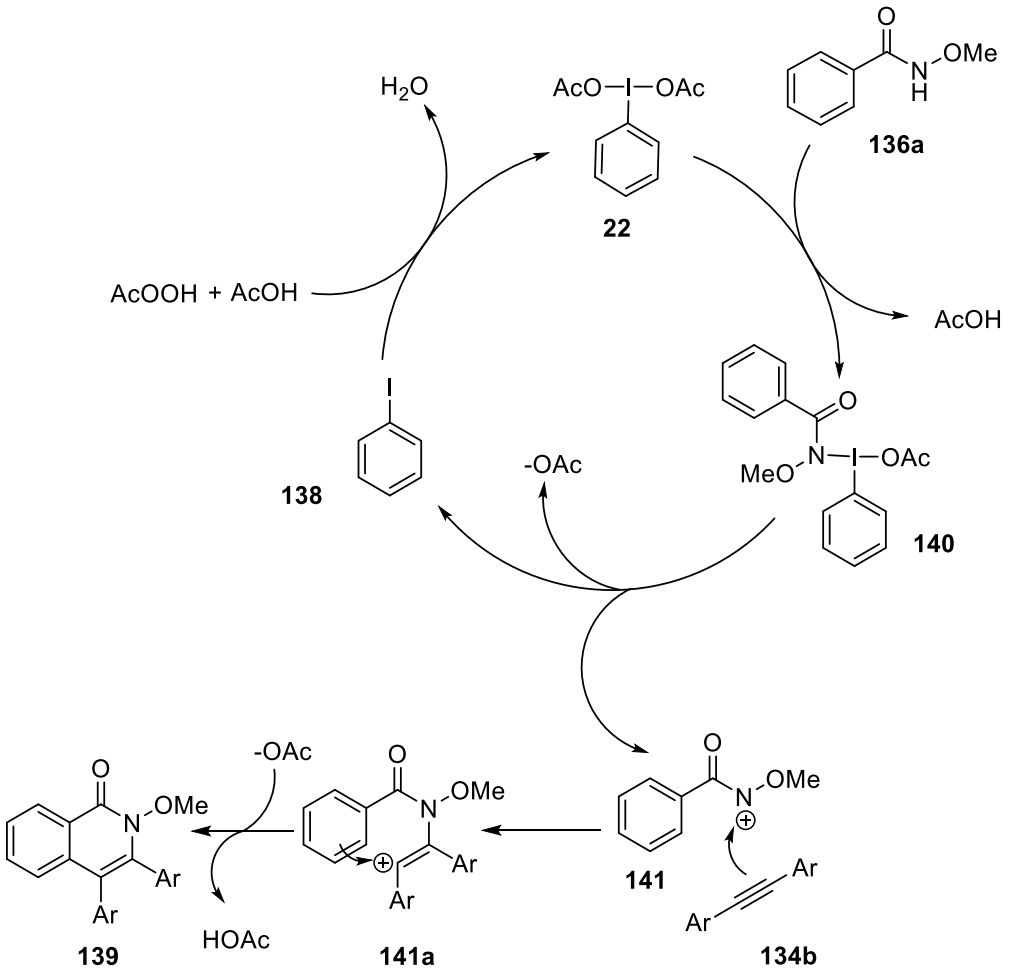


Figure 3.2. Identification of regioisomer of product **137d** by NOE experiments.

3.6 Mechanism

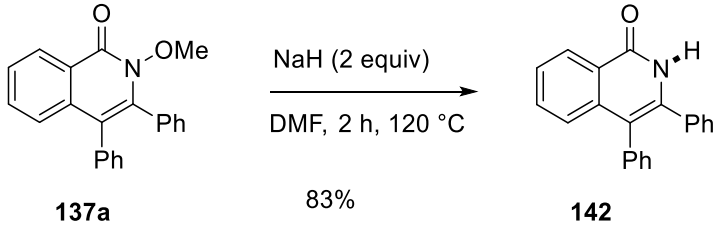
Based on our preliminary investigation and experimental studies, a plausible mechanism has been shown in Scheme 3.2. The active species **22** was generated *via in-situ* oxidation of iodobenze **138** in the presence of peracetic acid. Afterwards, the intermediate **140** produced *via* the ligand exchange of *N*-methoxybenzamide **136a** after reacting with the intermediated **22**. Then nitrenium intermediate **141** was generated through reductive elimination of intermediated **140** which subsequently trapped by alkyne **134a** to give probable intermediate **141a**. Finally, isoquinolone **139** was formed followed by hydrogen abstraction by acetate anion and the producing acetic acid as byproducts.



Scheme 3.2. Proposed mechanism for organocatalyzed annulation.

3.7 Synthetic Application of Product 137a

To apply follow up reaction, we examined N–O bond cleavage to N–H bond by applying reported method (Scheme 3.3).[146] N-H bond formation could be applied using NaH by the reduction of N–O bond. Finally, we anticipated compound **137a** with 2 equivalents of NaH in DMF at 120 ºC to afford **142** in 83% yields.

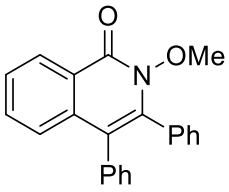
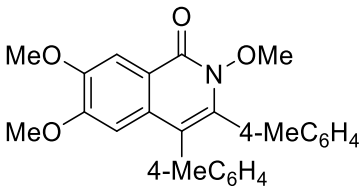
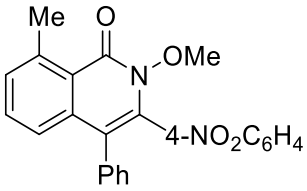
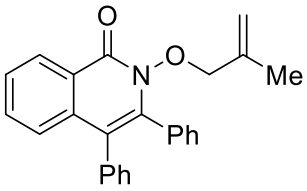


Scheme 3.3. N–O bond cleavage of product **137a**.

3.8 Identification of Biological Activity of Isoquinolones

According to our plan, we synthesized compound libraries of isoquinolone derivatives. Afterwards, we submitted all compound to COMAS (Compound Management and Screening Centre) in Dortmund to find the biological activity. Several cell-based assays such as hedgehog signaling pathway and Wnt signaling pathway and autophagy were tested. After screening different assays, four compounds **137a**, **137b, 137h** and **139e** inhibited the hedgehog signaling pathway in the low micro molar range (Table 3.8.1).

Table 3.8.1. Results of hedgehog signaling pathway.

Entry	Product	IC_{50} [µM]	Viability [µM]
1	 **137a**	5.52 ± 0.38	inactive
2	 **137b**	4.69 ± 0.21	inactive
3	 **137h**	4.31± 0.56	inactive
4	 **139e**	5.10 ± 0.46	inactive

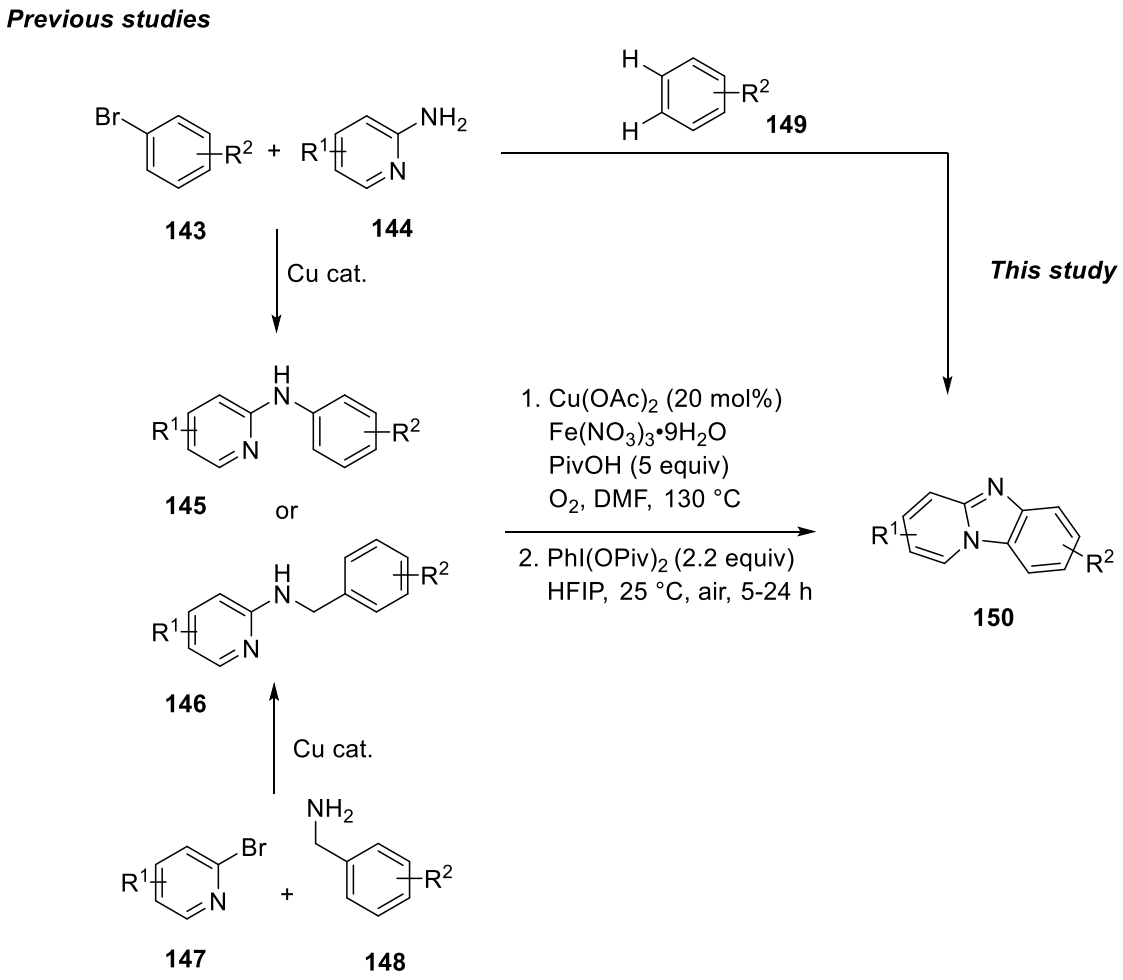
Chapter 4

Hypervalent Iodine (III) Mediated Oxidative Annulation of 2-Aminopyridines with Arenes

(Part of this result already published: S. Manna, K. Matcha, A. P. Antonchick, *Angew. Chem*. **2014**, *126*, 8302-8305; *Angew. Chem. Int. Ed*, **2014**, *53*, 8163-8166).

4.1 Introduction

Hypervalent iodine (III) mediated oxidative C–N bond formation is one of the most fascinating reactions in organic chemistry due to its efficient and cost reliable to build up diverse compound libraries.[78] It has been used in many fields such as pharmaceutical, biological relevant molecules development and natural products synthesis.[147-152] One of the key objectives of this method is the utilization of readily available starting materials to get a wide range of molecular diversities under simple reaction conditions. Utilization of I(III) reagents has seen explosive growth in modern organic synthesis due to its easily available and user friendly.[153] Nevertheless, the synthesis of nitrogen-containing heterocycles such as pyridoimidazoles and pyridobenzimidazoles *via* oxidative annulation approaches without prefunctionalized building blocks would be highly desirable transformation.



Scheme 4.1. Various routes in the synthesis of pyrido[1,2-*a*]benzimidazoles.

In the recent years, several methods for intramolecular pyridobenzimidazoles synthesis were developed using hypervalent iodine (III) reagents from prefunctionalized feedstocks.[88, 91, 154-155] Synthesis of pyridobenzimidazole of *N*-aryl-2-aminopyridines was disclosed by Zhu and

co-workers employing copper(II) and iron(III) as catalyst (Scheme 4.1).[156] Later, Zhu and co-workers developed hypervalent iodine (III) mediated pyrido[1,2-*a*]benzimidazoles with *N*-aryl-2-aminopyridines and *N*-benzylpyridin-2-amines (Scheme 4.1).[81, 157] However the reported methods are only intramolecular approaches (Scheme 4.1). Synthesis of pyrido[1,2-*a*]benzimidazoles *via* intermolecular way has never been reported.[158] In this context, it would be a significant advantage to discover a direct intermolecular annulation of 2-aminopyridines with non-prefunctionalized arenes. In the continue of our studies, we were interested to develop PhI(OAc)$_2$ (**22)** mediated oxidative annulation of 2-aminopyridine derivatives **144** with simple arenes **149** for the synthesis of the pyrido[1,2-*a*]benzimidazole scaffolds.

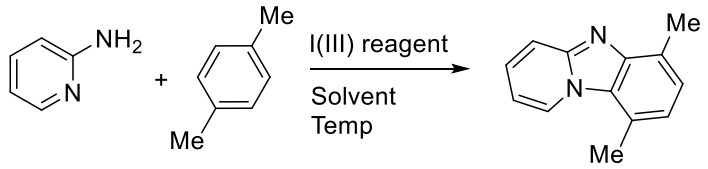
4.2 Results and Discussion

4.3 Studies on the Optimization of Reaction Conditions

Having interests from our previous studies on the annulation of benzamides with alkynes, we were motivated to develop a new method for oxidative annulation of 2-aminopyridine (**144a**) with non-functionalized arene under metal-free conditions. We began our initial studies with 2-aminopyridine (**144a**) and *para*-xylene (**159a**) as model substrates to examine the annulation by employing hypervalent iodine (III) reagents. While the reaction was carried out with 2-aminopyridine (**144a**) and *para*-xylene (**149a**) in the presence of two equivalents PhI(OAc)$_2$ (**22**) as oxidant at room temperature in HFIP, the desired product pyrido[1,2-*a*]benzimidazoles derivative (**151a**) was isolated in 63% yield. Afterwards, we tested different temperature for the annulation reaction. To our delight, when reaction was performed at 70 ^{0}C, the desired product formation decreased to 19% yield. Changing the reaction temperature to 40 ^{0}C, formation of the desired product **151a** was increased to 74% yield. After screening different solvents, we found that HFIP was to be the best solvent in this transformation. We did not obtain target product **151a** while dichloromethane, 1,2-dichloroethane, 2,2,2-trifluoroethanol or toluene were used as a solvent. The solvent combination with HFIP and dichloromethane (1:1) did not give promising results. Later, we investigated the application of various hypervalent iodine (III) reagents for oxidative annulation reaction. Surprisingly, highly reactive PhI(OCOCF$_3$)$_2$ (**23**) did not provide the desired product **151a**. Less reactive PhI(OCO^{t}Bu)$_2$ (**22a**) was able to produce the desired product **151a** in 33% yield. Notably, the yield was decreased with increase or decrease the amount of PhI(OAc)$_2$ (**22**) instead of 2 equivalents reagents. Finally, we found that 2 equivalents of PhI(OAc)$_2$ (**22**) was to be the best reagent for this transformation. However, increasing the amount of the arene did not give

the benefit for the oxidative annulation reaction (Table 4.3.1, entry 16), but decreasing amount of arene provided lower yield (Table 4.3.1, entry 15).

Table 4.3.1. Optimization of oxidative annulation reaction conditions.[a]



144a **149a** **151a**

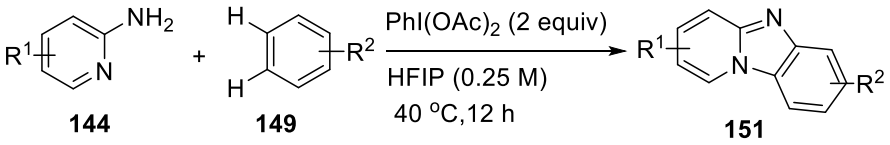
Entry	Solvent (0.25M)	I(III) reagent (equiv)	Temp (^{o}C)	Yield (%)
1	HFIP	PhI(OAc)$_2$ (2)	RT	63
2	HFIP	PhI(OAc)$_2$ (2)	40	74
3	HFIP	PhI(OAc)$_2$ (2)	70	19
4	DCM	PhI(OAc)$_2$ (2)	40	n.d.
5	HFIP:DCM (1:1)	PhI(OAc)$_2$ (2)	40	31
6	CF_3CH_2OH	PhI(OAc)$_2$ (2)	40	n.d.
7	Toluene	PhI(OAc)$_2$ (2)	40	n.d.
8	DCE	PhI(OAc)$_2$ (2)	40	n.d.
9	HFIP	PhI(OCOCF$_3$)$_2$ (2)	40	n.d.
10	HFIP	PhI(OCO^{t}Bu)$_2$ (2)	40	33
11	HFIP	PhI(OAc)$_2$ (1.5)	40	48
12	HFIP	PhI(OAc)$_2$ (1.75)	40	63
13	HFIP	PhI(OAc)$_2$ (2.5)	40	68
14	HFIP	PhI(OAc)$_2$ (3)	40	44
15[c]	HFIP	PhI(OAc)$_2$ (2)	40	55
16[d]	HFIP	PhI(OAc)$_2$ (2)	40	75
17	DCM	PhI(OCOCF$_3$)$_2$ (2)	40	n.d.

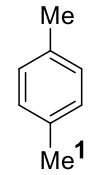
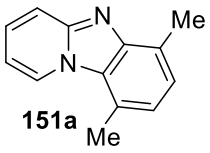
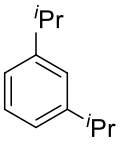
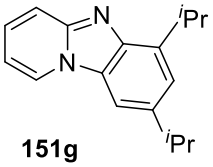
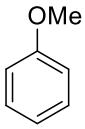
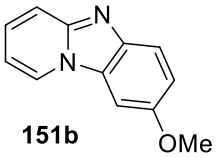
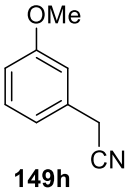
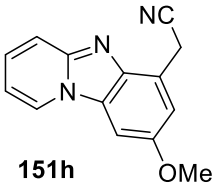
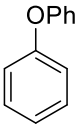
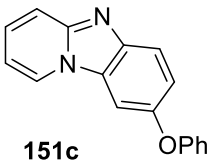
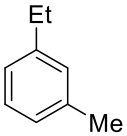
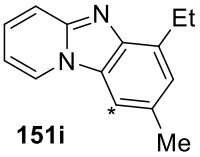
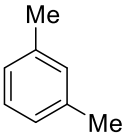
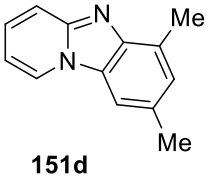
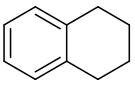
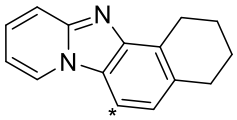
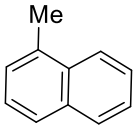
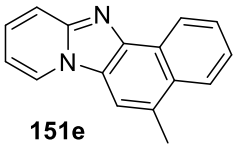
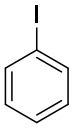
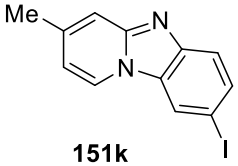
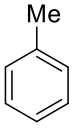
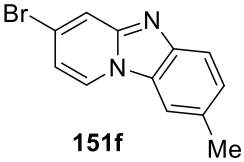
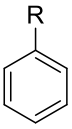
[a] Reaction conditions: **144a** (0.2 mmol), **149a** (1.0 mmol), I(III) reagent (equiv) in solvent (0.25 M) and temperature for 12 h. [b] **149a** (0.4 mmol) used. [c] **149a** (2.0 mmol) used. DCE = 1.2-Dichloroethane. n.d. = not detected.

4.4 Substrate Scope of PhI(OAc)$_2$ Mediated Oxidative Annulation

With the optimized reaction conditions in hand, we moved to explore the oxidative annulation reaction. At first, a series of simple arenes were examined for the annulation (Table 4.4.1). To our delight, the reaction was found to be very facile with various electron- rich arenes.

Table 4.4.1. Scope of oxidative annulation of different arenes.[a]



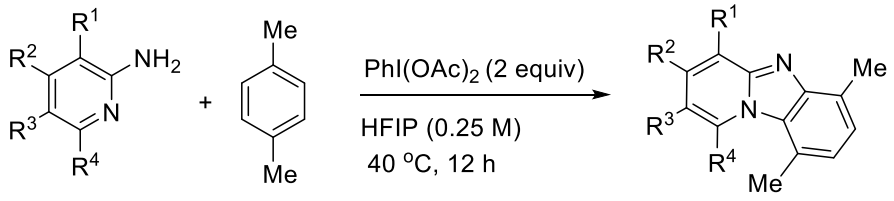
Entry	Arene	Product	Yield (%)	Entry	Arene	Product	Yield (%)
1	 **149a**	 **151a**	75	7	 **149g**	 **151g**	52
2	 **149b**	 **151b**	77	8	 **149h**	 **151h**	68[b]
3	 **149c**	 **151c**	80	9	 **149i**	 **151i**	73 (2.1:1)[e]
4	 **149d**	 **151d**	62	10	 **149j**	 **151j**	82 (1.3:1)[e]
5	 **149e**	 **151e**	67 (5:1)[b]	11	 **138**	 **151k**	49[c,f]
6	 **149f**	 **151f**	43[c,d]	12		**149k** = Cl **149l** = F **149m** = NO_2	n.d.

[a] Reaction conditions: **144** (0.2 mmol), **149** (1.0 mmol), PhI(OAc)$_2$ (0.4 mmol) in HFIP (0.25 M) at 40 °C for 12 h. [b] **149** (0.6 mmol) used. [c] After 12 h, PhI(OAc)$_2$ (0.2 mmol) was added and the reaction continued for 24 h. [d] 4-bromo-2-aminopyridine was used. [e] Major isomer is shown, minor isomer is indicated with star and the yields were reported for mixtures. [f] 4-Me-2-aminopyridine was used. n.d. = not detected.

Simple electron-rich arenes such as anisole (**149a**) and diphenyl ether (**149b**) provided the corresponding products **151b** and **151c** in excellent yields. After successfully established

monosubstituted arenes, we then examined multisubstituted arenes and found disubstituted arenes were well tolerated under optimal reaction conditions and provided products in good to excellent yield (Table 4.4.1, entries 4, 7-10). Various disubstituted arenes also were well tolerated and provided the desired products with excellent to moderate yields **151g-151j**. Naphthalene derivatives **149e** was investigated in the metal-free annulation reaction and obtained the desired products **151e** in 67% yield with regioisomer in 5:1 ratio. Furthermore, toluene (**149f**) also provided the desired annulation products in acceptable yields. Tetrahydronapthalene (**149j**) worked well and gave a mixture of regioisomers with 1.3:1 ratio. Interestingly, less electron-deficient iodobenzene (**138**) also provided the desired product **151k** in 49% yield. An electron-deficient arenes such as nitrobenzene, chlorobenzene and

Table 4.4.2. Scope of oxidative annulation of different 2-aminipyridines.[a]



144(a-i) **149a** **152**

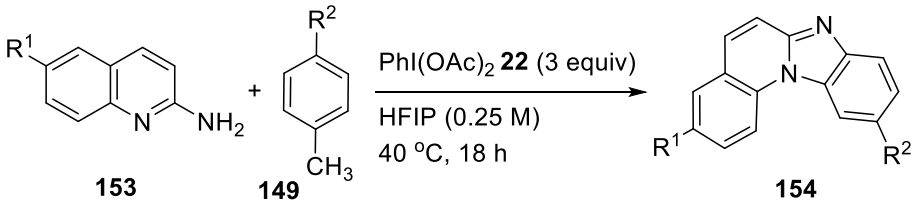
Entry	R^1	R^2	R^3	R^4	Product	Yield (%)
1	H	H	Br	H	**152a**	86
2	H	H	F	H	**152b**	59
3	H	H	Me	H	**152c**	75
4	H	Me	H	H	**152d**	72
5	H	H	H	Me	**152e**	72
6	H	Me	H	Br	**152f**	76
7	Br	H	Br	H	**152g**	57
8	H	Me	Br	Me	**152h**	87
9	OAc	H	H	Me	**152i**	80

[a] Reaction conditions: **144** (0.2 mmol), **149a** (1.0 mmol), PhI(OAc)$_2$ (0.4 mmol) in HFIP at 40 ^{o}C for 12 h. [b] **152b** (0.6 mmol) used. [b] After 12 h PhI(OAc)$_2$ (0.2 mmol) was added and the reaction continued for 24 h. [c] Obtained from product **152e** by adding additional PhI(OAc)$_2$ (0.2 mmol) and reaction time of 24 h.

fluorobenzene did not provide the desired product under optimized conditions. Phenol and benzene did not yield the desired product under develop reaction conditions.

Having established the scope of different arenes, we next investigated the scope of various 2-aminopyridine derivatives in the metal-free oxidative annulation reaction conditions (Table 4.4.2). We found that various functionalized 2-aminopyridine derivatives worked very well and provided the corresponding desired products **(152a-152i**) in good to excellent yield. We observed that the oxidative annulation was very facile with 2-aminopyridines bearing electron-donating as well as electron-withdrawing groups at various position of pyridines. Further, disubstituted 2-aminopyridines were investigated and obtained the corresponding products **152f-152g** in moderate to good yields. Disubstituted electron-withdrawing 2-aminopyridine worked well and provided the desired product **152h** in 57% yield. Trisubstituted 2-aminopyridine also provided the desired product **152g** in excellent yield. It is notable that product **152i** could be directly obtained using excess amount of PhI(OAc)$_2$ (**22**) in the one-pot reactions with product **152e**.

Table 4.4.3. Scope of oxidative annulation of 2-aminoquinolines.[a]



[a] Reaction conditions: **153** (0.2 mmol), **149** (1.0 mmol), PhI(OAc)$_2$ (0.6 mmol was added in 3 portions every 6 h) in HFIP (0.25 M) at 40 °C for 18 h.

Later, we found interesting demethylated benzo[4,5]imidazo[1,2-*a*]quinolinee derivative formation while 2-aminoquinoline (**153a**) was used instead of 2-aminopyridine (**144a**) with *para*-xylene (Table 4.4.3). Afterwards, we were interested to expand the scope of demethylation of arene for the demonstration of biologically relevant benzo[4,5]imidazo[1,2-*a*]quinolinee scaffolds. In this context, 2-aminoquinoline and *para*-xylene (**149a**) were subjected to our optimized reaction conditions and obtained the corresponding product **154a**

in 60% yield. Then, we examined the generality of this unprecedented oxidative annulation under developed reaction conditions. To our delight, 4-iodotoluene also provided the desired annulation product **154b** in 45% yield. 6-Fluro-2-aminoquinoline worked well under developed conditions and provided the desired product **154c** in 57% yield.

4.5 Determination of the Regioisomers

4.5 1-D NOE Experiments for Product 151i

NOE experiment was carried out for product **151i** (Figure 3.2) to identify regioisomer. Upon irradiation of proton $\mathbf{H^a}$ which shows the correlation with proton $\mathbf{H^b}$ and $\mathbf{Me^a}$ but there is no correlation between $\mathbf{H^a}$ with proton $\mathbf{H^c}$. Upon irradiation of proton $\mathbf{H^c}$ which shows correlation with proton $\mathbf{H^d}$ but there is no correlation with $\mathbf{H^b}$. NOE experimental result suggested that **Et** group in 6th position of product **151i**.

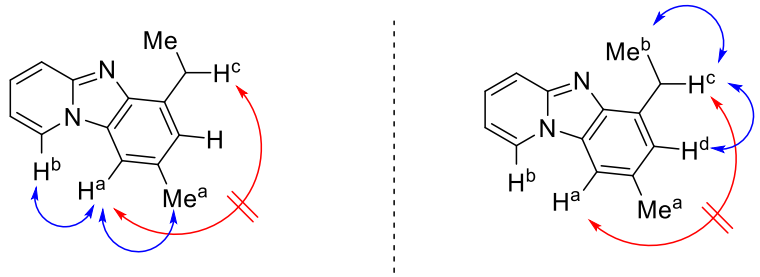
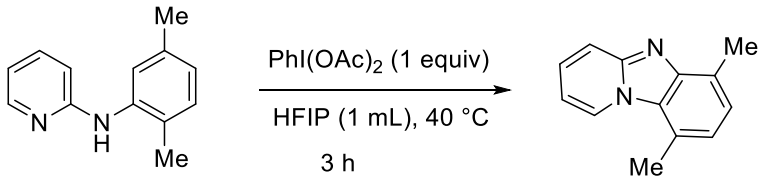


Figure 4.1. Identification of regioisomer of product **151i** by NOE experiments.

4.6 Studies on Reaction Mechanism

Further, we performed several experimental studies to gain insight into the reaction mechanism. We thought that reaction underwent through *N*-arylpyridine intermediate. According to our hypothesis, we have prepared the probable intermediates and conducted the control experiments in our standard protocol.

4.6.1 Reaction with Probable Intermediate 155



155 95% **151a**

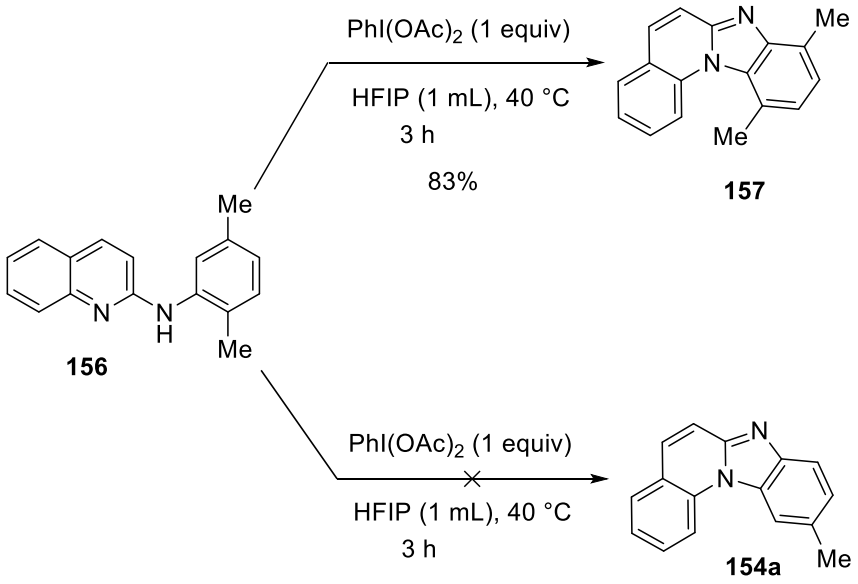
Scheme 4.2. Control experiment with the intermediate **155**

The intermediate **155** was investigated under standard protocol for oxidative annulation. We found that the intermediate **155** provided the desired product **151a** in 95% yield (Scheme 4.2).

This result suggested that the reaction of 2-aminopyridine (**144a**) underwent *via* the intermediate **155**.

4.6.2 Reaction with Probable Intermediate 156

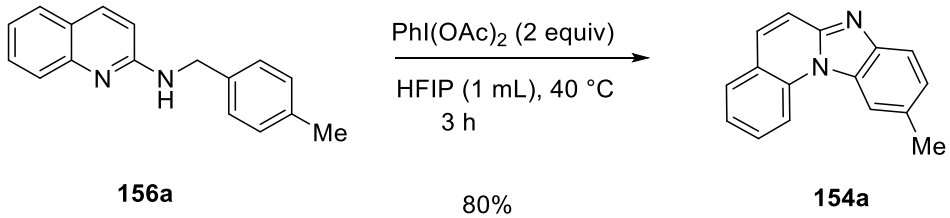
Later, we thought that annulation of 2-aminoquinoline occurred similar type of 2-aminopyridine intermediate. Afterwards, we tested our standard protocol with probable intermediate **156** (Scheme 4.3). We obtained product **157** instead of product **154a** with excellent yield under standard reaction conditions.



Scheme 4.3. Control experiment with the intermediate **156**.

After this experiment, we were confirmed that the reaction of 2-aminoquinoline did not undergo through intermediate **156**. From this experiment, we hypothesized that reaction underwent *via* benzylamine intermediate.

4.6.3. Reaction with Probable Intermediate 156a

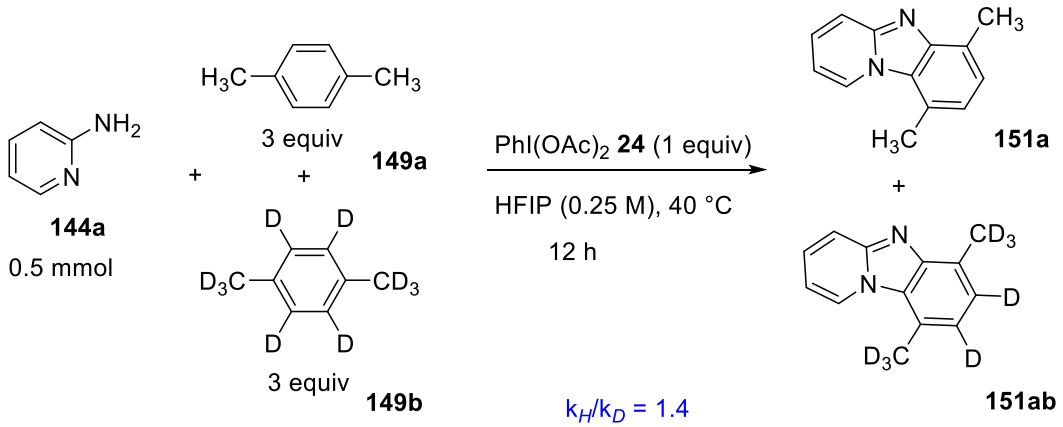


Scheme 4.4. Control experiment with the intermediate **156a**.

Additionally, we performed control experiment with benzylamine intermediate **156a** under optimized reaction conditions and obtained the desired product **154a** in 80% yield (Scheme 4.4). This result suggested that the annulation reaction of 2-aminoquinoline underwent through benzylamine intermediate.

4.6.4 Kinetic Isotope Effect Study of 2-Aminopyridine[159]

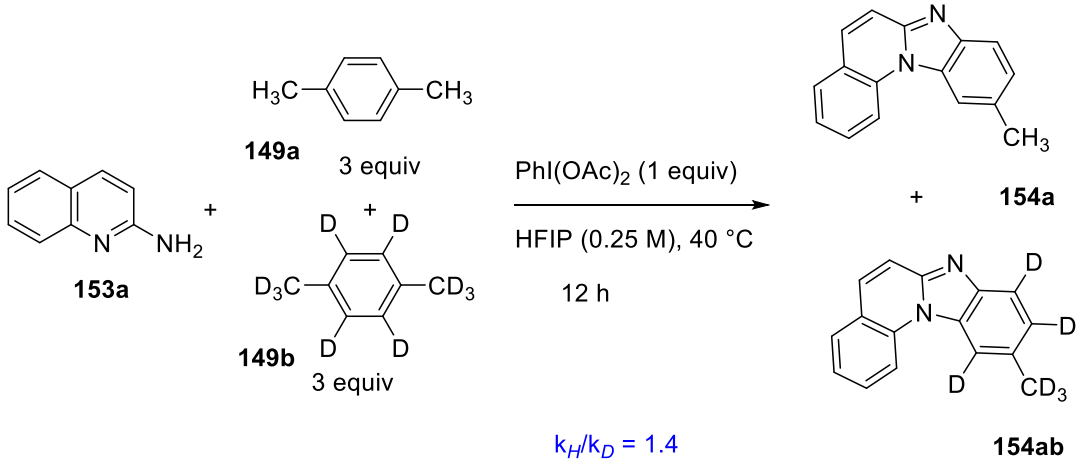
After intermediate studies, we conducted a kinetic isotope effect experiment of *p*-xylene (**149a**) and deuterated *p*-xylene (**149b**) with 2-aminopyridine (**144a**) under our optimal reaction conditions (Scheme 4.5). We observed small kinetic isotope effect (k_H/K_D = 1.4). This result suggested that the abstracting of hydrogen is not rate-limiting step in the oxidative annulation reaction.



Scheme 4.5. Kinetic study of *p*-xylene (**149a**) and deuterated *p*-xylene (**149b**).

4.6.5 Kinetic Isotope Effect Study of 2-Aminoquinoline

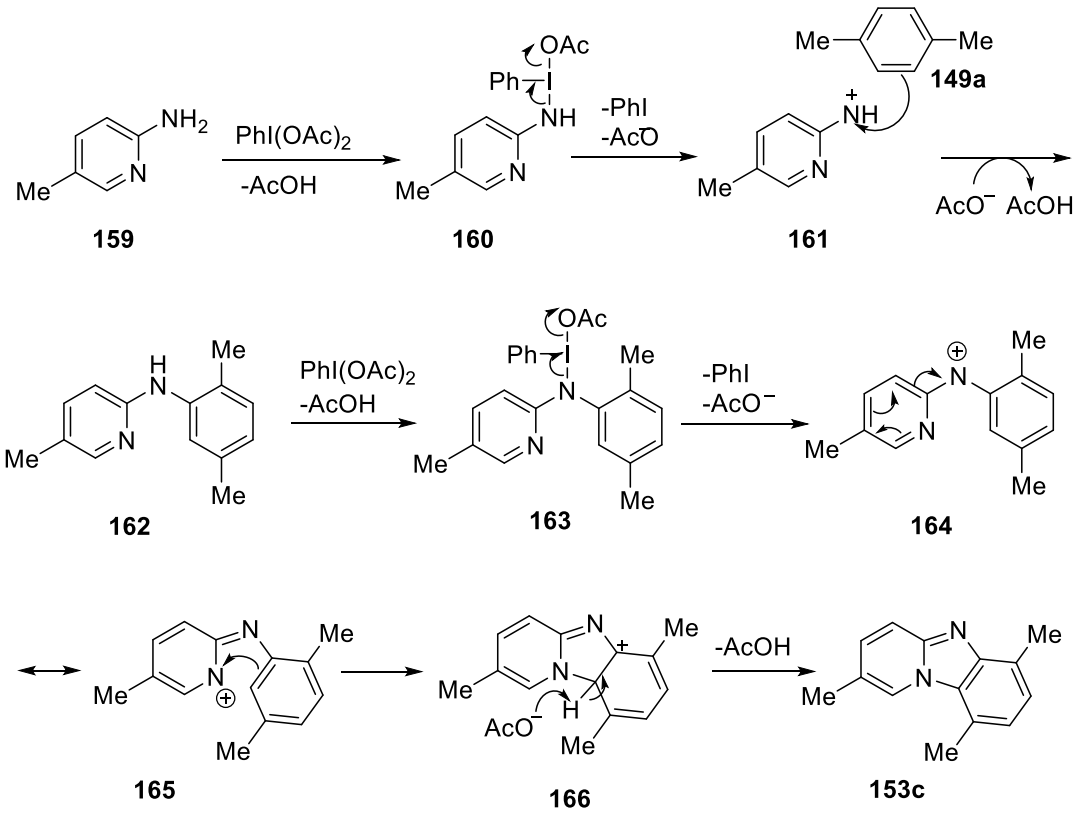
Further, we set up a kinetic isotope effect experiment of 2-aminoquinoline (**153a**) with *p*-xylene (**149a**) and deuterated *p*-xylene (**149b**) and obtained kinetic isotope effect equal to 1.4 (Scheme 4.6). This result suggested that the hydrogen abstraction of *p*-xylene is not rate-limiting step.



Scheme 4.6. Kinetic study of *p*-xylene (**149a**) and deuterated *p*-xylene (**149b**).

4.7 Mechanism

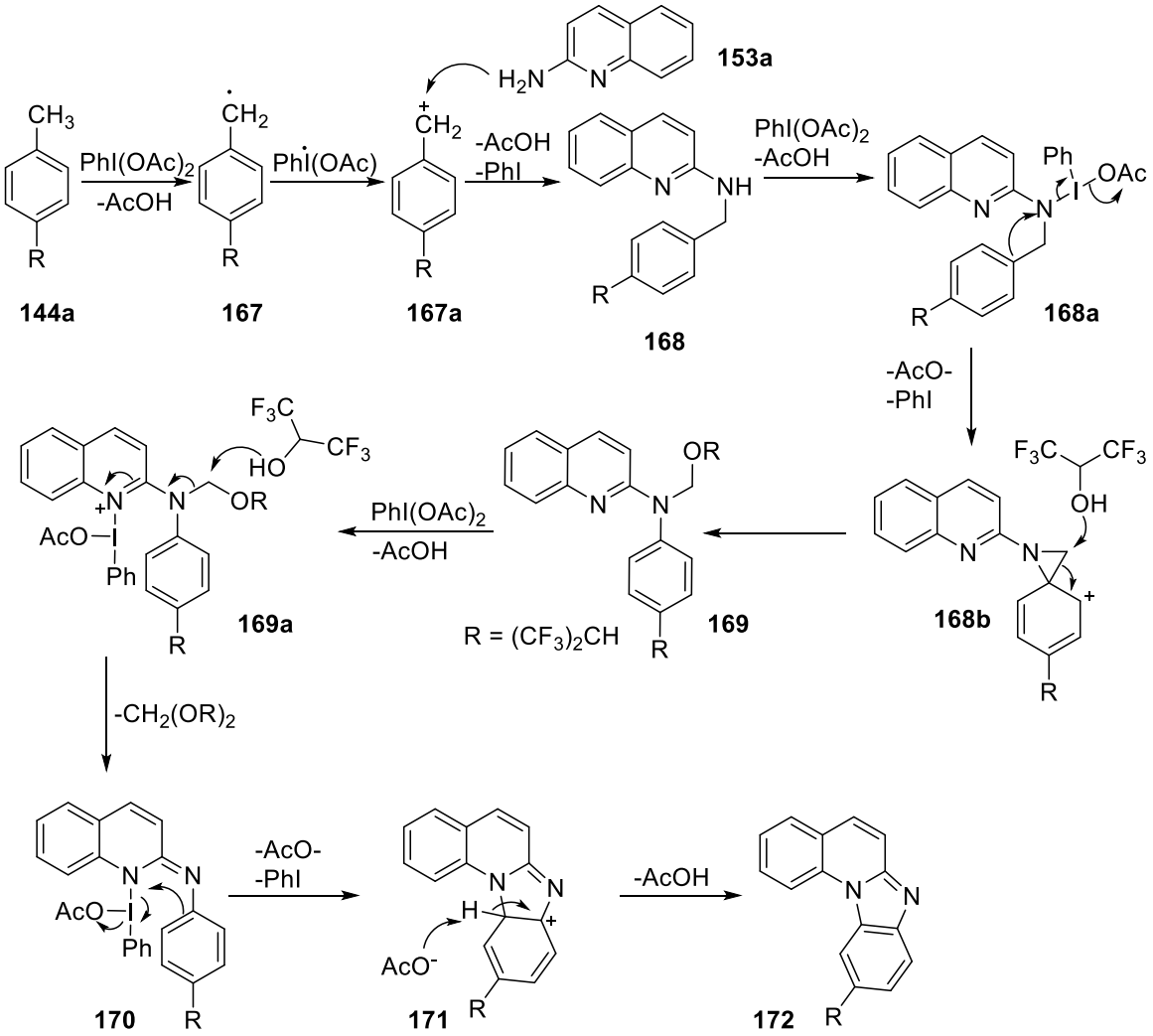
Based on our experimental studies and literatures reports, a plausible mechanism for oxidative annulation of 2-aminopyridine derivative with *p*-xylene (**149a**) has showed in Scheme 4.7.



Scheme 4.7. Proposed mechanism for 2-aminopyridine.

The intermediate **160** was formed after reacting with PhI(OAc)$_2$ (**22)** and 2-aminopyridine derivative (**159**) *via* ligand exchange of acetate. Then, the intermediate (**160**) led to generate the nitrenium ion (**161**) *via* reductive elimination of the intermediate **160** which subsequently trapped by arene (**149a**) and provided *N*-arylated-2-aminopyridine **162**. Following oxidation of the intermediate **162** with one equivalent of PhI(OAc)$_2$ (**22**) produced nitrenium ion **164**. The intermediate **164** could be stabilized *via* resonance which generated the more stable ion **165**. The intermediate **165** readily underwent intramolecular cyclization to form intermediated **166**. Finally, aromatization of intermediate **166** followed by hydride abstraction in the presence of acetate anion provided the annulated product **152c**.

In the case of 2-aminoquinoline (**153a**), initially the intermediate **167** was generate by the oxidation of methyl group of the **144a** through successive single-electron transfer from PhI(OAc)$_2$ (**22**) to generate the benzylic carbocation **167a**.[84] The carbo cation was readily attacked by 2-aminoquinoline (**153a**) to form the intermediate **168 (**Scheme 4.8). Then, the



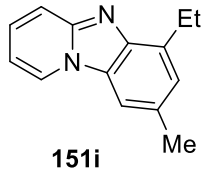
Scheme 4.8. Proposed mechanism for 2-aminoquinoline.

intermediate **168a** was formed by reacting with one equivalent of PhI(OAc)$_2$ (**22**), which underwent oxidative degradation through an *ipso*-attack to form the cationic species **168b**. The tertiary amine intermediate **169** was generated by the aziridine ring opening through attacking of HFIP molecules. Afterwards, attacks of HFIP lead to cleavage of the carbon-nitrogen bond of the intermediate **169a** which represents the formal loss of a methyl group from the arene substrate. This step initiates the intramolecular cyclization to form the cationin species **171**, which rearomatizes to provide the final product **172**.

4.8 Identification of Biological Activity of Pyrido[1,2-*a*]benzimidazole Derivatives

According to our plan, we synthesized compound libraries of pyrido[1,2-*a*]benzimidazole derivatives. Afterwards, we submitted all compound to COMAS (Compound Management and Screening Centre) in Dortmund to find the biological activity. Several cell-based assays such as hedgehog signaling pathway and Wnt signaling pathway and autophagy were tested.

After screening different assays, compounds **151i** inhibited the hedgehog signaling pathway in the low micro molar range (Figure 4.8).



151i

IC_{50} [µM] = 9.15±0.59
Viability [µM] = inactive

Figure 4.8. Results of hedgehog signaling pathway.

Chapter 5

Hypervalent Iodine (III) Mediated Oxidative Amination of Heteroaromatic Amines with Arenes

(This part already published: S. Manna[#], P. O. Serebrennikova[#], I. A. Utepova, A. P. Antonchick, O. N. Chupakhin, *Org. Lett.* **2015**, *17*, 4588-4591)

[#] Both authors contributed equally

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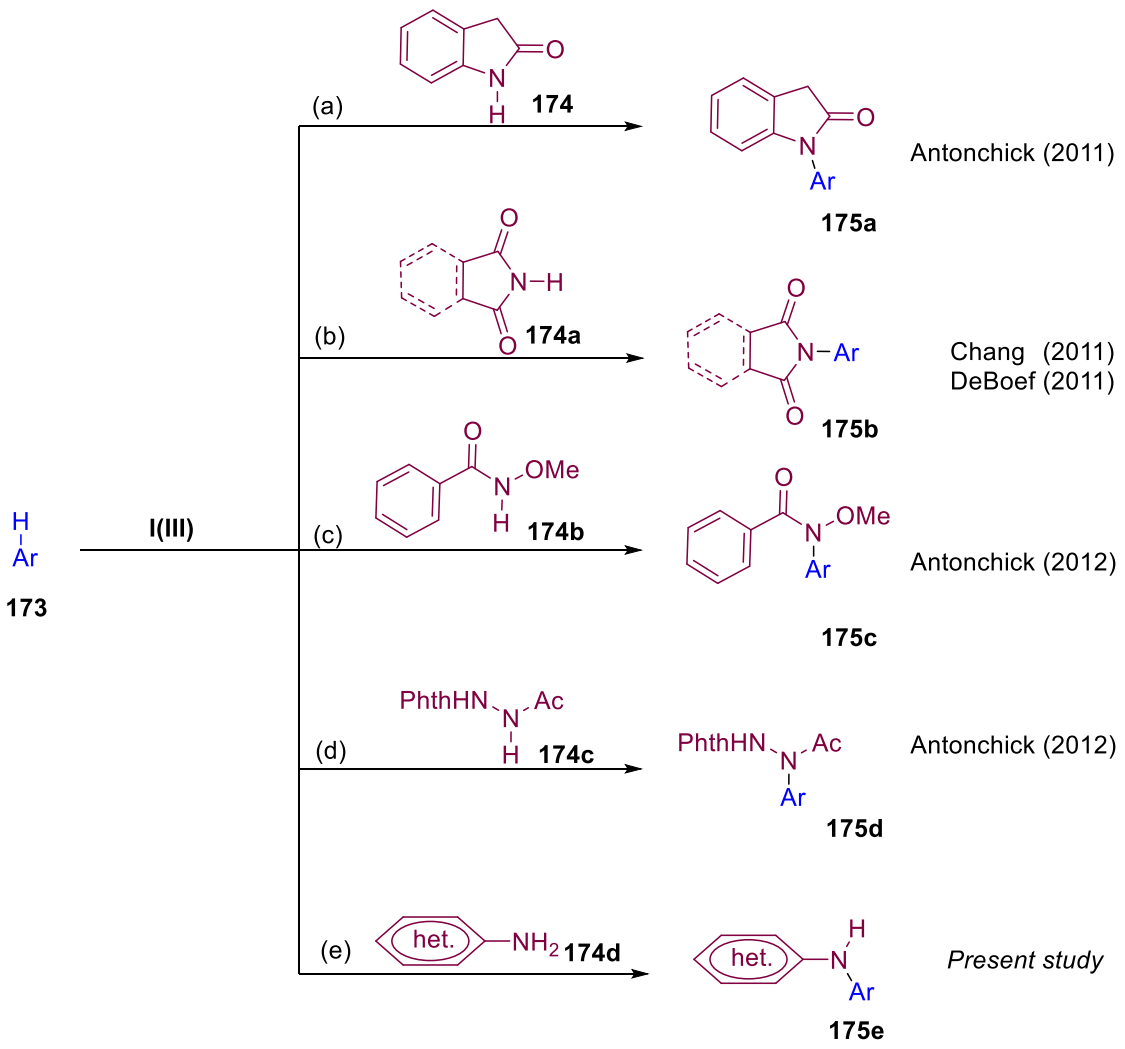
5.1 Introduction

Metal-free carbon-nitrogen (C–N) bond formation is highly attractive method from the atom-economic point of view, least amount of chemical waste and sustainable green process.[160-161] In the last few decades, hypervalent iodine (III) reagents have found very important roles in organic synthesis. In this context, hypervalent iodine (III) mediated C–H bond amination is becoming an attractive field because of many advantages such as the simplicity of this method and efficiency. Nevertheless, hypervalent iodine (III) mediated oxidative amination has emerged as a prime topic in organic chemistry for the construction of C–N bond without prefunctionalized building block. *N*-Arylated heteroaryl amines represents in many natural products and biologically active drug molecules.[77, 162-164] Despite their importance in organic synthesis, the discovery of a new method for the practically valuable *N*-aryled heteroaryl amines synthesis with non-prefunctionalized arenes under metal-free conditions would be highly attractive method.



Scheme 5.1. Oxidative amination of arene.

Reported synthetic routes to *N*-aryl amines require harsh reaction conditions and higher temperature.[165-167] Recently, several attractive methods to *N*-arylamines synthesis employing non-prefunctionalized arenes were developed using protected amines.[78, 83, 168] Antonchik and co-workers disclosed hypervalent (III) mediated oxidative aminations of simple arenes [Scheme 5.1, (a), (c) and (d)].[79, 90, 169-170] Very recently, Chang and Deboef group reported hypervalent iodine (III) mediated amination of simple arene with protected amine [Scheme 5.1, (b)].[83-84] During our studies on metal-free intermolecular amination of 2-aminopyridine with simple arene employing hypervalent iodine (III) reagents for the synthesis of pyridobenzimidazoles, we envisaged that development of oxidative amination of heteroarylamines with non-prefunctionalized arenes would be highly attractive method. Animation of heteroarylamines with unactivated arene has never been investigated. Therefore, we were interested in the development of a novel method for the *N*-arylated heteroaromatic amines synthesis with simple arenes under metal-free conditions.

5.2. Results and Discussion

5.3. Studies on the Optimization of Reaction Conditions

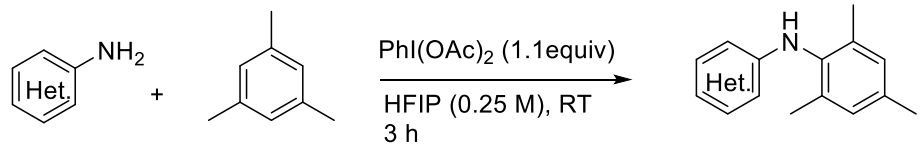
We began our studies by the investigation of oxidative amination of 2-aminopyridine (**144a**) with mesitylene (**177a**) in the presence of $PhI(OAc)_2$ (**22**) as oxidant in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at room temperature and the desired product was obtained in 86% yield. Afterwards, Ms. Polina O. Serebrennikova optimized the reaction conditions along with me. Having fully optimization reaction conditions in hand, we next explored the substrate scope with various 3-aminopyridine derivatives having differently functional groups with mesitylene (**177a**). Part of this project was included in this thesis.

5.4 Substrate Scope of $PhI(OAc)_2$ Mediated Oxidative Amination

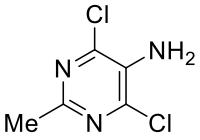
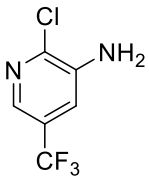
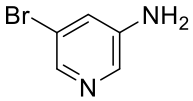
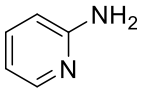
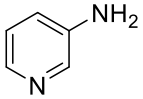
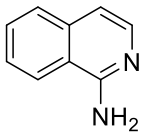
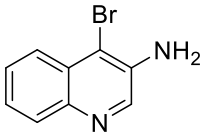
Having optimized reaction conditions in hand, we next explored the substrate scope with various pyridine derivatives with mesitylene (**177a**). We were pleased to find out that various heteroaromatic amine derivatives could be transferred into the oxidative aminated products in moderate to good yields (Table 5.4.1). Electron-withdrawing groups onto the heterocycles were well tolerated and provided the corresponding product **178a**-**178c** in excellent yield. Interestingly, highly substituted pyrimidine derivative could be efficiently converted into the corresponding desired product **178a** in 93% yield. Afterwards, various substituted 3-aminopyridine were tested and obtained excellent yield. It was noteworthy that 1-

aminoquinoline (**176e**) and 2-aminoquinoline (**176f**) also gave the corresponding products **178f** and **178g** in 48% and 85% yield.

Table 5.4.1. Scope of oxidative aminations.[a]



176 **177** **178**

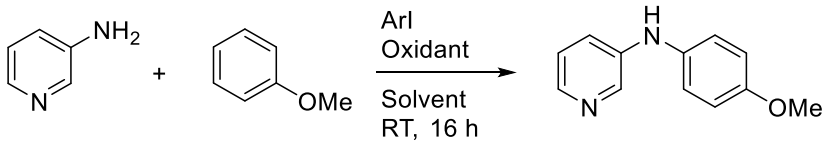
Entry	Ar-NH$_2$		Product	Yield (%)
1		**176a**	**178a**	93
2		**176b**	**178b**	94
3[b]		**176c**	**178c**	89
4		**144a**	**178d**	86
5		**176d**	**178e**	97
6		**176e**	**178f**	48
7		**176f**	**178g**	85

[a] Reaction conditions: **176** (0.25 mmol), mesitylene **177** (2.5 mmol), PhI(OAc)$_2$ (1.1 equiv) in HFIP (0.25 M).
[b] Reaction was carried out at 0 ˚C.

5.5 Organocatalytic Oxidative Amination

Having motivation of $PhI(OAc)_2$ (**22**) mediated oxidative amination of heteroaromatic amine derivatives with simple arenes, we were interested to develop organocatalytic oxidative amination of nonfunctionalized arenes to minimize the least amount of side product. Afterwards, we initiated the optimization studies between 3-aminopyridine (**176d**) and anisole (**177a**) with a catalytic amount of iodobenzene (**138**) in combination with peracetic acid as oxidant (Table 5.5.1). We found that catalytic amount of iodobenzene (**138**) was effective in this transformation and provided the desired product **178a** in 45% yield. After screening of several oxidants, solvents and catalysts for the *N*-arylated heteroaromatic amines synthesis, finally we found that peracetic acid was to be the best oxidant for oxidative amination and provided the desired product **178a** in 60% yield.

Table 5.5.1. Optimization of oxidative amination reaction conditions.[a]



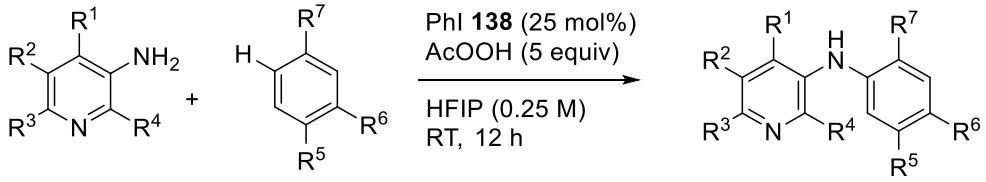
176d **177a** **178a**

Entry	Solvent	ArI (mol%)	Oxidant (equiv)	Yield (%)
1	HFIP	**138** (25)	AcOOH (3)	45
2	HFIP	**138** (25)	AcOOH (5)	60
3	HFIP	**138e** (10)	AcOOH (3)	30
4	HFIP	**138** (25)	*m*-CPBA (2)	45
5	DCE	**138** (25)	AcOOH (5)	n.d.
6	DCE	**138e** (10)	AcOOH (2)	n.d.
7	HFIP	-	$PhI(OAc)_2$ (2)	56
8	$CHCl_3$	-	$PhI(OAc)_2$ (2)	trace
9	HFIP	-	$PhI(OCOCF_3)_2$ (2)	n.d.
10	DCE	-	$PhI(OCOCF_3)_2$ (2)	n.d.

[a] Reaction conditions: **176d** (0.25 mmol), arene **177a** (2.5 mmol), ArI (x mol%), AcOOH (y equiv), added portion wise in 6 h) in HFIP (0.25 M). DCE = 1,2-Dichloroethane. n.d. = not detected.

We did not obtain our target product **178a** while $PhI(OCOCF_3)_2$ (**23**) was used for optimization. To our delight, HFIP was found considerably better solvent to give in 60% yield of the desired product **178a**. The aminated product **178a** was not obtained in $CHCl_3$ or DCE as a solvent.

Table 5.5.2. Scope of oxidative aminations.[a]



176 **177(a-e)** **180**

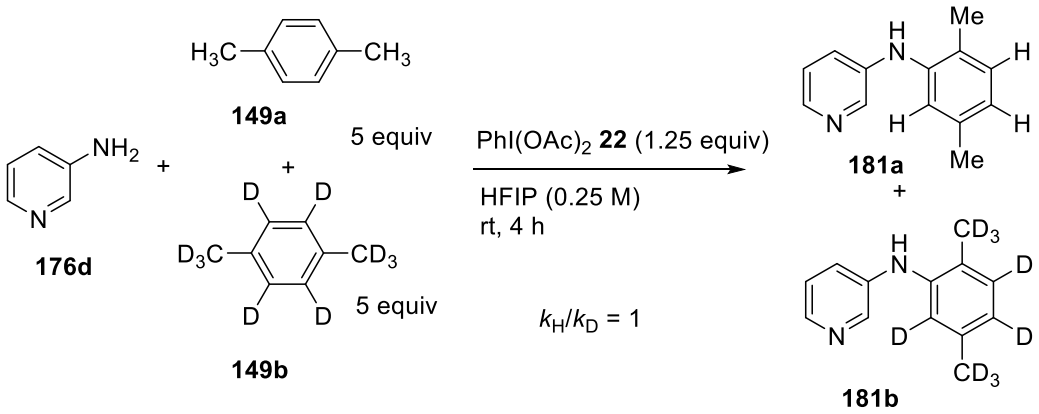
Entry	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Product	Yield (%)
1	H	H	H	H	H	OMe	H	**180a**	60
2	Cl	H	H	Cl	H	OMe	H	**180b**	58
3	H	CF_3	H	Cl	H	OMe	H	**180c**	65
4	H	Br	H	H	H	OMe	H	**180d**	54
5	Me	H	H	H	Me	H	Me	**180e**	75
6	Cl	H	H	Cl	Me	H	Me	**180f**	78
7	H	H	H	H	H	H	OH	**180g**	n.d.
8	H	H	H	H	H	H	NH_2	**180h**	n.d.
9	H	H	H	H	H	H	Cl	**180i**	n.d.

[a] Reaction conditions: **176** (0.25 mmol), arene **177** (2.5 mmol), PhI (25 mol%), AcOOH (5 equiv, added portion wise in 6 h) in HFIP (0.25 M). n.d. = not detected.

Pleasingly, we found that a wide array of 3-aminopyridine derivatives were well tolerated under organocatalytic conditions and provided the corresponding desired products in moderates to good yields (Table 5.5.2). Various electron-withdrawing groups such as chloro, bromo, and trifluoromethyl onto the pyridines were able to yield the corresponding desired products **180b-180d** and **180f**. Electron-donating group onto the pyridine also worked well and delivered the desired product **180e** in 75% yield. Electron-withdrawing arene such as chlorobenzene as well as electron-donating arene such as phenol and aniline were not tolerated under organocatalytic conditions.

5.6 Kinetic Isotope Effect (KIE) Study

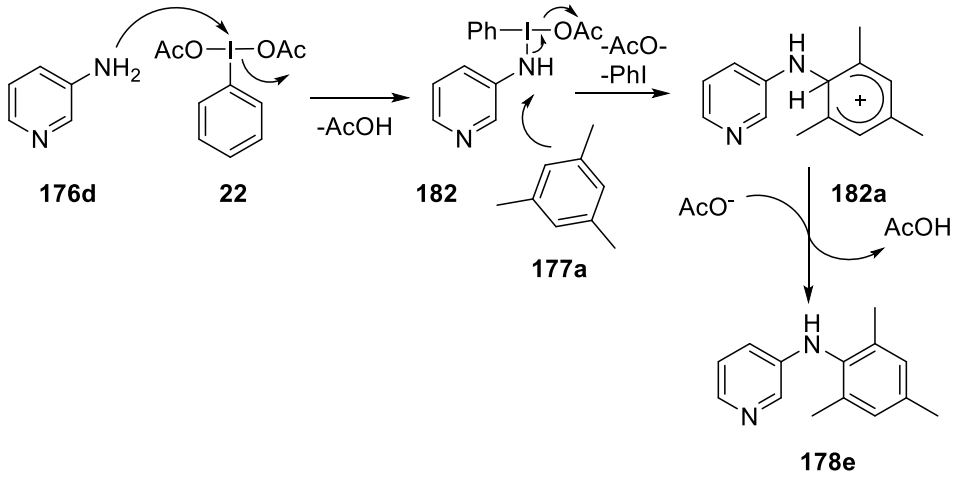
In addition, we conducted kinetic isotope effect (KIE) experiment between *p*-xylene (**149a**) and deuterated *p*-xylene (**149b**) with 3-aminopyridine (**176d**) under optimized reaction conditions and obtained kinetic isotope effect equal to 1 ($k_H/k_D \approx 1$). This result suggested that the hydrogen abstraction from arene is not rate-determine step (Scheme 5.2).



Scheme 5.2. Kinetic isotope effect (KIE) experiment.

5.7 Mechanism

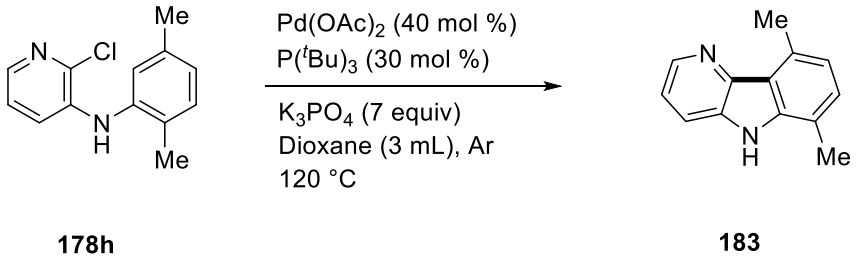
On the basis of our experimental studies, a plausible mechanism has been described in the Scheme 5.3. The intermediate **182** could be obtained after reacting 3-aminopyridine (**176d**) with hypervalent iodine (III) reagent (**22**) *via* ligand exchange. After nucleophilic attacks of



Scheme 5.3. Proposed mechanism for oxidative amination.

mesitylene (**177a**) to the intermediate **182** which produced the intermediate **182a**. Iodobenzene (**138**) and acetate anion was generated as a side product after reductive elimination of the intermediated **182**. Afterward, rearomatization of intermediate **182a** in the presence of acetate anion and provided the desired product **178e**.

5.8 Synthesis of Carboline Scaffold[171]



178h **183**

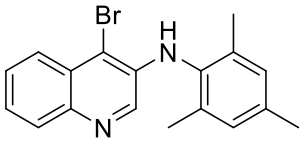
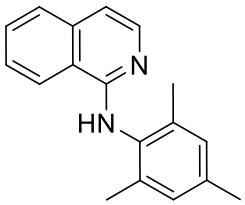
Scheme 5.4 Synthesis of Carboline.

We were interested in the synthesis of the important carboline scaffold from the *N*-arylated heteroaromatic amine. Palladium catalyzed C–H activation was applied in the synthesis of carboline derivative (**183)**. The desired product **183** was obtained in 53% yield from *N*-arylated heteroaromatic amine **178h**.

5.9 Identification of Biological Activity of *N*-Arylated Heteroaromatic Amines

According to our plan, we synthesized compound libraries of *N*-arylated heteroaromatic amines. Afterwards, we submitted all compound to COMAS (Compound Management and Screening Centre) in Dortmund to find the biological activity. Several cell-based assays such as hedgehog signaling pathway and Wnt signaling pathway and autophagy were tested. After screening different assays, compounds **178f** inhibited the hedgehog signaling pathway and compound **178d** inhibited autophagy in the low micro molar range (Table 5.9.1).

Table 5.9.1. Results of hedgehog signaling pathway and autophagy.

Entry	Product	Pathway	IC_{50} [µM]	Viability [µM]
1	 **178f**	hedgehog signaling	1.63±0.07	inactive
2	 **178d**	autophagy	0.50±0.21	inactive

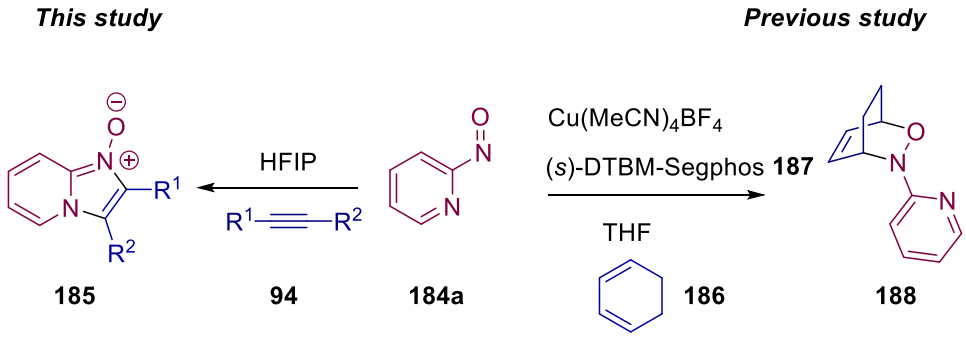
Chapter 6

Regioselective Annulation of Nitrosopyridines with Alkynes and Alkenes in the Synthesis of *N*–Oxide-imidazopyridines

(Part of this work already published: S. Manna, R. Narayan, C. Golz, C. Strohmann, A. P. Antonchick, *Chem. Commun*. **2015**, *51*, 6119- 6122)

6.1 Introduction

During the studies on oxidative annulation of 2-aminopyridines with arenes under metal-free conditions,[172] we were motivated to develop a novel oxidative annulation of 2-aminopyridines with alkynes in the synthesis of imidazopyridine derivatives. Unfortunately, we did not obtain our target product due to instability of alkyne under oxidative conditions in the presence of hypervalent iodine reagents. Despite huge importance of pyridoimidazole in biological studies, the development of an efficient method for pyridoimidazole scaffolds under metal-free conditions would be highly desirable.[173-174]



Scheme 6.1. Annulation of nitrosopyridine.

Over the past few decades, the strategy based on cycloaddition of nitrosoarene has emerged as a new route to construct heterocyclic compounds.[175-176] Transition-metal catalyst has played a leading role in these fields for the transformation of cyclic compounds. Recently, the groups of Yamato and Studer disclosed nitrosopyridine[47]as a dienophile for nitroso Diels-Alder (NDA) reactions employing copper catalyst.[48] Recently, Liu and co-workers independently demonstrated gold-catalyzed [3+3] cycloaddition of nitrosoarenes with alkenyldiazo esters.[177] Arguably, the annulation of nitrosoarene require lower temperature and transition metal catalyst. However, the annulation of nitrosopyridine with various alkynes under metal-free conditions for the synthesis of pyridoimidazole has never been investigated. Therefore, a mild and efficient metal-free condition for the synthesis of pyridoimidazole scaffolds is highly demanded.

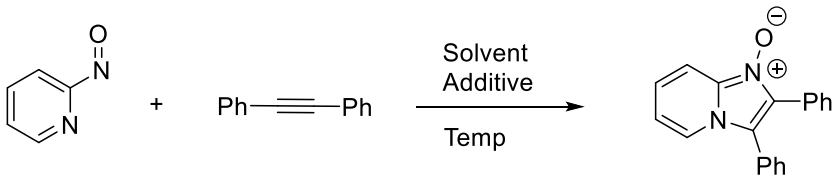
6.2 Results and Discussion

6.3 Studies on the Optimization of Reaction Conditions

We initiated our investigation with 2-nitrosopyridine (**184a**) and diphenylacetylene (**134a**) as a model substrate to explore annulation in acetonitrile without oxidant and catalyst (Table 6.3.1). Initially, we obtained our desired product **189a** in 20% yield. Encouraged by the initial

result, next various solvents were screened for the annulation reaction. We observed that acetonitrile, dichloromethane or chloroform were less effective to produce annulated product

Table 6.3.1. Optimization of metal-free annulation reaction conditions.[a]



184a **134a** **189a**

Entry	Solvent (1 mL)	Additive (equiv)	Time (h)	Yield (%)
1	MeCN	-	24	20
2	CH_2Cl_2	-	24	45
3	$CHCl_3$	-	12	65
4	H_2O	-	12	n.d.
5	MeOH	-	12	n.d.
6	CF_3CH_2OH	-	24	40
7	HFIP	-	12	86
8	EtOAc	-	12	n.d.
9	EtOH	-	12	n.d.
10	PhH	-	12	n.d.
11[b]	HFIP	-	12	70
12	HFIP: CH_2Cl_2 (1:1)	CF_3CO_2H (2)	12	50
13	MeOH	CH_3CO_2H (2)	12	n.d.
14	$CHCl_3$	CF_3CO_2H (2)	12	20
15	$CHCl_3$	CF_3CO_2H (2)	12	15
16	HFIP	CF_3CO_2H (2)	12	54

[a] Reaction conditions: **184a** (0.25 mmol), **134a** (0.28 mmol) in solvent (0.25 M) at 40 °C for 12 h. [b] Reaction was carried out at ambient temperature. n.d. = not detected. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol

189a under catalyst and additive free reaction conditions. Protic solvents such as MeOH or EtOH did not provide the desired product **189a**. While reaction was performed in nonpolar solvents such as benzene or 1,2 dichloroethane (DCE), we did not obtain the corresponding product **189a**. After screening various solvents, we found that HFIP was to be the best solvent to provide (3+2) annulated product **189a** in 70% yield at room temperature. Afterward, we tested 2,2,2-trifluoroethanol (TFE) for annulation and found the reaction is less effective, resulting the desired product in 40% yield. In the presence of additive, we did not get promising yield. Finally, the changing of temperature to 40 ºC, obtained the best result in 86% yield after 12 h.

6.3.1 Structure Determination of Imidazo[1,2-*a*]pyridine 1-oxide

The structure of the imidazo[1,2-*a*]pyridine 1-oxide was confirmed by X-ray single crystal structural analysis (Figure 6.1).

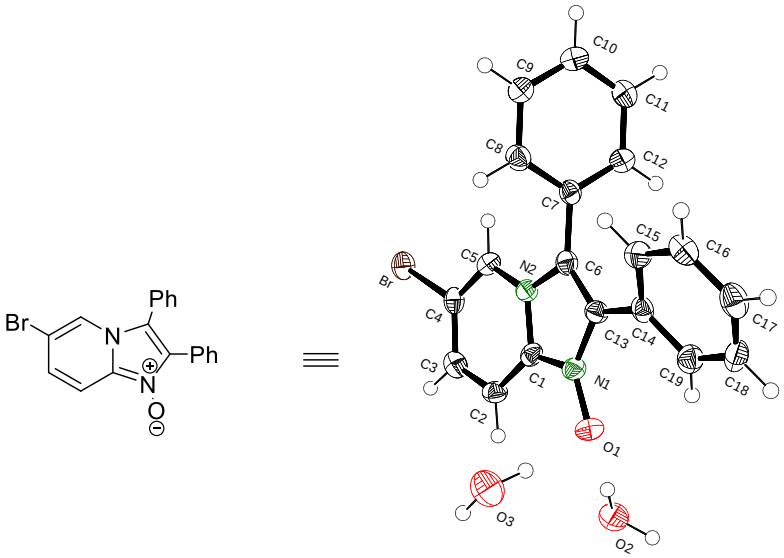


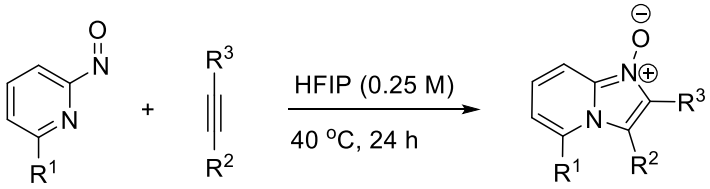
Figure 6.1. Crystal structure of product **194f**.

6.4 Scope of Annulation with Nitrosopyridines and Alkynes

With fully optimized reaction conditions in hand, we then started to explore the scope of annulation reaction with symmetrical alkynes (Table 6.4.1). Various functional groups onto the alkynes were well tolerated under optimized conditions. To our delight, the alkyne bearing electron-donating groups as well as electron-withdrawing groups were able to produce the desired products in good to excellent yields (Table 6.4.1). Reactions of nitrosopyridine with

functionalized alkynes found to be facile to deliver the desired product. Simple, *para*-substituted electron-donating alkynes such as methyl, methoxy and *tert*-butyl group onto the

Table 6.4.1. Scope of metal-free annulation of alkynes.[a]



184 **94** **189**

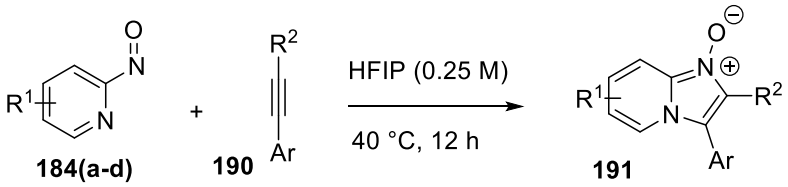
Entry	R^1	R^2	R^3	Product	Yield (%)
1	H	Ph	Ph	**189a**	86
2	H	4-^{t}BuC$_6$H$_4$	4-^{t}BuC$_6$H$_4$	**189b**	95
3	H	4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	**189c**	88
4	Me	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	**189d**	87
5[b]	H	4-CF$_3$C$_6$H$_4$	4-CF$_3$C$_6$H$_4$	**189e**	77
6[b]	Me	4-FC$_6$H$_4$	4-FC$_6$H$_4$	**189f**	91
7	H	thiophen-2-yl	thiophen-2-yl	**189g**	86
8	H	Ph	4-NO$_2$C$_6$H$_4$	**189h**	84
9	H	4-MeOC$_6$H$_4$	Ph	**189i**	85
10	Me	4-MeOC$_6$H$_4$	4-CNC$_6$H$_4$	**189j**	86

[a] Reaction conditions: **184** (0.25 mmol), **94** (0.28 mmol) in HFIP (0.25 M) at 40 ºC for 12 h. [b] The reaction was performed at 60°C.

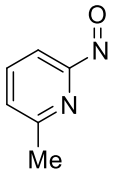
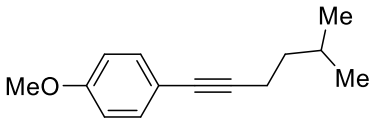
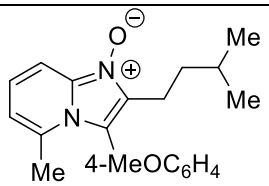
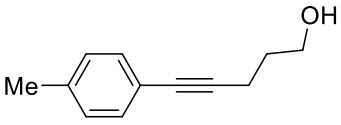
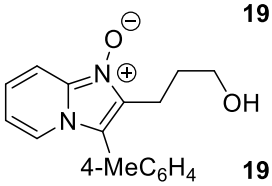
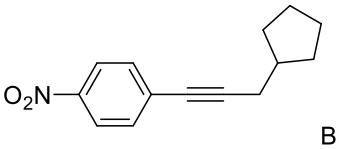
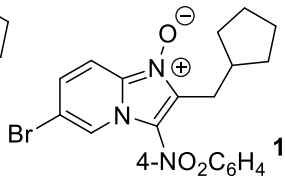
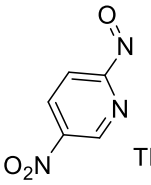
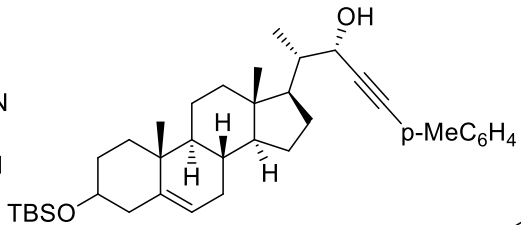
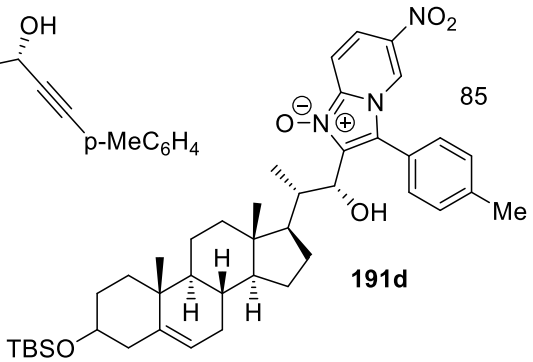
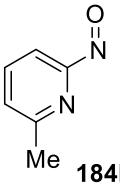
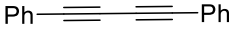
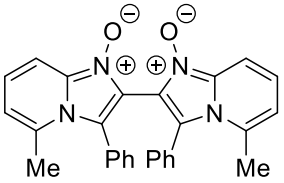
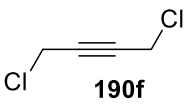
aryl part provided corresponding products **189b**-**189d** in excellent yields. To our delight, *para*-substituted electron-withdrawing alkynes such as trifluoromethyl and fluoro group also provided the desired product **189e**-**189f** in excellent yields. Notably, 1,2-di(thiophen-2-yl)ethyne reacted smoothly and delivered the corresponding product **189g** in 92% yield. Having established scope of symmetrical alkynes, we next examined the scope of unsymmetrical diphenylacetylene derivatives under optimal conditions (Table 6.4.2, entries 8-10). Pleasingly, we found that the reactions of unsymmetrical alkynes with nitrosopyridine

also were well tolerated. Pleasingly, an excellent yields were obtained when alkynes having various functional

Table 6.4.2. Scope of metal-free annulation of alkynes.[a]



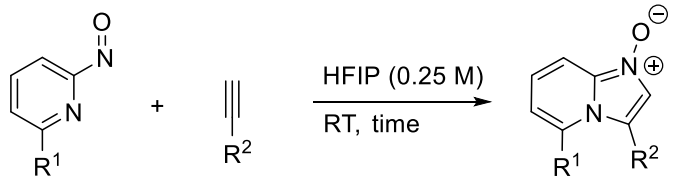
184(a-d) **190** **191**

Entry	Nitrosoarene	Alkyne	Product	Yield (%)
1	 **184b**	 **190a**	 **191a**	83
2	**184a**	 **190b**	 **191b**	53
3	**184a**	 **190c**	 **191c**	82
4	 **184c**	 **190d**	 **191d**	85
5[b]	 **184b**	 **190e**	 **191e**	63
6	**184a**	 **190f**	-	n.d.

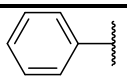
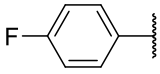
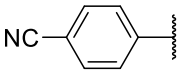
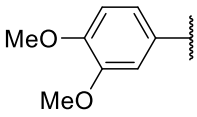
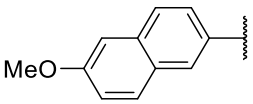
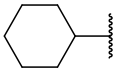
[a] Reaction conditions: **184** (0.25 mmol), **190** (0.28 mmol) in HFIP (0.25 M) at 40 ºC for 12 h. [b] 2-Nitroso-5-methyl-pyridine (2 equiv) was used, yield is given for a mixture of di- and mono adduct with ratio 8:1. n.d. = not detected.

group such as methoxy, nitro and cyano at the *para*-positions onto the aryl part of diphenylacetylene and provided the corresponding products **191h-191j**.Notably, one side electron-donating group and other side electron-withdrawing group at the *para*-position of unsymmetrical diphenylacetylene derivative provided regioselectively single isomer **191j** in 86% yield under standard conditions. One side attached with aliphatic chain in the arylalkynes were examined under developed reaction conditions and obtained the desired products **191k-191m** excellent yield with regioselectively single isomer (Table 6.4.2, entries 1-4). Notably, steroid-derived complex molecule **190d** was investigated under annulation conditions, and obtained the corresponding product **191d** in 85% yield. Further, conjugate bis-alkyne **190e** was employed and found to be facile to provide the desired product **191e** in 63% yield.

Table 6.4.3. Scope of metal-free annulation of various terminal alkynes.[a]



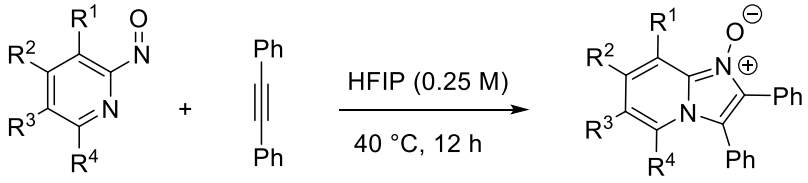
184(a-b) **63** **192**

Entry	R^1	R^2	Time (h)	Product	Yield (%)
1[b]	H	 **63a**	3	**192a**	76 (2:1)
2[b]	H	 **63b**	4	**192b**	78 (5:1)
3[b]	Me	 **63c**	5	**192c**	65 (3:1)
4	Me	 **63d**	2	**192d**	74
5	H	 **63e**	2	**192e**	87
6	H	 **63f**	12	**192f**	n.d.

[a] Reaction conditions: **184(a-b)** (0.25 mmol), **63** (0.28 mmol) in HFIP (0.25 M). [b] Major isomer is shown, and the yields were reported for mixtures. n.d. = not detected.

Having described internal alkynes, next we investigated the scope of various terminal alkynes under annulation reaction conditions (Table 6.4.3). Interestingly, we found that a wide range of functional groups onto the aryl part of terminal alkynes were tolerated and afforded the *N*–oxideimidazo[1,2-*a*]pyridine derivatives in good to excellent yield. The election-rich disubstituted phenyl acetylene derivative (**63d**) produced the corresponding product **192d** with selectively single isomer in 74% yield. The terminal alkyne of naphthalene derivative (**63e**) provided the desired product **192e** with selectively single isomer in 87% yield. Unfortunately, aliphatic terminal alkyne did not provide the desired product.

Table 6.4.4. Scope of metal-free annulation of various nitrosopyridines.[a]



193 **134a** **194**

Entry	R^1	R^2	R^3	R^4	Product	Yield (%)
1	H	Me	H	H	**194a**	67
2	H	H	Me	H	**194b**	82
3	H	H	NO_2	H	**194c**	96
4	Cl	H	CF_3	H	**194d**	64
5	Br	H	Br	H	**194e**	81
6	H	H	Br	H	**194f**	95
7	H	H	H	Me	**194g**	87

[a] Reaction conditions: **193** (0.25 mmol), **134a** (0.28 mmol) in HFIP (0.25 M) at 40 ºC for 12 h.

Later, we sought to evaluate 2-nitrosopyridine derivatives **193** for annulation with symmetrical alkynes (Table 6.4.4). We were interested to expand the scope of various nitrosopyrines with diphenylacetylene **134a**. To our gratification, various functional groups such as chloro, bromo, trifluoromethyl, methyl and nitro on the nitrosopyridine, provided the corresponding annulated products **194a-194g** in good to excellent. Nitrosopyridine bearing electron-withdrawing groups such as nitro, trifluoromethyl, chloro and bromo were well tolerated and provide annulated products **194c-194f** in excellent yield. Furthermore, electron-

rich nitrosopyridines were investigated under developed reaction conditions and obtained the corresponding products **194a-194b** and **194g** in good to excellent yields.

6.5 Determination of the Regioisomers

6.5.1 1-D NOE Experiments for Product 189i

NOE experiment was carried out for product **189i** (Figure. 6.1) to identify regioisomer. Upon irradiation of proton $\mathbf{H^a}$ which correlated with proton $\mathbf{H^b}$ and **Me** group. Upon irradiation of **Me** group which shows correlation with proton $\mathbf{H^a}$ and $\mathbf{H^d}$ and there was no correlation with proton $\mathbf{H^c}$. After irradiation of proton $\mathbf{H^b}$ which showed correlated with proton $\mathbf{H^a}$ and **OMe**. NOE experimental result suggested that 4-methoxybenzene group close to **Me** group.

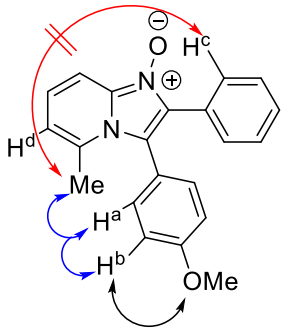


Figure 6.1. Identification regioisomer of product **189i** by NOE experiments.

6.5.2 1-D NOE Experiments for Product 191c

NOE experiment was carried out for product **191c** (Figure 6.2) to identify regioisomer. Upon irradiation of proton $\mathbf{H^a}$**,** which correlated with proton $\mathbf{H^b}$ and $\mathbf{H^c}$. There was no correlation between proton $\mathbf{H^a}$ and proton $\mathbf{H^d}$. Upon irradiation of proton $\mathbf{H^c}$ which shows correlation with proton $\mathbf{H^a}$ only but there was no correlation between $\mathbf{H^c}$ and $\mathbf{H^d}$. NOE experimental result suggested that 4-nitrobenzene group close to proton $\mathbf{H^c}$.

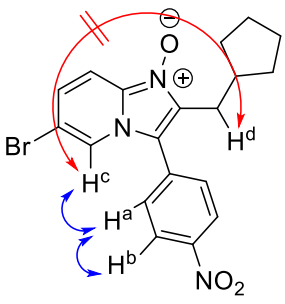
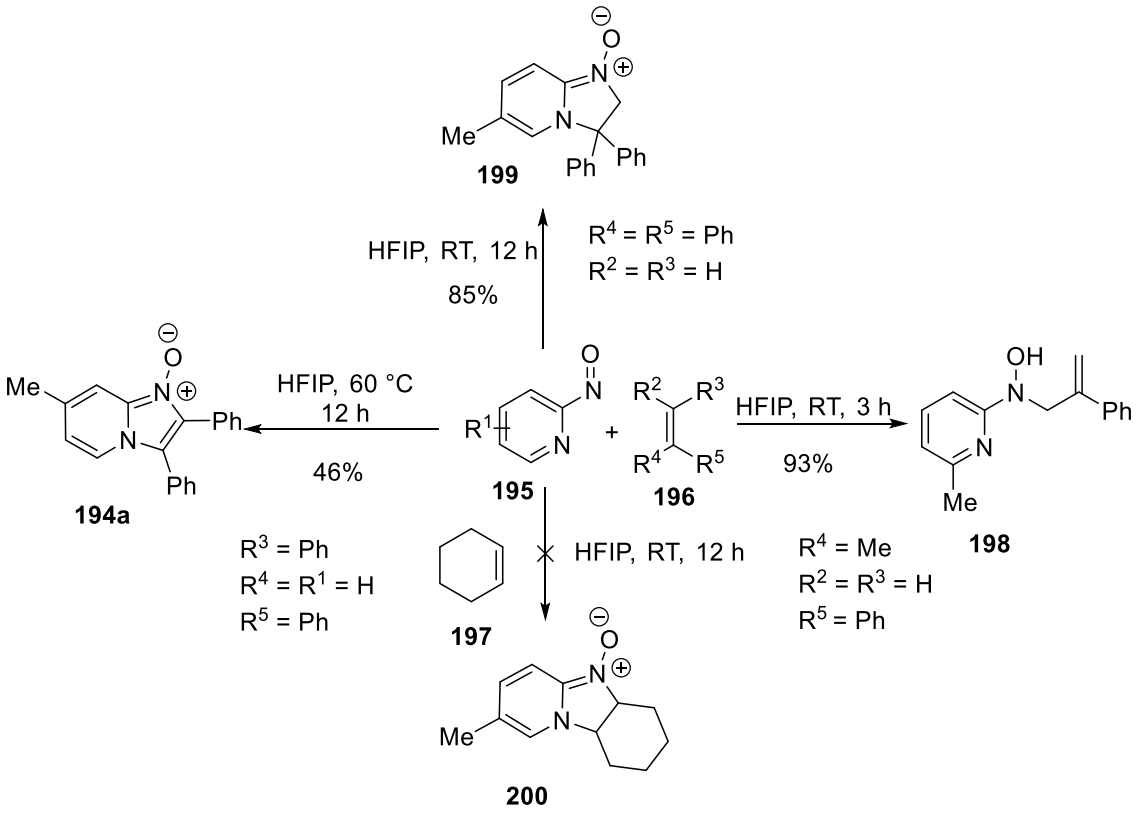


Figure 6.2. Identification regioisomer of product **191c** by NOE experiments.

6.6 Scope of Annulation with Nitrosopyridines and Alkenes

Having described the scope of alkynes, we further explored the scope of alkenes under optimal reaction conditions (Scheme 6.2). To our delight, we found that nitrosopyridine reacted with *α* methylstyrene to give the product **198** *via* ene-reaction.[178-179] Notably, the



Scheme 6.2. Reaction of nitrosopyridines with alkenes.

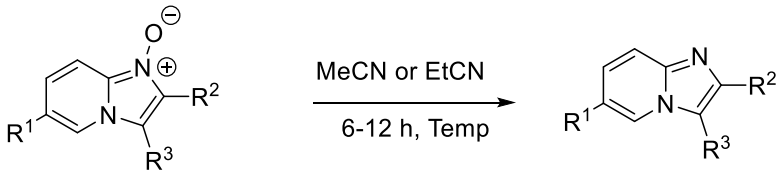
reaction between 4-methyl-6-nitrosopyridine and *cis*-stilbene, obtained product **194a** which underwent through annulation and over oxidation with most probable dissolved oxygen of air. Furthermore, α-phenylstyrene was employed for the annulation reaction with nitrosopyridine and the target product **199** was isolated in 85% yield. Unfortunately, aliphatic alkene such as cyclohexene and butene did not give the desired product under developed reaction conditions.

6.7 Scope of Deoxygenation of Imidazo[1,2-*a*]pyridine 1-oxide

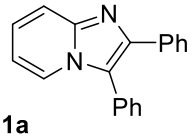
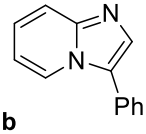
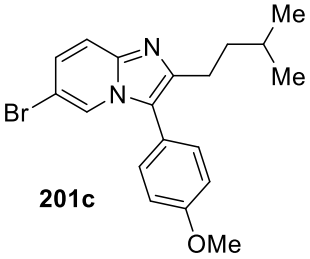
Further, we were interested to explore the cleavage of N–O bonds to obtain biologically important imidazo[1,2-*a*]pyridines scaffolds (Table 6.4.5).[180] We were delighted to find that *N*–oxides of imidazo[1,2-*a*]pyridines could be deoxygenated under heating conditions. Notably, 2,3-diphenylimidazo[1,2-*a*]pyridine could be obtained from **189a** upon heating at 125 ºC. 3-Phenylimidazo[1,2-*a*]pyridine 1-oxide **192a** was used for deoxygenation and obtained the target product **201b** in 86% yield. Alkyl-substitution at C2 position of

imidazo[1,2-*a*]pyridine 1-oxide also provided the deoxygenated product **201c** in 65% yield under heating conditions.

Table 6.4.5. Scope of deoxygenations.



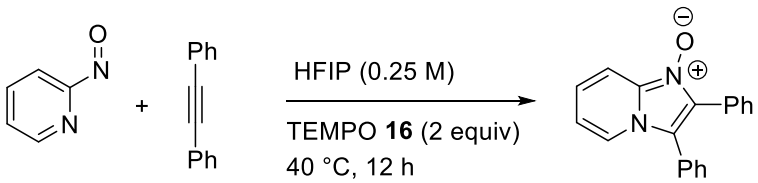
189a-191a **201**

Entry	3	Temp (°C)	Product	yield (%)
1[a]	**189a**	125	 **201a**	95
2[b]	**192a**	140	 **201b**	86
3[c]	**191a**	150	 **201c**	65

Reaction conditions: 0.25 mmol *N*–oxide-imidazopyridines in solvent (0.5 M). [a] In MeCN at 125°C for 6 h, [b] In MeCN at 140°C for 12 h. [c] In EtCN at 150°C for 12 h.

6.8 Studies on Reaction Mechanism

6.8.1 Radical Inhibition Test



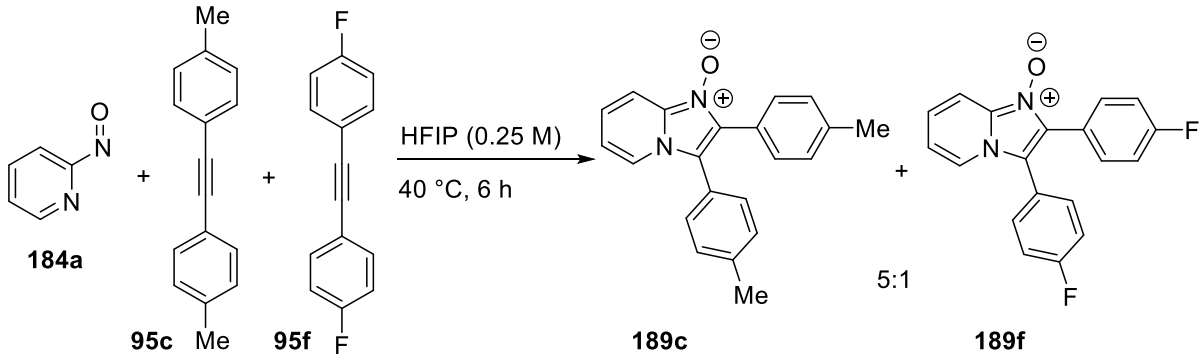
184a **134a** **189a**

Scheme 6.3. Reaction with radical scavenger.

In addition, we performed radical inhibition test with 2 equivalents of 2,2,6,6-tetramethylpiperidine 1-oxyl (**16**) under standard reaction conditions (Scheme 6.3). We

observed formation the desired product only in 40 % yield after 12 h. Unfortunately, we did not observe any TEMPO (**16**) adduct product. Hence, reaction did not undergo *via* radical mechanism.

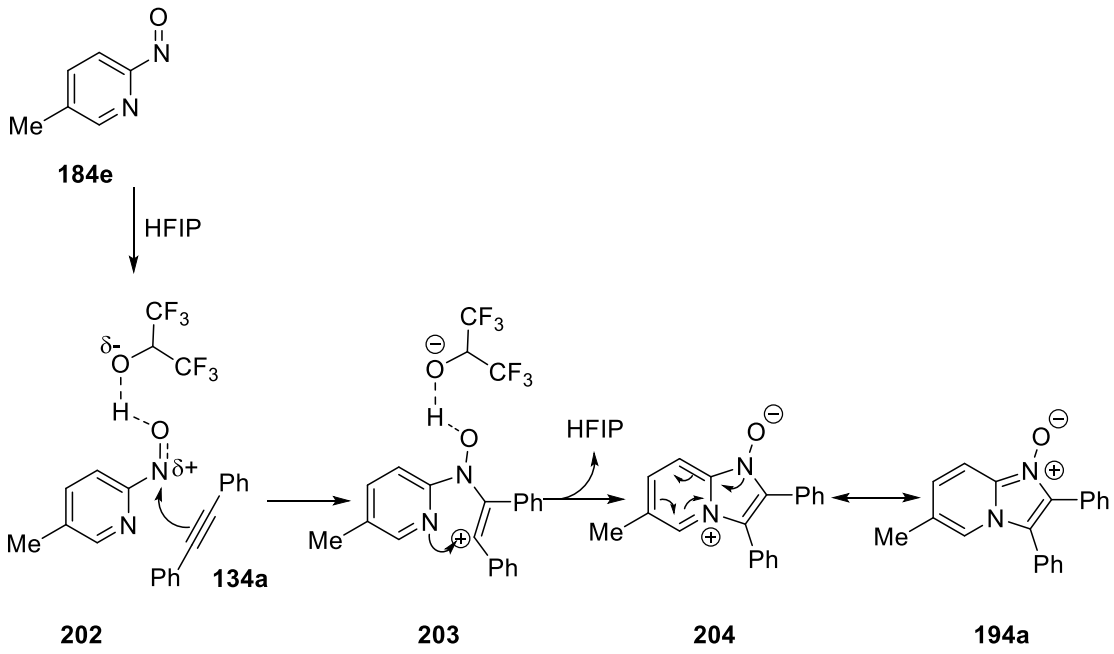
6.8.2 Competition Study



Scheme 6.4. Competition experiment.

Furthermore, a competition experiment was carried out between electron-rich alkyne **95c** and electron-deficient alkyne **95f** with nitrosopyridine (**184a**) under standard reaction conditions (Scheme 6.4). We found that reaction of the electron-rich alkyne much faster than electron-deficient alkyne. This result indicated that annulation reaction underwent through nucleophilic addition and followed by intramolecular cyclization.

6.9 Mechanism



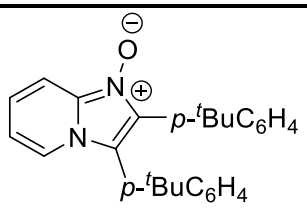
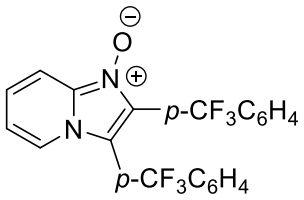
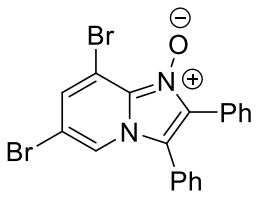
Scheme 6.5. Proposed mechanism for metal-free annulation.

A plausible mechanism for (3+2) annulation has been described in Scheme 6.5. The nitroso group of pyridine (**184e**) was activated by HFIP solvent through the hydrogen bonding and it led nitrenium ion intermediate **202** formation which was subsequently trapped by alkyn**e 134a** to form the intermediate **203**. Then the vinyl cationic species was attacked by nucleophilic nitrogen of pyridine to generate intermediate **204**. Afterwards, the rearrangement of nitrogen lone pair provided the desired produce **194a**.

6.10 Identification of Biological Activity of Imidazo[1,2-*a*]pyridine 1-oxides

According to our plan, we synthesized compound libraries of imidazo[1,2-*a*]pyridine 1-oxide derivatives. Afterwards, we submitted all compound to COMAS (Compound Management and Screening Centre) in Dortmund to find the biological activity. Several cell-based assays such as hedgehog signaling pathway and Wnt signaling pathway and autophagy were tested. After screening different assays, three compounds **189b**, **189e** and **194e** inhibited the hedgehog signaling pathway in the low micro molar range (Table 6.9.1).

Table 6.9.1. Results of hedgehog signaling pathway.

Entry	Product	IC_{50} [µM]	Viability [µM]
1	 **189b**	5.24 ± 0.39	inactive
2	 **189e**	7.93 ± 0.29	inactive
3	 **194e**	≥ 10	inactive

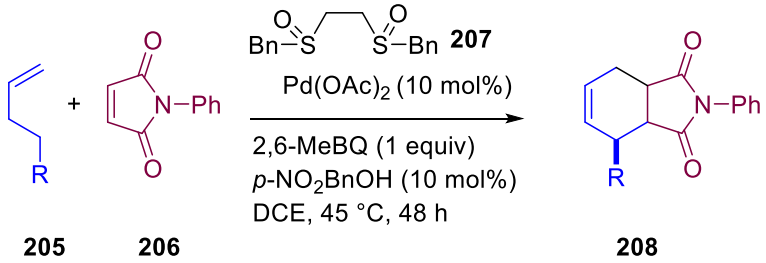
Chapter 7

Metal-Free Oxidative Dehydrogenative Diels-Alder Reaction of Alkylarenes with Electron-Deficient Alkenes

(This part already publish: S. Manna, A. P. Antonchick, *Chem. Eur. J.* **2017**, *23*, 7825-7829.)

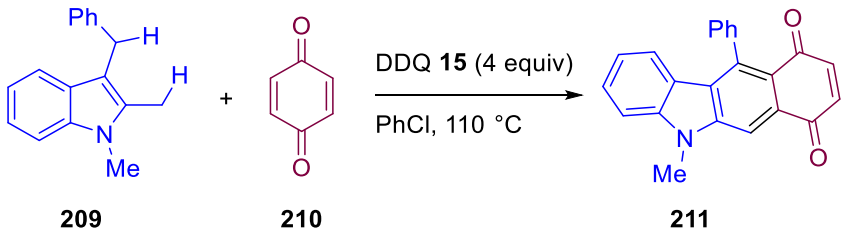
7.1 Introduction

Cross-dehydrogenative coupling (CDC) has become an attractive method due to their inherent economic and environmentally benign nature. [121, 181] In the last decades, CDC represents an efficient, atom economic and sustainable green methods for the construction of C–C bond and occupy an important space of modern chemistry.[182] Several synthetic routes to cross-dehydrogenative coupling reactions were developed under metal-free conditions.[118] Notably, oxidative CDC reaction represents state of arts in organic synthesis. In this regard, metal-free cross-dehydrogenative coupling are highly interesting method for the functionalization of C(sp^3)–H bonds.[183] Among them, metal-free CDC reactions were also applied for oxidative Diels-Alder reaction employing low cost and easy handling reagent.[184-185] Diels-Alder reactions represent one of the most fundamental, atom-economic, and efficient reactions in organic synthesis and used in many fields such as the natural products synthesis,[186] materials and biologically relevant molecules synthesis.[187] Over the last few decades, Diels-Alder reactions were developed employing diene and dienophile to obtain unsaturated carbocycles. Despite its importance in organic synthesis, development of the dehydrogenative Diels-Alder (DDA) reactions paid great attention nowadays.[122] Therefore, syntheses of carbocycles by functionalization of unactivated C–H bonds are highly interesting method to the chemists.



Scheme 7.1 Palladium catalyzed dehydrogenative Diels-Alder reactions.

Interestingly, dehydrogenative Diels-Alder reactions with electron-deficient dienophiles were first developed by the group of White[188] and Stahl[189] employing palladium catalyzed *via* -



Scheme 7.2 Metal-free dehydrogenative Diels-Alder reaction.

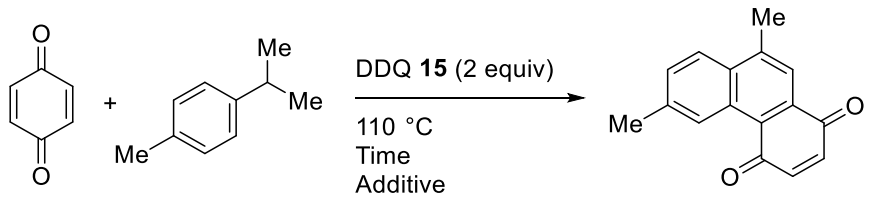
C–H bonds activation (Scheme 7.1). Very recently, metal-free dehydrogenative Diels-Alder reaction has been developed by Zhang and co-workers employing DDQ as oxidant (Scheme 7.2).[58] Similarly Yao and co-workers developed oxidative Diels-Alder reaction of 3-ethylindoles using excess amount of 1,4-benzoquinones.[190] However, this method only was applied to electron-rich indole scaffolds. It is notable that metal-free dehydrogenative Diels-Alder reaction of alkylbenzene with electron-deficient alkene has never been studied. Therefore, a mild and metal-free dehydrogenative Diels-Alder reaction of simple alkylbenzenes would be a significant advance for the synthesis of phenanthraquinone and isoindolone scaffolds.[191]

7.2 Results and Discussion

7.3 Studies on the Optimization of Reaction Conditions

To test our hypothesis, *p*-cymene (**212a**) was treated with 1,4-benzoquinone (**210a**) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (**15**) as oxidant in the presence of acetic acid in chlorobenzene as solvent at 110 °C under argon (Table 7.3.1). We obtained dehydrogenative Diels-Alder product **213a** in 42% isolated yields after 24 h. Encouraged by the initial result,

Table 7.3.1. Optimization of reaction conditions with different additives.[a]



210a **212a** **213a**

Entry	Additive (x equiv)	Solvent (2 mL)	Yield (%)
1	-	PhCl	trace
2	CH_3CO_2H (2)	PhCl	42
3	CF_3CO_2H (2)	PhCl	trace
4	4-$NO_2C_6H_4CO_2H$ (2)	PhCl	45
5	2-$FC_6H_4CO_2H$ (2)	PhCl	20
6	4-$CNC_6H_4CO_2H$ (2)	PhCl	15
7	$PhCO_2H$ (2)	PhCl	46
8	Ac_2O (2)	PhCl	38
9	Ac_2O (1.5)	PhCl	35
10	Ac_2O (3)	PhCl	22

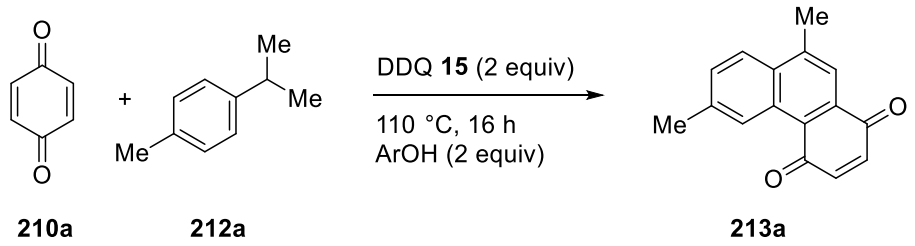
Continuation of **Table 7.3.1**			
11	Tetrafluorophthalic anhydride (1.5)	PhCl	25
12	$(CF_3CO)_2O$ (2)	PhCl	trace
13	BOP (2)	PhCl	trace
14	HFIP (5)	PhCl	30
15	DDQ (3)+ AcOH (2)	PhCl	50
16[b]	PhOH (2)	PhCl	65

[a] Reaction conditions: **210a** (1.25 mmol), **212a** (0.25 mmol), DDQ (2 equiv), additive (x equiv) in solvent (0.125 M) at 110 °C for 12-24 h under argon [b] Additive and 1,4-benzoquinone were added after 4h.

we next tested various additives for dehydrogenative Diels-Alder reaction. To our delight, various additives were examined under oxidative reaction conditions. Notably, we found that annulation reaction was proceeded very smoothly. After the screening various additives, we did not observe the improvement of the yield (Table 7.3.1, entries 3-7). We envisioned that acidic anhydride as additive could be accelerated the yield of the desired product **213a** instead of acid derivatives. Unfortunately, various acidic anhydride as additives did not give improvement of yield (Table 7.3.1, entries 8-12). To our delight, the yield was increased to 65% while phenol used as additive.

Afterwards, we examined different phenolic derivatives as additive. We observed that phenolic additives were very effective to increase the yield of the desired product **213a** (Table 7.3.2, entries 1-5). After screening of various phenolic derivatives, we found that benzenediol were effective to provide a good yield under oxidative reaction conditions. Remarkably, the desired product **213a** was obtained in 72% yield when 2 equivalents of hydroquinone were used instead of catechol and resorcinol. The yield was decreased while the reaction was carried out at 90 °C instead of 110 °C. The increasing of the temperature, the yield of the desired product **213a** did not increase. Afterwards, we moved to screen different polar as well as non-polar solvents for oxidative Diels-Alder reaction. Finally, we found that chlorobenzene was to be the best solvent to achieve the corresponding product **213a** in 72% yield. We did not observe the desired product formation when reaction was carried out in polar solvents such as MeCN, ^{t}BuOH or DMF. Later, we found that aromatic halogenated solvents were suitable for metal-free oxidative annulation reaction. Among them, PhCl was found to be the best solvent for the dehydrogenative Diels-Alder reaction.

Table 7.3.2. Optimization of reaction condition with phenolic additives and solvents.[a]



210a **212a** **213a**

Entry	ArOH (2 equiv)	Solvent (2 mL)	Yield (%)
1[b]	4-$NO_2C_6H_4OH$	PhCl	25
2[b]	PhOH	PhCl	65
3[b]	1,2-Dihydroxybenzene	PhCl	70
4[c]	1,3-Dihydroxybenzene	PhCl	44
5[c]	**Hydroquinone**	**PhCl**	**72**
6[c]]	Hydroquinone	DCE	trace
7[c]]	Hydroquinone	PhF	44
8[c]	Hydroquinone	PhBr	65
9[c]	Hydroquinone	MeCN	trace
10[c]	Hydroquinone	DMF	trace
11[c]	Hydroquinone	PhH	15
12[c]	Hydroquinone	^{t}BuOH	trace
13[c,d]	Hydroquinone	PhCl	60
14[e]	Hydroquinone	PhCl	50
15[f]	Hydroquinone	PhCl	70

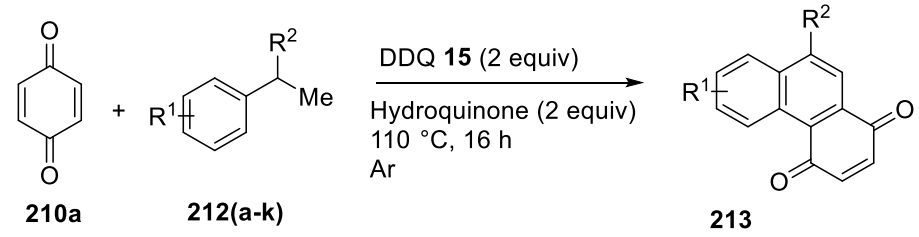
[a] Reaction conditions: **210a** (1.25 mmol), **212a** (0.25 mmol), oxidant (2 equiv), additive (2 equiv) in solvent (0.125 M) at 110 °C for 12-24 h under argon [b] Additive and 1,4-benzoquinone were added after 4h. [d] Reaction was carried out with 1.5 equiv hydroquinone [e] Reaction was carried out at 90 °C. [f] Reaction was performed at 120 °C.

7.4 Scope of Oxidative Dehydrogenative Diels-Alder Reaction

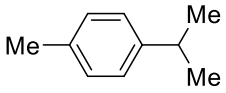
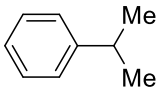
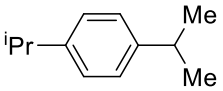
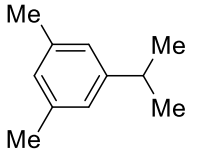
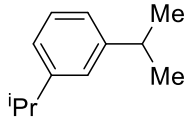
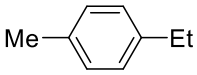
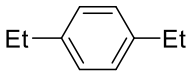
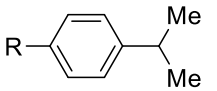
With the optimized reaction conditions in hand, we next explored the substrate scope of metal-free oxidative dehydrogenative Diels-Alder reactions. We investigated the scope of metal-free dehydrogenative Diels-Alder reaction of different arenes with *p*-benzoquinone (**210a**) under optimal reaction conditions (Table 7.4.1). Various substituted arenes were well tolerated under developed reaction conditions. It was notable that a wide array of arenas were able to yield the corresponding desired products (**213a-213f**) in moderate to good yield. 3,5-

Dimethylisopropylbene was employed under developed reaction conditions and obtained the corresponding desired product **213c** in 46% yield under developed reaction conditions. It is

Table 7.4.1. Substrate scope of different arenes.[a]



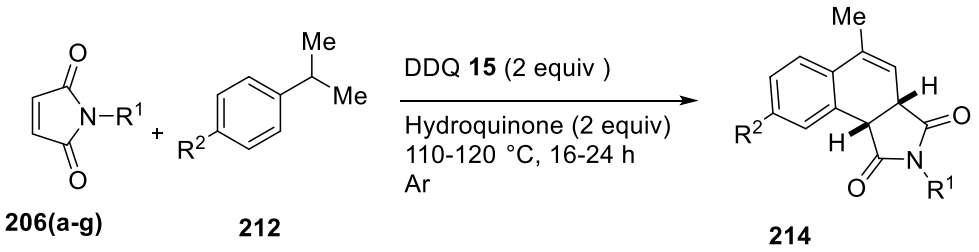
210a **212(a-k)** **213**

Entry	Arene	Product	Yield (%)
1	 **212a**	**213a**	50
2	 **212b**	**213b**	56
3	 **212c**	**213c**	46
4	 **212d**	**213c**	46
5[b]	 **212e**	**213d**	56
6[b]	 **212f**	**213e**	38
7[b]	 **212g**	**213f**	43
8	 R = OH,**212h** R = OAc,**212i** R = NHAc,**212j** R = NH_2,**212k**		n.d.

[a] Reaction conditions: **210a** (0.25 mmol), **212** (1.25 mmol), DDQ (0.5 mmol) and hydroquinone (0.5 mmol) in PhCl (0.125 M) at 110 ˚C for 24 h under argon. n.d. = not detected.

notable that selectively mono annulated product was obtained when 1,4-diethylbenzene was used for oxidative annulation reaction. Unfortunately, electron-rich alkene, alkyne such as diphenylacetylene, phenylacetylene and stilbene were not working under optimal conditions.

Table 7.4.2. Substrate scope of different maleimides.[a]



206(a-g) 212 214

Entry	R^1	R^2	Product	Yield (%)
1	Me	Me	**214a**	64
2	Me	$C_2H_4NO_2$	**214b**	64
3	Me	H	**214c**	46(61[b])
4[c]	Me	Br	**214d**	43
5	Me	2-tolyl	**214e**	48
6	nBu	Me	**214f**	72
7	CH_2CF_3	Me	**214g**	78
8	Ph	Me	**214h**	56
9	4-BrC_6H_4	Me	**214i**	62
10	4-ClC_6H_4	Me	**214j**	53
11	4-$NO_2C_6H_4$	Me	**214k**	66

[a] Reaction conditions: **206** (0.25 mmol), **212** (1.25 mmol), DDQ (0.5 mmol) and hydroquinone (0.5 mmol) in PhCl (0.125 M) at 110 ˚C for 24 h under argon. [b] Reaction was performed without hydroquinone. [c] Reaction carried out at 120˚C for 24 h.

Further, various arenes were investigated with *N*-methylmaleimide (**213a**) and obtained good to moderates yield of the corresponding products **214a-214d**. Selectively single product **214b** was obtained when 1-isopropyl-4-(2-nitroethyl)benzene was used under optimal conditions. Furthermore, electron-withdrawing group onto the *para*-positions were compatible under the developed reaction conditions and provided the desired products **214d** and **214e** in 43% and 48% yield. Afterwards, different *N*-substituted maleimide derivatives were examined under oxidative annulation reaction conditions. We observed that various maleimide derivatives afforded the corresponding products (**214f-214k**) in moderate to good yields. Later, electron-donating maleimide was investigated and obtained the corresponding product **214e** in 72% yield. To our delight, different *para* substituted *N*-arylmaleimides also well examined and obtained the desired products **214h-214j** without any difficulty under developed reaction conditions.

7.4.1 Determination of the Diastereoisomer of Product 214i

NOE experiment was carried out for product **214i** (Figure 7.1) to identify diastereomer. Upon irradiation of proton $\mathbf{H^a}$ which correlated with proton $\mathbf{H^b}$ and $\mathbf{Me^a}$. Proton $\mathbf{H^c}$ shows nice correlation with proton $\mathbf{H^b}$ and $\mathbf{H^d}$. NOE experimental result suggested that $\mathbf{H^b}$ and $\mathbf{H^c}$ are *cis* -configuration.

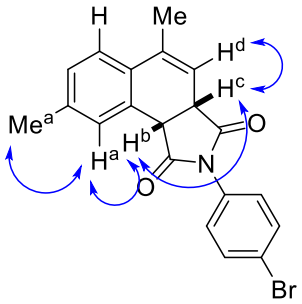
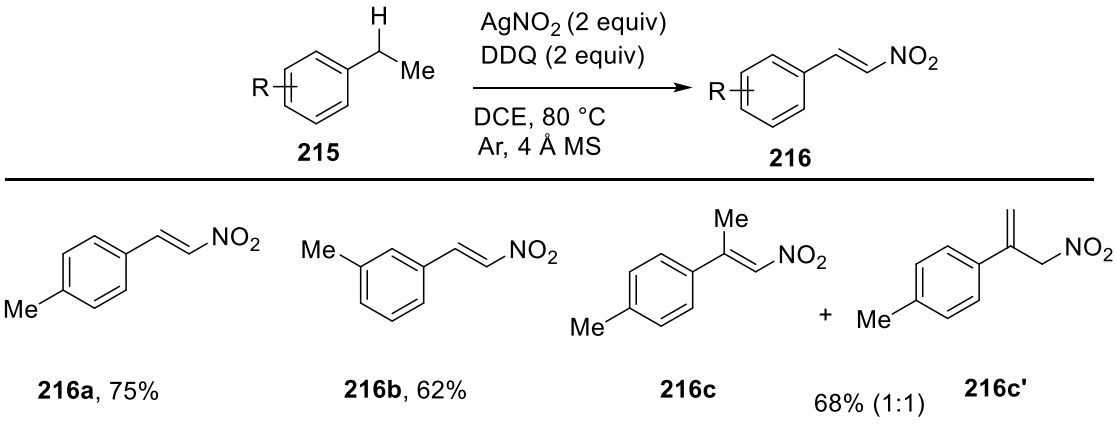


Figure 7.1. Identification diastereoisomer of product **214i** by NOE experiments.

7.5 Scope of Dehydrogenative Nitration

Having established dehydrogenative Diels-Alder reaction between alkylbenzenes and electron-deficient alkenes, next we investigated dehydrogenative nitration of simple arene for nitrostyrene synthesis. Generally, nitrostyrenes are synthesized using aldehydes and ketones

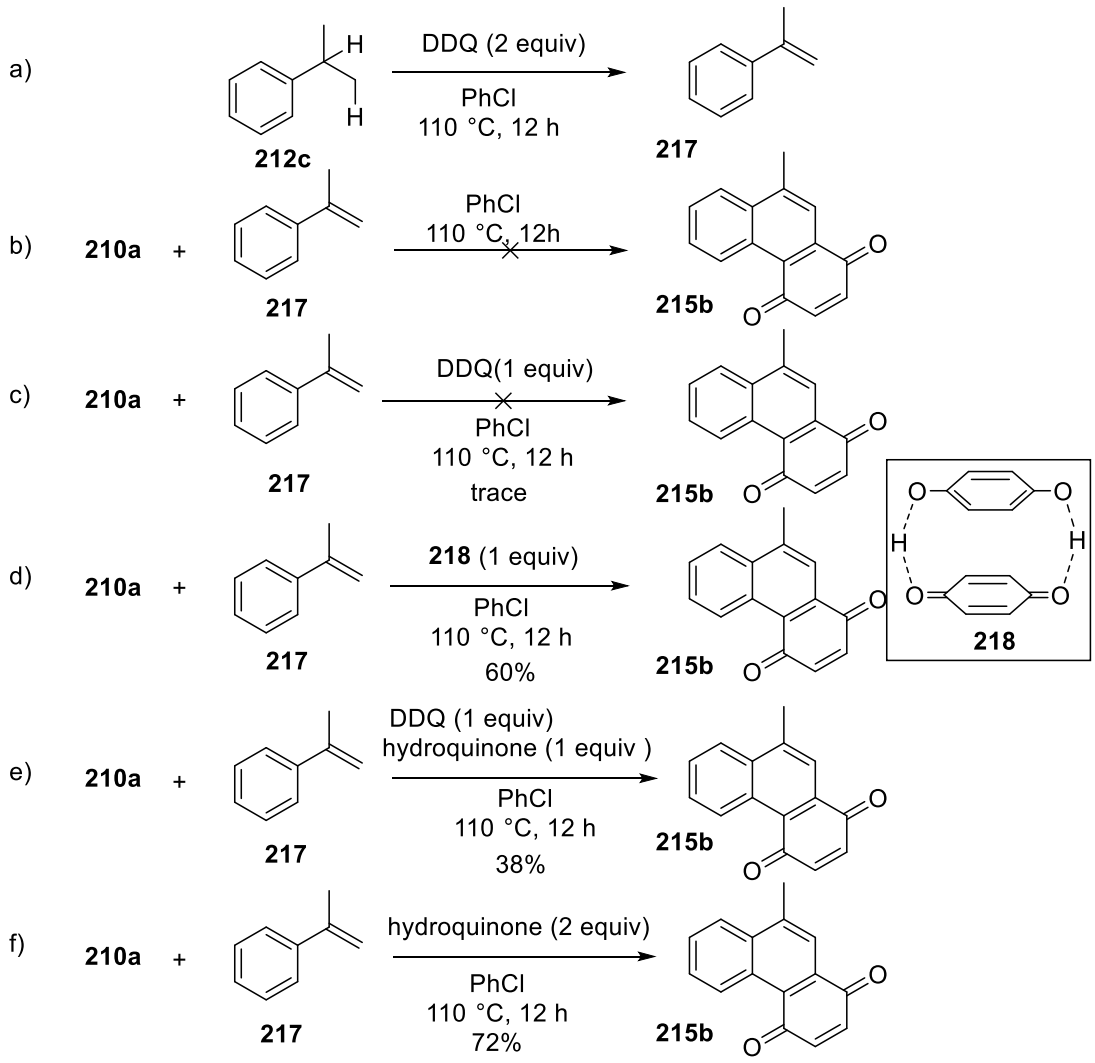


Scheme 7.3. Reaction conditions: **215** (0.5 mmol), DDQ (2 equiv), $AgNO_2$(2 equiv), 50 mg Å molecular sieve in 1,2-dichloroethane (2.0 mL) at 80 °C for 10 h under argon.

with nitroalkanes under basic mediated condensation at higher temperature.[192] Recently. Maiti and co-workers developed synthesis of nitroolefins from different building blokes using metal nitrate or *tert*-butylnitrate.[193-194] It is notable that the metal-free dehydrogenative nitration of ethylbenzene have never investigated. Nevertheless, we were interested to develop new method for dehydrogenative nitrostyrene synthesis from alkylbenzene. We investigated nitrostyrenes synthesis employing silver nitrate as a nitrating reagent with DDQ **15** (Scheme

7.3). We observed that the nitrostyrene derivatives (**216a-216b**) were formed selectively in *trans*-isomer in good yield. Furthermore, isopropyl group of benzene was investigated and obtained nitrated product with (1:1) mixtures of **216c** and **216c'** in 68% yield.

7.6 Studies on Reaction Mechanism

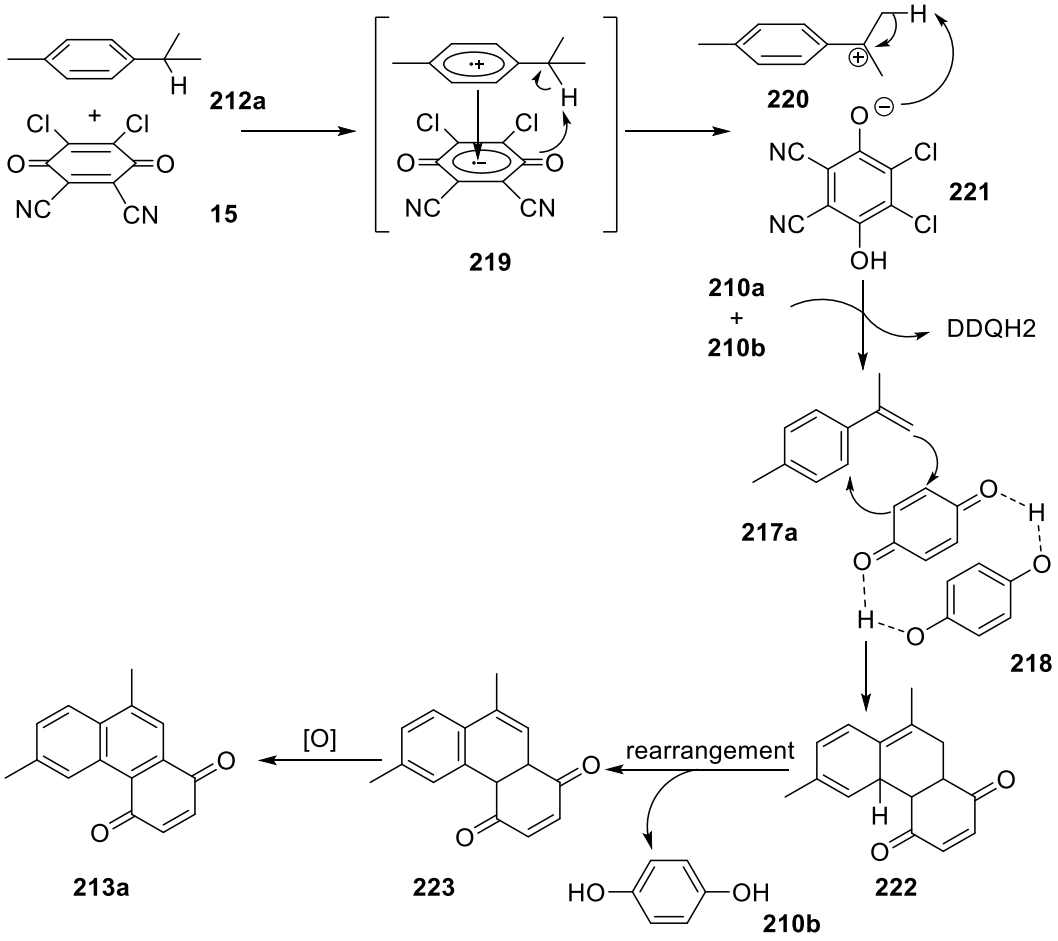


Scheme 7.4. Reaction conditions: **210a** (0.25 mmol), **217** (1.25 mmol), additive (x mmol) in PhCl (0.125 M) at 110 ˚C for 12 h under argon.

In order to gain insight into the reaction mechanism of dehydrogenative Diels-Alder reaction, we conducted several control experiments (Scheme 7.4). First, we did control experiment with possible intermediate **217** which formed by the oxidation of cumene (**212c**).[195] When the reaction was performed between cumene (**212c**) and DDQ (**15**) without **210a**, observed the formation of probable intermediate **217** (Scheme 7.4, entry a). The reaction between **210a** and **217** with 1 equivalent of DDQ (**15**), the desired product was not obtained (Scheme 7.4, entry c). Afterwards, control experiment was carried out with intermediate **217** in the presence

quinhydrone (**218**). The desired product **215b** was obtained in 60% yield (Scheme 7.4. d). After understanding the role of quinhydrone (**218**), we set out the reaction with 1:1 DDQ **15** and hydroquinone and obtained the desired product **215b** in 38% yields (Scheme 7.4 entry e). Finally, we conducted the cycloaddition reaction between **210a** and **217** with 2 equivalents of hydroquinone, found the desired products **215b** formation in 72% yield (Scheme 7.4, entry f). Mechanistic studies revealed that dehydrogenative Diels-Alder reaction underwent *via* styrene intermediate *via* acid promoted cycloaddition.[196]

7.7 Mechanism



Scheme 7.5. Proposed mechanism for dehydrogenative Diels-Alder reaction.

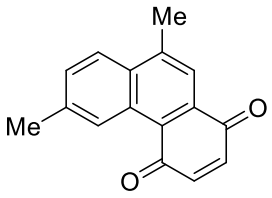
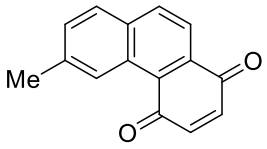
Based on our mechanistic studies, a proposed reaction mechanism of metal-free Diels-Alder reaction has been shown in the Scheme 7.5. Initially, the complex **219** was formed by a single-electron transfer from *p*-cymene (**212a**) to electron-deficient DDQ (**15**) which led to generate radical cation species of arene.[197] Afterwards, the intermediate **220** was formed after abstraction of hydrogen atom from radical cationic species of *p*-cymene by radical anion of DDQ (**15**). Subsequently the anion species **221** abstract hydrogen atom from the benzyl

cation species **220** to form intermediate **217a**. In the presence of hydroquinone, the complex intermediate **218** could be generated through hydrogen bonding of hydroxy groups which are well known in literature for activation of quinone **210a** through hydrogen bonding of hydroxy group.[198] Then styrene derivative facilitated the Diels-Alder reaction with intermediate **218** to lead intermediate **222**. In the next step, intermediate **223** could be obtained from the intermediate **222** *via* rearrangement. Finally, oxidation of the intermediate **223**, provided the desired product **213a**.

7.8 Identification of Biological Activity of 1,4-Phenanthraquinone Derivatives

According to our plan, we synthesized compound libraries of 1,4-phenanthraquinone scaffolds. Afterwards, we submitted all compound to COMAS (Compound Management and Screening Centre) in Dortmund to find the biological activity. Several cell-based assays such as hedgehog signaling pathway and Wnt signaling pathway and autophagy were tested. After screening different assays, two compounds **213d**, and **213f** inhibited the autophagy signaling pathway in the low micro molar range (Table 7.8.1).

Table 7.8.1. Results of autophagy pathway inhibition.

Entry	Product	IC_{50} [µM]	Viability [µM]
1	 **213d**	≥ 10	inactive
2	 **213f**	≥ 10	inactive

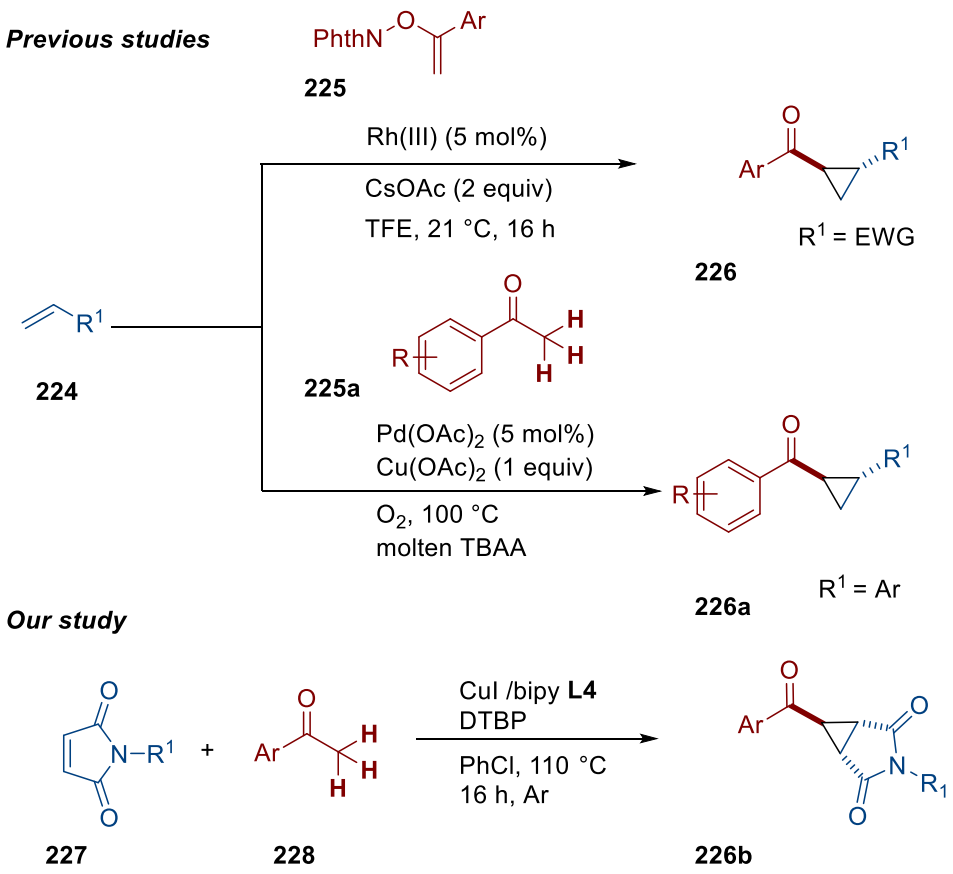
Chapter 8

Copper(I)-Catalyzed Oxidative (2+1) Annulation of Acetophenones with Maleimides in the Synthesis of Cyclopropanes

(This part already published: S. Manna, and A. P. Antonchick, *Angew. Chem.* **2015**, *127*, 15058-15061; *Angew. Chem. Int. Ed.* **2015**, *54*, 14845-14848.)

8.1 Introduction

Cyclopropanes represents one of the most useful molecules and have found many applications[199-201] in organic synthesis due to its unique reactivity and ring strain.[202-205] This small molecule is widely used in many fields such as natural products,[200, 206-207] biologically relevant compound and materials.[208-211] Traditionally cyclopropanes were synthesized by Simmon-Smith reaction[212] employing diiodomethane and zinc copper with alkene.[126-131] Recent years, transition metal catalyst such as Rh[213], Ru[214], Fe[215-216], Co[217], Cu[218-219], Ir[220-222], Pd[223], Au[135] and Ni[131] played important roles in the novel cyclopropane synthesis. Among them, metal carbene has been used for cyclopropane synthesis using diazo compound with alkene. It is notable that metal-free method for cyclopropanation also was established applying ylide precursors.[136] Simmon-Smith method, Michael-initiated ring closure reaction[129, 224-227] and diazo compounds with metal catalysis are the most useful and valuable synthetics route for cyclopropane synthesis. Though, these methods are useful for the synthesis of cyclopropanes, drastic reaction conditions and explosive nature of many chemicals open room for further development. Therefore, the development of new method for cyclopropane synthesis under mild conditions is in high demand.



Scheme 8.1. Cyclopropanation *via* C–H bond functionalization.

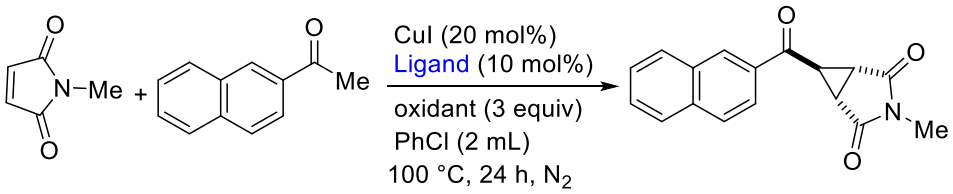
In the recent years, development of cyclopropanes *via* C–H bond functionalization have been reported employing transition metal-catalyst. Very recently, the group of Rovis disclosed cyclopropanation of alkenes with phenyl-*N*-enoxyphthalimide (**225**) *via* rhodium-catalyzed C–H activation (Scheme 8.1).[228] The group of Monopoli and Nacci developed palladium catalyzed cyclopropanation of alkene with acetophenone (Scheme 8.1).[223] Although, a variety of cyclopropane synthesis have been reported using functionalized precursors, the development of a novel method for the synthesis of cyclopropane *via* C–H bond functionalization is still high demand. We were interested in developing cyclopropane though acetophenones functionalization with electron-deficient alkenes.

8.2. Results and Discussion

8.3. Studies on the Optimization of Reaction Conditions

We began our optimization studies of cyclopropanation with 2-acetylnaphthalene (**228a**) and *N*-methylmaleimide (**227a**) under oxidative conditions. Initially, the optimization was started

Table 8.3.1. Optimization of cyclopropanation with different ligands and oxidants.[a]



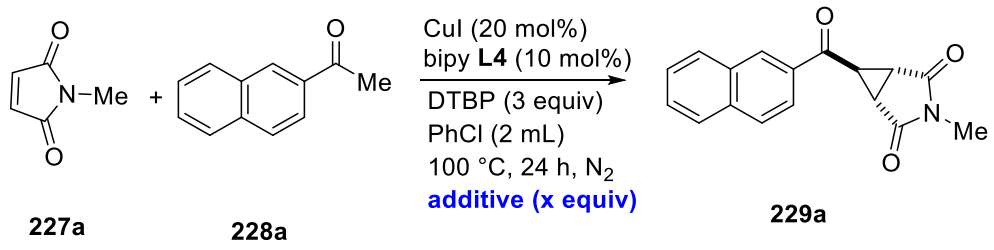
227a **228a** **229a**

Entry	Ligand (10 mol%)	Oxidant (3 equiv)	Yield (%)
1	1,10-Phenanthroline **(L1)**	DTBP	52
2	2,9-Dimethyl-1,10-phenanthroline (**L2**)	DTBP	trace
3	3,4,7,8-Tetramethyl-1,10-phenanthroline (**L3**)	DTBP	35
4	2,2'-Bipyridine (**L4**)	DTBP	63
5	4,4'-Di-*tert*-butyl-2,2'-bipyridine (**L5**)	DTBP	64
6	4,4'-Dimethoxy-2,2'-bipyridine (**L6**)	DTBP	49
7	Picolinic acid (**L7**)	DTBP	0
8	**L4**	TBHP	trace
9	**L4**	$PhI(OAc)_2$	n.d.
10[b]	**L4**	H_2O_2	n.d.
11	**L4**	$K_2S_2O_8$	n.d.

[a] Reaction conditions: **227a** (0.25 mmol), **228a** (0.5 mmol), in PhCl (2.0 mL) for 24 h under argon. [b] Reaction carried out at 80 °C. DTBP = Di-*tert*-butyl peroxide, TBHP = *tert*-Butyl hydroperoxide. n.d. = not detected.

with 20 mol% CuI as catalyst in combination with 10 mol% 1,10-phenanthrolene (**L1**) as ligand in the presence of di-*tert*-butylperoxide (**20)** as oxidant in chlorobenzene at 100 ºC for 24 h and obtained the desired product **229a** in 52% yield.[229] Encouraged by the initial result, we further tested different nitrogen-based ligands under oxidative reaction conditions (Table 8.3.1, entries 1-7). We observed that the cyclopropanation reaction was highly ligand dependent. After screening of several ligands, we found 2,2′-bipyridine (**L4**) and 4-4′-dimethoxy-2-2′-bipyridine (**L6**) ligands were to be optimal to provide the desired product **229a** in 63% and 65% yields. Later, we screened different oxidants. After testing various

Table 8.3.2. Optimization of cyclopropanation with different additives and Cu-catalysts.[a]



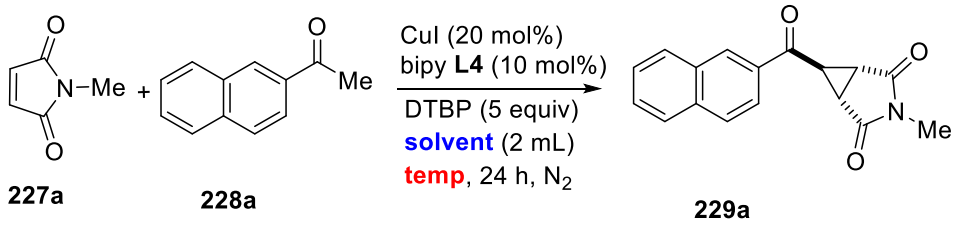
227a **228a** **229a**

Entry	Cu-salt (20 mol%)	Additive (x equiv)	Yield (%)
1	CuI	-	66
2[b]	CuI	-	72
3	CuBr	-	65
4	CuCl	-	62
5	$CuBr{\cdot}SMe_2$	-	42
6	$Cu(OAc)_2$	-	35
7[c]	CuI	-	83
8	CuI	KI (0.2)	n.d.
9	CuI	I_2 (0.2)	trace
10	CuI	DBU (0.5)	n.d.
11	CuI	Et_3N (1)	n.d.
12	CuI	MS (50 mg, 4 Å)	45
13[d]	CuI	-	trace

[a] Reaction conditions: **227a** (0.25 mmol), **228a** (0.5 mmol), in solvent (2.0 mL) for 24 h under argon. [b] 30 mol% **L4** was used. [c] Reaction was carried out with 5 equiv DTBP. [d] Reaction was performed under oxygen atmosphere MS = Molecular sieve. n.d. = not detected.

oxidants, DTBP was found to be the best oxidant to provide cyclopropane **229a** in 64% yields. We did not observe the desired product formation while *tert*-butyl-hydroperoxide (**19**),

Table 8.3.3. Optimization of cyclopropanation with different temperature and solvents.[a]



227a 228a 229a

Entry	Solvent (2 mL)	Temp (ºC)	Yield (%)
1	Toluene	110	trace
2	*p*-Xylene	110	trace
3	DMSO	110	n.d.
4	DMF	110	n.d.
5	H_2O	110	n.d.
6	PhCl	110	83
7	PhBr	110	72
8	PhF	110	41
9	*tert*-Amyl alcohol	110	n.d.
10	NMP	110	n.d.
11	EtCN	110	n.d.
12	PhCl	90	63
13	PhCl	100	65
14	PhCl	110	83
15	PhCl	120	68
16[b]	PhCl	110	45

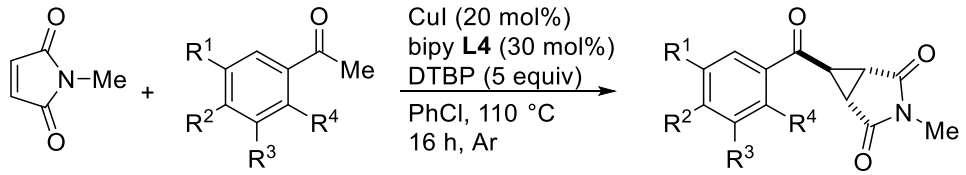
[a] Reaction conditions: **227a** (0.25 mmol), **228a** (0.5 mmol), in solvent (2.0 mL) for 24 h under argon. [b] 10 mol% CuI was used. DTBP = Di-*tert*-butyl peroxide. [b] 10 mol% catalyst was used. n.d. = not detected.

hydrogen peroxide (H_2O_2) or $PhI(OAc)_2$ (**22**) were used as oxidant (Table 8.3.1, entries 8-11). After screening various copper catalysts, next we moved to examine various additives for oxidative cyclopropanation reaction. We did not observe cyclopropane formation when KI, I_2, DBU or NEt_3 were used as additives (Table 8.3.2, entries 8-11). In the presence of molecular sieve, the desired product formation decreased to 45 % yield. The desired cyclopropane did not obtain while reaction was carried out under oxygen atmosphere (Table 8.3.2, entry 13). In order to investigate copper-catalyzed oxidative annulation of acetophenone, a series of copper salts were tested (Table 8.3.2, entries 1-6). However, the yield was slightly decreased while

CuBr or CuCl were used instead of CuI. It is notable that lower yield was obtained when copper(II) diacetate was used (Table 8.3.2, entry 6). After screening of various copper catalysts, 72% yield of the desired product **229a** was obtained using 30 mol% of CuI in the present of 3 equivalents of DTBP. To our delight, after increase the amount of oxidant, the yield of the desired product **229a** also increased to 83%. Further, we examined various solvents (Table 8.3.3). We did not observe the formation of the desired product while reaction was carried out in H_2O, DMSO or DMF. Only trace amount of product **229a** was obtained in non-polar solvent such as toluene or *p*-xylene. Yield was increased by using halogenated solvents such as PhCl, PhBr or PhF. Notably, chlorobenzene was found to be the best solvent to achieve corresponding product **229a** in 83% yield. When the amount of copper catalyst was decreased to 10 mol%, the yield of **229a** dramatically decreased to 45%. While the reaction was carried out below 100 ºC, surprisingly the yield of product **229a** was decreased to 65% at 90 ºC. Finally, we found that 110 ºC was the best temperature for oxidative cyclopropanation.

8.4 Scope of Oxidative Cyclopropanation

Table 8.4.1. Substrate scope with different acetophenone derivatives.[a]



227a **228** **229**

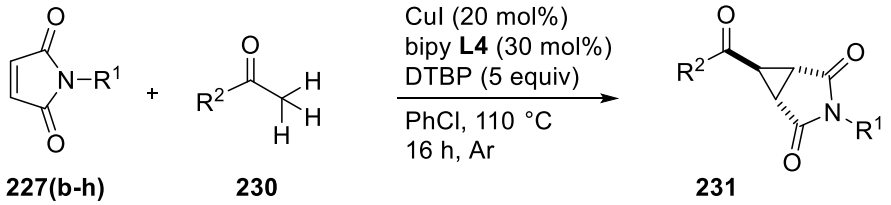
Entry	R^1	R^2	R^3	R^4	Product	Yield (%)
1	H	NO_2	H	H	**229b**	62
2	H	CO_2Me	H	H	**229c**	82
3[b]	H	Ac	H	H	**229d**	56
4	H	F	H	H	**229e**	72
5	H	3-ClC_6H_4	H	H	**229f**	62
6	H	H	H	H	**229g**	65
7	H	Br	H	H	**229h**	78
8	H	Me	H	H	**229i**	52
9	H	Cl	H	H	**229j**	76
10	H	H	Br	H	**229k**	76
11	H	H	CN	H	**229l**	84

Continuation of **Table 8.4.1**						
12	H	H	CF_3	H	**229m**	82
13	H	Br	NO_2	H	**229n**	69
14	H	Cl	H	Cl	**229o**	48
15	F	H	H	F	**229p**	76
16[c]		2-Acylpyridine			**229q**	62

[a] Reaction conditions: **227a** (0.25 mmol), **228** (0.5 mmol), 5 equiv DTBP, CuI 20 mol%, bipy (**L4**) 30 mol% in PhCl (2.0 mL) at 110 ºC for 16 h. [b] Methyl aryl ketone was use 3 equiv. [c] 10 mol% 1,10-phen (**L1**) and 4 equiv DTBP were used. All products were formed with d.r. >20:1.

With the optimization reaction conditions in hand, we then started investigation the scope of the cyclopropanation reaction of acetophenone derivatives with *N*-methyl maleimide (Table 8.4.1). Various functional groups such as nitro, bromo, chloro, fluoro, acetyl, ester, trifluoromethyl and also protected phenol (R^2 = 3-$ClC_6H_4CO_2$) on the acetophenones were well tolerated under standard reaction conditions. Notably, both electron-rich as well as electron-deficient aryl groups were found to be compatible for the cyclopropanation reaction. Further, various functional groups onto the *para*-position of acetophenone were investigated and obtained the corresponding products (**229b-229g** and **229h-229j**) in good to excellent yield. Selectively mono-addition product **229c** was obtained in 56% yield when 1,4-diacetylbenzene was employed under optimal conditions. Furthermore, various functional groups such as nitro, bromo, cyano and trifluoromethyl group on the *meta*-position of acetophenone derivatives were investigated under the developed reaction conditions and obtained the corresponding desired products (**229k-229n**) in good yield. Next, we focused on cyclopropanation of di-substituted aryl methyl ketone under developed reaction conditions (Table 8.4.1, entries 13-15). The desired product **229n** was obtained when 2,4-dichlroacetophenone was employed. Interestingly, 3,5-difluoroacetophenone provided corresponding product **229p** in 69% yield. To our delight, 2-acetylpyridine was used and found the desired product **229q** in 62% yield. It is notable that all desired products were obtained single and *trans* isomer which was confirmed by NOE studies.

Table 8.4.2. Substrate scope with different maleimide derivatives.[a]



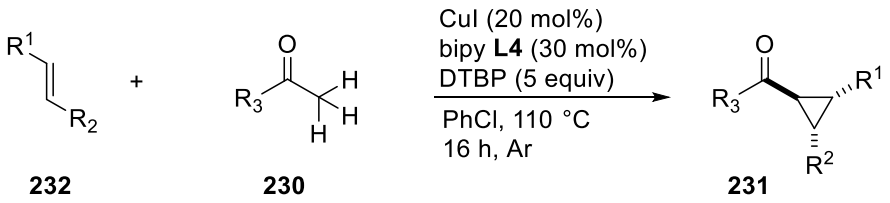
227(b-h) **230** **231**

Entry	R	R^1	Product	Yield (%)
1	*n*-Pr	4-BrC_6H_4	**231a**	63
2	*n*-Hexyl	4-BrC_6H_4	**231b**	86
3	*c*-Hexyl	4-BrC_6H_4	**231c**	77
4	CH_2CF_3	4-BrC_6H_4	**231d**	56
5	but-3-en-1-yl	4-$CO_2MeC_6H_4$	**231e**	59
6[b]	CH_2Ph	4-$CO_2MeC_6H_4$	**231f**	72
7	(*R*)-1-(1-phenylethyl)	4-$CO_2MeC_6H_4$	**231g**	87
8	(*R*)-1-(1-cyclohexylethyl)	4-BrC_6H_4	**231h**	60
9	H	4-BrC_6H_4	**231i**	n.d.

[a] Reaction conditions: **227** (0.25 mmol), **230** (0.5 mmol), 5 equiv DTBP, CuI 20 mol%, bipy **L4** 30 mol% in PhCl (2.0 mL) at 110 ºC for 16 h. [b] Reaction time was 12 h. [c] using CuI 10%, **L4** (20 mol%), DTBP (3 equiv), methacrylate (10 equiv). Reaction was performed at 100 °C. n.d. = not detected. All products were formed with d.r. >20:1.

Encouraged by the acetophenone scopes, we further explored the scope of cyclopropanation reaction with a series of *N*-substituted maleimide **227** under our standard reaction conditions (Table 8.3.2). Various substituted maleimide derivatives were investigated and found good compatible for cyclopropanation. *N*-Alkylsubstituted electron-rich maleimides were found to be facile for the products formation (**231a-231c**). Importantly, *N*-substituted terminal alkene maleimide gave the desired product **231e** in 59% yield under radical reaction conditions without radical species addition of terminal alkene (Table 8.3.2, entry 231e). *N*-Benzylmaleimide underwent smoothly conversion to give the desired product **231f** in 72% yield. Afterwards, *N*-substituted chiral maleimides were examined and found excellent yield of the corresponding products **231g** and **231h**. Maleimide did not give the desired product under developed reaction conditions.

Table 8.4.3. Substrate scope with different alkenes.[a]]



232 230 231

Entry	R^1	R^2	R^3	Product	Yield (%)
9	CN	H	4-$CO_2MeC_6H_4$	**231j**	35
10[b]	CO_2Me	H	4-CNC_6H_4	**231k**	70
11	4-ClC_6H_4CO	4-ClC_6H_4CO	4-$CO_2MeC_6H_4$	**231l**	61
12	CO_2Me	CO_2Me	4-BrC_6H_4	**231m**	n.d.

[a] Reaction conditions: **232** (0.25 mmol), **230** (0.5 mmol), 5 equiv DTBP, CuI 20 mol%, bipy **L4** 30 mol% in PhCl (2.0 mL) at 110 ºC for 16 h. using CuI 10%, **L5** (20 mol%), DTBP (3 equiv), methacrylate (10 equiv). Reaction was performed at 100 °C. n.d. = not detected. All products were formed with d.r. >20:1.

Having described scope of maleimides and acetophenone derivatives, next we investigated the scope of various internal and terminal alkenes in the cyclopropane synthesis (Table 8.4.3). Interestingly, we found that various alkenes were very facile to provide cyclopropane (**231j-231l**) in moderate to good yield. Cyclopropane **231k** was obtained in good yield under developed conditions. Internal alkene such as (*E*)-1,4-bis(4-chlorophenyl)but-2-ene-1,4-dione well tolerated and provide the corresponding cyclopropane **231l** in 61% yield. Unfortunately, methyl fumarate did not provide the desired product.

8.4.1 Determination of the Stereoisomer

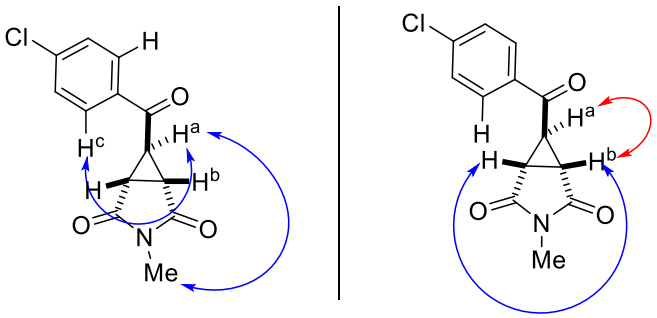


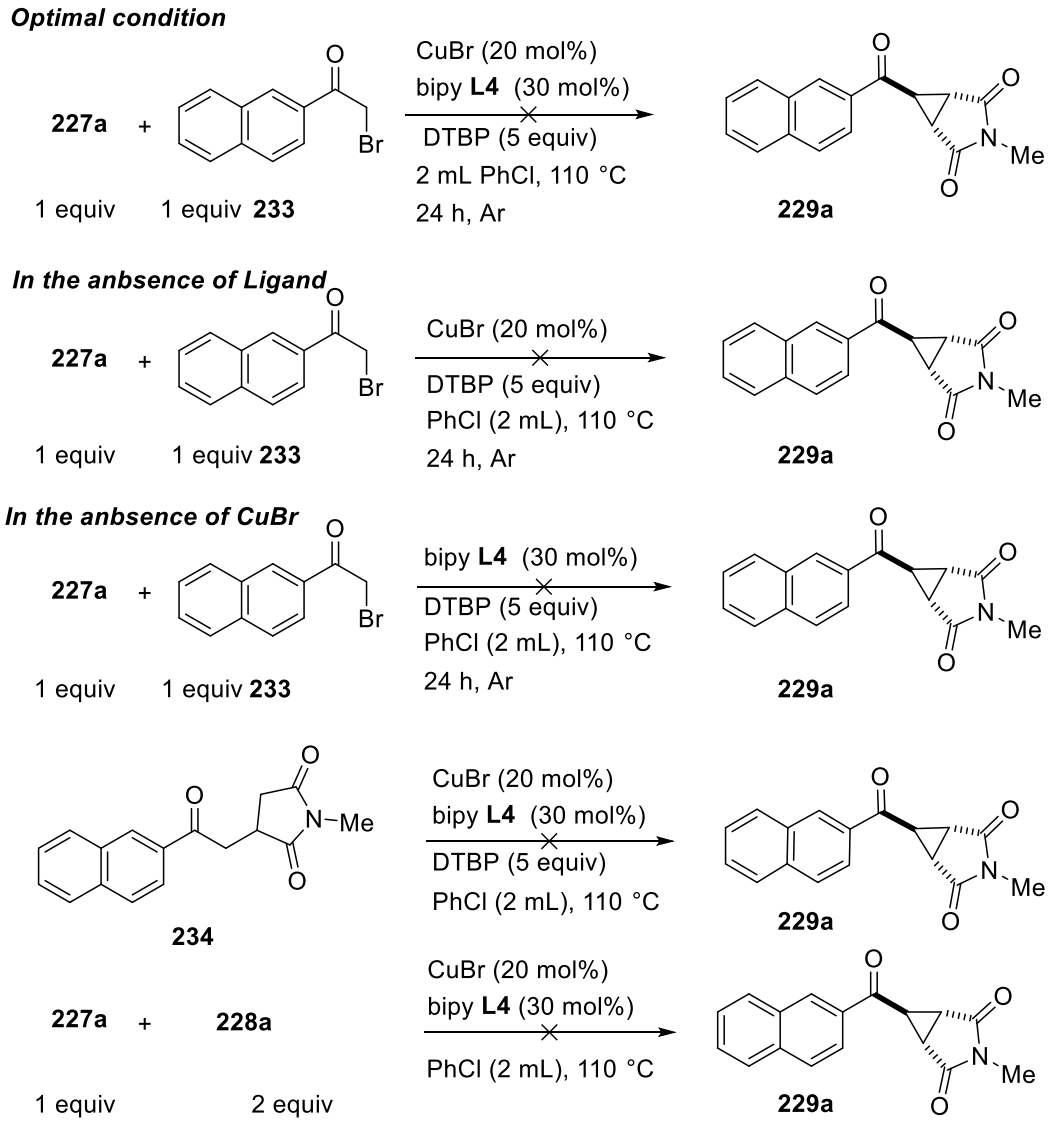
Figure 8.1. Identification of stereoisomer of product **229j** by NOE experiments.

NOE experiment was performed to identify stereoisomer of product **229j** (Figure 8.1). According to the NOE analysis, proton $\mathbf{H^a}$ correlated with proton $\mathbf{H^b}$ and **Me** group. Proton $\mathbf{H^b}$ on irradiation did not shows strong correlation with proton $\mathbf{H^a}$ which indicated that proton $\mathbf{H^a}$ and $\mathbf{H^b}$ are *tran* configuration.

8.5 Studies on Reaction Mechanism

8.5.1 Control Experiments

Next we turned out our attention to understand the reaction mechanism of copper-catalyzed cyclopropanation. In this regards, we conducted several experimental studies with the probable intermediate (Scheme 8.2). Initially, we were wondering whether cyclopropanation reaction proceeds *via in-situ* formation of *α*-halocarbonyl intermediate **233** or different pathway. While the reaction was performed between **233** and **227a** under optimized reaction conditions, did not observe any desired product formation. While the reaction was carried out



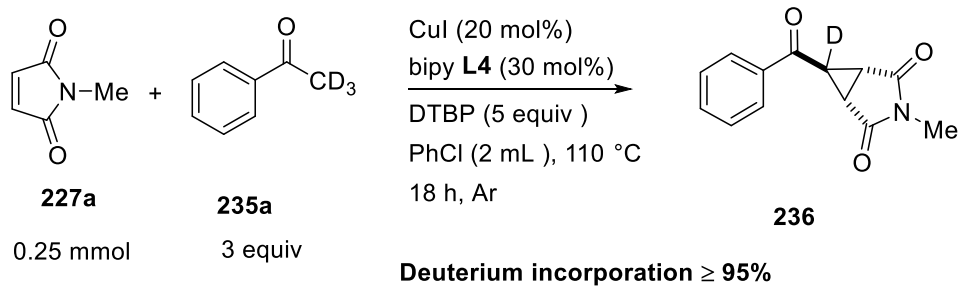
Scheme 8.2. Control experiment with probable intermediate

without ligand or without catalyst with probable intermediate **233**, we did not obtain target product **229a**. This result indicated that cyclopropanation did not undergo *via* *α*-halocarbonyl intermediate. Afterwards, we thought that cyclopropanation underwent different pathway.

Finally, we examined our standard reaction condition with probable intermediate **234**. Unfortunately, we did not observe any desired product formation under developed reaction conditions.

8.5.2 Reaction of 2,2,2-[$^2H_3$]-1-Phenylethan-1-one with Maleimide

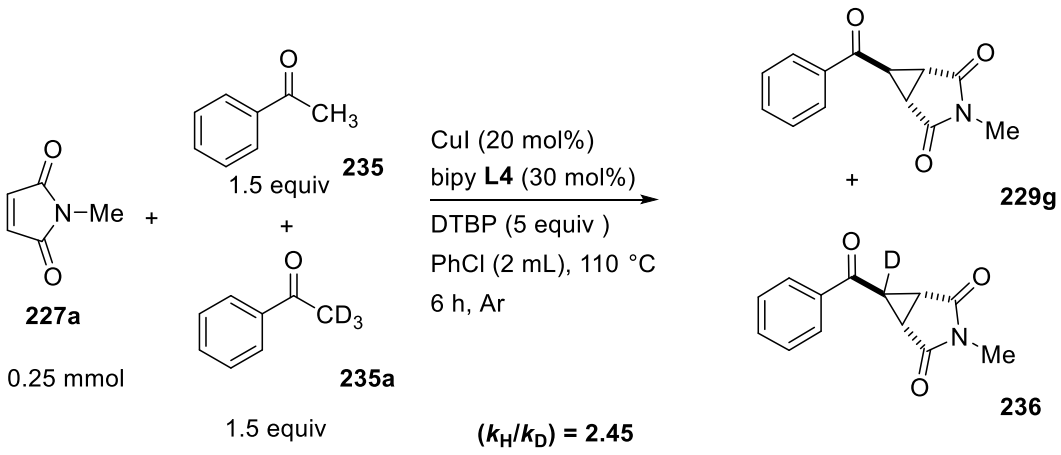
In order to gain insight into the reaction mechanism, we conducted the control experiment with 2,2,2-[$^2H_3$]-1-phenylethan-1-one under developed reaction conditions (Scheme 8.3). Pleasingly, we obtained target product **236** in 41% yield with deuterium incorporation greater than 95%. This result suggested that deuterium and hydride exchange not occurred under radical reaction conditions.



Scheme 8.3. Reaction of deuterated acetophenone.

8.5.3 Kinetic Isotope Effect (KIE) Study

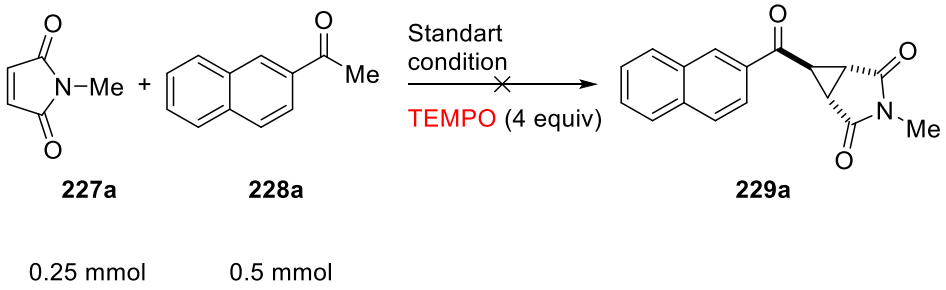
Subsequently, a kinetic isotope effect experiment was performed between **235** and **235a** with *N*-methylmaleimide under developed reaction conditions and obtained kinetic isotope effect equal to 2.45 (Scheme 8.4). Hence, abstraction of both hydrogen atom is not rate-limiting step.



Scheme 8.4. Kinetic isotope effect (KIE) experiment.

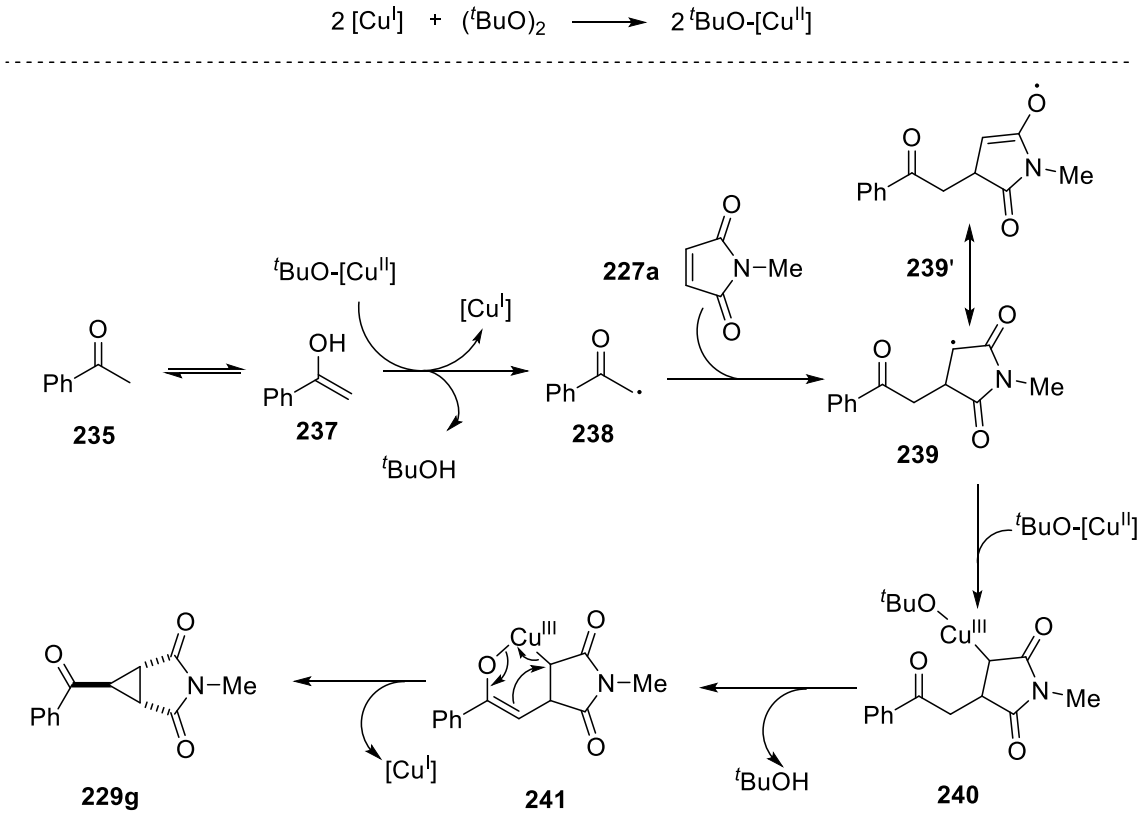
8.5.4 Radical Trapping Experiment with TEMPO

Furthermore, a radical trapping experiment was performed with TEMPO (**16)** as a radical scavenger. The yield of the desired product **229a** dramatically decreased in the presence of TEMPO (Scheme 8.5). This result suggested that the reaction proceeded through radical pathway.



Scheme 8.5. Radical trapping experiment.

8.6 Mechanism



Scheme 8.6. Proposed mechanism for Cu-catalyzed cyclopropanation.

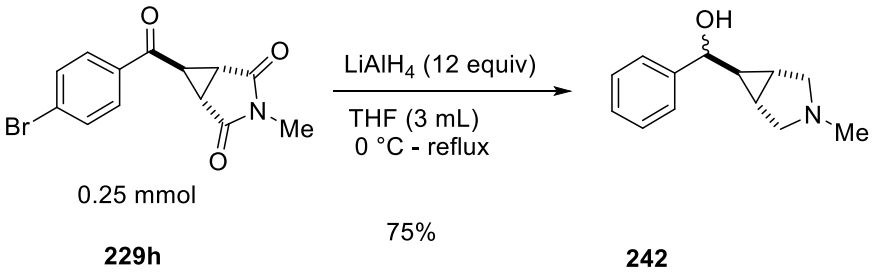
Based on our mechanistic studies and literature reports, a plausible reaction mechanism has been proposed in the Scheme 8.6. First, ^{t}BuO-[Cu^{II}] species was formed by the oxidation of Cu(I) with DTBP.[230] In the next step, intermediate **237** was formed *via* enolization of

acetophenone. After oxidation of the intermediate **237** with Cu(II) species to yield the intermediate **238** which attack the electron-deficient maleimide **227a** to form intermediate **239**. The intermediate **239** could be stabilized by resonance to generate the intermediate **239'**. Upon reaction of r Cu(II) species with the intermediate **239**, generate the intermediate **240**. The intermediate **241** could be obtained *via* enolization of keto group of **240** and ligand exchange and followed by cyclization. The cyclic intermediate **241** determined the stereo-selectivity of developed annulation. Finally, reductive elimination of Cu(I) provided the final product **229g**. The Cu(II) species was regenerated in the presence of DTBP *via* oxidation of Cu(I) species.

8.7 Products Derivatization

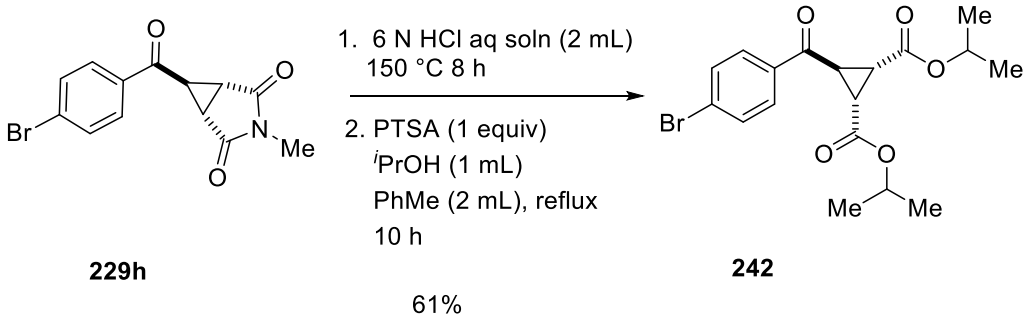
8.7.1 Reduction of Product 229h

Further, we were interested to reduce the amide bonds of cyclopropane scaffolds.[231] Importantly, cyclopropane **229h** could be transferred into product **242** upon reduction of amide and carbonyl groups in the presence of $LiAH_4$ (Scheme 8.6). The desired product **242** was obtained in 75% isolated yield.



Scheme 8.6. Reduction of product **229h**.

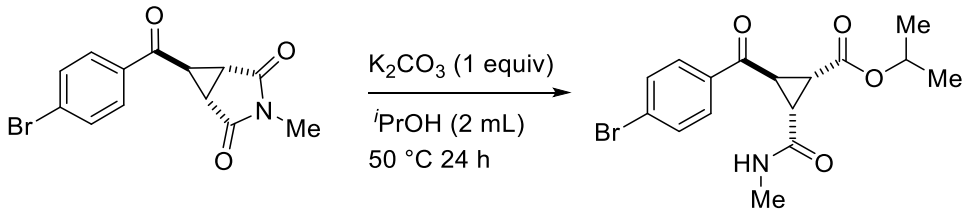
8.7.2 Ring Opening of the Product 229h



Scheme 8.7. Ring opening of the product **229h**.

In addition, we investigated the ring opening of obtained product **229h** (Scheme 8.7).[232] Ester derivative of cyclopropane **243** could be obtained from product **229h** in 61% yield**,** upon

hydrolysis of amide followed by esterification of the hydrolyzed product in one-pot.[233] Further, unsymmetrical ring opening of obtained cyclopropane was applied in the presence of K_2CO_3 and the desired product **244** was isolated in 53% yield.[234]



229h 53% **244**

Scheme 8.8. Unsymmetrical ring opening of the product **229h**.

8.8 Identification of Biological Activity of 3-Azabicyclo[3.1.0]hexane-2,4-diones

According to our plan, we synthesized compound libraries of 3-azabicyclo[3.1.0]hexane-2,4-dione scaffolds. Afterwards, we submitted all compound to COMAS (Compound Management and Screening Centre) in Dortmund to find the biological activity. Several cell-based assays such as hedgehog signaling pathway and Wnt signaling pathway and autophagy were tested. After screening different assays, we did not obtain biological result.

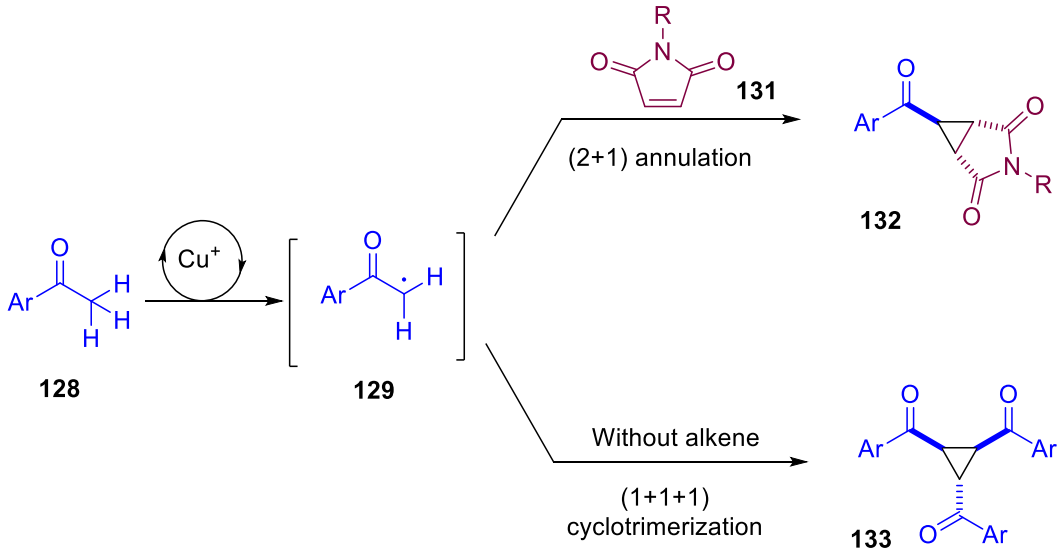
Chapter 9

Copper(I)-Catalyzed Oxidative (1+1+1) Annulation of Acetophenones for Cyclopropanes Synthesis

(This part already published: S. Manna, and A. P. Antonchick, *Angew. Chem.* **2016**, *128*, 5376-5379; *Angew. Chem. Int. Ed.* **2016**, *55*, 5290-5293)

9.1 Introduction

During studies on cyclopropanation of acetophenones with electron-deficient alkenes under oxidative conditions, we envisaged that the development of a novel method for the oxidative cyclopropanation through C–H bond functionalization without alkene would be highly desirable transformation (Scheme 9.1). It is notable that synthesis of small carbocycles *via* three C(sp^3)–H bonds functionalization has never been reported. Therefore, discovery of a new method for the synthesis of strain cyclopropane without prefunctionalized starting material would be a significant advantage. Moreover, a mild and efficient method *via* C–H bond functionalization is in high demand.



Scheme 9.1. Oxidative Cyclopropanation of acetophenone.

Cyclotrimezation reactions were applied for the synthesis of polysubstituted benzenes using acetophenones in the recent years.[235-237] The development of cyclopropane from acetophenone *via* oxidative cyclotrimerization has never been reported. In this regard, we were interested to demonstrate the first catalytic approach for the synthesis of strained cyclopropanes by an unprecedented (1+1+1) cyclotrimerization of simple aryl methyl ketones under oxidative conditions.

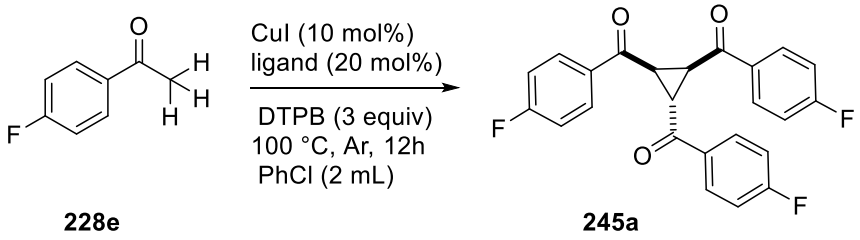
9.2 Result and Discussion

9.3 Studies on the Optimization of Reaction Conditions

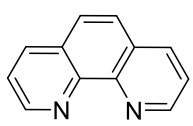
We initiated our optimization studies on the oxidative cyclopropanation of 4-fluoroacetophenone (**228e**) as model substrate. We started our exploration of the reaction with 10 mol% CuI in combination with 20 mol% bipy (**L4**) as ligand and 3 equivalents of DTBP as

oxidant in PhCl as solvent at 100 °C for 12 h under argon (Table 9.3.1). At the beginning, the desired cyclopropane (**245a**) was isolated in 41% yield. Encouraged by the initial result of oxidative (1+1+1) annulation, we further tested different ligands (Table 9.3.1). Pleasingly, we found that 4,4′-ditertbutyl-2-2′-bipyridine (**L5**) was to be the best ligand for the copper(I)-catalyzed annulation of 4-fluoroacetophenone (**228e**) and could be obtained the desired

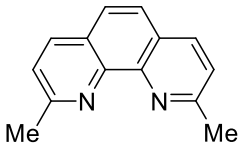
Table 9.3.1. Optimization of cyclopropanation with different ligands.[a]



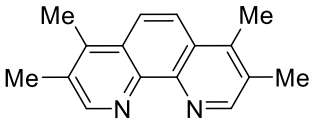
228e **245a**



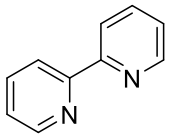
L1, trace



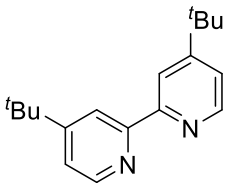
L2, trace



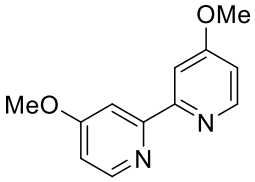
L3, trace



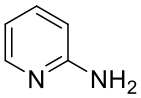
L4, 41%



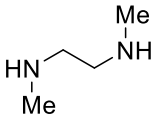
L5, 73%



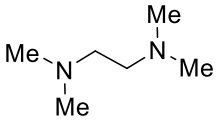
L6, 55%



L7, trace



L8, n.d.

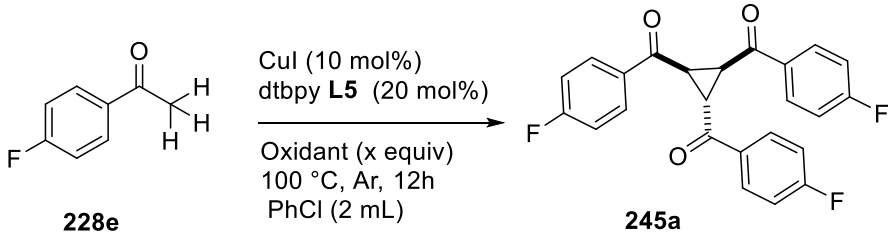


L9, n.d.

[a] Reaction conditions: **228e** (0.5 mmol), DTBP (3 equiv), CuI (10 mol%), ligand (20 mol%) in PhCl (2.0 mL) at 100 °C for 12 h under argon. n.d. = not detected

product 245a in 73% yield using ligand **L5**. Unfortunately, 1,10-phenanthroline derivatives (**L1-L3)** and aliphatic nitrogen-based ligands (**L8-L9)** did not give promising yield of the desired product **245a** under oxidative conditions. After screening various ligands, next we examined various oxidants for cyclopropanation (Table 9.3.2). To our delight, the desired product **245a** was isolated in 73% yield using 3 equivalents of DTBP. Formation of cyclopropane was decreased when *tert*-butyl hydroperoxide or di-cumylperoxide were employed (Table 9.3.2 entries 2-3). We did not observe the desired product **245a** formation when hydrogen peroxide, benzoyl peroxide or $PhI(OAc)_2$ (**22**) were used as oxidant (Table 9.3.2 entries 4-8).

Table 9.3.2. Optimization of cyclopropanation with different oxidants.[a]

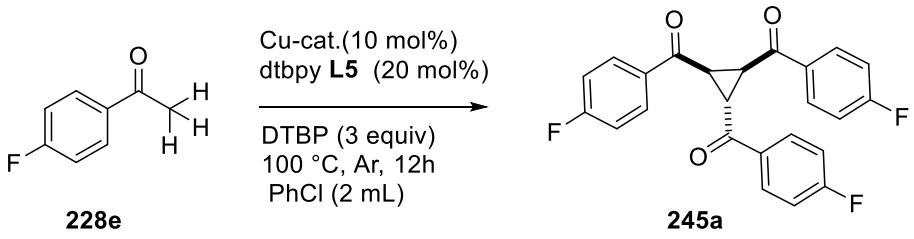


228e **245a**

Entry	Oxidant (x equiv)	Yield (%)	Entry	Oxidant (x equiv)	Yield (%)
1	DTBP (3)	73	6	$K_2S_2O_8$ (2)	n.d.
2	DCP (3)	55	7	$PhI(OAc)_2$ (2)	n.d.
3	TBHP (3)	15	8	H_2O_2 (4)	n.d.
4	TBPB (3)	trace	9	DTBP (2)	55
5	BPO (3)	n.d.	10	DTBP (4)	70

[a] Reaction conditions: **228e** (0.5 mmol), oxidant (x equiv), CuI (10 mol%), dtbpy **L5** (20 mol%) in PhCl (2.0 mL) at 100 °C for 12 h under argon. BOP = Benzoyl peroxide. DCP = Dicumyl peroxide. TBPB = *tert*-Butyl peroxybenzoate. TBHP = *tert*-Butyl hydroperoxide. n.d.= not detected.

Table 9.3.3. Optimization of cyclopropanation with different copper-salts.[a]



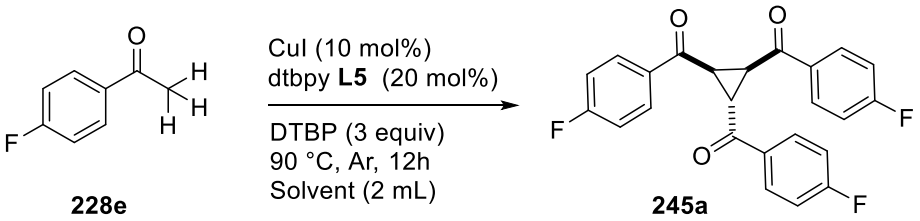
228e **245a**

Entry	Cu-salt	Yield (%)	Entry	Cu-salt	Yield (%)
1	CuCl	72	5	$CuCl_2$	34
2	CuBr	68	6	$Cu(OAc)_2$	trace
3	CuI	73	7	$Cu(OSO_2CF_3)_2$	trace
4	$CuBr{\cdot}SMe_2$	56	8[b]	CuI	86

[a] Reaction conditions: **228e** (0.5 mmol), DTBP (3 equiv), Cu-salt (10 mol%), dtbpy **L5** (20 mol%) in PhCl (2.0 mL) at 100 °C for 12 h under argon. [b] Reaction was carried out at 90 °C for 8 h.

To identify the best catalyst, various copper salts were examined for oxidative cyclopropanation and finally CuI was found to be the best catalyst for the transformation (Table 9.3.3). However, the yield of the desired product was slightly decreased when CuBr or CuCl were used. When $Cu(OAc)_2$ or $Cu(OTf)_2$ were employed, the desired product was not obtained under optimal reaction conditions.

Table 9.3.4. Optimization of cyclopropanation with different solvents.[a]



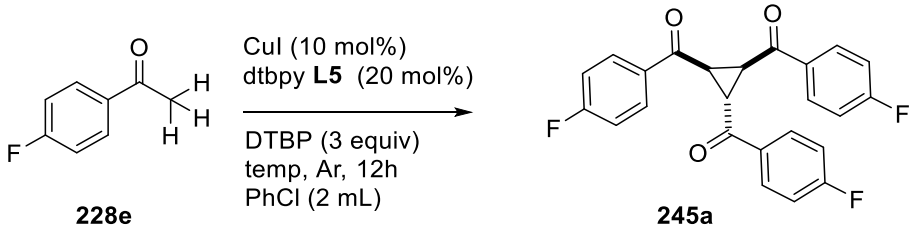
228e **245a**

Entry	Solvent (2 mL)	Yield (%)	Entry	Solvent (2 mL)	Yield (%)
1	Benzene	trace	9	PhCl	86
2	Toluene	trace	10	PhBr	74
3	*p*-Xylene	trace	11	PhF	68
4	ClCHCHCl	trace	12	$PhNO_2$	10
5	DMSO	trace	13	NMP	n.d.
6	DMF	43	14	^{t}AmOH	n.d.
7	DMF(1mL)	51	15	EtCN	15
8	H_2O	n.d.	16[b]	PhCl	48

[a] Reaction conditions: **229e** (0.5 mmol), DTBP (3 equiv), CuI (10 mol%), dtbpy **L5** (20 mol%) in different solvent (2.0 mL) at 90 °C for 8 h under argon. [b] Reaction was carried out with 5 mol% CuI. n.d.= not detected.

After screening different catalysts, we next tested different solvents as well (Table 9.3.4). We did not observe the formation of target product **245a** in protic solvent such as H_2O, ^{t}AmOH. Trace amount of the desired product was obtained when non-polar solvents such as benzene, toluene or *p*-xylene were used. Finally, we found that aromatic halogenated solvents such as PhCl, PhBr or PhF were suitable for the copper-catalyzed oxidative cyclopropanation. After that, chlorobenzene was found to be the best solvent for the discovery of oxidative cyclopropanation of methyl aryl ketone. The effect of temperature was examined under copper-catalyzed cyclopropanation reaction (Table 9.3.5). The best yield of oxidative cyclopropanation could be obtained at 90 °C using 3 equivalents of DTBP. Increasing or decreasing of temperature, formation of the desired product **245a** also was decreased instead of 90 °C (Table 9.3.5, entries 1 and 5). The formation of the desired product **245a** drastically decreased under atmospheric conditions.

Table 9.3.5. Optimization of cyclopropanation with different temperature.[a]



228e 245a

Entry	Temp (°C)	Yield (%)	Entry	Temp. (°C)	Yield (%)
1	70	54	5	110	45
2	80	78	6[b]	90	48
3	90	85	7[c]	90	86
4	100	83	8[d]	90	n.d.

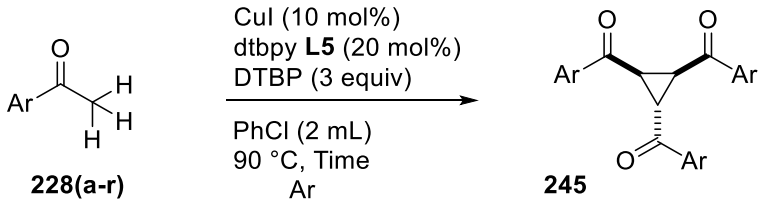
[a] Reaction conditions: **228e** (0.5 mmol), DTBP (3 equiv), CuI (10 mol%), dtbpy **L5** (20 mol%) in PhCl (2.0 mL) at different temperatures for 12 h under argon. [b] Reaction was carried out with 5 mol% CuI; [c] Reaction time 8 h. [d] Reaction was carried out in oxygen. n.d.= not detected.

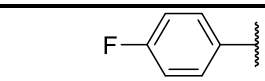
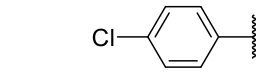
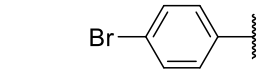
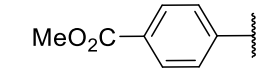
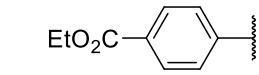
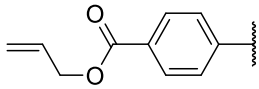
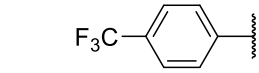
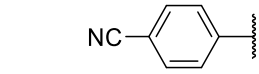
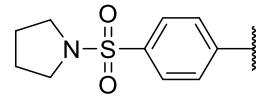
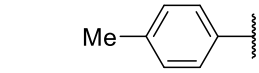
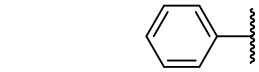
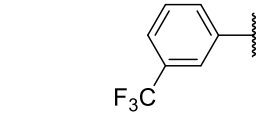
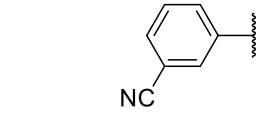
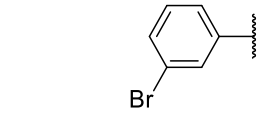
9.4 Scope of Cu(I)-Catalyzed Oxidative (1+1+1) Annulation of Acetophenones

With the optimal reaction conditions in hand, we next explored the substrate scope of the copper-catalyzed oxidative cyclopropanation of methyl aryl ketone derivatives (Table 9.4.1). We found that various acetophenone were well tolerated and obtained the corresponding products in moderate to good yields. Interestingly, various functional groups such as fluoro, chloro, bromo, ester, sulphonamide, methyl and trifluoromethyl on the acetophenones were tolerated under standard conditions. To our delight, various electron-withdrawing groups such as fluoro, chloro, bromo, cyano, ester, sulphonamide and trifluoromethyl on the *para*-position of acetophenones provided the desired products **245a-245j** smoothly. Afterwards, we tested electron-donating group on the acetophenone and obtained the desired products **245j**, **245o** in moderate yield. Substituents at *meta*-positions of acetophenones were well tolerated and provided the corresponding desired products **245l-245m** in good to moderate yield. Furthermore, polysubstituted acetophenones were employed for the cyclopropane synthesis under oxidative conditions (Table 9.4.1, 15 and 16). 3,4-Dimethylacetophenone was well tolerated and provided the desired product **245o** in 53% yield. After that, we assessed the potential of this (1+1+1) cycloaddition of 2-acetylnaphthalene moiety that could be formed three member strained ring without any difficulty. It is remarkable that heterocyclic derivative was found to give the desired product **245t** in 52% yield under developed conditions.

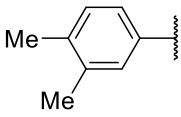
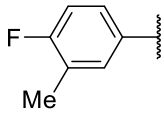
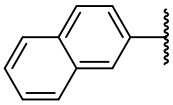
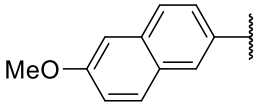
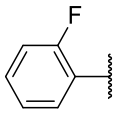
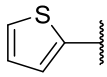
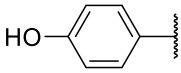
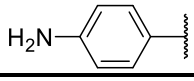
Electron-donating groups such as hydroxyl and anino onto the acetophenone did not provide the desired product under optimized reaction conditions.

Table 9.4.1. Scope of acetophenones.[a]



Entry	Ar	Time (h)	Product	Yield (%)
1		8	**245a**	86
2		8	**245b**	66
3		8	**245c**	73
4		8	**245d**	88
5		8	**245e**	65
6		6	**245f**	43
7		5	**245g**	79
8		6	**245h**	62
9		8	**245i**	35
10		8	**1245j**	43
11[b]		12	**245k**	69
12		8	**245l**	46
13		7	**245m**	68
14		8	**245n**	77

Continuation of **Table 9.4.1**

15[c]		18	**245o**	53
16		18	**245p**	43
17		8	**245q**	65
18[b]		12	**245r**	46
19		8	**245s**	41
20		8	**245t**	52
21		12	**245u**	n.d.
22		12	**245w**	n.d.

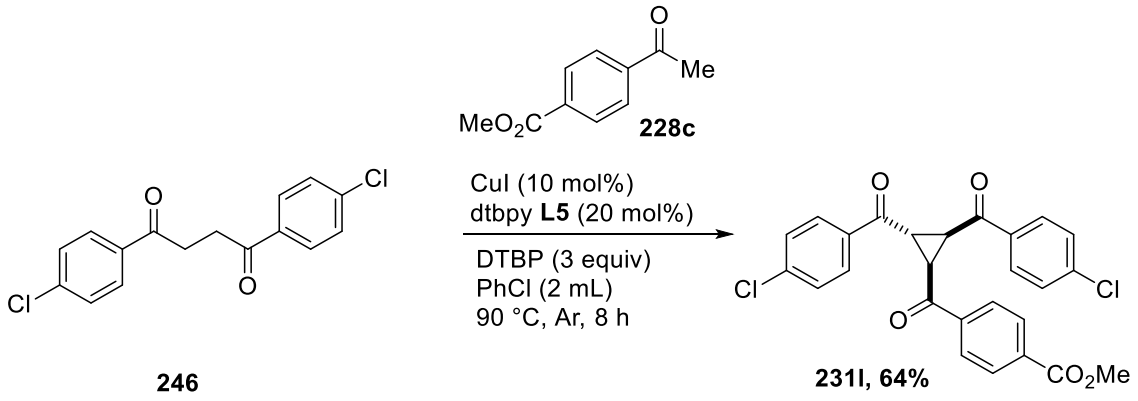
[a] Reaction conditions: **228** (0.5 mmol), DTBP (3 equiv), CuI (10 mol %), **L5** (20 mol%) in PhCl (2.0 mL) at 90 °C for 5-8 h under argon. All products were formed with d.r. >20:1. [b] CuI (20 mol %), **L5** (30 mol %) were used at 75 °C for 12 h under argon. [c] Reaction was carried out in 1 mL DMF for 18 h. n.d. = not detected.

9.5 Studies on Reaction Mechanism

In order to gain insight into the reaction mechanism of copper-catalyzed oxidative cyclopropanation, we conducted several control experiments for understanding the reaction mechanism. We hypothesized that reaction underwent step-wise mechanism. In this context, we prepared several potential intermediates to examine oxidative cyclopropanation under developed reaction conditions.

9.5.1. Reaction with Probable Intermediate 246

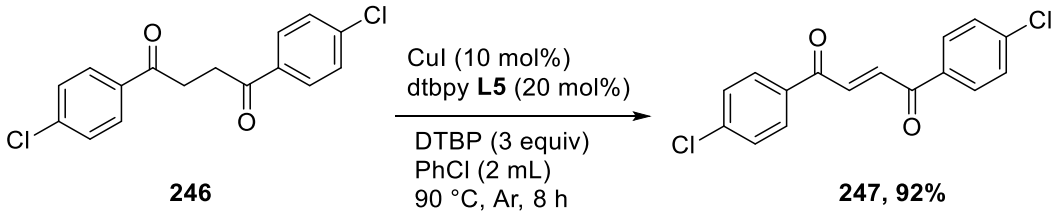
In addition, we performed annulation reaction with probable intermediate **246** with **228c** under optimized reaction conditions and obtained the desired product in 64% yield (Scheme 9.2). This result suggested that annulation reaction proceeded through intermediate **246**.



Scheme 9.2. Reaction with the intermediate **246**.

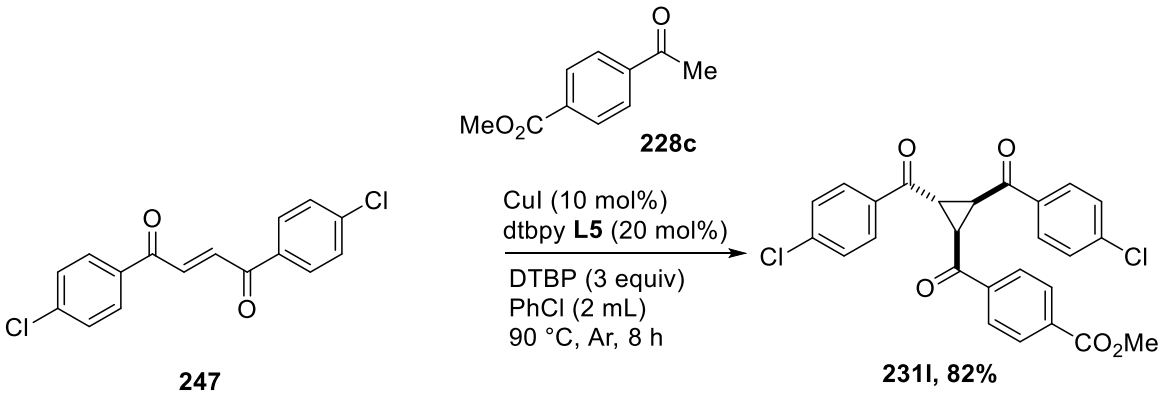
9.5.2 Reaction with Probable Intermediate 246 without 228c

When the control experiment was carried out with intermediate **246** without **228c** under optimal conditions, we observed the formation of (*E*)-1,4-bis(4-chlorophenyl)but-2-ene-1,4-dione **247** in 92% yield (Scheme 9.3). This result indicated that reaction underwent *via* probable intermediate **247**.



Scheme 9.3. Reaction with the intermediate **246** without **228c**.

9.5.3 Reaction with Probable Intermediate 247



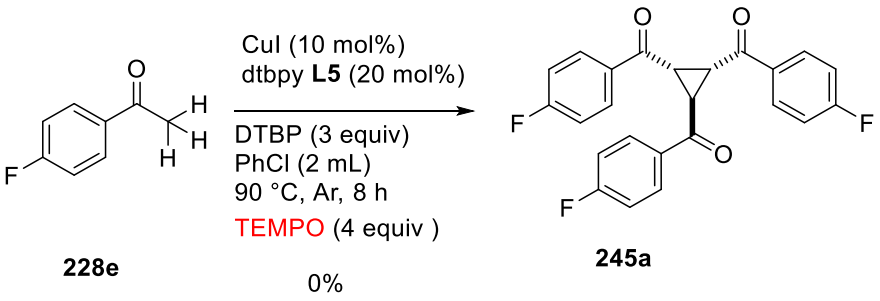
Scheme 9.4. Reaction with the intermediate **247** without **228c**.

Afterwards, we performed the annulation reaction between **228c** and (*E*)-1,4-bis(4-chlorophenyl)but-2-ene-1,4-dione (**247**) (Scheme 9.4). We observed the desired product

formation in 82% yield under optimal reaction conditions. This result supported that the reaction underwent *via* intermediate **247**.

9.5.4 Radical Inhibition Test

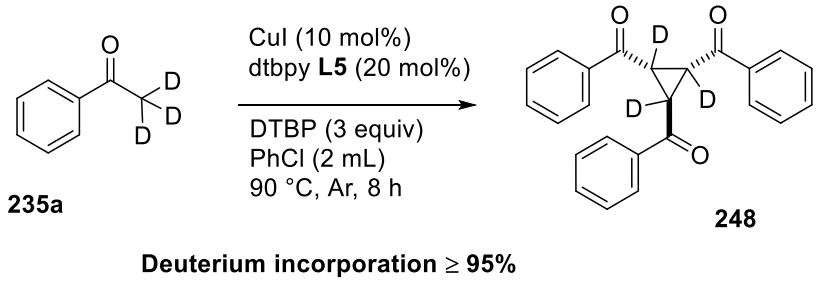
Radical inhibition test was conducted in the presence of radical scavenger TEMPO (**16**). Formation of the desired product was suppressed under optimized reaction conditions in the presence TEMPO (Scheme 9.5). This experimental result supported that cyclopropanation reaction proceeded *via* methyl radical species of acetophenone.



Scheme 9.5. Radical inhibition test.

9.5.5 Reaction with 2,2,2-[$^2H_3$]-1-Phenylethan-1-one

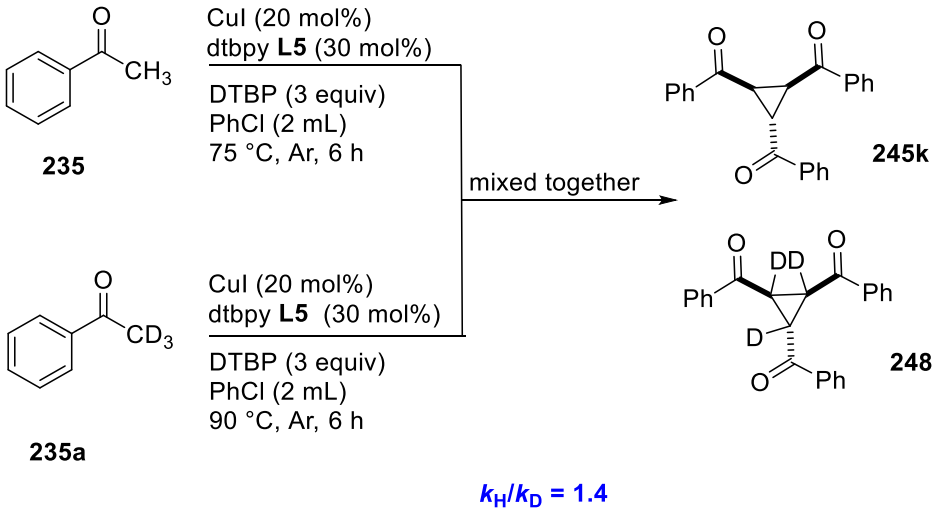
Interestingly, when reaction was carried out with deuterated acetophenone (**235a**) under oxidative reaction conditions, the desired product **248** was obtained in 55% yield with deuterium incorporation ≥ 95% (Scheme 9.6).



Scheme 9.6. Synthesis of product trideuterated product (**248**).

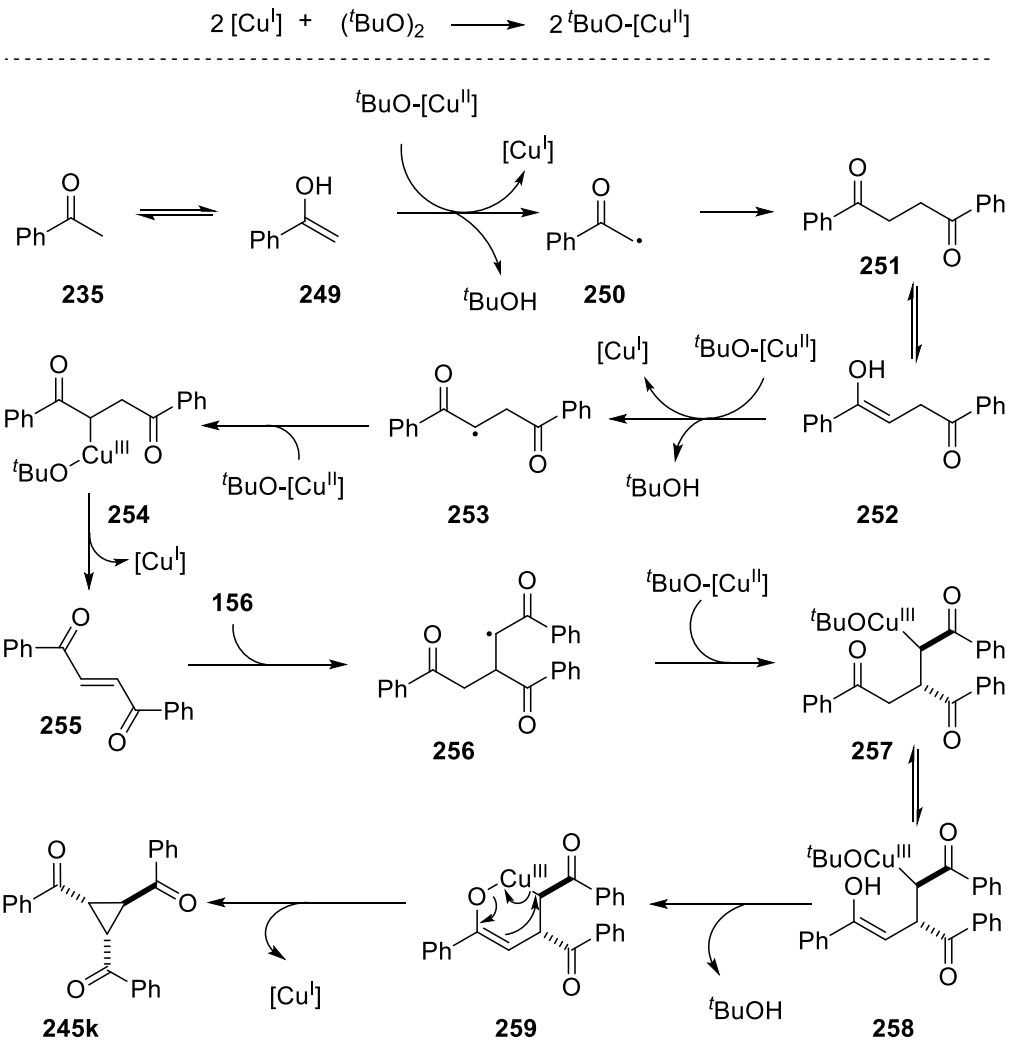
9.5.6 Kinetic Isotope Effect (KIE) Study

Additionally, kinetic isotope effect experiment was performed between **235** and **235a** under standard conditions (Scheme 9.7). The value of k_H/k_D was equal to 1.4 which suggesting that the hydrogen abstraction process from acetophenone is not rate-limiting step.



Scheme 9.7. Kinetic isotope effect experiment.

9.6 Mechanism



Scheme 9.8. Proposed mechanism for Cu-catalyzed trimerization.

Based on our experimental results, a proposed mechanism has been shown in the Scheme 9.8. We described the mechanism for the synthesis of cyclopropane through triple C(sp^3)–H functionalization. First, Cu(II) species was generated in the presence of DTBP *via* oxidation of Cu(I) species. The radical species **250** was formed by oxidation of intermediate **249**. Afterwards, two radical species **250** dimerized to generate the intermediate **251**. The intermediate **253** could be generated from the intermediate **251** *via* oxidation with Cu(II)-species which generated the intermediate **254** after addition of copper(II) species. The intermediate **254** lead to form **255** which could react with **250** and produced the intermediate **256**. Afterwards, the intermediate **257** was formed from the intermediate **256** after addition of Cu(II) species which could be genrated intermediate **258** *via* enolization. The intermediate **258** could be led to form the intermediate **259** *via* ligand exchange of copper centre. Finally, product **245k** was generated by reductive elimination of Cu(I) from **259**. Cu(II) species was regenerated by the oxidation of Cu(I) in the presence of DTBP.

9.7 Identification of Biological Activity of Cyclopropane Derivatives

According to our plan, we synthesized compound libraries of cyclopropane derivatives. Afterwards, we submitted all compounds to COMAS (Compound Management and Screening Centre) in Dortmund to find the biological activity. Several cell-based assays such as hedgehog signaling pathway and Wnt signaling pathway and autophagy were tested. After screening different assays, we did not obtain biological results.

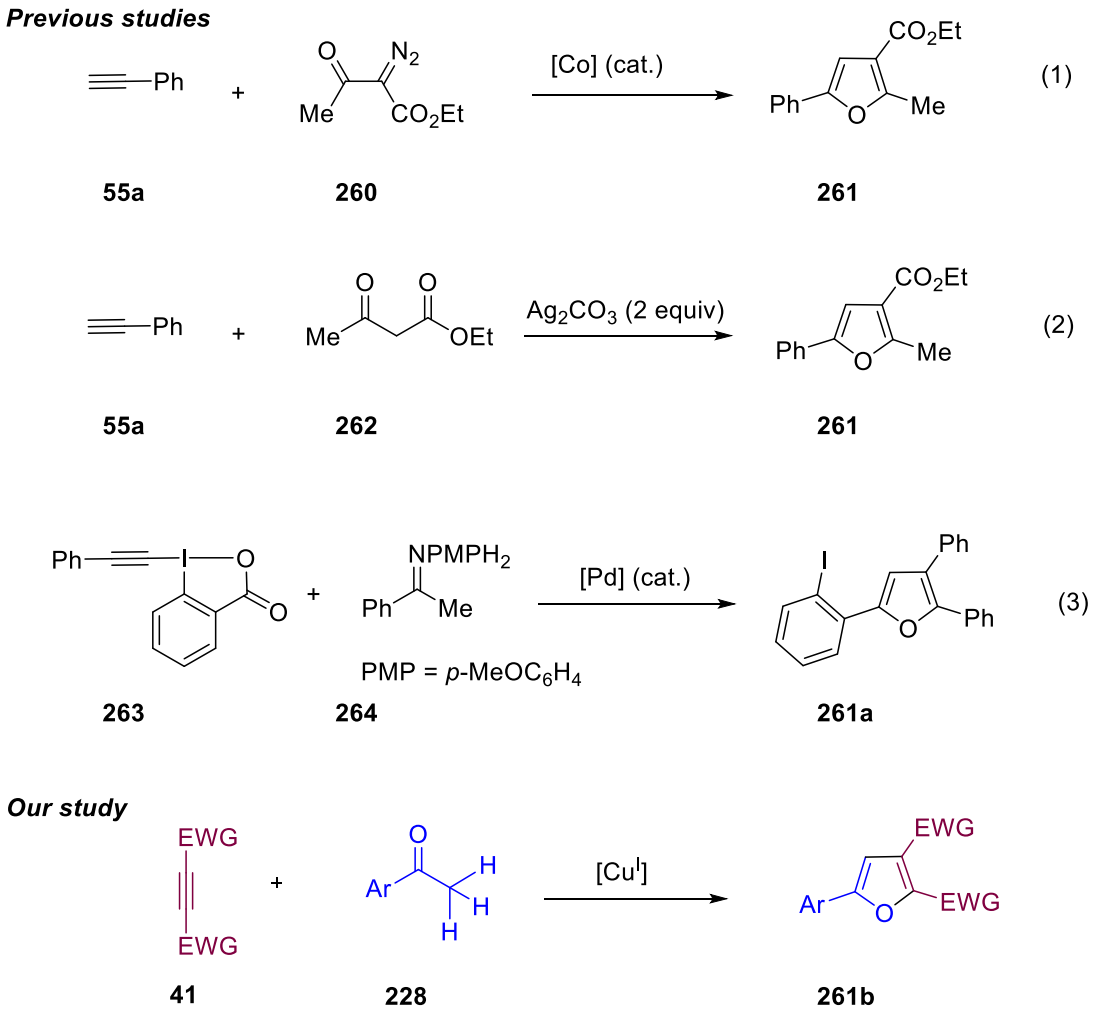
Chapter 10.

Copper(I)-Catalyzed (3+2) Oxidative Annulation of Acetophenones with Electron-Deficient Alkynes

(This part of the work already published: S. Manna, and A. P. Antonchick, *Org. Lett.* **2015**, *17*, 4300-4303.)

10.1 Introduction

Oxygen containing heterocycles represents one of the most important classes of compounds.[238-242] Among them, furans are ubiquitous structural motif found in many natural products, agrochemicals, pharmaceuticals and biologically active drug molecules.[124-125, 243] Multisubstituted furans have found a widespread application in organic synthesis as building blocks.[240-241, 244-247] In this regard, several attractive methods for the synthesis of furans were developed using various transition-metal catalyst and under metal-free conditions employing functionalized feedstocks.[57, 248-252]



Scheme 10.1. Metal catalyzed furan synthesis.

Conventionally furan derivatives are synthesized by Paal-Knorr method which relies upon acid catalyzed cyclization of 1,4-dicarbonyl compound.[248, 251] Multisubstituted furans are prepared intermolecular approach using Feist-Benary method from α-haloketones and β-dicarbonyl.[253-254] In the recent years, transition-metal catalyzed intramolecular approaches to the synthesis of multisubstituted furan derivatives have been reported employing allenyl

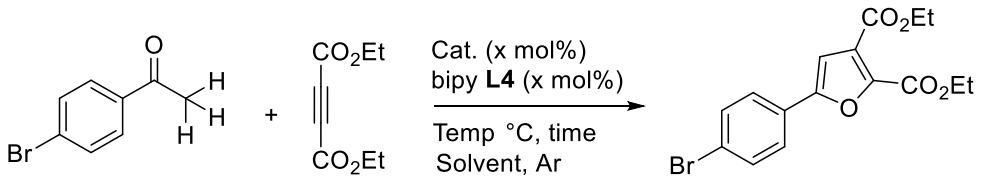
ketone.[255-261] Very recently, Zhang and co-workers developed the synthesis of furans with alkynes and *α*-diazocarbonyls through Co-catalyzed metalloradical cyclization.[262] Lei and co-workers disclosed a novel silver mediated an efficient method to furans using alkynes and 1,3-diketones compounds.[263] Recently, palladium-catalyzed synthesis of furans has been developed by Yoshikai and co-workers employing imine derivatives of acetophenones and alkynylbenziodoxolones.[264-265] However, reported methods require prefunctionalized precursors, stoichiometric amount of metals and longer reaction time. It is notable that synthesis of multisubstituted furan employing acetophenone with electron-deficient alkyne has never investigated. Therefore, development of a novel method to multisubstituted furans *via* C–H bond functionalization would be highly attractive method in organic synthesis. In this regards, we were interested to develop a novel strategy for copper(I)-catalyzed oxidative (3+2) annulation of acetophenones with electron-deficient alkynes to access multisubstituted furan derivatives.

10.2 Result and Discussion

10.3 Studies on the Optimization of Reaction Conditions

During the study on oxidative annulation of acetophenones with maleimides for the synthesis of cyclopropanes, we envisaged that synthesis of furan derivatives by employing aryl methyl ketones with electron-deficient alkynes would be significant advantage.[266] To test our hypothesis, the reaction was initiated with 4-bromoacetophenone (**228h**) and diethyl acetylenedicarboxylate (**265a**) in the presence of CuI (20 mol%), 2,2'-bipyridine (30 mol%) and 3 equivalents of di-*tert*-butylperoxide (DTBP) in PhCl at 110 ºC for 12 h (Table 10.3.1). Interestingly, the desired product **266a** was isolated in 45% yield under oxidative conditions. Encouraged by the initial result, we first examined different ligands. Pleasingly, 2,2'-bipyridine (**L4**) was found to be the best ligand in this transformation and the yield could be obtained in 64% using CuI as a pre-catalyst. It was notable that while reaction was performed at higher or lower temperature resulted in a lower yield (Table 10.3.1 entries 4 and 20). Afterwards, various solvents were tested and the reaction showed strongly solvent dependent (Table 10.3.1, entries 7-14). We observed that chlorinated solvent such as PhBr, PhCl, PhF or 1,2-dichloroethane were efficient solvents to deliver the desired product **266a**. Finally, 1,2-dichloroethane was found to be the best solvent for the annulation of **228h** with **265a** to obtain product **266a** in 64% yield (Table 10.3.1, entry 14).

Table 10.3.1. Optimization of reaction conditions.[a]



228h **265a** **266a**

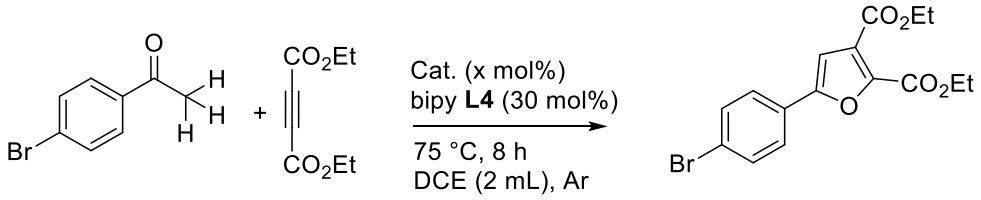
Entry	Solvent (2 mL)	Oxidant (equiv)	Metal salt (mol%)	Temp (°C)	Ligand (mol%)	Yield (%)
1	PhCl	DTBP (3)	CuI (15)	110	30	42
2	PhCl	DTBP (3)	CuI 30)	110	30	40
3	PhCl	DTBP (3)	CuI (20)	110	30	45
4	PhCl	DTBP (3)	CuI (20)	110	40	34
5	DCE	DTBP (3)	CuI (20)	80	30	47
6	DCE	DTBP (3)	CuI(20)	60	30	25
7	MeCN	DTBP (3)	CuI (20)	75	30	trace
8	$PhNO_2$	DTBP (3)	CuI (20)	75	30	25
9	PhF	DTBP (3)	CuI (20)	75	30	39
10	PhBr	DTBP (3)	CuI (20)	75	30	46
11	PhH	DTBP (3)	CuI (20)	75	30	trace
12	DCE	DTBP (3)	CuI (20)	75	30	45
13	2-^{i}PrOH	DTBP (3)	CuI (20)	75	30	n.d.
14[b,c]	DCE	DTBP (3)	CuI (20)	75	30	64

[a] Reaction conditions: **288h** (0. 75 mmol), **265a** (0. 25 mmol), DTBP (3 equiv), CuI (20 mol%), 2,2'-bipyridine **L4** (30 mol%) in DCE (2.0 mL) at 75 °C for 5-8 h under argon. [b] Solid starting mixture was degassed by freezing it in liquid nitrogen, replacing the atmosphere with argon and allowing it to warm to room temperature (repeated two times). [c] Reaction time 8 h. DCE = 1,2-dichloroethane. n.d.= not detected.

After screening different solvents, we next screened different copper salts such as CuBr, CuI, CuCl, Cu_2O, CuF_2 or $CuBr{\cdot}SMe_2$ as a catalyst. Notably, $CuBr{\cdot}SMe_2$ was to be the best catalyst for oxidative furan synthesis and desired produce product **266a** was isolated in 70% yield (Table 10.3.2, entry 9). Furthermore, we examined various oxidants for multisubstituted furan synthesis. Several oxidants, such as TBHP, BPO or H_2O_2 were failed to produce the

desired annulated product **266a (**Table 10.3.2, entries 12-14**)**. Interestingly, di-cumyl-peroxide (DCP) and di-*tert*-butylperoxide (**20**) were suitable to produce the product **266a** under

Table 10.3.2. Optimization of reaction condition with different catalysts and oxidants.[a]



228h **265a** **266a**

Entry	Oxidant (equiv)	Cat. (mol%)	Yield (%)
1	DTBP (3)	CuCl (20)	32
2[b]	DTBP (3)	CuBr (20)	53
3	DTBP (3)	CuCN (20)	trace
4	DTBP (3)	CuF_2 (20)	n.d.
5	DTBP (3)	Cu_2O (20)	trace
6	DTBP (3)	$Fe(acac)_3$ (20)	n.d.
7[c,d]	DTBP (3)	CuI (20)	64
8[c,d]	DTBP (3)	CuBr (20)	68
9[c,d]	DTBP (3)	$CuBr{\cdot}SMe_2$ (20)	70
10[b,d]	DTBP (5)	CuBr (20)	44
11[b,d]	DTBP (4)	CuBr (20)	65
12	BPO (3)	CuI (20)	trace
13	H_2O_2 (3)	CuI (20)	trace
14	TBHP (3)	CuI (20)	trace
15	DCP (3)	CuI (20)	55
16[e]	DTBP (3)	CuBr (20)	44
17	DTBP (3)	CuI (20)	trace

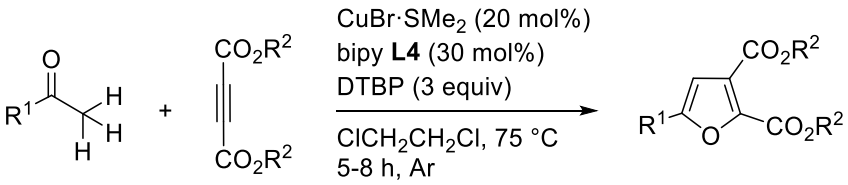
[a] Reaction conditions: **288h** (0. 75 mmol), **265a** (0. 25 mmol), DTBP (3 equiv), CuI (20 mol%), 2,2'-bipyridine **L4** (30 mol%) in DCE (2.0 mL) at 75 °C for 8 h under argon. [b] Fresh degassed DCE was used. [c] Solid starting mixture was degassed by freezing it in liquid nitrogen, replacing the atmosphere with argon and allowing it to warm to room temperature (repeated two times). [d] Reaction time 8 h. [e] 1 equiv SMe_2 was used. DTBP = Di-*tert*-butyl hydrogen peroxide. TBHP = *tert*-Butyl hydrogen peroxide. BPO = Dibezyl peroxide. DCP = Dicumyl peroxide.

oxidative conditions. The temperature effect of furan synthesis was examined. The best yield was obtained while reaction was conducted at 75 ºC. The formation of product **266a** drastically decreased under atmospheric condition.

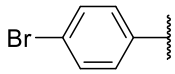
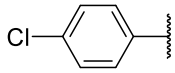
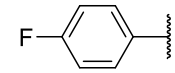
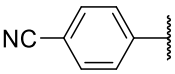
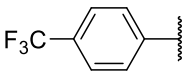
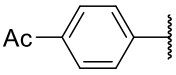
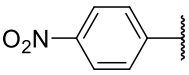
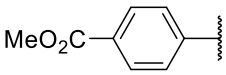
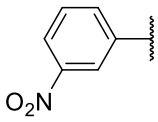
10.4 Scope of Copper(I)-Catalyzed Oxidative Furans Synthesis

With fully optimized reaction conditions in hand, a wide range of aryl methyl ketones were then examined with **265a** under copper(I)-catalyzed annulation reaction conditions (Table 10.4.1). The formations of multisubstituted furan derivatives were observed with various functionalized acetophenones. We were pleased to find that various acetophenones could be transferred into the corresponding products in moderate to good yield. To our delight, *meta*-

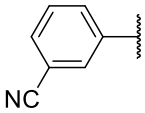
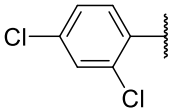
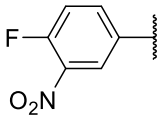
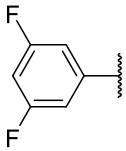
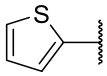
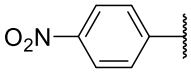
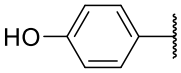
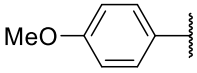
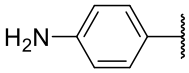
Table 10.4.1. Scope of Aryl methyl ketones.[a]



228 (a-r) **265 (a-b)** **266**

Entry	R^1	R^2	Product	Yield (%)
1		Et	**266a**	70
2		Et	**266b**	75
3		Et	**266c**	45
4		Et	**266d**	76
5		Et	**266e**	66
6		Et	**266f**	67
7		Et	**266g**	78
8		Et	**266h**	65
9		Et	**266i**	56

Continuation of **Table 10.4.1**

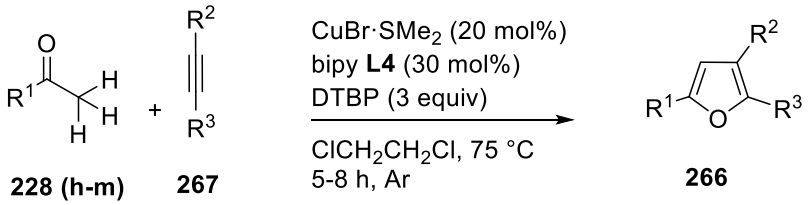
10		Et	**266j**	72
11		Et	**266k**	56
12		Et	**266l**	70
13		Et	**266m**	61
14		Et	**266n**	48
15		Me	**266o**	66
16		Me	**266p**	n.d.
17		Me	**266q**	n.d.
18		Me	**266r**	n.d.

[a] Reaction conditions: **228** (0. 75 mmol), **265** (0. 25 mmol), DTBP (3 equiv), CuBr·Me2S (20 mol%), bipy **L4** (30 mol%) in DCE (2.0 mL) at 75 °C for 5-8 h under argon. [b] 4 Equiv aryl methyl ketone was used. n.d. = not detected.

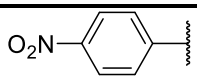
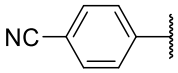
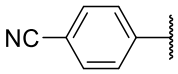
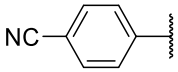
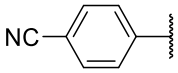
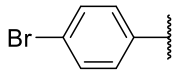
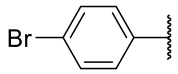
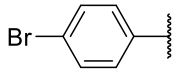
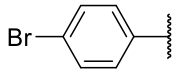
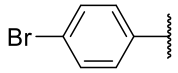
substituted acetophenones were well tolerated and the desired products (**266i-266j**) proceeded in moderate to good yield. Various functional groups on the aryl part were compatible with oxidative conditions and annulation reaction afforded the desired products (**266k-266m**) smoothly. Gratifyingly, 2-acetylthiophene provided the corresponding desired product **266n** in 48 % yield efficiently under developed reaction conditions. Unfortunately, electron-donating groups such as hydroxyl, methoxy and amino onto the acetophenone were not tolerated under optimal conditions.

After successfully established the scope of acetophenones, we further explored the scope of the copper(I)-catalyzed oxidative furans synthesis with a series of alkyl acetylenedicarboxlate under developed reaction conditions (Table 10.4.2). To our delight, various alkyl substituted

Table 10.4.2. Scope of different alkynes.[a]



228 (h-m) **267** **266**

Entry	R^1	R^2	R^3	Product	Yield (%)
1		CO_2n-Pr	CO_2n-Pr	**266s**	76
2		CO_2n-Hex	CO_2n-Hex	**266t**	72
3		CO_2allyl	CO_2allyl	**266u**	51
4[b]		CO_2(+)-menthol	CO_2(+)-menthol	**266v**	80
5[b]		CO_2(+)-borneol	CO_2(+)-borneol	**266w**	47
6		Ph	CO_2H	**266x**	n.d.
7		Me	CO_2H	**266y**	n.d.
8		CO_2H	CO_2H	**266z**	n.d.
9		Ph	Ph	**266ab**	n.d.
10		Ph	H	**266ac**	n.d.

[a] Reaction conditions: **228** (0. 75 mmol), **267** (0. 25 mmol), DTBP (3 equiv), CuBr·Me_2S (20 mol%), **L4** (30 mol%) in DCE (2.0 mL) at 75 °C for 5-8 h under argon. [b] 4 equiv arylmethylketone were used. n.d. = not detected.

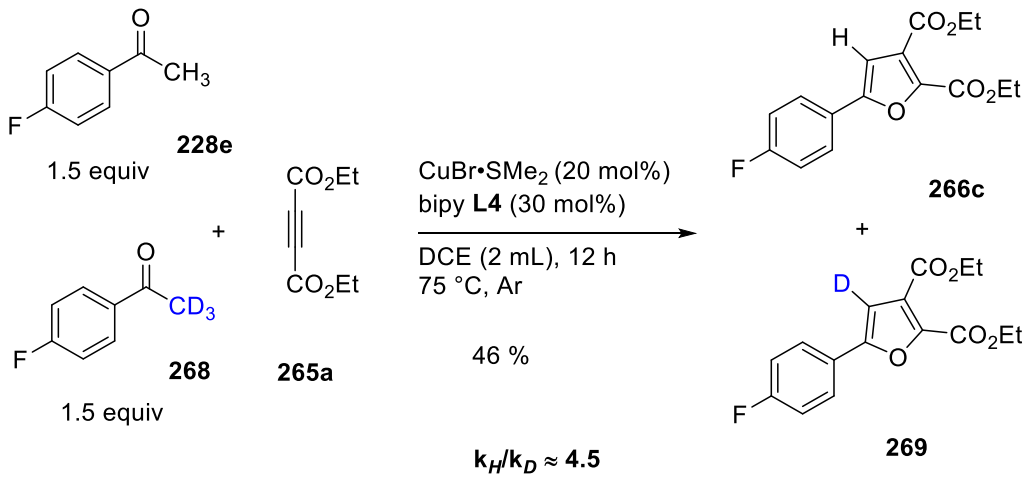
esters of acetylenedicarboxylic acid provided the corresponding furan derivatives (**226s-226w)** under oxidative reaction conditions. Long-chain-aliphatic substituted acetylenedicarboxylate ester derivatives were anticipated and observed formation of products **226s-226u** in good yield. Interestingly, diallyl but-2-ynedioate well tolerated under radical reaction conditions and obtained the desired product **266u** in 51% yield. Gratifyingly, an ester derivative of (+)-menthol and (+)-borneol of but-2-ynedioic acid, gave the desired products **266v** and **266w** smoothly in moderate to good yield. Ethylpropiolate, phenylacetylene and

diphenylacetylene derivatives did not give the desired products under optimized reaction conditions.

10.5 Studies on Reaction Mechanism

10.5.1 Kinetic Isotope Effect (KIE) Study

In order to gain insight into the reaction mechanism of the copper-catalyzed furan synthesis, we performed several experimental studies. We next conducted kinetics isotope effect (KIE) experiment between **228e** and **268** under optimal reaction condition. We observed large kinetic isotope effect equal to 4.5 ($k_H/k_D \approx 4.5$). This study suggested that the hydrogen abstraction from the acetophenone derivative is not the rate-determining step.

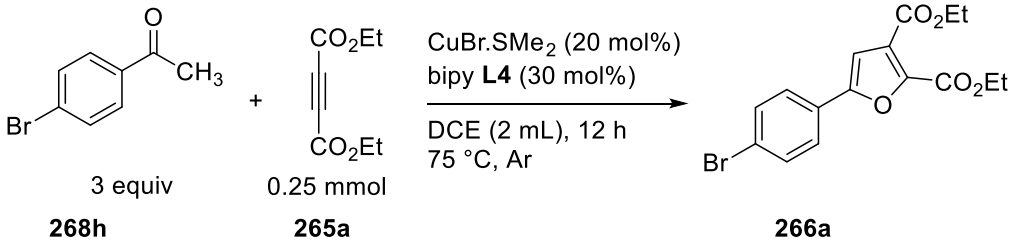


Scheme 10.2. Kinetics isotope effect (KIE) experiment.

10.5.2 Radical Inhibition Studies

Initially, we were wondering whether the annulation reaction underwent *via* radical pathway or other reaction pathway. In this regards, we have performed radical trapping experiment under our optimized reaction conditions using radical scavenger. In the presence of radical scavenger such as TEMPO (**16**), (*Z*)-*N*-*tert*-butyl-1-phenylmethanimine oxide (**270**) and 2,6-di-*tert*-butylphenol (**271**), we did not observe the desired product formation. These result suggested that reaction proceeded *via* radical intermediate.

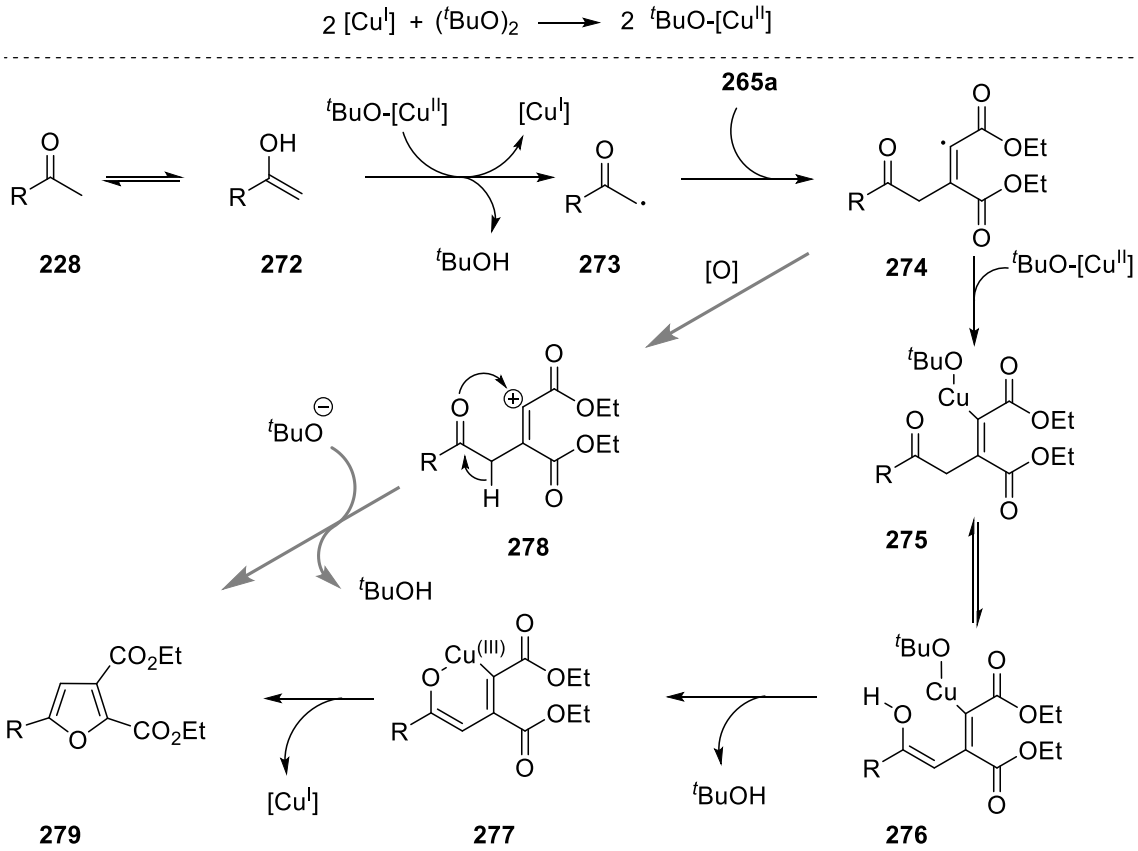
Table 10.5.1. Reaction with different radical scavengers.[a]



Entry	Additive	Yield (%)
1	none	68
2	TEMPO (**16**)	
3	(*Z*)-*N*-*tert*-butyl-1-phenylmethanimine oxide (**270**)	n.d.
4	2,6-di-*tert*-butylphenol (**271**)	n.d.

[a] Reaction conditions: **268h** (0.75 mmol), **265a** (0. 25 mmol), DTBP (3 equiv), CuBr·Me_2S (20 mol%), bipy **L4** (30 mol%), additive (2 equiv) in DCE (2.0 mL) at 75 °C for 12 h under argon.

10.6 Mechanism



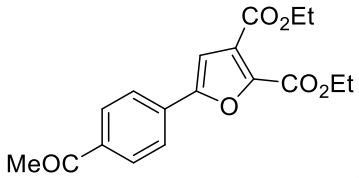
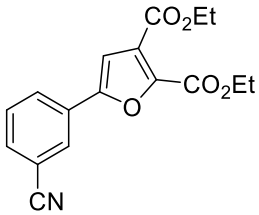
Scheme 10.3. Proposed mechanism for furan synthesis.

Based on our previous studies and preliminary experimental results, a plausible mechanism has been proposed in the Scheme 10.3. At the beginning, the copper (II) species was generated from cupper(I) species by oxidation with DTBP.[230] Then, the reaction of enol form of acetophenone (**228**) with copper(II) species could be generated the intermediate **273** which reacted with electron-deficient alkyne (**265a**) to form the intermediate **274**. Afterwards, the intermediate **275** was formed from the intermediate **274** after addition of copper(II) species which could be formed intermediate **276**. The intermediate **276** could be led to form intermediate **277** *via* ligand exchange of copper center of intermediate **276**. Finally, product **279** was produced by reductive elimination of copper(I) from **277**. Alternative way of product **279** could be formed *via* oxidation of intermediate **274** to lead the intermediate **278** which C–O cyclized followed by oxidation. The Cu(II) species was regenerated by oxidation of Cu(I) with DTBP.

10.7 Identification of Biological Activity of Furan Derivatives

According to our plan, we synthesized compound libraries of furan derivatives. Afterwards, we submitted all compound to COMAS (Compound Management and Screening Centre) in Dortmund to find the biological activity. Several cell-based assays such as hedgehog signaling pathway and Wnt signaling pathway and autophagy were tested. After screening different assays, two compounds **266f**, and **266j** inhibited the hedgehog signaling pathway in the low micro molar range (Table 10.7.1).

Table 10.7.1. Results of hedgehog signaling pathway.

Entry	Product	IC_{50} [µM]	Viability [µM]
1	 **266f**	6.01±0.44	inactive
2	 **266j**	6.51±0.38	inactive

11 Summary

In the present work, emphasis is given on the synthesis of biologically relevant compound libraries *via* oxidative annulation of non-prefunctionalized precursors. The thesis is mainly focused on the development of new methods for the synthesis of nitrogen, oxygen-containing

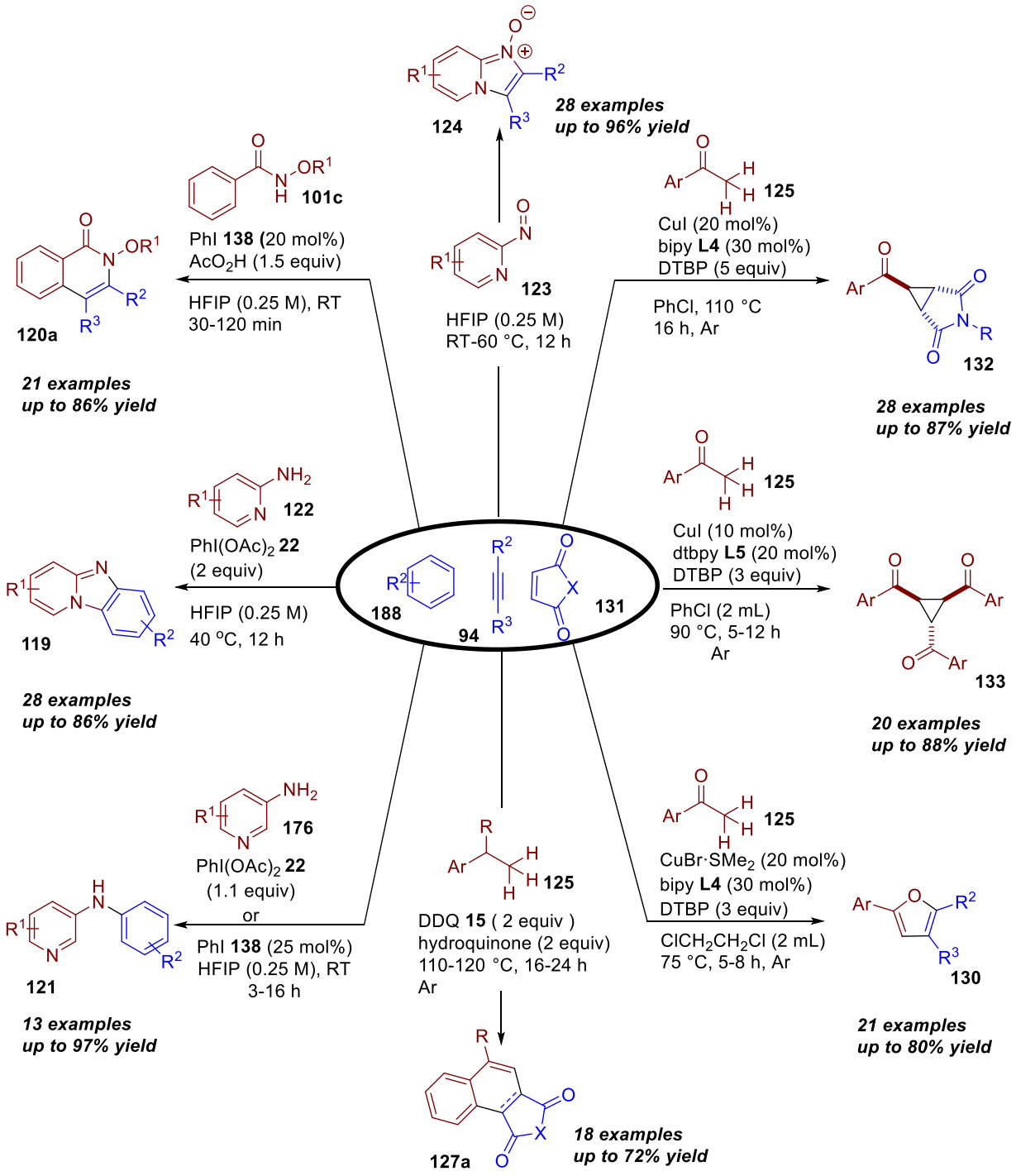
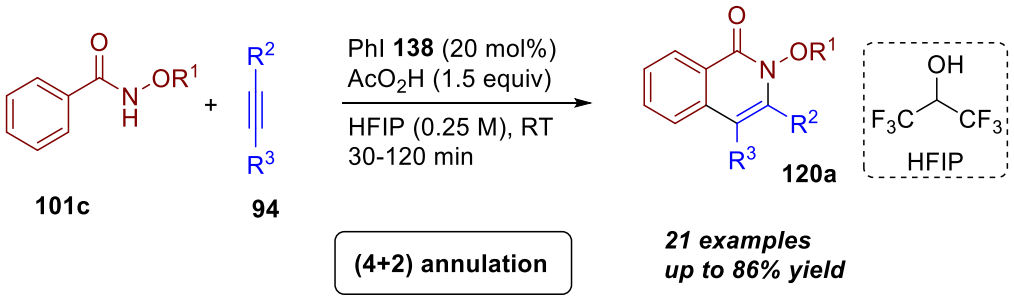


Figure 11.1. Summary of oxidative annulation *via* C–H bond functionalization in the syntheses of biologically relevant compounds.

heterocycles and carbocycles under annulation conditions. The "privileged scaffolds" were obtained employing metal-free conditions and copper catalyst. In the first part of this work, the focus was oriented in the synthesis of isoquinolones, pyrido[1,2-*a*]benzimidazoles and *N*-arylated pyridine scaffolds using hypervalent iodine (III) reagents. Furthermore, synthesis of imidazo[1,2-*a*]pyridine 1-oxide derivatives were described *via* annulation of various nitrosopyridines with alkynes and alkenes. In the second part of the work, oxidative annulations *via* C(sp^3)–H bond functionalization were investigated. In this respect, a novel dehydrogenative Diels-Alder reaction of alkylbenzenes and electron-deficient alkenes and dehydrogenative nitration of alkyl benzenes were demonstrated using DDQ as oxidant. Development of novel methods for the syntheses of fully substituted cyclopropanes and furans *via* functionalization of acetophenones were described.

11.1 Hypervalent Iodine (III) Mediated Oxidative Annulations

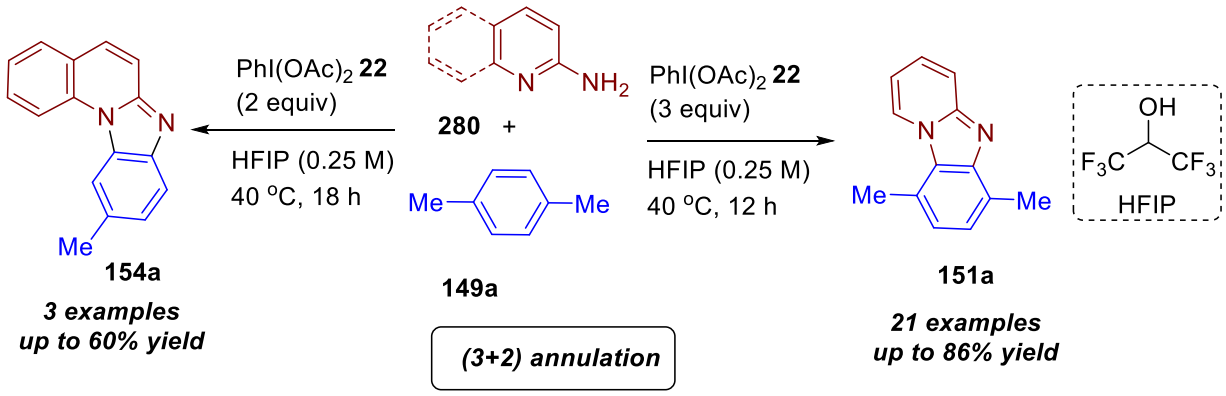
In the first project, organocatalyzed regioselective oxidative annulation of *N*-alkoxybenzamides (**101c**) with readily available alkynes (**94**) was described. The iodobenzene as a simple catalyst in combination with peracetic acid as oxidant was employed for the synthesis of biologically important isoquinolone scaffolds under mild reaction conditions. The developed method was applied in the annulation of various symmetric as well as unsymmetrical alkynes with different substituted benzamide derivatives. Unsymmetrical alkynes provided regioselectively single isomer which was confirmed by NOE and COSY analysis. The yields of this methodology ranged from moderate to excellent with very short reaction time. Furthermore, N–O bond cleavage of alkoxyisoquinolone was carried out to obtain the corresponding isoquinolone scaffold.



Scheme 11.1. Organocatalyzed isoquinolone synthesis.

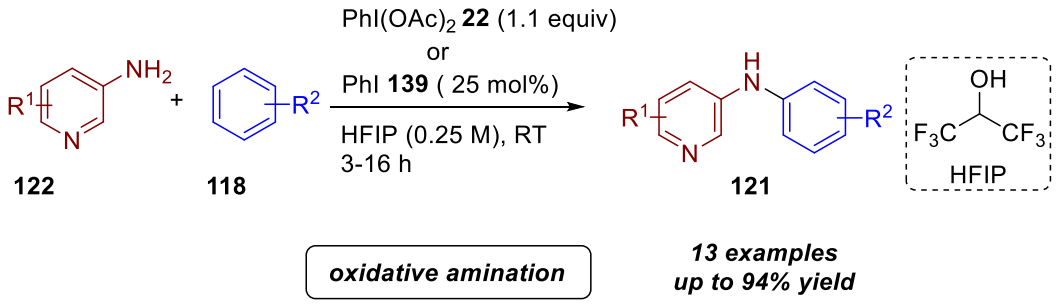
In the second project, a novel (3+2) annulation of 2-aminopyridine and 2-aminoquinoline derivatives with simple arenes were demonstrated under oxidative conditions employing $PhI(OAc)_2$ (**22**) as oxidant. The developed method tolerated a broad range of diversely

functionalized 2-aminopyridine derivatives to access biologically important pyrido[1,2-*a*]benzimidazole scaffolds under mild reaction conditions. In addition, the methyl group of arenes as a traceless directing group in the synthesis of benzo[4,5]imidazo[1,2-*a*]quinolone derivatives were developed.



Scheme 11.2. Hypervalent iodine (IIII) mediated pyrido[1,2-*a*]benzimidazole and benzo[4,5]imidazo[1,2-*a*]quinolone synthesis.

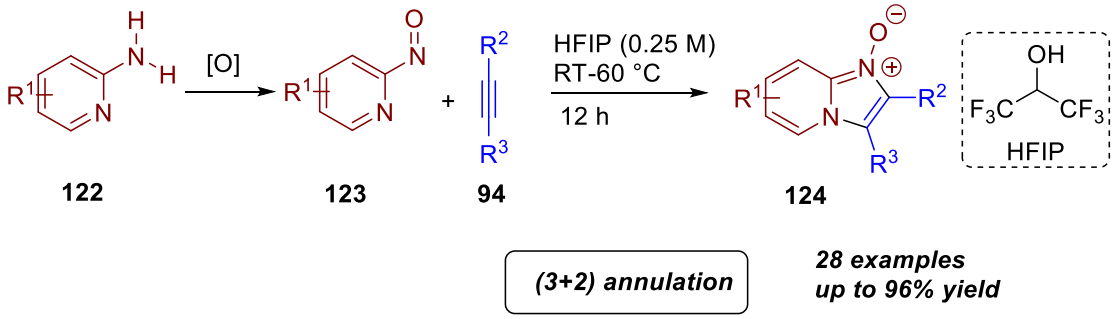
In the third project, metal-free amination of heteroarylamines with non-prefunctionalized arenes were established. This process realized pharmaceutically useful scaffolds of *N*-arylated heteroaromatic amines using $PhI(OAc)_2$ (**22**) as oxidant. Various 3-aminopyridine derivatives bearing differently functional groups were well tolerated and the yields of amino compounds were excellent in these conditions. Further, the development of an organocatalytic version of aforementioned reaction was developed. The oxidative amination reaction was successful under organocatalytic conditions and the corresponding products were obtained in moderate to good yields.



Scheme 11.3. Hypervalent iodine (III) in oxidative amination.

11.2 Metal-free Regioselective Annulation of Nitrosopyridines with Alkynes

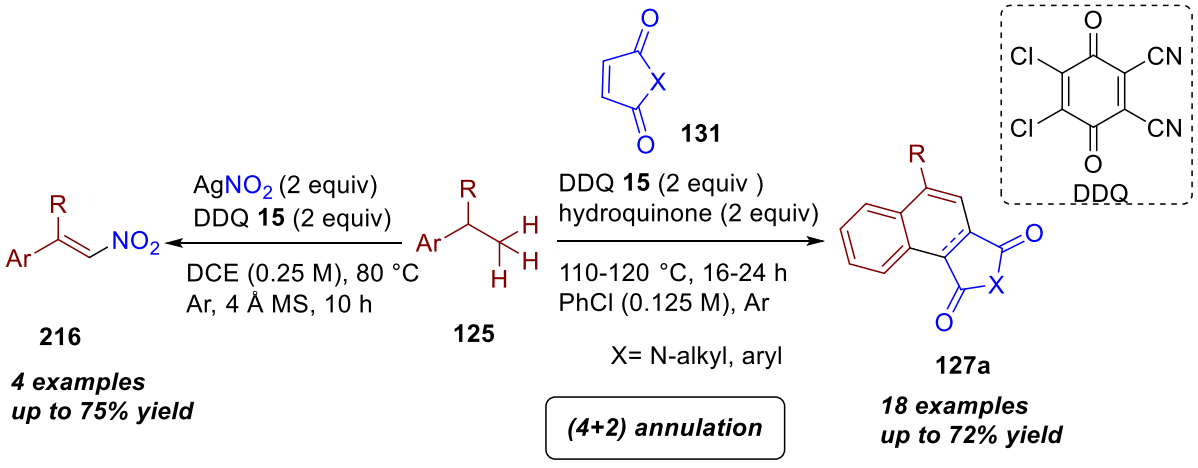
In the course of these studies, effort was also put to develop a new method for the synthesis of imidazo[1,2-*a*]pyridines under metal and reagents free conditions (Scheme 11.4). This was achieved through a metal-free regioselective (3+2) annulation of nitrosopyridines with alkynes and alkenes. According to our knowledge, for the first time regioselective annulation of nitrosopyridines was developed under both catalyst and additive free conditions. In the annulation reaction, various functional groups were well tolerated and provided imidazo[1,2-*a*]pyridine 1-oxide derivatives in good to excellent yield. Furthermore, *N*–oxides products could be deoxygenated under heating condition to obtain imidazo[1,2-*a*]pyridine motifs.



Scheme 11.4. Metal free imidazo[1,2-*a*]pyridine 1-oxide synthesis.

11.3 Oxidative Annulation of Alkylarenes with Electron-Deficient Alkenes

Carbon-hydrogen (C–H) bonds are ubiquitous in nature and have found many significant advantages to utilize C–H bond functionalization for the construction C–C bond in an atom and the step economical way. In this regards, oxidative dehydrogenative Diels-Alder (DDA) reaction and nitration of alkylarenes *via* C–H bond functionalization were studied in details. DDQ (**15**) mediated oxidative dehydrogenative Diels-Alder reaction of alkylarenes and

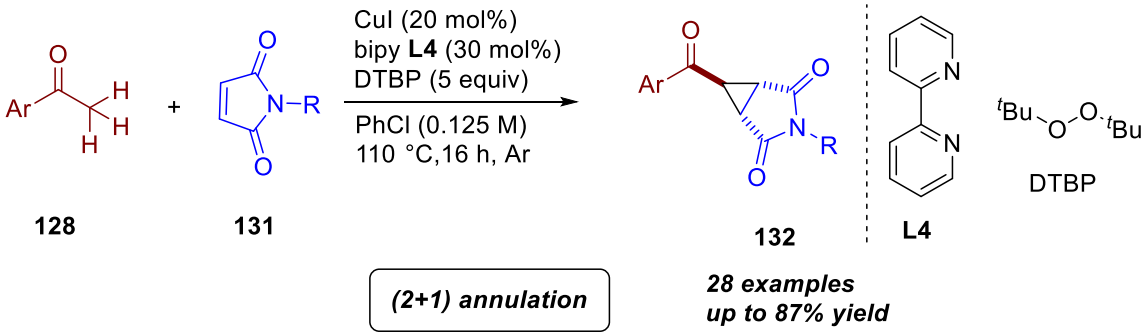


Scheme 11.5. Oxidative dehydrogenative Diels-Alder reaction and nitration.

electron deficient alkenes was developed (Scheme 11.5). The process was carried out with 2 equivalents of DDQ (**15**) as oxidant, 2 equivalents of hydroquinone as additive in chlorobenzene under argon atmosphere and the synthesis of 1,4-phenanthraquinone and isoindolone scaffolds were realized. The reaction showed tolerance to various substituted arenes yielding the corresponding desired product. Mechanistic studies suggested that oxidative annulation reaction underwent *via* styrene intermediate with *in-situ* formation of quinhydrone. Furthermore, a dehydrogenate stereoselective nitroalkenes synthesis from alkylbenzenes was also developed employing $AgNO_2$ as nitrating agent (Scheme 11.5).

11.4 Oxidative Annulation of Acetophenones *via* C(sp^3)–H Bond Functionalization

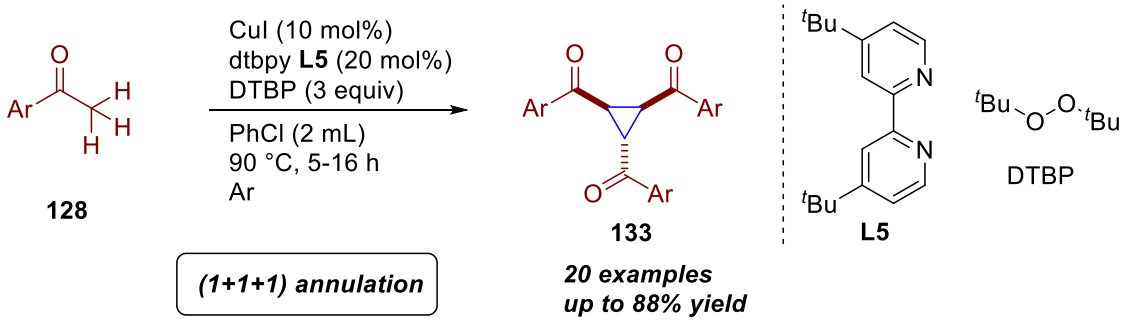
Furthermore, the investigations of acetophenones for the oxidative annulation *via* C–H bond functionalization were described. In the sixth project, a novel Cu(I)-catalyzed oxidative (2+1) cyclopropanation of aryl methyl ketones with electron-deficient alkenes were demonstrated using 20 mol% CuI in combination with 30 mol% 2,2'-bipyridine (**L4**) as ligand in the presence of DTBP as oxidant in chlorobenzene (Scheme 11.6). Diverse ranges of acetophenones and maleimide derivatives were tolerated under such mild reaction conditions. Interestingly, the method allowed stereoselectively (2+1) annulation of acetophenones with electron-deficient alkenes and provided the straightforward way in the synthesis of strain cyclopropanes. Mechanistic studies revealed that the reaction underwent *via* a novel radical oxidative pathway.



Scheme 11.6. Synthesis of cyclopropane *via* (2+1) annulation.

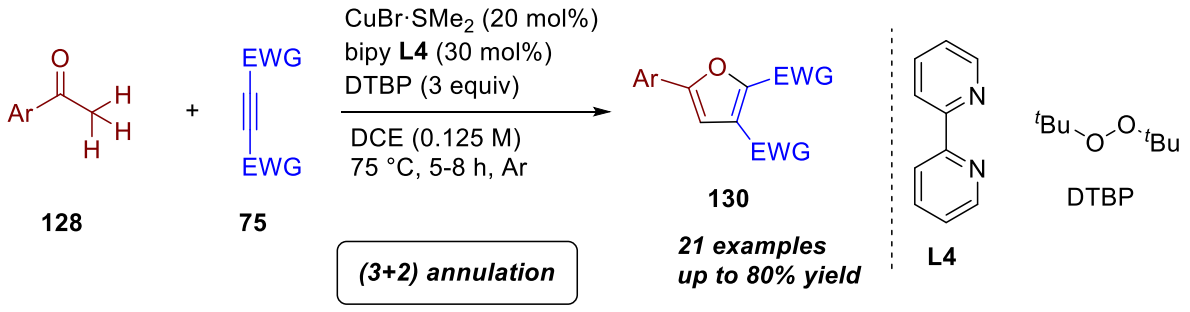
In the seventh project, Cu(I)-catalyzed (1+1+1) oxidative annulation of acetophenone derivatives without alkenes was also developed for the synthesis of fully substituted cyclopropanes (Scheme 11.7). The process was developed using 10 mol% CuI in combination of 20 mol% 4,4'-di-*tert*-butyl-2,2'-bipyridyl (**L5**) as ligand in the presence of DTBP as oxidant in chlorobenzene at 90 ºC. Wide ranges of functional groups were tolerated under mild

conditions and good to excellent yield was achieved. The process is highly practical and a wide array of acetophenones could be used in the stereoselective synthesis of cyclopropanes.



Scheme 11.7. Oxidative (1+1+1) cyclotrimerization in cyclopropane synthesis.

During the studies on oxidative cyclopropanation, we envisaged that a new route to multisubstituted furans *via* acetophenone radical addition to alkynes would be highly interesting method from simple starting materials. In an attempt towards this direction a Cu(I)-catalyzed (3+2) annulation of acetophenone derivatives with alkyl acetylenedicarboxylates was demonstrated under oxidative reaction conditions (Scheme 11.8). The method was developed using $CuBr{\cdot}SMe_2$ as catalyst, bipy (**L4**) as ligand and DTBP as oxidant under radical reaction conditions. The developed method provided polysubstituted furan derivatives with various substituted acetophenones in moderate to good yield. Mechanistic studies revealed that reaction underwent a novel a radical addition to the electron-deficient alkynes. The developed reaction is highly practical because readily available starting materials were used without prefunctionalization.



Scheme 11.8. Cu(1)-catalyzed oxidative furan synthesis.

After establishing several interesting reaction methodologies, they were used for the synthesis of biologically relevant compound collections. Finally, all developed compounds were submitted to the COMAS for various cell-based assays which resulted in identifying of

some analogous as inhibitors of the hedgehog signaling pathway, Wnt signaling pathway and autophagy.

11 Zusammenfassung

In der vorgelegten Arbeit wurde die Synthese von biologisch relevanten Substanzbibliotheken durch oxidative Anellierung von nicht-funktionalisierten Startmaterialien durch C-H Bindungsfunktionalisierung adressiert. Dabei fokussierten sich die Studien in dieser Arbeit auf die Entwicklung neuer Methoden zur Synthese von Stickstoff- und Sauerstoff-

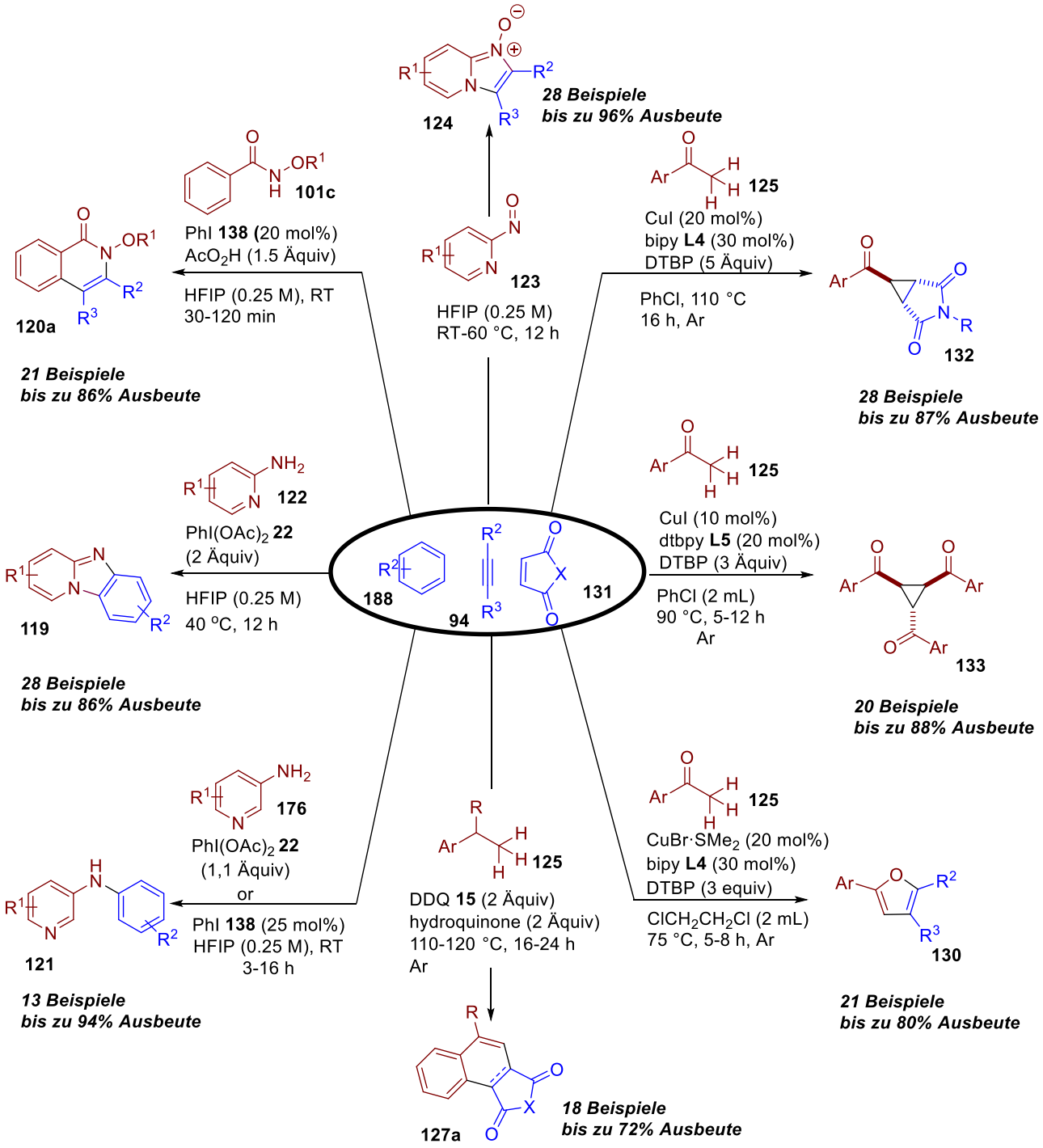


Abbildung 11.1. Zusammenfassung der oxidativen Anellierung durch C-H Bindungsfunktionalisierung zur Synthese biologisch relevanter Verbindungen.

haltigen Heterocyclen als auch von Carbocyclen unter Anellierungsbedingungen. Die privilegierten Gerüstmoleküle wurden unter Metall-freien Reaktionsbedingungen und Kupferkatalyse erhalten. Im ersten Teil dieser Arbeit lag der Fokus auf der Synthese von Isoquinolonen, Pyrido[1,2-*a*]benzimidazolen, und *N*-arylierten Pyridinen unter Verwendung von hypervalenten Iod(III) Reagenzien. Darüber hinaus wurde die Synthese von Imidazopyridin *N*-Oxide durch Anellierung verschiedener Nitrosopyridine mit Alkinen und Alkenen beschrieben. Im zweiten Teil dieser Arbeit wurde eine neue dehydrogenative Diels-Alder Reaktion von Alkylbenzolen und elektronenarmen Alkenen als auch die dehydrogenative Nitrierung von Alkylbenzol durch den Einsatz von DDQ als Oxidationsmittel beschrieben. Des Weiten wurde die Entwicklung neuer Methoden zur Synhese vollständig substituierter Cyclopropane und Furane durch Funktionalisierung von Acetophenonen beschrieben.

11.1 Hypervalentes Iod(III) vermittelte oxidative Anellierungen

Im ersten Projekt wurde die organokatalytische regioselektive oxidative Anellierung von *N*-Alkoxybenzamiden (**101c**) mit leicht zugänglichen Alkinen (**94**) beschrieben (Abbildung 11.2). Iodbenzol als einfacher Katalysator in Verbindung mit Peressigsäure als Oxidationsmittel wurde zur Synthese des biologisch wichtigen Isoquinolon-Gerüsts unter milden Reaktionsbedingungen verwendet. Die entwickelte Methode wurde zur Anellierung verschiedenster symmetrischer und asymmetrischer Alkine mit unterschiedlich substituierten Benzamid-Derivaten genutzt. Asymmetrische Alkine lieferten ein einziges Regioisomer, was durch NOE und COSY-NMR Analyse bestätigt wurde. Diese neue Methode erzielte gute bis ausgezeichnete Ausbeuten in kurzen Reaktionszeiten. Darüber hinaus wurde die N-O Bindungsspaltung der Alkoxyisoquinolone zu den entsprechenden Isoquinolonen demonstriert.

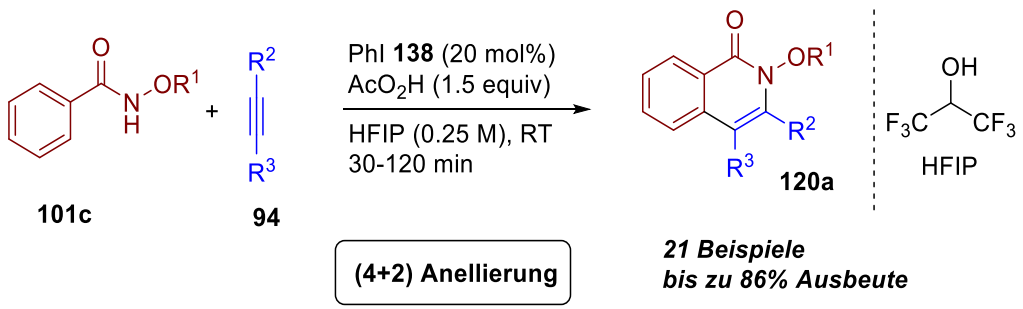


Abbildung 11.2. Organokatalytische Isoquinolon-Synthese.

Im zweiten Projekt wurde eine neue (3+2) Anellierung von 2-Aminopyridinen und 2-Aminoquinolinen mit einfachen Arenen unter oxidativen Reaktionsbedingungen durch die Verwendung von $PhI(OAc)_2$ (**22**) als Oxidationsmittel demonstriert (Abbildung 11.3). Die entwickelte Methode tolerierte ein breites Spektrum an funktionalisierten 2-Aminopyridinen zur Synthese des biologisch relevanten Pyrido[1,2-*a*]benzimidazol-Gerüsts unter milden Reaktionsbedingungen. Zusätzlich wurde der Einsatz der Methylgruppe von Arenen als spurlose dirigierende Gruppe in der Synthese von Benzo[4,5]imidazo[1,2-*a*]quinolone-Derivaten entwickelt.

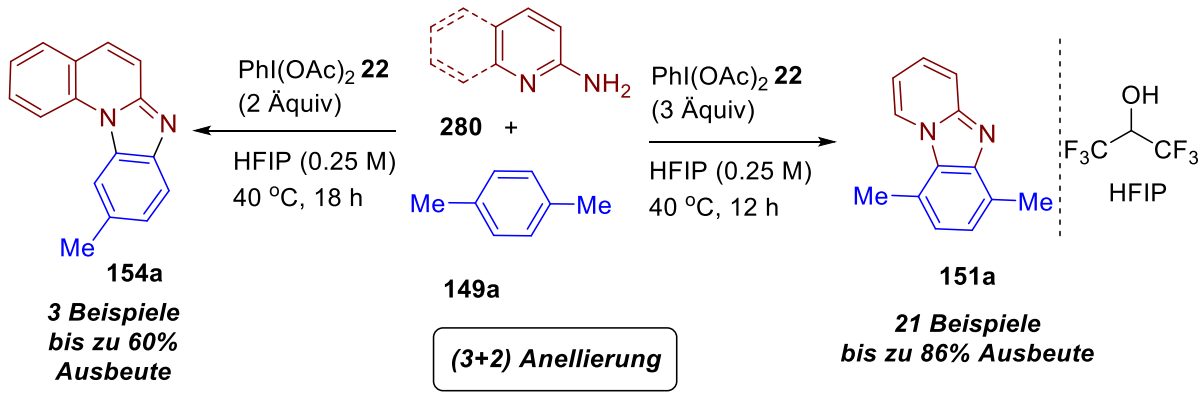


Abbildung 11.3. Hypervalentes Iod(III) vermittelte Synthese von Pyrido[1,2-*a*]benzimidazolen und Benzo[4,5]imidazo[1,2-*a*]quinolonen.

Im dritten Projekt wurde die Metall-freie Aminierung von Heteroaryl-Aminen mit nicht-prefunktionalsierten Arenen etabliert. Dieser Prozess realisierte die Synthese von pharmazeutisch nützlichen *N*-arylierten heteroaromatischen Aminen durch Verwendung von $PhI(OAc)_2$ (**22**) als Oxidationsmittel (Abbildung 11.4). Eine Vielzahl an 3-Aminopyridin-Derivaten mit verschiedenen funktionellen Gruppen wurde unter den Reaktionsbedingungen mit exzellenten Ausbeuten toleriert. Die oxidative Aminierung wurde darüber hinaus erfolgreich unter organokatalytischen Bedingungen durchgeführt, wobei die entsprechenden Produkte in moderaten bis guten Ausbeuten erhalten wurden.

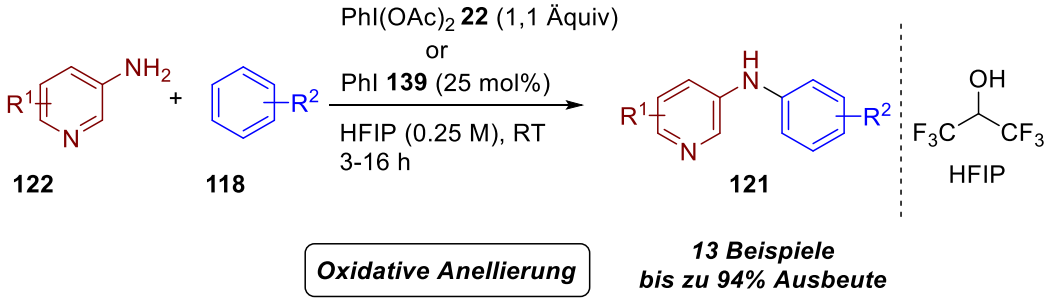


Abbildung 11.4. Hypervalent iodine (III) in oxidative amination.

11.2 Metal-freie regioselektive Anellierung von Nitrosopyridinen mit Alkinen

Im weiteren Verlauf dieser Arbeit wurde die Entwicklung einer neuen Methode zur Synthese von Imidazo[1,2-*a*]pyridinen unter Metall-freien Bedingungen und ohne den Einsatz von weiteren Reagenzien erzielt (Abbildung 11.5). Diese Transformation wurde durch die Metall-freie und regioselektive (3+2) Anellierung von Nitrosopyridinen mit Alkinen und Alkenen erreicht. Nach unserem Wissen wurde damit zum ersten Mal die regioselektive Anellierung von Nitrosopyridinen ohne Verwendung von Katalysatoren oder Additiven beschrieben. In der Annellierungsreaktion wurden verschiedene funktionelle Gruppen gut toleriert und lieferte Imidazopyridin *N*–Oxide in guten bis ausgezeichneten Ausbeuten. Zusätzlich wurden die *N*-Oxide durch Erhitzen desoxygeniert, wodurch die entsprechenden Imidazo[1,2-*a*]pyridine erhalten wurden.

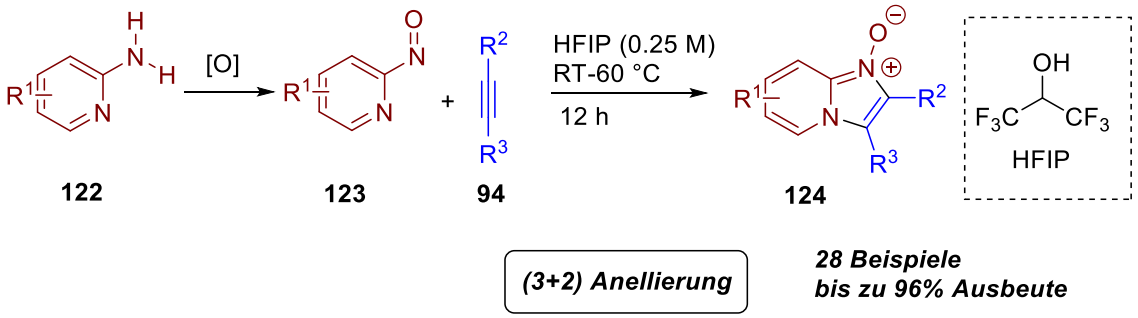


Abbildung 11.5. Metal-freie Synthese von Imidazopyridin *N*–Oxiden.

11.3 Oxidative Anellierung von Alkylarenen mit elektronenarmen Alkenen

Kohlenstoff-Wasserstoff (C-H) Bindungen sind allgegenwertig in der Natur und es finden sich viele signifikante Vorteile C-H Bindungen zu nutzen, um neue C-C Bindungen in einer Atom- und syntheseschrittökonomischen Weise zu konstruieren. Im diesem Kontext wurde die oxidative dehydrogenative Diels-Alder (DDA) Reaktion und Nitrierung von Alkylarenen durch C-H Bindungsfunktionalisierung im Detail studiert. Mit diesem Ziel wurde die DDQ (**15**) vermittelte oxidative und dehydrogenative Diels-Alder Reaktion von Alkylarenen und elektronenarmen Alkenen entwickelt (Abbildung 11.6).

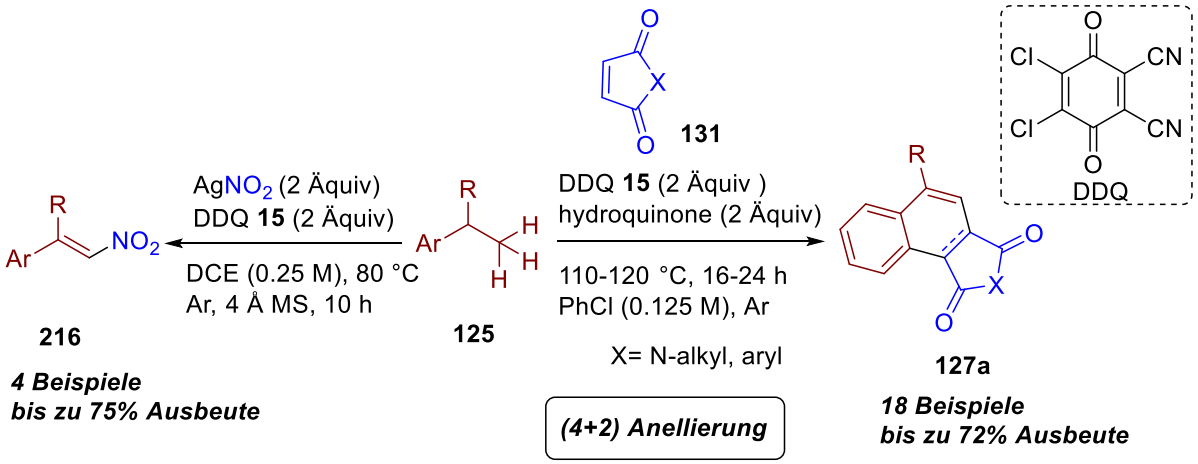


Abbildung 11.6. Oxidative dehydrogenative Diels-Alder Reaktion und Nitrierung.

Dieser Prozess wurde mit zwei Äquivalenten DDQ (**15**) als Oxidationsmittel, zwei Äquivalenten Hydrochinon als Additiv in Chlorbenzol unter Argonatmosphäre durchgeführt, wodurch 1,4-Phenanthrachinone und Isoindole erhalten wurden. Die Reaktionsbedingungen zeigten gute Toleranz gegenüber verschieden substituierter Arene, welche die gewünschten Produkte in guten Ausbeuten lieferten. Mechanistische Studien legten nahe, dass die oxidative Anellierungsreaktion über ein Styrol-Intermediat und die *in situ* Bildung von Quinhydrone verläuft. Zusätzlich wurde die dehydrogenative und stereoselektive Synthese von Nitroalkenen ausgehend von Alkylbenol durch den Einsatz von $AgNO_2$ als Nitrierungsreagenz beschrieben (Abbildung 11.5).

11.4 Oxidative Anellierung von Acetophenonen durch C(sp^3)–H Bindungsfunktionalisierung

Des Weiteren wurde die oxidative Annelierung durch C(sp^3)–H Bindungsfunktionalisierung beschrieben. In diesem 6. Projekt wurde eine neue Cu(I)-katalysierte oxidative (2+1) Cyclopropanierung von Acetophenon-Derivaten mit elektronenarmen Alkenen durch den Einsatz von 20 mol% CuI in Verbindung mit 30 mol% 2,2‘-Bipyridin (**L4**) als Liganden in der Anwesenheit von DTBP als Oxidationsmittel in Chlorbenzol demonstriert (Abbildung 11.7). Ein vielseitiges Spektrum an Acetophenonen und Maleimid-Derivaten wurde unter den milden Reaktionsbedingungen toleriert. Interessanterweise erlaubte die Methode die stereoselektive (2+1) Anellierung von Acetophenonen mit elektronenarmen Alkenen und ermöglichte dadurch die Synthese gespannter Cyclopropane. Mechanistische Studien deckten auf, dass die Reaktion durch einen neuen oxidativ radikalischen Weg erfolgte.

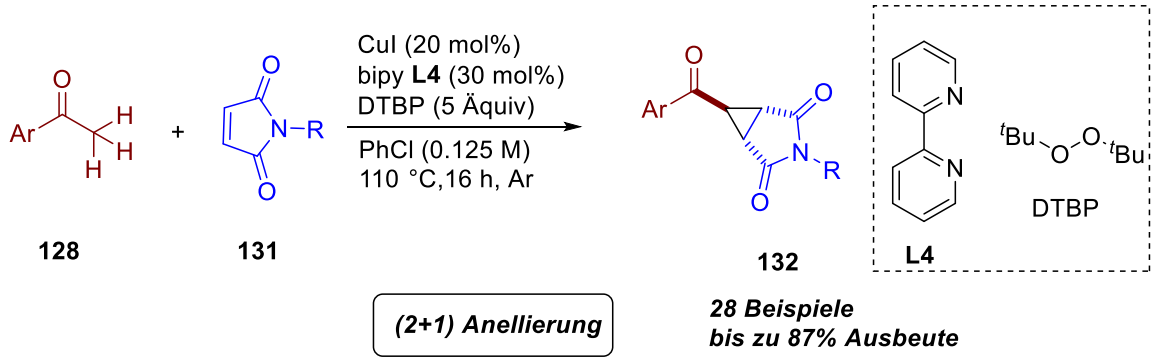


Abbildung 11.7. Synthesis von Cyclopropanen *via* (2+1) Anellierung.

Im 7. Projekt wurde die Cu(I)-katalyisierte oxidative (1+1+1) Anellierung von Acetophenon-Derivaten ohne die Verwendung von Alkenen zur Synthese vollständig substituierter Cycopropanen entwickelt (Abbildung 11.8). Dieser Prozess wurde durch Verwendung von 10 mol% CuI in Kombination mit 20 mol% 4,4'-di-*tert*-Butyl-2,2'-bipyridin (**L5**) als Ligand in Gegenwart von DTBP als Oxidationsmittel in Chlorbenzol bei 90 °C verwirklicht. Ein breites Spektrum an funktionellen Gruppen wurde unter den milden Reaktionsbedingungen toleriert und erzielte gute bis ausgezeichnete Ausbeuten. Dieser Prozess ist von hohem praktischem Nutzen, da eine Vielzahl an Acetophenonen für die stereoselektive Synthese von Cyclopropanen eingesetzt werden konnte.

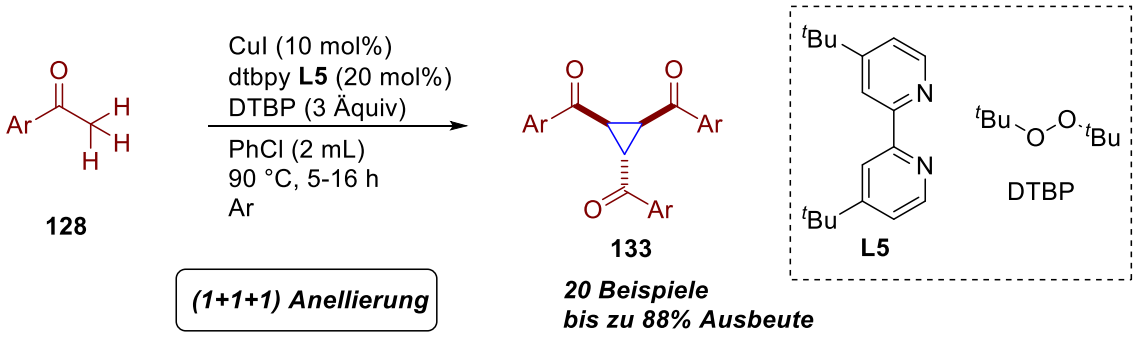


Abbildung 11.8. Oxidative (1+1+1) Cyclotrimerisierung in der Synthese von Cyclopropanen.

Während der Studien zur oxidativen Cyclopropanierung postulierten wir eine neue Route für multisubstituierte Furane durch Acetophenon-Radikaladdition an Alkine als hoch interessante Methode ausgehend von einfachen Startmaterialien. Mit dem Ziel diesen Ansatz zu verwirklichen wurde die Cu(I)-katalyisierte (3+2) Anellierung von Acetophenon-Derivaten mit elektronenarmen Alkinen unter oxidativen Reaktionsbedingungen demonstriert (Abilldung 11.9). Die Methode wurde durch den Einsatz von $CuBr{\cdot}SMe_2$ als Katalysator, bipy

(**L4**) als Ligand und DTBP als Oxidationsmittel unter radikalischen Reaktionsbedingungen. Die entwickelten Reaktionsbedingungen lieferten polysubstituierte Furan-Derivate mit verschieden substituierten Acetophenonen in moderaten bis guten Ausbeuten. Mechanistische Studien deckten auf, dass die Reaktion über die radikalische Addition von Acetophenon an elektronenarme Alkine erfolgte. Die entwickelten Reaktionsbedingungen erwiesen sich als äußert praktisch, da einfache Startmaterialien ohne Prefunktionalisierung genutzt werden konnten.

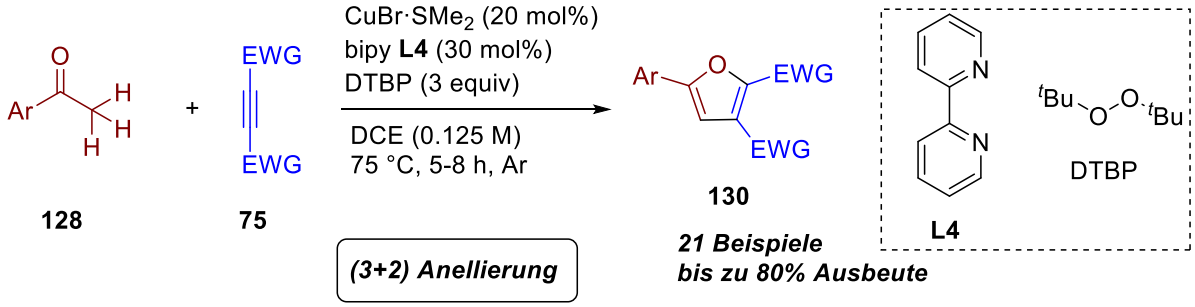


Abbildung 11.9. Cu(1)-katalysierte oxidative Furansynthese.

Nach der Etablierung mehrerer Reaktionsmethoden, wurden diese zur Synthese biologisch relevanter Substanzbibliotheken genutzt. Letztendlich wurden alle erhaltenen Verbindungen im COMAS in verschiedenen Zell-basierten Assays untersucht, was die Identifikation mehrerer Analoga mit inhibitorischer Aktivität in den Hedgehog und Wnt Singalwegen als auch gegen Autophagie erzielte.

Chapter 12

Experimental Section

12.1 Materials and methods

12.2 General Remarks

Unless otherwise noted, all commercially available compounds were used as provided without further purification. Solvents for chromatography were technical grade. Dry solvents were purified by the Solvent Purification System Glovebox *Technology M-BRAUN SPS-800*.

12.2.1 Nuclear Magnetic Resonance Spectroscopy (NMR)

^{1}H-NMR and ^{13}C-NMR were recorded on *Varian Mercury (200 MHz)*, *Bruker DPX400 (300 MHz)*, *Bruker DRX400 (400 MHz)*, *DRX500 (500 MHz)* or *DRX600 (600 MHz)* spectrometers in $CDCl_3$. Data are reported in the following order: chemical shift (d) in ppm; multiplicities are indicated s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (*J*) are given in Hertz (Hz).

12.2.2 Chromatography

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium plates with *F-254* indicator, visualized by irradiation with UV light. Column chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm). Solvent mixtures are understood as volume/volume.

12.2.3 High resolution mass spectra (HRMS)

HRMS were recorded on a LTQ Orbitrap mass spectrometer coupled to an Accela HPLC-System (HPLC column: Hypersyl GOLD, 50 mm × 1 mm × 1.9 µm). Mass spectra (MS-EI, 70 eV) were collected using a GC-MS (GC system 7890A equipped with 5975C detector) produced by Agilent Technologies (column: HP-5MS, 30 m × 0.250 mm × 0.25µm).

12.2.4 Fourier transform infrared spectroscopy (FT-IR)

IR spectra were obtained with a Bruker Tensor 27 spectrometer (ATR, neat) and are reported in terms of frequency of absorption (cm^{-1}).

11.2.5 Optical rotations

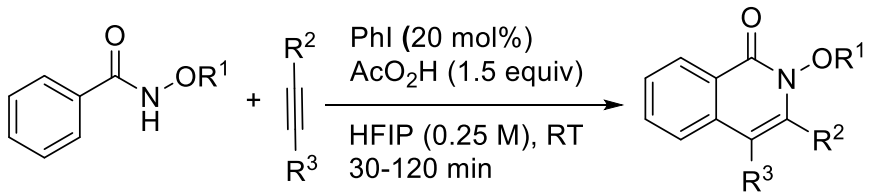
Optical rotation [α] was measured in a *Schmidt + Haensch Polartronic HH8* polarimeter in cuvettes with a path length of 10 cm at ambient temperature. The concentration is given as g/100 mL

12.2.6 Reagents

Chemicals were brought form commercial sources with purity above 97% which used without further purification. Nitrosopyridine derivatives were taken from Dr. Rishikesh Narayan and benzamide derivatives were taken from Dr. Rajarshi Samanta for substrate scope.

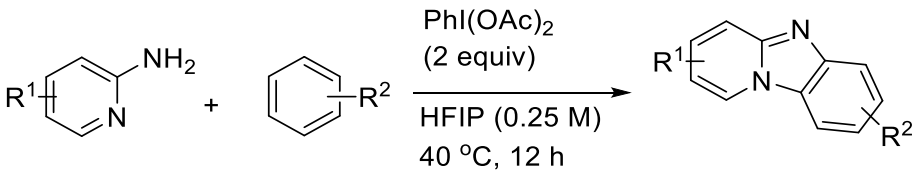
12.3 General Procedure for A-J

General Procedure A: Synthesis of *N*-Methoxyisoquinolone Derivatives



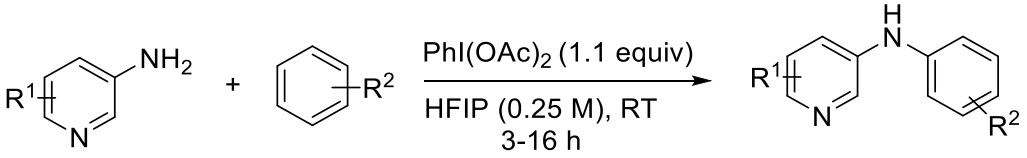
To a screw capped reaction vial containing benzamide (1 equiv, 0.25 mmol) diphenylacetylene derivative (1.2 equiv, 0.3 mmol), iodobenzene (0.2 equiv) in 1 mL 1,1,1,3,3,3-hexafluoro-2-propanol (0.25 M), and peracetic acid (1.5 equiv; 0.75×2) were added portion-wise (second portion was added after 15 min) at room temperature under air. After stirring 30-50 min, the reaction mixture was diluted with mesitylene (2 mL) and the crude reaction mixture was concentrated under reduced pressure until almost evaporation of HFIP. Crude reaction mixture was subsequently purified by flash column chromatography over neutral alumina using petroleum ether/ethyl acetate as an eluent system.

General Procedure B: Synthesis of Pyrido[1,2-*a*]benzimidazoles Derivatives



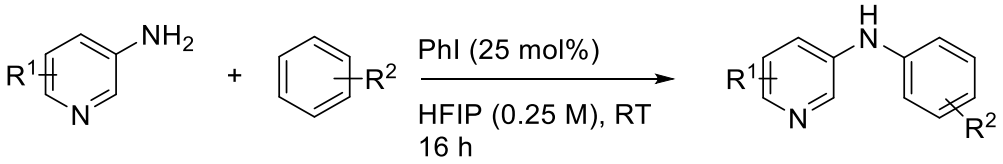
To a screw cap reaction vial 2-aminopyridine derivatives (1 equiv, 0.25 mmol), phenyliodine diacetate (2 equiv, 0.5 mmol), arene (3-5 equiv, 0.75-1.25 mmol) and HFIP (0.25 M) were added. The reaction mixture was heated to 40 ^{o}C and stirred until completion. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as an eluent system.

General Procedure C: Synthesis of *N*-Arylated Heteroaromatic Amines



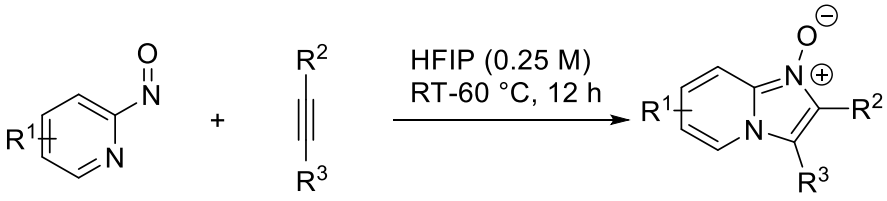
To a screw capped reaction vial containing heteroaromatic amine (0.25 mmol), arene (2.5 mmol, 10 equiv) and HFIP (0.25 M) were added. Then $PhI(OAc)_2$ (0.257-0.375 mmol) was added to the reaction mixture and the reaction was stirred at room temperature under air until completion. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as eluent system.

General Procedure D for Organocatalytic Amination



To a screw capped reaction vial containing heteroaromatic amine (0.25 mmol), arene (2.5 mmol, 10 equiv), iodobenzene (25 mol %) in 1 mL HFIP (0.25 M) and peracetic acid (5 equiv; 39% solution in acetic acid) was added portion-wise (3 equiv was added initially and second portion 2 equiv was added after 6 h) at room temperature under air and the reaction mixture was stirred at room temperature under air until completion. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ ethyl acetate as eluent system.

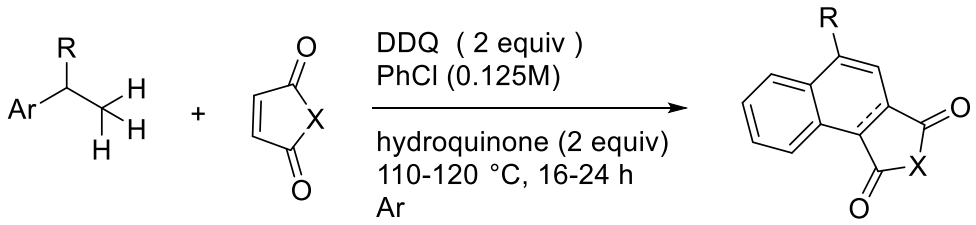
General Procedure E: Synthesis of *N*–Oxide-imidazopyridines



To a screw cap reaction vial 2-nitrosopyridine derivatives (0.25 mmol, 1 equiv), alkyne (0.28 mmol, 1.1 equiv), and HFIP (0.25 M) were added under air. The reaction mixture was stirred vigorously at RT-60 ^{o}C until completion. The crude reaction mixture was concentrated under

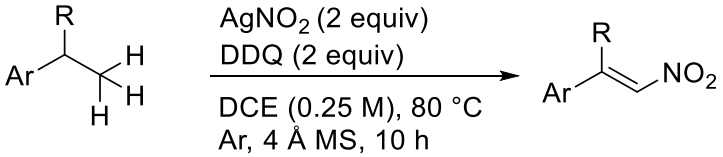
reduced pressure and subsequently purified by flash column chromatography over silica gel using dichloromethane/methanol as an eluent system.

General Procedure F: Synthesis of Oxidative Diels-Alder Reaction



To a screw cap reaction vial charged with a magnetic stir-bar, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.5 mmol, 2 equiv) was added. Then the reaction tube was evacuated and back-filled with argon. The evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, 2 mL chlorobenzene (0.125 M) and arene (1.25 mmol, 5 equiv were added and the reaction was allowed to warm to 110-120°C. After 6 h, hydroquinone (0.5 mmol, 2 equiv) and maleimide or quinone (0.25 mmol, 1 equiv) were added. The reaction mixture was stirred vigorously for completion of reaction (12 h). Afterwards, the reaction mixture was cooled to room temperature. Acetone (4 mL) was added and subsequently the reaction mixture was concentrated *in vacuo* and purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether/acetone/ethyl acetate as eluent.

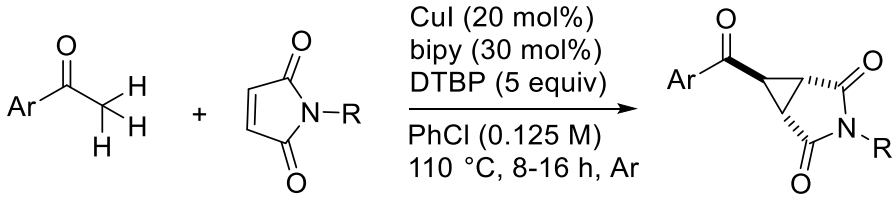
General Procedure G: Synthesis of Nitroolefins



To a screw cap reaction vial charged with a magnetic stir-bar, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.25 mmol, 2 equiv) was added. Then the reaction tube was evacuated and back-filled with argon. The evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, 2 mL of 1,2-dichloroethane (0.25 M) and arene (0.25 mmol, 1 equiv were added and the reaction was allowed to warm to 80 °C. After 4 h, AgNO2 (0.5 mmol, 2 equiv) was added. The reaction mixture was stirred vigorously for completion of reaction (6 h). Afterwards, the reaction mixture was cooled to room temperature. Acetone (4 mL) was added and subsequently the reaction mixture was concentrated in vacuum and

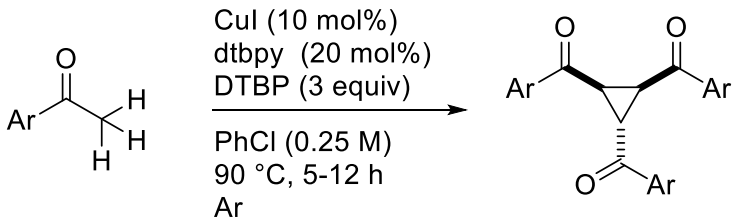
purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether/ ethyl acetate as eluent.

General Procedure H: Synthesis of Cyclopropanes



To a screw cap reaction tube charged with a magnetic stir-bar, maleimide (0.25 mmol), acetophenone (0.5 mmol), CuI (20 mol%) and 2,2'-bipyridine (30 mol%) were added. The tube was then evacuated and back-filled with argon. This evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, solvent (2 mL of degased chlorobenzene) and di-*tert*-butyl peroxide (5 equiv) were added. The reaction mixture was allowed to warm up to 110 °C and stirred vigorously for completion of reaction (12-24 h). Then the reaction mixture was cooled to room temperature. Dichloromethane (4 mL) and ethyl acetate (2 mL) were added and the reaction mixture was filtered through Celite. Afterwards, the reaction mixture was concentrated and purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether/ acetone as eluent.

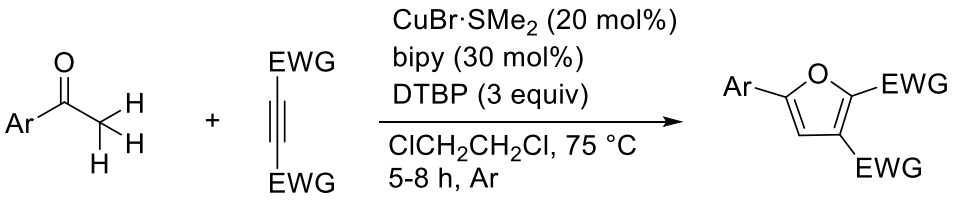
General Procedure I: Synthesis of Cyclopropane from Acetophenones



To a screw cap reaction vial charged with a magnetic stir-bar, acetophenone derivative (0.5 mmol), CuI (10 mol%), dtbpy **L5** (20 mol%) were added. The vial was then evacuated and back-filled with argon. This evacuation/back-fill sequence was repeated three additional times. Under a counter flow of argon, 2 mL (0.25 M) of degassed solvent and DTBP (3 equiv) were added by syringe. The reaction mixture was allowed to warm up to 80-90 °C and was stirred vigorously for completion of reaction. Then the reaction mixture was cooled to room temperature. To the reaction mixture was added dichloromethane (20 mL), washed with HCl (1M) for two times, dried over Na2SO4 and evaporated in vacuum to afford the crude

product, which was purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether/ acetone as the eluent.

General Procedure J: Synthesis of Furan Derivatives

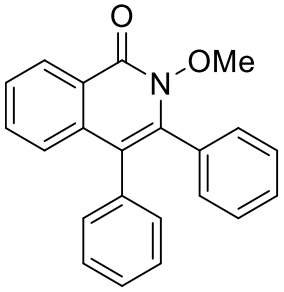


To a screw cap reaction tube with septum charged with a magnetic stir-bar, acetylendicarboxylic acid ester (0.25 mmol, if it is solid), aryl methyl ketone (0.75 mmol, if it is solid), CuBr.SMe_2 (20 mol%) and bipy **L4** (30 mol%) were added. The tube was then evacuated and back-filled with argon. This evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, solvent (2 mL of degased 1,2-dichloroethane) was added. The resulting mixture was then degassed by freezing in liquid nitrogen, replacing the atmosphere with argon and allowing warming to room temperature (repeated two times). Then liquid samples (acetylendicarboxylica acid ester and aryl methyl ketone) and DTBP (3 equiv) were added. The reaction mixture was allowed to warm to 75 °C and stirred vigorously for completion of reaction (5-8 h). Afterwards, the reaction mixture was cooled to room temperature. Dichloromethane (4 mL) and ethyl acetate (2 mL) were added and the reaction mixture was filtered through celite. Subsequently, the reaction mixture was concentrated and purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether/ acetone/ethyl acetate as eluent.

12.4 Experimental Part for Iodobenzene-Catalyzed Oxidative Annulation of Benzamide Derivatives with Alkynes

12.4.1 Characterization of Isoquinolone Derivatives (137a-139l)

2-Methoxy-3,4-diphenylisoquinolin-1(2H)-one (137a)



Compound **137a** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (10:90 v/v); the product was obtained as brown amorphous solid in 78% yield.

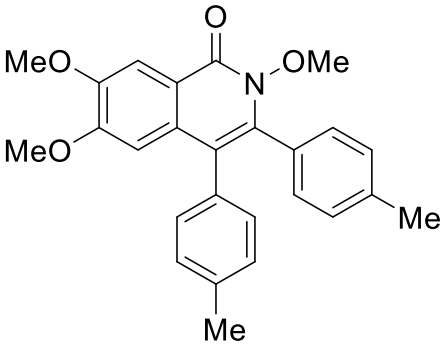
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.29 – 7.20 (m, 9H), 7.12 – 7.06 (m, 2H), 3.73 ppm (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.27, 140.06, 136.61, 135.53, 133.03, 132.40, 131.71, 130.78, 128.40, 128.22, 127.90, 127.62, 127.28, 126.89, 126.48, 125.87, 118.45, 63.60 ppm.

FT-IR: $\tilde{\nu}$ = 3027, 2934, 1757, 1604, 1444, 1419, 1277, 1174, 1025 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{22}H_{18}O_2N$: 328.13305found: 328.13321.

2,6,7-Trimethoxy-3,4-di-p-tolylisoquinolin-1(2*H*)-one (137b)



Compound **137b** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 82% yield.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.90 (s, 1H), 7.21 – 7.17 (m, 2H), 7.12-7.10 (m, Hz, 4H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.60 (s, 1H), 4.04 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 2.35 ppm (s, 6H).

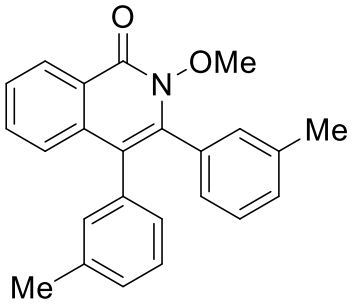
^{13}C NMR (126 MHz, CD_2Cl_2) δ 157.79, 153.90, 149.90, 139.20, 138.55, 137.31, 133.63, 132.79, 131.96, 131.18, 129.98, 129.35, 128.70, 120.94, 118.08, 107.96, 106.91, 63.82, 56.67, 56.19, 21.59, 21.50 ppm.

FT-IR: $\tilde{\nu}$ = 3015, 2958, 1771, 1656, 1503, 1422, 1181, 1020 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{26}H_{26}O_2N$: 416.18563 found: 416.18553.

2-Methoxy-3,4-di-m-tolylisoquinolin-1(2*H*)-one (137c)

Compound **137c** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (10:90 v/v); the product was obtained as brown amorphous solid in 60% yield.



^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.53 (d, *J* = 7.6 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.18 – 7.14 (m, 2H), 7.13-7.06 (m, 3H), 7.00-6.96 (m, 2H), 3.76 (s, 3H), 2.31 (s, 3H), 2.29 ppm (s, 3H).

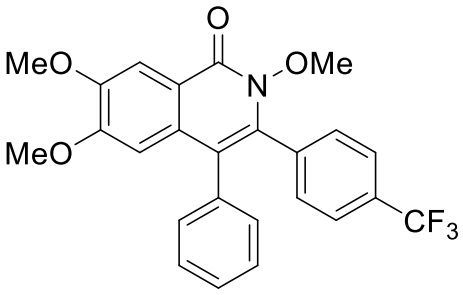
^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.38, 140.73, 138.24, 137.75, 137.31, 136.05, 132.86, 132.61, 132.41, 131.75, 129.44, 129.17, 128.36, 128.30, 128.11, 127.85, 127.79, 127.07, 126.98, 126.35, 118.60, 63.91, 21.55 ppm.

FT-IR: $\tilde{\nu}$ = 3015, 2958, 1771, 1656, 1503, 1422, 1181, 1020 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{24}H_{22}O_2N$: 356.16451 found: 356.16461.

6,7-Dimethoxy-4-phenyl-3-(4-(trifluoromethyl)phenyl)isoquinolin-1(2*H*)-one (137d)

Compound **137d** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 53% yield.



^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.87 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.28-7.23 (m, 3H), 7.16 – 7.08 (m, 2H), 6.57 (s, 1H), 4.01 (s, 3H), 3.69 (s, 3H), 3.66 ppm(s, 3H).

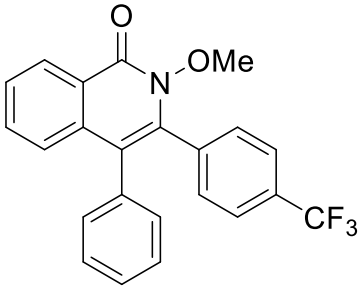
^{13}C NMR (101 MHz, CD_2Cl_2) δ 157.56, 153.97, 150.17, 143.96, 139.13, 137.40, 136.74, 135.85, 132.74, 132.16, 132.01, 131.87, 130.49, 130.16, 128.82, 127.96, 126.57, 124.97, 124.93, 124.90, 124.86, 121.14, 118.56, 107.90, 106.79, 63.94, 56.67, 56.16 ppm.

FT-IR: $\tilde{\nu}$ = 3040, 2934, 1661, 1605, 1555, 1506, 1324, 1271, 1172, 1091 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{25}H_{21}O_4NF_3$: 456.14172 found: 456.14150.

2-Methoxy-4-phenyl-3-(4-(trifluoromethyl)phenyl)isoquinolin-1(2*H*)-one (137e)

Compound **137e** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 71% yield.



^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.52 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.23 (m, 4H), 7.12 (dd, *J* = 7.3, 1.7 Hz, 2H), 3.72 ppm (s, 3H).

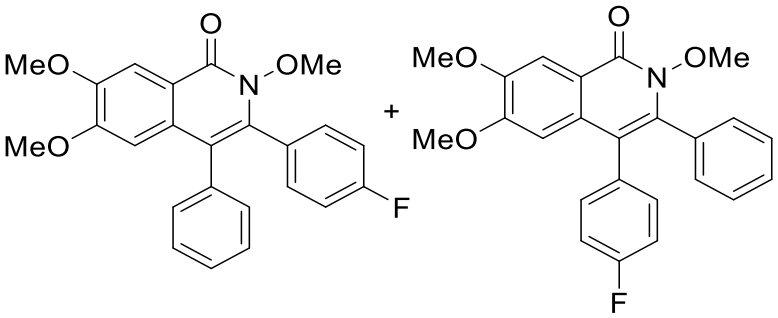
^{13}C NMR (126 MHz, CD_2Cl_2) δ 158.33, 139.12, 137.03, 136.35, 135.59, 132.94, 132.16, 131.81, 131.10, 130.50, 129.75, 128.86, 128.08, 128.06, 127.68, 127.35, 126.50, 125.68, 125.10, 125.07, 125.04, 125.01, 119.09, 64.04 ppm.

FT-IR: $\tilde{\nu}$ = 3031, 2923, 1736, 1647, 1605, 1567, 1448, 1389, 1316, 1172, 1069 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{23}H_{17}O_2NF_3$: 396.12059 found: 396.11938.

3-(4-Fluorophenyl)-2,6,7-trimethoxy-4-phenylisoquinolin-1(2*H*)-one (137f) and 4-(4-fluorophenyl)-2,6,7-trimethoxy-3-phenylisoquinolin-1(2*H*)-one (137f') (2:1)

Mixture of compounds **137f** and **137f'** were obtained by using the general procedure A and products were isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 61% yield.



^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.87 (s, 1H), 7.25 (s, 5H), 7.13-7.10 (m, 2H), 7.00 – 6.90 (m, 2H), 6.55 (s, 1H), 4.00 (s, 3H), 3.70 (s, 3H), 3.68 ppm (s, 3H).

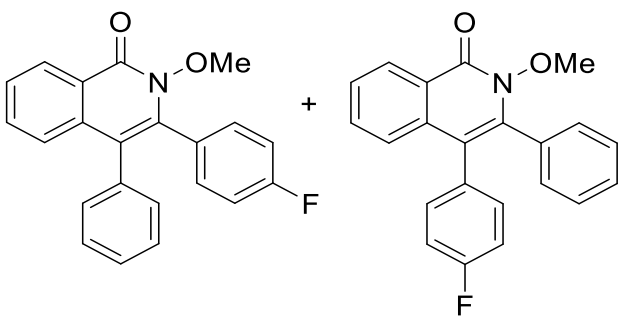
^{13}C NMR (101 MHz, CD_2Cl_2) δ 164.04, 163.54, 163.07, 161.58, 161.10, 157.66, 153.94, 149.94, 139.41, 137.96, 136.32, 135.57, 133.86, 133.78, 133.30, 133.22, 132.56, 132.54, 132.50, 132.34, 132.26, 132.05, 131.20, 128.73, 128.69, 128.08, 127.72, 120.88, 115.69, 115.47, 115.13, 114.91, 107.91, 107.86, 106.69, 106.41, 63.88, 63.80,73, 53.46 ppm.

FT-IR: $\tilde{\nu}$ = 3068, 2935, 1791, 1606, 1503, 1396, 1351, 1271, 1115, 1015 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{24}H_{21}O_4NF$: 406.14491 found: 406.14426.

3-(4-Fluorophenyl)-2,6,7-trimethoxy-4-phenylisoquinolin-1(2*H*)-one (137g) and 4-(4-fluorophenyl)-2-methoxy-3-phenylisoquinolin-1(2*H*)-one (137g') (2:1)

Mixture of compounds **137g** and **137g'** were obtained by using the general procedure A and



products were isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 53% yield.

^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.52 – 8.50 (m, 1H), 7.61 – 7.56 (m, Hz, 1H), 7.55 – 7.51 (m, 1H), 7.31 – 7.25 (m, 5H), 7.22 (t, *J* = 8.7 Hz, 1H), 7.15 – 7.09 (m, 2H), 6.95 (t, *J* = 8.8 Hz, 2H), 3.72 ppm (s, 3H).

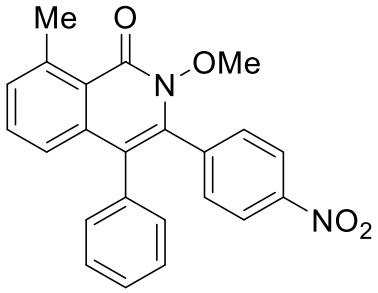
^{13}C NMR (126 MHz, CD_2Cl_2) δ 166.30, 163.97, 163.44, 162.00, 161.48, 158.42, 158.40, 141.14, 140.69, 139.67, 137.49, 137.18, 137.10, 136.79, 136.07, 135.13, 134.00, 133.93, 133.24, 133.18, 132.84, 132.81, 132.43, 132.21, 131.12, 128.90, 128.77, 128.20, 128.09, 128.03, 127.81, 127.39, 127.34, 127.22, 127.15, 126.36, 126.10, 118.99, 117.50, 115.68, 115.51, 115.24, 115.07, 63.98, 63.90, ppm.

FT-IR: $\tilde{\nu}$ = 3035, 2940, 1660, 1604, 1508, 1326, 1219, 1155, 1015 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{22}H_{17}O_2NF$: 346.12378 found: 346.12380.

2-Methoxy-8-methyl-3-(4-nitrophenyl)-4-phenylisoquinolin-1(2*H*)-one (137h)

Compound **137h** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 46% yield.



^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.48 (dd, *J* = 6.6, 2.6 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.40 – 7.36 (m, 2H), 7.18 – 7.13 (m, 3H), 7.09 (dd, *J* = 6.6, 3.1 Hz, 2H), 3.74 (s, 3H), 1.77 ppm (s, 3H).

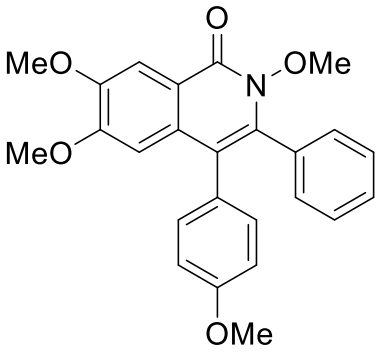
^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.31, 147.75, 139.71, 138.78, 138.62, 137.31, 136.54, 134.66, 132.84, 132.45, 132.20, 129.13, 128.66, 128.44, 127.98, 127.63, 126.80, 125.16, 123.05, 118.89, 64.02, 24.12 ppm.

FT-IR: $\tilde{\nu}$ = 3051, 2943, 1661, 1586, 1515, 1343, 1103, 1016 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{23}H_{19}O_4N_2$: 342.14886 found: 342.14888.

2,6,7-Trimethoxy-4-(4-methoxyphenyl)-3-phenylisoquinolin-1(2*H*)-one (137i)

Compound **137i** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 50% yield.



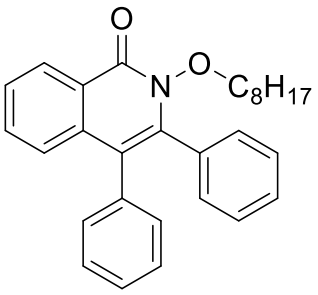
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.86 (s, 1H), 7.26 (s, 5H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.60 (s, 1H), 4.00 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 3.68 (s, 3H) ppm.

^{13}C NMR (126 MHz, CD_2Cl_2) δ 159.19, 157.79, 154.65, 153.99, 149.99, 146.90, 139.28, 133.21, 133.00, 132.94, 131.36, 128.57, 128.03, 120.94, 117.88, 114.97, 114.06, 107.99, 106.89, 63.88, 56.69, 56.24, 55.65 ppm.

FT-IR: $\tilde{\nu}$ = 3038, 2939, 1655, 1603, 1248, 1216, 1156, 1031 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{25}H_{24}O_5N$: 418.16490 found: 418.16477.

2-(Octyloxy)-3,4-diphenylisoquinolin-1(2*H*)-one (139a)



Compound **139a** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (3:97 v/v); the product was obtained as brown amorphous solid in 81% yield.

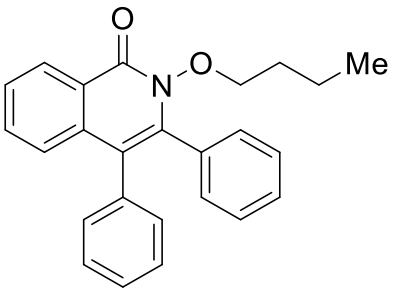
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.53 – 8.43 (m, 1H), 7.59 – 7.47 (m, 3H), 7.26 (tdd, *J* = 7.0, 5.1, 2.3 Hz, 8H), 7.17 – 7.11 (m, 2H), 3.95 (t, *J* = 6.3 Hz, 2H), 1.35-1.04 (m, 12H), 1.02-0.85 ppm (m, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.53, 144.12, 141.05, 137.18, 136.29, 132.59, 132.24, 131.36, 130.37, 128.69, 128.57, 127.92, 127.59, 127.09, 126.21, 125.24, 118.34, 76.35, 54.72, 32.25, 29.71, 29.57, 28.20, 25.84, 23.19, 14.42 ppm.

FT-IR: $\tilde{\nu}$ = 3061, 2923, 1658, 1603, 1465, 1322, 1271, 1106, 1027 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{29}H_{32}O_2N$: 426.24276 found: 426.24265.

2-Butoxy-3,4-diphenylisoquinolin-1(2H)-one (139b)



Compound **139b** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (5:95 v/v); the product was obtained as brown amorphous solid in 85% yield.

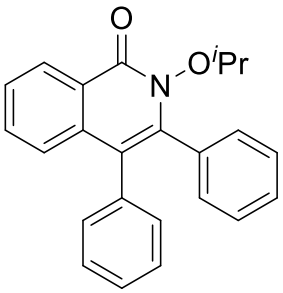
^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.50 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.25 (dt, *J* = 10.5, 7.9 Hz, 9H), 7.16 – 7.11 (m, 2H), 3.95 (t, *J* = 5.8 Hz, 2H), 1.32 – 1.25 (m, 2H), 1.02 – 0.93 (m, 2H), 0.68 ppm (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.52, 141.03, 137.17, 136.28, 132.58, 132.24, 132.07, 131.35, 130.36, 129.07, 128.65, 128.56, 127.93, 127.89, 127.59, 127.09, 127.06, 126.20, 118.33, 75.99, 30.21, 19.07, 13.99 ppm.

FT-IR: $\tilde{\nu}$ = 3058, 2952, 16461, 1602, 1552, 1478, 1444, 1320, 1175, 1060 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{25}H_{24}O_2N$: 370.18016 found: 370.18019.

2-Isopropoxy-3,4-diphenylisoquinolin-1(2*H*)-one (139c)



Compound **139c** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (5:95 v/v); the product was obtained as brown amorphous solid in 76% yield.

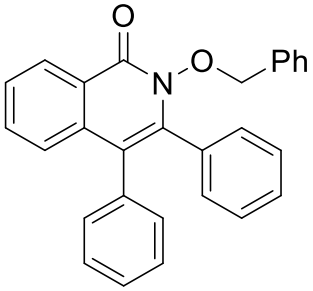
^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.49 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.58-7.50 (m, 2H), 7.27 – 7.19 (m, 9H), 7.13 (d, *J* = 5.8 Hz, 2H), 4.39 (sep, 6.3 Hz, 1H), 0.94 (s, 3H), 0.92 ppm (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.46, 141.78, 137.15, 136.52, 132.97, 132.52, 132.33, 132.05, 130.78, 129.22, 129.06, 128.98, 128.55, 128.46, 128.07, 127.61, 127.54, 127.07, 126.98, 126.17, 118.27, 79.38, 54.54, 54.27, 54.00, 53.73, 53.46, 20.74 ppm.

FT-IR: $\tilde{\nu}$ = 3057, 2977, 2923, 1647, 1606, 1491, 1445, 1372, 1175, 1071 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{24}H_{22}O_2N$: 356.16451 found: 356.16466.

2-(Benzyloxy)-3,4-diphenylisoquinolin-1(2*H*)-one (139d)



Compound **139d** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 56% yield.

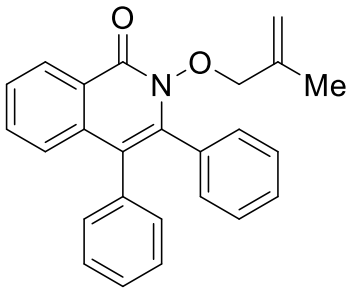
^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.56 (d, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.62 – 7.48 (m, 3H), 7.32 -7.23 (m, 10H), 7.19 – 7.14 (m, 2H), 6.84 (d, *J* = 7.6 Hz, 2H), 4.93 ppm (s, 2H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.64, 140.88, 137.23, 136.13, 134.21, 134.09, 132.76, 132.60, 132.21, 131.48, 130.52, 130.16, 129.37, 129.02, 128.89, 128.83, 128.78, 128.74, 128.60, 128.10, 128.00, 127.67, 127.26, 127.04, 126.31, 77.88 ppm.

FT-IR: $\tilde{\nu}$ = 3031, 2925, 1655, 1602, 1443, 1210, 1173, 1105, 1028 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{28}H_{22}O_2N$: 404.16451 found:404.16405.

2-(2-Methylallyl)oxy)-3,4-diphenylisoquinolin-1(2*H*)-one (139e)



Compound **139e** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (10:90 v/v); the product was obtained as brown amorphous solid in 75% yield.

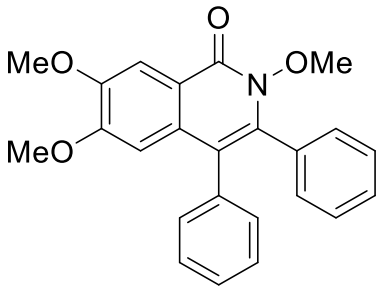
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.55 – 8.46 (m, 1H), 7.54 (m, 3H), 7.28 – 7.21 (m, 8H), 7.16 – 7.11 (m, 2H), 4.83 – 4.74 (m, 2H), 4.37 (s, 2H), 1.31 ppm (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.56, 140.93, 139.63, 137.19, 136.18, 132.67, 132.50, 132.21, 131.40, 128.73, 128.57, 128.45, 128.16, 128.01, 127.94, 127.62, 127.31, 127.17, 127.03, 126.25, 118.47, 116.44, 79.69, 69.91, 19.55 ppm.

FT-IR: $\tilde{\nu}$ = 3059, 2928, 1658, 1491, 1444, 1319, 1173, 1105, 1024 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{25}H_{22}O_2N$: 368.16451 found: 368.16493.

2,6,7-Trimethoxy-3,4-diphenylisoquinolin-1(2*H*)-one (139f)[267]



Compound **139f** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 64% yield.

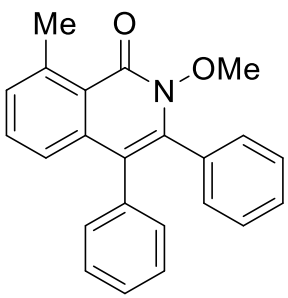
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.26 – 7.18 (m, 8H), 7.12 – 7.08 (m, 2H), 6.60 (s, 1H), 4.05 (s, 3H), 3.73 (s, 3H), 3.70 ppm (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.67, 153.44, 149.42, 138.67, 135.94, 132.07, 131.97, 131.65, 130.94, 128.28, 128.26, 127.58, 127.32, 120.56, 118.03, 107.83, 106.24, 63.62, 56.47, 55.95 ppm.

FT-IR: $\tilde{\nu}$ = 3040, 2941, 1660, 1603, 1508, 1444, 1249, 1173, 1094, 1015 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{24}H_{22}O_2N$: 388.15433 found: 388.15502.

2-Methoxy-8-methyl-3,4-diphenylisoquinolin-1(2*H*)-one (139g)



Compound **139g** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 68% yield.

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.51 – 8.42 (m, 1H), 7.43 – 7.38 (m, 2H), 7.23 – 7.14 (m, 5H), 7.17 – 7.08 (m, 5H), 3.73 (s, 3H), 1.74 ppm (s, 3H).

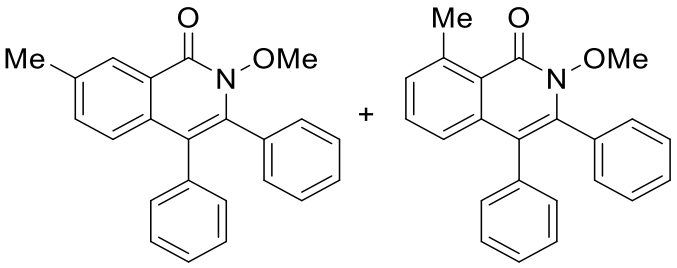
^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.44, 141.17, 139.51, 137.01, 136.17, 135.49, 135.11, 133.01, 132.65, 131.00, 130.32, 129.59, 128.42, 128.35, 127.99, 127.82, 127.36, 127.00, 126.68, 118.42, 63.83, 54.72, 54.36, 54.00, 53.64, 53.28, 24.13 ppm.

FT-IR: $\tilde{\nu}$ = 3000, 2940, 1655, 1584, 1488, 1442, 1310, 1094, 1026 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{23}H_{20}O_2N$: 342.14886 found: 342.14883.

2-Methoxy-7-methyl-3,4-diphenylisoquinolin-1(*2*H)-one (139h) and 2-methoxy-8-methyl-3,4-diphenylisoquinolin-1(*2*H)-one (139h') (3:1)

Mixture of compounds **139h** and **139h'**were obtained by using the general procedure A and products were isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (10:90 v/v); the product was obtained as brown amorphous solid in 65% yield.



^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.32 (s, 1H), 7.44 – 7.38 (m, 2H), 7.31 – 7.18 (m, 10H), 7.12 (dd, *J* = 8.0, 3.6 Hz, 4H), 3.70 (s, 3H), 2.51 ppm (s, 3H).

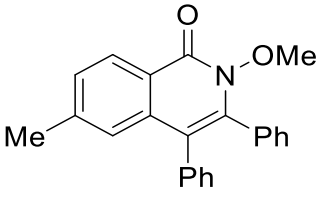
^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.29, 139.64, 137.59, 137.01, 136.32, 134.84, 134.20, 132.65, 132.59, 132.17, 131.23, 131.00, 128.65, 128.52, 127.98, 127.81, 127.55, 127.50, 126.94, 126.20, 63.81, 21.60 ppm.

FT-IR: $\tilde{\nu}$ = 3058, 2937, 1656, 1491, 1442, 1333, 1213, 1174, 1073 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{23}H_{20}O_2N$: 342.14886 found: 342.14888.

2-Methoxy-6-methyl-3,4-diphenylisoquinolin-1(2*H*)-one (139i)

Compound **139i** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (10:90 v/v); the product was obtained as brown amorphous solid in 74% yield.



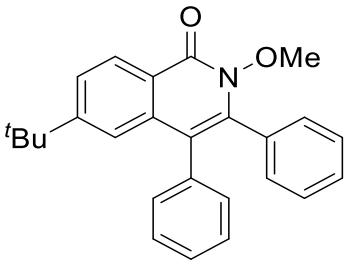
^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.32 (s, 1H), 7.40 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.28 – 7.21 (m, 8H), 7.13 – 7.10 (m, 3H), 3.70 (s, 3H), 2.51 ppm (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.29, 139.65, 137.59, 136.32, 134.84, 134.20, 132.59, 132.17, 131.23, 128.65, 128.52, 127.97, 127.54, 127.50, 126.94, 126.20, 118.51, 63.81, 21.60 ppm.

FT-IR: $\tilde{\nu}$ = 3058, 2937, 1656, 1602, 1495, 1441, 1334, 1214, 997 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{23}H_{20}O_2N$: 342.14886 found: 342.14878.

6-(*tert*-Butyl)-2-methoxy-3,4-diphenylisoquinolin-1(2*H*)-one (139j)



Compound **139j** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 69% yield.

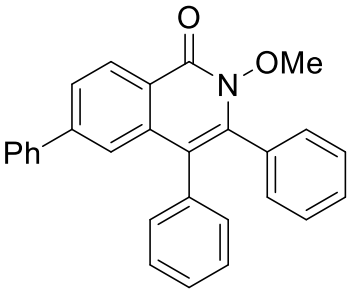
^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.50 (d, *J* = 2.1 Hz, 1H), 7.64 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.28 – 7.21 (m, 8H), 7.16 (d, *J* = 8.6 Hz, 1H), 7.14 – 7.10 (m, 2H), 3.70 (s, 3H), 1.41 ppm (s, 9H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.52, 150.74, 139.88, 136.32, 134.85, 132.60, 132.16, 131.22, 130.78, 129.06, 128.66, 128.53, 127.98, 127.56, 126.69, 126.12, 123.73, 118.38, 63.81, 35.43, 31.54 ppm.

FT-IR: $\tilde{\nu}$ = 3057, 2960, 1654, 1588, 1491, 1442, 1332, 1176, 1072 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{26}H_{26}O_2N$: 384.19581 found: 384.19660.

2-Methoxy-3,4,6-triphenylisoquinolin-1(2*H*)-one (139k)



Compound **139k** was obtained by using the general procedure A and product was isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 65% yield.

^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.76 (d, *J* = 2.1 Hz, 1H), 7.84 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.77 – 7.74 (m, 2H), 7.49 (t, *J* = 7.6 Hz, 3H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.30 – 7.24 (m, 8H), 7.18 – 7.14 (m, 2H), 3.73 ppm (s, 3H).

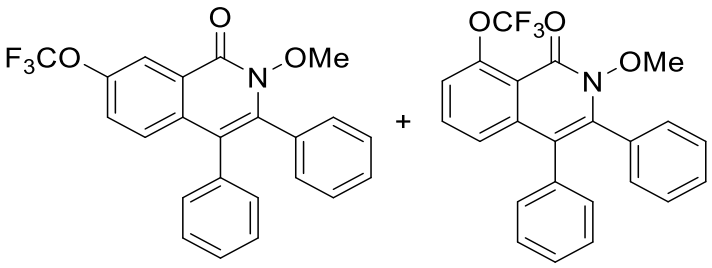
^{13}C NMR (75 MHz, CD_2Cl_2) δ 158.49, 140.63, 140.21, 139.87, 136.16, 134.94, 132.67, 132.47, 132.20, 131.50, 131.19, 129.51, 129.00, 128.80, 128.64, 128.39, 128.05, 127.70, 127.41, 127.19, 126.97, 125.83, 123.56, 118.46, 63.93 ppm.

FT-IR: $\tilde{\nu}$ = 3057, 2960, 1654, 1609, 1491, 1442, 1332, 1265, 1176, 1072 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{28}H_{22}O_2N$: 404.16451 found: 404.16405.

2-Methoxy-3,4-diphenyl-7-(trifluoromethoxy)isoquinolin-1(2*H*)-one (139l) and 2-methoxy-3,4-diphenyl-8-(trifluoromethoxy)isoquinolin-1(2H)-one (139l') (5:4)

Mixture of compounds **139l** and **139l'** were obtained by using the general procedure A and products were isolated by column chromatography with neutral alumina. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as brown amorphous solid in 54% yield.



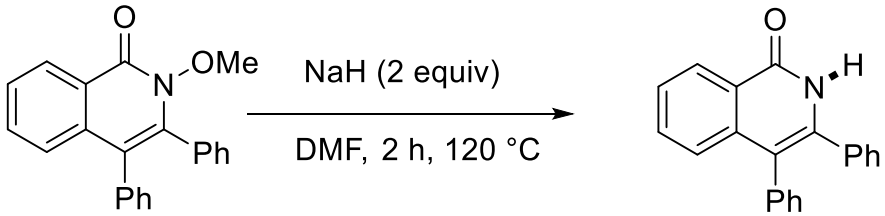
^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.35 (d, *J* = 1.2 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.29 – 7.22 (m, 9H), 7.14 – 7.08 (m, 2H), 3.72 ppm (s, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 157.65, 148.16, 141.33, 135.94, 135.78, 135.50, 132.16, 131.13, 130.37, 129.63, 129.01, 128.80, 128.73, 128.30, 128.16, 127.96, 125.99, 119.33, 118.10, 64.06 ppm.

FT-IR: $\tilde{\nu}$ = 3058, 2944, 1662, 1593, 1491, 1254, 1212, 1158, 1022 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{23}H_{17}O_3NF_3$: 412.11550 found: 412.11532.

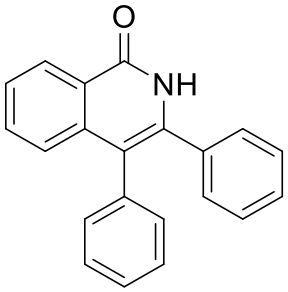
12.4.2 Synthesis of 3,4-Diphenylisoquinolin-1*(2H)*-one (142)



139a 83% **142**

To a screw capped reaction vial containing compound **139a** (0.25 mmol), NaH (2 equiv) and DMF (2 ml) were added and the reaction was allowed to warm to 120 °C for 2 h. After completing, the reaction mixture was allowed to cool down to room temperature, and saturated aqueous $Na_2S_2O_3$ (20 mL) was added, extracted with CH_2Cl_2 (10 mL x 2). The combined organic layer was dried over anhydrous Na_2SO4, concentrated under reduced pressure. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as eluent system (80:20 v/v).

3,4-Diphenylisoquinolin-1(2*H*)-one (142)



^{1}H NMR (500 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.47 (d, *J* = 7.9 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.27 – 7.21 (m, 5H), 7.18 – 7.16 ppm (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 138.82, 135.74, 135.11, 132.88, 131.92, 129.31, 128.79, 128.51, 128.49, 127.57, 127.47, 126.82, 125.84, 117.63 ppm.

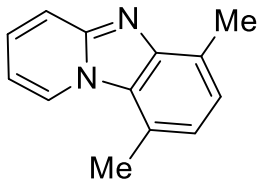
FT-IR: $\tilde{\nu}$ = 3048, 2922, 1715, 16444, 1554, 1514, 11315, 1155, 114, 1016 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{21}H_{16}ON$: 298.12264 found: 298.12222.

12.5 Hypervalent Iodine (III) Mediated Oxidative Annulation of 2-Aminopyridines with Arenes

12.5.1. Characterization of Pyrido[1,2-*a*]benzimidazole Derivatives (151a-154a)

6,9-Dimethylpyrido[1,2-*a*]benzimidazole (151a)



Compound **151a** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (20:80 v/v); the product was obtained as light yellow amorphous solid in 75% yield.

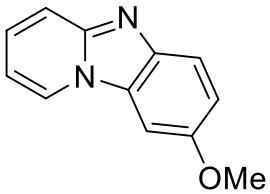
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 7.2 Hz, 1H), 7.74 (d, *J* = 9.3 Hz, 1H), 7.36 (ddd, *J* = 9.3, 6.6, 1.2 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 6.9, 1.2 Hz, 1H), 2.85 (s, 3H), 2.73 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.04, 143.79, 128.59, 127.55, 127.30, 127.19, 125.44, 123.31, 120.67, 118.12, 110.41, 19.67, 17.08 ppm.

FT-IR: $\tilde{\nu}$ = 3034, 2914, 1819, 1749, 1508, 1319, 1279, 1209 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{13}N_2$: 197.1073 found: 197.1075.

8-Methoxypyrido[1,2-*a*]benzimidazole (151b)



Compound **151b** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (20:80 v/v); the product was obtained as brown solid in 77% yield.

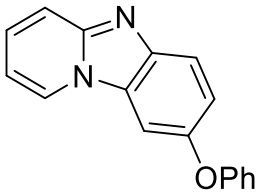
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 6.9 Hz, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.48 – 7.31 (m, 1H), 7.30 (d, *J* = 6.9 Hz, 1H), 7.19 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.82 (t, *J* = 6.9 Hz, 1H), 3.94 ppm (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.56, 147.91, 138.59, 128.77, 128.50, 124.82, 120.47, 118.05, 116.19, 110.45, 93.34, 56.12 ppm.

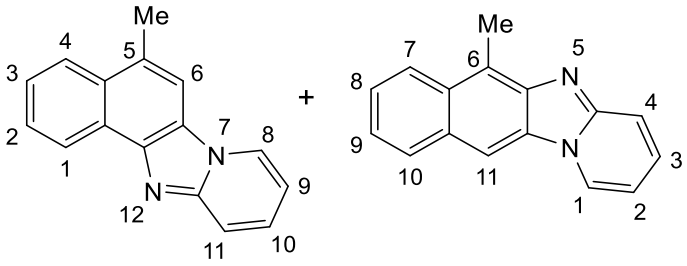
FT-IR: $\tilde{\nu}$ = 3072, 2956, 2834, 2282, 1758, 1487, 1359, 1283, 1207, 1027 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{12}H_{11}ON_2$: 199.0868 found: 199. 0865.

8-Phenoxypyrido[1,2-*a*]benzimidazole (151c)



Compound **151c** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel.



Eluent: EtOAc/petroleum ether (20:80 v/v); the product was obtained as brown solid in 80% yield.

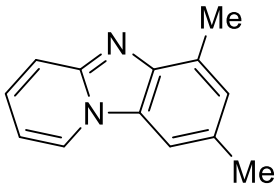
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 6.9 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.50 (d, *J* = 2.2 Hz, 1H), 7.43 – 7.28 (m, 4H), 7.11 (m, 1H), 7.03 (d, *J* = 6.9 Hz, 2H), 6.82 ppm (t, *J* = 6.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.31, 151.99, 148.71, 140.43, 129.94, 129.36, 128.84, 125.17, 123.20, 120.73, 119.43, 118.36, 118.13, 110.75, 101.08 ppm.

FT-IR: $\tilde{\nu}$= 3067, 2923, 2325, 1585, 1434, 1219, 1160 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{17}H_{13}ON_2$: 261.1025 found: 261.1022.

6,8-Dimethylpyrido[1,2-*a*]benzimidazole (151d)



Compound **151d** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (15:85v/v); the product was obtained as light yellow amorphous solid in 62% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 6.8 Hz, 1H), 7.74 (d, *J* = 9.3 Hz, 1H), 7.46 (s, 1H), 7.42 – 7.27 (m, 1H), 7.15 (s, 1H), 6.78 (m, 1H), 2.73 (s, 3H), 2.52 ppm (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.58, 141.32, 131.39, 129.16, 128.93, 128.23, 127.92, 125.12, 117.89, 110.47, 107.64, 21.90, 17.22 ppm.

FT-IR: $\tilde{\nu}$ = 3015, 2913, 2854, 1693, 1640, 1497, 1464, 1355, 1174, 1099 cm^{-1}.

HRMS: calc. for [M+H]+ $C_{13}H_{13}N_2$: 197.1073 found: 197.1075.

5-Methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (151e) and 6 methylnaphtho[2',3':4,5] -imidazo [1,2-*a*]pyridine (151e')

Mixture of compounds **151e** and **151e'** were obtained by using the general procedure B and products were isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (20:80 v/v); the product was obtained as light yellow amorphous solid in 75% yield.

Prepared according to the general procedure using PIDA (2 equiv) and the product was obtained as amorphous solid in 67% yield;

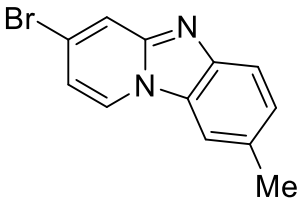
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, *J* = 8.1 Hz, 1H), 8.36 (d, *J* = 6.8 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.84 – 7.79 (m, 1H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.38 – 7.31 (m, 1H), 6.86 (t, *J* = 6.4 Hz, 1H), 2.78 ppm (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.92, 140.14, 131.81, 129.19, 128.12, 127.59, 127.00, 126.77, 126.29, 125.35, 124.57, 123.80, 121.66, 118.96, 118.09, 111.58, 110.51, 20.79 ppm.

FT-IR: $\tilde{\nu}$= 3070, 2929, 1732, 1526, 1349, 1323, 1263 cm^{-1}.

HRMS: calc. for [M+H]+ $C_{16}H_{13}N_2$: 233.1075 found: 233.1073.

3-Bromo-8-methylpyrido[1,2-*a*]benzimidazole (151f)[268]



Compound **151f** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (15:85 v/v); the prod-uct was obtained as light yellow amorphous solid in 43% yield.

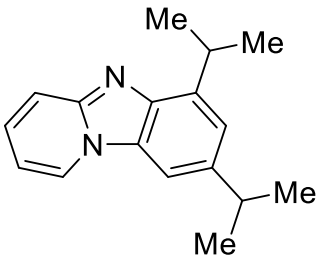
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, *J* = 1.1 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 9.4 Hz, 2H), 7.48 (dd, *J* = 9.4, 1.8 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 2.59 pmm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.81, 141.31, 133.00, 132.77, 128.62, 128.26, 125.44, 119.41, 118.46, 110.34, 105.17, 22.03 ppm.

FT-IR: $\tilde{\nu}$=3052, 2919, 1498, 1454, 1383, 1256, 1217, 1073 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{12}H_{10}{}^{79}BrN_2$: 261.0029 found: 261.0022.; HRMS: calc. for $[M+H]^+$ $C_{12}H_{10}{}^{81}BrN_2$: 263.0002 found: 263.0001.

6,8-Diisopropylpyrido[1,2-*a*]benzimidazole (151g)



Compound **151g** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (10:90 v/v); the product was obtained as light yellow amorphous solid in 52% yield.

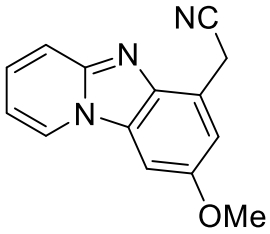
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 6.8 Hz, 1H), 7.72 (d, *J* = 9.2 Hz, 1H), 7.55 (s, 1H), 7.35 (dd, *J* = 5.1, 4.0 Hz, 1H), 7.28 (s, 1H), 6.78 (t, *J* = 6.8 Hz, 1H), 3.96 – 3.68 (m, 1H), 3.13 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.46 (d, *J* = 6.9 Hz, 6H), 1.37 ppm (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.67, 142.88, 141.08, 140.20, 128.63, 125.10, 121.05, 118.08, 110.12, 107.85, 104.59, 34.75, 29.20, 24.74, 23.35 ppm.

FT-IR: $\tilde{\nu}$= 3073, 2957, 2868, 1639, 1507, 1422, 1356, 1229, 1146 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{17}H_{21}N_2$: 253.1626 found: 253.253.1703.

2-(8-Methoxybenzo[4,5]imidazo[1,2-*a*]pyridin-6-yl)acetonitrile (151h)



Compound **151h** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (25:75v/v); the product was obtained as light yellow amorphous solid in 68% yield (ratio = 2.1:1).

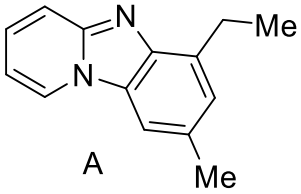
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 6.8 Hz, 1H), 7.68 (d, *J* = 9.3 Hz, 1H), 7.40 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.31 (s, 1H), 7.27 (d, *J* = 1.9 Hz, 1H), 6.86 (t, *J* = 6.8 Hz, 1H), 4.30 (s, 2H), 3.95 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.64, 155.25, 129.00, 125.05, 122.22, 118.28, 117.77, 115.07, 110.93, 93.44, 56.35, 19.69 ppm.

FT-IR: $\tilde{\nu}$= 3075, 2923, 2835, 2249, 1643, 1500, 1462, 1349, 1230, 1206, 1079 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{12}ON_3$: 238.0977 found: 238.0975.

6-Ethyl-8-methylpyrido[1,2-*a*]benzimidazole (151i)



Compounds **151i and 151i'** were obtained by using the general procedure B and products were isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (10:90 v/v); the product was obtained as light yellow amorphous solid in 73% yield (2.1:1 ration).

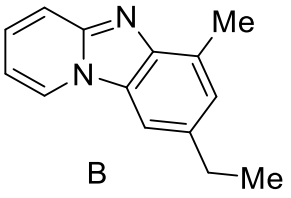
Major product: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.38 (d, *J* = 6.8 Hz, 1H), 7.73 (d, *J* = 9.2 Hz, 1H), 7.52 (s, 1H), 7.37 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.20 (s, 1H), 6.81 (t, *J* = 6.7 Hz, 1H), 2.84 (q, *J* = 7.6 Hz, 2H), 2.76 (s, 3H), 1.34 ppm (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.98, 141.61, 135.84, 131.64, 128.90, 126.20, 118.42, 110.46, 107.96, 106.67, 24.75, 22.34, 15.15 ppm.

FT-IR: $\tilde{\nu}$ = 3074, 2964, 2928, 1639, 1506, 1458, 1356, 1206, 1051 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{15}N_2$: 211.1231, found 211.1229.

6-Methyl-8-ethylpyrido[1,2-*a*]benzimidazole (151')



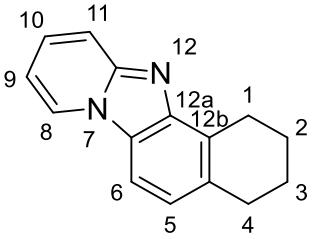
Minor product: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.40 (d, *J* = 6.8 Hz, 1H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.54 (s, 1H), 7.39 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.22 (s, 1H), 6.83 (t, *J* = 6.7 Hz, 1H), 2.86 (q, *J* = 7.6 Hz, 2H), 2.79 (s, 3H), 1.36 ppm (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.01, 142.14, 138.30, 129.71, 129.10, 128.63, 127.12, 125.51, 118.35, 110.64, 106.69, 29.65, 17.59, 16.71 ppm.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{15}N_2$: 211.1231, found 211.1229.

1,2,3,4-Tetrahydronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (151j)

Compounds **151j** and **151j'** were obtained by using the general procedure B and products were isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as light yellow amorphous solid in 82% yield (ratio = 1.3:1).



Major product: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.43 (d, *J* = 6.8 Hz, 1H), 7.79 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.49 – 7.36 (m, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.87 (t, *J* = 6.8 Hz, 1H), 3.29 (t, *J* = 5.9 Hz, 2H), 2.98 (t, *J* = 5.8 Hz, 2H), 2.07 – 1.82 ppm (m, 4H).

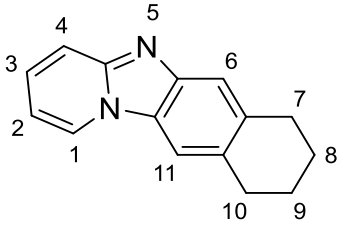
^{13}C NMR (126 MHz, $CDCl_3$) δ 147.70, 134.60, 129.08, 128.31, 126.10, 125.17, 123.31, 117.86, 110.68, 109.73, 107.43, 29.91, 24.82, 23.51, 22.81 ppm.

FT-IR: $\tilde{\nu}$ = 3074, 2925, 1726, 1642, 1503, 1356, 1195, 1049 cm^{-1}.

HRMS: calc. for [M+H]+ $C_{15}H_{15}N_2$: 223.1232 found: 223.1229.

7,8,9,10-Tetrahydronaphtho[2',3':4,5]imidazo[1,2-*a*]pyridine (151j')

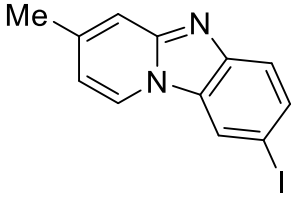
Minor product: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.41 (d, *J* = 6.8 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.85 (t, *J* = 6.8 Hz, 1H), 3.27 (s, 2H), 3.04 – 2.84 (m, 2H), 2.01 – 1.86 ppm (m, 4H).



^{13}C NMR (126 MHz, $CDCl_3$) δ 148.08, 136.81, 136.57, 132.10, 129.82, 125.29, 118.40, 117.46, 110.76, 109.82, 31.03, 30.39, 30.36, 23.47, 23.37 ppm.

3-Methyl-8-iodopyrido[1,2-*a*]benzimidazole (151k)

Compound **151k** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (20:80 v/v); the product was obtained as light yellow amorphous solid in 49% yield.



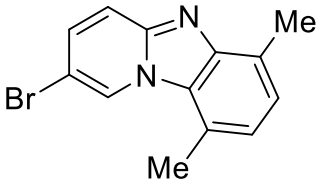
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.0 Hz, 1H), 8.17 (s, 1H), 7.74 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.43 (s, 1H), 6.70 (d, *J* = 7.0 Hz, 1H), 2.46 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.10, 143.85, 141.94, 134.45, 130.23, 124.29, 121.33, 119.49, 116.09, 114.06, 82.96, 22.10 ppm.

FT-IR: $\tilde{\nu}$ = 3050, 2958, 1651, 1609, 1258, 1036 cm^{-1}. HRMS: calc. for $[M+H]^+$ $C_{12}H_{10}IN_2$: 308.9885found: 308.9883.

HRMS: calc. for $[M+H]^+$ $C_{12}H_{10}IN_2$: 308.9885found: 308.9883.

2-Bromo-6,9-dimethylpyrido[1,2-*a*]benzimedazole (152a)



Compound **152a** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (15:85v/v); the product was obtained as light yellow amorphous solid in 86% yield.

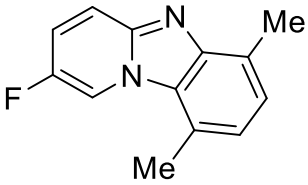
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 0.8 Hz, 1H), 7.64 (d, *J* = 9.7 Hz, 1H), 7.40 (dd, *J* = 9.7, 0.8 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 7.3 Hz, 1H), 2.82 (s, 3H), 2.72 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.08, 143.82, 131.93, 127.61, 127.52, 127.10, 125.92, 124.11, 120.67, 118.77, 104.61, 19.54, 17.04 ppm.

FT-IR: $\tilde{\nu}$ = 3031, 2926, 1692, 1588, 1514, 1450, 1423, 1371, 1279, 1113. cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{12}{}^{79}BrN_2$: 275.0186 found: 275.0178. HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}{}^{81}BrN_2$: 277.0159 found: 277.0158.

2-Fluoro-6,9-dimethylpyrido[1,2-*a*]benzimidazole (152b)



Compound **152b** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as light yellow amorphous solid in 59% yield.

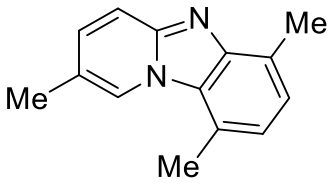
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (dd, *J* = 3.9, 2.4 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.42 – 7.27 (m, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 7.3 Hz, 1H), 2.83 (s, 3H), 2.72 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.60 (d, *J* = 235.8 Hz), 145.63, 144.59, 127.99, 127.75, 125.52, 123.67, 120.89 (d, *J* = 26.0 Hz), 120.51, 118.55 (d, *J* = 8.6 Hz), 113.93 (d, *J* = 40.9 Hz), 19.29, 17.02 ppm.

FT-IR: $\tilde{\nu}$ =3013, 2926, 1659, 1533, 1514, 1439, 1308, 1204, 1103, 1037 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{12}N_2F$: 215.0982 found: 215.0979.

2,6,9-Trimethylpyrido[1,2-*a*]benzimidazole (152c)



Compound **152c** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (15:85 v/v); the prod-uct was obtained as light yellow amorphous solid in 72% yield.

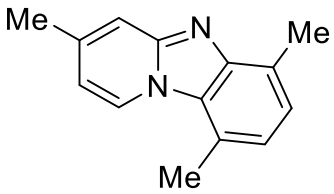
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.67 (d, *J* = 9.3 Hz, 1H), 7.21 (dd, *J* = 9.3, 1.4 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.94 (d, *J* = 7.3 Hz, 1H), 2.83 (s, 3H), 2.72 (s, 3H), 2.36 ppm (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.16, 143.74, 131.83, 127.16, 126.99, 125.07, 124.88, 123.05, 120.60, 119.87, 117.31, 19.75, 18.54, 17.08 ppm.

FT-IR: $\tilde{\nu}$ = 3026, 2967, 2921, 1650, 1511, 1417, 1347, 1251, 1105 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{15}N_2$: 211.1233 found: 211.1229.

3,6,9-Trimethylpyrido[1,2-*a*]benzimidazole (152d)



Compound **152d** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as light yellow amorphous solid in 72% yield.

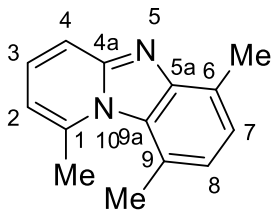
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 7.2 Hz, 1H), 7.48 (s, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 6.92 (d, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 7.2 Hz, 1H), 2.79 (s, 3H), 2.70 (s, 3H), 2.41 ppm (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.45, 143.44, 140.15, 127.05, 126.65, 126.50, 125.32, 122.91, 120.38, 115.83, 113.32, 21.76, 19.50, 17.07 ppm.

FT-IR: $\tilde{\nu}$ = 3027, 2920, 2867, 1649, 1554, 1536, 1459, 1418, 1376, 1260, 1037 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{15}N_2$: 211.1233 found: 211.1229.

1,6,9-Trimethylpyrido[1,2-*a*]benzimidazole (152e)



Compound **152e** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (10:90v/v); the product was obtained as

light yellow amorphous solid in 72% yield.

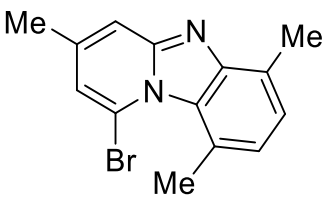
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 6.9 Hz, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 6.9 Hz, 1H), 6.95 (d, *J* = 7.3 Hz, 1H), 6.66 (dd, *J* = 6.9, 6.9 Hz, 1H), 2.82 (s, 3H), 2.78 (s, 3H), 2.71 ppm (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.68, 143.80, 127.85, 127.73, 127.27, 126.66, 125.14, 125.03, 123.07, 120.48, 110.11, 19.61, 17.88, 17.12 ppm.

FT-IR: $\tilde{\nu}$ = 3016, 2962, 2915, 1831, 1634, 1557, 1518, 1382, 1356, 1252, 1084 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{15}N_2$: 211.1232 found: 211.1229.

1-Bromo-3,6,9-trimethylpyrido[1,2-*a*]benzimidazole (152f)



Compound **152f** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (10:90 v/v); the product was obtained as light yellow amorphous solid in 76% yield.

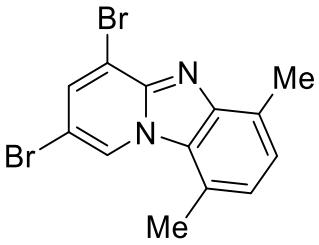
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.52 (s, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 2.83 (s, 3H), 2.78 (s, 3H), 2.37 ppm (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.93, 144.01, 133.97, 128.37, 128.04, 125.62, 124.55, 123.93, 120.61, 119.69, 111.46, 19.59, 18.23, 16.84 ppm.

FT-IR: $\tilde{\nu}$ = 2917, 1522, 1489, 1380, 1342, 1257, 1159, 1048 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{14}{}^{79}BrN_2$: 289.0341 found: 289.0335. HRMS: calc. for $[M+H]^+$ $C_{14}H_{14}{}^{81}BrN_2$: 291.0313 found: 291.0314.

2,4-Dibromo-6,9-dimethylpyrido[1,2-*a*]benzimidazole (152g)



Compound **152g** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (5:95 v/v); the product was obtained as light yellow amorphous solid in 57% yield.

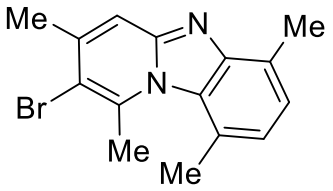
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, *J* = 1.5 Hz, 1H), 7.73 (d, *J* = 1.5 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 2.83 (s, 3H), 2.77 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 144.27, 144.09, 133.22, 128.60, 128.28, 126.73, 126.14, 124.82, 120.68, 112.60, 103.01, 19.49, 17.06 ppm.

FT-IR: $\tilde{\nu}$ = 3074, 2964, 1727, 1485, 1374, 1335, 1274, 1196 cm^{-1}.

HRMS: $C_{13}H_{11}{}^{79}Br_2N_2$ $[M+H]^+$ calc.: 352.9298 found: 352.9283; $C_{13}H_{11}{}^{79}Br^{81}BrN_2$ $[M+H]^+$ calc.: 354.9270 found: 354.9263, $C_{13}H_{11}{}^{81}Br_2N_2$ $[M+H]^+$ calc.:356.9244 found : 356.9242

2-Bromo-1,3,6,9-tetramethylpyrido[1,2-*a*]benzimidazole (152h)



Compound **152h** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (10:95 v/v); the product was obtained as light yellow amorphous solid in 87% yield.

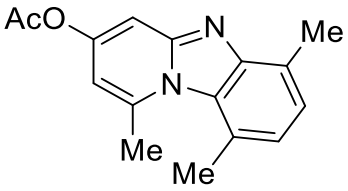
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.27 (d, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 3.03 (s, 3H), 2.74 (s, 6H), 2.54 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.23, 141.50, 137.58, 129.68, 126.51, 126.40, 125.29, 121.66, 114.11, 113.87, 25.85, 24.36, 24.18, 17.18 ppm.

FT-IR: $\tilde{\nu}$ =3031, 2956, 2918, 1644, 1531, 1374, 1346, 1299, 1195 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{15}H_{16}{}^{79}BrN_2$: 303.0499 found: 303.0491. HRMS: calc. for $[M+H]^+$ $C_{15}H_{16}{}^{81}BrN_2$: 305.0474 found: 305.0471.

3-Acetoxy-1,6,9-trimethylpyrido[1,2-*a*]benzimidazole (152i)



Compound **152i** was obtained by using the general procedure B and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (15:85 v/v); the product was obtained as light yellow amorphous solid in 80% yield.

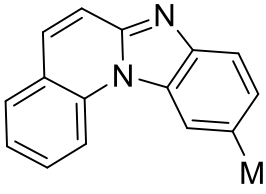
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 9.1 Hz, 1H), 7.29 (dd, *J* = 6.8, 2.1 Hz, 1H), 7.09 (s, 1H), 6.56 (d, *J* = 6.6 Hz, 1H), 2.89 (s, 3H), 2.75 (s, 3H), 2.53 (s, 3H), 2.39 ppm (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.11, 151.29, 144.06, 142.98, 128.93, 127.57, 120.40, 115.80, 113.84, 112.62, 24.28, 20.87, 17.29, 17.07 ppm.

FT-IR: $\tilde{\nu}$ = 3063, 30178, 2921, 2230, 1760 1519, 1350, 1058 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{17}O_2N_2$: 269.1288 found: 269.1284.

10-Methylbenzo[4,5]imidazo[1,2-*a*]quinolone (154a)



Compound **154a** prepared according to the general procedure B using PIDA (3 equiv PIDA was added in 3 portions every 6 h and reaction continued for 18 h) and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (25:75 v/v); the product was obtained as light yellow amorphous solid in 60% yield. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.52 (d, *J* = 8.5 Hz, 1H), 8.13 (s, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.79 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.77

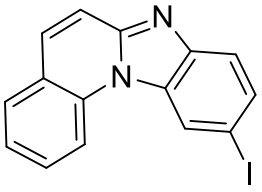
– 7.68 (m, 1H), 7.60 (q, *J* = 9.5 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 2.64 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.99, 142.72, 135.79, 132.83, 131.15, 130.84, 129.61, 129.54, 126.20, 124.17, 123.58, 119.96, 117.85, 115.36, 114.06, 22.44 ppm.

FT-IR: $\tilde{\nu}$ = 2930, 2855, 1605, 1560, 1525, 1415, 1225 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{13}N_2$: 233.1073 found: 233.1069.

10-Iodobenzo[4,5]imidazo[1,2-*a*]quinolone (154b)



Compound **154b** prepared according to the general procedure B using PIDA (3 equiv PIDA was added in 3 portions every 6 h and reaction continued for 18 h) and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (20:80 v/v); the product was obtained as brown amorphous solid in 45% yield.

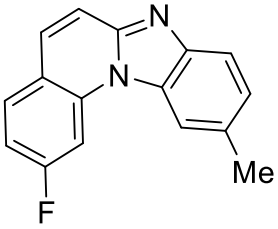
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.43 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.84 – 7.78 (m, 2H), 7.77 (dd, *J* = 9.0, 4.6 Hz, 2H), 7.67 (d, *J* = 9.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.02, 143.13, 134.94, 133.45, 131.99, 131.78, 130.16, 129.84, 124.87, 123.40, 122.59, 121.67, 116.94, 115.24, 86.04 ppm.

FT-IR: $\tilde{\nu}$ = 3040, 2945, 2856, 1575, 1520, 1403, 1340, 1170, 1109 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{15}H_{10}N_2I$: 344.9882. found: 344.9883.

2-Fluoro-10-methylbenzo[4,5]imidazo[1,2-*a*]quinolone (154c)



Compound 1**54c** prepared according to the general procedure B using PIDA (3 equiv PIDA was added in 3 portions every 6 h and reaction continued for 18 h) and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (25:75 v/v); the product was obtained as brown amorphous solid in 57% yield.

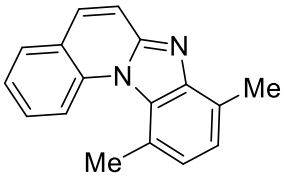
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 8.8, 4.4 Hz, 1H), 8.06 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.67 (d, *J* = 9.5 Hz, 1H), 7.59 (d, *J* = 9.5 Hz, 1H), 7.46 (dt, *J* = 8.3, 2.8 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 1H), 2.64 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.83 (d, *J* = 245.4 Hz), 147.08, 141.61, 133.53, 132.11, 130.36, 130.33, 126.68, 125.07 (d, *J* = 8.5 Hz), 119.86, 118.72, 117.46 (d, *J* = 24.0 Hz), 117.02 (d, *J* = 8.3 Hz), 114.72 (d, *J* = 22.5 Hz), 113.73, 22.46 ppm.

FT-IR: $\tilde{\nu}$ = 3050, 2955, 2850, 1630, 1550, 1490, 1380, 1220, 1113 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{12}N_2F$: 251.0979 found: 251.0973.

8,11-Dimethylbenzo[4,5]imidazo[1,2-*a*]quinoline (157)[81]



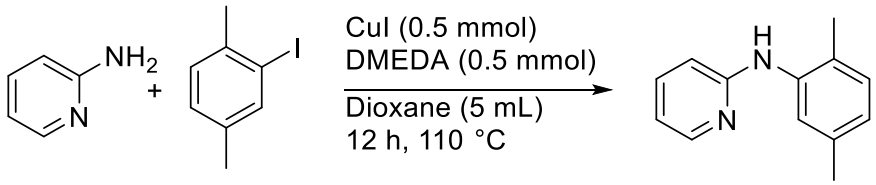
Compound **157** prepared according to the general procedure B using PIDA (1 equiv) and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (25:75 v/v); the product was obtained as light yellow amorphous solid in 83% yield.

^{1}H NMR (400 MHz, CDCl3) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.66 –7.57 (m, 3H), 7.43 – 7.37 (m, 1H), 7.28 – 7.24 (m, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 2.78 ppm (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.65, 144.95, 135.66, 130.84, 130.58, 128.55, 128.03, 127.24, 126.09, 125.18, 124.11, 124.02, 120.73, 119.79, 118.06, 23.25, 17.02 ppm.

MS-EI: m/z (%): 246.1 (100); 231.1 (41); 115.1 (8).

12.5.2 Synthesis of *N*-Heteroarylamines[269]

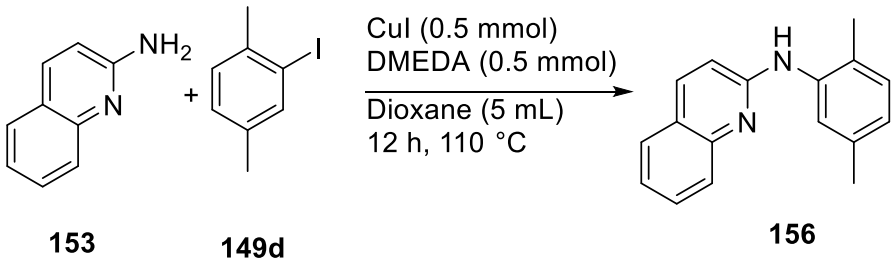


144a **149d** **155**

To the seal tube, 2-aminopyridine **144a** (1 mmol), CuI (0.5 mmol) and K_2CO_3 (2.0 mmol) were added, magnetic stir bar and septum. The seal tube was evacuated and back filled with nitrogen gas three times. Dioxane (5 mL), 2-iodo-1,4-dimethylbenzene (1.5 mmol) and DMEDA (0.5 mmol) were added by syringe at room temperature. The reaction mixture was stirred at 100 °C for 12 h. Upon completion the reaction, cooled down to room temperature. Saturated ammonium chloride (25 mL) added, and the mixture was extracted with ethyl acetate (3×10 mL). The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as an eluent system. The product was obtained as yellow solid in 45% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, *J* = 6.3 Hz, 1H), 7.21 (s, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.82 (t, *J* = 48.5 Hz, 3H), 2.32 (s, 3H), 2.23 ppm (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.10, 137.57, 136.61, 130.95, 128.72, 125.97, 125.48, 123.97, 21.16, 17.76.



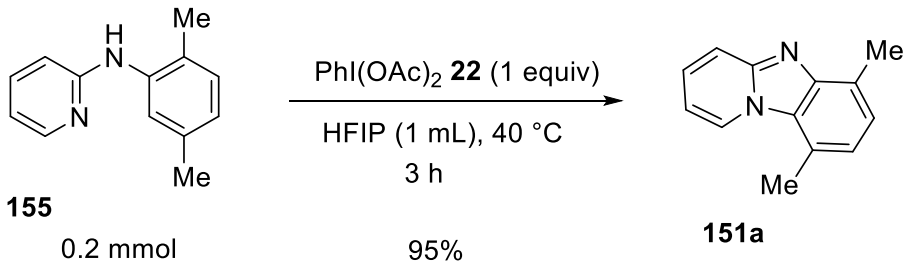
153 **149d** **156**

To the seal tube, 2-aminoquinoline **153a** (1 mmol), CuI (0.5 mmol) and K_2CO_3 (2.0 mmol) were added, magnetic stir bar and septum. The seal tube was evacuated and back filled with nitrogen gas three times. Dioxane (5 mL), 2-iodo-1,4-dimethylbenzene (1.5 mmol) and DMEDA (0.5 mmol) were added by syringe at room temperature. The reaction mixture was stirred at 100 °C for 12 h. Upon completion the reaction, cooled to room temperature. Saturated ammonium chloride (25 mL) added, and the mixture was extracted with ethyl acetate (3×10 mL). The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as an eluent system. The product was obtained as yellow solid in 33% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.0 Hz, 1H), 7.72 (s, 1H), 7.63 (t, *J* = 8.3 Hz, 1H), 7.57 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.37 (s, 1H), 7.31 – 7.26 (m, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 2.35 (s, 3H), 2.27 ppm (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.71, 147.78, 138.08, 136.72, 130.98, 129.98, 129.63, 127.62, 127.23, 126.18, 125.95, 124.61, 124.12, 122.95, 110.72, 21.21, 17.81 ppm.

12.5.3 Procedure for probable Intermediate 155 Test



155 0.2 mmol

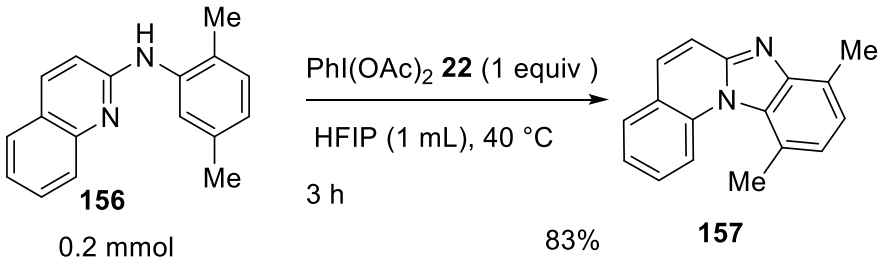
95%

151a

To a screw cap reaction vial *N*-(2,5-dimethylphenyl)pyridin-2-amine **155** (0.20 mmol, 1 equiv), $PhI(OAc)_2$ (0.20 mmol, 1 equiv) and HFIP (1 mL) were added. The reaction mixture was heated to 40 ^oC for 3 h. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate or acetone as an eluent system. The product was obtained as yellow solid in 95% yield

12.5.4 Procedure for Probable Intermediate 156 Test

To a screw cap reaction vial *N*-(2,5-dimethylphenyl)quinolin-2-amine (0.20 mmol, 1 equiv), $PhI(OAc)_2$ (0.20 mmol, 1 equiv) and HFIP (1 mL) were added. The reaction mixture was heated to 40 ^oC for 3h. Then the reaction mixture was analysis by GC-MS and only 8,11-dimethylbenzo[4,5]imidazo[1,2-*a*]quinoline was obtained. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ ethyl acetate or acetone as an eluent system. The product was obtained as yellow solid in 83% yield



8,11-Dimethylbenzo[4,5]imidazo[1,2-*a*]quinoline (157)

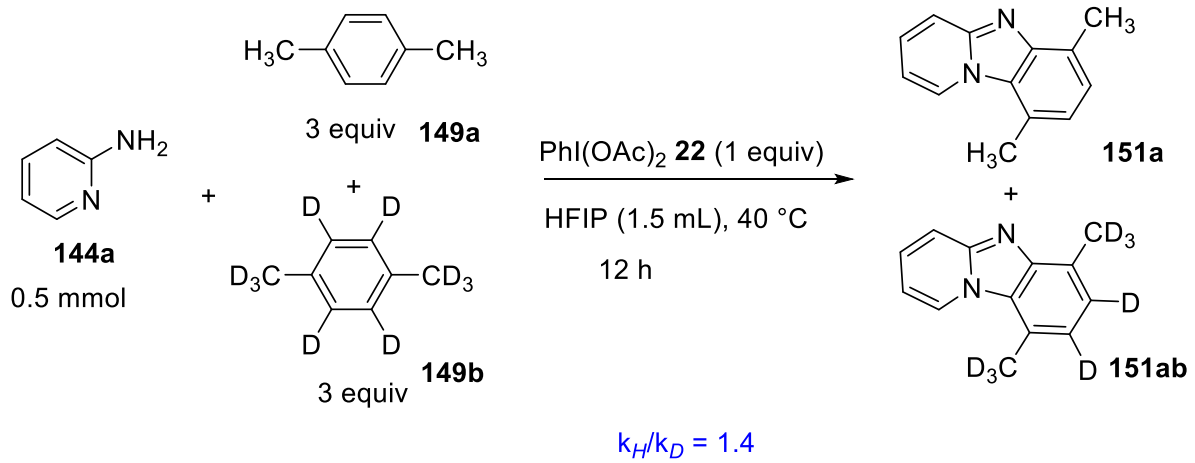
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.77 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.66 – 7.57 (m, 3H), 7.45 – 7.37 (m, 1H), 7.30 – 7.22 (m, 1H), 7.14 (d, *J* = 7.4 Hz, 1H), 2.78 ppm (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.65, 135.66, 130.84, 130.58, 128.55, 128.03, 127.24, 126.09, 125.18, 124.11, 124.02, 120.73, 119.79, 118.06, 23.25, 17.02 ppm.

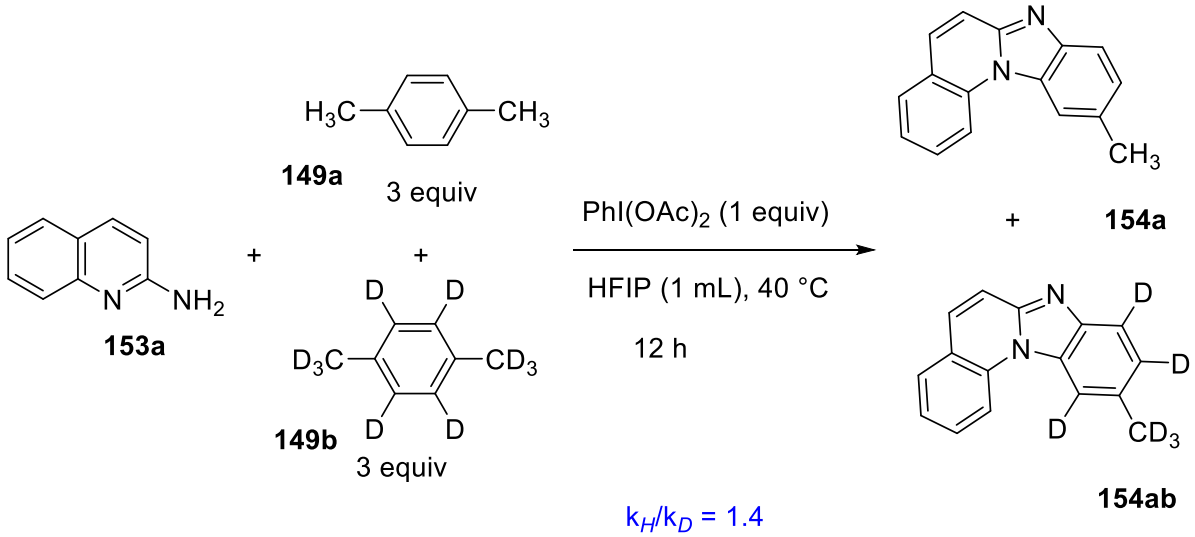
12.5.5. Procedure for Kinetic Isotope Experiment Study with 2-Aminopyridine

To a screw cap reaction vial 2-aminopyridine (0.5 mmol, 1 equiv), $PhI(OAc)_2$ (0.20 mmol, 1 equiv), *p*-xylene (3 equiv), deuterated *p*-xylene (3 equiv) and HFIP (1.5 mL) were added. The reaction mixture was heated to 40 ^oC for 12 h. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica

gel using petroleum ether/ethyl acetate or acetone as an eluent system. Ratio was calculated by ^{1}H NMR analysis and k_H/k_D is equal to 1.

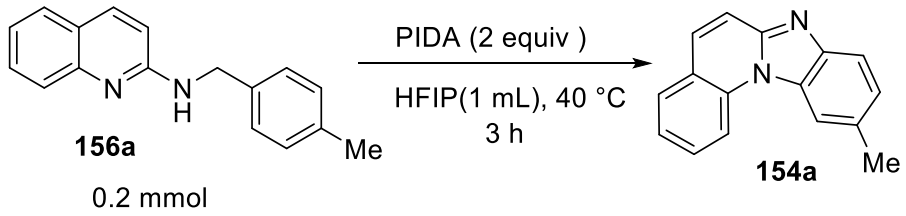


12.5.6 Procedure for Kinetic Isotope Effect Study with 2-Aminoquinoline



To a screw cap reaction vial 2-aminopyridine (0.5 mmol, 1 equiv), $PhI(OAc)_2$ (0.20 mmol, 1 equiv), *p*-xylene (3 equiv), deuterated *p*-xylene (3 equiv) and HFIP (1.5 mL) were added. The reaction mixture was heated to 40 ^{o}C for 12 h. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by lash column chromatography over silica gel using petroleum ether/ethyl acetate or acetone as an eluent system. Ratio was calculated by ^{1}H NMR analysis and K_H/K_D is equal to1.42.

12.5.7 Reaction of *N*-Benzylamine Intermediate



156a

0.2 mmol

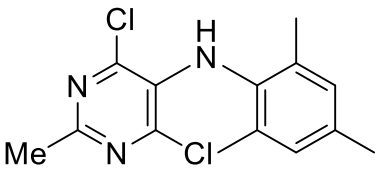
154a

To a screw reaction vial *N*-(4-methylbenzyl)quinolin-2-amine (0.20 mmol, 1 equiv), $PhI(OAc)_2$ **22** (0.4 mmol, 2 equiv) and HFIP (1 mL) were added. The reaction mixture was heated to 40 ^oC for 3 h and the reaction mixture was monitored by TLC and GC-MS analysis. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate or acetone as an eluent system. The product was obtained as yellow solid in 90% yield.

12.6 Hypervalent Iodine (III) Mediated Oxidative Amination of Arenes with Heteroaromatic Amines

12.6.1. Characterization of *N*-Arylated Heteroaromatic Amines (189a-194g)

4,6-Dichloro-*N*-mesityl-2-methylpyrimidin-5-amine (178a)



Compound **178**a was obtained by using the general procedure C and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (5:95 v/v); The product was obtained as brown solid in 93% yield.

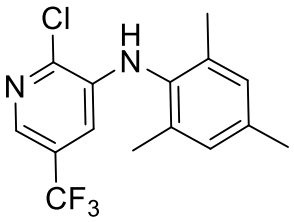
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 2H), 5.48 (s, 1H), 2.59 (s, 3H), 2.28 (s, 3H), 2.11 ppm (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.64, 146.66, 136.43, 135.52, 134.48, 133.08, 129.10, 24.43, 21.03, 19.00 ppm.

FT-IR: $\tilde{\nu}$ = 3265, 2918, 2854, 1610, 1508, 1482, 1434, 1370, 1292, 1186, 1028 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{16}{}^{35}Cl_2N_3$: 296.07158 found: 296.07167; calc. for $[M+H]^+$ $C_{14}H_{16}Cl^{37}ClN_3$: 298.06863 found: 298.06869; calc. for $[M+H]^+$ $C_{14}H_{16}{}^{37}Cl_2N_3$: 300.06568 found: 300.06534.

2-Chloro-*N*-mesityl-5-(trifluoromethyl)pyridin-3-amine (178b)



Compound **178b** was obtained by using the general procedure C and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (5:95 v/v); The product was obtained as light yellow solid in 94% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.0 Hz, 1H), 7.00 (s, 2H), 6.55 (d, *J* = 2.0 Hz, 1H), 5.90 (s, 1H), 2.33 (s, 3H), 2.14 ppm (s, 6H).

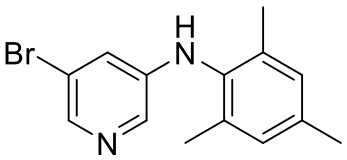
^{13}C NMR (126 MHz, $CDCl_3$) δ 139.82, 139.75, 137.66, 136.13, 133.57 (q, *J* = 4.4 Hz), 132.24, 129.91, 127.01 (d, *J* = 32.9 Hz), 123.37 (q, *J* = 272.8 Hz), 114.65 (q, *J* = 3.5 Hz), 21.09, 18.04 ppm.

FT-IR: $\tilde{\nu}$ = 3265, 2918, 2854, 1508, 1482, 1434, 1370, 1292, 1186, 1028, 1011 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{15}H_{15}{}^{35}ClF_2$: 315.0804 found: 315.08797; $[M+H]^+$ $C_{15}H_{15}{}^{37}ClF$: 317.08409 found: 317.08487.

5-Bromo-*N*-mesityl-3-amonopyridine (178c)

Compound **178c** was obtained by using the general procedure C and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (20:80 v/v); The product was obtained as brown crystals in 89% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 2.1 Hz, 1H), 7.95 (d, *J* = 2.1 Hz, 1H), 6.96 (s, 2H), 6.76 (t, *J* = 2.1 Hz, 1H), 5.50 (s, 1H), 2.31 (s, 3H), 2.15 ppm (s, 6H).

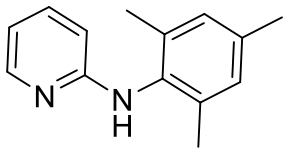
^{13}C NMR (126 MHz, $CDCl_3$) δ 144.27, 139.31, 136.85, 136.12, 134.41, 133.26, 129.67, 121.39, 121.10, 21.04, 18.22 ppm.

FT-IR: $\tilde{\nu}$ = 3204, 2673, 1698, 1575, 1443, 1323, 1004 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{16}{}^{79}BrN_2$: 291.04914 found: 291.05045; $[M+H]^+$ $C_{14}H_{16}{}^{81}BrN_2$: 293.04709 found: 293.04827.

***N*-Mesityl-2-aminopyridine (178d)**

Compound **178d** was obtained by using the general procedure C and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (40:60 v/v); The product was obtained as light brown amorphous solid in 86% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 4.4 Hz, 1H), 7.43 – 7.31 (m, 1H), 6.95 (s, 2H), 6.69 (s, 1H), 6.60 (dd, *J* = 6.6, 5.6 Hz, 1H), 6.01 (d, *J* = 8.4 Hz, 1H), 2.31 (s, 3H), 2.19 ppm (s, 6H).

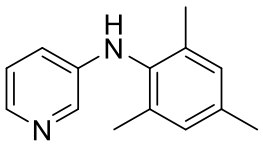
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.99, 147.72, 138.25, 136.65, 136.55, 133.69, 129.34, 113.34, 105.98, 21.06, 18.36 ppm.

FT-IR: $\tilde{\nu}$ = 3155, 2920, 1716, 1684, 1593, 1454 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{17}N_2$: 213.13863 found: 213.13909.

***N*-Mesityl-3-aminopyridine (178e)**

Compound **178e** was obtained by using the general procedure C and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (20:80 v/v); The product was obtained as light brown amorphous solid in 97% yield.



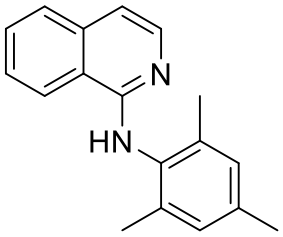
^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.6 Hz, 1H), 7.95 (d, *J* = 4.6 Hz, 1H), 7.03 (dd, *J* = 8.3, 4.6 Hz, 1H), 6.95 (s, 2H), 6.65 (ddd, *J* = 8.3, 2.6, 1.3 Hz, 1H), 5.46 (s, 1H), 2.30 (s, 3H), 2.15 ppm (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.18, 138.65, 136.12, 136.00, 135.99, 134.24, 129.37, 123.83, 118.83, 20.90, 18.13 ppm.

FT-IR: $\tilde{\nu}$ = 3229, 2968, 2916, 1579, 1480 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{17}N_2$: 213.13863 found:213.13909.

***N*-Mesitylisoquinolin-1-amine (178f)**



Compound **178f** was obtained by using the general procedure C and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (40:60 v/v); The product was obtained as light brown amorphous solid in 47% yield.

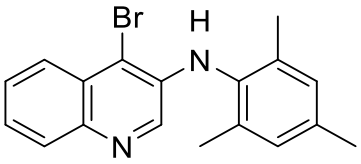
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.4 Hz, 1H), 7.69 – 7.39 (m, 3H), 7.25 – 7.20 (m, 2H), 6.99 (s, 2H), 2.37 (s, 3H), 1.93 ppm (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.69, 137.98, 137.64, 136.69, 135.28, 132.45, 131.86, 128.41, 126.96, 125.34, 124.01, 123.01, 21.23, 20.46 ppm.

FT-IR: $\tilde{\nu}$ = 3395, 2915, 1663, 1610, 1505, 1454, 1284, 1025 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{18}H_{19}N_2$: 263.15428 found: 263.15431.

4-Bromo-*N*-mesitylquinolin-3-amine (178g)



Compound **178g** was obtained by using the general procedure C product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (10:90 v/v); The product was obtained as brown solid in 85% yield.

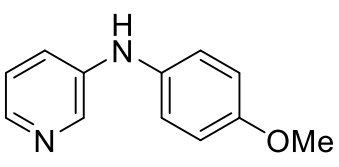
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.97-7.95 (m, 2H), 7.57 (ddd, *J* = 8.4, 7.0, 1.1 Hz, 1H), 7.48 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 7.00 (s, 2H), 5.89 (s, 1H), 2.34 (s, 3H), 2.20 ppm (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.88, 139.40, 137.99, 137.13, 136.58, 133.73, 129.70, 129.58, 128.44, 128.26, 125.80, 124.73, 112.97, 21.12, 18.30 ppm.

FT-IR: $\tilde{\nu}$ = 3347, 2946, 2853, 1592, 1479, 1407, 1340, 1239, 1215, 1029 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{17}H_{16}BrN_2$: 327.04914 found: 327.05006; $[M+H]^+$ $C_{17}H_{16}{}^{81}BrN_2$: 329.04709 found: 329.04786.

***N*-(4-Methoxyphenyl)pyridin-3-amine (180a)**



Compound **180a** was obtained by using the general procedure D and the product was isolated by column chromatography with

silica gel. Eluent: EtOAc/petroleum ether (30:70 v/v); The product was obtained as brown amorphous solid in 60% yield.

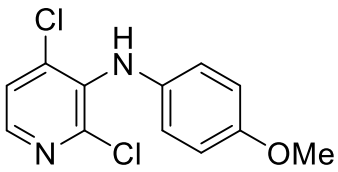
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 2.6 Hz, 2H), 8.05 (d, *J* = 4.6 Hz, 2H), 7.22 – 7.17 (m, 2H), 7.11 – 7.09 (m, 1H), 7.08 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.70 (s, 2H), 3.80 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.10, 141.97, 140.42, 138.24, 134.45, 123.86, 122.91, 121.39, 115.00, 55.70 ppm.

FT-IR: $\tilde{\nu}$ = 3247, 3176, 3041, 2923, 2852, 1505, 1324, 1246, 1030 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{12}H_{13}N_2O$: 201.09832 found: 201.10224.

2,4-Dichloro-*N*-(4-methoxyphenyl)pyridin-3-amine (180b)



Compound **180b** was obtained by using the general procedure D and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (20:80 v/v); The product was obtained as brown amorphous solid in 58% yield.

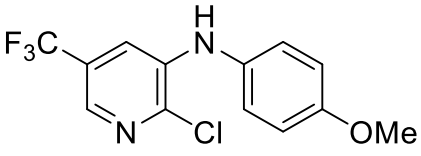
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 2.2 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.03 (s, 1H), 3.83 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.07, 140.56, 136.40, 135.38, 131.87, 131.76, 126.35, 119.25, 115.57, 55.95 ppm.

FT-IR: $\tilde{\nu}$ = 3369, 3005, 2938, 2838, 1592, 1509, 1417, 1286, 1246, 1112, 1060, 1036 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{12}H_{11}{}^{35}Cl_2N_3$: 269.02429 found: 269.02505; calc. for $[M+H]^+$ $C_{12}H_{11}Cl^{37}ClN_3$: 271.02134 found: 271.02180; calc. for $[M+H]^+$ $C_{11}H_{12}{}^{37}Cl_2N_3$: 273.01839 found: 273.01863.

2-Chloro-*N*-(4-methoxyphenyl)-5-(trifluoromethyl)pyridin-3-amine (180c)



Compound **180c** was obtained by using the general procedure D and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (15:85 v/v); The product was obtained as brown amorphous solid in 65% yield.

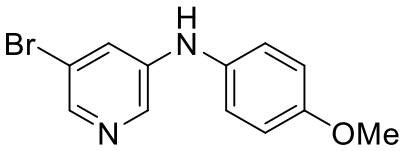
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.84 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.98, 140.27, 139.88, 134.15 (d, *J* = 4.5 Hz), 131.17, 126.74 (d, *J* = 33.0 Hz), 126.13, 124.42, 123.34 (d, *J* = 272.9 Hz), 115.56 (d, *J* = 3.5 Hz), 115.43, 55.67 ppm.

FT-IR: $\tilde{\nu}$ = 3314, 2915, 2838, 1654, 1514, 1453, 1340, 1243, 1117, 1068, 1033 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}{}^{35}ClN_2F_3$: 303.05065 found: 303.05143; calc. for $[M+H]^+$ $C_{13}H_{11}Cl^{37}N_2F_3$: 305.04770 found: 305.04818.

5-Bromo-*N*-(4-methoxyphenyl)pyridin-3-amine(180d)



Compound **180d** was obtained by using the general procedure D and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (20:80 v/v); The product was obtained as brown amorphous solid in 54% yield.

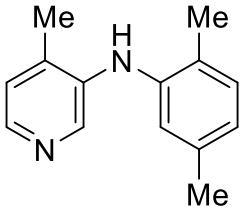
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 8.07 (s, 1H), 7.31 (t, *J* = 1.9 Hz, 1H), 7.10 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 5.82 (s, 1H), 3.82 ppm(s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.98, 146.33, 140.04, 135.57, 132.94, 124.24, 123.01, 115.20, 55.72 ppm.

FT-IR: $\tilde{\nu}$ = 3238, 3002, 2929, 1566, 1505, 1439, 1246, 1178, 1033, 1006 cm^{-1}.

HRMS: calc. for $[M]^+$ $C_{12}H_{12}O^{79}BrN_2$: 279.01275 found: 279.01382; calc. for $[M+H]^+$ $C_{12}H_{12}O^{81}BrN_2$: 281.01071 found: 281.01131.

***N*-(2,5-Dimethylphenyl)-4-methylpyridin-3-amine (180e)**



Compound **180e** was obtained by using the general procedure D and product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (15:85 v/v); The product was obtained as brown amorphous solid in 75% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 8.14 (d, *J* = 3.8 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.72 (s, 1H), 5.11 (s, 1H), 2.25 (s, 6H), 2.23 ppm (s, 3H).

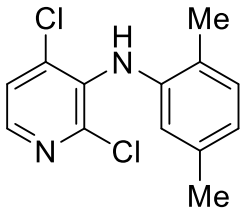
^{13}C NMR (126 MHz, $CDCl_3$) δ 142.72, 141.04, 140.79, 139.05, 136.79, 136.58, 130.89, 125.54, 124.75, 123.00, 119.10, 21.20, 17.40, 17.36 ppm.

FT-IR: $\tilde{\nu}$ = 3236, 3027, 1600, 1585, 1481, 1395, 1310, 1289, 1213, 1120, 1004 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{15}N_2O$: 213.13863 found: 213.13860.

2,4-Dichloro-*N*-(2,5-dimethylphenyl)pyridin-3-amine (180f)

Compound **180f** was obtained by using the general procedure D and the product was isolated by column chromatography with silica gel. Eluent: EtOAc/petroleum ether (25:75 v/v); The product was obtained as brown amorphous solid in 75% yield.



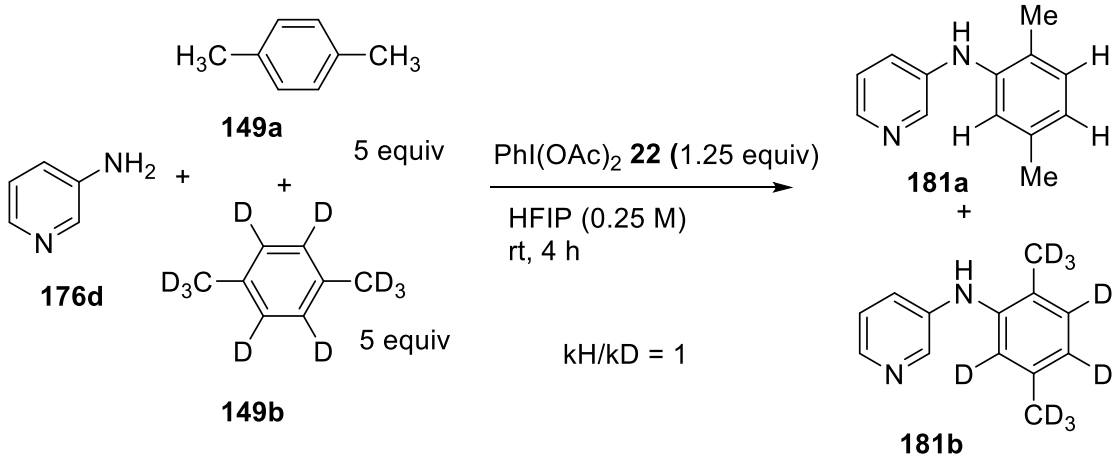
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.2 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.03 (s, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 5.92 (s, 1H), 2.34 (s, 3H), 2.19 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 139.72, 137.34, 136.88, 136.23, 135.35, 131.66, 131.50, 130.38, 127.34, 125.61, 119.39, 21.09, 17.44 ppm.

FT-IR: $\tilde{\nu}$ = 3329, 2920, 1567, 1473, 1424, 1364, 1251, 1196, 1112, 1061 cm^{-1}.

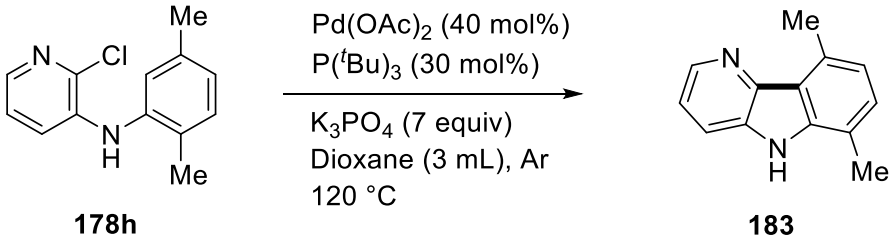
HRMS: calc. for $[M+H]^+$ $C_{13}H_{13}{}^{35}Cl_2N_2$: 267.04503 found: 267.04517; calc. for $[M+H]^+$ $C_{13}H_{13}Cl^{37}ClN_2$: 269.04208 found: 269.04196; calc. for $[M+H]^+$ $C_{13}H_{13}{}^{37}Cl_2N_2$: 271.03913 found: 271.03857.

12.5.1 Procedure for Kinetic Isotope Experiment of 3-Aminopyridine



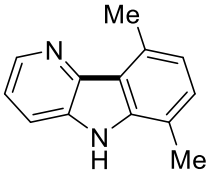
To a screw capped reaction vial containing, 3-aminopyridine **176d** (1 equiv.), *p*-xylene **149a** (5 equiv.), deuterated *p*-xylene **149b** and HFIP (0.25 M) were added. Then 1.1 equiv (diacetoxy)iodobenzene **22**, was added to the reaction mixture and was stirred at room temperature under air for 4 h. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as an eluent system. KIE ($K_H/K_D \approx 1$) was determined from ^{1}H NMR.

12.6.2 Synthesis of Compound 183



In a seal tube equipped with a magnetic stirring bar, were added dry dioxane (3 mL), $Pd(OAc)_2$ (40 mol %), $P(^tBu)_3$ (30 mol %), then 2-chloro-*N*-(2,5-dimethylphenyl)pyridin-3-amine and finely ground K_3PO_4 (7 equiv) under argon atmosphere. The mixture was heated under argon atmosphere for 24 h at 12 °C. After cooling ethyl acetate was added and the mixture was filtered. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as an eluent system.

6,9-dimethyl-5*H*-pyrido[3,2-*b*]indole



^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.72 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.26 (dd, *J* = 8.3, 4.6 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 7.3 Hz, 1H), 3.03 (s, 3H), 2.52 ppm(s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 141.66, 139.79, 133.06, 132.93, 132.35, 128.12, 121.56, 119.25, 117.56, 117.50, 117.31, 19.70, 16.37 ppm.

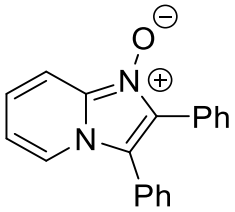
FT-IR: $\tilde{\nu}$ = 3015, 2913, 2854, 1693, 1640, 1497, 1464, 1355, 1174, 1099 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{13}N_2$: 197.10732 found: 197. 1080.

12.7 Regioselective Annulation of Nitrosopyridine with Alkynes and Alkenes in the Synthesis of *N*–Oxide-imidazopyridines

12.7.1. Characterization of *N*–Oxide-imidazopyridine derivatives (189a-194g)

2,3-Diphenylimidazo[1,2-*a*]pyridine 1-oxide (189a)



Compound **189a** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); The product was obtained as light yellow solid in 86% yield. This reaction was carried out in 4 mmol scale and the pure product was obtained; 75% yield.

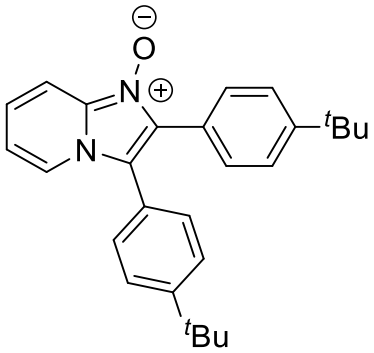
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.91 (m, 2H), 7.75 – 7.68 (m, 2H), 7.49 – 7.42 (m, 3H), 7.39 – 7.32 (m, 2H), 7.32 – 7.27 (m, 3H), 7.20 (ddd, *J* = 9.1, 6.7, 0.8 Hz, 1H), 6.78 ppm (td, *J* = 6.9, 1.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.97, 132.91, 130.51, 130.13, 129.75, 129.71, 128.98, 128.26, 126.72, 126.50, 124.92, 122.60, 117.28, 114.48, 112.87 ppm.

FT-IR: $\tilde{\nu}$ = 3015, 2926, 1630, 1506, 1514, 1450, 1423, 1371, 1279, 1113 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{19}H_{15}N_2O$: 287.11789 found: 287.11743.

2,3-Bis(4-(*tert*-butyl)phenyl)imidazo[1,2-*a*]pyridine 1-oxide (189b)



Compound **189b** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); the product was obtained as light yellow solid; yield 95%.

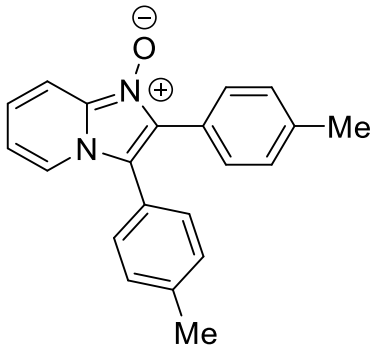
^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 – 7.87 (m, 2H), 7.76 – 7.64 (m, 2H), 7.54 – 7.45 (m, 2H), 7.39 – 7.28 (m, 4H), 7.20 (ddd, *J* = 9.4, 6.7, 0.9 Hz, 1H), 6.83 – 6.72 (m, 1H), 1.36 (s, 9H), 1.29 ppm(s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 152.92, 151.88, 133.92, 132.90, 130.29, 129.73, 126.64, 125.29, 124.69, 123.86, 123.67, 122.78, 117.19, 114.24, 112.82, 35.02, 34.85, 31.35, 31.33 ppm.

FT-IR: $\tilde{\nu}$ = 2962, 2915, 1605, 1492, 1363, 1283, 1177, 1089 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{27}H_{31}N_2O$: 399.24310 found: 399.24309.

2,3-Di-*p*-tolylimidazo[1,2-*a*]pyridine 1-oxide (189c)



Compound **189c** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); the product was obtained as light yellow solid; yield 88%.

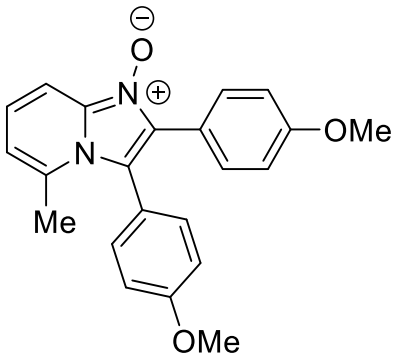
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.0 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7-317.28 (m, 4H), 7.26 – 7.21 (m, 1H), 7.17 (d, J = 8.0 Hz, 2H), 6.86-8.81 (m, 6.9, 1H), 2.45 (s, 3H), 2.35 ppm(s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 139.84, 138.92, 133.83, 132.75, 130.36, 130.30, 129.89, 128.95, 124.97, 123.60, 123.50, 122.62, 117.19, 114.32, 112.59, 21.47, 21.44 ppm.

FT-IR: $\tilde{\nu}$ =2988, 2921, 1620, 157, 1407, 1360, 1232, 1110 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{21}H_{19}N_2O$: 315.14919 found: 315.15023.

2,3-Bis(4-methoxyphenyl)-5-methylimidazo[1,2-*a*]pyridine 1-oxide (189d)



Compound **189b** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); the product was obtained as light yellow solid; yield 87%.

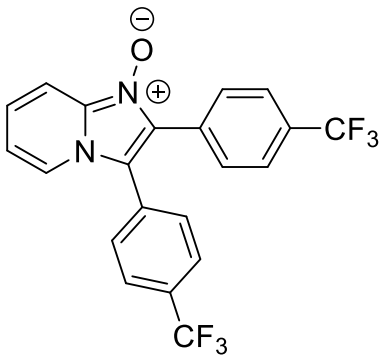
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.1 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.9 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.73 (t, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 6.8 Hz, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 2.04 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.62, 159.66, 136.43, 135.16, 134.22, 133.57, 131.38, 124.81, 121.42, 118.94, 117.75, 115.51, 113.49, 113.46, 110.55, 55.35, 55.15, 21.51 ppm.

FT-IR: $\tilde{\nu}$ = 2996, 2837, 1609, 1519, 1494, 1395, 1293, 1247, 1160, 1027 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{22}H_{21}N_2O_3$: 361.15467 found: 361.15525.

2,3-Bis(4-(trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridine 1-oxide (189e)



Compound **189e** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); the product was obtained as light yellow solid; yield 77%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.6 Hz, 2H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 2H), 7.32 (dd, *J* = 9.5, 6.8 Hz, 1H), 6.91 ppm (t, *J* = 7.4 Hz, 1H).

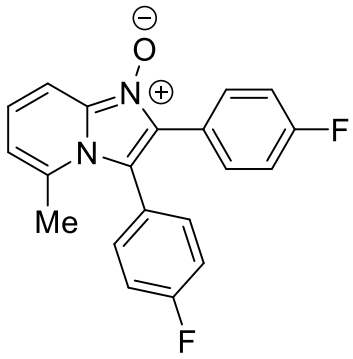
^{13}C NMR (75 MHz, $CDCl_3$) δ 134.73, 132.33, 132.18, 131.89 (q, *J* =31.02 Hz), 131.41 (q, *J* =30.68 Hz), 130.97, 130.51, 130.03, 129.67, 127.02 (q, *J* = 3.6 Hz), 126.16, 125.53 (q, *J* =3.7 Hz), 122.12 (q, *J* =271.09 Hz), 121.82 (q, *J* =272.35 Hz), 116.30, 115.55, 113.31 ppm.

FT-IR: $\tilde{\nu}$ = 3158, 2950, 1620, 1413, 1320, 1159, 1008 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{21}H_{13}N_2OF_6$: 423.09266 found: 423.09283.

2,3-Bis(4-fluorophenyl)-5-methylimidazo[1,2-*a*]pyridine 1-oxide (189f)

Compound **189f** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); the product was obtained as light yellow solid; yield 91%.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.1 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.42 – 7.36 (m, 2H), 7.19 – 7.13 (m, 1H), 7.09 (t, *J* = 8.5 Hz, 2H), 6.95 (t, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 6.8 Hz, 1H), 2.07 ppm (s, 3H).

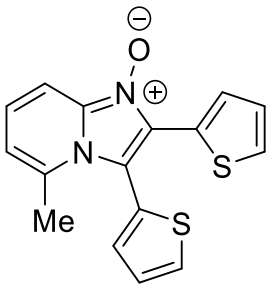
^{13}C NMR (126 MHz, $CDCl_3$) 163.63 (d, *J* = 251.80 Hz), 162.87 (d, *J* = 249.6 Hz), 136.28, 135.49, 134.87 (d, *J* = 8.4 Hz), 133.31, 132.17 (d, *J* = 8.4 Hz), 125.46 (d, J = 3.7 Hz), 125.32, 122.47 (d, *J* = 3.3 Hz), 117.10, 115.58, 115.52 (d, *J* = 21.8 Hz), 115.30 (d, *J* = 21.7 Hz), 111.03ppm.

FT-IR: $\tilde{\nu}$ = 3093, 3051, 1637, 1595, 1517, 1493, 1377, 1222, 1158, 1070 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{15}N_2OF_2$: 337.11470 found: 337.11470.

5-Methyl-2, 3-di (thiophen-2-yl)imidazo[1,2-*a*]pyridine 1-oxide (189g)

Compound **189g** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); the product was obtained as brown solid; yield 92%.



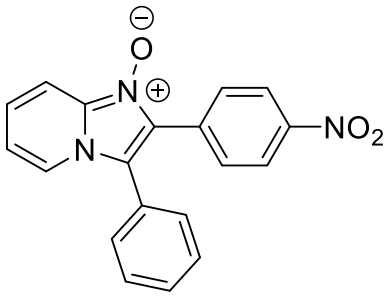
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.0 Hz, 1H), 7.68 (dd, *J* = 5.3, 1.2 Hz, 1H), 7.38 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.34 – 7.32 (m, 1H), 7.22 (dd, *J* = 5.3, 3.5 Hz, 1H), 7.16 (dd, *J* = 9.0, 6.9 Hz, 1H), 7.11 (dd, *J* = 3.9, 1.0 Hz, 1H), 6.93 (dd, *J* = 5.0, 3.9 Hz, 1H), 6.56 (d, *J* = 6.8 Hz, 1H), 2.28 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.85, 135.90, 134.89, 131.54, 130.97, 129.70, 128.55, 127.63, 127.41, 127.33, 126.25, 125.29, 116.28, 110.52, 106.36, 20.14 ppm.

FT-IR: $\tilde{\nu}$ = 3055, 2960, 1627, 1537, 1441, 1421, 1387, 1197, 1151, 1035 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{13}N_2OS_2$: 313.04638 found: 313.04711.

2-(4-Nitrophenyl)-3-phenylimidazo[1,2-*a*]pyridine 1-oxide (189h)



Compound **189h** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); the product was obtained as brown solid; yield 84%.

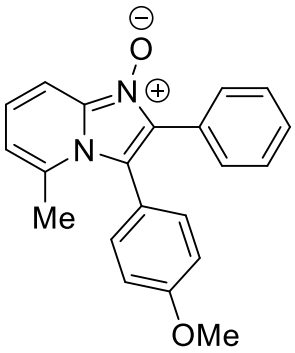
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 2H), 8.10 (d, *J* = 7.0 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.61 (dd, *J* = 6.6, 3.2 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.34 (dd, *J* = 5.3, 1.9 Hz, 3H), 7.31 – 7.26 (m, 1H), 6.91 ppm (dd, *J* = 6.6, 1.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 147.87, 134.85, 134.21, 133.40, 131.09, 130.31, 129.69, 128.66, 125.97, 125.63, 124.85, 122.34, 115.52, 114.86, 113.31, ppm.

FT-IR: $\tilde{\nu}$ = 3025, 2929, 1597, 1514, 1443, 1383, 1345, 1104 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{19}H_{14}N_3O_3$: 332.10297 found: 332.10432.

3-(4-Methoxyphenyl)-5-methyl-2-phenylimidazo[1,2-*a*]pyridine 1-oxide (189i)



Compound **189i** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); the product was obtained as brown solid; yield 85%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 9.1 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.27 (d, *J* = 8.7 Hz, 2H), 7.22 (m, 3H), 7.11 (dd, *J* = 9.1, 6.8 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 6.49 (d, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 2.05 ppm (s, 3H).

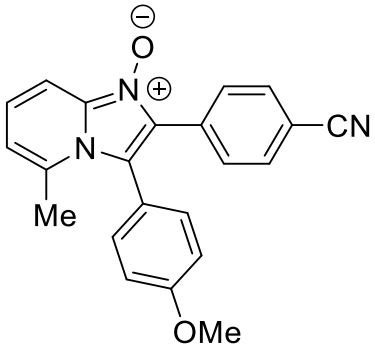
^{13}C NMR (75 MHz, $CDCl_3$) δ 160.65, 136.57, 135.25, 133.78, 130.14, 128.64, 127.96, 126.64, 125.10, 121.16, 118.38, 115.65, 113.45, 110.75, 55.36, 21.54 ppm.

FT-IR: $\tilde{\nu}$ = 2987, 2963, 1631, 1605, 1542, 1391, 1290, 1246, 1161, 1027 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{21}H_{19}N_2O_2$: 331.14410 found: 331.14496.

2-(4-Cyanophenyl)-3-(4-methoxyphenyl)-5-methylimidazo[1,2-*a*]pyridine 1-oxide (189j)

Compound **189g** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); the product was obtained as brown solid; yield 86%.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.1 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.16 (dd, *J* = 9.1, 6.8 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 6.8 Hz, 1H), 3.84 (s, 3H), 2.08 ppm (s, 3H).

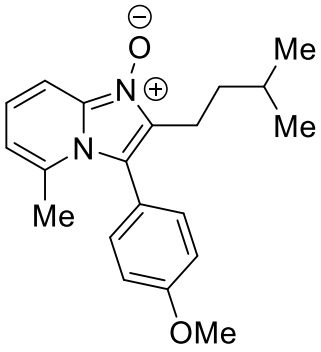
^{13}C NMR (75 MHz, $CDCl_3$) δ 161.16, 136.96, 135.80, 134.16, 131.79, 131.48, 130.52, 126.12, 124.69, 120.35, 119.30, 118.68, 116.33, 113.94, 112.15, 110.91, 55.51, 21.58 ppm.

FT-IR: $\tilde{\nu}$ = 3006, 2967, 2839, 1912, 1609, 1546, 1333, 1291, 1253, 1180, 1071 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{22}H_{18}N_3O_2$: 356.13935 found: 356.14013.

2-Isopentyl-3-(4-methoxyphenyl)-5-methylimidazo[1,2-*a*]pyridine 1-oxide (191a)

Compound **191a** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (2:98 v/v); the product was obtained as brown solid; yield 83%.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 9.1 Hz, 1H), 7.33 – 7.22 (m, 2H), 7.07 (dd, *J* = 9.1, 6.8 Hz, 1H), 6.98 – 6.81 (m, 2H), 6.45 (d, *J* = 6.8 Hz, 1H), 3.85 (s, 3H), 2.69 – 2.56 (m, 2H), 2.03 (s, 3H), 1.51-1.46 (m, 3H), 0.76 (s, 3H), 0.74 (s, 3H).

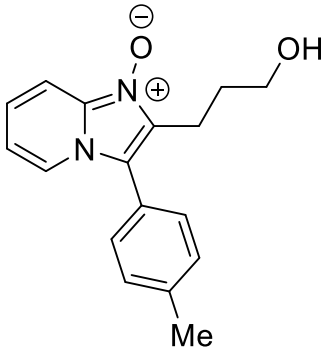
^{13}C NMR (75 MHz, $CDCl_3$) δ 160.71, 136.74, 136.33, 134.91, 133.73, 124.63, 121.26, 117.80, 114.96, 113.40, 110.08, 55.47, 36.91, 27.86, 22.30, 21.43, 20.61 ppm.

FT-IR: $\tilde{\nu}$ = 3056, 2949, 2866, 1638, 1580, 1505, 1310, 1247, 1142, 1033 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{25}N_2O_2$: 325.19105 found: 325.19229.

2-(3-Hydroxypropyl)-3-(*p*-tolyl)imidazo[1,2-*a*]pyridine 1-oxide (191b)

Compound **191b** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); the product was obtained as brown solid; yield 53%.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.0 Hz, 1H), 7.89 (d, *J* = 9.2 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H),

7.31 – 7.26 (m, 1H), 6.83 (t, *J* = 7 Hz, 1H), 3.69 – 3.57 (m, 2H), 3.11 – 2.96 (m, 2H), 2.46 (s, 3H), 1.95 – 1.77 ppm (m, 2H).

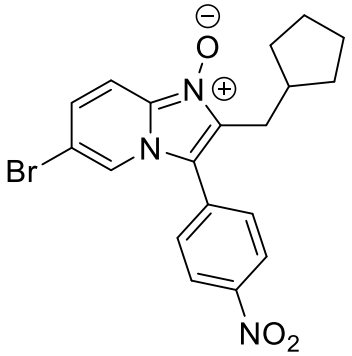
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.34, 135.15, 133.56, 130.52, 129.94, 125.74, 123.07, 122.98, 118.06, 114.43, 112.23, 60.80, 32.91, 21.58, 19.17 ppm.

FT-IR: $\tilde{\nu}$ = 2920, 1738, 1543, 1391, 1108, 1056, 1011 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{17}H_{19}N_2O_2$: 383.14410 found: 283.14481.

6-Bromo-2-(cyclopentylmethyl)-3-(4-nitrophenyl)imidazo[1,2-*a*]pyridine 1-oxide (191c)

Compound **191c** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v); The product was obtained as brown solid; yield 76%.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 8.8 Hz, 2H), 8.01 (s, 1H), 7.81 (d, *J* = 9.6 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.28 – 7.24 (m, 1H), 2.90 (d, *J* = 7.5 Hz, 2H), 2.39 (dt, *J* = 15.5, 7.8 Hz, 1H), 1.60 (dt, *J* = 11.3, 6.5 Hz, 2H), 1.54 – 1.45 (m, 2H), 1.41 (m, 2H), 1.01 ppm (m, 2H).

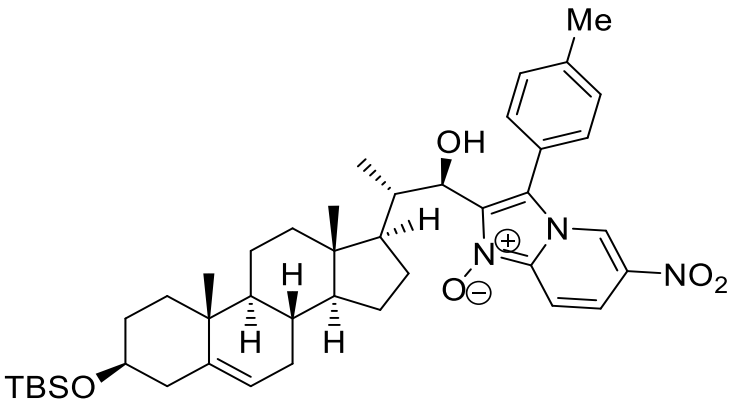
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.37, 137.07, 132.88, 131.89, 130.91, 128.59, 125.10, 122.11, 115.41, 113.44, 109.83, 38.29, 32.52, 28.23, 24.70 ppm.

FT-IR: $\tilde{\nu}$ = 3093, 2951, 2862, 1611, 1515, 1382, 1345, 1206, 1055 cm^{-1}.

HRMS: $[M+H]^+$ $C_{19}H_{19}{}^{79}BrN_3O_3$: 416.06043 found: 416.06132. HRMS: calc. for $[M+H]^+$ $C_{19}H_{19}{}^{81}BrN_3O_3$: 418.05838 found: 418.05834.

2-((1*R*,2*S*)-2-((3*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*R*)-3-((tert-butyldimethylsilyl)oxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-1-hydroxypropyl)-6-nitro-3-(*p*-tolyl)imidazo[1,2-*a*]pyridine 1-oxide (191d)

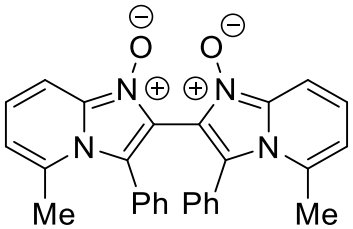
Compound **191d** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (1:99 v/v).The product was obtained as orange solid; yield 85%.



^{1}H NMR (600 MHz, $CDCl_3$) δ 8.85 (d, *J* = 1.0 Hz, 1H), 7.93 (s, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 5.29 (dd, *J* = 2.9, 2.1 Hz, 1H), 4.90 (d, *J* = 4.9 Hz, 1H), 3.47 – 3.42 (m, 1H), 2.49 (s, 3H), 2.26 – 2.21 (m, 1H), 2.17 – 2.10 (m, 2H), 1.94 – 1.83 (m, 1H), 1.78 – 1.73 (m, 2H), 1.68 (d, *J* = 12.4 Hz, 1H), 1.54 – 1.47 (m, 1H), 1.47 – 1.39 (m, , 3H), 1.38 – 1.31 (m, 2H), 1.26 – 1.18 (m, 2H), 1.10 – 1.04 (m, 1H), 0.98 (dd, *J* = 11.6, 5.4 Hz, 5H), 0.94 (s, 3H), 0.87 (s, 9H), 0.69 (dd, *J* = 11.3, 4.1 Hz, 1H), 0.63 (s, 3H), 0.04 ppm (s, 6H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 141.89, 141.77, 138.92, 136.43, 133.01, 130.96, 130.79, 123.91, 121.17, 121.04, 120.58, 118.82, 112.24, 72.73, 72.06, 56.72, 53.26, 50.31, 45.56, 43.08, 42.89, 39.85, 37.48, 36.61, 32.15, 31.97, 31.83, 28.23, 26.04, 24.61, 21.67, 21.06, 19.49, 18.37, 15.10, 11.66, -4.48 ppm.
FT-IR: $\tilde{\nu}$ = 2928, 2855, 1525, 1509, 1515, 1460, 1332, 1249, 1195, 1078 cm^{-1}.
HRMS: calc. for $[M+H]^+$ $C_{42}H_{60}N_2O_5Si$: 714.42967 found: 714.43019.

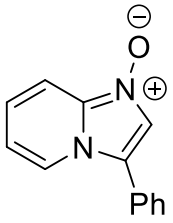
5,5'-Dimethyl-3,3'-diphenyl-[2,2'-biimidazo[1,2-*a*]pyridine] 1,1'-dioxide (191e)

Prepared according to the general procedure E using 1 equiv alkyne, 2 equiv 6-methyl-2-nitrosopyridine and the product could be isolated as light yellow solid by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v) in 65 % yield;



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.0 Hz, 2H), 7.58 – 7.49 (m, 4H), 7.33 – 7.23 (m, 8H), 6.74 (d, *J* = 6.9 Hz, 2H), 2.09 ppm (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 138.69, 137.33, 135.68, 130.11, 128.98, 128.78, 126.99, 125.58, 117.79, 111.77, 104.13, 18.90 ppm.
FT-IR: $\tilde{\nu}$ = 3063, 2926, 2915, 1634, 1546, 1444, 1406, 1209, 1114 cm^{-1}.
HRMS: calc. for $[M+H]^+$ $C_{28}H_{23}N_4O_2$: 447.18155 found: 447.18190.

3-Phenylimidazo[1,2-*a*]pyridine 1-oxide (192a)



Compound **192a** was obtained according to the general procedure E and the products were formed in 2:1 regioisomeric ratio in 76% combined yield and the major product could be isolated as light yellow solid by column chromatography with silica gel. Eluent: MeOH/DCM (3:97 v/v) in 40% yield in pure form which was fully characterized.

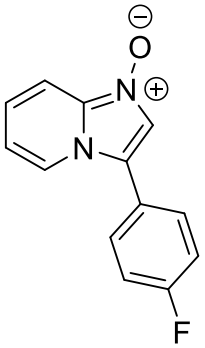
^{1}H NMR (400 MHz, $CDCl_3$+ CD_3OD 10:1) δ 8.20 (d, *J* = 7.0 Hz, 1H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.79 (s, 1H), 7.60 – 7.48 (m, 5H), 7.34 – 7.27 (m, 1H), 6.90 ppm (t, *J* = 7.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.67, 130.01, 129.80, 128.82, 126.06, 125.93, 123.25, 122.81, 121.12, 114.95, 112.93 ppm.

FT-IR: $\tilde{\nu}$ = 3052, 2954, 1641, 1474, 1416, 1327, 1147cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}N_2O$: 211.08659 found: 211.08659.

3-(4-Fluorophenyl)imidazo[1,2-*a*]pyridine 1-oxide (192b)



Compound **192b** was obtained according to the general procedure E and the products were formed in 4:1 regioisomeric ratio in 78% combined yield and the major product could be isolated as light yellow solid by column chromatography with silica gel. Eluent: MeOH/DCM (3:97 v/v) in 51% yield in pure form which was fully characterized.

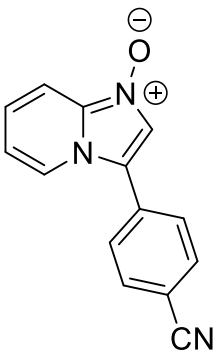
^{1}H NMR (300 MHz, $CDCl_3$+ CD_3OD 10:1) 8.18 (d, *J* = 7.1 Hz, 1H), 7.92 (d, *J* = 9.1 Hz, 1H), 7.78 (s, 1H), 7.60 – 7.50 (m, 2H), 7.42 (dd, *J* = 9.1, 6.9 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.00 (t, *J* = 6.9 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.61 (d, *J* = 251.7 Hz), 134.57, 131.06 (d, *J* = 8.6 Hz), 127.06, 123.22, 122.27, 121.68 (d, *J* = 3.5 Hz), 120.53, 117.04 (d, *J* = 22.1 Hz), 115.32, 112.34 ppm.

FT-IR: $\tilde{\nu}$ = 3037, 1719, 1495, 1413, 1335, 1225, 1088 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{10}N_2OF$: 229.07717 found: 229.07791.

3-(4-Bromo)imidazo[1,2-*a*]pyridine 1-oxide (3s)



Compound **192b** was obtained Eaccording to the general procedure E using 2 equiv of alkyne and the products were formed in 3:1 regioisomeric ratio in 65% combined yield and the major product could be isolated as light yellow semi-solid by column chromatography with silica gel. Eluent:

MeOH/DCM (5:95 v/v) in 43% yield in pure form which was fully characterized;

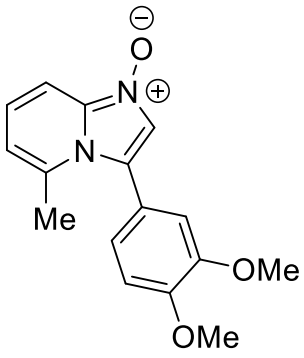
^{1}H NMR (500 MHz, DMSO) δ 8.49 (d, *J* = 7.0 Hz, 1H), 8.18 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 9.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.34 (dd, *J* = 9.1, 6.7 Hz, 1H), 7.00 ppm(t, *J* = 6.8 Hz, 1H).

^{13}C NMR (126 MHz, DMSO) δ 133.90, 132.24, 130.26, 125.64, 125.30, 124.25, 122.81, 122.24, 118.79, 114.76, 111.87 ppm.

FT-IR: $\tilde{\nu}$ = 3090, 2935, 2229, 1684, 1495, 1395, 1173, 1123 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{10}N_3O$: 236.08184 found: 236.08252.

3-(3,4-Dimethoxyphenyl)-5-methylimidazo[1,2-*a*]pyridine 1-oxide (192d)



Compound **192d** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v). The product was obtained as light yellow solid; yield 74%.

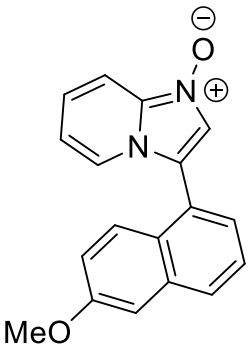
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.1 Hz, 1H), 7.61 (s, 1H), 7.17 (dd, *J* = 9.1, 6.8 Hz, 1H), 6.98 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.89 (m, 2H), 6.55 (d, *J* = 6.8 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 2.15 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.59, 148.25, 137.10, 135.59, 125.78, 125.21, 124.43, 121.35, 120.69, 115.51, 115.12, 110.60, 110.31, 56.22, 56.10, 21.10 ppm.

FT-IR: $\tilde{\nu}$ = 2954, 2931, 1640, 1582, 1461, 1250, 1233, 1130 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{17}N_2O_3$: 285.12337 found: 285.12435.

3-(6-Methoxynaphthalen-1-yl)imidazo[1,2-*a*]pyridine 1-oxide (192e)



Compound **192d** was obtained by using the general procedure E product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v). The product was obtained as light yellow solid; yield 87%.

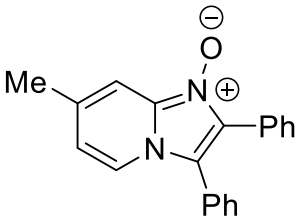
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.1 Hz, 1H), 7.91-7,84 (m, 3H), 7.82 – 7.73 (m, 2H), 7.48 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.25 – 7.13 (m, 3H), 6.84 (t, *J* = 6.8 Hz, 1H), 3.92 (s, 3H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.89, 134.92, 134.36, 129.71, 128.81, 128.34, 128.08, 126.00, 125.12, 123.20, 122.92, 121.05, 121.00, 120.28, 114.64, 112.89, 105.84, 55.51 ppm.

FT-IR: $\tilde{\nu}$ = 3042, 2929, 1628, 1607, 1416, 1394, 1113, 1035 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{18}H_{15}N_2O_2$: 291.11280 found: 291.11361.

7-Methyl-2,3-diphenylimidazo[1,2-a]pyridine 1-oxide (194a)



Compound **194a** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v). The product was obtained as light yellow solid; yield 67%.

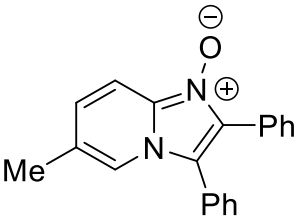
^{1}H NMR (400 MHz, $CDCl_3$) 7.87 (d, *J* = 7.1 Hz, 1H), 7.68-7.65 (m, 3H), 7.47 – 7.41 (m, 3H), 7.34 – 7.29 (m, 2H), 7.29 – 7.25 (m, 3H), 6.66 (dd, *J* = 7.1, 1.1 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.39, 134.35, 132.51, 130.43, 130.07, 129.66, 128.90, 128.20, 126.64, 126.45, 122.10, 117.37, 116.82, 110.70, 21.45 ppm.

FT-IR: $\tilde{\nu}$ = 2999, 1635, 1505, 1444, 1457, 1241, 1174, 1040 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{17}N_2O$: 301.13354 found: 301.13354.

6-Methyl-2,3-diphenylimidazo[1,2-a]pyridine 1-oxide (194b)



Compound **194b** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v). The product was obtained as light yellow solid; yield 82%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 9.2 Hz, 1H), 7.73 (s, 1H), 7.66 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.49 – 7.42 (m, 3H), 7.33 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.30 – 7.24 (m, 3H), 7.10 (d, *J* = 9.2 Hz, 1H), 2.25 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 133.30, 132.50, 130.57, 130.07, 129.71, 128.89, 128.63, 128.21, 126.77, 126.49, 124.73, 119.97, 116.99, 112.05, 18.42 ppm.

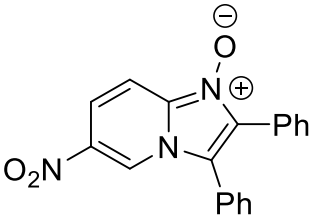
FT-IR: $\tilde{\nu}$ = 3063, 2960, 1645, 1513, 1380, 1369, 1259, 1182, 1068 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{17}N_2O$: 301.134354 found: 301.13439.

6-Nitro-2,3-diphenylimidazo[1,2-*a*]pyridine 1-oxide (194c)

Compound **194c** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (10:90 v/v). The product was obtained as light yellow solid; yield 96%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.00 (d, *J* = 10.0 Hz, 1H), 7.84 (dd, *J* = 10.0, 1.6 Hz, 1H), 7.72 (dd, *J* = 7.1, 2.1 Hz, 2H), 7.60 – 7.52 (m, 3H), 7.42-7.34 ppm (m, 5H).

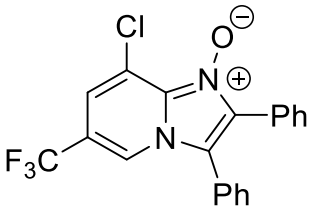


^{13}C NMR (75 MHz, $CDCl_3$) δ 138.84, 136.33, 133.33, 130.87, 130.42, 130.25, 130.06, 129.92, 128.52, 125.33, 125.08, 123.65, 120.32, 117.83, 113.28 ppm.

FT-IR: $\tilde{\nu}$ = 3060, 2996, 1726, 1605, 1503, 1369, 1325, 1126, 1075 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{19}H_{14}N_3O_3$: 332.10297 found: 332.10374.

8-Chloro-2,3-diphenyl-6-(trifluoromethyl)imidazo[1,2-*a*]pyridine 1-oxide (3f)



Compound **194b** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (3:97 v/v). The product was obtained as light yellow solid; yield 64%.

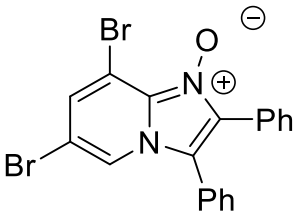
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.72 – 7.68 (m, 2H), 7.58 – 7.52 (m, 3H), 7.39 – 7.36 (m, 2H), 7.34 (dd, *J* = 5.7, 4.6 Hz, 3H), 7.15 ppm (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.44, 130.88, 130.52, 130.28, 130.24, 129.90, 129.79, 128.37, 125.29, 125.25, 123.46, 123.12, 122.38 (q, *J* = 272.52 Hz), 120.69, 120.62 (q, *J* = 5.9 Hz), 118.49, 118.21 ppm.

FT-IR: $\tilde{\nu}$ = 3050, 2940, 1636, 1531, 1416, 1309, 1231, 1121, 1074 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{21}H_{12}ClF_3N_2O$: 389.05903 found: 389.06982.

6,8-Dibromo-2,3-diphenylimidazo[1,2-*a*]pyridine 1-oxide (194e)



Compound **194e** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v). The product was obtained as light yellow solid; yield 81%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.3 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.52 – 7.49 (m, 3H), 7.36 – 7.32 (m, 3H), 7.31 – 7.27 ppm (m, 3H).

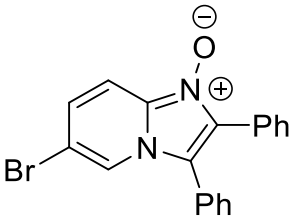
^{13}C NMR (126 MHz, $CDCl_3$) δ 134.97, 130.99, 130.55, 130.48, 130.15, 130.03, 129.37, 129.00, 128.17, 125.70, 125.65, 121.75, 118.18, 108.12, 107.55 ppm.

FT-IR: $\tilde{\nu}$ = 3035, 2980, 1602, 1599, 1504, 1488, 1361, 1329, 1244, 1140, 1031 cm^{-1}.

HRMS: $C_{19}H_{13}{}^{79}Br_2N_2O$ $[M+H]^+$ calc.: 442.93891 found: 442.94002; $C_{19}H_{13}{}^{79}Br^{81}BrN_2O$ $[M+H]^+$ calc.: 444.94687 found: 444.93711, $C_{19}H_{13}{}^{81}Br_2N_2$ $[M+H]^+$ calc.: 446.93482found : 446.93442.

6-Bromo-2,3-diphenylimidazo[1,2-*a*]pyridine 1-oxide (194f)

Compound **194f** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v). The product was obtained as light yellow solid; yield 95%.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.92 (d, *J* = 9.6 Hz, 1H), 7.70 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.51 (dd, *J* = 6.5, 3.6 Hz, 3H), 7.40 – 7.28 ppm (m, 6H).

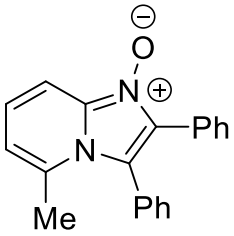
^{13}C NMR (75 MHz, $CDCl_3$) δ 133.55, 132.85, 130.53, 130.32, 130.16, 130.01, 129.47, 128.73, 128.46, 126.01, 125.82, 122.51, 117.87, 113.75, 109.76 ppm.

FT-IR: $\tilde{\nu}$ = 3096, 3004, 1625, 1510, 1376, 1355, 1175, 1078 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{19}H_{14}{}^{79}BrN_2O$: 365.03004 found: 365.02840. HRMS: calc. for $[M+H]^+$ $C_{19}H_{14}{}^{79}BrN_2O$: 367.02726 found: 367.02636.

5-Methyl-2,3-diphenylimidazo[1,2-*a*]pyridine 1-oxide (194g)

Compound **194g** was obtained by using the general procedure E and the product was isolated by column chromatography with silica gel. Eluent: MeOH/DCM (5:95 v/v).The product was obtained as light yellow solid; yield 87%.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.1 Hz, 1H), 7.56 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.50 – 7.30 (m, 5H), 7.28 – 7.14 (m, 4H), 6.57 (d, *J* = 6.8 Hz, 1H), 2.06 ppm (s, 3H).

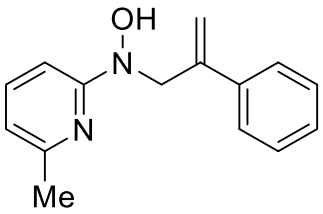
^{13}C NMR (75 MHz, $CDCl_3$) δ 136.66, 135.45, 133.80, 133.01, 130.19, 130.00, 129.32, 128.82, 128.12, 128.02, 126.32, 125.60, 118.63, 115.95, 110.71, 21.60 ppm.

FT-IR: $\tilde{\nu}$ = 3064, 2955, 1633, 1517, 1393, 1336, 1221, 1106 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{17}N_2O$: 301.13354 found: 301.13353.

***N*-(6-methylpyridin-2-yl)-*N*-(2-phenylallyl)hydroxylamine (198)**

To a screw cap reaction vial 6-methyl-2-nitrosopyridine (0.25 mmol, 1 equiv), *α*-methyl-styrene (0.5 mmol, 2 equiv), and HFIP (1.0 mL) were added under air. The reaction mixture was stirred vigorously at RT for 3 h. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using ethyl acetate/petroleum ether (10:90 v/v) as an eluent system. The product was obtained as light yellow liquid in 93% yield



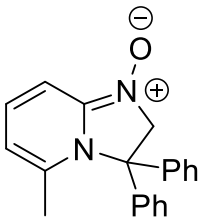
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.34-7.26 (m, 3H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 7.2 Hz, 1H), 5.55 (s, 1H), 5.37 (s, 1H), 4.67 (s, 2H), 2.45 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.52, 155.98, 143.65, 139.38, 138.13, 128.41, 127.84, 126.45, 115.45, 115.40, 106.18, 59.12, 24.25 ppm.

FT-IR: $\tilde{\nu}$ = 3058, 2925, 2854, 1632, 1589, 1449, 1333, 1263, 1195, 1029 cm^{-1}.

5-Methyl-3,3-diphenyl-2,3-dihydroimidazo[1,2-*a*]pyridine 1-oxide (199)

To a screw cap reaction vial 6-methyl-2-nitrosopyridine (0.25 mmol, 1 equiv), alpha-phenyl-styrene (0.5 mmol, 2 equiv), and HFIP (1.0 mL) were added under air. The reaction mixture was stirred vigorously at RT for 12 h. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using methanol/ dichloromethane (2:98 v/v) as an eluent system. The product was obtained as light yellow solid in 85% yield;



1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 6H), 7.27 – 7.23 (m, 4H), 6.61 (d, J = 6.4 Hz, 2H), 5.77 – 5.69 (m, 1H), 4.65 (s, 2H), 2.14ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.39, 147.04, 140.63, 132.52, 129.25, 129.14, 127.53, 109.00, 107.75, 73.45, 70.00, 21.97 ppm.

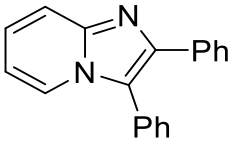
FT-IR: $\tilde{\nu}$ = 3059, 2955, 1655, 1538, 1493, 1446, 1356, 1130, 1081 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{19}H_{17}N_2O$: 289.13354 found: 289.13333.

12.7.1 Synthesis of Imidazo[1,2-*a*]pyridine Scaffolds (201a-201c)

2,3-Diphenylimidazo[1,2-a]pyridine (201a)

To a screw cap reaction vial 2,3-diphenylimidazo[1,2-*a*]pyridine 1-oxide (**189a**, 0.25 mmol) and acetonitrile (2.0 mL) were added under air. The reaction mixture was stirred vigorously at 125-130 ^{o}C for 3 h. After completion the crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using acetone/petroleum ether (20:80) as an eluent system. The product was obtained as brown solid in 95% yield;



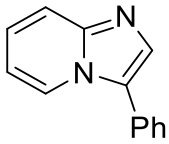
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 6.8, 1.0 Hz, 1H), 7.68 (d, *J* = 9.1 Hz, 1H), 7.62-7.57 (m, 2H), 7.50 – 7.44 (m, 2H), 7.44 – 7.42 (m, 1H), 7.41 – 7.37 (m, 2H), 7.24 – 7.19 (m, 3H), 7.18 – 7.14 (m, 1H), 6.70 ppm (dd, *J* = 6.8, 1.0 Hz, 1H).

^{13}C NMR (126 MHz, CDC_3) δ 144.60, 133.73, 130.90, 129.75, 129.19, 128.47, 128.26, 127.82, 125.32, 123.49, 121.24, 117.50, 112.76 ppm.

FT-IR: $\tilde{\nu}$ = 3058, 2925, 1666, 1600, 1505, 1442, 1344, 1212, 1027 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{19}H_{15}N_2$: 271.12298 found: 271.12367.

3-Phenylimidazo[1,2-*a*]pyridine (201b)



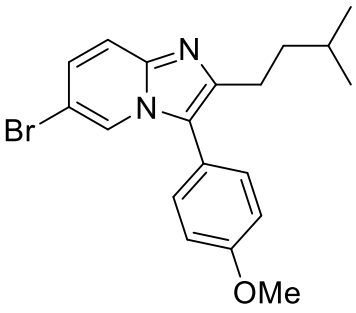
To a screw cap sealed reaction tube 3-phenylimidazo[1,2-*a*]pyridine 1-oxide (**192a**, 0.25 mmol) and acetonitrile (2.0 mL) were added under air. The reaction mixture was stirred vigorously at 140 ^oC for 12 h. After completion the crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using acetone/petroleum ether (15:85) as an eluent system. The product was obtained as brown liquid in 86% yield;

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 – 8.31 (m, 1H), 7.72-7.70 (m, 2H), 7.58 – 7.54 (m, 2H), 7.54 – 7.50 (m, 2H), 7.45 – 7.40 (m, 1H), 7.23 (s, 1H), 6.83 ppm (dd, *J* = 6.8, 1.0 Hz, 1H). ^{13}C **NMR (126 MHz, $CDCl_3$)** δ 146.01, 132.11, 129.42, 129.26, 128.46, 128.26, 124.72, 123.55, 118.26, 112.89 ppm.

FT-IR: $\tilde{\nu}$ = 3055, 2936, 2851, 1643, 1499, 1353, 1297, 1148, 1010 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}N_2O$: 195.09167 found: 195.0912.

6-Bromo-2-isopentyl-3-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine (201c)



To a screw cap sealed reaction tube 6-bromo-2-isopentyl-3-(4-methoxyphenyl)imidazo[1,2-*a*]pyridine 1-oxide (**191f**, 0.15 mmol) and propionitrile (2.0 mL) were added under air. The reaction mixture was stirred vigorously at 150 ^oC for 12 h. After completion the crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using acetone/petroleum ether (10:90) as an eluent system. The product was obtained as black semi solid in 65% yield;

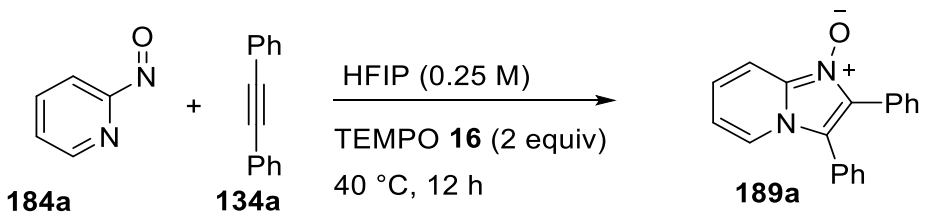
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 1.0 Hz, 1H), 7.56 (d, *J* = 9.4 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.24 (dd, *J* = 9.4, 1.6 Hz, 1H), 7.11 – 7.06 (m, 2H), 3.90 (s, 3H), 2.78 – 2.69 (m, 2H), 1.69 – 1.61 (m, 2H), 1.56 (td, *J* = 13.2, 6.6 Hz, 1H), 0.87 ppm (d, *J* = 6.5 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.03, 142.10, 131.20, 127.88, 124.56, 123.25, 120.11, 117.28, 114.88, 107.12, 55.38, 38.82, 27.92, 25.34, 22.33.

FT-IR: $\tilde{\nu}$ = 3060, 2966, 1656, 1538, 1493, 1446, 1355, 1278, 1130 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{19}H_{22}{}^{79}BrN_2O$: 373.09100 found: 373.09266. HRMS: calc. for $[M+H]^+$ $C_{19}H_{22}{}^{81}BrN_2O$: 375.08896 found: 375.08997.

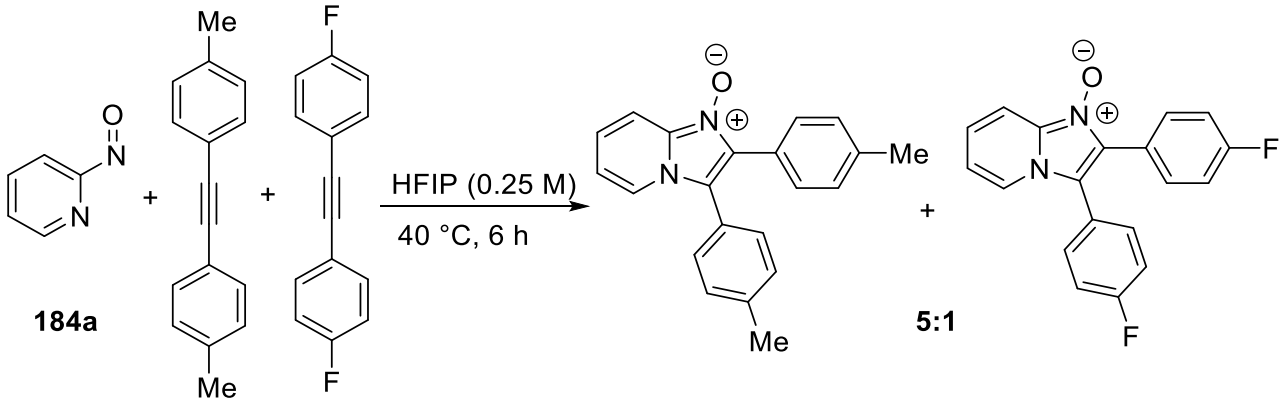
12.7.2 Radical Trapping Experiment



184a 134a 189a

To a screw cap reaction vial 2-nitrosopyridine (0.25 mmol, 1 equiv), diphenylacetylene (0.28 mmol, 1.1 equiv), TEMPO (2 equiv) and HFIP (1.0 mL) were added. The reaction mixture was heated to 40 ^oC for 12 h. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using dichloromethane/methanol as an eluent system and isolated yield was 40%.

12.7.3 Competition Study

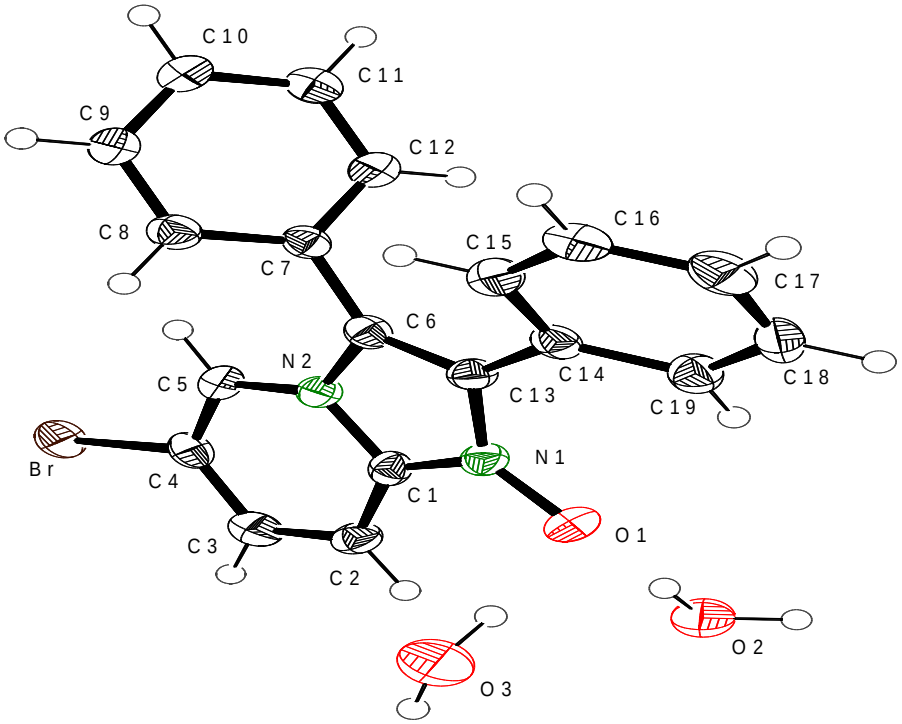


184a 95c 95f 189c 189f

To a screw cap reaction vial, 2-aminosopyridine **184**a (0.25 mmol, 1 equiv), 1,2-di-*p*-tolylethyne 95c (0.24 mmol, 1.0 equiv), 1,2-bis(4-fluorophenyl)ethyne **95f** (0.24 mmol, 1.0 equiv), and HFIP (1.0 mL) were added. The reaction mixture was heated to 40 ^oC for 6 h. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by

flash column chromatography over silica gel using dichloromethane/methanol as an eluent system. The ratio of the product was checked by ^{1}H NMR analysis and it was 5:1.

12.7.4. Crystallographic data for the compound 194f



Crystal structure of the *N*–Oxide product. ORTEP of (**194f**) Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 1018375.

Table 12.7.4.1. Crystal data and structure refinement for **194f.**

Identification code	CCDC 1018375	
Empirical formula	C_{19} H_{17} Br N_2 O_3	
Formula weight	401.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.6130(4) Å	a= 90°.
	b = 16.0480(14) Å	b= 90°.

	c = 18.9931(15) Å g = 90°.
Volume	1710.8(2) $Å^3$
Z	4
Density (calculated)	1.558 Mg/m^3
Absorption coefficient	2.424 mm^{-1}
F(000)	816
Crystal size	0.401 x 0.043 x 0.023 mm^3
Theta range for data collection	2.492 to 25.997°.
Index ranges	-6<=h<=6, -19<=k<=19, -23<=l<=23
Reflections collected	54577
Independent reflections	3355 [R(int) = 0.1113]
Completeness to theta = 25.242°	99.8 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3355 / 4 / 242
Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma(I)]	R1 = 0.0358, wR2 = 0.0688
R indices (all data)	R1 = 0.0542, wR2 = 0.0753
Absolute structure parameter	-0.026(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.336 and -0.235 $e.Å^{-3}$

Table 12.7.4.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)

for 5965. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br	322(1)	10416(1)	6744(1)	34(1)
O(1)	9155(6)	7405(2)	6644(2)	34(1)
O(2)	10153(8)	7653(3)	5239(2)	46(1)
O(3)	5984(8)	6143(3)	6554(2)	49(1)
N(1)	8282(7)	8015(3)	7048(2)	26(1)
N(2)	6009(7)	9032(3)	7417(2)	24(1)

C(1)	6468(8)	8508(3)	6861(3)	25(1)
C(2)	5054(9)	8524(3)	6255(2)	28(1)
C(3)	3207(9)	9075(3)	6222(3)	30(1)
C(4)	2846(7)	9636(3)	6794(2)	28(1)
C(5)	4233(8)	9625(3)	7376(2)	26(1)
C(6)	7578(8)	8855(3)	7960(3)	25(1)
C(7)	7452(8)	9324(3)	8632(2)	25(1)
C(8)	5538(9)	9187(3)	9082(2)	30(1)
C(9)	5399(8)	9617(3)	9718(2)	34(1)
C(10)	7127(10)	10186(4)	9897(3)	39(1)
C(11)	9005(9)	10334(4)	9445(3)	40(1)
C(12)	9165(9)	9901(3)	8806(3)	34(1)
C(13)	8979(8)	8210(3)	7735(2)	25(1)
C(14)	10777(8)	7730(3)	8129(3)	25(1)
C(15)	10537(9)	7653(3)	8863(2)	30(1)
C(16)	12201(9)	7201(3)	9243(3)	33(1)
C(17)	14100(9)	6821(3)	8914(3)	37(1)
C(18)	14335(8)	6891(3)	8185(3)	34(1)
C(19)	12679(9)	7332(3)	7797(3)	33(1)

Table 12.7.4.3. Bond lengths [Å] and angles [°] for 5965.

Br-C(4)	1.892(5)
O(1)-N(1)	1.338(5)
N(1)-C(1)	1.336(6)
N(1)-C(13)	1.398(6)
N(2)-C(1)	1.375(6)
N(2)-C(5)	1.381(6)
N(2)-C(6)	1.385(6)
C(1)-C(2)	1.399(7)
C(2)-C(3)	1.364(7)
C(3)-C(4)	1.425(7)
C(4)-C(5)	1.351(6)
C(6)-C(13)	1.369(7)

C(6)-C(7)	1.483(7)
C(7)-C(12)	1.376(7)
C(7)-C(8)	1.391(7)
C(8)-C(9)	1.392(6)
C(9)-C(10)	1.375(7)
C(10)-C(11)	1.380(7)
C(11)-C(12)	1.402(7)
C(13)-C(14)	1.473(6)
C(14)-C(19)	1.394(7)
C(14)-C(15)	1.407(7)
C(15)-C(16)	1.385(7)
C(16)-C(17)	1.377(7)
C(17)-C(18)	1.395(7)
C(18)-C(19)	1.381(7)

C(1)-N(1)-O(1)	124.0(4)
C(1)-N(1)-C(13)	109.2(4)
O(1)-N(1)-C(13)	126.6(4)
C(1)-N(2)-C(5)	120.9(4)
C(1)-N(2)-C(6)	109.1(4)
C(5)-N(2)-C(6)	130.0(4)
N(1)-C(1)-N(2)	107.5(4)
N(1)-C(1)-C(2)	131.5(4)
N(2)-C(1)-C(2)	121.0(4)
C(3)-C(2)-C(1)	118.7(4)
C(2)-C(3)-C(4)	118.9(5)
C(5)-C(4)-C(3)	122.2(4)
C(5)-C(4)-Br	118.7(4)
C(3)-C(4)-Br	119.1(3)
C(4)-C(5)-N(2)	118.1(4)
C(13)-C(6)-N(2)	106.7(4)
C(13)-C(6)-C(7)	132.8(4)
N(2)-C(6)-C(7)	120.4(4)
C(12)-C(7)-C(8)	119.9(5)

C(12)-C(7)-C(6)	121.0(4)
C(8)-C(7)-C(6)	119.1(4)
C(7)-C(8)-C(9)	119.9(5)
C(10)-C(9)-C(8)	120.3(5)
C(9)-C(10)-C(11)	120.0(5)
C(10)-C(11)-C(12)	120.2(5)
C(7)-C(12)-C(11)	119.8(5)
C(6)-C(13)-N(1)	107.4(4)
C(6)-C(13)-C(14)	129.1(4)
N(1)-C(13)-C(14)	123.3(4)
C(19)-C(14)-C(15)	118.8(5)
C(19)-C(14)-C(13)	122.3(4)
C(15)-C(14)-C(13)	118.9(4)
C(16)-C(15)-C(14)	119.8(5)
C(17)-C(16)-C(15)	121.2(5)
C(16)-C(17)-C(18)	119.2(5)
C(19)-C(18)-C(17)	120.5(5)
C(18)-C(19)-C(14)	120.6(5)

Symmetry transformations used to generate equivalent atoms:

Table 12.7.4.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 5965. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br	28(1)	34(1)	40(1)	5(1)	-4(1)	2(1)
O(1)	36(2)	31(2)	34(2)	-10(2)	4(2)	4(2)
O(2)	44(3)	59(2)	34(2)	-8(2)	-5(2)	2(2)
O(3)	52(3)	41(2)	54(3)	5(2)	-3(2)	-8(2)
N(1)	27(2)	27(2)	24(2)	-2(2)	4(2)	-3(2)

N(2)	24(2)	26(2)	22(2)	0(2)	1(2)	-1(2)
C(1)	24(2)	24(3)	27(3)	2(2)	7(2)	-2(2)
C(2)	33(3)	28(3)	22(2)	-2(2)	3(2)	-2(2)
C(3)	32(3)	32(3)	28(3)	6(2)	-3(2)	-7(2)
C(4)	23(2)	28(3)	31(3)	7(3)	1(2)	-4(2)
C(5)	27(2)	25(3)	26(2)	1(2)	5(2)	2(3)
C(6)	23(3)	26(3)	27(3)	2(2)	1(2)	-3(2)
C(7)	21(2)	26(3)	26(3)	2(2)	-4(2)	2(2)
C(8)	30(3)	29(3)	30(3)	0(2)	-1(2)	-4(3)
C(9)	30(2)	41(3)	30(2)	-3(3)	4(2)	-3(3)
C(10)	36(3)	49(4)	32(3)	-12(3)	4(2)	2(3)
C(11)	31(3)	44(3)	45(3)	-12(3)	-1(2)	-7(3)
C(12)	31(3)	41(3)	29(3)	-5(2)	4(2)	-3(2)
C(13)	26(3)	27(3)	22(3)	-2(2)	0(2)	-3(2)
C(14)	22(2)	20(2)	34(3)	0(2)	-2(2)	-4(2)
C(15)	31(3)	29(3)	29(3)	1(2)	2(2)	-2(2)
C(16)	36(3)	32(3)	31(3)	3(3)	-6(2)	-7(3)
C(17)	33(3)	30(3)	48(4)	6(3)	-10(3)	-1(3)
C(18)	22(2)	29(3)	52(3)	-1(3)	4(3)	1(2)
C(19)	29(3)	30(3)	39(3)	-1(3)	2(2)	-1(2)

Table 12.7.4.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 5965.

	x	y	z	U(eq)
H(1O)	11720(70)	7450(50)	5140(40)	100(30)
H(2O)	9890(140)	7530(50)	5721(17)	110(30)
H(3O)	7160(110)	6580(40)	6540(40)	100(30)
H(4O)	5070(120)	6190(50)	6130(20)	100(30)

H(2)	5375	8159	5873	33
H(3)	2179	9085	5825	37
H(5)	3994	10015	7745	32
H(8)	4328	8800	8957	36
H(9)	4106	9517	10029	40
H(10)	7027	10478	10331	47
H(11)	10192	10730	9568	48
H(12)	10454	10006	8494	40
H(15)	9238	7911	9098	36
H(16)	12030	7151	9739	40
H(17)	15236	6516	9180	44
H(18)	15645	6635	7954	41
H(19)	12836	7363	7300	39

Table 12.7.4.6. Torsion angles [°] for 5965.

O(1)-N(1)-C(1)-N(2)	177.4(4)
C(13)-N(1)-C(1)-N(2)	1.1(5)
O(1)-N(1)-C(1)-C(2)	1.0(8)
C(13)-N(1)-C(1)-C(2)	-175.3(5)
C(5)-N(2)-C(1)-N(1)	179.1(4)
C(6)-N(2)-C(1)-N(1)	-0.2(5)
C(5)-N(2)-C(1)-C(2)	-4.1(7)
C(6)-N(2)-C(1)-C(2)	176.7(4)
N(1)-C(1)-C(2)-C(3)	176.3(5)
N(2)-C(1)-C(2)-C(3)	0.3(7)
C(1)-C(2)-C(3)-C(4)	2.5(7)
C(2)-C(3)-C(4)-C(5)	-1.8(7)
C(2)-C(3)-C(4)-Br	178.8(4)
C(3)-C(4)-C(5)-N(2)	-1.9(7)
Br-C(4)-C(5)-N(2)	177.5(3)
C(1)-N(2)-C(5)-C(4)	4.8(6)
C(6)-N(2)-C(5)-C(4)	-176.2(5)
C(1)-N(2)-C(6)-C(13)	-0.9(5)

C(5)-N(2)-C(6)-C(13)	180.0(4)
C(1)-N(2)-C(6)-C(7)	-179.1(4)
C(5)-N(2)-C(6)-C(7)	1.8(7)
C(13)-C(6)-C(7)-C(12)	74.6(7)
N(2)-C(6)-C(7)-C(12)	-107.7(6)
C(13)-C(6)-C(7)-C(8)	-106.8(6)
N(2)-C(6)-C(7)-C(8)	70.9(6)
C(12)-C(7)-C(8)-C(9)	-1.9(7)
C(6)-C(7)-C(8)-C(9)	179.6(4)
C(7)-C(8)-C(9)-C(10)	1.0(7)
C(8)-C(9)-C(10)-C(11)	0.1(8)
C(9)-C(10)-C(11)-C(12)	-0.4(8)
C(8)-C(7)-C(12)-C(11)	1.6(8)
C(6)-C(7)-C(12)-C(11)	-179.9(5)
C(10)-C(11)-C(12)-C(7)	-0.4(8)
N(2)-C(6)-C(13)-N(1)	1.5(5)
C(7)-C(6)-C(13)-N(1)	179.4(5)
N(2)-C(6)-C(13)-C(14)	-173.6(5)
C(7)-C(6)-C(13)-C(14)	4.3(9)
C(1)-N(1)-C(13)-C(6)	-1.7(5)
O(1)-N(1)-C(13)-C(6)	-177.9(4)
C(1)-N(1)-C(13)-C(14)	173.8(4)
O(1)-N(1)-C(13)-C(14)	-2.3(7)
C(6)-C(13)-C(14)-C(19)	-154.2(5)
N(1)-C(13)-C(14)-C(19)	31.3(7)
C(6)-C(13)-C(14)-C(15)	27.4(7)
N(1)-C(13)-C(14)-C(15)	-147.1(5)
C(19)-C(14)-C(15)-C(16)	1.2(7)
C(13)-C(14)-C(15)-C(16)	179.7(4)
C(14)-C(15)-C(16)-C(17)	0.0(7)
C(15)-C(16)-C(17)-C(18)	-0.4(8)
C(16)-C(17)-C(18)-C(19)	-0.4(8)
C(17)-C(18)-C(19)-C(14)	1.6(8)
C(15)-C(14)-C(19)-C(18)	-1.9(7)

C(13)-C(14)-C(19)-C(18) 179.6(5)

Symmetry transformations used to generate equivalent atoms:

Table 12.7.4.7. Hydrogen bonds for 5965 [Å and °].

D-H.A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(2)–H(2)...O(2)#1	0.95	2.48	3.409(6)	164.4
C(5)–H(5)...O(3)#2	0.95	2.25	3.176(6)	165.4
O(3)–H(3O)...O(1)	0.97(3)	1.74(3)	2.701(5)	172(7)
O(3)–H(3O)...N(1)	0.97(3)	2.57(5)	3.402(6)	145(6)
O(2)–H(2O)...O(1)	0.95(3)	1.81(3)	2.754(5)	173(7)

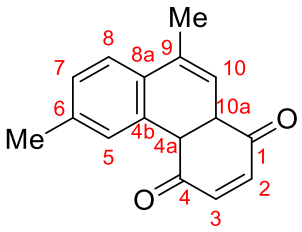
Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+3/2,-z+1 #2 -x+1,y+1/2,-z+3/2

12.8 Metal-Free Oxidative Dehydrogenative Diels-Alder Reaction of Alkylarenes with Electron-Deficient Alkenes

12.8.1 Characterization of Compounds (213a-216c)

6,9-Dimethylphenanthrene-1,4-dione (213a)



Compound **3a** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and ethyl acetate (98:2 v/v) as an orange amorphous in 72% yield.

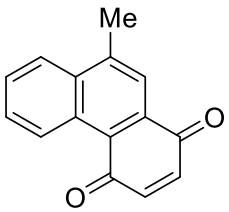
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 – 9.36 (m, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.91 (d, *J* = 0.7 Hz, 1H), 7.49 (dd, *J* = 8.6, 1.7 Hz, 1H), 6.89 (dd, *J* = 10.1 Hz, 2H), 2.77 (s, 3H), 2.59 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.05, 186.33, 142.57, 140.69, 139.93, 135.41, 133.93, 131.78, 130.60, 130.40, 127.37, 125.08, 124.24, 121.89, 22.22, 20.42 ppm.

FT-IR: $\tilde{\nu}$ = 3303, 3110, 3012, 2920, 1664, 1647, 1614, 1589, 1372, 1295, 1082 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{13}O_2$: 237.09077 found: 237.09101.

9-Methylphenanthrene-1,4-dione (213b)



Compound **213b** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and ethyl acetate (98:2 v/v) as an orange amorphous solid in 56% yield.

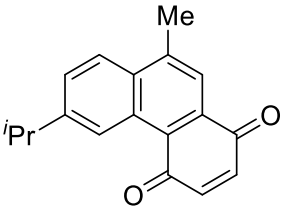
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (d, *J* = 8.7 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.98 (s, 1H), 7.77 – 7.70 (m, 1H), 7.69 – 7.64 (m, 1H), 6.91 (dd, *J* = 10.1 Hz, 2H), 2.80 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.20, 186.41, 142.96, 140.79, 135.72, 135.63, 131.75, 130.21, 129.79, 128.66, 128.59, 125.79, 124.59, 122.76, 20.68 ppm.

FT-IR: $\tilde{\nu}$ = 3052, 2920, 2894, 1706, 1651, 1587, 1424, 1336, 1290, 1109, 1976 cm^{-1}.

MS-EI: m/z (%):) 222.1(100); 207.0 (31); 194.0 (31); 165.1 (38), 139.1 (36).

6-Isopropyl-9-methylphenanthrene-1,4-dione (213c)



Compound **213c** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and ethyl acetate (98:2) as an orange amorphous

in 46% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (d, *J* = 1.1 Hz, 1H), 8.00 (d, *J* = 8.7 Hz, 1H), 7.94 – 7.87 (m, 1H), 7.59 (dd, *J* = 8.7, 1.6 Hz, 1H), 6.89 (dd, *J* = 10.1 Hz, 2H), 3.17 (sep, *J* = 6.9 Hz, 1H), 2.77 (s, 3H), 1.38 ppm (d, *J* = 6.9 Hz, 6H).

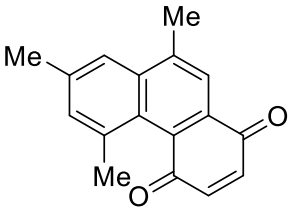
^{13}C NMR (126 MHz, $CDCl_3$) δ 188.32, 186.56, 150.75, 142.73, 140.85, 135.55, 134.46, 131.87, 130.63, 128.25, 125.40, 125.09, 124.63, 122.11, 34.79, 23.99, 20.62 ppm.

FT-IR: $\tilde{\nu}$ = 3067, 2957, 2713, 1659, 1646, 1586, 1554, 1460, 1423, 1343, 1291, 1074 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{18}H_{17}O_2$: 265. 12231 found: 265.12207.

5,7,9-Trimethylphenanthrene-1,4-dione (213d)

Compound **213d** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and ethyl acetate (98:2 v/v) as an orange amorphous solid in 50% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.67 (s, 1H), 7.36 (s, 1H), 6.99 (d, *J* = 10.1 Hz, 1H), 6.83 (d, *J* = 10.1 Hz, 1H), 2.75 (s, 3H), 2.53 (s, 3H), 2.47 ppm (s, 3H).

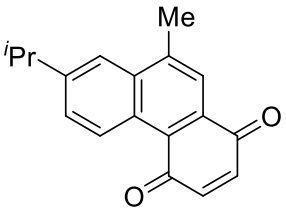
^{13}C NMR (126 MHz, $CDCl_3$) δ 187.64, 185.93, 141.63, 140.05, 138.81, 137.20, 137.15, 135.37, 134.56, 132.33, 131.90, 128.05, 122.07, 121.77, 25.27, 21.91, 20.82 ppm.

FT-IR: $\tilde{\nu}$ = 3059, 2976, 2928, 1651, 1615, 1588, 1449, 1301, 1079 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{17}H_{15}O_2$: 251.1066 found: 251.10690.

7-Isopropyl-9-methylphenanthrene-1,4-dione (213e)

Compound **213e** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and ethyl acetate (98:2 v/v) as an orange amorphous in 56% yield.



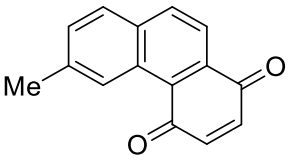
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.51 (d, *J* = 9.0 Hz, 1H), 7.97 (s, 1H), 7.84 (d, *J* = 1.3 Hz, 1H), 7.65 (dd, *J* = 9.1, 1.8 Hz, 1H), 6.90 (dd, *J* = 10.1 Hz, 1H), 3.12 (sep, *J* = 6.8 Hz, 1H), 2.80 (s, 3H), 1.37 ppm (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.35, 186.52, 149.47, 142.43, 140.70, 136.14, 135.74, 131.10, 129.55, 128.70, 128.58, 125.77, 122.84, 121.06, 34.64, 23.89, 20.73 ppm.

FT-IR: $\tilde{\nu}$ = 3043, 2958, 2868, 1656, 1617, 1588, 1357, 1287, 1075, 1045 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{18}H_{17}O_2$: 12231 found: 265.12180.

6-Methylphenanthrene-1,4-dione (213f)[270]



Compound **213f** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and ethyl acetate (98:2 v/v) as an orange amorphous in 38% yield.

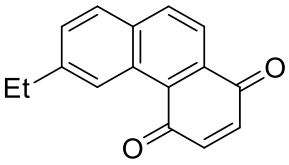
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.15 – 8.05 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 6.93 (dd, *J* = 10.1 Hz, 2H), 2.60 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.47, 186.24, 140.79, 140.72, 135.85, 135.05, 132.40, 131.03, 130.28, 128.62, 126.84, 126.55, 121.16, 22.60 ppm.

FT-IR: $\tilde{\nu}$ = 2921, 1649, 1613, 1591, 1450, 1373, 1301, 1153, 1074 cm^{-1}.

MS-EI: m/z (%):) 222.1(100); 207.0 (31); 194.0 (31); 165.1 (38).

6-Ethylphenanthrene-1,4-dione (213g)



Compound **213g** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and ethyl acetate (98:2 v/v) as an orange amorphous in 43% yield.

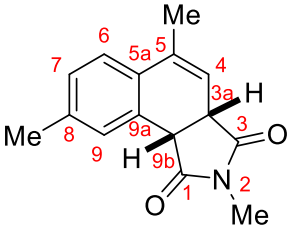
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (d, *J* = 0.6 Hz, 1H), 8.12 (dd, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.53 (dd, *J* = 8.4, 1.5 Hz, 1H), 6.95 (dd, *J* = 10.1 Hz, 2H), 2.90 (q, *J* = 7.6 Hz, 2H), 1.37 ppm (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.51, 186.26, 147.01, 140.77, 135.91, 135.38, 135.05, 132.48, 130.47, 130.02, 128.79, 126.80, 125.79, 121.26, 29.85, 15.67 ppm.

FT-IR: $\tilde{\nu}$ = 3115, 3081, 2856, 1777, 1707, 1597, 1548, 1498, 1377, 1346, 1162, 1070 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{13}O_2$: 237.09101 found: 237.09072.

***rel*-(3a*S*,9b*S*)-2,5,8-Trimethyl-3a,9b-dihydro-1*H*-benzo[*e*]isoindole-1,3(2*H*)-dione (214a)**



Compound **214a** was prepared according to general procedure F and the product compound was isolated by column chromatography with silica gel using petroleum ether and acetone (90:10 v/v) as a white amorphous solid in 64%) yield.

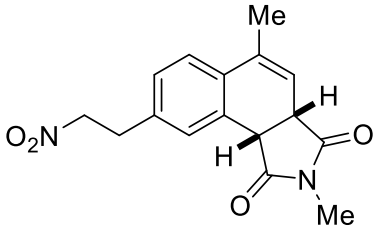
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.11 (d, *J* = 7.9 Hz, 1H), 5.68 (d, *J* = 2.2 Hz, 1H), 4.10 (d, *J* = 10.5 Hz, 1H), 3.92 – 3.81 (m, 1H), 3.01 (s, 3H), 2.39 (s, 3H), 2.07 – 2.05 ppm (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.52, 178.01, 138.53, 133.10, 130.97, 129.89, 129.24, 127.26, 124.37, 117.12, 43.05, 42.47, 25.66, 21.63, 20.07 ppm.

FT-IR: $\tilde{\nu}$ = 3045, 2962, 2856, 1769, 1686, 1504, 1430, 1375, 1282, 1157, 1092 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{15}H_{16}O_2N$: 242.11756 found: 242.11747.

***rel*-(3a*S*,9b*S*)-2,5-Dimethyl-8-(2-nitroethyl)-3a,9b-dihydro-1*H*-benzo[*e*]isoindole-1,3(2*H*)-dione (214b)**



Compound **214b** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether: acetone (90:10) as an orange amorphous solid in 64% yield.

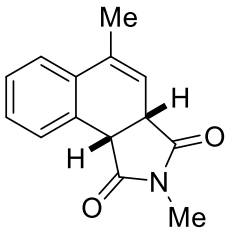
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 1.1 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.15 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.76 (dd, *J* = 3.7, 1.4 Hz, 1H), 4.77 – 4.36 (m, 2H), 4.13 (d, *J* = 10.6 Hz, 1H), 3.89 (ddd, *J* = 10.6, 3.8, 2.1 Hz, 1H), 3.36 (dd, *J* = 15.2, 7.5 Hz, 2H), 3.02 (s, 3H), 2.07 ppm (t, *J* = 1.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.93, 177.47, 135.74, 132.40, 131.57, 130.16, 128.50, 127.87, 124.71, 118.06, 76.14, 42.54, 42.07, 33.18, 25.47, 19.78 ppm.

FT-IR: $\tilde{\nu}$ = 3050, 2919, 2855, 1774, 1692, 1547, 1432, 1377, 1285, 1094 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}O_4N$: 323.10023 found: 323.10032.

***rel*-(3a*S*,9b*S*)-2,5-Dimethyl-3a,9b-dihydro-1*H*-benzo[*e*]isoindole-1,3(2*H*)-dione (214c)**



Compound **214c** was prepared according to general procedure F and the product was isolated by column chromatography (petroleum ether: acetone, 90:10) as a light yellow amorphous solid in 61% yield.

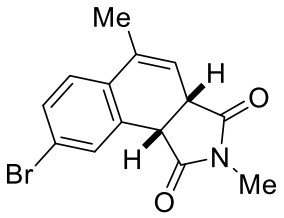
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.50 (m, 1H), 7.34 – 7.28 (m, 3H), 5.75 (dd, *J* = 3.6, 1.4 Hz, 1H), 4.15 (d, *J* = 10.5 Hz, 1H), 3.94 – 3.83 (m, 1H), 3.02 (s, 3H), 2.09 ppm (t, *J* = 1.8 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.09, 177.60, 132.76, 132.11, 129.91, 128.26, 128.21, 126.98, 124.06, 117.81, 42.61, 42.03, 25.34, 19.74 ppm.

FT-IR: $\tilde{\nu}$ = 3105, 3078, 2894, 1772, 1698, 1455, 1378, 1285, 1117, 1092 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{14}O_2N$: 228.10191 found: 228.10210.

rel-(3a_S_,9b_S_)-8-Bromo-2,5-dimethyl-3a,9b-dihydro-1_H_-benzo[_e_]isoindole-1,3(2_H_)-dione (214d)



Compound **214d** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and acetone (90:10) as a yellow amorphous solid in 43% yield.

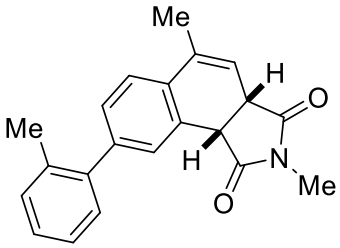
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 1.5 Hz, 1H), 7.43 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 1H), 5.77 (dd, *J* = 3.6, 1.3 Hz, 1H), 4.10 (d, *J* = 10.6 Hz, 1H), 3.98 – 3.71 (m, 1H), 3.02 (s, 3H), 2.08 – 2.00 ppm (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.71, 177.03, 132.79, 132.13, 131.40, 131.22, 129.11, 125.67, 122.00, 118.39, 42.25, 42.02, 25.54, 19.78 ppm.

FT-IR: $\tilde{\nu}$ = 3065, 2922, 2853, 1766, 1728, 1614, 1444, 1371, 1281, 1092 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{13}O_2N^{79}Br$: 306.01242 found: 306.01225; **HRMS**: calc. for $[M+H]^+$ $C_{14}H_{14}O_2N^{81}Br$: 308.01037 found: 308.01035.

rel-(3a_S_,9b_S_)-2,5-Dimethyl-8-(o-tolyl)-3a,9b-dihydro-1_H_-benzo[_e_]isoindole-1,3(2_H_)-dione (214e)



Compound **214e** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and ethyl acetate (95:5 v/v) as a yellow amorphous solid in 48% yield.

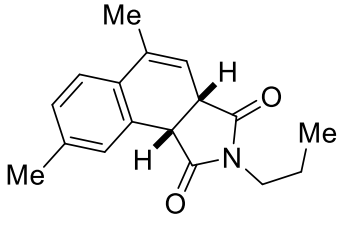
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.26 (m, 5H), 5.78 (d, *J* = 2.3 Hz, 1H), 4.18 (d, *J* = 10.6 Hz, 1H), 3.99 – 3.68 (m, 1H), 3.03 (s, 3H), 2.35 (s, 3H), 2.12 ppm (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.25, 177.66, 141.92, 141.13, 135.62, 132.73, 131.10, 130.83, 130.63, 129.88, 129.12, 127.65, 126.87, 126.02, 124.00, 117.8542.78, 42.21, 25.48, 20.68, 19.87 ppm.

FT-IR: $\tilde{\nu}$ = 3059, 2958, 2851, 1708, 1654, 1417, 1398, 1244, 1112, 1073 cm^{-1}.

EIMS $[M^+]$ $C_{14}H_{14}O_2N$: 317.24123.

rel-(3a_S_,9b_S_)-5,8-Dimethyl-2-propyl-3a,9b-dihydro-1_H_-benzo[_e_]isoindole-1,3(2_H_)-dione (214f)



Compound **214f** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and acetone (95:5 v/v) as a yellow amorphous solid in 72% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.13 – 7.09 (m, 1H), 5.67 (dd, *J* = 3.5, 1.4 Hz, 1H), 4.07 (d, *J* = 10.5 Hz, 1H), 3.90 – 3.75 (m, 1H), 3.49 (t, *J* = 7.4 Hz, 2H), 2.39 (s, 3H), 2.09 – 1.95 (m, 3H), 1.59 (ses, *J* = 7.4 Hz, 2H), 0.86 ppm(t, *J* = 7.4 Hz, 3H).

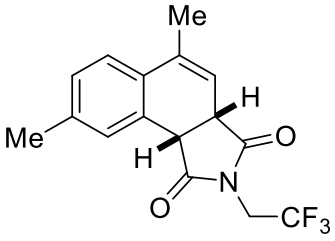
^{13}C NMR (126 MHz, $CDCl_3$) δ 178.32, 177.69, 138.21, 132.81, 130.78, 129.66, 128.95, 127.13, 124.08, 117.05, 42.79, 42.24, 40.95, 21.37, 21.09, 19.80, 11.32 ppm.

FT-IR: $\tilde{\nu}$ = 2969, 2929, 2873, 1768, 1694, 1503, 1436, 1397, 1345, 1234, 1205, 1153, 1127, 1056 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{17}H_{22}O_2N$: 270.14886 found: 270.14884.

***rel*-(3a*S*,9b*S*)-5,8-Dimethyl-2-(2,2,2-trifluoroethyl)-3a,9b-dihydro-1*H*-benzo[*e*]isoindole-1,3(2*H*)-dione (214g)**

Compound **214g** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and acetone (95:5) as a yellow amorphous solid in 38% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 5.65 (d, *J* = 1.9 Hz, 1H), 4.21 (d, *J* = 10.6 Hz, 1H), 4.14 (q, *J* = 8.6 Hz, 2H), 3.98 (d, *J* = 10.0 Hz, 1H), 2.39 (s, 3H), 2.07 ppm (s, 3H).

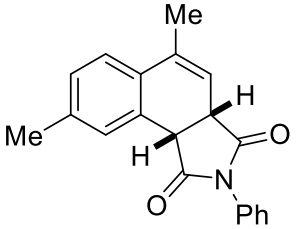
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.63, 176.22, 138.57, 133.64, 130.81, 129.54, 129.32, 126.12, 124.30, 122.95 (q, *J* = 279.9 Hz), 115.96, 42.86, 42.19, 40.01 (q, *J* = 36.4 Hz), 21.38, 19.84 ppm.

FT-IR: $\tilde{\nu}$ = 3020, 2979, 2927, 1787, 1796, 1503, 1412, 1385, 1267, 1153, 1127, 1104, 1026 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{25}O_2NF_3$: 310.10494 found: 10478.

***rel*-(3a*S*,9b*S*)-5,8-Dimethyl-2-phenyl-3a,9b-dihydro-1*H*-benzo[*e*]isoindole-1,3(2*H*)-dione (214 h)**

Compound **214h** was prepared according to general procedure F and the product was isolated by column chromatography with



silica gel using petroleum ether and ethyl acetate (95:5) as a yellow amorphous solid in 56% yield.

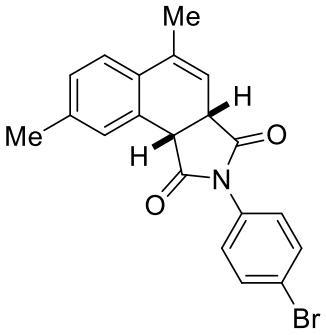
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 3H), 7.81 – 7.75 (m, 1H), 7.71 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.69 – 7.64 (m, 1H), 7.59 – 7.51 (m, 1H), 6.21 – 6.14 (m, 1H), 4.69 (d, *J* = 10.7 Hz, 1H), 4.47 – 4.36 (m, 1H), 2.81 (s, 3H), 2.54 – 2.52 ppm (t, *J* = 1.71H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.17, 176.65, 138.38, 134.33, 133.40, 132.15, 130.88, 129.75, 129.19, 129.13, 128.66, 126.90, 126.51, 124.18, 116.78, 43.04, 42.43, 21.38, 19.87 ppm.

FT-IR: $\tilde{\nu}$ = 3062, 2920, 1773, 1703, 1548, 1498, 1377, 1186, 1176, 1073 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{18}O_2N$: 304.13321 found: 304.13321.

***rel*-(3a*S*,9b*S*)-2-(4-Bromophenyl)-5,8-dimethyl-3a,9b-dihydro-1*H*-benzo[*e*]isoindole-1,3(2*H*)-dione (214i)**



Compound **214i** was prepared according to general procedure A and the product was isolated by column chromatography with silica gel using petroleum ether: acetone (90:10) as a yellow amorphous solid in 62% yield.

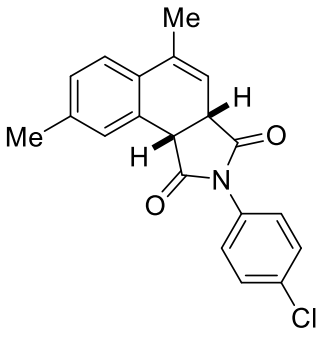
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.7 Hz, 2H), 7.40 – 7.37 (m, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 1H), 5.76 – 5.66 (m, 1H), 4.27 (d, *J* = 10.6 Hz, 1H), 4.06 – 3.98 (m, 1H), 2.40 (s, 3H), 2.11ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.82, 176.34, 138.50, 133.60, 132.38, 131.15, 130.86, 129.71, 129.24, 128.01, 126.67, 124.26, 122.49, 116.52, 43.07, 42.43, 21.40, 19.88 ppm.

FT-IR: $\tilde{\nu}$ = 3098, 2919, 2855, 1774, 1709, 1491, 1378, 1184, 1118, 1069 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{17}O_2N^{79}Br$: 382.04372 found: 382.04332; **HRMS**: calc. for $[M+H]^+$ $C_{20}H_{17}O_2N^{81}Br$: 384.04167 found: 384.04123.

***rel*-(3a*S*,9b*S*)-2-(4-Chlorophenyl)-5,8-dimethyl-3a,9b-dihydro-1*H*-benzo[*e*]isoindole-1,3(2*H*)-dione(214 j)**



Compound **214 j** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and acetone (90:10) as a light yellow amorphous solid in 53% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 3H), 7.26 (t, *J* = 8.1 Hz, 3H), 7.15 (d, *J* = 7.8 Hz, 1H), 5.73 (d, *J* = 2.0 Hz, 1H), 4.28 (d, *J* = 10.7 Hz, 1H), 4.03 (d, *J* = 10.6 Hz, 1H), 2.40 (s, 3H), 2.11 ppm (s, 3H).

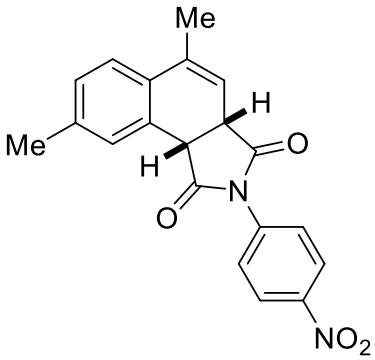
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.85, 176.35, 138.39, 134.34, 133.47, 130.74, 130.42, 129.57, 129.31, 129.14, 127.62, 126.52, 124.15, 116.40, 42.90, 42.27, 21.30, 19.81 ppm.

FT-IR: $\tilde{\nu}$ = 3107, 3062, 2852, 1775, 1709, 1494, 1378, 1184, 1120, 1090 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{17}O_2N^{35}Cl$: 338.09423 found: 338.09395; calc. for $[M+H]^+$ $C_{20}H_{17}O_2N^{37}Cl$: 340.09128 found: 340.09118.

rel-(3a*S*,9b*S*)-5,8-Dimethyl-2-(4-nitrophenyl)-3a,9b-dihydro-1*H*-benzo[*e*]isoindole-1,3(2*H*)-dione (214k)

Compound **214k** was prepared according to general procedure F and the product was isolated by column chromatography with silica gel using petroleum ether and acetone (85:15) as a yellow amorphous solid in 66% yield



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.1 Hz, 2H), 7.61 (d, *J* = 9.1 Hz, 2H), 7.40 (s, 1H), 7.29 – 7.23 (m, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 5.73 (d, *J* = 2.0 Hz, 1H), 4.32 (d, *J* = 10.7 Hz, 1H), 4.08 (d, *J* = 10.6 Hz, 1H), 2.41 (s, 3H), 2.12 ppm (s, 3H).

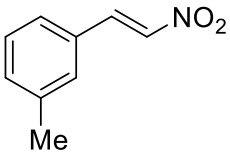
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.31, 175.93, 146.91, 138.57, 137.56, 133.87, 130.74, 129.51, 129.33, 126.84, 126.18, 124.35, 124.27, 116.00, 43.02, 42.36, 21.32, 19.82 ppm.

FT-IR: $\tilde{\nu}$ = 3115, 3081, 2856, 1776, 1707, 1597, 1522, 1498, 1377, 1346, 1162, 1111, 1017 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{17}O_4N$: 349.11828 found: 349.11828.

(*E*)-1-Methyl-3-(2-nitrovinyl)benzene (216a)

Compound **215a** was obtained according to general procedure G and the product was isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (2:98 v/v); light yellow liquid with 62% yield.



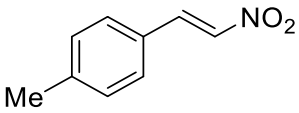
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 13.7 Hz, 1H), 7.50 (d, *J* = 13.7 Hz, 1H), 7.31 – 7.21 (m, 4H), 2.32 ppm (s, 3H).

^{13}C NMR (126 MHz, CDCl3) δ 139.41, 139.31, 136.96, 133.15, 130.03, 129.82, 129.35, 126.48, 77.41, 77.16, 76.91, 21.35 ppm.

FT-IR: $\tilde{\nu}$ = 3110, 2972. 2921, 1652, 1633, 1515, 1425, 1338, 1289, 1265, 1108, 1076 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_9H_{10}O_2N$: 164.07061 found: 164.07048.

(*E*)-1-Methyl-4-(2-nitrovinyl)benzene (216b)



Compound **215b** was obtained according to general procedure B and the product was isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (2:98 v/v); light yellow amorphous solid with 75% yield.

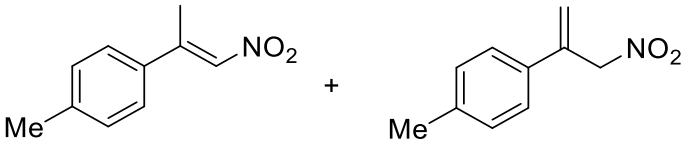
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 13.6 Hz, 1H), 7.56 (d, *J* = 13.6 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 2.41 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.22, 139.27, 136.45, 130.28, 129.31, 127.44, 21.79 ppm.

FT-IR: $\tilde{\nu}$ = 3107, 3029, 2854, 1631, 1605, 1516, 1495, 1333, 1264, 1185, 964 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_9H_{10}O_2N$: 164.07061 found: 164.07020.

(*E*)-1-Methyl-4-(1-nitroprop-1-en-2-yl)benzene (216c) and 1-methyl-4-(3-nitroprop-1-en-2-yl)benzene (216c') (1:1)[1]



Compounds **216c** and **215c'**were obtained according to general procedure B and the products were isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (2:98 v/v); light yellow amorphous solid with 68% yield.

Compound **215c: ^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.36 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.31 (m, 3H), 2.40 (s, 3H), 2.36 ppm (s, 3H).

Compound **215c': ^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.24 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 5.79 (s, 1H), 5.48 (s, 1H), 5.34 (d, *J* = 0.7 Hz, 2H), 2.40 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.10, 141.02, 138.87, 137.93, 135.92, 135.43, 134.07, 129.86, 129.62, 126.90, 125.78, 120.91, 79.79, 21.40, 21.25, 18.54 ppm.

FT-IR: $\tilde{\nu}$ = 3101, 3030, 28580, 1617, 1607, 1553, 1509, 1334, 1258, 1190, 1037 cm^{-1}.

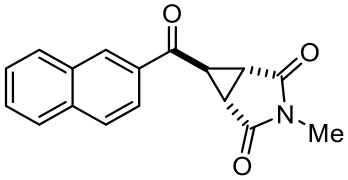
MS-EI: m/z (%):) 163.1(37); 146.1 (16); 115.1 (100); 91.1 (61), 78.1 (26).

12.9 Copper(I)-Catalyzed Oxidative (2+1) Annulation of Acetophenones with Maleimides in the Synthesis of Cyclopropanes

12.9.1 Characterization of Cyclopropane Derivatives (229a-231l)

(1*R*,5*S*,6*s*)-6-(2-Naphthoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229a)

Compound **3a** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 83% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.01-7.89 (m, 4H), 7.70 – 7.56 (m, 2H), 3.53 (t, *J* = 2.8 Hz, 1H), 3.10 (d, *J* = 2.8 Hz, 2H), 2.97 ppm (s, 3H).

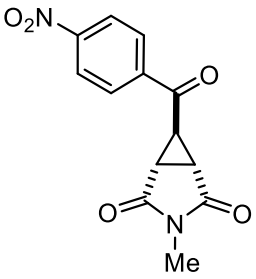
^{13}C NMR (126 MHz, $CDCl_3$) δ 191.86, 173.18, 136.17, 133.21, 132.50, 130.91, 129.86, 129.40, 129.15, 128.04, 127.39, 123.70, 35.90, 28.38, 24.81 ppm.

FT-IR: $\tilde{\nu}$ = 3085, 2929, 1698, 1667, 1624, 1433, 1378, 1264, 1181, 1122, 1015 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{17}H_{14}O_3N$: 280.09682 found: 280.09643.

(1*R*,5*S*,6*s*)-3-Methyl-6-(4-nitrobenzoyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (229b)

Compound **229b** was obtained by using the general procedure H and the product product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 62% yield.



^{1}H NMR (200 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.0 Hz, 2H), 8.15 (d, *J* = 9.0 Hz, 2H), 3.35 (t, *J* = 2.8 Hz, 1H), 3.08 (d, *J* = 2.8 Hz, 2H), 2.94 ppm (s, 3H).

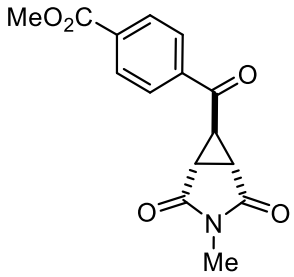
^{13}C NMR (50 MHz, $CDCl_3$) δ 191.06, 172.45, 151.06, 140.12, 129.72, 124.30, 35.69, 28.66, 24.89 ppm.

FT-IR: $\tilde{\nu}$ = 3087, 2955, 2857, 1695, 1665, 1603, 1522, 1435, 1381, 1347, 1321, 1222, 1181, 1120, 1025 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}O_5N_2$: 275.06625 found: 275.06575.

Methyl-4-(1*R*,5*S*,6*s*)-3-methyl-2,4-dioxo-3- azabicyclo[3.1.0]hexane-6-carbonyl)benzoate (229c)

Compound **229c** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 82% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.5 Hz, 2H), 8.03 (d, *J* = 8.5 Hz, 2H), 3.96 (s, 3H), 3.37 (t, *J* = 2.8 Hz, 1H), 3.05 (d, *J* = 2.8 Hz, 2H), 2.93 ppm (s, 3H).

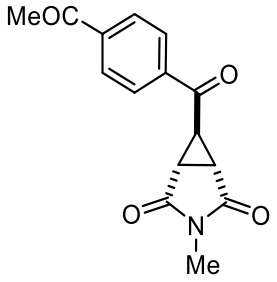
^{13}C NMR (75 MHz, $CDCl_3$) δ 191.84, 172.80, 165.98, 138.89, 135.05, 130.23, 128.56, 52.76, 35.77, 28.49, 24.81 ppm.

FT-IR: $\tilde{\nu}$ = 3092, 2970, 2898, 1695, 16177, 1514, 1453, 1435, 1383, 1290, 1257, 1042 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{15}H_{14}O_5N$: 288.08665 found: 288.08619.

(1*R*,5*S*,6*s*)-6-(4-Acetylbenzoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229d)

Compound **229d** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 56% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 4H), 3.37 (t, *J* = 2.8 Hz, 1H), 3.06 (d, *J* = 2.8 Hz, 2H), 2.94 (s, 3H), 2.66 ppm (s, 3H).

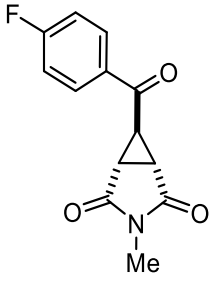
^{13}C NMR (75 MHz, $CDCl_3$) δ 197.28, 191.80, 172.80, 141.10, 138.82, 128.88, 35.79, 28.51, 27.08, 24.84 ppm.

FT-IR: $\tilde{\nu}$ = 3090, 2950, 1697, 1675, 1433, 1378, 1259, 1180, 1122, 1024 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{15}H_{14}O_4N$: 272.09173 found: 272.09147.

(1*R*,5*S*,6*s*)-6-(4-Fluorobenzoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229e)

Compound **229e** was obtained by using the general procedure H andtThe product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 72% yield.



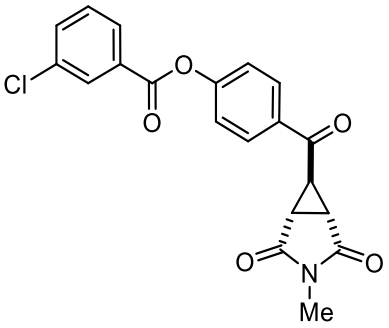
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 – 7.97 (m, 2H), 7.26-7.16 (m,2H), 3.31 (t, *J* = 2.8 Hz, 1H), 3.03 (d, *J* = 2.8 Hz, 2H), 2.93 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.49, 172.99, 166.60 (d, *J* = 257.4 Hz), 132.24, 131.44 (d, *J* = 9.6 Hz), 116.40 (d, *J* = 22.1 Hz), 35.60, 28.27, 24.79 ppm.

FT-IR: $\tilde{\nu}$ = 3091, 2967, 2928, 1699, 1676, 1592, 1453, 1434, 1378, 1257, 1181, 1041 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}NO_3F$: 248.07175 found: 248.07164.

4-(1*R*,5*S*,6*s*)-3-Methyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carbonyl)phenyl 3-chlorobenzoate (229f)



Compound **229f** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 62% yield.

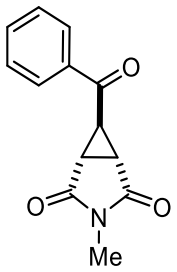
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (t, *J* = 1.8 Hz, 1H), 8.11 – 8.06 (m, 3H), 7.64 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.42 – 7.35 (m, 2H), 3.36 (t, *J* = 2.8 Hz, 1H), 3.05 (d, *J* = 2.8 Hz, 2H), 2.93 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.83, 172.97, 163.36, 155.44, 135.06, 134.22, 133.55, 130.69, 130.45, 130.40, 130.19, 128.52, 122.42, 35.68, 28.30, 24.79 ppm.

FT-IR: $\tilde{\nu}$ = 3106, 3074, 2922, 1743, 1702, 1664, 1598, 1475, 1418, 1344, 1283, 1202, 1161, 1061 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{15}O_5NCl$: 384.06333 found: 384.06301.

(1*R*,5*S*,6*s*)-6-Benzoyl-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229g)



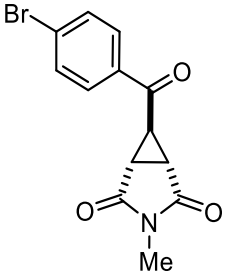
Compound **229g** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 65% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 2H), 7.64 (ddd, *J* = 6.8, 4.0, 1.3 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 3.37 (t, *J* = 2.8 Hz, 1H), 3.03 (d, *J* = 2.8 Hz, 2H), 2.93 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 192.08, 173.12, 135.82, 134.46, 129.12, 128.66, 35.80, 28.29, 24.78 ppm.

FT-IR: $\tilde{\nu}$ = 3093, 2927, 1697, 1666, 1593, 1455, 1380, 1286, 1264, 1224, 1124, 1026 cm^{-1}.**HRMS**: calc. for $[M+H]^+$ $C_{13}H_{12}NO_3$: 230.08117 found: 230.08116.

(1*R*,5*S*,6*s*)-6-(4-Bromobenzoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229h)



Compound **229h** was obtained by using the general procedure H and the product was isolated by column chromatography

with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 78% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 3.30 (t, *J* = 2.8 Hz, 1H), 3.03 (d, *J* = 2.8 Hz, 2H), 2.93 ppm (s, 3H).

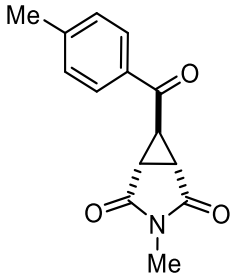
^{13}C NMR (75 MHz, $CDCl_3$) δ 190.99, 172.73, 134.33, 132.32, 129.90, 129.81, 35.35, 28.18, 24.64 ppm.

FT-IR: $\tilde{\nu}$ = 3087, 2930, 1698, 1672, 1434, 1379, 1263, 1182, 1122, 1017 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}{}^{79}BrNO_3$: 307.99168 found: 307.99098 HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}{}^{81}BrNO_3$: 309.98964 found: 309.98864.

(1*R*,5*S*,6*s*)-3-Methyl-6-(4-methylbenzoyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (229i)[271]

Compound **229i** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 52% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.34 (t, *J* = 2.8 Hz, 1H), 3.00 (d, *J* = 2.8 Hz, 2H), 2.92 (s, 3H), 2.43 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.49, 173.20, 145.58, 133.37, 129.77, 128.77, 35.77, 28.19, 24.72, 21.88 ppm.

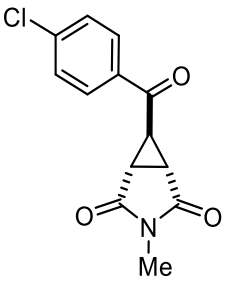
FT-IR: $\tilde{\nu}$ = 3112, 3082, 2945, 1694, 1664, 1603, 1540, 1523, 1416, 1346, 1266, 1225, 1117, 1010 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{14}O_3N$: 244.09682 found: 244.09656.

(1*R*,5*S*,6*s*)-6-(4-Chlorobenzoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229j)

Compound **229j** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 76% yield.

^{1}H NMR (500 MHz,$CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 3.30 (t, *J* = 2.8 Hz, 1H), 3.01 (d, *J* = 2.8 Hz, 1H), 2.91 ppm (s, 3H).

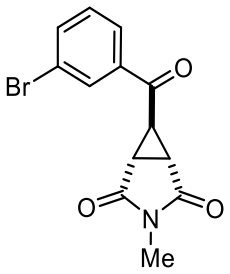


^{13}C NMR (126 MHz, $CDCl_3$) δ 190.89, 172.84, 141.12, 134.12, 129.99, 129.46, 35.55, 28.29, 24.75 ppm.

FT-IR: $\tilde{\nu}$ = 3093, 2965, 1696, 1664, 1600, 1527, 1456, 1435, 1417, 1348, 1226, 1160, 1042 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}O_3NCl$: 264.04220 found: 264.04185.

(1*R*,5*S*,6*s*)-6-(3-Bromobenzoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229k)



Compound **229k** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with76% yield.

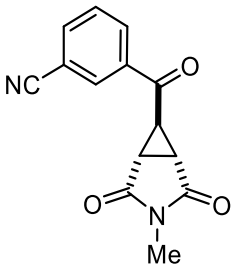
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (t, *J* = 1.8 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.78 – 7.72 (m, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 3.31 (t, *J* = 2.8 Hz, 1H), 3.02 (d, *J* = 2.8 Hz, 2H), 2.92 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.95, 172.76, 137.44, 137.24, 131.57, 130.63, 127.14, 123.42, 35.46, 28.39, 24.79 ppm.

FT-IR: $\tilde{\nu}$ = 3083, 2972, 1699, 1670, 1435, 1378, 1281, 1267, 1212, 1160, 1045 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{10}{}^{79}BrNO_3$: 307.99168 found: 307.99110: HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}{}^{81}BrNO_3$: 309.98964 found: 309.98897.

3-(1*R*,5*S*,6*s*)]-3-Methyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carbonyl)benzonitrile (229l)



Compound **229l** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 84% yield.

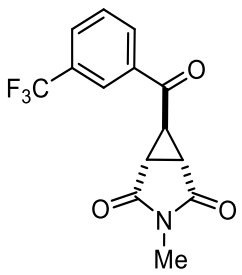
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (t, *J* = 1.4 Hz, 1H), 8.24 – 8.18 (m, 1H), 7.94 – 7.87 (m, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 3.34 (t, *J* = 2.8 Hz, 1H), 3.06 (d, *J* = 2.8 Hz, 2H), 2.94 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.53, 172.50, 137.14, 136.55, 132.44, 132.29, 130.20, 117.57, 113.83, 35.27, 28.52, 24.85 ppm.

FT-IR: $\tilde{\nu}$ = 3075, 2955, 2235, 1701, 1673, 1435, 1380, 1246, 1183, 1126, 1023 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{11}O_3N_2$: 255.07642 found: 255.07603.

(1*R*,5*S*,6*s*)-3-Methyl-6-(3-(trifluoromethyl)benzoyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (229m)



Compound **229m** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 73% yield.

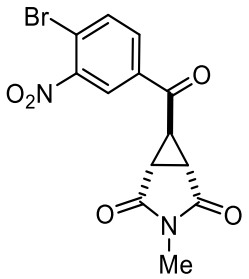
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 3.37 (t, *J* = 2.8 Hz, 1H), 3.05 (d, *J* = 2.8 Hz, 2H), 2.93 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.11, 172.68, 136.30, 132.1.65 (q = *J*, 33.2 Hz) 131.74, 130.61 (q, *J* = 3.5 Hz), 129.85, 125.30 (q, *J* = 3.8 Hz), 123.37 (q, *J* = 272.8 Hz), 35.36, 28.51, 24.80 ppm.

FT-IR: $\tilde{\nu}$ = 3099, 2952, 1697, 1675, 1436, 1378, 1331, 1211, 1119, 1073 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}O_3NF_3$: 298.06855 found: 298.06805.

(1*R*,5*S*,6*s*)-6-(4-Bromo-3-nitrobenzoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229n)



Compound **229n** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 69% yield.

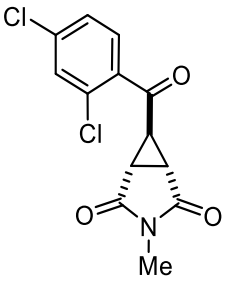
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, *J* = 1.5 Hz, 1H), 8.01 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 3.32 (t, *J* = 2.8 Hz, 1H), 3.05 (d, *J* = 2.8 Hz, 2H), 2.93 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.65, 172.29, 150.34, 136.26, 135.68, 132.13, 125.42, 121.33, 35.06, 28.67, 24.88 ppm.

FT-IR: $\tilde{\nu}$ = 3084, 2951, 1697, 1674, 1592, 1536, 1437, 1333, 1267, 1214, 1118, 1072 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{10}{}^{79}BrN_2O_5$: 352.97676 found: 352.97616 HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}{}^{81}BrN_2O_5$: 354.97471 found: 354.97402.

(1*R*,5*S*,6*s*)-6-(2,4-Dichlorobenzoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229j)



Compound **229j** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 48% yield.

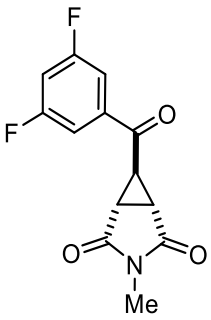
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 10.5 Hz, 1H), 7.49 (s, 1H), 7.36 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.21 (t, *J* = 2.8 Hz, 1H), 3.07 (d, *J* = 2.8 Hz, 2H), 2.90 ppm (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 193.69, 172.51, 139.32, 135.67, 133.16, 131.27, 130.83, 127.93, 39.35, 29.24, 24.79 ppm.

FT-IR: $\tilde{\nu}$ = 3083, 2974, 1701, 1672, 1551, 1435, 1379, 1285, 1265, 1213, 1140, 1017 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{10}NO_3Cl_2$: 298.00323 found: 298.00289.

(1*R*,5*S*,6*s*)-6-(3,5-Difluorobenzoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229p)



Compound **229p** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 75% yield.

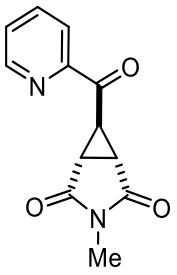
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 2H), 7.09 (tt, *J* = 8.3, 2.2 Hz, 1H), 3.24 (t, *J* = 2.7 Hz, 1H), 3.03 (d, *J* = 2.7 Hz, 2H), 2.93 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 190.01, 172.50, 163.30 (dd, *J* = 252.5, 11.8 Hz), 138.54 (t, *J* = 7.8 Hz), 111.69 (dd, *J* = 19.9, 6.6 Hz), 109.75 (t, *J* = 25.3 Hz), 35.40, 28.48, 24.82 ppm.

FT-IR: $\tilde{\nu}$ = 3090, 2971, 2931, 1698, 1676, 1480, 1453, 1380, 1290, 1258, 1181, 1042 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{10}NO_3F_2$: 266.06233 found: 166.06198.

(1*R*,5*S*,6*s*)]-3-Methyl-6-picolinoyl-3-azabicyclo[3.1.0]hexane-2,4-dione (229q)



Compound **229q** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (15:85 v/v); light yellow amorphous solid with 62% yield.

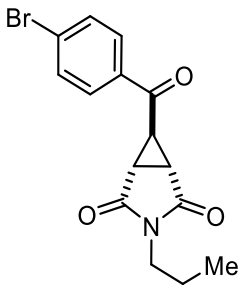
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 – 8.69 (m, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz, 1H), 7.56- 7.53 (m, 1H), 4.37 (t, *J* = 2.9 Hz, 1H), 2.98 (d, *J* = 2.9 Hz, 2H), 2.92 ppm (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 193.30, 173.25, 151.88, 149.40, 137.36, 128.22, 122.64, 34.14, 28.63, 24.71 ppm.

FT-IR: $\tilde{\nu}$ = 3092, 2971, 2899, 1698, 1678, 1582, 1567, 1481, 1433, 1377, 1260, 1026 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{12}H_{15}N_2O_3$: 231.07642 found: 231.07652.

(1*R*,5*S*,6*s*)-6-(4-Bromobenzoyl)-3-propyl-3-azabicyclo[3.1.0]hexane-2,4-dione (231a)



Compound **231a** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (3:97 v/v); light yellow amorphous solid with 61% yield.

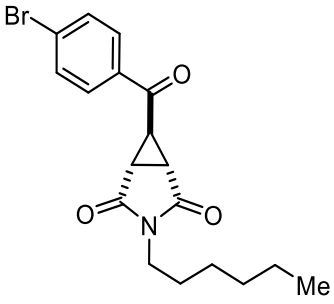
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 3.41 – 3.30 (m, 2H), 3.22 (t, *J* = 2.8 Hz, 1H), 3.00 (d, *J* = 2.8 Hz, 2H), 1.62 – 1.52 (m, 2H), 0.90 ppm (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.17, 172.88, 138.46, 134.57, 132.46, 130.01, 129.87, 77.41, 77.16, 76.91, 40.29, 35.57, 28.27, 21.35, 11.33 ppm.

FT-IR: $\tilde{\nu}$ = 3089, 2970, 2931, 1698, 1676, 1622, 1453, 1379, 1260, 1181, 1122 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{15}H_{15}{}^{79}BrNO_3$: 336.02298 found: 336.02232: HRMS: calc. for $[M+H]^+$ $C_{15}H_{15}{}^{81}BrNO_3$: 338.02094 found: 338.02054.

(1*R*,5*S*,6*s*)-6-(4-Bromobenzoyl)-3-hexyl-3-azabicyclo[3.1.0]hexane-2,4-dione (231b)



Compound **231b** was obtained by using the general procedure and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (2:98 v/v); light yellow amorphous solid with 86% yield.

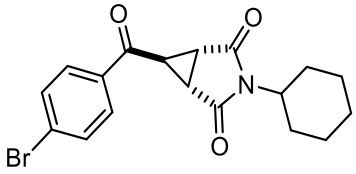
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 3.44 – 3.37 (m, 2H), 3.20 (d, *J* = 2.8 Hz, 1H), 3.01 (d, *J* = 2.8 Hz, 2H), 1.58 – 1.49 (m, 2H), 1.34 – 1.26 (m, 6H), 0.89 ppm (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.20, 172.88, 138.51, 134.62, 132.51, 130.03, 38.82, 35.61, 31.42, 28.31, 27.99, 26.57, 22.63, 14.11 ppm.

FT-IR: $\tilde{\nu}$ = 3091, 2914, 1698, 1665, 1596, 1436, 1381, 1347, 1283, 1161, 1010 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{18}H_{21}{}^{79}BrNO_3$: 378.06993 found: 378.06903: HRMS: calc. for $[M+H]^+$ $C_{18}H_{21}{}^{81}BrNO_3$: 380.06789 found: 380.06789.

(1*R*,5*S*,6*s*)-6-(4-Bromobenzoyl)-3-cyclohexyl-3-azabicyclo[3.1.0]hexane-2,4-dione (231c)



Compound **231c** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (3:97 v/v); light yellow amorphous

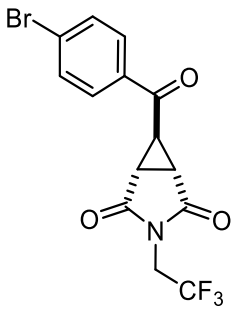
solid with 77% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 3.97 – 3.61 (m, 1H), 3.13 (t, *J* = 2.8 Hz, 1H), 2.95 (d, *J* = 2.8 Hz, 1H), 2.12 – 2.00 (m, 1H), 1.82 (d, *J* = 13.5 Hz, 1H), 1.66-1.57 (m, 2H), 1.34 – 1.13 ppm (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.25, 172.98, 138.45, 134.64, 132.45, 130.01, 129.82, 77.41, 77.16, 76.91, 51.64, 35.54, 29.16, 28.18, 25.94, 25.06 ppm.

FT-IR: $\tilde{\nu}$ = 3087, 2969, 1699, 1674, 1434, 1379, 1263, 1219, 1182, 1043 cm^{-1}.

(1*R*,5*S*,6*s*)-6-(4-Bromobenzoyl)-3-(2,2,2-trifluoroethyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (231d)



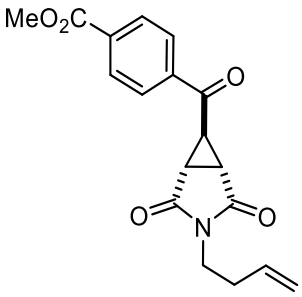
Compound **231d** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 56% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 4.09 (q, *J* = 8.6 Hz, 2H), 3.29 (t, *J* = 2.9 Hz, 1H), 3.10 ppm (d, *J* = 2.9 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 190.63, 171.06, 138.61, 134.29, 132.62, 130.25, 123.03 (q, *J* = 279.9 Hz), 24 (q, *J* = 36.4 Hz), 34.80, 28.07 ppm.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{10}{}^{79}BrNO_3F_3$: 375.97907 found: 375.97970: HRMS: calc. for $[M+H]^+$ $C_{14}H_{10}{}^{81}BrNO_3F_3$: 377.97702 found: 377.97754.

Methyl 4-(1*R*,5*S*,6*s*)-3-(but-3-en-1-yl)-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carbonyl)benzoate (3231e)



Compound **231e** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 59% yield.

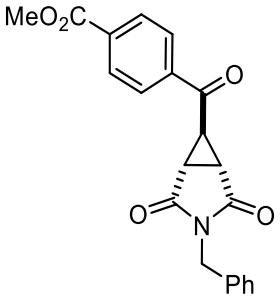
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 2H), 7.99 (d, *J* = 8.6 Hz, 2H), 5.79-7.70 (m, 1H), 5.14 (s, 1H), 5.09 (dd, *J* = 6.9, 1.9 Hz, 1H), 3,96 (s, 3s), 3.54 (t, *J* = 6.7 Hz, 2H), 3.33 (t, *J* = 2.8 Hz, 1H), 3.02 (d, *J* = 2.8 Hz, 2H), 2.36 ppm (q, *J* = 6.8 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.92, 172.75, 165.99, 138.98, 135.07, 130.27, 128.48, 117.86, 52.78, 37.18, 35.81, 32.29, 28.34 ppm.

FT-IR: $\tilde{\nu}$ = 3083, 2952, 1698, 1670, 1579, 1436, 1379, 1267, 1212, 1106, 1014 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{18}H_{18}O_4N$: 328.11795 found: 328.11748.

Methyl 4-(1*R*,5*S*,6*s*)-3-benzyl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carbonyl)benzoate (231f)



Compound **231f** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 72% yield.

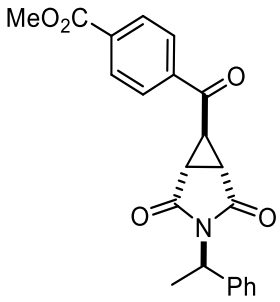
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.28 (m, 5H), 4.57 (s, 2H), 3.95 (s, 3H), 3.23 (t, *J* = 2.8 Hz, 1H), 3.03 ppm (d, *J* = 2.8 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.73, 172.35, 165.94, 138.90, 135.77, 135.04, 130.21, 128.93, 128.80, 128.51, 128.30, 52.72, 42.39, 35.38, 28.38 ppm.

FT-IR: $\tilde{\nu}$ = 3045, 2949, 2924, 1698, 1655, 1597, 1540, 1435, 1380, 1262, 1222, 1123, 1017 cm^{-1}

HRMS: calc. for $[M+H]^+$ $C_{21}H_{18}NO_5$: 364.11795found: 364.11742.

Methyl 4-(1*R*,5*S*,6*s*)-2,4-dioxo-3-((*R*)-1-phenylethyl)-3-azabicyclo[3.1.0]hexane-6-carbonyl)benzoate (231g)



Compound **231** was obtained by using the general procedure Hand the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 87% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 2H), 7.96 (d, *J* = 8.6 Hz, 2H), 7.44 – 7.29 (m, 5H), 5.28 (q, *J* = 7.3 Hz, 1H), 3.96 (s, 3H), 3.17 (t, *J* = 2.7 Hz, 1H), 2.98 (d, *J* = 2.8 Hz, 2H), 1.80 ppm (d, *J* = 7.4 Hz, 3H).

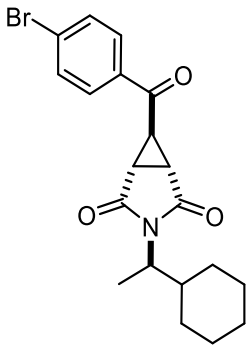
^{13}C NMR (75 MHz, $CDCl_3$) δ 191.80, 172.50, 172.46, 165.96, 139.50, 138.92, 134.96, 130.20, 128.69, 128.48, 128.14, 127.47, 52.74, 50.31, 35.10, 28.31, 28.25, 16.74 ppm.

FT-IR: $\tilde{\nu}$ = 3084, 2951, 1697, 1674, 15736, 14367, 1351, 1267, 1214, 1118, 1072 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{22}H_{20}O_5N$: 378.13360 found: 378.13330.

$[\alpha]^{RT}_D$ = -53.1 (CH_2Cl_2, *c* = 1.0).

(1*R*,5*S*,6*s*)-6-(4-bromobenzoyl)-3-((*R*)-1-cyclohexylethyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (231h)



Compound **231h** was obtained by using the general procedure H and the product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (3:97 v/v); light yellow amorphous solid with 60% yield.

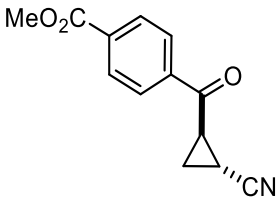
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 3.66-3.76 (m, 1H), 3.18 (t, *J* = 2.7 Hz, 1H), 2.98 (dd, *J* = 2.7, 1.4 Hz, 2H), 1.32 (d, *J* = 7.0 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 191.25, 173.13, 173.06, 134.67, 132.51, 129.99, 129.86, 53.03, 39.23, 35.36, 30.60, 30.31, 28.23, 28.18, 26.18, 25.85, 25.79, 15.94 ppm.

HRMS: calc. for $[M+H]^+$ $C_{20}H_{23}{}^{79}BrNO_3$: 404.08558 found: 404.08474: HRMS: calc. for $[M+H]^+$ $C_{20}H_{23}{}^{81}BrNO_3$: 406.08354 found: 406.08279.

$[\alpha]^{RT}_{D}$ = -6.1 (CH_2Cl_2, *c* = 1.0).

***rel*-Methyl 4-(1*R*,2*R*)-2-cyanocyclopropanecarbonyl)benzoate (231j)**



Compound **3z** was obtained by using the general procedure from methyl 4-acetylbenzoate (0.25 mmol) and acrylonitrile (1.0 mmol). The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 35% yield.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 2H), 8.07 (d, *J* = 8.4 Hz, 2H), 3.97 (s, 3H), 3.27 (ddd, *J* = 8.7, 5.8, 4.3 Hz, 1H), 2.24 – 2.08 (m, 1H), 1.73-1.66 ppm (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.86, 166.08, 139.47, 134.90, 130.24, 128.41, 119.62, 52.73, 24.54, 17.34, 7.89 ppm.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{12}O_3N$: 230.08117 found: 230.08087.

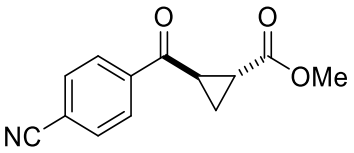
FT-IR: $\tilde{\nu}$ = 3091, 2970, 2929, 1697, 1678, 1481, 1453, 1376, 1258, cm^{-1}.

***rel*-Methyl (1*R*,2*R*)-2-(4-cyanobenzoyl)cyclopropane-1-carboxylate (231k)**

To a screw cap reaction vial charged with a magnetic stir-bar 4-cyanocetophenone (0.25 mmol), CuI (10 mol%), dtbpy **L5** (20 mol%) were added. The tube was then evacuated and back-filled with argon. This evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, solvent (2 mL of degased chlorobenzene), 10 equiv methylacraylate and di-*tert*-butyl peroxide (3 equiv) were added. The reaction mixture was

allowed to warm up to 90 °C and was stirred vigorously for completion of reaction (12 h). Then the reaction mixture was cooled to room temperature. To the reaction mixture was added dichloromethane (20 mL), washed by 1(N) HCl for two times, dried over Na_2SO_4 and evaporated in vacuum to afford the crude product and purified by column chromatography using silica. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 70% yield.

***rel*-Methyl (1*R*,2*R*)-2-(4-cyanobenzoyl)cyclopropane-1-carboxylate (231k)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.6 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 1H), 3.73 (s, 2H), 3.24 – 3.01 (m, 1H), 2.47 – 2.33 (m, 1H), 1.65 ppm (dd, *J* = 7.8, 6.4 Hz, 1H).

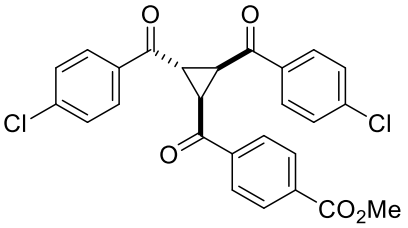
^{13}C NMR (75 MHz, $CDCl_3$) δ 196.02, 172.36, 139.94, 132.66, 128.77, 117.94, 116.72, 52.47, 26.23, 25.13, 18.58 ppm.

FT-IR: $\tilde{\nu}$ = 3084, 2951, 1697, 1674, 15736, 14367, 1351, 1267, 1214, 1118, 1072 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{12}O_3N$: 230.08117 found: 230.08076.

Methyl 4-((2*S*, 3*S*)-2,3-bis(4-chlorobenzoyl)cyclopropane-1-carbonyl)benzoate (231l)

Compound **231l** was obtained by using the general procedure H from 0.25 mmol (*E*)-1,4-bis(4-fluorophenyl)but-2-ene-1,4-dione. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 61% yield.



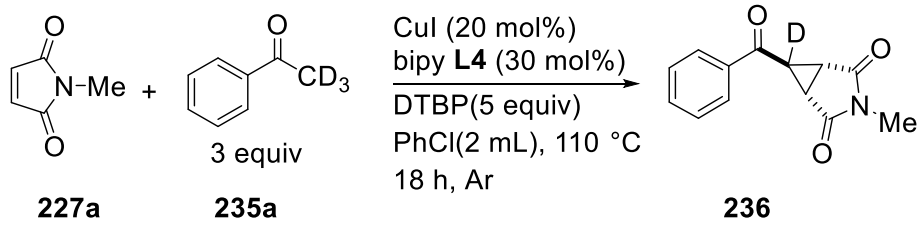
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 2H), 8.09 (d, *J* = 8.6 Hz, 2H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 4.15 (t, *J* = 5.6 Hz, 1H), 3.93 (s, 3H), 3.73 ppm (d, *J* = 5.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.47, 192.54, 191.70, 166.12, 140.89, 140.51, 139.53, 134.75, 134.70, 134.56, 130.29, 130.09, 129.94, 129.41, 129.27, 128.45, 52.64, 36.45, 36.35, 30.50 ppm.

FT-IR: $\tilde{\nu}$ = 3049, 2952, 1721, 1692, 1666, 1587, 1571, 1452, 1315, 1269, 1176, 1055, 1009 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{26}H_{19}O_5Cl_2$: 481.06041 found: 481.05939.

12.9.2 Procedure for Reaction of 2,2,2-[$^2H_3$]-1-phenylethan-1-one (235a)

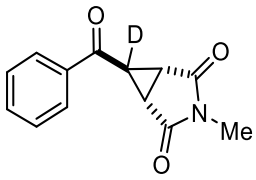


227a **235a** **236**

41%

To a screw cap reaction tube charged with a magnetic stir-bar *N*-methylmaleimide (0.25 mmol), 2,2,2-[$^2H_3$]-1-phenylethan-1-one (0.75 mmol), CuI (20 mol%), bipy **L4** (30 mol%) were added. The tube was then evacuated and back-filled with argon with the help of a syringe. This evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, solvent (2 mL degas chlorobenzene) and di-*tert* butyl peroxide (5 equiv) were added. The reaction mixture was allowed to warm up to 110 °C and stirred vigorously for completion of reaction (18 h). Then the reaction mixture was cooled to room temperature. Dichloromethane (4 mL) and ethyl acetate (2 mL) were added for dilution of reaction mixture. Finally, the reaction mixture obtained upon filtration through a celite bed was concentrated and was purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether / acetone as the eluent and isolated yield was 41%.

6-[^2H]-(1*R*,5*S*,6*s*)-6-benzoyl-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione



1H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.9, 0.5 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 3.02 (s, 1H), 2.93 ppm (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 192.05, 173.07, 135.84, 134.43, 129.11, 128.64, 28.27, 28.19, 24.76.

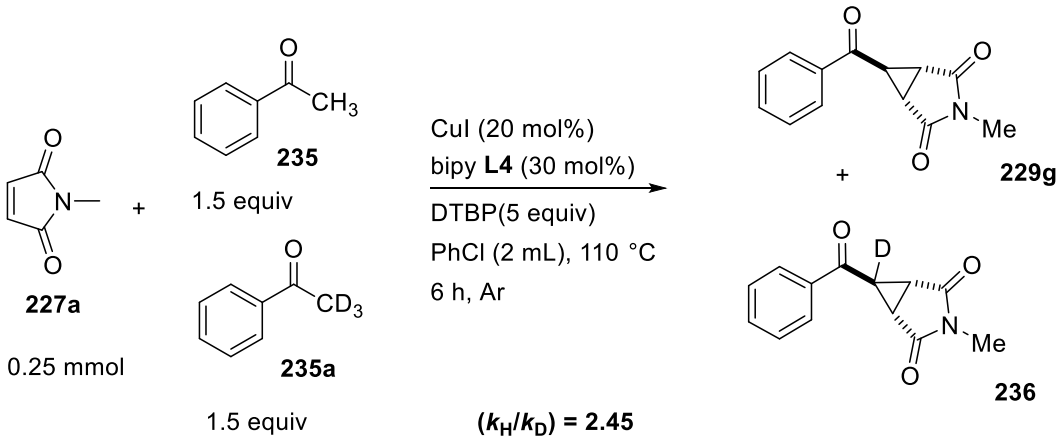
FT-IR: $\tilde{\nu}$ = 3092, 2946, 1768, 1694, 1675, 1437, 1382, 1229, 1125, 1017 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{11}DO_3N$: 231.08745 found: 231.08669.

12.9.3 Procedure for Kinetic Isotope Effect (KIE) study

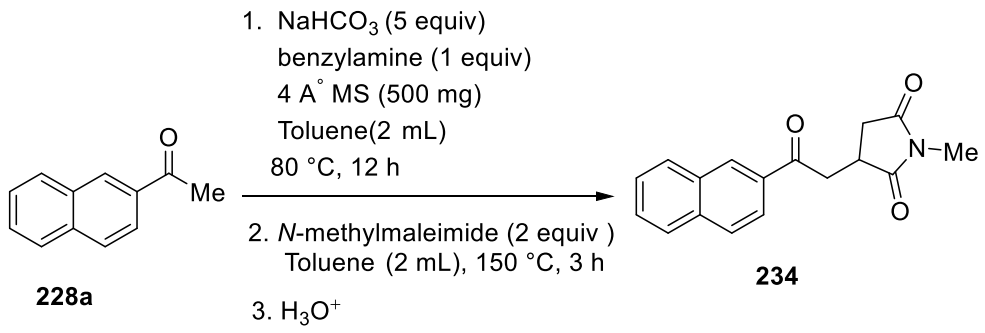
To a screw cap reaction tube charged with a magnetic stir-bar *N*-methylmaleimide (0.25 mmol), acetophenone (0.375 mmol), 2,2,2-[$^2H_3$]-1-phenylethan-1-one (0.375 mmol), CuI (20 mol%), **L4** (30 mol%) were added. The tube was then evacuated and back-filled with argon with the help of a syringe. This evacuation/backfill sequence was repeated three additional

times. Under a counter flow of argon, solvent (2 mL degas chlorobenzene) and di-*tert* butyl peroxide (5 equiv) were added. The reaction mixture was allowed to warm up to 110 °C and



stirred vigorously for completion of reaction (6 h). Then the reaction mixture was cooled to room temperature. Dichloromethane (4 mL) and ethyl acetate (2 mL) were added for dilution of reaction mixture. Finally, the reaction mixture obtained upon filtration through a celite bed was concentrated and purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether / acetone as the eluent. KIE (K_H/K_D = 2.45) was determined from ^{1}H NMR.

12.9.4 Synthesis of Compound 234[272]



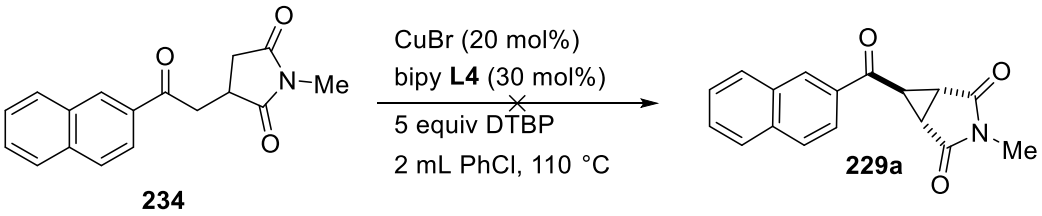
To screw-capped pressure vial (10 ml) equipped with a magnetic stirring bar was charged with aromatic ketimine (1, 0.25 mmol), *N*-methylmaleimide **227a** (2, 0.5 mmol), 2 mL toluene. The vial was closed and heated at 150 ℃ with a vigorous stirring for 3 hr. After cooling to room temperature, 10 mL 1 N HCl was added. The organic layer was extracted with Et_2O, and dried over anhydrous Na_2SO_4. The crude traction mixture was concentrated under vacuum. The product **234** was purified by column chromatography (petroleum-ether /acetone 90:10) on silica gel. The desired product was obtained 35%.

Methyl-3-(2-(naphthalen-2-yl)-2-oxoethyl)-pyrrolidine-2,5-dione (234)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.99 – 7.89 (m, 2H), 7.90 – 7.84 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 3.79-3.74 (m, 1H), 3.55-3.50 (m, 1H), 3.33 – 3.24 (m, 1H), 3.06 – 3.04 (m, 1H), 3.05)s, 1H) 2.53-2.40 ppm (m, 1H).

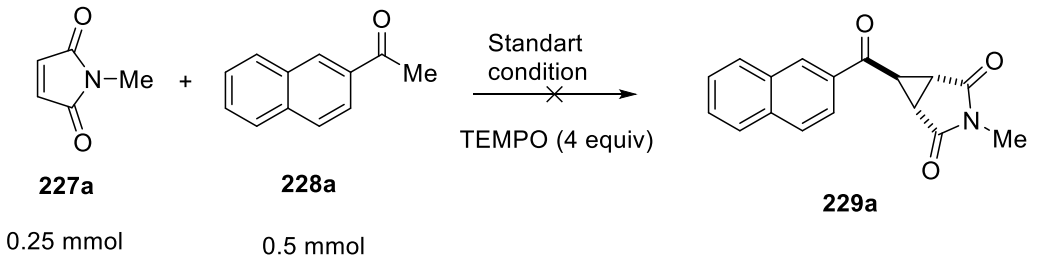
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.83, 179.86, 176.68, 135.90, 133.40, 132.50, 130.06, 129.68, 128.92, 128.77, 127.91, 127.10, 123.52, 39.23, 36.01, 34.98, 25.10 ppm.

12.9.5 Procedure for Control Experiment



To a screw cap reaction tube charged with a magnetic stir-bar 1-methyl-3-(2-(naphthalen-2-yl)-2-oxoethyl)pyrrolidine-2,5-dione **234** (0.25 mmol), CuI (20 mol%), bipy **L4** (30 mol%) were added. The tube was then evacuated and back-filled with argon with the help of a syringe. This evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, solvent (2 mL degas chlorobenzene) and DTBP (5 equiv) were added. The reaction mixture was allowed to warm up to 110 °C and stirred vigorously for completion of reaction (18 h). Then the reaction mixture was cooled to room temperature. Dichloromethane (4 mL) and ethyl acetate (2 mL) were added for dilution of reaction mixture. Finally, the reaction mixture was analyzed by GC-MS and the desired product was not found.

12.9.6 Procedure for Radical Inhibition Test

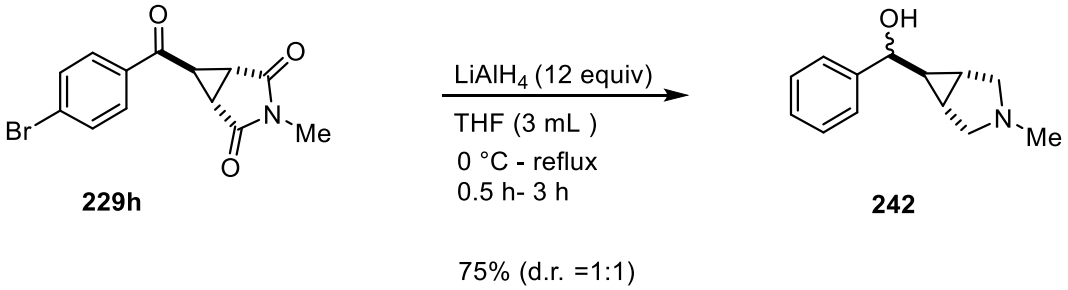


To a screw cap reaction tube charged with a magnetic stir-bar maleimide (0.25 mmol), 2-acetylnaphthalene (0.5 mmol), CuI (20 mol%), bipy (30 mol%) and TEMPO (4 equiv) were added. The tube was then evacuated and back-filled with argon with the help of a syringe. This evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, solvent (2 mL degas chlorobenzene) and DTBP (5 equiv) were added. The reaction mixture was allowed to warm up to 110 °C and stirred vigorously for completion of reaction

(24 h). Then the reaction mixture was cooled to room temperature. Dichloromethane (4 mL) and ethyl acetate (2 mL) were added for dilution of reaction mixture. Finally, the reaction mixture was analyzed by GC-MS and the desired product was not found.

12.9.7 Synthesis of Compound 242

To a seal tube charged with a magnetic stir-bar; slowly $LiAH_4$ (12 equiv) was added to a solution of amide in THF (3 mL) at 0 °C. The reaction mixture was stirred at reflux for 3h, then cooled to 0 °C and treated with water (1 mL) and 1N NaOH (2 mL). White solid was filtered out, the filtrate was extracted with ethyl acetate and further purified by column chromatography. The pure product was isolated with 75% yield.



229h **242**

75% (d.r. =1:1)

((1*R*,5*S*,6*r*)-3-Methyl-3-azabicyclo[3.1.0]hexan-6-yl)(phenyl)methanol (242)

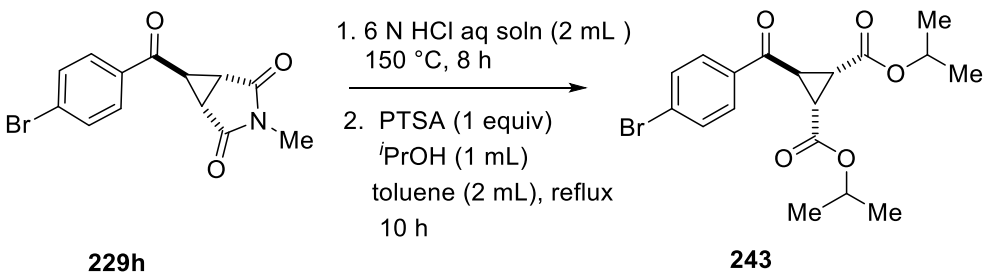
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.29 (dd, *J* = 7.9, 6.5 Hz, 1H), 4.08 (dd, *J* = 8.3, 4.3 Hz, 1H), 3.09 (dd, *J* = 8.8, 6.2 Hz, 1H), 2.97 – 2.91 (m, 1H), 2.37 (dd, *J* = 9.0, 3.9 Hz, 1H), 2.28 (s, 3H), 1.67 (dd, *J* = 7.3, 4.1 Hz, 1H), 1.59 (dd, *J* = 7.1, 3.5 Hz, 1H), 1.42 – 1.39 ppm (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.98, 128.44, 127.61, 126.33, 57.23, 56.88, 41.43, 27.56, 22.52, 21.63 ppm.

FT-IR: $\tilde{\nu}$ = 3317, 2969, 2898, 1652, 1451, 1401, 1347, 1245, 1071 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{13}H_{18}ON$: 204.13829 found: 204.13911.

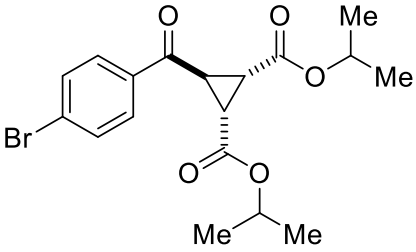
12.9.8 Synthesis of Compound 243



229h **243**

To a sled tube charged with a magnetic stir-bar was added (1*R*,5*S*,6*s*)-6-(4-bromobenzoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione **229h** (0.25 mmol), 2 mL 6 N HCl aqueous solution were added. The reaction mixture was heated under refluxed for 8 h with the oil bath maintained at 150 °C. Then the reaction mixture was cooled to room temperature. To the reaction mixture was added dichloromethane (20 mL) and extracted by separating funnel. Finally, the reaction mixture was concentrated and crude product was used for second step. For the second step, to a round bottom flux charged with a magnetic stir-bar was added crude reaction mixture, 1 equiv PTSA, 1 mL isopropanol and 2 mL toluene were added. The reaction mixture was heated under refluxed for 10 h with a Dean–Stark trap, with the oil bath maintained at 120 °C. Then the reaction mixture was cooled to room temperature. Finally, the reaction mixture was concentrated and was purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether / acetone as the eluent. The product was obtained as a white amorphous solid in 61% yield.

Diisopropyl (1*R*,2*S*,3*s*)-3-(4-bromobenzoyl)cyclopropane-1,2-dicarboxylate (243) **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.94 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 5.04 (hept, *J* = 6.3 Hz, 1H), 3.66 (t, *J* = 5.6 Hz, 1H), 2.67 (d, *J* = 5.6 Hz, 1H), 1.25 ppm (dd, *J* = 6.3, 3.7 Hz, 6H).

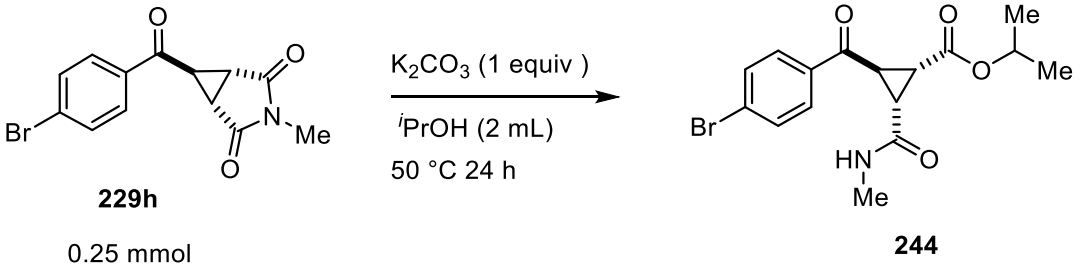


^{13}C NMR (75 MHz, $CDCl_3$) δ 194.40, 167.47, 135.33, 132.23, 130.16, 129.24, 69.39, 30.63, 29.06, 21.90, 21.85 ppm.

FT-IR: $\tilde{\nu}$ = 2979, 2934, 1723, 1674, 1583, 1373, 1416, 1296, 1211, 1181, 1106, 1037 cm^{-1}.

MS-EI: m/z (%): 155,0 (37); 156,9 (19); 182,9 (82); 184,9 (79); 294,9 (100); 296,9 (100); 355,0 (18); 357,0 (17); 396,1 (4); 398,0 (4).

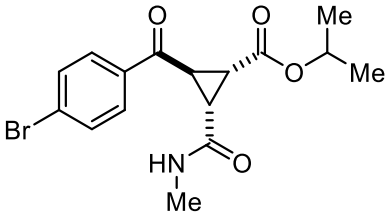
12.9.9 Synthesis of Compound 244



To a screw cap reaction tube charged with a magnetic stir-bar was added (1*R*,5*S*,6*s*)-6-(4-bromobenzoyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione **229h**, 1 equiv K_2CO_3 and 2 mL isopropanol were added. The reaction mixture was allowed to warm up to 50 °C and was

stirred vigorously for completion of reaction (24 h). Then the reaction mixture was cooled to room temperature. Finally, the reaction mixture was concentrated and was purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether / acetone as the eluent and isolated yield was 52%.

***rel*-Isopropyl (1*S*,2*R*,3*R*)-2-(4-bromobenzoyl)-3-(methylcarbamoyl)cyclopropane-1-carboxylate (244)**



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 5.96 (s, 1H), 5.05 (hept, *J* = 5.6 Hz, 1H), 3.69 (t, *J* = 5.6 Hz, 1H), 2.82 (d, *J* = 4.8 Hz, 3H), 2.54 (dd, *J* = 9.8, 5.5 Hz, 1H), 1.25 ppm (t, *J* = 5.6 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.91, 167.88, 167.22, 135.41, 132.26, 130.20, 129.26, 69.48, 32.21, 31.04, 29.01, 26.80, 21.91, 21.85 ppm.

FT-IR: $\tilde{\nu}$ = 3084, 2951, 1697, 1674, 15736, 14367, 1351, 1267, 1214, 1118, 1072 cm^{-1}.

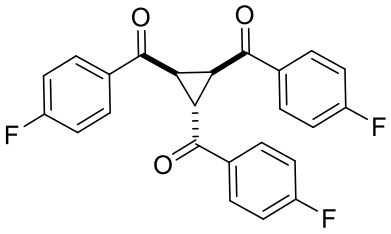
HRMS: calc. for $[M+H]^+$ $C_{16}H_{19}{}^{79}BrNO_4$: 368.04920 found: 375.97970: HRMS: calc. for $[M+H]^+$ $C_{14}H_{10}{}^{81}BrNO_3F_3$: 370.04715 found: 370.04770.

12.10 Copper(I)-Catalyzed Oxidative (1+1+1) Annulation of Acetophenone for Cyclopropane Synthesis

12.10.1 Characterization of Cyclopropane Derivatives (245-248)

(*r*)-Cyclo propane-1,2,3-triyltris((4-fluorophenyl)methanone

Compound **245a** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (3:97 v/v); light yellow amorphous solid with 86% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (dd, *J* = 8.4, 5.5 Hz, 2H), 8.03 (dd, *J* = 8.4, 5.5 Hz, 4H), 7.20 (t, *J* = 8.4 Hz, 2H), 7.11 (t, *J* = 8.4 Hz, 4H), 4.15 (t, *J* = 5.6 Hz, 1H), 3.69 ppm (d, *J* = 5.6 Hz, 2H).

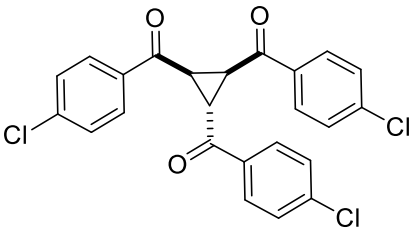
^{13}C NMR (126 MHz, $CDCl_3$) δ 194.23, 191.43, 166.50 (d, *J* = 256.7 Hz), 166.19 (d, *J* = 256.2 Hz), 132.98 (d, *J* = 3.0 Hz), 132.95 (d, *J* = 3.4 Hz), 131.65 (d, *J* = 9.5 Hz), 131.24 (d, *J* = 9.5 Hz), 116.24 (d, *J* = 20.7 Hz), 116.07 (d, *J* = 22.0 Hz), 36.14, 30.40 ppm.

FT-IR: $\tilde{\nu}$ = 3069, 3018, 1727, 1631, 1594, 1505, 1366, 1223, 1154, 1037 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3F_3$: 409.10461 found: 409.10452.

(*r*)-Cyclopropane-1,2,3-triyltris((4-bchlorophenyl)methanone) (245b)

Compound **245b** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (3:97 v/v); light yellow amorphous solid with 66% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 8.6 Hz, 4H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 4H), 4.13 (t, *J* = 5.6 Hz, 1H), 3.69 ppm (d, *J* = 5.6 Hz, 2H).

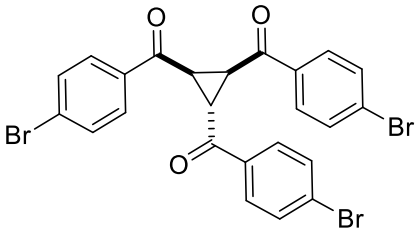
^{13}C NMR (126 MHz, $CDCl_3$) δ 194.57, 191.75, 140.89, 140.47, 134.76 (x 2), 130.30, 129.93, 129.42, 129.27, 36.24, 30.45 ppm.

FT-IR: $\tilde{\nu}$ = 3050, 1693, 1665, 1586, 1400, 1368, 1296, 1231, 1092, 1008 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3Cl_3$: 457.01595 found: 457.01529.

(*r*)-Cyclopropane-1,2,3-triyltris((4-bromophenyl)methanone) (245c)

Compound **245c** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 73% yield, we carried out the reaction at 6 mmol scale using 2 equiv DTBP. Product **245c** was obtained in 66% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 4H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 4H), 4.12 (t, *J* = 5.6 Hz, 1H), 3.68 ppm (d, *J* = 5.6 Hz, 2H).

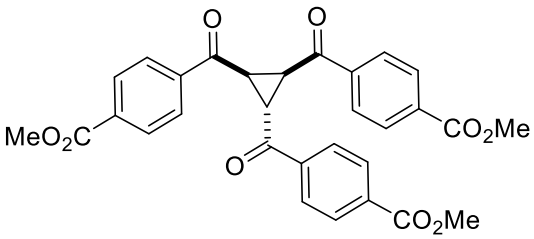
^{13}C NMR (126 MHz, $CDCl_3$) δ 194.75, 191.94, 135.14, 132.42, 132.28, 130.35, 130.00, 129.69, 129.27, 36.22, 30.42 ppm.

FT-IR: $\tilde{\nu}$ = 3053, 2925, 1695, 1664, 1585, 1486, 1370, 1297, 1204, 1073, 1007 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3{}^{79}Br_3$: 588.86441 found: 588.86293; HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3{}^{79}Br_2{}^{81}Br$: 590.86236 found: 590.86129; HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3{}^{79}\mathbf{Br}^{81}Br_2$: 592.86032 found: 592.85936; HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3{}^{81}Br_3$: 594.85827 found: 594.85936.

Trimethyl 4,4',4''-(cyclopropane-1,2,3-tricarbonyl)(*r*)-tribenzoate (245d)

Compound **245d** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 88% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 – 8.21 (m, 2H), 8.20 – 8.17 (m, 2H), 8.11 – 8.07 (m, 4H), 8.06 – 8.02 (m, 4H), 4.24 (t, *J* = 5.6 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 6H), 3.80 ppm (d, *J* = 5.6 Hz, 2H).

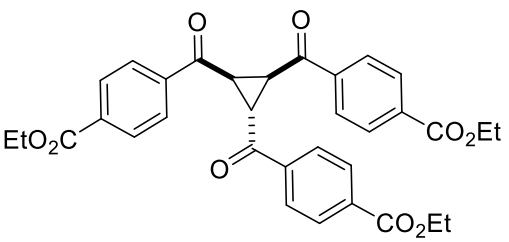
13C NMR (126 MHz, $CDCl_3$) δ 195.29, 192.39, 166.16, 166.12, 139.54, 139.47, 134.94, 134.64, 130.24, 130.12, 128.83, 128.48, 52.70, 52.65, 36.79, 30.86 ppm.

FT-IR: $\tilde{\nu}$ = 2925, 1719, 1695, 1662, 1586, 1438, 1409, 1315, 1197, 1107, 1012 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{30}H_{25}O_9$: 529.14931 found: 529.14892.

Triethyl 4,4',4''-(cyclopropane-1,2,3-tricarbonyl)(*r*)-tribenzoate (245e)

Compound **245e** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent:



acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 65% yield;

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 – 8.17 (m, 4H), 8.11 – 8.02 (m, 8H), 4.43 – 4.35 (m, 6H), 4.24 (t, *J* = 5.6 Hz, 1H), 3.80 (d, *J* = 5.6 Hz, 1H), 1.44 – 1.34 ppm (m, 9H).

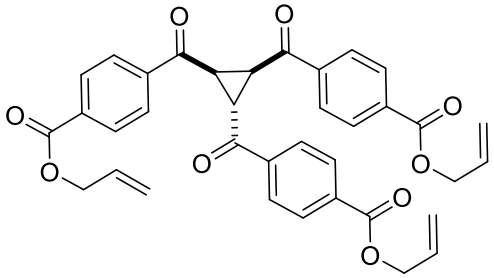
^{13}C NMR (75 MHz, $CDCl_3$) δ 195.36, 192.44, 165.68, 165.64, 139.40, 139.31, 135.23, 134.95, 130.17, 130.06, 128.78, 128.43, 61.74, 61.68, 36.78, 30.79, 14.39 (x 2) ppm.

FT-IR: $\tilde{\nu}$ = 3051, 2978, 1713, 1668, 1504, 1438, 1408, 1368, 1271, 1102, 1014 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{33}H_{31}O_9$: 571.19626 found: 571.19629.

Triallyl 4,4',4''-(cyclopropane-1,2,3-tricarbonyl)(*r*)-tribenzoate (245f)

Compound **245f** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 43% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25-8.20 (m, 4H), 8.11 (d, *J* = 8.5 Hz, 4H), 8.05 (d, *J* = 8.5 Hz, 4H), 6.09-5.58 (m, 3H), 5.45 – 5.38 (m, 3H), 5.35 – 5.24 (m, 3H), 4.86 (d, *J* = 5.7 Hz, 2H), 4.83 (d, *J* = 5.7 Hz, 4H), 4.24 (t, *J* = 5.6 Hz, 1H), 3.81 ppm (d, *J* = 5.6 Hz, 2H).

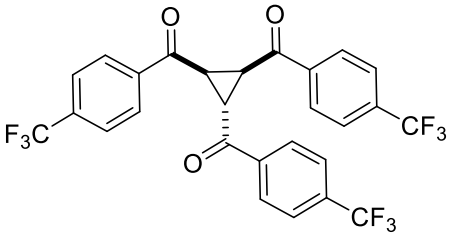
^{13}C NMR (126 MHz, $CDCl_3$) δ 195.26, 192.37, 165.31, 165.27, 139.56, 139.49, 134.95, 134.66, 131.93 (x2), 130.27, 130.17, 128.82, 128.47, 118.93, 118.90, 66.26, 66.20, 36.77, 30.87 ppm.

FT-IR: $\tilde{\nu}$ = 3082, 3031, 2933, 1716, 1670, 1681, 1576, 1456, 1364, 1315, 1266, 1102, 1017 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{36}H_{31}O_9$: 606.19626 found: 607.19636.

(*r*)-Cyclopropane-1,2,3-triyltris((4-(trifluoromethyl)phenyl)methanone) (245g)

Compound **245g** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (3:97 v/v); light yellow amorphous solid with 79% yield.



^{1}H NMR (500 MHz, Acetone) δ 8.41 (d, *J* = 8.1 Hz, 2H), 8.30 (d, *J* = 8.1 Hz, 4H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 4H), 4.24 (t, *J* = 5.7 Hz, 1H), 4.05 ppm (d, *J* = 5.7 Hz, 2H).

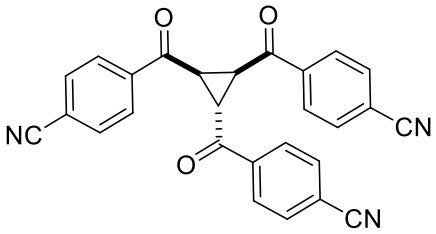
^{13}C NMR (126 MHz, Acetone) δ 195.23, 193.33, 140.79, 140.68, 134.90 (q, *J* = 32.3 Hz), 130.33, 130.20, 126.95 (q, *J* = 3.8 Hz), 126.74 (q, *J* = 3.7 Hz), 121.69, 110.66, 37.42, 32.01 ppm.

FT-IR: $\tilde{\nu}$ = 3058, 3024, 2932, 1698, 1672, 1512, 1367, 1317, 1301, 1207, 1164, 1120, 1011 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{27}H_{16}O_3F_9$: 559.09502 found: 559.09565.

(*r*)-4,4',4''-(Cyclopropane-1,2,3-tricarbonyl)tribenzonitrile (245h)

Compound **245h** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 62% yield.



^{1}H NMR (500 MHz, DMSO) δ 8.25 (d, *J* = 8.3 Hz, 2H), 8.16 (d, *J* = 8.3 Hz, 4H), 8.08 (d, *J* = 8.4 Hz, 2H), 7.98 (d, *J* = 8.4 Hz, 4H), 4.08 (t, *J* = 5.8 Hz, 1H), 4.01 ppm (d, *J* = 5.8 Hz, 2H).

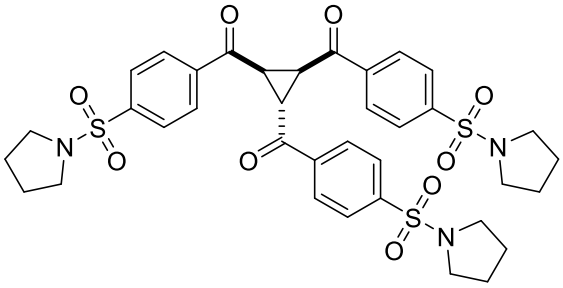
^{13}C NMR (126 MHz, DMSO) δ 194.03, 192.63, 139.24, 139.04, 132.97, 132.77, 128.96, 128.88, 118.03, 117.98, 115.72, 115.54, 36.13, 31.10 ppm.

FT-IR: $\tilde{\nu}$ = 3080, 2958, 2231, 1670, 1596, 1512, 1579, 1373, 1307, 1242, 1196, 1173, 1122 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{27}H_{16}O_3N_3$: 430.11862 found: 430.11837.

(*r*)-Cyclopropane-1,2,3-triyltris((4-(pyrrolidin-1-ylsulfonyl)phenyl)methanone (245i)

Compound **245i** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 35% yield.



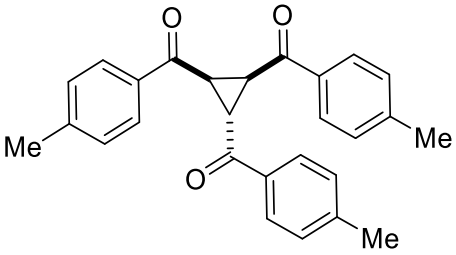
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.4 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 4H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 4H), 4.20 (t, *J* = 5.6 Hz, 1H), 3.81 (d, *J* = 5.6 Hz, 2H), 3.29-3.23 (m, 12H), 1.85 – 1.63 ppm(m, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.61, 192.23, 142.63, 142.47, 139.30, 139.26, 129.75, 129.40, 128.32, 128.22, 48.40, 48.36, 36.84, 31.38, 25.74, 25.72 ppm.

FT-IR: $\tilde{\nu}$ = 2975, 2880, 1674, 1595, 1569, 1398, 1343, 1291, 1208, 1157, 1092, 1005 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{36}H_{40}O_9N_3S_3$: 754.19212 found: 754.19293.

(*r*)-Cyclopropane-1,2,3-triyltris(*p*-tolylmethanone) (245j)



Compound **245j** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (2:98 v/v); light yellow amorphous solid with 43% yield;

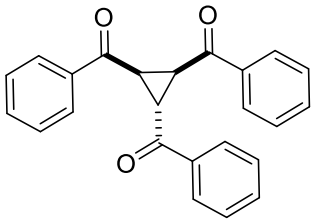
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 4H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 4H), 4.20 (t, *J* = 5.6 Hz, 1H), 3.72 (d, *J* = 5.6 Hz, 2H), 2.44 (s, 3H), 2.38 ppm (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.87, 192.74, 144.95, 144.44, 134.30, 134.26, 129.62, 129.44, 129.01, 128.70, 36.41, 30.33, 21.87, 21.79 ppm.

FT-IR: $\tilde{\nu}$ = 3030, 2967, 1722, 1664, 1605, 1408, 1367, 1224, 1178, 1013 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{27}H_{25}O_3$: 397.17982 found: 397.17989.

(*r*)-Cyclopropane-1,2,3-triyltris(phenylmethanone) (245k)[273]



Compound **245k** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (3:97 v/v); light yellow amorphous solid with 65% yield.

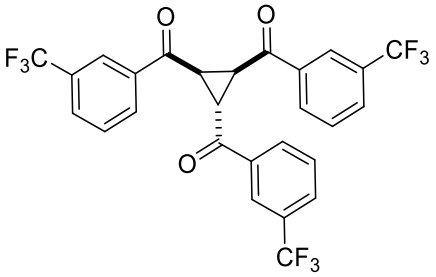
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 – 8.17 (m, 2H), 8.03 – 7.97 (m, 4H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.54 (q, *J* = 7.7 Hz, 4H), 7.43 (t, *J* = 7.7 Hz, 4H), 4.24 (t, *J* = 5.6 Hz, 1H), 3.76 ppm (d, *J* = 5.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 196.14, 193.11, 136.66, 134.06, 133.67 (x2), 129.00, 128.93, 128.82, 128.61, 36.52, 30.55 ppm.

FT-IR: $\tilde{\nu}$ = 3066, 2999, 1684, 1661, 1595, 1578, 1446, 1328, 1303, 1216, 1153, 1014 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{27}H_{16}O_3N_3$: 355.13287 found: 355.13336.

(*r*)-Cyclopropane-1,2,3-triyltris((3-(trifluoromethyl)phenyl)methanone) (245l)



Compound **245l** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 46% yield;

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 3.6, 2.9 Hz, 2H), 8.22 (s, 2H), 8.18 (d, *J* = 7.8 Hz, 2H), 7.94 – 7.88 (m, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.74 – 7.68 (m, 1H), 7.60 (t, *J* = 7.8 Hz, 2H), 4.26 (t, *J* = 5.6 Hz, 1H), 3.82 ppm(d, *J* = 5.6 Hz, 2H).

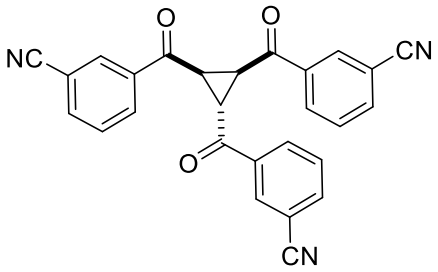
^{13}C NMR (75 MHz, $CDCl_3$) δ 194.41, 191.51, 136.85, 136.71, 132.19, 131.66 (q, *J* = 33.2 Hz), 131.88 (d, *J* = 33.3 Hz), 131.66, 130.75, 130.70, 130.66 (q, *J* = 3.5 Hz), (q, *J* = 3.5 Hz), 129.86, 129.72, 129.57, 125.58 (q, *J* = 3.9 Hz), (q, *J* = 3.8 Hz) 124.73, 123.57 (q, *J* = 272.7 Hz), 123.66 (q, *J* = 272.6 Hz), 121.75, 118.14, 36.44, 30.32 ppm.

FT-IR: $\tilde{\nu}$ = 3069, 2929, 1733, 1694, 1674, 1614, 1329, 1309, 1200, 1162, 1153, 1022 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{27}H_{16}O_3F_9$: 559.09502 found: 559.09564.

(*r*)-3,3',3''-(Cyclopropane-1,2,3-tricarbonyl)tribenzonitrile (245m)

Compound **245m** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 68% yield.



^{1}H NMR (500 MHz, DMSO) δ 8.54 (s, 1H), 8.52 (s, 2H), 8.39 (d, *J* = 7.9 Hz, 2H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 2H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 2H), 4.12 (t, *J* = 5.8 Hz, 1H), 4.01 ppm(d, *J* = 5.8 Hz, 2H).

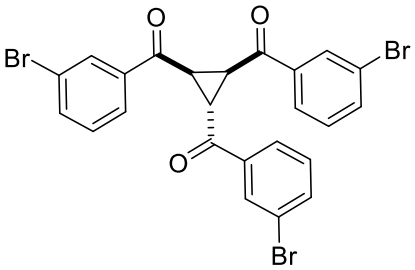
^{13}C NMR (126 MHz, DMSO) δ 193.43, 191.91, 136.93, 136.77(x2), 136.73, 132.69, 132.45, 132.28, 132.23, 130.32, 130.08, 118.00, 117.90, 112.19, 112.01, 35.99, 30.55 ppm.

FT-IR: $\tilde{\nu}$ = 3080, 2958, 2231, 1670, 1596, 1579, 1423, 1373, 1307, 1196, 1066, 1024 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{27}H_{16}O_3N_3$: 430.11862 found: 430.11837.

(*r*)-Cyclopropane-1,2,3-triyltris((3-bromophenyl)methanone) (245n)

Compound **245n** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 77% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.17 – 8.06 (m, 3H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 2H), 4.14 (t, *J* = 5.6 Hz, 1H), 3.71 ppm (d, *J* = 5.6 Hz, 2H).

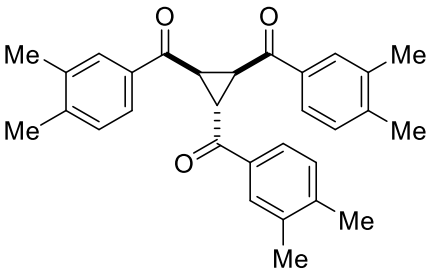
^{13}C NMR (126 MHz, $CDCl_3$) δ 194.44, 191.48, 138.10, 138.03, 137.08, 136.77, 131.71, 131.61, 130.64, 130.49, 127.59, 127.09, 123.48, 123.30, 36.46, 30.37 ppm.

FT-IR: $\tilde{\nu}$ = 3065, 2926, 1686, 1662, 1565, 1418, 1343, 1294, 1197, 1064, 1034 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3{}^{79}Br_3$: 588.86441 found: 588.86293; HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3Br_2{}^{81}Br$: 590.86236 found: 590.86129; HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3{}^{79}Br^{81}Br_2$: 592.86032 found: 592.85936; HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3{}^{81}Br_3$: 594.85827 found: 594.85936.

(*r*)-Cyclopropane-1,2,3-triyltris((3,4-dimethylphenyl)methanone) (245o)

Compound **245o** was obtained by using the general procedure I from 3,4-dimethylacetophenone (0.5 mmol) in 1 mL DMF for 18 h at 80 °C. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (3:97 v/v); light yellow amorphous solid with 53% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.77 (s, 2H), 7.75 (dd, *J* = 7.8, 1.7 Hz, 2H), 7.26 (d, *J* = 7.7 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 1H), 4.19 (t, *J* = 5.6 Hz, 1H), 3.70 (d, *J* = 5.6 Hz, 2H), 2.34 (s, 6H), 2.27 (s, 6H), 2.25 ppm (s, 6H).

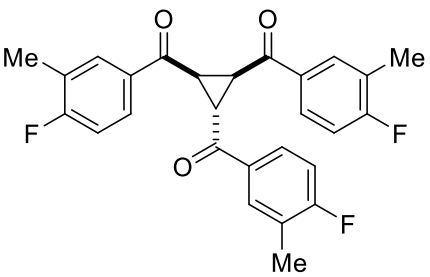
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.17, 192.86, 143.52, 142.99, 137.17, 136.91, 134.58, 134.55, 130.03, 129.81, 129.77, 129.59, 126.56, 126.23, 30.12, 28.18, 20.11, 20.02, 19.75, 19.70 ppm.

FT-IR: $\tilde{\nu}$ = 3097, 2927, 1722, 1637, 1512, 1545, 1408, 1316, 1216, 1170, 1052 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{30}H_{31}O_3$: 439.22677 found: 439.22698.

(*r*)-Cyclopropane-1,2,3-triyltris((4-fluoro-3-methylphenyl)methanone (245p)

Compound **245p** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (3:97 v/v); light yellow amorphous solid with 43% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (t, *J* = 7.1 Hz, 2H), 7.89 – 7.72 (m, 4H), 7.13 (t, *J* = 8.7 Hz, 1H), 7.03 (t, *J* = 8.8 Hz, 2H), 4.13 (t, *J* = 5.6 Hz, 1H), 3.67 (d, *J* = 5.6 Hz, 1H), 2.36 (s, 3H), 2.27 ppm (s, 6H).

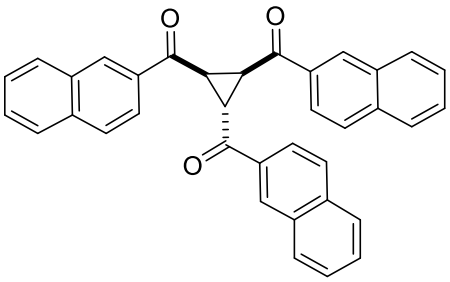
^{13}C NMR (151 MHz, $CDCl_3$) δ 165.13 (d, *J* = 255.2 Hz), 164.81 (d, *J* = 254.6 Hz), 132.74, 132.73, 132.71, 132.70, 132.42 (d, *J* = 6.8 Hz), 129.03 (d, *J* = 9.5 Hz), 128.60 (d, *J* = 9.5 Hz), 125.99 (d, *J* = 18.0 Hz), 125.79 (d, *J* = 18.0 Hz), 115.77 (d, *J* = 23.2 Hz), 115.56 (d, *J* = 23.2 Hz), 36.34, 30.27, 14.74, 14.71, 14.69, 14.67 ppm.

FT-IR: $\tilde{\nu}$ = 3064, 2958, 1741, 1684, 1661, 1584, 1545, 1496, 1411, 1317, 1246, 1155, 1067 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{27}H_{22}O_3F_3$: 451.15156 found: 451.15137.

(*r*)-Cyclopropane-1,2,3-triyltris(naphthalen-2-ylmethanone) (245q)

Compound **245q** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 65% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.66 (s, 2H), 8.29 – 8.22 (m, 1H), 8.10 – 8.06 (m, 3H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.92 (t, *J* = 8.5 Hz, 3H), 7.87 – 7.84 (m, 4H), 7.70 – 7.64 (m, 1H), 7.63 – 7.58 (m, 4H), 7.52 (t, *J* = 7.5 Hz, 2H), 4.57 (t, *J* = 5.5 Hz, 1H), 4.08 ppm (d, *J* = 5.5 Hz, 2H).

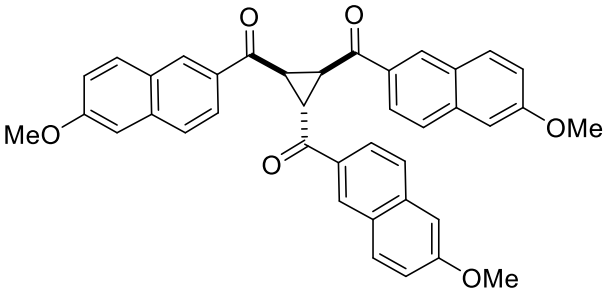
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.23, 193.12, 136.14, 135.91, 134.11, 134.05, 132.72, 132.56, 131.42, 130.67, 130.11, 129.77, 129.11, 128.91, 128.83, 128.75, 127.93, 127.90, 127.14, 126.97, 124.03, 36.94, 30.72 ppm.

FT-IR: $\tilde{\nu}$ = 3050, 2970, 2928, 1727, 1662, 1596, 1595, 1492, 1393, 1251, 1217, 1153, 1022, cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{27}H_{16}O_3N_3$: 505.17982 found: 505.17932.

(*r*)-Cyclopropane-1,2,3-triyltris((6-methoxynaphthalen-2-yl)methanone) (**245r**)

Compound **245r** was obtained by using the general procedure I from 1-(6-methoxynaphthalen-2-yl)ethan-1-one (0.5 mmol), CuI (20 mol%) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (30 mol%) at 75 °C. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (10:90 v/v); light yellow amorphous solid with 46% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.54 (s, 2H), 8.20 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.03 (dd, *J* = 8.6, 1.6 Hz, 2H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.22 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.14 (dd, *J* = 9.0, 2.4 Hz, 2H), 7.09 (d, *J* = 2.1 Hz, 2H), 4.49 (t, *J* = 5.6 Hz, 1H), 3.99 (d, *J* = 5.6 Hz, 2H), 3.96 (s, 3H), 3.91 ppm(s, 6H).

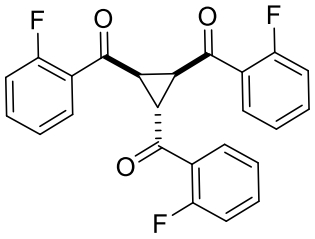
^{13}C NMR (126 MHz, $CDCl_3$) δ 196.01, 192.88, 160.29, 160.04, 137.90, 137.63, 132.31, 132.20, 131.71, 131.34, 131.23, 130.50, 128.05, 127.89, 127.52, 127.35, 124.85, 120.00, 119.86, 106.00, 105.90, 55.59, 55.53, 36.79, 30.51 ppm.

FT-IR: $\tilde{\nu}$ = 3029, 2929, 1713, 1679, 1574, 1512, 1410, 1362, 1264, 1213, 1099, 1173, 1031 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{39}H_{31}O_6$: 595.21152 found: 595.21133.

(*r*)-Cyclopropane-1,2,3-triyltris((2-fluorophenyl)methanone) (245s)

Compound **245s** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (2:98 v/v); light yellow amorphous solid with 41% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.87 (m, 1H), 7.86-7.83 (m, 2H), 7.59 – 7.48 (m, 3H), 7.28 – 7.24 (m, 1H), 7.23 – 7.18 (m, 2H), 7.15 (dd, *J* = 9.7, 1.2 Hz, 1H), 7.11 (dd, *J* = 10.1, 8.5 Hz, 2H), 4.15 (ddd, *J* = 5.6, 4.6, 1.1 Hz, 1H), 3.76 ppm(d, *J* = 5.6 Hz, 2H).

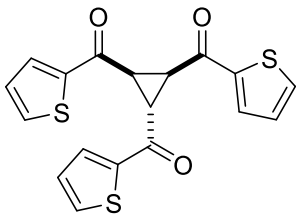
^{13}C NMR (126 MHz, $CDCl_3$) δ 194.87, 191.62, 163.54, 163.43, 161.51, 161.38, 135.44, 135.37, 131.26, 131.09, 126.36, 126.26, 125.82, 125.73, 124.85, 117.40, 117.22, 117.19, 117.00, 41.20, 41.16, 41.12, 35.16, 35.09 ppm.

FT-IR: $\tilde{\nu}$ = 3079, 2928, 1726, 1665, 1607, 1577, 1480, 1452, 1315, 1269, 1206, 1120, 1014 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{24}H_{16}O_3F_3$: 409.10461 found: 409.10487.

(*r*)-Cyclopropane-1,2,3-triyltris(thiophen-2-ylmethanone) (245t)

Compound **245t** was obtained by using the general procedure I. The product was isolated by column chromatography with silica gel. Eluent: acetone/petroleum ether (5:95 v/v); light yellow amorphous solid with 52% yield;



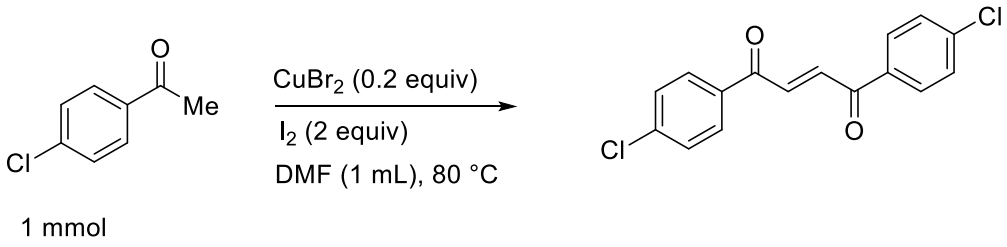
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 3.8, 0.8 Hz, 1H), 7.82 (dd, *J* = 3.8, 0.8 Hz, 2H), 7.74 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.62 (d, *J* = 0.9 Hz, 2H), 7.21 – 7.15 (m, 1H), 7.09 (dd, *J* = 4.9, 3.9 Hz, 2H), 4.10 (t, *J* = 5.5 Hz, 1H), 3.64 ppm (d, *J* = 5.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.18, 184.97, 143.71, 143.64, 135.40, 134.54, 134.15, 132.86, 128.78, 128.36, 36.39, 30.65 ppm.

FT-IR: $\tilde{\nu}$ = 3097, 2927, 1722, 1637, 1512, 1408, 1352, 1316, 1235, 1216, 1067, 1052 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{18}H_{13}O_3S_3$: 373.00213 found: 373.00249.

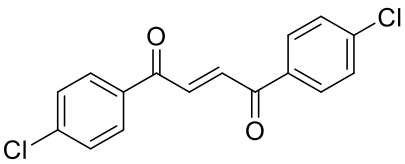
12.10.2 Synthesis of Compound 247[216]



1 mmol

228b **247**

To a sealed tube (25 mL) was added 4-chloroacetophenone **228b** (1 mmol), $CuBr_2$ (0.2 mmol), I_2 (2 mmol) and dry DMF (1 mL). Then the mixture was heated to 80 ºC for 20 h. Afterward, the reaction mixture was cooled to room temperature, saturated $Na_2S_2O_4$ (15 mL) was added. The resulting mixture was extracted with diethyl ether (3 × 10 mL). The combined organic phase was dried with Na_2SO_4. The reaction mixture was concentrated and purified by column chromatography using silica gel (100-200 mesh) and petroleum ether /ethyl acetate as eluent (95:5 v/v).



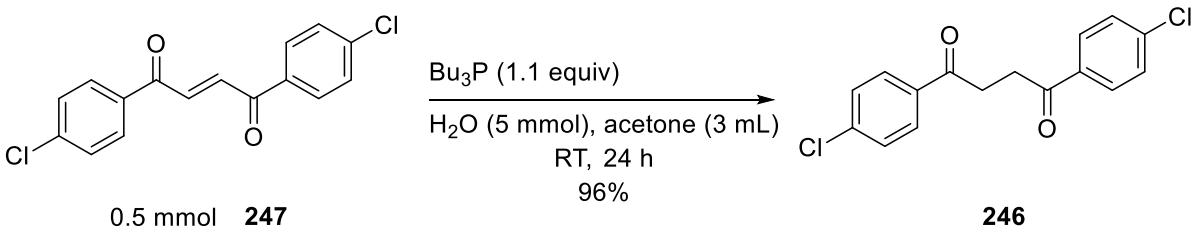
(*E*)-1,4-Bis(4-chlorophenyl)but-2-ene-1,4-dione

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (d, *J* = 8.7 Hz, 4H), 7.97 (s, 2H), 7.51 ppm (d, *J* = 8.7 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.48, 140.76, 135.28, 135.03, 130.40, 129.47 ppm.

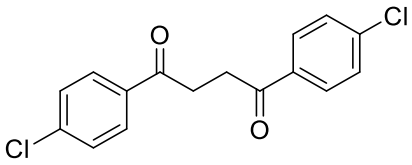
12.10.3. Synthesis of Compound 246[274]

To a screw cap reaction tube with septum charged with a magnetic stir-bar, PBu_3 (112 mg, 0.55 mmol) was added into a mixture of (*E*)-1,4-Bis(4-chlorophenyl)but-2-ene-1,4-dione **249**



0.5 mmol **247** **246**

(152 mg, 0.5 mmol) and H_2O (90 mg, 5.0 mmol) in 3 mL of acetone under argon. Reaction mixture stirred vigorously at room temperature for 24 h. The crude reaction mixture was concentrated under reduced pressure and subsequently purified by flash column chromatography over silica gel using petroleum ether/ethyl acetate as eluent system (150 mg, 95%).

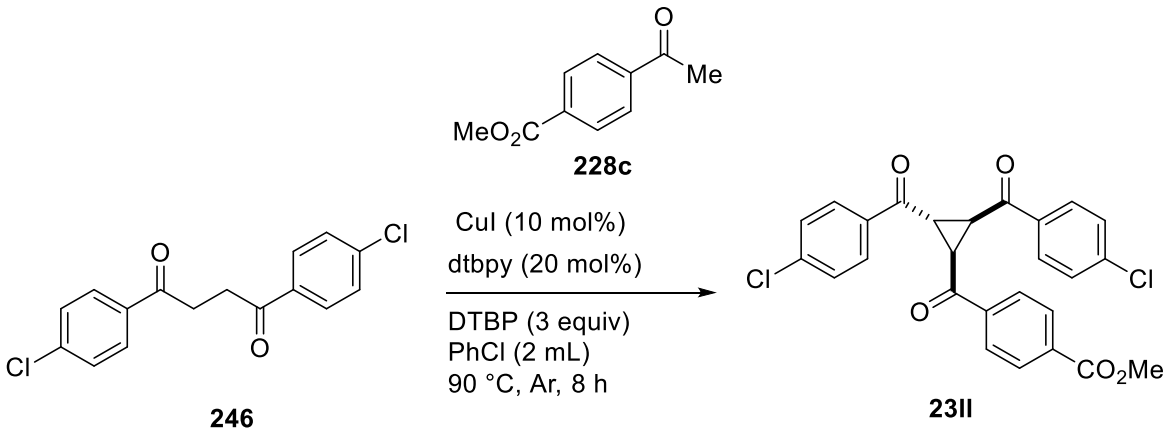


1,4-Bis(4-chlorophenyl)butane-1,4-dione

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.6 Hz, 4H), 7.38 (d, *J* = 8.6 Hz, 4H), 3.40 ppm (s, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 197.41, 139.75, 135.05, 129.63, 129.04, 32.54 ppm.

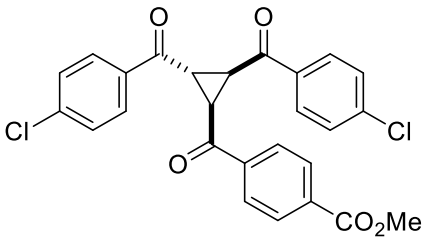
12.10.4. Synthesis of Compound 231l



To a screw cap reaction vial charged with a magnetic stir-bar 1,4-bis(4-chlorophenyl)butane-1,4-dionee **248** (0.25 mmol, 1 equiv), 4-acetylbenzoate (0.375 mmol, 1.5 equiv), CuI (10 mol%), dtbpy **L5** (20 mol%) were added. The vial was then evacuated and back-filled with argon. This evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, 2 mL of degased chlorobenzene and DTBP (3 equiv) were added by syringe.

The reaction mixture was allowed to warm up to 90 °C and was stirred vigorously for 8 h. Then the reaction mixture was cooled to room temperature. To the reaction mixture was added dichloromethane (15 mL), washed with HCl (1N) for two times, dried over Na_2SO_4 and evaporated in vacuum to afford the crude product, which was purified by column chromatography using silica gel (100-200 mesh) and petroleum ether / acetone as eluent. The pure isolated product was light yellow amorphous with 64% yield.

Methyl 4-((2*S*,3*S*)-2,3-bis(4-chlorobenzoyl)cyclopropane-1-carbonyl)benzoate (247)



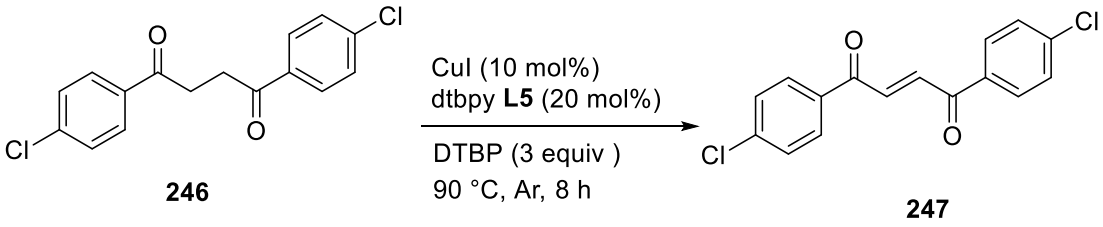
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 2H), 8.09 (d, *J* = 8.6 Hz, 2H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 4.15 (t, *J* = 5.6 Hz, 1H), 3.93 (s, 3H), 3.73 ppm (d, *J* = 5.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.47, 192.54, 191.70, 166.12, 140.89, 140.51, 139.53, 134.75, 134.70, 134.56, 130.29, 130.09, 129.94, 129.41, 129.27, 128.45, 52.64, 36.45, 36.35, 30.50 ppm.

FT-IR: $\tilde{\nu}$ = 3049, 2952, 1721, 1692, 1666, 1587, 1571, 1452, 1315, 1269, 1176, 1055, 1009 cm^{-1}.

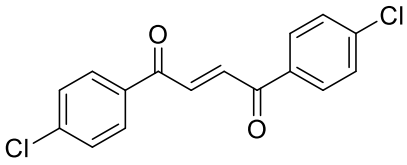
HRMS: calc. for $[M+H]^+$ $C_{26}H_{19}O_5Cl_2$: 481.06041 found: 481.05939.

12.10.5 Control Experiment with 246



To a screw cap reaction vial charged with a magnetic stir-bar, 1,4-bis(4-chlorophenyl)butane-1,4-dione **248** (0.5 mmol), CuI (10 mol%), dtbpy **L5** (20 mol%) were added. The vial was then evacuated and back-filled with argon. This evacuation/back-fill sequence was repeated three additional times. Under a counter flow of argon, 2 mL of degased chlorobenzene and DTBP (3 equiv) were added by syringe. The reaction mixture was allowed to warm up to 90 °C and was stirred vigorously for 8 h. Then the reaction mixture was cooled to room temperature. To the reaction mixture was added dichloromethane (15 mL), washed with HCl (1M) for two times, dried over Na_2SO_4 and evaporated in vacuum to afford the crude product,

which was purified by flash column chromatography using silica gel (100-200 mesh) and petroleum-ether / acetone as eluent (95:5 v/v). The pure isolated product was light yellow amorphous and yield was 92%.



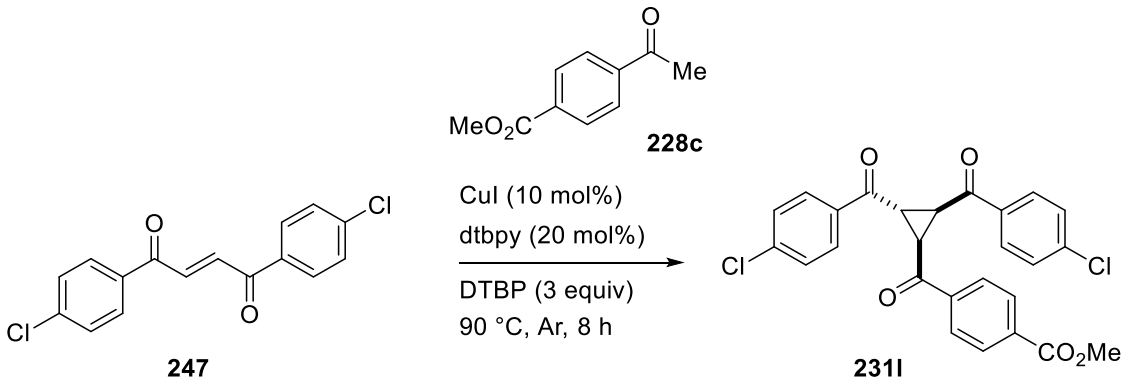
(*E*)-1,4-Bis(4-chlorophenyl)but-2-ene-1,4-dione (247)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.98 (d, *J* = 8.7 Hz, 4H), 7.97 (s, 2H), 7.51 ppm (d, *J* = 8.7 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 188.48, 140.76, 135.28, 135.03, 130.40, 129.47 ppm.

12.10.6 Synthesis of Compound231l with Probable Intermediate 247

To a screw cap reaction vial charged with a magnetic stir-bar, (*E*)-1,4-bis(4-chlorophenyl)but-2-ene-1,4-dione **247** (0.25 mmol, 1 equiv), 4-acetylbenzoate **228d** (0.375 mmol, 1.5 equiv) CuI (10 mol%), dtbpy **L5** (20 mol%) were added. The vial was then evacuated and back-filled with argon. This evacuation/back-fill sequence was repeated three additional times. Under a counter flow of argon, 2 mL of degassed chlorobenzene and DTBP (3 equiv) were added by



syringe. The reaction mixture was allowed to warm up to 90 °C and was stirred vigorously for 8 h. Then the reaction mixture was cooled to room temperature. To the reaction mixture was added dichloromethane (15 mL), washed by 1 M HCl for two times, dried over Na_2SO_4 and evaporated in vacuum to afford the crude product which was purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether / acetone (95;5 v/v) as the eluent. The pure isolated product was light yellow amorphous and its yield was 82%.

Methyl 4-((2*S*, 3*S*)-2,3-bis(4-chlorobenzoyl)cyclopropane-1-carbonyl)benzoate (231l)

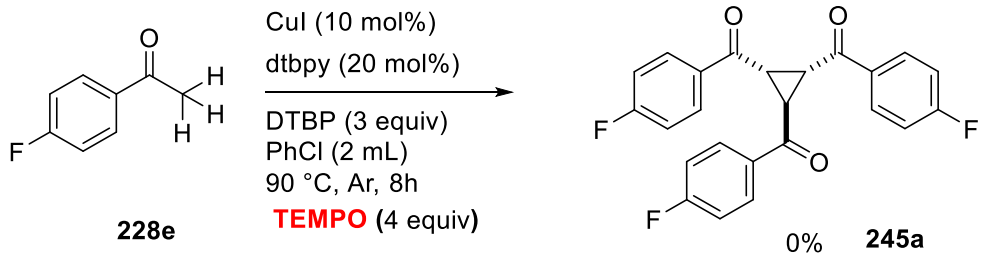
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 2H), 8.09 (d, *J* = 8.6 Hz, 2H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.92 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 4.15 (t, *J* = 5.6 Hz, 1H), 3.93 (s, 3H), 3.73 ppm (d, *J* = 5.6 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.47, 192.54, 191.70, 166.12, 140.89, 140.51, 139.53, 134.75, 134.70, 134.56, 130.29, 130.09, 129.94, 129.41, 129.27, 128.45, 52.64, 36.45, 36.35, 30.50 ppm.

FT-IR: $\tilde{\nu}$ = 3049, 2952, 1721, 1692, 1666, 1587, 1571, 1452, 1315, 1269, 1176, 1055, 1009 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{26}H_{19}O_5Cl_2$: 481.06041 found: 481.05939.

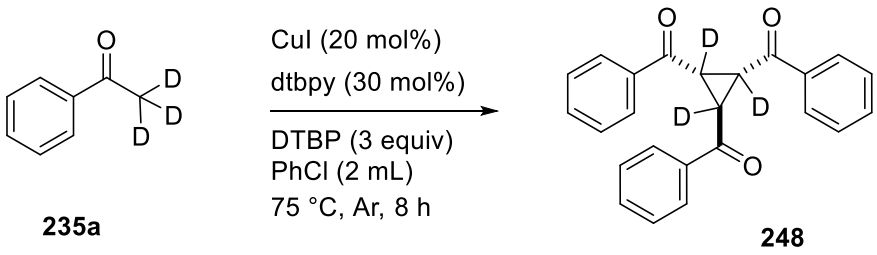
12.10.7 Procedure for Radical Inhibition Test



To a screw cap reaction vial charged with a magnetic stir-bar, 4-fluoroacetophenone **228e** (0.5 mmol), CuI (10 mol%), dtbpy **L5** (20 mol%) and 4 equiv TEMPO **16** were added. The vial was then evacuated and back-filled with argon. This evacuation/back-fill sequence was repeated three additional times. Under a counter flow of argon, 2 mL of degassed chlorobenzene and DTBP (3 equiv) were added. The reaction mixture was allowed to warm up to 90 °C and was stirred vigorously for 8 h. Then the reaction mixture was cooled to room temperature. Ethyl acetate (2 mL) was added for dilution of reaction mixture. Finally, the reaction mixture was checked by GC-MS analysis and we did not observe the desired product.

12.10.8 Procedure for the Reaction of 2,2,2-[$^{2}H_3$]-1-Phenylethan-1-one (235a)

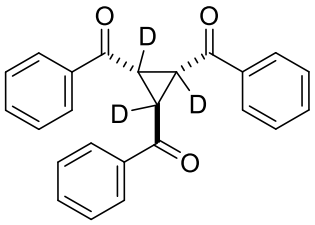
To a screw cap reaction vial charged with a magnetic stir-bar, 2,2,2-[$^{2}H_3$]-1-phenylethan-1-one (0.5 mmol), CuI (20 mol%), dtbpy **L5** (30 mol%) were added. The vial was then evacuated and back-filled with argon. This evacuation/back-fill sequence was repeated three additional times. Under a counter flow of argon, 2 mL of degassed chlorobenzene and DTBP



235a **248**

(3 equiv) were added. The reaction mixture was allowed to warm up to 75 °C and was stirred vigorously for 12 h. Then the reaction mixture was cooled to room temperature. To the reaction mixture was added dichloromethane (15 mL), washed with 1M HCl for two times, dried over Na_2SO_4 and evaporated in vacuum to afford the crude product which was purified by column chromatography using silica gel (100-200 mesh) and petroleum ether/acetone (97:3 v/v). as the eluent and isolated yield was 55%.

(*r*)-(Cyclopropane-1,2,3-triyl-($^2H_3$)tris(phenylmethanone) (248)



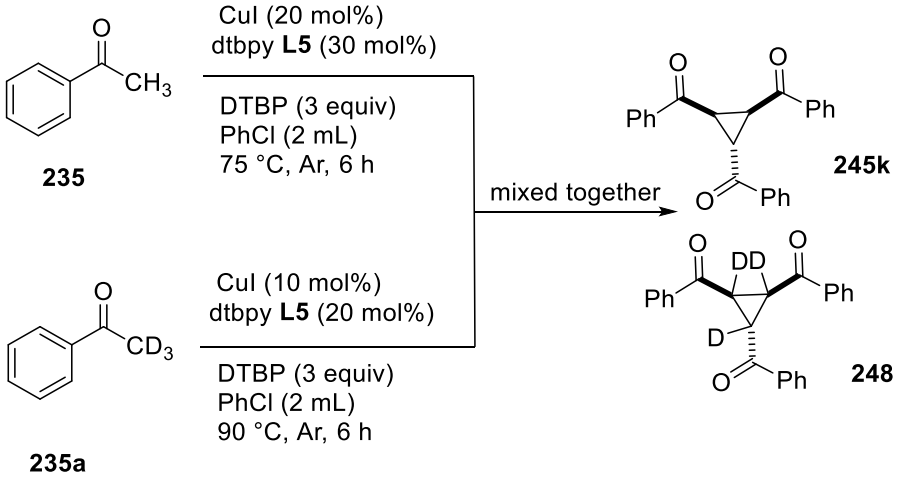
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.17 (m, 2H), 8.11 – 7.96 (m, 4H), 7.63 (dd, *J* = 10.5, 4.3 Hz, 1H), 7.60 – 7.50 (m, 4H), 7.43 ppm (t, *J* = 7.7 Hz, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.01, 192.96, 136.41, 133.93, 133.55, 128.83, 128.75, 128.67, 128.44, 36.10 (t, *J* = 25.1 Hz), 30.10- (t, *J* = 25.1 Hz) ppm.

FT-IR: $\tilde{\nu}$ = 3061, 2969, 1727, 1684, 1663, 1580, 1476, 1320, 1272, 1176, 1046 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{26}H_{16}D_3O_3$: 358.15170 found: 358.15210.

12.10.9 Procedure for Kinetic Isotope Effect (KIE) Study



235 **245k**

235a **248**

k_H/k_D = 1.4

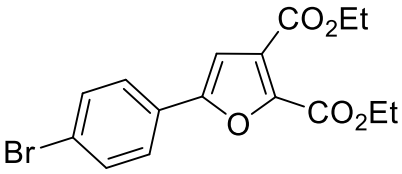
Two reaction vials were set up separately for acetophenone **235** (0.5 mmol) and 2,2,2-[$^{2}H_{3}$]-1-phenylethan-1-one (0.5 mmol) and CuI (20 mol%), dtbpy **L5** (30 mol%) were added to each vial. Then the vial was evacuated and back-filled with argon. This evacuation/back-fill sequence was repeated three additional times. Under a counter flow of argon, 2 mL of degassed chlorobenzene and DTBP (3 equiv) were added by syringe. Then the reaction mixtures were allowed to warm up to 75 °C and stirred vigorously for 6 h. Afterwards, the reaction mixtures were cooled to room temperature and mixed together in a single separation funnel. To the reaction mixture was added dichloromethane (20 mL), washed by 1M HCl for two times, dried over Na_2SO_4 and evaporated in vacuum to afford the crude product, which was purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether/ acetone as the eluent. KIE (k_H/k_D = 1.4) was determined by ^{1}H NMR analysis.

12.11 Copper(I)-Catalyzed (3+2) Oxidative Annulation of Acetophenone with Electron-Deficient Alkyne

12.11.1 Characterization of Furan Derivatives (266a-266w)

Diethyl 5-(4-bromophenyl)furan-2,3-dicarboxylate (266a)[275]

Compound **266a** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (2:98 v/v); light yellow amorphous solid with 70% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.7 Hz, 2H), 7.56 (d, *J* = 8.7 Hz, 2H), 6.97 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.46 – 1.35 ppm (m, 6H).

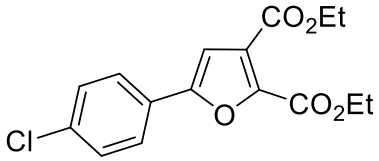
^{13}C NMR (75 MHz, $CDCl_3$) δ 162.48, 157.96, 154.79, 142.96, 132.27, 127.74, 126.46, 125.94, 123.67, 108.10, 61.80, 14.34, 14.29 ppm.

FT-IR: $\tilde{\nu}$ = 3069, 3018, 2985, 1711, 16981, 1594, 1505, 1410, 1322, 1298, 1223, 1154, 1011 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}O_5{}^{79}Br$: 367.01756 found: 367.01833 HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}O_5{}^{81}Br$: 369.01552 found: 369.01633.

Diethyl 5-(4-chlorophenyl)furan-2,3-dicarboxylate (266b)

Compound **266b** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (2:98 v/v); white solid with 75% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 6.98 (s, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.46 – 1.37 ppm (m, 6H).

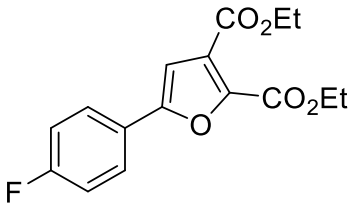
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.50, 157.96, 154.79, 142.98, 135.46, 129.34, 127.37, 126.28, 125.95, 108.01, 61.77, 61.74, 14.35, 14.30 ppm.

FT-IR: $\tilde{\nu}$ = 3067, 2958, 1716, 1664, 1593, 1542, 1449, 1409, 1368, 1304, 1240, 1183, 1140, 1065 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}O_5{}^{35}Cl$: 323.06808 found: 323.06863 HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}O_5{}^{37}Br$: 325.06513found: 325.06566.

Diethyl 5-(4-fluorophenyl)furan-2,3-dicarboxylate (266c)

Compound **266c** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (2:98 v/v); light yellow amorphous solid with 45% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.66 (m, 2H), 7.17 – 7.07 (m, 2H), 6.91 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.44 – 1.34 ppm (m, 6H).

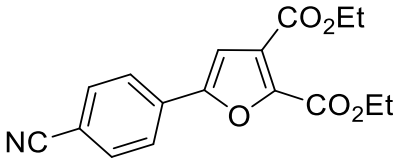
^{13}C NMR (75 MHz, $CDCl_3$) δ 163.24 (d, *J* = 250.1 Hz), 162.45, 157.84, 154.87, 142.51, 126.86 (d, *J* = 8.4 Hz), 125.84, 125.04 (d, *J* = 3.3 Hz), 116.07 (d, *J* = 22.2 Hz), 107.20, 61.56 (x2), 14.18, 14.12 ppm.

FT-IR: $\tilde{\nu}$ = 3066, 2980, 1692, 1602, 1542, 1492, 1424, 1314, 1248, 1141, 1072, 1010 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}O_5F$: 307.09820 found: 307.09763.

Diethyl 5-(4-cyanophenyl)furan-2,3-dicarboxylate (266d)

Compound **266d** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (4:96 v/v); white solid with 76% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.12 (s, 1H), 4.47– 4.35 (m, 4H), 1.43– 1.37 ppm (m, 6H).

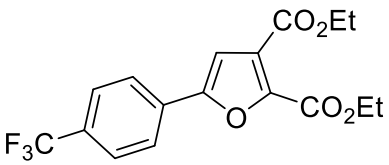
^{13}C NMR (75 MHz, $CDCl_3$) δ 162.12, 157.75, 153.40, 144.03, 132.90, 132.65, 125.81, 125.30, 118.50, 112.66, 110.20, 62.04, 61.90, 14.32, 14.28 ppm.

FT-IR: $\tilde{\nu}$ = 3124, 2984, 2230, 1692, 1615, 1542, 1492, 1424, 1368, 1306, 1276, 1186, 1108, 1074 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{17}H_{16}O_5N$: 314.10302 found: 314.10230.

Diethyl 5-(4-(trifluoromethyl)phenyl)furan-2,3-dicarboxylate (266e)

Compound **266e** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); light yellow amorphous solid with 66% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.08 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 4.8 Hz, 3H), 1.39 ppm (t, *J* = 4.8 Hz, 3H).

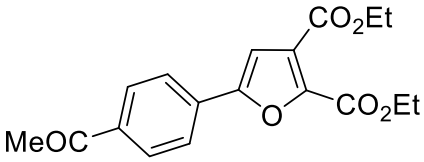
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.30, 157.87, 154.10, 143.67, 132.01, 131.10 (q, *J* = 32.7 Hz), 126.07 (q, *J* = 3.7 Hz), 123.96 (q, *J* = 272.1 Hz), 125.04, 109.30, 61.90, 61.80, 14.31, 14.27 ppm.

FT-IR: $\tilde{\nu}$ = 3119, 2985, 1699, 1619, 1541, 1497, 1423, 1322, 1309, 1164, 1108, 1065 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{17}H_{16}O_5F_3$: 357.09443 found: 357.09548.

Diethyl 5-(4-acetylphenyl)furan-2,3-dicarboxylate (3f)

Compound **266f** was obtained by using the general procedure J from 1,4-diacetylbenzene (0.75 mmol). The product was isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); white amorphous solid with 67% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.09 (s, 1H), 4.53 – 4.29 (m, 4H), 2.62 (s, 3H), 1.43 – 1.36 ppm (m, 6H).

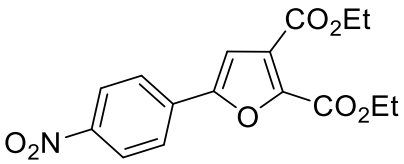
^{13}C NMR (75 MHz, $CDCl_3$) δ 197.33, 162.32, 157.89, 154.44, 143.60, 137.25, 132.71, 129.09, 125.86, 124.95, 109.57, 61.90, 61.79, 26.79, 14.31, 14.27 ppm.

FT-IR: $\tilde{\nu}$ = 3112, 2984, 1713, 1679, 1609, 1538, 1487, 1442, 1297, 1241, 1187, 1064, 1020 cm^{-1}.

MS-EI: m/z (%):) 201,0(13); 243,0 (32); 285,0 (15); 330,0 (100); 331,0 (19).

Diethyl 5-(4-nitrophenyl)furan-2,3-dicarboxylate (266g)

Compound **266g** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); yellow amorphous solid with 78% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 – 8.19 (m, 2H), 7.94 – 7.77 (m, 2H), 7.16 (s, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.47 – 1.24 ppm (m, 6H).

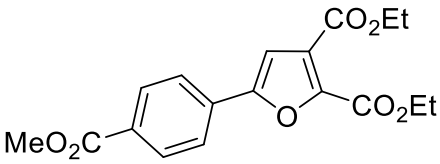
^{13}C NMR (126 MHz, $CDCl_3$) δ 161.99, 157.70, 153.06, 147.93, 144.40, 134.37, 125.82, 125.49, 124.50, 110.76, 62.06, 61.88, 14.29, 14.25 ppm.

FT-IR: $\tilde{\nu}$ = 3122, 2988, 1715, 1605, 1517, 1478, 1384, 1340, 1297, 1243, 1190, 1065, 1017 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}O_7N$: 334.09303 found: 334.09213.

Diethyl 5-(4-(methoxycarbonyl)phenyl)furan-2,3-dicarboxylate (266h)

Compound **2h** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); light yellow amorphous solid with 65% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.08 (s, 1H), 4.51 – 4.26 (m, 4H), 3.92 (s, 3H), 1.46 – 1.32 ppm (m, 6H).

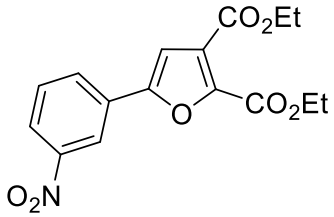
^{13}C NMR (75 MHz, $CDCl_3$) δ 166.51, 162.33, 157.89, 154.55, 143.53, 132.65, 130.60, 130.32, 125.85, 124.76, 109.43, 61.87, 61.77, 52.41, 14.32, 14.27 ppm.

FT-IR: $\tilde{\nu}$ = 3122, 2986, 1716, 1613, 1541, 1491, 1433, 1251, 1177, 1143, 1107, 1065 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{18}H_{19}O_7$: 347.11253 found: 347.11320.

Diethyl 5-(3-nitrophenyl)furan-2,3-dicarboxylate (266i)

Compound **266i** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); light yellow amorphous solid with 56% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 – 8.40 (m, 1H), 8.21 – 8.12 (m, 1H), 8.04 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.11 (s, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 5.8 Hz, 3H), 1.37 ppm (t, *J* = 5.8 Hz, 3H).

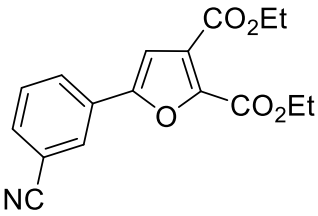
^{13}C NMR (126 MHz, $CDCl_3$) δ 161.96, 157.62, 152.92, 148.79, 143.82, 130.32, 130.18, 125.72, 123.69, 119.65, 109.53, 61.92, 61.77, 14.23, 14.18 ppm.

FT-IR: $\tilde{\nu}$ = 3090, 2987, 1716, 1692, 1522, 1473, 1349, 1299, 1246, 1195, 1148, 1110, 1063 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{16}O_7N$: 334.09213found: 334.09306.

Diethyl 5-(3-cyanophenyl)furan-2,3-dicarboxylate (266j)

Compound **266j** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); white amorphous solid with 72% yield.



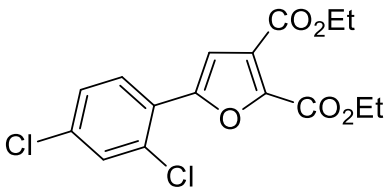
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.05 (s, 1H), 4.46 – 4.31 (m, 4H), 1.43 – 1.34 ppm (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.11, 157.71, 153.07, 143.70, 136.11, 132.47, 129.99, 128.83, 128.29, 125.78, 118.18, 113.53, 109.23, 61.98, 61.84, 14.30, 14.24 ppm.

FT-IR: $\tilde{\nu}$ = 3112, 2984, 2230, 1709, 1597, 1535, 1471, 1438, 1259, 1190, 1148, 1064, 1023 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{17}H_{16}O_5N$: 314.10230 found: 314.10302.

Diethyl 5-(2,4-dichlorophenyl)furan-2,3-dicarboxylate (266k)



Compound **266k** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); light yellow amorphous solid with 52% yield.

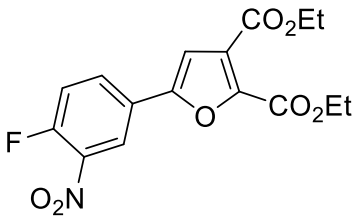
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.40 (s, 1H), 7.33 (dd, *J* = 8.6, 2.0 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.42 – 1.37 ppm (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.38, 157.86, 151.02, 142.82, 135.36, 131.85, 130.75, 129.61, 127.68, 125.97, 125.53, 113.27, 61.88, 61.76, 14.30, 14.28 ppm.

FT-IR: $\tilde{\nu}$ = 2987, 2938, 1724, 1584, 1466, 1404, 1385, 1300, 1241, 1195, 1112, 1067 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{15}O_5{}^{35}Cl_2$: 357.02911 found: 357.03020; calc. for $[M+H]^+$ $C_{16}H_{15}O_5{}^{35}Cl^{37}Cl$: 359.02616 found: 359.02698 calc. for $[M+H]^+$ $C_{16}H_{15}O_5{}^{37}Cl_2$: 361.02321 found: 361.02344.

Diethyl 5-(4-fluoro-3-nitrophenyl)furan-2,3-dicarboxylate (266l)



Compound **266l** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (2:98 v/v); light yellow amorphous solid with 56% yield.

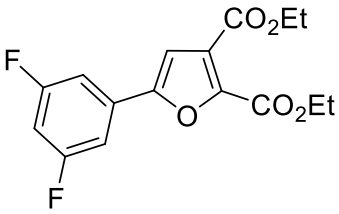
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 6.8, 2.1 Hz, 1H), 8.01 (ddd, *J* = 8.7, 3.9, 2.3 Hz, 1H), 7.44 – 7.33 (m, 1H), 7.07 (s, 1H), 4.46 – 4.34 (m, 4H), 1.50 – 1.26 ppm (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.97, 157.65, 155.60 (d, *J* = 268.3 Hz), 152.02, 143.90, 137.84, 131.49 (d, *J* = 8.8 Hz), 126.05 (d, *J* = 4.3 Hz), 125.82, 122.49, 119.54 (d, *J* = 21.7 Hz), 109.36, 62.06, 61.91, 14.29, 14.24 ppm.

FT-IR: $\tilde{\nu}$ = 3113, 2995, 1716, 1601, 1533, 1487, 1423, 1360, 1318, 1249, 1195, 1162, 1018 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{15}O_7NF$: 352.08324 found: 352.08271.

Diethyl 5-(3,5-difluorophenyl)furan-2,3-dicarboxylate (266m)



Compound **266m** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (2:98 v/v); yellow amorphous solid with 61% yield.

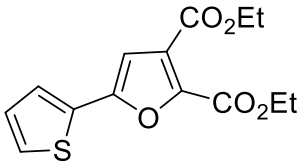
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 2H), 7.00 (s, 1H), 6.85 – 6.74 (m, 1H), 4.44 – 4.33 (m, 4H), 1.42 – 1.33 ppm (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.54 (d, *J* = 249.2 Hz), 162.14, 163.37 (d, *J* = 249.2 Hz), 157.72, 153.21, 143.54, 131.57 (t, *J* = 10.5 Hz), 125.72, 109.35, 108.13, 107.77, 104.73 (t, *J* = 25.4 Hz), 61.93, 61.81, 14.28, 14.24 ppm.

FT-IR: $\tilde{\nu}$ = 3119, 2995, 1708, 1622, 1589, 1442, 1497, 1368, 1302, 1226, 1177, 1116, 1054 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{16}H_{15}O_5F_2$: 325.08821 found: 325.08900.

Diethyl 5-(thiophen-2-yl)furan-2,3-dicarboxylate (266n)



Compound **2n** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (3:97 v/v); reddish liquid with 48% yield.

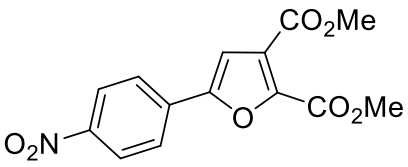
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.36 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.07 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.80 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.45 – 1.34 ppm (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.47, 157.87, 151.44, 142.09, 131.31, 128.12, 126.99, 126.03, 125.85, 107.41, 61.70, 14.32, 14.26 ppm.

FT-IR: $\tilde{\nu}$ = 3120, 2954, 2927, 1716, 1612, 1599, 1487, 1455, 1387, 1301, 1242, 1180, 1140, 1063 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{15}O_5S$: 295.06347 found: 295.06355.

Dimethyl 5-(4-nitrophenyl)furan-2,3-dicarboxylate (266o)



Compound **266o** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); yellow amorphous solid with 66% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 – 8.02 (m, 2H), 7.97 – 7.67 (m, 2H), 7.17 (s, 1H), 3.96 (s, 3H), 3.91 ppm (s, 3H).

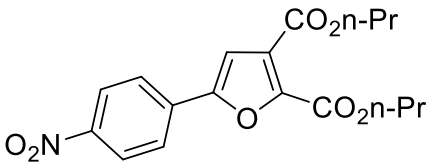
^{13}C NMR (75 MHz, $CDCl_3$) δ 162.22, 157.98, 153.15, 147.90, 144.19, 134.20, 125.65, 125.49, 124.51, 110.85, 52.83, 52.79 ppm.

FT-IR: $\tilde{\nu}$ = 3110, 2949, 1716, 1601, 1446, 1514, 1441, 1342, 1292, 1255, 1197, 1136, 1067 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{12}O_7N$: 306.06083 found: 306.06150.

Dipropyl 5-(4-nitrophenyl)furan-2,3-dicarboxylate (266s)

Compound **266s** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); light yellow solid with 76% yield.



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 – 8.26 (m, 2H), 7.95 – 7.88 (m, *J* = 9.0 Hz, 2H), 7.17 (s, 1H), 4.34 (t, *J* = 6.7 Hz, 2H), 4.29 (t, *J* = 6.7 Hz, 2H), 1.85 – 1.72 (m, 4H), 1.05 – 1.00 ppm (m, 6H).

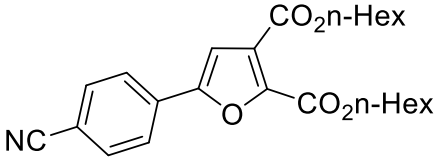
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.08, 157.82, 153.06, 147.96, 144.43, 134.43, 125.82, 125.51, 124.54, 110.75, 67.62, 67.50, 22.13, 22.09, 10.55, 10.51 ppm.

FT-IR: $\tilde{\nu}$ = 3115, 2966, 1708, 1604, 1619, 1514, 1341, 1315, 1293, 1245, 1178, 1149, 1069 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{18}H_{20}O_7N$: 362.12343 found: 362.12429.

Dihexyl 5-(4-cyanophenyl)furan-2,3-dicarboxylate (266t)

Compound **266t** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (2:98 v/v); light yellow semi solid with 72% yield.



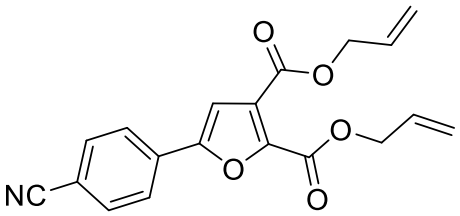
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.10 (s, 1H), 4.36 (t, *J* = 6.8 Hz, 2H), 4.31 (t, *J* = 6.8 Hz, 2H), 1.81 – 1.67 (m, 4H), 1.44 – 1.40 (m, 4H), 1.37 – 1.29 (m, 8H), 0.90 ppm (t, *J* = 6.0 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.16, 157.83, 153.37, 144.12, 132.90, 132.73, 125.80, 125.30, 118.47, 112.71, 110.15, 66.18, 66.09, 31.57, 31.55, 28.66, 25.72, 25.65, 22.67, 14.12 ppm.

FT-IR: $\tilde{\nu}$ = 2955, 2929, 2858, 2228, 1718, 1612, 1487, 1419, 1268, 1242, 1182, 1142, 1067 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{14}H_{12}O_7N$: 426.22750 found: 426.22830.

Diallyl 5-(4-cyanophenyl)furan-2,3-dicarboxylate (266u)



Compound **266u** was obtained by using the general procedure J and isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); yellow amorphous solid with 51% yield.

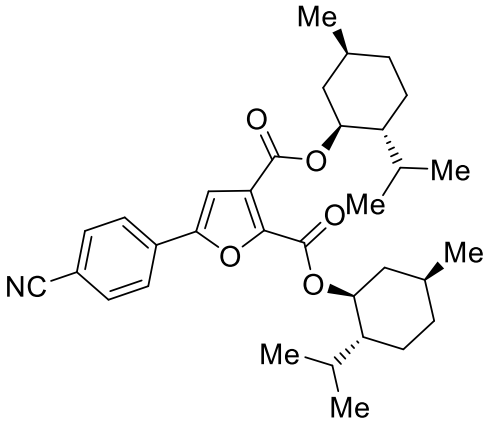
^{1}H NMR (500 MHz, $CDCl_3$) 7.86 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.14 (s, 1H), 6.12 – 5.93 (m, 2H), 5.50 – 5.34 (m, 2H), 5.33 – 5.21 (m, 2H), 4.88 – 4.84 (m, 2H), 7.95 – 7.78 ppm (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.62, 157.32, 153.64, 143.94, 132.92, 132.57, 131.63, 131.46, 125.72, 125.35, 119.39, 119.27, 118.43, 112.84, 110.28, 66.49 ppm.

FT-IR: $\tilde{\nu}$ = 3123, 2948, 2227, 1716, 1693, 16539, 1488, 1419, 1363, 1301, 1271, 1181, 1145, 1074 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{19}H_{16}O_5N$: 338.10230 found: 338.10324.

Bis-((1*S*, 2*R*, 5*S*)-2-isopropyl-5-methylcyclohexyl)-5-(4-cyanophenyl)furan-2,3-dicarboxylate (266u)



Compound **266u** was obtained by using the general procedure J from bis((1*S*, 2*R*, 5*S*)-2-isopropyl-5-methylcyclohexyl) but-2-ynedioate (0.25 mmol) and 4-cyanoacetophenone (1.0 mmol). The product was isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); white amorphous solid with 80% yield.

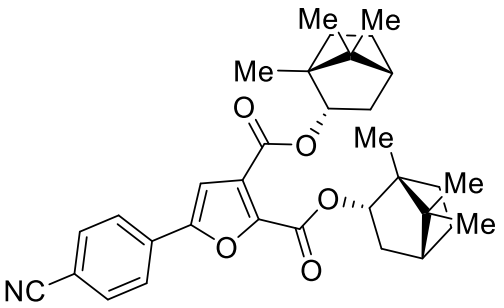
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.08 (s, 1H), 4.98 (td, *J* = 10.9, 4.5 Hz, 1H), 4.93 (td, *J* = 10.9, 4.4 Hz, 1H), 2.20 – 2.11 (m, 2H), 2.01 – 1.91 (m, 2H), 1.73 (dt, *J* = 4.6, 3.2 Hz, 4H), 1.60 – 1.51 (m, 5H), 1.22 – 1.08 (m, 5H), 0.96 – 0.93 (m, *J* = 6.5, 4.2 Hz, 6H), 0.92 (d, *J* = 1.5 Hz, 3H), 0.91 (d, *J* = 1.5 Hz, 3H), 0.82 (d, *J* = 1.9 Hz, 3H), 0.81 ppm (d, *J* = 1.9 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 161.64, 157.47, 153.17, 144.19, 132.86, 132.82, 125.86, 125.29, 118.52, 112.56, 110.20, 76.35, 76.00, 47.13, 47.11, 40.91, 40.77, 34.37, 31.62, 31.60, 26.47, 26.41, 23.67, 23.61, 22.20, 22.17, 20.93, 20.89, 16.54, 16.53 ppm.

FT-IR: $\tilde{\nu}$ = 2954, 2226, 2869, 2228, 1719, 1612, 1541, 1487, 1418, 1243, 1180, 1142, 1066 cm^{-1}.

HRMS: calc. for $[M+H]^+$ $C_{33}H_{44}O_5N$: 534.32140 found: 534.32238.

Bis((1*R*, 2*S*, 4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-5-(4-cyanophenyl)furan-2,3-dicarboxylate (266w)



Compound **266w** was obtained by using the general procedure J from bis((1*R*, 2*S*, 4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) but-2-ynedioate (0.25 mmol) and 4-cyanoacetophenone (1.0 mmol). The product was isolated by column chromatography with silica gel. Eluent: ethyl acetate/petroleum ether (5:95 v/v); white amorphous solid with 47% yield.

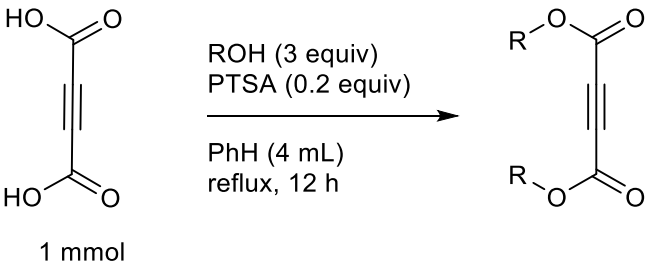
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.09 – 7.06 (m, 1H), 5.16 (ddd, *J* = 10.0, 3.2, 2.2 Hz, 1H), 5.13 (ddd, *J* = 9.9, 3.2, 2.2 Hz, 1H), 2.53 – 2.43 (m, 2H), 2.13 – 2.07 (m, 1H), 2.02 – 1.98 (m, 1H), 1.83 – 1.75 (m, 2H), 1.74 (d, *J* = 3.6 Hz, 2H), 1.40 – 1.28 (m, 3H), 1.18 (ddd, *J* = 14.6, 7.1, 3.9 Hz, 3H), 0.96 (s, 6H), 0.93 (d, *J* = 6.4 Hz, 6H), 0.91 ppm (d, *J* = 3.6 Hz, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.19, 158.10, 153.08, 144.67, 132.99, 132.94, 126.04, 125.32, 118.61, 112.65, 110.04, 82.25, 81.82, 57.01, 49.38, 49.23, 48.19, 45.14, 45.13, 36.96, 36.82, 28.24, 28.23, 27.48, 27.44, 19.94, 19.93, 19.13, 19.11, 13.82, 13.77 ppm.

FT-IR: $\tilde{\nu}$ = 2952, 2875, 2228, 1722, 1612, 1541, 1487, 1418, 1304, 1245, 1185, 1146, 1067 cm^{-1}.

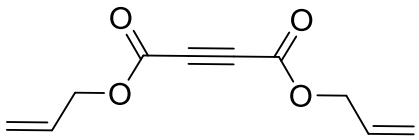
HRMS: calc. for $[M+H]^+$ $C_{33}H_{40}O_5N$: 530.29010 found: 530.29045.

12.11.2 Synthesis of Acetylendicarboxylic Acid Esters[276]



To the round bottom flask, acetylenedicarboxylic acid (1 mmol), corresponding alcohol (3 equiv.) and *p*-toluenesulfonic acid (0.2 equiv) in benzene (4 mL) was refluxed using a Dean–Stark trap apparatus for 12 h. The reaction mixture was concentrated and the products were

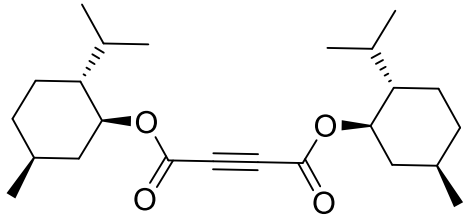
isolated by column chromatography using silica gel (100-200 mesh) and petroleum-ether/ acetone as eluent.



Diallyl but-2-ynedioate

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (t, *J* = 6.8 Hz, 4H), 2.57 (td, *J* = 6.8, 2.7 Hz, 4H), 2.02 ppm (t, *J* = 2.7 Hz, 2H).

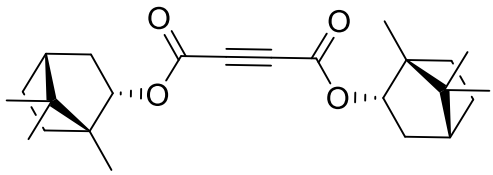
^{13}C NMR (126 MHz, $CDCl_3$) δ 151.39, 79.00, 74.83, 70.72, 64.39, 18.76 ppm.



Bis(2-isopropyl-5-methylcyclohexyl) but-2-ynedioate

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (dd, *J* = 3.3, 2.1 Hz, 1H), 4.90 (dd, *J* = 3.3, 2.0 Hz, 1H), 2.36 – 2.18 (m, 2H), 1.94 – 1.79 (m, 2H), 1.72 – 1.60 (m, 2H), 1.55 – 1.48 (m, 2H), 1.26 – 1.15 (m, 4H), 0.80 (s, 6H), 0.78 (s, 6H), 0.77 (s, 6H), 0.74 – 0.67 ppm (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.58, 83.60, 49.16, 48.14, 44.88, 36.56, 28.02, 27.10, 19.80, 18.92, 13.57 ppm.

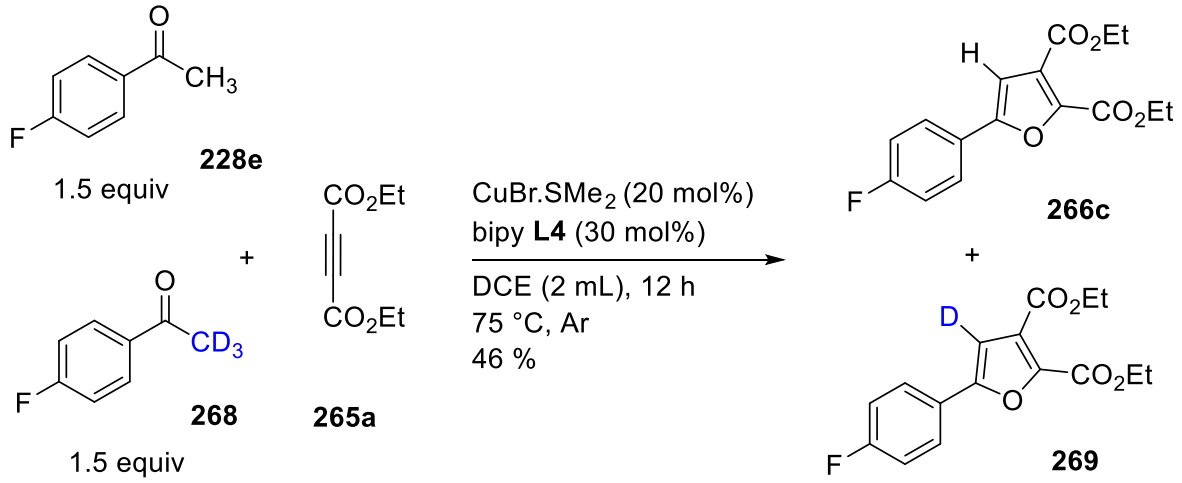


Bis((2S)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) but-2-ynedioate

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 – 4.74 (m, 2H), 2.02 (d, *J* = 11.9 Hz, 2H), 1.94 – 1.79 (m, 2H), 1.69 (d, *J* = 11.6 Hz, 4H), 1.46 (d, *J* = 11.5 Hz, 3H), 1.16 – 1.02 (m, 3H), 0.93 – 0.8 (m, 12H), 0.76 ppm (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.80, 77.80, 75.00, 46.89, 40.55, 34.08, 31.59, 26.16, 23.31, 22.05, 20.85, 16.19 ppm.

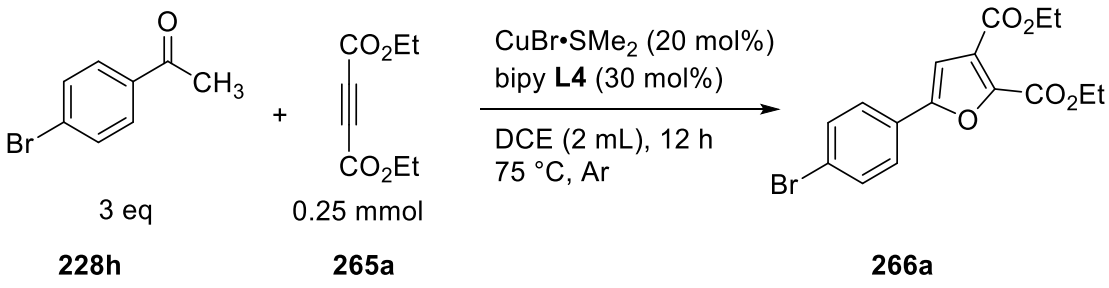
12.11.3 Procedure for Kinetic Isotope Effect (KIE) Study



$k_H/k_D \approx 4.5$

To a screw cap reaction tube with septum charged with a magnetic stir-bar, CuBr·SMe_2 (20 mol%) and bipy **L4** (30 mol%) were added. The tube was then evacuated and back-filled with argon. This evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, diethyl but-2-ynedioate (0.25 mmol), 2,2,2-[$^2H_3$]-1-(4-fluorophenyl)ethan-1-one(1,5 equiv), 1-(4-fluorophenyl)ethan-1-one (1.5 equiv) and solvent (2 mL of degased 1,2-dichloroethane) were added. The resulting mixture was then degassed by freezing in liquid nitrogen, replacing the atmosphere with argon and allowing warming to room temperature (repeated two times). Then DTBP (3 equiv) was added. The reaction mixture was allowed to warm up to 75 °C and stirred vigorously for completion of reaction (12 h). Then the reaction mixture was cooled to room temperature. Dichloromethane (4 mL) and ethyl acetate (2 mL) were added and the reaction mixture was filtered through celite. Afterwards, the reaction mixture was concentrated and purified by column chromatography using silica gel (100-200 mesh) and petroleum-ether/ethyl acetate as eluent. KIE (k_H/k_D = 4.5) was determined from ^{1}H NMR.

12.11.4 Procedure for Radical Trapping Experiment



To a screw cap reaction tube with septum charged with a magnetic stir-bar, 4-bromo-acetophenone **228h** (0.75 mmol), radical quencher (0.5 mmol), $CuBr{\cdot}SMe_2$ (20 mol%) and bipy **L4** (30 mol%) were added. The tube was then evacuated and back-filled with argon. This evacuation/backfill sequence was repeated three additional times. Under a counter flow of argon, diethyl but-2-ynedioate (0.25 mmol) and solvent (2 mL of degassed 1,2-dichloroethane) were added. The resulting mixture was then degassed by freezing in liquid nitrogen, replacing the atmosphere with argon and allowing warming to room temperature (repeated two times). Then DTBP (3 equiv) was added. The reaction mixture was allowed to warm up to 75 °C and stirred vigorously for completion of reaction (12 h). Then the reaction mixture was cooled to room temperature and diluted with ethyl acetate (2 mL). Finally, the reaction mixture was analyzed by GC-MS and the desired product was not found.

Entry	**Additive**	**Yield (%)**
1	none	68
2	TEMPO (**16**)	
3	(*Z*)-*N*-*tert*-butyl-1-phenylmethanimine oxide y (**270**)	n.d.
3	2,6-di-*tert*-butylphenol (**271**)	n.d.

13 Biological Methods

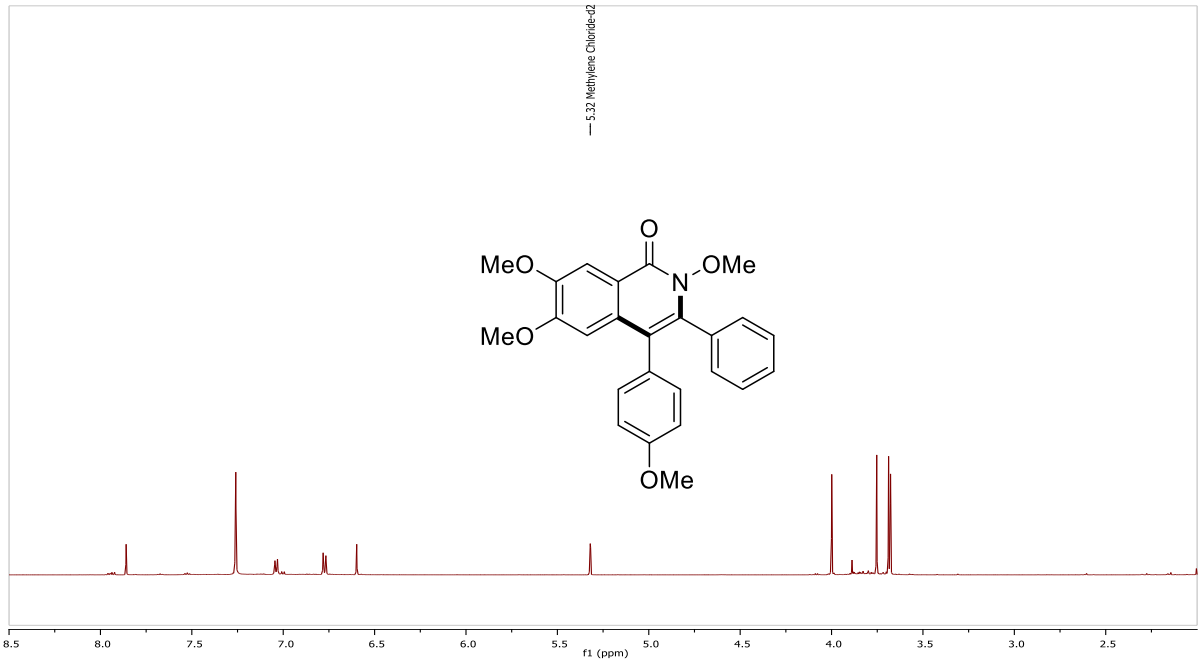
The hedgehog signaling inhibition and cell viability

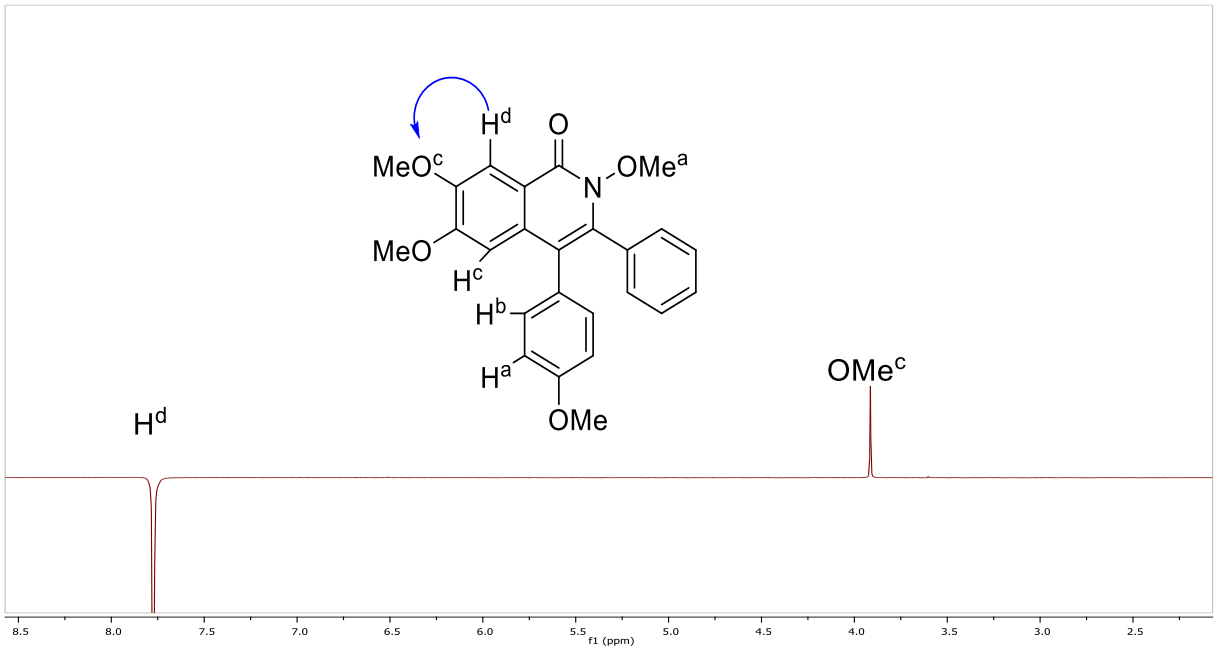
To assay the signal transduction through the Hh pathway mouse embryonic mesoderm fibroblast C3H10T1/2 cells were used. These multipotent mesenchymal progenitor cells can differentiate into osteoblasts upon treatment with the Smoothened agonist Purmorphamine. During differentiation osteoblast specific genes such as alkaline phosphatase (ALK), which plays an essential role in bone formation, are highly expressed. Activity of ALK can directly be monitored by following substrate hydrolysis yielding a highly luminescent product. Inhibition of the pathway results in reduction of luminescence.[277-279]

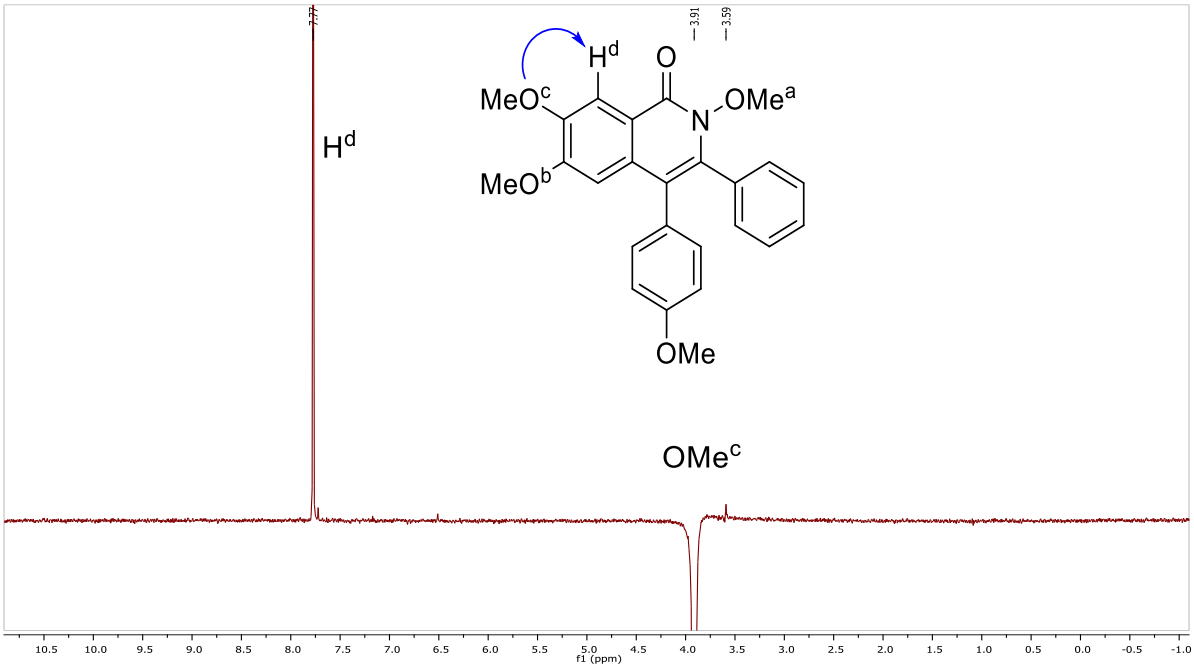
The screening for small molecule inhibitors of the Hh pathway was carried out in 384 well formats. Shortly, 800 cells per well were seeded and allowed to grow overnight. The next day, compounds were added to a final concentration of 10µ M using the acoustic nanoliter dispenser ECHO 520. After one hour, Purmorphamine was added to a final concentration of 1.5 µ M; control cells did not receive Purmorphamine. After four days, the cell culture medium was aspirated and a commercial luminogenic ALK substrate (CDP-Star, Roche) was added. After one hour, luminescence was read. To identify and exclude toxic compounds that also lead to a reduction in the luminescent signal, cell viability measurements were carried out in parallel. The cell viability assay followed the same workflow as the Hh assay, except that only 200 cells per well were seeded. Cell culture medium alone served as control for the cell viability assay. For the measurement of cell viability, Cell Titer Glo reagent (Promega) which determines the cellular ATP content was used. Hits were scored as showing at least a 50% reduction in the luminescent signal in the Hh assay, and a minimum of 80% cell viability. Dose-response analysis for hit compounds was done using a three-fold dilution curve starting from 30 µ M. IC_{50} values were calculated using the Quattro software suite
(Quattro Research GmbH).

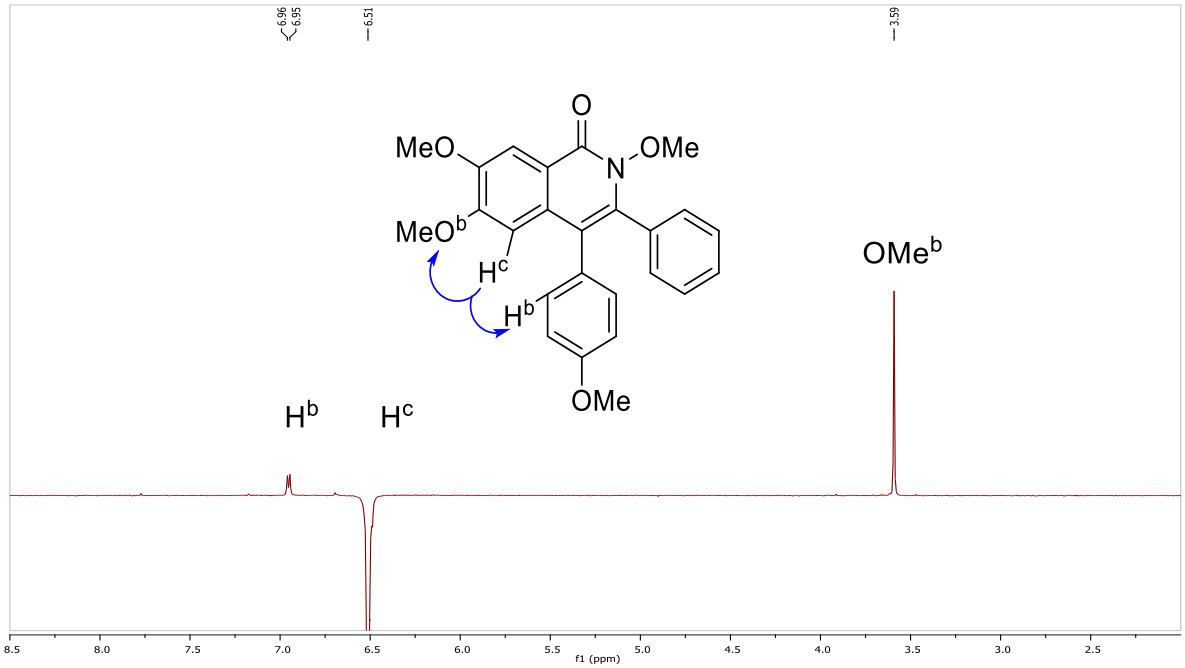
14 Selected NMR Spectra

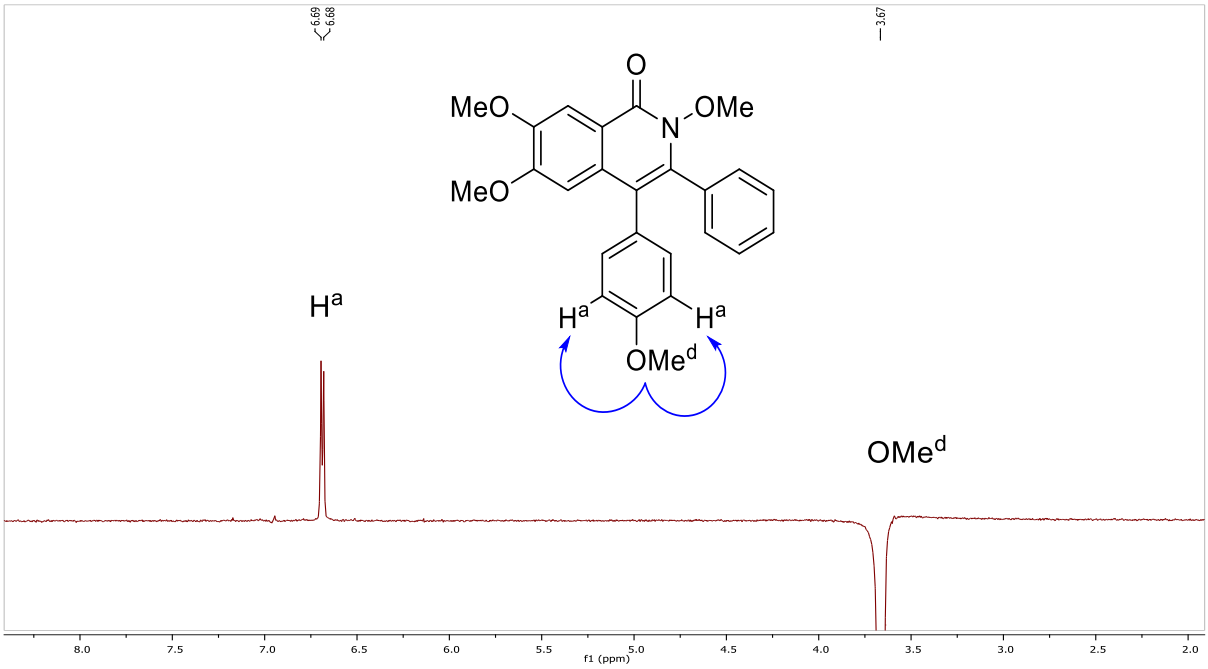
1-D NOE Spectra of Product 137h

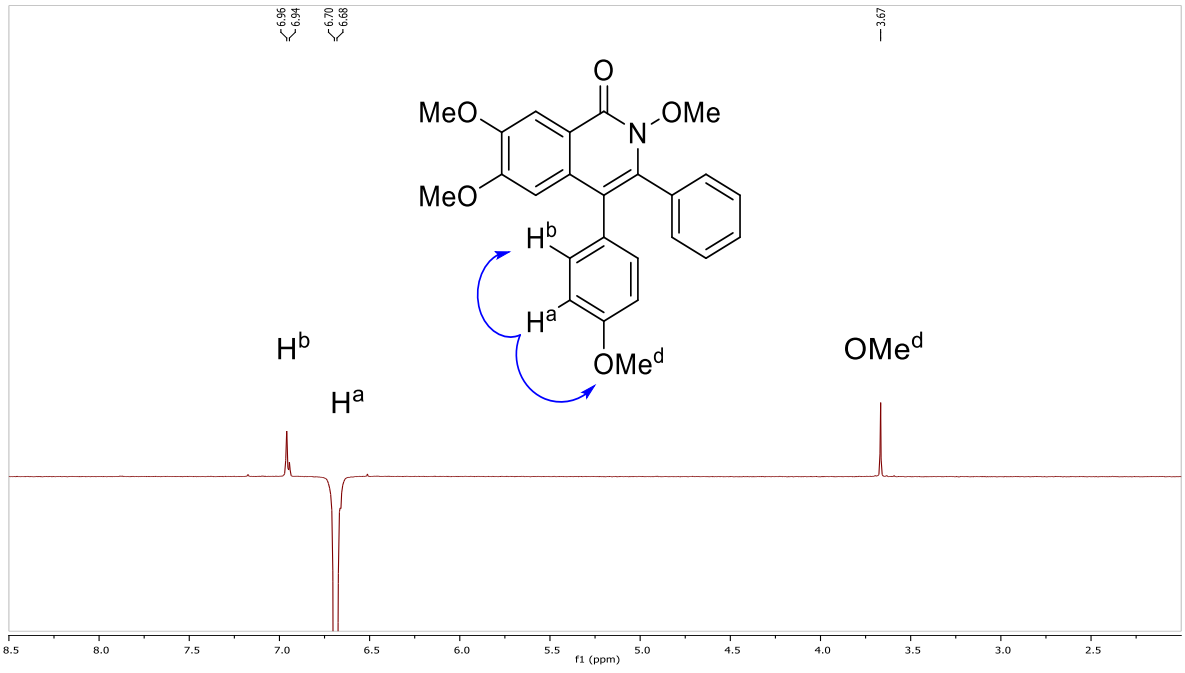




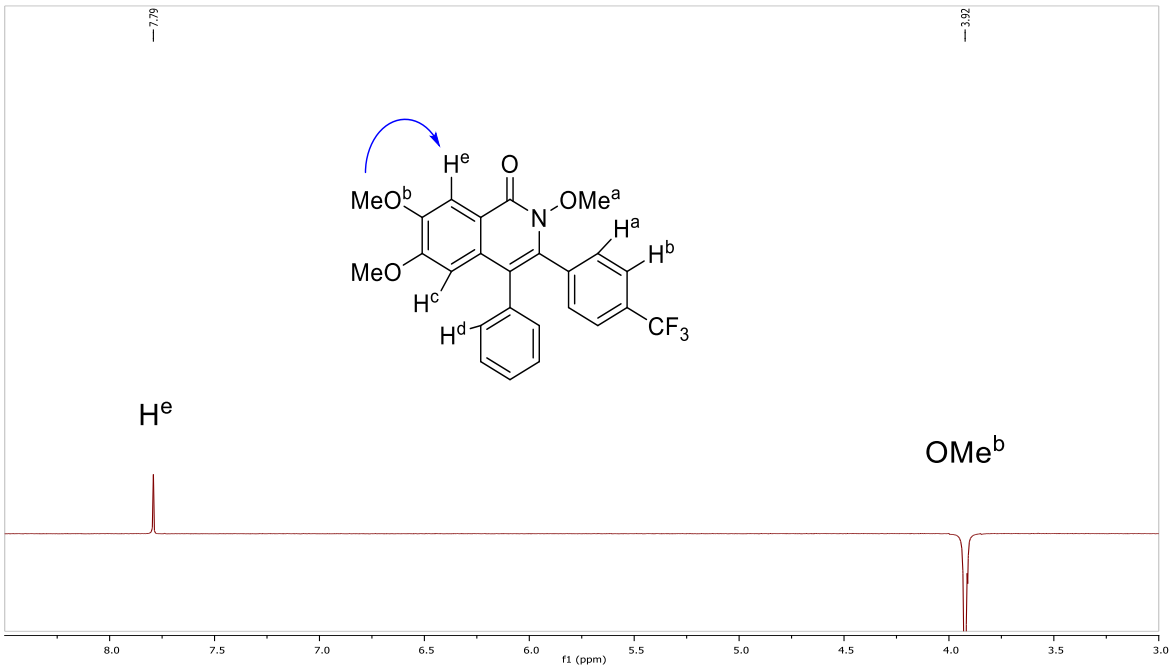

7.77
3.91
3.59
H^d
MeO^c
H^d
O
N
OMe^a
MeO^b
OMe
OMe^c
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

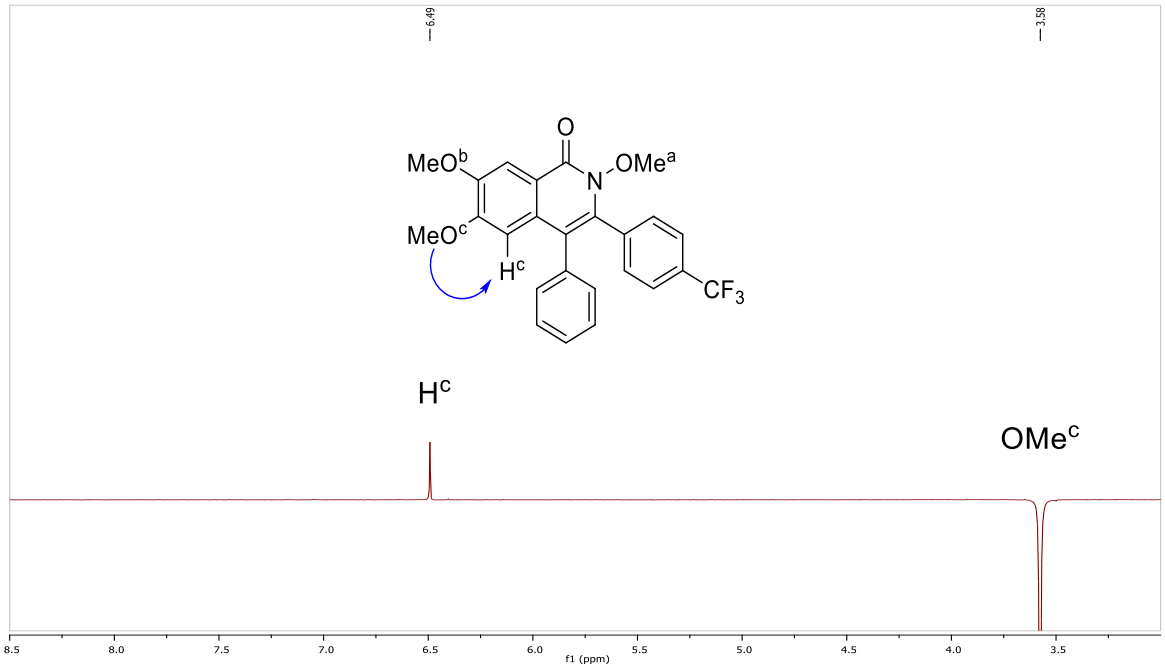

6.96
6.95
6.51
3.59
O
MeO
N
OMe
MeO^b
H^c
H^b
OMe
OMe^b
H^b
H^c
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5
f1 (ppm)

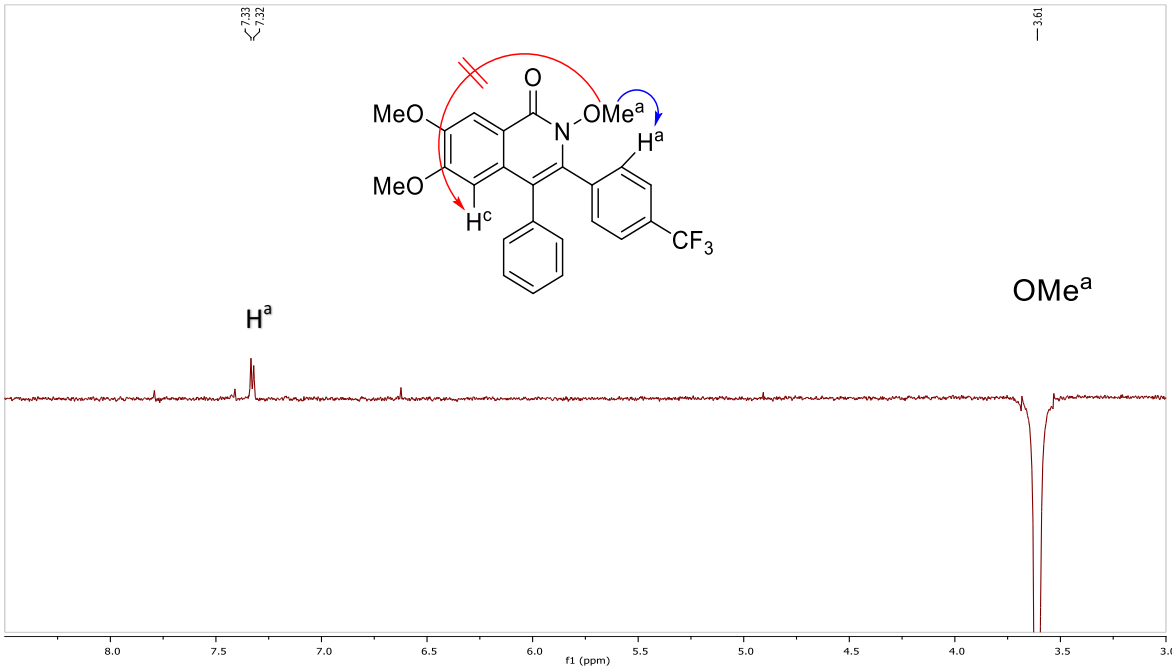

6.69
6.68
3.67
O
MeO
OMe
N
MeO
Ha
Ha
Ha
OMed
Ha
OMed
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

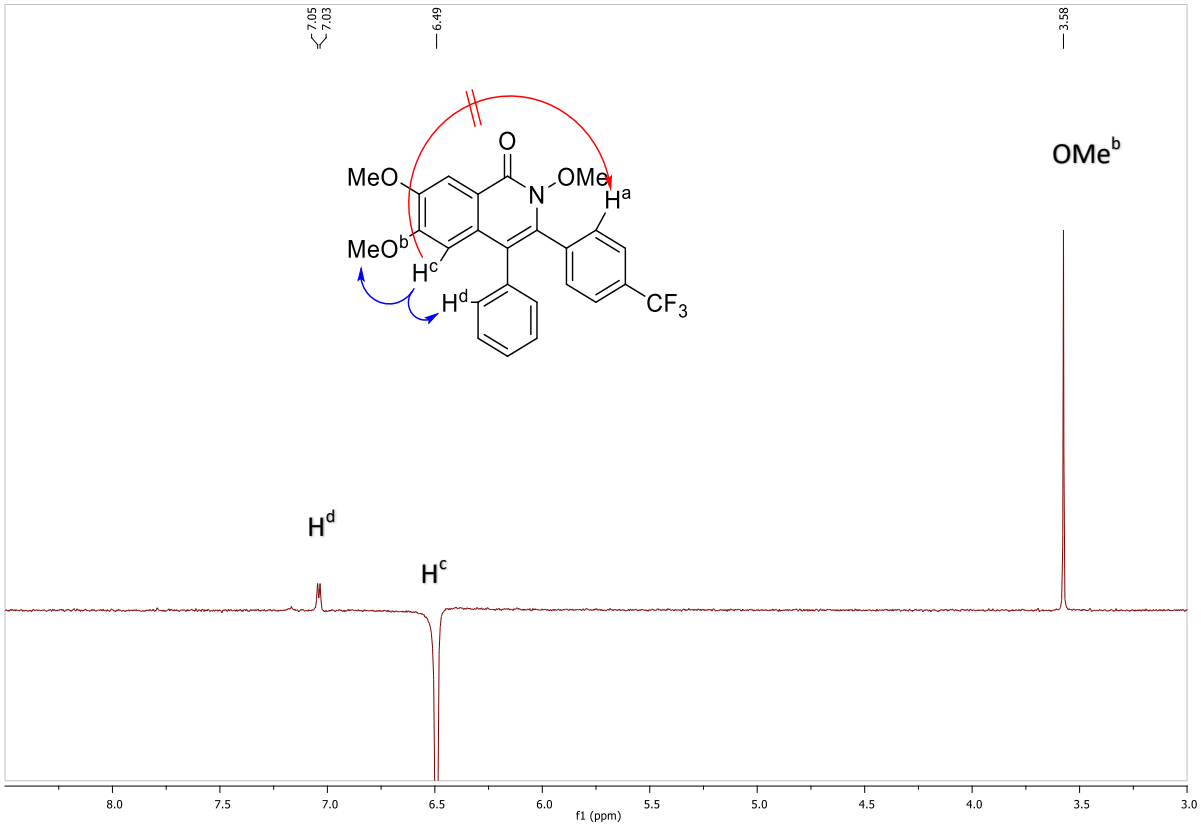

6.96
6.94
6.70
6.68
3.67
O
MeO
OMe
N
MeO
Hb
Ha
OMed
Hb
Ha
OMed
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
f1 (ppm)

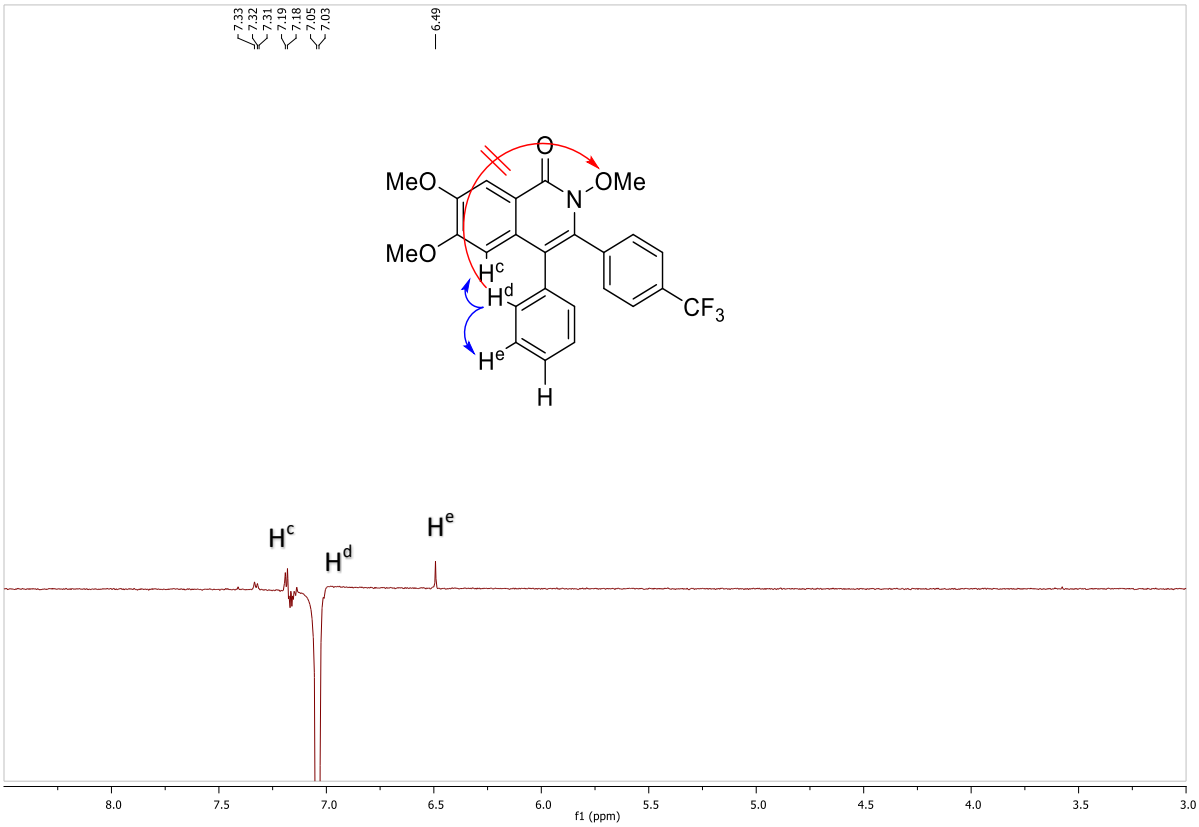
1-D NOE Spectra of Product 137d



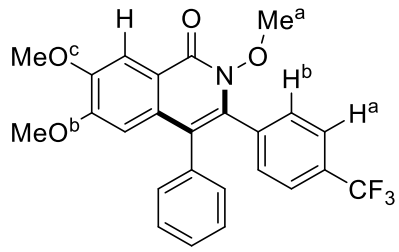


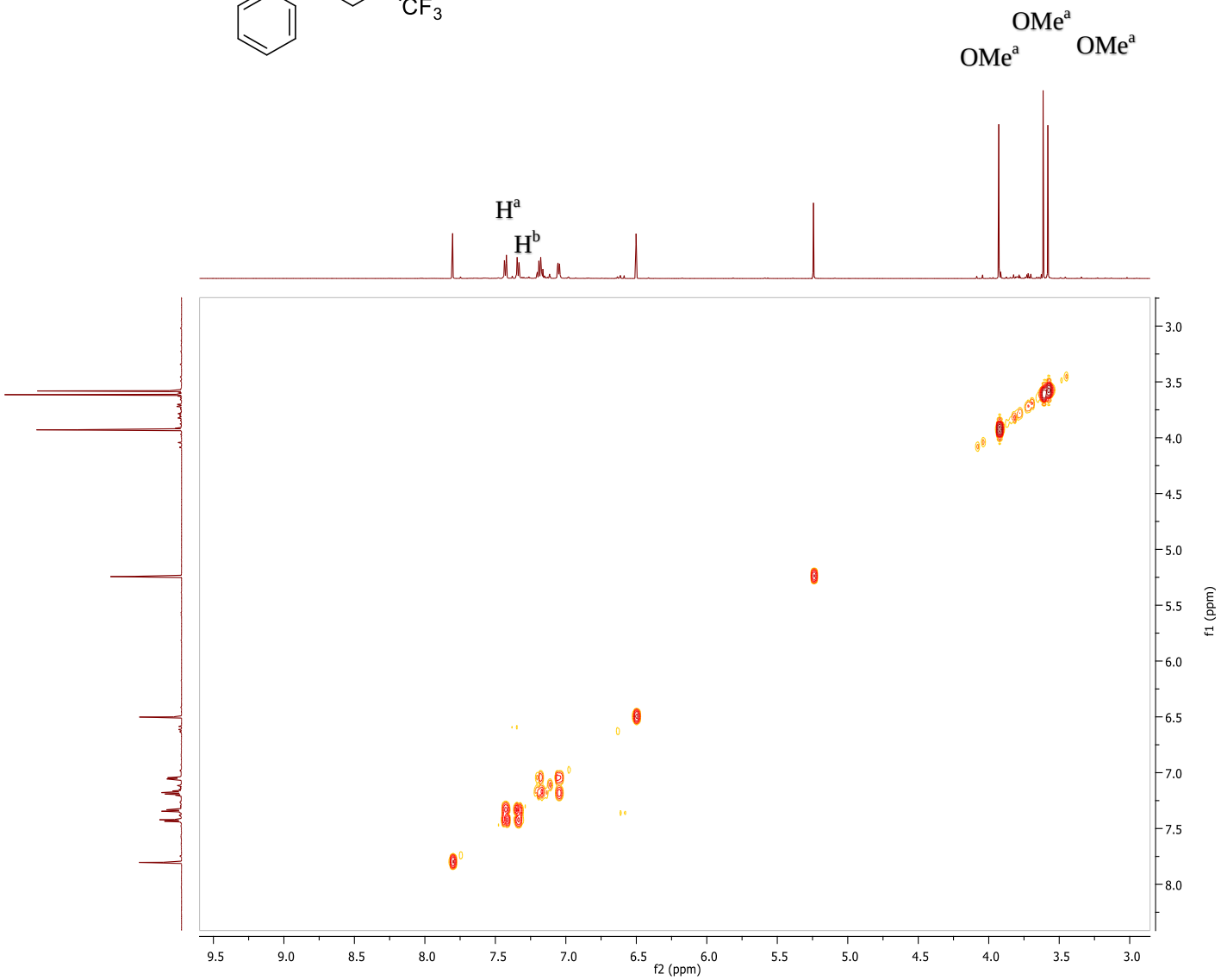

7.33
7.32
3.61
MeO
MeO
O
N
OMe^a
H^a
H^c
CF3
OMe^a
H^a
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
f1 (ppm)

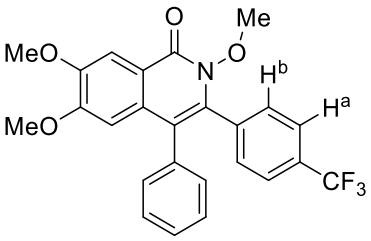

7.05
7.03
6.49
3.58
MeO
MeO^b
O
N
OMe
H^a
H^c
H^d
CF3
OMe^b
H^d
H^c
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
f1 (ppm)

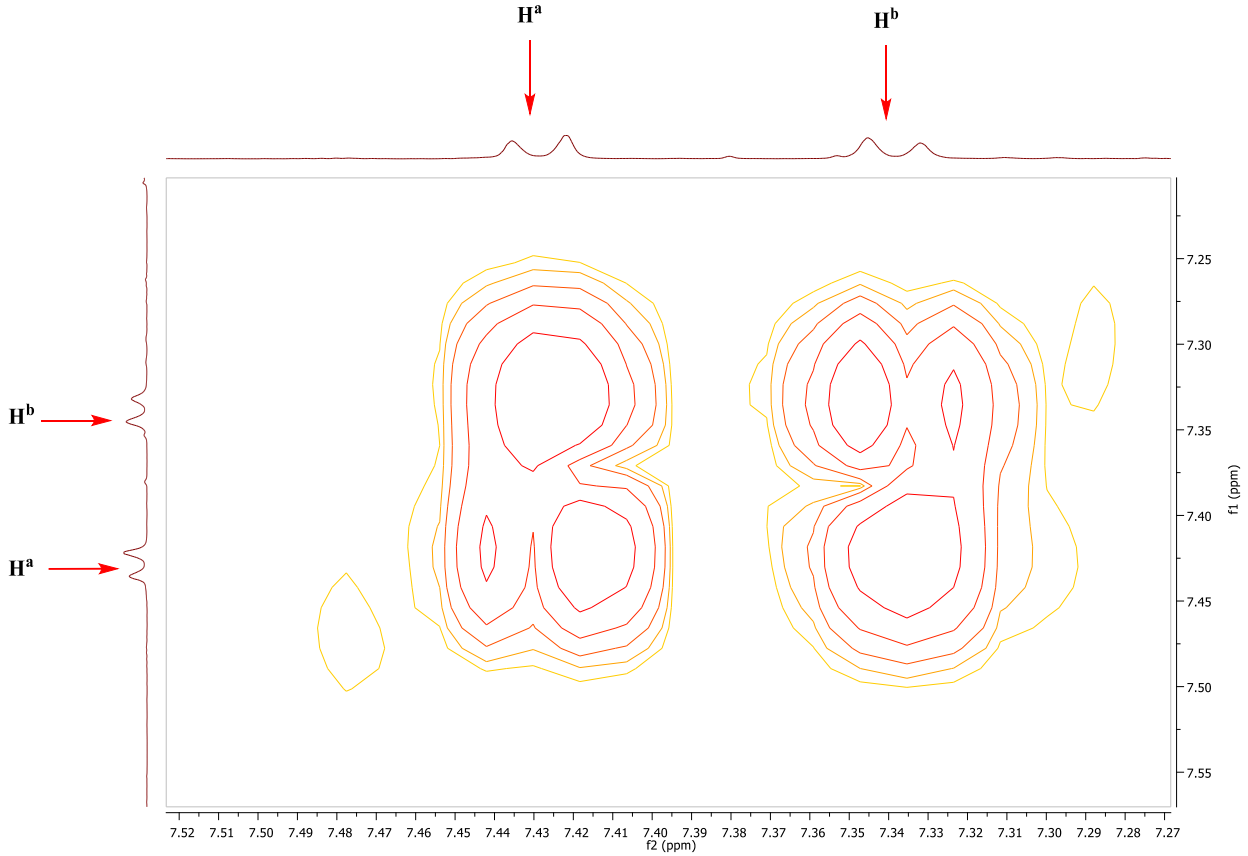

7.33
7.32
7.31
7.19
7.18
7.05
7.03
6.49
MeO
MeO
O
N
OMe
CF3
Hc
Hd
He
H
Hc
Hd
He
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
f1 (ppm)

2-D COSY Spectra for the Product 137d

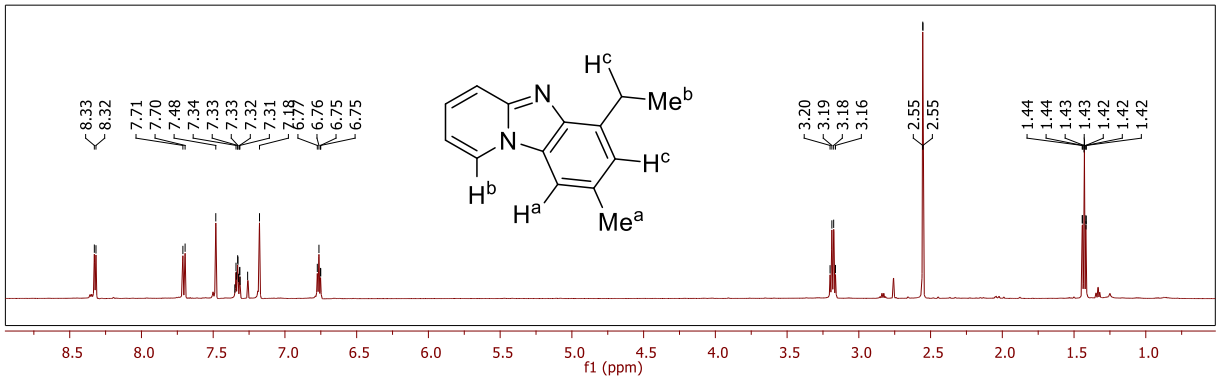


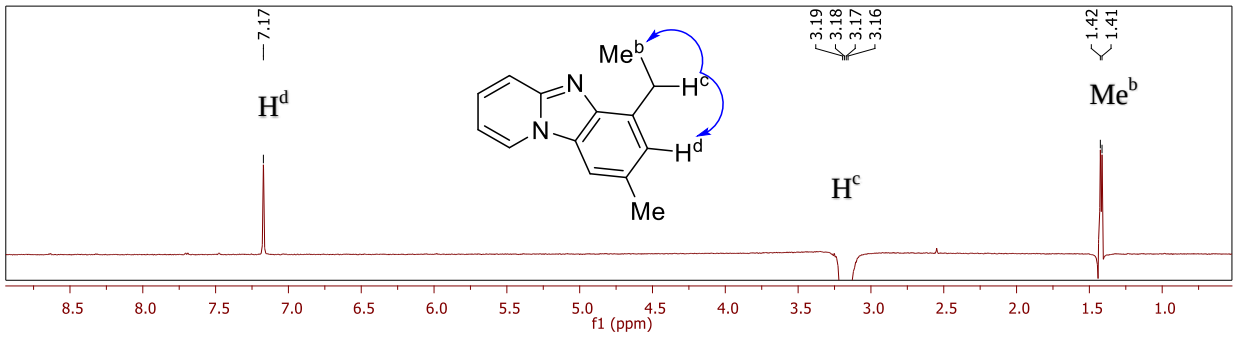


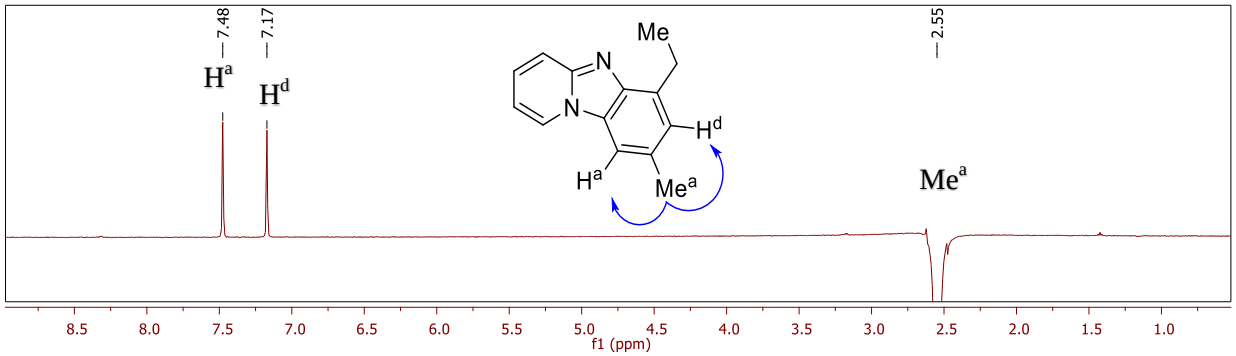

O
Me
MeO
N
O
H^b
H^a
MeO
CF3

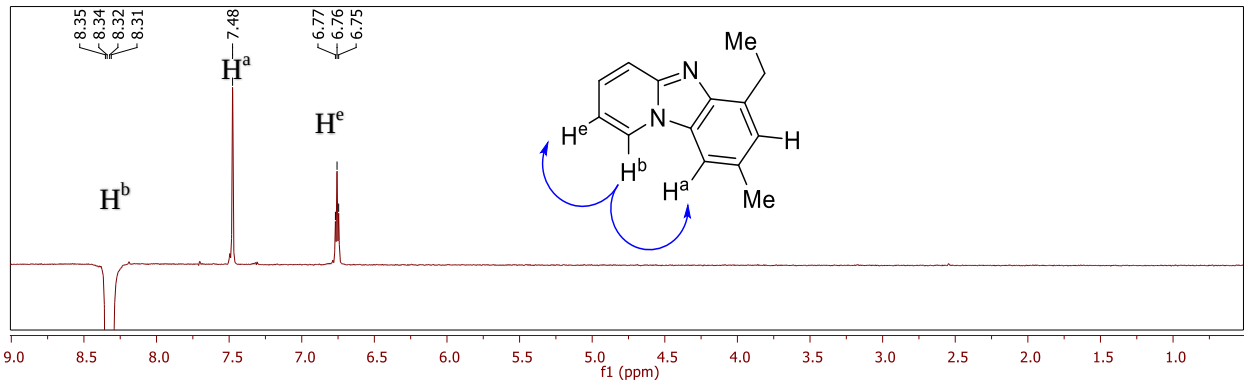

H^a
H^b
H^b
H^a
7.25
7.30
7.35
7.40
7.45
7.50
7.55
f1 (ppm)
7.52 7.51 7.50 7.49 7.48 7.47 7.46 7.45 7.44 7.43 7.42 7.41 7.40 7.39 7.38 7.37 7.36 7.35 7.34 7.33 7.32 7.31 7.30 7.29 7.28 7.27
f2 (ppm)

1-D NOE Spectra of Product 151i

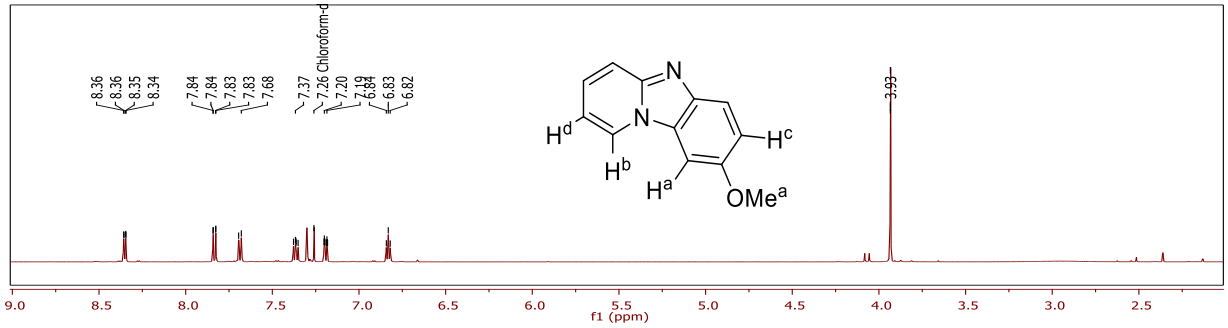


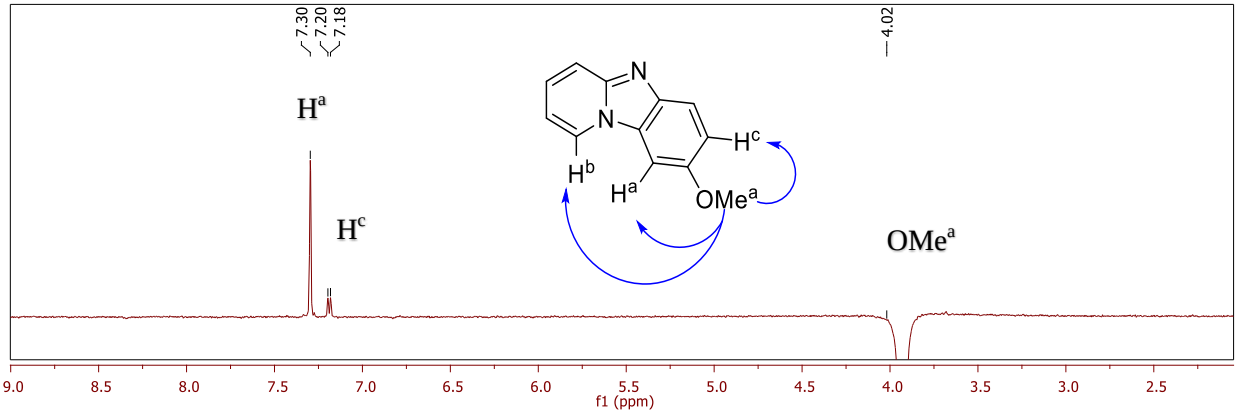


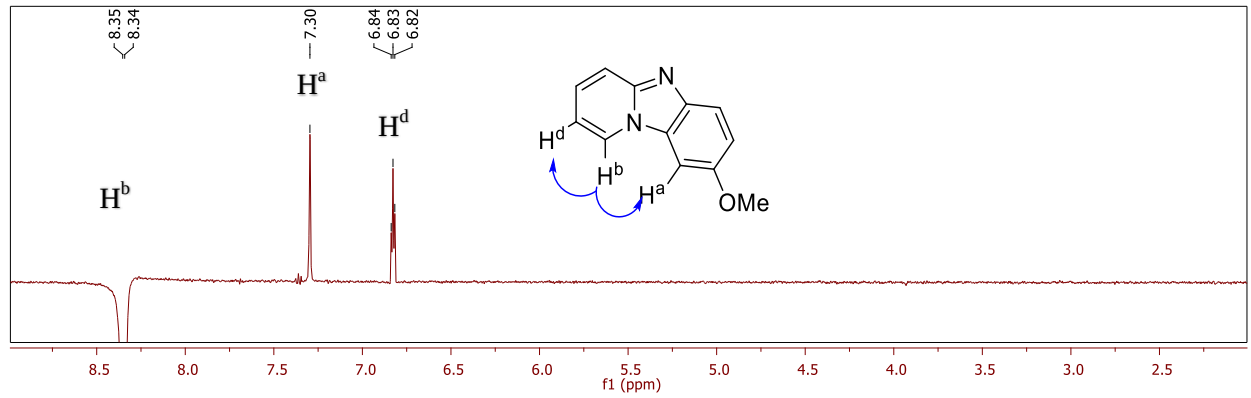




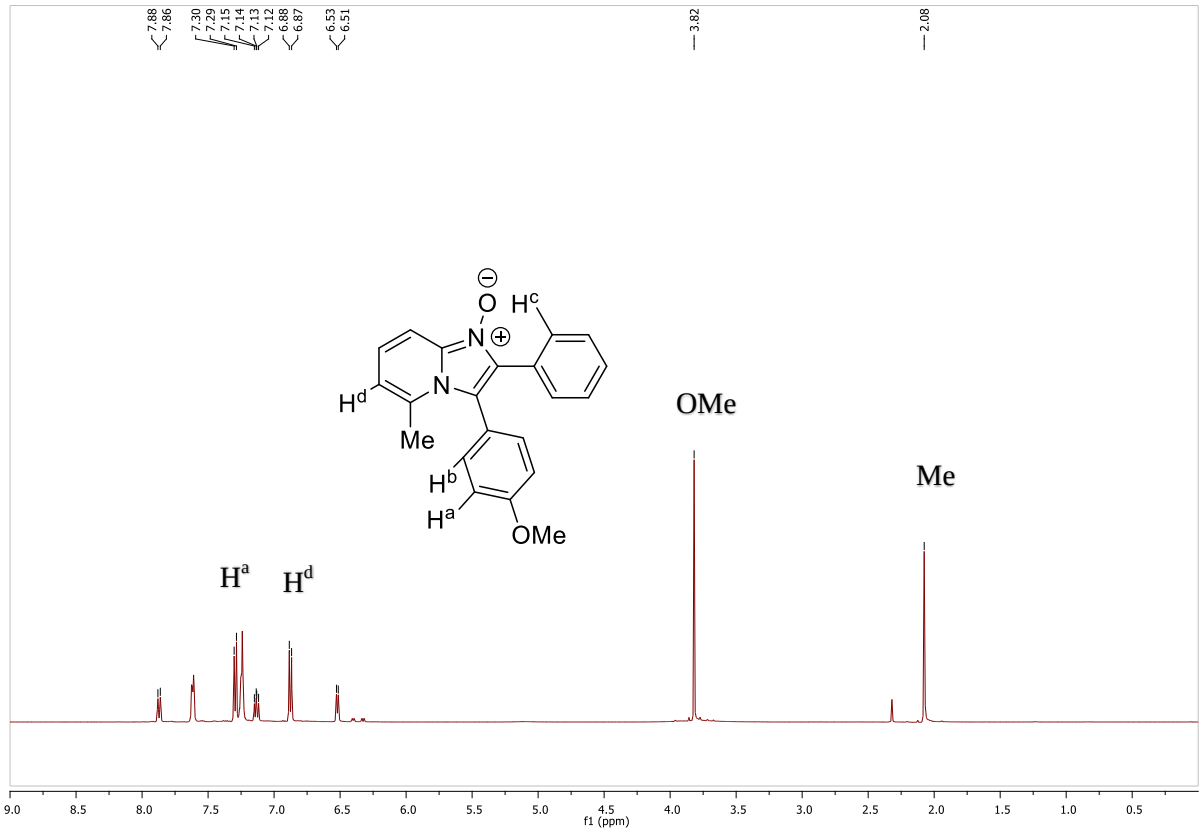
1-D NOE Spectra of Product 151b

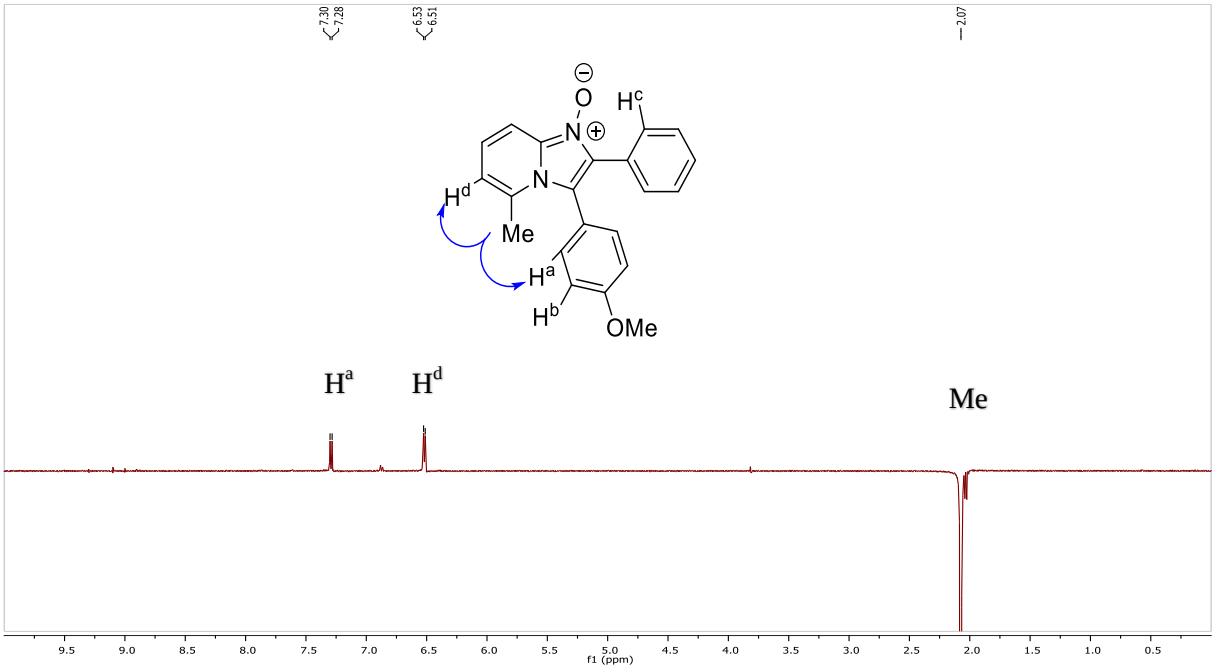


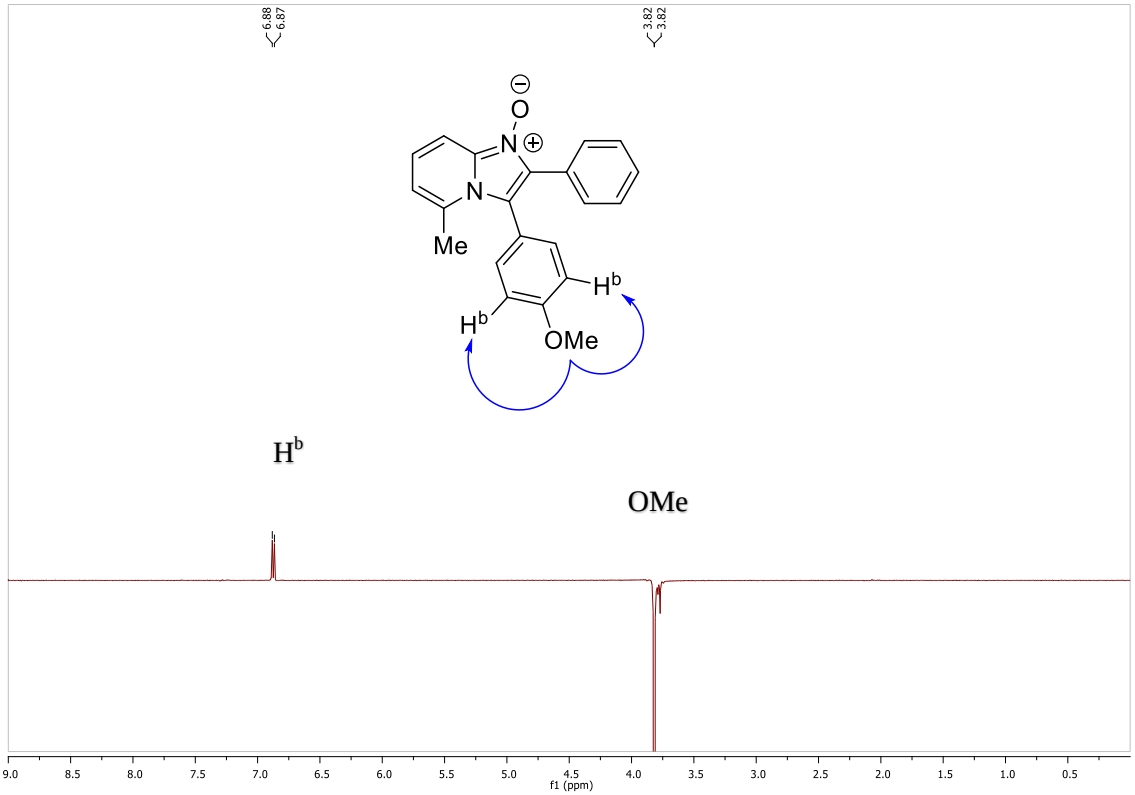


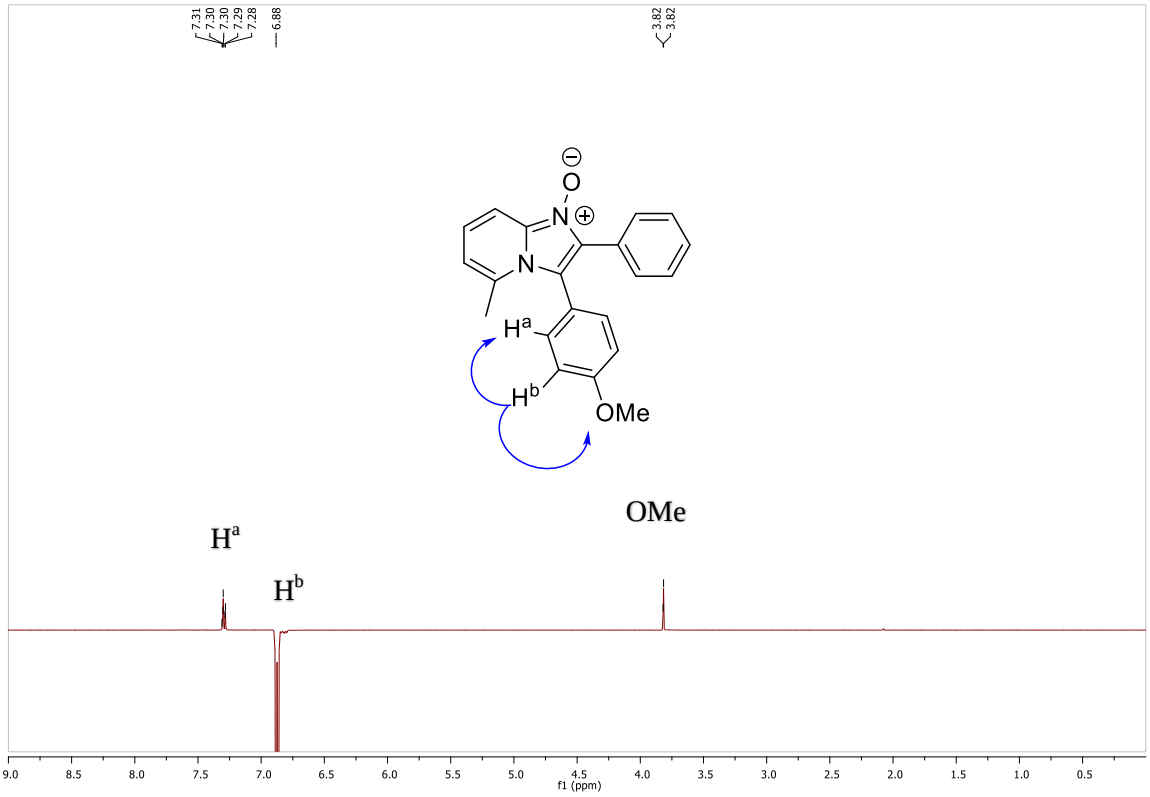


1-D NOE Spectra of Product 189j

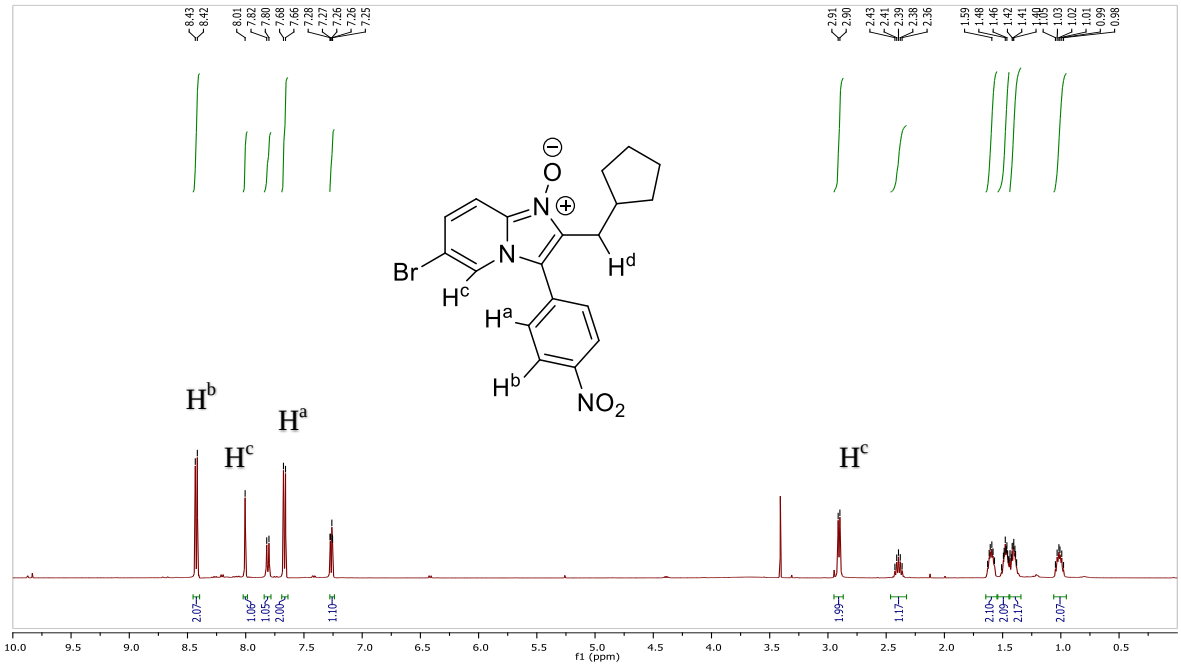


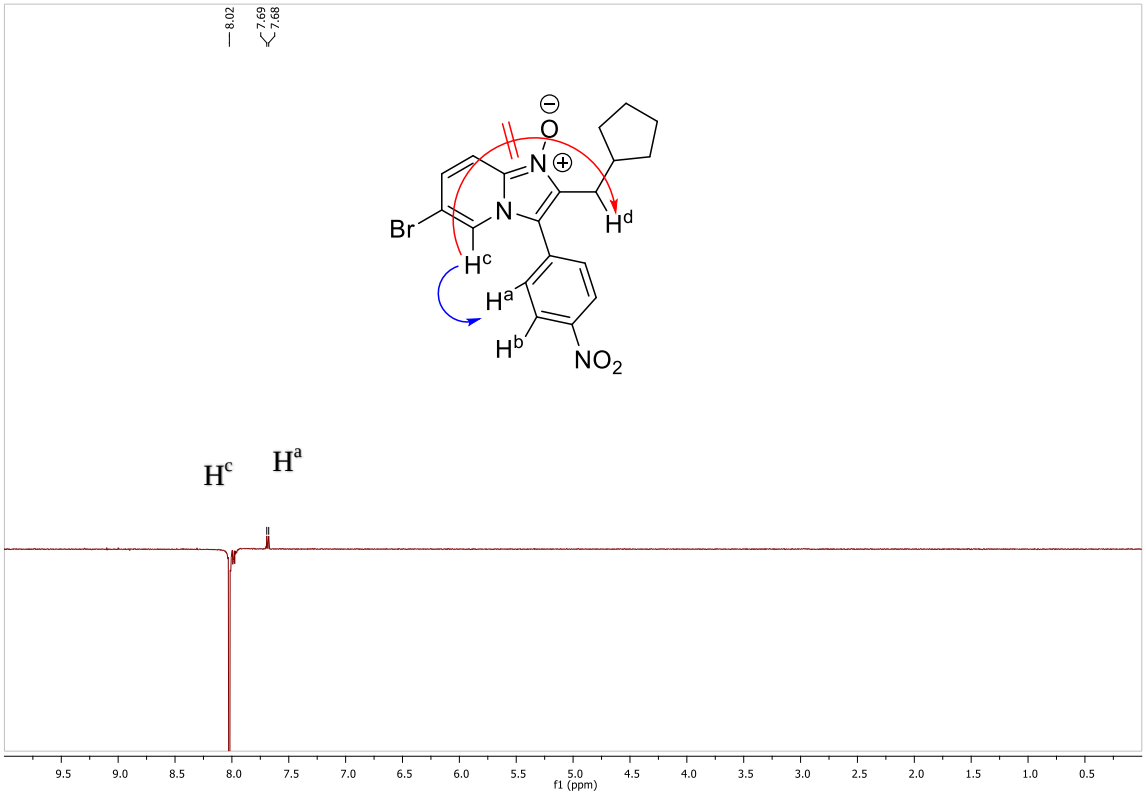


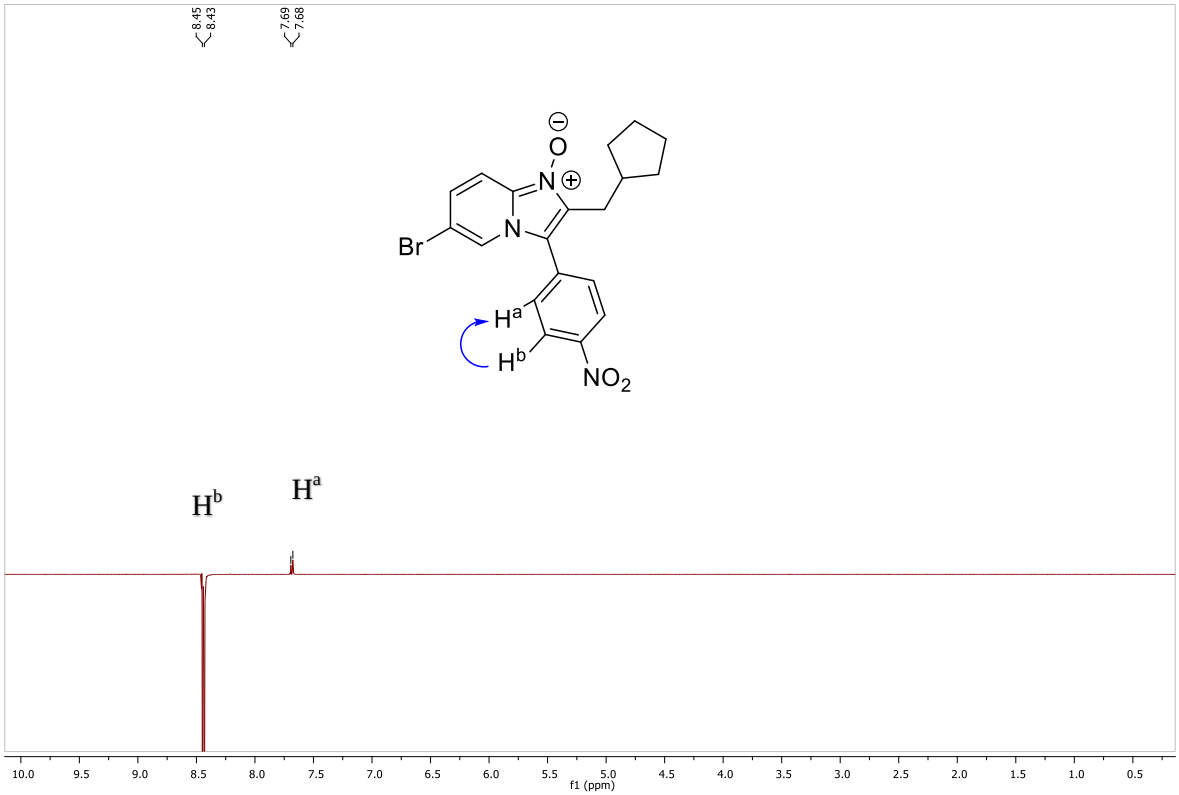

6.88
6.87
3.82
3.82
O
N
N
Me
H^b
H^b
OMe
H^b
OMe
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

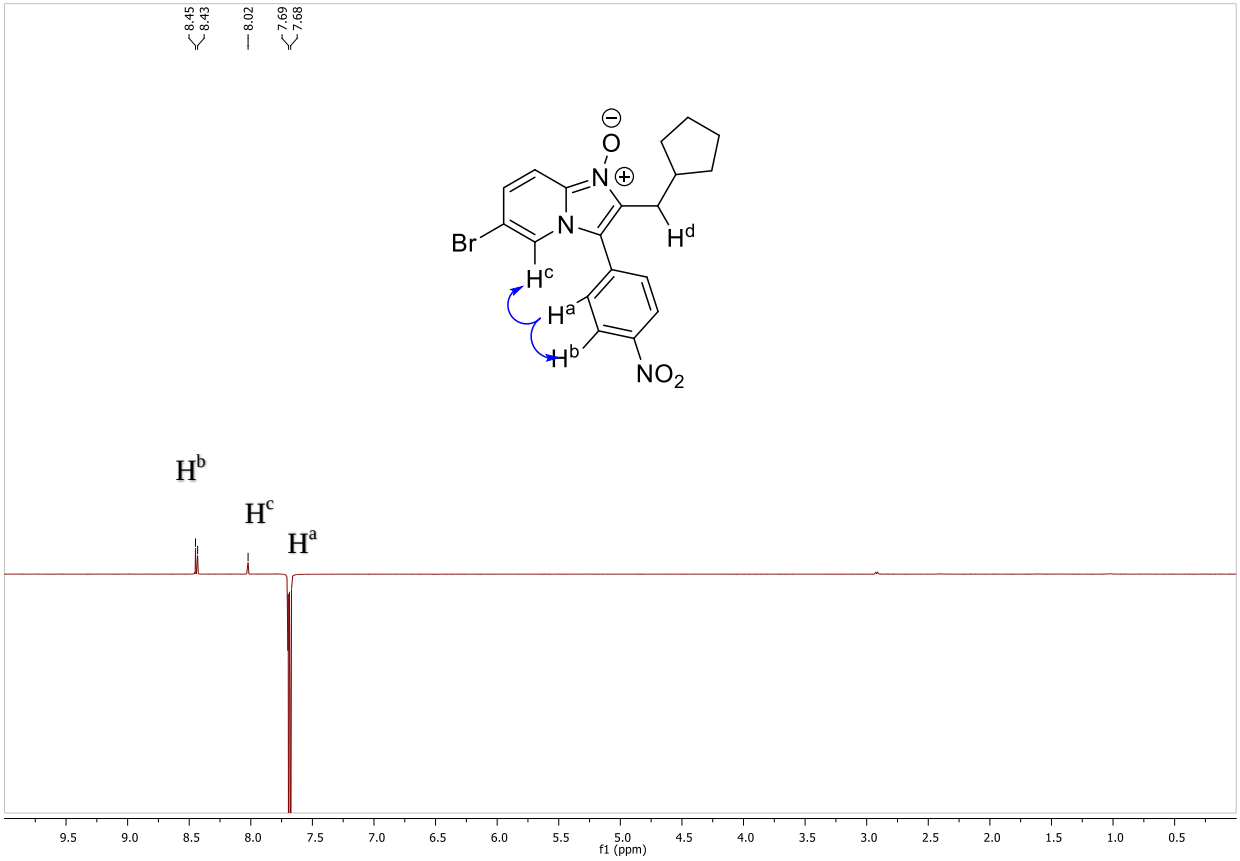

7.31
7.30
7.30
7.29
7.28
6.88
3.82
3.82
O
N
N
H^a
H^b
OMe
OMe
H^a
H^b
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

1-D NOE Spectra of Product 191c

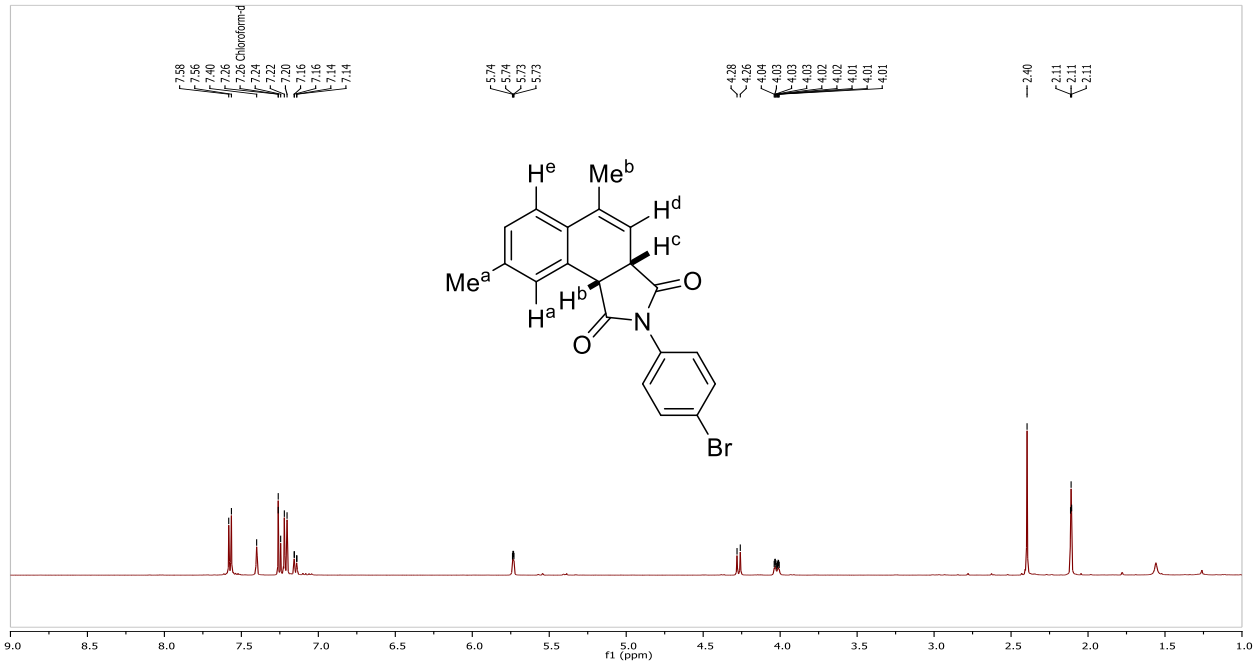


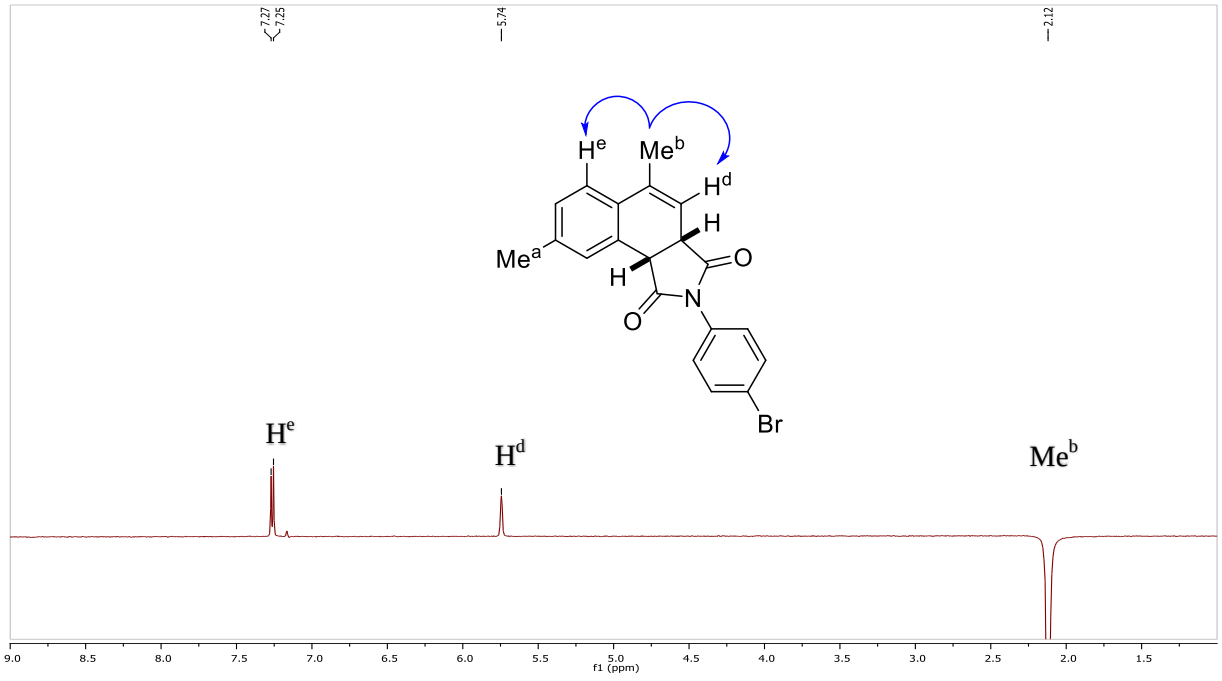


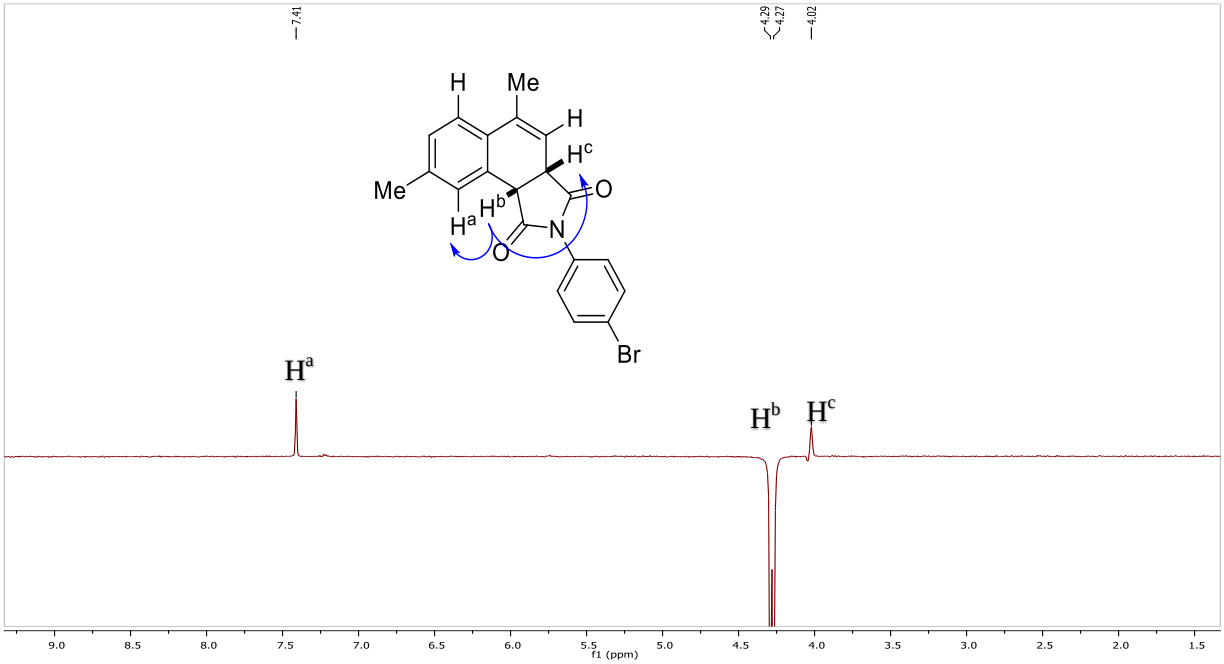

8.45
8.43
7.69
7.68
O
N
N
Br
Ha
Hb
NO2
Hb
Ha
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

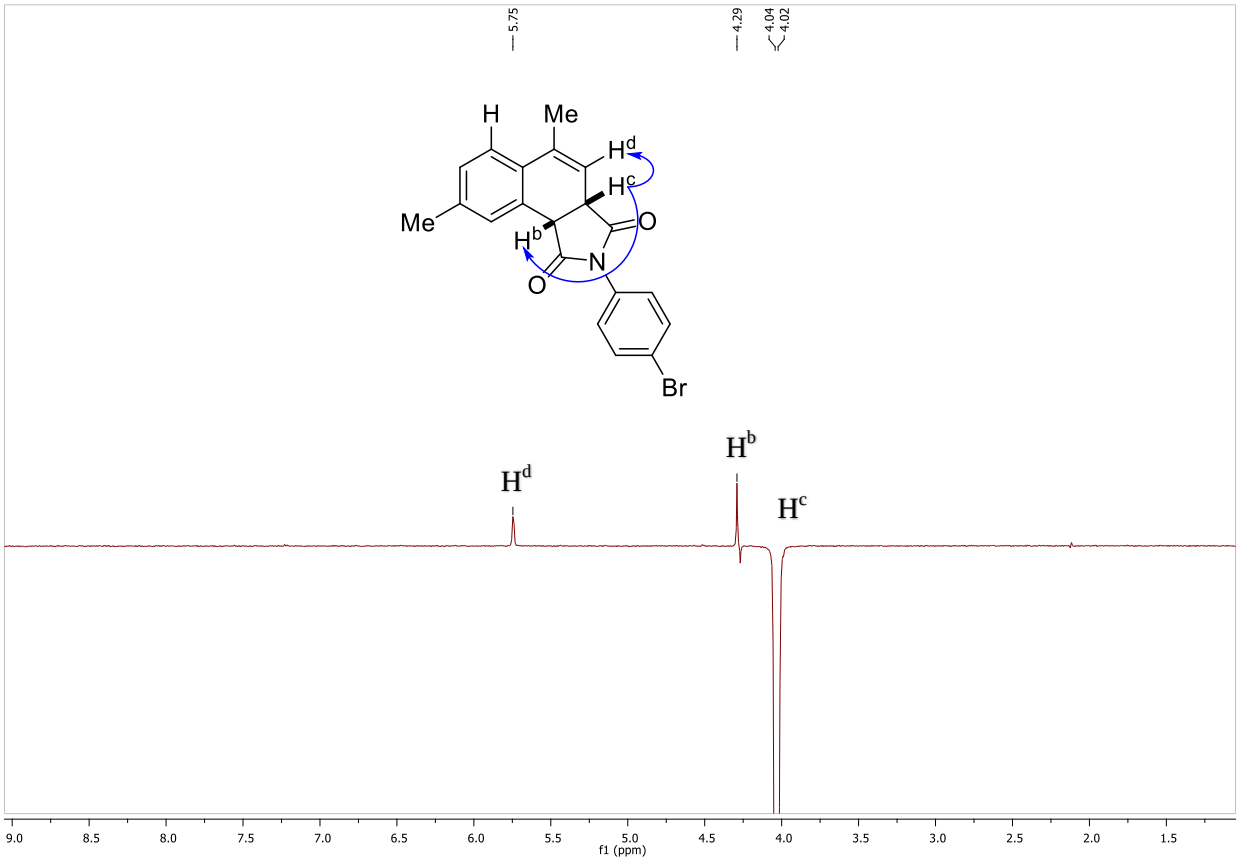

8.45
8.43
8.02
7.69
7.68
O
N
N
Br
Hd
Hc
Ha
Hb
NO2
Hb
Hc
Ha
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

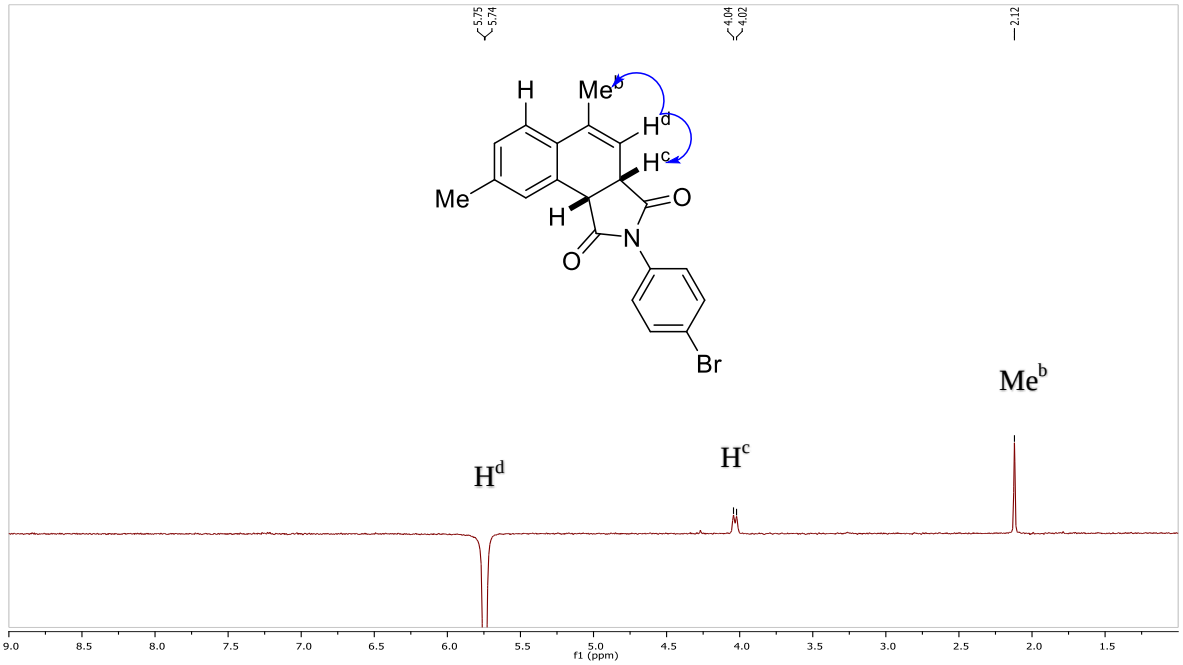
1-D NOE Spectra of Product 214i

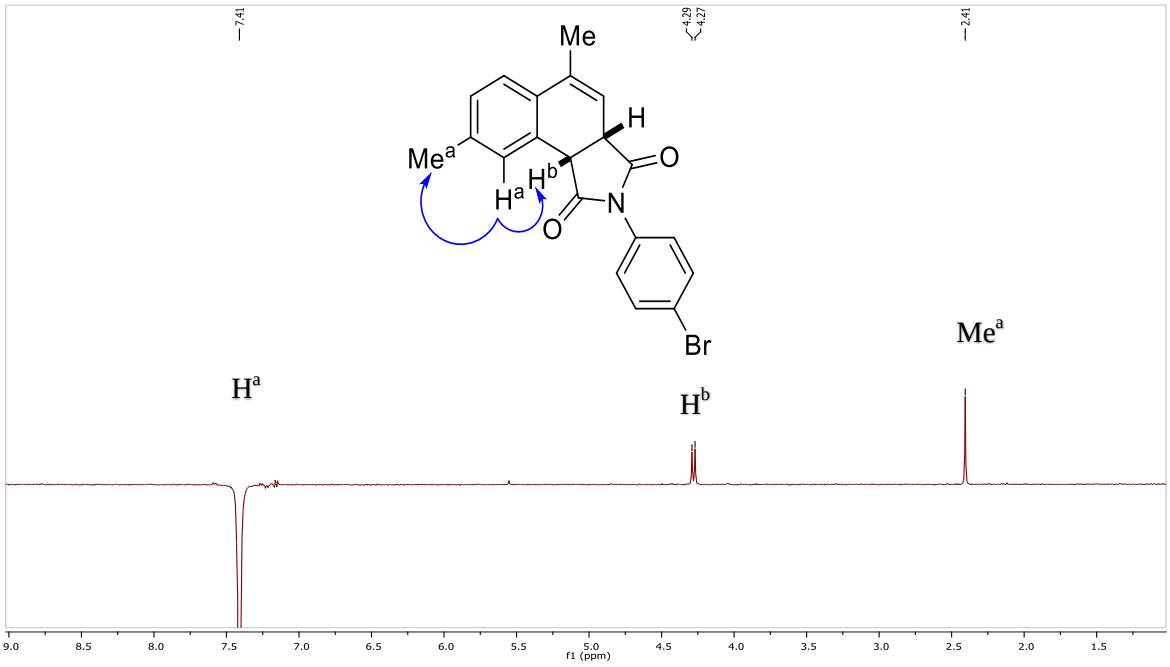




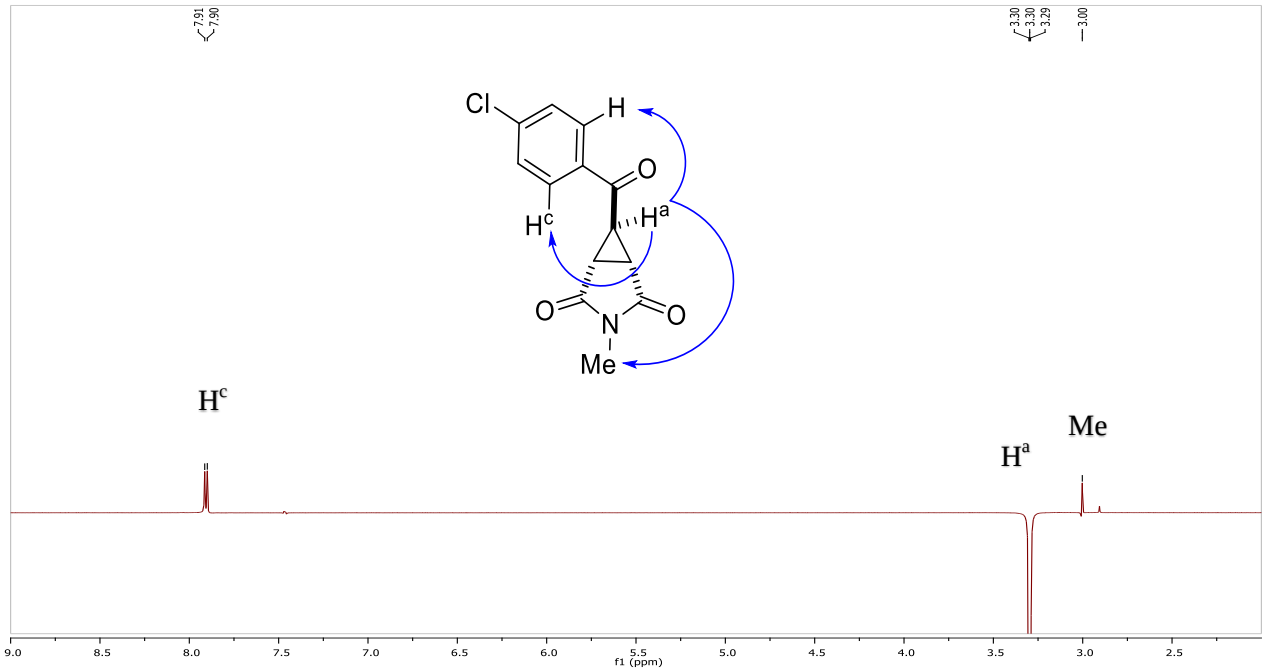

7.41
4.29
4.27
4.02
H
Me
H
H^c
Me
H^b
H^a
O
N
O
Br
H^a
H^b
H^c
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

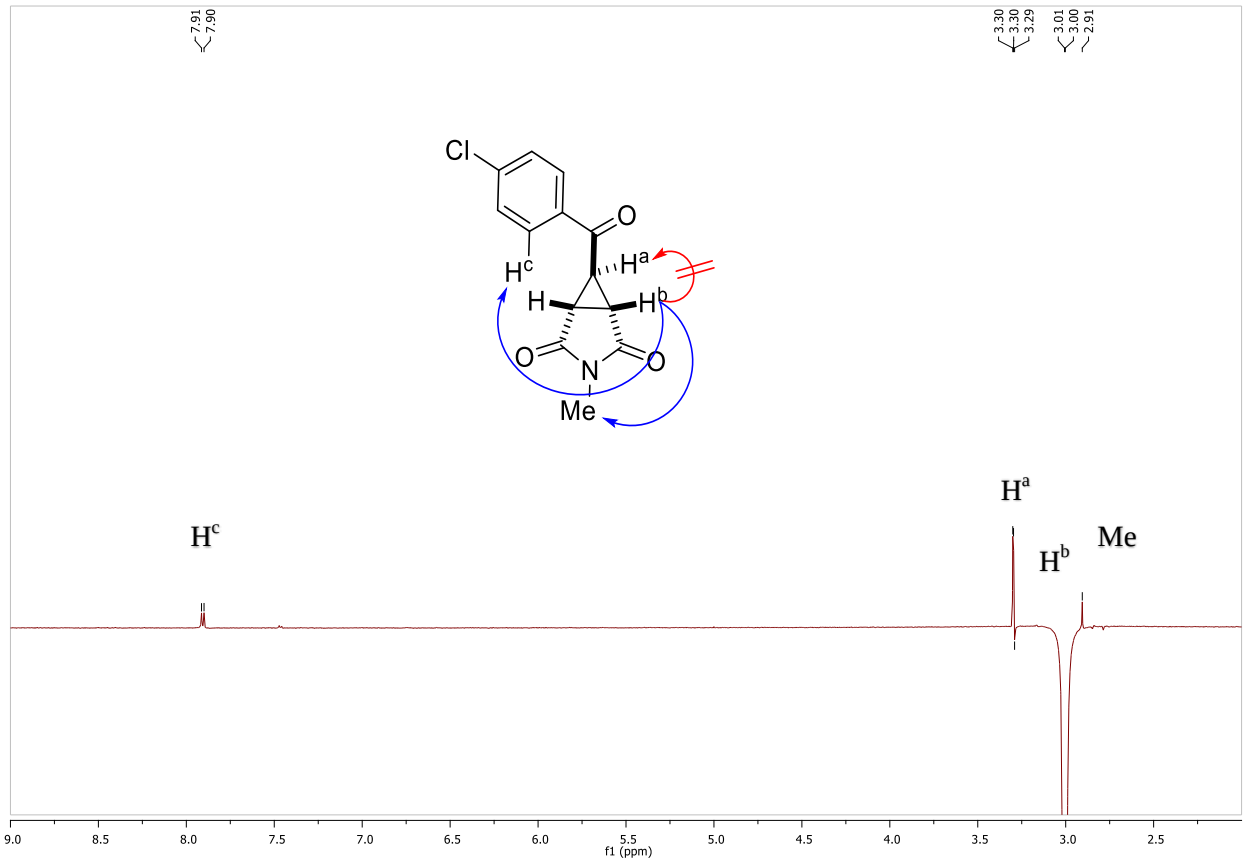

5.75
4.29
4.04
4.02
H
Me
H^d
H^c
Me
H^b
O
N
O
Br
H^b
H^d
H^c
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


5.75
5.74
4.04
4.02
2.12
H
Me
b
H
d
H
c
Me
H
O
N
O
Br
Me
b
H
d
H
c
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)


7.41
4.29
4.27
2.41
Me
H
Me
a
H
b
H
a
O
N
O
Br
Me
a
H
a
H
b
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
f1 (ppm)

1-D NOE Spectra of Product 229j





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II List of Abbreviations

Å	Ångström
Ac	acetyl
Alk	alkyl
aq.	aqueous
Ar	aryl
atm	atmospheric pressure
BHT	2,6-di-*tert*-butyl-4-methylphenol
bipy	2,2'-bipyridine
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
BDE	bond dissociation energy
Bz	benzoyl
BPO	benzoyl peroxide
BQ	1,4-benzoquinone
c-	cyclo
CDC	cross-dehydrogenative coupling
calc.	calculated
cat.	catalyst
cod	1,5-cyclooctadien
conv.	conversion
COMAS	Compound Management and Screening Center
Cu	copper
Cp*	pentamethylcyclopentadiene
Cy	cyclohexyl
δ	chemical shift
d	doublet
DCE	1,2-dichloroethane
DCP	di-cumyl-peroxide
DCM	dichloromethane
dd	doublet of doublet
DG	directing group

DTBP	di-*tert*-butyl peroxide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DME	dimethoxyethane
DMSO	dimethyl sulfoxide
DTBP	di-*tert*-butyl peroxide
dt	doublet of triplet
d.r.	diastereomeric ratio
dtbpy	4,4'-di-*tert*-butyl-2,2'-bipyridyl
E	electrophile
Ed.	edition
(*E*)	trans-isomer
EWG	electron-withdrawing group
EI	electron ionization
equiv	equivalent
ESI	electronspray ionization
Et	ethyl
FG	functional group
g	gram
GC	gas chromatography
h	hour
Hal	halogen
Het	hetero(aryl)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
Hex	hexyl
HPLC	high performance liquid chromatography
HR-MS	high resolution mass spectrometry
Hz	Hertz
i	iso
^{i}Pr	isopropyl
IC_{50}	half maximal inhibitory concentration
IR	infrared spectroscopy
J	coupling constant
KIE	kinetic isotope effect
L	ligand

LED	light-emitting diode
m	multiplet
m-	meta
M	molar
$[M]^+$	molecular ion peak
Me	methyl
mg	milligram
MHz	megahertz
m-CPBA	*meta*-chloroperoxybenzoic acid
min	minute
mL	milliliter
mmol	millimol
MS	molecular sieve
m/z	mass-to-charge ratio
n	normal
N	normality
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
NOE	nucler overhauser effect
Nu	nucleophile
o-	ortho
oct	octane
p-	para
pent	pentyl
Ph	phenyl
Piv	pivaloyl
PIDA	iodosobenzene Diacetate
PTSA	*p*-toluenesulfonic acid
PIFA	iodosobenzene bis(trifluoroacetate)
PMP	*p*-methoxyphenyl
ppm	parts per million
Pr	propyl
Py	pyridyl
q	quartet

RT	room temperature
rel	relative configuration
ref.	reference
s	singlet
sat.	saturated
sec	secondary
SET	single electron transfer
t	triplet
T	temperature
TBAA	tetra-n-butylammonium acetate
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TEMPO	2,2,6,6-tetramethylpiperidin-1-yloxy
TMEDA	tetramethylethylenediamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TM	transition metal
UV	ultraviolet
v/v	volume/volume percent
$\tilde{\nu}$	frequency
wt%	weight by volume
X	(pseudo)halide
(*Z*)	*cis*- isomer
[α]	specific rotation
'''''''	relative configuration
▬	relative configuration

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IV Eidesstattliche Versicherung (Affidavit)

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Belehrung:	**Official notification:**
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2. Oral presentation, *Metal Free C-H Bond Amination: A Novel Method for Synthesis of Heterocycles*, 24th July, 2016, Academie Klausenhof meeting, Germany.

3. Poster presentation, *Copper Catalyzed C (sp^3)-H Bond Functionalization : Synthesis of Cyclopropanes*, 5th July 2016, BOS Symposium, Riga, Latvia.

4. Poster presentation, *Metal Free C-H Bond Functionalization: A Novel Method for Synthesis of Heterocycles*, 22nd April 2016, MSCEC, Münster, Germany.

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